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No Effect of Hippocampal Lesions on Perirhinal Cortex-Dependent Feature-Ambiguous Visual Discriminations

Lisa M. Saksida,[1*] Timothy J. Bussey,[1] Cindy A. Buckmaster,[2] and Elisabeth A. Murray[2]

ABSTRACT: Previous studies have shown that perirhinal cortex lesions in monkeys impair visual discriminations with a high degree of "feature ambiguity," a property of visual discriminations that can emerge when features are a part of both rewarded and unrewarded stimuli. The effects of damage to the hippocampus on these perirhinal-dependent feature-ambiguous tasks are, however, unknown. Prominent theories of medial temporal lobe function predict similar effects of perirhinal cortex and hippocampal lesions on cognitive tasks. In contrast, our hypothesis is that perirhinal cortex, and not the hippocampus, is important for nonspatial complex feature-ambiguous discriminations. We sought to distinguish between these competing theories in a straightforward way, by testing rhesus monkeys with hippocampal lesions on the same feature-ambiguous tasks shown previously to depend on perirhinal cortex. It was found that hippocampal lesions had no effects on any of these tasks. The findings support the perceptual-mnemonic/feature conjunction model of perirhinal cortex function, and provide further evidence for heterogeneity of function within the putative medial temporal lobe memory system. © 2006 Wiley-Liss, Inc.

KEY WORDS: medial temporal lobe; discrimination learning; object recognition; inferotemporal cortex; ventral visual stream; rhesus monkey

INTRODUCTION

Structures in the medial temporal lobe (MTL), including the hippocampus and perirhinal cortex, are often regarded as working in concert to mediate "declarative" memory selectively, and are held to have little or no role in other "nondeclarative" functions such as perception (Squire and Zola-Morgan, 1991; Zola-Morgan et al., 1994; Squire et al., 2004). We and others have argued that (1) although the subregions of the MTL can and do work in concert, they have distinct functions that can be experimentally dissociated (Gaffan, 1994a; Murray and Bussey, 1999; Aggleton and Brown, 1999; Bussey et al., 1999; Buckley and Gaffan, 2000; Baxter and Murray, 2001; Mumby, 2001; Murray and Wise, 2004; Winters et al., 2004; Forwood et al., 2005), and (2) perirhinal cortex may have a role in other functions such as perception (Eacott et al., 1994; Buckley and Gaffan, 1997; Murray and Bussey, 1999; Buckley et al., 2001; Bussey and Saksida, 2002; Bussey et al., 2003; Buckley, 2005; Bussey et al., 2005; Lee et al., 2005a,b,c). Evidence for the first proposal has come from lesion studies demonstrating functional double dissociations between the effects of lesions of the perirhinal cortex and hippocampus (Winters et al., 2004). Evidence for the second comes from recent work indicating that lesions of perirhinal cortex can impair the discrimination of visual stimuli (Buckley and Gaffan, 1997; Buckley et al., 2001; Bussey et al., 2002, 2003; Barense et al., 2005; Lee et al., 2005a,b,c). Perirhinal cortex does not, however, have a general perceptual role, as it is not important for all types of visual discrimination (Buckley and Gaffan, 1997; Hampton and Murray, 2002), only for those requiring representations of complex conjunctions of features (Murray and Bussey, 1999; Buckley et al., 2001; Eacott et al., 2001; Bussey and Saksida, 2002; Bussey et al., 2002, 2003). Indeed, it had been predicted, on the basis of the hierarchical organization of the ventral visual stream, that perirhinal cortex might be important for representing complex conjunctions of features (Murray and Bussey, 1999; Bussey and Saksida, 2002; Saksida and Bussey, 1998). To test this idea we have required monkeys to learn certain types of visual discrimination problems, which can only be solved if the monkeys can represent conjunctions of features. These perirhinal cortex-dependent discriminations possess a high degree of "feature ambiguity," a property of visual discriminations that can emerge when features are a part of both rewarded and unrewarded stimuli (Saksida and Bussey, 1998; Bussey and Saksida, 2002).

There remains a gap in our knowledge; however, the effects of damage to the hippocampus on feature-ambiguous tasks are unknown. The standard "medial temporal lobe memory system" view outlined earlier predicts that the nature of impairment caused by damage to the putative medial temporal lobe memory system depends not on the location of the lesion—which of the component structures is damaged—but only on the size of the lesion, larger lesions having larger effects on the single function of declarative memory (Zola-Morgan et al., 1994). On this view, hippocampal lesions should impair performance on any task disrupted by perirhinal cortex lesions, including complex nonspatial feature-ambiguous discriminations. Our view is that the resolution of complex nonspatial feature-ambiguous discriminations via conjunctive representations is the domain of the perirhinal cortex, and not the hippocampus (Bussey and Saksida, 2002).

[1] **Department of Experimental Psychology, University of Cambridge, Cambridge, UK;** [2] **Laboratory of Neuropsychology, National Institute of Mental Health, Bethesda, Maryland**
*Correspondence to: Dr. L.M. Saksida, Department of Experimental Psychology, University of Cambridge, Downing Street, Cambridge CB2 3EB, UK. E-mail: lms42@cam.ac.uk
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We sought to distinguish between these competing theories in a straightforward way, by testing rhesus monkeys with selective hippocampal lesions on the same feature-ambiguous tasks shown previously to depend on perirhinal cortex (Bussey et al., 2002, 2003). If the "MTL memory system" account is correct, then hippocampal lesions should impair the same feature-ambiguous discriminations that are impaired by perirhinal cortex lesions. If our view is correct, hippocampal lesions should have little or no effect on these tasks. In the present study we manipulated feature ambiguity in two different ways. In Experiment 1 we examined acquisition of four-pair concurrent discriminations, in three different conditions corresponding to three levels of feature ambiguity (Bussey et al., 2002). We used specially constructed "objects," each comprised of a pair of images adjoined. This allowed us systematically to vary the number of features shared between objects in a given pair. In Experiment 2, we examined acquisition of single-pair discriminations of photographs that had been morphed together to create pairs with more or fewer features in common (Bussey et al., 2003, Experiment 1). In Experiment 3, we examined postacquisition performance on similar morphed-picture discriminations (Bussey et al., 2003, Experiment 2).

MATERIALS AND METHODS

Subjects

Eight experimentally naive male rhesus monkeys (*Macaca mulatta*), weighing between 5.4 and 8.6 kg at the beginning of testing, were the subjects of the present study. The monkeys were housed individually and were fed a controlled diet of Purina Primate Chow (Purina Mills Inc., St. Louis, MO), supplemented with fruit. Four of these monkeys received excitotoxic lesions of the hippocampus (H), and four monkeys were retained as unoperated controls.

Surgery

Selective H lesions ($n = 4$) were performed using magnetic resonance imaging (MRI)-guided stereotaxic procedures combined with injection of the excitotoxin *N*-methyl-D-aspartate (NMDA). After induction of anesthesia, the animal was placed in a stereotaxic frame and draped to establish an aseptic field. Then an incision was made in the skin, and the skin and underlying galea were retracted. During surgery, all monkeys received an intravenous drip of isotonic fluids containing an antibiotic (Cefazolin), and heart rate, respiration rate, body temperature, blood pressure and expired CO_2 were monitored closely throughout the procedure. At the completion of surgery, the galea was closed with Vicryl sutures, and the skin was closed with either surgical steel staples or Vicryl. Dexamethasone sodium phosphate (0.4 mg/kg, i.m.) and an antibiotic (Di-Trim, 0.1 ml/kg, 24% w/v solution, i.m., Syntex Animal Health Inc, West Des Moines, IA, or Cefazolin) were administered for 1 week following surgery to reduce swelling and to prevent infection, respectively. Monkeys also received ketoprofen (10–15 mg, i.m.), acetaminophen (40 mg), or Banamine (flunixin meglumine, 5 mg) as an analgesic for at least 3 days following surgery.

Because ketamine hydrochloride blocks NMDA receptors, and might interfere with the neurotoxic action of NMDA, monkeys were restrained with a combination of medetomidine (0.1 mg/kg; Domitor, Pfizer) and butorphanol (0.3 mg/kg). After intubation, the monkeys were anesthetized with isoflurane (1–3%, to effect), and the medetomidine was reversed with atipamezole (0.5 mg/kg, Antisedan, Pfizer). The NMDA injections were made from two different stereotaxic approaches. First, a large bone flap was turned over the dorsal cranium. Each monkey received 2–3 injections in the uncus, made via a 10-µl Hamilton syringe needle held in a Kopf electrode manipulator; the needle was introduced via a dorsal approach. At each site, 2.0 µl of NMDA (0.2 M) was injected at a rate of 0.2 µl/min. The injections were made in one hemisphere at a time. Second, NMDA injections in the body of the hippocampus were made via one longitudinal needle penetration using the methods developed by Hampton et al. (2004a). Small bone openings about 1 cm diameter were made over the occipital cortex. The needle of a 25-µl Hamilton syringe was introduced through a slit in the dura and lowered to the site of the most rostral injection. Then 7 to 10 separate injections, 2 mm apart, were made along the length of the hippocampus. At each site 2.0 µl NMDA (0.2 M) was injected at a rate of 0.25 µl/min. This second set of injections was carried out in both hemispheres simultaneously using two manipulators, one mounted on each arm of the stereotaxic frame. After the injection was at each site completed, the needle was left in place for 3 min before being withdrawn to the next site. Each monkey in group H received a T2-weighted MR scan within 7d of surgery. Based on the extent of hypersignal visible in the MR scan, indicative of edema at injection sites, additional surgeries were planned and carried out as needed (Málková et al., 2001). T2-weighted scans from one representative monkey in group H are shown in Figure 1.

Lesion Assessment Using MRI

The extent of the lesions in monkeys in group H was estimated using the method of Málková et al. (2001). The method is based on a comparison of the preoperative and postoperative volumes of each hippocampus. For this purpose, we defined the hippocampus as including not only the dentate gyrus (DG) and CA1-CA3 fields, but also the subicular complex, which is difficult to discriminate from the hippocampus proper in MR scans. The area of the hippocampus in each 1-mm coronal section in the preoperative T1-weighted MR scan of each monkey was determined using Scion Image (Scion Corp., Frederick, MD). Because the measurements were taken at 1-mm intervals, the sum of areas for each hemisphere yields an estimate of the volume of that hippocampus, in mm^3. The same procedure was applied to T1-weighted postoperative scans obtained an average of 23.5 months (range 16–33) after surgery. T1-weighted

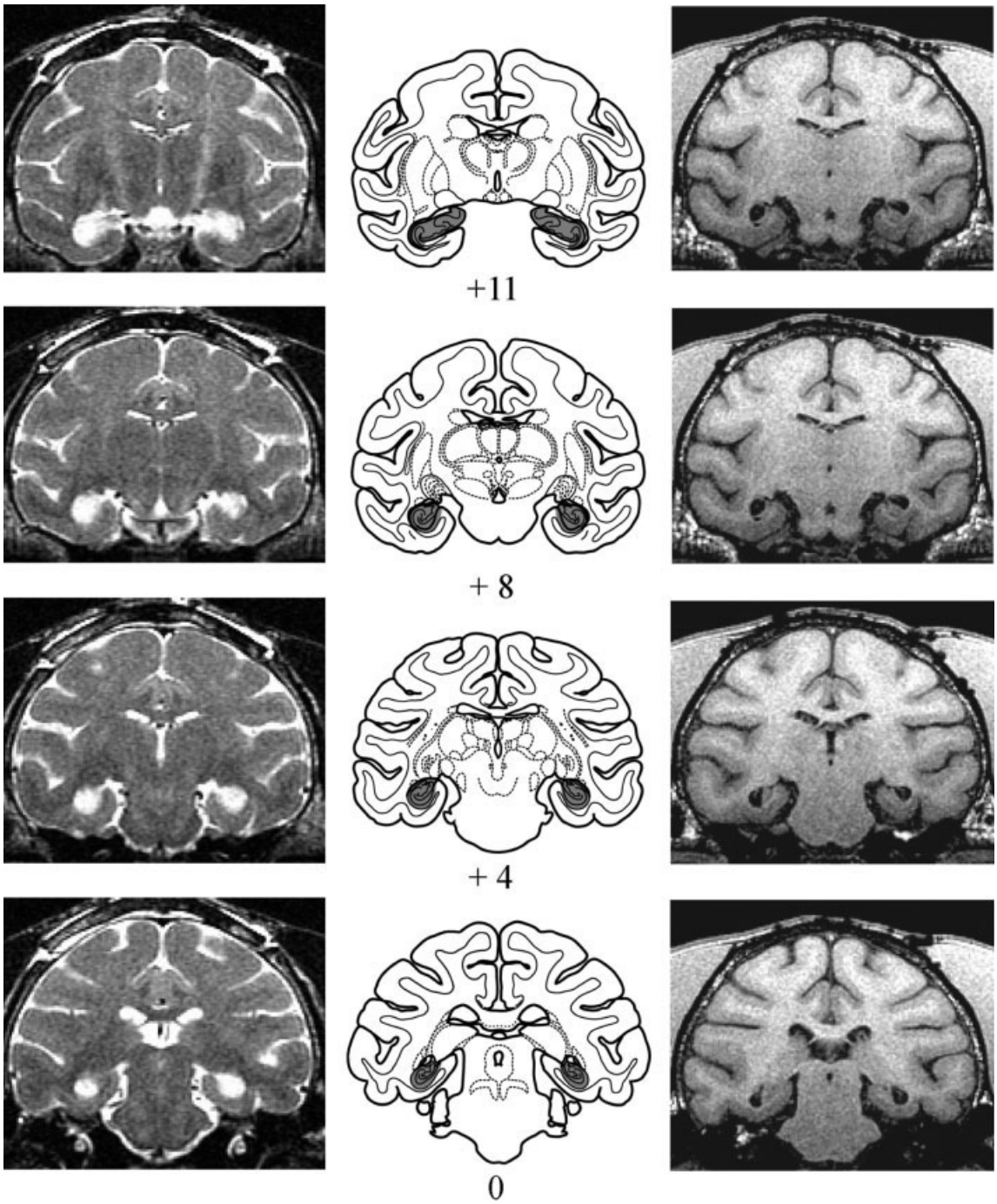

FIGURE 1. Extent of the hippocampal lesion in one representative monkey (H3). The intended lesion (gray) is shown in the central column on coronal sections from a standard rhesus monkey brain. Images taken from corresponding levels from a T2-weighted MR scan obtained 4 days after surgery and from a T1-weighted scan obtained 16 months after surgery are shown in the left and right columns, respectively. The hypersignal (white) in the images in the left column shows the region in which the NMDA injections were made. Postoperative shrinkage of the hippocampus and ensuing enlargement of the adjacent portion of the ventricle are evident in the images in the right column. The numerals indicate the distance in millimeters from the interaural plane (0).

coronal images obtained 16 months after surgery from a representative case in group H are shown in Figure 1. From the preoperative and postoperative measurements, the proportion of hippocampal volume lost was determined. Based on the regression function generated by Málková et al. (2001), the extent of damage was estimated to be 83, 80, 65, and 28% of the total volume of the hippocampus (Table 1). In each monkey, including the monkey with the smallest lesion, damage to the anterior and posterior portions of the hippocampus constituted roughly half of the total damage.

TABLE 1.

Estimated Percent Damage to the Hippocampus

	Percent shrinkage		Estimated percent damage		
	Left	Right	Left	Right	Mean
H1	59.5	71.4	75.4	91.2	83.3
H2	48.9	54.0	61.4	68.1	64.6
H3	57.4	68.5	72.7	87.2	79.9
H4	17.6	29.4	20.1	35.6	27.9

Test Apparatus and Materials

Monkeys were trained and tested in an automated apparatus consisting of an IBM compatible computer linked to a 15-in. color monitor fitted with a touch-sensitive screen (Microtouch Systems, Woburn, MA) and an automatic pellet dispenser (BRS/LVE, Laurel, MD). Reward pellets (190 mg banana flavored; Noyes, Lancaster, NH) were delivered via a copper tube into a food cup located directly below the center of the monitor. During each test session, the monkey was seated in a primate chair inside a test cubicle. The monkey's head was approximately 230 mm from the monitor screen.

Visual stimuli consisted of grayscale photographs, 4×4 cm^2, obtained from a commercially available collection of stock photographs ("Masterclips"; IMSI, San Rafael, CA, USA; Figures 2 and 4). Complex pictures of this type elicit selective responses from neurons in perirhinal cortex (Erickson et al., 2000).

Testing Procedure

Monkeys were tested for the ability to learn to choose the correct one of a pair of simultaneously presented visual stimuli. On each trial two different stimuli were presented—one on the left and one on the right side of the monitor screen—set ~8 cm apart from center to center. In each pair, one stimulus was the S+ and the other was the S−. The stimuli remained on the screen until the monkey made a response by touching one or the other. Touching the S+ resulted in offset of the stimulus display concomitant with delivery of a reward pellet. Touching the S− resulted in offset of the stimulus display with no reward delivery. Whether the S+ was on the right or left on a given trial was determined by a pseudorandom series. There was a 10 s interval between each trial.

Monkeys were trained on three tasks measuring discrimination performance under conditions of varying feature ambiguity. Testing procedures and stimulus materials used in this series of experiments were identical to those used in our previous studies (Bussey et al., 2002, 2003). The monkeys proceeded directly from one experiment to the next, with no breaks or intervening training on other tasks.

Experiment 1. Concurrent Discrimination

In Experiment 1, monkeys were trained on a set of concurrent discriminations in which the number of object pairs was held constant, but the degree of feature ambiguity was varied systematically. For this purpose we prepared a specially constructed set of "objects". Each object consisted of two images adjoined, one above the other, in a vertical format (Fig. 2). To manipulate feature ambiguity, we presented pairs of objects in which the component images overlapped to different degrees. If one considers that each object is comprised of two "features" (the two images), the conditions were as follows: Maximum Feature Ambiguity, in which all features were explicitly ambiguous (AB+, CD+, BC−, AD−; known as the biconditional problem); Minimum Feature Ambiguity, in which no features were explicitly ambiguous (AB+, CD+, EF−, GH−); and Intermediate Feature Ambiguity, in which half the features were explicitly ambiguous (AB+, CD+, CE−, AF−). Using this task, we have shown that even though the number of object pairs to be discriminated is held constant, perirhinal cortex lesions have a greater effect on discrimination learning as the degree of feature ambiguity is increased (Bussey et al., 2002).

Methods

In each test session, a stimulus set consisting of four different pairs of objects (i.e., a four-pair concurrent discrimination) was presented for a total of 96 trials. Each pair was presented in 24 trials in each daily session, and the order in which pairs appeared across trials was determined pseudorandomly. To control for the amount of exposure to the objects, each stimulus set was presented for two consecutive daily sessions (a total of 192 trials), irrespective of whether criterion had been reached. The number of errors committed in reaching a criterion of eight correct responses in 10 consecutive trials was recorded. The same object pairs were used for all monkeys. Objects were presented in pairs as shown in Figure 2. Which condition was presented in a given pair of sessions was determined by pseudorandom series. Monkeys were trained on four different stimulus sets per condition, and data were averaged across the four stimulus sets for each condition.

Results and discussion

Monkeys with lesions of the hippocampus were unimpaired in the Minimum Feature Ambiguity condition, the Intermediate Feature Ambiguity condition and the Maximum Feature Ambiguity condition (Fig. 3). Analysis of variance (ANOVA) with Group as between-subjects and Condition as within-subjects factors revealed a significant main effect of Feature Ambiguity ($F_{2,12} = 22.43$, $P < 0.001$), but no main effect of Group ($F_{1,12} < 1$), and no Group by Feature Ambiguity interaction ($F_{2,12} < 1$). Thus, there was no effect of hippocampal lesions on this perirhinal cortex-dependent task.

Experiment 2. Acquisition of Single-Pair Discriminations

In Experiment 2, a second method of increasing feature ambiguity in grayscale picture discriminations was used, that is

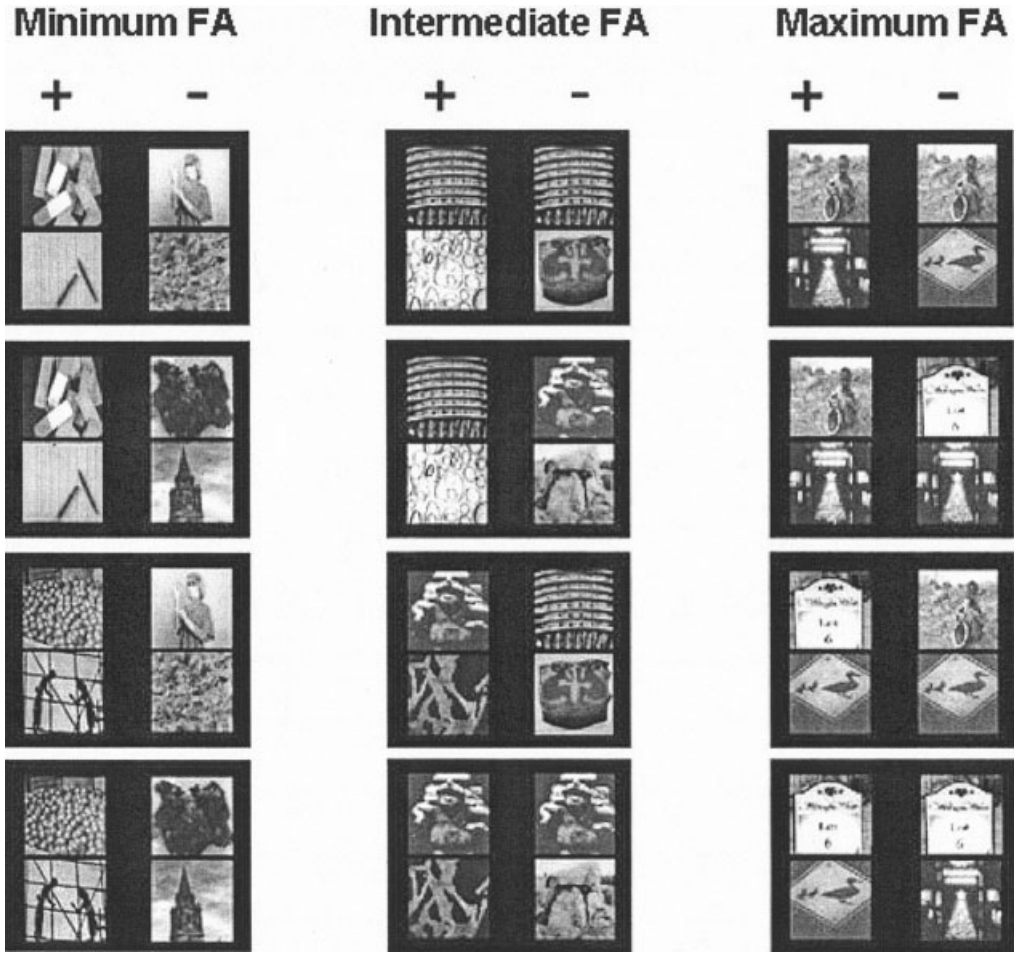

FIGURE 2. Example of stimulus pairs in the Minimum, Intermediate, and Maximum Feature Ambiguity conditions of Experiment 1. In the Minimum condition, no features were explicitly ambiguous (i.e., each feature was consistently either rewarded or nonrewarded). In the Intermediate condition, two features were explicitly ambiguous; in the Maximum condition, all four features were explicitly ambiguous. The "features" comprising each two-feature stimulus were randomly selected grayscale photographs obtained from a commercially available clip–art collection. The + and − indicate that the stimuli on the left were the correct (rewarded) images in the pair, whereas those on the right were incorrect (unrewarded). For pairs of stimuli presented in the test sessions, the location of the S+ (left or right) followed a pseudorandom order.

blending together the stimuli using commercially available "morphing" software (Fig. 4). As the pictures are blended together, they contain more features in common. As in the case of the constructed objects used in Experiment 1, we reasoned that successful discrimination in Experiment 2 would require representations of feature conjunctions. Perirhinal cortex lesions impair such discriminations, but only when complex stimuli are used that share many features in common (Bussey et al., 2003, Experiment 1).

Methods

Problems were of two types: low feature ambiguity and high feature ambiguity. Stimuli used for the "Low feature ambiguity" discriminations were grayscale photographs and drawings obtained from a commercially available clip–art collection ("Masterclips"; IMSI, San Rafael, CA, USA). Stimuli used for the "High feature ambiguity" discriminations were grayscale photographs and drawings, obtained from the same source that had been blended together using a commercially available image morphing program (Gryphon Software Corporation, San Diego, CA, USA). The morphing software was used as a means of systematically manipulating feature ambiguity; images generated in this way had more features in common than the original pair. To create each pair of stimuli, two pictures were morphed together to create a series of 40 new images, the first images in this series consisting mostly of features from picture 1, the latter images consisting mostly of features from picture 2. For each discrimination problem, the 14th and 27th images from this series were chosen to be the "High feature ambiguity" test pair. A representative subset of images generated by the morphing software, including sample Low and High Feature Ambiguity test pairs, is shown in Figure 4. Each monkey was trained on five problems of each type. The type of discrimination (High or Low feature ambiguity) tested in a given session was determined by a pseudorandom series.

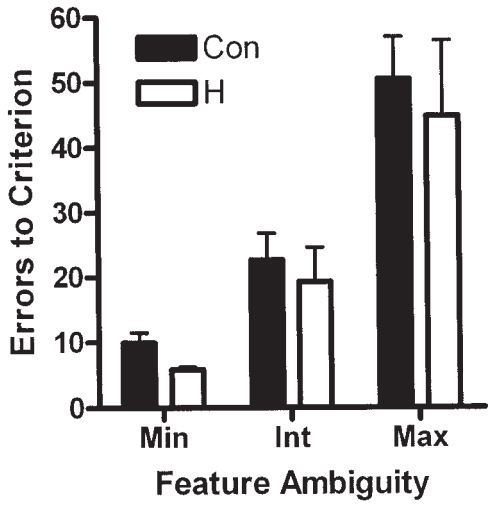

FIGURE 3. Data from Experiment 1: Acquisition by control monkeys and monkeys with selective lesions of the hippocampus of four-pair concurrent discriminations in each of the Minimum, Intermediate, and Maximum Feature Ambiguity conditions. Scores are the group mean errors to criterion for four sets of problems in each condition. Error bars indicate ± standard error of the mean. There were no significant differences between the control and lesion groups. Abbreviations: Con, unoperated control monkeys (n = 4); H, monkeys with bilateral lesions of the hippocampus made with the excitotoxin NMDA (n = 4).

Results and discussion

Monkeys with hippocampal lesions were unimpaired in acquisition of single-pair discrimination problems with low feature ambiguity (Fig. 5A). ANOVA with Group as between-subjects factor and Block as within-subjects factor revealed a significant main effect of Block ($F_{11,66} = 18.43$, $P < 0.0001$) but no effect of Group ($F_{1,66} < 1$), and no Group–Block interaction ($F_{11,66} = 1.72$). Monkeys with hippocampal lesions were also unimpaired in acquisition of single-pair discrimination problems with high feature ambiguity (Fig. 5B). ANOVA with Group as between-subjects factor and Block as within-subjects factor revealed a significant main effect of Block ($F_{11,66} = 8.67$, $P < 0.0001$) but no effect of Group ($F_{1,66} < 1$), and no Group–Block interaction ($F_{11,66} < 1$). Thus, there was no effect of hippocampal lesions on this perirhinal cortex-dependent task.

Experiment 3. Performance on Single-Pair Discriminations

Experiments 1 and 2 were designed so that the memory demands were equal in both high and low feature-ambiguous discriminations. That is, both high and low feature ambiguity conditions required the monkey to learn across trials to associate a stimulus with a reward, and the number of pairs to be learned was equivalent across the conditions. The impairments found on these tasks following perirhinal cortex lesions are therefore dependent on the perceptual demands of the tasks, suggesting a role for perirhinal cortex in perception. Still, this approach could be criticized on the grounds that acquisition of discriminations contains a memory component, as new learning was required. Therefore, in Experiment 3 we measured the effects of manipulating feature ambiguity in a situation requiring no new learning. As in Experiment 2, we used the morph method to manipulate feature ambiguity. Unlike Experiment 2, however, which focused on acquisition, this experiment examined the effect of increasing feature ambiguity in previously acquired, low feature-ambiguity single-pair discriminations. This was tested in the present experiment by first training monkeys on a perceptually easy, low feature ambiguity grayscale

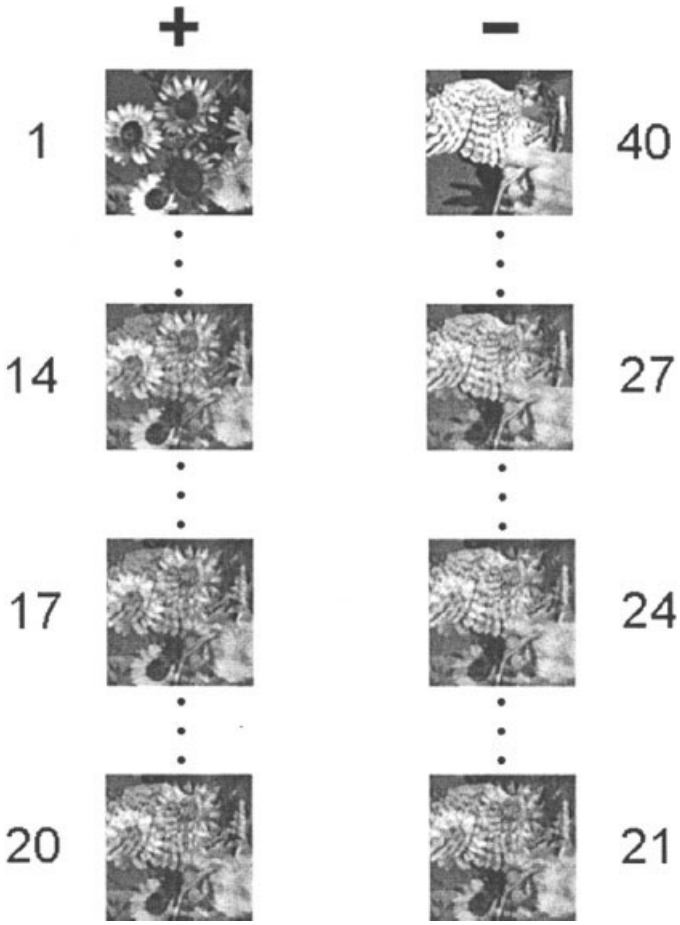

FIGURE 4. Example of grayscale picture stimuli used in experiments 2 and 3. To create each pair of stimuli, two pictures were "morphed" (blended) together to create a series of 40 images, the first images in this series consisting mostly of features from picture number 1, the latter images consisting mostly of features from picture number 40. The numbers next to an image indicate the position of the image in the series. In experiment 2 the original pictures, images 1 and 40, were used as the Low feature ambiguity pair, and the 14th and 27th images were used as the high feature ambiguity test pair. In experiment 3, the original images were used as the Trained Pair, the 14th and 27th images were used as Morph Pair 1, and the 17th and 24th images were used as Morph Pair 2. In both of these experiments, monkeys were tested on four such stimulus sets, and the data were averaged across sets. The + and − indicate that the images on the left, in this example those most similar to the photograph of the sunflowers, were the correct (rewarded) images in the pair, whereas those on the right were incorrect (unrewarded).

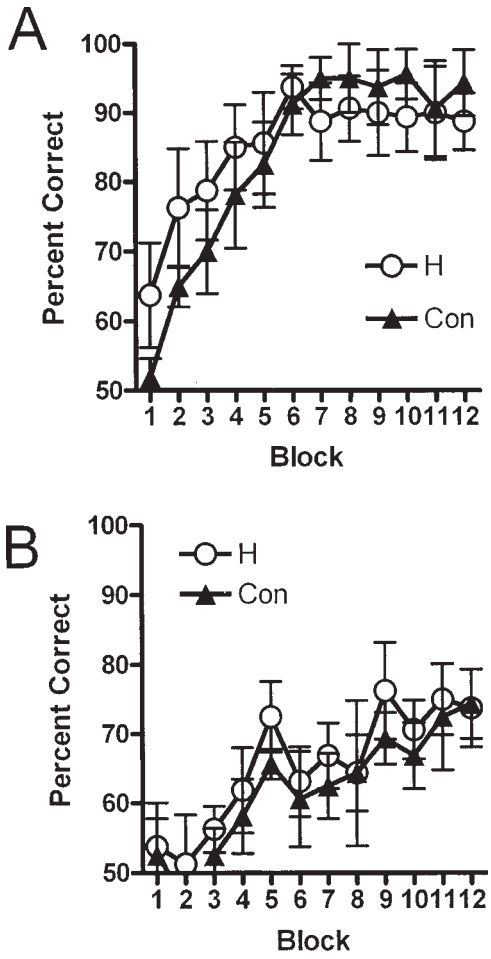

FIGURE 5. Data from experiment 2: (A) Acquisition of discriminations of stimuli with low feature ambiguity, by control monkeys and monkeys with lesions of the hippocampus. (B) Acquisition of discriminations of stimuli with high feature ambiguity, by control monkeys and monkeys with lesions of the hippocampus. There were no significant differences between the control and lesion groups. Conventions are as in Figure 3.

picture discrimination problem, and then assessing discrimination performance when the discriminanda were blended together, thereby increasing feature ambiguity and perceptual difficulty. In this series the low feature ambiguity Trained Pair corresponded to images 1 and 40, and High Feature Ambiguity Pairs 1 and 2 corresponded to images 14 and 27, and 17 and 24, respectively, from the morph series (Fig. 4). Impaired performance under conditions of greater perceptual difficulty would indicate perceptual impairments in the absence of learning. Such perceptual impairments are observed after perirhinal cortex lesions (Bussey et al., 2003, Experiment 2).

Methods

Monkeys were first trained to discriminate a single pair of grayscale picture stimuli (the Trained Pair). In each pair, one stimulus was arbitrarily designated as the S+, and the other the S−. With the exception of number of trials per session, training parameters were identical to those in the previous task. Now, rather than receiving 96 trials per session, monkeys were trained to a criterion of 17 out of 20 correct responses. The following day, a reminder session was given in which monkeys were again given the same discrimination problem until a criterion of 17 out of 20 correct had been attained. This was followed immediately by a critical test session in which performance was assessed on the Trained Pair, and on each of the two High Feature Ambiguity Pairs. This procedure was repeated for each of four different sets of picture stimuli, and the data were averaged across the four stimulus sets. During each critical test session monkeys were tested on a 32-trial block of the Trained Pair, a 32-trial block of High Feature Ambiguity Pair 1 and a 32-trial block of High Feature Ambiguity Pair 2. The order in which these three blocks were presented was either Trained Pair first, followed by High Feature Ambiguity Pair 1, followed by High Feature Ambiguity Pair 2 (blocking order "A"), or High Feature Ambiguity Pair 2 first, followed by High Feature Ambiguity Pair 1, followed by the Trained Pair (blocking order "B"). To control for potential order effects the blocking order was varied according to an A, B, B, A design; i.e., stimulus set 1 was tested using blocking order A; stimulus set 2 using blocking order B; stimulus set 3, blocking order B; and stimulus set 4, blocking order A. Following each critical test session, monkeys were trained to criterion on the Trained Pair of the stimulus set to be tested the following day, in which again a reminder session was given followed by a critical test session. This two-day procedure was repeated four times, once for each of the four different sets of picture stimuli.

Results and discussion

Monkeys with hippocampal lesions were not impaired when previously acquired stimulus pairs were made more difficult to discriminate by increasing feature ambiguity (Fig. 6). ANOVA

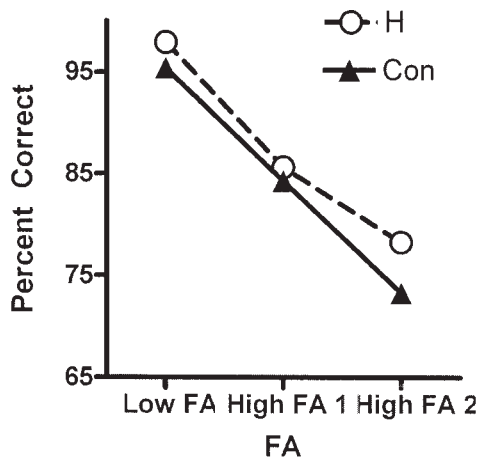

FIGURE 6. Data from experiment 3: Discrimination performance of control monkeys and monkeys with selective lesions of the hippocampus on the Low feature ambiguity Trained Pair (Low FA), and on the morphed High feature ambiguity Pair 1 (High FA 1) and Pair 2 (High FA 2). There were no significant differences between the control and lesion groups. Conventions are as in Figure 3.

with Group as between-subjects factor and Feature Ambiguity as within-subjects factor revealed a significant main effect of Feature Ambiguity ($F_{2,12} = 82.87$, $P < 0.0001$) but no effect of Group ($F_{1,12} < 1$), and no Group–Feature Ambiguity interaction ($F_{2,12} < 1$). Thus, there was no effect of hippocampal lesions on this perirhinal cortex-dependent task.

DISCUSSION

The present study tested whether rhesus monkeys with selective lesions of the hippocampus would be impaired on feature-ambiguous visual discriminations previously shown to depend on perirhinal cortex (Bussey et al., 2002, 2003). No hint of impairment was observed on any of these tasks. Thus, the present findings support the view that the perirhinal cortex, and not the hippocampus, contains complex conjunctive representations that can resolve feature ambiguity in complex nonspatial visual discriminations.

It might be asked whether the hippocampal lesions in the present study were functionally effective. A recent study showed that the same monkeys with hippocampal lesions studied here were *facilitated* in acquisition of the transverse patterning task, another example of a feature-ambiguous visual discrimination (Saksida et al., 2003, 2006). This latter study demonstrates not only the functional efficacy of the lesion, but also provides another example of spared feature-ambiguous discrimination learning following lesions of the hippocampus. Moreover, the same study demonstrated an impairment on transverse patterning following lesions of the perirhinal cortex (see also Alvarado and Bachevalier, 2005). This finding, taken together with those of the present study, our previous studies (Introduction), and those of others (Eacott et al., 2001; Gilbert and Kesner, 2003; Norman and Eacott, 2004), provides converging evidence for a role for the perirhinal cortex, and not the hippocampus, in resolving feature ambiguity in complex nonspatial visual discriminations.

These demonstrations of differential effects of perirhinal cortex and hippocampal lesions, along with many other studies showing such dissociations (Murray et al., 1993; Gaffan, 1994a; Murray and Mishkin, 1998; Aggleton and Brown, 1999; Bussey et al., 1999; Buckley and Gaffan, 2000; Bussey et al., 2000; Mumby, 2001; Bussey and Aggleton, 2002; Winters et al., 2004; Forwood et al., 2005), indicate that subregions of the medial temporal lobe have distinct and dissociable functions. They do not, however, support currently influential theories of medial temporal lobe function that preclude the possibility of double dissociations between these structures (Eichenbaum et al., 1994; Zola-Morgan et al., 1994; Squire et al., 2004).

Do these dissociations hold in humans, as well as monkeys? Barense et al. (2005) tested patients with either selective hippocampal damage, or with combined damage to hippocampus and extra-hippocampal damage predominantly in perirhinal cortex (the "MTL group") on the same task used in Bussey et al. (2002) and in Experiment 1 of the present study. Whereas patients in the MTL group were severely impaired in acquiring visual discrimination problems with high feature ambiguity, the performance of patients with selective hippocampal damage was indistinguishable from that of controls. These findings held over four replications, with four different classes of feature-ambiguous stimuli. Furthermore, Lee et al. (2005c) tested the same patients studied by Barense et al. (2005) on complex morph discriminations of faces using methods similar to those used in Bussey et al. (2003) and in Experiments 2 and 3 of the present study. Again the MTL patients were impaired on these discriminations, but patients with selective hippocampal lesions were not. Thus, the view that perirhinal cortex, and not the hippocampus, contains conjunctive representations for the resolution of nonspatial feature ambiguity is supported by studies in humans as well as in monkeys.

These findings from human studies are controversial, and indeed others have reported no such perceptual effects in their medial temporal lobe patients (Stark and Squire, 2000; Levy et al., 2005). These studies, however, have been criticized on a number of grounds, including the suggestion that they did not manipulate perceptual difficulty in a way that might be expected to recruit perirhinal cortex (Bussey et al., 2005; Lee et al., 2005a).

The present study indicates that the hippocampus has little or no role in nonspatial visual perceptual discrimination, even in tasks with high feature ambiguity. Instead, the perirhinal cortex, lesions of which impair performance on these same tasks, appears to be involved in both perception and memory for such stimuli. In our view these data indicate that the perirhinal cortex, but not the hippocampus, is essential for representing conjunctions of features comprising objects. Perirhinal cortex lesions do not, however, necessarily disrupt performance on spatial memory tasks (Bussey et al., 1999, 2000; Bussey and Aggleton, 2002; Winters et al., 2004). In contrast, the hippocampus is critical for spatial and "scene" memory (Olton et al., 1979; Morris et al., 1982; Aggleton et al., 1986; Gaffan, 1994b; Bohbot et al., 1998; Burgess et al., 2002; King et al., 2002; Hampton et al., 2004b). Could it be that, like the perirhinal cortex for nonspatial visual perception, the hippocampus has a role in both perception and memory for spatial or "scene" stimuli? New evidence suggests that it does. Lee et al. (2005c) found that patients with selective hippocampal lesions were selectively impaired in the visual discrimination of morphed scenes (but not faces). In another experiment, Lee et al. (2005b) found that these same patients were impaired in the perceptual task of selecting the "odd one out" of an array of stimuli—but only when the stimuli were spatial in nature (virtual reality rooms). These findings provide further evidence for dissociations of function within the MTL, for a role for human perirhinal cortex in visual perception and, most strikingly, a role for the hippocampus in the perceptual discrimination of scenes.

The perception of spatial scenes in such patients has not yet been tested by other laboratories. Clearly, the suggestion that the hippocampus is involved in spatial perception will strike many as radical, and thorough investigation will be required before the idea can finally be accepted, or rejected.

CONCLUSIONS

In conclusion, the present study has shown that nonspatial feature-ambiguous discriminations, known to depend on perirhinal cortex, are unaffected by lesions of the hippocampus. These findings provide support for the hypothesis that the resolution of nonspatial feature ambiguity in complex visual discriminations is the domain of perirhinal cortex, and not the hippocampus. It is possible that just as the perirhinal cortex resolves ambiguity in the nonspatial domain, so the hippocampus resolves ambiguity by operating at a higher level in the representational hierarchy (Bussey and Saksida, 2005). This idea is compatible with the view that both perirhinal cortex and the hippocampus have a role in pattern separation, the former in the nonspatial and the latter in the spatial domain (Gilbert and Kesner, 1993; Gilbert, Kesner and DeCoteau, 1998). In addition, the present findings provide further evidence for a clear dissociation of function between subregions within the putative medial temporal lobe memory system.

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