The Role of the Medial Temporal Lobe in Discriminating Complex Object and Scene Stimuli

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Summary

The emergent memory account (EMA) proposes that the medial temporal lobe (MTL), a region implicated in declarative memory, supports perception. EMA hypothesises that the perirhinal cortex (PRC) and hippocampus (HC), form complex conjunctions of objects and scenes, respectively, which can support fine-grained perceptual discriminations. This thesis combined both neuropsychological and functional imaging approaches, to examine the representations supported by the MTL. The final experiment applied one of the tasks in cognitive-genetic neuroimaging of Alzheimer's disease (AD).

Consistent with EMA, patients with focal HC damage showed impaired learning of spatial, but not object, conjunctions (Chapter 2), and showed specific deficits in scene perception (Chapter 3). A complementary functional imaging study examined contributions of PRC and HC to the detection of object and scene differences, respectively; the predicted effects – PRC activation for object discrimination; HC for scene discrimination – were evident only at a relaxed statistical threshold. Significant MTL effects were demonstrated using an oddity task with items presented from different views (Chapter 4). Increasing object and scene feature overlap, however, did not increase PRC and HC activity; the opposite pattern was evident for scenes, with a novel context by feature overlap interaction for objects. In the final experimental Chapter (Chapter 5), it was found that young healthy adults at increased genetic risk of AD (ApoE-e4 carriers) showed increased scene-related activity in posterior cingulate cortex (PCC); a region affected, structurally, early in AD.

The novel contributions of these findings are detailed in the General Discussion (Chapter 6). Briefly, they partially confirm EMA's predictions that the HC is necessary for learning conjunctive scenes, and that MTL involvement fractionates according to the stimulus to-be-processed. It also describes limitations of the experiments, proposes future challenges for representational accounts, and outlines experiments to elucidate the effect of ApoE-e4 on scene-related activity in PCC.

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Chapter 1: Introduction

Memory is fundamental to our beliefs, social interactions and the ways in which we navigate around the world. Developing a good understanding of the cognitive and neuroanatomical architecture of memory, and how it can be affected after brain injury, is, therefore, a major goal of cognitive neuroscience. Damage to particular brain structures, such as the hippocampus and adjacent sub-structures within the medial temporal lobe (MTL), results in every-day memory problems, including poor memory for details of a holiday, who called on the telephone previously and the location of objects in an environment (e.g., where one parked the car). These problems are often mirrored in sensitive laboratory tasks, such as poor memory for details of a spoken passage, slower learning of words and impaired retrieval of details about a previously presented complex visual figure. A key question in this research field is how the hippocampus and related brain structures in the MTL, in particular the perirhinal cortex, support memory; for example, it is not clear what types of memory are critically dependent upon these brain regions and whether they play a role only in memory (or go beyond memory to other cognitive domains, such as perception).

These questions are addressed here in a series of studies that focus on the contribution of MTL structures to the representation of object and spatial information, and how perceptual representations stored in these brain regions might underpin memory. The reason for investigating these specific questions is that they are of particular relevance to recent representational models of MTL function. Briefly, in one of these models, the Emergent Memory Account (EMA),

the division of labour in the MTL is governed by the type of stimulus to-be-processed, with the perirhinal cortex and hippocampus supporting the processing of conjunctive object and scene stimuli, respectively (Graham, Barense, & Lee, 2010).

This framework differs markedly from more longstanding memory models in which different regions in the MTL are considered to form a unitary system (e.g., Squire, Wixted, & Clark, 2007), to be distinguishable on the basis of the processes they support (e.g., Aggleton & Brown, 1999), or in terms of the kinds of information that are subject to processing (e.g., Diana et al., 2007). Of at least equal importance for EMA and its departure from other models is the assumption that memory for material is supported by the same regions that are involved in the perception of that material. The experiments described in this thesis, therefore, have been designed to address whether, and if so how, different sub-regions in the MTL support perception, with the outcomes also being of relevance to the question of how the MTL supports memory. The specifics of the individual experiments are given within Chapters 2-5, and summarised at the end of this Introduction. This summary is preceded by an account of competing memory models of MTL function, emphasising data points that have prompted the development of models in which content rather than process is to the fore. The Introduction also details the literature relevant to the question of the roles of the MTL in perception, on which issue long-standing memory models either stand in opposition (e.g., Squire, Wixted, & Clark, 2007) or are agnostic by dint of no direct consideration of the issue (e.g., Aggleton & Brown, 1999).

The data points relevant to this proposed role of the MTL in perception stem from findings in studies in human participants, but also in non-human primates and rats. Different species, populations and experimental approaches permit different kinds of inferences, and provide a powerful means of understanding neural and cognitive function. For this reason, the experiments described in this thesis are a mix of neuropsychological and functional magnetic resonance imaging (fMRI) studies, with the findings in combination offering new insights into the cognitive processes the MTL supports and how the MTL contributes to human memory.

1.1. Overview of Chapter 1

This Chapter provides an account of relevant research examining the role of the MTL in memory and perception, leading to an overview of the experiments detailed in this thesis. In Part 1 (Section 1.3), I review evidence from early lesion studies that led researchers to propose that the MTL supports declarative memory in a relatively undifferentiated way (a unitary account), before moving onto a discussion of the dual process accounts, which suggests different composite structures of this region support different declarative memory processes. Part 2 (Section 1.4) provides details of research that motivated a paradigm shift in the study of the MTL by suggesting that the type of information to-be-processed may be the governing principle for the involvement of different subregions (binding of item and context), and more controversially that these regions may support perception (representational accounts). Finally, Part 3 (Section 1.5) outlines the experiments detailed in this thesis and describes how they address some outstanding questions of particular relevance to EMA.

1.2. The anatomy of the MTL

The MTL comprises a number of interconnected structures; the perirhinal cortex (PRC), entorhinal cortex (ERC), parahippocampal cortex (PHC) (collectively referred to as the parahippocampal gyrus (PHG)), and hippocampus (HC). The PRC is located in the antero-medial portion of the MTL, whereas the PHC is located at the posterior extent of the MTL, and lies inferior to the HC and ERC. The HC formation consists of HC subfields CA1-4, the dentate gyrus and the subiculum. Due to the limited spatial resolution in the imaging experiments detailed in this thesis, I will not distinguish between subregions of the HC in the experimental chapters.

The ERC is the primary route through which information enters the HC, and the PRC and PHC (the PHC is known as the postrhinal cortex in rats; Burwell, 2000) provide the majority of input to the ERC (there are also a number of direct connections between the PRC and PHC: Suzuki & Amaral, 1994). The PRC and PHC, however, have different cortical afferents, and in turn project onto different regions of the ERC. Whilst the PRC receives the majority of its inputs from unimodal visual areas in the temporal lobe such as TE and TEO, the PHC receives the majority of its inputs from polymodal sensory areas including the cingulate gyrus, retrosplenial cortex, and posterior parietal lobe (Burwell, 2000). This unimodal and polymodal sensory information remains segregated by distinct connections from the PRC and PHC to the lateral and medial ERC, respectively. In turn, the ERC projects onto the HC maintaining this rostral-caudal distinction; PRC, therefore, has indirect connections to rostral HC, whereas PHC has a greater number of indirect connections with caudal HC (Aggleton, 2012). Information is fed forward through the ERC into the HC,

where it passes through the dentate gyrus, CA3 – CA1 subfields and the subiculum.

Although there are between-species differences in the anatomy of structures within the MTL, for example the primate PRC is thicker than the rodent's (Burwell, 2000), there is considerable consistency in the organisation of this region across rats, monkeys, and humans (see Figure 1.1). This anatomical consistency benefits translational research as it allows for the use of similar experimental paradigms across a number of different species, and has been of particular importance in establishing the representational accounts of MTL function that are the focus of this thesis.

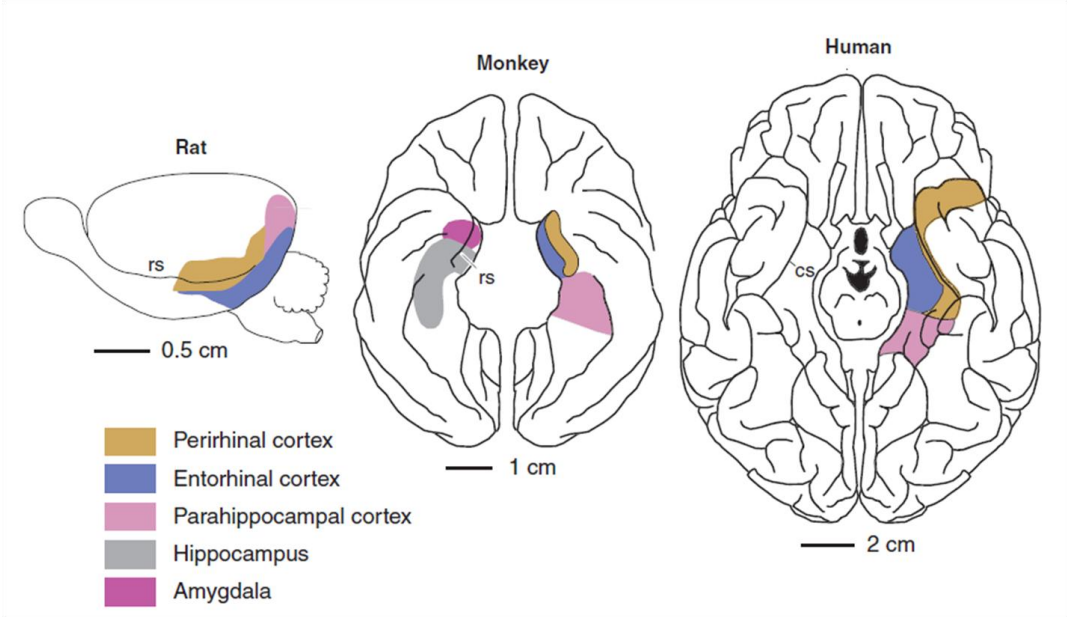

Figure 1.1. ***The medial temporal lobe and composite structures in the rat (lateral view), monkey, and human brain (medial view). Figure from Murray, Bussey, and Saksida (2007).***

1.3. Part 1: The MTL memory system and declarative memory

1.3.1. Early lesion research and the unitary account of memory

The MTL, and particularly the HC, became the focus of memory research after patient HM underwent pioneering surgery to alleviate his severe epilepsy. Scoville (1954) excised a large portion of patient HM's MTL bilaterally, from the tip of the temporal pole extending 8cm posteriorly. The surgery resulted in the removal of brain various structures including the amygdala, ERC, HC and PHG. After the operation, HM was left with profound anterograde amnesia (an inability to create new memories of events); consequently, he was unable to recall having had the operation or recent discussions with hospital staff. Performance in other cognitive domains, however, was thought to be unaffected. For example, HM's intelligence score improved after surgery. On tests of rule learning/switching, such as the Wisconsin Card Sorting Task, HM made very few errors. Equally, his perceptual abilities appeared normal. When asked to detect a face from shaded component elements (Mooney faces) his performance matched controls, and he was able to detect objects from impoverished line drawings at the same rate and with the same accuracy as controls (Milner, Corkin, & Teuber, 1968).

Formal neuropsychological testing revealed the extent of HM's selective memory impairment. For example, on the "associate learning" subtest of the Wechsler Memory Scale (Wechsler, 1945) in which he was required to remember word pairs, HM scored zero for difficult word associations, and achieved low scores, relative to population norms, for easy word associations (Scoville & Milner, 1957). Similarly, relative to a patient with frontal damage, HM made a greater number of errors in a task requiring him to select faces to which

he had been previously exposed (Milner et al., 1968). Furthermore, when asked to remember a list of numbers, HM performed normally if he was allowed to rehearse them; his memory for the numbers rapidly declined when he was prevented from doing this.

Critically, HM's performance on other tasks suggested that he did not have a global problem with retaining new information. In one such task, HM was asked to trace in between two star shapes whilst viewing his hand only in a mirror's reflection. He made fewer errors over successive days of testing on this task despite reporting that he did not remember completing the task previously (Milner, 1962). This effect was later seen in a group of amnesic patients with MTL damage who became progressively quicker at reading words reflected in a mirror (Cohen & Squire, 1980). Unlike healthy control participants, however, during a subsequent test the patients were not quicker to identify words they had seen previously versus those that were novel. These data suggested that although the amnesic patients could learn the skill of mirror reading, they had no memory for the content of the learning episode. It was argued, therefore, that there must be two different kinds of memory, and these must have different neural substrates (Squire, 1992). This argument led to an account where declarative memory, comprising conscious memory for facts and events, is reliant upon the integrity of the MTL. Nondeclarative memory, in contrast, comprises all forms of non-conscious memory (such as skill-learning), and is reliant on other neural substrates (see Figure 1.2) (Squire, 1992).

In order to understand how damage to these brain structures affected HM's memory, researchers attempted to develop an animal model of MTL amnesia, to test systematically the exact structures required to support

declarative memory. The first challenge for researchers was to develop an analogue of human declarative memory tasks in animals. Discrimination learning paradigms were commonly used to test animal memory in the 1960s and 70s (Squire & Zola-Morgan, 1991), but these tasks were not particularly sensitive to HC lesions. In discrimination learning, items are presented either singly, or in pairs (e.g., two different junk objects) and there is gradual learning, over many hundreds of trials, of the items associated with reward. Notably, however, application of this approach in animals with focal HC lesions did not impair memory performance, and this led to the conclusion that the HC may not contribute to declarative memory (for review see Douglas, 1967). It was proposed, however, that, as learning occurs slowly over a relatively large number of trials, these tasks may be more akin to skill learning and reflect the nondeclarative memory that is spared in human amnesic patients (Gaffan, 1972).

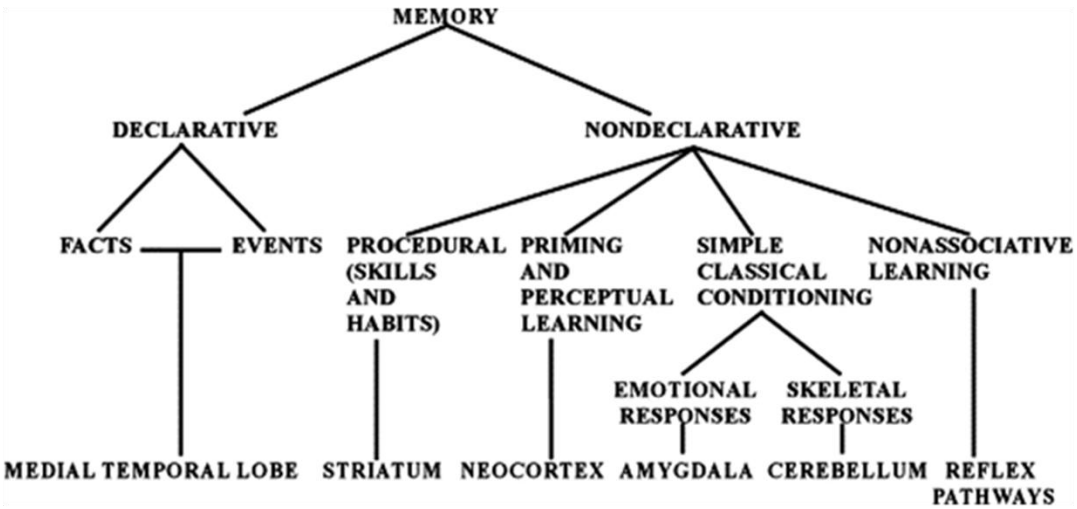

Figure 1.2. ***The declarative versus nondeclarative memory distinction proposes that conscious memory for facts and events is supported by the MTL, whereas as all other types of learning and memory are supported by other neural substrates. Figure from Squire (1992).***

The delayed match to sample (DMS) task benefitted from not requiring extensive exposure to stimuli. In this paradigm, a number of target items (for example junk object items) are presented singly. These items are then presented again paired with a new item; for reward, the animal is required to select the item to which it has already been exposed (Gaffan, 1974). More recent versions of this task include the delayed non-match to sample (DNMS) task which takes advantage of an animal's natural tendency to explore novel items, and the novel object recognition (NOR) task where the dependent variable is the amount of time spent viewing or exploring a novel stimulus. The latter has the advantage of requiring no overt training of the animal. These tasks are thought to tap recognition memory, which operationally is the identification (which can be measured in various ways) of items to which a subject has already been exposed.

Gaffan (1974) tested monkeys with fornix lesions on a DMS and a discrimination learning task. Fornix lesions functionally lesion the HC by removing cortical connections to this structure; an advantage of this approach is that it limits extra-HC damage during surgery. In the DMS task, fornix lesions resulted in significantly poorer memory for the previously exposed item, and accuracy decreased as the delay (10-130 seconds) between sample and test presentation increased. In contrast, performance on the discrimination learning task was matched across control animals and the fornix group. This outcome was consistent with the view emerging from the human literature that the HC supports only some kinds of memory, and provides evidence for a potential separation between declarative and nondeclarative memory.

In early animal models, the amygdala was also identified as being integral for normal declarative memory performance, given that damage to both the HC and amygdala resulted in profound memory deficits (e.g., Mishkin, 1978; Zola-Morgan, Squire, & Mishkin, 1982). It was noted, however, that surgical procedures used to excise the amygdala caused inadvertent damage to surrounding cortex (including PRC, ERC, and PHG), and it was this inadvertent damage that resulted in impaired DNMS performance in monkeys (Zola-Morgan, Squire, & Amaral, 1989). Stereotaxic lesions of the HC and surrounding cortex resulted in more profound memory impairments than focal amygdala, or combined amygdalo-HC lesions. Furthermore, in a separate DNMS task with monkeys, memory deficits resulting from lesions to the PRC and PHG were equivalent to those resulting from combined amygdalo-HC lesions (Zola-Morgan, Squire, Amaral, & Suzuki,1989). These data suggested, therefore, that declarative memory was supported by a MTL memory system comprising the HC, PRC, ERC, and PHG.

These studies highlight the importance of MTL regions in memory and a number of theories have been proposed for how these structures interact to support declarative memory. One of these is the unitary process account (Squire & Zola-Morgan, 1998). Although this account does not necessarily ascribe the same role in memory to all structures within the MTL (Squire, Wixted, & Clark, 2007), it suggests that they work in concert as a declarative memory system, distinct from other cognitive faculties such as perception (Squire & Wixted, 2011). There are a number of key predictions from this account: 1) the degree of declarative memory impairment will correlate with the extent of MTL damage (Scoville & Milner, 1957; Squire, Wixted, & Clark, 2007), 2) perception is a separate cognitive function and will not be affected by MTL

damage, and 3) memory impairments after MTL damage will not be modulated by the type of information to-be-remembered, for example different types of stimuli (all other factors being equal). As described below, none of these predictions have gone unchallenged. First, however, a competing class of theoretical accounts is introduced.

1.3.2. Dual process accounts of memory

Consistent with the unitary account of memory, dual process accounts propose that the MTL supports declarative memory. These accounts are based on cognitive models in which recognition memory is supported by two processes, familiarity and recollection (for review see Yonelinas, 2002, for an important precursor see Mandler, 1980). Familiarity is a scalar strength signal that permits judgments of prior occurrence. Recollection is recovery of contextual information about an event. Aggleton and Brown (1999) mapped these memory processes onto distinct structures within the MTL, with the PRC and HC supporting familiarity and recollection, respectively.

In the next section, animal studies relevant to the role of the PRC in familiarity, and human neuropsychological and fMRI data supporting evidence of a division of labour within the MTL according to memory process, will be reviewed.

Despite the initial finding that fornix lesions resulted in impaired DMS performance (Gaffan, 1974), in subsequent research these lesions had little or no effect on recognition memory performance using DNMS and DMS tasks in monkeys (Bachevalier, Parkinson, and Mishkin, 1985; Bachevalier, Saunders, and Mishkin, 1985), and DNMS tasks in rats (e.g., Rothblat & Kromer, 1991).

These data prompted a re-evaluation of the unique contribution of individual regions of the MTL to recognition memory. Studies previously implicating the HC in successful DMS/DNMS task performance had used ischemic lesions, the exact pathology of which is difficult to quantify (Aggleton & Brown, 1999). By contrast, focal HC lesions, that spared the surrounding rhinal cortices, did not impair DNMS performance in rats (Mumby et al., 1996), and deficits in memory were evident in monkeys only after a delay of 10 minutes between sample and test (Alvarez, Zola-Morgan, & Squire, 1995). Furthermore, combined excitotoxic lesions of bilateral amygdala and HC failed to elicit a DNMS deficit in monkeys even after a delay of up to 40 minutes (Murray & Mishkin, 1998), replicating the relatively mild effects of fornix lesions on DNMS task performance (Gaffan, 1994). These data suggested that the HC is not necessary for performance on these tasks. In so far as successful DMS and DNMS performance can be based on relative familiarity, these data suggest that MTL regions other than HC support this process.

The outcomes of studies using a number of different methods including lesion studies, c-fos expression, and single cell recordings, converge on the view that non-HC MTL regions, in particular the PRC, can support familiarity. Meunier, Bachevalier, Mishkin, and Murray (1993) found that rhinal lesions (comprising both ERC and PRC) impaired DNMS performance in monkeys. This impairment stemmed, however, from PRC damage, as indicated by the relatively mild effects of focal ERC lesions. Furthermore, the extent of the memory deficit correlated with the level of damage to the PRC (Meunier et al., 1993, 1996; Murray & Mishkin, 1986), and was not exacerbated by lesions to the HC (Meunier et al., 1996). Similarly, levels of c-fos expression in the rat PRC (an indirect marker of neuronal activity) revealed greater concentrations of

this protein associated with new items relative to ones to which the rats had already been exposed (Zhu, McCabe, Aggleton, & Brown, 1997). Finally, the profile of cell firing rates within the monkey PRC revealed that this region could provide a familiarity signal (Brown & Xiang, 1998); PRC cells fired more frequently when presented with a new item, but declined in firing rate after repeated exposure. Together, these data suggest that the PRC can support decisions about the prior occurrence of an item, presumably based on a familiarity signal.

To what extent do these findings converge with those from human neuropsychological studies? It is important to note here that patients with focal PRC lesions that spare the HC are particularly rare. There is one case described in the literature, however, in which the outcomes of three separate assessments suggest a selective impairment in the use of familiarity for memory judgments (Bowles et al., 2007). In light of this difficulty, researchers have commonly used a subtraction method in which the performance of patients with focal HC lesions and patients with extensive MTL lesions (encompassing both the HC and PRC) is compared. In the subtraction approach, relative to controls, deficits in task performance common to both HC and MTL groups would be attributed to the lesions evident in both patients (i.e., the HC). More extensive memory deficits in the MTL group relative to the HC group would be attributed to the extra-HC damage (i.e., the PRC and surrounding cortex). Given that patient HM had gross damage to the MTL encompassing both the PRC and HC, the dual process account would predict impairments in both familiarity and recollection. Focal HC lesions, however, should impair recollection but spare familiarity. This pattern has been demonstrated in patients with lesions limited to the HC (or fornix); such cases show a disproportionate impairment in free recall

(which is not cued) relative to an old/new recognition decision, which is often in the normal range (Aggleton & Shaw, 1996; Tsivilis et al., 2008; Vann et al., 2009).

A number of different paradigms have been developed in an attempt to delineate the contributions of recollection and familiarity to memory decisions and an extensive review of this literature is not provided here (for reviews, see Parks & Yonelinas, 2007; Wixted, 2007; Yonelinas, 2002; Yonelinas & Parks, 2007). The focus below is on evidence from paradigms where recovery of contextual (source) information has been required, as this method is employed in the experiment detailed in Chapter 4 in this thesis.

Recollection entails the recovery of contextual information about an item, for example when or where an item was encountered. Contributions of recollection can therefore be assessed by employing tasks requiring source decisions. In experiments of this kind, items are commonly presented in one of at least two different study contexts (for example, two different colours or screen locations). At test, the study items are presented again (commonly interspersed with foils) and the participant is required to indicate whether the item is old or new, and, if old, the source or context in which it was studied. Correctly identifying an item as ‘old’ but failing to recover the study context can be supported by familiarity because, although the participant is aware the item has been encountered before, recovery of relevant (or at least sufficient) contextual information has not occurred (for considerations of non-criterial recollection see Yonelinas & Jacoby, 1996). Correctly identifying both the item as old and its encoding context is often assumed to be evidence for the contribution of recollection.

Deficits in source memory have been demonstrated in patients with focal HC lesions. Relative to controls, patients have demonstrated intact item memory, but impaired memory for when an item was presented (e.g. Aggleton et al., 2000), or where it was presented (e.g., Chalfonte, Verfaille, Johnson, and Reiss, 1996). These findings suggest a clear link between the HC and the process of recollection.

FMRI studies have been complemented by these neuropsychological findings. FMRI allows researchers to localise regions of the brain that show significantly increased blood oxygen level dependent (BOLD) response, which is commonly used as an index of neural activity. In fMRI studies of human memory, the study portion of the task is often scanned prior to participants completing a subsequent memory test outside of the scanner. This allows the researcher to determine how the level of neural activity at encoding correlates with later memory (also know as 'Dm' effects; Paller, Kutas, & Mayes, 1987; Paller & Wagner, 2002). Study trials are back-sorted to identify those where subsequent judgments were correct or incorrect. In source memory studies activity at study is separated according to whether: 1) both the item and its source have been identified (hit-hit), 2) the item has been identified but the source has not (hit-miss), and 3) the item has not been identified correctly (miss). It is commonly assumed that hit-hit responses are based on recollection, while hit-miss responses are based on familiarity. If the HC is involved in recollection then trials attracting a hit-hit response should elicit greater activity in this region than hit-miss trials. If PRC codes for familiarity then both the hit-hit and hit-miss responses should be associated with greater activity in this region than miss trials, because in both of these trials the item has been correctly recognised as ‘old’. The majority of studies described in the next section

examined encoding-related activity, but there are also studies in which neural activity at retrieval has been investigated. For these studies, the same logic described above is employed to separate responses based upon the processes of recollection and familiarity. In the experiments described below, neural activity was measured at encoding unless it is stated explicitly that activity at retrieval was assessed.

A number of fMRI studies have revealed outcomes consistent with the dual process model. For example, greater activity in the HC was seen when participants subsequently judged correctly whether they had read a word or imagined a scene during study, in comparison to circumstances when they could not do so (Davachi, Mitchell, & Wagner, 2003). Activity in the PRC, however, was greater for words judged correctly to be old and attracting either correct or incorrect context judgments relative to misses. Similarly, the BOLD response in the HC predicted whether participants would recall whether they had made an animacy versus common decision for words and pictures with emotional connotations (Kensinger & Schacter, 2006), whereas PRC/ERC activity was found to predict memory for the items irrespective of the recovery of study context. Moreover, HC activity has been found to correlate with the number of pieces of contextual information retrieved about an item while again PRC only distinguished the prior occurrence of an item (Uncapher, Otten, & Rugg, 2006; but see Gold et al., 2006).

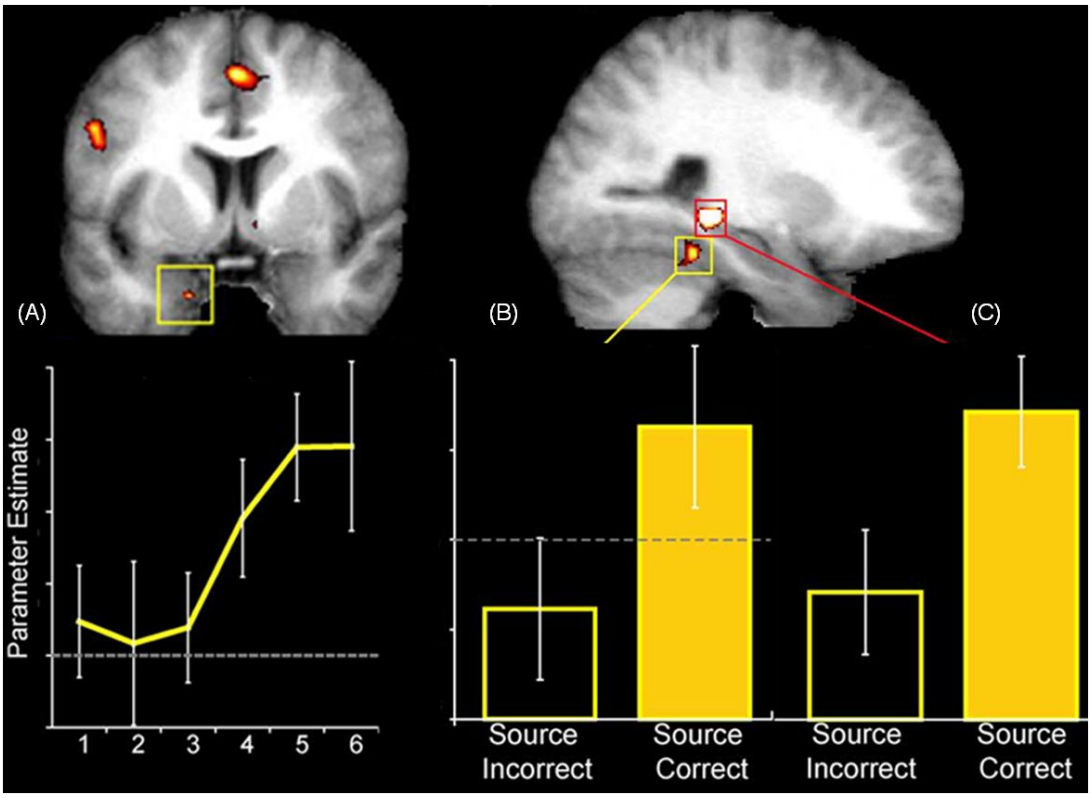

Figure 1.3. ***Subsequent memory effects after recovery of item (A) and source (B, C) information. (A) In PRC there is evidence of a graded pattern of data associated with item memory strength, whereas in (B) posterior PHG, and (C) HC, significantly greater activity is associated with subsequent retrieval of contextual information (Figure adapted from Ranganath et al., 2004).***

In a conceptually related study, Ranganath et al. (2004) presented words in one of two encoding contexts (people made either size or animacy judgments to visually presented words) and in a subsequent memory test were required to indicate their memory confidence for the item (1-6) and the study context. Greater activity in HC was associated with successful retrieval of context. BOLD response in the PRC, however, correlated with the memory strength judgment (see Figure 1.3). This effect in PRC has been replicated in a different study,

involving memory for scenes, over a four point confidence decision (Montaldi et al. 2006). In both of these experiments, confidence judgments were employed as a means of measuring memory strength, the assumption being that regions that show a graded change in activity levels with confidence are associated with the process of familiarity. From the dual-process perspective, recollection is commonly associated with highly confident responses, with confidence ratings thereby providing a means of distinguishing regions that support one or other of these processes. The assumption that only highly confident responses are linked with recollection, however, has not gone unchallenged (e.g., Rotello, Macmillan, Reeder, & Wong, 2005; Wixted, 2007). Resolving this question is important for interpreting neural as well as behavioural data, and many of these arguments have focused around how receiver operating characteristics (ROCs) are interpreted. ROCs plot the profile of hits versus false alarms over a range of confidence levels. They have been employed in animal and human neuropsychological investigations, as well as imaging studies, and while their interpretation remains contentious, the findings in several experiments are consistent with predictions from dual-process models. More specifically, high confidence responses most likely reflect recollection and lead to asymmetric plots shifted to the left, whereas lower confidence responses, most likely to reflect familiarity, result in more curvilinear, symmetrical plots.

The role of the HC in recovery of source memory has also been inferred from increased activity in this region when scanning has been conducted during retrieval. A greater level of signal was evident when participants correctly remembered the location of an object within a grid relative to when the location was forgotten (Cansino, Maquet, Dolan, & Rugg, 2002).

Together, these animal, human neuropsychological and imaging data are consistent with a division of labour within the MTL according to memory process. This account predicts that: 1) familiarity decisions are supported by the PRC, 2) the recovery of contextual information should require the HC. There are data points and theoretical proposals that challenge this account, however, some of which have been acknowledged above. Below, a third class of views is considered where an important division is made around the kinds of memory contents that are processed by MTL sub-structures.

1.4. Part 2: Paradigm shifts towards information/representations in the MTL

1.4.1. Informational accounts of memory

The dual process account maps specific memory processes onto distinct structures within the MTL. Other accounts, however, propose that the type of information, rather than the memory process *per se*, determines whether a particular MTL structure will be recruited during a declarative memory task (Diana et al., 2007). Informational accounts are of relevance to this thesis because they provide an alternate explanation to the findings of a fourth class of model, representational accounts, addressed in Section 1.4.2.

Guided by anatomical connections within the MTL, it was proposed that item and spatial information are processed separately prior to convergence in the HC (Eichenbaum, Yonelinas, & Ranganath, 2007). Specifically, inputs to the PRC come from areas of the brain that process unimodal sensory information about the qualities of objects (“what”) and project to the medial entorhinal area.

Inputs to the posterior PHG contain polymodal spatial ("where") information, and converge on the lateral entorhinal area (see Figure 1.4).

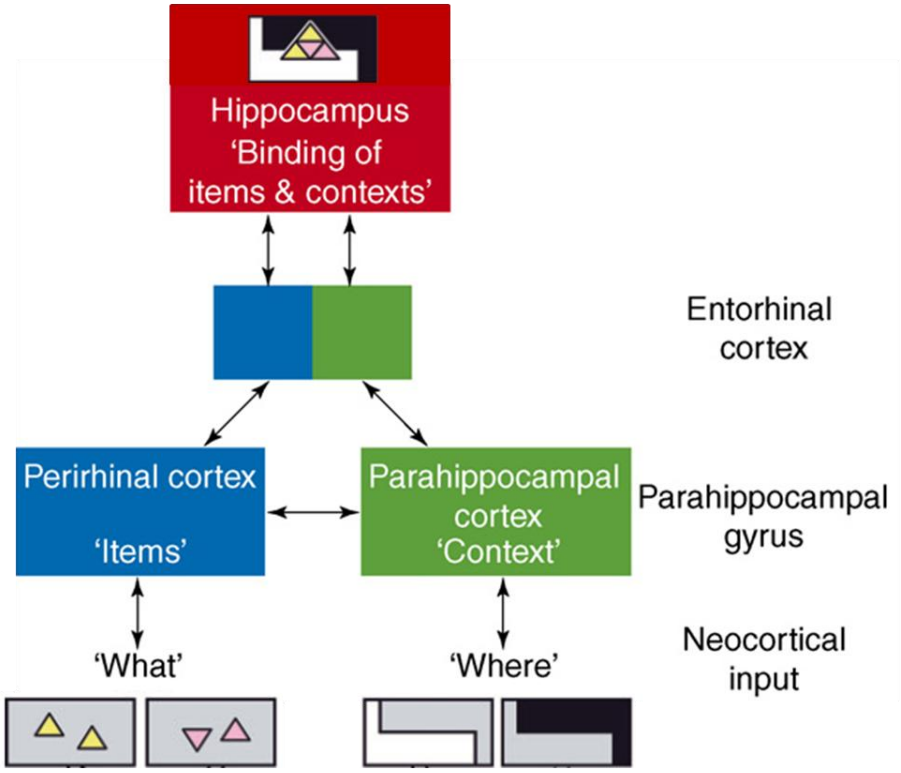

Figure 1.4. ***Functional organisation of the MTL according to the binding of item and context model (BIC). Neocortical input regarding "what" and "where" information is, for the most part, anatomically segregated until these disparate pieces of information and bound in the HC (Figure adapted from Eichenbaum et al., 2007, and Diana et al., 2007).***

The binding of item and context (BIC) model, a hybrid of the dual process account, does not predict a simple mapping of memory process to specific MTL structures (Diana et al., 2007). Instead it proposes that the type of information required to support a memory decision governs the involvement of different

MTL structures. For example, in a source memory experiment, if the contextual information to-be-remembered comprises an item feature, BIC proposes that PRC can support memory for both the item and this contextual information. Importantly, linking with the dual process accounts, BIC predicts that familiarity supports this item-feature contextual memory. In an extension of the dual process account, BIC proposes that the PHC also supports memory for contextual information. This hypothesis was based on the observation that in 14 of 26 source memory imaging studies (Diana et al., 2007), increased PHC activity was associated with recovery of contextual information. Finally, BIC proposes that the HC performs domain-general, or relational processes, such as pattern separation/completion (Norman & O'Reilly, 2003), or match-mismatch detection (Kumaran & Maguire, 2006, 2007a, 2009), and binds together different informational elements that comprise an episodic memory.

BIC offers explanations for extant data not easily accommodated by dual process accounts. First, informational accounts can accommodate spared recollection in patients with focal HC damage (there are, however, dual process accounts that also provide an explanation of these effects, for example the domain-dichotomy account; Mayes, Montaldi, & Migo, 2007). Second, they can explain why increased PHC activity is often evident during successful retrieval of source information in imaging tasks (Diana et al., 2007). In the next section neuropsychological and functional imaging data consistent with BIC will be reviewed, starting with a description of studies involving associative memory.

Associative memory experiments involve the presentation of pairs of items, for example words, and at test the presentation of intact pairs and recombined pairs, with the latter consisting of previously studied words that

were not paired together at study. Because at test all individual items are likely to be equally familiar, it has been argued that discriminating between 'old' versus 'recombined' pairs relies on recollection (Yonelinas, 2002).

Associative memory deficits have often been observed in patients with HC damage and interpreted as evidence for a role of this region specifically in recollection (e.g., Giovanello, Verfaellie, & Keane, 2003; Holdstock et al., 2005; Mayes et al., 2002; Mayes et al., 2004; Turriziani et al., 2004; Vargha-Khadem et al., 1997). Changing the encoding instructions in associative tasks, however, has led to normal associative memory performance in hypoxic patients (hypoxia leads to HC dysfunction) who normally show impairments in recollection. Quamme, Yonelinas, and Norman (2007) presented word pairs either as a compound ('*CLOUD-LAWN'* – "A yard used for sky-gazing"), along with a fictional definition, or separated in a sentence. At test, intact and recombined word pairs were presented. Intact/recombined discrimination was significantly better, and ROCs more curvilinear, when the words were processed as a compound compared to when they were separated in a sentence. This effect was replicated in an imaging study with healthy individuals; processing word pairs as a compound rather than a sentence significantly increased behavioural estimates of familiarity derived from ROCs. Furthermore, there was greater PRC activity associated with the compound encoding condition (Haskins, Yonelinas, Quamme, & Ranganath, 2008). These data suggested that the PRC can support associative memory judgments under some circumstances. The behavioural data implied that familiarity was the process supporting these judgments and it was proposed that this effect comes about because the encoding manipulation enabled the fusion of disparate elements of the study episode into a single item representation.

Diana, Yonelinas, and Ranganath (2010) used combined neuropsychological and imaging experiments to explore whether, and if so how, PRC can support memory for context when the contextual information has been encoded as an item feature (for earlier studies examining how the PRC may support contextual information, see Staresina & Davachi, 2006, 2008). Nouns were presented on one of two coloured backgrounds (green or red). There were two different encoding conditions. In the 'item' condition, participants were required to imagine the noun in the background colour; in the 'context' condition, participants were required to imagine the noun interacting with a dollar bill (green) or a stop sign (red). Subsequent memory test responses for each item were made using a 6-point scale allowing ROCs to be plotted. Source discrimination in patients, who had suffered mild hypoxic events and had previously exhibited impairments in recollection, was modulated by the encoding condition. Source discrimination was better in the 'item' rather than in the 'context' encoding condition. It was argued that by unitising the item and source information, this encoding manipulation had enabled the memory decision to be supported by familiarity. Consistent with this idea, in a complementary imaging experiment, healthy controls exhibited more curvilinear ROCs in the 'item' condition, thought to reflect the greater contribution of familiarity; this encoding manipulation, however, did not affect estimates of recollection. Relative to the 'context' detail, successful recovery of the 'item' detail resulted in significantly greater PRC activity; activity in the HC was reliably greater than baseline for recovery of either source details but did not differentiate between the two conditions. These data suggested that the PRC can (presumably on the basis of familiarity) support certain kinds of context judgements (depending on how the item is encoded).

The BIC model proposes that PHC supports memory for spatial information (Awipi & Davachi, 2008; Litman, Awipi, & Davachi, 2009; Staresina, Duncan, & Davachi, 2011). BIC suggests, however, that the PHC supports memory for generic contextual associations not limited to spatial information (Diana et al., 2007). For example, successful retrieval of the encoding task (size versus animacy) associated with a noun was also associated with increased activity in right posterior PHG (Ranganath et al., 2004). Given that there was no overt demand for scene memory in this task (although there is the possibility that imagery was employed to make judgments at encoding), it was suggested that this region must play a more generic role in the processing of contextual associations, including schema or gist.

To assess further whether posterior PHG processes non-spatial as well as spatial contextual information, Diana, Yonelinas, and Ranganath (2012) used an adaptation paradigm in which object items were presented alongside an encoding question (for example, “Could you use this thing as an ingredient when cooking?”). Throughout the experiment either the object image or the encoding question was repeated. The aim was to identify regions that showed adaptation (i.e., attenuation of BOLD signal due to repetition; for further discussion of this method, see Grill-Spector, Henson, & Martin, 2006) to either a repeat of the object item, or the encoding question. Regions sensitive to the repetition of stimuli were identified by contrasting all repeated items with those that were not repeated during the experiment. Within the identified brain regions, the pattern of BOLD response associated with item repeats and question repeats was analysed. A reduced response was evident in PRC and PHC for the object and encoding conditions, respectively. Although it is possible that the encoding questions engendered the imagination of scene stimuli, these

data seem to suggest a role for the PHC in the processing of, and memory for, non-spatial contextual information.

The BIC model garners support from the context framework hypothesis, which suggests that the posterior PHG processes both spatial and non-spatial contextual associations (Aminoff, Schacter, & Bar, 2008; Bar, 2004). Bar and colleagues have shown increased activity in the PHC for items that have non-spatial contextual associations, for example, a picture of 'lipstick' that might be associated with the context of 'beauty' (Bar & Aminoff, 2003), and for famous faces in whom there is likely to be large number of contextual associations (Bar, Aminoff, and Ishai, 2008). Bar and Aminoff (2003) also propose that objects can differ in the strength of their spatial contextual association, and found that items strongly associated with a particular environment (e.g., a deckchair is strongly associated with the beach) elicit equivalent levels of activity in the posterior PHG as real world scenes (Bar, Aminoff, and Schacter, 2008). This supports the BIC model by demonstrating that activity in the MTL corresponds with the type of information being retrieved (i.e., increased PHC activity with the recovery of associated spatial contextual associations). The predictions of the context framework hypothesis will be discussed in more detail in relation to representational accounts in Section 1.4.2.1.

The BIC model predicts that individual structures in the MTL interact to support declarative memory, but these structures will be recruited depending upon the type of memory cue, and the type of information recovered to support the memory decision. Hannula, Libby, Yonelinas, and Ranganath (2013) scanned participants whilst they viewed unique object-scene pairings for which they were required to make explicit associations. During a scanned test

session, either the object item, or the scene was presented and the participant was required to decide whether the item was new, whether the item was familiar, whether they could recollect the associated object/scene, or whether they could recollect something else about the item (for example, a thought during the encoding episode). By scanning the test session it allowed activity associated with the memory cue to be assessed. Consistent with the predictions of the BIC model, successful recollection of an associated scene from the presentation of an item cue led to significantly greater activity in the posterior PHG, relative to those scenes that were classed as familiar. This level of activity, however, was still significantly less than the signal associated with the presentation of a context cue (i.e., a scene). Contrary to predictions of BIC, however, activity in PRC was modulated by successful recollection of the associate for both item and context cues, suggesting that this region is sensitive to both types of information.

In summary, key tenets of the BIC model include: 1) PRC supports item information (frequently operationalised as object items although the model is not explicit in stating that it is limited to any one particular stimulus category), 2) the posterior PHC supports generic contextual information, including spatial contextual information, and 3) the HC performs domain-general mnemonic processes.

1.4.2. Representational accounts

The accounts described above differ in terms of the roles attributed to individual structures of the MTL. While the unitary account proposes that these structures work in concert to support declarative memory (Squire et al., 2007), dual process accounts map specific memory processes onto the PRC and HC

(Aggleton & Brown, 1999). A paradigm shift in the last few years has focused attention away from process towards the type of information to-be-remembered and highlighted potential contributions from PRC to both item and context memory (Diana et al., 2007). Importantly, for all these accounts, the HC is proposed to bind together different elements of an event that comprise an episodic memory, and to do this in a way that does not distinguish between the different components (or representations) that might make up these events. In contrast, representational accounts of MTL function explain the different recruitment of the PRC and HC during memory processing in terms of the demand placed upon access to distinct perceptual representations within these structures. Given the focus on representations, these models propose that the roles of the PRC and HC are to form flexible stimulus specific representations that support perception and are also used to serve memory. The following sections review the current literature on the role of MTL in perception and memory for different stimulus types. Given its relevance to the predictions of the BIC model, I will begin by reviewing work on scene-specific processing in posterior PHG.

1.4.2.1. The role of the posterior PHG in spatial processing

Epstein and Kanwisher (1998) identified an area of the posterior PHG in which increased BOLD response was associated with the processing of scene stimuli. Activity in this region was greater during the presentation of scenes relative to other categories of stimuli including objects, faces, houses (Experiment 1), which could not be explained simply by the increased number of objects in the scenes (Experiment 2), and was only evident when cohesive spatial relationships between scene elements were maintained (Experiment 3).

Furthermore, lower-level perceptual differences between stimuli could not explain the category-specificity of this region as Lego blocks arranged into a scene configuration elicited greater activity in posterior PHG than the same component parts arranged into an object (Epstein et al., 1999). As a result, this region was coined the parahippocampal place area (PPA). The view that the posterior PHG is sensitive specifically to scene stimuli will be referred to as the 'spatial layout' hypothesis.

Subsequent research aimed to understand the precise nature of the representations supported by this region, and whether they supported memory. To test whether the PPA supported flexible views of scenes, participants were scanned whilst they viewed images of scenes containing a central object. After a scene was presented, participants were shown either: 1) the identical image, 2) the same scene with a different object, 3) a different view of the same scene, 4) the same object in a different scene, or 5) extra objects added to the periphery of the scene. Repetition of the same scene, or the same scene with a different object, resulted in attenuated activity in the PPA. Changing the viewpoint of the same scene, however, resulted in increased activity in the PPA suggesting that the current percept differed from the stored representation (Epstein, Graham, & Downing, 2003). The results of this study suggest that the PPA houses viewpoint-specific scene representations. Contrary to the predictions of BIC, familiar scenes, which would be accompanied by mnemonic information, were not associated with increased activity in the PPA relative to unfamiliar ones. Familiarity of landmark, however, was shown to modulate

activity in this region with greater signal associated with familiar relative to unfamiliar landmarks (Epstein et al., 1999), but this level of activity was still less than that associated with full scenes. These data support the notion that this region of posterior PHG is exquisitely sensitive to scene stimuli and that although memory for related scene information can modulate activity in PPA, its primary role is the processing of scene geometry.

The spatial layout hypothesis suggests that the posterior PHG processes scene geometry specifically, and that related spatial information can modulate activity in this region (i.e., for familiar landmarks), but that this is a top-down, rather than automatic process. In contrast, the central tenets of the context framework account are that: 1) the posterior PHG processes both spatial contextual and non-spatial contextual associations equivalently (as evidenced by the equivalent level of BOLD response for these two categories of stimuli), and 2) these associations are brought to mind rapidly. To test how top-down processes may influence activity in the PPA, Epstein and Ward (2010) contrasted the BOLD response associated with faces (famous and non-famous), scenes (famous and non-famous), strong and weak spatial context objects presented in isolation, and scrambled objects. Participants were scanned whilst they performed a one-back task in which images were presented either rapidly (400ms), or slowly (2800ms). First, comparing activity for scenes and objects revealed significantly greater signal in the PPA associated with scenes for both the fast and slow presentation rates. During fast presentation there was a slight increase in BOLD response for the famous

places, and strong context objects relative to the non-famous places and weak context objects. This effect, however, was also evident for the *'scrambled strong context objects > scrambled weak context objects'* contrast, suggesting that some lower-level perceptual properties might explain these effects. For the slow presentation rates, there was a stronger effect of contextual association; greater activity was associated with famous, relative to nonfamous places, and strong, relative to weak context objects, but there was no difference for famous versus nonfamous faces. The authors proposed that the slow presentation condition provided opportunity to imagine the spatial contextual association, which was not possible during the fast presentation.

These data suggest that the PPA rapidly codes spatial geometry. Activity in this region may be increased, however, when a participant is provided with time to imagine related spatial information. One criticism of the Epstein and Ward (2010) experiment is that the novel scene stimuli comprised real-world locations. Similar to the rationale for including Lego scenes in Epstein et al. (1999), one might argue that the novel real-world scenes are reminiscent of a previously visited environment, and therefore result in increased activity for both the famous and novel scenes.

1.4.2.2. The role of the HC in spatial processing

Whilst it is proposed that the PPA processes viewpoint-specific scene representations, representational accounts suggest that the HC stores viewpoint variant, allocentric spatial representations. Due to ease of testing, spatial tasks have often been employed with non-human animals, for example

rats, and have led to the notion of the HC forming a cognitive map of the local environment (O'Keefe & Nadel, 1978). Recent extensions of this account have proposed that the human HC performs an analogous role in spatial processing (BBB; Byrne, Becker, & Burgess, 2007). In this next section, data from animal, human neuropsychological, and imaging studies that implicate the HC in spatial processing will be reviewed briefly.

A number of different paradigms have been developed to test spatial memory in non-human animals. First, the water maze paradigm requires animals (often rats) to find a submerged platform in a water-filled arena. On the first trial, the rat will swim randomly until it finds the platform and exits the water; on subsequent trials, it will swim more directly towards the platform, suggesting that it has memory for the spatial location of the platform. Rats with HC lesions, however, do not show this improved learning; they continue to swim in a random pattern in the arena. This impairment can be ameliorated when there is a visible cue indicating the location of the platform, suggesting that the impairment stems from a deficit in spatial memory rather than memory for the task *per se*. Subsequent research revealed that lesions to the HC, rather than the subiculum or ERC, resulted in this particular memory impairment (Galani, Weiss, Cassel, & Kelche, 1998).

In another approach, using the T-maze, rats are placed in a T-shaped maze and required to retrieve food placed in either the left or right tip of the 'T'. After the rat has been allowed to explore the maze and consume the food contained in one of the arms, it is removed before being returned for the test trial. Successful performance is measured by the rat selecting the novel arm of the T (i.e., the one that had not previously contained food) and consuming the

food reward now located there. Relative to controls, rats with fornix lesions made significantly greater errors when having to locate the novel arm of the maze (Ennaceur, Neave, & Aggleton, 1996). Furthermore, in the same study, fornix lesions impaired rats' memory for: 1) the novel location of a lever in a delayed non-match to position (DNMP) task, and 2) which lever (left versus right) was associated with reward.

A third approach, the radial maze, assesses spatial memory by requiring the rat to remember a number of different spatial locations visited previously. The radial maze comprises a central section with arms extending from it, each containing food. The rat is required to retrieve food from each arm; revisiting an arm is classed as an error. Fornix lesions resulted in a greater number of errors on this task relative to control rats (Ennaceur & Aggleton, 1997).

Together, these data implicate the HC in spatial memory, and support the notion of this region forming a cognitive map of the local environment (O'Keefe & Nadel, 1978). The mechanism underpinning the HC cognitive map has been studied over many decades, starting with the original identification of cells in the rat HC whose firing rate correlated with specific spatial locations and were therefore termed "place cells" (O'Keefe & Dostrovsky, 1971; O'Keefe, 1976). Importantly, these cells: 1) coded for the shape of the local spatial environment (O'Keefe & Burgess, 1996; O'Keefe & Speakman, 1987), but not for changes in the local features of the spatial environment (Cressant, Muller, and Poucet, 1997), 2) were not altered by changes in perceptual input caused by changes in direction, and 3) maintained their firing rate for the same location over several weeks, suggesting that this region stored a memory of a particular

spatial location (Lever, Wills et al., 2002). The HC, therefore, appeared to support a sense of location which would aid spatial navigation.

Whilst the idea of a cognitive map was accepted as an explanation for the spatial memory deficits in rats after HC lesions, some researchers viewed this account as too simplistic a characterisation of the declarative memory impairments evident in humans after HC damage (Squire & Cave, 1991). Human neuropsychological research has, however, highlighted (albeit rather inconsistently) that HC damage can be associated with a disproportionate impairment in memory for scenes. In one notable study, developmental amnesic, Jon, who had bilateral reduction of the HC after perinatal anoxia, was tested for memory of objects, people, and places using a computer-generated game environment (King, Trinkler, Hartley, Vargha-Khadem, & Burgess, 2004). Jon showed memory impairment for the location in which objects had been encountered, but not the objects themselves. Similarly, Taylor, Henson, and Graham (2007) found that patients with HC damage showed a scene-specific memory impairment when scenes were presented from different views. Participants viewed blocks of single face and single scene stimuli. At test, the studied items were presented in pairs alongside a within-category foil; old items could be presented either in the same or different orientation as study. For faces, the HC patients' performance matched controls, regardless of which viewpoint was presented at test. For scene stimuli, however, the HC patients were significantly impaired in the different view condition compared to controls.

The HC appears particularly important for forming allocentric spatial representations. In King et al.'s (2004) study, amnesic Jon also showed deficits in remembering an object in a particular spatial location when his viewpoint was

changed from the study to test phase. This topographical memory deficit was replicated with the four mountains test in a group of patients with HC damage (Hartley et al., 2007). At study, participants were presented with a computer generated scene comprising four mountain components. At test, four scenes were presented (all from different views) and the participant was required to select the matching item; the test items could be presented concurrently, or two seconds after the sample. The participant was cued to select the item that matched the non-spatial characteristics of the sample scene (foliage colour, cloud cover etc.) or the topographical characteristics (i.e., the spatial relationship between the component mountains). All patients were significantly impaired when required to remember the topographical details of the scene after a delay. These effects were replicated in patients with mild cognitive impairment (MCI) and Alzheimer's disease (AD) (Bird et al., 2010); AD is thought to result in HC dysfunction and increasing brain atrophy, and impairments in episodic memory are characteristic of disease presentation. Finally, relative to controls, patients with transient global amnesia (which causes minor focal lesions of the CA1 field of the HC) did not show improvement over successive trials of a virtual water maze (Bartsch et al., 2010). Replicating the animal findings, therefore, HC damage in humans, across a number of different disease aetiologies, impairs spatial, topographic memory.

A number of studies have implicated the HC in spatial processing by showing links between HC integrity and spatial expertise, and providing evidence to suggest that this region supports the imagination of spatially coherent environments. For example, in terms of HC volume, increases in posterior HC grey matter in taxi drivers has been shown to reflect increased navigational expertise (Maguire, Woollett, & Spiers, 2006; Maguire et al., 2000;

Woollett & Maguire, 2011). Similarly, estimates of both anterior and posterior HC grey matter correlated positively with participants' performance on the four mountains test (described above) (Hartley & Harlow, 2012). Moving beyond the mnemonic domain, the HC has also been implicated in the imagination of spatially coherent scenes. Similar levels of activity in HC have been observed when participants have been required to imagine scenes as when recalling scenes (Hassabis, Kumaran, & Maguire, 2007). Supporting these data, relative to controls, patients with HC damage show difficulties when required to imagine scenes from a brief verbal description (Hassabis, Kumaran, Vann, & Maguire, 2007), particularly in terms of the spatial coherence of the imagined scene. Imaging data suggest that this may be attributable to the HC's role in binding together elements comprising the local spatial environment. Bird, Capponi, King, Doeller, and Burgess (2010) scanned healthy participants and presented scenes comprising towers and perimeter boundaries; the number of boundaries was parametrically manipulated from 0-4 across trials. Consistent with "place cell" findings in rats (O'Keefe & Burgess, 1996), increased HC activity was associated with the presentation of an increasing number of physical boundaries. These data suggest that, rather than performing a purely mnemonic role, the human HC can also support the processing of complex spatial environments.

The BBB model (Byrne et al., 2007), which is an extension of the earlier cognitive map account, proposes that the HC codes for one's allocentric position in the local spatial environment, whilst through reciprocal connections the PRC and PHC code for the objects within, and the physical boundaries of, the environment, respectively. Relating this model to the mnemonic accounts of MTL function, BBB proposes that recognition memory tasks, particularly those

in which memory for contextual information is queried, require the imagination of a spatially coherent mental image which necessarily taxes the HC. Furthermore, the model argues that it is this formation of the spatial mental image that gives rise to the phenomenological feeling of recollection (Bird & Burgess, 2008).

1.4.3. Representational accounts and perception

The BBB model provides a mechanistic account as to how the HC may form allocentric spatial representations that support both perceptual and mnemonic processes. Evidence for the role of the HC in perception of complex spatial stimuli will be reviewed in more detail in Sections 1.4.4, and 1.4.5. Recent models of PRC function have proposed that this region supports both perception of, and memory for, complex object stimuli, particularly under conditions of high feature ambiguity (Graham et al., 2010; Saksida & Bussey, 2010). In the next sections, animal data will be reviewed that prompted a change in the conceptualisation of the role of the PRC, and I will examine the conditions under which this region is proposed to contribute to higher order perception.

1.4.3.1. The role of the PRC in object processing: animal data

In Section 1.3.2, it was noted that damage to the PRC resulted in deficits in DMS/DNMS memory performance, and this deficit was exacerbated by increases in the delay between sample and test presentation. Deficits in discrimination performance have been observed, however, in zero-second delay, and concurrent discrimination manipulations, prompting a change in the conceptualisation of the role of this region (Eacott, Gaffan, & Murray, 1994).

Preoperatively, monkeys were trained on a DMS task comprising two sets of ASCII characters of different sizes and colours. In one set, there were a large number of items, in the other set there were only four items. Bilateral lesions of the rhinal cortex, including the PRC, led to impaired performance on the task relative to the control group when there was a demand to remember items over a delay. When the test items were presented immediately after the sample stimulus (0-second delay), however, the lesion group was still impaired relative to controls. Given that the PRC was thought to be involved in memory, it was striking that the animals showed poor performance even when there was no delay between study and test items. Furthermore, the deficit persisted even in a concurrent discrimination in which the original sample stimulus was presented alongside the target and foil. Notably the stimulus set size was crucial as to whether a deficit was observed; impairments were only evident when the stimulus to be discriminated was drawn from a large set of stimuli. It was suggested that, by increasing the number of foils, in order to discriminate the target from a number of similar foils placed greater demand on the stimulus representation.

Deficits in discrimination accuracy after PRC lesions were evident when greater demand was placed on object representations by increasing the number of stimuli to-be-discriminated, or increasing the number of foils presented along with the target. Buckley and Gaffan (1997) found that monkeys with PRC lesions made a significantly greater number of discrimination errors relative to controls when required to learn a large set of object discrimination trials.

Furthermore, this deficit worsened when the number of foils presented alongside the target item was increased. These findings support the data from Murray et al. (1994) and suggest that the discrimination deficits observed after PRC damage result from increased demand to remember the precise object representation. Similarly, changes in viewpoint between study and test led to impairments in monkeys with PRC lesions (Buckley & Gaffan, 1998). Monkeys learned 40 concurrent discriminations that comprised everyday-object pairs presented in isolation. Relative to presentation during training, at test the items were presented from: 1) the same viewpoint, 2) a different viewpoint, or 3) a different viewpoint combined with the backdrop of a complex scene. Relative to controls, PRC lesions resulted in impaired performance when the object pairs were presented from a different viewpoint; the addition of the complex scene did not exacerbate this deficit. That the monkeys with PRC ablation performed normally on the same view discriminations, and that the addition of scenes as a backdrop to the objects did not increase impairment, suggested that the PRC was required for flexible, viewpoint invariant representations of object stimuli.

A potential explanation for the previous findings was that the different view condition was simply more difficult than the same view. To demonstrate that the deficits associated with PRC lesions were specific to complex visual stimuli rather than task difficulty *per se*, Buckley, Booth, Rolls, and Gaffan (2001) used an oddity paradigm with simple (colour, size, and shape), and complex (objects, human faces, monkey faces, and scenes) stimuli, with different levels of difficulty (see **Error! Reference source not found.**). In an oddity

task, a number of items are presented concurrently and the participant has to select the item that differs from the others in the array. For example, if four faces were presented, three would comprise the same face whilst the fourth would be a similar but different face. For the simple stimuli, the PRC lesion group's performance matched controls' even at the highest difficulty level. Conversely, the PRC group was significantly impaired relative to the control group when discriminating complex stimuli. Together these data suggested that the PRC is necessary for discriminating complex rather than simple stimuli, and that this deficit cannot be easily explained by task difficulty. Moreover, the PRC seems to form flexible, view-invariant representations of object/face stimuli necessary for identifying items from different angles given that PRC lesions resulted in impaired discrimination accuracy for objects presented at different views at test than at training (Buckley & Gaffan, 1998), and impaired oddity performance for face stimuli (Buckley et al., 2001). Interestingly, the PRC group also exhibited deficits in the real-world scene oddity comprising a number of foreground objects. Given that discrimination deficits for scene stimuli would not be predicted after PRC damage, one potential explanation is that the objects in the scene were diagnostic of the odd item. The PRC group, therefore, would not be able to use this object information to identify the odd item. This possibility is further supported by the finding that the inclusion of scenes did not exacerbate the impairment of the PRC group previously (Buckley & Gaffan, 1998). These data suggest that it is the requirement to use the objects within the scene, rather than scenes *per se* that resulted in the PRC associated deficit.

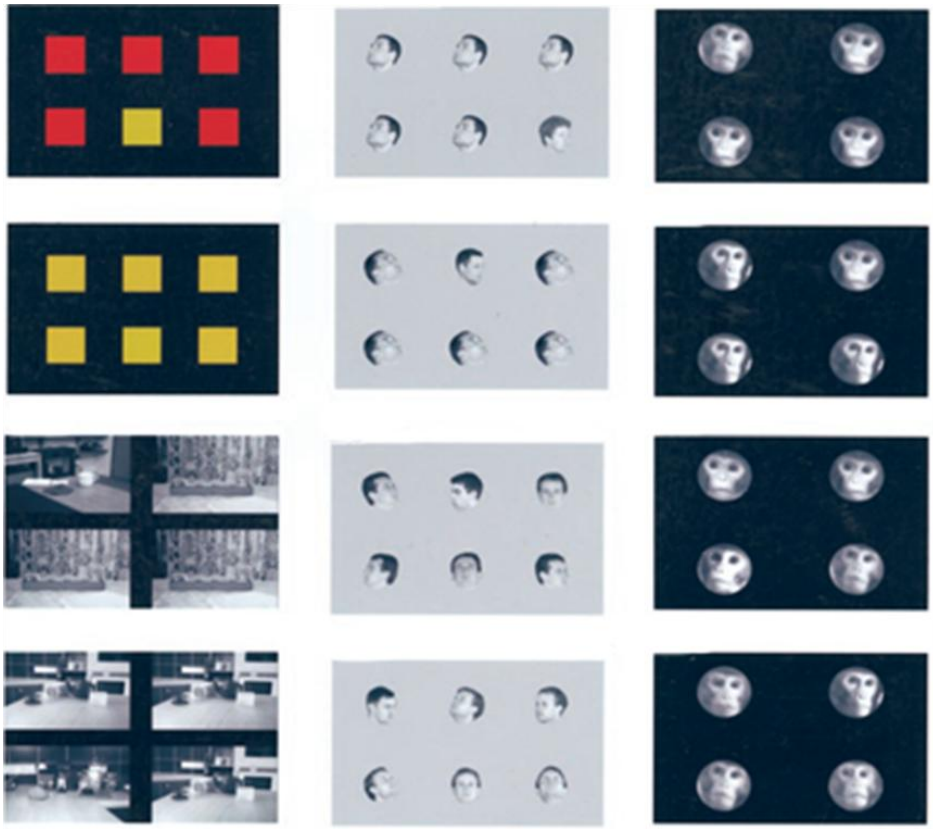

Figure 1.5. ***Examples of oddity stimuli from Buckley et al. (2001). Monkeys with PRC ablation were impaired on complex scene, and face oddity; they showed spared performance, however, for equally difficult size and colour discriminations.***

The notion that PRC damage results in deficits in the perception of complex object stimuli has not gone unchallenged. Other researchers proposed that they in fact resulted from inadvertent damage to proximal cortical regions TE and TEO which support visual processing in the macaque monkey (Buffalo et al., 1998; 1999; 2000). These counter studies can be criticised, however, by methods used to assess perceptual/mnemonic deficits, as they used small stimuli sets, simple geometric stimuli, and required memory over a delay.

Accordingly, they may have failed to tax the animals' perceptual abilities (Buckley, 2005). To summarise, these early animal studies highlighted a critical role for PRC in object-level discriminations in tasks with limited mnemonic demand.

1.4.3.2. Object perception and ambiguity

Given that PRC lesions seemed to impair the formation of abstract representations of face and object stimuli, a more systematic approach was adopted to identify the exact conditions under which these deficits would be elicited. Deficits in oddity and discrimination learning tasks were often evident when there was a high level of features shared between the target and foils, or low-level features could not be used to discriminate items. This led to the notion that the PRC may be taxed under conditions of high object feature ambiguity. Broadly, ambiguity has been manipulated in two different ways. First, the degree of feature overlap between target and foils has been manipulated either by morphing together different stimuli, or selecting visually similar stimuli. Second, feature overlap has been manipulated by controlling the component features of stimuli and making them common to both targets and foils.

1.4.3.2.1. The role of the PRC in discriminating visually similar items

To test whether PRC lesions impaired high ambiguity object-level representations, Bussey, Saksida, and Murray (2003) morphed between distinct greyscale photographs (e.g., pictures of flowers or birds). After PRC ablation, monkeys were trained to discriminate between two images, one of which was

rewarded (S+ versus S-). Ambiguity was operationalised by the amount of feature overlap between images, achieved by morphing between the S+ and S- items. In the high ambiguity condition, test pairs were morphs that contained a high degree of feature overlap; in the low ambiguity condition the S+ and S- items were visually distinct. The performance of the monkeys with PRC lesions was modulated by the degree of feature overlap; they were impaired relative to controls in the high ambiguity condition with performance remaining at chance level even after many blocks of testing. In the low ambiguity condition, however, they acquired the discrimination rapidly and matched controls' performance. These data suggested, therefore, that the qualities of the stimulus (i.e., level of feature ambiguity) are key to PRC involvement.

One possible explanation for the deficit in discrimination learning for the high ambiguity condition was that these item pairs placed greater demand on memory. A deficit in memory rather than perception, therefore, could explain the pattern of data (Suzuki & Baxter, 2009; Suzuki, 2010). In an attempt to rule out a mnemonic explanation for the deficit in the high ambiguity condition, Bussey et al. (2003) trained monkeys to discriminate a pair of low ambiguity S+ and S- images. In subsequent testing, pairs of images were presented that were either high ambiguity, or low ambiguity morphs between the two stimuli. Replicating the results of the first experiment, the PRC group showed impairments in discrimination learning for the high ambiguity items only. Because the monkeys had demonstrated that they could discriminate between the S+ and S- items prior to testing, it was argued that any impairment specific to the high ambiguity

condition must result from a deficit in perception, sensitive to the degree of feature overlap between the target and foil. Furthermore, the results were contrary to the predictions of the unitary account and the declarative/nondeclarative memory distinction. Performance was spared for the rapidly learnt discriminations, thought to be reliant upon declarative memory and MTL integrity, but impaired for the items that required slow learning over many trials, thought to tax nondeclarative memory mediated by brain regions outside of the MTL.

The level of feature overlap was also found to modulate performance of rats with PRC lesions in the NOR paradigm with minimal delay between sample and test (Bartko, Winters, Cowell, Saksida, and Bussey, 2007a). The NOR paradigm utilises rats' natural tendency to explore novel stimuli and benefits, therefore, from the animal not requiring extensive training with the experimental apparatus. An item's perceived novelty is inferred from the rats' behaviour; investigating a stimulus for an extended period of time is indicative that the rat perceives the item as new. Animals were placed in a Y-shaped maze with identical sample stimuli (Lego blocks) in each arm. After the sample stimulus had been explored, a guillotine door was removed immediately (zero-second delay) revealing the test items – the sample stimulus and a foil. To examine the effect of feature-overlap, in one condition the target and foil were visually distinct (low ambiguity); in the other condition the foil was perceptually similar to the target (high ambiguity). In both low and high ambiguity conditions, control rats spent a greater proportion of time exploring the novel stimulus. Similarly, in

the low ambiguity condition, PRC lesioned rats preferentially explored the novel stimulus indicating that this stimulus was perceived as new. In the high ambiguity condition, however, the PRC rats divided their time equally between the target and foil suggesting that they could not discriminate between items that shared a high degree of feature overlap.

To ensure that a memory deficit could not explain the observed effect (i.e., the demand of having to remember the sample stimulus over even a minimal delay), the task was replicated using an oddity paradigm. Three items were presented simultaneously, comprising two identical foils and one different target item. The level of visual similarity between the foils and target was manipulated to create four levels of ambiguity (low, medium, medium-high, and high). Control rats spent a greater amount of time exploring the odd item across all levels of ambiguity suggesting that they had identified the novel stimulus. In the PRC group, however, the time spent exploring the odd item decreased as the degree of feature overlap increased. This resulted in a significant group difference for high ambiguity items, and a marginal group effect for medium-high ambiguity. Replicating the earlier findings, these data suggested that the PRC is required when distinguishing between perceptually similar items. Moreover, by using an oddity paradigm in a task that required no overt training, these data suggest that the role of this MTL structure may not be limited to memory.

1.4.3.2.2. The role of the PRC in discriminating feature conjunctions

Feature conjunctions provide greater control over the exact features that overlap between targets and foils. Bussey, Saksida, and Murray (2002) tested monkeys' ability to solve discrimination-learning problems whilst manipulating feature overlap. Stimuli comprised eight greyscale images (ABCDEFGH) that were combined in object pairs. Three levels of ambiguity were created: 1) low ambiguity comprised item pairs AB+ CD+ EF- GH- in which none of the features present in the rewarded stimuli (+) were shown in the non-rewarded stimuli (-), 2) intermediate ambiguity comprised stimuli where half of the features were present in the non-rewarded stimuli (AB+, CD+, CE-, AF-), and 3) high ambiguity comprised stimulus conjunctions AB+ CD+ AC- BD- (see Figure 1.6). In this condition all four elements of the stimuli were equally rewarded and non-rewarded; only the conjunction of images was diagnostic of whether reward would be administered. As predicted, after receiving PRC lesions, monkeys were significantly impaired, relative to the control group, in both the intermediate and high ambiguity conditions. They performed normally, however, in the low ambiguity condition. These data suggested that, rather than being selectively involved in memory, the PRC is crucial for conjoining item features analogous to an object-level representation.

Equally, PRC lesions impaired discrimination performance of monkeys when the reward status of individual items was ambiguous (Saksida, Bussey, Buckmaster, & Murray, 2007). In the transverse pattern problem, each item is equally rewarded and non-rewarded in the experiment; its reward status depends on the item with which it is paired. Success on this task, therefore, relied on the animal understanding the relationship between the two objects

presented. Relative to controls, monkeys with PRC lesions made a significantly greater number of errors. The monkeys were not, however, impaired on a concurrent discrimination problem in which there was no overlap between rewarded and non-rewarded items, reminiscent of the low ambiguity condition in Bussey et al. (2002). Together, these data suggested that the PRC supports the conjunction of features that comprise an object.

This effect was replicated in rats using the NOR paradigm with minimal delay between sample and test (Bartko, Winters, Cowell, Saksida, & Bussey, 2007b). The rats were again placed in a Y-shaped maze and presented with a sample configural item comprising two junk objects (BC). Unlike the previous experiment employing the Y-shaped maze and a zero-second delay test, the animal was then exposed to a second configural item (AD). The test items were subsequently presented and comprised the sample configural item (BC) and a configural foil (AB). In the high ambiguity condition (described here), all individual elements of the stimuli were familiar to the rat; only the conjunction of features was novel. In the control condition, the same procedure was used but in this case there was no overlap between the sample configural item, second configural item, or foil. Control rats successfully identified the novel configural items in both conditions. The PRC group, however, divided their exploration time equally between the sample and novel configural items on the high ambiguity trials; performance was spared in the low ambiguity condition.

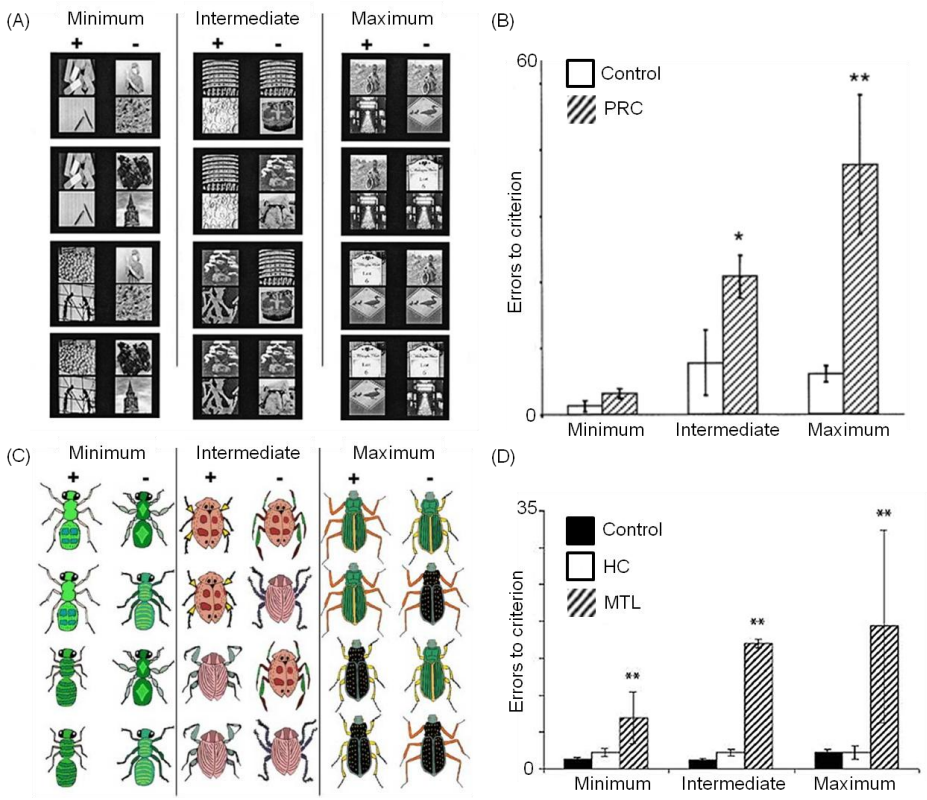

Figure 1.6. ***Conjunction learning stimuli comprising (A) object pairs and (C) object feature conjunctions. Participants were required to remember the rewarded items (+) and ignore foils (-). The level of feature overlap was manipulated between the targets and non-targets so that they could share none (minimum), or all component objects/features (maximum). In both monkeys with PRC ablation (B), and patients with damage including the PRC (D), performance was modulated by the degree of feature overlap with the most errors occurring when there was maximum degree of feature overlap (these data are discussed in Section 1.4.4).***

In a second experiment, the same configural items were used in an oddity paradigm in an attempt to assess whether the deficit stemmed from a perceptual rather than a mnemonic impairment. Again, there were low and high ambiguity conditions. In the low ambiguity condition the odd item did not share

any features with its foils; the animal was presented with two pairs of identical items (AB1, AB2, CD1, CD2), and an odd item (EF). In the high ambiguity condition, the odd item shared individual features with its foils but only the conjunction of features was diagnostic of the odd item (AB1, AB2, CD1, CD2, and AD). Replicating the results of the visual-similarity oddity, relative to controls the PRC lesion group were impaired only in the high ambiguity condition.

1.4.3.3. The representational-hierarchical account of MTL function

In combination, these data suggest that the PRC houses viewpoint-invariant object representations that support both memory and perception. Moreover, PRC support is required under conditions of high ambiguity (i.e., when required to distinguish between items that contain a high degree of overlapping features). It is proposed that the ventral visual stream (VVS) contains hierarchically organised representations of visual stimuli (Ungerleider & Haxby, 1994). Posterior regions of the VVS code for simple feature components. More anterior regions, however, process conjunctions of these simple features with each layer of the VVS coding for more complex conjunctions than the layer preceding it (Riesenhuber & Poggio, 1999; Tanaka, 1996). The PRC forms the apex of this stream and processes object-level feature conjunctions (Bussey et al., 2002; Graham et al., 2010; Murray, Bussey, & Saksida, 2007; Saksida & Bussey, 2010).

The representational-hierarchical model (Saksida & Bussey, 2010) predicts that lower-level (posterior) regions of the VVS, that code for individual stimulus features, can distinguish between items that can be differentiated on the basis of these features. When these individual features are shared across a number of items to-be-discriminated (increasing ambiguity), however, and only the conjunction of features is indicative of the correct item, a more complex configural representation is required which is more likely to require a contribution from the PRC. The model predicts that "a lesion at any point of the VVS will cause impairments in visual discrimination learning, if the to-be-discriminated stimuli possess a level of complexity best represented by the neurons in the lesioned area" (Cowell, Bussey, & Saksida, 2010, p.13). Therefore, if posterior regions of the VVS were damaged, this would result in a deficit in the ability to discriminate between items comprising simple, distinct features. A more anterior lesion, for example in the PRC, would result in deficits for configural stimuli, but spared performance for visually-distinct items that would be supported by the posterior regions of the VVS.

1.4.3.4. The PRC buffers against interference from low-level feature conjunctions

One question that arises from the representational accounts is how PRC damage, leading to a loss in the ability to form complex object representations, results in the mnemonic deficits commonly observed after MTL damage. One explanation is that the PRC forms unique object representations that buffer against interference from low-level feature conjunctions common to a number of

different object stimuli. For example, in the DNMS tasks sensitive to PRC integrity, a sample object is presented followed by the sample object paired with a novel item. Whilst control rats can form a distinct object representation of the sample object allowing them to distinguish it from the foil, rats with PRC damage must base their memory judgment on intact lower-level conjunctions that may be common to the sample, foil, and even other objects in the testing environment. Furthermore, given that the lower-level feature conjunctions are common to a number of object items it leads to a paradoxical situation in which novel object conjunctions may seem familiar. In terms of behaviour, for the NOR paradigm it would predict less time spent exploring the novel item, reflecting familiarity, rather than an increase in exploration time, indicating novelty.

This prediction was upheld by findings in an NOR paradigm where the memory performance of rats with PRC lesions was improved when the opportunity for interference was reduced. McTighe, Cowell, Winters, Bussey, and Saksida (2010) presented rats with a sample object item, then, after a one hour delay, showed either the sample item or a novel item. During the delay, the rat was placed in a holding cage in which the testing room was visible (‘interference’) or a visual restriction cage which comprised a black box from which the outside room was not visible (‘no interference’). Regardless of the delay condition, control rats spent a greater proportion of time exploring the novel object compared to the repeated object. The performance of rats with PRC lesions, however, was modulated by the delay condition. In the ‘interference’ condition, PRC rats spent an equal amount of time exploring the

novel and repeated stimuli; they spent significantly less time exploring the novel item relative to control rats. In the 'no interference' condition, however, their performance matched the controls and they spent significantly more time exploring the novel, relative to the repeated item. The fact that the PRC rats spent less time exploring the novel object after the interference condition supports the assertion that both the sample and foil appeared equally familiar.

These data imply that the memory deficits commonly observed after MTL damage stem from an inability to form distinct, object-level representations. Manipulating the degree of feature overlap between objects so that they share more features, therefore, results in poorer discrimination performance because these similar representations cause interference (Bartko et al., 2007a, 2007b). Consistent with this hypothesis, Bartko, Cowell, Winters, Bussey, and Saksida (2010) found that the presentation of a visually similar (high ambiguity) item immediately before or after the sample stimulus led to impaired NOR performance in rats with PRC lesions; visually distinct items, however, did not affect performance.

1.4.4. Object and scene processing in the MTL: Human neuropsychological data

The data presented thus far suggest that the HC is required to form allocentric spatial representations (Section 1.4.2.2), whilst the PRC forms complex conjunctive representations of object stimuli that buffer against interference for visually similar items (Section 1.4.3.4). In the next section, evidence is reviewed from human neuropsychological studies that have

replicated the paradigms used in the animal literature to demonstrate a division of labour in the MTL according to the type of stimulus to-be-processed.

Early attempts to replicate in humans the perceptual deficits associated with PRC damage did not support predictions from the animal research. Buffalo, Reber, and Squire (1998) tested two patients with lesions of the MTL encompassing the PRC on a recognition memory task with varying delays between sample and test. Novel object quartets comprising colourful geometric objects were shown sequentially after which a sample stimulus was presented. Participants had to decide whether this target item had been presented in the previous object quartet. The sample stimulus was presented either immediately after the object quartet (0 seconds) or in increasing delays relative to the study presentation (2, 6, 10, 25 or 40 seconds later). Consistent with the unitary and dual process models of MTL function, memory performance declined as the length of time between sample and test presentation increased; at short delays (0-2 seconds), patients were not impaired relative to controls, but they were impaired at long delays (25-40 seconds). Interestingly, however, when analysing patients' discrimination accuracy according to the sample stimuli's position in the object quartet, either 1, 2, 3 or 4, the patients' performance matched controls at long delays when the sample stimulus was presented in position 1; the deficit at the long delays, therefore, resulted from performance on the items presented at positions 2-4. Given that when the sample stimulus was presented first in the quartet followed by a 25-40 second delay before test, this represented the most mnemonically demanding trial in the experiment (as

measured by time elapsed between sample and test), it is not clear, from a mnemonic view, why the patients were not impaired at this data point.

Similarly Holdstock, Gutnikov, Gaffan, and Mayes (2000) used a DMS task in patients with MTL lesions encompassing the PRC and found spared performance when the sample item was presented concurrently. Unlike Buffalo et al. (1998), the study included a concurrent discrimination condition that was designed to tax perceptual, rather than mnemonic processes. A novel object stimulus was presented in the centre of the screen. In the concurrent condition, the sample stimulus remained in the centre of the screen and the participant was required to pick the corresponding target from an array surrounding it. In the delay condition, the sample stimulus was removed and the target and foils were presented after a variable delay. Consistent with mnemonic accounts of MTL function, patients performed normally in the concurrent condition but made significantly more errors when a 10 second delay was introduced between sample presentation and test. The authors note that one possible explanation for the absence of an impairment in a patient with damage to the PRC was that the stimuli comprised basic geometric shapes (identifiable by colour and shape); Buckley et al. (2001) found that discrimination of similar basic visual properties was intact in monkeys with PRC lesions.

Human neuropsychological experiments found deficits in patients for object and scene processing consistent with the animal literature when the methods used in human studies replicated those applied in animal experiments. Using a paradigm similar to Bussey et al. (2002), Lee, Bussey, et al. (2005)

demonstrated that lesion location, focal HC versus MTL (encompassing PRC) (see Section 1.2.2 for a description of the subtraction method commonly used in neuropsychological experiments), led to different patterns of impairment in perceptual discrimination for distinct classes of stimuli in two experiments. In Experiment 1, a pair of images was presented and the participant was taught which one was the 'correct' (akin to rewarded) item. In subsequent trials, pairs of images were presented that had been morphed together so that they shared 0-49% of features, thereby creating low to high ambiguity pairs. The participants were required to select the image that they felt contained more of the features from the original 'correct' item. Stimuli comprised faces, objects, scenes, abstract art, and colour. Compared to matched controls, the MTL group (with PRC damage) showed deficits (as measured by overall performance) in the discrimination of faces, objects, and scenes. There was a borderline impairment for abstract art also. Replicating the animal data, the MTL group was impaired in discrimination of object and art stimuli only when they contained a high degree of feature overlap; the deficit for faces was evident across all morph levels. By contrast, the HC group showed poor performance on high ambiguity scene stimuli only. These patterns were also apparent in Experiment 2, in which the original item was presented concurrently with the morphed pairs; this suggests that the deficit was perceptual in nature, rather than mnemonic, as there was no requirement to remember the target item across trials. Importantly, these data highlight a particular role for PRC when there is a need to discriminate between highly similar, but not visually distinct, stimuli (however, see Shrager, Gold, Hopkins, & Squire, 2006). Moreover, these data extend the

conclusions from the animal studies by highlighting a role for the HC in scene specific perception/memory.

The PRC and HC appear necessary, therefore, for forming abstract, view-invariant representations of object/face and scene stimuli, respectively. Lee, Buckley, et al. (2005) replicated Buckley et al.'s (2001) oddity task (used in PRC lesioned monkeys) using colour swatches, simple geometric shapes, faces, and novel and familiar objects in the same patients. Again, the pattern of MTL damage (MTL versus HC) modulated successful performance in oddity across different stimulus types. The MTL group were impaired on face and novel object oddity judgements, whereas the HC group's performance matched the controls all conditions. Both groups, like the monkeys, showed normal performance for colour, size and shape oddity (e.g., normal perceptual discrimination for lower level visual features). In a second oddity experiment, faces and scenes were presented and the view of the stimuli was manipulated. In the same view condition, all items were presented from the same viewpoint; in the different view condition, the target and foils were all presented from different views, meaning that the participant was required to form an abstract, view-invariant representation of the item. The latter condition is akin to that tested in the first experiment. Both groups of patients performed normally in both same view conditions but when the items were presented from a different view, the HC and MTL group were impaired on scene oddity judgements. In addition, damage to the MTL (which included the PRC) led to impaired face oddity decisions compared to matched control participants. This pattern of data

was replicated in patients with AD (Pengas, Hodges, Watson, & Nestor, 2010), who were impaired on scenes, whereas patients with semantic dementia, which particularly affects the PRC early in the disease, showed impairments for faces (Lee et al., 2006).

To address these striking findings, proponents of mnemonic accounts of MTL function have suggested that, relative to patients, controls may benefit from learning when trials are repeated (Suzuki, 2009). The use of trial-unique stimuli in Experiment 2 of Lee, Buckley, et al. (2005) deals with this criticism and suggests that the deficits in oddity tasks reflect perceptual rather than mnemonic impairments. Consistent with this, in Lee, Buckley, et al. (2005) the controls' accuracy did not improve over the experiment, suggesting that they did not benefit from memory.

Damage to PRC impaired discrimination accuracy when objects were morphed together to contain a high degree of feature overlap (Lee, Bussey et al., 2005). The morphing procedure, however, can lead to small featural differences that could also be diagnostic of the correct item (e.g., the level of contrast in the stimuli). Discrimination impairments in patients with MTL damage have not, therefore, always been observed when using this method (Levy, Shrager, & Squire, 2005), and more recent studies have attempted to implement a more systematic approach to feature ambiguity.

Using a concurrent discrimination task similar to that reported by Bussey et al. (2002, see Section 1.4.3.2.2), Barense et al. (2005) gained greater control

over the individual components of the stimuli by parametrically manipulating the level of feature overlap between items. Stimuli comprised blobs, bugs, barcodes, and beasts, and each stimulus consisted of two component features, the combination of which was manipulated to create feature overlap (see Figure 1.6). There were four items in each category, two of them designated correct. Pairs of images were presented and each pair comprised one target (to-be-remembered) and one non-target (to-be-avoided). Participants learned through trial and error the targets versus non-targets, and were required to make eight consecutive correct responses; the number of errors to reach this criterion was recorded. Three levels of ambiguity were created: 1) minimum: targets and non-targets did not share any component features, 2) intermediate: the targets and non-targets shared one component feature, and 3) maximum: targets and non-targets comprised the same four features; like Bussey et al. (2002), only the conjunction of features discriminated the target from non-target items. Relative to controls, patients with damage encompassing the PRC were impaired on both the intermediate and maximum ambiguity conditions, but performed normally when there was minimal feature ambiguity. The performance of patients with damage limited to the HC, however, did not differ from controls. Supporting the animal data, PRC damage resulted in discrimination learning deficits only when the patients were required to use conjunctions of features to discriminate items.

Given that the task required participants to learn conjunctions of features associated with the correct response, it was not possible to rule out that a deficit

in memory could explain the effects. Indeed, consistent with the unitary account of memory, the pattern of data could be interpreted as demonstrating that patients with more extensive MTL damage exhibit poorer discrimination learning performance. Unlike the unitary account, however, representational accounts propose that the HC supports discrimination learning of complex spatial stimuli, and would therefore predict a stimulus specific deficit in scene learning after HC damage. This question was the motivation for the experiment outlined in Chapter 2 of this thesis. Two patients with HC lesions were tested using a conjunction learning paradigm utilising different stimuli, including objects and scenes. It was predicted that patients would show a scene-specific impairment.

1.4.4.1. Could deficits in declarative memory underpin stimulus specific perceptual impairments?

Despite patients with different profiles of MTL damage showing stimulus specific deficits in trial-unique oddity, proponents of the unitary account continue to explain these effects in terms of a deficit in memory. Kim et al. (2011) presented participants with a pair of computer generated or novel face stimuli. Underneath these, an image comprising a morph between the two stimuli was presented and the participant was required to select which of the pair the morph most closely resembled. In the trial unique condition, the pair of images and the morph changed on every trial. In the repeat condition, the pair of images remained the same, and the morph changed. The prediction was that, unlike the HC patients, the controls should be able to benefit from remembering the pair of images in the repeat condition; there should be no difference, however, in

performance during the trial-unique condition. In line with their predictions, controls showed significant learning across blocks in the repeat condition for both faces and scenes, but did not improve in accuracy in the trial unique condition. Furthermore, in contrast to predictions of representational accounts, there was no evidence of a scene-specific deficit in discrimination accuracy resulting from the HC damage. It was argued, therefore, that patients' apparent perceptual deficits may reflect an inability, unlike the controls, to use declarative memory.

This explanation, however, still does not account for deficits in trial-unique oddity discriminations that are modulated by the perceptual qualities of the stimulus. For example, Barense, Gaffan, and Graham (2007) tested two groups of patients, one with MTL lesions and the other with focal HC lesions, on a trial-unique oddity task in which the level of feature overlap between target and foil was parametrically manipulated. In the first experiment, novel object stimuli (fribbles) were created which comprised a number of appendages. In each oddity trial, seven fribbles were presented; three matching pairs and one odd-one-out. In the minimum ambiguity condition, the appendages that formed the odd item were unique to it. In the intermediate condition, the odd item shared half of its features with the foils. In the maximum ambiguity condition, all of the appendages that formed the odd item were also used in the creation of the foils; the conjunction of features was diagnostic of the odd-one-out. The MTL group was significantly impaired in the intermediate and high ambiguity conditions, whereas the HC group's discrimination accuracy matched controls.

In the second experiment, ambiguity was manipulated in a four-choice oddity using size, colour, and high and low ambiguity novel (greebles) and familiar object stimuli. In the low ambiguity condition, the odd item could be identified on the basis of a single feature; in the high ambiguity, the odd item and foils shared a number of overlapping features. Relative to controls, the MTL and HC groups were not impaired on the size, colour, or low ambiguity oddity discriminations. In the high ambiguity condition, however, the MTL group made significantly more errors than controls and the HC group. Importantly, control performance was matched across the high ambiguity object, size, and colour discriminations meaning that a difference in difficulty between conditions could not explain the deficit. Furthermore, the use of trial-unique stimuli limited the opportunity for controls to benefit from memory because, as was evident in Kim et al. (2011), controls showed learning only when the same stimuli were repeated over trials. More recent proposals in support of the unitary account have explained these deficits, even in perceptual tasks, in terms of subspan and supraspan memory (Jeneson & Squire, 2012).

While original instantiations of the unitary account proposed that the memory performance of temporal lobe amnesic patients will diminish over a delay (e.g.,Milner et al., 1968), a relatively recent modification of this account has placed more emphasis on the amount of information to-be-remembered. Subspan memory comprises memory for items whilst the participant's attention is directed toward the stimulus. For example, this might refer to the constant rehearsal of information, thought to explain HM's spared digit-span memory. Supraspan memory relies on more permanent memory storage and is

employed after the participant is distracted from the stimulus, or the stimulus is too complex (e.g., comprising a high number of visually similar items). The view proposes that patients with damage to the MTL can maintain information indefinitely in subspan memory as long as this capacity is not exceeded by the demands of the task (Jeneson & Squire, 2012). Once a task requires the maintenance of a number of different elements in an array or the switching of attention between different items, however, it will then more likely require supraspan memory.

To test this prediction, Knutson, Hopkins, and Squire (2012) created a fribble (novel object) oddity task and manipulated the difficulty of the task by changing the array size, and ambiguity of the items (by virtue of number of appendages, colour of appendages, and the visual similarity of the appendages). Two groups of patients were tested: a group with focal HC lesions and a group with larger lesions encompassing the PRC (MTL). It was predicted that when the perceptual load was low (i.e., smaller arrays with discriminable features), the patients' performance would match controls. When the arrays involved a large number of items and were perceptually similar, however, this would exceed working memory capacity and the patients would be impaired. The authors predicted, contrary to the representational account described above, that as both lesion groups had damage to the HC both should be impaired on the task. These predictions were borne out, suggesting that previously observed patient deficits result from mnemonic, rather than perceptual deficits.

The impairments seen in this object perceptual discrimination task are challenging to representational accounts, but as the authors did not fully cross

the factors of array size and feature overlap, the findings remain difficult to interpret. It is not possible to determine, therefore, the individual contribution of these factors or how they interact. Given that the stimuli comprised objects, representational accounts of MTL function would predict that high feature overlap, even in small arrays, should result in impairments in the MTL group. Increasing the number of items in the array would necessarily exacerbate any deficit because it would require the maintenance of a greater number of object-level representations. The data cannot speak to this hypothesis because, in the small arrays, the item features were visually distinct, and feature overlap was only increased in larger arrays. That said, representational accounts would predict that the HC patients should perform normally on this task given that the task uses object stimuli (Barense et al., 2007). Contrary to this, the HC patients showed greater impairments in discrimination accuracy than the MTL group.

A potential explanation for the poorer performance of the HC group in this task relative to Barense et al. (2007) is that the feature change was implemented differently. In Knutson et al. (2012), the high ambiguity changes comprised differences in the size or shape of an appendage; in Barense et al. (2007) the feature change was replacement of an appendage with a different appendage. If the role of the HC extends beyond scene/spatial environments to processing the spatial features of object stimuli, it is possible that changes to the size or shape of an appendage might stress the HC. In support of this idea, Buckley, Charles, Browning, and Gaffan (2004) found that monkeys with fornix lesions were impaired when required to discriminate pairs of object stimuli

(tadpoles) in which spatial aspects of the stimuli had been manipulated (length of the tail and orientation) (see Figure 1.7). To test whether the human HC supports processing of spatial object features, tadpole stimuli were used in the conjunction learning task reported in Chapter 2.

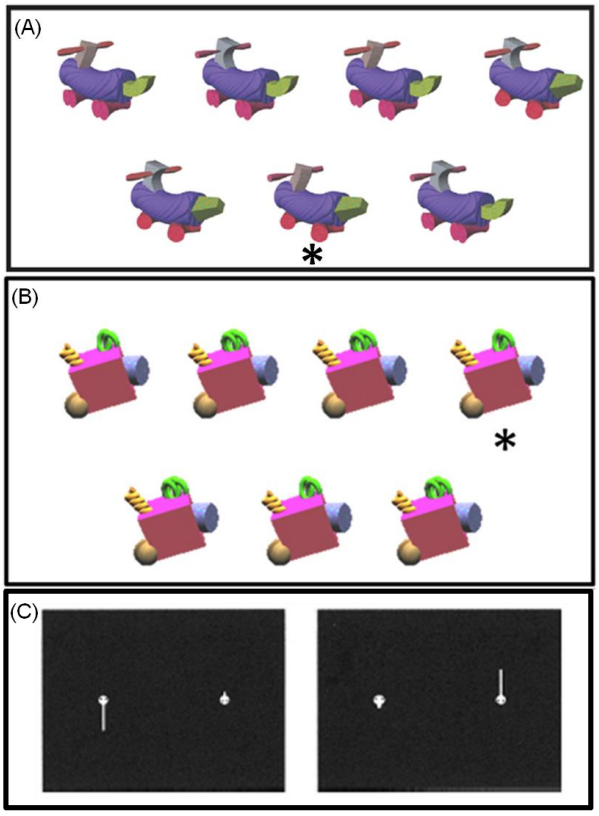

Figure 1.7. ***High ambiguity trials from novel object (fribble) oddity tasks in (A) Barense et al. (2007), and (B) Knutson et al. (2012). Each concurrent array contains three identical pairs and one odd item (denoted with *). (C) Conjunction learning task with spatial objects (tadpoles). Monkeys with fornix lesions were impaired when required to discriminate items on the basis of ambiguous spatial features (orientation and length of tail).***

An alternative explanation for perceptual deficits in patients with MTL damage is that they may have impaired trans-saccadic memory. This means that even when all items to-be-discriminated are presented concurrently, the patient may not remember information when switching their gaze across the different items. Abnormal eye movements in patients with MTL damage, therefore, might be indicative of a subtle memory deficit. Eye-tracking data suggest that patients with MTL or HC do not show abnormal eye-movements during oddity tasks. Erez, Lee, and Barense (2013) used novel object, familiar object, face, and scene stimuli in an oddity task and examined the saccadic eye-movements of patients. Behaviourally, the patients performed consistently with previous outcomes; HC patients showed impairments for scenes whilst MTL patients were impaired on scenes, objects, and faces. The eye-tracking data, however, did not reveal any differences between patients and controls in the way in which items were visually searched, regardless of stimulus category. Importantly, there was no evidence that they needed to switch their gaze between items any more than the controls, which would be expected if the patients had greater difficulty representing the items over this delay.

In order to reduce working memory load in a perceptual task, Lee and Rudebeck (2010) used single object items and analysed eye-movements to examine how patients with damage to the PRC process these stimuli. Two patients, one with focal HC damage and one with damage to the MTL including the PRC, and controls were presented with object items comprising line drawings. Half of the stimuli contained a region that was structurally incoherent

and therefore rendered the object ‘impossible’ in the real world. In the first experiment, participants were presented with pairs of items (both possible and impossible) and were required to say whether the two items were the same or different. In the second experiment, single items were presented and they were required to say whether the item was ‘possible’ or ‘impossible’ and the patient’s eye-movements were analysed. Both patients and controls performed normally on the discrimination task in the first experiment. The MTL patient, however, made a significantly greater number of errors during the presentation of the single impossible items. Eye-tracking data revealed that controls and the HC patient spent a greater proportion of time fixating on the structurally incoherent element of the impossible stimulus. The MTL patient only showed this pattern of data for correct responses; for incorrect responses they looked beyond this element. It was argued that this demonstrated that patients with damage to the PRC could not represent the conjunctions of features that comprise an object.

The apparent disparity between eye-tracking results (normal for oddity but impaired for single items) can be explained by the difference in experimental paradigm. The oddity task requires the participant to examine a number of items, and only the conjunction of features is indicative of the odd-one-out. This means that the participant is required to look between several different stimuli and there is not one individual feature that is indicative of the odd item. The single object item, however, has one area critical to success in the task, and is therefore a more sensitive approach for identifying how participants use visual information in perceptual tasks. The use of trial-unique stimuli, single items, and

abnormal eye-tracking performance during the processing of structurally incoherent objects suggest that the deficits are perceptual rather than mnemonic.

1.4.4.2. The human PRC buffers against interference

Analogous to the animal data, Barense et al. (2012) demonstrated that the human PRC also buffers against interference in object stimuli. Novel 'blob' stimuli were created comprising three features; an outer shape (A), an inner shape (B), and a texture (C). Participants were presented with a pair of 'blobs' and required to say whether the two items were the same or different; to make the task more difficult the items were presented rotated. Two levels of ambiguity were created: 1) high ambiguity, in which one feature differed between the blobs (e.g., ABC versus ABD), or 2) low ambiguity in which there was no overlap in features (e.g., ABC versus DEF). Replicating previous ambiguity effects, patients with MTL damage made significantly more errors on the high ambiguity relative to low ambiguity trials relative to patients with focal HC lesions, and controls. Analysing the patients' performance by trial schedule supported the notion of the PRC buffering against the interference of similar conjunctions. Relative to controls, the MTL patients' performance declined over the course of the high ambiguity condition. This effect was ameliorated, however, with the inclusion of trials (real world objects) that contained no features that overlapped with the high ambiguity blob stimuli.

The data from Lee Buckley et al. (2005), Lee Bussey et al., (2005), and Barense et al. (2007) support the findings of the animal research using relatively similar paradigms and addressed some of the criticisms associated with the animal research, such as alleviating the need for extensive training. In a relatively diverse set of manipulations of featural ambiguity, including blended images, manipulations of viewpoint, and conjunctions of features, patients with MTL lesions that included the PRC were impaired on discrimination learning and oddity tasks employing object stimuli under conditions of high featural ambiguity relative to patients with HC lesions and controls. The representational-hierarchical model provides a convincing explanation for these data, however there was also evidence that patients with HC lesions were impaired when discriminating high ambiguity spatial stimuli, manipulated by changing the viewpoint of scenes in oddity or by morphing together two scenes to create overlapping features (Lee, Buckley, et al., 2005; Lee, Bussey, et al., 2005). Currently, the representational-hierarchical model does not account for these spatial deficits, although there is some evidence that the dorsal HC in mice is recruited under conditions of high spatial ambiguity (McTighe, Mar, Romberg, Bussey, & Saksida, 2009). EMA (Graham et al., 2010) proposes an explanation for the extant data and this will be discussed in relation to converging fMRI data addressing these research questions.

1.4.5. Object and scene processing in the MTL: fMRI evidence

The contribution of PRC and HC to object and scene processing, respectively, has been supported by a number of imaging studies. Prior to

scanning, Pihlajamäki et al. (2004) presented participants with a 3 × 3 array containing five colour objects arranged in a random configuration (baseline). Whilst in the scanner, subjects passively viewed the same baseline image and, after a short delay the array was presented again. In an item change condition, stimuli were presented in the same configuration but one object was replaced by a distinct novel object. In a location change condition, the same objects were presented but one object occupied a different spatial location in the array. Contrasting activity associated with item change trials with baseline and location change trials revealed activity in PRC and anterior HC. Conversely, location change trials (contrasted with item change and baseline) were associated with posterior HC and posterior PHG activity. This task suggested a division of labour within the MTL with the PRC supporting object discriminations and the HC supporting spatial discriminations.

This effect was replicated in a perceptual discrimination task that, unlike Pihlajamäki et al. (2004), contained no demand to remember items and configurations over a delay. Lee, Bandelow, Schwarzbauer, Henson, and Graham (2006) scanned participants whilst they were presented with two, 2*3, arrays each containing three object items. Similar to Pihlajamäki et al. (2004), there were three conditions; item change, location change, and match. In the item change condition, objects were arranged in the same configuration across the grids but one pair of items differed. In the location change condition, the three item pairs were the same, but one of the items occupied a different spatial location across grids. In the match condition, the two grids contained the same

items and they were located in the same spatial locations across grids. Participants were required to indicate whether the grids contained an item change, a location change, or were the same. In attempt to rule out any contribution of memory, all stimuli were trial-unique. Replicating the previous findings, relative to match trials, item change trials were associated with significantly greater activity in the PRC. Location change trials, however, were not associated with an increase in HC activity.

The absence of HC activity associated with object location change trials was unsurprising given that the spatial stimuli used in the experiment were quite different to those that elicit deficits in HC patients (i.e., real-world or virtual reality scenes). In a further experiment, Lee, Scahill, and Graham (2008) scanned participants whilst they performed the different view condition of the oddity task with face and scene stimuli that had elicited stimulus specific deficits in patients (Lee, Buckley, et al., 2005, 2006). Four-choice face, scene, and size oddity trials were presented in a blocked design with trials repeated over three runs. This design allowed the researchers to observe regions of the MTL in which activity correlated with object and scene stimuli, respectively. Furthermore, it provided an opportunity to test whether these regions showed an attenuated response to items that were repeated (Grill-Spector et al., 2006). Correct responses to face oddity trials were associated with increased BOLD response in the PRC and anterior HC. Conversely, correct responses for scene trials activated the posterior HC and PHC. Furthermore, the BOLD signal in

these stimulus specific regions was attenuated when the stimuli were repeated over the three runs.

Changing the view of objects in a perceptual discrimination task has also been associated with an increase in PRC activity. Devlin and Price (2007) presented participants with a four-choice oddity task comprising object, shape and colour stimuli, at two levels of ambiguity; low and high. For the objects (animals and artefacts), low ambiguity trials comprised items presented from the same view with a visually distinct target item. In the high ambiguity condition, the target and foils were presented from different views and all items shared a number of overlapping features. For the colour and shape stimuli, in the low ambiguity condition the target item was either a distinct colour or shape or was a perceptually similar colour or shape. Relative to baseline, only the high ambiguity object condition was associated with significantly increased PRC activity. Activity in the left PRC tracked the level of ambiguity with greater activity associated with high ambiguity object trials relative to low ambiguity trials which in turn was greater than high and low ambiguity colour and shape trials. Given that the task manipulated both the level of feature overlap and viewpoint in the high ambiguity condition, it was not possible to attribute the increased PRC activity solely to either manipulation.

This effect was replicated and extended to demonstrate that successful oddity discrimination for scenes from different views increased HC activity (Barense, Henson, Lee, & Graham, 2010). Participants viewed three-choice oddity trials comprising novel object (greeble), face, virtual reality scene, and

size stimuli. In the low ambiguity condition, all items in the triad were presented from the same view and the odd item could be identified on the basis of a single feature. In the high ambiguity condition, all items were presented from different views and shared a number of overlapping features. These trials, therefore, required a complex and view-invariant representation of the item. Supporting the findings of Devlin and Price (2007), significantly greater PRC activity was associated with high ambiguity relative to low ambiguity objects. The same pattern of data was true for scenes in the HC. The level of ambiguity for face stimuli modulated activity in both the PRC and HC. These data suggested that the greater demand placed upon a representation is mirrored in the level of activity in stimulus specific regions. Like the Devlin and Price (2007) study, however, the level of ambiguity was confounded by the change in viewpoint. It is difficult, therefore, to ascertain whether the level of activity in these regions is modulated by the demand to process items from a different view, distinguish the target from similar foils, or a combination of the two.

Disentangling viewpoint and level of ambiguity, Barense et al. (2012) scanned participants whilst they discriminated high versus low ambiguity blob stimuli in an fMRI version of the patient task described earlier. Parameter estimates were extracted from probabilistic masks of the PRC and revealed significantly greater activity associated with high relative to low ambiguity stimuli. Corroborating the findings of the animal data, these findings suggest that the PRC is recruited when one is required to discriminate between visually similar stimuli.

1.4.5.1. Could the fMRI data be explained by incidental encoding activity?

Mnemonic accounts of MTL function would propose that the level of BOLD response correlates with subsequent memory for these items. Increased activity evident during a perceptual discrimination task, therefore, may reflect incidental encoding of these items. For example, the unitary account could propose that the participants form stronger memories for the scenes therefore engaging the HC rather than the PRC. Equally, dual process accounts might suggest that subsequent memory for the different stimulus categories may be supported by different memory processes. For example, it has been argued that face stimuli are more configural and can be unitised therefore meaning that a PRC-mediated familiarity signal could support subsequent memory for this category of stimuli (Aly, Knight, and Yonelinas, 2010).

Efforts have been made, therefore, to control for the BOLD response associated with subsequent memory performance. Barense, Henson, and Graham (2011) presented participants with oddity triads of novel and familiar objects, and novel and familiar faces. After scanning, participants viewed the single odd items from each trial plus new foils and indicated whether they had seen them before (old/new) and their confidence in their decisions (sure/unsure). Parameter estimates revealed that even when items had been subsequently forgotten or poorly remembered (unsure old), activity in the PRC was still significantly above baseline, and subsequent memory performance did not modulate activity for the novel stimuli. These data argue against an incidental encoding interpretation of the stimulus specific effects reported in the

MTL. It must be noted, however, that by including poorly remembered items in the subsequent memory analysis, this may have increased the level of activity in the PRC and therefore it is not possible to rule out entirely the contribution of incidental encoding.

Similarly, for HC activity associated with scene processing cannot be explained simply by incidental encoding. Lee, Brodersen, and Rudebeck (2013) scanned participants whilst they completed a large number (200) of scene oddity trials; outside of the scanner they performed a subsequent memory task. The large number of trials provided the power to categorise trials into one of four bins: 1) perceptual hit and subsequent memory hit, 2) perceptual hit and subsequent memory miss, 3) perceptual miss and subsequent memory hit, or 4) perceptual miss and subsequent memory miss. Contrasting activity for correct versus incorrect oddity trials revealed two bilateral anterior HC clusters of activity, and one in right posterior HC. Parameter estimates extracted from these clusters revealed that the BOLD response was modulated by perceptual oddity performance, not subsequent memory success; correct responses to oddity trials were associated with greater activity than incorrect responses to oddity trials, and activity was not modulated subsequent memory for the item. Although the same pattern of data was evident in all three clusters, the difference in activity between correct and incorrect responses was most apparent in the anterior HC clusters.

Another possible explanation for increased MTL activity associated with oddity tasks is that this reflects the working memory demand of the task. Lee

and Rudebeck (2010b) found that the demand to process complex spatial representations modulated activity in the HC, not working memory demand per se. Participants viewed single virtual reality scenes, or arrays of geometric shapes and were required to either press when an image immediately repeated (1-back), or was a repeat of an image was presented two items before (2-back). Greater activity in the HC was associated with virtual reality scenes relative to the simple geometric stimuli. Furthermore, the memory demand, 2-back vs 1-back, only modulated activity for the virtual reality scenes with greater activity associated with the former relative to latter. These data suggest that the stimulus specific activity evident in oddity tasks cannot be explained simply in terms of incidental encoding. The scene working memory task, however, suggests that the HC supports memory for scenes.

Similarly, O'Neil, Cate, and Köhler (2009) provided evidence to suggest that face representations stored in the PRC can flexibly support both memory and perception. Prior to each scanning run, participants were presented with a number of faces presented singly. During scanning, they were then presented with a three-choice oddity in which two images were the same face and the third was a similar but different face. Two different trial-types were used in an attempt to distinguish between mnemonic and perceptual processes. In the memory condition the participant was required to select the face to which they had been exposed prior to the scanning run; in the perception condition, they were required to select the different face of the trio. For both conditions, performance was above chance but contained enough errors to allow a comparison of activity for correct versus incorrect trials. For both the memory and perception

conditions, relative to incorrect trials, correct trials were associated with significantly greater activity in PRC. Contrary to mnemonic accounts of MTL function therefore, these data suggested that PRC may signal, by way of increased BOLD response, the prior occurrence of an item, or perceptual differences between items.

1.5. Part 3: The emergent memory account and aims of this thesis

At the outset of this Introduction EMA was introduced briefly, as predictions of the model are tested in the experiments described in Chapters 2-5. The preceding sections have outlined competing models and provided a review of the relevant memory and perception literature. A more detailed account of EMA is provided here, with reference to how this account differs in its predictions to the other models discussed in the Introduction. Following this, the experiments comprising the bulk of this thesis are outlined.

First, EMA proposes that the MTL supports both perception *and* memory. It proposes, therefore, that memory deficits following MTL damage may arise from an inability to perceive, and form representations of, object and scene stimuli. In contrast, the unitary account (Squire et al., 2007), dual process account (e.g., Aggleton & Brown, 1999), and BIC model (Diana et al., 2007) suggest that the role of the MTL is limited to declarative memory, and does not extend to perception. EMA, therefore, can account for the deficits on perceptual tasks exhibited by patients with MTL damage (e.g., Lee, Buckley et al., 2005, however see Jeneson & Squire, 2012). Second, EMA proposes a division of labour within the MTL, with the PRC forming complex conjunctions of features comprising object-level representations, and the HC processing complex conjunctions of spatial features comprising scenes. Whereas the unitary and

dual process accounts make few predictions as to the involvement of different MTL regions according to the stimulus to-be-processed, the BIC model accommodates the PRC in the processing of object item stimuli. In contrast to EMA, however, BIC suggests that the HC performs domain-general binding of episodic elements (i.e., object + spatial information) and combines these disparate elements into a bound memory representation. Unlike EMA, therefore, BIC would not predict a scene-specific impairment in memory, and/or perception, in a patient with focal HC damage. Moreover, EMA predicts that these MTL subregions will only be recruited when object and scene stimuli cannot be discriminated on the basis of simple features; the mnemonic accounts discussed here make no predictions as to the involvement of MTL subregions due to an object or scene's conjunctive complexity. Finally, EMA suggests that the HC is recruited when discriminating scene stimuli that share a high degree of overlapping features, even when there is no demand to process the scene from different views (e.g., Lee et al., 2007; Lee, Yeung, & Barense, 2012). In contrast, the BBB model (Byrne et al., 2007) posits that the HC supports allocentric spatial processing. EMA agrees that the HC is recruited during allocentric processing, but suggests that this reflects greater demand to process complex spatial conjunctions. EMA, therefore, would predict that patients with HC damage should show impairments when discriminating scenes presented from the same viewpoint if they share a high degree of overlapping features; in contrast, the BBB model would predict that HC patients should perform normally when scenes are presented from the same viewpoint, but make a greater number of errors when there is a demand for allocentric processing.

Predictions that follow from EMA will be tested throughout the thesis using neuropsychological data (in patients with HC damage), but also applying new fMRI versions of tasks that have successfully recruited PRC and HC during perceptual tasks.

The first experimental Chapter is a short neuropsychological investigation in two HC patients, using a version of the conjunction learning task from Barense et al. (2005). In Barense et al., HC patients showed normal performance on all conditions, while MTL patients were impaired on high ambiguity object discriminations. This pattern has been explained in terms of a working memory deficit (Jeneson & Squire, 2012). A potential challenge to this explanation would be to demonstrate a stimulus specific deficit in conjunction learning performance, where patients with focal HC lesions show impairment on scene, but not object, conjunction learning. Furthermore, it would be difficult to argue for a deficit in working memory if the number of features to be remembered was equivalent across different stimulus types (i.e., a conjunction of two features).

Chapter 3 follows on from this experiment by developing a novel version of Lee, Bandelow et al.'s (2006) discrimination task. In Lee et al., participants had to identify object item changes across two simultaneously presented arrays; this resulted in significant PRC activity. The experiment in Chapter 3 aimed to extend this finding by investigating the role of the HC and PRC in scene and object item changes, respectively, using fMRI, and then asking whether HC patients would show particular difficulties with scene item changes (which would be consistent with the conjunction learning impairments for scenes predicted in Chapter 2).

Chapter 4 tests whether increasing the feature overlap between object and scene stimuli results in commensurate increases in PRC and HC activity, respectively. Although there have been attempts previously to modulate feature overlap across objects in oddity (Devlin and Price, 2007; Barense et al., 2011), these have confounded a change of viewpoint with an increase in feature ambiguity. This experiment controlled for effects of viewpoint whilst manipulating feature overlap. Given that patients with damage to the MTL show impairments during object oddity tasks in which the items share a large number of overlapping features, but not when the items are visually distinct (Barense et al., 2007), it was predicted that activity in PRC should be greater for high ambiguity relative to low ambiguity items. Similarly, patients with HC damage show impairments when discriminating scenes that contain a high degree of feature overlap (Lee, Bussey, et al., 2005) therefore it was predicted that in HC the BOLD response associated with high ambiguity scenes would be greater than low ambiguity scenes. This experiment also aimed to test the role of the posterior PHG in the processing of scenes, and objects associated strongly with a particular spatial context, one of the divergent points between the BIC and representational accounts. In support of the representational accounts, it was predicted that greater activity in this region would be associated with scenes relative to objects with strong spatial contextual associations.

As briefly alluded to above, one of the striking clinical implications of this research has been the finding that patients with AD show poor performance on scene, but not face, oddity tasks (Lee, Buckley, et al., 2006). Similarly, Lee, Levi, Davies, Hodges, and Graham (2007) found that patients with AD also showed deficits on the morph task used in Lee, Buckley, et al. (2005). Other researchers have started to focus on the possibility that spatial perception and

memory may be highly sensitive to the early cognitive changes that precede transition from MCI to Alzheimer's disease (Bird et al., 2010; Pengas, Hodges, et al., 2010; Pengas, Patterson, et al., 2010b). In a novel departure here, this approach is extended to individuals at genetic risk of developing Alzheimer's disease; the final chapter describes an oddity imaging study, complemented by a recognition experiment, in which the aim is to ask whether participants who are carriers of an ApoE-e4 allele, which increases risk of developing Alzheimer's disease later in life, show functional brain alterations (compared to non-carriers) particularly for scene perception and memory.

These experimental chapters are complemented by a General Discussion (Chapter 6) in which the findings from the four experiments are summarised, and integrated, and where key outstanding questions are considered in the context of the diverse literature presented in this Introduction.

Chapter 2: Conjunctive scene learning in the human hippocampus

2.1. Introduction

As outlined in Chapter 1, there is considerable debate regarding the putative roles of the HC and PRC in memory, a discussion that has been extended recently to a potential role in perception. A number of different MTL models were discussed in the Introduction to this thesis, only some of which (representational accounts, Graham et al., 2010; Saksida & Bussey, 2010) assume a contribution for MTL structures in memory *and* perception. In one of these views, EMA (Graham et al., 2010), the HC and PRC are involved in the higher order perception of different types of complex visual stimuli, with the PRC necessary for discriminating between, learning and remembering conjunctive object representations (Saksida & Bussey, 2010), while the HC is involved in both perceptual discrimination, learning and memory for complex scene representations. Evidence supporting this view and a related model, the representational-hierarchical account, has mostly come from animal lesion experiments, with many of these studies examining the role of the PRC in higher order perception (see Section 1.4.3.1). A successful research strategy was the extension of these tasks into human participants with static lesions of the MTL that resulted in memory impairment, as evidenced by performance on standard neuropsychological tests of memory. These studies have revealed a striking level of similarity in the patterns of preservation and impairment seen after broader MTL damage (including the PRC), including a key study in humans, in which feature ambiguity for objects was systematically controlled

(Barense et al., 2005, see Section 1.4.4). The combined findings from these animal and human studies, including the complementary fMRI investigations discussed in the Introduction (e.g., Barense et al., 2012, 2011; Devlin & Price, 2007; Mundy, Downing, & Graham, 2012; O'Neil et al., 2009, see Section 1.4.5), clearly highlight a role for PRC in perceptual discrimination of object and face stimuli, and demonstrate that these patterns cannot easily be accounted for by mnemonic processes. While there is still debate about the role of the PRC, in particular how these representations may be used in the service of perception and memory, many memory researchers are now comfortable with the idea that the contributions of PRC go beyond declarative memory (e.g., Dew & Cabeza, 2013).

By contrast, there has been far less research testing predictions from representational accounts regarding the role of the HC in perceptual discrimination (i.e., in particular studies that show preservation of object perception alongside impaired scene perception). This Chapter, therefore, addresses whether the HC supports discrimination learning of scenes, but not objects, including objects in which there are changes to the spatial location of features (similar to Buckley et al., 2004, tadpoles, see Section 1.4.4.1). Importantly, to address mnemonic explanations of stimulus specific effects, in this experiment, memory load across different stimulus categories was controlled by systematically manipulating two features of the stimuli. Prior to describing the experiment, I will provide a brief review of relevant studies, and highlight how the study helps address outstanding questions in the literature.

The most robust findings in this area come from neuropsychological studies that have adopted paradigms in which the feature overlap between

objects has been systematically controlled. For example, Barense et al. (2005) demonstrated that the PRC forms highly conjunctive object representations using a discrimination learning paradigm in which the level of feature overlap between targets and foils was manipulated (see Figure 1.6). Patients with damage limited to the HC (including patients HC2 and HC3 that participated in the experiment described in the current Chapter), and patients with MTL damage encompassing both the PRC and HC, viewed pairs of object images which contained varying degrees of feature overlap (two of the overlap conditions are described here). In the low ambiguity condition there was no overlap between the S+ and S- stimuli, whereas in the high ambiguity condition each component part of the stimulus was present equally often in S+ and S- items; only the conjunction of features was indicative of the S+ item. The patients' pattern of performance was modulated by the profile of MTL damage. Patients with HC lesions made the same number of errors as controls, regardless of the level of feature overlap; patients with MTL damage, however, made a significantly greater number of errors, but only for the high ambiguity condition (i.e., where feature conjunctions were necessary to successfully complete the task). These data, therefore, support the idea of the PRC housing complex and conjunctive object representations. They do not, however, speak to the hypothesis that the HC stores complex, conjunctive scene representations.

To ask whether the HC supports scene learning specifically, Mundy, Downing, Dwyer, Honey, and Graham (2013) tested two patients (patient HC3 and a patient with MTL damage) using a perceptual learning paradigm with pairs of face, scene, and dot stimuli. Two images were presented in quick succession. Pairs were either identical, or morphed to share a small degree of

features from another similar image; the participant was required to indicate whether the two images were the ‘same’ or ‘different’. Over a number of repetitions, control participants learned to successfully discriminate between the similar images in all stimulus categories. The patients, however, showed a pattern of discrimination impairment commensurate with the location of their MTL damage. Specifically, the MTL patient showed impaired learning for faces and scenes but, over repeated trials, was able to discriminate between dot patterns to the same level as controls. The HC patient showed learning for both dot patterns *and* face stimuli, but did not learn to discriminate scene pairs. Together, the two studies highlight a division of labour in the MTL with the PRC and HC supporting object/face and scene learning, respectively. It is important to note, however, that unlike the PRC evidence discussed above (and in Section 1.4.3.2.2), the composite features of scene stimuli were not controlled in Mundy et al. (2013); rather, morphs or changes in viewpoint were implemented to create potential feature ambiguity.

As was described in Section 1.4.4.1, the unitary account of MTL function explains these apparent stimulus specific deficits in terms of the extent of MTL damage, and a resultant deficit in 'supraspan' memory (Jeneson & Squire, 2012; Jeneson, Wixted, Hopkins, & Squire, 2012; Kim et al., 2011; Knutson et al., 2012). One of the key predictions of the unitary account is that the level of MTL damage will correlate with the degree of memory impairment. Consistent with this prediction, Barense et al. (2005) showed that patients with widespread MTL lesions showed greater learning impairments relative to patients with focal HC lesions. Second, the unitary account proposes that memory comprises both subspan and supraspan memory (Jeneson & Squire, 2012). It is argued that patients with MTL damage can maintain information within subspan memory for

an infinite length of time as long as the information can be rehearsed, and the stimulus is not too complex; this is consistent with HM's preserved digit span memory when he was free from other distractions (Corkin, 2002). Once subspan memory capacity has been exceeded, supraspan memory is required to maintain accurate task performance.

This supposed deficit in supraspan memory was demonstrated by impaired performance in HC and MTL patients in a fribble oddity task in which the array was large, and the individual fribbles contained a high degree of feature overlap (Knutson et al., 2012); only small spatial changes such as the size and orientation of an appendage were indicative of the odd-one-out. As deficits were only observed in the large array/high feature overlap condition, it was argued that this had exceeded the patients' intact subspan memory. The scene specific deficit in learning for patient HC3 (Mundy et al., 2013), therefore, might be explained by differences in the inherent complexity of the stimuli themselves. For example, scenes may require maintenance of a greater number of component features, which may, in turn, cause subspan memory to be exceeded. Critically, therefore, a stimulus specific deficit may actually reflect the absence of supraspan memory in the patients.

That patients with HC damage were impaired on spatial manipulations (orientation, size) of object stimuli in Knutson et al. (2012) may reveal more about the types of representations supported by the HC. Fornix lesions in macaque monkeys have been shown to impair learning of object stimuli (tadpoles) in which spatial features, such as the length of tail and its orientation, were manipulated (Buckley et al., 2004). Similar to Barense et al. (2005), monkeys were presented with pairs of images and required to remember the

rewarded items. In the high ambiguity condition, monkeys could not use an individual feature to discriminate the tadpole pairs. Instead, they were required to remember the conjunction of tail length and the tadpole's orientation. Fornix lesions impaired the learning of these highly ambiguous spatial object conjunctions, suggesting that the HC may support spatial processing of object stimuli when there are spatial changes to object features.

It must be noted, however, that there is an inevitable tautology with the subspan/supraspan memory explanation for these findings, because the exact conditions under which deficits will be observed in patients has not been made explicit. Rather, the unitary account uses the point at which a patient begins to show impairment on perceptual discrimination tasks as the moment at which subspan memory has been exceeded (Knutson et al., 2012). Stimulus specific accounts of MTL function are particularly vulnerable to criticisms regarding stimulus complexity. For example, in comparison to a single object, a real world scene could be considered a collection of spatially related object items, and is therefore more complex than an individual object. Feature conjunctions have provided a viable method of controlling for the complexity, and degree of feature overlap, between object items but there have been no attempts thus far to control this factor across stimulus categories. Implementing such an experiment would be a step forward, therefore, in addressing potential criticisms of existing studies.

The experiment outlined in this Chapter addressed this issue by testing two patients with damage limited to the HC on a novel visual conjunctive learning task similar to that of Barense et al. (2005). Four conditions were

tested: colour, scenes, objects (fribbles, see Barense et al., 2007), and tadpoles (see Buckley et al., 2004).

There were two principal aims. First, by comparing scene and object stimuli, both created by undertaking feature manipulations analogous to those used previously to test PRC contributions to object learning, I was able to ask whether the HC is necessary for learning to discriminate between featurally overlapping scene, but not object, representations. To control for feature overlap between targets and non-targets, and the level of stimulus complexity across the four experimental conditions, each item was created from two component parts (features). This allowed for control over feature overlap between items, and provided a control for potential differences in the complexity, and resultant memory load, across different stimulus classes. It was predicted that the HC patients would show impaired scene, but not object, learning. Second, a key prediction of EMA is that the contribution of the MTL to perception and memory task fractionates according to the type of stimulus to-be-processed (i.e., objects versus scenes processed in PRC and HC, respectively). It is not clear, however, whether the HC is required when discriminating object items in which the critical features driving task success would comprise spatial elements. Tadpole stimuli, similar to those described by Buckley et al. (2004), were also presented to test whether the HC supports discrimination of these items, as would be predicted by impairments shown in fornix lesioned monkeys. The colour condition was added as a control, based on Lee, Buckley, et al.'s (2005, see also Buckley et al., 2001) findings that colour oddity is preserved after PRC lesions.

2.2. Method

2.2.1. Participants

Two patients (previously reported under the codes HC2 and HC3 in Barense et al., 2005, 2007; Erez et al., 2013; Graham et al., 2006; Lee & Rudebeck, 2010a; Lee, Buckley, et al., 2005; Lee, Bussey, et al., 2005; Rudebeck, Filippini, & Lee, 2013) and seven age and education matched healthy controls (four for patient HC2; three for HC3) participated in the experiment. Patients HC2 and HC3 were first described in Lee, Bussey, et al. (2005) and throughout this thesis, these patient labels are maintained for consistency. The patients and controls described here also participated in the experiment described in Chapter 3.2. All participants gave informed consent, and the research gained ethical approval from the Cambridge National Health Service Research Ethics Committee, and the Cardiff University School of Psychology Ethics Committee. Age-matched controls were recruited using Cardiff University's School of Psychology Community Panel, and they were remunerated for their participation in the study according to standard procedures for the panel.

Patient HC2, a 51 year old female with 17 years of education, sustained brain injury after viral encephalitis. Patient HC3, a 54 year old female with 10 years of education, sustained brain damage after carbon monoxide-induced hypoxia. Visual assessment of structural scans confirmed significant HC atrophy in the patients relative to controls (Lee, Buckley, et al., 2005; Lee, Bussey, et al., 2005), and more detailed volumetric analyses involved estimates from a number of bilateral regions of interest (ROIs) (temporopolar cortex, amygdala, ERC, PRC, HC, PHC, anterior fusiform gyrus, posterior fusiform

gyrus, anterior temporal cortex, posterior lateral temporal cortex). These analyses confirmed that, relative to age-matched controls, patient HC2 (Erez et al., 2013) and patient HC3 (Lee & Rudebeck, 2010a) had significantly reduced bilateral HC volume (see Table 2.1). It is important to note that there was little atrophy to other surrounding areas of cortex in both cases. Furthermore, recent functional imaging of patient HC3 revealed that other regions of cortex show normal response to different categories of visual stimuli (see Figure 2.1), and structural analyses confirmed no gross white matter structural differences relative to controls. Although it is possible that there is covert brain pathology not detectable via imaging, these data provide some confidence that any behavioural deficits observed in the patients most likely result from their focal HC lesions.

Table 2.1. ***Results of volumetric analyses from 10 bilateral ROIs in patients HC2 and HC3 relative to age matched controls (Z > -1.96 indicates significantly reduced brain volume in an ROI). (Table adapted from Erez et al., 2013).***

	Temporopolar cortex	*Amygdala*	*Entorhinal cortex*	*Perirhinal cortex*	*Hippocampus*	*Parahippocampal cortex*	*Anterior fusiform gyrus*	*Posterior fusiform gyrus*	*Anterior lateral temporal cortex*	*Posterior lateral temporal cortex*
LEFT										
HC2	0.83	0.24	1.01	0.04	**-2.48**	1.58	0.03	1.82	-0.34	1.89
HC3	1.06	1.86	1.44	0.18	**-4.78**	-0.74	-0.57	0.39	-0.43	0.49
RIGHT										
HC2	3.63	0.41	0.24	0.3	**-2.3**	1.95	1.15	0.12	-0.09	1.33
HC3	0.43	0.94	0.31	-0.9	**-3.92**	-0.73	-0.09	0.78	-0.33	-0.53

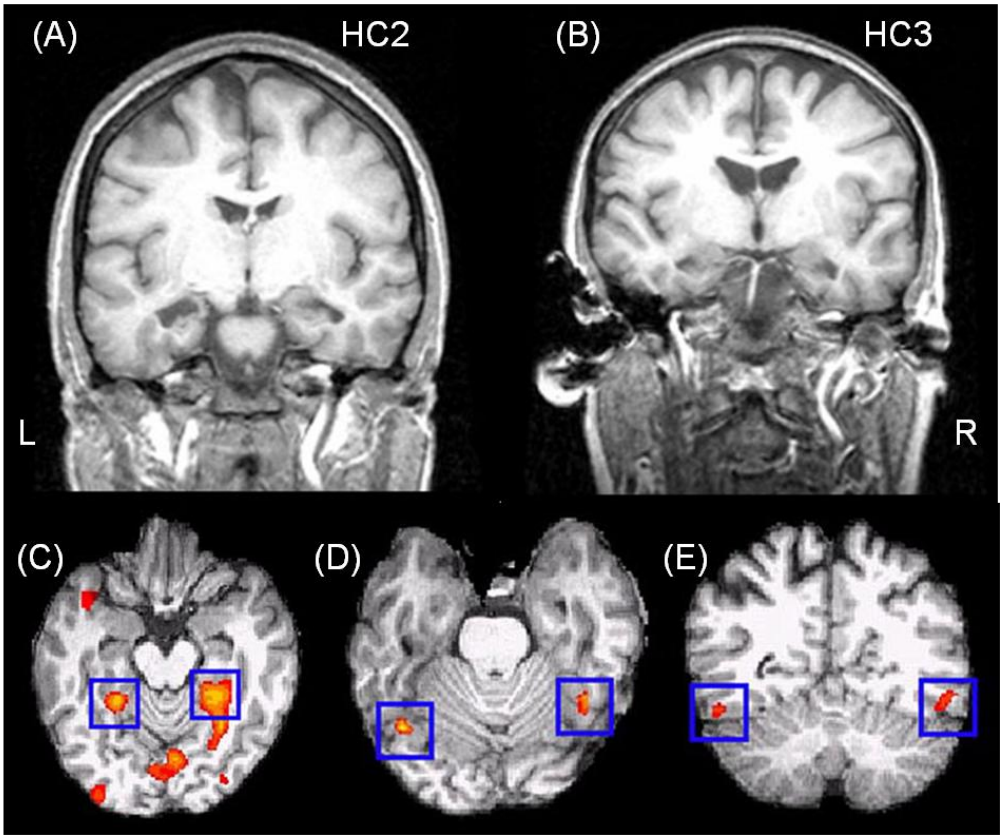

Figure 2.1. ***Coronal slices from T1 weighted scans of patients (A) HC2 and (B) HC3 showing HC atrophy in both patients. Lee and Rudebeck (2010) scanned patient HC3 during a 1-back localiser task comprising scenes, faces, and objects and found the predicted response in extrastriate regions, (C) the PPA (D) the fusiform face area, and (E) the lateral occipital cortex, respectively (Figure adapted from Lee and Rudebeck, 2010).***

On neuropsychological tests, both patients showed evidence of impaired memory. For delayed recall of a prose passage in the Wechsler Memory Scale 3rd edition (WMS III; Wechsler, 1997), patient HC3 showed very poor memory (4/50), with performance more than two standard deviations below that of the matched controls who participated in the current study. Patient HC2 showed a

more subtle memory deficit with memory performance just below control average (see Table 2.2). Patient HC2 showed normal recognition memory for the prose passage, whereas patient HC3 was again impaired relative to matched controls. On the Warrington Recognition Memory Test (WRMT; Warrington, 1984), both patients' memory for words was poor (HC2 = 10-25th percentile; HC3 = <5th percentile), whilst memory for faces was in the normal range (HC2 = 95th percentile; HC3 = 50th percentile). Supporting the structural imaging findings, there was no evidence of any perceptual deficits as evidenced by near perfect performance when required to copy the Rey-Osterrieth Complex Figure (RCF; Osterrieth, 1944) (HC2 = 36/36; HC3 = 35/36); performance declined, however, when required to remember this image over a delay (delayed recall: HC2 = 18, HC3 = 3), and HC3's performance was more than two standard deviations below matched control mean. Visuospatial abilities were normal in both patients, with near perfect performance on the dot counting, position discrimination, and cube analysis subtests of the visual object and space perception battery (VOSP; Warrington & James, 1991). Similarly, semantic knowledge (assessed by naming; Adlam et al., 2010), word-picture matching (Adlam et al., 2010), and the Pyramid and Palm Tree test (PPT; Howard & Patterson, 1992), and executive functions (assessed by the Wisconsin Card Sorting Task; Nelson, 1976) and Raven's coloured progressive matrices (RPCM; Raven, 1962) were within the normal range.

Table 2.2. ***Neuropsychological test battery. Where applicable, maximum scores are contained within parentheses. Individual scores are provided for patients HC2 and HC3. Mean scores of age-matched control groups are provided (parentheses contain one standard deviation (S.D.). Where percentiles given, norms are based on the test manual. Patient scores in bold reflect performance two standard deviations below matched-control mean.***

	HC2	HC3	HC2 controls	HC3 controls
Age	51	54	51 (1.83)	50 (3.61)
Years of education	17	10	16 (0.82)	10.67 (0.58)
Recall				
WMS III immediate story recall (/75)	31	**22**	43.5 (10.85)	54.67 (6.11)
WMS III delayed story recall (/50)	24	**4**	31.5 (8.35)	34.67 (3.21)
RCF delayed recall (/36)	18	**3**	16.75 (5.33)	18.83 (8.25)
Recognition				
WMS III delayed story recognition (/30)	24	**19**	26.5 (1.73)	28.33 (1.53)
WRMT faces (/50)	48 (95%ile)	44 (50%ile)		
WRMT words (/50)	42 (10-25%ile)	33 (<5%ile)		
Visuospatial				
RCF copy (/36)	36	35	34.75 (1.89)	36 (0)
VOSP dot counting (/10)	10	9	10 (0)	10 (0)
VOSP position discrimination (/20)	20	19	20 (0)	20 (0)
VOSP cube analysis (/10)	10	10	9.75 (0.5)	10 (0)
Semantic			**Controls**	
Naming (/64)*	62	64	62.3 (1.7)	
Word Picture matching (/64)*	64	64	63.8 (0.4)	
PPT pictures (/52)$^{\Delta}$	51	52	51.2 (1.4)	
Executive				
WCST (categories/6)$^{+}$	6	6	5.8 (0.5)	
Digit span-forwards*	6	6	7.2 (0.9)	
Digit span-backwards*	4	6	5.3 (1.3)	
RPCM (/36)	34 (>95%ile)	34 (>95%ile)		

Controls from Adlam, Patterson, Bozeat, and Hodges (2010);** $^{\Delta}$ **Controls from Howard and Patterson (1992);** $^{+}$ **Controls from Graham, Emery, and Hodges (2004).

2.2.2. Experiment procedure and materials

The experiment procedure replicated Barense et al. (2005). Participants viewed four different classes of stimuli: colour, objects (fribbles; Williams and Simons, 2000), scenes, and tadpoles (details provided below). On each trial, two items were presented concurrently on a touch screen monitor. Each item was sized approximately 225*300 pixels and the items were presented 5cm apart. Within each pair of items, one was designated correct (S+) whilst the other item was incorrect (S-); participants were required to learn, through trial and error, the S+ items. When pressed, S+ items were surrounded by a yellow box and accompanied by a 'chime' sound effect. Conversely, S- items were surrounded by a grey box and were accompanied by an aversive 'chord' sound effect; stimuli remained on the screen until a response had been made at which time the trial ended. Within each condition, stimuli comprised four items (S+ = AB, CD; S- = AD, CB), resulting in four comparisons in total (AB vs AD; AB vs CB; CD vs AD; CD vs CB) (see Figure 2.2).

The discrimination pairs were presented in blocks of four so that each discrimination appeared only once in a block; the order of pairs was randomly determined within each block. The screen position (left versus right) of items was randomly determined on each trial meaning participants could not use screen position as an additional cue to the S+ items. After eight consecutive correct responses per condition the experiment ended; the number of errors to criterion for each condition was recorded.

A practice condition, comprising the letters 'A' and 'B' in different orientations (left versus right leaning) was given prior to the conditions of interest, to allow participants an opportunity to familiarise themselves with the

touch screen apparatus and ask any questions. Participants were told that within each of the pair of items being presented, one item was correct whilst the other was incorrect; the participant's aim was to work out, through trial and error, the correct items and to select them for the remainder of the experiment. In the practice, it was made clear to participants that they could not use individual features of the stimuli to identify the correct item and instead must focus on the use of a combination of features. Two different task orders were created: patient HC2 and her matched controls completed the task in the order: 1) colour, 2) tadpoles, 3) objects, 4) scenes. Patient HC3 and her controls were presented with the following order: 1) colour, 2) objects, 3) scenes, 4) tadpoles.

2.2.2.1. Colour

Colour blocks were created using Adobe Photoshop 6.0.1. Using the 'greyscale slider' option, different shades can be created ranging on a continuum (0-100) from white (0) to black (100), with values in between these two points reflecting different shades of grey. Each 225*300 colour block was divided vertically into two 225*150 component colour blocks. Component 'A' was grey ('50' on the greyscale slider); 'B' was white ('0'); 'C' was dark grey ('75'), and 'D' was black ('100') (see Figure 2.2).

2.2.2.2. Objects

The objects comprised novel 'fribbles' (Williams & Simons, 2000), as used by Barense et al. (2007), but differed from the stimuli reported in the original conjunction learning paper of Barense et al. (2005). The fribbles were selected from the same fribble 'family' (Fa3), meaning that the basic features of (colour, texture etc) were the same across items. The fribbles were identical except for the manipulation of two appendages: the antennae and base. This

task required the participant to remember unique antennae + base combinations.

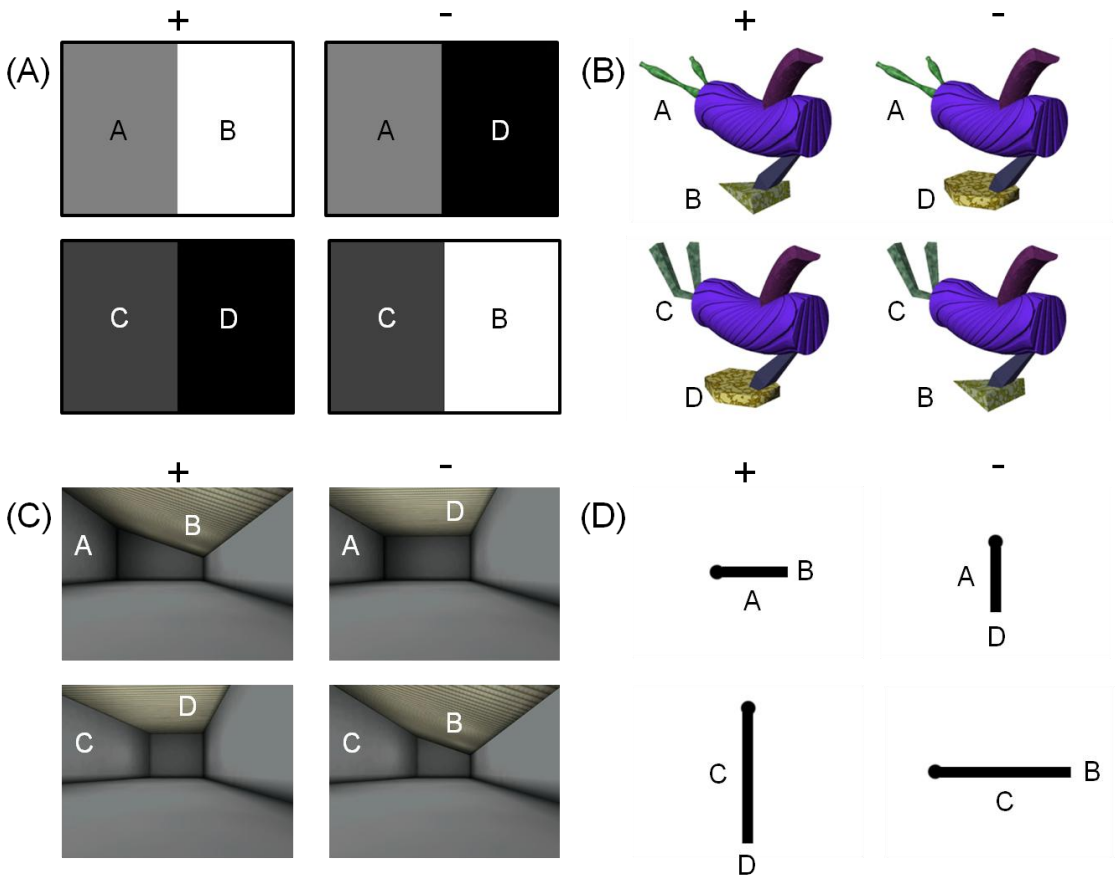

Figure 2.2. ***Stimuli comprised (A) colour blocks (B) fribbles (C) scenes, and (D) tadpoles. Each stimulus comprised two component features that were manipulated to control for feature overlap between S+ and S- items. Importantly, all component features were equally rewarded; only the conjunction of features was indicative of the S+ items.***

2.2.2.3. Scenes

Scenes were created using Deus Ex (Ion Storm L.P., Austin, TX, USA) with software development package (Deus Ex Software Development Kit v1112f). The scenes comprised a room with grey walls with a yellow textured ceiling. The angles of the left hand wall and ceiling were manipulated across rooms to create unique conjunctions that altered the spatial geometry. The angle of the left hand wall could either be straight ('A'), or angled inwards ('C'). Similarly, the ceiling was either angled downwards ('B') or straight ('D').

2.2.2.4. Tadpoles

Tadpoles were created using Adobe Photoshop 6.0.1. The tadpoles were identical except for tail length and tail orientation. These were changed across items to create ambiguity. Tail lengths were either 85 ('A') or 170 pixels ('C'). The orientation of the head could either be leftward ('B') or upward ('D') facing. Participants, therefore, were required to remember unique spatial feature conjunctions of length and orientation.

2.2.3. Statistical analysis

Replicating Barense et al. (2005), performance in patients and controls was assessed by analysing the number of errors to criterion for each stimulus category.

Prior to undertaking a comparison between patients and controls, behavioural performance for the two groups of age-matched controls was assessed by submitting to ANOVA the number of errors to criterion for each stimulus class. A Group (HC2 controls; HC3 controls)*Stimulus (colour; objects; scenes; tadpoles) ANOVA revealed that the number of errors was statistically

equivalent across different stimulus classes ($F(3, 15) = 1.73$, $p = .21$), performance was matched across control groups ($F(1, 5) = 0.46$, $p = .53$), and the factors Group and Stimulus did not interact ($F(3, 15) = 1.78$, $p = .19$). For subsequent analyses, therefore, a single, larger, control group (n = 7), that did not differ in age or years in education to the patients (ts(7) < 0.98, ps > .36), was used for comparison with the patients.

To determine whether there were any differences in learning performance between patients and controls, the number of errors to criterion for each stimulus class were submitted to a Group (HC patients; normal controls)*Stimulus (colour; objects; scenes; tadpoles) mixed ANOVA. A significant interaction between these two factors was investigated with Crawford t-tests (Crawford & Garthwaite, 2002; Crawford & Howell, 1998) to compare the number of errors for each patient separately relative to controls for each stimulus category. Briefly, the Crawford t-test is a modification of the independent samples t-test, in which the patient and controls are treated as two independent samples but, unlike independent samples t-tests, the patient's score does not contribute to the estimate of within-group variance. It has been proposed that this approach is more sensitive to group differences when comparing the scores of individual patients with small samples of control participants (Crawford & Garthwaite, 2002; Crawford & Howell, 1998).

2.3. Results

The Group (HC patients; normal controls)*Stimulus (colour; objects; scenes; tadpoles) mixed ANOVA revealed a main effect of Stimulus ($F(3, 21) = 3.23$, $p < .05$), qualified by a Group*Stimulus interaction ($F(3, 21) = 2.97$, $p < .05$). Patient HC2 showed a significant difference compared to controls on the

scene conjunction learning condition ($t(6) = 2.23$, $p < .05$); as shown in Figure 2.3, this difference reflected poorer performance (a greater number of errors) than the control group. There was also a significant difference between this patient and controls for learning of the colour blocks, but as shown in Figure 2.3, this reflected marginally better memory performance on this condition relative to controls ($t(6) = 1.92$, $p < .05$). Performance was not significantly different between HC2 and controls on the objects and tadpoles ($t(6) < 0.14$, $p > .44$). Like patient HC2, case HC3 also showed a significant difference compared to controls for scene learning ($t(6) = 5.06$, $p < .01$), but also for tadpoles ($t(6) = 9.68$, $p < .01$). In both cases, this difference reflected poorer performance than controls, particularly in the computer generated scene condition where almost 40 errors to criterion were made (compared to the controls average of 4.3). Performance on the objects was matched to that of controls ($t(6) = 0.33$, $p = .38$), although this patient did show a significant difference with controls on the colour blocks ($t(6) = 38.53$, $p < .01$), which reflected extremely poor performance on this condition (see Figure 2.3).

To check that all comparisons were of equivalent difficulty for controls, both within and across stimulus categories, the number of errors for each comparison within each stimulus condition was submitted to a three way ANOVA with the factors: Group (HC2 controls; HC3 controls)*Stimulus (colour; objects; scenes; tadpoles)*Discrimination (AB-AD; AB-CB; CD-AD; CD-CB). There were no significant effects or interactions (Fs < 1.79, ps > 0.19).

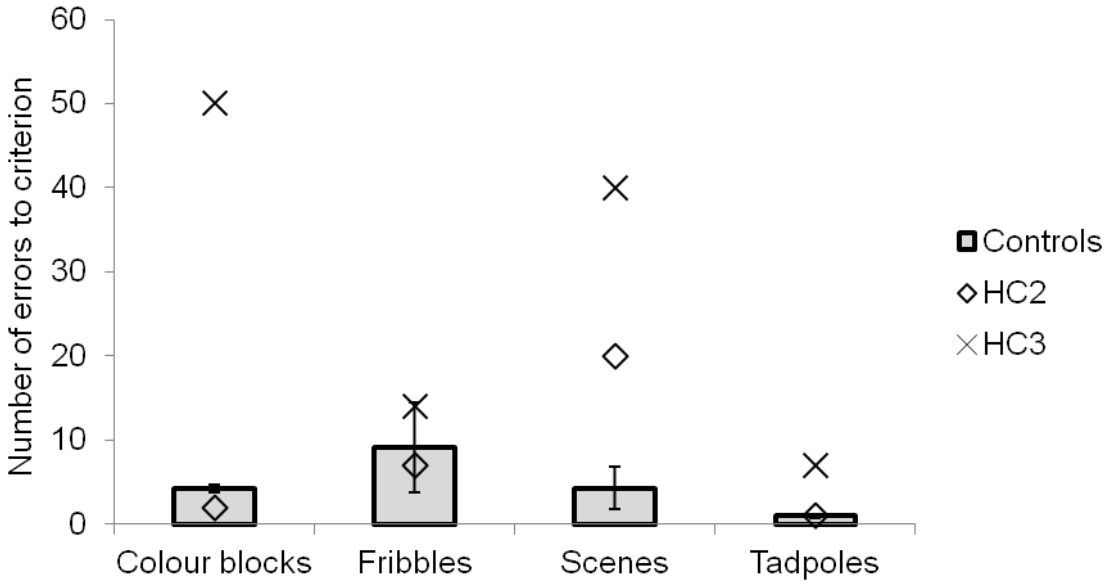

Figure 2.3. ***The number of errors to criterion (eight consecutive correct responses) for each stimulus category, for patients (HC2 and HC3) and controls (error bars represent the standard error of the mean).***

2.4. Discussion

In this study, two patients with focal HC damage were tested to see if they would show impairments in discrimination learning for scene stimuli in which the presence or absence of key features was systematically manipulated, thereby placing a demand on the need to process feature conjunctions within objects and scenes. Four conditions were tested (colour, objects, scenes, and tadpoles). These were designed to answer two key questions: 1) whether we would see scene, but not object, concurrent discrimination learning impairments in our patients (consistent with the predictions of EMA), and 2) whether patients would also show difficulties on concurrent discrimination learning of 'spatial

objects', as shown by Buckley et al. (2004) in monkeys with fornix transections. Critically, for the interpretation of such data, it was important to see that the memory demand across the four stimulus categories was matched in control participants, with similar levels of behavioural performance in all conditions. To our knowledge, this is the first concurrent discrimination learning task that has controlled for the degree of feature overlap between targets and non-targets, whilst matching the level of memory load across different stimulus categories. Moreover, it is the first study that has systematically manipulated features within scenes to create a high ambiguity scene concurrent learning task.

Supporting the findings of Barense et al. (2005), both HC patients showed normal learning when asked to discriminate between visually overlapping fribbles (the object condition). This finding is important by extending evidence of normal discrimination learning of objects in HC cases, but also in demonstrating similar patterns for fribbles when presented in an oddity task and in a concurrent discrimination learning paradigm. Given the focal HC lesions in the two cases, this finding reveals that the HC is not necessary for some aspects of learning, in particular when that involves objects and even when there is high featural ambiguity between stimuli.

Both patients showed impairments in scene learning, as evidenced by a significantly greater number of errors to reach the criterion of eight consecutive correct responses. This result complements that reported in Mundy et al. (2013) and, as explained in the introduction to this Chapter, addresses some of the criticisms of this study regarding a lack of control over the composite elements of the stimuli (e.g., visual similarity between stimuli was created by morphing rather than systematic featural changes within rooms). Patient HC3 also

showed a broader spatial impairment than HC2 by demonstrating difficulties (albeit milder than for virtual reality scenes) when asked to learn to discriminate between object stimuli (tadpoles) that contain conjunctions of spatial features (i.e., length, orientation). In combination, these findings partially support the predictions presented in Section 1.5; they will now be discussed in light of other relevant research.

Both HC patients showed clear evidence of a difficulty with concurrent discrimination learning of high ambiguity scene stimuli. Moreover, this deficit in scene learning cannot be explained on the basis of the number of features to-be-remembered; successful task performance required memory for the same number of features across all conditions. These findings, therefore, are consistent with EMA, which proposes that the HC stores conjunctive scene representations (Graham et al., 2006, 2010; Lee et al., 2007; Lee, Buckley, et al., 2005, 2006; Lee, Bussey, et al., 2005; Mundy et al., 2013). These data are not, however, consistent with one possible basis for accommodating some previous findings within a unitary account, according to which specific impairments on scene stimuli arise from a greater demand on supraspan memory by virtue of scenes being more complex relative to other conditions (Jeneson & Squire, 2012; Jeneson et al., 2012; Knutson et al., 2012).

Data from animal (Bartko et al., 2007a; Bussey et al., 2002, 2003), computational modelling (Cowell et al., 2006), human neuropsychological (Barense et al., 2005), and combined human neuropsychological and imaging (Barense et al., 2012) studies provide evidence to support the idea that the PRC forms the apex of the VVS, forming conjunctive representations of object stimuli. In the current literature, however, it was not clear whether this region

processed only high ambiguity object-feature conjunctions or a more domain-general role in the conjunction of features. For example, could the PRC support conjunctions of features comprising other stimulus categories (i.e., scenes), if a similar approach had been adopted to create the stimuli? The current data suggest that the conjunctions processed by the PRC are in fact object-specific (as evidenced by normal performance for fribbles by both HC patients), and that this region does not support feature conjunctions *per se*. The absence of a low feature ambiguity condition in this experiment means it is not possible to argue that, like object representations in the PRC, scene representations in the HC are organised hierarchically according to feature overlap. These data do, however, suggest a similar conjunctive mechanism may operate in the HC for spatial features that comprise a scene.

It is widely accepted that lesions to the rat HC result in spatial deficits due to this region's role in forming a cognitive map of the local environment (see Section 1.4.2.2). Similar scene-specific memory deficits have been noted in humans after HC damage. For example, amnesic Jon had difficulty remembering objects in places, and the topographical locations of objects (King et al., 2004). Moreover, Taylor, Henson, and Graham (2007) found that patients with HC damage had significantly poorer memory for scenes when these items were presented from a different viewpoint at test relative to study; performance was normal, however, for faces when viewpoint was manipulated. Similarly, patients with static HC lesions exhibit deficits in detecting a different scene when, in an oddity task, items were presented from different viewpoints, suggesting that this region is necessary for allocentric processing of scenes (Lee, Buckley, et al., 2005). Deficits have also been noted, however, in tasks using stimuli that do not require the imagination of scenes from different views,

for example in tasks where two scene items have been morphed together so that they share a high degree of overlapping features (Lee, Bussey, et al., 2005), and in the scene conjunction learning described in this Chapter. It remains unclear, therefore, as to the nature of the spatial representations supported by the HC. Furthermore, it is also unclear as to whether this region is limited to the processing of scenes, or whether the HC may process spatial features more broadly such as spatial features comprising objects.

Lee, Yeung, and Barense (2012) suggest that the role of the HC is to form complex conjunctions of spatial features, not necessarily limited to scenes. They argue that this property of the HC may enable one to both form flexible allocentric representations of scenes, and to distinguish two visually similar scenes even when there is no requirement to imagine the scene from a different view. Unlike other accounts of HC function, which suggest that this region processes scenes specifically (e.g., Maguire & Mullally, 2013), Lee et al. (2012) propose that the HC may play a role in processing of spatial representations more broadly. For example, mirroring the performance of patient HC3, monkeys with fornix lesions are impaired during discrimination learning of objects that contain a high degree of overlap in spatial features (tadpoles) (Buckley et al., 2004). Similarly, using a DMS task, Gilbert, Kesner, and DeCoteau (1998) tested rats' abilities to distinguish between proximal spatial locations after HC lesions. During training, rats were placed in an arena containing an object placed over a baited food well and required to displace the item to access a reward. At test, the rats were returned to the arena and required to choose between two identical objects; the target object occupied the same spatial location as at training and contained a reward, whilst the foil occupied a novel spatial location. The proximity of the foil was manipulated so that it could range

from 15 – 105cm from the target spatial location. Whilst control rats' performance was not affected by the proximity of the foil, rats with HC lesions performed more poorly (selected the object in the incorrect spatial location) the closer the foil was to the target location. These effects were replicated in a novel touch screen paradigm that required rats to distinguish between two lights in an array when the distance between the lights was manipulated (McTighe et al., 2009). Relative to a group of rats with sham lesions, rats with HC lesions made a significantly greater number of errors when the lights were proximal (separated by one spatial location), but performance was matched when the lights were distal (separated by three or five spatial locations). Together, these data suggest that the role of the HC may not be limited to the processing of scenes, but may extend to fine-grained discriminations of space, including spatial objects (for discussion of these findings in relation to other data in the thesis, see Section 6.1.2)

An outstanding question from the current experiment is why the performance of the two HC patients differed. Patient HC3 showed a deficit in discrimination learning consistent with the role of the HC processing spatial features; significantly greater errors were made when required to remember conjunctions of spatial object features in the tadpole stimuli. This was not true, however, of HC2, who was impaired for scenes only. This provides a quandary with regard to the interpretation of these findings. Testing more individuals with HC damage would be necessary to determine whether there is a consistent pattern across cases, and identify the robustness of the impairment/preservation of performance on tadpoles. A larger sample would also enable a systematic mapping of performance to lesion site. HC 2 – who showed preserved performance in the tadpoles compared to controls – has less

obvious HC damage compared to HC3 (when assessed by volumetric analysis). There are at least two possible interpretations for the differences between patients' learning impairments. First, the scenes, relative to the tadpoles, may have required more fine-grained representation of the spatial elements (i.e., the tadpoles contained more distinct changes in spatial configuration). It can be suggested, therefore, that the degree of spatial impairment in patients correlates with the degree of HC damage; less extensive HC damage impairs only fine-grained discriminations of space. Eliciting impairments on tadpoles (where there is less spatial demand than complex scenes), therefore, may require a larger HC lesion. Second, the location of the damage within the HC may be an important factor in eliciting spatial deficits. Replicating the paradigm of Gilbert et al. (1998), Gilbert, Kesner, and Lee (2001) examined the effects of focal lesions to either the dentate gyrus or the CA1 subfield of the HC in rats. Whilst lesions to the CA1 subfield had little effect on the discrimination of spatial locations, lesions of the dentate gyrus significantly impaired rats' abilities to distinguish between proximal spatial locations. These data suggest, therefore, that larger HC lesions (by virtue that these will more likely affect a greater number of subregions in the HC including the dentate gyrus) will lead to more pervasive impairments on spatial discrimination tasks.

The current findings also help to reconcile recent evidence that contradicts EMA. In a study by Knutson and colleagues (2012), patients with HC damage were found to be impaired on an object oddity task, contrary to Barense et al.'s (2007) previous study. There is, however, a critical difference between these two experiments: in Barense et al. (2007), the odd item needed to be identified on the basis of a different combination of object features, whereas the size and orientation of the feature was indicative of the odd item in

Knutson et al. (2012). Based on the impairments in tadpole learning for patient HC3, and the evidence discussed above, the object oddity deficits in Knutson et al. could be interpreted – instead – as a deficit in learning and representing spatial object changes, such as size and orientation. This study, therefore, may suggest, albeit indirectly, that the HC supports spatial judgments even for object stimuli.

2.5. Summary

Previous studies have found that the PRC supports conjunctive object representations. The experiment outlined in this Chapter asked whether patients with focal lesions to the HC would show deficits specifically for scene discrimination learning. Adopting the approach used previously to create conjunctive object stimuli, scenes were created by manipulating two component elements of the stimuli. By controlling for individual features of the stimuli, it allowed for memory demand to be equated across all stimulus categories employed in the task (colour blocks, fribbles, scenes, tadpoles). Relative to matched controls, both patients were impaired in scene discrimination learning, whilst showing spared memory for object feature conjunctions. Furthermore, patient HC3 also showed deficits when discriminating object stimuli on the basis of spatial features, such as size and orientation. This patient had evidence of greater HC damage, as measured by volumetric assessments of her scans. Although the finding of an impairment on tadpoles is not conclusive, given the variability across the two patients, it implies a possible role for the HC in representing conjunctions of spatial properties more broadly, rather than being specific to scenes. The data are not easily accommodated by unitary or dual process accounts of MTL function, but are predicted by representational

models, such as EMA, that proposes a fractionation of the MTL according to the type of stimuli to-be-processed.

Chapter 3: The role of the MTL in detecting object and scene differences

EMA and other related models (Murray & Bussey, 1999; Saksida & Bussey, 2010), propose that the PRC processes complex conjunctions of object features, whereas the HC represents complex conjunctions of spatial features often comprising scenes (Graham et al., 2010). In Chapter 2, a novel concurrent discrimination learning task was developed to test the prediction that the HC is necessary for discrimination between high ambiguity scene stimuli, but not high ambiguity objects. Supporting EMA, patients with focal HC lesions showed impaired learning for pairs of virtual reality scenes but spared memory for fribbles (novel computer generated objects). When these findings are considered alongside other relevant studies, such as the object concurrent learning data-set from Barense et al. (2005) and the perceptual learning data reported by Mundy et al. (2013), they support EMA's proposal of a stimulus-sensitivity division in responsibility within the MTL, with the HC necessary for scene learning and the PRC for object learning, particularly when high ambiguity stimuli are used. Although the study in Chapter 2 did not contrast high and low ambiguity conditions, in both Barense et al. (2005), and Barense, Gaffan, and Graham (2007), there was evidence of behavioural modulations by feature ambiguity for objects in patients (high ambiguity conditions impaired, low ambiguity normal). Moreover, fMRI studies, in which viewpoint and feature ambiguity have been contrasted (Barense et al., 2012, 2010; Devlin & Price, 2007; Mundy et al., 2012), have revealed differences in activity in MTL regions (greater activity for different compared to same viewpoint and high versus low ambiguity discriminations).

A further key prediction of EMA, however, is that stimulus specific representations in the MTL flexibly support both memory *and* perception. A number of studies have shown dissociations between the MTL structures involved in perceptual discrimination of faces, objects, and scenes (see Section 1.4.3). One possibility is that structures within the MTL signal the differences between two perceptually similar stimuli (inferred by way of increased BOLD response). The paradigms employed in these tasks, however, have meant that it is difficult to infer this. Consistent with EMA, and supporting the imaging data, patients with MTL damage show impairments in detecting the odd stimulus in an array in which all items are presented concurrently. Again, however, the paradigms employed mean that it is difficult to understand the nature of these deficits. The main focus of the second study in this thesis, therefore, is the prediction that PRC and HC signal item differences between familiar objects and real world scenes, respectively, during a perceptual discrimination task. The Chapter contains a description of two experiments: Section 3.1 details a functional imaging experiment and Section 3.2 describes a complementary neuropsychological study.

3.1. An event-related fMRI study examining the contribution of the MTL to item and location discriminations for objects and scenes

3.1.1. Introduction

To test whether the MTL supports higher order perception of objects using fMRI, Lee, Bandelow, et al. (2006) developed a perceptual discrimination task (based on Pihlajamäki et al., 2004) that did not require participants to retain information over a delay. During scanning, two, 2*3 arrays, each containing three familiar objects, were presented concurrently (see Figure 3.1).

Participants were required to indicate whether the grids: 1) contained an item change, in which the configuration of the objects within both grids was the same but one grid contained a different item, 2) contained a location change, in which the objects were matched across the grids but the spatial configuration of the items was different by virtue of one object occupying a different spatial location, or 3) were matched in both object identity and configuration. Activity for correct item change trials and correct match trials was contrasted; this revealed greater signal for item changes in the PRC. No regions in the MTL showed increased activity associated with the location change trials, which the authors proposed may have reflected the low spatial demand in this condition. These data suggest that the PRC is recruited during the perceptual discrimination of objects, and that this region signals, evidenced by way of increased BOLD response, situations in which two object items differ. One potential limitation of this experiment was that the different object item in the item change condition was from a different semantic category (e.g., cup versus cell phone). It has been shown that the requirement to name items is associated with increased activity in the PRC (Tyler et al., 2004; Wise et al., 2000). The increased activity associated with the item change condition, therefore, could reflect the naming of a greater number of items in this condition compared to the match condition.

Increased BOLD response in the HC has been associated with the perceptual discrimination of scene stimuli using the oddity task (see Section 1.4.5). Lee, Scahill and Graham (2008) scanned participants whilst they viewed oddity trials comprising four computer generated scenes, novel faces, or size stimuli presented concurrently. For each stimulus class, the participant was required to select the odd (or different) item from three visually similar, within-category foils. The first block of stimuli comprised trial-unique oddity

discriminations, which were subsequently repeated a further two times across the experiment. Contrasting activity for blocks of scenes over blocks of faces, for the initial presentation of the stimuli (i.e., when all trials were new to the participant), revealed greater signal in the posterior HC associated with scenes. Again, given that there was no demand to remember information over a delay, and that each trial was unique, these data suggest that the HC is recruited when required to disambiguate perceptually similar scene stimuli. Furthermore, because the oddity paradigm requires participants to detect a different item, and frequently only correct trials are analysed, one might argue that the associated activity reflects the successful detection of the odd item (i.e., that, similar to the role of the PRC in signalling the difference between perceptually similar objects, (Lee, Bandelow, et al. 2006), increased activity in the HC signals the discrimination of different scenes). This interpretation, however, may not be accurate. Lee, Bandelow, et al. (2006) contrasted trials containing item changes, versus trials in which the stimuli were matched. Differences in the BOLD response between these two conditions, therefore, could be interpreted as activity associated with detecting a difference between items. In contrast, in an oddity task, every trial contains an odd item. This means that it is not possible to determine whether increased activity associated with a specific stimulus class during oddity reflects the detection of the odd item in the trial, or the response to a preferred category of stimuli.

Another study elucidated whether HC activity reflected the signalling of differences between scene stimuli by comparing activity for correct versus incorrect scene oddity trials. Lee, Brodersen, and Rudebeck (2013) analysed scene oddity trials that had been binned according to behavioural performance. It was predicted that if the HC signals differences between scene stimuli, then

greater activity should be associated with correct relative to incorrect trials. The activity in scene-sensitive regions in posterior HC was not modulated by behavioural performance; in anterior HC, however, greater activity was associated with correct relative to incorrect perceptual oddity judgements. These data suggest that there may be some heterogeneity in the function of the HC, with anterior regions of this structure involved in the detection of differences between scenes. A limitation of this experiment, however, is that it was not clear why a participant made an incorrect response. For example, for incorrect trials, participants may not have been attending to the stimuli to the same degree as for the correct trials. This means that a comparison between the BOLD responses associated with correct and incorrect responses may be confounded by differences in the extent to which the participants attended to the stimuli. The paradigm of Lee, Bandelow, et al. (2006) did not suffer from this problem because it allowed for comparison between activity associated with correct 'item change' trials versus correct 'match' trials. Extending this approach to scene stimuli, and obtaining a comparable outcome, therefore, would allow the field to be more confident that the HC is necessary during perceptual discrimination of scene stimuli.

An alternative explanation for increased BOLD response associated with the item change trials in perceptual discrimination tasks is that the activity reflects the incidental encoding of a stimulus. For example, BIC proposes that the PRC supports item memory. Considering the paradigm used by Lee, Bandelow, et al. (2006), BIC would predict increased activity in the PRC associated with the item change condition as this would reflect incidental encoding of the 'extra' item (e.g. 'cup' versus 'phone' across the two arrays). For scene stimuli, however, the predictions are less clear. Although BIC

proposes that the use of objects provides a powerful way to observe item effects (Diana et al., 2012), it does not explicitly state that the PRC is limited to the processing of this stimulus-type. Contrary to the predictions of EMA, therefore, BIC might predict that the detection of differences between two scenes would also be associated with increased PRC activity, and that this reflects the encoding of the extra item. A further tenet of the BIC model is that the PHC supports memory for contextual information (Hannula et al., 2013), and scenes provide a viable spatial context. BIC predicts, therefore, increased activity in PHC when detecting scene item changes, with this activity increase reflecting the incidental encoding of these items. In contrast, EMA proposes that the HC supports the discrimination of perceptually similar scenes, and would therefore predict increased HC activity associated with the successful discrimination of these items.

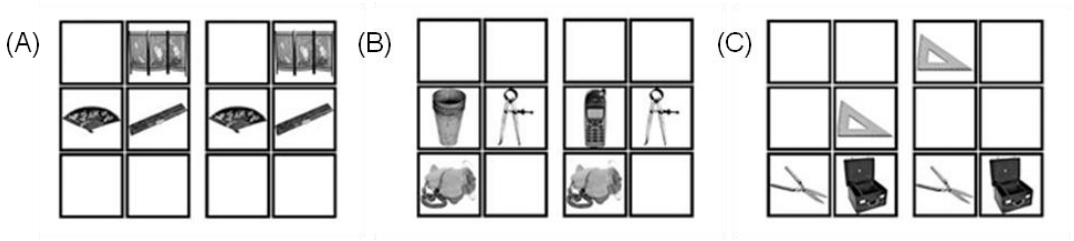

Figure 3.1. ***Examples of trials from the three different conditions in Lee, Bandelow et al. (2006). Participants were required to identify whether the two grids were the same (A), or differed due to: (B) a change in item, or (C) the configuration of items.***

To address these questions, I developed a novel version of the perceptual discrimination paradigm developed by Lee, Bandelow, et al. (2006) to test whether the PRC and HC support the discrimination of perceptually

similar object and scene items, respectively. Participants were presented with object, scene, and shape (baseline) stimuli, and required to judge whether two grid arrays were the same or different. The same manipulations were implemented here for each stimulus class; an item change condition, a location change condition, and a match condition. First, to test EMA's prediction that there will be differential sensitivity to object and scene processing in the PRC and HC, respectively, activity associated with all object and scene trials was contrasted. EMA would predict greater PRC activity associated with the contrast *'objects > scenes'*, and greater HC/PHC activity for the reverse of this contrast. Second, contrasts were implemented to identify brain regions sensitive to item and location changes for objects and scenes, respectively. This was achieved by contrasting '*item change > match'*; and *'location change > match'* for objects and scenes separately. As noted previously, the BIC model proposes that the PRC supports item memory but does not stipulate whether this involvement is limited to objects or extends to single items of any stimulus category (i.e., scenes). In contrast, EMA proposes that this region is recruited when required to discriminate between two object items that contain a number of overlapping features. The two accounts also make different predictions regarding the role of the HC in the perceptual discrimination of scene stimuli. EMA would predict a scene-specific item change effect in the HC, whereas BIC would predict equivalent activity for both objects and scenes consistent with the proposal that this region performs domain-general mnemonic processes. The study described here addressed some of the limitations of Lee, Bandelow, et al. (2006). First, the different item in the item change condition was from the same semantic category; here this confound was removed by having a different number of semantic categories in the item change and match conditions. Second, a

baseline condition was included which avoided having to contrast experimental conditions with downtime. To reiterate, the predictions are: 1) contrasting *'objects > scenes'* would elicit activity in the PRC, whereas the reverse of this contrast would be associated with increased activity in HC/PHC, 2) the contrast *'object item change > match'* would be associated with increased PRC activity, whilst the same contrast using scenes would result in increased HC activity, 3) detecting a difference in either an object (*'object location change > match'*) or a scene's (*'scene location change > match'*) location would be associated with increased BOLD response in the HC. If these predictions are upheld they have strong implications for mnemonic accounts that suggest the MTL does not support perceptual discrimination of object and scene stimuli.

3.1.2. Method

3.1.2.1. Participants

Twenty-one participants (11 male) were scanned (mean age = 25.2 years; S. D. = 4.8). All were right-handed native-English speakers with no self-reported neurological and/or psychiatric disorders and normal or corrected to normal vision. All participants gave written informed consent prior to the experiment and were paid £20 for their participation. The experiment and its procedures received ethical approval from the Cardiff University School of Psychology Ethics Committee.

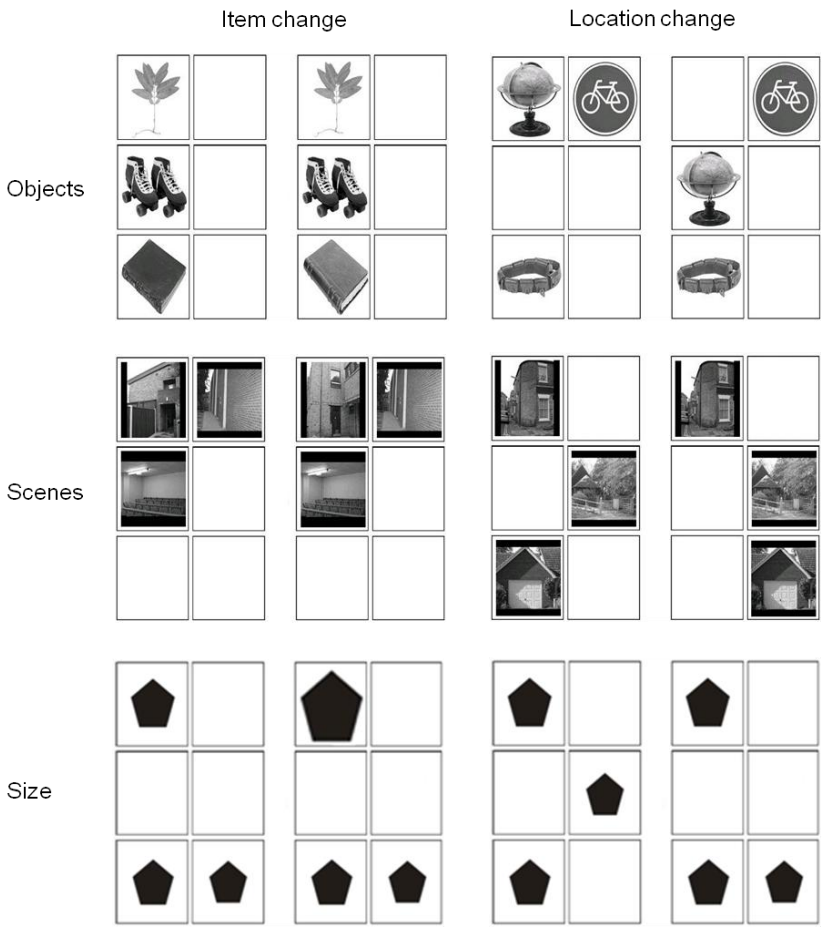

Figure 3.2. ***Examples of the three different classes of stimuli and the item and location change trials (match trials are not displayed). Two 2*3 arrays were presented, with each containing three items; the participant was given four seconds to respond by pressing a button to indicate whether they thought the two grids were the same or differed (based on a change to an item or location).***

3.1.2.2. Experiment procedure and materials

Participants were presented concurrently with two, 2*3 arrays. Each array was divided into six 125*125 pixel squares and contained three items; the remaining three squares of each grid were empty (see Figure 3.2). During

scanning participants were required to identify, via the appropriate button-box response, whether the two grids were the same or different. The grids could differ in one of two ways – an *item change* or a *location change*. In the *item change* condition, the three pairs of items were in the same configuration across the two grids but one of the pairs differed in identity across the two grids. The differing pair shared a number of overlapping features and, unlike Lee, Bandelow, et al. (2006), was selected from the same semantic category (e.g., two different exemplars of a telephone). In the *location change* condition the grids contained three pairs of items but the configuration of the items differed; one item was located in a different square relative to the other grid (see Figure 3.2). *Match* trials were identical in both the items contained, and the configuration of these objects within the arrays.

Three classes of stimuli were used: 1) familiar *objects* (taken from Photo Objects 50,000 Vol 1-3, Hemera Technologies Inc, Quebec, Canada), 2) real-world *scenes* (both indoor and outdoor vistas of Cambridge University and the surrounding area) and 3) geometric shapes (pentagons, hexagons, octagons, circles, triangles, and squares). An item change in the geometric shapes condition was made by having items from one pair of shapes differ in size. This class of stimuli shall be referred to as *size* for the remainder of this Chapter.

There were 144 trials per stimulus type divided equally into *item change*, *location change*, and *match* trials. Scanning was conducted in three runs, each containing an equal number of trials from each stimulus type, and condition. Trial presentation order was randomised and the run presentation order counterbalanced across participants. To minimize mnemonic demand, all stimuli were trial unique: 160 images per stimulus class were required, therefore, per

run (480 images per stimulus class across the entire experiment). Each trial was presented for 4 seconds with a mean 1 second ITI (range 0.5-3.5s) during which the screen was blank. In each run, an equal number of 'change' events occurred in each of the six squares of the array to eliminate the possibility of participants focussing their attention on one particular grid location. In addition, the location of the remaining items was balanced so that each square of the grid contained an equivalent number of items across the experiment. The experiment was run using E-Prime Version 1.0 (Psychology Software Tools, Pittsburgh, PA).

3.1.2.3. Scanning parameters

The majority of scanning parameters described here are also relevant to the imaging experiments outlined in Chapters 4 and 5. These parameters, therefore, will be outlined in detail here; in subsequent chapters, only details of deviations from these approaches will be noted. Data were collected at the Cardiff University Brain Research Imaging Centre (CUBRIC) using a General Electric 3-T HDx MRI system with an 8 channel receive-only head coil. An echo-planar imaging (EPI) pulse sequence was used to acquire T2*-weighted image volumes with BOLD contrast (TR/TE = 2750/35ms, FOV = 220mm, 64*64 data matrix, and ASSET (acceleration factor), 90° flip angle). The same scanning protocol was used for all participants. Forty-nine slices were collected in an interleaved fashion per image volume for whole brain coverage. Each slice was 2.4mm thick with a 1mm inter-slice gap (3.4*3.4*2.4 mm voxels). Slices were acquired with a 30° axial-to-coronal tilt relative to the AC - PC line (anterior upwards) to reduce signal dropout in the medial temporal lobe. The first four volumes of each scanning run were discarded to allow for signal equilibrium.

Two 3D SPGR images were acquired at the beginning of the first scanning session to improve registration and reduce image distortion as a result of magnetic-field inhomogeneity (TE = 7ms and 9ms, TR = 20ms, FOV = 384* 192* 210mm, 128*64*70 data matrix, 10° flip angle). The SPGR used the same slice orientation as the EPI data. High resolution anatomical images were acquired using a standard T1-weighted 3D FSPGR sequence comprising 178 axial slices (TR/TE = 7.8/3.0s, FOV = 256*256*176mm, 256*256*176 data matrix, 20° flip angle, and 1mm isotropic resolution).

Stimuli were projected for viewing from a stimulus presentation machine to an angled mirror within the scanner. Participants manually adjusted the viewing angle of the mirror to ensure the image was centred correctly. The MR projector system was a Canon SX60 LCOS system coupled to a Navitar SST300 zoom converter lens. An MR compatible button box was used to allow participants to make a 2-way-response (index and middle finger buttons on the right hand).

3.1.2.4. Data pre-processing

Similarly, the pre-processing steps described below were mostly applied for the experiments outlined in Chapters 4 and 5; again, therefore, only differences to these methods will be described in these later chapters. Pre-processing and analysis of fMRI data was carried out using FEAT (FMRI Expert Analysis Tool) Version 5.63, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Pre-processing comprised motion correction (Jenkinson, Bannister, Brady, & Smith, 2002); the removal of non-brain tissue (Brain Extraction Tool (BET); Smith, 2002); spatial smoothing using a Gaussian kernel of full width at half maximum (FWHM) 5mm; mean-based intensity

normalisation; high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma = 20.0s). Phase information from the two SPGR images was unwarped using PRELUDE (Phase Region Expanding Labeller for Unwrapping Discrete Elements; Jenkinson, 2003). The unwrapped phase images were then subtracted and the resulting fieldmap used to unwarp the EPI data using FUGUE (FMRIB's Utility for Geometrically Unwarping EPIs). Time-series statistical analysis was carried out using FILM (FMRIB's Improved Linear Model) with local autocorrelation correction (Woolrich, Ripley, Brady, & Smith, 2001). Registration to high resolution 3D anatomical T1 scans (per participant) and to a standard Montreal Neurological Institute (MNI152) template image (for group average) was carried out using FLIRT (FMRIB's Linear Image Registration Tool; Jenkinson et al., 2002; Jenkinson & Smith, 2001). Stereotactic co-ordinates of significant effects are reported in MNI space.

3.1.2.5. Object and scene item and location change analysis

Analyses were first conducted at the single-subject level on each individual EPI run using the FILM. The BOLD signal was modelled using a standard model of hemodynamic response function (HRF). 10 explanatory variables were used to model the time course data. These comprised the correct responses for each stimulus and condition (i.e., *item change*, *location change*, and *match* conditions for *object*, *scene*, and *size* stimuli), and one regressor containing all incorrect responses. Twelve contrasts of interest were implemented. The first two contrasts aimed to test the veracity of the stimulus specific account by contrasting all scene and object trials to identify regions in which activity correlated with object and scene stimuli, respectively ('*object (item + location + match) > scene (item + location + match)'*; and the reverse of

this contrast). Four contrasts were implemented to determine brain regions that signalled item and location changes for object and scene stimuli; *'object item change > object match'*; *'object location change > object match'*; *'scene item change > scene match'*; *'scene location change > scene match'*. Finally, six contrasts comprised each scene and object condition contrasted to the appropriate size baseline, for example *'object item change > size item change*' etc., so that parameter estimates could be extracted for these contrasts. The three individual runs for each participant were combined using a fixed effects model. Finally, a group analysis was carried out using FLAME (FMRIB's Local Analysis of Mixed Effects tool; Beckmann, Jenkinson, & Smith, 2003; Woolrich, Behrens, Beckmann, Jenkinson, & Smith, 2004). The resulting Z statistic images were thresholded using a $Z > 2.3$, and a family-wise error (FWE) corrected cluster extent of $p < .05$ (unless otherwise stated), based on the theory of Gaussian Random Fields.

Analyses were first conducted at a whole-brain level (details provided in Appendix A.1), followed by detailed analyses of effects in the MTL (reported here). To examine the MTL effects, higher level cluster-based analyses were constrained to a combined mask of the PRC, HC, and PHG, comprising a bilateral PRC probabilistic mask created by Devlin and Price (2007), and bilateral HC, and PHG regions of interest (ROIs), created using probabilistic masks from the Harvard-Oxford Subcortical Structural Atlas (see Figure 3.3). Percent signal change values for each contrast versus size baseline were extracted from significant clusters of activity and entered into a ROI*Stimulus (object; scene)*Condition (item change; location change; match) ANOVA. Follow-up pair-wise comparisons were Bonferroni-corrected for multiple comparisons.

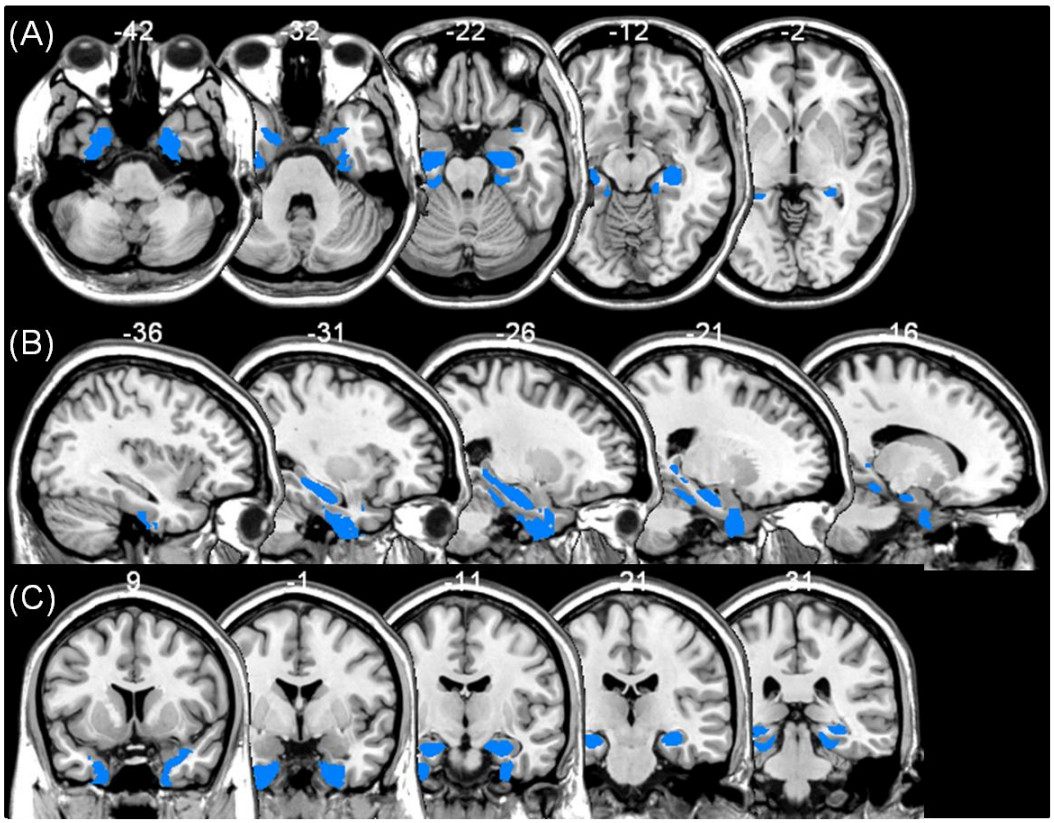

Figure 3.3. ***(A) Axial, (B) sagittal, and (C) coronal slices illustrating the probabilistic mask of the MTL used to constrain fMRI analyses in Chapters 3, 4, and 5. The mask comprised bilateral probabilistic masks of the HC, PHG (both derived from the Oxford subcortical atlas), and PRC (from Devlin & Price, 2007).***

3.1.3. Results

3.1.3.1. Behavioural data

Figure 3.4 illustrates the mean accuracy and reaction time in each stimulus type and each experimental condition. A Stimulus (object; scene; size)*Condition (item change; location change; match) repeated-measures

ANOVA revealed differences in accuracy across Condition ($F(2, 40) = 48.78$, $p < .01$), and a Stimulus*Condition interaction ($F(4, 80) = 10.82$, $p < .01$).

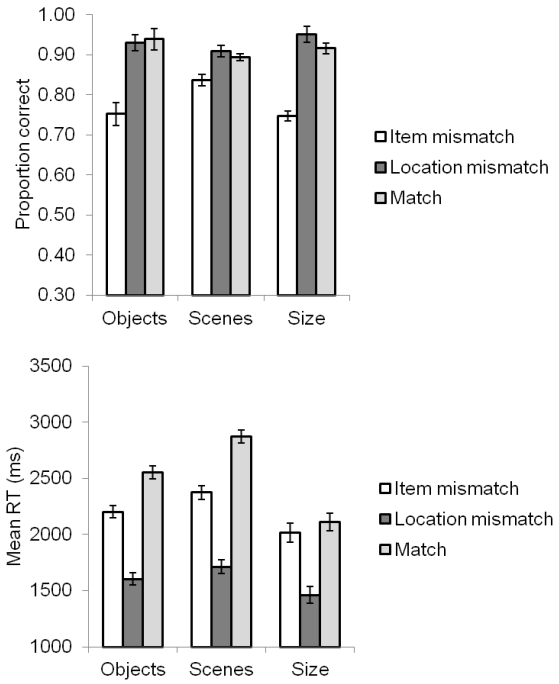

Figure 3.4. ***Proportion correct and mean response times for each stimulus and condition.***

Follow-up one-way ANOVAs were used to investigate the interaction by comparing accuracy across condition (item change; location change; match) within each stimulus class individually. There was evidence of significant difference in accuracy across the different conditions for objects, scenes and size (all Fs(2, 40) > 7.14, ps < .01), and these significant effects were subsequently interrogated using pair-wise t-tests. A similar pattern of data was evident across all stimulus types; participants were reliably more accurate during location change and match trials relative to item change trials (ts(20) > 2.75, ps < .017; Bonferroni correction = .05/3 α = .017). The Stimulus*Condition

interaction was then interrogated by comparing accuracy for each condition between the different stimuli. For item changes there was a main effect of Stimulus ($F(2, 40) = 9.07$, $p < .01$) resulting from significantly greater accuracy on scene item changes, relative to object and size item change trials ($t(20) = 4.44$, $p < .017$, and $t(20) = 3.61$, $p < .017$, respectively; Bonferroni correction = .05/3 $\alpha = .017$). There was also a main effect of stimulus in the location change condition ($F(2, 40) = 5.91$, $p < .01$) due to better accuracy on size relative to scene trials ($t(20) = 3.41$, $p < .017$); no other comparisons were statistically different ($ts(20) < 2.06$, $ps > .05$). Finally, there was a main effect of stimuli in the match condition ($F(2, 40) = 4.16$, $p < .05$); participants performed better on object relative to scene stimuli ($t(20) = 3.28$, $p < .05$). Again, no other comparisons were statistically different ($ts(20) < 1.79$, $ps > .08$).

An identical repeated-measures ANOVA for reaction times revealed a main effect of Stimulus ($F(2, 40) = 177.56$, $p < .001$), a main effect of Condition ($F(2, 40) = 109.5$, $p < .001$), and a Stimulus*Condition interaction ($F(4, 80) = 24.76$, $p < .001$). Follow-up one-way ANOVAs for object, scene, and size stimuli revealed significant differences across item change, location change and match conditions ($Fs(2, 40) > 43.41$, $ps < .01$). For both objects and scenes, responses were fastest for location change trials, relative to item change trials, which in turn were quicker than responses to match trials ($ts(20) > 5.65$, $ps < .017$; Bonferroni correction = .05/3 $\alpha = .017$). Size stimuli location changes were detected more quickly than item changes ($t(20) = 14.07$, $p < .017$) and matches ($t(20) = 14.07$, $p < .017$), but reaction times for item change and match trials were equivalent ($t(20) = 1.16$, $p > .25$). There were also reliable differences in reaction times between stimulus-type within each condition ($Fs > 35.42$, $ps < .01$). For item change, location change and match trials, reaction times were

fastest for size stimuli, which were significantly quicker than responses to object stimuli, which in turn were quicker than responses to scene stimuli (*t*s(20) > 3.37, *p*s < .017).

3.1.3.2. Imaging data

3.1.3.2.1. Whole brain analyses

Activation maps and details of local maxima from the whole brain analysis are contained in Appendix A (Section 7.1). Briefly, the contrast *'objects > scenes'* was associated with a large swathe of activation in lateral occipital cortex, extending forward into PRC. The reverse of this contrast revealed significant activity in regions that have been previously implicated in scene processing (i.e., the posterior PHG, and precuneus, extending into posterior cingulate). Activity did not, however, extend into the HC.

3.1.3.2.2. MTL effects

3.1.3.2.2.1. Objects > scenes

To remind the reader of the key predictions being tested here, based on EMA, for the contrast *'objects > scenes'*, greater activity was predicted in the PRC and anterior HC. Conversely, for *'scenes > objects'*, greater activity was predicted in the posterior HC and posterior PHG.

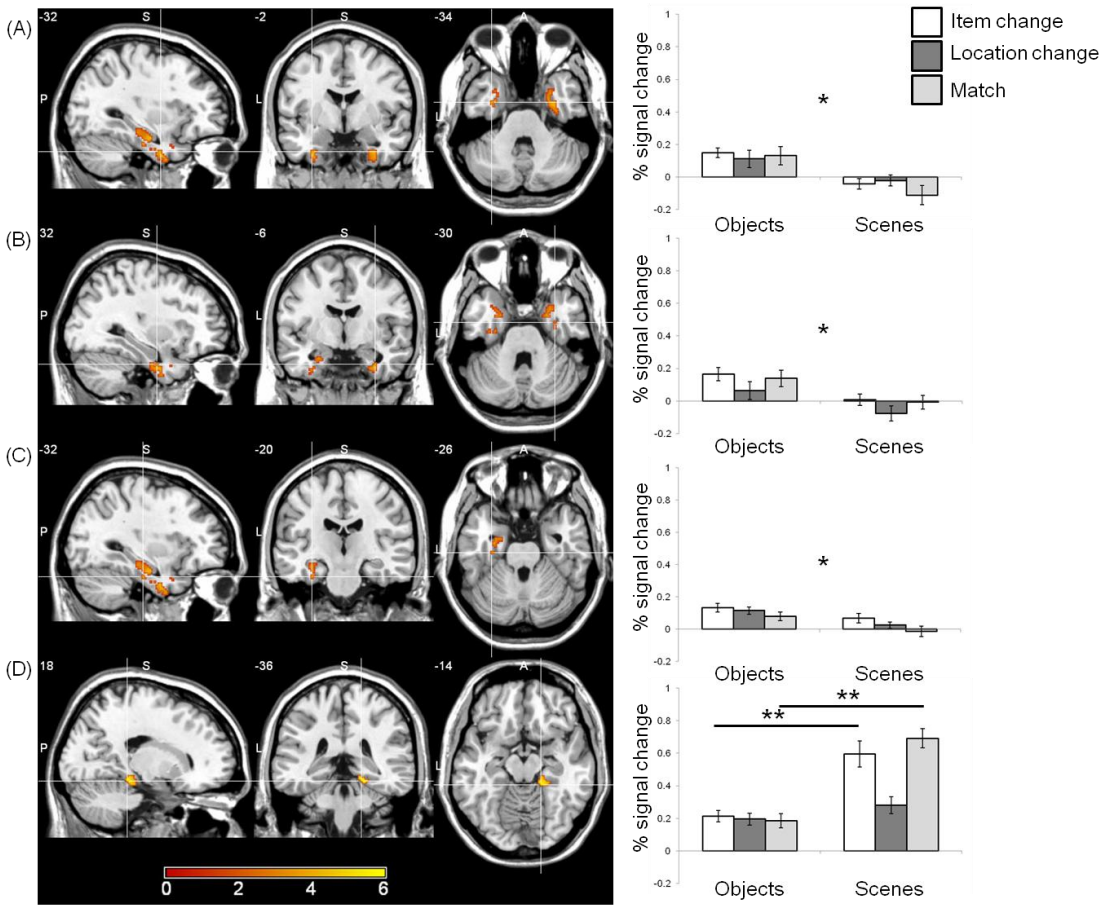

Figure 3.5. ***Clusters of activity associated with contrast 'objects > scenes' (collapsed across condition) (A) left PRC (-32, -2, -34; 138 voxels), (B) right PRC (32, -6, -30; 176 voxels), (C) Left PHG (-32, -20, -26; 173 voxels), and 'scenes > objects' (D) right PHG (18, -36, -14; 115 voxels). Corresponding plots show percent signal change values extracted from each cluster for all object and scene conditions contrasted with the appropriate size baseline; * = p < .05; ** = p < .017***

Contrasting activity for correct object trials (collapsed across all conditions) with correct scene trials (collapsed across the three conditions) revealed three significant clusters of activity. These were located in left and right PRC, and left PHG (extending into left posterior HC) (see Figure 3.5). Next, the six conditions (*object item change; object location change; object match*; *scene item change*; *scene location change*; *scene match*) were contrasted to the appropriate size baseline, for example *'object item change trials > size item change'* trials, and the resulting percent signal change values entered into an ROI (left HC; right HC; left posterior PHG)*Stimulus (objects; scenes)*Condition (item change; location change; match) repeated-measures ANOVA. This analysis revealed a main effect of Stimulus ($F(1,20) = 42.19$, $p < .01$) and an ROI*Stimulus interaction ($F(2, 40) = 7.01$, $p < .01$).

Collapsing across condition, a one-way ANOVA comparing scene-related activity in the three ROIs (left PRC; right PRC; left posterior PHG) revealed a significant effect of ROI ($F(2, 40) = 5.67$, $p < .01$). Follow-up pair-wise comparisons found significantly greater activity in left posterior PHG relative to the left PRC ($t(20) = 3.06$, $p < .017$; Bonferroni correction = .05/3 comparisons; $\alpha = .017$). Interestingly, activity for objects did not differ across the same three ROIs ($F(2, 40) = 0.25$, $p = .78$), but this level of activation for objects, in all three ROIs, was greater than activity associated with scenes ($ts(20) > 5$, $p < .017$; Bonferroni correction = .05/3 comparisons; $\alpha = .017$).

3.1.3.2.2.2. Scenes > objects

Contrasting activity for correct scene trials with correct object trials (again, both collapsed across condition) revealed a significant cluster of activity in right posterior PHG (see Figure 3.5). Percent signal change values were

extracted from this cluster for each stimulus class and condition, contrasted to the appropriate size baseline, and entered into a Stimulus (objects; scenes)*Condition (item change; location change; match) ANOVA. This resulted in significant main effects of Stimulus ($F(1,20) = 54.03$, $p < .01$), Condition ($F(2, 40) = 12.82$, $p < .01$), and a significant Stimulus*Condition interaction ($F(2, 40) = 25.01$, $p < .01$).

A one-way ANOVA compared activity associated with scenes across the three conditions (item change; location change; match) and revealed a main effect of Condition ($F(2, 40) = 24.87$, $p < .01$). Activity for both item change and match trials was reliably larger than activity for location change trials (both ts > 4.61, ps < .017; Bonferroni correction = .05/3 α = .017). Furthermore, pair-wise comparisons revealed that the level of BOLD response associated with item change and match conditions for scenes was significantly greater than for objects ($t(20) = 5.59$, $p < .017$, and $t(20) = 9.28$, $p < .017$, respectively; Bonferroni correction = .05/3 comparisons; α = .017). For objects, the level of signal was not modulated by condition ($F(2, 40) = 0.25$, $p = 0.77$).

3.1.3.2.3. Summary of MTL analysis

As predicted, relative to scenes, objects were associated with greater activity in bilateral PRC. Furthermore, there was also a significant cluster in left posterior PHG. Consistent with stimulus specific accounts of MTL function, the BOLD response for scenes was significantly greater in left posterior PHG relative to left PRC. Greater activity for scenes was also identified in right posterior PHG, and was driven by a larger neural response associated with the scene item change and scene match conditions.

3.1.3.2.4. Item and location change effects in MTL

The statistical threshold of Z = 2.3 and $p < .05$ resulted in significant clusters only for the contrasts *'objects > scenes' and 'scenes > objects'*. In an attempt to investigate item and location change effects in the MTL more thoroughly, a more liberal threshold was used for the remaining contrasts. Clusters were interrogated further if they surpassed a Z > 2.3 ($p = .05$ uncorrected) and consisted of at least 10 contiguous voxels.

3.1.3.2.4.1. Object item change > object match

Replicating Lee, Bandelow, et al. (2006), it was predicted that the BOLD response in PRC for object item change trials would be significantly greater than the response associated with object location change, and object match trials.

The contrast *'object item change > object match'* was associated with four clusters of activity in the MTL; right PRC, bilateral anterior HC, and right posterior HC (see Figure 3.6). Percent signal change values were extracted from these clusters for each stimulus class and condition and then entered into a ROI (right PRC; left anterior HC; right anterior HC; right posterior HC)*Stimulus (objects; scenes)*Condition (item change; location change; match) ANOVA. There was a main effect of ROI ($F(3, 60) = 4.07$, $p < .05$), Stimulus ($F(1, 20) = 6.34$, $p < .05$), and Condition ($F(2, 40) = 6.65$, $p < .01$), a ROI*Stimulus interaction ($F(3, 60) = 7.77$, $p < .01$), and a ROI*Stimulus*Condition interaction ($F(6, 120) = 2.49$, $p < .05$).

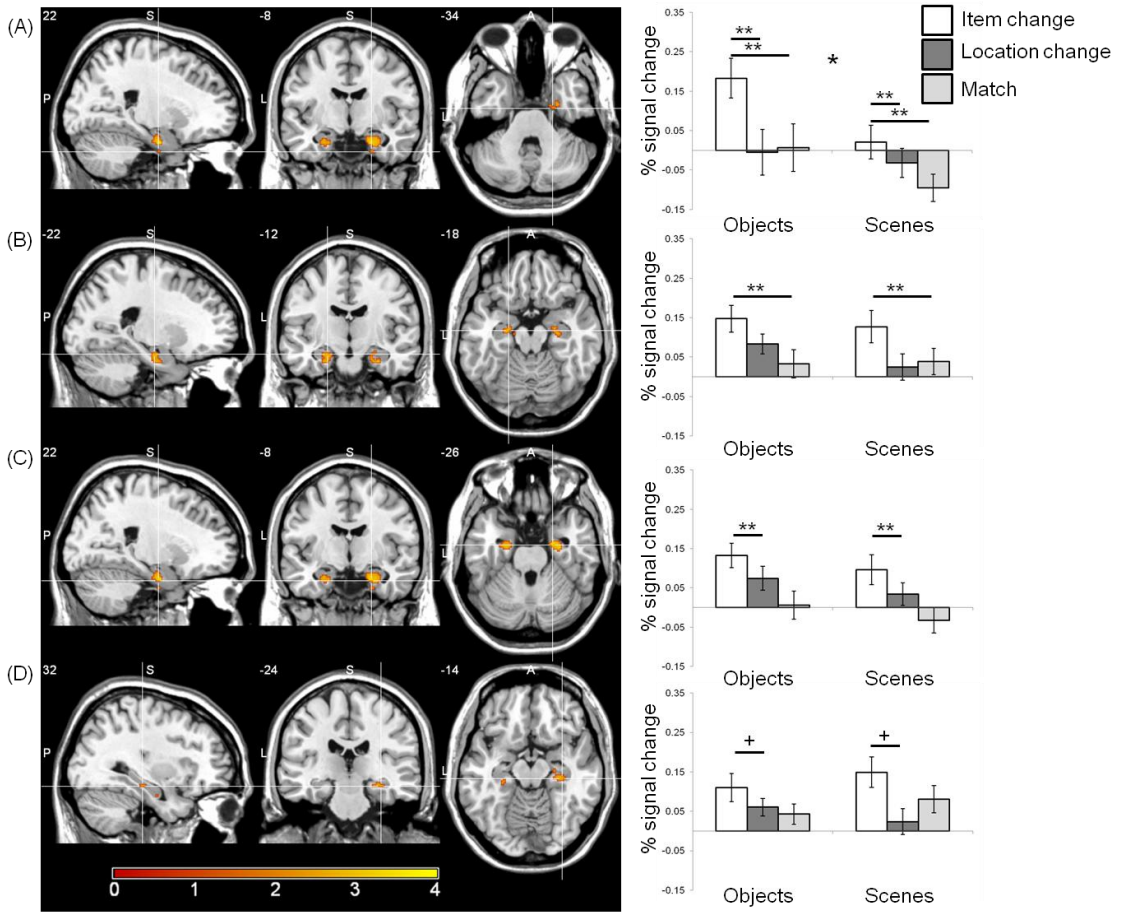

Figure 3.6. ***Clusters of activity associated with the contrast 'object item change > object match' (A) right PRC (22, -8, -34; 14 voxels), (B) left anterior HC (-22, -12, -18; 82 voxels), (C) right anterior HC (22, -8, -26; 92 voxels), (D) right posterior HC (32, -24, -14; 16 voxels). Corresponding plots show percent signal change values extracted from each cluster for all object and scene conditions and contrasted with the appropriate size baseline; * = p<0.05; ** = p<0.017; + = 0.018.***

The three-way interaction was investigated first by individual ROI, resulting in four Stimulus*Condition ANOVAs which will be addressed in turn. In right PRC, significantly greater activity was associated with objects relative to scenes ($F(1, 20) = 23.03$, $p < .01$), and activity differed across condition ($F(2, 40) = 4.64$, $p < .05$). Follow-up pair-wise comparisons found that this stemmed from significantly greater activity associated with item change relative to location

change ($t(20) = 2.65$, $p < .017$; Bonferroni correction = .05/3 α = .017), and match conditions ($t(20) = 2.8$, $p < .017$); location change and match trials did not differ ($t(20) < 1$, $p > 0.63$).

In both left and right anterior HC ROIs, the pattern of BOLD response distinguished between the different conditions ($F(2, 40) = 5.71$, $p < .01$, and $F(2, 40) = 4.84$, $p < .05$, respectively). In left anterior HC significantly greater activity was associated with item change relative to match trials ($t(20) = 3.12$, $p < .017$; Bonferroni correction = .05/3 α = .017). Item change and location change trials, and location change and match trials did not differ ($ts(20) < 2.02$, $ps > .06$). In the right anterior HC, greater activity was associated with item change relative to location change trials ($t(20) = 2.88$, $p < .017$), with a trend towards greater activity for item change relative to match trials ($t(20) = 2.48$, $p = .02$); location change and match trials did not differ ($t(20) < 1$, $p > 0.59$).

In right posterior HC there was a main effect of Condition ($F(2, 40) = 3.76$, $p < .05$), resulting from a trend towards greater activity associated with item change relative to location change trials ($t(20) = 2.58$, $p = .018$; Bonferroni correction = .05/3 α = .017). Location change and match trials, and item change trials and match trials did not differ ($ts(20) < 2$, $ps > .08$).

ANOVAs were conducted across the four ROIs to determine whether the three-way interaction resulted from a different profile of activity for each stimulus class and condition across these different regions. The activity for objects did not differ across the four ROIs, regardless of condition ($Fs < 2.2$, $ps > 0.1$). For scenes, however, there was a main effect of region for item change trials ($F(3, 60) = 5.66$, $p < .01$). Follow-up pair-wise comparisons, however, did not survive Bonferroni correction, but there was a marginal effect of greater activity in right

posterior HC relative to right PRC ($t(20) = 3.37$, $p = .02$; Bonferroni correction = .05/5, adjusted $\alpha = .01$). Similarly, activity associated with match trials differed across region ($F(3, 60) = 12.33$, $p < .01$). The BOLD response associated with scene match trials in right posterior HC was significantly greater than the response in left anterior HC ($t(20) = 6.14$, $p < .01$) and right PRC ($t(20) = 4.47$, $p < .01$). Equally, greater activity was evident in right anterior HC relative to left anterior HC ($t(20) = 3.08$, $p < .01$), and right PRC ($t(20) = 3.28$, $p < .01$). Activity for location change trials did not differ across the four ROIs ($F < 2$, $p > .2$).

To summarise, the right PRC ROI was the only one in which there was significantly greater activity associated with objects relative to scenes. Furthermore, the BOLD response for the item change condition was reliably larger than the response associated with location change and match conditions. This effect, however, was domain-general, as it was evident for both objects and scenes. Activity in the anterior HC did not distinguish between objects and scenes, but was modulated by condition; significantly greater signal was associated with item change trials relative to match trials in left HC, whereas in right HC the neural response to item change trials was reliably larger than location change trials. Activity associated with objects did not differ across the four ROIs, but right posterior HC, and right anterior HC showed the largest response to scene item, and match conditions.

3.1.3.2.4.2. Object location change > object match

In Lee, Bandelow, et al. (2006), contrary to predictions, the contrast *'object location change > object match'* was not associated with activity in the HC. There was, however, no control baseline task, and it is possible that the comparison with the noisy downtime baseline may have masked any significant

effects of this contrast. The predictions here, therefore, were the same as Lee et al.'s original study; that there would be greater activity in HC associated with detecting an object location change.

Consistent with predictions, the contrast *'object location change > object match'* revealed three clusters of activity; right anterior HC, and bilateral HC, located around the mid-point of the HC (see Figure 3.7). A ROI (right anterior HC; left middle HC; right middle HC)*Stimulus (objects; scenes)*Condition (item change; location change; match) ANOVA resulted in a main effect of Condition ($F(2, 40) = 6.12$, $p < .01$), that was qualified by a Stimulus*Condition interaction ($F(2, 40) = 4.36$, $p < .05$). Given that the factor of ROI did not interact with Stimulus and Condition ($F(4,80) = 2.19$, $p = .08$), the Stimulus*Condition interaction was analysed by collapsing across region.

The interaction was analysed first by stimulus type. Object item change, location change and match conditions were submitted to a one-way ANOVA which revealed a main effect of Condition ($F(2, 40) = 5.21$, $p < .01$), resulting from greater activity for item change relative to match conditions ($t(20) = 2.68$, $p < .017$; Bonferroni correction = .05/3, adjusted $\alpha = .017$) and location change relative to match conditions ($t(20) = 2.58$, $p = .017$); activity for item and location change trials did not differ ($t(20) = .79$, $p = .44$). For scenes, a main effect of Condition ($F(2, 40) = 5.77$, $p < .01$) resulted from significantly greater activity for item change trials relative to location change trials ($t(20) = 3.43$, $p < .017$); the BOLD response for item change and match conditions ($t(20) = 2.24$, $p = .04$), and location change and match trials ($t(20) = .87$, $p = .39$) did not differ.

Finally, the interaction was investigated by comparing activity for each condition between stimulus-type. Significant differences were only evident in the

location change condition with greater activity associated with objects compared to scenes ($t(20) = 2.87$, $p < .017$).

Consistent with predictions, relative to match trials, detecting an object location change was associated with increased activity in the HC. Parameter estimates revealed, however, that this response was equivalent during detection of an item change. For scenes, item changes were associated with greater activity than location change trials, but were not reliably larger than activity for match trials. Finally, the HC response was larger for detection of an object location change, relative to a scene location change.

3.1.3.2.4.3. Scene item change > scene match

It was predicted that greater HC activity would be associated with successful detection of a difference between two scenes relative to successful identification that two scenes were the same.

Four clusters, all located in the HC, showed greater activity for scene item change trials relative to scene match trials (see Figure 3.8). These were located in the left and right anterior HC, and in the middle left and right HC. The ROI (left anterior HC; right anterior HC; left middle HC; right middle HC)*Stimulus (objects; scenes)*Condition (item change; location change; match) ANOVA revealed a ROI*Stimulus interaction ($F(3, 60) = 9.76$, $p < .01$) and a significant three-way ROI*Condition*Stimulus interaction ($F(6,120) = 6.66$, $p < .01$).

The three-way interaction was interrogated first by ROI. For left anterior HC, the Stimulus*Condition ANOVA revealed a main effect of Stimulus ($F(1, 20) = 14.53$, $p < .01$) resulting from greater activity associated with objects relative

to scenes. In right anterior HC, there was a main effect of Condition ($F(2, 40) = 3.72$, $p < .05$), reflecting greater activity for item change relative to location change trials ($t(20) = 3.07$, $p < .017$; Bonferroni correction = .05/3, adjusted $\alpha = .017$). Similarly, in left HC, there was a main effect of Condition ($F(2, 40) = 5.55$, $p < .01$), however, this resulted from significantly greater activity for item change relative to match trials ($t(20) = 2.86$, $p < .017$). In right HC, there was a significant Stimulus*Condition interaction ($F(2, 40) = 3.94$, $p < .05$), which was driven by a difference in parameter estimates across conditions for scene stimuli ($F(2, 40) = 7.79$, $p < .01$), that was not apparent in the objects ($F(2, 40) = 2.71$, $p = .08$). For scenes, greater activity was associated with item change relative to location change trials ($t(20) = 3.9$, $p < .017$) and match trials ($t(20) = 2.7$, $p = .017$); location change and match trials did not differ ($ts < 1.2$, $ps > .25$). Pair-wise comparisons between stimulus type for each condition revealed greater activity for scenes relative to objects in the item change condition ($t(20) = 2.91$, $p < .017$).

To investigate whether the ROI*Stimulus*Condition interaction resulted from a different profile of activity for each condition across the four regions, percent signal change values for each stimulus and condition were entered into four, one-way ANOVAs. For object match trials there was a significant effect of ROI ($F(3, 60) = 2.77$, $p < .05$) resulting from greater activity in left anterior HC relative to left HC ($t(20) = 3.39$, $p < .01$; Bonferroni correction = .05/5, adjusted $\alpha = .01$); activity for object item and location change trials did not differ across the ROIs ($Fs < 1.1$, $ps > .35$). Activity for scene item change trials differed across ROI ($F(3, 60) = 8.39$, $p < 0.01$) with significantly greater activity in right HC relative to left anterior HC ($t(20) = 3.95$, $p < .01$) and in left HC relative to left anterior HC ($t(20) = 2.87$, $p < .01$). Similarly there was a main effect of ROI for

scene match trials ($F(3, 60) = 2.65$, $p < .05$), however, pair-wise comparisons did not survive Bonferroni correction ($ts < 2.16$, $ps .> .04$). Activity for scene location change trials did not differ across the ROIs ($F(3, 60) = 1.06$, $p = .37$).

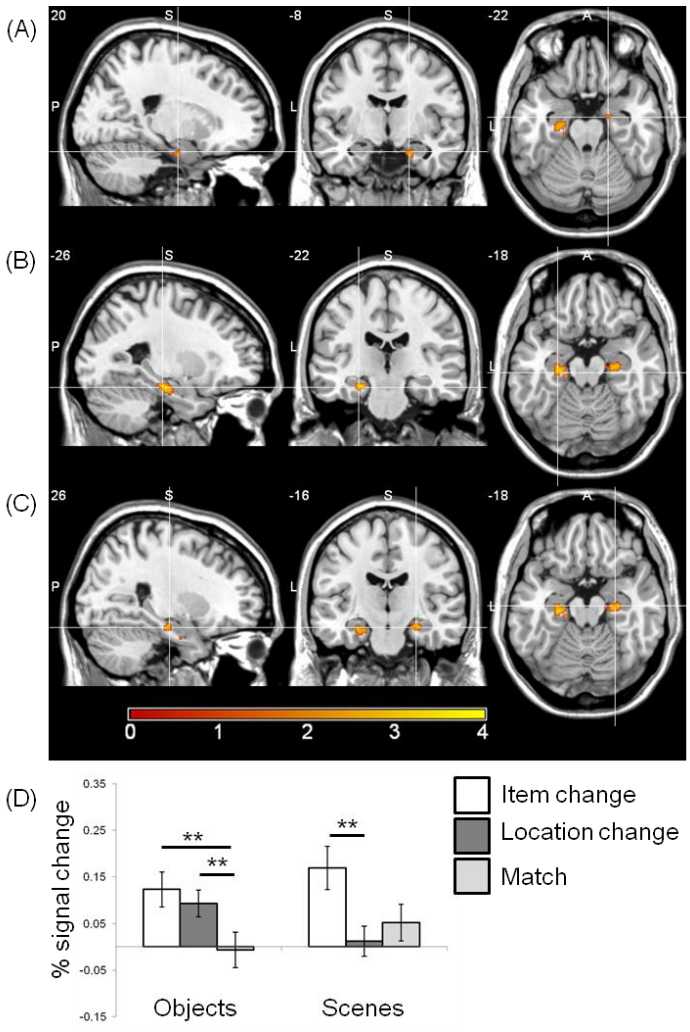

Figure 3.7. ***Clusters of activity from the contrast 'object location change > object match' (A) right anterior HC (20, -8, -22; 17 voxels), (B) left HC (-26, -22, -18; 68 voxels) (C) right HC (26, -16, -18; 30 voxels), (D). Plot of the Stimulus*Condition interaction; ** = p < .017.***

In summary, similar to the effect in left PRC for objects, the right HC showed a scene-specific effect in which greater activity was associated with scene item change trials relative to scene location change, and scene match trials. In anterior HC, greater activity was associated with object relative to scene processing, and the identification of item rather than location changes. In the two more posterior HC clusters, activity in left HC was associated with item changes rather than matches.

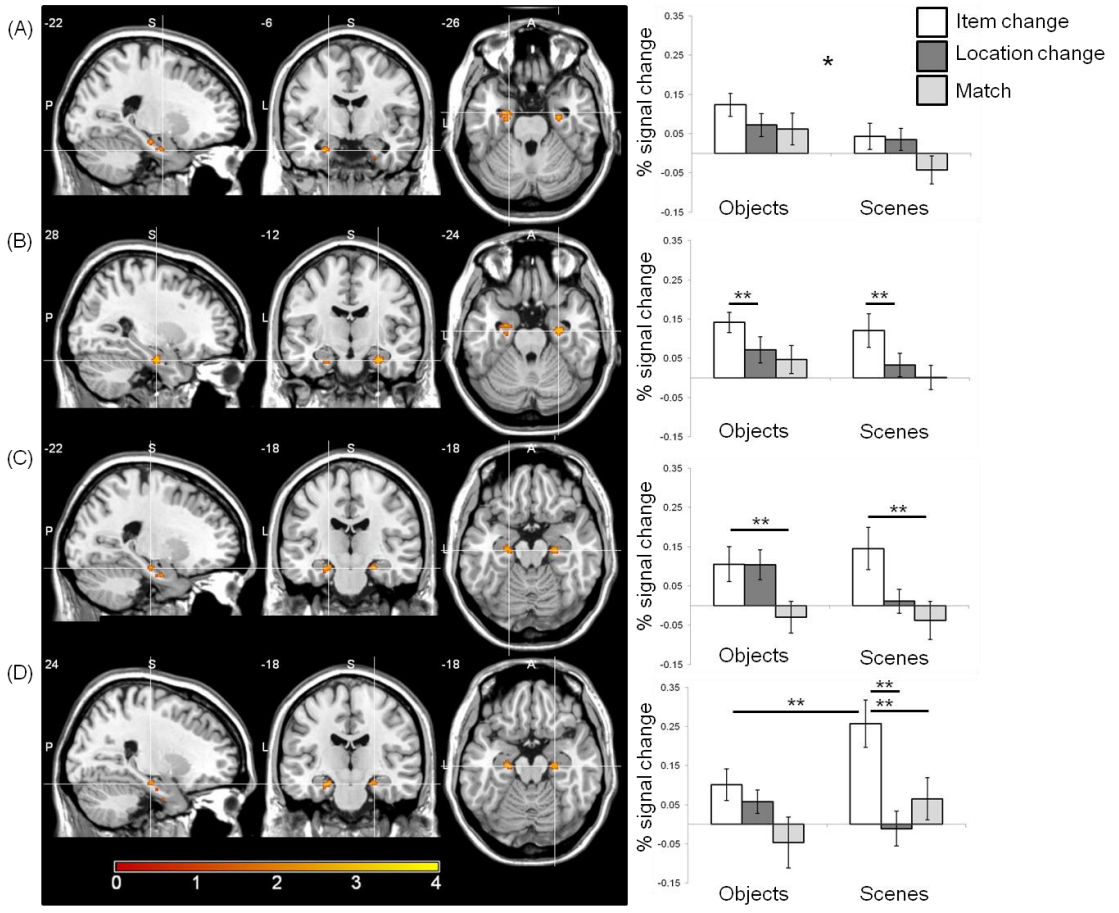

Figure 3.8. ***Clusters of activity from the contrast 'scene item change > scene match' (A) left anterior HC (-22, -6, -26; 22 voxels), (B) right anterior HC (28, -12, -24; 34 voxels), (C) left HC (-22, -18, -18; 32 voxels), (D) right HC (24, -18, -18, 13 voxels). Corresponding plots display percent signal change values extracted from each cluster for object and scene conditions contrasted to the appropriate size baseline; * = p < .05; ** = p < .017.***

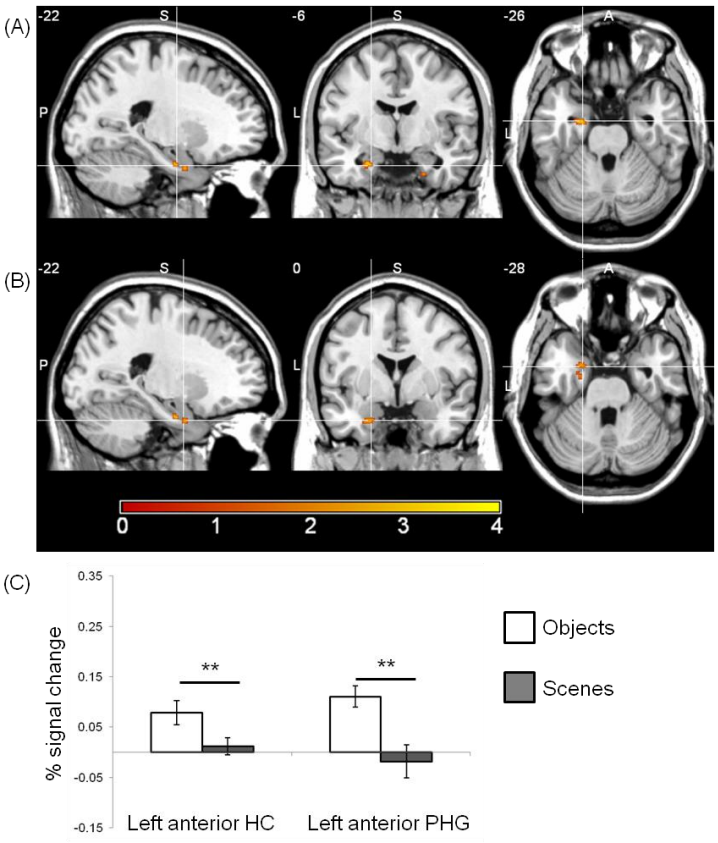

Figure 3.9. ***Clusters of activity from the contrast 'scene location > scene match' contrast (A) left anterior HC (-22, -6, -26; 19 voxels), and (B) left anterior PHG (-22, 0, -28; 12 voxels), (C) Plot of the ROI*Stimulus interaction*; ** = p < .025.***

3.1.3.2.4.4. Scene location change > scene match

Changing the arrangement of individual scene stimuli has not been formally tested previously so we predicted a similar pattern of results to objects (i.e., increased HC activity).

Two regions of the MTL were associated with greater BOLD response for scene location change trials relative to scene match trials (see Figure 3.9). One cluster was located in anterior HC, and the other was in anterior PHG. Percent signal change values were entered into a ROI (anterior HC; anterior

PHG)*Stimulus (objects; scenes)*Condition (item change; location change; versus match) ANOVA and revealed a main effect of Stimulus ($F(1, 20) = 25.03$, $p < .01$) and a ROI*Stimulus interaction ($F(1, 20) = 4.94$, $p < .05$). Collapsing across condition to investigate the interaction, both regions revealed greater activity associated with objects relative to scenes, however this difference was greater in the anterior PHG ($t(20) = 4.51$, $p < .025$, Bonferroni correction = .05/2, adjusted α = .025) compared to anterior HC ($t(20) = 3.51$, $p < .025$).

Consistent with earlier analyses, greater BOLD response in anterior PHG and anterior HC was associated with object, rather than scene, processing.

3.1.4. Discussion

This study was designed to identify regions in the MTL where the level of neural activity correlated with object and scene stimuli. The paradigm of Lee, Bandelow, et al. (2006) was employed to ask whether there was evidence to suggest that these MTL regions support higher order perception. Specifically, do the PRC and HC, show increased activity associated with the detection of a different object and scene, respectively.

Supporting the predictions of EMA, the contrast *'objects > scenes'* using the probabilistic mask of the MTL revealed greater activity in PRC associated with objects relative to scenes. The role of the PRC in signalling differences between object items ('*object item change > object match'*), however, was less clear. Activity was evident in the PRC for this contrast only when a liberal threshold was employed (i.e., $Z > 2.3$, $p = 1$). Increased PRC activity associated with object item changes has been demonstrated previously (Köhler, Danckert, Gati, & Menon, 2005; Pihlajamäki et al., 2004), including in a study using the same paradigm (Lee, Bandelow, et al., 2006). Furthermore, stimulus

manipulations in the current study were predicted to be more likely to elicit PRC activity than those used before. Relative to Lee, Bandelow, et al., the item pairs for the object item change condition in the current study contained a greater degree of feature overlap - a property thought to be important in eliciting PRC activity (Barense et al., 2012, 2010; Devlin & Price, 2007). There are at least two possible explanations for why the manipulations implemented in the current experiment may not have resulted in as strong an effect as has been reported previously.

First, increasing feature overlap of the object item change pairs may have inadvertently made participants pay more attention to the object match trials. In the object item change condition of Lee, Bandelow, et al. (2006), visually distinct items were used, and participants detected these differences very rapidly (item change condition RT = ~1850ms). Consequently, in Lee, Bandelow et al.'s study, participants may have adopted a response strategy whereby, if they did not immediately notice a different object, they would respond 'same', a response that would most likely be correct as the item changes were very obvious. In the current study, the increased feature overlap between object pairs meant that the difference between items was not immediately apparent and more attention needed to be paid to the items in order to be successful in making an appropriate 'same/different' decision (as evidenced by the longer RTs; mean item change condition RT = 3042ms). By this account, participants would need to search the match trials to determine whether the objects contained any subtle differences. As a consequence, an increased level of activity in PRC associated with match trials (because the object features were studied in more detail) would be predicted, and would therefore make it more difficult to attain a significant difference in activity

between the object item change and object match trials. This notion is supported by examining the plots of the BOLD response for each condition in the two different studies: in Lee, Bandelow, et al. (2006) the match (no change) condition was associated with a decrease in signal whereas in the current study there was a slight increase in BOLD signal relative to baseline. Reassuringly, given that the manipulation is identical in both studies, activity in the right PRC associated with object location trials was equivalent in both studies (comprising a slight decrease in activity relative to baseline).

Second, a critique of the original Lee, Bandelow, et al. (2006) experiment was that activity in the PRC associated with the item change condition may have reflected the naming of an additional object exemplar (as these changed items were from different semantic categories). BOLD signal in PRC has been shown to be increased when there is a requirement to name objects at the "basic" level vs "domain" level (e.g. *donkey* vs *living thing*) (Tyler et al., 2004; Wise et al., 2000). It is possible, therefore, that in Lee, Bandelow, et al. (2006), the presentation of an extra object item led to the automatic naming of this exemplar during the object item change condition, resulting in increased BOLD response in PRC. In the current study, the differing objects in the item change condition were selected from the same category, and consequently had the same semantic label (for example, two different books or cameras). The number of semantic categories in the item change, and match conditions, therefore, was equivalent, and there was no additional demand placed on naming. This may have reduced the level of activity in PRC in the current study. When these two points are considered together, therefore, increased PRC signal due to an additional object to name in the item change condition, combined with less activity associated with the match trials reflecting less need

to study the object items, may explain why the *'object item change > object match'* contrast yielded a significant PRC cluster in Lee, Bandelow, et al. (2006), but not so strongly in this experiment. It should be noted, however, that PRC activity associated with perceptual discriminations cannot be explained purely in terms of semantic processing (or naming). For example, although familiar objects were associated with greater activity in PRC relative to novel object stimuli (greebles), there was still above baseline activity in this region associated with the novel objects for which there was no prior semantic knowledge (Barense et al., 2011) (for further discussion of the nature of representations supported by PRC, see Section 6.3.1).

The pattern of BOLD response in right PRC suggests that this region signals differences between items, regardless of stimulus type (Figure 3.6, A). There was a main effect of condition, resulting from greater activity for item change relative to location change and match conditions, across both object and scene stimuli. This is contrary to the predictions of EMA, according to which this pattern of data would be evident for objects only. As Lee, Bandelow, et al. (2006) only used objects, it was not possible to test the specificity of the PRC item effect; a key question of the current study. Although this finding is challenging to EMA, it is possible to explain a PRC contribution to the scene task as follows. First, real-world scenes were used that, in many instances, contained objects. It is conceivable that differences between the objects contained within the scenes, and not the spatial features of the scene itself, were diagnostic of a scene item change. Supporting this idea, Buckley, Booth, Rolls, and Gaffan (2001) found that after PRC ablation, monkeys were impaired on scene oddity, where the scenes comprised many objects. Where objects

within scenes were diagnostic of a difference between scenes, EMA would predict increased PRC activity.

The pattern of data in PRC is consistent with predictions from mnemonic accounts of MTL function. BIC, for example, would predict increased activity in PRC associated with the item change condition relative to location change and match conditions for objects and scenes, reflecting incidental encoding of the extra item across grids. That this region showed a main effect of stimulus, with greater activity associated with objects relative to scenes, however, is not easily reconciled with the BIC model. Consistent with EMA, these data suggest that the primary role of this region is to form unique representations of object-level feature conjunctions, necessary to disambiguate perceptually similar object items. An alternative interpretation supporting BIC, which was alluded to in a recent paper (Diana et al., 2012), suggests that objects provide a more powerful way of testing item effects and therefore greater activity might be expected to be associated with this stimulus class relative to scenes that comprise a combination of object items. Although cases could be made for both interpretations of this main effect of stimulus, they are more easily accommodated by EMA, which proposes that the role of this region is to process complex conjunctions of features comprising an object item.

For one cluster located at the mid-point of the right HC, significantly greater activity was associated with scenes relative to objects. Moreover, this activity was modulated by condition with reliably greater BOLD response associated with scene item change relative to location change and match conditions. Consistent with EMA, this pattern of data could reflect the signalling of a difference between two perceptually similar scenes. As noted above,

however, the real-world scenes contain objects that may be indicative of scene item differences. This effect, therefore, may not reflect a pure scene item detection effect.

These data extend the findings of Lee et al. (2012) by addressing several concerns raised because of methodological issues in their study. As described in Section 3.1.1, in Lee et al.'s study, activity in anterior HC was modulated by behavioural performance in scene oddity, with greater signal associated with correct versus incorrect responses; accuracy, however, did not modulate activity in posterior HC. Moving beyond Lee et al. (2012), the analysis of correct responses to both item change and match trials means that one can be more confident that participants were attending to the stimuli in both conditions. By analysing correct versus incorrect responses, like in Lee et al. (2012), activity associated with performance might be confounded with differences in attention across the two behavioural outcomes (i.e., participants could be attending more to the stimuli in the correct rather than incorrect trials). Second, the current study used both objects and scenes meaning that it was possible to test whether increased activity associated with item change relative to location change and match conditions, was specific to one stimulus type. In Lee et al., only scenes were tested meaning that it was not possible to say whether increased activity in anterior HC associated with correct versus incorrect oddity performance for scenes was specific to this stimulus, or common to all stimulus types. In summary, the current findings suggest that the HC shows a scene-specific effect in the discrimination of two perceptually similar items.

The BIC model finds increased HC activity associated specifically with the scene item change condition more difficult to reconcile than the PRC

effects. BIC proposes that the HC supports domain-general (i.e., consistent for both objects and scenes) mnemonic processes, whereas the PHC supports memory for contextual (including spatial) information. If it is assumed that the activity evident during a perceptual discrimination reflects incidental encoding of items, this model would predict increased activity in PHC for the scene item change, reflecting the encoding of an additional scene exemplar, but that the level of neural activity in HC should not differ between objects and scenes. The current data, therefore, are inconsistent with the BIC account of MTL function. Dual process accounts, however, could explain this scene specific effect in relation to the type of memory process that supports subsequent memory for these stimuli. For example, it could be suggested that, relative to objects, scenes may encourage different encoding strategies that makes them more likely to be recollected later. Equally, the unitary account could suggest that the BOLD signal reflects strength of memory for items, and therefore the participants would have subsequently stronger memory for scenes relative to objects (Shrager, Kirwan, & Squire, 2008; Song, Wixted, Smith, & Squire, 2011; Squire et al., 2007). Without a subsequent memory paradigm, in which it would be possible to look at encoding related activity associated with individual trials, it is difficult to adjudicate between these accounts and argue against the view that these activations do not reflect incidental encoding.

Detecting changes in the configuration of objects across two grids was associated with increased activity in anterior HC. Parameter estimates revealed, however, that the level of signal was equivalent for both object item change and location change conditions. These data are consistent with domain-general processes such as match-mismatch, which are proposed to be supported by the HC (Duncan, Ketz, Inati, & Davachi, 2012; Kumaran & Maguire, 2006, 2007a,

2007b, 2009). For example, Kumaran and Maguire (2007a) showed four single objects sequentially in specific spatial locations. These items were presented again either with a change in object order (temporal), or the spatial location of one of the object items. Significantly greater activity in HC was associated with the mismatches (both temporal and spatial) relative to matches. It was proposed that this increase in activity reflects a domain-general match-mismatch mechanism, in which mnemonic predictions are compared with current sensory input. Where there is a mismatch between these, increased activity in HC reflects the encoding of the novel stimulus elements. The current data do not rule out the involvement of domain-general match-mismatch processes in the HC as several of the anterior clusters showed increased activity for item change relative to match trials regardless of stimulus type. They do, however, suggest that: 1) these processes operate during a perceptual discrimination, rather than over a delay, and 2) stimulus specific processes for detecting differences between objects and scenes also operate in the PRC and HC, respectively.

For the object and scene '*item change* > *match*' and '*location change* > *match*' MTL analyses (detailed in Section 3.1.3.2.4), it must be noted that the contrasts, from which percent signal change values were extracted, were not orthogonal and therefore there is a degree of circularity in this analysis. Specifically, stimulus conditions used in the contrasts to identify significant ROIs were again used in a contrast to baseline to extract the percent signal change values. For example, the '*object item change* > *object match*' contrast was associated with a significant cluster of activity in the right PRC. Percent signal change values, for each object and scene condition relative to the appropriate size baseline, were then extracted from this ROI and submitted to ANOVA.

Given that the initial contrast used to identify the ROI was sensitive to voxels showing increased activity associated with the object item change condition (i.e., '*object item change* > *object match*'), assessments of statistical significance of the effect of this condition relative to baseline (i.e., '*object item change* > *size item change*'), are likely to have been inflated. In the right PRC ROI, therefore, the BOLD response for object item change trials may appear larger, relative to other stimulus conditions, as a result of this analysis approach. Assessments of statistical significance are most likely inflated for stimulus conditions that were used to identify the ROI (e.g., voxels identified via the contrast '*object location change* > *object match*', are more likely to show a significant effect for the contrast '*object location change* > *size location change*' because the object location change condition was used in the contrast to create the ROI). The percent signal change values associated with the other stimulus conditions, however, should not be affected by this voxel selection bias because they are orthogonal to the contrast used to create the ROI.

The use of non-independent ROIs in fMRI research, known as circularity of analysis, or "double-dipping", has required to use of alternative methods to identify independent ROIs (Kriegeskorte, Lindquist, Nichols, Poldrack, & Vul, 2010; Kriegeskorte, Simmons, Bellgowan, & Baker, 2009; Vul, Harris, Winkielman, & Pashler, 2009). These include the use of anatomical masks, or functional ROIs identified using a separate dataset orthogonal to the experimental data. In Chapters 4 and 5, the latter approach is adopted to circumvent this issue of circularity, and a separate functional localiser (comprising a "one-back" task) is used to identify voxels sensitive to object, and scene stimuli, respectively (see Section 4.2.2.1 for details of this localiser).

The current imaging experiment demonstrated stimulus specific processing in the PRC and posterior PHG for objects and scenes, respectively. Despite evidence of greater activity associated with objects relative to scenes in PRC, there was a domain general effect associated with successful identification of differences between object and scene items. These data suggest that it is possible for the PRC to support discriminations between visually similar items, and that its role is not necessarily limited to object stimuli. There was, however, a scene specific signal in right HC that was modulated by condition; the largest BOLD response was associated with item change relative to location change and match conditions.

The domain-general response to item change relative to match trials in PRC was not predicted by EMA, and is inconsistent with reports of stimulus specific impairments in patients with MTL damage (e.g., Barense et al., 2005, 2007). It is hard to test the role of PRC in scene item detection directly in this type of task, as comparisons between patients are generally subtractive; patients with broader MTL damage have involvement of the HC and PRC, and generally show poor scene and object/face discrimination (Erez et al., 2013; Graham et al., 2006; Lee, Buckley, et al., 2005, 2006). Examination of the performance of patients with focal HC lesions, such as those reported in Chapter 2 (see Section 2.2.1), could be helpful in this regard: the imaging findings predict that HC patients should be able to identify both object and scene item changes using the domain-general item change signal in the PRC (which was proposed above to reflect an object signal that could also be applied to scene detection). The patients, however, should not benefit from the HC signal evident in the *'scene item change > scene match'* contrast, which is more likely to be scene-specific, available to controls, and therefore might show less

efficient detection of scene, relative to object, changes (as evidenced by longer RTs).

3.2. Neuropsychological study examining the contribution of the HC to item discriminations of objects and scenes

3.2.1. Introduction

The unitary account proposes that the MTL supports declarative memory only, and that perception should be unaffected by damage to this region, or any of its composite structures (Squire et al., 2007). This view suggests that any deficits evident in patients with MTL lesions during perceptual discriminations stem from the impact of an impairment in long-term (or more recently supraspan) memory, rather than a deficit in higher order perception (See Section 1.4.4.1) (e.g., Jeneson & Squire, 2012; Jeneson, Wixted, Hopkins, & Squire, 2012; Knutson, Hopkins, & Squire, 2012).

For example, Kim et al. (2011) tested patients with HC lesions and age-matched controls on a concurrent discrimination task. Participants were presented with two stimulus conditions: faces and scenes. A pair of images (either faces or scenes), and a morph between these two images, were presented. The participant was required to select which of the two items the morph more closely resembled. In the trial-unique condition, the pair of images and the morph changed on every trial. In the repeat condition, the pair of images remained the same, and the morph changed. The prediction was that, unlike the HC patients, the controls should be able to benefit from memory for the pair of images in the repeat condition; there should be no such benefit, however, in performance during the trial-unique condition. Confirming their

predictions, in the repeat condition, controls showed significant learning across blocks for both faces and scenes that resulted in significantly better accuracy relative to patients over the course of the experiment. In the trial unique condition, however, performance was matched across controls and patients for both stimulus classes. Furthermore, contrary to predictions of EMA, the performance of patients was not modulated by stimulus category (i.e., they did not show a deficit in scene learning but spared learning for faces). Replicating previous findings (e.g., Buffalo, Reber, & Squire, 1998; Levy, Shrager, & Squire, 2005; Shrager, Gold, Hopkins, & Squire, 2006), these data suggest that apparent perceptual deficits in patients in fact stem from controls benefitting from memory.

The current experiment used an amended version of the imaging task described in Section 3.1 to answer outstanding questions raised by the imaging study, and to test whether patients show impairments in perception that cannot be explained by a mnemonic benefit in controls. Specifically, do patients with focal HC damage show difficulties in scene, but not object, detection in a paradigm that places no explicit demand on declarative memory, and in which all stimuli are trial-unique, thereby ensuring no advantage from memory transfer across trials in controls? The findings from the imaging study outlined in Section 3.1 would suggest that PRC can signal differences between both objects and scenes (the latter being driven by the presence of objects within the scenes). There was also evidence, however, of a HC signal that was associated with successful identification of scene item change trials relative to match trials. As noted previously, it was predicted that the HC patients should be able to discriminate objects and scene stimuli, but may show less efficiency (as indexed by longer reaction times) in the discrimination of scenes.

3.2.2. Method

3.2.2.1. Participants

Two patients with focal HC damage (patients HC2 and HC3) and seven matched controls participated in the experiment. See Section 2.2.1 for details about the patients and information about their matched controls.

3.2.2.2. Experiment procedure and methods

A simplified version of the fMRI paradigm was created. Given that object and scene specific activity was evident in PRC and HC, respectively, for the contrast *'item change > match'*, we used these conditions in the neuropsychological task (i.e., the location change trials were removed). Stimuli comprised objects, scenes and size. In contrast to the fMRI experiment, the trials were presented in blocks according to stimulus-type; item change and match trials were randomly presented within these blocks throughout the experiment. Testing took place over two experimental runs, each comprising 16 trials per condition for object, scene and size stimuli. The order of the blocks within each run was manipulated so that the first block of each run always comprised size stimuli; this was to ensure that the patients understood the task requirements in advance of doing the two experimental conditions of particular interest. The object and scene block order was counterbalanced so that, for one run, the objects were presented first followed by scenes, and vice-versa in the other block. The run order was also counterbalanced across patients, and the two matched control groups were given the appropriate run order of their patient match. Participants responded using a two-choice button-box and, unlike the fMRI task, prompts on the bottom left and right of the screen reminded the

patient of the buttons assigned to ‘Same’ and ‘Different’ responses. This was to ensure that any deficit in performance was not a result of poor memory for the task instructions. Participants were told that they would see two grids each containing three items. They were asked to indicate, via a button box response, whether the two grids were identical (‘same’), or differed on the basis of the items contained within them (‘different’). The task was self-paced but participants were asked to respond as quickly and accurately as possible. The experiment comprised the same stimuli as the imaging experiment described in Section 3.1. Trials from one run of the fMRI experiment were used as a practice prior to starting the task which includes the stimuli from the remaining two fMRI runs.

3.2.2.3. Statistical analysis

Performance on this task was assessed through discrimination accuracy and a measure of inverse efficiency (reaction time/proportion of correct responses, for previous use of this method, see Graham et al., 2006). Given the two choice response required on this task, and that the patients had as long as they wished to make a response, it was anticipated that accuracy might be quite high, which makes it difficult to obtain sensitive assessments of behavioural impairment using accuracy measures alone. Combining accuracy measures with reaction time data, however, allows the experimenter to interpret whether accuracy performance reflects an unusually long response time on each trial. For example, in Graham et al. (2006), patients (including those reported here) showed good perceptual discrimination accuracy but this ‘preservation’ of performance reflected extremely long RTs compared to controls.

Prior to undertaking a comparison between patients and controls, behavioural performance for the two groups of age-matched controls was assessed by submitting their accuracy, reaction time, and inverse efficiency data to an ANOVA. A Group (HC2 controls; HC3 controls)*Stimulus (objects; scenes; size)*Condition (item change; match) mixed model ANOVA was conducted for each dependent measure. For accuracy, reaction times, and inverse efficiency scores, there was no evidence of any group differences (*F*s < 3.26, *p*s > .12), the factor Group did not interact with Stimulus or Condition, and there was no evidence of a significant three-way interaction (*F*s < 1.75, *p*s > .24). For subsequent analyses, therefore, a single, larger, control group (n = 7) was used for comparison with the patients.

To determine whether there were any differences in discrimination performance between patients and controls, accuracy and inverse efficiency scores for each stimulus class and condition were submitted to a Group (HC patients; normal controls)*Stimulus (objects; scenes; size)*Condition (item change; match) mixed ANOVA. A significant three-way interaction (indicative of a group difference in performance between patients and controls) was followed up with subsidiary ANOVAs investigating the pattern of performance for patients and controls across item change and match conditions, for each stimulus type; Group (HC patients; normal controls)*Condition (item change; match) for objects, scenes, and size separately. A significant interaction between Group and Condition in these subsidiary ANOVAs was then investigated with Crawford t-tests (Crawford & Garthwaite, 2002; Crawford & Howell, 1998) (see Section 2.2.7 for more details about this statistical test).

3.2.3. Results

Mean accuracy and reaction times for each stimulus class are shown, by condition for both patients and controls, in Table 3.1. Accuracy measures were submitted to a Group (HC patients; normal controls)*Stimulus (objects; scenes; size)*Condition (item change; match) ANOVA and revealed a main effect of Condition ($F(1, 7) = 13.76$, $p < .01$) that was qualified by a Group*Stimulus*Condition interaction ($F(2, 14) = 4.41$, $p < .05$). A subsidiary ANOVA examining accuracy across Group (HC patients; normal controls)*Condition (item change; match) for object stimuli revealed a main effect of Condition resulting from significantly better accuracy for match trials relative to item change ($F(1, 7) = 9.42$, $p < .05$); there was no statistical differences between HC and control groups ($F(1,7)=2.06$, $p=0.19$), and no evidence of a Group*Condition interaction ($F(1, 7) = 2.35$, $p = .17$). The same ANOVA for scene stimuli, however, revealed a main effect of Group ($F(1, 7) = 11.41$, $p < .05$), a main effect of Condition ($F(1, 7) = 11.49$, $p < .05$), and a significant Group*Condition interaction ($F(1, 7) = 9.5$, $p < .05$). Follow-up Crawford t-test showed that compared to controls, patient HC2 made significantly more errors when discriminating perceptually similar scenes in the item change condition ($t(6) = 2.21$, $p < .05$). This deficit was even more apparent in patient HC3 who made a large number of errors in this condition ($t(6) = 10.19$, $p < .01$). Finally, for size stimuli, there was a trend towards greater accuracy for match relative to item change conditions ($F(1, 7) = 4.58$, $p = .07$), but there was no effect of Group, or Group*Condition interaction (Fs < 2.82, ps > .12).

The same analyses were conducted for the inverse efficiency measures. This revealed a main effect of Stimulus ($F(2, 14) = 25.97$, $p < .01$), qualified by a Group*Stimulus interaction ($F(2, 14) = 9.44$, $p < .01$) (see Figure 3.10). To investigate further the statistical interaction between group and stimulus (collapsed across item change and match conditions), Crawford adjusted t-tests were used to test each patient's performance with that of the control group.

Table 3.1. ***Proportion correct and response times for controls (n=7) and patients HC2 and HC3 (parentheses contain the SE of the mean).***

		Object		Scene		Size	
		Item change	Match	Item change	Match	Item change	Match
Accuracy	Controls	0.92 (0.03)	0.99 (0.01)	0.98 (0.01)	0.99 (0.01)	0.92 (0.02)	0.97 (0.01)
	HC2	0.94	1.00	0.91	0.97	0.94	0.94
	HC3	0.66	0.97	0.66	0.97	0.81	0.88
Reaction time (ms)	Controls	2518 (72)	3835 (115)	3053 (204)	4468 (443)	2808 (346)	3292 (82)
	HC2	3382	6017	4287	7386	2147	3335
	HC3	3365	3648	3797	3881	3137	2827

Relative to controls, both patients showed normal performance for size stimuli (HC2: $t(6) = .41$, $p = .35$; HC3: $t(6) = .49$, $p = .32$). Considering the scene stimuli, patient HC2 was found to be significantly impaired for scenes ($t(6) = 3.63$, $p < .01$); in the case of HC3, this was a marginal impairment ($t(6) = 1.65$, $p = .07$). For objects, HC2 showed a trend towards impaired object processing ($t(7) = 1.79$, $p = .06$); HC3 matched control performance for objects ($t(6) = 1.36$, $p = .11$).

To check that the deficit in patients could not be explained by learning in the controls, each of the two runs was divided into blocks and the accuracy and inverse efficiency scores calculated for each block. In each run, there were 32 trials per stimulus class (16 item change, and 16 match trials) resulting in four blocks (see Appendix A, Section 7.2).

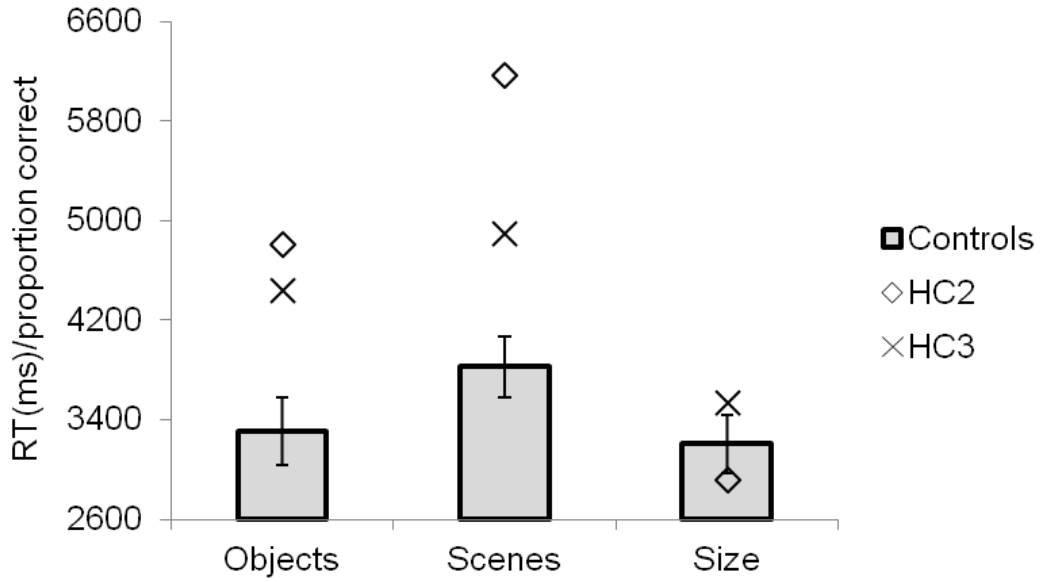

Figure 3.10. ***Inverse efficiency scores of patients HC2 and HC3 plotted with control data, for the three stimulus classes, collapsed across item change and match conditions.***

These data were submitted to separate Run (one; two)*Block (one; two; three; four)*Stimulus (object; scene; size) ANOVAs. Given that the stimuli were trial unique, it is little surprise that the participants showed no evidence of learning in their accuracy or inverse efficiency scores across run one to two,

across blocks within runs one and two, and these factors did not interact with Stimulus (*F*s < 3.68, *p*s > .1).

3.2.4. Discussion

The patient experiment outlined here asked whether patients with HC lesions would show particular difficulties on the scene item change condition, compared to the object and size item change conditions, given the stimulus specific effect (*'scene item change > match'*) that was evident in HC during the imaging task. Consistent with the predictions based on the imaging data, both patients with focal HC lesions showed significant impairments relative to healthy controls when required to discriminate between two scenes that contained a high degree of feature overlap. Furthermore, both patients exhibited greater difficulty in the processing of scenes as evidenced by the larger inverse efficiency scores for this stimulus category. The pattern of performance for objects, however, was not consistent across patients. Patient HC2's discrimination accuracy matched controls, whereas patient HC3's object item change performance was much poorer than both HC2 and controls.

A prediction of EMA is that HC damage should lead to impairments in both the perception of, and memory for, scenes. Supporting this prediction, two patients with focal HC damage made a significantly greater number of errors when discriminating two perceptually similar scenes, and had significantly (or marginally) larger inverse efficiency scores when required to process scene stimuli. Furthermore, contrary to the predictions of Kim et al. (2011), this deficit could not be explained in terms of a memory benefit for controls, but not for patients, as there was no evidence of learning across blocks in the control group. These data are consistent with those in a number of other studies that

have demonstrated impairments specifically for scenes in patients with HC damage (see Section 1.4.3 for references and further details).

Oddity tasks have shown that patients with HC damage have significant difficulty in selecting a different scene from a number of concurrently presented scene items (Erez et al., 2013; Lee, Buckley, et al., 2005). They provide limited insight, however, into why these patients make significantly more errors on scene conditions. Considering the theoretical proposals of EMA, there are at least two possible explanations as to why HC patients may make more errors on scene trials during oddity. First, if patients are unable to form complex conjunctions of spatial features, their scene representations may lack spatial coherence, which leads to the patient selecting the incorrect scene item. For this type of error, the patient may believe (incorrectly) that the item they have selected is the odd-one-out. Second, HC patients may be forced to rely on less complex conjunctions of spatial features, perhaps supported by extrastriate regions, to inform their oddity decision (Graham et al., 2010; Mundy et al., 2012). These lower-level spatial conjunctions are common to a number of scene items within the oddity trial, and, as a result of these impoverished scene representations, all of the items appear the same. Errors here may reflect the patient guessing at one of the concurrently presented items leading to poorer discrimination accuracy. In line with this second suggestion, one HC patient, when commenting on her impairments for scenes, stated “Whichever angle I look, everything looks the same” (p. 832, Graham et al., 2010). The second proposal is similar to the hypothesised role of the PRC in disambiguating perceptually similar object items (e.g., Barense et al., 2012; Bartko, Cowell, Winters, Bussey, & Saksida, 2010). It was argued that deficits in discriminating perceptually similar object items after PRC damage result from the interference

of intact lower-level object feature conjunctions (McTighe et al., 2010). Normally, the PRC buffers against this interference by forming unique object-level representations; in the absence of this region, however, all complex object items appear to look the same by virtue of the intact lower-level feature conjunctions common to all items. It is possible, therefore, that the HC performs an analogous role in disambiguating perceptually similar scenes.

Given that the current experiment contained trials in which the scene items were different, and those in which they were the same, it allowed for greater insight, than oddity tasks, into the nature of the patients' deficits by examining the pattern of errors across these two conditions. If patients make errors because they cannot form complex conjunctions of spatial features (i.e., the first proposal), one would expect errors to be distributed across both item change and match conditions. If, however, the second interpretation is correct, and all scenes appear the same to the patients, then one would expect to observe a bias towards responding 'same', and therefore more errors in the item change condition. Consistent with the second interpretation, both patients made a significantly greater number of errors in the scene item change condition relative to controls (i.e., the patients could not detect differences between two perceptually similar scenes). These data suggest that the HC is required to form complex scene representations that disambiguate perceptually similar scene items. Moreover, supporting the imaging data, this region may signal the differences between two perceptually similar scene items.

These patient data also suggest that the imaging data outlined in Section 3.1 cannot be explained purely in terms of mnemonic processes. Reliance on just the imaging data leaves open the possibility that the increased BOLD

response in HC associated with the scene item change condition is due to incidental encoding of the extra scene item, rather than a HC-mediated signal that two complex scenes differ. By complementing these findings with data from patients with HC damage, it is possible to be more confident the HC is supporting a process necessary for perceptual discrimination rather than subsequent memory for the items in healthy controls. Consistent with EMA, these patient data suggest that the HC forms complex conjunctions of spatial features, which allow for the disambiguation of two perceptually similar scene items that cannot be discriminated on the basis of lower-level feature conjunctions.

Examination of the inverse efficiency scores supports the broader conclusion that, as well as showing an impairment in detecting differences between perceptually similar scenes, the patients with HC may also have more general impairments in scene processing (i.e., for both item change and match trials). Relative to controls, patients showed significantly larger inverse efficiency scores across both scene item change and match trials. This pattern of data, however, may not be unexpected. The patients were aware that the experiment comprised both trials in which the items differed and trials in which the items were the same. If it is assumed that the HC response in the imaging data reflects a signal that two perceptually similar scenes differ, one possible explanation is that because patients do not benefit from this signal, they were more cautious in their responses for this category of stimuli. Specifically, even when presented with grids containing identical scenes, they had difficulty forming complex conjunctions of these spatial features and therefore spent longer on these items to ensure that they did not differ. These data, therefore,

are still consistent with a role for the HC in higher order perception of scene stimuli.

Similar to Chapter 2, in comparison to HC2, patient HC3 showed greater variability in discrimination accuracy across stimuli. Moreover, HC3 achieved the same level of accuracy for both object and scene item change conditions (0.66 correct). In comparison with scenes, the Group*Condition interaction for objects did not reach significance due to slightly less accurate, and more variable performance in the control group for this stimulus. HC3's impairment across both objects and scenes, therefore, might be interpreted as reflecting a domain-general impairment in match-mismatch detection, a role ascribed to the HC (Kumaran & Maguire, 2006, 2007a, 2007b, 2009), rather than a stimulus specific deficit in scene processing. It is not clear, however, why patient HC2 shows a scene specific deficit in the item change condition but spared performance for object item change trials, if the HC supports domain-general match-mismatch processes. As discussed in Chapter 2, patient HC3 has more extensive HC damage compared to patient HC2 and this may explain the more profound deficits for both scene, and object stimuli. As noted previously, larger patient sample sizes are required to better establish the consistency of these effects. Supporting Chapter 2's findings of scene conjunction learning deficits in patients, however, it is reassuring that in the current experiment both HC patients showed a significant impairment when required to detect scene item changes.

It is not clear why there is a discrepancy between the findings of the current study and those of Kim et al. (2011). In Kim et al., patients with HC damage performed at the same level as control participants when face and

scene stimuli were trial-unique. One possibility is that differences in task demands explain the differences in results. In Kim et al., participants were required to match a target stimulus to one of two foils, whereas in the current study participants were required to look for similarities, and differences between stimuli. It is possible that the paradigm used in Kim et al. may have afforded the use of a piecemeal search strategy. For example, patients may have picked an individual feature of the scene to-be-discriminated, and then compared this one feature with the pair of scenes presented above. This would allow them to make a binary decision as to which of the two scenes it more closely resembled. In the current paradigm, this strategy would be less effective. For example, if participants selected one of the features of the scene stimuli and found that it matched the corresponding scene, they would not be sure whether this indicated that this pair of scenes was the same, whether a different feature of the same scene differed, or whether one of the other pairs of scenes within the trial differed. The current task, therefore, may have placed more demand on processing the scene as a gestalt, requiring the patient to form complex conjunctions of spatial features, rather than focussing on the discrimination of an individual feature.

In summary, these patient data suggest that the HC supports the discrimination of perceptually similar, complex scene items. Furthermore, these patient deficits were evident during a trial-unique task with no overt memory component, in which there was no evidence of control participants benefitting from memory. The latter point is important because it rules out an explanation that can be offered for previous ostensibly similar findings in which this factor was not controlled for.

3.3. Summary

The imaging and patient study described here were designed to test the accuracy of some elements of EMA, via the identification of regions of MTL associated with successful discrimination of object and scene stimuli, respectively. Increased activity in the PRC and posterior PHG was associated with objects and scenes, respectively. Consistent with the predictions of EMA, detecting a difference between visually similar objects was associated with increased activity in PRC. Contrary to this account, however, the same pattern of BOLD response was evident for scenes. In the HC, there was evidence of increased activity associated with detecting differences between two visually similar scenes. A linked neuropsychological study revealed complementary data; patients with HC damage showed poorer discrimination accuracy for scene item change trials, relative to matched controls; there was no evidence of impairment, however, in the scene match condition. For the imaging study, the scene item change effects in the HC were identified by using a liberal statistical threshold ($Z > 2.3$, $p = .05$, uncorrected). A question that remains outstanding, therefore, is why this effect was not more robust. One possible explanation is that changes in viewpoint are necessary to elicit these HC effects for scenes, such as those implemented in oddity judgement tasks (Barense et al., 2010; Lee et al., 2008). This question is addressed in the following Chapter, in an experiment where a further prediction of EMA was tested, namely that there should be increased activity for high relative to low feature overlap in the HC and PRC for scene and object stimuli, respectively.

Chapter 4: The role of the MTL in the processing of spatial context and ambiguity

4.1. Introduction

In Experiment 3.1, there was a pattern of activity partially consistent with representational accounts of MTL function. Increased PRC activity was evident when contrasting objects over scenes, but the contrast '*scenes* > *objects*' was not associated with increased HC activity, which contradicts a number imaging findings, and does not correspond with the deficits in scene processing that have been reported after damage to this region (see Section 1.4.4). The '*scenes* > *objects*' contrast did reveal increased activity for scenes in the posterior PHG, or PPA, which is consistent with literature in which this region is involved in scene processing (see Section 1.4.2.1). The aim of the experiment outlined in this chapter was to follow-on from the earlier imaging study by examining the conditions under which activity is modulated in stimulus specific regions of cortex, focussing on the impact of increasing the level of feature overlap between stimuli.

Both the representational-hierarchical account and EMA propose that the PRC supports object-level, conjunctive representations that disambiguate perceptually similar object items (see Section 1.4.3.2). FMRI data have appeared to support these findings, with BOLD response in PRC increasing in association with the degree of feature overlap between object items (Barense et al., 2010; Devlin & Price, 2007). These studies, however, are confounded by a change in viewpoint for the high ambiguity discriminations. For example, in Barense et al., the low ambiguity oddity trials comprised all items presented

from the same view with one visually distinct ‘odd’ item. In the high ambiguity trials, however, the items were presented from different views *and* contained a high degree of feature overlap; this was also true of the object oddity task used by Devlin and Price (2007) (see Figure 4.1). In monkeys, PRC ablation has been shown to impair the discrimination of objects when there was increased demand to process the items from a different view (Buckley & Gaffan, 1998). After PRC ablation, monkeys were trained to discriminate object pairs. After reaching criterion on this task, the items were presented again in one of three different views relative to study. Relative to controls, the PRC group made over twice as many errors to reach criterion on the new discriminations in which the same items were presented from a different view. Similarly, patients with MTL damage encompassing the PRC show impairments in oddity task performance when discriminating faces from different views; discrimination accuracy is normal, however, when faces are presented from the same viewpoint. As a result, it was not clear whether the increase in PRC activity in the imaging data reflects the role of this region in discriminating high ambiguity object stimuli, or the demand to process objects from different views. One aim of the experiment described in this Chapter, therefore, was to test key tenets of the representational-hierarchical account and EMA, and ask whether greater activity in PRC is associated with high, relative to low ambiguity, object discriminations. Importantly, to control for effects of viewpoint, all items were presented from different views, whilst manipulating the level of feature overlap.

The experiment was designed to test whether the BOLD response associated with objects during a perceptual discrimination task could be explained by subsequent memory for the items. The increased PRC activity associated with objects in the experiment described in Chapter 3 is not

inconsistent with mnemonic accounts of MTL function. Despite the task comprising a perceptual discrimination with no overt memory component, the unitary account of memory could explain greater PRC activity associated with objects in terms of incidental encoding; participants may have had subsequently stronger memory for the objects compared to scenes. Similarly, BIC could explain the object and scene activity in PRC and posterior PHG, respectively, as reflecting the encoding of object items in the PRC and spatial/contextual information in the posterior PHG (although see Barense, Henson, and Graham (2011), and Lee, Brodersen, and Rudebeck (2013) for evidence that MTL activity may not be explained simply in terms of mnemonic processes).

To examine how the BOLD response associated with the object oddity task correlates with subsequent memory performance, participants' memory for high ambiguity objects was tested outside of the scanner. This test included a manipulation of source in which participants were required to remember the orientation of items. If the MTL activity evident during the oddity task reflects incidental encoding of items, then greater activity should be associated with those items later recognised as old versus those old items later incorrectly endorsed as new. If, however, the level of activity is not modulated by subsequent memory performance, then this would suggest that the MTL activity present during perceptual tasks does not simply reflect incidental encoding, and that this region plays a role in higher order perception.

In Experiment 3.1 (Chapter 3), the contrast '*scenes* > *objects*' was not associated with increased HC activity. These data, therefore, did not support the predictions of EMA, and contradicted a number of neuropsychological and imaging findings. For example, patients with damage limited to the HC were

impaired when discriminating scenes, presented from the same view, when the target and foil were morphed together to contain a high degree of feature overlap; they performed normally, however, when the scenes were visually distinct (Lee, Bussey, et al., 2005). Similarly, patients with HC lesions were impaired when required to identify the different scene during an oddity task in which all items were presented from a different view; they showed spared performance when scenes items were presented from the same view (Lee, Buckley, et al., 2005). Complementing this finding in imaging, Lee, Scahill, and Graham (2008) found increased HC BOLD signal when healthy participants completed the different view scene oddity task, relative to the same view condition. These data suggested, therefore, that akin to the role of the PRC in object processing, the HC supports the discrimination of highly similar scenes, and the processing of scenes from different views. It has not yet been formally tested in fMRI, however, as to whether HC activity increases with the degree of feature overlap for these stimuli. Towards this end, in this experiment, the level of feature overlap between target and foils in the oddity task was manipulated by using two scene categories: 1) high ambiguity computer generated scenes that could only be differentiated due to the movement of one of the component features, and 2) low ambiguity visually distinct real world scenes in which it was possible to identify the odd item on the basis of the objects contained within the scene. Furthermore, all scenes were presented from different views, which we predicted would lead to significantly greater HC activity relative to objects.

The role of the posterior PHG in memory and/or perception is a point of contention between BIC and representational accounts, such as EMA. The BIC model proposes that the posterior PHG supports the recovery of contextual information (Diana et al., 2007). This was based on the observation that in 14 of

26 source memory experiments, successful recovery of contextual information was associated with increased posterior PHG activity. It must be noted, however, that in all but four of these studies, the contextual information was of a spatial nature. The 'context framework' account of PHG function lends support to the BIC model. It proposes that this region processes generic contextual associations, and, reflecting the role of this region in processing contextual associations, equivalent activity was noted across scenes and objects presented in isolation that have strong contextual associations (Aminoff, Gronau, & Bar, 2007; Aminoff, Schacter, & Bar, 2008; Bar, Aminoff, & Ishai, 2008; Bar, Aminoff, & Schacter, 2008; Bar, 2004).

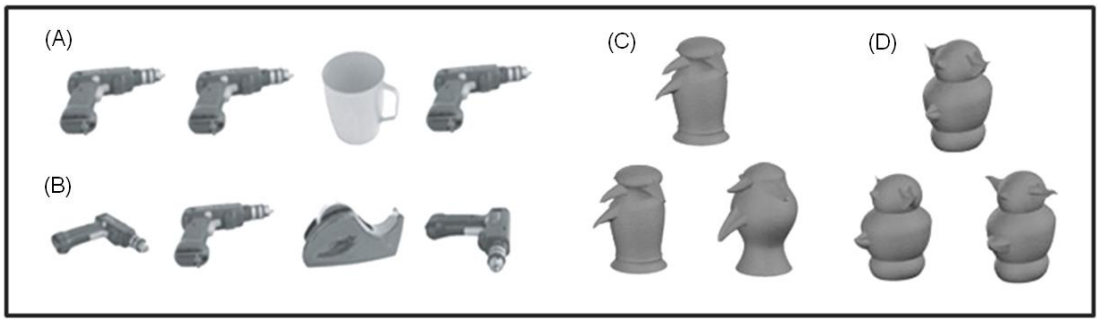

Figure 4.1. ***Examples of high and low ambiguity stimuli from Devlin and Price (2007) (A and B, respectively) and Barense et al. (2010) (C and D, respectively) that confound the level of feature overlap in objects with a change of viewpoint.***

In contrast, there is evidence that posterior PHG is exquisitely sensitive to viewpoint-specific scene geometry (Epstein & Kanwisher, 1998). Although EMA does not make explicit predictions about the role of posterior PHG in scene processing (Graham et al., 2010), several studies testing this account have demonstrated greater activity in this region for scenes relative to faces

(Mundy et al., 2013), and relative to faces and objects combined (Mundy et al., 2012). Based on these data, it would be fair to assume that EMA would align itself with the view that the primary role of this region is to process scene stimuli. It has been demonstrated that under certain conditions, posterior PHG may show increased activity associated with objects presented in the absence of geometric information if they have associated scene information, for example with a familiar landmark (Epstein et al., 1999). Findings such as this have prompted the 'spatial layout' hypothesis, which explains the context framework account in terms of top-down processes (i.e., that increased posterior PHG activity associated with strong context objects results from the participant having time to elaborate about the stimuli and think about associated spatial environments; Epstein & Ward, 2010). Epstein and Ward (2010) tested this hypothesis by presenting famous scenes, unfamiliar real world scenes, as well as strong and weak context objects at two different speeds (fast versus slow). It was predicted that the context effects would only be evident at the slow presentation rate as participants would have more time to think about related spatial associations. BOLD signal for scenes, both famous and novel, was greater than for strong and weak context objects at both fast and slow presentation rates. Significant modulations of famous versus novel scene, and strong versus weak context, were only evident during slow presentation rates. These data suggest that it is the imagination of the associated scene information that leads to increased posterior PHG activity for strong context objects. One critique of this proposal was that the novel scenes comprised real world stimuli that may have been reminiscent of a location visited by the participant and therefore activated associated spatial information that increased the level of activity in the posterior PHG (Epstein et al., 1999). A more stringent

test, therefore, would be to compare activity for strong context objects versus geometric spatial scenes that are novel to the participant (such as computer generated scenes).

The aims of the experiment described in this chapter will be reviewed briefly. The experiment asked whether there was: 1) evidence of a division of labour in the MTL, with PRC and HC associated with object and scene processing, respectively, 2) significantly greater BOLD response in PRC and HC associated with increased object and scene overlap, respectively, 3) greater activity in posterior PHG for novel computer generated scenes relative to strong context objects, and if activity in this region was modulated by an object's spatial contextual association, and 4) evidence that PRC activity associated with high ambiguity objects could be explained in terms of subsequent memory for the items.

4.2. Method

4.2.1. Participants

Twenty-four participants (14 male) were scanned (mean age = 26.9 years; S.D. = 3.9). One participant's data was removed from the localiser task due to a scanning error, and one participant from the oddity task analysis due to excessive movement (>3mm). A computer error during the memory task meant that two further participants were removed from the subsequent memory analysis only (subsequent memory n = 21). All participants were right-handed native-English speakers with no self-reported neurological and/or psychiatric disorders and normal or corrected to normal vision. They provided written informed consent prior to the experiment and were paid £20 for their

participation. The experiment and its procedures received ethical approval from the Cardiff University School of Psychology Ethics Committee.

4.2.2. Experiment procedure and materials

4.2.2.1. "One-back" localiser task

The "one-back" localiser task described in this section was also used for the experiment outlined in Chapter 5. Participants viewed single items presented sequentially and were required to respond with a button press when they saw an immediate item repeat. Stimuli comprised: scenes (computer generated using the game Deus Ex, Ion Storm L.P., Austin, TX, USA, with software development package Deus Ex Software Development Kit v1112f); faces (created using FaceGen Modeller 3.3, Singular Inversions Inc); objects (chairs, acquired from Hemera object database Vol. 1-3); and scrambled objects. For the scenes, faces, and objects, there were 32 exemplars per class; for the scrambled objects there were 16 exemplars. All stimuli were orthogonal to those used in the oddity task.

During the task 192 items per class were displayed, drawn randomly from their respective sets. Items were presented in a blocked design, with 16 items per class presented per block. Images were presented for 200ms, with an ISI of 800ms, resulting in an individual block length of 16 seconds. There were 52 blocks in total. Blocks 1, 18, 35, and 52 comprised fixation crosshairs to allow the participant to rest or prepare for the upcoming experimental blocks. Blocks 2-17 followed the sequence objects/faces/scenes/scrambled objects (with this sequence repeated four times); blocks 19-34 followed the sequence scrambled objects/scenes/faces/objects (repeated four times); finally, blocks 36-51 followed the sequence scrambled objects/faces/scenes/objects (repeated

four times). Images were shown during scanning using Presentation (Neurobehavioral Systems, Albany, California, USA) software at a size of 400 by 400 pixels.

4.2.2.2. Oddity task

Subjects were scanned whilst they viewed a series of oddity discriminations. In each trial, three images were presented concurrently and comprised two examples of the same item and one different item. Participants were required to select the unique item from the array using a corresponding button-box response. Stimuli comprised: 1) strong context objects, 2) weak context objects (both as defined by Bar et al., 2003), 3) scenes, and 4) size (baseline). Within each stimulus class there was a manipulation of ambiguity defined as the amount of feature overlap between the odd item and its foils. In the low ambiguity (LA) trials the odd item was perceptually distinct and could be differentiated on the basis of a lower level feature, such as the shape or colour of the item (see below for further details). In the high ambiguity (HA) condition the target shared a number of overlapping features with its foils (see Figure 4.2). For both HA and LA trials, items were presented from different views. This resulted in eight conditions: 1) HA strong context objects, 2) LA strong context objects, 3) HA weak context objects, 4) LA weak context objects, 5) HA scenes, 6) LA scenes, 7) Difficult size, and 8) Easy size. Each item within the triad was approximately 125 by 125 pixels. All stimuli were trial-unique and presented on a white background.

There were 60 trials per condition and scanning was divided into three runs each comprising 160 trials; the location of the odd-item in the array was balanced within each condition and within each run. The presentation order of

trials within each of the three runs was pseudo-randomised so that no more than three trials of the same condition appeared in a row; run order was balanced across participants. Trials were presented for 5 seconds with a mean 1 second ISI resulting in a scanning run length of approximately 16 minutes.

4.2.2.2.1. Object oddity (strong and weak context)

Stimuli comprised colour objects from the Hemera object database Vol. 1-3. Strong and weak context object categories were defined using Bar et al.'s (2003) context functional localiser. For example, strong context items include 'oven', 'coffin', and 'tractor', whereas weak context items include 'bag', 'glass', and 'light bulb'. In instances where it was not possible to create oddity trials from a context category included in Bar et al.'s functional localiser, due to a lack of stimuli in the object database, other semantically related object categories were used. For example, there were too few items in the object database to create an oddity trial for Bar et al.'s strong context object 'roulette wheel'. An oddity trial using 'playing card' stimuli was used, therefore, as a semantically related replacement for this category. Object categories were matched across HA and LA conditions for both strong and weak context stimuli (e.g., for strong context objects there was a 'playing card' oddity trial in both the HA and LA conditions).

4.2.2.2.2. Scene oddity

LA scene oddity trials comprised images of real world scenes, such as parks, streets, rivers etc. (acquired by the experimenter) that could be differentiated on the basis of the objects contained within them (e.g., a different tree or building). HA scenes comprised computer generated rooms created using the game Deus Ex (Ion Storm L.P., Austin, TX, USA, with software

development package Deus Ex Software Development Kit v1112f). The odd scene differed due to the location of one component feature, for example a pillar or door. A similar approach to manipulating feature overlap in real world scenes versus computer generated was used in a recent paper that examined the contribution of MTL and extrastriate regions to the processing of scene stimuli (Mundy et al., 2012).

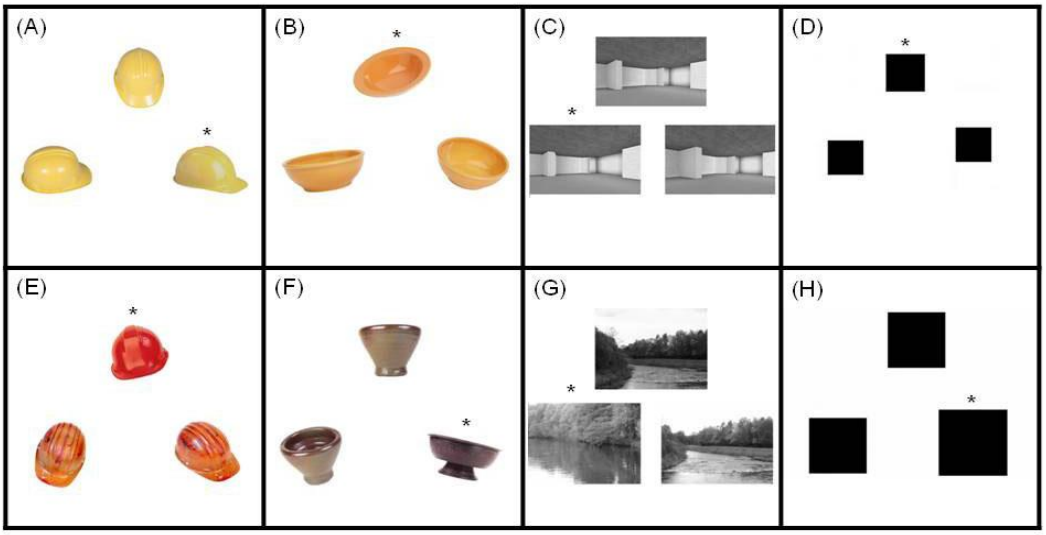

Figure 4.2. ***Examples of oddity trials - the top row comprise HA stimuli (A) strong context objects, (B) weak context objects, (C) scenes, (D) difficult size. The bottom row comprises corresponding LA categories (asterisk denotes odd item).***

4.2.2.2.3. Size Oddity (Baseline)

For the baseline task, black squares were presented in which the length of each side varied between 40 and 268 pixels. Two squares in the array were the same size whereas the third was a different size (either smaller or larger than the other two squares). For difficult size trials, the odd item differed

between 9 and 15 pixels; in the easy size trials it differed between 16 and 40 pixels, meaning it was easier to identify the uniquely sized item. Given that HA trials were necessarily more difficult than LA, it was important to have two different baselines to attempt to control for these differences in difficulty (see also the design of Barense et al., 2010). HA trials, therefore, were contrasted with difficult size trials whereas LA trials were contrasted with easy size trials.

4.2.2.3. Subsequent memory

Participants completed a surprise memory test outside of the scanner. They were presented with the odd items from the HA strong and weak context object trials (n=120) plus an equal number of semantically matched foils. Piloting had revealed that memory for the other conditions was at floor and these were not tested in an attempt to maximise performance on the HA object items.

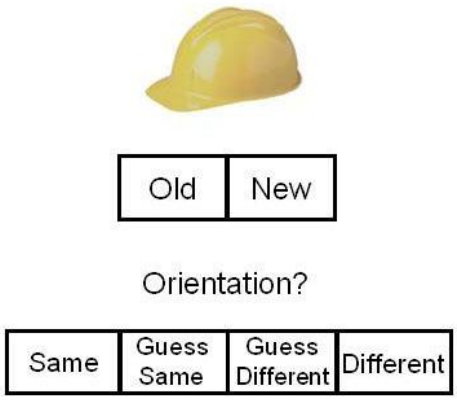

Figure 4.3. ***In the subsequent memory test, participants were presented with the individual odd items from the HA object trials presented in either the same, or different orientation to study. They were first required to make a binary 'old/new' decision, followed by a decision about the item's orientation relative to study.***

Individual object items were presented individually and, for half of the items, their orientation was manipulated so that they appeared the same as during the oddity task, or in a different orientation. The change in orientation was achieved by flipping the image on its horizontal plane, or, in the case of symmetrical items (e.g., a football), rotated. Participants made an initial 'old' or 'new' judgement for each item. If the item was designated 'old' they were then asked to judge its current orientation relative to presentation during the oddity task; response options comprised: 'Same', 'Guess same', 'Guess different' or 'Different'. Participants were instructed to only use the 'Guess' responses if they had absolutely no memory for the orientation of the stimulus (see Figure 4.3).

4.2.3. Analysis strategy

Analyses were conducted using two different approaches. Firstly, targeted contrasts between conditions of interest were used to examine different profiles of cluster-based activity at both the whole brain level, and within a bilateral probabilistic mask of the MTL (as used in Chapter 2). Secondly, the one-back localiser task was used to identify unbiased and orthogonal functional regions of interest (fROIs) within the MTL from which percent signal change values were extracted and subsequently tested using the statistics package SPSS (PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc.).

4.2.3.1. Data pre-processing

Unless stated otherwise, the pre-processing steps replicate those described in Chapter 3.

4.2.3.2. fROI one-back localiser

Four explanatory variables were used to model the localiser run comprising faces, objects, scenes, and scrambled objects.

To identify object sensitive fROIs, voxels that responded preferentially to object stimuli were identified via the contrast *'objects > faces + scenes + scrambled objects'.* Similarly, scene sensitive voxels were identified with the contrast *'scenes > faces + objects + scrambled objects'*. This approach has been used to identify stimulus specific regions in the visual cortex (Epstein & Kanwisher, 1998; Grill-Spector, Kourtzi, & Kanwisher, 2001; Kanwisher, McDermott, & Chun, 1997), but has more recently been adopted to examine stimulus specific perceptual (Lee & Rudebeck, 2010; Mundy et al., 2012; Mundy et al., 2013), and mnemonic effects (Watson, Wilding, & Graham, 2012) in the MTL. These analyses were constrained within a probabilistic MTL mask (described previously in Chapter 3). Group contrasts were thresholded liberally at Z > 1.64, uncorrected.

4.2.3.3. Oddity

Eight explanatory variables were used to model the HRF for each run of a participant's oddity data. These comprised correct responses to each condition (1) HA strong context objects, (2) LA strong context objects, (3) HA weak context objects, (4) LA weak context objects, (5) HA scenes, (6) LA scenes, (7) Difficult size, and (8) Easy size.

15 contrasts of interest were implemented. First, to examine evidence of stimulus specific activity, activity associated with all object and scene conditions was contrasted: 1) *'objects (HA strong context + LA strong context + HA weak*

context + LA weak context) > scenes (HA + LA)', 2) *'scenes (HA + LA) > objects (HA strong context + LA strong context + HA weak context + LA weak context)'*. Second, regions sensitive to the level of feature overlap for both objects and scenes, respectively, were examined: 3) '*HA (strong context objects + weak context objects) > LA (strong context objects + weak context objects)',* 4) '*LA (strong context objects + weak context* objects) > *HA (strong context objects + weak context objects)', (5) 'HA scenes > LA scenes',* (6) '*LA scenes > HA scenes'*. Third, to test whether spatial contextual association modulated the level of activity in posterior PHG, activity associated with strong context objects and weak context objects was contrasted: (7) '*strong context objects (HA + LA) > weak context objects (HA + LA)'*. Finally, to provide a rigorous test of the spatial layout versus contextual framework hypothesis, activity associated with HA strong context objects, and activity associated with HA scenes was contrasted: (8) '*HA strong context objects > HA scenes' (9) 'HA scenes > HA strong context objects'.*

Six contrasts of interest were implemented for the fROI analysis which comprised each condition contrasted to its appropriate difficulty baseline; (10) *'HA strong context objects > difficult size'*, (11) *'LA strong context objects > easy size'*, (12) *'HA weak context objects > difficult size'*, (13) *'LA weak context objects > easy size'*, (14) *'HA scenes > difficult size'*, and (15) *'LA scenes > easy size'*. The three runs for each participant were then combined using a fixed effects model.

Percent signal change values were extracted for contrasts 11-15, from each of the ROIs identified by the localiser for object and scene stimuli,

respectively. These values were entered into a ROI*Stimulus (strong context; weak context; scene)*Ambiguity (high; low) repeated measures ANOVA.

4.2.3.4. Subsequent memory

The HA object subsequent memory data were used to back sort oddity trials to examine both mnemonic and perceptual contributions to the BOLD signal in object-sensitive regions (Note, only HA object trials were used because piloting revealed that memory performance for LA objects and both HA and LA scenes was at floor). 12 EVs were used to model the subsequent memory trials. Trials were binned according to orientation presentation during test (same; different), item and source memory performance (hit-hit; hit-miss; miss), and confidence (confident; guess). Mnemonic accounts of MTL function suggest that activity associated with perceptual discriminations reflects incidental memory encoding. If this is true, then activity for both the hit-hit, and hit-miss categories should exceed the memory for those trials that were forgotten (misses). Analyses were limited to the confident (sure) responses only given that there were very few 'guess' responses.

4.3. Results

4.3.1. Behavioural data

4.3.1.1. Localiser

The number of "one-back" targets across the localiser task was randomly determined and on average there were 18.57 (S.D. = 4.24) targets per stimulus class. These were submitted to one-way, repeated measures ANOVA with four levels (faces; objects; scenes; scrambled objects), which revealed that the number of targets was matched ($F(3, 69) = 0.27$, $p = .85$).

Behavioural performance for each category was assessed via the relative frequency of hits (correctly identifying that an image had repeated) minus false alarms (FA, incorrectly indicating that an image had repeated) rate (see Table 4.1). These values were entered into a one-way repeated measures ANOVA with four levels (faces; objects; scenes; scrambled objects). Performance differed across the different stimulus types ($F(3, 66) = 19.23$, $p < .01$) resulting from significantly greater accuracy for objects relative to faces ($t(22) = 5.35$, $p < .01$), and scrambled objects ($t(22) = 6.62$, $p < .01$). "One-back" accuracy did not differ between faces and scrambled objects ($t(22) = 1.23$, $p = 1$). Accuracy for scene stimuli was better than accuracy for faces ($t(22) = 2.88$, $p = 0.05$) and scrambled objects ($t(22) = 4.72$, $p<0.01$). Finally, accuracy for objects was marginally better than for scenes ($t(22) = 2.89$, $p = .06$).

Table 4.1. ***Discrimination accuracy (as measured by p(hit)-p(FA) in one-back localiser task (parentheses contain SE of the mean) .***

Stimulus	Hit - FA
Objects	0.75 (0.04)
Faces	0.59 (0.04)
Scenes	0.67 (0.04)
Scrambles	0.54 (0.04)

4.3.1.2. Oddity

Participants' oddity performance was submitted to a two-way repeated measures ANOVA. The Stimulus (strong context objects; weak context objects;

scenes; size)*Ambiguity (high; low) ANOVA revealed a main effect of Stimulus ($F(3,66) = 21.47$, $p < .01$), Ambiguity ($F(1, 22) = 389.68$, $p < .01$) and an interaction between the two factors ($F(3, 66) = 7.69$, $p < .01$). The interaction stemmed from a difference in performance across stimulus type within both high ($F(3, 66) = 4.62$, $p < .01$) and low ($F(3, 66) = 51.45$, $p < .01$) ambiguity manipulations. For HA conditions, accuracy for scenes was significantly poorer than size ($t(22) = 2.93$, $p < .05$). For LA conditions, accuracy for scenes was significantly poorer than all other stimuli (all ts > 6, ps < .01), and performance for strong context objects exceeded that of size ($t(22) = 2.99$, $p < .05$). Importantly, all HA conditions were significantly more difficult than LA (ts > 10, ps < .01) (see Table 4.2).

Table 4.2. ***Proportion correct and mean RTs for all stimulus condition during oddity. (parentheses contain SE of the mean).***

Stimulus	Ambiguity	Accuracy	RT (ms)
Strong context objects	High	0.68 (0.02)	3167 (66)
	Low	0.98 (0.01)	1877 (73)
Weak context objects	High	0.69 (0.02)	2919 (66)
	Low	0.97 (0.01)	1908 (65)
Scenes	High	0.64 (0.03)	3684 (58)
	Low	0.85 (0.02)	2978 (80)
Size	Difficult	0.71 (0.02)	2428 (94)
	Easy	0.95 (0.01)	1729 (69)

Reaction times were submitted to the same analysis and revealed a main effect of Stimulus ($F(3, 66) = 350.73$, $p < .01$), Ambiguity ($F(1, 22)=1050.25$, $p < .01$) and a significant interaction between these two factors ($F(3, 66) = 35.99$, p

< .01). Again, the interaction stemmed from a different pattern of performance across stimulus type within HA (F(3, 66) = 184.89, p < .01) and LA conditions (F(3, 66) = 266.45, p < .01). For the HA conditions, responses were fastest for size trials, followed by weak context objects, strong context objects, and scenes (reaction times for all conditions were significantly different from one another; ts > 5, ps < .01). For LA conditions, responses to scenes were significantly longer than all other stimulus categories (ts > 20, ps <. 01), and responses to size trials were quicker than responses to weak context objects (t(22) = 3.33, p < .05). Again, reaction times to HA conditions were all significantly longer than LA conditions (ts > 11, ps < .01).

4.3.1.3. Subsequent memory

Item discrimination accuracy, calculated via p(hit) – p(false alarm) rate, was analysed first to determine whether memory performance differed across Context (strong context; weak context), or the Orientation of the item at test relative to study (same; different). A Context*Orientation ANOVA revealed that discrimination accuracy was better for strong relative to weak context objects (strong context: 0.52, SE = 0.3; weak context: 0.47, SE = 0.3; F(1, 20) = 4.88, p < .05) but was not affected by the orientation of the item at test, and these factors did not interact (Fs < .09, ps > .77). The hit rates for each condition were submitted to the same ANOVA and revealed a greater proportion of hits for strong context relative to weak context objects (strong context: 0.73, SE = 0.03; weak context: 0.67, SE = 0.03; F(1, 20) = 15.41, p < .01) but no difference in the false alarm rate across strong and weak context object foils (t(20) = 0.8, p = .43) (see Table 4.3).

Table 4.3. ***Proportion of correct responses to old items (hits), incorrect responses to new items (FA). Hit-hit shows the proportion of correct old items for which the participant also correctly remembered the orientation of the object item, and the proportion of those responses that were accompanied by a 'confident' response (parentheses contain SE of the mean).***

		Hits	False alarms	Hit-hit	Hit-hit Confident	Hit-miss Confident
Context	Orientation					
Strong	Same	0.74 (0.03)	0.22 (0.03)	0.65 (0.02)	0.85 (0.05)	0.76 (0.05)
	Different	0.74 (0.03)	0.22 (0.03)	0.56 (0.03)	0.81 (0.05)	0.80 (0.05)
Weak	Same	0.68 (0.03)	0.20 (0.02)	0.64 (0.04)	0.77 (0.06)	0.66 (0.07)
	Different	0.67 (0.03)	0.20 (0.02)	0.53 (0.03)	0.78 (0.05)	0.79 (0.05)

Source memory accuracy scores, calculated via (p(item hit-source hit)/p(item hit-source hit + item hit-source miss), were submitted to the same repeated-measures ANOVA. Source memory was reliably better when, at test, the item was presented in the same orientation as study (same: 0.65, SE = 0.2; different: 0.55, SE = 0.2; $F(1, 20) = 6.09$, $p < .05$). Furthermore, this was significantly greater than chance (0.5) for the 'same' ($t(20) = 5.98$, $p < .01$) but not 'different' ($t(20) = 1.88$, $p = .08$) orientation test items. Source memory for strong and weak context objects was matched, and there was no evidence of a Context*Orientation interaction (Fs < 0.3, ps > .59). Accurate source memory judgments were analysed according to the proportion of confident (as opposed to guess) responses, and revealed that participants were more confident in their accurate source judgments for strong relative to weak context objects (proportion of strong context source responses rated confident: 0.83, SE=0.43; weak context: 0.77, SE = 0.5). Examining the source responses for false alarms revealed a response bias for strong context objects; participants were more

likely to respond different rather than same (chance = 0.50; proportion of different responses for strong context objects: 0.60, SE = 0.05; $t(20) = 2.11$, $p < .05$), but this was not apparent for source responses to weak context objects (0.52, SE = 0.05; $t(20) = 0.37$, $p = .71$).

Reaction times for the item discrimination were entered into a Context (strong; weak)*Orientation (same; different)*Item accuracy (hit; miss) ANOVA. Participants' responses were significantly slower for hits, relative to misses (hit: 2487, SE = 201; miss: 2116, SE = 274; $F(1, 20) = 9.21$, $p < .01$); there were no other main effects or interactions between the other factors (Fs < 1.74, ps > .20) (see Table 4.4).

Table 4.4. ***Reaction times (ms) for hits, misses, and source accuracy broken down by confidence (parentheses contain SE of the mean).***

		Hit	Miss	Hit-hit		Hit-miss	
				Confident	Guess	Confident	Guess
Context	Orientation						
Strong	Same	2537 (265)	2275 (393)	764 (83)	769 (171)	1030 (85)	805 (181)
	Different	2482 (222)	2291 (389)	1005 (78)	1025 (232)	821 (76)	448 (116)
Weak	Same	2387 (203)	1849 (141)	866 (98)	797 (180)	1118 (174)	990 (179)
	Different	2541 (232)	2049 (292)	1030 (85)	985 (214)	1366 (475)	1153 (237)

Reaction times for the source memory decision were submitted to a Context (strong; weak)*Orientation (same; different)*Source accuracy (hit; miss)*Confidence (confident; guess) ANOVA. Source memory decisions were

quicker for strong relative to weak context objects (strong: 833ms, SE = 82; weak: 1038, SE = 96; $F(1, 20) = 6.87$, $p < .05$) and there was an interaction between Context and Source accuracy ($F(1, 20) = 4.25$, $p = .05$). Pair-wise comparisons revealed that strong context source misses were made more quickly than weak context source misses ('strong' context miss: 775ms, SE = 83; 'weak' context miss: 1157, SE = 147; $t(20) = 2.54$, $p < .05$). There were no other significant main effects, or interactions between factors (Fs < 2.48, ps > .12).

4.3.2. Imaging data

4.3.2.1. Whole brain analysis

Details of the whole brain analyses are contained in Appendix B. Briefly, the contrasts *'objects (HA strong context + LA strong context + HA weak context + LA weak context) > scenes (HA + LA)',* and *'scenes (HA + LA) > objects (HA strong context + LA strong context + HA weak context + LA weak context)'* revealed stimulus specific patterns of activity. Relative to scenes, objects were associated with increased BOLD signal in the lateral occipital cortex, which has been implicated in object processing (Grill-Spector et al., 2001; Kourtzi & Kanwisher, 2001), and this activity extended into bilateral PRC. In contrast, scenes were associated with a network of regions involved in spatial processing, including the lingual gyrus (Menon, White, Eliez, Glover, & Reiss, 2000), posterior PHG, with activity extending into posterior HC. Increasing the level of feature overlap between objects resulted in increased activity in extrastriate lateral occipital cortex. For scenes, relative to LA items, HA items were associated with increased activity in posterior PHG, whereas the reverse of this contrast was associated with increased activity in lingual gyrus.

Contrasting activity associated with *'strong context objects > weak context objects'* revealed clusters in bilateral occipital pole leading into the lateral occipital cortex. There was also evidence of increased activity in the lingual gyrus and posterior PHG for strong context relative to weak context objects. Activity in similar regions (i.e., posterior PHG/lingual gyrus, and posterior HC) was greater for HA scenes compared to HA strong context objects. The reverse of this contrast revealed increased PRC activity associated with HA strong context objects relative to HA scenes.

4.3.2.2. MTL effects

The same analyses were conducted within a probabilistic mask of the MTL (see Figure 4.4, with local maxima detailed in Table 4.5). Relative to scenes, objects were associated with increased activity in the PRC. Scenes, however, were associated with increased activity in the posterior PHG. Increasing feature overlap, for both objects and scenes, was not associated with increased activity in the MTL. Relative to HA objects, however, LA objects were associated with increased anterior HC activity, whereas as LA scenes were associated with increased posterior PHG and posterior HC activity. Contrary to predictions, no regions of the MTL were associated with greater activity for *'HA scenes > HA strong context objects"* the reverse of this contrast, however, was associated with greater activity in anterior HC.

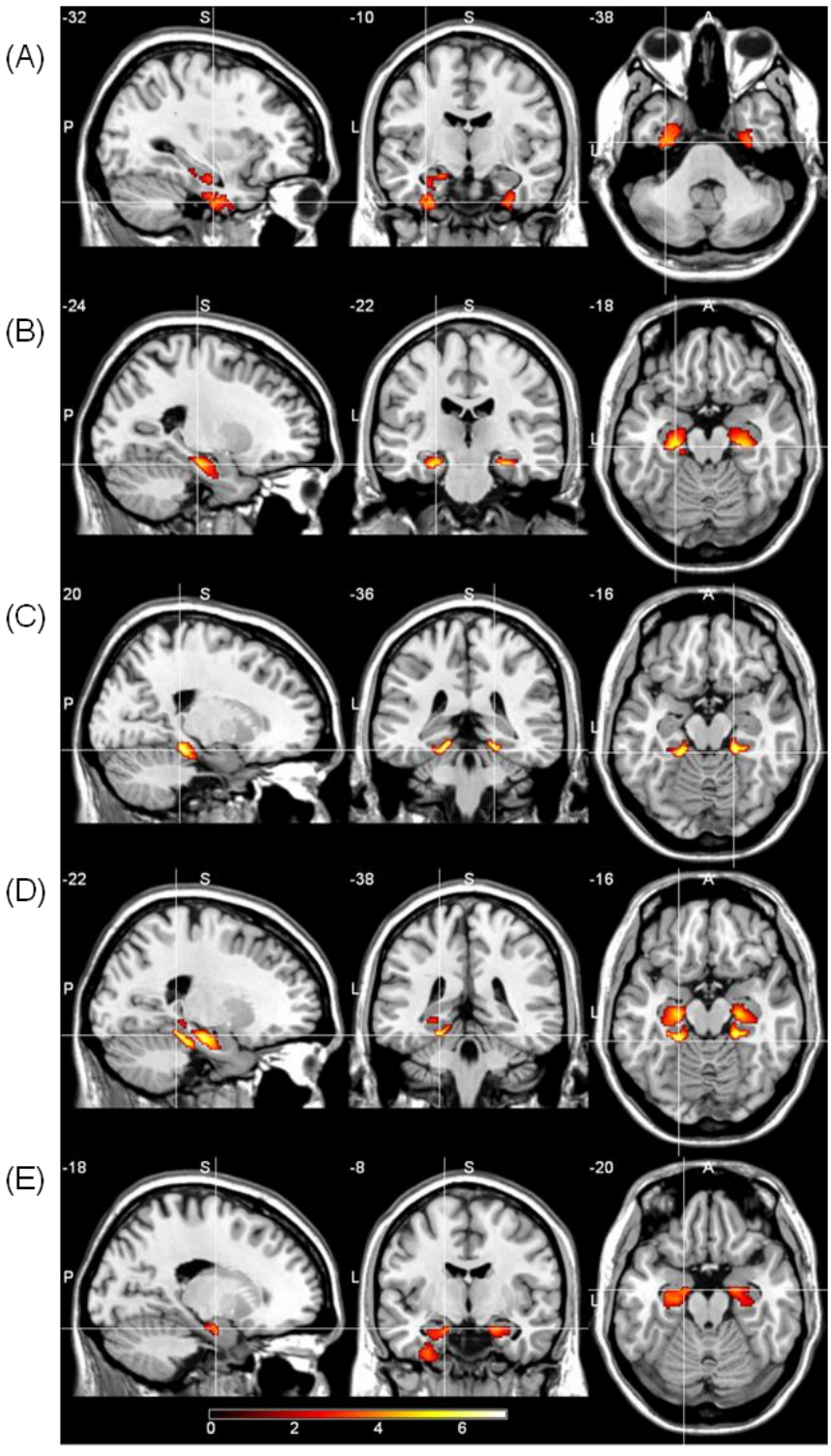

Figure 4.4. ***(A) 'Objects > scenes', (B) 'LA objects > HA objects', (C) 'Scenes > Objects', (D) 'LA scenes > HA scenes', (E) 'HA strong context objects > HA scenes'.***

Table 4.5. ***Local maxima in MTL associated with experimental contrasts.***

Region	Z	*x*	*y*	*z*
'Objects > scenes'				
Left perirhinal cortex	4.45	-32	-10	-38
Right perirhinal cortex	3.8	30	-8	-38
Left parahippocampal gyrus, posterior division	2.94	-30	-26	-16
Left anterior hippocampus	4.19	-20	-10	-18
Left temporal pole	2.79	-28	8	-28
'LA objects > HA objects'				
Left parahippocampal gyrus, posterior division	6.23	-22	-38	-16
Right parahippocampal gyrus, posterior division	6.41	20	-34	-18
Left hippocampus	3.75	-32	-28	-14
Right hippocampus	6.03	22	-16	-20
'Scenes > objects'				
Right parahippocampal gyrus, posterior division	6.15	20	-36	-16
Left parahippocampal gyrus, posterior division	6.12	-16	-38	-12
'LA scenes > HA scenes'				
Left parahippocampal gyrus, posterior division	5.26	-24	-22	-18
Right parahippocampal gyrus, anterior division	5.18	24	-20	-20
Left hippocampus	2.95	-24	-10	-28
Right hippocampus	4.22	28	-12	-24
'HA strong context objects > HA scenes'				
Left hippocampus	4.15	-18	-8	-20
Right hippocampus	4.29	22	-8	-20
Left temporal fusiform cortex, anterior division	3.87	-30	-8	-40

4.3.2.3. Localiser fROIs

To identify voxels sensitive to object stimuli, the contrast *'objects > faces + scenes + scrambled objects'* was implemented. It revealed two clusters of activity; one located in left PRC, and one in left PHG (see Figure 4.5). Scene-sensitive voxels, derived from the contrast *'scenes > faces + objects + scrambled objects',* were identified in bilateral posterior HC and bilateral posterior PHG (see Figure 4.7).

4.3.2.4. Oddity

4.3.2.4.1. Object fROIs

Percent signal change values were extracted for each of the six contrasts and entered into a fROI (left PRC; left PHG)*Stimulus (strong context; weak context; scenes)*Ambiguity (high; low) ANOVA. A significant ROI*Stimulus*Ambiguity interaction ($F(2, 44) = 19.91$, $p < .01$) led to investigation of effects within each of the two ROIs.

In the left PRC there was a main effect of Stimulus ($F(2, 44) = 31.22$, $p < .01$) and an interaction between Stimulus and Ambiguity ($F(2, 44) = 3.32$, $p < .05$). For HA conditions, the BOLD response differed across the different contexts ($F(2, 44) = 20.08$, $p < .01$) with significantly greater activity associated with strong context objects relative to weak context objects ($t(22) = 4.35$, $p < .017$; Bonferroni correction = .05/3 $\alpha = .017$) and scenes ($t(22) = 5.50$, $p < .017$); activity associated with weak context objects was also greater than scenes ($t(22) = 2.86$, $p < .017$). For LA conditions, again there was a significant difference in neural activity associated with the different contexts ($F(2, 44) = 23.24$, $p < .01$). Greater activity was associated with both strong and weak

context objects relative to scenes (both $t(22) > 4.8$, $p < .017$). Activity for strong and weak context LA objects, however, did not differ ($t(22) = 0.70$, $p = .49$). Contrasting activity between the HA and LA conditions revealed marginally greater activity associated with HA strong context objects relative to LA weak context objects ($t(22) = 2.03$, $p = .05$); the BOLD response for HA relative to low ambiguity scenes, and weak context objects, did not differ across levels of ambiguity ($t(22) < 1.90$, $p > .07$) (see Figure 4.6).

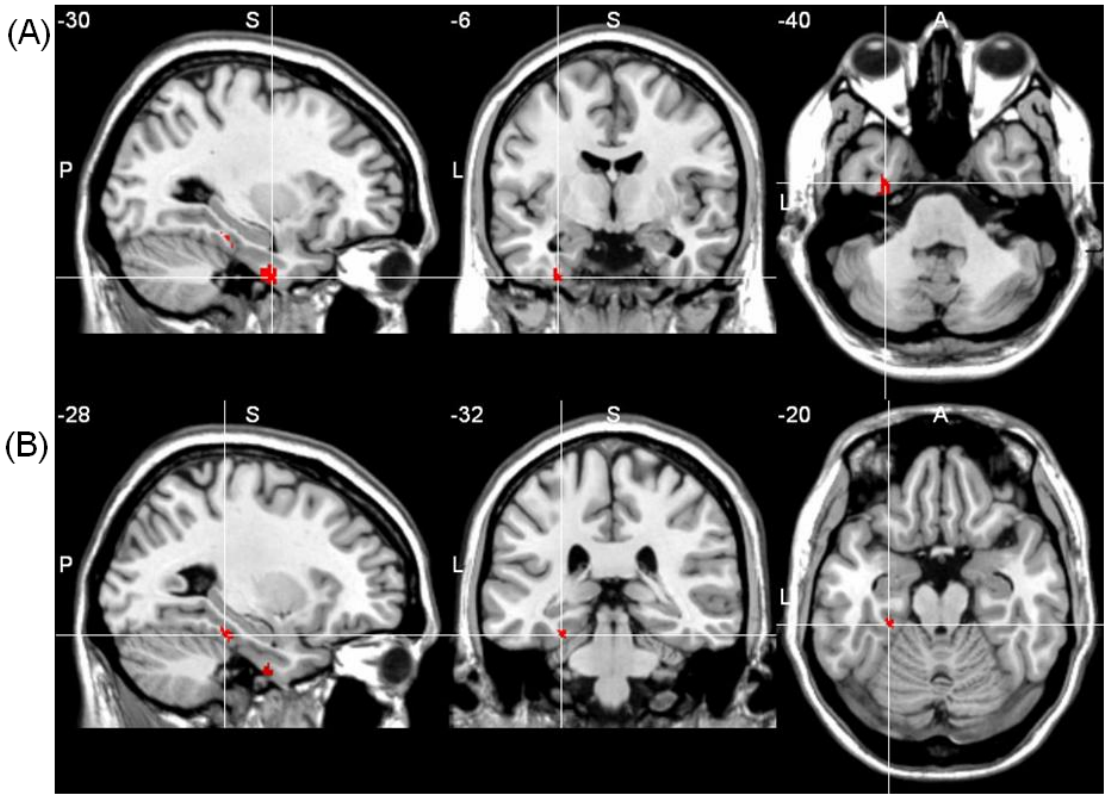

Figure 4.5. ***Object sensitive fROIs (A) left PRC (67 voxels), (B) left PHG (24 voxels).***

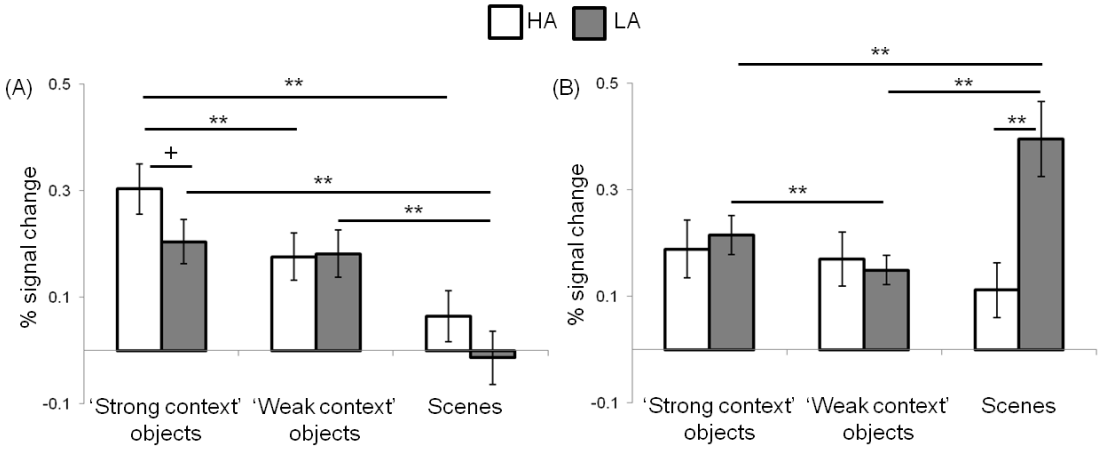

Figure 4.6. ***Percent signal change values for oddity task extracted object sensitive fROIs (A) left PRC, and (B) left posterior PHG fROIs; ** = p < .017; + = p = .05.***

The same analyses were conducted for the left posterior PHG fROI and revealed main effects of Stimulus ($F(2, 44) = 4.47$, $p < .05$) and Ambiguity ($F(1, 22) = 8.42$, $p < .01$) and a significant interaction between these two factors ($F(2, 44) = 18.99$, $p < .01$). The interaction resulted from a difference in the BOLD response in the LA ($F(2, 44) = 16.84$, $p < .01$), but not HA ($F(2, 44) = 2.22$, $p = .12$) conditions. For LA conditions, scenes elicited the largest change in signal relative to strong context objects ($t(22) = 3.84$, $p < .01$; Bonferroni correction = .05/3 α = .017) and weak context objects ($t(22) = 4.05$, $p < .017$); in turn, the BOLD response for strong context objects was greater than weak context objects ($t(22) = 2.70$, $p < .017$). Testing for differences in signal between HA and LA conditions revealed greater activity associated with LA scenes relative to HA scenes ($t(22) = 6.05$, $p < .017$); there was no effect of ambiguity manipulation for strong and weak context objects (ts < 0.65, ps > .55).

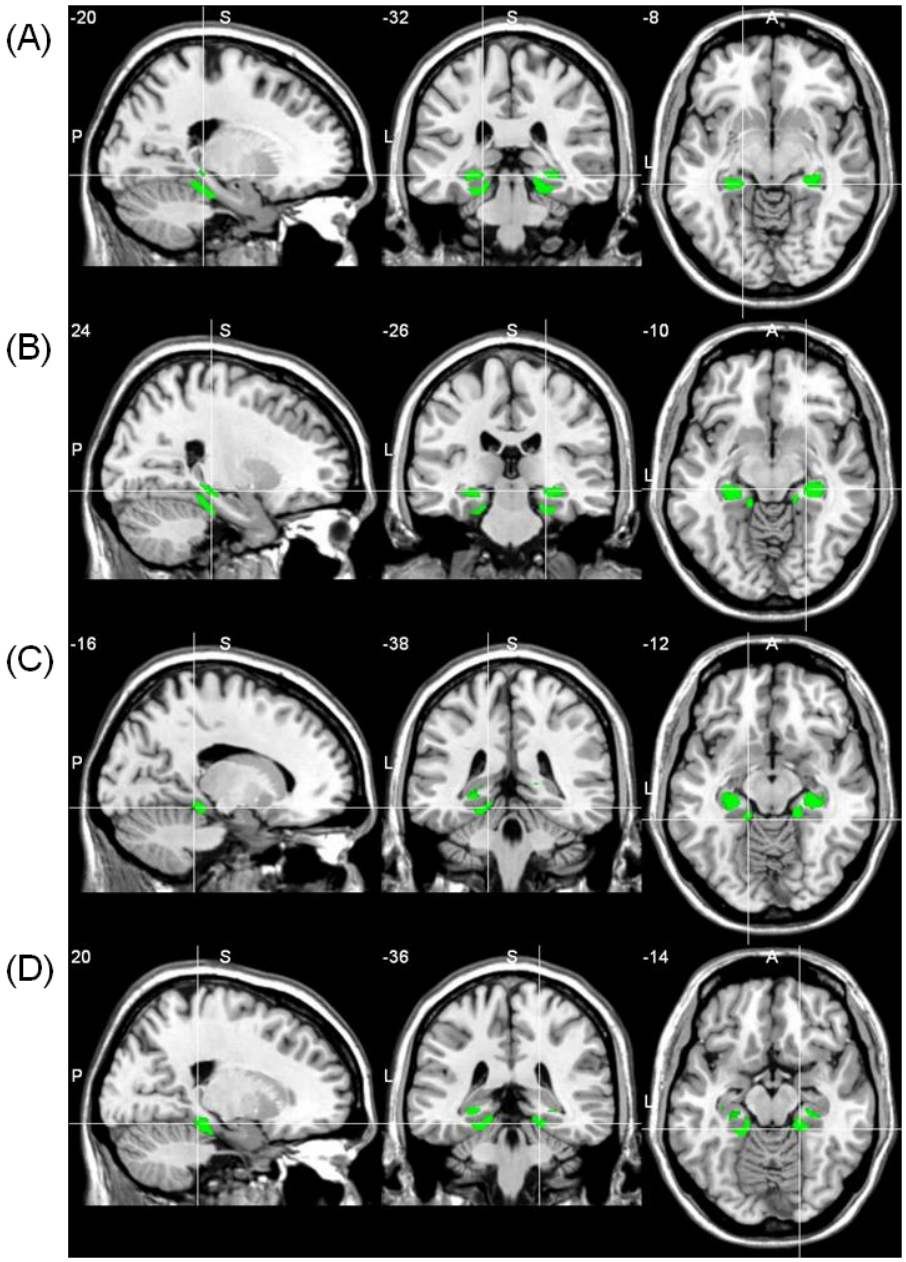

Figure 4.7. ***Scene sensitive fROIs (A) left posterior HC (167 voxels), (B) right posterior HC (143 voxels), (C) left posterior PHG (140 voxels), and (D) right posterior PHG (131 voxels).***

4.3.2.4.2. Scene fROIs

The three-way fROI (left HC; right HC; left PHG; right PHG)*Stimulus (strong context; weak context; scenes)*Ambiguity (high; low) repeated measures ANOVA revealed a significant interaction between the three factors ($F(6, 132) = 13.99$, $p < .01$). Each individual fROI, therefore, will be considered separately (see Figure 4.8).

In the left HC, there was a marginal interaction between Stimulus and Ambiguity ($F(2, 44) = 2.91$, $p = .07$), resulting from a different profile of BOLD response across stimuli in the LA conditions ($F(2, 44) = 4.42$, $p < .05$). Significantly greater activity was associated with scenes relative to weak context objects ($t(22) = 2.83$, $p < .017$; Bonferroni correction = .05/3 α = .017); the neural response did not differ between the other conditions (ts < 2.1, ps > .17).

In the right HC, the BOLD response was modulated by Stimulus ($F(2, 44) = 9.66$, $p < .01$); the main effect of Ambiguity, and the interaction between Stimulus and Ambiguity, did not reach significance (Fs < 2.5, ps > 0.1). The main effect of Stimulus resulted from significantly greater activity associated with scenes relative to strong context ($t(22) = 2.67$, $p < .017$; Bonferroni correction = .05/3 α = .017) and weak context objects ($t(22) = 3.90$, $p < .017$); percent signal change values for strong and weak context objects were equivalent ($t(22) = 1.87$, $p = .08$).

In the left PHG there was a main effect of Stimulus ($F(2, 44) = 41.78$, $p < .01$), Ambiguity ($F(2, 44) = 21.27$, $p < .01$) and an interaction between these factors ($F(2, 44) = 18.47$, $p < .01$). Follow up analyses revealed that the interaction stemmed from a difference in percent signal change values in the LA

(F(2, 44) = 62.80, p < .01) but not HA (F(2, 44) = 2.29, p = .11) conditions. In the LA conditions, significantly greater neural response was associated with scenes relative to strong context (t(22) = 10.09, p < .017; Bonferroni correction = .05/3 α = .017) and weak context objects (t(22) = 7.86, p < .017); there was no evidence of a modulation in BOLD response for strong versus weak context objects (t(22) = 1.35, p = 0.19). The level of ambiguity modulated activity for scenes only, with significantly greater activity associated with LA relative to HA scenes (t(22) = 7.13, p < .017); HA and LA strong and weak context objects did not differ (ts<1.27, ps > .22).

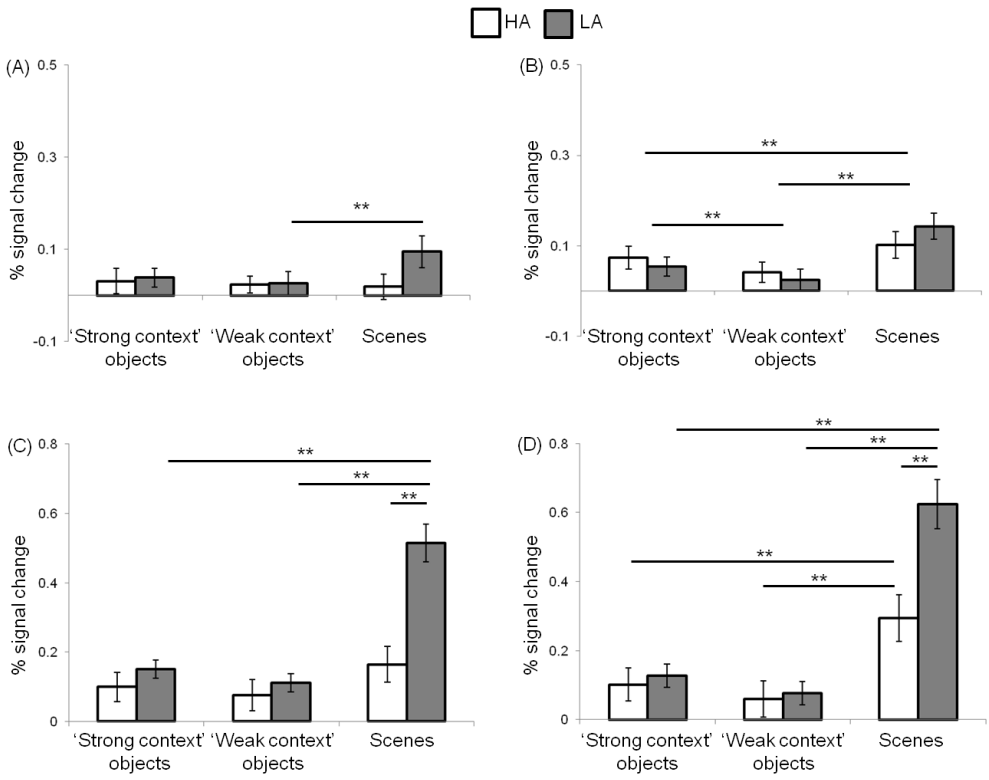

Figure 4.8. ***Percent signal change values for oddity task extracted from scene sensitive fROIs (A) left posterior HC, (B) right posterior HC, (C) left posterior PHG, and (D) right posterior PHG fROIs. ; ** = p < .017.***

A different pattern of BOLD response was evident in the right PHG. There was a main effect of Stimulus ($F(2, 44) = 67.23$, $p < .01$), Ambiguity ($F(1, 22) = 17.56$, $p < .01$) and a significant interaction between the two factors ($F(2, 44) = 14.90$, $p < .01$). In contrast to the left PHG, however, there was a significant modulation of percent signal change for both HA ($F(2, 44) = 13.61$, $p < .01$) and LA ($F(2, 44) = 71.75$, $p < .01$) conditions in the right PHG. For both HA and LA conditions, significantly greater activity was associated with scenes relative to strong context and weak context objects (ts > 3.89, ps < .01). Furthermore, there was no difference in the level of activity associated with strong context and weak context objects (ts < 1.8, ps > .26). For scenes, pair-wise comparisons revealed significantly greater activity associated with LA relative to HA conditions ($t(22) = 6.42$, $p < .01$); there was no modulation of BOLD response according to ambiguity in the left PHG for strong context or weak context objects (ts < 0.69, ps > .50).

In summary, for object-sensitive fROIs, in left PRC there was an interaction between ambiguity and contextual association for objects, with the highest level of activity being associated with HA strong context objects. The BOLD response associated with objects in left posterior PHG was modulated by an item's contextual association; larger percent signal change values were associated with strong context relative to weak context objects. In scene-sensitive fROIs, in right HC greater neural activity was associated with scenes relative to objects, and the neural signal for objects was modulated by contextual association with greater signal for strong, relative to weak context objects. In right posterior PHG, there was a stimulus specific pattern of data with the largest BOLD response associated with LA scenes relative to all other conditions; HA scenes also elicited greater activity than both object categories.

In left HC the effects were less prominent - there was a small (but significant) difference between LA scenes and LA weak context objects. Finally, in left posterior PHG, the strongest response was associated with LA scenes, relative to all other conditions.

4.3.2.5. Subsequent memory

Dual process accounts of memory propose that subsequent memory performance may explain stimulus specific MTL activity; for example increased activity in the PRC associated with objects may reflect better subsequent memory for those items. To test whether the subsequent memory status of the object item could explain the BOLD response in the left PRC fROI, percent signal change values were submitted to a Stimulus (strong context; weak context)*Orientation (same; different)*Memory (hit-hit; hit-miss; miss) ANOVA. First, there was a marginal main effect of Memory ($F(2, 40) = 2.74$, $p = .08$); follow up comparisons, however, did not reveal any differences in BOLD response associated with subsequent memory performance (ts < 2.04, ps > .17). Mirroring the oddity data, there was a main effect of Stimulus resulting from significantly greater activity associated with strong context relative to weak context objects ($F(1, 20) = 7.15$, $p < .05$). There was also an interaction between Orientation and Memory ($F(1, 20) = 5.13$, $p < .05$), reflecting greater activity associated with hit-miss responses when (at test) items were presented in a different orientation to study ($t(20) = 3.34$, $p < .017$; Bonferroni correction = .05/3 α = .017). There was a trend towards the opposite pattern for hit-hit responses, with significantly greater activity associated with items that were presented in the same orientation at study and test ($t(20) = 2.25$, $p = .04$). Follow up one-way ANOVAs for ‘same’ and ‘different’ orientation across

memory performance (hit-hit; hit-miss; miss) revealed a significant main effect for the different orientation items ($F(2, 40) = 4.23$, $p < .05$). Follow up comparisons, however, revealed that the greater BOLD signal associated with hit-miss trials, relative to hit-hit and miss, did not survive Bonferroni correction ($t(20) = 2.29$, $p = .03$; $t(20) = 2.30$, $p = .03$, respectively) (see Figure 4.9).

The same analyses were conducted for the left posterior PHG fROI and revealed a significant Orientation*Memory interaction ($F(2, 40) = 5.07$, $p < .05$), resulting from greater BOLD response associated with hit-miss trials in the 'different' relative to 'same' orientation ($t(20) = 2.74$, $p < .017$; Bonferroni correction = .05/3 α = .017).

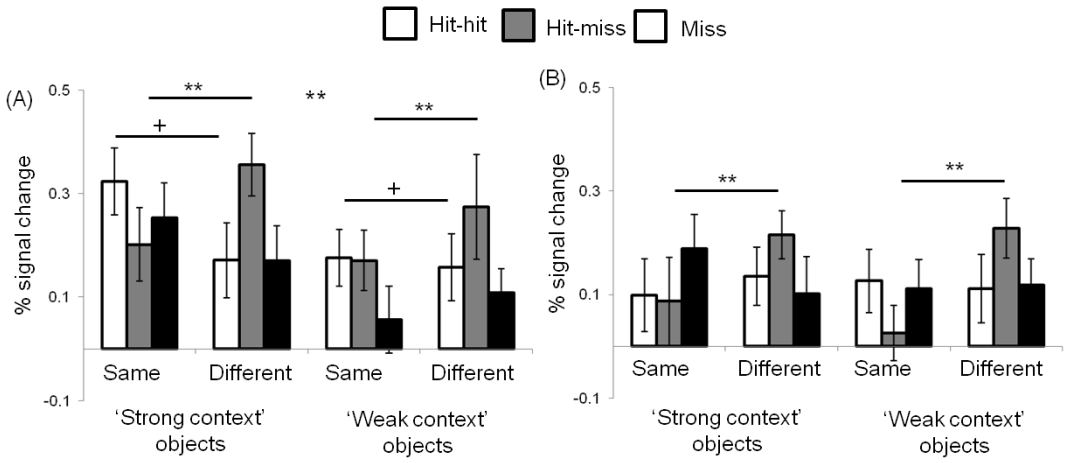

Figure 4.9. ***Percent signal change values for HA object oddity trials, binned according to subsequent memory performance, extracted from object-sensitive fROIs (A) Left PRC, and (B) Left PHG fROI; ** p< .017; + p = .04.***

4.4. Discussion

The experiment outlined here was designed to test a number of predictions from representational accounts of memory. First, it asked whether

the level of BOLD response in PRC correlates with the degree of feature overlap in objects in an oddity task. Although this has been tested previously (Barense et al., 2010; Devlin & Price, 2007), studies have confounded an increase in feature overlap (from LA to HA) with a corresponding change in viewpoint. This means it has not been possible to determine which of these manipulations places the most demand on PRC. Second, the experiment investigated whether a similar pattern of data was evident in HC for scene stimuli. It has been demonstrated that patients with HC damage show impairments when discriminating pairs of scenes that have been morphed to contain a large number of overlapping features (Lee et al., 2007; Lee, Bussey, et al., 2005); no fMRI studies, however, have demonstrated an increase in BOLD response in HC associated with greater feature overlap of scenes. Third, the experiment allowed comparison of the level of activity in posterior PHG associated with scene processing relative to objects that have strong spatial contextual associations. The 'context framework' hypothesis, that provides support for the BIC model, proposes that the level of activity in PHC should be equivalent for these two categories of stimuli. EMA, on the other hand, suggests that PHC processes scene stimuli primarily.

4.4.1. The role of the PRC in solving feature ambiguity

EMA and the representational-hierarchical account of MTL function propose that PRC supports object-level, conjunctive representations (Graham et al., 2010; Saksida & Bussey, 2010). According to these views, greater demand is placed on PRC when there is a requirement to discriminate between two object items that share a number of overlapping features (i.e., high ambiguity). In the experiment described here, activity for HA and LA object trials

was contrasted, with the prediction that the HA trials should be associated with greater activity in PRC. This main effect of ambiguity, however, was not obtained. Instead, there was an interaction between ambiguity and context with significantly greater activity associated with HA strong context objects relative to HA weak context objects; the level of BOLD response for HA weak context objects and LA weak context objects did not differ (the interaction between ambiguity and contextual association is discussed in Section 4.4.2). These data are surprising given the impairments evident in patients with damage to PRC on a very similar oddity task using familiar object stimuli (Barense et al., 2007). Furthermore, a recent study that manipulated the feature overlap of novel object pairs found increased activity in PRC associated with HA relative to LA trials (Barense et al., 2012).

There are at least three possible reasons for the discrepancy between the current data and previous findings. First, while the familiar object oddity task used in the current study was very similar to the oddity task that found deficits in patients with damage encompassing the PRC, the two paradigms differed in the number of items shown concurrently on each oddity trial; there were four items in the patient study (Barense et al., 2007) but only three in the current imaging task. It has been proposed that the role of the PRC is to form distinct object-level representations that buffer against interference from other visually similar items (e.g., Barense et al., 2012; McTighe, Cowell, Winters, Bussey, & Saksida, 2010). One potential explanation, therefore, is that by using fewer items in each trial there was relatively less demand on the PRC. This raises an interesting question with regards to the nature of object interference, particularly whether it operates within an oddity trial, as is being proposed here, or across trials, as has been demonstrated previously (Barense et al., 2012).

Second, in Barense et al. (2012), increases in feature overlap were found to modulate activity in PRC; unlike the current study, however, their LA condition did not contain objects presented from different views. Participants completed a 'same/different' discrimination in which item pairs were presented and the level of feature overlap between items was manipulated (HA: ABC vs ABD; LA: ABC vs DEF). In the low ambiguity condition, therefore, the participant viewed two distinct objects that shared no overlapping features. In the study described here, however, the foils in the low ambiguity condition comprised two images of the same object presented from different views, which may have led to increased levels of activity in PRC even for low ambiguity trials. Changes in viewpoint have been associated with increased levels of BOLD response in PRC (Barense et al., 2010; Devlin & Price, 2007), and damage to this region impaired the ability of monkeys to discriminate object pairs when presented in a different view at test, relative to study (Buckley & Gaffan, 1998). In the current study, it seems highly plausible that the presentation of an object from different views (i.e., the foils in the low ambiguity condition) resulted in the formation of a flexible representation of this item and therefore increased PRC activity.

Third, in the current study, the BOLD response associated with familiar objects, which have semantic associations, may have masked any effects of feature overlap. The anterior temporal lobe, including PRC, has been implicated in conceptual/semantic processing (Patterson, Nestor, & Rogers, 2007). Barense et al. (2011) found that greater activity in bilateral PRC was associated with familiar (real-world) object oddity trials, relative to novel (fribble) object oddity trials. It was proposed that the conceptual information associated with the familiar objects modulated the level of activity in this region. In the current study, therefore, even the low ambiguity objects would have associated conceptual

information, which may have resulted in increased BOLD response in PRC and consequently masked any effects of feature overlap. This confound was avoided in Barense et al. (2012) by using novel 'blob' stimuli for which the participant would have little prior knowledge meaning the only difference between the two conditions was the level of feature overlap. For considerations as to how contextual association may be tested in future experiments see Section 6.3.1.

4.4.2. The PRC and context

A novel finding of the fROI analysis was the interaction between the level of feature overlap, and the strength of spatial contextual associations, with significantly greater activity in left PRC associated with high ambiguity, strong context objects. Although it was predicted that contextual association would modulate activity in PHC, a main effect of ambiguity was predicted for PRC, and it was not thought that an object's contextual association would influence activity in this region. Some reasons for this finding are now considered. The 'context framework' hypothesis, proposed by Bar and colleagues (Bar, 2004), suggests that rapidly determining the spatial context of an item allows for representations of objects associated with that context to be activated, thereby, speeding their identification. One possible explanation for increased BOLD response in PRC associated with the strong context objects, therefore, is that it reflects the imagination of related object items. For example, seeing a roulette wheel may evoke thoughts of a deck of cards, a card table, a croupier etc. This explanation would be consistent with predictions of EMA and BIC, as both models predict that the PRC can support memory for associated object items,

and that activation in PRC would be positively related to the number of objects associated semantically with another item.

It is also possible that the increased activity in PRC may reflect imagination of spatial contextual information for the strong context objects. Hannula, Libby, Yonelinas, and Ranganath (2013) presented unique object-scene pairs that participants were required to remember. At test, either the object or the scene from the pair was presented as a cue and the participant was required to retrieve the associated item and make a confidence judgment about the strength of the recovered memory (whether the memory for the associated item would be classed as 'familiar' or if the participant could 'recollect' the associate). Contrary to predictions of EMA, activity in PRC was equivalent for both objects and scenes. Furthermore, contrary to predictions of BIC, relative to familiar responses, recollect responses for either the associated object (from the scene cue) or the associated scene (from the object cue) resulted in significantly greater PRC activity. Given the direct cortical connections between PHC and PRC (Suzuki & Amaral, 1994), it was suggested that recovery of the scene associate in PHC may lead to reinstatement of this representation in PRC. In the current study, increased PRC activity associated with the strong context objects might, therefore, reflect recovery of associated spatial contextual information. It should be noted, however, that, contrary to Hannula et al. (2013), in the current study there was evidence of domain specificity in the PRC with greater activity associated with objects (both HA and LA, strong context and weak context) relative to scenes.

If the increased activity in PRC associated with HA strong context objects reflects the activation of a greater number of associated object items, greater

conceptual information about the items and/or recovery of spatial context, a logical question is why this effect was only evident in the HA condition. Given that reaction times were longer for the HA relative to LA condition, this may be explained in terms of increased opportunity for top-down processing. Epstein and Ward (2010) scanned participants whilst they presented stimuli, with either strong or weak contextual associations, at two different speeds. When the stimuli were presented rapidly, there was no modulation of strong relative to weak contextual association on the BOLD response. At longer presentation speeds, however, there was a significant effect of contextual association, with greater activity associated with strong relative to weak context items. It was suggested that the increased presentation time allowed the participant greater opportunity to elaborate about the stimuli and imagine contextual associations. In the current study, the longer responses to the HA trials may have provided more opportunity for the participant to bring to mind contextual information associated with the strong context stimuli.

4.4.3. How does this activity relate to mnemonic accounts of MTL function?

Given that the MTL has classically been implicated in declarative memory, evidence of increased activity in this region associated with perceptual discriminations has been explained in terms of subsequent memory for those items (e.g., Lee et al., 2006). For example, BIC could explain increased PRC activity associated with object perceptual discriminations as being driven by subsequent memory for the items.

In an effort to address this in the current study, a subsequent memory task was used to assess the memory activity associated with the high ambiguity objects. Importantly, there was no evidence of a simple mapping of memory

strength to the level of BOLD activity (i.e., hit-hit => hit-miss > miss) in the PRC. These data suggest, therefore, that the MTL activity evident during perceptual discriminations cannot be explained simply in terms of mnemonic processes and may implicate these regions in perceptual processing also. One potential caveat here is that the initial 'old/new' decision comprised a binary response (i.e., there was no item confidence measure), and therefore the BOLD signal may have been contaminated by low confidence and 'guess' responses for both hits and misses. This would necessarily provide a noisier measure and therefore make potential differences between memory conditions more difficult to detect. This aside, the current data replicate previous findings where above baseline activity in PRC associated with objects is evident even when these items have been weakly remembered or forgotten (Barense et al., 2011).

Consistent with the oddity data, in the subsequent memory data there was a main effect of context in left PRC with greater activity associated with strong relative to weak context objects. As the behavioural data suggested better memory for the strong versus weak context items, the increased BOLD response in left PRC for strong context objects may reflect processes that lead to better subsequent memory for these items. Analysis of the miss trials, however, suggests that this context effect occurs independently of an item's subsequent memory status. A pair-wise t-test revealed significantly greater percent signal change associated with miss trials for strong relative to weak context objects ($t(20) = 2.43$, $p < .05$). In short, the subsequent memory data suggest that activity in PRC cannot be accommodated easily by an incidental encoding interpretation.

4.4.4. The HC and spatial processing

At the whole brain level, contrasting activity for '*scenes* > *objects*' revealed significantly greater BOLD response in posterior HC. This pattern of data was confirmed in the fROI analysis with significantly greater activity associated with scenes relative to objects in the right HC, whilst in the left posterior HC greater activity was associated with scenes relative to weak context objects.

The finding that the HC is preferentially involved in scene processing replicates the findings in a number of imaging and patient studies (e.g., Barense et al., 2010; Lee et al., 2007; Lee et al., 2008; Lee, Buckley, et al., 2005, 2006; Pengas et al., 2010), and supports the notion of a division of labour within the MTL according to the category of stimulus-to-be-processed. Comparing the results of the experiment described here in relation to those discussed in Chapter 3 might suggest that the increased demand to form an allocentric representation of the scenes (by changing the viewpoint) engages HC processing, and this is consistent with the findings from a number of studies (Bird & Burgess, 2008; Byrne et al., 2007; Hartley & Harlow, 2012; Hartley et al., 2007). It is not clear, however, whether the increased HC activity reflects the demand for allocentric spatial processing, or the requirement to form and maintain a greater number of spatial feature conjunctions relative to real world scenes presented from the same view (i.e., in Chapter 3). As discussed in Section 2.4, it has been proposed that the HC is required to support complex spatial feature conjunctions, and that presenting scenes from a different view (as in the current experiment) places greater demand on these conjunctions in order to form a flexible representation of the environment (Lee et al., 2012). The

data outlined in this Chapter are consistent with both arguments (i.e., allocentric processing versus spatial feature conjunctions) but will be considered in relation to the findings of Chapter 2 in Section 6.3.2.

It is also notable that the manipulation of feature overlap did not support our predictions; significantly greater activity was associated with LA relative to HA scenes as evidenced in the cluster analysis constrained by the MTL mask. The difference in stimulus class (real world versus computer generated) may explain this effect. First, the real world scenes may have provided a richer spatial environment and therefore resulted in increased HC activity. Second, as the real world scenes contained objects, activity here may not only reflect the processing of spatial feature conjunctions but also the processing of objects-in-place which has been shown to be sensitive to HC function (e.g., Duncan, Ketz, Inati, & Davachi, 2012; Hannula & Ranganath, 2008). Related to this point, it may be that because they comprised more individual features, the real world scenes required more 'relational' processing, which has also been ascribed to the role of the HC (Dusek & Eichenbaum, 1997; Konkel, Warren, Duff, Tranel, & Cohen, 2008). It must be noted, however, that the HC is not responsible for relational processing *per se*; in Chapter 2 patients with HC damage showed learning impairments for scenes but not objects even though they comprised the same number of constituent features. One possibility, therefore, is that rather than reflecting domain-general stimulus complexity, increases in HC activity reflect increases in scene complexity. Finally, there is a possibility that the real world scenes may be more likely to remind the participant of events from their past, and therefore the increased activity reflects activation of associated memory during the task. It must be noted, however, that in the scene-sensitive fROI in right posterior HC, there was a main effect of stimulus

class that did not interact with ambiguity. Specifically, greater activity was associated with scene stimuli (real world scenes = computer generated) relative to both strong context and weak context object conditions. This suggests that this region of posterior HC may be sensitive to processing of complex spatial conjunctions regardless scene content (i.e., object-full in the real-world scenes or empty in the computer generated ones). Consistent with EMA, the role of the posterior HC, therefore, may be to form conjunctions of complex spatial features that provide the perception of a spatially coherent environment.

4.4.5. The role of the posterior PHG in spatial/contextual processing

A point of divergence between representational accounts and BIC/context framework hypothesis is the role of the posterior PHG in spatial processing. The context framework account proposes that this region processes spatial context (i.e., both scenes, and individual object items with strong spatial contextual associations). This model predicts, therefore, that the level of activity should be equivalent for these two categories of stimuli (Aminoff, Kveraga, & Bar, 2013; Bar & Aminoff, 2003; Bar, 2004). The spatial layout hypothesis, however, proposes that the primary role of the posterior PHG is to process scene geometry. Modulations of activity in this region may be evident if an item has strong associations with scene information (i.e., in the case of a familiar landmark). This level of activity, however, is still less than that associated with the processing of scenes. For the current study, therefore, the context framework account would predict equivalent activity for scenes and strong context objects, which in turn should be greater than items with weak contextual associations. The spatial layout hypothesis would predict the greatest level of activity in the posterior PHG for scenes relative to both object categories; spatial

contextual association for objects may modulate activity, however, because it activates representations of spatial information (see Section 1.4.2.1).

Consistent with the spatial layout hypothesis, when contrasting '*scenes* > *objects*' there was significantly greater posterior PHG activity, and this was consistent even when contrasting activity associated with novel computer generated scenes (HA), for which there would be no contextual associations, with HA strong context objects. Similarly, for the fROI analysis, in right posterior PHG both computer generated and real world scenes elicited greater activity than object categories. It must also be noted that in the whole brain analysis there was a small but significant modulation of activity in the posterior PHG associated with strong context relative to weak context objects.

These data suggest that the posterior PHG primarily processes scene geometry; activity, however, may be modulated according to an item's spatial association. These findings are reminiscent of those in the object-scene association experiment described above (Hannula et al., 2013). In their study, there was evidence of a domain-specific effect in posterior PHG with greater activity associated with scenes compared to objects. The level of activity in this region associated with objects, however, was modulated by the strength of memory for the associated scene; greater activity was evident in posterior PHG when participants reported that they could 'recollect' the scene associate rather than feeling that the associated scene was 'familiar'. This could be interpreted in terms of the strength of contextual association; objects with strong contextual associations (recollect) elicit greater activity in posterior PHG than those with weak contextual associations (familiar), but both of these are less than activity associated with the scene cues. Supporting our findings, these data suggest

that the posterior PHG processes primarily spatial geometry but activity in this region can be modulated for object stimuli if there is a strong association with spatial information.

The task demand in the experiment described in this Chapter is different to that employed by Bar et al. (2003) and it could be argued that this explains why posterior PHG activity was not modulated by contextual association. In Bar et al. (2003) participants either passively viewed stimuli or pressed a button when they had identified them. The oddity task, however, encourages participants to look for differences between concurrently presented stimuli. It is possible that attentional resources were being directed to detecting the odd item rather than elaborating about the stimuli. There are at least two reasons, however, why this might not be the case. First, for LA object stimuli, the odd item was visually distinct which led to short reaction times and presumably little demand for the participant to study the items in more detail. As a result, the LA object conditions were very similar to the Bar et al. paradigm and yet there was no manipulation of context in these conditions. Second, the context framework hypothesis suggests that the identification of the context develops almost with immediate onset of the stimulus; task demand, therefore, should be irrelevant.

4.5. Summary

The current experiment provides support for the notion of a division of labour in the MTL according to the stimulus type to-be-processed with greater activity associated with objects and scenes in the PRC and HC, respectively. Contrary to predictions, for objects there was no main effect of ambiguity in the PRC. Instead, there was an interaction between ambiguity and contextual association, with HA strong context objects associated with the highest level of

activity in this region. This pattern of data, however, could not be explained easily in terms of incidental encoding. For scenes, LA items were associated with greater activity than HA items in both left and right posterior HC. This pattern of data may reflect the greater number of spatial feature conjunctions in the real world scenes relative to the computer generated scenes. Contrary to the context framework hypothesis the posterior PHG appears exquisitely sensitive to scene geometry but can show modulation of activity if there is a strong spatial contextual association.

Chapter 5: Scene processing as a marker of increased genetic risk of developing Alzheimer's disease

5.1. Introduction

The experiments in this thesis have found evidence of a discrimination learning, and perceptual discrimination impairment for scenes in patients with focal HC damage (Chapters 2 and 3), and evidence of a partial fractionation of the MTL according to the type of stimulus to-be-processed, with activity in the PRC (Chapters 3 and 4) and HC (Chapter 4), being associated with perceptual discriminations of object and scene stimuli, respectively. These studies are valuable in developing strong and predictive theoretical accounts of how the brain supports memory and perception and this increased knowledge also provides an opportunity to understand better the nature of the behavioural impairments that can ensue when these structures are affected in neurological diseases. The earlier chapters focused on neuropsychological studies involving patients with damage to the HC from anoxia and encephalitis, but there are also key implications of such findings for neurodegenerative disorders, such as Alzheimer's disease (AD). In particular, given the increased longevity of the population and predicted increases in the prevalence of dementia in future years, a key question in the field is whether cognitive paradigms can be applied to the early identification of those individuals at risk of developing the disease. Prior to outlining the key aims of the experiment reported here, I will provide some background to AD, focusing on early detection of the disease, including genetic markers of increased risk.

AD is a neurological disorder characterised by progressive neurodegeneration of the cortex, associated with beta-amyloid deposition, and neurofibrillary tangles (Braak & Braak, 1991; Chesser, Pritchard, & Johnson, 2013; Gilbert, 2013; Mucke, 2009; Ramachandran & Udgaonkar, 2013). The disease is associated with global cortical atrophy, including that of MTL regions. Preceding the disease state is a presymptomatic stage called Mild Cognitive Impairment (MCI). In MCI, patients do not fulfil criteria for AD but have some mild changes in cognitive performance (Petersen, 2004), which may be limited to memory (amnestic MCI), or include deficits in memory and at least one other cognitive domain (amnestic MCI multiple domain) (Petersen et al., 2001). Consistent with mnemonic accounts of MTL function, impairments in declarative memory are common early in MCI and AD (for review, see Salmon, 2000). Spatial processing deficits, however, are also a common feature of the disease, and a large proportion of patients demonstrate problems navigating both familiar and unfamiliar environments (Lithfous, Dufour, & Després, 2013; Monacelli, Cushman, Kavcic, & Duffy, 2003; Pai & Jacobs, 2004). Formal testing has revealed that both MCI and AD patients show significant difficulties in remembering previously travelled routes (DeIpolyi, Rankin, Mucke, Miller, & Gorno-Tempini, 2007). Participants completed a novel circuit of a hospital ward. Subsequently, they were required to navigate the route again (both forwards and backwards), draw a map of it, identify images of landmarks that they had passed, and place these landmarks in the order in which they were encountered on the route. Relative to age-matched controls, both MCI and AD patients made significantly more errors when retracing the route (regardless of direction). Furthermore, they were less accurate when drawing a map of the circuit, and

could not place the landmarks in the correct temporal order. They showed spared recognition, however, for the items that they had encountered.

This navigational deficit was replicated using a virtual reality route (Cushman, Stein, & Duffy, 2008), and extended to show that patients demonstrate particular difficulties in forming associations between images of scenes and the spatial location of these images. Participants viewed ten images of objects or location from the novel route and were required to indicate on a map where these photos had been taken (photo location). Similarly, they viewed short video clips of the route and had to indicate on a map the location in which these clips had been filmed, and the direction in which the camera had travelled (video location). In a factor analysis, both photo location and video location subtests accounted for the most variance in MCI and AD patients' performance. It was suggested, therefore, that AD-related neurodegeneration impairs patients' abilities to form bound representations of scene images and spatial locations, which may support allocentric processing of spatial environments (Hort et al., 2007; Laczó et al., 2010; Laczó et al., 2009).

As has been discussed throughout this thesis, research has suggested that the role of the MTL may not be limited to supporting declarative memory, and that the PRC and HC also support perception under conditions of high ambiguity. An interesting question, therefore, is whether MCI and AD patients would also show difficulties on tasks that extend to perceptual discrimination, consistent with the findings in patients with static lesions of the MTL. This question has been investigated using a topographical memory task that required patients to remember the spatial arrangement of four mountain components of a scene (Bird, Chan, et al., 2010; Hartley et al., 2007). In the

perceptual discrimination condition, the target image was presented above the same target image (presented from a different viewpoint) along with three foils (see Figure 5.1). Although this task is reminiscent of the oddity tasks used in this thesis and in a number of previous studies, it differs in that there is a target item presented alongside a number of comparison stimuli. In the memory condition the target image was presented briefly prior to the presentation of the comparison stimuli. Both MCI and AD patients were impaired on the scene memory condition but showed spared performance in the perceptual discrimination condition. The absence of an effect in the perceptual condition, however, may have resulted from the small sample size and therefore a lack of power to detect a group difference. Supporting this assertion, when replicated in a larger sample, both MCI and AD patients showed impairments in the perception condition (Pengas, Patterson, et al., 2010b). These data suggest that patients with AD, or probable AD, show deficits in scene memory/perception, consistent with the theoretical arguments being proposed as part of this thesis.

A further study provides a clearer indication of the specificity around the scene difficulties evident above (Lee, Buckley, et al., 2006). Similar to the oddity task used in Chapter 4, four images (computer generated scenes or faces) were presented concurrently. Three of the images were of the same face or scene presented from different viewpoints, whilst the fourth was a similar but different item; the participant was required to select the odd-one-out (see Figure 5.1). In one condition, all items were presented from the same view, in the other all items were presented from different views. Relative to healthy controls, AD patients were impaired when discriminating scenes, regardless of the viewpoint manipulation. This deficit, however, was specific to scene stimuli; AD patients'

performance matched controls for the face stimuli even when presented from different viewpoints. This scene-specific impairment in AD was replicated using a discrimination learning paradigm (Lee et al., 2007). Participants viewed pairs of distinct images (scenes, faces, objects, or colour blocks) in which one of the items was arbitrarily designated correct. Over subsequent trials pairs of images were presented that comprised morphs of the two original stimuli; the pairs varied in difficulty so that the images either shared very few overlapping features, or a high degree of overlapping features. Patients with AD discriminated object, face, and colour items, even when the pair of items had been morphed together at the highest level. Performance for scenes, however, was significantly poorer than controls at even the lowest level of morphing, and this deficit was apparent throughout the rest of the trials on this condition (see Figure 5.1).

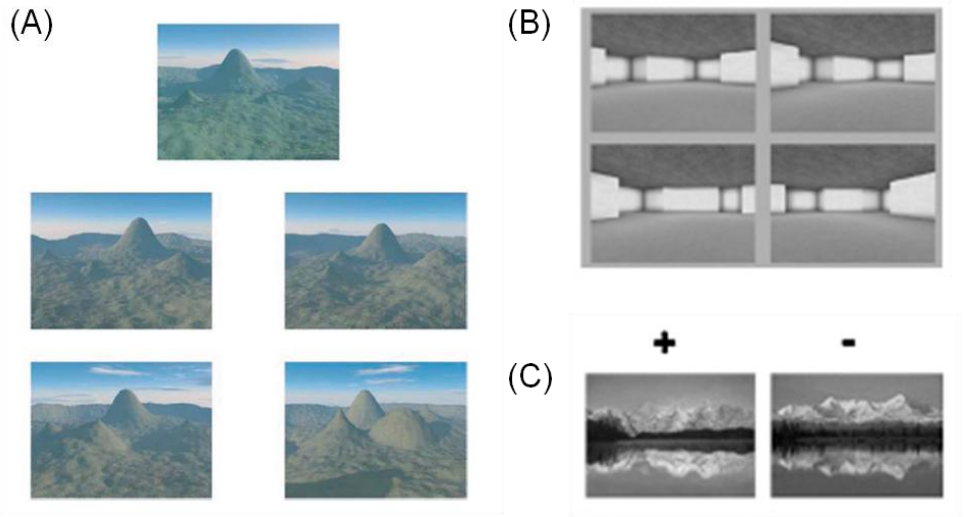

Figure 5.1. ***Examples of stimuli from neuropsychological tasks that have revealed spatial processing deficits in patients with MCI or early AD. (A) topographic matching task (Hartley, Bird et al., 2007), (B) scene oddity (Lee, Buckley et al., 2006), and (C) scene discrimination learning (Lee et al., 2007).***

Although later manifest disease is associated with global cortical atrophy, including significant atrophy of MTL regions, earlier in AD there is evidence of more focal brain alterations, often in advance of behavioural impairments. The posterior cingulate cortex (PCC) is one such region that shows changes (Baron et al., 2001; Chételat et al., 2002; Scahill, Schott, Stevens, Rossor, & Fox, 2002), and focal atrophy of PCC is predictive of progression from MCI to AD. For example, a group of 56 patients with MCI, and an age-matched control group, had structural scans and were then followed up for approximately three years to identify participants who did (progressive MCI) and did not (stable MCI) later develop AD (Hämäläinen et al., 2007). During the follow up period, 13 of the MCI sample progressed to develop AD. Comparing atrophy in the progressive MCI patients relative to the stable MCI patients revealed greater focal atrophy in the PCC and precuneus for the progressive MCI patients. This pattern of data was replicated in a study using a within-subjects design using a smaller sample of 18 MCI patients, seven of whom later progressed to AD (Chételat et al., 2005). Again, participants were scanned at the beginning of the study but they were also scanned at the end of the study (after 18 months) meaning that within-subject comparisons of grey matter density could be made between the scans at the start of the study relative to the end. For the progressive MCI patients, relative to the start of the study, greater grey matter atrophy was evident in PCC, precuneus, and PHG. Increased atrophy in the PCC for progressive MCI patients was again confirmed in a larger sample using a ROI analysis strategy (Pengas, Hodges, et al., 2010). The PCC, HC, and anterior cingulate were identified in each MCI patient's scan and the level of atrophy assessed. Relative to controls, there was significantly greater atrophy of the PCC and HC. This atrophy, however, was not global; grey matter volume of

the anterior cingulate did not differ between patients and controls. These grey matter structural changes mirror the findings of positron emission tomography (PET) studies in which glucose metabolism has been found to be significantly reduced in the PCC in both MCI (Nestor, Fryer, Ikeda, & Hodges, 2003; Nestor, Fryer, Smielewski, & Hodges, 2003) and AD patients (Minoshima, Foster, & Kuhl, 1994; Nestor, Fryer, Smielewski, & Hodges, 2003).

The PCC is one of the most heavily interconnected structures of the brain. For example, in an analysis of the default mode network (DMN - a network of regions in which there is highly correlated BOLD response when there is no explicit cognitive demand, Raichle et al., 2001), BOLD signal in the PCC and anterior medial prefrontal cortex correlated strongly with a number of other regions in the network, and these two regions were considered “hubs” due to their extensive connectivity (Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010; Buckner et al., 2009). Moreover, the degree of cortical connectivity within these hub regions has been shown to correlate with the level of beta-amyloid deposition in MCI and AD (Buckner et al., 2009; Klunk et al., 2004).

de Haan, Mott, van Straaten, Scheltens, and Stam (2012) developed a computational model to explain why these regions of high connectivity may be particularly vulnerable to AD pathology. Using neural mass models, the authors created a network that mirrored the structural topology of the brain. The network was then lesioned by adding random degeneration (RD) to circuits across the brain, or activity dependent degeneration (ADD), in which the level of damage within a region was based on the level of activity within local neurons. Relative to RD, ADD led to greater reductions in connectivity throughout the network.

Furthermore, measuring the spike density within hub regions, ADD led to an initial increase in firing of neurons followed by a rapid decline in spike density within neurons, and connectivity across the network. It was proposed, therefore, that increased neuronal activity in the DMN (as evidenced through increased BOLD response in imaging) may contribute to rapid degeneration of heavily inter-connected hub regions of the brain (e.g., the PCC). It was hypothesised that this increased brain activity in itself is toxic to neurons, but also contributes to the accumulation of beta-amyloid resulting in aberrant neuronal activity and consequently further cell damage. Parietal hub areas, including the PCC, may be particularly vulnerable to pathological processes because, as they are some of the last brain regions to develop, they have thinner myelination (Jacobs, Van Boxtel, Jolles, Verhey, & Uylings, 2012).

Of relevance to this thesis, and linking together the behavioural impairments and the focal brain damage predictive of conversion from MCI to AD, is that the PCC forms a connection between the posterior parietal lobe and the MTL (Kravitz, Saleem, Baker, & Mishkin, 2011). This pathway has been implicated in spatial attention (Small et al., 2003), and shifting between egocentric spatial representations in the posterior parietal cortex to allocentric spatial representations supported by the HC in the MTL (Vogt, Finch, & Olson, 1992). The role of the PCC in spatial processing, therefore, accords with the spatial behavioural deficits that have been observed prior to, or early in AD (Bird et al., 2010; Cushman et al., 2008; deIpolyi et al., 2007; Hort et al., 2007; Laczó et al., 2010; Laczó et al., 2009; Lee et al., 2006, 2007; Monacelli et al., 2003; Pengas, Hodges, et al., 2010); and may be attributable to functional and/or structural changes in this region.

The studies described thus far have focused on the early behavioural changes that might be associated with AD. A more recent approach, aiming to ask whether brain changes can be seen many years in advance of the onset of AD, has focused on whether differences in brain activity can be elicited using brain imaging in individuals who are considered to be at increased genetic risk for AD. Recent genome-wide association studies (GWAS) have identified a number of genetic variants that seem to map onto AD risk (e.g., presenilin 1 and clusterin; for review, see Hollingworth, Harold, Jones, Owen, & Williams, 2011), but the strongest genetic marker for AD is Apolipoprotein E (ApoE) (Kamboh et al., 2012). The ApoE allele is coded on chromosome 19 and has three isoforms (e2, e3, and e4). It is involved in the transport of cholesterol to neurons via ApoE receptors (Liu, Kanekiyo, Xu, & Bu, 2013), synaptogenesis (Han & Bondi, 2008), and aids in the brain response to injury (Poirier & Sévigny, 1998). The e4 allele is associated with increased risk of both early and late-onset AD (Barral et al., 2012; Chartier-Harlin et al., 1994; Houlden et al., 1998), and critically, there is a dose-response effect of the allele with carriers of two e4 alleles at greater risk of developing AD than carriers of one allele (Corder et al., 1993). The ApoE-e4 allele is associated with greater levels of beta-amyloid deposition (Kok et al., 2009; Namba, Tomonaga, Kawasaki, Otomo, & Ikeda, 1991), and poorer cognitive performance later in life (Caselli et al., 2004).

PET studies comparing glucose metabolism in ApoE-e4 carriers and non-carriers have found strikingly similar results to those from MCI and AD patients. Relative to age-matched non-carriers, healthy older-adult ApoE-e4 homozygotes showed decreased metabolism in the PCC and lateral temporal cortex (Reiman et al., 1996). This pattern was also found in the same regions for healthy older adults who carried a single ApoE-e4 allele (Small et al., 2000).

Furthermore, there was evidence of a dose-response effect in healthy older adult carriers of the ApoE-e4 allele with greater decreases in glucose metabolism in a network of regions including the PCC in carriers of two copies of the ApoE-e4 allele relative to carriers of one allele (Reiman et al., 2005). These effects, however, were not limited to older-adults; young adult (20-39 years old) ApoE-e4 heterozygotes showed reduced metabolism in the PCC relative to non-carriers (Reiman et al., 2004).

Consistent with the findings using PET, fMRI studies have found differences in the BOLD response between young healthy ApoE-e4 carriers and non-carriers. During study of novel blocks of animal and scene stimuli, carriers of the ApoE-e4 allele showed increased BOLD response in posterior HC and retrosplenial cortex (Filippini et al., 2009). Similarly, in a working memory task that required participants to indicate the immediate repeat (one-back) of an object in a specific grid location, ApoE-e4 carriers showed increased neural activity in a network of regions including the precuneus and the cingulate cortex (both posterior and anterior) (Filbey, Slack, Sunderland, & Cohen, 2006). Furthermore, carriers of the ApoE-e4 allele were shown to have increased connectivity between the PCC and HC during an object memory task (Dennis et al., 2010). These studies suggest that young adult carriers of the ApoE-e4 allele show increases in neural activity.

There is evidence that the direction of the BOLD effect changes over the course of the lifespan (Filippini et al., 2011), and this may result from the activity-related neural degeneration discussed earlier (Buckner et al., 2009; de Haan et al., 2012). Specifically, relative to age-matched non-carriers, young ApoE-e4 carriers show increases in neural activity, whereas older adult carriers

show decreases in activity. One hypothesis for the change in direction of the ApoE-e4 effect on neural activity (increases when young, but decreases when old) is that this reflects increased neural effort to maintain 'normal' cognitive performance that eventually leads to neural degeneration of the same regions in old age (Filippini et al., 2011). Alternatively, Jagust and Mormino (2011) propose that ApoE-e4 carriers may have lower cognitive reserve (factors such as neural efficiency thought to protect against the effects of pathology) meaning that beta-amyloid deposition has a more detrimental effect on carrier's cognitive abilities. As a compensatory mechanism for this low cognitive reserve, ApoE-e4 carriers show increased BOLD response even before there are any signs of AD pathology. The additional burden of beta-amyloid accumulation, combined with low cognitive reserve, however, leads to a rapid decline of neuronal function and cognitive abilities.

Despite the relative consistency of the direction of the BOLD effect in young ApoE-e4 carriers (i.e., increases in neural activity for carriers relative to non-carriers), there have been instances where young ApoE-e4 carriers do not show increases in BOLD response (for review, see Trachtenberg, Filippini, & Mackay, 2012). One potential reason for this discrepancy is that the effect is modulated by the task employed. A number of experiments that have found an effect of ApoE status on neural activity have used cognitive tasks that require the maintenance of spatial information, for example remembering a scene or an object in a specific spatial location. Greater activity was evident in ApoE-e4 carriers during the first run of a memory task that required participants to imagine a face and associated verbal information in a scene representation (Mondadori et al., 2007). This effect, however, was not replicated when a simple pleasant/unpleasant judgment was required about the faces. Similarly, a

working memory task (“2-back”) undertaken in the same study using single letters did not differentiate between ApoE-e4 carriers and non-carriers. It is possible that spatial processing demand may be an important factor in eliciting differences in ApoE-e4 carriers and non-carriers.

The notion that tasks placing greater demand on spatial processing may be more sensitive to differences in ApoE status was supported in a study that used a scene memory, and a verbal stroop task (Trachtenberg, Filippini, Cheeseman, et al., 2012). In the scene memory task, participants were presented with grey-scale scenes and performed a subsequent memory test outside of the scanner. Contrasting activity for scenes that were subsequently remembered between carriers and non-carriers resulted in significantly greater activity in a network of regions for the ApoE-e4 carriers. The greatest neural response was in a cluster comprising bilateral occipital cortex, superior parietal cortex, precuneus and PCC. In the same experiment, the verbal stroop task again revealed greater activity in the ApoE-e4 carriers but in fewer regions than the episodic memory task. Moreover, in regions activated consistently across both tasks (i.e., the PCC and precuneus), the level of BOLD response associated with scene memory was greater than that associated with the stroop task.

There are at least two possible reasons for the discrepancy between the magnitude of effects in these two studies. One possibility is that the ApoE-e4 allele disproportionately affects episodic memory rather than executive function (as indexed by scene memory and the stroop task, respectively), and therefore the scene memory task is more sensitive to differences in ApoE status. This interpretation is consistent with the episodic memory deficits seen early in AD.

An alternative interpretation, however, is that ApoE status affects some types of stimuli more than others, and that tasks that place demand on scene processing, in particular, are more likely to elicit differences in BOLD response. Again, this interpretation would be consistent with the spatial processing deficits evident in MCI and AD patients. A task that allowed comparison of activity across a number of different stimuli classes in one experiment would provide further insight into this issue.

The work carried out in this thesis, in particular where I was interested in the networks underpinning scene stimuli, provides a useful way to address outstanding questions in this field. In particular, there is a need for studies in which the BOLD response elicited in young healthy ApoE-e4 carriers and non-carriers in response to different categories of stimuli is compared. This would allow us to determine whether the effects in risk carriers are cognitively specific (e.g., particularly affect scene stimuli). This was accomplished in the experiment described here, in which participants were separated according to e4 presence/absence, by applying an oddity task comprising scenes, faces, objects, and size discrimination

Consistent with the analyses and theme of this thesis, contrasts were made between different categories of stimuli to identify stimulus specific regions in the MTL across the entire sample. In line with the results of Chapter 4, it was predicted that objects would be associated with significantly greater activity in PRC whereas scenes would be associated with greater activity in posterior PHG and HC. To address differences in neural activity associated with genetic risk of AD (i.e., the presence of the ApoE-e4 allele) I first used a localiser task (comprising scenes, faces, objects, and scrambled objects) to identify regions of

significant difference in BOLD response between the two ApoE groups. These group differences were then used as fROIs to interrogate data from the oddity task. Based on previous literature, it was predicted that ApoE-e4 carriers would show increased BOLD response most prominently in the PCC compared to non-carriers. Furthermore, given the selective behavioural deficits early in AD, this activity should be most evident for scene stimuli, but not in other conditions tested in the oddity task.

5.2. Method

5.2.1. Participants

A large sample of (mainly) first year undergraduates was genotyped for ApoE using a cheek swab. Based on genotype status, a subset of 30 participants was selected to form two groups matched for age, education, and gender. Fifteen participants carried one ApoE-e4 allele (these participants comprised the allele combination e3-e4, and will be referred to as ApoE-e4 carriers throughout this Chapter); the remaining fifteen comprised any other combination of ApoE alleles (predominantly e3-e3; these will be referred to as non-carriers throughout this Chapter).

These 30 participants (28 female; mean age = 19.7 years; S.D. = 0.8) were scanned on a series of imaging tasks and given a number of complementary behavioural tasks. The researchers collecting and analysing the data (including myself) were blind to the ApoE status of the participants. All were right-handed native-English speakers with no self-reported neurological or psychiatric disorders and normal or corrected to normal vision. All participants gave written informed consent prior to the experiment and were paid £20 for

their participation. The experiment and its procedures received ethical approval from the Cardiff University School of Psychology Ethics Committee.

In this Chapter, data from two of the imaging tasks is reported: a localiser and an oddity task. These tasks were selected as they are consistent with tasks used elsewhere in this thesis (Chapter 4). In the analyses, a participant's data was not included if their movement exceeded 3mm (i.e., one voxel). Based on this, data for all participants was included in the localiser analysis ("one-back" localiser task: ApoE-e4 carriers n = 15, non-carriers n = 15). In the oddity task, four participants data were removed (two from each group) due to excessive movement, and a further participant's data excluded from the non-carriers due to scanner error (oddity task: ApoE-e4 carriers n = 13, non-carriers n = 12).

As can be seen in Table 5.1, and based on the behavioural assessment carried out alongside the imaging experiments, the carrier and non-carrier groups were well matched in memory recall and recognition, visuospatial abilities, and executive functions (ts < 1.75, ps > .9). There was a small but significant advantage for the ApoE-e4 group in their associative semantic knowledge ($t(27) = 2.29$, $p < .05$), as measured by the Camel and Cactus Task (Bozeat, Lambon Ralph, Patterson, Garrard, & Hodges, 2000); both groups, however, performed well on this task.

Table 5.1. ***Neuropsychological battery used to compare memory, visuospatial, semantic and executive abilities (parentheses contain SE of the mean).***

	ApoE-e4 carriers	Non-carriers
Age	19.65 (0.23)	19.67 (0.21)
Recall		
WMS III immediate story recall (/75)	40.27 (2.33)	41.53 (1.75)
WMS III delayed story recall (/50)	27.73 (1.9)	26.93 (1.39)
RCF delayed recall (/36)*	26.47 (1.41)	24.81 (1.64)
Recognition		
WMS III delayed story recognition (/30)	26.2 (0.72)	26.67 (0.45)
Visuospatial		
RCF copy (/36)*	34.33 (0.29)	35.23 (2.15)
Semantic		
CCT (/64)$^{\Delta}$	58.53 (0.67)	56.64 (0.46)
Executive		
RPCM (/36)	34.33 (0.29)	30.53 (2.15)

* scores based on 15 ApoE-e4 carriers and 13 non-carriers; Δ scores based on 15 ApoE-e4 carriers and 14 non-carriers.

WMS III (Wechsler Memory Scale 3rd edition; Wechsler, 1997); RCF (Rey-Osterrieth Complex Figure; Osterrieth, 1944); RPCM (Raven's coloured progressive matrices; Raven, 1962); CCT (Camel and cactus test; Bozeat et al., 2000).

5.2.2. Experiment procedure and materials

5.2.2.1. "One-back" localiser task

The "one-back" localiser was the same as the task described in Chapter 4 (see Section 4.2.2.1 for details). Briefly, during scanning, participants viewed single items presented sequentially and were required to respond with a button press when they saw an immediate item repeat (1-back). Stimuli comprised scenes (computer generated using the game Deus Ex, Ion Storm L.P., Austin, TX, USA, with software development package Deus Ex Software Development Kit v1112f); faces (created using Facegen Modeller 3.3, Singular Inversions Inc); objects (chairs, acquired from Hemera object database Vol. 1-3); and scrambled objects.

5.2.2.2. Oddity task

Participants viewed a series of trial-unique arrays in which they had to identify the odd-one-out (see Figure 5.2). Consistent with the oddity task used in Chapter 4, three images were presented concurrently, one placed centrally above two images, located to the left and right of the screen. There were four classes of stimuli; scenes (real world vistas acquired by the experimenter); novel faces; objects (acquired from Hemera object database, Vol. 1-3); and square blocks. For the scenes, faces, and objects, two of the images comprised the same item presented from different viewpoints, whilst the third was a perceptually similar item. For the square blocks (baseline), two of the square blocks were the same size whilst the third was a different sized square (for the remainder of this Chapter, this condition will be referred to as 'size').

Participants identified the different item using a three-choice button-box and were required to make their decision whilst the oddity trial was still present.

There were 54 trials per stimulus class presented in mini-blocks. A mini-block comprised three trials of each stimulus class presented sequentially. There were six mini-blocks per run and three runs in total. Four counterbalanced presentation orders of the mini-blocks were created and these versions were balanced across the entire sample. Trials were presented for six seconds with a mean one second inter-stimulus-interval (range 500-4000ms). The task was run using E-Prime Version 1.0 (Psychology Software Tools, Pittsburgh, PA).

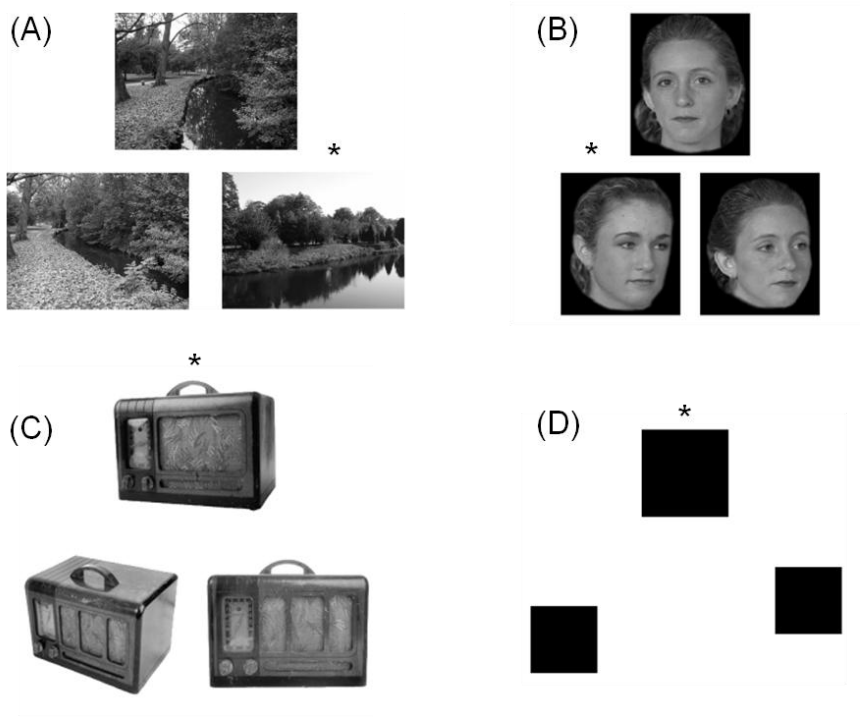

Figure 5.2. ***Examples of oddity trials comprising (A) scenes, (B) faces, (C) objects, and (D) size. Participants were required to select the odd item from the array with a corresponding button press (asterisks denote odd item).***

5.2.3. Analysis strategy

5.2.3.1. "One-back" task analysis

For the one-back task, EVs were used to model the time course data. These comprised scenes, faces, objects, and scrambled objects blocks.

As noted in Chapter 4, the "one-back" localiser task provides an unbiased and orthogonal approach to interrogating imaging data. In FEAT, a general linear model was used to distinguish two groups on the basis of ApoE status (ApoE-e4 carriers and non-carriers). The mean BOLD response for scenes, faces, objects and scrambled objects was contrasted between-groups. Group analyses were carried out using the FMRIB Local Analysis of Mixed Effects tool (Beckmann et al., 2003; Woolrich et al., 2004). To account for potential between-group differences in brain structure, grey matter (GM) images were included in the model as a covariate. FMRIB's Automated Segmentation Tool (FAST; Zhang, Brady, & Smith, 2001) was used to extract the GM image for each participant, registered to standard space, smoothed to the same extent as the fMRI data, and demeaned within each group (consistent with methods employed in Filippini et al., 2009). The resulting Z statistic images were thresholded using a $Z > 3.1$, and a family-wise error (FWE) corrected cluster extent of $p < .05$, based on the theory of Gaussian Random Fields. Clusters surviving this analysis were then used as fROIs to interrogate the oddity data.

5.2.3.2. Oddity task analysis

For the oddity task, each of the three runs was modelled separately. Five EVs were used to model the time course data. These comprised correct

responses to scene, face, object, and size trials, and one regressor comprising all incorrect responses. Three contrasts were created: 1) *'scenes > size'*, 2) *'faces > size'*, and 3) *'objects > size'*. The three individual runs for each participant were then combined using a fixed effects model. Percent signal change values were extracted for each of these contrasts from within each of the fROIs identified by the localiser task.

Consistent with the other analyses within this thesis, stimulus specific regions were identified, with a further two contrasts, by contrasting activity associated with different classes of stimuli; 1) *'objects > scenes'*, and 2) *'scenes > objects'*. Again, these contrasts were modelled for each participant in each individual run and then combined across three runs. Higher level analyses were conducted at the whole brain level, before being thresholded by a probabilistic mask of the MTL (all $Z > 2.3$, $p < .05$).

5.2.4. ApoE group-difference fROIs derived from the "one-back" localiser task

The BOLD response for each stimulus class (scenes, faces, objects, and scrambled objects) was contrasted between ApoE-e4 carriers and non-carriers. Significantly greater activity was evident in ApoE-e4 carriers for scenes, objects, and scrambled objects; no group differences were associated with faces. For scenes, there were three regions in which activity was greater for the ApoE-e4 carriers relative to non-carriers. These were located in the PCC, the cuneus, and the cingulate. For objects and scrambled objects, ApoE-e4 carriers showed greater activity in the frontal pole (see Figure 5.3). These five ROIs were used to interrogate the oddity data.

5.3. Results

5.3.1. Behavioural data

5.3.1.1. "One-back" localiser task

To check that the number of one-back targets was equivalent across stimulus-class and ApoE group, the number of targets were entered into an ApoE group (carriers; non-carriers)*Stimulus (faces; objects; scenes; scrambled objects) ANOVA and revealed no significant effect of ApoE group, Stimulus, or interaction between these two factors (Fs < 1.5, ps > 0.2).

Behavioural performance was assessed via the ratio of hits-FA (for a description of this method, see Section 4.3.1.1) (see Table 5.2). These values were submitted to a mixed ANOVA comprising a between-group factor of ApoE group (carriers; non-carriers) and a within-subject factor of Stimulus (faces; objects; scenes; scrambled objects). Discrimination accuracy differed across stimulus type ($F(3, 84) = 20.03$, $p < .01$), with greater discrimination accuracy for objects and scenes relative to faces ($t(29) = 6.59$, $p < .008$, and $t(29) = 4.36$, $p < .008$; Bonferroni correction = .05/6 $\alpha = .008$, respectively), and scrambled objects ($t(29) = 6.29$, $p < .008$, and $t(29) = 3.94$, $p < .008$, respectively). Discrimination accuracy for objects and scenes ($t(29) < 2.29$, $p = .03$), and for faces and scrambled objects ($t(29) = 0.87$, $p = .38$) did not differ. ApoE group was not associated with differences in discrimination accuracy ($F(1, 28) = 1.21$, $p = .28$), and did not interact with Stimulus ($F(3, 84) = 1.08$, $p = .14$).

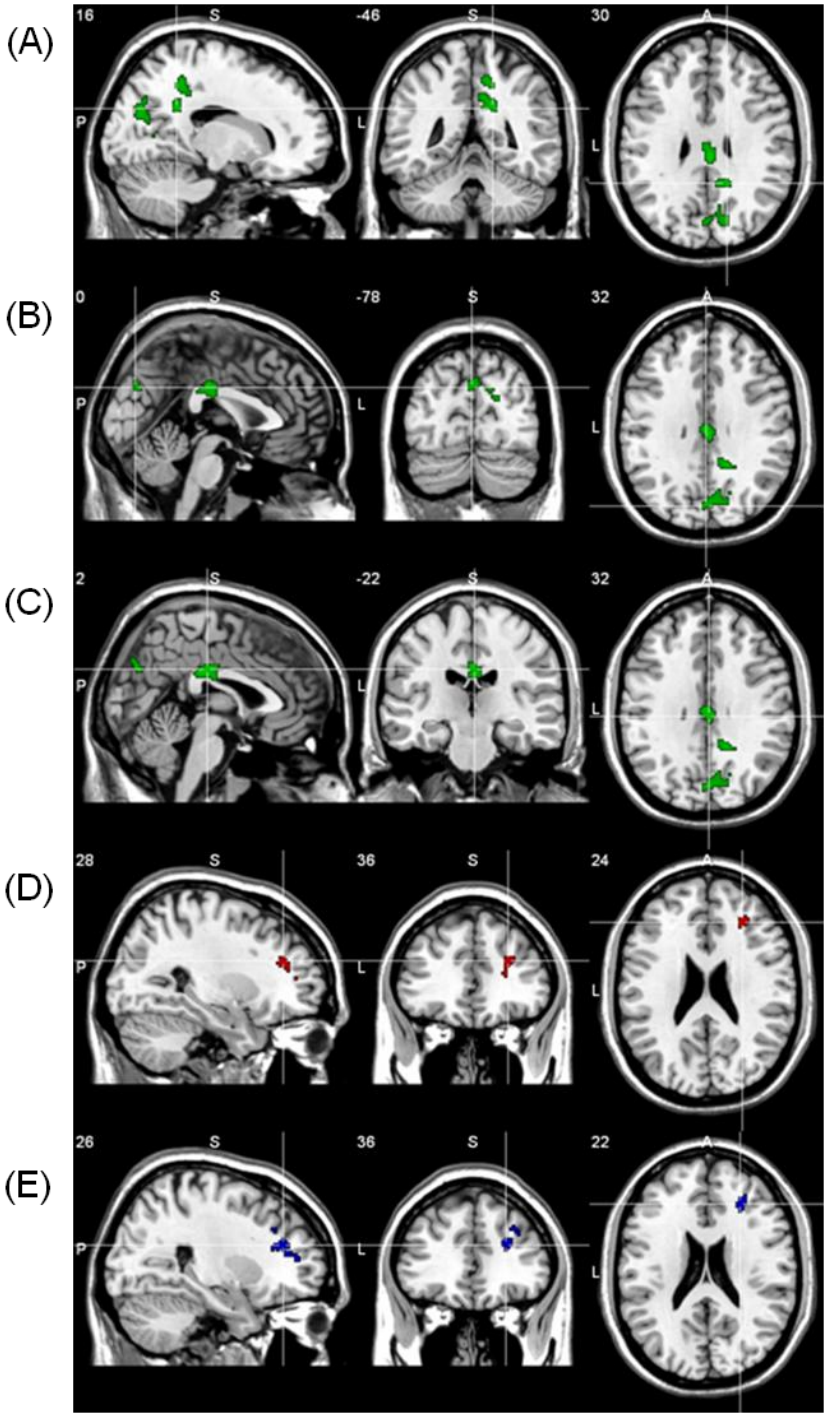

Figure 5.3. ***The localiser task revealed greater activity in the ApoE-e4 carriers relative to non-carriers in five fROIs. Scene-sensitive fROIs comprised (A) PCC, (B) cuneus, and (C) cingulate. Object-sensitive ROIs comprised (D) frontal pole, and scrambled object fROIs comprised (E) frontal pole.***

Table 5.2. ***Hit-FA rate for localiser task according to ApoE status.***

	ApoE-e4 carriers (n=15)	Non-carriers (n=15)
	Hit - FA (S.D)	Hit - FA (S.D)
Objects	0.78 (0.03)	0.70 (0.06)
Faces	0.55 (0.05)	0.52 (0.06)
Scenes	0.75 (0.03)	0.61 (0.05)
Scrambled objects	0.57 (0.06)	0.56 (0.05)

5.3.1.2. Oddity task

There was a high level of accuracy across all stimulus types in the oddity task (see Table 5.3). A mixed-model ANOVA comprising ApoE group (carriers; non-carriers) and Stimulus (faces; objects; scenes; size) revealed that performance was matched across ApoE group ($F(1, 23) = 0.003$, $p = .95$) and Stimulus ($F(3, 69 = 1.65$, $p = .19$). There was no interaction between these two factors ($F(3, 69) = 1.39$, $p = .25$). Reaction times were also matched across ApoE group ($F(1, 23) = 0.67$, $p = .42$), with no statistical evidence of an interaction between ApoE group and Stimulus ($F(3, 69) = 1.67$, $p = .18$). There was an overall main effect of Stimulus in reaction times ($F(3, 69) = 54.14$, $p < 0.001$); this reflected significantly quicker responses to size trials relative to faces ($t(24) = 7.80$, $p < .008$; Bonferroni correction = .05/6 $\alpha = .008$), objects ($t(24) = 10.27$, $p < .008$), and scenes ($t(24) = 10.28$, $p < .008$). There was a marginally significant effect of faster responses to faces relative to scenes ($t(24) = 2.87$, $p = .05$).

5.3.2. Imaging data

5.3.2.1. Stimulus specific effects

Consistent with analyses in Chapters 3 and 4, contrasts were made between the object and scene conditions. The whole brain and MTL analyses are contained in Appendix C (Sections 9.1 and 9.2, respectively). Briefly, the contrast *'objects > scenes'* was associated with increased activity in regions of extrastriate cortex that have previously been associated with object processing (i.e., the lateral occipital cortex). Similar to stimulus specific contrasts throughout this thesis, the reverse of this contrast was associated with increased activity in the lingual gyrus extending into posterior PHG.

In the MTL, the contrast *'objects > scenes'* was associated with significantly greater activity in left PRC; in the reverse of this contrast, scenes with increased activity in bilateral HC and posterior PHG.

5.3.2.2. Comparison of ApoE-e4 carriers and non-carriers

As noted in the methods section, the application of the localiser revealed five fROIs that were differentially affected, during a working memory task for scenes, objects, and scrambled objects in the ApoE carriers versus non-carriers. These fROIs will each be addressed in turn for oddity task data

To analyse the oddity imaging data, percent signal change values, for the contrasts of each stimulus condition relative to size baseline, were extracted from within each fROI and entered into a mixed ANOVA comprising a between-group factor of ApoE group (carriers; non-carriers) and a within-group factor of Stimulus (faces; objects; scenes). If there was evidence of a significant

interaction between the two factors in the fROI, then the percent signal change values were interrogated with separate one-way ANOVAs to examine the profile of BOLD response for individual stimulus classes within each group. Independent-sample t-tests were then used to test for between-group differences in percent signal change values associated with each stimulus class.

Table 5.3. ***Mean proportion correct and reaction items (RT) for oddity task broken down by ApoE status.***

	ApoE-e4 carriers (n=13)	Non-carriers (n=12)
Proportion correct	Mean (S.D)	Mean (S.D)
Scenes	0.85 (0.06)	0.86 (0.07)
Faces	0.89 (0.08)	0.88 (0.07)
Objects	0.87 (0.05)	0.83 (0.08)
Size	0.82 (0.12)	0.86 (0.13)
RT (ms)		
Scenes	2629 (586)	2809 (321)
Faces	2505 (424)	2582 (249)
Objects	2648 (447)	2635 (275)
Size	1944 (407)	2163 (312)

5.3.2.2.1. PCC scene fROI

In PCC there was a main effect of ApoE group ($F(1, 23) = 8.11$, $p = .01$) and Stimulus ($F(2, 46) = 15.86$, $p = .01$) modulated by an ApoE group*Stimulus interaction ($F(2, 46) = 9.35$, $p = .01$). This interaction resulted from a different

profile of activity across Stimulus in ApoE-e4 carriers ($F(2, 24) = 26.53$, $p = .001$), but not non-carriers ($F(2, 22) = 0.45$, $p = .65$). For ApoE-e4 carriers, there was significantly greater activity associated with scenes relative to faces ($t(12) = 5.24$, $p < .017$; Bonferroni correction = .05/3 α = .017) and objects ($t(12) = 5.59$, $p < .017$); activity for faces and objects did not differ ($t(12) = 0.34$, $p = 1$). Pair-wise comparisons for each stimulus class found greater activity in ApoE-e4 carriers relative to non-carriers for scenes ($t(23) = 4.01$, $p < .017$), but not faces ($t(23) = 1.30$, $p = 0.21$) or objects ($t(23) = 1.47$, $p = .16$) (see Figure 5.4).

5.3.2.2.2. Cuneus scene fROI

There was a main effect of Stimulus ($F(2, 46) = 36.36$, $p = .001$) and an ApoE group*Stimulus interaction ($F(2, 46) = 3.75$, $p = .03$). Both ApoE-e4 carriers and non-carriers showed a main effect of Stimulus ($F(2, 24) = 33.63$, $p = .001$; $F(2, 22) = 7.93$, $p = 0.01$, respectively), with greater activity associated with scenes relative to objects and faces. This effect, however, was more prominent in the ApoE-e4 carriers (scenes > faces, $t(12) = 8.28$, $p < .017$; scenes > objects, $t(12) = 5.27$, $p < .017$; objects = faces, $t(12) = 0.5$, $p = 1$) compared to non-carriers (scenes > faces, $t(11) = 3.55$, $p < .017$; scenes > objects, $t(11) = 2.95$, $p = .04$; faces = objects, $t(11) = 0.9$, $p = 1$). Similar to the PCC, there was evidence of between-group differences with greater activity in the ApoE-e4 carriers relative to non-carriers for scenes. This difference, however, did not survive Bonferroni correction ($t(23) = 2.33$, $p = .03$; Bonferroni correction = .05/3 α = .017); activity for faces ($t(23) = 0.56$, $p = .58$) and objects ($t(23) = 0.28$, $p = .78$) did not differ between groups.

5.3.2.2.3. Cingulate scene fROI

There was only a main effect of Stimulus in the cingulate ($F(2, 46) = 5.73$, $p = .01$) resulting from greater activity associated with faces relative to scenes ($t(24) = 3.87$, $p < .017$; Bonferroni correction = .05/3 α = .017).

5.3.2.2.4. Frontal pole object fROI

ANOVA revealed a main effect of Stimulus ($F(2, 46) = 4.99$, $p = .01$) that was qualified by a ApoE group*Stimulus interaction ($F(2, 46) = 3.62$, $p = .04$). The interaction stemmed from a significant difference in activity across the Stimulus in the non-carrier group ($F(2, 24) = 6.55$, $p = .01$). In this group, significantly greater activity was associated with objects relative to scenes ($t(11) = 3.24$, $p < .017$; Bonferroni correction = .05/3 α = .017), and faces, however this did not survive Bonferroni correction ($t(11) = 2.16$, $p = .03$); activity associated with faces and scenes did not differ ($t(11) = 1.45$, $p = .70$). The BOLD response for ApoE-e4 carriers did not differ across stimulus type ($F(2, 24) = 0.71$, $p = .5$) in this brain region. Furthermore, there were no ApoE group differences in activity for any stimulus class (ts < 1.78, $p > .09$).

5.3.2.2.5. Frontal pole scrambled object ROI

In the frontal pole ROI derived from the group contrast for scrambled objects, the oddity data revealed a main effect of Stimulus ($F(2, 46) = 3.99$, $p = .03$), resulting from greater activity associated with objects relative to scenes. This difference, however, did not survive Bonferroni correction (.05/3 α = .017) ($t(24) = 2.33$, $p = .04$); activity for faces and objects, and faces and scenes did not differ ($t(24) < 1.83$, $p > .08$).

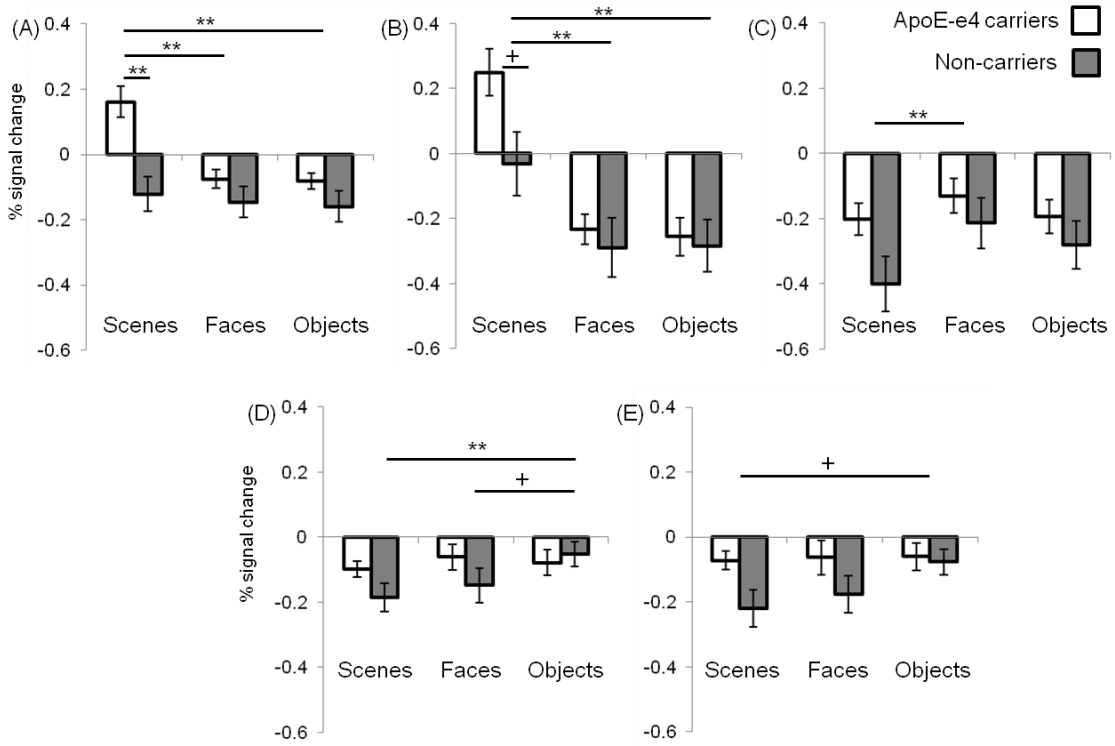

Figure 5.4. ***Percent signal change values extracted from scene fROIs (A) PCC (B) cuneus (C) cingulate; object fROI (D) frontal pole; and scrambled object fROI (E) frontal pole. ** = <0.017; + = <0.05).***

5.4. Discussion

The experiments outlined in previous Chapters in this thesis were designed to test whether there is a fractionation of the MTL according to the stimulus to-be-discriminated, with evidence accruing that the PRC forms complex conjunctions of features comprising object stimuli, and with a similar role for the HC in supporting complex spatial representations. Elucidating the

nature of the representations supported by MTL structures will necessarily allow researchers to better capture the nature of the deficits likely to result from neurological disorders that affect these structures, as well as adjacent regions. Here I focused on one such disorder, AD, and conducted an experiment designed to investigate whether functional imaging can help provide biological markers to identify individuals at increased risk of the disease. In the current study, I compared the BOLD response associated with different classes of stimuli in young healthy carriers of the ApoE-e4 allele relative to non-carriers, a genetic risk factor for AD, to determine whether these groups show different levels of neural activity for scenes specifically. To constrain our analysis, particularly due to low participant numbers, a “1-back” localiser task employing scenes, faces, objects and scrambled objects was used to identify regions of the brain that differed in terms of their neural activity in ApoE-e4 carriers and non-carriers. These ROIs were then used to interrogate the data from an oddity task comprising scene, face, object, and size stimuli. This task has been shown to be sensitive to the earliest behavioural changes seen in AD (Lee et al., 2007; Lee, Buckley, et al., 2006), and consequently, provides a useful tool to determine the sensitivity of fMRI in young carriers of genes that place them at increased risk later in life.

In fROIs that were identified on the basis of ApoE group differences in BOLD response at the whole brain level, greater activity in the PCC and cuneus (although the latter did not survive Bonferroni correction) was associated with scenes during an orthogonal oddity task in ApoE-e4 carriers relative to non-carriers. In the same regions, there were no group differences in activity associated with the object and face stimuli. Furthermore, there were no group differences in activation in two fROIs in the frontal pole. Scene-related activity in

the PCC, therefore, seemed particularly sensitive to ApoE-e4 genotype status. These differences were noted, however, in the absence of any behavioural differences between ApoE groups. I will now consider the role of the PCC in spatial processing and the use of spatial tasks as a marker for AD risk.

The PCC has previously been identified as a region that shows structural or metabolic changes in advance of AD. For example, focal atrophy of the PCC has been shown to be predictive of progression from MCI to AD (Baron et al., 2001; Chételat et al., 2005; Chételat et al., 2002; Hämäläinen et al., 2007; Pengas, Hodges, et al., 2010; Scahill et al., 2002), and increased glucose metabolism is evident in this region in ApoE-e4 carriers relative to non-carriers years in advance of behavioural symptoms (Reiman et al., 2004). The current data advance these findings by showing that differences in the BOLD response in the PCC are apparent in young adults, many years in advance of behavioural symptoms, but are specifically associated with scene stimuli.

The influence of ApoE-e4 over the lifespan is currently not well understood, particularly in relation to how differences in BOLD response in young adults at genetic risk of AD relate to structural changes in the same regions later in life. For example, Filippini et al. (2011) scanned both young and older ApoE-e4 carriers and non-carriers and compared the level of neural activity across these two groups. Relative to non-carriers, young ApoE-e4 carriers showed increases in BOLD response; the reverse was true, however, for the older adult carriers and non-carriers. One hypothesis for the increased BOLD response evident in young adults is that this reflects increased neural effort to maintain normal behavioural performance, that subsequently leads to more rapid decline in brain function (and subsequently reduced neural signal) in

old age (Filippini et al., 2011). Similarly, Jagust and Mormino (2011) propose that, due to low cognitive reserve in ApoE-e4 carriers, increases in neural effort (inferred by the increased BOLD response) are required to maintain normal performance on cognitive tasks. When challenged with the extra burden of neurological pathology, as in AD, this results in a rapid decline in neuronal function leading to a reduced level of neural activity evident in imaging (Filippini et al., 2011). In the current study, therefore, the increased BOLD response in the PCC for ApoE-e4 carriers associated with scene processing might reflect increased neural effort that results in greater atrophy in this region later in life (de Haan et al., 2012), consistent with the observed structural changes in progression from MCI to AD.

A logical question, therefore, is how dysfunction of the PCC might result in the behavioural deficits commonly observed in AD. In a number of neuropsychological studies of patients with static lesions to the HC, behavioural deficits often mimic those evident in early AD (i.e., impairments in spatial processing and episodic memory). As noted in Section 5.1, the PCC forms a pathway between the posterior parietal cortex (which has been associated with visuospatial processing), and the MTL, in particular the HC (which has been implicated in the formation of allocentric spatial representations). Functional or structural changes in this region, therefore, may result in an inability to form complex spatial representations that aid one's ability to discriminate visually similar scenes (Lee et al., 2007; Lee, Buckley, et al., 2006), or form allocentric topographical representations of spatial environments (Bird, Chan, et al., 2010; Hartley et al., 2007; Pengas, Patterson, et al., 2010). Furthermore, given that the PCC is also strongly interconnected with a number of different brain regions such as HC, PHC, and retrosplenial cortex (Andrews-Hanna et al., 2010),

atrophy in this region resulting from increased neural effort during the processing of scenes might also eventually lead to more widespread atrophy throughout the brain and more pervasive behavioural impairments in other cognitive domains.

Some previous studies have reported increases in the BOLD response associated with ApoE-e4, while others have reported decreases. The direction of the effect, therefore, has been difficult to predict, and interpretation has not been aided by the use of different cognitive tasks each employing different stimulus-types across studies. The current experiment benefitted from examining the BOLD response associated with different stimulus classes within the same paradigm. The data suggest recent findings may need to be re-evaluated according to the stimuli employed in the tasks. Greater increases in the BOLD response for ApoE-e4 carriers were reported during a scene episodic memory task compared to a verbal stroop task (Trachtenberg, Filippini, Cheeseman, et al., 2012). This led to the conclusion that, mirroring declarative memory impairments in AD, the ApoE-e4 allele may disproportionately affect memory. Given the current findings, in which effects were evident on a task that did not place an overt demand on memory, however, one might suggest that it was the difference in stimuli (scenes versus words) that resulted in the more prominent effect during the memory task in Trachtenberg's study.

Similarly, increased BOLD response was evident in ApoE-e4 carriers in a memory task that required participants to encode a face in an imagined scene (Mondadori et al., 2007). This effect was not replicated in the same participants, however, in a memory task that required a simple pleasant/unpleasant judgment about the faces or a "2-back" working memory task using letter

stimuli. Although there were different cognitive demands across tasks, there was also a difference in the amount of spatial processing required; the task in which there was increased neural activity required the encoding of an associated scene. Experiments that have elicited an increase in BOLD response in ApoE-e4 carriers relative to non-carriers include a “one-back” task requiring the memory for an object in a specific spatial location (Filbey et al., 2006), and a memory task in which blocks of animal and scene stimuli were presented (Filippini et al., 2009). Given that the latter task was not designed to compare between different stimulus types, the limited trial numbers meant that it was not possible to contrast memory activity associated with the scenes to that of the animals. The current findings, however, would suggest that the neural response to the scene, rather than the animal, stimuli may have driven the effect seen in Filippini’s initial study.

Given the deleterious effects of the ApoE-e4 allele later in life, researchers have debated the evolutionary benefit of this gene and specifically why it has survived. It has been hypothesised that this allele survives because it may be cognitively advantageous at a young age (for review, see Tuminello & Han, 2011). For example, young carriers of the e4 allele have been shown to have higher IQ than age-matched non-carriers (Yu, Lin, Chen, Hong, & Tsai, 2000). Furthermore, in a large study of 87 ApoE-e4 carriers versus 253 non-carriers, carriers had better memory for a word list after a five minute delay (Mondadori et al., 2007). A subset of these participants was then scanned during encoding and retrieval of faces (either presented singly or with a piece of contextual information). The same items were presented over three runs of encoding and, relative to non-carriers who showed increased activity over repeats, e4 carriers showed a reduction in brain activity. Furthermore, they

showed decreased activity during retrieval of the same items. This pattern of activity was interpreted as reflecting increased neural efficiency in the ApoE-e4 carriers. One interpretation of the current data, therefore, is that the increased activity associated with scenes in the current study reflects some cognitive benefit for scenes specifically that the current paradigm did not have the power to detect. Performance on the oddity task was high across both groups, and a more demanding task, or larger sample, might allow behavioural differences to emerge. For example, differences between ApoE-e4 carriers and non-carriers in behavioural measures have been identified in much larger samples. When comparing a sample of 29 ApoE-e4 carriers and 97 non-carriers, carriers were shown to have higher IQs; this effect, however, did not survive correction for multiple comparisons (Yu et al., 2000). Given the potentially small effect sizes, the current sample size may have not been powerful enough to capture any subtle differences in behavioural performance.

A larger sample of participants would also allow for the stratification of allele combinations to examine their effect on neural activity, particularly the e2 allele. Relative to e3 homozygotes, e2 carriers, who are at a decreased risk of developing AD, also showed increased BOLD response (Trachtenberg, Filippini, Cheeseman, et al., 2012). These data suggest, therefore, that caution must be exercised when associating increased blood flow with AD risk as the same pattern of data was evident in those both at increased and decreased risk of developing the disease. Examining the percent signal change plots for the two tasks (scene memory task and verbal stroop task) in Trachtenberg's study, however, reveals that the neural response to scene stimuli may be more sensitive to this genotype difference. Not only was the scene memory task associated with a greater number of regions showing increased activity in the

ApoE-e4 carriers, it also showed a dose response effect with greater activity associated with e4 homozygotes relative to heterozygotes in a cluster comprising PCC. Furthermore, there was a numerical trend for greater activity in the e3-e4 participants relative to e2-e3 carriers (see Figure 5.5). These data suggest that tasks requiring scene processing may be more sensitive to AD risk than tasks employing other types of stimuli such as words.

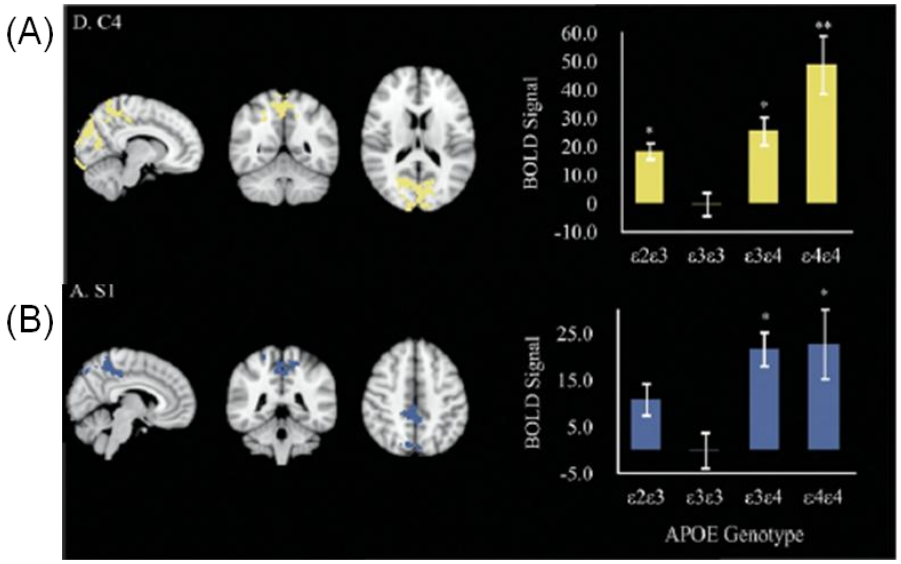

Figure 5.5. ***Comparison of parameter estimates extracted from clusters in or around PCC for different combinations of ApoE alleles, in (A) an episodic memory task that contained scene stimuli, and (B) a verbal stroop task (Trachtenberg, Filippini, Cheeseman, et al., 2012).***

5.5. Summary

The current data suggest that scene processing tasks may be a fruitful approach to developing a biomarker of AD risk. By using different stimulus types within the same task, the present study was able to examine the contribution of the stimulus to neural activity without confounding it with different

task demands. Increased activity in the PCC for ApoE-e4 carriers associated with scene processing may provide a useful metric by which early therapeutic intervention can be measured. These data therefore provide a link between the structural and metabolic changes, and spatial processing impairments evident in the earliest stages of AD. For representational accounts, future directions for research might include investigating how the PCC contributes to the formation of flexible allocentric spatial representations, through its connections between posterior parietal lobe, PHG and HC. Furthermore, in relation to genetic AD risk, it will be important to test whether activity in PCC associated with allocentric scene processing is more sensitive to ApoE genotype status (Laczó et al., 2010). For the research field in general, it is important that the academic pursuit of understanding how different structures within the MTL contribute to perception and memory translates into clinical application and aids in the early identification of neurological disease.

Chapter 6: General discussion

The aim of this thesis has been to test the predictions of representational accounts of MTL function, with a particular focus on EMA and the proposed contribution of the PRC and HC to the discrimination of complex conjunctive objects and scenes, respectively (Graham et al., 2010) This aim was achieved through the combined use of human neuropsychological and functional imaging studies in which activity associated with object and scene stimuli was contrasted, and where feature ambiguity was sometimes manipulated either by increasing the perceptual similarity of items or by requiring participants to form unique conjunctions of features comprising object and scene stimuli. A variation of one of the tasks used in the thesis to test EMA (oddity judgement) was then applied to young healthy participants at increased genetic risk of AD, to determine whether differences in the BOLD response associated with scene oddity would be apparent between ApoE-e4 carriers and non-carriers. In this final Chapter of my thesis, I will review the results from these experiments, in particular examining the consistency of findings, highlight how they have helped inform our understanding of the role of the MTL in perception and memory, and consider future directions for research.

6.1. Summary of findings

6.1.1. Evidence for the role of the PRC in processing complex conjunctive object representations

A central tenet of EMA is that the PRC comprises the apex of the VVS and forms complex, object-level conjunctions of features; simpler feature

conjunctions are represented in VVS regions posterior to the PRC (Bartko, Winters, Cowell, Saksida, & Bussey, 2007a; Buckley et al., 2001; Buckley & Gaffan, 1997; Bussey, Saksida, & Murray, 2002, 2003). A key prediction for EMA, therefore, is that the degree of feature overlap between object items should modulate performance in patients with damage encompassing the PRC. When items can be discriminated on the basis of simple, lower-level features (low ambiguity), patients should show spared performance; on tasks requiring the processing of complex conjunctions of features (high ambiguity), then deficits should be observed. This pattern has been demonstrated in the literature (Barense et al., 2005, 2007, 2012; Lee, Barense, & Graham, 2005). Equally, in imaging, the discrimination of perceptually similar object items should be associated with increased activity in PRC relative to visually distinct items; again, this pattern has now been reported in a few studies (Barense et al., 2010, 2012; Devlin & Price, 2007). There is a need, however, for further investigation of the circumstances under which these patterns are seen, as not all studies show these feature ambiguity effects for objects, particularly in patients (Kim et al., 2011; Knutson et al., 2012; Levy et al., 2005; Shrager et al., 2006).

The experiments detailed in this thesis examined the contribution of the PRC to the discrimination of complex object stimuli as follows. In Chapter 2, patients with damage restricted to the HC were tested on discrimination learning for object stimuli (fribbles); the same stimuli as adopted by Barense et al. (2007) was applied in the experimental paradigm reported in Barense et al. (2005), thereby bridging the gap between these studies. Complementing this, fMRI was used in: 1) a grids paradigm, in which participants discriminated between simultaneously presented object and scene stimuli (Chapter 3) and 2) an oddity

task in which the degree of feature overlap between object targets and foils was manipulated (Chapter 4). Across all experiments, it was possible to compare the pattern of activity in MTL regions associated with objects compared to scenes, and vice versa. Whole brain analyses from Chapters 3-5 are reported in the Appendices. Within the Chapters, themselves, MTL analyses involved anatomical and/or functional ROI comparisons.

Supporting EMA, in all the imaging Chapters (3, 4, and the MTL analyses for Chapter 5, contained in Appendix C, Section 9.2) there was evidence of significantly greater activity in PRC for object stimuli, when tested using a *'objects > scenes'* contrast. There was less consistent evidence, however, for the notion that the PRC supports complex object item discriminations (Chapter 3), or that the level of activity in this region is modulated by the degree of feature overlap between object items (Chapter 4). By contrast, at least one of the HC patients, across both neuropsychological experiments (Chapters 2 and 3), showed object discrimination abilities within the normal range of controls, in the context of difficulties with scene discrimination.

Considering the imaging findings alongside previously published studies (e.g., Lee, Bandelow et al., 2006), when contrasting *'object item change > object match'* in Chapter 3, a significant effect was only evident when the statistical threshold was relaxed. Moreover, the item change effect thought to be specific to objects, was in fact also evident for the *'scene item change > scene match'* contrast. Lee, Bandelow, et al. (2006) found significantly increased activity in PRC when contrasting *'object item change > object match'*, but it was not possible to comment on the specificity of this effect because the study used only object stimuli. A discussion as to why the PRC may show increased BOLD

response for the detection of item changes in both objects and scenes is detailed in Section 3.1.4. Inconsistent with EMA, the contrast *'high ambiguity objects > low ambiguity objects'* in Chapter 4 was also not associated with increased activity in PRC. Instead, a fROI analysis examining object sensitive voxels revealed that activity in this region was modulated by both feature overlap, and spatial contextual association, with greatest activity associated with high ambiguity, strong context objects. The notion that the degree of object feature overlap modulates activity in PRC, therefore, is not well supported in this thesis. Considerations as to why the experiments contained in this thesis failed to replicate previous effects of ambiguity are discussed in Section 6.3.1.

6.1.2. Evidence for the role of the HC in the processing of complex spatial representations

Since the seminal finding that cells in the rat HC fire consistently in relation to specific spatial locations, research has examined how this region might support the processing of spatial environments (Bird et al., 2010; Burgess et al., 2000; O'Keefe, Burgess, Donnett, Jeffery, & Maguire, 1998; O'Keefe & Burgess, 1996; O'Keefe & Nadel, 1978). Whilst one representational account, BBB (for a description of this model, see Section 1.4.2.2), proposes that the HC forms allocentric representations of spatial environments (Byrne et al., 2007), EMA notes that this region forms complex conjunctions of spatial features, analogous to the role of the PRC in forming conjunctive, object-level representations. Relative to BBB, EMA places less emphasis on allocentric processing and suggests that any spatial task that taxes complex conjunctions (i.e., discriminating two perceptually similar scenes) will require the contribution of the HC (Buckley, Charles, Browning, & Gaffan, 2004; Lee, Yeung, &

Barense, 2012). This proposal is supported by the findings that patients with static lesions of the HC are impaired when discriminating between two same view scenes morphed to share a high degree of features (Lee, Buckley, et al., 2005; Mundy et al., 2013). Although EMA is not explicit about the role of extrastriate regions in the processing of scenes, activity for low ambiguity stimuli has been associated with increased activity in the posterior PHG (or PPA), and therefore these regions may support less complex, or less conjunctive (low ambiguity) scene representations (Mundy et al., 2012).

The role of the HC in spatial processing was tested in this thesis using a combination of functional imaging and neuropsychological tasks. In imaging, 1) the grids paradigm tested whether activity in the HC was associated with the successful detection of scene item changes (Chapter 3) and 2) the oddity task, examined whether the level of activity in the HC was modulated by the degree of feature overlap in scene stimuli, as measured by comparing virtual reality and real world scenes (Chapter 4). As mentioned above, a novel part of this thesis was that patients with focal HC damage were also tested on a subset of the experimental tasks: this enabled examination of: 1) the contribution of the HC to the learning of conjunctive scene representations (Chapter 2), and 2) whether patients with HC damage show particular difficulties in detecting scene, relative to object, item changes when presented in a simultaneous array (Chapter 3).

The imaging data partially supported the predictions of EMA. In Chapter 3, there was evidence of a stimulus specific item change effect in the HC associated with scenes. Like the objects, however, this was only apparent at a relaxed statistical threshold (when thresholded with a probabilistic mask of the MTL), and notably, when contrasting *'scenes > objects'*, there was no evidence

of significantly greater HC activity associated with scenes (again, in analyses limited to the MTL). In contrast, in the oddity task described in Chapter 4, scenes were associated with increased posterior HC activity relative to objects. Contrary to predictions, this effect was driven by the increased BOLD response associated with the low ambiguity scenes (real world) rather than the high ambiguity scenes (computer generated). Replicating this effect, in Chapter 5, real world scenes again elicited greater activity in HC relative to objects (details of this analysis are contained in Appendix C, Section 9.2). In conclusion, the most robust scene-sensitive BOLD effects in the HC were associated with the discrimination of real world scenes presented from different views.

The neuropsychological experiments provided more novel insights into the role of the HC in scene processing. First, both patients showed a scene specific impairment in the discrimination learning of high ambiguity conjunctive scenes, in the context of spared performance for objects. Furthermore, patient HC3 also demonstrated a significant impairment when required to discriminate objects comprising spatial features that changed within objects (tadpoles). The modified version of the grids paradigm used in Chapter 3 also revealed that both patients showed particular difficulties when detecting differences between concurrently presented scenes, although in HC2, this conclusion needs to be tempered given some difficulties with object item change decisions as well.

6.1.3. The role of the PHG in the processing of scenes and objects with strong spatial context associations

A point of contention between representational accounts and a mnemonic account of MTL function, BIC, is the role of the posterior PHG in the processing of context. As mentioned previously, although EMA does not

explicitly state the types of representations supported by the posterior PHG, this account would seem compatible with the notion that this region processes scene geometry (e.g., Epstein et al., 1999), due to evidence of increased activity in posterior PHG associated with the viewing of real world scenes (Mundy et al., 2012). Supporting BIC, other accounts propose that the posterior PHG supports the processing of more generic contextual associations, even in the absence of spatial information (e.g., Bar, 2004). In the oddity task outlined in Chapter 4, stimuli comprised scenes, objects strongly associated with a spatial context (presented in isolation, without any background information), and objects not associated with any particular spatial context. Consistent with Epstein et al., significantly greater activity was associated with scenes relative to strong context objects. It must be noted, however, that there was also a modulation of activity according to an item's contextual association, with a reliably larger BOLD response associated with strong context relative to weak context objects. As evidenced by the level of BOLD response, these data suggest that the primary role of the posterior PHG is to process scene geometry. It may, however, also support memory for associated spatial information in non-scene items, as has been demonstrated previously by findings of increased BOLD response for familiar, relative to novel, landmarks (Epstein et al., 1999)

6.1.4. Scene tasks as an indicator of AD risk

The final aim of the thesis was to examine the use of the oddity task as a marker of ApoE-e4 carrier status; ApoE-e4 is a gene that places individuals at increased risk of AD later in life. Given the scene processing and navigational deficits evident early in AD, and evidence of early involvement of PCC in

individuals who go onto to subsequently develop the disease (e.g., Chételat et al., 2005; Hämäläinen et al., 2007, see Section 5.1), it was hypothesised that ApoE-e4 carriers would show increased activity associated with scene, but not object/face, oddity in the PCC. This prediction was borne out in the findings, and suggests that scene discrimination tasks may provide a way of identifying individuals at increased risk of developing AD early in life (e.g., Filippini et al., 2009; Lee et al., 2007; Pengas et al., 2010; Trachtenberg, Filippini, & Mackay, 2012) (see Section 5.4).

6.2. Limitations of the work presented in this thesis

6.2.1. Examining the contribution of incidental encoding to the BOLD response during perceptual tasks

In Chapter 4, a subsequent memory test for the high ambiguity object oddity stimuli allowed assessment of the contribution of incidental encoding to the level of BOLD response in a PRC fROI (for imaging results of this subsequent memory analysis, see Section 4.3.2.5). Briefly, there was no difference in the level of activity for objects subsequently recognised as old accompanied by recovery of contextual information (orientation), compared to items later recognised as old without this contextual information, or items subsequently forgotten. In the same Chapter, however, there was no subsequent memory test for the low ambiguity objects or scenes (both high and low ambiguity). Similarly, memory was not assessed for the object and scene stimuli in the item discrimination task outlined in Chapter 3. As such, for a number of these conditions, it is not possible to be sure that MTL activity associated with the discrimination of objects and scenes reflects perceptual, rather than mnemonic processes. This is a considerable problem for

representational accounts and there have been several attempts to address it previously. For example, after a scanned oddity task comprising objects and faces, Barense et al. (2011) gave participants a surprise memory task in which they were required to decide whether an (object or face) item had been studied in the oddity task, and indicate their confidence in their memory judgment. Consistent with the notion that the MTL supports the perception of complex object and face stimuli, even weakly remembered items (misses and low confidence hits) were associated with above baseline activity in PRC. Similarly, after a scanned scene oddity experiment, Lee et al. (2013) presented the same trials again alongside a number of foils, and asked participants to make an 'old/new' discrimination. This allowed for trials to be binned according to perceptual and mnemonic accuracy: perception hit-memory hit, perception hit-memory miss, perception miss-memory hit, and perception miss-memory miss. In HC, the level of activity was modulated by perceptual accuracy (i.e., greater activity associated with correct versus incorrect oddity decisions), but not memory accuracy (equivalent for hits and misses). Together, these data, combined with the subsequent memory task employed in Chapter 4 for high ambiguity objects, suggest that MTL activity cannot be explained solely in terms of incidental encoding.

One of the difficulties in trying to demonstrate stimulus specific contributions to perception and memory is that this necessarily involves a large number of trials. For example, Lee et al. (2013) used 200 scene oddity trials to enable them to have adequate trial numbers so that the imaging data could be analysed according to perceptual and mnemonic accuracy. Moreover, if one then wanted to examine the potential contribution of different memory processes to these memory judgments, by plotting ROCs, it is advised to ask

participants to respond over six different confidence levels (Yonelinas & Parks, 2007), which involves the use of an even greater number of stimuli. As was demonstrated by Lee et al. (2013), increasing the number of trials can lead to suboptimal memory performance. These constraints make it relatively difficult to undertake a sufficiently powered imaging study that facilitates comparison across stimulus conditions, as well as sensible contrasts between perception and subsequent memory. Nevertheless, the inclusion of a subsequent memory task as a matter of course to rule out the contribution of memory seems vital when testing the contribution of the MTL to perceptual discriminations.

6.2.2. Variability in patient performance

Two patients with focal HC damage were tested in this thesis. These patients have been used in a number of previous neuropsychological investigations, and there is detailed information about the extent of their structural damage (Barense et al., 2005, 2007; Erez et al., 2013; Graham et al., 2006; Lee & Rudebeck, 2010a; Lee, Buckley, et al., 2005; Lee, Bussey, et al., 2005; Rudebeck, Filippini, & Lee, 2013). Given the small sample size, one way of interpreting the data from the two experiments reported here is to examine consistencies in performance across the patients. Consistent with EMA, in the conjunction learning task (Chapter 2), both patients showed impaired discrimination learning for scenes, but spared performance for objects. Similarly, for the item change detection task of Chapter 3, relative to controls, both patients showed deficits in discriminating perceptually similar scenes but there was no group difference (between HC patients and healthy controls) in the discrimination of objects.

In a number of conditions across the two neuropsychological experiments, however, Patient HC3, performed more poorly than patient HC2. In the conjunction learning task, HC3 showed learning impairments for tadpoles and colour blocks; in the latter it had been predicted that she should show spared performance. Similarly, in Chapter 3, slightly more variable control performance in the object item change condition, relative to the scene item change condition, masked HC3's poor discrimination accuracy for these stimuli; she performed at the same level for both objects and scenes (0.66 correct). Examination of the inverse efficiency scores, however, reveals that she took longer to respond to the scene stimuli relative to objects, perhaps indicative of impairment for this stimulus class (Graham et al., 2006).

Volumetric analyses revealed that patient HC3 has more extensive HC damage than HC2 (see Table 2.1, Section 2.2.1). This analysis, however, did not allude to regional differences in HC volume (i.e., whether this damage is located in anterior or posterior divisions of the HC). In Barense et al. (2005), visual assessments of scans were conducted to estimate the extent of cortical damage, ranging from 0, indicating no damage, to 3 (4 in anterior HC), indicating the complete absence of cortex. It revealed that patient HC3 had moderate damage to the entirety of the HC (rated 1.25 in anterior HC compared to 1 in posterior HC), whereas HC2's hippocampal damage was more apparent in anterior HC (assessed as a 2) rather than in posterior HC (rated 0.25). Furthermore, relative to HC2, patient HC3 has more extensive damage in PHG as demonstrated in both the volumetric, and scan rating, analyses. Both the greater extent of HC damage and greater damage to areas surrounding the HC (i.e., the PHG) might explain the more severe scene discrimination deficits in HC3.

Turning to the evident difficulties in objects, which was not predicted, consistent with her performance in the experiment detailed in Chapter 3, recent testing in patient HC3 by other research groups has revealed significantly poorer performance relative to controls for both scene and familiar object oddity (Erez et al., 2013). Interestingly, HC3 showed normal performance for novel object and face oddity in this study. Reassuringly, Erez et al. also found, however, that the only consistent deficit across HC2 and HC3 was for scene oddity. It is difficult to make any firm conclusions on the basis of data from two patients, who show quite different patterns of performance on object discrimination tasks and different degrees of damage to key MTL structures; moving forward, therefore, it would be important to test a larger sample of patients in order to determine the consistency, and strength of predicted discrepancies in performance, on scene and object discriminations.

6.2.3. Manipulations of scene ambiguity

In Chapter 4, one of the primary aims was to examine how activity in the HC was modulated by the degree of feature overlap in scenes. Similar to Mundy et al. (2012), this task utilised computer generated and real world scenes for the high and low ambiguity manipulation, respectively. In contrast to Mundy et al. (2012), the low ambiguity scenes (real world) were associated with greater activity in HC than the high ambiguity scenes (computer generated).

It is possible that variables not related to feature ambiguity may explain these differences in the level of activity seen in the HC. For example, there is evidence that the PPA responds preferentially to high spatial frequencies (Rajimehr, Devaney, Bilenko, Young, & Tootell, 2011; Zeidman, Mullally, Schwarzkopf, & Maguire, 2012). It is possible, therefore, that the real world

scenes have a higher spatial frequency than the computer generated items, and that activity in HC may also be modulated by this basic property of the stimuli. This would not explain, however, why Mundy et al. (2012) observed greater activity in HC for computer generated relative to real world scenes. The two scene categories also differed in the number of composite object items within the scenes. Predictably, the real world scenes comprised a number of object stimuli, whereas the computer generated stimuli contained very few object items. It is possible, therefore, that increased demand to process object-in-place relationships (e.g., in the oddity task to detect the different item) may particularly tax the HC and result in greater activity in this region. In Mundy et al., the task involved passive viewing of the scenes which may mean that it was not necessary to process object-in-place relationships (for further discussion of the nature of the representations supported by HC, see Section 6.3.2).

6.3. Outstanding questions and future directions

6.3.1. The nature of the representations supported by the PRC

Given the converging animal (Bartko, Cowell, Winters, Bussey, & Saksida, 2010; Bartko et al., 2007a; Bartko et al., 2007b; Bussey et al., 2002; McTighe, et al., 2010; Murray, Bussey, & Saksida, 2007), computational (Cowell et al., 2006, 2010), imaging (Barense et al., 2010; 2012; Devlin & Price, 2007; Lee, Bandelow, et al., 2006), and neuropsychological research (Barense et al., 2005, 2007, 2012; Lee, Buckley, et al., 2006) implicating the PRC in the discrimination of perceptually similar, complex object representations, it was predicted that changing the level of ambiguity would modulate the level of activity in this region. As mentioned above, this prediction was not supported in

the imaging data. I will next consider instances in which manipulations of ambiguity have found associated modulations of activity in PRC, suggest why differences in paradigm might account for the discrepancy between those data and those reported in this thesis, and what this might mean about the representations supported by the PRC.

At least four imaging studies have previously shown that activity in PRC is modulated by the degree of feature overlap in object stimuli (Barense et al., 2010, 2012; Devlin & Price, 2007; Mundy et al., 2012). Two of these studies, as outlined in Chapter 4, confounded a change in viewpoint with a change in the degree of feature overlap (Barense et al., 2010; Devlin & Price, 2007). One study, however, removed this confound and provided compelling evidence that the PRC forms unique, object-level conjunctions of features that permit the discrimination of perceptually similar objects (Barense et al., 2012). Barense et al. (2012) presented participants with novel object pairs comprising three features (ABC) and manipulated the level of feature overlap between them. Compared to low ambiguity trials in which there was no feature overlap between items, high ambiguity discriminations (e.g., ABC vs ABD) were associated with significantly greater activity in PRC. These data were not supported by the findings of Chapter 4, in which an oddity task contrasting high versus low ambiguity conditions did not modulate activity in PRC, although there was greater activity seen for a high ambiguity, high context oddity condition.

There are at least two possible reasons for the discrepancy between Barense et al. (2012), and the findings in Chapter 4. First, unlike the stimuli in Chapter 4, in Barense et al. (2012), the degree of feature overlap between objects was controlled by using predefined composite stimulus elements (inner

shape, outer shape, and fill pattern). The high ambiguity real world objects used in Chapter 4 were selected on the basis of them being perceptually similar. It is possible, however, that individual, lower-level features may have identified the odd item, and therefore not taxed conjunctive representations. By strictly controlling the stimulus elements, Barense et al. encouraged the processing of relationships between individual stimulus elements of the object items, a conclusion that is supported by complementary eye-tracking data reported in the paper. The eye-tracking confirmed that participants examined the intra-item relationship between stimulus elements, rather than the inter-item differences between features, a pattern that implies conjunctive processing of the stimuli. Tasks placing greater processing demand on feature conjunctions, therefore, may be required to elicit greater activity in PRC, and – as employed by Barense and colleagues – it would be prudent to test (using eye-tracking) how participants are processing these stimuli in advance of using them in fMRI paradigms.

Similarly, differences in the tasks employed may have encouraged the use of different conjunctive strategies; Barense et al. (2012) may have observed increased PRC activity associated with high ambiguity items due to the inclusion of both match and non-match trials in their experiment. This manipulation involves participants looking for differences between the stimuli (as required in the oddity task), but also needing to gauge the similarity between the presented pairs. In contrast, the oddity task requires participants to detect any difference between stimuli. As a result, for Barense et al. (2012), participants had to form holistic item representations to ensure that the items matched. In contrast, for oddity tasks, a successful strategy might be to search for lower-level feature differences, particularly for familiar object stimuli in which

feature overlap is more difficult to control. These stimuli and the task employed, therefore, mean it is less likely to tax complex conjunctive representations supported by the PRC. It is notable both same, and different, trials were included in Experiment 3.1 (Chapter 3), and did not elicit an effect at standard levels of significance. Again, the use of familiar objects, in which the level of feature overlap was not strictly controlled, means that it is possible that lower-level features were used to discriminate items, and not conjunctive object representations.

In contrast to the findings of Chapter 4 one study has shown that the level of activity in PRC is modulated by the degree of feature overlap in real world objects (Mundy et al., 2012). Participants were scanned whilst they passively viewed high ambiguity (perceptually similar) or low ambiguity (perceptually distinct) objects. In PRC, greater activity was associated with high, relative to low ambiguity items; in lateral occipital cortex, the reverse was true. The task demand, however, might explain the differences. As mentioned above, the oddity paradigm encourages the detection of lower-level featural differences. When objects are passively viewed and presented individually, as in Mundy et al. (2012), this may encourage participants to focus on the entire image, rather than local featural differences.

Together these data suggest that both the level of feature overlap and task demand modulate the contribution of the PRC for object discriminations, although the circumstances under which such patterns are elicited (particularly using fMRI) is still decidedly unclear. It seems likely that oddity tasks, particularly those using real world object stimuli, encourage the use of lower-level featural differences, and therefore a modified version of the oddity task, in

which ‘same’ trials were inserted might stress a more conjunctive processing approach in participants. Furthermore, there is an urgent need to understand how complex, conjunctive, object representations formed by the PRC, interact with lower-level feature conjunctions in extrastriate areas, during perceptual discrimination. For example, are local featural differences between stimuli detected early in the ventral visual stream, and signalled in these regions before being passed up to PRC, or are the conjunctive object representations first formed by passing these conjunctive representations to the PRC before being fed back through the lower level conjunctions to detect featural differences? The PRC may support perceptual discriminations by forming object-level representations, and then guiding a visual search of local item features, supported by extrastriate regions. Due to the speed at which this is likely to occur, fMRI may not provide a useful tool to address this question, but magnetoencephalography (MEG) in which both time course and (a degree of) cortical localisation is available may be more appropriate.

In Chapter 4, activity in the left PRC fROI was modulated by spatial contextual association, but it was not clear exactly what properties of the stimuli resulted in this increased activity, be it the spatial association of the objects (Hannula et al., 2013), associated related object items (Bar, 2004), or the familiarity of the items. Activity in PRC has been shown to be modulated by an item’s familiarity, with familiar objects/faces associated with significantly greater activity than novel objects/faces (Barense et al., 2011). It has been argued that the PRC forms the interface between perceptual processes and conceptual knowledge stored in the anterior temporal lobe (Patterson et al., 2007). It seems apparent that the role of the PRC in the processing of conceptual knowledge warrants further investigation, and elucidating exactly what information is being

recovered for an object item, and how this modulates the level of associated PRC activity, would be important. Given that real world items already have contextual associations, future research should involve the use of novel object stimuli (such as greebles) and the training of participants to associate different types of information with different greeble items, and this would also provide an opportunity to test some of the predictions from mnemonic accounts of MTL functions.

For example, one dual process model proposes that the PRC can support memory for within-domain, but not between-domain associations (e.g., object-object, but not object-location associations – domain dichotomy model; Mayes, Montaldi, & Migo, 2007); the latter association, it is proposed, requires the HC. Similarly, other dual process models suggest that the familiarity signal propagated by PRC can support memory for object-object, or object-item feature associations as long as encoding strategies have encouraged unitisation of the information to-be-remembered (Bastin et al., 2013; Diana, Yonelinas, & Ranganath, 2008; Haskins et al., 2008; Quamme et al., 2007). EMA predicts that the PRC forms unique, conjunctive object-level representations, and that the level of activity in this region is modulated by the degree of feature overlap between object items. One prediction, therefore, might be that an object with a number of highly conjunctive object associates would elicit greater activity in PRC than an object with visually distinct object associates. It is not clear that the dual process models mentioned above would make any predictions regarding the level of feature overlap amongst associated object items. Similarly, although not explicitly stated, it would seem logical to assume that EMA would predict a modulation of activity in HC based upon the degree of conjunctive overlap in associated scene items. Specifically, objects

associated with highly conjunctive scene representations should be associated with greater HC activity than visually distinct scene items. The domain dichotomy model would predict that HC involvement would be required to support memory for this between-domain association. In contrast, BIC would predict increased activity in both posterior PHG (for spatial contextual information), as well as HC for domain-general memory processes such as pattern completion. Neither of these accounts, however, would predict a modulation of HC activity according to the degree of conjunctive overlap between associated scene items.

6.3.2. The nature of the representations supported by the HC

One of the main aims of this thesis was to understand the nature of the representations supported by the HC. Whilst some representational accounts suggest that this region processes allocentric scene representations (e.g., BBB), EMA predicts that this region supports complex conjunctions of spatial features not necessarily limited to scene stimuli. As noted above for PRC, there are outstanding questions about how extrastriate and MTL (particularly the HC) support spatial perception, including whether the HC is involved in spatial conjunctions, and whether this extends to spatial feature changes in objects.

Contrary to BBB, the patient data from the conjunction learning task reported in Chapter 2 suggest that the HC is required to support the learning, and discrimination of, high ambiguity conjunctions of spatial features comprising a scene, not necessarily limited to allocentric processing. The imaging data, however, revealed that activity associated with different view scenes was greater than that associated with same view scenes, as evidenced by the significant HC activity for the *'scenes > objects'* contrast in the different view

oddity tasks in the scene fROI analysis of Chapter 4 (Section 4.3.2.4.2) but not the same view scene item discrimination task (Chapter 3). This larger effect for different view scenes, however, may not mean that the HC only performs allocentric processing. As argued by Lee et al. (2012), presenting scenes from different views necessarily taxes the spatial relations between scene elements to enable the participant to form a flexible representation of the spatial environment. Allocentric processing, therefore, may represent a more complex level of spatial feature conjunctions in comparison to same view scenes.

It is also not clear why real world scenes were associated with increased activity in HC relative to computer generated ones (Chapter 4). As mentioned previously, there are differences in the basic properties of the stimuli which may affect the level of BOLD response. Moreover, the real world scenes may remind participants of previous events and are therefore be associated with increased HC activity due to episodic and/or semantic familiarity. An alternative suggestion is that because the real world scenes often contain a greater number of composite objects, the increased HC activity may reflect the processing of spatial relationships between these object items when presented from different views. Increased activity in the HC has been shown to be associated with greater accuracy on a working memory task requiring maintenance of object location information (Hannula & Ranganath, 2008). Participants were required to remember the identity, and location of four object items in a three-dimensional grid. After a brief delay, the grid was presented again, rotated 90 degrees, and was either identical, or contained a change to one of the objects, or to the location of one of the objects. Comparing activity for correct versus incorrect responses revealed significantly increased activity when the participant was correct. Furthermore, changes in the position of the

item were associated with greater activity relative to changes in item identity. Supporting these findings, Olson, Page, Moore, Chatterjee, & Verfaellie (2006) demonstrated impaired object-location working memory in a group of patients with heterogonous MTL damage. Together, these data suggest that the activity associated with the real world scenes might reflect not only the processing of spatial feature conjunctions, but also the processing of object-in-place feature conjunctions. Moreover, this region might also process the spatial properties of the object stimuli, as evidenced by patient HC3's impaired performance for tadpoles, replicating the spatial object discrimination learning deficits in monkeys after fornix transection (Buckley et al., 2004). The evidence from this thesis suggests that the HC supports spatial feature conjunctions, often required for, but not limited to, the processing of scenes.

For future research, these various factors could be addressed in the conjunction learning paradigm from Chapter 2 as follows. First, it would be important to ask whether patients with HC damage can learn to discriminate between virtual reality scene stimuli in which there were no overlapping geometric spatial features. This would elucidate whether, like object representations in the PRC, scene representations are organised hierarchically in the HC. Second, to understand the nature of the object-location deficit, patients could be tested on rooms that are differentiated on the basis of the locations of the objects within them. Given the increased HC activity associated with remembering objects in locations (Hannula & Ranganath, 2008), the greater level of activity associated with object-full, real world scenes relative to computer generated scenes (Chapter 4), and the working memory deficits of patients in remembering objects in grid locations (Olson et al., 2006), I would predict that patients should show impairments in this task.

6.3.3. Scene oddity as a marker of AD risk

The final chapter in this thesis focused on the possible clinical translation of EMA. The study of individuals at increased genetic risk of AD revealed increases in BOLD response in carriers of ApoE-e4 for scenes in the PCC; this region has been associated with early anatomical and metabolic brain changes in prodromal AD (e.g., Nestor, Fryer, Ikeda, & Hodges, 2003; Nestor, Fryer, Smielewski, & Hodges, 2003; Pengas, Hodges, Watson, & Nestor, 2010). Previous experiments comparing activity levels in ApoE-e4 carriers and non-carriers have used a variety of different cognitive tasks, and stimulus types, leading to a number of contradictory findings (Trachtenberg, Filippini, & Mackay, 2012). The experiment outlined in Chapter 5, therefore, was novel because it examined the effect on the BOLD response, of different stimulus types within the same cognitive task (oddity), and was based on a clear theoretical framework (i.e., EMA). Of relevance to interpreting this finding, and generating further sensitive cognitive paradigms, are the points discussed in Section 6.3.2., in particular what it is about scene stimuli that drives this effect in PCC. For example, the PCC has been implicated in the transformation of egocentric viewpoints in posterior parietal cortex to allocentric representations in HC (Jacobs, Van Boxtel, Jolles, Verhey, & Uylings, 2012; Vogt et al., 1992). An important next step, therefore, would be to compare activity for same and different view scene processing to see whether this effect is only evident for the different view items. Furthermore, if, as discussed in Section 6.3.1, the inclusion of both same and different trials encourages more conjunctive processing, including these trials might increase further the level of activity in ApoE-e4 carriers.

In terms of the sensitivity of applying fMRI as an effective early biomarker for AD, it is essential to understand the stability of this effect over time in the same individuals. More specifically, if an ApoE-e4 participant shows increased functional activity in PCC compared to a carrier group during one session, do they show this again the next time they are tested? To address this question, it would be useful to replicate the findings reported in Chapter 5 with a larger sample, but also scan the participants on two separate occasions with different, counterbalanced versions of the task, to understand the reliability of increased brain responses in this region. A further interesting approach would be to investigate the impact of memory load. Specifically, consistent with a neural effort hypothesis (Filippini et al., 2009; Jagust & Mormino, 2011) (See Section 5.1 for a discussion of how increased neuronal activity might lead to cortical atrophy), would ApoE-e4 carriers show an even greater increase in the BOLD response in PCC compared to carriers when they are placed under particular spatial stress (e.g., a 2 back versus a 1 back working memory task). Finally, there is evidence that the pattern of BOLD response changes over the course of the lifespan, with increases in BOLD response observed in young carriers, whereas the reverse is true in older adult carriers (Filippini et al., 2011). One unanswered, but important, question is whether this reduction in neural activity would be more pronounced for scenes than any other category of stimuli in older adult ApoE-e4 carriers relative to non-carriers.

6.4. Concluding remarks

This thesis has tested the predictions of EMA (Graham et al., 2010), a relatively contemporary conceptualisation of the role of MTL in perception and memory. On the strength of the findings detailed here, there is evidence to suggest that the PRC supports the processing object stimuli, which cannot be accommodated easily by mnemonic explanations. The nature of representations processed by the HC remains less clear, but the patient data in this thesis suggests that this region may form complex conjunctions of spatial features comprising a scene.

A considerable theoretical challenge for representational accounts of MTL function has been the constraints imposed by the declarative/nondeclarative memory distinction. Even in tasks with no overt memory component (i.e., trial-unique perceptual discriminations), which should not tax declarative memory, mnemonic accounts of MTL function will often use the MTL patient's performance to characterise the mnemonic demands of a task. Specifically, if patients show impairments in perceptual discrimination task, then it is concluded that successful task performance must rely on declarative memory; if they show spared performance, however, it is suggested that performance must be supported by non-declarative memory. This necessarily leads to circularity in the debate regarding the role of the MTL in memory and perception, and means that it is impossible to demonstrate that these regions support anything other than declarative memory. Although recently there have been revisions of mnemonic accounts that attempt to accommodate the stimulus specific perceptual deficits observed in patients (e.g., subspan and

supraspan memory; Jeneson & Squire, 2012), they still subscribe to the theoretical view that the MTL supports declarative memory only.

Despite the pervasive declarative/nondeclarative memory distinction, it is apparent that representational accounts have changed the way in which memory researchers have conceptualised the role of the MTL; hybrids of dual process accounts have been proposed to incorporate stimulus specific effects in the MTL (BIC; Diana et al., 2007), and there is growing acceptance of a role for the PRC (Cabeza et al., 2013) and even the HC (Yonelinas, 2013), in non-mnemonic processes – a notion unthinkable ten years ago. For representational accounts, the onus is on proponents of these accounts to now provide explicit predictions as to the stimulus properties (i.e., conjunctions), and tasks that will modulate the recruitment of different MTL structures during perceptual and mnemonic tasks. For example, a number of explanations have been provided as to why the manipulations of stimulus ambiguity, and the tasks employed in this thesis did not modulate activity in stimulus specific regions; a frank appraisal, however, is that the results of increasing feature overlap between items did not support the predictions of EMA. It is important, therefore, to avoid a similar circularity in debate for representational accounts, in which patient performance or the level of associated brain activity is used to infer level of ambiguity in complex conjunctive stimuli.

The ultimate aim of academic debate is the translation of research findings into clinical application. Stemming from experiments examining the contribution of MTL regions to stimulus-sensitive modulations of performance in dementia (Lee et al., 2007; Lee, Buckley, et al., 2006), this thesis has shown how scene oddity discriminations may provide a biomarker for AD risk in healthy

young individuals. It is notable that none of the mnemonic accounts examined in this thesis would have predicted modulations of activity in PCC in ApoE-e4 carriers associated with the stimulus type to-be-processed during a perceptual oddity task. It is the generation of these novel predictions that are of paramount importance to the field, and to society.

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Appendix A

7.1. Whole brain analysis

7.1.1. Stimulus specific effects

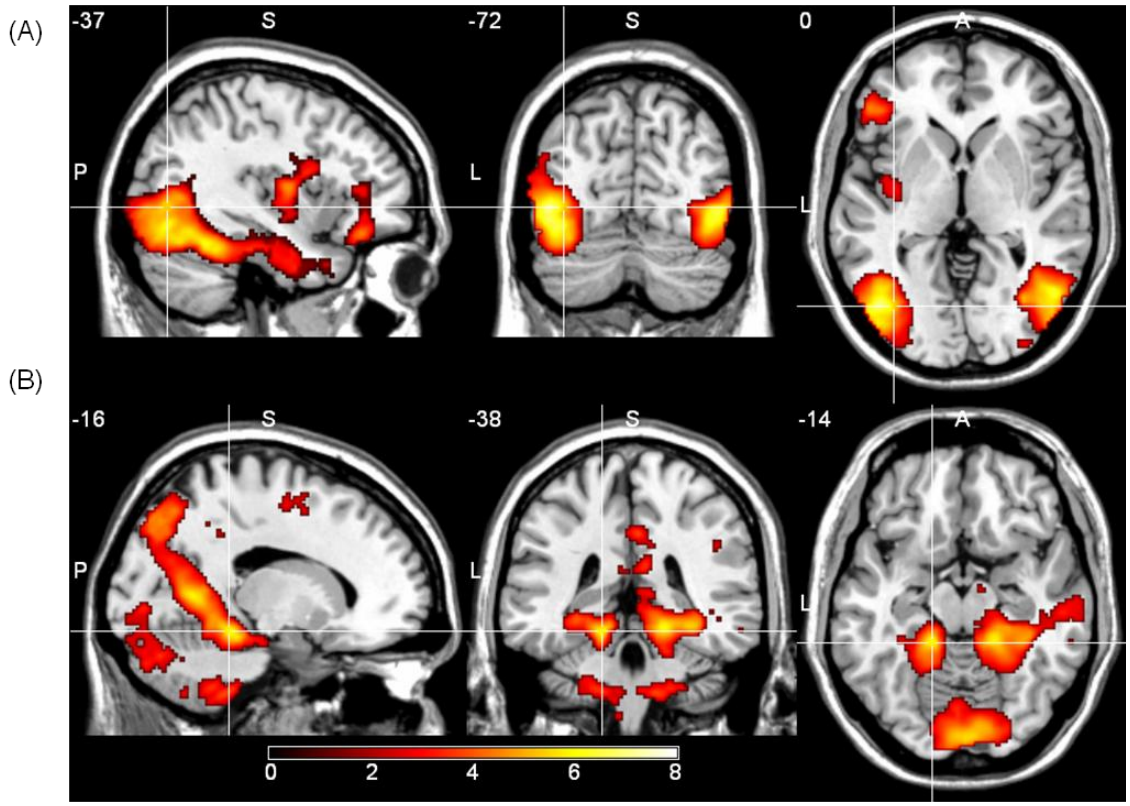

Figure 7.1. ***Significant regions of whole brain activity associated with (A) 'object > scenes', and (B) 'scenes > objects'.***

Table 7.1. ***Local maxima for contrast 'objects > scenes'.***

Region	Z	x	y	z
Left lateral occipital cortex	*7.18*	*-44*	*-72*	*0*
Right lateral occipital cortex	*6.68*	*46*	*-78*	*-4*
Left temporal occipital fusiform cortex	*6.49*	*-38*	*-50*	*-20*
Right temporal occipital fusiform cortex	*4.8*	*40*	*-58*	*-16*
Left occipital fusiform cortex	*5.78*	*-34*	*-74*	*-16*
Right occipital fusiform cortex	*5.24*	*34*	*-68*	*0*
Left fronal orbital cortex	*4.93*	*-34*	*34*	*-16*
Left insular cortex	*4.74*	*-36*	*-6*	*10*
Left frontal pole	*4.65*	*-48*	*38*	*4*
Left inferior frontal gyrus	*4.58*	*-50*	*36*	*0*
Right postcentral gyrus	*3.4*	*62*	*-18*	*28*
Right supramarginal gyrus, anterior division	*3.12*	*54*	*-28*	*52*
Left precentral gyrus	*3*	*-50*	*-4*	*18*
Left insular cortex	*2.8*	*-38*	*-4*	*-4*
Left planum polare	*2.6*	*-42*	*-10*	*-8*

Table 7.2. ***Local maxima for contrast 'scenes > objects'.***

Region	Z	x	y	z
Left parahippocampal gyrus, posterior division	*6.19*	*-16*	*-38*	*-14*
Right parahippocampal gyrus, posterior division	*6.06*	*18*	*-38*	*-12*
Left lingual gyrus	*5.81*	*-26*	*-50*	*-8*
Right lingual gyrus	*6.4*	*20*	*-54*	*4*
Right occipital pole	*6.15*	*4*	*-92*	*-12*
Left precuneous cortex	*5.98*	*-16*	*-58*	*4*
Left precentral gyrus	*4.74*	*-28*	*-6*	*46*
Left middle frontal gyrus	*3.91*	*-34*	*24*	*26*
Right middle frontal gyrus	*4.83*	*26*	*4*	*50*
Left frontal pole	*3.28*	*-36*	*48*	*2*
Right frontal pole	*3.72*	*34*	*46*	*10*
Left lateral occipital cortex	*3.81*	*-42*	*-64*	*38*
Left angular gyrus	*3.33*	*-56*	*-58*	*32*
Left superior frontal gyrus	*3.02*	*-22*	*8*	*62*
Left supramarginal gyrus, posterior division	*2.63*	*-54*	*-48*	*28*

7.1.2. Item and location change effects

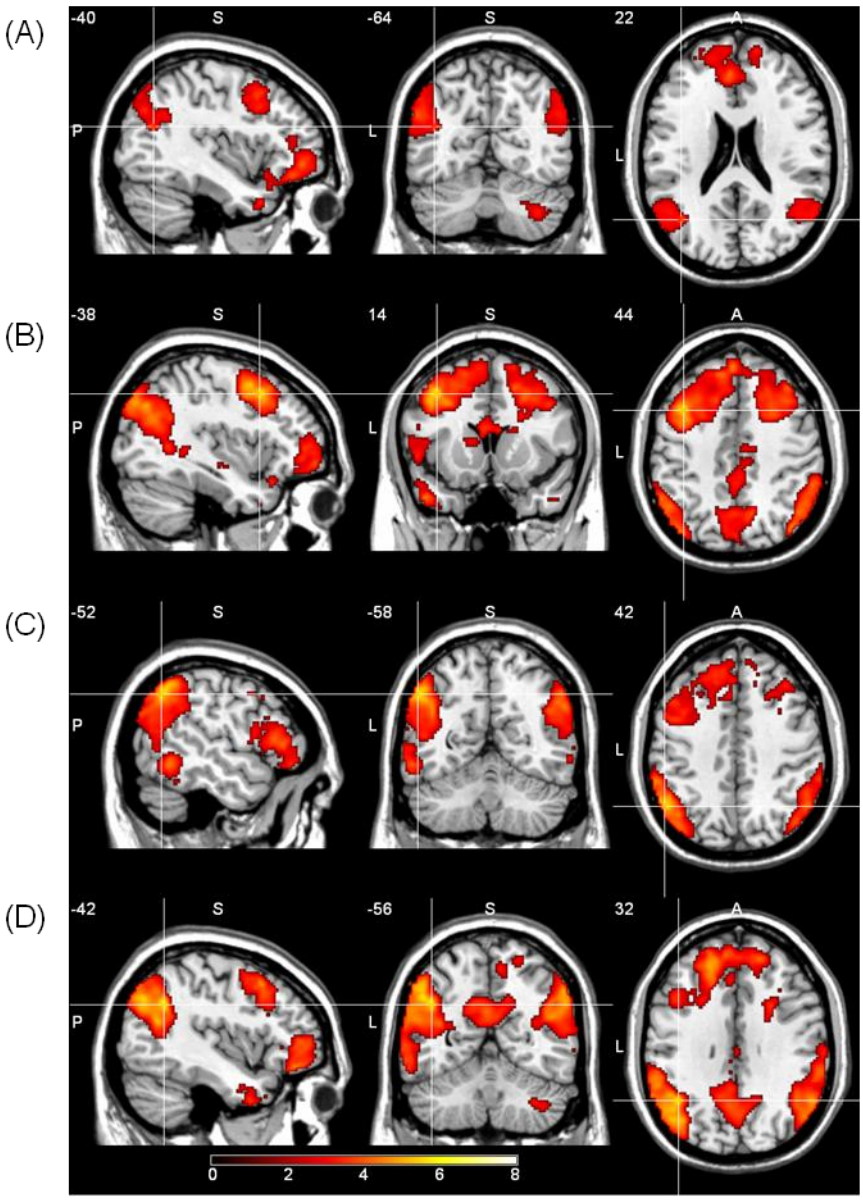

Figure 7.2. ***Whole brain contrasts for (A) 'object item location change > object match', (B) 'object location change > object match', (C) 'scene item change > scene match', and (D) 'scene location change > scene match'.***

Table 7.3. ***Local maxima from contrast 'object item change > object match'.***

Region	Z	*x*	*y*	*z*
Left lateral occipital cortex, superior division	4.27	-40	-64	22
Right lateral occipital cortex, superior division	3.19	46	-60	20
Left middle temporal gyrus	4.84	-62	-48	-8
Right middle temporal gyrus	4.16	68	-30	-6
Left angular gyrus	4.05	-56	-58	32
Right angular gyrus	4.32	54	-54	30
Left frontal pole	4.3	-42	46	-6
Left paracingulate gyrus	4.27	-4	42	22
Left superior frontal gyrus	4.12	-2	42	44
Left inferior frontal gyrus	3.89	-54	22	6
Left frontal orbital cortex	3.74	-48	34	-10
Left interior temporal gyrus	3.71	-58	-50	-16
Left lateral occipital cortex	3.52	-42	-70	34
Right supramarginal gyrus, posterior division	3.32	58	-40	38

Table 7.4. ***Local maxima from contrast 'object location change > object match'.***

Region	Z	*x*	*y*	*z*
Left middle fronal gyrus	5.61	-38	14	44
Left middle temporal gyrus	5.53	-60	-36	-10
Right lateral occipital cortex, superior division	5.37	48	-68	36

Table 7.5. ***Local maxima from contrast 'scene item change > scene match'.***

Region	Z	*x*	*y*	*z*
Left angular gyrus	5.65	-52	-58	42
Right angular gyrus	4.47	56	-58	32
Left lateral occipital cortex	5.09	-44	-62	30
Right lateral occipital cortex	4.4	50	-66	34
Left frontal pole	5	-44	42	-4
Left middle temporal gyrus	4.75	-56	-52	-10
Right middle temporal gyrus	4.56	62	-46	-6
Left superior frontal gyrus	4.36	-18	20	50
Left inferior frontal gyrus	4.24	-42	32	14

Table 7.6. ***Local maxima from contrast 'scene location change > scene match'.***

Region	Z	*x*	*y*	*z*
Left angular gyrus	*5.91*	*-42*	*-56*	*32*
Right angular gyrus	*5.35*	*54*	*-58*	*40*
Left lateral occipital cortex	*5.59*	*-48*	*-68*	*28*
Right lateral occipital cortex	*4.82*	*44*	*-68*	*44*
Left frontal pole	*5.2*	*-24*	*58*	*18*
Left superior frontal gyrus	*5.07*	*-18*	*20*	*52*
Left middle frontal gyrus	*4.97*	*-34*	*8*	*52*
Right middle frontal gyrus	*3.69*	*38*	*30*	*42*
Right supramarginal gyrus	*5.04*	*60*	*-38*	*42*
Right precuneous	*4.55*	*4*	*-68*	*38*
Posterior cingulate cortex	*4.52*	*0*	*-60*	*26*
Left middle temporal gyrus, anterior division	*4.3*	*-52*	*6*	*-30*
Right middle temporal gyrus	*4.04*	*66*	*-48*	*-2*
Right superior frontal gyrus	*4.02*	*18*	*16*	*60*
Right middle temporal gyrus, anterior division	*3.94*	*58*	*2*	*-32*
Right temporal pole	*3.93*	*50*	*10*	*-36*
Left inferior temporal gyrus	*4.14*	*-48*	*6*	*-38*
Left temporal pole	*3.26*	*-34*	*12*	*-42*
Right superior parietal lobule	*3.78*	*20*	*-48*	*64*
Right juxtapositional lobule cortex	*3.17*	*10*	*-10*	*44*
Right postcentral gyrus	*2.65*	*22*	*-36*	*58*

7.2. Inverse efficiency scores by schedule for controls and patients

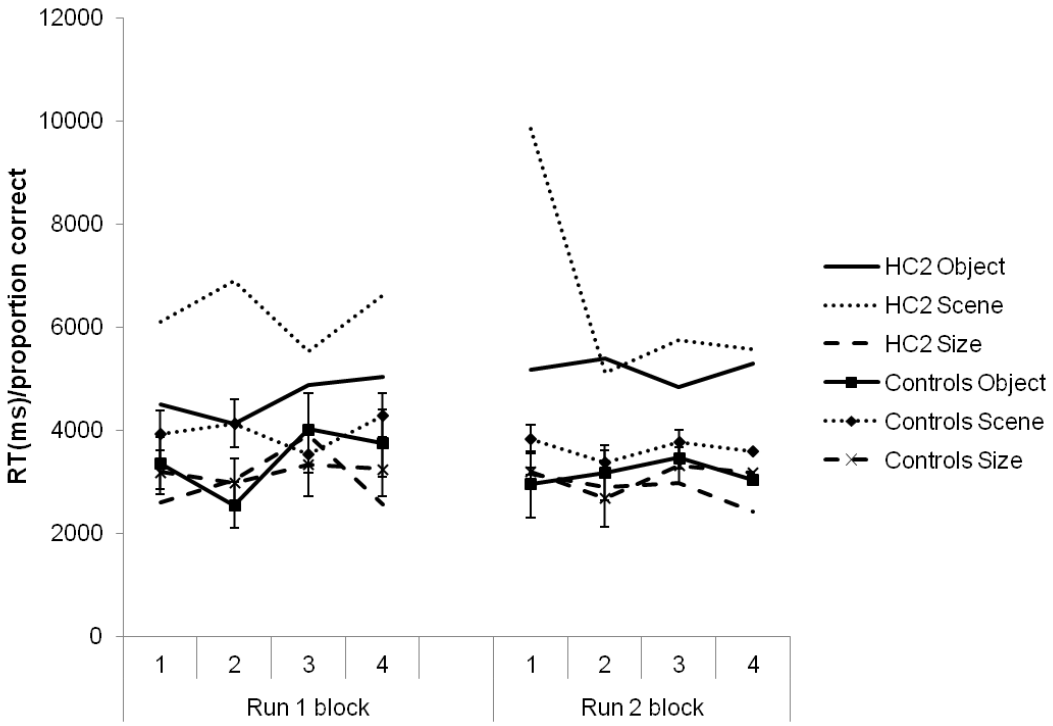

Figure 7.3. ***Inverse efficiency scores plotted by experiment schedule for controls and patient HC2. Values were calculated over blocks of 8 trials (32 trials per stimulus class per run/4 = 4 blocks per run).***

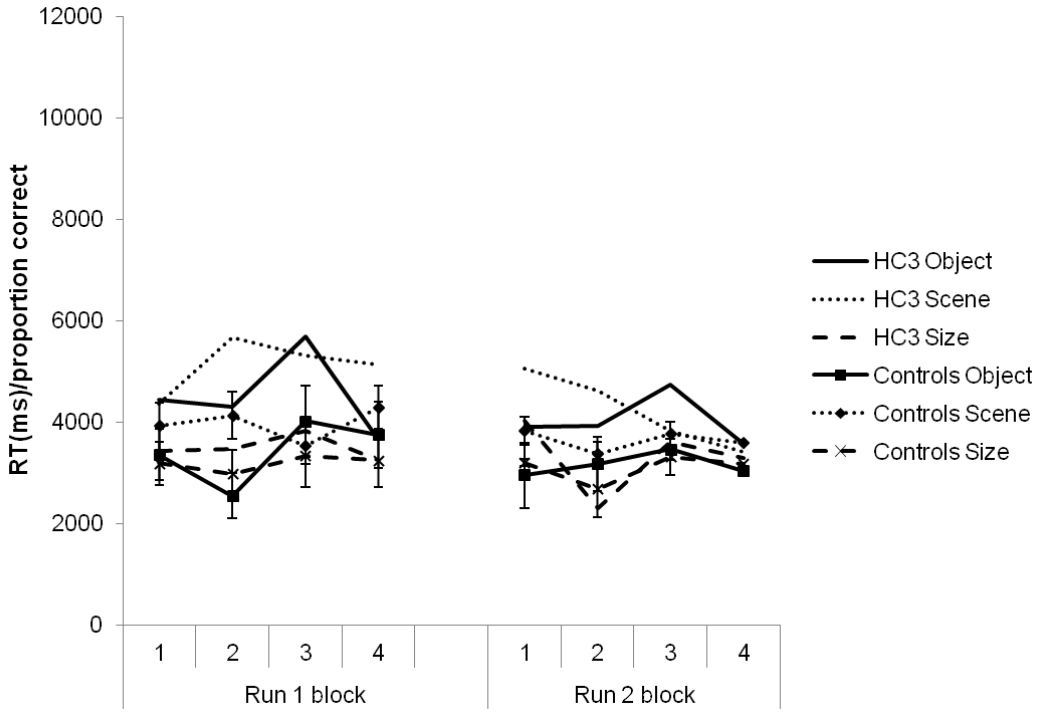

Figure 7.4. ***Inverse efficiency scores plotted by experiment schedule for controls and patient HC3. Values were calculated over blocks of 8 trials (32 trials per stimulus class per run/4 = 4 blocks per run).***

Appendix B

8.1. Whole brain analysis

8.1.1. Stimulus specific effects and modulations of activity according to feature ambiguity

Table 8.1. ***Local maxima for contrast 'objects > scenes'.***

Region	Z	*x*	*y*	*z*
Left precuneous cortex	5.87	-20	-44	12
Right lateral occipital cortex, inferior division	5.87	48	-78	-8
Left central opercular cortex	5.81	-58	-6	4
Left supramarginal gyrus, anterior division	5.64	-60	-28	24
Left insular cortex	5.49	-42	-4	-6
Right insular cortex	5.59	42	-14	-2
Left planum temporale	5.47	-58	-22	10
Right planum polare	5.42	62	-2	4
Left frontal pole	5.43	-2	60	20
Right parietal operculum cortex	6.16	50	-32	22
Parietal operculum cortex	5.18	42	-26	16
Heschl's gyrus	5.07	52	-14	6
Right occipital pole	3.65	32	-98	-6
Left postcentral gyrus	4.11	-22	-34	72
Left superior parietal lobule	3.04	-24	-50	72

Table 8.2. ***Local maxima for contrast*** **'scenes > objects'.**

Region	Z	*x*	*y*	*z*
Left lingual gyrus	7.46	-18	-46	-12
Right lingual gyrus	7.34	22	-44	-14
Left occipital fusiform gyrus	7.28	-16	-84	-14

Table 8.3. ***Local maxima for contrast 'HA objects > LA objects'.***

Region	Z	*x*	*y*	*z*
Left lateral occipital cortex	6.69	-42	-86	2
Right lateral occipital cortex	6.7	54	-66	-14
Right temporal occipital fusiform cortex	6.57	30	-54	-18
Right lateral occipital cortex, superior division	6.47	28	-68	38
Left paracingulate gyrus	6.38	-4	20	44
Right paracingulate gyrus	6.32	4	22	40
Right frontal orbital cortex	6.31	36	24	-6
Left middle frontal gyrus	6.22	-26	2	52
Left insular cortex	5.64	-30	24	-2
Right middle frontal gyrus	5.29	26	0	50
Right inferior frontal gyrus	5.42	54	12	24
Left precentral gyrus	5.29	-48	6	26
Right precentral gyrus	5.41	52	8	22
Left thalamus	5.32	-12	-18	10
Right thalamus	5.49	10	-18	10
Left inferior frontal gyrus	5.29	-44	8	24

Table 8.4. ***Local maxima for contrast 'LA objects > HA objects'.***

Region	Z	*x*	*y*	*z*
Right cingulate gyrus	6.28	6	-52	20
Right frontal pole	6.26	6	62	-6
Right frontal medial cortex	6.2	6	48	-10
Left precuneous cortex	6.13	-2	-56	24

Table 8.5. ***Local maxima for contrast 'HA scenes > LA scenes'*****.**

Region	Z	*x*	*y*	*z*
Right occipital pole	6.76	2	-92	18
Right cuneal cortex	6.76	4	-80	22
Left lingual gyrus	6.35	-10	-74	-2
Right lingual gyrus	6.52	10	-70	0
Left supramarginal gyrus, anterior division	6.35	-42	-38	40
Left frontal pole	4.94	-34	56	16
Right frontal pole	4.35	30	50	28
Left middle frontal gyrus	4.31	-44	30	30

Table 8.6. ***Local maxima for contrast 'LA scenes > HA scenes'*****.**

Region	Z	*x*	*y*	*z*
Left temporal fusiform cortex	6.74	-24	-42	-18
Right lingual gyrus	6.47	16	-52	2
Left parahippocampal gyrus, posterior division	6.29	-22	-34	-22
Right parahippocampal gyrus, posterior division	6.41	20	-34	-18
Left occipital pole	6.33	-10	-104	-2
Right temporal fusiform cortex, posterior division	6.27	30	-30	-24
Left lateral occipital cortex, superior division	5.09	-42	-74	30
Left superior frontal gyrus	4.05	-24	26	48
Frontal medial cortex	3.67	0	50	-20
Frontal pole	3.53	0	58	-16
Left frontal medial cortex	3.41	-8	46	-18
Left frontal pole	3.37	-6	62	-14

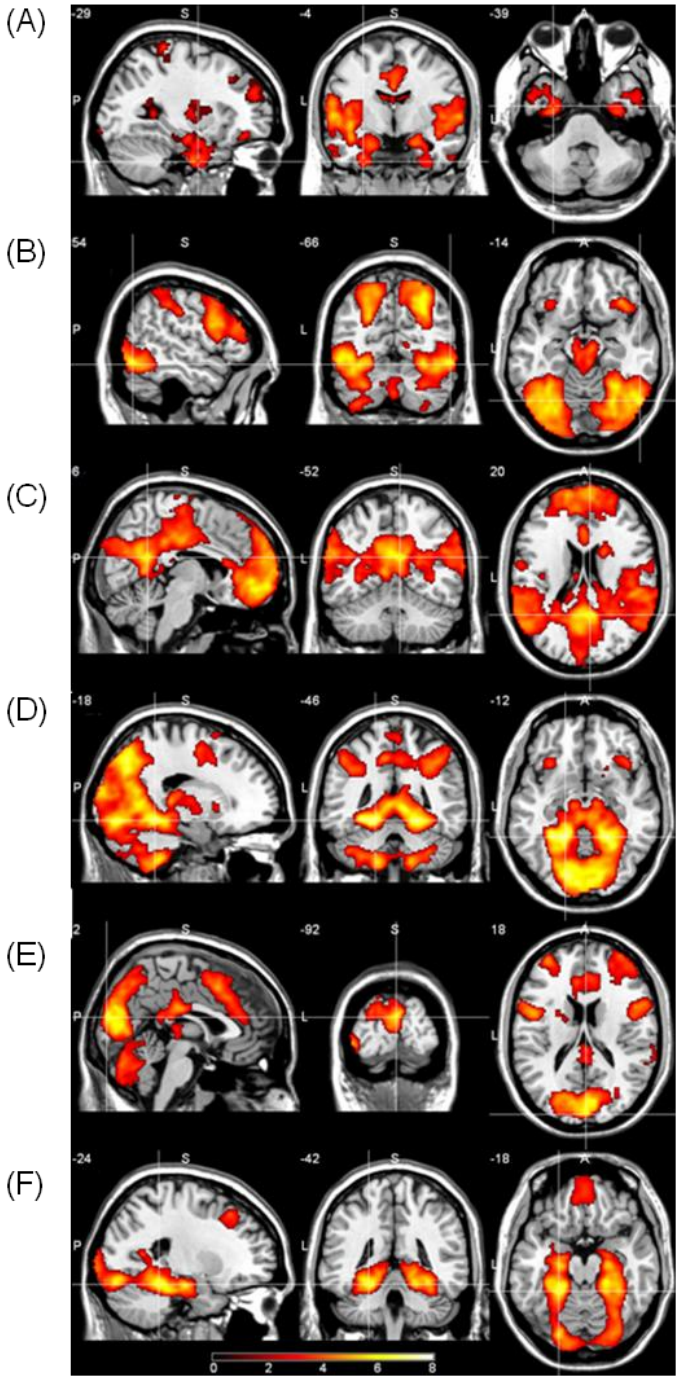

Figure 8.1. ***Whole brain contrasts (A) 'Objects > scenes', (B) 'HA objects > LA objects (C) 'LA objects > HA objects' (D) 'Scenes > objects' (E) 'HA scenes > LA scenes' (F) 'LA scenes > HA scenes'. All images Z > 2.3, p < .05.***

8.1.2. Context effects

Table 8.7. ***Local maxima for contrast 'strong context objects > weak context objects'.***

Region	Z	*x*	*y*	*z*
Left occipital pole	5.12	-12	-102	-4
Right occipital pole	5.19	24	-96	16
Right lateral occipital cortex	5.01	28	-86	16
Left occipital fusiform gyrus	5.01	-24	-74	-14
Left inferior frontal gyrus	3.95	-46	14	28
Right inferior frontal gyrus	4.08	40	18	20
Left middle frontal gyrus	4.23	-40	12	28
Right middle frontal gyrus	3.71	50	12	40
Right precentral gyrus	3.84	44	6	22
Right paracingulate gyrus	3.35	8	28	42
Left frontal orbital cortex	3.11	-52	34	-12
Right superior frontal gyrus	3.24	8	42	38
Right frontal pole	2.85	10	40	56

Table 8.8. ***Local maxima for contrast 'HA scene > HA strong context objects'*****.**

Region	Z	*x*	*y*	*z*
Left lingual gyrus	7.04	-6	-84	-6
Right lingual gyrus	6.69	24	-54	-6
Right lateral occipital cortex, superior division	6.79	18	-74	48
Right middle frontal gyrus	5.79	28	2	54
Left superior frontal gyrus	3.94	-26	4	66
Right superior frontal gyrus	4.12	20	8	66
Left precentral gyrus	6.04	-28	-2	52
Right precentral gyrus	4.03	44	2	48
Left frontal pole	4.35	-40	52	10
Right frontal pole	3.7	36	64	-6
Left paracingulate gyrus	3.29	-12	14	40
Right paracingulate gyrus	3.46	8	22	36
Left cingulate gyrus, anterior division	3.35	-8	30	22
Left insular cortex	3.95	-32	20	2
Left frontal operculum cortex	3.59	-42	14	-2
Left putamen	3.47	-18	14	-2
Left frontal orbital cortex	2.83	-26	6	-10

Table 8.9. ***Local maxima for contrast 'HA strong context objects > HA scenes'*****.**

Region	Z	*x*	*y*	*z*
Left hippocampus	4.15	-18	-8	-20
Right hippocampus	4.29	22	-8	-20
Left temporal fusiform cortex, anterior division	3.87	-30	-8	-40

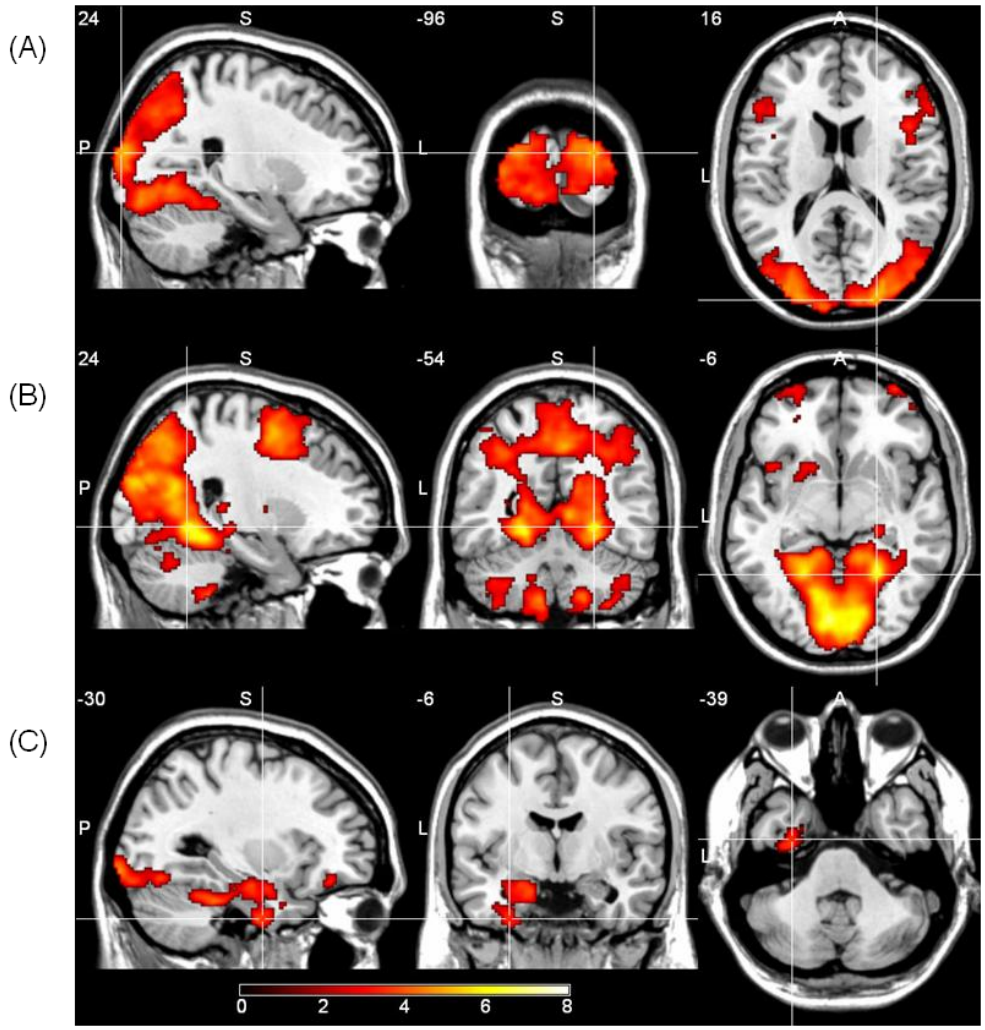

Figure 8.2. ***Whole brain contrasts (A) 'Strong context objects (HA+ LA) > weak context objects (HA + LA)', (B) 'HA scene > HA strong context objects', (C) 'HA strong context objects > HA scene'. All images Z > 2.3, p < .05.***

Appendix C

9.1. Stimulus specific effects at the whole brain level

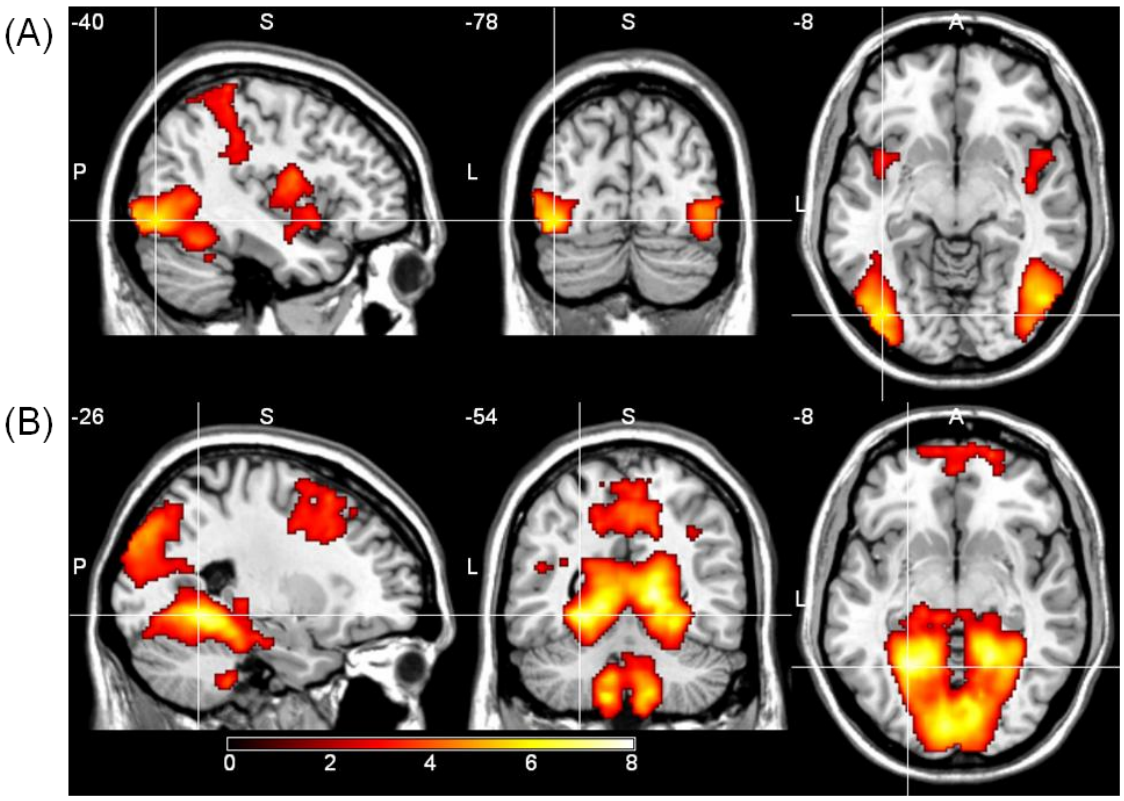

Figure 9.1. ***Stimulus specific activity at the whole brain level resulting from 'objects > scenes' in (A) left PRC, and from the contrast 'scenes > objects' in (B) left HC (Z > 2.3, p < .05).***

Table 9.1. ***Local maxima for contrast 'objects > scenes'*****.**

Region	Z	*x*	*y*	*z*
Left lateral occipital cortex	*6.02*	*-40*	*-78*	*-8*
Right lateral occipital cortex	*6.15*	*48*	*-70*	*-8*
Left supramarginal gyrus	*5.7*	*-52*	*-30*	*34*
Right supramarginal gyrus	*5.16*	*56*	*-30*	*40*
Right parietal operculum cortex	*5.23*	*60*	*-34*	*32*
Right superior parietal lobe	*5.04*	*40*	*-48*	*62*
Left postcentral gyrus	*4.47*	*-28*	*-34*	*72*
Right middle temporal gyrus	*4.74*	*38*	*-56*	*2*
Right temporal occipital fusiform cortex	*4.49*	*46*	*-54*	*-18*
Left insular cortex	*4.5*	*-36*	*-4*	*12*
Right insular cortex	*4.16*	*40*	*-2*	*8*
Left precentral gyrus	*4.32*	*-48*	*2*	*16*
Right precentral gyrus	*4.45*	*54*	*4*	*22*
Left anterior cingulate	*3.59*	*-2*	*16*	*28*
Right anterior cingulate	*3.54*	*2*	*18*	*14*

Table 9.2. ***Local maxima for contrast 'scenes > objects'*****.**

Region	Z	*x*	*y*	*z*
Left lingual gyrus	*7.65*	*-26*	*-54*	*-8*
Right lingual gyrus	*7.66*	*14*	*-54*	*4*
Right precuneous	*7.26*	*16*	*-56*	*12*
Left middle frontal gyrus	*5.09*	*-30*	*14*	*56*
Right middle frontal gyrus	*4.58*	*30*	*10*	*46*
Left superior frontal gyrus	*3.79*	*-24*	*18*	*36*
Right superior frontal gyrus	*3.52*	*26*	*26*	*50*
Right frontal pole	*4.12*	*22*	*62*	*-10*
Left frontal medial cortex	*3.73*	*-2*	*54*	*-10*
Right frontal medial cortex	*3.44*	*6*	*54*	*-16*

9.2. Stimulus specific effects in the MTL

Consistent with analyses in Chapter 4, relative to scenes, objects were associated with increased activity in left PRC (-30, -8, -36: 123 voxels). In the reverse of this contrast, scenes were associated with four clusters of activity. These comprised bilateral HC (-20, -16, -22: 138 voxels; 22, -16, -22: 113 voxels), and bilateral PHG (-22, -34, -18: 135 voxels; 22, -26, -24: 130 voxels) clusters (see Figure 9.2).

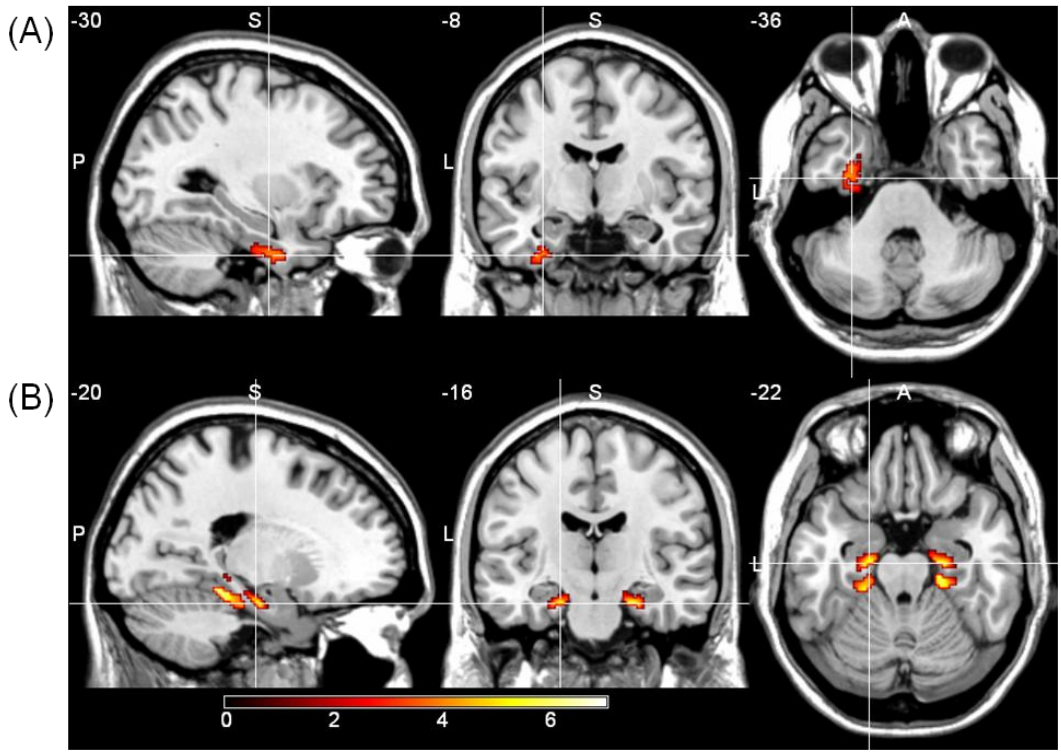

Figure 9.2. ***Stimulus specific activity in MTL resulting from 'objects > scenes' in (A) left PRC, and from the contrast 'scenes > objects' in (B) left HC (Z > 2.3, p < .05).***