

Impairment and Facilitation of Transverse Patterning after Lesions of the Perirhinal Cortex and Hippocampus, Respectively

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We have recently suggested that certain effects of perirhinal cortex removals in monkeys can be attributed to the lesion compromising complex configural representations of visual stimuli. On this view, monkeys with perirhinal cortex lesions will be impaired on acquisition of discrimination problems that possess high “feature ambiguity,” that is, those in which many of the same features belong to both rewarded and unrewarded stimuli. A subclass of feature-ambiguous problems includes “configural” discrimination problems in which all features are ambiguous. In the present study, we tested control monkeys and monkeys with bilateral lesions of perirhinal cortex on a configural discrimination problem, the transverse-patterning task (i.e., A+ vs. B-, B+ vs. C-, C+ vs. A-), using complex 2-dimensional visual stimuli. In addition, we investigated the effects of lesions to another structure that has been implicated in configural learning, the hippocampus. Monkeys with perirhinal cortex lesions were impaired, whereas monkeys with selective hippocampal lesions were facilitated, on acquisition of the transverse-patterning task. These data do not provide support for mass action theories of medial temporal lobe function, which cannot account for the opposing effects of the 2 lesions. These results are, however, compatible with a view that perirhinal cortex, and not the hippocampus, contains complex configural representations of visual stimuli critical to the solution of the transverse-patterning task.

Keywords: configural learning, discrimination learning, inferotemporal cortex, object recognition, rhesus monkey, ventral visual stream

Introduction

Recent work indicates that the perirhinal cortex plays an important role in the discrimination of visual stimuli. Perirhinal cortex is not, however, 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 (Saksida and Bussey 1998; Murray and Bussey 1999; Buckley and others 2001; Eacott and others 2001; Bussey and others 2002, 2003; Bussey and Saksida 2002). Such 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 (Bussey and Saksida 2002). Discrimination tasks with a high degree of feature ambiguity include “configural” learning tasks such as the biconditional problem, and, consistent with our hypothesis, damage to perirhinal cortex impairs the solution of this problem (Buckley and Gaffan 1998; Eacott and others 2001; Bussey and others 2002).

In the present study, we tested this view of perirhinal cortex function further using another well-studied configural task, transverse patterning. Transverse patterning requires subjects

to solve 3 pairwise discriminations concurrently: A+ versus B-, B+ versus C-, and C+ versus A-. Thus, if objects A and B are displayed, the subject should choose A; if B and C are displayed the subject should choose B; and if A and C are displayed the subject should choose C. Because each stimulus is rewarded as often as not, the subject must be able to represent the conjunction of stimuli to solve the problem.

The use of the transverse-patterning task extends our previous studies (Bussey and others 2002, 2003) in at least 2 ways. First, in our previous studies, stimuli were comprised of conjunctions of what we referred to as “features,” colocalized to form an “object.” In the transverse-patterning task, however, the components of “AB”—that is, “A” and “B”—are separated in space. This task therefore provides the opportunity to test whether perirhinal cortex is important for the representation of the co-occurrence of separate objects. Such representations in perirhinal cortex might underlie object-object paired associate learning (Murray and others 1993; Higuchi and Miyashita 1996; Buckley and Gaffan 1998) and the discrimination of visual scenes and contexts (Murray and others 1998; Burwell and others 2002). Accordingly, we evaluated the acquisition of the transverse-patterning task in monkeys with perirhinal cortex lesions. Second, because configural (Sutherland and Rudy 1989; Rudy and Sutherland 1995) and relational (Eichenbaum and others 1994) theories of hippocampal function predict an impairment on transverse patterning following hippocampal dysfunction (although for different reasons; see Discussion), we also evaluated the acquisition of the same task by monkeys with hippocampal lesions. Examination of the 2 operated groups allowed us to test for dissociable functions of separate elements within the putative “medial temporal lobe (MTL) memory system” (Squire and Zola-Morgan 1991).

Materials and Methods

Subjects

Sixteen young adult rhesus monkeys (*Macaca mulatta*) 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 aspiration lesions of the perirhinal cortex (group PRh), 4 received excitotoxic lesions of the hippocampus (group H), and 8 monkeys were retained as unoperated controls. Four of the controls were tested concurrently with group PRh and the 4 remaining controls were tested concurrently with group H. Before entering the present study, all monkeys had extensive experience in acquiring visual discrimination problems. Monkeys in group PRh and their controls are the same subjects reported in earlier papers from this laboratory (Bussey and others 2002, 2003). Monkeys in group H and their controls received a subset of the same training in the same sequence (Saksida and others, 2006). At the time of the experiment, monkeys in group PRh and their controls were somewhat older than monkeys in group H and their

controls (group PRh and their controls, mean = 6.7 years of age; group H and their controls, mean = 4.8 years).

Surgery

Bilateral aspiration lesions of perirhinal cortex ($n = 4$) were performed with sterile procedures under visual control with the aid of an operating microscope. Selective hippocampus lesions ($n = 4$) were performed using magnetic resonance imaging-guided stereotaxic procedures combined with injection of the excitotoxin *N*-methyl-D-aspartate (NMDA). After induction of anesthesia, the animal was draped to establish an aseptic field, 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 CO₂ 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, intramuscularly) and an antibiotic (Di-Trim, 0.1 ml/kg, 24% w/v solution, intramuscularly, 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, intramuscularly), acetaminophen (40 mg), or Banamine (flunixin meglumine, 5 mg) as an analgesic for at least 3 days following surgery.

Perirhinal Cortex Removals

On the day of surgery, the monkeys were restrained with an injection of ketamine hydrochloride (10 mg/kg, intramuscularly) and anesthetized with isoflurane (1–3%, to effect). After the skin and galea had been retracted, the zygoma was removed to allow access to the portion of the cranium overlying the ventrolateral surface of the frontal and temporal lobes. Then the temporalis muscle was reflected, and a large bone flap was taken, extending rostrally to the orbit, ventrally to the base of the temporal fossa, and caudally to the auditory meatus. The dura was first cut over the frontal and anterior temporal lobes. Using a supraorbital approach, the frontal lobe was gently retracted from the orbit with a brain spoon, the rhinal sulcus was identified, and the rostral part of the perirhinal cortex was removed with a small-gauge sucker. This part of the lesion extended along the rostral face of the temporal pole from the lateral fissure to the floor of the temporal fossa and included the cortex lining the lateral bank of the rhinal sulcus, together with about 2–3 mm of the cortex lateral to the sulcus. The medial boundary of the lesion was the fundus of the rhinal sulcus. After this part of the removal was completed, the dura was sewn over the frontal lobe, and the original dural opening was extended over the lateral temporal lobe. The monkey's head was now tilted at an angle of 120° from vertical, thereby allowing a subtemporal approach for ablation of the caudal half of the perirhinal cortex. Mannitol was administered at this time (30%; 30 ml intravenously over 30 min) to reduce brain volume and increase accessibility of the ventromedial cortex, which was retracted from the base of the temporal fossa. The lesion was continued caudally from the 1st ablation, along the lateral bank of the rhinal sulcus, to include the cortex lining the lateral bank as well as about 2–3 mm of cortex lateral to the sulcus. The medial boundary of the lesion was the fundus of the rhinal sulcus. After the removal was completed, the dura was sewn, and the bone flap was repositioned and held in place with Vicryl sutures.

Hippocampal Injections

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), placed in a stereotaxic apparatus, and the medetomidine was reversed with atipamezole (0.5 mg/kg, Antisedan, Pfizer). The NMDA injections were made from 2 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- μ l Hamilton syringe needle held in a Kopf electrode manipulator; the needle was introduced via a dorsal approach. At each

site, 2.0 μ l of NMDA (0.2 M) was injected at a rate of 0.2 μ l/min. The injections were made in 1 hemisphere at a time. Second, the NMDA injections in the body of the hippocampus were made via 1 longitudinal needle penetration using the methods developed by Hampton and others (2004). Small bone openings about 1 cm diameter were made over the occipital cortex. The needle of a 25- μ l Hamilton syringe was introduced through a slit in the dura and lowered to the site of the most rostral injection. Then 7–10 separate injections, 2 mm apart, were made along the length of the hippocampus. At each site 2.0 μ l of NMDA (0.2 M) was injected at a rate of 0.25 μ l/min. This 2nd set of injections was carried out in both hemispheres simultaneously using 2 manipulators, one mounted on each arm of the stereotaxic frame. After the injection at each site was completed, the needle was left in place for 3 min before being withdrawn to the next site.

Each monkey in group H received a T_2 -weighted magnetic resonance (MR) scan within 7 days 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 (Malkova, Lex, and others 2001). T_2 -weighted images from 1 representative monkey in group H are shown in Figure 1.

Lesion Assessment Using Magnetic Resonance Imaging

Location and extent of the perirhinal cortex lesions were evaluated using T_1 -weighted MR images, obtained at 1-mm intervals from each of the 4 monkeys. The lesions were plotted from digitized coronal sections from MR scans onto standard sections of a rhesus monkey brain at 1-mm intervals. The volumes of the lesions were then measured using Scion Image software (Scion Corporation, Frederick, MD).

A detailed description of the perirhinal cortex lesions is provided elsewhere (Bussey and others 2002). The lesions were generally as intended with damage to perirhinal cortex averaging 92% (range 79–96) of the total volume of this region (Table 1). The monkey with the smallest lesion, case PRh2, had sparing of the deepest portion of the lateral bank of the rhinal sulcus bilaterally. As for inadvertent damage, there was minimal involvement of entorhinal cortex, area TE, and areas TF/TH. T_1 -weighted images from 1 representative monkey in group PRh are shown in Figure 2.

The extent of the lesions in monkeys in group H was estimated using the method of Malkova, Lex and others (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 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 T_1 -weighted MR scan of each monkey was determined using Scion Image (Scion Corporation). Because the measurements were taken at 1-mm intervals, the sum of the areas for each hemisphere yields an estimate of the volume of that hippocampus, in cubic millimeters. The same procedure was applied to T_1 -weighted postoperative scans obtained on an average of 23.5 months (range 16 to 33) after surgery. T_1 -weighted 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 Malkova, Lex and others (2001), the extent of damage was estimated to be 83%, 80%, 65%, and 28% of the total volume of the hippocampus (Table 1).

Test Apparatus and Materials

Monkeys were trained and tested in an automated apparatus consisting of computer linked to a 15-inch 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 \times 4 cm, obtained from a commercially available collection of stock photographs

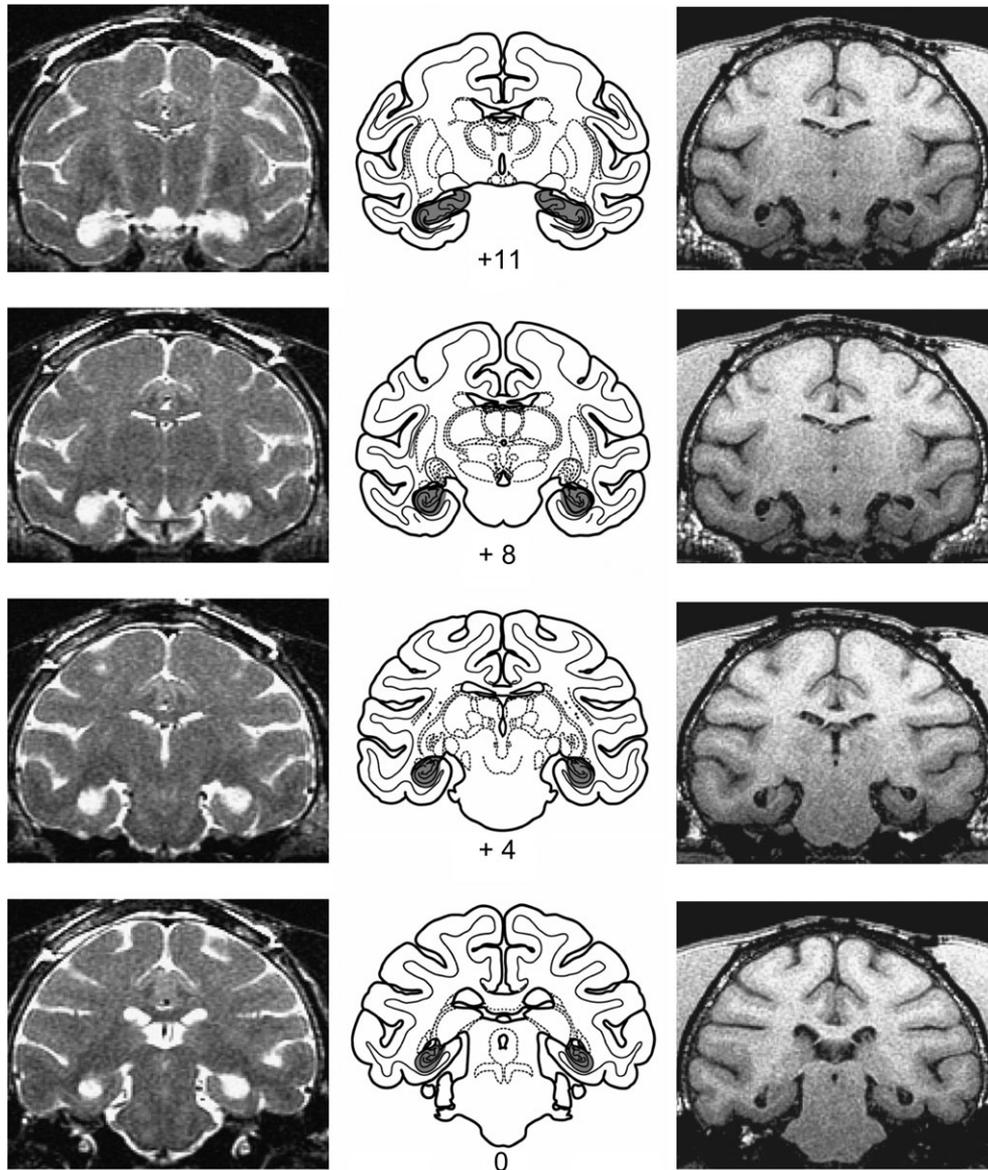


Figure 1. Extent of the hippocampal lesion in 1 representative monkey (H3). The intended lesion (gray shaded region) is shown in the central column on coronal sections from a standard rhesus monkey brain. Images taken from corresponding levels from a T_2 -weighted MR scan obtained 4 days after surgery and from a T_1 -weighted scan obtained 16 months after surgery for monkey H3 are shown in the left and right columns, respectively. The hypersignal (white) in the region of the hippocampus in the T_2 -weighted images (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 T_1 -weighted images (right column). The numerals indicate the distance in millimeters from the interaural plane (0).

(www.istockphoto.com see Fig. 3). Complex pictures of this type elicit selective responses from neurons in perirhinal cortex (Erickson and others 2000). Novel images were used for each problem.

Table 1
Estimated percent damage

	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
PRh1	—	—	96.6	95.1	95.8
PRh2	—	—	87.4	70.6	79.0
PRh3	—	—	95.4	97.1	96.2
PRh4	—	—	97.6	91.7	94.6

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, 2 different stimuli were presented—1 on the left and 1 on the right side of the monitor screen—set approximately 8 cm apart from center to center. In each pair, 1 stimulus was the S+ and the other was the S-. The stimuli remained on the screen until the monkey made a response by touching 1 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 2 transverse patterning problems and, as a control, 2 3-pair concurrent discrimination problems, in pseudorandom order. The data were averaged across the 2 problems for each condition. Each problem was trained in 3 phases, and monkeys were required to learn the discriminations in 1 phase before moving on to the next phase, as detailed below.

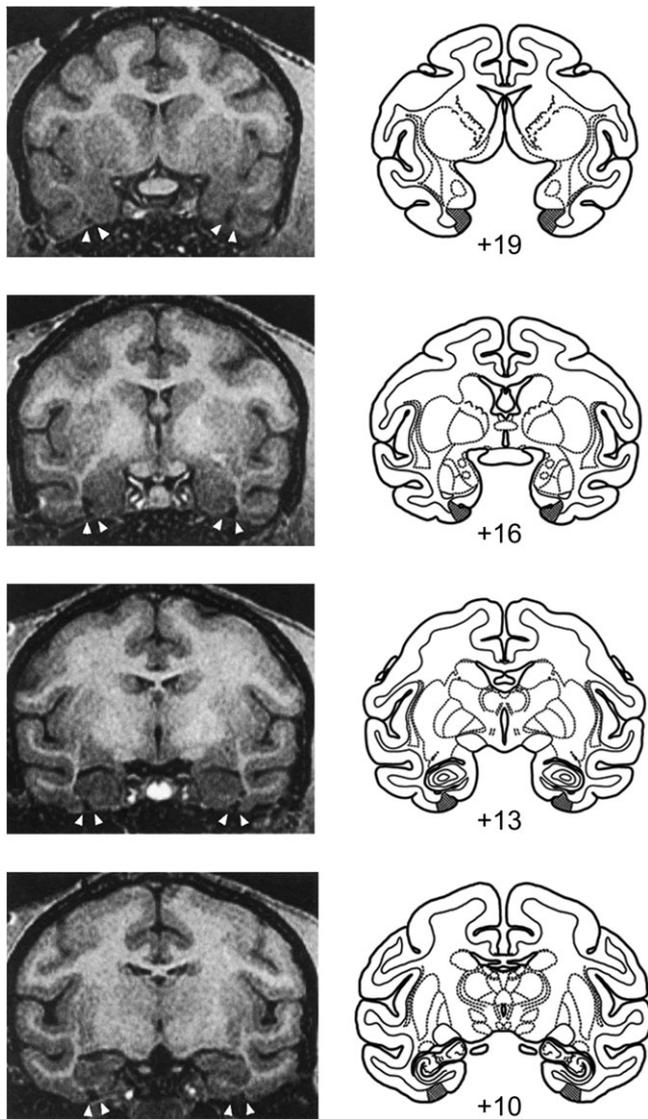


Figure 2. Extent of the perirhinal cortex lesion in 1 representative monkey (PRh1). The intended lesion (gray shaded region) is shown in the right column. The numerals indicate the distance in millimeters from the interaural plane (0). Corresponding sections from T_1 -weighted MR images are shown in the left column. Arrows indicate the medial and lateral extent of the lesion.

Transverse-Patterning Discriminations

The transverse patterning task consists of a 3-pair concurrent discrimination in which 3 stimuli are used and are reinforced differentially depending on which other stimulus is presented simultaneously. If the capital letters A, B, and C represent objects (in our case, 2-dimensional complex grayscale images) that are either reinforced (+) or not (-), then the task can be described schematically as A+ versus B-, B+ versus C-, and C+ versus A- (see Fig. 3A). Monkeys were trained on this task in 3 phases. In phase 1, they were trained on the 1st stimulus pair, A+ versus B-, to a criterion of 17 correct out of 20. Once they attained criterion on this discrimination, they were moved to phase 2, in which the 1st and the 2nd stimulus pair (A+ vs. B- and B+ vs. C-) were presented concurrently. In phase 2, the 2 stimulus pairs were presented in pseudorandom order with the constraint that equal numbers of the two were given in each session. Once they attained a criterion of 17 correct out of 20 on each of the 2 discriminations, monkeys were moved to phase 3, the full transverse-patterning discrimination, in which all 3 stimulus pairs (A+ vs. B-, B+ vs. C-, C+ vs. A-) were presented concurrently. In phase 3, the 3 pairs were presented in pseudorandom

order with the constraint that each pair appeared in 32 trials per session. Phase 3 continued for 32 daily sessions of 96 trials each.

Concurrent Discriminations

Each of the 3-pair concurrent discriminations used 6 novel stimuli (e.g., A+ vs. B-, C+ vs. D-, E+ vs. F-; see Fig. 3B). In each pair, 1 stimulus was arbitrarily designated as the S+ and the other the S-. Monkeys were trained on this task in 3 phases designed to match those used in the transverse patterning task. In phase 1, they were trained on the 1st stimulus pair, A+ versus B-, to a criterion of 17 correct out of 20. Once they attained criterion on this discrimination, they were moved to phase 2, in which the 1st and the 2nd stimulus pair (A+ vs. B- and C+ vs. D-) were presented concurrently. Once they attained a criterion of 17 correct out of 20 on each of the discriminations, monkeys were moved to phase 3, the 3-pair concurrent discrimination, in which all 3 stimulus pairs (A+ vs. B-, C+ vs. D-, E+ vs. F-) were presented concurrently. Phase 3 continued for 16 daily sessions of 96 trials each. As in the transverse-patterning task, the order of presentation of stimulus pairs across trials was pseudorandom for both phases 2 and 3.

Statistics

A preliminary 1-way analysis of variance (ANOVA) on the performance of the 2 control groups on the full transverse-patterning task (i.e., phase 3) showed no difference between groups ($F_{1,18} < 1$), no group by block interaction ($F_{3,18} < 1$), and a significant main effect of block ($F_{3,18} = 10.06$, $P < 0.01$). Because there was no difference between control groups, for all subsequent statistical analyses we combined the control groups for the 2 cohorts.

For both types of discrimination—transverse patterning and concurrent discrimination—data for each subject were averaged across the 2 problems of that type before analysis. Group means of errors to criterion were analyzed for phases 1 and 2 of transverse patterning and concurrent discrimination using 1-way (group) ANOVA. Group means of percent correct for each block of 8 sessions were analyzed for acquisition of phase 3 of transverse patterning, and group means of percent correct for each block of 4 sessions were analyzed for acquisition of phase 3 of concurrent discrimination. These data were submitted to 2-way (group by block) ANOVAs with repeated measures. Significant interaction effects were further analyzed with separate, planned independent-samples t -tests comparing performance of each lesion group with the control group. All statistical analyses were conducted with a significance level of $P = 0.05$.

Results

Transverse-Patterning Discriminations

One-way ANOVA indicated no difference between groups on phase 1 ($F_{2,15} < 1$) or phase 2 ($F_{2,15} < 1$) of transverse patterning. Monkeys required 1 session to attain criterion for phase 1 and 1 session for phase 2.

Acquisition curves for phase 3, showing percent correct scores for each block of 8 sessions, are shown in Figure 4. ANOVA with group as between-subjects and block as within-subjects factors revealed a significant main effect of group ($F_{2,39} = 5.09$, $P < 0.05$), a significant main effect of block ($F_{3,39} = 32.38$, $P < 0.001$), and a significant group by block interaction ($F_{6,39} = 4.05$, $P < 0.01$). Separate independent-samples t -tests were conducted on the means of the final block of sessions to compare performance of each lesion group with performance of the control group. The results of these tests indicated that group PRh was significantly impaired relative to controls ($t_8 = 2.44$, $P < 0.05$) and that group H was significantly facilitated relative to controls ($t_8 = 2.37$, $P < 0.05$). As suggested by the significant interaction of group and block, the groups did not differ early in acquisition: the results of separate independent-samples t -tests conducted on the means of performance scores from the 1st session indicated that there was

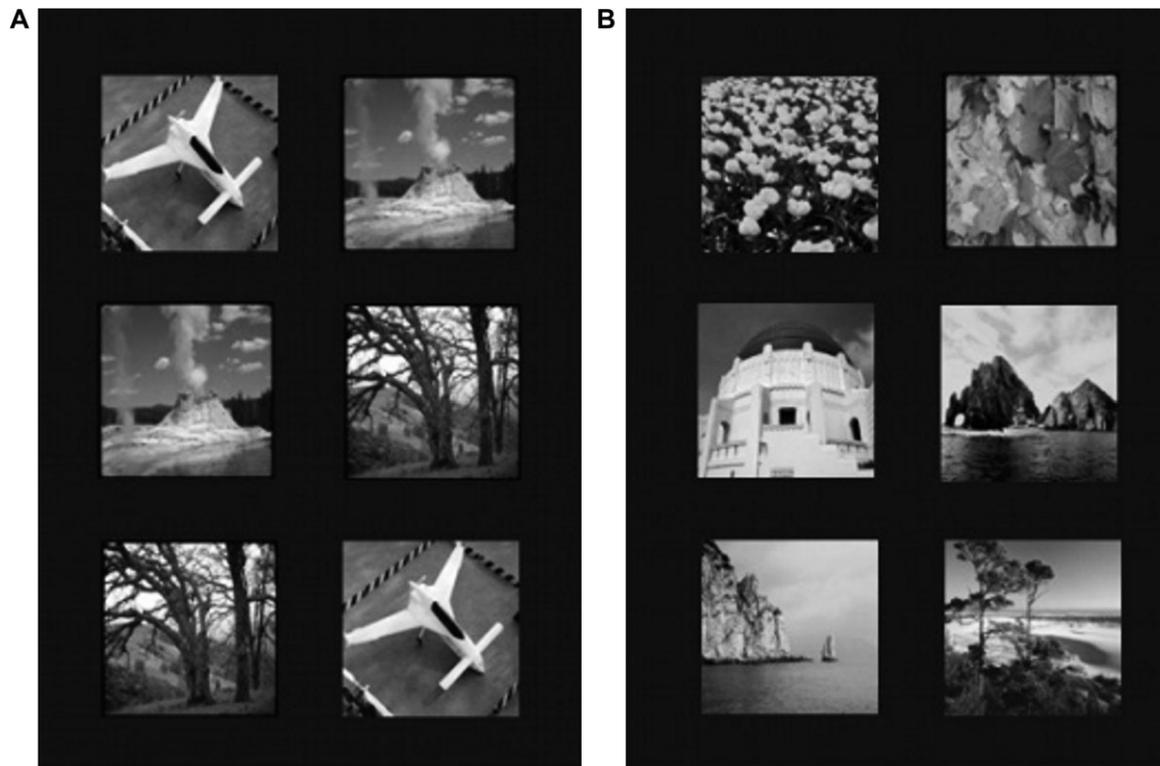


Figure 3. Examples of stimulus pairs used in testing. (A) The transverse-patterning condition, in which all stimuli are explicitly ambiguous. The 3 pairs comprise the 3 trial types that appeared within each session of phase 3. On each trial, 2 stimuli were presented for choice. If objects A and B are displayed, the subject should choose A; if B and C are displayed, the subject should choose B; and if A and C are displayed, the subject should choose C. Because each stimulus is rewarded as often as not, the subject must be able to represent the conjunction of stimuli to solve the problem. (B) A control procedure, the 3-pair concurrent discrimination condition, in which stimuli are not explicitly ambiguous. The 3 pairs comprise the 3 trial types that appeared within each session of phase 3. In practice, the side of presentation of rewarded stimuli was counterbalanced, and the stimuli were 8 cm apart; here they are shown closer together for ease of comparison.

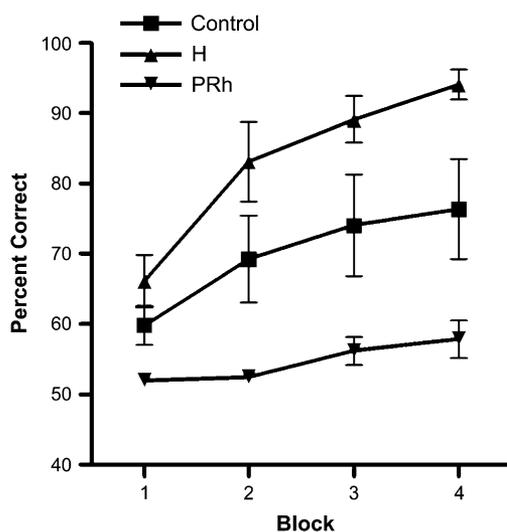


Figure 4. (A) Acquisition by unoperated control monkeys (Control, $N = 8$), monkeys with lesions of perirhinal cortex (PRh, $N = 4$), and monkeys with selective lesions of the hippocampus (H, $N = 4$) of the 3rd phase of the transverse-patterning problem. Percent correct scores for each block of 8 sessions were averaged across 2 stimulus sets.

neither a difference between group PRh and controls ($t_{10} < 1$) nor between group H and controls ($t_{10} = 1.12$). Although there appears at first inspection to be a relationship between total errors and size of lesion for 3 animals in group H (the larger the

lesion the fewer the errors), the 4th monkey does not fit this pattern. There is no apparent relationship between total errors and size of lesion for group PRh (see Table 2).

Concurrent Discriminations

One-way ANOVA indicated no difference between groups on phase 1 ($F_{2,15} < 1$) of the concurrent discrimination. There was, however, a difference between groups on phase 2 ($F_{2,15} = 11.85$, $P < 0.01$) of the concurrent discrimination. Newman-Keuls post hoc analysis revealed a significant difference between group PRh and controls ($P < 0.001$) and between group PRh and group H ($P < 0.01$). Impairment of the PRh group on phase 2 of the concurrent discrimination was unexpected, especially because these subjects were not impaired on phase 2 of transverse patterning. Furthermore, there was no difference between groups in acquisition of phase 3 of the concurrent discrimination (see below), suggesting that this instance of impairment was anomalous. In support of this contention, when analyzed separately, whereas one of the 2 problems used in phase 2 yielded a significant impairment ($F_{2,15} = 21.72$, $P < 0.0001$), the other problem did not ($F_{2,15} = 1$). Thus, it appears that the impairment holds for only 1 problem of 1 phase of concurrent learning and might therefore reflect factors related to either the stimulus set or the day of testing (as all monkeys in this group were tested on this phase on a single day). Taken together, the results from phases 2 and 3 indicate that monkeys with perirhinal cortex lesions do not have a general impairment in concurrent learning. This is consistent with several other

Table 2

Estimated percent damage to either the hippocampus (H1–H4) or the perirhinal cortex (PRh1–PRh4) and errors scored in each phase of the transverse patterning and concurrent discrimination problems. H1–H4: monkeys with bilateral excitotoxic lesions of the hippocampus; PRh1–PRh4: monkeys with aspiration lesions of the perirhinal cortex

Subject	Estimated percent damage	Transverse-patterning problem 1 errors			Transverse-patterning problem 2 errors			Concurrent problem 1 errors			Concurrent problem 2 errors		
		Phase 1	Phase 2	Phase 3	Phase 1	Phase 2	Phase 3	Phase 1	Phase 2	Phase 3	Phase 1	Phase 2	Phase 3
H1	83.3	2	0	404	1	28	173	1	1	2	2	1	7
H2	64.6	0	3	627	2	0	924	1	5	5	4	4	20
H3	79.9	1	2	382	1	5	373	1	2	2	4	4	6
H4	27.9	2	1	720	0	4	547	2	5	17	5	3	9
PRh1	95.8	27	10	1404	6	0	1467	1	62	15	7	20	31
PRh2	79.0	2	5	1258	3	6	1267	3	54	125	7	6	71
PRh3	96.2	11	20	1283	4	33	1480	9	42	69	17	16	72
PRh4	94.6	3	3	1076	2	3	1477	9	17	9	3	3	19

studies examining concurrent discrimination learning in monkeys with perirhinal cortex lesions (e.g., Gaffan and Murray 1992; Buckley and Gaffan 1997; Thornton and others 1997).

ANOVA with group as between-subjects and block as within-subjects factors revealed no significant main effect of group ($F_{2,39} \leq 1$), a significant main effect of block ($F_{3,39} = 3.48$, $P < 0.05$), and no significant group by block interaction ($F_{6,39} < 1$). There is no apparent relationship between total errors and size of lesion for either group H or group PRh (see Table 2).

Discussion

The main finding of the present study was that whereas monkeys with lesions of the perirhinal cortex were significantly impaired in acquisition of transverse patterning, monkeys with excitotoxic lesions of the hippocampus were significantly facilitated. Indeed, the monkeys with hippocampal lesions achieved levels of over 95% correct responses overall, a score that could be achieved only through good performance on all 3 problems. Monkeys with perirhinal cortex lesions were not impaired, however, in acquisition of the control task, a standard 3-pair concurrent discrimination. Studies using fornix lesions have reported similar facilitations of transverse patterning after hippocampal-system damage (Bussey and others 1998; Brasted and others 2003; but see Dusek and Eichenbaum 1998). Fornix lesions, however, may not be functionally equivalent to hippocampal lesions (Clark and others 2000; Vann and others 2000). The effects on transverse patterning reported in the present study can be attributed unequivocally to damage to the hippocampus.

Contributions of Perirhinal Cortex to Coding Object Representations

Transverse patterning requires the association of a response such as “choose A” with a configural cue AB. Such complex configural cues, we suggest, are stored in perirhinal cortex (Saksida and Bussey 1998; Murray and Bussey 1999; Bussey and Saksida 2002). The transverse-patterning task is different from most other configural tasks, however, in that the components of the configural cue AB—that is, objects A and B—are separated in space. Thus, it appears that perirhinal cortex is essential not only for representing conjunctions of features within an object but also for representing components that occur together in a scene, whether or not these components are colocalized in space to form an object. That perirhinal cortex can conjoin separate object components into a conjunctive representation is consistent with the finding that perirhinal cortex lesions can impair object-object paired associate learning (Murray and

others 1993; Higuchi and Miyashita 1996; Buckley and Gaffan 1998) and the discrimination of visual scenes and contexts (Murray and others 1998; Easton and Gaffan 2000; Burwell and others 2002).

Multiple Functional Subdivisions in the MTL

The findings of the present study argue against the view that the MTL structures work together as a single functional unit (Zola-Morgan and others 1994). Although several single and double dissociations between the effects of perirhinal cortex and hippocampal or fornix lesions have been reported (e.g., Murray and others 1993; Gaffan 1994; Murray 1996; Aggleton and Brown 1999; Bussey and others 1999, 2000; Winters and others 2004; Forwood and others 2005), this is, to our knowledge, the first study showing opposing effects of lesions of perirhinal cortex and hippocampus on a single task. Such a result suggests not only that these MTL structures have distinct functions but also that these functions may, in fact, compete. According to this view, hippocampal damage in the present study resulted in the removal of a function that normally competes with perirhinal cortex function. The finding of the reverse pattern, in which perirhinal cortex lesions produce facilitations on tasks sensitive to hippocampal function, is consistent with this idea (Bussey and others 1999, 2000). The nature of this competition and the level at which it operates is, however, unclear. One possibility is that intact monkeys may seek an incorrect “spatial” solution that is unavailable to monkeys with hippocampal lesions. This idea has been suggested to account for the facilitative effects of hippocampal lesions in other settings (Meunier and others 1996).

Neural Bases of Transverse Patterning

The transverse patterning task has traditionally been regarded as a configural task, requiring conjunctive representations for its solution (Sutherland and Rudy 1989; Rudy and Sutherland 1995; Alvarado and Rudy 1995a, 1995b; Couvillon and Bitterman 1996; Wynne 1996; Alvarado and others 2002). The reason it has been regarded as such is logical: animals must learn that when A and B are presented in conjunction, they must perform a different response to that required when, say, A and C are presented in conjunction. Recently, however, some authors have begun to regard the transverse-patterning task as a “relational” task, requiring relational representations for its solution (Dusek and Eichenbaum 1998; Alvarado and Bachevalier 2005a, 2005b). It is not clear to us what is the a priori reason—that is, before the effects of lesions are known—for reformulating transverse patterning in this way. Of course, it is possible that the

transverse-patterning problem might be solved in subtly different ways depending on the way the task is administered (Dusek and Eichenbaum 1998; Reed and Squire 1999). Holland (1991) has provided evidence that in ambiguous discriminations (involving stimulus presentations of the type $A \rightarrow B \rightarrow \text{reward}$), when A and B are presented simultaneously, such tasks are more likely to be solved using configural representations (i.e., $AB \rightarrow \text{reward}$), but when A and B are presented sequentially such tasks are more likely to be solved using a conditional (occasion setting) rule (i.e., if A then $B \rightarrow \text{reward}$). Note that in the 1st instance the required representation of A and B is conjunctive (AB), whereas in the latter instance A and B are represented individually. In the present study, and the studies of Bussey and others (1998) and Brasted and others (2003), all of which found facilitations, the 2 stimuli displayed on a given trial (e.g., A vs. B) were presented simultaneously on a computer monitor at a distance from the subject that allowed simultaneous viewing of the 2 stimuli. In addition, after a choice, the 2 stimuli disappeared at the same time. This arrangement might be expected, according to Holland's analysis, to encourage a configural solution (i.e., $AB \rightarrow \text{choose A}$), consistent with our interpretation. If, however, the stimuli were presented discontinuously, such an arrangement might encourage A and B to be represented individually. This analysis may provide an a posteriori explanation for why other studies find impairment on transverse patterning following hippocampus or fornix lesions (Dusek and Eichenbaum 1998; Alvarado and Bachevalier 2005b). These studies used hand-testing procedures in which stimuli were junk objects presented to monkeys, or pots of scented sand presented to rats. Such procedures require the subjects to sample the stimuli separately and might therefore have encouraged stimuli to be represented individually. As relational theory posits that the hippocampus houses individual stimulus representations and the "relationships" between them, such an analysis may be consistent with the authors' interpretation in terms of an impairment in relational memory. This idea would need to be tested, however, in the context of transverse patterning, perhaps using a procedure similar to that employed by Holland (1991). The prediction would be an impairment when A and B were presented sequentially, but not when presented simultaneously. Even if this pattern of results were found after hippocampal lesions, however, one would still need to explain exactly what relationship is being calculated to exist between the 2 stimuli and how this helps the solution of the task.

The foregoing discussion indicates that there may be a posteriori ways to justify reformulating transverse patterning as a relational task, thereby reconciling the findings of effects of lesions on this task. But perhaps a more ready reconciliation can be found by close consideration of the lesions in such studies. In the study of Alvarado and Bachevalier (2005b), for example, 4 of the 5 monkeys had damage to extrahippocampal regions, most notably parahippocampal cortex (area TF/TH). This unintended damage, although limited, may have contributed to the impairment in these animals; indeed these same authors report that lesions of TF/TH alone can impair transverse patterning (Alvarado and Bachevalier 2005a). These authors also report impairments following perirhinal cortex lesions, and the present study supports this latter finding (Alvarado and Bachevalier 2005a). Thus, a 2nd way in which the discrepant findings may be reconciled is with the suggestion that perirhinal cortex and perhaps TF/TH, and not the hippocampus, are critical for transverse patterning. Paradoxically, perhaps, if in the foregoing

studies subjects are solving transverse patterning in a configural manner, then the results taken together provide good support for relational theory. This is because relational theory posits configural representations in parahippocampal areas such as perirhinal cortex, but not the hippocampus (Eichenbaum and others 1994).

Conclusion

The present study finds impairment and facilitation on transverse patterning after lesions of the perirhinal cortex and hippocampus, respectively. The results confirm and extend our earlier findings regarding perirhinal cortex and provide support for the idea that perirhinal cortex plays a central role in representing complex configural cues (Saksida and Bussey 1998; Murray and Bussey 1999; Bussey and Saksida 2002). Furthermore, the results argue against the view that structures within the MTL operate as a single functional unit. Instead, it appears that MTL structures may have competing roles in visual learning.

Notes

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