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The representational–hierarchical view of amnesia: Translation from animal to human

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ABSTRACT

Animal research has, in our opinion, made an invaluable contribution to our understanding of human amnesia. In this article we summarise our and others' work in this area, focusing on a new view of amnesia we refer to as the representational–hierarchical view. According to this view—and in contrast to the prevailing paradigm in the field—the brain is best understood as a hierarchically organized continuum of representations, each of which is useful for a variety of cognitive functions. We focus our review on four visual discrimination paradigms that have been successfully translated into the human arena: configural concurrent discriminations, pair-wise "morph" discriminations, oddity discriminations, and configural oddity discriminations. The data from the animal studies are first reviewed, followed by illustrations of how the tasks have been utilized in human research. We then turn to the canonical impairment in animal models of amnesia, object recognition, and show how impairments in object recognition can be understood within the representational–hierarchical framework. This is followed by a discussion of predictions of the view related to classic issues in amnesia research, namely whether amnesia is due to a deficit of encoding, storage or retrieval, and the related issue of the role of interference in amnesia. Finally, we provide evidence from animal and human studies that even the hippocampus—almost universally regarded as a module for memory—may be better understood within the representational–hierarchical paradigm.

1. Introduction

The currently dominant view of amnesia is that selective impairments in memory arise from damage to regions of the brain specialized for memory. Specifically it is argued that regions affected in amnesia mediate a particular type of memory, which has been referred to in various ways, including "cognitive memory" (Mishkin, Suzuki, Gadian, & Vargha-Khadem, 1997), "explicit memory" (Graf & Schacter, 1985), "episodic memory" (Tulving & Markowitsch, 1998), and "declarative memory" (Eichenbaum, Dusek, Young, & Bunsey, 1996; Squire, Stark, & Clark, 2004; Squire & Zola-Morgan, 1991; Suzuki & Amaral, 2004; Tulving & Schacter, 1990). These putative memory systems can be contrasted with other cognitive systems, including a separate visual "perceptual representation system" (PRS; Tulving & Schacter, 1990), which includes the extrastriate visual cortex, and is critical both for representing the structure of visual stimuli and for non-declarative memory functions such as categorization, perceptual learning and perceptual discrimination.

This view stemmed initially from classic studies with amnesic patients such as HM who, after bilateral removal of the medial temporal lobe, presented with large deficits on tasks subsequently regarded as tests of declarative memory, but didn't appear to have any overt deficits in other aspects of cognition such as perception (Milner, 1972; Scoville & Milner, 1957; Warrington & Weiskrantz, 1968). Around the same time, a number of non-human primate researchers were using tests of visual cognition to investigate the effects of lesions in both anterior and posterior areas of the ventral visual stream (VVS) leading into the temporal lobe. Many of these studies revealed a dissociation between the behavioural effects of damage to anterior and posterior regions of this stream, which was interpreted as support for a functional distinction, with memory mediated in anterior areas and perception in posterior areas (Blake, Jarvis, & Mishkin, 1977; Cowey & Gross, 1970; Gross, Cowey, & Manning, 1971; Iwai & Mishkin, 1968; Wilson, Zieler, Lieb, & Kaufman, 1972). The subsequent development of the matching- and non-matching-to-sample object recognition tasks (Gaffan, 1974; Mishkin & Delacour, 1975) led to a more detailed description of the anatomical components of this putative 'medial temporal lobe (MTL) memory system' (Bachevalier, Parkinson, &

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Mishkin, 1985; Bachevalier, Saunders, & Mishkin, 1985; Gaffan, 1974; Mahut, Zola-Morgan, & Moss, 1982; Mishkin, 1978; Mishkin & Delacour, 1975; Saunders, Murray, & Mishkin, 1984; Zola-Morgan & Squire, 1985, 1986), now thought to include the hippocampus, and the perirhinal, entorhinal, and parahippocampal cortices. This and subsequent work has lead to the prevailing paradigm in which memory processes are assumed to be independent of processes involved in other cognitive functions such as categorization, perceptual learning, and perceptual discrimination.

Recently, however, a number of researchers have begun to question this paradigm, instead putting forward an alternative account of temporal lobe function, in which memory and other aspects of cognition such as perceptual discrimination are not necessarily segregated into dedicated modules (e.g., Bussey & Saksida, 2007; Fuster, 2003; Gaffan, 2002; Palmeri & Gauthier, 2004; Uttal, 2001). Consistent with this less modular, more distributed view of memory and cognition, we have introduced a novel framework for understanding impairments due to damage in brain regions associated with amnesia (Bussey & Saksida, 2002, 2005, 2007). Instead of emphasizing modules for different kinds of memory, or different processes such as encoding, storage, or retrieval, our view emphasizes the importance of the organization of representations in a hierarchical continuum throughout the ventral visual-perirhinal-hippocampal processing stream (hereafter we will refer to this alternative paradigm as the 'representational–hierarchical view'). This view has been instantiated in a connectionist model (Bussey & Saksida, 2002; Bussey, Saksida, & Murray, 2002, 2003; Cowell, Bussey, & Saksida, 2006) that formalizes the assumptions of the representational–hierarchical view and has been used to generate testable predictions. Because animal models allow relatively precise anatomical localization of brain damage, many of the experiments initially carried out to test this view were conducted in the macaque monkey and the rat, and focused in particular on perirhinal cortex, chosen because it lies at the interface of the putative MTL memory system and the putative perceptual representation system.

A number of studies testing the predictions of the model, some of which are reviewed below, have found strong support for this view. A considerable body of relevant empirical research has also now emerged from labs independent of our own, and the experimental paradigms used in the animal studies have also been very successfully translated to human subjects. Of these studies, several support the modular view and the remainder are either in favour of, or consistent with, the representational–hierarchical view.

In the present article, we outline some of the work that led us to begin to question the utility of the psycho-modular view and suggest that rather than trying to label brain regions as 'memory', 'perception', or other psychological functions, it may be more useful to focus our efforts on considering the representations that these regions contain, how these representations are organized across brain regions, and how this representational organization might help us to understand the effects of brain damage on cognition (Bussey et al., 2002). As a main aim of this special issue is to illustrate how ideas and paradigms from animal work can illuminate studies in human amnesia, we will then show how four broad paradigms designed to test the representational–hierarchical view—configural concurrent discriminations, pair-wise "morphed" discriminations, oddity discriminations, and configural oddity discriminations—have been translated into the human arena, with particular reference to perirhinal cortex. Next, again because the focus of this special issue is translation from animal to human, we will then examine what the representational–hierarchical view can tell us about object recognition memory, which is a task that has been widely used to assess memory in animal models of MTL amnesia (see Winters et al., Clark & Squire, this issue). This is followed by a discussion of predictions of the view related to classic issues in amnesia research, namely whether amnesia is due to a deficit of encoding, storage or retrieval, and the related issue of the role of interference in amnesia. We conclude with some ideas about how other MTL structures damaged in amnesia—namely the hippocampus—might fit into a representational–hierarchical framework.

2. The representational–hierarchical view

2.1. Perirhinal cortex as part of the ventral visual stream object processing pathway

Object recognition has been defined as the ability to identify which of two or more objects has been previously encountered. This has been taken to be a paradigm test of declarative memory in animals (e.g., Manns, Stark, & Squire, 2000), and various tasks that measure this ability have been used to investigate amnesia using animal models (see other papers this issue). Support for the critical role of perirhinal cortex in object recognition comes from electrophysiological recording work (Brown & Aggleton, 2001; Desimone, 1996; Fahy, Riches, & Brown, 1993) demonstrating in macaques that in visual recognition tasks up to 25% of neurons in the anterior parahippocampal region, centred in the perirhinal cortex, respond much more strongly to stimuli that are new than to stimuli that have been seen previously. This pattern of neuronal changes, which is often referred to as repetition suppression, is appropriate for making familiarity judgments because responses are attenuated after a single exposure to stimuli. Furthermore, damage to perirhinal cortex consistently leads to impairments in object recognition (Buffalo, Reber, & Squire, 1998; Eacott, Gaffan, & Murray, 1994; Meunier, Bachevalier, Mishkin, & Murray, 1993; Mumby & Pinel, 1994). As a result, this structure has been considered by many researchers to be a critical component of the putative "MTL memory system" that is damaged in amnesia[1] (Bachevalier, Parkinson et al., 1985; Bachevalier, Saunders et al., 1985; Gaffan, 1974; Mahut et al., 1982; Mishkin, 1978; Mishkin & Delacour, 1975; Saunders et al., 1984; Zola-Morgan & Squire, 1985, 1986), More recently, however, it has been discovered that perirhinal cortex lesions can impair certain visual discrimination tasks that are acquired more slowly over a number of trials—tasks that according to the multiple memory systems view should be non-declarative and therefore should not recruit structures of the putative MTL system (Buffalo et al., 1999; Poldrack & Gabrieli, 1997; Squire, 1992; Squire & Knowlton, 2000; Squire & Zola, 1996; Teng, Stefanacci, Squire, & Zola, 2000; Zola & Squire, 2000). In these tasks stimuli are repeated and the task does not rely on a judgment of novelty. This has led some researchers to suggest that perirhinal cortex is important not just for putative tests of declarative memory such as object recognition, but plays a more general role in the processing of coherent concepts of individual objects, or 'object identification' (Eacott et al., 1994; Murray, Málková, & Goulet, 1998). In the context of the above—with some researchers pointing to a role for perirhinal cortex in declarative memory, and others suggesting a role in object identification—it is interesting to note that the anatomical location of perirhinal cortex is at the interface of the putative MTL memory system and the ventral visual object processing pathway. As a result, we thought that a potentially fruitful way forward might be to explore the explanatory power of considering perirhinal cortex not as an exclusive part

[1] The controversy regarding whether the hippocampus is also critical for object recognition has been reviewed else where (e.g., Clark & Squire; Winters this issue), and so will not be revisited in detail here. For the present purposes it will suffice to summarise the standard view as assuming that structures within the putative MTL system specifically are involved in object recognition.

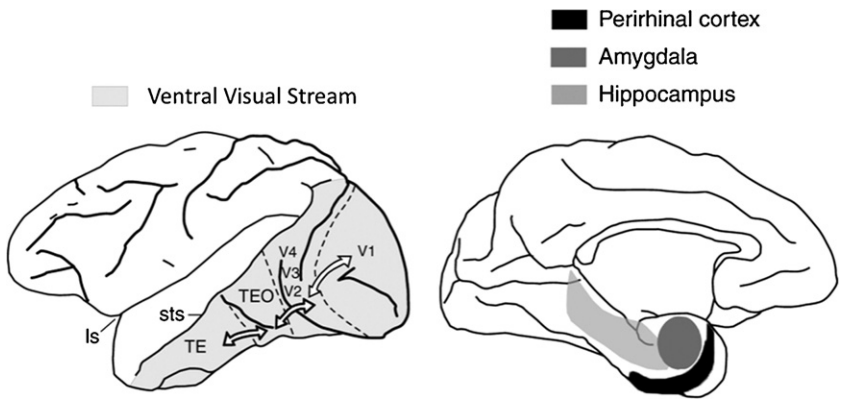

Fig. 1. (a) Lateral and (b) medial views of macaque cerebral cortex. The lateral view shows the ventral visual stream object processing pathway (shaded) and some of the anatomical connections between cortical areas (arrows). The medial view shows structures within the putative medial temporal lobe memory system including the perirhinal cortex and hippocampus. *Abbreviations*: ls, lateral sulcus; sts, superior temporal sulcus; V1–V4, TEO, and TE, visual cortical areas. Figure adapted from Murray et al. (2007).

of an MTL memory system, but instead as an extension of the ventral visual stream (Fig. 1).

The VVS is thought to contain hierarchically organized representations of visual stimuli (Desimone & Ungerleider, 1989). This idea receives much support from electrophysiological and anatomical studies providing evidence that in general, neurons respond to increasingly complex stimuli as you move downstream in the VVS (Tanaka, 1996), and has been referred to by Riesenhuber and Poggio (1999) as the "Standard Model" of object processing in the cortex. According to this view, when an object is presented to and encoded by a subject, it is represented not in a particular 'object' module, but throughout the entire pathway. Yet the object is represented in different ways in different parts of the pathway: as features in posterior regions, as conjunctions of features in more anterior regions, and as complex feature conjunctions—perhaps at the level of object wholes—in anterior regions such as perirhinal cortex (see Fig. 2).

We built a basic computational model to explore whether the location of perirhinal cortex anteriorly within the VVS, and therefore the high-level object representations that it maintains, might be sufficient to explain the effects of lesions in perirhinal cortex on a variety cognitive tests (see Fig. 3). In other words, how much can we understand about the processes that we label memory and perception, etc. simply by considering the hierarchical nature of visual representation in the brain, without postulating separate memory systems or processes? For simplicity, the model collapses the VVS to two layers: a "feature" layer (corresponding to regions posterior to perirhinal cortex) which contains representations of simple features of objects, and a "feature conjunction" layer (corresponding to perirhinal cortex) which contains representations of complex conjunctions of these visual features (Bussey & Saksida, 2002; Bussey, Saksida, & Murray, 2005; Cowell et al., 2006).

The initial test of the model involved damaging the component of the model corresponding to perirhinal cortex, and running simulations of the several findings related to object identification in the literature at the time. These findings include the report by Buckley and Gaffan (1997) that monkeys with perirhinal cortex lesions were impaired when learning a large, but not a small number of concurrent pair-wise visual discriminations, and the subsequent finding that monkeys with perirhinal cortex lesions were impaired on a configural concurrent discrimination learning task (in which discriminanda explicitly shared features), even when the stimulus set size was small (Buckley & Gaffan, 1998); these studies are discussed in more detail below). The model was able successfully to account for these data, and the fundamental reason for the impairment in lesioned networks was the same in all cases: Networks with a damaged perirhinal cortex component did not have the representations necessary to cope with problems in which the individual features alone did not provide a reliable solution. We refer to this situa-

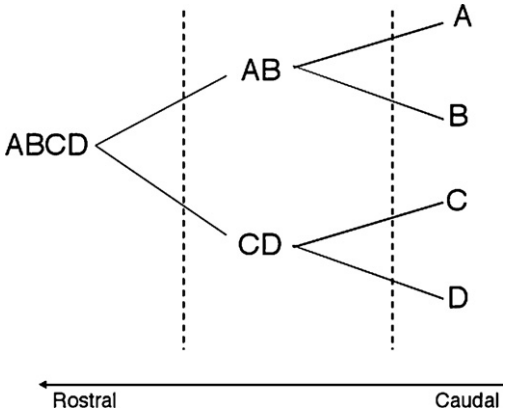

Fig. 2. The proposed organization of visual representations in the ventral visual stream object processing pathway. A, B, C and D refer to relatively simple features represented in caudal regions. More complex conjunctions of these features are stored in more rostral regions, including perirhinal cortex. Figure adapted from Bussey and Saksida (2002).

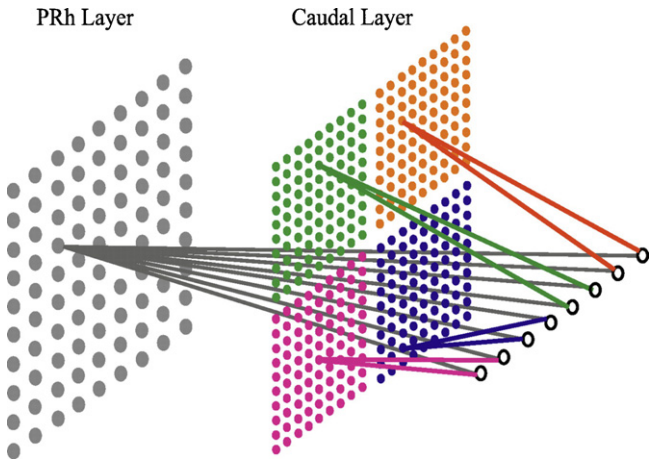

Fig. 3. Diagram of the connectionist model of Cowell et al. (2006). The network consists of two layers of units, a feature layer and a feature conjunction layer, and an outcome node representing a consequent event such as reward. The feature conjunction layer represents perirhinal cortex and the feature layer represents regions caudal to perirhinal cortex in the ventral visual stream. Figure adapted from Cowell et al. (2006).

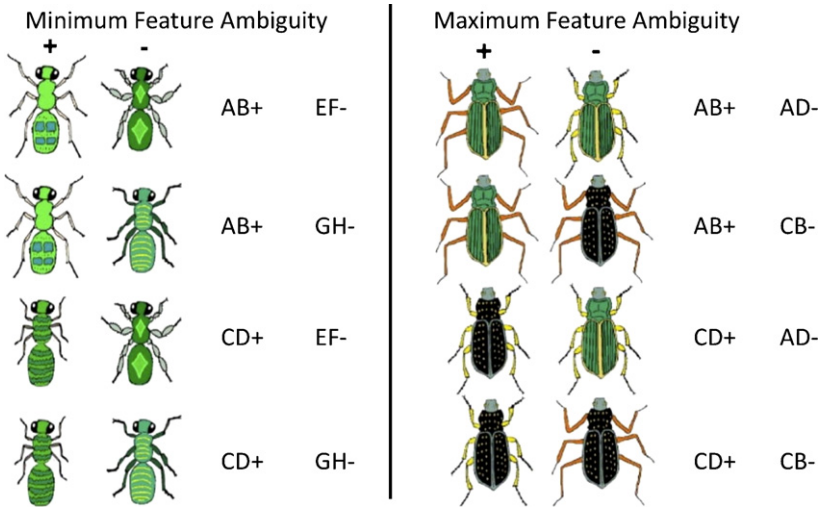

Fig. 4. The concept of feature ambiguity, illustrated with stimuli used in Barense et al. (2005). Within a set of discriminations, each bug is comprised of two features: legs and body plan. Each of these features can be represented by a distinct letter, and shown here are two conditions of a concurrent pair-wise discrimination task. (A) In the minimum ambiguity condition, each individual feature is consistently rewarded or unrewarded. For example, body plan A (four spots on abdomen) is always rewarded, and body plan E (diamonds on thorax and abdomen) is never rewarded. The same is true of all individual body plans and leg configurations. (B) In the maximum ambiguity condition, each individual feature is rewarded as often as not. For example, body plan A (stripes) is rewarded when paired with leg configuration B (longer, orange) but not when paired with leg configuration D (shorter, yellow). Body plan C is rewarded when paired with leg configuration D but not when paired with leg configuration B. However, conjunctions of features are consistently rewarded or unrewarded. For example, body plan A combined with leg configuration B is always rewarded. Body plan A combined with leg configuration D is never rewarded. Thus the configurations of features make it necessary to solve the problem by resolving feature-level ambiguity. We propose that this is achieved using conjunctive representations in perirhinal cortex.

tion, which can occur in visual discrimination tasks when individual features are inconsistently rewarded, as "feature ambiguity" (see Fig. 4). Our hypothesis is that perirhinal cortex contains complex conjunctive representations that can help to resolve such feature ambiguity.

Although it is important to simulate extant data, the real test of a model is to allow it to make novel predictions that can then be tested experimentally. The following section describes a number of experiments that have tested the hypothesis that perirhinal cortex maintains complex stimulus representations that are required when feature ambiguity occurs in visual discriminations, thus demonstrating that the critical factor influencing performance may not be whether the task measures, for example, declarative or non-declarative memory, or memory or perception, but the complexity of the stimulus representations required to solve the task. As described above, to illustrate the translational aspects of this work we focus here on the rationale, development and testing of four broad paradigms: configural concurrent discriminations, pair-wise "morphed" discriminations, oddity discriminations, and configural oddity discriminations. Following this we show how these paradigms have been translated from the animal to the human work.

2.2. Animals: configural concurrent discriminations

As mentioned earlier, Buckley and Gaffan (1997) showed that monkeys with perirhinal cortex lesions were impaired when learning a large, but not a small, number of concurrent pair-wise visual discriminations. This finding is congruent with the finding from object recognition studies that perirhinal cortex lesions impair delayed-match-to-sample with a large, but not a small, set-size (Eacott et al., 1994). Interestingly, in a subsequent study Buckley and Gaffan (1998) demonstrated that perirhinal cortex lesions can also lead to difficulties in discrimination of a very small set of stimuli if the stimuli are manipulated appropriately. In particular, they showed that monkeys with perirhinal cortex damage are impaired on the biconditional discrimination (see Fig. 4), in which four stimuli (A, B, C and D) are presented as compounds, two of which are rewarded (AB+, CD+) and two of which are not rewarded (CB−, AD−), a result later replicated in rats (Eacott, Machin, & Gaffan, 2001). Buckley and Gaffan (1998) concluded on the basis of these and other results that perirhinal cortex plays a role in the visual identification of objects, because "monkeys with perirhinal or combined perirhinal and entorhinal cortex damage have been shown to be specifically impaired on tasks that require a relatively high level of ability to process coherent concepts of multiple individual objects".

The question that we wanted to ask was: what specifically does perirhinal cortex contribute to the ability to identify objects? According to our model, the critical factor involved in all of these manipulations of the difficulty of object identification was the degree of feature ambiguity. For example, the biconditional discrimination manipulates feature ambiguity directly: individual features (A, B, C and D) are rewarded as often as not, so are completely ambiguous. As a result, the conjunctions of features (AB, CD, CB, AD), which are consistently rewarded or not rewarded, are required to solve the discrimination. Simulations with the model provided evidence that the same situation was at the heart of the deficit on large sets of concurrent discriminations: as stimulus set size increases, the likelihood that an individual feature appears in two different objects increases naturally, leading to impairments in the perirhinal cortex-damaged networks on large, but not small, sets of concurrent discriminations. So, according to the model, the critical feature is not set size *per se*; it is feature ambiguity.

To test this hypothesis explicitly, we needed to run an experiment in which the number of object pairs was held constant, but the degree of feature ambiguity was varied (see Fig. 5). Monkeys were tested in three conditions, Maximum Feature Ambiguity, in which all four features were explicitly ambiguous (AB+, CD+, BC−, AD−; the biconditional problem); Minimum Feature Ambiguity, in which no features were explicitly ambiguous (AB+, CD+, EF−, GH−); and Intermediate Feature Ambiguity, in which two features were explicitly ambiguous (AB+, CD+, CE−, AF−) (Bussey et al., 2002). The prediction of the model, of course, was that perirhinal cortex lesions should have a greater effect on discrimination learning of problems with greater feature ambiguity, even when the number of problems

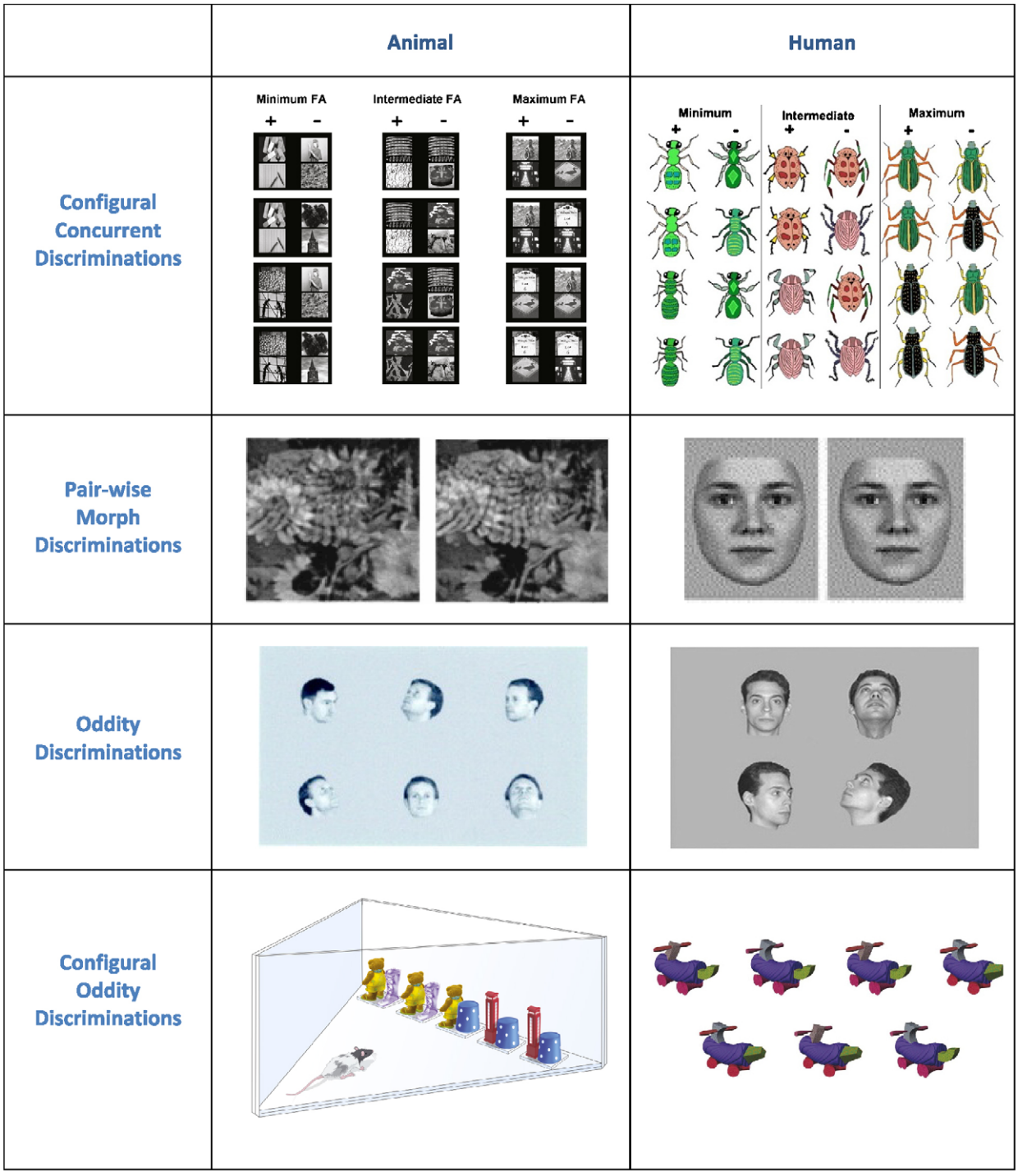

Fig. 5. Example stimuli used in animals and humans in the four categories of tasks reviewed here: concurrent configural discriminations, pair-wise "morphed" discriminations, oddity discriminations, and configural oddity discriminations.

to be discriminated is the same. As predicted, it was found that as the degree of feature ambiguity was increased, monkeys with lesions of perirhinal cortex became increasingly impaired. Note that we do not see perirhinal cortex as a configural module. Conjunctive visual representations, in our view, exist throughout the visual stream; those in perirhinal cortex are just those at a high (whole object) level in the hierarchy. In this way our view differs from others that suggest a role for parahippocampal regions specifically in housing configural representations (e.g., Eichenbaum, Otto, & Cohen, 1994; Gluck & Myers, 1993).

Additional evidence that perirhinal cortex contains high-level conjunctive representations comes from the observation that lesions of perirhinal cortex in monkeys severely impair the 'transverse patterning' task (Alvarado & Bachevalier, 2005; Saksida, Bussey, Buckmaster, & Murray, 2007). Transverse patterning requires subjects to solve 3 pair-wise discriminations concurrently: A+ versus B−, B+ versus C−, and C+ versus A−. Just as in the biconditional discrimination, individual stimuli are rewarded as often as not, and so the conjunction of features is required to solve the discrimination.

Finally, although it has sometimes been taken as evidence against the representational–hierarchical view (Squire et al., 2004), further support for the idea that feature ambiguity is a critical aspect of tasks that tax perirhinal cortex comes from a study by Hampton and Murray (2002). In this study, monkeys with perirhinal cortex damage were trained on a large number of visual discriminations. They were then required to discriminate versions of the same images (in probe trials) that were rotated, enlarged, shrunken, presented with colour deleted, or degraded by masks. Critically, none of these manipulations explicitly affected feature ambiguity, because components of the stimuli were not duplicated across discriminanda. For example, in the chequerboard mask manipulation, 50% of each stimulus was masked by a chequerboard pattern (various resolutions were used). This obviously makes the discrimination more difficult because of a reduction in information, but the remaining information is no more ambiguous than it was previously—the animal could, for example, simply focus on a feature in the top right corner of both discriminanda to make a successful discrimination. The same is true of the size, colour and rotation manipulations. In fact, size manipulations are often used as control conditions for difficulty in experiments testing the feature ambiguity hypothesis (e.g., Barense et al., 2005)—in these cases, subjects with PRh damage are impaired on the feature ambiguous tasks such as the biconditional but not on equally difficult size manipulation tasks. Interestingly, although performance of both controls and monkeys with perirhinal cortex damage was impaired, suggesting that the manipulations increased difficulty of discrimination, the lesioned group was not differentially affected by the manipulations. These results show that under a number of conditions not involving increased feature ambiguity, perirhinal cortex is not critical for the identification of stimuli, further supporting the hypothesis that perirhinal cortex contains complex conjunctive representations that enable the system to resolve such feature ambiguity at the object level.

As the tasks described here were tests of simple visual discrimination, and the critical factor affecting performance was feature ambiguity, this suggests that perirhinal cortex is not important exclusively for a specific type of memory, cognitive function or process, but that it may be important for any task that requires the complex, high-level stimulus representations that are supported by this region.

2.3. Animals: pair-wise "morph" discriminations

The representational–hierarchical view maintains that representations in any region within the ventral visual-perirhinal-hippocampal stream can be useful for a variety of cognitive functions, including both memory and perceptual discrimination. We therefore followed up the configural discrimination studies with a study using a "morph" paradigm that tests perceptual discrimination ability more explicitly (Bussey et al., 2003). Although morphing does not manipulate feature ambiguity in a controlled manner, the morphing algorithm creates pairs of stimuli with an increasing number of features shared in common, thus increasing feature ambiguity within a pair-wise discrimination paradigm (see Fig. 5). The degree to which two stimuli are morphed can be adjusted to produce pairs of stimuli that are relatively perceptually similar, and pairs that are relatively perceptually dissimilar.

We first tested monkeys on acquisition of discriminations of morphed stimuli, and found that monkeys with perirhinal cortex lesions were impaired only when the discriminanda were highly morphed and therefore relatively similar, showing once again that it is not number of object pairs *per se*, but the degree of feature ambiguity, that is the critical factor leading to impairments. In addition, an assumption of at least some versions of the standard view – that the more rapidly a discrimination is solved, the more declarative it will be, and the more it will require MTL regions (Broadbent, Squire, & Clark, 2007) – was shown to be wrong: perirhinal cortex lesions impaired the more slowly acquired, but not the more rapidly acquired, discrimination. So neither set-size *per se*, nor speed of acquisition, determines recruitment of the MTL; the critical factor is feature ambiguity. In a second experiment, which targets perceptual ability more directly, we trained monkeys to criterion on a single-pair discrimination of unmorphed stimuli, and then in probe trials tested their performance on morphed versions of the original stimuli. Monkeys with perirhinal cortex lesions were again impaired when perceptual demands were high, but not when they were low. Critically, no significant learning occurred across trials during the probe sessions, indicating that perceptual deficits in this task were not simply a result of learning demands (Bussey, Saksida, & Murray, 2006; Hampton, 2005; Levy, Shrager, & Squire, 2005). Furthermore, monkeys with perirhinal cortex damage performed no differently from controls on conditions in which stimuli were relatively dissimilar, suggesting that the fundamental problem was not one of memory for which of the stimuli was correct. In addition, monkeys with perirhinal cortex damage performed as well as controls on colour discriminations that were matched in terms of difficulty to the high feature ambiguity condition, suggesting that the pattern of effects was not simply a result of difficulty or ceiling effects (Bussey et al., 2003). This provides further evidence for the idea that that perirhinal cortex is not important exclusively for a specific type of memory, cognitive function or process, but that it may be important for any task that requires the complex, high-level stimulus representations that are supported by this region.

2.4. Animals: oddity discriminations

The foregoing experiments indicate what appear to be perceptual impairments following a lesion in the putative MTL memory system. Buckley, Booth, Rolls, and Gaffan (2001) also investigated a possible role for perirhinal cortex in perception. To this end, these authors devised several perceptual oddity tasks in which monkeys had to choose which stimulus of several presented simultaneously on a touch screen was the "odd one out". Because stimuli were presented to subjects simultaneously, within a given problem there was no requirement to remember the stimuli across a delay, minimizing the memory load in the task (see Fig. 5). Monkeys with damage to perirhinal cortex were selectively impaired on this task relative to control monkeys when stimuli were presented across different views, requiring object-level representations to solve the task. They remained unimpaired on the task when simple features were sufficient to solve the problem (e.g., when the odd stimulus was a different colour, a different shape, or a different size) even when these discriminations were extremely difficult, again suggesting that the issue was not discrimination difficulty *per se*. This led these authors to conclude that perirhinal cortex damage leads to impairments on perceptual discriminations at the object level.

Bartko, Winters, Cowell, Saksida, and Bussey (2007a) conducted a similar experiment using a spontaneous oddity paradigm for rats, which capitalizes on the fact that rats will naturally spend more time exploring novel objects compared to familiar ones. This robust phenomenon has been exploited thoroughly in the form of the spontaneous object recognition paradigm (see Winters paper this issue, and later section), and offered an opportunity to develop a version of oddity for the rat that was not subject to some of the difficulties that can occur in non-spontaneous, rewarded paradigms. In this study, three objects were presented simultaneously: two identical objects and a third "odd one out". Normal rats divided their exploration between the two identical objects, resulting in relatively increased exploration for the odd object. Rats with perirhinal cortex damage were impaired relative to the control group on objects with high perceptual similarity, but

when the objects were not perceptually similar, performance of the lesion group was indistinguishable from controls. As with the monkey paradigm described earlier, the failure of the perirhinal cortex group to show preference for the odd object can be viewed as primarily a perceptual, rather than a mnemonic deficit because all of the information necessary to make the oddity judgment was available to the animal at one time, supporting the idea that the stimulus representations maintained by this region may be the critical factor underlying the role of this region in any number of cognitive functions. Previous oddity studies have been criticized because monkeys require extensive training to learn the task, suggesting that learning or memory may play a role (Levy et al., 2005; Shrager, Gold, Hopkins, & Squire, 2006; Squire, Shrager, & Levy, 2006). Rats, however, perform the spontaneous oddity task immediately and without training, thereby eliminating any significant contributions of across-trial learning.

2.5. Animals: configural oddity discriminations

Feature ambiguity was manipulated indirectly in the rat oddity study by using perceptually similar stimuli with shared features in the high similarity condition. In order to determine more definitively whether feature ambiguity was the basis of the deficit in animals with perirhinal cortex lesions, we developed a configural version of the oddity paradigm in which feature ambiguity was manipulated directly (Bartko, Winters, Cowell, Saksida, & Bussey, 2007b). The biconditional discrimination (AB+, CD+, CB−, AD−) was again used as inspiration (see Fig. 5). Thus, in the configural version of the oddity task, rats were presented with a total of 5 objects: two copies of one object pair (CB1 and CB2), two copies of a second object pair (AD1 and AD2) and one copy of an "odd one out" (AB). The odd object in this condition can only be identified using conjunctions of features, because each individual feature in the odd object appears as often as not in the alternative, repeated objects. In the control condition, rats were also presented with a total of 5 objects: two copies of one object pair (EF1 and EF2), two copies of a second object pair (GH1 and GH2) and one copy of an "odd one out" (AB). The odd object in this condition can be identified using individual features alone since there is no overlap with the alternative object pairs. Normal rats divided their exploration between the two identical objects within the pairs in both the configural and control conditions, resulting in an overall apparent "preference" for the odd object. Rats with damage to perirhinal cortex were highly impaired in the configural, but not the control, condition. This study therefore provides additional support for the assertion of the representational–hierarchical view that it is the complex stimulus representations maintained by perirhinal cortex that are the critical factor, and any task that places demands on these representations will be affected when the region is damaged, whether the task measures memory, perception or some other psychological function.

3. Translation from animal to human

Amnesic patients do not present with obvious impairments in visual perception: they are rarely impaired on standardized neuropsychological tests of perception such as the copying condition of the Rey–Osterrieth figure (Osterrieth, 1944), which requires participants to copy a complex drawing, or the Visual Object Space Perception battery (Warrington & James, 1991), which is comprised of a number of tests assessing a range of perceptual abilities such as identifying incomplete pictures of letters and noting positions and quantities of items on the page (Lee, Barense, & Graham, 2005). In addition, early studies that examined the role of MTL structures in perception by adapting standard memory tasks to have low mnemonic demand found amnesics to be unimpaired (Buffalo et al., 1998; Holdstock, Gutnikov, Gaffan, & Mayes, 2000). When considered with the large and obvious impairments seen in memory in such patients, it is no wonder that the possibility of perceptual impairment in amnesia was not considered to be likely (although see Gaffan, 2001, 2002; Horel, 1978). However, what is less clear is why the foregoing evidence is still routinely used to argue that perirhinal cortex has no role in perceptual discrimination (Squire et al., 2004; Suzuki, 2009), in the face of the evidence such as that presented so far in this review showing that perceptual discrimination impairments can be revealed—but only under certain circumstances. The finding that animals or humans with MTL lesions are unimpaired at simple tests of perception does not indicate that perception is normal; nor does it support a modular versus representational view. Indeed spared performance on simple tests of perception is precisely what the representational–hierarchical view predicts.

Furthermore the representational–hierarchical view is clear that the critical factor that must be manipulated is feature ambiguity. A problem with both standardized neuropsychological tests of perception and the early studies in amnesics, therefore, is the fact that feature ambiguity was not addressed. Recently, however, a relatively large number of visual discrimination studies in humans in which feature ambiguity was manipulated directly or indirectly have been carried out. These consist of both patient studies and imaging studies in healthy individuals, and many are direct analogues of the animal studies reviewed earlier. The use of tasks essentially identical to those used in the animal studies with human patients is potentially a very powerful approach, allowing for more effective translation from animal to human. Converging evidence from animal studies, in which precise and consistent localization of damage is possible, and directly analogous patient studies has great potential to clarify inconsistencies from patient studies, in which brain damage is rarely circumscribed. If we also bring functional imaging in healthy participants into the picture, we can then investigate processing in the intact human brain. We now turn to a discussion of how our four broad paradigms—configural concurrent discriminations, pair-wise morphed discriminations, oddity discriminations and configural oddity discriminations—have been translated into human work, and how they are contributing to what we know about amnesia.

3.1. Humans: concurrent configural discriminations

Barense et al. (2005) assessed the performance of two groups of patients on the discrimination task described earlier (see Fig. 5), on which macaques with perirhinal cortex damage were impaired as a function of degree of feature ambiguity (Bussey et al., 2002). One group of patients had damage to the hippocampus, and a second group had more extensive damage to the medial temporal lobe including perirhinal cortex. Both patient groups had been tested earlier on general neuropsychological tests of perception (Osterrieth, 1944; Warrington & James, 1991), and all patients performed within the normal range on these tests, suggesting intact perceptual abilities as traditionally assessed. The discrimination task structure was identical to that used in the monkey study; for each stimulus type, three levels of feature ambiguity were used—minimum, intermediate, and maximum—and the number of objects to be remembered was constant for all conditions. However, the stimuli were altered to make them into coherent objects, more suitable for human subjects (see Fig. 5). For example, two of the conditions involved "blobs" and "bugs", and each stimulus item was composed of two explicitly defined components (e.g., shape and fill). Barense et al. (2005) found that the patients with selective hippocampal lesions performed no differently from age-matched controls on all conditions. The patients with larger MTL lesions including damage to perirhinal cortex, on

the other hand, showed the same feature-ambiguity-dependent pattern of results as the monkeys with perirhinal cortex damage in Bussey et al. (2002): they were significantly impaired in the intermediate and maximum feature ambiguity conditions, but performed normally on all minimum feature ambiguity conditions. Control subjects performed equally across all conditions and, although their performance was in general very good, controls performed well below ceiling on the "barcode" discriminations, making around 10 errors to criterion, suggesting that the deficits observed in the MTL group were unlikely to be a result of task difficulty. Furthermore, because more total features were present in the lower ambiguity conditions, the magnitude of impairment in the MTL group was inversely related to the number of features presented, suggesting that any differences in memory load were not critical to eliciting impairments in MTL patients (Suzuki, 2009).

3.2. Humans: pair-wise "Morphed" discriminations

Lee, Buckley et al. (2005) adapted the monkey morph paradigm described above (Bussey et al., 2003) for use with humans (see Fig. 5), and studied the same patients tested by Barense et al. (2005)—one group with selective hippocampal damage and a second group with more extensive medial temporal damage including perirhinal cortex. Again, the structure of the task was essentially identical to the task used with monkeys. Participants were presented with a pair of unfamiliar images for several trials, and asked to touch the "correct" one. During the remaining trials in the session, participants were presented with the same images, morphed together to various degrees to create several levels of difficulty, and were asked to select the image containing the greater proportion of features of the original correct stimulus. In addition, a simultaneous version of the same task was administered to these patients several months later. This version of the task was identical to the one just described, with the exception that on each trial the original correct stimulus was displayed above the two choice stimuli, obviating the need for subjects to retain a memory of the correct stimulus throughout the task.

In support of the previous monkey work, it was found that on both versions of the morph task, the patients with damage to MTL including perirhinal cortex were impaired at discriminating faces, whereas the group with damage to only the hippocampus performed no differently from controls. The patients with perirhinal cortex damage were also impaired at discriminating objects in the pair-wise discrimination, but not in the simultaneous matching, object condition. Neither patient group had any difficulties with difficult colour discriminations. Lee, Buckley et al. (2005) concluded—based on the similarity of findings across the two tasks, and the fact that the simultaneous version had a minimal mnemonic component—that the observed deficits were more likely to be perceptual than mnemonic in nature. Furthermore, as in the equivalent monkey study, neither of the subject groups showed an effect of learning across trials on either version of the task, suggesting that the deficits were not primarily deficits of learning.

Interestingly, Levy et al. (2005) and Shrager et al. (2006) also conducted versions of the morph experiment in humans, and came to very different conclusions from those of Bussey et al. (2003) and Lee, Buckley et al. (2005). Levy and colleagues attempted a direct replication, in humans, of the monkey morph experiments. The structure of the tasks was essentially identical to that used by Bussey and colleagues, although the stimulus sets were different. Their subjects were two patients with MTL damage including perirhinal cortex. In one condition, participants were shown two morphed images, and were asked to say whether they were the same or different. In a subsequent condition, participants were again shown two morphed images, but were required to learn across a number of trials which image was correct and which was incorrect. The images shown in this condition were images that the same subjects had successfully discriminated in the initial same-different condition. In the initial same-different condition, patients performed as well as controls. In the second condition, one patient was not distinguishable from controls whereas the other patient was somewhat impaired. Because of this difference in results across the two conditions, the authors suggested that the impairment was due to difficulties with learning rather than perception.

Shrager et al. (2006) attempted to replicate the human morph study by Lee, Buckley et al. (2005). Their subjects were four patients with hippocampal damage and two patients with large MTL lesions including the hippocampus. They used four versions of the morph tasks. The first two experiments were designed to replicate exactly the two experiments conducted by Lee, Buckley et al. (2005), although the stimuli used were similar but not identical to those used in that study. The third experiment was a trial-unique version of the simultaneous matching task, and the fourth experiment was a visual matching task in which participants were asked to scroll through an ordered series of 100 morphed images to try to find a match to the target image. Both patient groups performed as well as controls on most conditions. However, similar to the result found by Lee, Buckley et al. (2005), the MTL group were impaired on one of the faces tests in the simultaneous visual discrimination task.

Both Levy et al. (2005) and Shrager et al. (2006) interpret their data as supporting the psycho-modular view of memory, and state that their "results support the principle that the ability to acquire new memories is a distinct cerebral function, dissociable from other perceptual and cognitive functions." Shrager et al. (2006) suggest that the impairment that they found on the simultaneous visual discrimination task is most likely mnemonic, because no impairments were found on their trial-unique version of the task. Furthermore, they suggest that the discrepancy in results between their study and that of Lee, Buckley et al. (2005) is probably due to differences in extent of brain damage in the different subjects, and that the patients tested by Lee, Buckley et al. (2005) likely have damage in cortical regions beyond the hippocampus and perirhinal cortex, in areas known to be involved in higher visual processing. These two possibilities were subsequently addressed in patient and imaging studies using the oddity paradigm, discussed in the following section.

3.3. Humans: oddity discriminations

Oddity—arguably the task that most convincingly eliminates mnemonic confounds (Buckley & Gaffan, 2006)—has also been examined in both human patients and in healthy human participants via functional imaging. Similar to the morph experiments, the results are not completely consistent across laboratories. Stark and Squire (2000; also see Levy et al., 2005) conducted a version of the oddity task used in monkeys by Buckley et al. (2001). As in the monkey study, participants were required to choose the odd stimulus from 6, and various stimulus categories (e.g., shape, colour, size, objects, faces) were used. Some discriminations could be made on the basis of individual features (shape, colour, size), and others placed greater demand on conjunctions of features (objects and faces). Unlike monkeys with perirhinal cortex damage, amnesic patients were indistinguishable from controls across all stimulus conditions. As a result, the authors concluded that human perirhinal cortex is "functionally different from perirhinal cortex in monkeys with respect to visual perception", and that perirhinal cortex mediates memory exclusively in humans.

Lee, Bussey et al. (2005) also conducted a version of the oddity task used in monkeys by Buckley et al. (2001), in the same patients that were assessed in their morph experiments and configural discrimination learning experiments (Barense et al., 2005; Lee, Buckley et al., 2005; Lee, Bussey et al., 2005). As in Stark and Squire (2000), participants were required to select the odd stimulus from an array of six images (see Fig. 5). Consistent with the earlier monkey study, patients with MTL damage including perirhinal cortex were impaired at making oddity judgements for faces and objects. Patients with selective hippocampal damage were not impaired on this task, and neither group was impaired in the difficult colour condition. The control group was also above floor on the face condition, with performance levels at about 15% error. Thus, the profile of performance observed by Lee, Bussey et al. (2005) differed from that seen by Stark and Squire (2000). However, one critical difference between the studies is that, although the number of foils on a given trial was the same, the total number of problems (and therefore the number of stimuli) used by Lee and colleagues was double that used by Stark and Squire. This would have had the effect of increasing the degree of feature ambiguity across trials. This simple difference between the two experiments could have led to the opposing patterns of results, and points to the necessity of controlling degree of feature ambiguity explicitly if at all possible.

Devlin and Price (2007) conducted a study using fMRI in healthy participants, which sheds considerable light on the discrepancies in oddity judgement seen between laboratories. They conducted a four-item oddity task similar to those discussed in this section, in which object stimuli consisted of pictures of real three-dimensional animals or artifacts, and feature stimuli consisted of patches of colour or simple geometric shapes. Both easy and difficult feature trials could be solved on the basis of individual features. Difficult object trials, however, required the integration of multiple features in order to determine which three images depicted a single object presented from three different views. The difficult object condition was the only condition in which perirhinal cortex was activated above baseline levels; in no other condition was activation significantly different from baseline. Activations in perirhinal cortex showed a stimulus type by processing level interaction, and could not be explained as a linear function of overall task difficulty because reaction times were not a significant predictor of activation levels. Also, difficult conditions that could be solved by using single features did not activate perirhinal cortex. Devlin and Price therefore argue that the response properties of perirhinal cortex activation are consistent with the integration of features into an abstract representation (also see Lee, Scahill, & Graham, 2008 for imaging data consistent with this view). They further suggest that reasons for discrepancies between patient studies could include residual perirhinal cortex function in some patients, which can be difficult to detect using structural MRI alone, as well as the possibility of the development in patients of alternative strategies not requiring the use of perirhinal cortex.

Another recent imaging study, also using a version of the oddity task, provides further support for this view (O'Neil, Cate, & Kohler, 2009). In this study, O'Neil and colleagues found that right perirhinal cortex was selectively activated when subjects were discriminating between very similar morphed stimuli. Furthermore, subjects showed similar levels of right perirhinal cortex activity when engaged in forced-choice recognition memory task using the same stimuli. In both tasks, perirhinal cortex activity was directly related to accuracy of performance. This study suggests that a task with a significant mnemonic component does not lead to perirhinal cortex activation over and above that generated by a closely-matched visual discrimination task, contrary to what the psycho-modular view would predict.

3.4. Humans: configural oddity discriminations

The oddity studies discussed to this point did not manipulate feature ambiguity explicitly, and, as mentioned, this could be one reason for the discrepancy in results seen across laboratories. We have already seen some hints that this may be the case. For example, Stark and Squire (2000) used a smaller set size than Lee, Bussey et al. (2005), and we know from the monkey studies (Buckley & Gaffan, 1997) that set size can have an effect on feature ambiguity. In addition, Lee, Bussey et al. (2005) found an impairment in oddity discrimination in Semantic Dementia patients with predominant pathology in perirhinal cortex when they were required to integrate different views of objects, but not when objects were presented in consistent views. Barense, Gaffan, and Graham (2007), therefore, conducted an oddity study using trial-unique stimuli in which feature ambiguity was manipulated explicitly (see Fig. 5). In one experiment, participants were presented with an array of seven "fribble" stimuli (Williams & Simons, 2000), which consisted of novel objects, each composed of a body and four appendages. There were three identical pairs of fribbles in each array, along with a singleton fribble, and participants were asked to identify the odd-one-out. Similar to previous studies in which feature ambiguity has been manipulated explicitly, each trial could be of minimum, intermediate or maximum feature ambiguity, depending on the number of overlapping features across stimuli. A second experiment used "greeble" stimuli (Gauthier & Tarr, 1997) in a four-choice design, with a high and low ambiguity condition. In the high ambiguity condition, greebles were required to be from the same 'family', same 'gender' and be of the same symmetry (see Gauthier & Tarr, 1997). In the low ambiguity condition, greebles were required to be from different families, and could be the same or different gender and the same or different symmetry. Three groups of participants were tested: one group with hippocampal damage, one group with damage to MTL structures including hippocampus and perirhinal cortex, and a group of healthy controls. The MTL group was highly impaired relative to both hippocampal patients and healthy controls on the intermediate ambiguity fribble condition, the maximum ambiguity fribble condition and the high ambiguity greeble condition. Although control performance on the fribble discriminations was quite high at about 90% correct, control performance on the high ambiguity greeble condition was at about 80% correct, suggesting that the pattern is not simply due to ceiling effects. The MTL group performed as well as controls, however, on conditions that could be solved using single features, such as equally difficult size and colour discriminations.

3.5. Other relevant human studies

Several other human studies have used novel paradigms to test the ideas resulting from the foregoing animal work, in particular the idea that perirhinal cortex is important for processing detailed information about complex objects. Tyler and colleagues (Tyler et al., 2004; also see Moss, Rodd, Stamatakis, Bright, & Tyler, 2005), for example, conducted an imaging study in which they asked subjects to name pictures of animals and artefacts at either the basic level (e.g., horse, chair) or the domain level (e.g., living, man-made). The rationale was that more detailed information would be required in order to make the basic level distinction, as items within a category tend to share a large number of features (e.g., many living things have eyes and legs) whereas items across categories tend to share fewer features. Areas within left anteromedial temporal cortex were highly activated when participants named objects at the basic level, and activation was centered on perirhinal cortex. Similar activation was not observed, however, when participants named *the same items* at the domain level. These results are very interesting because they suggest that task demand is as critical to brain activa-

tion as stimulus material, and perirhinal cortex is recruited when the task necessitates the use of detailed information about objects.

3.6. What about memory across a delay?

The studies reviewed above provide evidence that rats and monkeys with damage in perirhinal cortex, and human amnesics with MTL damage that includes perirhinal cortex, are impaired on visual discrimination tasks that require the resolution of feature ambiguity at the object level. But the major deficit in amnesia is thought to be one of memory, and the classical impairment seen after damage to perirhinal cortex in animals is a delay-dependent deficit in object recognition (Buffalo et al., 1998; Eacott et al., 1994; Meunier et al., 1993; Mumby & Pinel, 1994). So the next question is: can the notion of feature ambiguity tell us anything about this canonical deficit in object recognition and, by extension, about the memory deficit in amnesia? And, as with visual discrimination, is the location of perirhinal cortex at the tail end of the VVS—and therefore the stimulus representations that it maintains—sufficient to explain the effects of damage to perirhinal cortex on object recognition? If so the representational–hierarchical paradigm could provide a common mechanism for both visual discrimination and object recognition, paving the way for a general theory of perirhinal cortex function based not on the task or type of memory, but on the representations that it maintains.

To explore this possibility, we adapted our computational model to give it the ability to perform object recognition tasks (Cowell et al., 2006). The original model (Bussey & Saksida, 2002) was equipped to perform visual discrimination tasks only, and as such the representations of stimuli were static, and the only learning possible in the model was stimulus–outcome associations. In order to perform object recognition, we needed to incorporate a mechanism for indicating degree of familiarity of objects. Critically, the new version of the model uses the same representational framework, with complex conjunctive representations located in perirhinal cortex and simpler ('feature') representations located in caudal regions of the VVS, each of which can be independently associated with an outcome. In the new version of the model, however, the stimulus representations are not static, but instead become tuned with experience. A given stimulus representation becomes sharper as the stimulus is repeatedly sampled by the network, and therefore the sharpness of the representation can be used as the basis of familiarity judgments. This sharpening mechanism is consistent with Brown and colleagues' electrophysiological recording work demonstrating a reduction in neuronal response as stimuli become familiar (Fahy et al., 1993). Other models use a similar index of familiarity (Norman & O'Reilly, 2003).

In addition to adapting our model, we also developed a version of the spontaneous object recognition task that allows the systematic manipulation of feature ambiguity while minimizing delay between sample and choice (Bartko et al., 2007b). In our lab, we run the standard spontaneous object recognition task in a Y-apparatus to mitigate spatial confounds (Forwood, Winters, & Bussey, 2005; Winters, Forwood, Cowell, Saksida, & Bussey, 2004). A modification of this apparatus allows us to follow the sample object with the choice object with almost no delay, and therefore mirrors the immediate delay condition often used in the delayed matching- and non-matching-to-sample tasks in monkeys, thought to reflect perceptual rather than mnemonic function (Buffalo et al., 1999; Eacott et al., 1994). We then designed a configural version of object recognition, again based on the biconditional discrimination. Thus, two compound stimuli BC and AD were presented in two sample phases (and would therefore be familiar when presented in the choice phase), and a third compound AB was presented as the novel stimulus in the choice phase. As a result, all of the features (A, B, C, and D) presented in the choice phase were familiar, and so the novel stimulus could not be determined using feature representations alone; only the conjunction of features AB was novel. Rats with damage to perirhinal cortex were impaired in the configural condition, and performed no differently from controls when the novel stimulus could be determined using features alone, a finding that was predicted by simulations run with the new version of the model. These data demonstrate that perirhinal cortex is critical for resolving feature ambiguity not only in visual discrimination tasks, but in object recognition as well.

While it is helpful that the new version of the model can make testable predictions about manipulation of feature ambiguity in an object recognition task with minimal delay, potentially more interesting is the fact that the model also demonstrates the canonical delay-dependent memory deficit seen after damage to perirhinal cortex. The mechanism behind this deficit, according to the model, is as follows. During the sample phase of the task, a subject is presented with a complex object, which becomes familiar over the course of the sample period. During the delay, the model assumes that the subject perceives many visual stimuli, both real and imagined. Simple features such as lines, shapes and colours are common to many objects and so will be encountered repeatedly and become highly familiar. Thus during the choice phase of the task, because many features will be familiar from experience during the delay, these individual features will not be useful for discriminating the novel from the familiar object. In other words, there is feature ambiguity. The conjunctive representations in perirhinal cortex, however, *are* useful. This is because perirhinal cortex contributes to a complex conjunctive representation that is *unique* to each object. Such representations thus help to shield the subject from interfering feature representations because even if all of the features of an object have been experienced during the delay, the specific, unique conjunction of features that makes up the sample object have not. Thus the object can be judged as familiar or novel despite the fact that many or all of its features are familiar. Thus, in exactly the same way as with visual discriminations, in object recognition an intact animal uses perirhinal cortex object-level representations to resolve feature ambiguity. A subject with a damaged perirhinal cortex, in contrast, must rely on spared representations in earlier regions of the VVS to try to judge which object is novel. The longer the delay, the more features that will be encountered, hence greater feature ambiguity, hence delay-dependent impairments.

An important point to make here is that the representational–hierarchical view suggests that familiarity judgments are likely not made on the basis of perirhinal cortex representations alone (i.e., perirhinal cortex is not a "familiarity module"), but that repetition suppression is likely to occur throughout the ventral visual stream in a stimulus-dependent manner. This point is consistent with data and views put forward by Brown and Aggleton: "*Current evidence suggests that the familiarity discrimination mechanism in the perirhinal and adjacent cortices is related to individual stimuli, so that it does not deal with the novel arrangement of familiar spatial stimuli, nor with associative and contextual aspects of recognition memory. Thus, there needs to be a further component to recognition memory that uses other brain structures (e.g. the hippocampal system) to deal with these more complex stimuli and events*" (Aggleton & Brown, 2006).

This feature-ambiguity based mechanism for producing a delay-dependent deficit is effectively an interference account of amnesia: perirhinal cortex damage compromises object-level conjunctive representations, leaving the subject susceptible to interference from incidental lower-level visual information. We next examined this idea directly in the model by manipulating interference explicitly, rather than relying on incidental experience of features during a delay. We ran simulations of a hypothetical object recognition experiment in which the delay between sample and choice was minimized, but an interfering stimulus was presented between the

sample and choice phases. Object recognition in lesioned networks was unaffected when the interpolated stimulus was not perceptually similar to the objects, but was highly impaired when the interpolated stimulus was similar to the objects. This is because the lesioned networks only had features in the intact caudal layer to work with, and since the perceptually similar interpolated item shared many features with the test objects, novelty could not be assessed using only feature representations. In contrast, intact control networks represented test items as well as interfering items not only as features in the caudal layer, but as unique conjunctions of features on the perirhinal cortex layer. Thus the perirhinal layer of the intact network helped to resolve the interference on the caudal layer by providing a unique object-level representation that tells the network: "you may have seen all these features before, but you have not seen this object before". This experiment was subsequently run in rats, and this prediction of the model was confirmed (Bartko, Winters, Saksida, & Bussey, 2005; also see Winters et al, this issue). These results provide support for the idea that delay-dependent impairments in object recognition following perirhinal cortex lesions may be explained by a similar interference account.

The idea that brain damage may lead to an increased susceptibility to interference has played an important part in human amnesia research. Warrington and Weiskrantz (1970) originally suggested that heightened susceptibility to interference and response competition is a fundamental characteristic of amnesia, largely to explain the beneficial effect of cues on retrieval in amnesia. This idea was subsequently retracted (Warrington & Weiskrantz, 1978), however, and largely replaced with the view that the beneficial effect of cues on retrieval reflects preserved implicit memory in amnesia, in other words, a psycho-modular account (e.g., Shimamura, 1986). This retraction is consistent with the general rejection in the psychology literature at the time of proactive interference as a plausible account of normal forgetting (seeWixted, 2004 for review). More recently, however, support for the role of interference in amnesia has started to reappear (e.g., Cowan, Beschin, & Della Sala, 2004; Della Sala, Cowan, Beschin, & Perini, 2005). Wixted (2004), for example, has compellingly argued that an interference account of normal forgetting should be resurrected. In particular, he suggests that the original studies of interference got it wrong by focusing on "cue-overload" studies, in which A–B associations were disrupted by subsequently learned A–C associations. Instead, he argues that retroactive interference from "ordinary mental exertion" is much more relevant to everyday forgetting than interference from cue overload, and that similarity of interfering stimuli is probably not the most critical factor in interference-based forgetting. In particular, he suggests that the hippocampus is critical for consolidation of new memories, and that ordinary mental exertion of any type interferes with this consolidation process and leads to forgetting. While we agree with Wixted's emphasis on interference, our view suggests that susceptibility to interference, at least when due to damage to perirhinal cortex, is a result of feature ambiguity and therefore is fundamentally related to the similarity of interfering representations, usually due to similarity of interfering stimuli—although it is possible that these interfering representations could be generated in part endogenously. Furthermore, the assumptions of the representational–hierarchical view lead to a novel conception of the nature of the impairment in amnesia, which potentially sheds light on the debate over whether the primary deficit in amnesia is one of encoding – i.e., conversion of incoming information into a representation in the brain – storage/consolidation, or retrieval, i.e., the ability to access previously stored information (Butters & Cermak, 1980; Kopelman, 2002; Meudell & Mayes, 1982; Warrington & Weiskrantz, 1970). Specifically, we suggest that brain damage can, at least with respect to object recognition, affect all three. Key to this view is the non-modular assumption, borne out by the extant data, that an object once encoded is represented throughout the ventral visual-perirhinal stream, and that damage to rostral regions such as perirhinal cortex affects only part of the representation of that object. Thus, although the complex conjunctive representation of the object is compromised, lower-level representations of the object, e.g., the individual features that make it up, remain intact. Following a rostral lesion, therefore, encoding and storage are affected because the complex stimulus representations normally maintained in rostral regions and important for the resolution of interference cannot be formed or stored after damage to rostral regions such as PRh. Retrieval is affected in that there is competition between the remaining feature representations when individual features are shared between interfering and novel stimuli. This account is consistent with transient inactivation experiments, which show that temporary 'lesions' of perirhinal cortex impair object recognition whether given during encoding (study phase), storage/consolidation (delay phase), or retrieval (test phase) (Winters, Bartko, Saksida, & Bussey, 2007; Winters & Bussey, 2005). Similar findings have been reported in hippocampus (Riedel et al., 1999).

4. Beyond perirhinal cortex

The focus of this review so far has been perirhinal cortex, for two reasons: (1) the representational–hierarchical view has focused on perirhinal cortex as a result of its location at the interface between the putative MTL memory system and the ventral visual object processing pathway and (2) perirhinal cortex is the region most associated with object recognition, the task most widely used to assess animal models of amnesia. However, amnesia in both humans and animal is associated with damage not just to perirhinal cortex, but with damage to other structures including, fundamentally, the hippocampus. Indeed, the hippocampus is the structure that is usually at the forefront of considerations of amnesia. So, what is the role of the hippocampus in the representational–hierarchical scheme?

An experiment simulated in Cowell et al. (2006) speaks to this issue. Object recognition memory is usually measured with trial-unique stimuli and, as mentioned earlier, many studies have shown that damage to perirhinal cortex impairs this task (Buffalo et al., 1998; Eacott et al., 1994; Meunier et al., 1993; Mumby & Pinel, 1994). However, a repeated-items version, in which a single set of items is presented on multiple trials, is also possible, and in this case, damage to perirhinal cortex does not typically lead to impairments (Eacott et al., 1994). When this task was simulated by Cowell et al. (2006), however, *neither* the peririhinal cortex lesioned group of networks *nor* the control group of networks could solve the task. The reason for this is that in contrast to the trial-unique version of the task, in the repeated-items version not only are features presented repeatedly, so are the objects themselves. As a result, over the course of the task, not just the features, but the *objects* become equally familiar. As described above, we assume that in normal, trial-unique object recognition features experienced during the delay cause many features to become familiar, resulting in feature representations being insufficient to judge novelty – that is, the task has feature ambiguity. However because in repeating-items object recognition even the objects on choice are equally familiar, a higher level of ambiguity is created, which we might call 'object ambiguity'. Thus, just as feature representations in caudal regions are impotent in the face of feature ambiguity, so object representations in perirhinal cortex are impotent in the face of object ambiguity. And just as feature ambiguity can be resolved using representations at a level in the hierarchy higher than the feature level, so object ambiguity must be resolved by representations at a level in the hierarchy higher than the object level. Thus we argue in Cowell et al. (2006) that solution of object-level ambiguity

requires an additional layer containing more complex representations that are able to resolve object-level ambiguity. The prime candidate for the maintenance of these more complex representations is, of course, the hippocampus. Current consensus is that the hippocampus is important for the representation of complex, "episodic" or relational (e.g., Eichenbaum, Schoenbaum, Young, & Bunsey, 1996; Squire et al., 2004) information, including information about "where" and "when". Such a higher-level representation is exactly what is needed for the resolution of object-level ambiguity.

If the hippocampus can be thought of as another, higher-level layer in the VVS-perirhinal-hippocampal stream, then can we regard the higher-level representations in the hippocampus as being, like those in perirhinal cortex, important for all kinds of cognitive functions, and not just "declarative memory"? The critical role of the hippocampus in representing "where" in the context of spatial memory has been particularly well-established in animal studies. Is there any evidence that the spatial representations in the hippocampus might be useful for perceptual discriminations? In a recent study, we examined the role of hippocampus in spatial discrimination learning (Clelland et al., 2009; McTighe, Mar, Romberg, Bussey, & Saksida, 2009). Rats were trained to discriminate locations on a computer screen that varied in terms of their distance apart (see Fig. 6). Animals with damage to dorsal hippocampus, or with impaired neurogenesis in the dentate gyrus, were impaired on this task when the locations were close together, but not when they were far apart. Note that this task is a spatial analogue of the pair-wise 'morph' discrimination paradigm described above (Bussey et al., 2003). Just as in that task, the learning and memory demands across conditions were the same, and only the perceptual similarity of the stimuli was varied. And in both cases, the lesion affected performance in only the perceptually similar condition. These results suggest that indeed, the hippocampus has functions outside of the realm of declarative memory. Although the discrimination paradigm we used has not yet been translated to humans, we would suggest this as a potentially fruitful direction for future research.

There is also mounting evidence from the human literature to support the idea that the hippocampus may be important for spatial perceptual discrimination. For example, in Lee, Buckley et al. (2005) morph study described earlier, a group of patients with damage to hippocampus alone, and another group of patients with MTL damage including perirhinal cortex and hippocampus were tested on discrimination of morphed stimuli. The MTL group, but not the hippocampal group, was impaired at discrimination of faces. However, both patient groups were impaired at the discrimination of spatial scenes, pointing to a selective role for the hippocampus in perceptual discrimination of scenes. In a subsequent study, Lee, Levi, Davies, Hodges, and Graham (2007) investigated the performance of patients with Alzheimer's Disease and Semantic Dementia on this task. Distinct profiles of MTL involvement in these two conditions have been reported (Chan et al., 2001; Davies, Graham, Xuereb, Williams, & Hodges, 2004; Galton et al., 2001); pathology is greater in hippocampus than other MTL regions in Alzheimer's Disease, and pathology is greater in perirhinal cortex than other MTL regions in Semantic Dementia. Patients with Alzheimer's Disease were impaired at scene, but not face, discrimination compared to healthy controls, and Semantic Dementia patients were impaired at face, but not scene, discrimination compared to healthy controls, demonstrating a double dissociation between these two patient groups. These data indicate perceptual functions for both the perirhinal cortex and hippocampus, the differences between them being the level within the representational hierarchy at which they operate.

Similar support for the idea that the hippocampus is important for processing spatial information in a perceptual discrimination

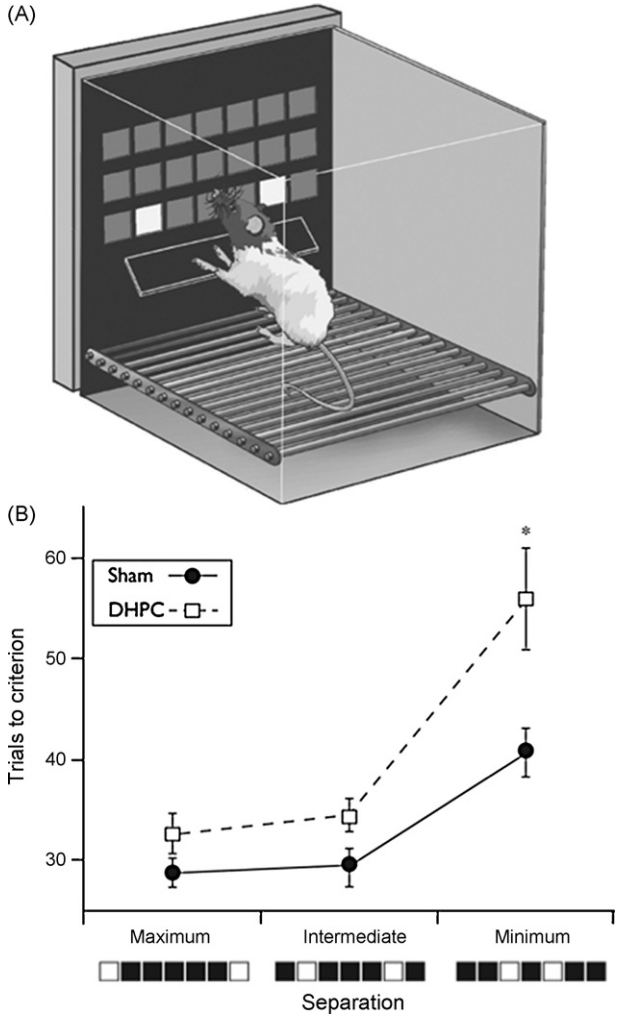

Fig. 6. (A) Touchscreen chamber showing the location discrimination task. (B) Rats were trained initially using the intermediate stimulus array, followed by probe sessions on the maximum and minimum conditions (shown below the *x* axis). After surgery, rats were tested in all conditions. The graph shows performance of the dorsal hippocampal lesion (DHPC) and sham groups during eight post-lesion probe sessions on each of the three separations. A clear difference in performance can be seen at the minimum separation, but not at either the maximum or intermediate separations. $^{*}P < 0.01$. Figure adapted from McTighe et al. (2009).

task comes from Lee, Bussey et al. (2005) oddity study. Participants were assessed on oddity judgment for colour, faces and objects, as well as spatial scenes. MTL patients were impaired at making oddity judgments for faces and spatial scenes, whereas hippocampal patients were impaired at making oddity judgements for spatial scenes. This study was followed up by looking at oddity in patients with Alzheimer's Disease and patients with Semantic Dementia (Lee et al., 2006). The Alzheimer's Disease patients were impaired at judging oddity for scenes, but not faces, presented from different views. In contrast, the Semantic Dementia patients were impaired at judging oddity for faces, but not scenes, presented from different views. Again, this double dissociation is easily understood within the representational–hierarchical framework.

Hartley et al. (2007) have also looked at the role of the hippocampus in spatial perceptual processing. They constructed a spatial non-match-to-sample task that they presented to four patients with hippocampal damage. In one condition, sample and choice stimuli were presented simultaneously, whereas in a second condition, choice stimuli were presented after a 2 second delay. All four patients were impaired in the delay condition, whereas two patients were impaired, and two patients were unimpaired, in the

perceptual condition. An additional patient with parahippocampal and hippocampal damage was severely impaired in the perceptual condition, and these authors conclude that the hippocampus is critical for processing spatial information over short delays, but that spatial perception is possible without the hippocampus, perhaps via a parahippocampal representation. In any case, these data and those above show that to understand the role of MTL structures in cognition, we must move beyond simply labeling these structures as a module or modules for long-term declarative memory.

Thus, the data summarized above provide strong evidence that the hippocampus is important for representing spatial information outside the context of tasks that tax long-term mnemonic function, in many cases in tasks with minimal mnemonic component. These data also suggest, contrary to the traditional view (Murray, Bussey, & Saksida, 2007; Squire et al., 2004), that lesions in the different structures within the putative MTL system do not necessarily have the same effect (e.g., Bussey, Duck, Muir, & Aggleton, 2000; Ennaceur, Neave, & Aggleton, 1996; Gaffan, 1994; Murray et al., 2007; Murray & Mishkin, 1998; Winters et al., 2004). Additional evidence comes from studies in which we tested monkeys with hippocampal damage on the visual discriminations reviewed earlier. For example, Saksida et al. (2007) have shown that monkeys with hippocampal lesions are not impaired on the morph and biconditional visual discrimination tasks on which monkeys with perirhinal cortex damage are severely impaired. Furthermore, Saksida, Bussey, Buckmaster, and Murray (2006) have shown that monkeys with hippocampal damage are *better* on the transverse patterning task than control monkeys, again in contrast to monkeys with perirhinal cortex damage, who are substantially impaired. The observation of different effects of damage within two MTL structures on the same task argues strongly against the idea that lesions in these structures have the same effects on cognition. The fact that the findings were in opposite directions further suggests that these two regions of the putative MTL system may actually be offering competing solutions to problems, and the removal of the non-optimal solution leads to a facilitation. These findings are consistent with the representational–hierarchical view, in which different regions within the VVS-perirhinal-hippocampal stream contain different levels of representations, and in which the region most useful for the solution of the task – the one which resolves ambiguity at lower levels – is the one that is recruited and the one in which lesions will produce the greatest deficit. Computational work has shown that such double-dissociations are accommodated within the representational–hierarchical view without needing to postulate modules based on psychological function (Cowell, Bussey, & Saksida, 2009).

5. It's not just about memory vs perception

Many of the above experiments have focused on the issue of memory versus perception, and specifically, whether damage to regions such as the perirhinal cortex and hippocampus, traditionally thought to contribute to memory only, might also impair perceptual discrimination tasks as well. Many findings, some of which are reviewed above, suggest that it can. And indeed, more recent evidence suggests that changes in regions such as V2, traditionally thought to be part of a "perceptual representation system" only (Tulving & Schacter, 1990), can affect a standard 'declarative' object recognition task in a way that, within the standard paradigm, would be taken as evidence for a role in declarative memory (Lopez-Aranda et al., 2009; Saksida, 2009). The emphasis on the issue of memory versus perception is underscored by a recent series of review articles in Neuron, in which two independent researchers debate this issue specifically (Baxter, 2009; Suzuki, 2009; Suzuki & Baxter, 2009).

The issue of memory versus perception is indeed an important one. But we would emphasize that this issue is only one example of the implications of the representational–hierarchical view for understanding cognition. We have argued above that a given representation, and thus a given brain region, is likely to be useful for many aspects of cognition (Bussey & Saksida, 2005, 2007). Thus we would predict that not just perceptual discrimination, but other functions—perceptual categorization and perceptual learning, for example—could depend on a number of regions throughout the VVS-perirhinal-hippocampal stream, the region that is most important for the task being the one that houses the most critical representations for its solution. So although it is no surprise according to the representational–hierarchical view that, for example, categorization and perceptual learning of dots and lines – that is, categorization using representations at the feature level – can be preserved in amnesic patients (Fahle & Daum, 2002; Squire & Knowlton, 1995), our prediction is that even regions within the putative MTL declarative memory system may be involved in categorization and perceptual learning tasks that are best solved using high-level representations stored in the MTL. Although antithetical to the standard, textbook view of amnesia, there is indeed some evidence for this already, as it has been reported that the hippocampus is important for categorization and perceptual learning tasks which are best solved using high-level, 'spatial' representations (Chun & Phelps, 1999; Graham et al., 2006). With respect to amnesia, then, the strong claim of the representational–hierarchical view is that the reason that amnesic patients are unimpaired on certain tasks subsequently labelled as 'non-declarative', is not that these tasks are recruiting a qualitatively different memory system, but that they tax representations stored outside of the area that is typically damaged in amnesia.

These are strong claims. Some of these ideas may turn out to be wrong. But it seems to us that in the face of the evidence summarized in this review, there must be something to what we are saying. And it is equally clear that, at the very least, the standard view of amnesia must somehow be revised.

We hope that this review has shown the advantages of the translational approach to understanding amnesia, and cognition in general. We think it is a powerful approach that should be encouraged.

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