Change in background context disrupts performance on visual paired comparison following hippocampal damage

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Abstract (217 words; max=250)

The medial temporal lobe plays a critical role in recognition memory but, within the medial temporal lobe, the precise neural structures underlying recognition memory remain equivocal. In this study, visual paired comparison (VPC) was used to investigate recognition memory in a human patient (YR), who had a discrete lesion of the hippocampus, and a group of monkeys with neonatal hippocampal lesions, which included the dentate gyrus, and a portion of parahippocampal region. Participants were required to view a picture of an object on a coloured background. Immediately afterwards, this familiar object was shown again, this time paired with a novel object. All participants displayed a novelty preference, provided the background on which the objects were shown was the same as the one used during the learning phase. When the background of the familiar object was changed between initial familiarization and test, only the control subjects showed a novelty preference; the hippocampal-lesioned monkeys and patient YR showed null preference. The results are interpreted within Eichenbaum and Bunsey's (Eichenbaum & Bunsey (1995) *Current Directions in Psychological Science*, *4*, 19-23) proposal that the hippocampus facilitates the formation of a flexible representation of the elements that make up a stimulus whereas the parahippocampal region is involved in the formation of a fused representation.

Introduction

The ability to recognise familiar objects, scenes and faces is one of the most important cognitive functions in humans. Recognition can occur after a short or long period of time, in an old or new environment. The ability to recognize people and objects in different environments is fundamental for our social life, and this flexibility represents a specific feature of an effective memory system. There is current controversy regarding the precise neural structures underlying recognition memory. One view is that there is hippocampal involvement only when recognition depends upon the recollection of associations, such as those between an item and its context (Aggleton & Brown, 1999). According to this view, when recognition can be based on item familiarity alone, it relies not upon the hippocampus but upon the integrity of the perirhinal cortex. Recently, attempts have been made to differentiate the relative contributions to recognition memory of the hippocampus and parahippocampal region (comprising perirhinal cortex, parahippocampal cortex and entorhinal cortex). (See Eichenbaum et al., 2007 and Diana et al., 2007 for reviews.) Both Eichenbaum et al. and Diana et al. argue that the hippocampus is critical for recollection but not familiarity-based responses, and that it supports recollection by facilitating the association between item and contextual information. They suggest that the parahippocampal cortex also contributes to recollection, possibly through the encoding and retrieval of contextual information. They argue that, in contrast, the perirhinal cortex is involved in, and is essential for, familiarity-based recognition. Others have argued, however, that although the medial temporal lobes may show some functional heterogeneity, the available evidence does not support the view that familiarity-based recognition responses are independent of the hippocampus (Squire et al., 2007).

Hippocampal involvement in the recollective component of recognition is consistent with a large body of evidence demonstrating its role in various aspects of associative memory, including contextual processing and retrieval (Hirsch, 1974; 1980; Selden at al., 1991; Kim & Fanselow, 1992; Phillips & LeDoux, 1992), formation of configural associations (Sutherland & Rudy, 1989) and storage of relational representations of items in memory (Cohen & Eichenbaum, 1993; Eichenbaum, Otto & Cohen, 1994; Chun & Phelps, 1999). The overall agreement is that the hippocampus is required to form a flexible association between elements of a scene or event in which the elements can also be kept separate for use in different contexts or episodes (O'Reilly & Rudy, 2001). For example, recognising your postman in the local pub as well as at your doorstep!

Amnesic patients with damage to the hippocampal region show hyperspecificity in associative learning since retrieval of the associations can only occur under highly constrained conditions in which the material presented during the retrieval episode closely resembles that present during the learning episode (Glisky & Schacter, 1988; Thoene & Glisky, 1995). Eichenbaum & Bunsey (1995) proposed that, whereas the hippocampus facilitates a flexible association between items, the parahippocampal region mediates the encoding of elements as *fused* or *unitized* memory representations. These fused representations are inflexible, in that individual elements cannot be retrieved separately in a new context. Therefore, in the absence of a functional hippocampus, hyperspecificity results from fused representations that are encoded by one or more cortices within the parahippocampal region. This proposal also has implications for performance on recognition memory tests when items and the context in which they appear are relevant for performance. A new combination of previously studied components could be fused into a novel representation and perceived as a new stimulus at recognition test. Thus, hippocampal-damaged patients/animals should respond to familiar yet recombined components of a stimulus as if they constitute a novel stimulus. Similarly, a familiar object displayed on a novel background (or on a familiar background previously paired with a different object) may be perceived as a novel stimulus because the object-background association constitutes a new, fused representation.

Support for this view has been provided by studies of rats in which it has been demonstrated that hippocampal lesions disrupt place memory and context memory leaving object memory intact (Mumby et al., 2002). More specifically, using odor discrimination, Eichenbaum and colleagues (Bunsey & Eichenbaum, 1993; Sauvage et al., 2008) have demonstrated that the hippocampus is essential for the formation of flexible representations that allow responses to be made based on the relationship between separate components of a stimulus. The current study extends this work across species in an investigation of the role of the hippocampus in the formation of flexible representations comprising an object and its contextual background.

The association between an item and its background context has been termed ‘contextual binding’ (Chalfonte & Johnson, 1996; Mitchell et al., 2000), and is thought to be mediated by the medial temporal lobe structures. Thus, monkeys with fornix transections are more severely impaired in object-in-place discrimination trials than on either object discrimination or place discrimination trials alone (Gaffan, 1994). Similarly, activations of the hippocampus and parahippocampal cortex occur not only during effortful associative encoding of pictures (Henke et al., 1997, 1999; Montaldi et al., 1998) but also during incidental associations between objects and the context in which they are presented (Goh et al., 2004; Hayes et al., 2007). These findings

are consistent with the view that the hippocampus mediates the encoding of a *flexible* representation of the objects and their context such that responses to the objects or backgrounds can subsequently be made independently of the object/background compound. In contrast, the parahippocampal region mediates the encoding of an *inflexible* representation of the object/background compound fused into a single stimulus, like a snapshot. In this case an object cannot be responded to independently of its background, and presentation of a familiar object on a new background would be perceived as a new stimulus.

To further substantiate this proposal, the aim of the present study is to investigate contextual binding in monkeys with lesions of the hippocampal formation and an amnesic patient (YR) who has a discrete hippocampal lesion using an incidental recognition task. The visual paired comparison task (VPC) exploits a subject's natural tendency to look preferentially at novel stimuli relative to familiar stimuli. VPC task performance has been found to be sensitive to damage to the hippocampal formation in both amnesic patients (McKee & Squire, 1993; Pascalis et al., 2004) and adult monkeys (Pascalis & Bachevalier, 1999; Zola et al., 2000; Nemanic et al. 2004) when increasing delays were used. In the present experiment, we manipulated the backgrounds onto which the objects appeared such that in some trials the backgrounds were identical during familiarization (study) and test, but on other trials they differed between familiarization and test (See Figure 1). Incidental encoding and retrieval of object/background association was assessed in adult monkeys with neonatal hippocampal lesions and the amnesic patient (YR). We predicted that, relative to controls, subjects with damage to the hippocampal formation will be selectively impaired on trials in which the backgrounds differed between familiarization and test. In other words, when the background context is kept constant between familiarization and test, all subjects will show a novelty preference, indicating memory for the familiar objects. However, when the background context is changed between familiarization and test, it is predicted that only the controls will show a novelty preference. It is predicted that the hippocampal-operated monkeys and patient YR will show null preference indicating that, for them, both a familiar object on a new background and a new object on a new background constitute novel stimuli.

The use of the VPC task allows a direct comparison of performance in monkeys and humans, since the task and responses made by the two types of participant are identical. A major strength of this approach is that we can compare the performance of a human patient with *presumed* focal hippocampal pathology with a group of monkeys for whom the lesion is *precise* and, in one of the monkeys, histologically verified.

Figure 1 about here

Experiment 1: Non-human primates

Methods

Subjects

Six adult rhesus monkeys (*Macaca mulatta*) participated in the present study. Three monkeys (2 males and 1 female) had received neonatal hippocampal lesions (Group H) and three (2 males and 1 female) were unoperated controls (Group N). Subjects were 11 years of age and weighed 3.8 – 7.1 kg at the beginning of the experiment.

All monkeys were born at the breeding colony of National Institute of Health Animal Center (Bethesda, MD) and raised in the primate nursery of the Laboratory of Neuropsychology (National Institute of Mental Health, Bethesda, MD). During the first year of life, they were tested on a series of cognitive tasks including a concurrent object discrimination task (24-hr ITI) at the age of 3 months, and the object delayed nonmatching-to-sample (DNMS) task at 10 months of age (Bachevalier et al., 1999). In addition, their social interactions with peers were measured at 2 months, 6 months, and 5 years (Bachevalier, 1994). Upon reaching adulthood, they were sent to the Department of Neurobiology and Anatomy (University of Texas, Houston) where they received further cognitive testing, which included re-tests on the 24-hr ITI and DNMS tasks at 6 and 7 years of age, respectively (Bachevalier et al., 1999), and training on Transverse Patterning and DNMS for locations task at 9 years of age (Alvarado, Wright & Bachevalier, 2002), before participating in the VPC task at 9 years of age (Pascalis & Bachevalier, 1999).

At the time of testing, the monkeys were housed in individual cages and maintained on a diet of Purina Monkey Chow plus fresh food. Water was always available, except for 5 hours prior to testing. The study was approved by the Institutional Animal Care and Use Committee of the University of Texas Health Science Center at Houston, TX, USA.

Surgery and verification of the lesion

The surgical procedure and the extent of brain damage of the operated animals has been described in detail in Bachevalier et al. (1999), although only cases H-1, H-4 and H-6, participated in the present experiment. Briefly, a two-stage aspiration lesion was performed aseptically under anesthesia when the animals were approximately 7 and 20 days old. The hippocampal removal included the dentate gyrus, all CA fields, the subicular complex as well as the underlying parahippocampal cortex (cortical areas TH and TF) lying medial to the occipitotemporal sulcus. The extent of the lesions was verified histologically in one case (see case H-6, Bachevalier et al., 1999) and through Magnetic Resonance Imaging in the two remaining cases (cases H-1 and H-4, Bachevalier et al., 1999) when the animals were 5-7 years old. In all cases, the lesions were as intended, and included the hippocampus proper, subicular complex, and a portion of cortical areas TH and TF. The entorhinal cortical area 28 and perirhinal cortical areas 35 and 36 were spared, except for the most caudal dorsomedial portion of the entorhinal cortex, bilaterally in cases H-4 and H-6, and unilaterally in case H-1. Finally, small unintended damage was found in the inferior temporal cortical area TEO, unilaterally in cases H-4 and H-6 and bilaterally in case H-1. This damage was judged to be potentially significant only in case H-1 where it extended caudally on the ventromedial surface of the right hemisphere to include the occipital cortex (see Fig. 3, Bachevalier et al., 1999).

Stimuli

The stimuli were coloured slides of objects. They were sorted into pairs which were matched for size, brightness and complexity, and the objects were shown either on plain coloured backgrounds (e.g., blue) or on coloured wallpaper patterns. Each stimulus measured approximately 10cm by 10cm. In the ‘same context’ condition, the background remained the same between familiarization and test. In the ‘different context’ condition, the background was changed between familiarization and test, i.e. different colour (e.g., yellow) or different pattern. All backgrounds were novel and had not been presented before. See Figure 1 for examples of stimuli used in the two conditions.

Apparatus

Behavioral testing was carried out in a standard Wisconsin General Testing Apparatus (WGTA) located inside a darkened sound-shielded room. A white-noise generator provided extraneous sound masking. As previously described (Pascalis & Bachevalier, 1998; 1999), a

Plexiglas cage was used to constrain the monkey during behavioural testing. The front of the cage was positioned 30 cm in front of a translucent screen onto which the stimuli (slides of objects) were rear projected. At the centre-front of the cage, a sipper tube was attached and delivered orange juice during training to keep the animal facing the translucent screen and to allow capture of the monkey's eye movements via a camera mounted above the screen during stimulus presentation.

Procedure

The animals had already been trained to perform the task. They were required to sit quietly at the front of the cage and to drink from the sipper tube while looking at stimuli (see Pascalis and Bachevalier, 1999). Each trial involved new stimuli and comprised two parts: familiarization (or study) and test. During familiarization, a sample stimulus was presented in the middle of the screen. The stimulus remained on the screen until the monkey had looked at it for a total cumulative time of 20 seconds. Measurements of the cumulative looking time at the stimulus during the familiarization period were made by the experimenter watching the monkey's fixation on the stimulus displayed on a TV monitor. The length of the familiarization phase was recorded for each trial.

After a 5-second retention interval, during which the participant's view of the stimulus was prevented, the participant was confronted with the familiarized stimulus presented together with a new stimulus, for two successive recognition tests. These two recognition tests were separated by a 5-second interval, in which the left/right position of the stimuli on the screen was reversed to minimise lateral bias. The retention interval used for the recognition tests was selected from our previous study (Pascalis & Bachevalier, 1999) showing that animals with a lesion of the hippocampal formation can demonstrate a novelty preference with delays up to 10 seconds. The two recognition tests, each of which lasted 5 seconds**,** began when the monkey started to look at one of the two stimuli. In the recognition test, the backgrounds onto which the familiar and novel objects were presented were either identical (same context condition) or different (different context condition) to those onto which the objects had been previously presented in the familiarization phase. Ten trials were run for each condition.

The time spent looking at each stimulus (novel or familiar) during the two recognition tests was measured with the aid of a frame by frame video-recording system, which allowed detailed analyses of the corneal reflection of the stimuli (see Pascalis & Bachevalier, 1999).

Results

Length of familiarization period

The total amount of time needed to reach the criterion of 20 cumulative seconds spent looking at each stimulus did not differ between groups across the two context conditions (same: t(18)=.84, NS; different: t(18)=.91, NS). For the control monkeys, it averaged 28.1 seconds (SD 9.3) and 30.7 seconds (SD 12.0) for the same and different context conditions, respectively. For the operated monkeys, it averaged 31.5 seconds (SD 8.75) and 35.7 seconds (SD 12.38) for the same and different context conditions, respectively.

Total looking time during the two recognition tests

For each of the two background conditions, the total time spent looking at the two stimuli during the two recognition tests was summed and then averaged across the 10 trials. The two groups explored the stimuli for a similar amount of time in each background condition (same: t(18)=.07, NS; different: t(18)=-.23, NS). For the control animals, mean total looking time was 2.67 (SD 1.31) and 2.39 (SD 1.16) seconds for the same context and different context conditions, respectively. For the operated animals, mean total looking time was 2.62 (SD 1.41) and 2.51 (SD 1.00) seconds for the same context and different context conditions, respectively.

Percent time looking at each stimulus during the two recognition tests

To determine novelty preference in the two groups of monkeys, the proportion of time spent looking at the novel stimuli was analysed for each trial in each condition. Novelty preference was defined as the time spent looking at the novel stimulus as a proportion of the total looking time during the retention test. The mean percent time spent looking at novel stimuli in the same context and different context conditions for each group is shown in Table 1A. A two-way ANOVA using group (control/hippocampal) and condition (same context/different context) as main factors revealed that both main effects were significant (group: $F(1,4) = 11.730$, $p = .0267$; condition: $F(1,4) = 24.883$, $p = .0076$). This reflected an overall greater novelty preference in the control animals relative to the operated animals, and greater novelty preference in the same context condition than in the different context condition. Of critical importance was the significant group x condition interaction ($F(1,4) = 21.470$, $p = .0098$). One-way ANOVAs were carried out for each condition separately and indicated that, in the same context condition

the two groups did not differ, but in the different context condition the controls showed greater novelty preference than the hippocampal-operated animals (see Table 1A).

Additional t-tests were carried out to determine whether or not novelty preference exhibited by each monkey was significantly above chance. Whereas each control animal in each condition showed a novelty preference that was significantly above chance (all ps < .025, one tailed), the hippocampal-operated monkeys' novelty preference was significantly above chance in the 'same context' condition (all ps < .025, one tailed), but not in the 'different context' condition (all ps > .10, one tailed).

Table 1A. Mean percent fixation time (SD) for novel pictures during retention test in monkeys

Condition	Group N	Group H	F-ratio (df 1, 4)	Probability
Same context	61.47 (2.48)	60.95 (1.69)	.093	.7760
Different context	61.08 (0.87)	50.26 (3.76)	23.582	.0083

Table 1B. Mean percent fixation time (SD) for novel pictures during retention test in YR and Controls

Condition	Controls	YR	t value	Probability
Same context	62.86 (13.83)	67.73 (18.35)	-.870	0.199
Different context	63.06 (13.44)	51.68 (21.49)	1.765	0.050

Experiment 2: Patient YR

Methods

Subjects

The subjects were patient YR and five age- and IQ-matched healthy control subjects. YR is a 62 year old female who has a memory impairment following a possible ischaemic infarct, arising from the administration of an opiate drug to relieve severe back pain 14 years previously in 1986. YR's neuropathology and neuropsychological profile are reported in detail by Holdstock, Mayes, Cezayirli et al. (2000) and Mayes, Holdstock, Isaac et al. (2004). For clarification, an overview of YR's neuropathological and neuropsychological details is included here.

Magnetic resonance imaging (MRI) was carried out in September 1997 using a 1.5T SIGNA whole-body magnetic imaging system (General Electric, Milwaukee, WI). A 3D T1-weighted radio-frequency spoiled gradient echo (SPGR) image revealed a selective lesion affecting the hippocampus bilaterally along its full anterior-posterior extent. Volumetric analysis indicated that the volumes of the hippocampi (corrected for intracranial volume) were 2.5 and 3 SDs smaller than the mean volumes in a group of healthy controls subjects (matched for sex, age and IQ) on the right and left, respectively. In contrast, there was no pathology evident in the parahippocampal gyrus, and the corrected volume of this region, which included the perirhinal, entorhinal and parahippocampal cortices, was at least 1 SD greater than that of the control subjects. Although the amygdala appeared small, there was no evidence of pathology. Frontal lobe structures were intact, and grey to white matter ratios were normal. There was some evidence of parietal lobe atrophy, but this was not atypical for a woman of YR's age, and her corrected parietal lobe volume was within the control range on the right, and only just below the control range on the left.

YR's memory performance has been reported extensively (Mayes et al., 2001, 2002, 2004; Holdstock, Mayes, Roberts et al., 2002), and is briefly summarised here. Her current FSIQ (WAIS-R; Wechsler, 1981), measured at the time of scanning, was in the average range (FSIQ 102). Although this represented a decrement of 13 points from her estimated pre-morbid IQ (115; NART; Nelson, 1991), this was a drop of less than 1 SD in IQ points. On tests of memory function, YR showed a consistent pattern in that she had a severe impairment on tests of verbal and non-verbal recall, but relatively intact performance on tests of verbal and non-verbal item recognition. This pattern of impairment is shown clearly by her performance on the Doors and People Test (Baddeley, Emslie & Nimmo-Smith, 1994) on which she scored below the fifth percentile on tests of verbal and visual recall (Scaled scores: People 4; Shapes 5), but at the 50th

percentile or above on tests of verbal and visual recognition (Scaled scores: Names 16; Doors 9). Similarly, her performance on the Warrington Recognition Memory Test (WRMT; Warrington, 1984) was above the 50th percentile for both verbal and visual subtests (Scaled scores: 11 and 16, respectively). On the Wechsler Memory Scale-Revised (WMS-R; Wechsler, 1987), which tends to rely more heavily on recall, she showed impairment on the Verbal Memory (62), General (66) and Delay (73) indexes. In contrast, her Visual Memory (102) and Attention indexes (112) were at, or above, average. YR's good Visual Memory index contrasts with her impaired visual recall score on the Doors and People Test, and may have been influenced by the recognition scores contributing to this index. Mayes et al. (2002) have confirmed the dissociation that YR shows between visual and verbal recall and recognition using over 70 recall and recognition tests. In particular, this study confirmed that YR's recall of several kinds of visual test materials is clearly impaired. Using another large battery of tests, Mayes et al. (2004) have shown that YR's recognition of associations between items of the same kind was relatively preserved whereas her recognition of associations between different kinds of information (for example, faces and voices) was as impaired as her recall**.** In addition to tests of memory, YR's perceptual function was assessed with the Visual Object and Space Perception Battery (VOSP; Warrington & James, 1991). YR scored within 1 SD of the mean of the normative sample for all subtests. (See Footnote.)

Five control participants were recruited. These were healthy, female volunteers who were matched to YR in terms of age (mean age 63.20 years, SD 2.17) and WAIS-R FSIQ (mean IQ 101.60, SD 5.03). These participants were the same as those reported in a separate study by Pascalis et al. (2004).

Stimuli

A new set of stimuli produced in the same way as those used in Experiment 1 was created to measure visual recognition memory in our amnesic patient and her controls. (See Figure 1.)

Procedure

YR and the controls were investigated individually. Experimental conditions were as follows: First, each participant was shown a single target stimulus to inspect during a 5 second familiarization period. After a very brief delay during which a blank screen was presented (approximately 1 second, the time taken to change the slide), the participant was shown the target object paired with a new stimulus, for 5 seconds. The length of the familiarization period

and the retention interval were chosen from our previous study (Pascalis et al., 2004), which showed that these conditions were sufficient to elicit a novelty preference in YR and her controls at short delays. The left-right position of the novel stimulus was counterbalanced across trials. As in Experiment 1, for 12 trials the background onto which the familiar and novel stimuli were shown was identical to the background used in the familiarization phase (same context condition) and for the remaining 12 trials the background was different (different context condition). Trials from the two conditions were mixed and presented in random order. Participants were told that they were part of a vision study, and we explained to YR that she was the control of a patient with a visual problem. Participants were told that one picture would appear on the screen followed by a brief period of rest, then two pictures would be simultaneously presented. Participants were asked to “look at the screen as if you were watching TV". The dependent variable was actual looking time directed to the new (novel) and to the old (familiar) stimulus.

A video camera with a videotimer was fixed above the screen and recorded participants’ eye movements onto videotape. Stimulus fixation was indicated by corneal reflection of the stimuli. Inspection of the videotape after the experiment allowed the time spent inspecting the right and left images in the 5-second recognition phase to be measured.

Results

Length of familiarization period and total looking time during the recognition tests

Each participant spent 100% of the 5-second familiarization period looking at the stimulus and spent more than 95% of their time looking at either the familiar or the novel picture during the recognition tests.

Percent of time looking at each stimulus during the recognition test

To determine whether there was a significant difference between the novelty preference of YR and that of the control subjects, the proportion of time spent looking at the novel stimuli was analysed. As in Experiment 1, novelty preference was defined as the time spent looking at the novel stimulus as a proportion of the total looking time. This was calculated for each subject on each of the 12 trials in each condition. YR's novelty preference in each condition was then compared with that of the control subjects using a t-test. Since it cannot be assumed that the

variance of YR's performance was equivalent to that of the group of control subjects, Welch's procedure was adopted, which tests for the significance of the difference between means when the population variances are unequal (Ferguson, 1976; p168). The results of this analysis are shown in Table 1B. YR showed a similar novelty preference to that of the controls in the 'same context' condition, but showed a significant difference from the controls in the 'different context' condition.

Additional t-tests were carried out to determine whether or not the novelty preference exhibited by YR and the control subjects was significantly above chance. The results indicated that, whereas each control subject in each condition showed a novelty preference that was significantly above chance (all ps<.025, one-tailed), YR's novelty preference was significantly above chance in the 'same context' condition ($t(11) = 3.346$, $p < .005$), but not in the 'different context' condition ($t(11) = 0.271$, $p > .10$).

General Discussion

In Experiment 1, both monkeys with neonatal hippocampal lesions (which included a portion of the parahippocampal region) and controls showed a novelty preference when objects' background context remained the same between familiarization and recognition tests. In contrast, only the control animals showed a novelty preference when the background context was modified between familiarization and recognition tests; under these conditions, monkeys with hippocampal lesions demonstrated a novelty preference that was not significantly above chance. A similar pattern of results was observed in Experiment 2. Both YR and her control subjects showed a significant novelty preference when the background context was consistent between familiarization and recognition tests. However, when the background context was modified between familiarization and test, only the controls showed a significant novelty preference. The results of the two experiments are therefore consistent. Furthermore, in both experiments, controls demonstrated the same degree of novelty preference in the two experimental conditions. This rules out an explanation that the absence of a novelty preference in the lesioned subjects in the different context condition is simply due to the relative difference in the novelty of the paired stimuli.

Given that the lesion in the operated monkeys included not only the hippocampus but also the parahippocampal cortex, either (or both) of these structures may be critical for novelty

preference when an object's background is changed between familiarization and test. However, there is no evidence that the parahippocampal cortex is damaged in patient YR. Since YR and the operated monkeys show an identical pattern of VPC performance, it seems plausible that it is the integrity of the ***hippocampus*** that is critical for novelty preference following a change in background context.

As suggested in the Introduction, a plausible interpretation of these results is that selective hippocampal lesions disrupt the ability to create flexible, recollection-supporting representations of associations between pictures of objects and their background context. Monkeys and humans with such lesions can only form ***fused*** associative memory representations such that the different elements of these representations cannot be attended to separately. Consequently, each newly formed associative representation is experienced as novel even when one of the elements is familiar. In contrast, for the control subjects, it is possible to attend selectively to different elements of ***flexible*** associative representations. So newly formed associative representations, which depend on the hippocampus, may be experienced as old if at least one of their elements has just been studied. This is particularly pertinent for objects as these are more likely to draw attention than background context.

Based on the VPC data, neither the hippocampal-operated monkeys nor YR seemed to experience studied objects paired with a new background context as old, even following very short, unfilled delays. This suggests that the hippocampal-operated monkeys and YR may have been impaired not only at creating long-term flexible object-context memories, but also at creating short-term flexible object-context memories. Mayes et al.'s (2004) findings on YR's associative recognition support this interpretation. In this study, YR was found to be impaired at recognition of associations between different kinds of information, such as pictures of scenes and environmental sounds, even at unfilled delays of a few seconds. It was argued that, in normal subjects, these memory representations are mediated by recollection and are therefore highly flexible. Object-background context associations are also associations between different kinds of information so YR would also probably have failed to create stable and flexible object-context representations in the current experiment. Given the very short delays at which YR (and the hippocampal-operated monkeys) showed their deficits, this would suggest that they could not form normal short-term memory, let alone long-term memory, representations of object-context associations that have flexibly accessible components. This proposal is consistent with recent findings from both lesion studies (Hannula, Tranel & Cohen, 2006; Olson, Page, Moore et al., 2006) and neuroimaging studies (Hannula & Ranganath, 2008) that have demonstrated hippocampal involvement in relational memory at short lags.

Our results appear inconsistent with those of Ryan and Cohen (2004). Using an eye tracking device with a 'change blindness' procedure, Ryan and Cohen showed that, although amnesic patients failed to show memory for the relations between elements of a scene over a long delay, these patients (including a patient with discrete hippocampal damage) performed similarly to controls over short delays (mean 1.77 seconds). This pattern of results contrasts with our current findings that both YR and the hippocampal-operated monkeys were impaired relative to controls at a very short delay. This apparent inconsistency may be explained by considering the type of representation that subjects' responses may be based upon in the two studies. In the current study, we suggested that in the absence of a functional hippocampus, YR and the operated monkeys form an inflexible, unitized representation of an object on its original background. When the background is consistent between familiarization and test, subjects indicate that the previously viewed object is a familiar stimulus by gazing preferentially at the novel object. In contrast, when the background is modified between familiarization and test, subjects respond as if the familiar object on a new background is a novel stimulus, by showing null preference at test. In the study of Ryan and Cohen, the amnesic patients may also form an inflexible, unitized representation of the scene they are viewing. Thus, when subjects were presented with a slightly modified scene, in which some of the elements of the scene had been added, deleted or changed location, they could utilize this unitized representation (at an unconscious level) to direct their eye movements. These eye movements reflected increased looking in the area where the change occurred, and suggests short-term retention of relational information may be accessed from a unitized representation. This view would appear to be consistent with the results of Haskins et al. (2008) which demonstrated that the perirhinal cortex is involved in a unitized encoding of novel associations. According to Haskins and colleagues, the perirhinal cortex supports associative recognition when responses can be based on familiarity. Alternatively, it may be the nature of the task that is critical in explaining the discrepancy between our present findings and those of Ryan and Cohen (2004). It is possible that the hippocampus is essential for relational memory but not for online processing of relationships between stimulus components. The viewing of sequential scenes in the Ryan and Cohen study may place more emphasis on online processing, whereas the VPC procedure in which subjects' relative gaze at one of two stimuli with varying degrees of familiarity may place more emphasis on short-term relational memory.

Our results are consistent with a growing body of evidence indicating that the hippocampus is critical to form flexible representation of objects and the environments in which they occur. (See Eichenbaum et al., 2007 and Diana et al., 2007 for reviews.) As indicated in the Introduction, it is proposed that recognition involves two independent processes, recollection and familiarity; recollection relies upon the integrity of the hippocampus whereas familiarity relies upon the

integrity of the perirhinal cortex. According to Eichenbaum et al. (2007), information about a given stimulus is processed by the perirhinal and lateral entorhinal cortices, information about the context surrounding the stimulus is processed by the parahippocampal and medial entorhinal cortices, and these two sets of information converge in the hippocampus. Thus, the hippocampus is involved in processing information about an item *and* its context. When a previously encountered stimulus is presented, it is processed by the perirhinal and lateral entorhinal cortices which can signal a match to a pre-existing representation. According to Eichenbaum et al. (2007), this match signal can be propagated back to neocortical areas where it elicits a sense of familiarity. Eichenbaum et al. also suggest that presentation of a previously encountered stimulus elicits the recovery of object-context associations within the hippocampus; back-propagation (via the parahippocampal and medial entorhinal cortices) to neocortical areas in which the context was originally processed can give rise to recollection. A possible mechanism for the matching procedure underlying familiarity and recollection may be pattern completion which has been associated with activity not only in the hippocampus, but also in the entorhinal and parahippocampal cortices (Bakker et al., 2008).

In terms of the current study, the perirhinal cortex (which is presumed to be intact in both patient YR and the operated monkeys) is sufficient to support recognition when an object is presented on the same background at familiarization and test. However, the representation formed by the perirhinal cortex does not have the flexibility to allow recognition when the background is changed. Whether or not this pattern of results extends to tests of explicit memory is an interesting question. In an earlier study (Pascalis et al., 2004), we observed intact performance on a delayed matching to sample task despite impaired performance on a VPC task at the same delay. It is possible that instructing patient YR to try and remember the object on each trial may be sufficient to direct her attention to that object such that she is able to select that object using familiarity in a subsequent forced-choice recognition test.

Finally, we can make predictions about the effect of background variability on VPC performance. Eichenbaum et al. (2007) propose that the parahippocampal cortex is involved in processing contextual information before this information converges with item information within the hippocampus. It would be useful to examine VPC performance further under conditions in which an item was presented repeatedly on a series of novel backgrounds. It is predicted that the parahippocampal cortex would be sensitive to this continued change in background. Since the parahippocampal cortex is intact in patient YR, but is damaged in our hipppocampal-operated monkeys, we would predict that YR would develop a novelty preference

across trials in which the background continually changed, whereas the operated monkeys would not.

Footnote

Since the psychometric data reported here were collected, YR's performance on a range of tests of intelligence, perception and memory has shown deterioration, and she is currently being investigated clinically for a dementing illness. However, there is no evidence that YR's pattern of memory impairment during the course of the current study (1999-2000) differed from the psychometric profile reported here or from the pattern of memory deficit reported by Mayes et al. (2002; 2004). To the contrary, as indicated in Pascalis et al. (2004), we have evidence that on reassessment at the end of 2000, YR's visual recognition, at least for faces, was intact.

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Figure 1. Examples of stimuli used in the (a) same context and (b) different context conditions in both Experiment 1 and Experiment 2.