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Heightened susceptibility to interference in an animal model of amnesia: Impairment in encoding, storage, retrieval – or all three?

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ABSTRACT

There has recently been a resurgence in the idea that amnesia may be characterized by an increased susceptibility to interference. In the present study we tested this idea using a well-controlled and well-established animal model of amnesia: impairment in object recognition following perirhinal and postrhinal cortical (PPRh) damage. We used this paradigm to test whether memory impairment was exacerbated by the interpolation of a potentially interfering item either before (proactive interference) or after (retroactive interference) the to-be-remembered item. Rats with PPRh damage were impaired in object recognition memory, with a minimal delay, when the interfering stimulus was perceptually similar to the test stimuli. When the interfering stimulus was less perceptually similar to the test stimuli, the PPRh-lesioned rats performed similarly to Controls. Both proactive and retroactive interference were observed, and both depended on the similarity of the interfering item to the test items. These findings provide support for the idea that amnesia can indeed be characterized by increased vulnerability to interference, and we illustrate, using simulations generated by a computational model of amnesia, how the mechanism for this vulnerability to interference can be understood, not in terms of an impairment in encoding, storage or retrieval, but in terms of an impairment in encoding, storage and retrieval.

1. Introduction

The idea that brain damage may lead to an increased susceptibility to interference has occupied an important place in amnesia research. Warrington and Weiskrantz (1970) originally introduced the idea, largely to explain the beneficial effect of cues on retrieval in amnesia. This approach, however, subsequently went out of favor (Warrington & Weiskrantz, 1978) and the beneficial effect of cues on retrieval is now usually explained by the idea that amnesics display preserved implicit memory in the absence of explicit or declarative memory (e.g., Shimamura, 1986).

Recently, however, the notion that interference may be an important factor in amnesia has begun to resurface (e.g., Wixted, 2004). Loewenstein et al. (2004), for example, found that a group of Alzheimer's disease (AD) patients showed a larger effect of proactive interference than a group of participants with mild cognitive impairment (MCI); both of these groups were more susceptible to interference than age-matched controls. In addition, several recent studies have indicated that performance in amnesic patients may be enhanced in tasks with reduced interference. Cowan, Beschin, and Della Sala (2004), for example, manipulated activity during the delay in a delayed recall task and found that when amnesic patients spent the delay in a quiet room, their rate of forgetting was less than under conditions in which the delay was filled with activity. Della Sala, Cowan, Beschin, and Perini (2005) carried out a similar experiment and examined patients with MCI in a task that required either immediate recall or recall following a 1-h delay. The MCI patients and controls performed similarly in the immediate recall condition. However, whereas controls performed well in both a "usual" and a "reduced interference" delay condition, the MCI patients performed relatively poorly in the usual interference condition. These results suggest that patients with memory impairments are susceptible to retroactive interference and that a reduction in interference can greatly improve memory performance.

Wixted (2004) has linked the notion of heightened susceptibility to interference with a storage/consolidation impairment, arguing that structures in the medial temporal lobe are critical for consolidation of new memories (Squire & Zola-Morgan, 1991; Squire &

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Zola, 1996; Squire, Stark, & Clark, 2004), and that damage to these structures, for example in amnesia, may lead to a reduction in "consolidation resources". As a result, whereas an intact system has sufficient consolidation resources to remain robust to interference, a compromised system in amnesia will be particularly susceptible to interference.

Recently, we have been refining and testing a novel "representational-hierarchical" framework for understanding impairments due to damage in brain regions associated with amnesia (Bussey & Saksida, 2002, 2005, 2007). We have used connectionist modeling to show how amnesia can be understood in terms of damage compromising high-level conjunctive representations, leaving only lower-level representations intact (Cowell, Bussey, & Saksida, 2006). These conjunctive representations, we suggest, 'provide the additional information that the features present in the stimulus belong together: the whole is more than merely the sum of the parts. In this way, these complex conjunctive representations serve to reduce interitem interference' (Bussey & Saksida, 2002). Thus, memory impairments in amnesia can be understood as being due to the inability to resolve interference from incidental, irrelevant lower-level information. Several studies have provided support for this view (Bartko, Winters, Cowell, Saksida, & Bussey, 2007a; Bartko, Winters, Cowell, Saksida, & Bussey, 2007b; Bussey, Saksida, & Murray, 2002, Bussey, Saksida, & Murray, 2003).

In the present study we sought to test further whether amnesia can be characterized as an increased susceptibility to interference. As with much of our previous work (Bartko et al., 2007b; Winters & Bussey, 2005b; Winters, Forwood, Cowell, Saksida, & Bussey, 2004), we use an animal model of object recognition impairment. This approach has a number of advantages. For example, we are able to produce discrete, selective damage to regions of interest; in human amnesia damage rarely respects the anatomically defined boundaries of areas of interest and in cases of AD and MCI, even less so. In addition, the use of an animal model eliminates the possibility of strategies such as verbal rehearsal. Furthermore, the object recognition paradigm is a well-established and well-understood model of amnesia (Winters, Saksida, & Bussey, 2008) that translates well to the human condition (Buffalo et al., 1999; Buffalo, Reber, & Squire, 1998; Manns, Stark, & Squire, 2000). The task allows the interpolation of interfering items during the retention interval which can be similar to, or different from, the study and test materials, allowing conditions of high and low interference. This approach, we believe, is preferable to those that use either interference or no interference, or methods using sleep, both of which can introduce unwanted confounds (Wixted, 2004).

Specifically, we examined whether rats with damage to temporal lobe regions known to be critical for visual recognition memory (PPRh; perirhinal plus postrhinal cortices) are more susceptible than controls to interference in a visual recognition task. We found that animals with PPRh lesions were able to perform well on this minimal-delay test when the interpolated item was not perceptually similar to the test items, but were severely impaired when the interpolated item was perceptually similar. This effect was seen whether the interpolated item was presented prior to (proactive interference) or after (retroactive interference) the to-be-remembered item. Thus even very specific, perirhinal cortex-dependent object recognition impairments can be elicited – under conditions of minimal delay – simply by increasing interference. These data provide additional support, from a well-controlled animal model of amnesia, for the suggestion that amnesia can be characterized by an increased susceptibility to interference (Della Sala et al., 2005; Warrington & Weiskrantz, 1970; Wixted, 2004). Finally we discuss, in the context of the representational-hierarchical paradigm (Bussey & Saksida, 2002; Bussey et al., 2002, 2003), how such effects can be understood, not in terms of amnesia affecting *either* encoding, storage/consolidation, or retrieval, but as an impairment in all three.

2. Experiment 1: simulations using a connectionist model

2.1. Materials and methods

2.1.1. Architecture

Recently we have introduced a novel framework for understanding impairments due to damage in brain regions associated with amnesia (Bussey & Saksida, 2002, 2005, 2007). This view, which has generated much experimental support (Devlin & Price, 2007; Gilbert & Kesner, 2003; Lee, Levi, Davies, Hodges, & Graham, 2007; Lee, Scahill, & Graham, 2008; Norman & Eacott, 2004; Tyler et al., 2004), does not emphasize heterogeneous anatomical modules for different kinds of memory (e.g., declarative vs. non-declarative) or different processes (e.g., storage vs. retrieval). Instead, it emphasizes the importance of the organization of representations in a hierarchical continuum throughout the ventral visual–perirhinal–hippocampal processing stream (Bussey & Saksida, 2005, 2007). Many of the experiments carried out to test this view have focused on perirhinal cortex (PRh), a region at the interface of putative 'perceptual' and 'mnemonic' systems. The perceptual-mnemonic feature-conjunction (PMFC) model (Bussey & Saksida, 2002; Bussey et al., 2002, 2003), which formalizes the assumptions of this representational-hierarchical view in a connectionist model, has been found to account for the effects of PRh damage on visual discrimination learning (Barense et al., 2005; Bussey & Saksida, 2005; Bussey et al., 2002, 2003; Lee et al., 2005). Within the same theoretical framework, Cowell et al. (2006) have presented a connectionist model of object recognition memory, which accounts for impairments in visual memory in amnesia in terms of PRh damage compromising object-level conjunctive representations of objects, leaving only lower-level representations intact. As a result, delay-dependent memory impairments in amnesia can be understood as being due to the inability to resolve interference from incidental, irrelevant lower-level visual information. Thus the model predicts that damage to regions such as PRh should lead not to modular impairments in either encoding, storage or retrieval, but to partial impairments in both encoding/storage (inability to represent and store critical object-level conjunctive representations) and retrieval (the inability to retrieve object-level conjunctive representations leads to increased response competition at retrieval because the remaining intact representations are at the lower, feature-level) that can result in a heightened susceptibility to visual interference.

This section provides a brief overview of the connectionist network [see Fig. 1 panel A; for details, see Cowell et al. (2006)]. The model assumes that regions of the ventral visual stream, including PRh, contain visual representations that are organized hierarchically, with simple features located in caudal regions of the ventral visual stream, and representations of the conjunctions of those features residing in more rostral regions. In the connectionist network, this system of representations is reduced for simplicity to a two-stage scheme, in which the first layer corresponds to a caudal region of the ventral visual stream, and the second layer to PRh.

The caudal layer of the model combines two stimulus dimensions into a single representation; each two-dimensional combination corresponds to a visual 'feature' of an object. One could think of this simple feature as the conjunction of, say, a color and a line orientation, although we do not make specific claims about the exact nature of these features. The PRh layer combines eight stimulus dimensions into a single representation, forming a unique and fully specified representation of a visual object possessing four features. Both layers of the model are implemented using Kohonen grids. The caudal layer comprises four Kohonen grids, each of which receives two-dimensional inputs, and the PRh layer comprises one Kohonen grid receiving an eight-dimensional input. Thus, a given stimulus is represented as single complex conjunction on the PRh layer, and as a series of separate, two-dimensional conjunctions in the more caudal layer.

Kohonen grids are designed to model cortex, including computational abstractions of cortical mechanisms such as lateral inhibition, which makes their use appropriate in systems level investigations of cognitive function. Each Kohonen grid comprises a two-dimensional array of processing units that receives stimulus inputs and is characterized by lateral inhibitory feedback between neighboring units. The grids are trained by the successive presentation of a number of stimulus inputs; the weights of each unit are incrementally adapted on each presentation. This gives an automatic mapping of stimulus inputs onto a set of representations with the same topological order as the stimuli, that is, similar stimuli are represented in neighboring locations on the grid. The self-organization process involves the sharpening of representations of stimuli on which the network is trained. A novel stimulus will elicit a moderate level of activity, broadly distributed across a large number of units in the grid (for details, see top panel of Fig. 3 in Cowell et al., 2006); as that stimulus is presented repeatedly, the activation pattern it elicits becomes more selective until only a small area of the grid contains highly active units, producing a peak of activation (for details, see bottom panel of Fig. 3 in Cowell et al., 2006). The development of sharply tuned representations thus can be used as the basis for familiarity judgments: as a stimulus representation becomes sharper, so it is judged to be more familiar (Norman & O'Reilly, 2003). The model may be used to simulate the effects of damage to PRh by removing the PRh layer so that object recognition performance depends on the caudal layer alone.

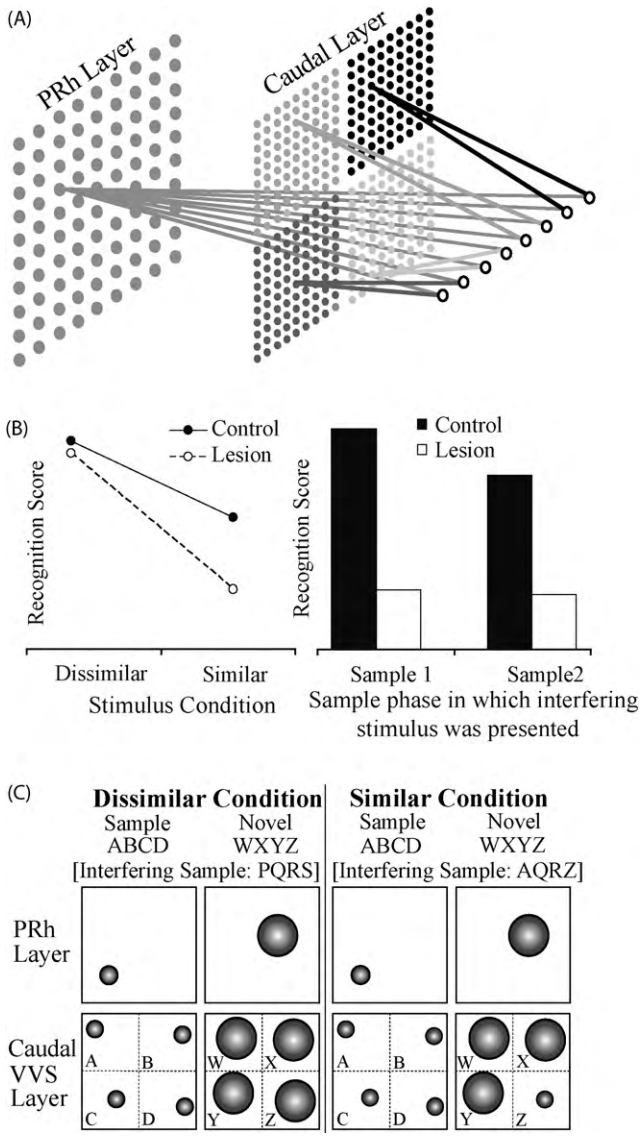

Fig. 1. (A) Illustration of the connectionist model. The input layer, containing eight nodes, is shown on the far right; the two layers of stimulus representations [PRh and caudal] are shown to the left of the input layer. Stimulus inputs to the network have eight "stimulus dimensions" (attributes); each dimension is represented in the diagram by an individual input node. On the caudal layer, stimulus dimensions are paired into four simple conjunctions. Each simple conjunction is shown in a different shade of gray and is represented individually on the caudal layer. On the PRh layer, the eight stimulus dimensions are combined into a conjunction, shown in gray, which represents the whole stimulus. (B) Performance of the model during object recognition in two conditions, Similar and Dissimilar. Filled circles represent recognition of the Control group and open circles represent recognition scores of the Lesion group. (C) Stimulus representations on the Kohonen grids of the model in the choice phase for the Similar (left) and Dissimilar (right) object recognition conditions. The PRh layer represents the object stimulus with a single conjunctive representation. The caudal layer represents individual object features separately; stimulus representations in the caudal layer are shown as chunked according to object features; there are four features per object stimulus. Small circles indicate sharply tuned ('familiar') representations, and large circles indicate coarsely tuned ('unfamiliar') representations. See Section 2.4 and the Discussion for more details.

2.1.2. Simulation methods

2.1.2.1. Stimuli. Object stimuli in this experiment were created by constructing four-featured objects from a pool of visual features. Each feature comprises two stimulus dimensions or attributes and each four-featured object comprises eight stimulus dimensions. On the caudal layer, each two-dimensional feature is represented as a simple conjunction and a four-featured object is represented as four separate simple conjunctions. On the PRh layer, a four-featured object is represented as a single complex conjunction. In practice, real-world objects may in fact contain more than four two-dimensional features, but the model is designed to illustrate a principle rather than reproduce the real-world in a strictly veridical manner.

Eight sets of stimuli were created for the present experiment; each set comprised two sample objects (the to-be-remembered sample and the interfering sample) and a novel object (*N*). In keeping with previous simulations using this model (Bartko et al., 2007a, 2007b; Cowell et al., 2006), the novel and the sample objects were assumed to be perceptually easily discriminable, having no features in common. Four of the eight stimulus sets were assigned to the 'Perceptually Dissimilar' condition (the interfering sample object was not similar to the to-be-remembered sample object or the novel object) and four stimulus sets were 'Perceptually Similar' (the interfering sample object was similar to both the to-be-remembered sample object and the novel object). In the Dissimilar sets, the interfering object shared no features with the to-be-remembered sample object and the novel object. In the Similar condition, the interfering object shared one feature with the to-be-remembered sample object and one feature with the novel object. Neither of the sample objects nor the novel stimulus in any set was replicated in any other set, but individual features were allowed to appear in more than one object set.

Nested within the Perceptually Dissimilar and Perceptually Similar conditions were two 'retroactive' and 'proactive' conditions, which refer to the order of presentation of the two sample objects. In retroactive trials, the to-be-remembered sample object was presented in phase 1 and the interfering object in phase 2, so that any interference arising from presentation of the interfering object occurred after encoding the to-be-remembered stimulus. In proactive trials, the interfering object was presented in phase 1 and the to-be-remembered sample object was presented in phase 2, so that any interference from the interfering object occurred before encoding the to-be-remembered object.

2.2. Simulation procedure

Two groups of twelve networks were tested: Group 'Control' consisted of intact networks and Group 'Lesion' consisted of networks in which the PRh layer had been removed to simulate PRh lesions. Each network was tested on four object sets under each condition – Dissimilar and Similar – giving eight trials per network. In each of the Dissimilar and Similar conditions, networks performed two retroactive trials and two proactive trials. Networks were initialized and pre-trained before testing on the eight trials. On each trial, a network was presented with the first sample object and allowed to 'encode' the object for 20 cycles; each cycle sharpened incrementally the peak of activation representing the sample object (see Appendix 1, Cowell et al., 2006 for details). Next, the network was presented with the second sample object and allowed to encode it for 20 cycles. Following encoding of the two sample objects, each network was presented with the to-be-remembered sample object (whether this had been presented in phase 1 or phase 2 depended on whether the trial type was retroactive or proactive) and the novel object in a choice phase. No learning occurred in the choice phase; the representations of the two objects were simply assessed to obtain an index of their relative familiarity (the recognition score). At the beginning of every new trial, each network was reset to the state it had assumed at the end of pre-training.

2.3. Results

As shown in the left panel of Fig. 1B, networks in both group Control and group Lesion performed well on object recognition in the Dissimilar condition. Both groups of networks were unimpaired by the presentation of an interfering stimulus that was dissimilar to the to-be-remembered sample and the novel objects. However, in the Similar condition, networks in group Lesion showed a recognition memory deficit relative to Control networks that had not been seen in the Dissimilar condition. Thus, the model predicts that introducing an interfering stimulus that is perceptually similar to the to-be-remembered sample and novel objects will impair object recognition memory in subjects with PRh lesions relative to Controls. This prediction of the model arises because, whereas the intact networks can represent the conjunction of stimulus features corresponding to the whole object, as well as simple conjunctions corresponding to individual features, the lesioned networks can represent only simple conjunctions corresponding to individual features (see Fig. 1C). In the Dissimilar condition, two objects are presented to networks in the choice phase – one of which is composed entirely of familiar features and one of which contains only novel features – and both layers of the model are able to discriminate the stimuli on the basis of familiarity. On the caudal layer, where low-dimensional conjunctions of stimuli are represented separately, all four features are sharply tuned for the familiar stimulus whereas all four are coarsely tuned for the novel stimulus. Similarly, on the PRh layer, the single conjunctive representation of the familiar stimulus is sharply tuned and can be discriminated from the coarsely tuned conjunctive representation of the novel stimulus. However, in the Similar condition, the novel object is composed of three unfamiliar features and one feature that has been presented as part of the interfering sample stimulus. This means that on the caudal layer of the model, one of the four features possessed by the novel stimulus appears familiar since its representation has been tuned through encoding of the interfering stimulus; the representations of the novel and sample stimuli are therefore less discriminable on the basis of familiarity than in the Dissimilar condition. In contrast, on the PRh layer, the representations of the whole conjunction are entirely distinct for the familiar and novel stimuli, even though one of the features of the novel object has been presented to the network as part of the interfering stimulus;

only the representation of the familiar object is sharply tuned and therefore the novel and familiar objects are just as discriminable as they were in the Dissimilar condition. It is clear from the schematic illustration of the model's representations shown in right panel of Fig. 1C that removal of the PRh layer, leaving only the caudal layer to solve the discrimination, will result in a deficit in object recognition performance.

In addition, the model makes a clear prediction for the effect of presentation order of the to-be-remembered and interfering sample stimuli. The effect of sample stimulus presentation order on recognition memory performance in the similar condition – i.e. the condition in which interference has an impact on performance – is shown in the right panel of Fig. 1B. The model predicts that the performance of subjects with PRh lesions should be impaired by both proactive and retroactive interference – the interfering stimulus should have the same detrimental impact on recognition performance for lesioned subjects whether it is presented before or after the to-be-remembered sample object. Furthermore, the two types of interference (retroactive and proactive) had a very similar influence on recognition memory performance for both Control and Lesion networks.

3. Experiment 2: validation of interfering stimuli using visual discrimination

The main aim of this study was to determine whether perirhinal lesion-induced amnesia for objects is characterized by an increased susceptibility to perceptual interference. This was tested in Experiment 3 in which potentially interfering items were interpolated between study and test; these items were either similar (made of Lego) or dissimilar (Picture Cards) to the (Lego) test items. In Experiment 2 we sought to first validate the stimuli by testing to ensure that the rats found the Lego objects sufficiently similar to other Lego objects, and sufficiently dissimilar to the Picture Cards. Thus, we pre-tested these sets of stimuli with naive rats in a two-choice discrimination procedure to provide a measure of the subjective perceptual similarity of the object in each pair. Animals were tested in two conditions: Perceptually Similar and Perceptually Dissimilar. We used these stimuli for the object recognition experiment examined in PPRh-lesioned and Control rats in Experiment 3.

3.1. Materials and methods

3.1.1. Subjects

The subjects were 12 experimentally naive adult male Lister hooded rats (Harlan Olac, Bicester, UK), weighing 270–320 g and housed in pairs in a room with a 12 h light/dark cycle (lights on at 7:00 P.M.). All behavioral testing was conducted during the dark phase of the cycle. During testing, rats were fed ~15 g of laboratory chow after daily behavioral sessions to maintain weights at 85–90% of free-feeding body weight. Water was available *ad libitum* throughout the experiment. All experimentation was conducted in accordance with the United Kingdom Animals (Scientific Procedures) Act (1986). These rats were previously tested in an object recognition pilot experiment; no objects from this pilot experiment were re-used in the present experiment.

3.1.2. Visual discrimination

3.1.2.1. Apparatus. The visual discrimination task was conducted in a Y-shaped apparatus as described previously (Bartko et al., 2007b). Briefly, in each of the arms, a Foamalux insert (40 cm tall and 9.9 cm wide) was added where there was previously a door between the second phase and choice phase. Small, transparent food wells (4.5 cm in diameter) were placed 12 cm from the start of the Y-apparatus in each arm and were located against the left side of both of the arms. Stimuli were placed directly beside the food wells.

3.1.2.2. Stimuli. For pre-training two wooden blocks (one white and one black) were used (9.5 cm tall and 9.5 cm wide). Wood was chosen since none of the stimuli used in the discrimination experiment proper were made of wood. For the discrimination experiment proper, the stimuli were the sample and interfering stimuli used in Experiment 3 (both Lego objects and Picture Cards). Therefore, the discrimination in the Perceptually Similar condition was between a Lego object and a Lego object and the discrimination in the Perceptually Dissimilar condition was between a Picture Card and a Lego object.

3.1.2.3. Habituation. All rats were given four habituation sessions on separate consecutive days, 24 h apart, and prior to their first testing day. For habituation sessions one and two, the rat was placed in the start box, the guillotine door opened, and the rat was free to explore the apparatus for 5 min. Nestlé Cheerios (Nestlé UK Ltd, York, UK) were scattered throughout the arms of the apparatus. In habituation sessions three and four, food was placed only in the food wells and the rat was left in the maze for 5 min; 24 h later, testing began.

3.1.2.4. Pre-training. Pre-training consisted of 9 sessions of 20 trials each. Half of the rats were rewarded for approaching the black wooden block and half were rewarded for approaching the white wooden block. The side on which the reward stimulus was presented on a given trial was determined pseudorandomly. Each rat was placed in the start box at the beginning of a trial; the guillotine door was raised and then shut after the rat entered the exploration area of the apparatus. A response was scored as correct if the rat approached (within 0.5 cm of the correct stimulus) and/or touched the object with its nose. If the rat chose correctly, one half of a Cheerio was placed in the food well directly in front of the stimulus. The experimenter waited for the rat to finish eating, then placed the rat back in the start box. Next, the guillotine door was raised to continue to the next trial. If the rat performed incorrectly, the rat was picked up without any reward and placed back in the start box for 15 s. The animals had to reach a criterion of 75% correct (15/20) on two consecutive days before the discrimination experiment proper began. Discrimination testing did not occur until all rats reached criterion. Since some rats reached criterion before day 9, all rats were run on the pre-training discrimination, one day prior to the visual discrimination experiment, to ensure they could still perform at criterion (all rats attained 15/20 or better).

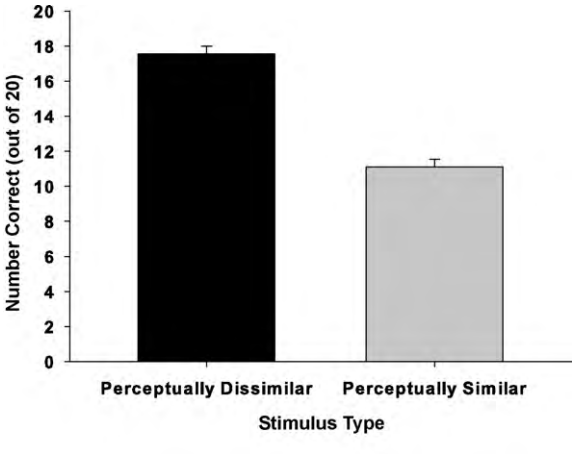

Fig. 2. Visual discrimination performance by naive rats using two different conditions of perceptual similarity (Dissimilar and Similar) in Experiment 2. Performance levels in the Perceptually Similar condition were significantly lower than performance in the Perceptually Dissimilar. Data are presented as average number of correct trials (out of 20 trials) ± SEM.

3.1.2.5. Visual discrimination. The same method was used as in pre-training. However, correction trials were now included. If a rat performed incorrectly, the rat was placed in the start box for 15 s, and then the same trial would be repeated until the correct choice was made. However, only the first choice on a given trial was scored, not the correction trials. Each rat was given 20 consecutive trials, plus correction trials, for 4 consecutive days, which were separated by at least 24 h.

3.2. Results

3.2.1. Visual discrimination accuracy

Univariate analysis of the group means of rats' trial performance in the two conditions, Perceptually Similar and Perceptually Dissimilar, on day 4 of the visual discrimination revealed a highly significant effect of group. Discrimination levels in the Perceptually Similar condition were significantly lower than in the Perceptually Dissimilar condition ($F_{(1,11)} = 47.85$, $p < 0.0001$) (Fig. 2). Furthermore, analysis of learning across sessions was examined using a two-way ANOVA where the first factor was the between-subjects factor of condition (Perceptually Similar or Perceptually Dissimilar) and the second factor was the within-subjects factor of session (1–4). A two-way ANOVA revealed a significant effect of session ($F_{(3,30)} = 5.91$, $p = 0.003$), condition ($F_{(1,10)} = 72.62$, $p < 0.0001$), and a significant session by condition interaction ($F_{(3,30)} = 3.20$, $p = 0.03$) (Fig. 3).

Therefore, the systematic examination of the perceptual difficulty of stimuli in the Perceptually Similar (discrimination between a Lego object and another Lego object) and Perceptually Dissimilar (discrimination between a Picture Card and a Lego object) conditions in the visual discrimination task confirmed that the Picture Card and Lego object stimuli are easily discriminable and when a Lego object has to be discriminated from another Lego object, the discrimination becomes more difficult. We used these same stimuli from this visual discrimination experiment for the following object recognition experiment (Experiment 3).

4. Experiment 3: interference task

Recognition memory is commonly impaired in human amnesics affected by neurodegenerative diseases or who have suffered brain injury (Buffalo et al., 1998; Hajilou & Done, 2007; Holdstock, 2005; Irle, Kessler, Markowitsch, & Hofmann, 1987; Laatu, Revonsuo, Jaykka, Portin, & Rinne, 2003; Lee, Rahman, Hodges, Sahakian, & Graham, 2003; Manns & Squire, 1999; Purdy, McMullen, & Freedman,

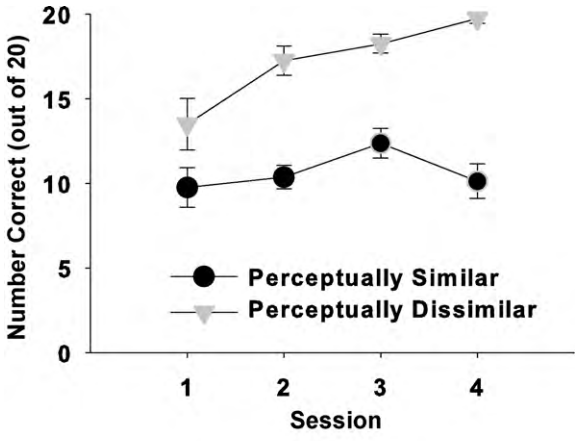

Fig. 3. Learning curve of visual discrimination performance by naïve rats in Experiment 2. Data are presented as average number of correct trials (out of 20 trials) ± SEM.

2002; Reed & Squire, 1997). For this reason, animal models of object recognition have figured prominently in the investigation of the neural basis of memory (Gaffan, 1994; Mumby & Pinel, 1994; Murray & Mishkin, 1998; Winters & Bussey, 2005c; Zola-Morgan, Squire, Amaral, & Suzuki, 1989). Recognition memory is commonly assessed in rodents using the spontaneous object recognition memory task (Ennaceur & Delacour, 1988). In this task, the subject is presented with two identical copies of the same object during a sample phase; after completing exploration of the sample stimuli, a delay is usually imposed, and then the subject is presented with a third copy of the sample object and a novel object. A normal animal will explore the novel object more than the familiar object in the choice phase, indicating that the subject 'remembers' seeing the familiar object in the previous sample phase. Neurotoxic lesions of PRh or PPRh have been shown to disrupt object recognition memory in the spontaneous object recognition task in a delay-dependent manner while leaving performance on standard allocentric spatial memory tasks (e.g., Morris water maze, delayed non-matching to position, and delayed spatial alternation in the t-maze) relatively intact (Bussey, Muir, & Aggleton, 1999; Bussey, Duck, Muir, & Aggleton, 2000; Ennaceur, Neave, & Aggleton, 1996). Furthermore, Winters et al. (2004) provided a clear functional double dissociation between effects of damage on PPRh and another medial temporal lobe structure, the hippocampus: PPRh lesioned rats were impaired on object recognition and unimpaired on radial maze performance whereas hippocampal lesioned animals showed the opposite pattern of effects. Furthermore, the stimulus material used in the spontaneous object recognition task lends itself to the interpolation of interfering items before or after the to-be-remembered object.

Experiment 3 was thus designed to investigate whether introducing an extra phase to the traditional object recognition paradigm would lead to interference in the PPRh-lesioned rats when the extra ('interfering') phase contained a perceptually similar object to the sample phase. We chose PPRh lesions because a selective lesion of PRh only might be argued not to adequately model amnesia, while very large lesions including the hippocampus would not be appropriate since complete lesions of the hippocampus have no effect whatsoever on object recognition using this method, as discussed previously. Therefore, we went with the PPRh lesion, which includes damage to the PRh, postrhinal, and entorhinal cortices, but not the hippocampus. Rats were tested in two conditions, Perceptually Similar and Perceptually Dissimilar. In the Perceptually Similar condition, the 'sample' phase consisted of the presentation of two identical Lego objects and the 'interfering sample' phase consisted of the presentation of a further two Lego objects, identical to each other but different from the other, 'sample' pair. In half of the trials, the interfering sample followed the sample (retroactive condition) whereas in the other half of the trials, the interfering sample preceded the sample (proactive condition). During the choice phase, the apparatus contained an identical copy of the sample (familiar) object in one arm and a new Lego object in the other. In the Perceptually Dissimilar condition, two identical Lego objects were presented in one of the sample phases and two (identical) Picture Cards were presented in the interfering sample phase. Again, half of the trials were retroactive and half were proactive. During the choice phase, the apparatus contained an identical copy of the familiar Lego object in one arm and a new Lego object in the other. Note that in order to retain consistency with previous work and to establish the basic interference effect, we decided that in the first instance we should increase the similarity of the interfering stimuli in the rat experiment simply by making them of Lego (i.e., the same material as the sample and choice objects). The model makes more specific predictions that could be tested using more complicated experimental designs (e.g., differential effects of similarity of the interfering stimulus with the familiar or novel stimulus only; these more specific predictions will be tested in future studies). Importantly, no explicit delay was imposed between the sample and choice phases, as is usually required to see a deficit in spontaneous object recognition tasks. As indicated by the simulations in Experiment 1, we predicted that when the interfering object was perceptually similar to the sample object, the PPRh-lesioned rats would be impaired in discrimination of the novel stimulus in the choice phase.

4.1. Materials and methods

4.1.1. Subjects

The subjects were 24 adult male Lister hooded rats (Harlan Olac, Bicester, UK) weighing 270–320 g before surgery. The animals were housed and fed in the same manner as the rats used in Experiment 2.

4.1.2. Surgery

Rats were divided into two groups: perirhinal plus postrhinal cortex lesions (PPRh; $n = 11$) and surgical controls (Control, $n = 13$). Before surgery, all animals were deeply anaesthetized by intraperitoneal injection (60 mg/kg, i.p.) of sodium pentobarbital (Sagatal; Rhône Mérieux, Essex, UK) and placed in a stereotaxic frame (Kopf Instruments, Tujunga, CA) with the incisor bar set at +5.0. The scalp was cut and retracted to expose the skull. Craniotomies were then performed directly above the target region, and the dura was cut to expose the cortex.

For the PPRh lesions, injections of 0.2 μl of 0.9 M NMDA (Sigma, Poole, UK) dissolved in phosphate buffer, pH 7.4, were made through a 1 μl Hamilton syringe into five sites in each hemisphere. Each injection was made gradually over a 2 min period, and the needle was left *in situ* for an additional 4 min before being withdrawn. The stereotaxic coordinates relative to ear-bar zero were: anteroposterior (AP) + 3.9, lateral (L) ± 5.9, dorsoventral (DV) + 2.0; AP + 2.4, L ± 6.1, DV + 1.6; AP + 0.6, L ± 6.2, DV + 2.5; AP − 0.8, L ± 6.2, DV + 2.7; and AP − 0.8, L ± 6.2, DV + 4.3.

Control animals received sham PPRh surgeries. For sham surgeries, the same initial surgery was performed (including craniotomy and insertion of needle), but no injections were made. At the completion of surgery, the skin was sutured, and an antibiotic powder (Acramide; Dales Pharmaceuticals, Skipton, UK) was applied. Animals were then administered subcutaneously with 5 ml of glucose saline (Aquapharm; Animalcare Limited, York, UK).

4.1.3. Histology

After behavioral testing, rats were anesthetized by intraperitoneal injection of 2 ml of Euthatal (Rhône Mérieux) and perfused transcardially with 100 ml of PBS, pH 7.4, followed by 250 ml of 4% paraformaldehyde (PFA), pH 7.4. The brains were removed, postfixed in 4% PFA at 4 °C for 24 h, and then immersed in 25% sucrose in PBS until they sank. Coronal sections (60 μm) were cut on a freezing microtome through the extent of the lesioned area, and every fifth section was mounted on a gelatin-coated glass slide, and stained with cresyl violet. Slides were examined under a light microscope to determine the extent of excitotoxin-induced damage.

The extent of tissue damage in perirhinal, postrhinal, lateral entorhinal, and medial entorhinal cortices was quantified in PPRh lesioned rats by measuring the pixel volume of the drawings of the intact areas (perirhinal, postrhinal, lateral entorhinal, and medial entorhinal cortices) from Paxinos & Watson (Paxinos & Watson, 1998) and comparing these with the pixel volume of the drawings of the lesioned PPRh area for each rat. This was accomplished using ImageJ software (http://rsbweb.nih.gov/ij/). The percentage of lesioned area for each rat and the mean percentage lesioned area for each lesion group were calculated from these values. The boundaries for measuring these areas was determined from those previously defined by Burwell et al. (Burwell, 2001; Burwell & Amaral, 1998; Burwell, Witter, & Amaral, 1995).

4.1.4. Spontaneous object recognition

4.1.4.1. Apparatus. Spontaneous object recognition was conducted in a Y-shaped apparatus, as described previously (Bartko et al., 2007b) (see Fig. 4). Briefly, the Y-shaped apparatus had high, homogeneous white walls constructed from Foamalux (Brett Martin, Lancashire, UK) to prevent the rat from looking out into the room and, thereby, maximizing attention to the stimuli. All walls were 40 cm high and each arm was 27 cm in length and 10 cm wide. The start arm contained a guillotine door 18 cm from the rear of the arm. This provided a start box area within which the rat could be confined at the start of a given trial. The floor and walls were wiped down with a dry paper towel between trials but otherwise were not cleaned during the experiment. A lamp illuminated the apparatus and a white shelf, 50 cm from the top of the apparatus, created a ceiling on which a video camera was mounted to record trials.

To facilitate immediate viewing between test phases (0-s delay), eight metal posts (four per test arm, each 33.40 cm in height) were inserted and positioned 12 cm apart from each other, which in turn created holders for two sliding doors in each arm of the Y-apparatus. The doors (composed of white Foamalux) were 33 cm tall and 10 cm wide. To create immediate viewing between test phases, modifications were made to the original Y-apparatus.

4.1.4.2. Lego objects. The Lego objects were composed entirely from Lego (LEGO group, Billund, Denmark). All Lego objects were between 6.5 and 15.6 cm tall and 5.2 and 8.9 cm wide and were affixed to an 8.50 cm × 8.50 cm black Lego sheet. Lego objects were secured to the floor of the apparatus with Blu-Tack (Bostik, Stafford,

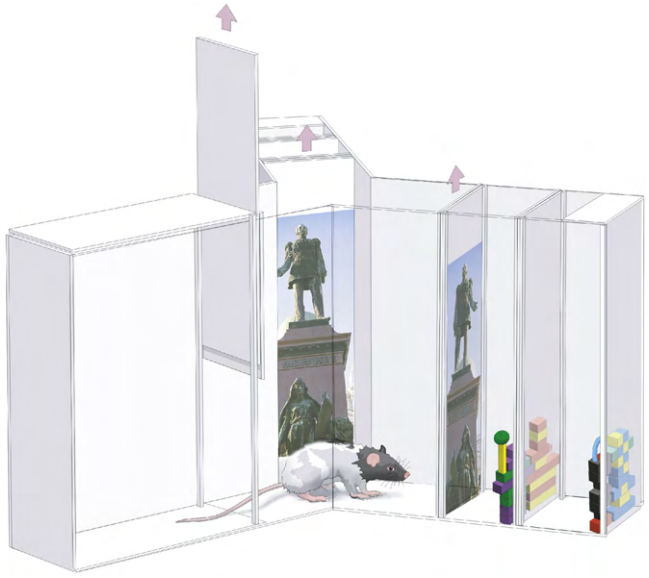

Fig. 4. Illustration of the phases of the zero-delay, two-sample object recognition task (figure illustrates the proactive, Perceptually Dissimilar condition). The nearest wall appears transparent for illustrative purposes and the guillotine door is shown raised. All stimuli (sample object, interfering item, and the choice object) are placed in the apparatus before testing begins. At the beginning of a trial, the rat is released from the start box when the experimenter raises the guillotine door. In phase 1, the rat is exposed to identical versions of the interfering object (Picture Card). At the end of phase 1, the Picture Card objects are removed and the door between phase 1 and phase 2 is immediately raised. In phase 2, the rat is exposed to identical versions of the sample object (Lego object). At the end of phase 2, the Lego objects are removed and the door between phase 2 and choice is immediately raised. In the choice phase, the rat is exposed to a third, identical copy of the sample at the end of the one exploration arm and a novel Lego object at the end of the other arm.

UK). As far as could be determined, the Lego objects had no natural significance for the rats, and they had never been associated with a reinforcer.

4.1.4.3. Picture Cards. The Picture Cards were composed from two photographic pictures (istockphoto™, Calgary, Alberta, Canada). The Picture Cards were printed with a Hewlett Packard Laser Jet printer onto white paper and then laminated. Two photographic pictures were placed side by side to create a single Picture Card that was 30 cm tall and 9.3 cm wide. The Picture Cards were secured to the sliding doors by Velcro (3M, UK). As far as could be determined, the Picture Cards had no natural significance for the rats, and they had never been associated with a reinforcer.

4.1.4.4. General procedure. All rats were habituated in two consecutive daily sessions in which they were allowed to explore the empty Y-apparatus for 5 min. For these habituation sessions, the rats were placed in the start box, and the guillotine door was opened to allow the rat to explore the main area of the apparatus. The guillotine door was lowered when the rat exited the start box to prevent re-entry into this area of the apparatus. The experimenter did not begin timing the trial until the rat exited the start box. Testing began 24 h after the second habituation session. Rats were given a series of test trials (one per day) with a minimum interval of 24 h between trials. A different object pair was used for each trial for a given animal, and the order of exposure to object pairs as well as the designated sample and novel objects for each pair were counterbalanced within and across groups. The time spent exploring objects was assessed from video recordings of the sample and choice phases. Data were collected by scoring exploratory bouts using a personal computer running a program in Visual Basic 6.0 (Microsoft, Redmond, WA).

4.1.4.5. Zero-delay object recognition. All object sets used in a given trial were placed in the apparatus before the rat was placed in the start box. The rat was then placed in the start box with the guillotine door lowered. Next, the guillotine door was raised to allow the rat into the exploration area of the apparatus. When the rat exited the start box, the guillotine door was lowered to prevent re-entry, and the test phases began. The time spent exploring the two objects in a testing phase was scored by an experimenter viewing the rat on a video screen. The cumulative duration of exploratory bouts, the beginning and end of which were indicated by pressing a given key on the computer keyboard, was calculated by the computer program. Exploration of an object was defined as directing the nose to the object at a distance of <2 cm and/or touching it with the nose.

Rats were tested in two conditions, Perceptually Similar and Perceptually Dissimilar; the presentation order of the two conditions was counterbalanced between rats and across trials. Nested within these conditions were the proactive and retroactive conditions. Therefore, each trial consisted of three phases and there were two possible trial types within each condition: retroactive (phase 1 = sample, phase 2 = interfering sample, and phase 3 = choice) and proactive (phase 1 = interfering sample, phase 2 = sample, and phase 3 = choice).

4.1.4.6. Perceptually Similar condition. In the perceptually similar condition, we used two pairs of Lego objects as 'sample' stimuli; the two objects within each pair were identical, but the objects in one pair (labeled A1 and A2, signifying two copies of the object 'A') were different from those in the other pair (B1 and B2). A1 and A2 were always the 'interfering' sample objects and B1 and B2 were always the 'to-be-remembered' sample objects. In phase 1, one pair of objects was presented to the rat; in phase 2, the other pair was presented. Whether the interfering items A1 and A2 were presented in phase 1 or phase 2 was counterbalanced between rats and across trials. During the choice phase, the apparatus contained an identical copy of the to-be-remembered sample object (B3) in one arm, and a new Lego object (C) in the other (see Fig. 5A).

4.1.4.7. Perceptually Dissimilar condition. In the Perceptually Dissimilar condition, two identical Lego objects (D1 and D2) were presented in one of the phases and two Picture Cards (E1 and E2 – the interfering stimuli) were presented in the other sample phase. During the choice phase, the apparatus contained an identical copy of the familiar Lego object (D3) in one arm and a new Lego object (F) in the other (see Fig. 5B). Whether the interfering items (E1 and E2) were presented in either phase 1 or phase 2 was counterbalanced between rats and across trials.

Each of the sample phases of a given trial ended when the rat had explored the identical objects for 15 s or when 5 min had passed, whichever occurred first. At the end of the first sample phase, the identical objects were removed and the dividing door was immediately opened, thus presenting the second pair of sample objects to the rat. After the rat explored these objects, the objects were removed, and the dividing door was opened to immediately expose the choice objects to the rat. The choice phase contained an identical copy of the sample (familiar) object in one arm and a novel object in the other. The arm in which the novel object was placed was counterbalanced between rats and across trials. The time spent exploring the novel and familiar objects was recorded for 3 min of the choice phase, but attention was focused on the first minute, during which object discrimination is typically greatest (Dix & Aggleton, 1999). We calculated a discrimination ratio, the proportion of total exploration time spent exploring the novel object (i.e., the difference in time spent exploring the novel and familiar objects divided by the total time spent exploring the objects), for the first minute of the choice phase on each object recognition trial. This measure takes into account individual differences in the total amount of exploration time.

4.1.5. Data analysis

Group means of three measures taken from object recognition testing (duration of sample and interfering item phase, total exploration time in the choice phase, and the discrimination ratio) were analyzed. Means from total exploration in the choice phase and recognition in the choice phase were submitted to a two-way ANOVA where the first factor was the between-subjects factor of lesion group and the second factor was the within-subjects factor of condition (Perceptually Similar or Perceptually Dissimilar). Means from the duration of sample and interfering item phase as well as the discrimination ratio from the choice phase were submitted to a three-way ANOVA. The first factor was lesion group (between-subjects), the second factor was condition (within-subjects), and the third factor was the phase of the interfering item (within-subjects). Planned comparison *t*-tests were used when hypotheses predicted an effect of group in one trial condition, but not the other. All tests of significance were performed at $\alpha = 0.05$.

4.2. Results

4.2.1. Histology

The excitotoxin-induced brain damage was centred on the targeted structures, with only minimal unintended damage to nearby regions seen in a few cases. In the PPRh group, cell loss was observed throughout the rostral-caudal extent of PRh and continued caudally throughout PPRh (Fig. 6). The estimated average percentage of lesioned areas was: PRh area = 84% (range: 67–97%) and postrhinal area = 81% (range = 66–99%). Although the lesion extended ventrally to include the lateral entorhinal cortex in all PPRh animals, the estimated average percentage of damage to lateral entorhinal cortex was minimal: lateral entorhinal cortex = 12% (range: 8–19%). Furthermore, no damage was apparent in medial entorhinal cortices of PPRh animals.

There was some unilateral sparing of the most rostral PRh in one animal. Minor unilateral damage to area CA1 in the ventral hippocampus was observed in one animal. Minor, incidental TE damage (bilateral in 6 PPRh rats and unilateral in 5 PPRh rats) was observed in all PPRh animals. However, analysis of discrimination scores of PPRh rats according to TE damage (unilateral and bilateral) revealed no significant difference between groups ($F < 1$) and no interaction with condition ($F_{(1,9)} = 1.75$). Histological analysis revealed no cellular loss in the PPRh of the Control group. However, unilateral cortical damage was observed in two Control rats, visible in

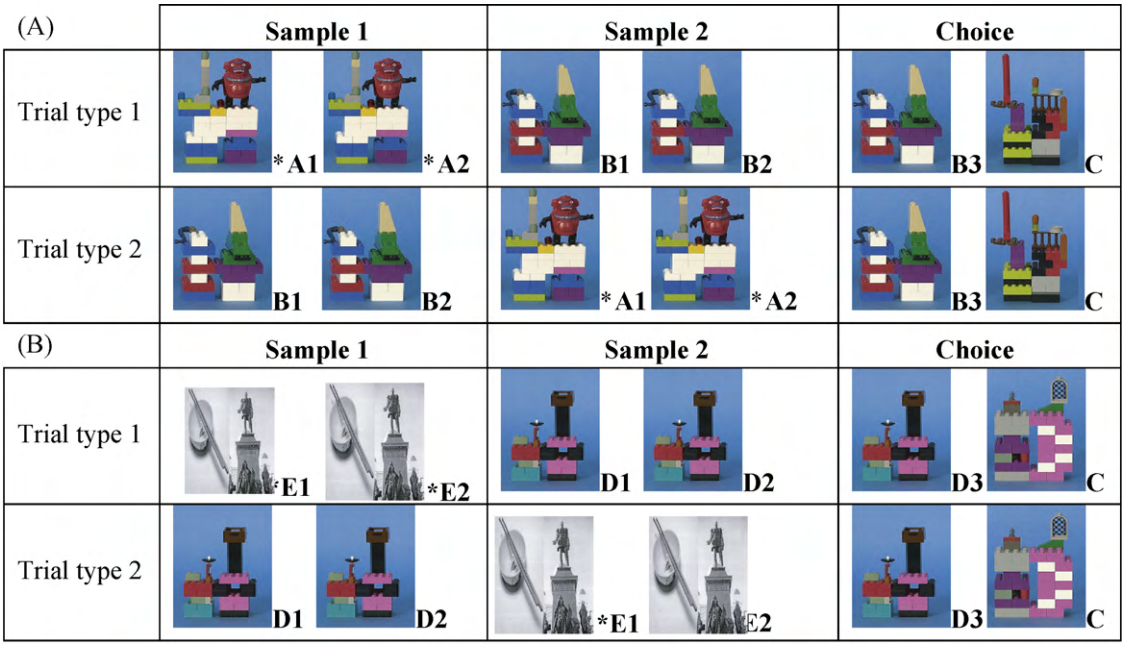

Fig. 5. Illustration of the two possible trial types which could occur during each condition (A: Perceptually Similar and B: Perceptually Dissimilar) of the zero-delay, two-sample object recognition task. The interfering stimulus could appear in either phase 1 or 2. During a proactive trial, the interfering item (*) was presented in phase 1 and the interfering item was presented in phase 2 during a retroactive trial.

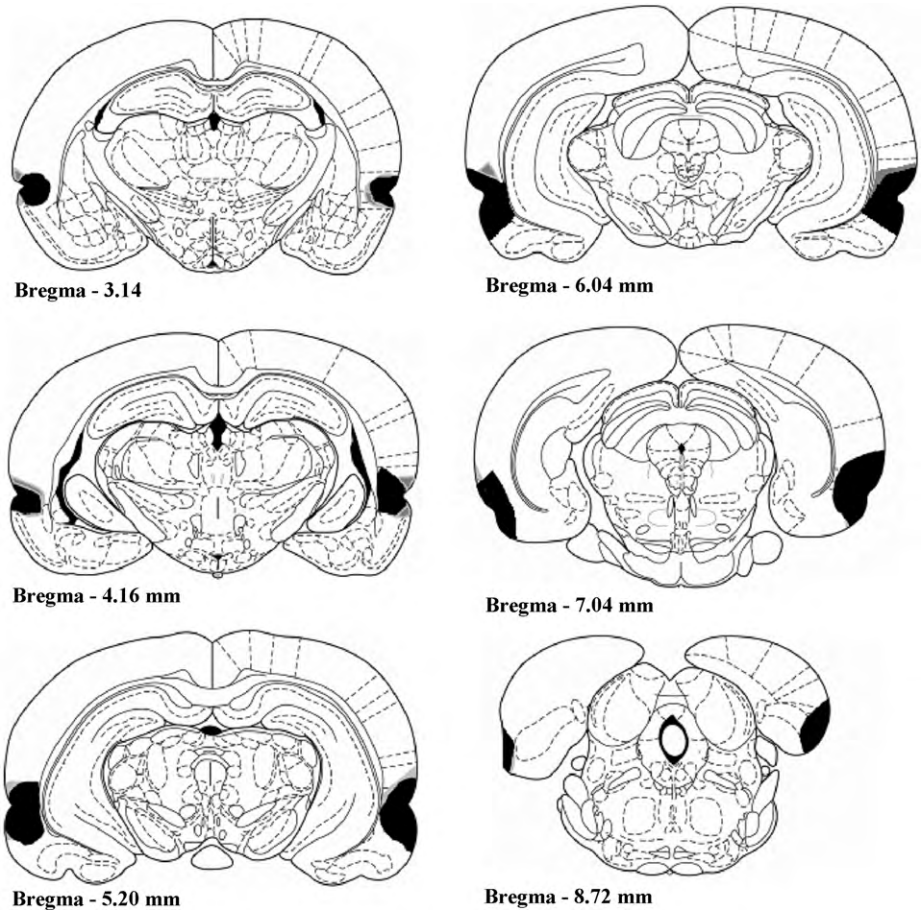

Fig. 6. Coronal sections illustrating the extent of the largest (black) and the smallest (gray) lesions of the perirhinal and postrhinal cortices from 2.12 to 8.72 mm bregma (Paxinos and Watson, 1998).

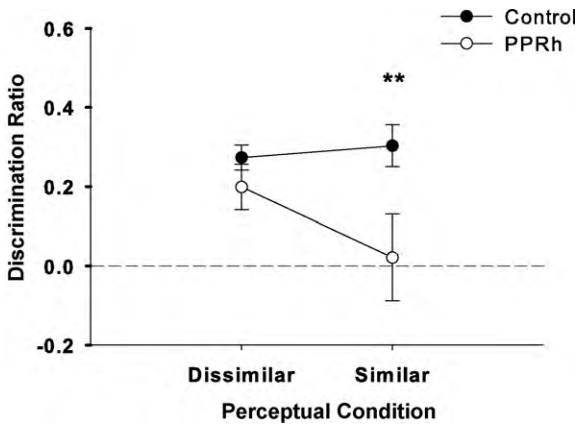

Fig. 7. Spontaneous object recognition performance by Control and PPRh animals in the zero-delay, two-sample, Experiment 3. Data are presented as average discrimination ratio ± SEM and $p < 0.01$.

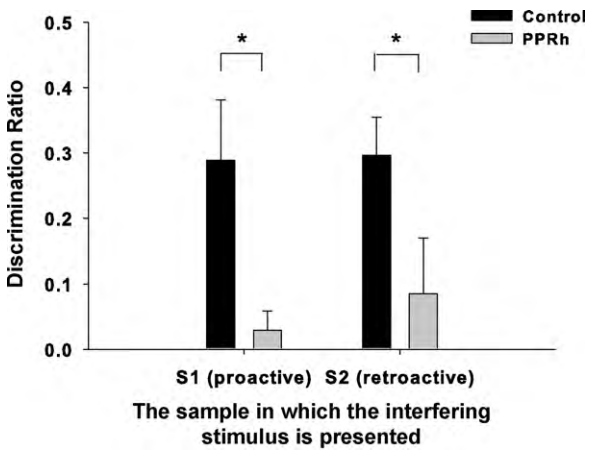

Fig. 8. Zero-delay, two-sample spontaneous object recognition performance by PPRh and Control animals in the Perceptually Similar condition in Experiment 3. In PPRh animals, a significant object recognition impairment relative to Controls occurred both when the interfering item was presented in phase 1 (proactive interference) and when the interfering item was presented in sample 2 (retroactive interference). Data are presented as average discrimination ratio ± SEM and $p < 0.05$.

the parietal cortex from 0.49 mm to 3.60 mm posterior to bregma. The damage is possibly a result of the craniotomies or from inserting the needle during surgery.

4.3. Spontaneous object recognition

4.3.1. Duration of the sample phase

In the present study, all animals explored the sample and the interfering item for 15 s in under 5 min on all trials. The total time required to meet the criterion for phase 1 and phase 2 exploration (15 s cumulative for each phase) was analyzed, because a group difference at this stage of trial might influence subsequent recognition performance. Time to complete 15 s of object exploration in each of phase 1 and phase 2 was analyzed using a three-way ANOVA (group × condition × phase of the interfering item). Analysis of the total time in the apparatus revealed no significant difference between the groups ($F_{(1,22)} = 1.04$) and no significant difference between conditions ($F_{(1,22)} = 3.87$). The sample in which the interfering stimulus was located (proactive or retroactive) ($F < 1$) and the three-way interaction of lesion × condition × sample of the interfering stimulus were also not significant ($F < 1$).

4.3.2. Object exploration during choice phase

There was no interaction of condition by group ($F < 1$), nor was there a significant difference in exploration by group ($F < 1$). However, there was a highly significant difference in exploration according to condition ($F_{(1,22)} = 15.63$, $p = 0.001$). Both PPRh and Control groups explored the novel and familiar choice objects in the Perceptually Dissimilar condition more than in the Perceptually Similar condition.

4.3.3. Recognition during the choice phase

The PPRh group performed significantly more poorly than Controls in the Perceptually Similar condition, both when the interfering stimulus was presented in phase 1 and when the interfering stimulus was presented in phase 2 (Fig. 7), even though the delay between sample and choice was minimal. A two-way ANOVA revealed no significant effect of condition ($F < 1$) or condition by group interaction ($F_{(1,22)} = 1.54$). However, there was a highly significant effect of group ($F_{(1,22)} = 12.11$, $p < 0.01$). Additional analyses revealed a significant group effect in the Perceptually Similar condition ($t_{(22)} = 2.54$, $p < 0.05$) but not the Perceptually Dissimilar condition ($t_{(22)} = 1.24$, $p > 0.05$). Therefore, as predicted and made explicit by the simulations in Experiment 1, PPRh lesions in the rat produced performance deficits in a spontaneous object recognition task when a perceptually similar interfering stimulus was interpolated.

4.3.4. Interference analysis for the Perceptually Similar condition

We examined whether there was a significant group difference according to whether the interfering object was presented as a phase 1 or a phase 2 object in the Perceptually Similar condition, since there was a significant group effect in this condition. A two-way ANOVA (group × phase of the interfering item) was used to analyze PPRh and Control performance. The PPRh group were more susceptible than controls to both proactive and retroactive interference in the Perceptually Similar condition (Fig. 8). The phase of the interfering item ($F < 1$) and the interaction of phase of the interfering item by group ($F < 1$) were not significant. There was a highly significant main effect of group ($F_{(1,22)} = 5.19$, $p < 0.05$). Further analysis of the discrimination ratios for PPRh and Controls when the interfering item was presented in phase 1 showed that proactive interference was significant ($t_{(10)} = 2.04$, $p < 0.05$). Analysis of the discrimination ratios for the groups when the interfering item was presented in phase 2 showed that retroactive interference was also significant ($t_{(10)} = 2.24$, $p < 0.05$). The failure of the PPRh-lesioned rats to discriminate the novel from the familiar stimulus in the choice phase occurred irrespective of whether the interfering item was presented before or after the to-be-remembered item, i.e., whether the interference was proactive or retroactive.

5. Discussion

It has been suggested that damage to temporal lobe regions can result in a heightened susceptibility to interference (Bussey & Saksida, 2002; Cowell et al., 2006; Della Sala et al., 2005; Warrington & Weiskrantz, 1970; Wixted, 2004). The present study tested this prediction using a well-studied rodent model of visual recognition memory impairment. We found that animals with PPRh lesions were able to perform well under conditions of minimal delay when the interpolated item was not perceptually similar to the test items, but were severely impaired when the interpolated item was perceptually similar. This effect was seen whether the interpolated item was presented prior to (proactive interference) or after (retroactive interference) the to-be-remembered item. Thus even very specific, perirhinal cortex-dependent object recognition impairments can be elicited simply by increasing interference. These data provide additional support, from a well-controlled animal model of amnesia, for the suggestion that amnesia is characterized by an increased susceptibility to interference (Bussey & Saksida, 2002; Cowell et al., 2006; Della Sala et al., 2005; Warrington & Weiskrantz, 1970; Wixted, 2004). These findings from an animal model complement recent studies that suggest that susceptibility to interference as an important feature of amnesia should be re-examined (Cowan et al., 2004; Della Sala et al., 2005; Dewar, Garcia, Cowan, & Della Sala, 2009; Loewenstein et al., 2004).

We have introduced a "representational-hierarchical" approach to understanding cognitive impairments following damage to brain regions associated with amnesia, which, as demonstrated by the simulations in Experiment 1, predicts and provides a mechanistic account for the heightened susceptibility to interference seen in amnesia. Our approach is very different from that typically taken. The predominant approach to amnesia is to view the brain as being organized according to modules, each of which performs a different function, such as declarative or explicit memory, each using a different computational mechanism. The representational-hierarchical view, however, emphasizes not psychological modules, but the hierarchical organization of representations through the ventral visual–perirhinal–hippocampal stream. When an object is presented to a subject, it is encoded not in a single representation in a single module, but throughout the object processing pathway,

with object features encoded caudally, and conjunctions of those features encoded rostrally within this system. This assumption of hierarchy – which is made in many models of object representation and is widely accepted (Riesenhuber & Poggio, 1999; Rolls, 1992; Ungerleider & Mishkin, 1982) – leads to a very different conception of the nature of the impairment in amnesia. Specifically it emphasizes that damage to temporal lobe structures such as PRh affects only a portion of the full representation of an object. The relevance of this assumption to the understanding of the nature of the impairment in amnesia is perhaps best understood with reference to the simulations presented in Experiment 1. Lesioned networks and animals with PPRh damage were impaired in discriminating the novel and familiar stimuli in the Similar but not in the Dissimilar condition. The impairment arose in the model because removing the PRh layer removed the object-level conjunctive representations, and the remaining caudal layer representations of simple visual features were not sufficient to resolve the perceptual similarity between the interfering stimulus and the novel item. On presentation of the interfering stimulus during the 'interference sample' phase, all of its features were encoded individually on the caudal layer. Since the interfering stimulus and the novel item shared a feature – corresponding to the similarity induced by constructing both from Lego – on subsequent presentation of the novel stimulus in the choice phase, the shared feature in the novel object appeared familiar, even though the whole novel object had never been seen. Therefore, the novel object appeared partially familiar to networks possessing only a caudal layer so that discrimination of the novel and familiar objects was more difficult. In contrast, Control networks possessing a PRh layer could represent all stimuli as unique conjunctions of features, so that the representation of the novel stimulus remained coarsely tuned (unfamiliar) on the PRh layer, despite its perceptual similarity to the encoded interfering stimulus. Control networks were thus unimpaired in the Similar condition. However, no performance impairment was seen in lesioned networks and animals in the Dissimilar Condition; because the novel and interfering stimuli shared few features – being constructed of Lego and Picture Cards, respectively – the representations of all features of the novel stimulus on the caudal layer remained coarsely tuned, i.e. unfamiliar. Therefore the novel and familiar stimuli were easily discriminable even by networks and animals possessing only caudal representations.

This leads to a second way in which the representational-hierarchical approach differs from the standard approach to amnesia: because only a portion of an object memory representation is compromised in amnesia, the representational-hierarchical approach allows for an explanation of heightened interference not in terms of a modular impairment in *either* encoding, storage/consolidation or retrieval, but in terms of "partial" impairments in encoding, storage/consolidation, *and* retrieval. Encoding and storage are affected in that although the stimuli are encoded and stored in terms of ventral-visual stream based representations after damage to rostral regions such as PRh, the additional, complex stimulus representations normally maintained in rostral regions and important for the resolution of interference cannot be formed. Retrieval is affected in that the feature-based encoded and stored representations are sufficient for retrieval under conditions in which there is minimal feature-based interference, however, when individual features are shared between interfering and novel stimuli there is competition between responses to these feature representations. In effect, what is happening is that a storage deficit caused by damage to rostral regions such as PRh leads to both a deficit in retrieval of PRh-based complex stimulus representations – because those representations are no longer there – and a further knock-on retrieval deficit resulting from response competition between the remaining relatively simple feature representations. Thus the amnesia for these two types of representations occurs due to different underlying mechanisms. The result is a dense amnesia because the complex representations are not available and the simpler level representations are not useful for the solution of the task.

It is important to note that the recognition experiments in this paper were run with a minimal delay between the sample and choice phases, a condition under which deficits are not usually seen in animals with damage to PRh (see Bartko et al., 2007b); typically a delay between sample and choice is required to see deficits in this task (Eacott, Gaffan, & Murray, 1994; Malkova, Bachevalier, Mishkin, & Saunders, 2001; Meunier, Bachevalier, Mishkin, & Murray, 1993; Mumby & Pinel, 1994; Wiig & Bilkey, 1995). Consistent with this, a deficit was not obtained when a dissimilar stimulus was interpolated between sample and choice. Interestingly, however, the mechanism outlined above to explain the detrimental effect of the interpolation of a similar stimulus between sample and choice can also be used to explain the effect of a delay between sample and choice. In a large set of potentially interfering items, the same features will tend to occur with relatively high frequency compared to specific conjunctions of those features corresponding to unique objects. Cowell et al. (2006) suggested that during the choice phase of the object recognition task, when an animal is trying to choose between a novel and a familiar object, many of the features of the novel object appear familiar because they have been encountered during the delay as part of other, interfering items. Therefore, the intact ventral visual stream based representations of features in an animal with PRh damage are not clear indicators of novelty. However, the specific conjunction of features belonging to a novel object is unlikely to have been encountered during the delay. Thus, the conjunctive representations in the PRh are by far the most useful representations for judging object novelty, consistent with the many reports suggesting that PRh is critical for object familiarity detection (Aggleton & Brown, 2005; Wan, Aggleton, & Brown, 1999; Zhu, McCabe, Aggleton, & Brown, 1996). The magnitude of impairment increases as delay increases because, as the delay lengthens, more interfering features are encountered and the conjunctive representations in PRh become increasingly important for resolving the interference. This mechanism for delay-dependent impairments was supported with simulations using the same computational model described here.

Thus, although we agree wholeheartedly with Wixted's (2004) view that the role of interference in amnesia should be reconsidered, the details of how we account for interference effects is very different. In particular, Wixted suggests that the original studies of interference in forgetting focused too much on "cue-overload" studies, in which A-B associations are disrupted by subsequently learned A–C associations, and that retroactive interference from "ordinary mental exertion" is much more relevant to everyday forgetting. Wixted further suggests, therefore, that similarity of interfering stimuli is probably not that important in normal forgetting. The mechanism that he puts forward for normal forgetting is that the hippocampus is critical for consolidation/storage of new memories, and that ordinary mental exertion of any type interferes with this consolidation process and leads to forgetting. While we support Wixted's emphasis on interference, and acknowledge that there is evidence for a role for non-specific interference in amnesia (see Wixted, 2004), our view suggests that susceptibility to interference, at least when due to damage to perirhinal cortex, can be fundamentally related to the similarity of interfering representations. This would usually be due to similarity of interfering stimuli, although it is of course possible that these interfering representations could be generated in part endogenously. However, because the representational-hierarchical view suggests that there are multiple representations of an individual stimulus of different levels of complexity in different parts of the brain, the manipulation

and interpretation of similarity may be somewhat more complex than assumed in the original cue-overload studies.

Our view of interference effects as due to alterations in encoding, storage/consolidation, and retrieval is consistent with our recent experiments using the same model of amnesia used here. This model allows, in additional to the permanent lesion approach used here, temporary pharmacological inactivation of brain regions. Combining pharmacological inactivation with the perirhinal cortex-dependent object recognition test, which has discrete encoding, storage/consolidation, and retrieval phases, allows us to inactivate perirhinal cortex during each of these processes selectively, leaving perirhinal cortex to function normally during the other two putative processes. Using this method we find that perirhinal inactivation impairs performance when administered during the encoding, storage/consolidation, *and* retrieval phases (Winters & Bussey, 2005a, 2005c; the same result has been reported for the hippocampus by Riedel et al., 1999). Furthermore, we have mapped the time-course of consolidation using this method: perirhinal inactivation prior to about 40 min into the consolidation period impairs memory, but after that period (when, the interpretation goes, the memory is consolidated), inactivation has no effect (Winters & Bussey, 2005a, 2005c). And importantly, when we inactivate perirhinal cortex during retrieval 180 min after encoding – that is, long after the memory has been consolidated – memory is still affected (Winters & Bussey, 2005c). As perirhinal cortex is still required for retrieval long after consolidation has occurred, these data are incompatible with the idea of the memory trace being consolidated for storage and eventual retrieval outside of the medial temporal lobe memory system, as standard systems-level consolidation theory suggests (e.g., Marr, 1971; Squire, Cohen, & Nadel, 1984). And finally, and most relevant to theories of the mechanism of interference effects in amnesia, we have observed interference effects in perirhinal cortex – which can be ameliorated by blocking encoding of interfering information by scopolamine (Winters, Bartko, Saksida, & Bussey, 2007) – immediately after encoding, 20 h after encoding, and at many points in-between. In other words, there is no relationship between the time-course of consolidation and the effects of interference. Thus our studies using a well-controlled animal model find little support for the idea that interference involves a selective disruption of systems-level consolidation, or that interference effects are apparent in amnesia only as a result of limited consolidation resources. Instead, damage to structures such as perirhinal cortex can induce amnesia by disrupting encoding, storage/consolidation, *and/or* retrieval, and the simulations in the present study show how interference effects can be understood as a disruption of any of these three processes.

In summary, the present study shows that when a perceptually interfering stimulus is presented, either before (proactive) or after (retroactive) the sample stimulus, rats with PPRh lesions are highly impaired in discriminating the novel stimulus from the familiar stimulus in the choice phase of object recognition. This study demonstrates that animals with memory impairments, like humans, can be highly susceptible to interference (also see Daumas et al., 2008), and supports previous work that has shown that PRh contains conjunctive representations that are important for the perceptual processing of complex objects. Furthermore, we suggest that this susceptibility to interference after damage to PRh is due, not to a modular impairment in either encoding, storage or retrieval, but instead may be due to partial impairments in both encoding/storage and retrieval. The present findings add to a growing body of evidence in support of a representational, computationally uniform view of cortical organization (Bussey, 2004; Bussey & Saksida, 2005; Gaffan, 2002), suggesting that the dominant heterogeneous modular view of the brain – in which different structures perform different cognitive functions using different mechanisms – may not be the only, or even the best, way of understanding brain organization.

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