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# A Reexamination of the Concurrent Discrimination Learning Task: The Importance of Anterior Inferotemporal Cortex, Area TE

Elizabeth A. Buffalo and Lisa Stefanacci
University of California, San Diego

Larry R. Squire and Stuart M. Zola
Veterans Affairs San Diego Health Care System, La Jolla, California and University of California, San Diego

For 30 years, the concurrent discrimination learning task has figured prominently in studies used to determine the effects of medial temporal lobe damage in monkeys. However, the findings from these studies have been contradictory. We explored the contribution to concurrent discrimination performance of inadvertent damage to area TE by reexamining the behavioral data and histological material from monkeys with medial temporal lobe lesions previously tested in our laboratory. The amount of inadvertent damage to area TE was more predictive of impaired performance on the concurrent discrimination learning task than was the amount of damage to any medial temporal lobe structure, including the perirhinal cortex. These findings resolve earlier inconsistent findings regarding the concurrent discrimination learning task by demonstrating that performance on this task depends on area TE and not on perirhinal cortex or other medial temporal lobe structures.

When the devastating effects on human memory of large medial temporal lobe lesions were first described (Scoville & Milner, 1957), work was immediately begun to try to establish an animal model of impaired memory in the monkey (Orbach, Milner, & Rasmussen, 1960). One of the tasks that figured prominently in this early work was concurrent discrimination learning (Corell & Scoville, 1965). In this task, the animal must learn several pairs of objects concurrently. One member of each pair is consistently rewarded, and training continues until the animal learns the correct member of each pair. A common version of the task involved training on eight pairs of objects with each pair appearing several times within a session (e.g., Iwai & Mishkin, 1968; Moss, Mahut, & Zola-Morgan, 1981). In an early review of the status of the animal model, Squire and Zola-Morgan (1983) identified concurrent discrimination learning as a memory task that seemed suitable for studying the effects of medial temporal lobe lesions in monkeys. This task appeared to require just the kind of learning that was deficient in humans with medial temporal lobe damage. Indeed, later studies confirmed that amnesic patients, including patients with medial temporal lobe damage, are impaired on the concurrent discrimination learning task when it is administered in the same way that it is administered to monkeys (Oscar-Berman & Zola-Morgan, 1980; Squire, Zola-Morgan, & Chen, 1988).

Despite this promising beginning, the published record on the effects of medial temporal lobe lesions on concurrent discrimination learning in monkeys has proven to be contradictory. Even though several studies have reported impaired performance after medial temporal lobe lesions (Correll & Scoville, 1965, 1970; Mahut, Zola-Morgan, & Moss, 1982; Moss, Mahut, & Zola-Morgan, 1981; $H^+A^+$ group: Zola-Morgan & Squire, 1985; $H^+$ group: Zola-Morgan, Squire, & Amaral, 1989a; PRPH II group: Zola-Morgan, Squire, Amaral, & Suzuki, 1989; $H^+$ group: Buckley & Gaffan, 1997; Zola-Morgan, Squire, Clower, & Rempel, 1993), other studies have found normal or near-normal performance (Gaffan & Murray, 1992; Malamut, Saunders, & Mishkin, 1984; Phillips, Malamut, Bachevalier, & Mishkin, 1988; PRPH II group; Suzuki, Zola-Morgan, Squire, & Amaral, 1993; $H^+A$ group: Zola-Morgan et al., 1989a; $H^{++}$ group: Zola-Morgan et al., 1993). Finally, some studies have found impaired retention of preoperatively acquired concurrent discrimination problems and normal or near-normal postoperative learning following medial temporal lobe lesions (Thornton, Rothblat, & Murray, 1997; Gaffan & Murray, 1992; Malamut, Saunders, & Mishkin, 1984).

Three possibilities have been suggested to explain this inconsistency. First, Phillips et al. (1988) suggested that medial temporal lobe lesions may spare concurrent discrimination learning when the set of discrimination pairs is presented only once each day (intertrial interval = 24 hr). Second, Suzuki et al. (1993) suggested that some monkeys, despite medial temporal lobe lesions, might have had

Elizabeth A. Buffalo, Graduate Program in Neurosciences, University of California, San Diego; Lisa Stefanacci, Department of Psychiatry, University of California, San Diego; Larry R. Squire and Stuart M. Zola, Veterans Affairs San Diego Health Care System, La Jolla, California, and Departments of Neurosciences and Psychiatry, University of California, San Diego.

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Correspondence concerning this article should be addressed to Stuart M. Zola, Department of Psychiatry 0603, University of California, San Diego, La Jolla, California 92037. Electronic mail may be sent via Internet to szola@ucsd.edu.

enough sparing of medial temporal lobe tissue to support task performance. Third, it was suggested that the concurrent discrimination learning task can be solved by monkeys using either of two fundamentally different learning strategies (Phillips et al., 1988; Suzuki et al., 1993; Zola-Morgan et al., 1993; Zola-Morgan, Squire, & Ramus, 1994). On the one hand, monkeys may approach the task as humans do, by trying to acquire specific facts about which of the stimuli are rewarded. This strategy, which requires declarative memory (Squire & Zola-Morgan, 1991), would depend on the integrity of the medial temporal lobe. If monkeys with medial temporal lobe damage adopted this strategy, they would not be able to perform normally. On the other hand, monkeys may approach the task nondeclaratively, as a task of habit learning, and gradually form dispositions or habits for each object pair. Habit learning is independent of the medial temporal lobe (Knowlton, Mangels, & Squire, 1996; Malamut et al., 1984; Squire & Zola-Morgan, 1991). Accordingly, if monkeys adopted this strategy, they should be able to perform normally, despite medial temporal lobe damage.

Another possible way to explain the inconsistent findings associated with concurrent discrimination learning is to consider the effect of inadvertent damage to structures outside the medial temporal lobe. Monkeys with bilateral lesions of anterior inferotemporal cortical area TE (which lies adjacent to the medial temporal lobe) are impaired on the concurrent discrimination learning task (Buffalo, Ramus, Zola-Morgan, & Squire, 1995; Iwai & Mishkin, 1968; Malkova, Mishkin, & Bachevalier, 1995; Moss et al., 1981; Phillips et al., 1988). Additionally, in the case of the 20 object-pair version of this task that uses 24-hr intertrial intervals, poor performance of monkeys with medial temporal lobe lesions was correlated with the extent of inadvertent damage to area TE (Malamut et al., 1984). These studies indicate that area TE is important for the performance of the concurrent discrimination learning task. The question that remains is whether the presence of inadvertent area TE damage can also explain the variable findings on this task from monkeys with intended medial temporal lobe lesions.

A consideration of the role of area TE in the concurrent discrimination learning task is best accomplished not only by examining concurrent discrimination performance as a function of damage to area TE but also by examining performance as a function of damage to the perirhinal (PR) cortex. The PR cortex lies immediately adjacent and medial to area TE and is thought to be a component of the medial temporal lobe memory system (Meunier, Bachevalier, Mishkin, & Murray, 1993; Mishkin & Murray, 1994; Murray, 1996; Squire & Zola-Morgan, 1991; Suzuki, 1996; Suzuki et al., 1993; Zola-Morgan, Squire, Amaral, & Suzuki, 1989; Zola-Morgan & Squire, 1993). PR cortex and area TE are strongly interconnected (Suzuki & Amaral, 1994a). The reason for considering the PR cortex along with area TE is that most studies that have evaluated performance on the concurrent discrimination learning task after intended lesions of area TE were based on earlier interpretations of the border between area TE and the PR cortex. Additionally, earlier interpretations of this border were used in a previous study that evaluated the effects of inadvertent area TE damage after medial temporal lobe lesions (Malamut et al., 1984). Convergent evidence from cytoarchitectonic and neuroanatomical tracing studies (Suzuki & Amaral, 1994a) shows that the border of area TE that adjoins PR cortex is more lateral than previously thought. As a result, the PR cortex is now recognized to occupy some of the territory previously considered part of area TE. Accordingly, what might have been identified as area TE damage in earlier studies might actually have been PR damage.

We have reexamined the behavioral data and the histological material from 34 monkeys previously tested in our laboratory. Twenty-three monkeys had been prepared with medial temporal lobe lesions; 1 monkey had been prepared with a lesion restricted to area TE. Ten unoperated control monkeys were used for comparison. In one analysis, we used a 4-point scale to estimate for each operated monkey the amount of unintended damage to area TE as well as the amount of damage to the PR cortex. We then determined the relationship between damage to each of these two cortical regions and performance on the concurrent discrimination learning task. In a second analysis for the same 23 monkeys, we also estimated the amount of damage to additional structures in the temporal lobe; that is the hippocampal region and the entorhinal (ER) and parahippocampal (PH) cortices. We then compared the effect of area TE damage to the effect of damage to these medial temporal lobe structures on performance of the concurrent discrimination learning task. Finally, we determined the effect of damage to each of these structures on the delayed nonmatching to sample (DNMS) task. The DNMS task was chosen as a comparison task because performance of this task is known to be sensitive to medial temporal lobe damage (Mishkin & Murray, 1994; Squire & Zola-Morgan, 1991). In summary, we compared the effects of damage to area TE and four medial temporal lobe structures on two tasks: the concurrent discrimination learning task and the DNMS task.

## Materials and Method

### *Subjects*

The findings from 34 cynomolgus monkeys (*Macaca fascicularis*) are presented. Twenty-eight monkeys were male and 6 were female, and they weighed between 2.4 and 5.2 kg at the start of behavioral testing. Twenty-four of the monkeys had bilateral lesions and belonged to nine surgical groups (described later). Ten monkeys were unoperated control monkeys used for comparison. Table 1 shows the references in which the surgical procedures, behavioral testing and results, and the neurohistological analyses of the lesions were previously reported. For 1 monkey that received a bilateral lesion of cortical area TE, behavioral and histological data have not been published previously, and they are presented here in detail.

### *Surgery*

Monkeys received bilateral lesions that damaged one or more temporal lobe regions, including the amygdala; the hippocampal region (hippocampus proper, dentate gyrus, and subicular complex); the ER, PR, and PH cortices; and cortical area TE. We have defined these areas as shown in Figure 1 and as follows:

Table 1
*References to Surgical Procedures, Behavioral Results, and Original Histological Findings*

| Group | *n* | Reference |
|---|---|---|
| A | 3 | Zola-Morgan, Squire, and Amaral, 1989b |
| H | 4 | Alvarez, Zola-Morgan, and Squire, 1995 |
| $H^{+}$ [a] | 4 | Zola-Morgan et al., 1989a; Zola-Morgan et al., 1993 |
| $H^{+}A$ | 3 | Zola-Morgan et al., 1989b |
| $H^{++}$ [b] | 4 | Zola-Morgan et al., 1993 |
| $H^{+}A^{-}$ | 4 | Zola-Morgan, Squire, and Mishkin, 1982; Zola-Morgan and Squire, 1985 |
| PRPH II[c] | 1 | Suzuki et al., 1993 |
| TE | 1 | Present study |

*Note.* A = bilateral stereotaxic radiofrequency lesions of the amygdala; H = bilateral stereotaxic radiofrequency lesions of the hippocampal region; $H^{+}$ = bilateral aspiration lesions of the hippocampal region, the posterior entorhinal (ER) cortex, and the parahippocampal (PH) cortex; $H^{+}A$ = bilateral aspiration lesions of the hippocampal region, the amygdala, the posterior ER cortex, and the PH cortex; $H^{++}$ = bilateral aspiration lesions of the hippocampal region and the ER, perirhinal (PR), and PH cortices; $H^{+}A^{+}$ = bilateral aspiration lesions of the hippocampal region, the amygdala, and the ER, PR, and PH cortices; PRPH II = bilateral aspiration lesion of the PR and PH cortices; TE = bilateral aspiration lesion of visual cortical area TE.

[a]One monkey in this group ($H^{+}$ 5) was excluded from the analysis because the lesion resulted in severe ventricular enlargement in the right hemisphere. The enlargement appeared to compress rather than destroy tissue in the temporal cortical regions. Because none of the other brains in our study sustained such profound tissue compression, it was impossible to apply comparable criteria for estimating damage in the case of $H^{+}$ 5.

[b]One monkey in this group ($H^{++}$ 5) was excluded from the analysis because he obtained anomalously good scores on nine separate behavioral measures (see Zola-Morgan et al., 1993). This monkey was likewise excluded from the statistical analyses in the original published report.

[c]Three monkeys in this group (PRPH II 5, PRPH II 7, PRPH II 8) were excluded from the analysis because they failed to reach criterion on the delayed nonmatching to sample task.

*Area TE.* Area TE lies in the medial temporal lobe on the inferior and middle temporal gyri (see Figure 2A–C). We defined the cytoarchitectonic boundaries of area TE according to Bonin and Bailey (1947) with modifications by Suzuki and Amaral (1994a). Rostrally, area TE extends the rostral limit of the superior temporal sulcus. Caudally, area TE extends to approximately 10 mm in front of the ascending inferior occipital sulcus and it is bordered by area TEO, approximately at the level of the posterior middle temporal sulcus (Baizer, Ungerleider, & Desimone, 1991). Medially, area TE is bordered by the PR cortex (rostrally) and the PH cortex (caudally). Laterally, it extends to the fundus of the superior temporal sulcus.

*PR cortex.* The PR cortex in the macaque monkey is located on the ventromedial surface of the temporal lobe. For most of its rostrocaudal extent, it lies lateral to the rhinal sulcus. We followed the nomenclature of Suzuki and Amaral (1994b) and Insausti et al. (Insausti, Amaral, & Cowan, 1987) in establishing the cytoarchitectonic boundaries of the PR cortex with other cortical regions. The PR cortex (see Figure 2, A and B) extends rostrally onto the temporal pole and caudally beyond the rhinal sulcus to the PH cortex. Medially, it is bordered by the ER cortex; laterally, it abuts area TE (rostrally) and the PH cortex (caudally).

*ER cortex.* The ER cortex lies in the rostral third of the ventromedial temporal lobe (see Figure 2, A and B). We have followed Amaral et al. (Amaral, Insausti, & Cowan, 1987) in establishing its location and topographic limits. Rostromedially, the ER cortex borders the piriform cortex. Moving caudally, its medial border is formed first by the periamygdaloid cortex then by the parasubiculum. The lateral border of the ER cortex is formed by the rhinal sulcus for most of its rostrocaudal extent, although near its rostral and caudal poles it directly abuts Area 35 and Area 36, respectively. At its caudal limit, the ER borders the parasubiculum and area TH of the PH cortex.

*PH cortex.* The PH cortex (areas TH and TF) is also located on the ventromedial surface of the temporal lobe (see Figure 2C). We followed Suzuki and Amaral (1994b) and Insausti et al. (1987) and considered the PH cortex as bordered by the PR cortex (rostrally) and by area VTF (caudally) (Gattass, Sousa, & Covey, 1985). Medially, PH is bounded by the PR cortex (rostrally) and the subicular complex (caudally). Laterally, PH borders area TE (rostrally) and area TEO (caudally).

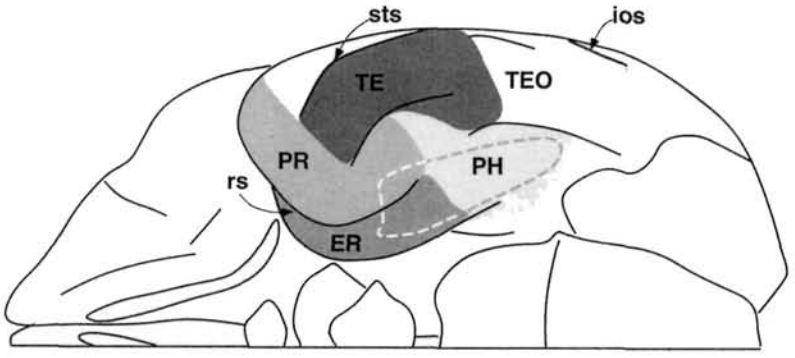


*Figure 1.* Drawing of the ventral surface of the left hemisphere from a macaque monkey brain showing the components of the medial temporal lobe memory system: the hippocampal region (consisting of the dentate gyrus, the cell fields of the hippocampus proper, and the subicular complex) is indicated by dashed lines; PR = perirhinal cortex; PH = parahippocampal cortex; ER = entorhinal cortex. Area TE is also shown. Rostrally, area TE extends approximately to the rostral limit of the superior temporal sulcus. Caudally, area TE extends to approximately 10 mm in front of the ascending inferior occipital sulcus (ios) and it is bordered by area TEO. Medially, it is bordered by the perirhinal cortex (rostrally) and by the parahippocampal cortex (caudally). Laterally, it extends to the fundus of the superior temporal sulcus. sts = superior temporal sulcus; rs = rhinal sulcus.

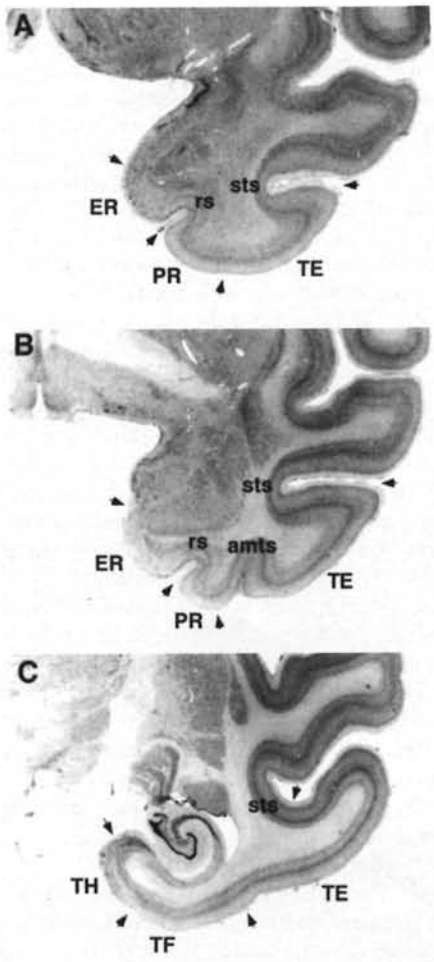


*Figure 2.* Coronal, Nissl-stained sections through rostral (A), mid-rostrocaudal (B), and caudal (C) levels of a normal right temporal lobe. Arrows indicate borders between cortical regions. ER = entorhinal cortex; PR = perirhinal cortex; TE = inferotemporal cortex, area TE; TH and TF = medial and lateral components of parahippocampal cortex. The surface extent of each cortical region is described in the Materials and Method section and is shown in Figure 1. amts = anterior middle temporal sulcus; sts = superior temporal sulcus; rs = rhinal sulcus.

The surgical groups in Table 1 include the following: A group, $n = 3$, bilateral stereotaxic radiofrequency lesions of the amygdala; H group, $n = 4$, bilateral stereotaxic radiofrequency lesions of the hippocampal region (hippocampus proper, dentate gyrus, and subicular complex); $H^+$ group, $n = 4$, bilateral aspiration lesions of the hippocampal region, the posterior ER cortex, and the PH cortex; $H^+A$ group, $n = 3$, bilateral aspiration lesions of the hippocampal region, the amygdala, the posterior ER cortex, and the PH cortex; $H^{++}$ group, $n = 4$, bilateral aspiration lesions of the hippocampal region and the ER, PR, and PH cortices; $H^+A^+$ group, $n = 4$, bilateral aspiration lesions of the hippocampal region, the amygdala, and the ER, PR, and PH cortices; PRPH II group, $n = 1$, bilateral aspiration lesion of the PR and PH cortices; TE group, $n = 1$, bilateral aspiration lesion of visual cortical area TE.

## *Behavioral Testing*

All testing took place in a modified Wisconsin General Test Apparatus (Harlow & Bromer, 1938). Four to 8 weeks after surgery, the monkeys were given four to six pretraining sessions during which they learned to obtain a food reward by displacing objects covering any of three food wells on a stimulus tray in front of the testing chamber. The monkeys were then tested on the following six behavioral tasks: trial-unique DNMS, pattern discrimination learning, delayed retention of object discriminations, concurrent discrimination learning, retest of DNMS, and motor skill learning. Descriptions of all the behavioral tasks and all of the behavioral findings can be found in the references listed in Table 1. The present article is concerned with the findings from only two of the tasks—the concurrent discrimination learning task and the DNMS task—which are described in the following discussion.

*Concurrent discrimination learning.* Eight pairs of junk objects were presented in an intermingled fashion during each testing session so that all eight discrimination pairs had to be learned simultaneously. Specifically, on each trial, one pair of objects was presented, and, over the course of each daily testing session of 40 trials, each pair was presented five times randomly intermixed with the other pairs. The intertrial interval was 15 s. The same object of the pair was always the correct one. By displacing it, monkeys revealed a food reward. The position of the correct object (left or right) was determined by a Gellerman sequence (Gellerman, 1933). Testing was continued until a learning criterion of 39 correct responses in 40 consecutive trials was achieved during one test session.

*DNMS.* In the first part of the trial, the monkey displaced an object covering the central food well and obtained a food reward. An opaque door was then lowered to block the monkey's view of the food wells. Eight seconds later, the opaque door was raised and the monkey saw two objects, the original object and a new one, each covering one of the two lateral food wells. The monkey had to displace the new object to obtain a food reward. The position of the correct object (left or right) varied on each trial according to a Gellerman sequence (Gellerman, 1933). Twenty such trials were presented daily with an intertrial interval of 15–20 s. Each trial used a new pair of objects, selected randomly from a collection of more than 300 junk objects. After reaching a learning criterion of 90 correct choices in 100 trials at the 8-s delay, monkeys were tested successively at delays of 15 s (for 100 trials), 60 s (for 100 trials), and 10 min (for 50 trials). One monkey (PRPH II 6; see Table 1) was given only 25 trials at the 10-min delay. Three groups of monkeys (H, TE, and 4 of the normal monkeys) were also tested with a delay of 40 min between the sample and choice trials, but these data will not be considered here.

## *Neurohistological Analyses*

Upon completion of behavioral testing, the operated monkeys were euthanized and the brains were frozen in cold isopentane and processed for neurohistological analysis of the lesions. Tissue was sectioned in the coronal plane at a thickness of 50 μ. Every fifth section was collected in 0.1 M $PO_4$ (pH 7.2), mounted onto gelatin-coated glass slides, and stained with thionin.

For the present study, each brain was reanalyzed microscopically to determine the extent of damage to temporal lobe regions. Five temporal lobe areas were reevaluated: area TE and PR cortex (Analyses 1 and 2; see Results section), the PH cortex, the ER cortex, and the hippocampal region (Analysis 2; see Results section). Two raters independently assigned a score from 0–3 to each temporal lobe region, corresponding to the estimated extent of damage. The raters were blind to the monkeys' behavioral scores. Separate scores were assigned to the left and right hemisphere for each region. A score of 0 corresponded to no damage, 1 corresponded to minimal (up to approximately 35%) damage, 2 corresponded to moderate (up to approximately 65%) damage, and 3 corresponded to extensive (up to 100%) damage (see Figure 3,

A–C). Raters used half-point increments in assigning scores. Every 10th section, corresponding to 0.5-mm increments (Rater 1), or every 20th section, corresponding to 1.0-mm increments (Rater 2) through the temporal lobe, was analyzed. For each brain and each brain region, scores for the analyzed sections from the two raters were averaged by hemisphere and then averaged with the scores from the contralateral hemisphere to produce a single measure of damage for each temporal lobe region (interrater reliability, $r = .99$). The two raters' scores were averaged, and these data (along with the corresponding behavioral results for the DNMS and concurrent discrimination tasks) are presented in Table 2. Behavioral data for 10 unoperated control monkeys (N) are presented in Table 2 for comparison.

### *Statistical Analyses*

*Analysis 1.* Simple regression and multiple regression analyses were performed to determine whether damage to area TE or the PR cortex correlated with performance on the concurrent discrimination task.

*Analysis 2.* The 23 lesioned monkeys were grouped according to the amount of damage to area TE. If the amount of area TE damage was rated as being less than 1, monkeys were placed in the no TE damage group. If the amount of area TE damage was rated as being greater than or equal to 1, monkeys were placed in the TE damage group. The performance of these two groups on the concurrent discrimination learning task and the DNMS task were then compared to each other and to 10 unoperated control monkeys. One-way analyses of variance (ANOVAs) and Bonferroni/Dunn post hoc analyses were used to compare the three groups and their performance on the two tasks.

Additionally, a canonical correlation was used to determine the relative importance of each of the five structures (area TE, ER, PR, PH cortex, and the hippocampal region) for performance on the concurrent discrimination learning task and the DNMS task. We used a canonical correlation analysis because we wanted to describe the importance of each of these structures for performance on two behavioral tasks. A canonical correlation analysis, unlike a multiple regression analysis, allows a determination of simultaneous correlation with two dependent variables.

Monkey TE 1 was not included in any of the statistical analyses, but his data are presented in Figure 4, A and B, for comparison.

### *Area TE Lesion*

A group of monkeys with bilateral lesions intended to be limited to cortical area TE is currently undergoing behavioral testing in our laboratory. As a result of gastrointestinal illness, it was necessary to euthanize 1 monkey from this group. This monkey had already completed the behavioral tasks that were relevant to the present study, and his data are presented here for comparison with the other groups.

*Histological findings.* The lesion of area TE extended bilaterally through the full rostrocaudal extent of the temporal lobe. Likewise, the mediolateral extent of area TE damage was virtually complete, with the exception of sparing within the ventral bank of the superior temporal sulcus. In the left hemisphere, there was minimal damage to the lateral portion of area TF, which extended for approximately 1 mm in the rostrocaudal plane. In the right hemisphere, there was minor damage to the rostral 2.5 mm of area TEO. There was no evidence of damage to any other medial temporal lobe region (see Figure 4, A–C). There was minimal damage to the white matter deep to Layer 6 of area TE, which was more prominent in the left hemisphere than in the right.

*Behavioral results.* This monkey completed the laboratory's standard battery of behavioral testing (see *Behavioral Testing* section). The scores for pattern discrimination (615 trials to criterion), delayed retention of object discrimination (95%), and the motor skills task were within the normal range, whereas the score for concurrent discrimination (1,040 trials to criterion) was well outside the normal range. The scores for DNMS (average of performance on the 15-s, 60-s, and 10-min delays = 82%) and the retest of DNMS (average of performance on the 15-s, 60-s, and 10-minute delays = 80%) were at the low end of normal performance.

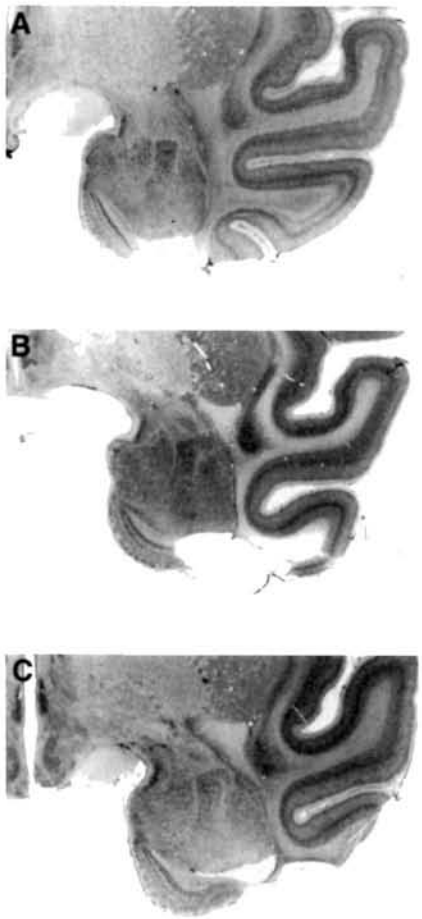


*Figure 3.* Coronal, Nissl-stained sections of one level (mid-rostrocaudal) through the right temporal lobe of 3 monkeys with lesions of the medial temporal lobe. Panels illustrate different extents of inadvertent damage to area TE, corresponding to different experimenter ratings (see *Materials and Method* section). A, Damage to area TE was minimal (a rating of 1). B, Damage to area TE was moderate (a rating of 2). C, Damage to area TE was extensive (a rating of 3).

## Results

### *Analysis 1*

We conducted two simple regression analyses to determine the relationship between the amount of damage to area TE and the PR cortex and performance on the concurrent discrimination learning task. An additional analysis, a multiple regression, assessed the relative importance of area TE versus the PR cortex for performance of the concurrent discrimination learning task. Monkey TE 1 was not included in the statistical analyses, but his data are presented for comparison in Figure 5.

Table 2
*Estimated Damage to Temporal Lobe Regions and Behavioral Scores*

| | Estimated damage to temporal lobe regions | | | | | Behavioral scores | |
|---|---|---|---|---|---|---|---|
| Monkey | TE | PR cortex | ER cortex | PH cortex | H | DNMS | Concurrent discrimination |
| N 1 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 90 | 440 |
| N 2 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 89 | 480 |
| N 3 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 81 | 680 |
| N 4 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 87 | 360 |
| N 5 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 91 | 480 |
| N 6 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 91 | 600 |
| N 7 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 82 | 720 |
| N 8 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 84 | 640 |
| N 9 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 87 | 240 |
| N 10 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 91 | 240 |
| *M* | | | | | | **87** | **488** |
| $H^+A^+$ 1 | 0.7 | 1.5 | 3.0 | 3.0 | 2.9 | 62 | 960 |
| $H^+A^+$ 2 | 0.6 | 2.3 | 3.0 | 2.6 | 2.5 | 59 | 1,160 |
| $H^+A^+$ 3 | 0.7 | 1.8 | 3.0 | 2.5 | 2.9 | 58 | 760 |
| $H^+A^+$ 4 | 1.2 | 2.2 | 3.0 | 3.0 | 3.0 | 66 | 1,520 |
| *M* | | | | | | **61** | **1,100** |
| $H^+A$ 1 | 0.6 | 0.7 | 1.1 | 2.4 | 1.9 | 77 | 720 |
| $H^+A$ 2 | 0.6 | 0.3 | 1.1 | 1.4 | 2.2 | 69 | 720 |
| $H^+A$ 3 | 0.5 | 0.3 | 0.7 | 1.9 | 2.7 | 79 | 520 |
| *M* | | | | | | **75** | **653** |
| $H^{++}$ 1 | 0.9 | 2.6 | 1.9 | 2.2 | 2.1 | 71 | 360 |
| $H^{++}$ 2 | 1.6 | 2.6 | 1.9 | 2.6 | 2.6 | 72 | 820 |
| $H^{++}$ 3 | 1.1 | 2.6 | 0.9 | 2.7 | 2.5 | 69 | 300 |
| $H^{++}$ 4 | 2.0 | 1.7 | 1.4 | 2.9 | 2.3 | 81 | 830 |
| *M* | | | | | | **73** | **577** |
| $H^+$ 1 | 0.3 | 0.1 | 1.0 | 1.9 | 2.7 | 74 | 760 |
| $H^+$ 2 | 0.4 | 0.0 | 0.9 | 1.5 | 2.9 | 77 | 720 |
| $H^+$ 3 | 0.8 | 0.9 | 0.0 | 2.8 | 2.0 | 82 | 880 |
| $H^+$ 4 | 2.2 | 1.3 | 0.4 | 3.0 | 2.0 | 86 | 1,510 |
| *M* | | | | | | **80** | **968** |
| H 1 | 0.0 | 0.0 | 0.0 | 0.0 | 1.5 | 84 | 320 |
| H 2 | 0.1 | 0.0 | 0.0 | 0.4 | 0.9 | 84 | 360 |
| H 3 | 0.0 | 0.0 | 0.0 | 0.0 | 1.4 | 85 | 400 |
| H 4 | 0.0 | 0.0 | 0.0 | 0.0 | 1.3 | 83 | 320 |
| *M* | | | | | | **84** | **350** |
| A 1 | 0.0 | 0.0 | 0.3 | 0.0 | 0.3 | 83 | 360 |
| A 2 | 0.0 | 0.3 | 0.6 | 0.0 | 0.1 | 84 | 520 |
| A 3 | 0.0 | 0.0 | 0.0 | 0.0 | 0.3 | 84 | 380 |
| *M* | | | | | | **84** | **420** |
| PRPH II 6 | 0.6 | 2.7 | 0.3 | 2.0 | 0.0 | 72 | 400 |
| TE 1 | 2.4 | 0.0 | 0.0 | 0.0 | 0.0 | 82 | 1,040 |

*Note.* Boldface numbers indicate means (*M*). See *Surgery* section for description of surgical groups. TE = area TE; PR = perirhinal; ER = entorhinal; PH = parahippocampal; H = hippocampal region; DNMS = delayed nonmatching to sample, percent correct (average of 15-s, 60-s, and 10-min delays); Concurrent discrimination = trials to criterion.

*Simple regression.* Simple regression analyses were first carried out to determine whether a linear relationship existed between the amount of damage to area TE and the PR cortex and performance on the concurrent discrimination learning task. That is, for each cortical region, we were interested in whether performance worsened as the amount of damage increased. Alternatively, an impairment might occur only when the damage extended beyond a certain level, or there might be no relationship at all between the amount of cortical damage and performance. As shown in Figure 5A, we found that there was a linear relationship between the amount of damage to area TE and performance on the concurrent discrimination learning task. Specifically, as the amount of damage to area TE increased, performance on

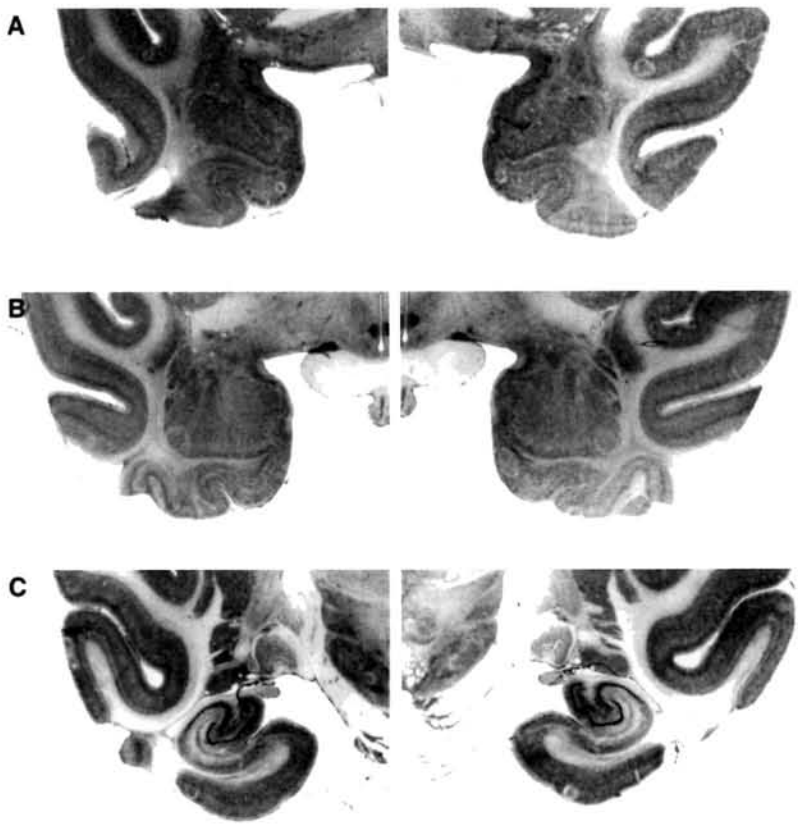


*Figure 4.* Coronal, Nissl-stained sections through rostral (A), mid-rostrocaudal (B), and caudal (C) levels of the left and right temporal lobes of monkey TE 1. Overall, the amount of bilateral area TE damage was rated as 2.35 (moderate-to-extensive damage). Bilateral damage to area TE was extensive and circumscribed, entirely sparing the perirhinal cortex (A and B). The lesion spared the ventral bank of the superior temporal sulcus on both sides as well as much of the anterior middle temporal sulcus (B). There was minimal damage to the parahippocampal cortex on the left (C), and minimal damage to the white matter subjacent to area TE.

the concurrent discrimination learning task worsened (Pearson product–moment correlation yielded a coefficient of .65, $p < .001$). By contrast, there was no significant relationship between the amount of damage to the PR cortex and performance on the concurrent discrimination learning task ($r = .34, p > .1$; see Figure 5B). Monkey TE 1 showed a relationship between performance and amount of damage that was similar to the other monkeys (Figure 5, A and B).

*Multiple regression.* A multiple regression analysis was carried out to determine whether damage to either cortical region (area TE or PR cortex) was predictive of performance on the concurrent discrimination learning task. Table 3 shows that the amount of damage to area TE, but not the amount of damage to the PR cortex, was predictive of performance on the concurrent discrimination learning task (area TE; $p < .01$; the PR cortex: $p > .1$).

## *Analysis 2: Part 1*

Five of the 23 lesioned monkeys sustained inadvertent damage to area TE that was rated as being greater than or equal to 1. The performance of this group of monkeys was compared to that of the remaining 18 monkeys whose damage to area TE was rated as being less than 1 (i.e., no TE damage) and to that of 10 unoperated control monkeys. A one-way ANOVA revealed a significant group effect, $F(2, 30) = 5.528, p < .01$. Figure 6A shows that the group with area TE damage was significantly impaired on the concurrent discrimination learning task relative to the group with no area TE damage ($p < .01$) and also relative to the normal group ($p < .01$). The group with no area TE damage was not different from the normal group ($p > .1$). That is, monkeys with unintended damage to area TE were impaired on the concurrent discrimination learning task, whereas monkeys without unintended damage to area TE were unimpaired. A different pattern of performance was observed for the DNMS task. A one-way ANOVA revealed a significant group effect, $F(2, 30) = 7.767, p < .01$. Figure 6B shows that the group with area TE damage was not different from the group with no area TE damage ($p > .1$). Both groups of lesioned monkeys were different from the normal group ($p < .01$). That is, monkeys with medial temporal lobe

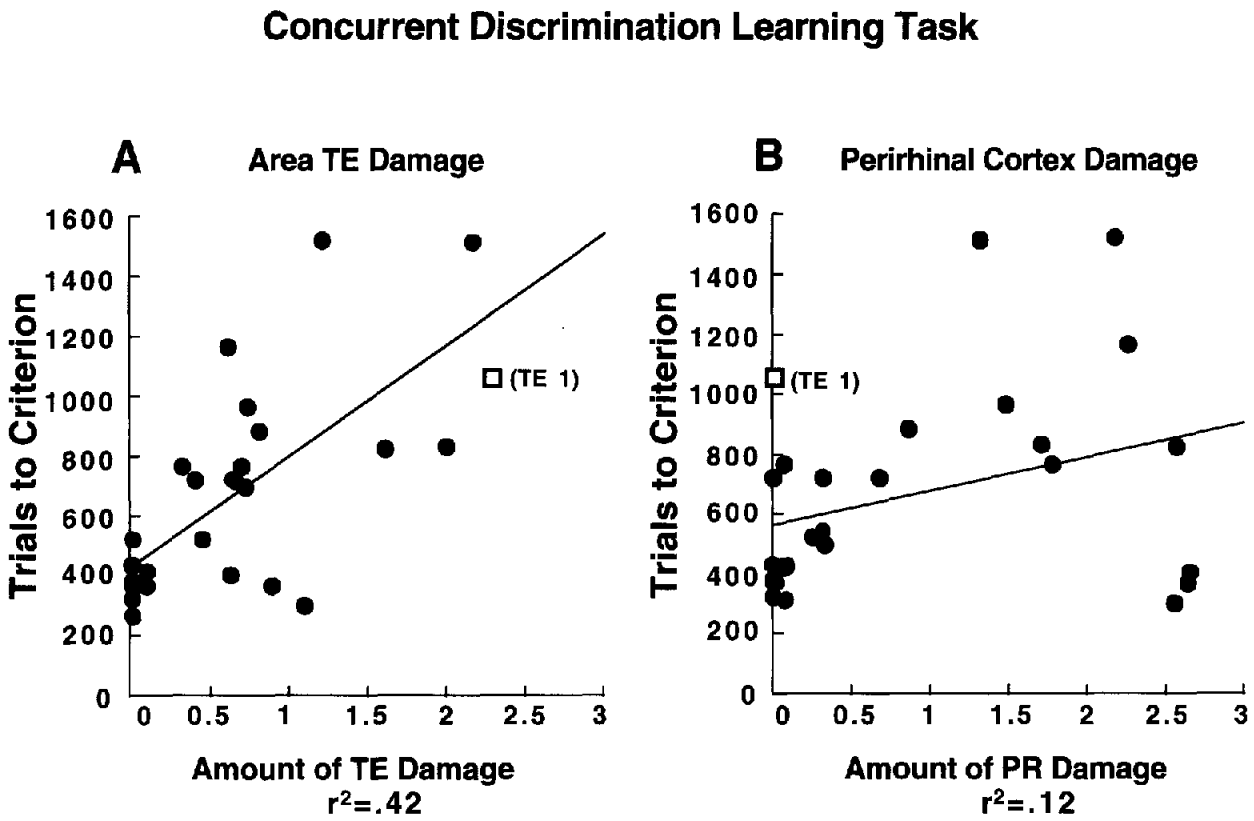


*Figure 5.* Concurrent discrimination learning task. The regression function in A shows the relationship between the amount of damage to area TE (on a scale from 0, *no damage*, to 3, *extensive damage*) and the number of trials required for monkeys to reach criterion on the concurrent discrimination learning task (trials to criterion). All 23 monkeys with medial temporal lobe lesions were included in this analysis. Monkey TE 1 was not included in the statistical analysis, but his score is shown here for comparison. A higher score on the trials to criterion measure indicates poorer performance. This analysis revealed that progressively more extensive damage to area TE was associated with progressively poorer performance on the concurrent discrimination learning task. The regression function in B shows the relationship between the amount of damage to the perirhinal (PR) cortex (on a scale from 0, *no damage*, to 3, *extensive damage*) and the number of trials required for monkeys to reach criterion on the concurrent discrimination learning task (trials to criterion). All 23 monkeys with medial temporal lobe lesions were included in this analysis. Monkey TE 1 was not included in the statistical analysis, but his score is shown here for comparison. A higher score on the trials to criterion measure indicates poorer performance. This analysis revealed no significant relationship between the amount of damage to the PR cortex and performance on the concurrent discrimination learning task.

lesions were impaired on the DNMS task, regardless of the extent of unintended damage to area TE.

### *Analysis 2: Part 2*

Part 1 of the second analysis contrasted the effects of area TE lesions and medial temporal lobe lesions on performance of the concurrent discrimination learning task. However, because monkeys with area TE damage sustained variable amounts of damage to several different medial temporal lobe structures, the analysis in Part 1 on its own could not identify a unique contribution of area TE to performance. Accordingly, a canonical correlation was used to determine the simultaneous association between (a) the amount of damage to area TE and the amount of damage to other structures of the medial temporal lobe; and (b) performance on the concurrent discrimination learning task and on the delay portion of the DNMS task (see Table 4). For each of the 23 lesioned monkeys used in the first analysis, the amount of damage to area TE, the PR cortex, the PH cortex, the ER cortex, and the hippocampal region was measured, and these scores were included in this canonical correlation. This canonical correlation revealed a significant relationship

Table 3
*Multiple Regression Analysis for the Concurrent Discrimination Learning Task*

| Cortical area | Coefficient | *SE* | *t* | *p* |
|---|---|---|---|---|
| Area TE | 426.1 | 127.9 | 3.33 | .0033 |
| PR cortex | −54.7 | 76.9 | −0.71 | .49 |

*Note.* PR = perirhinal.

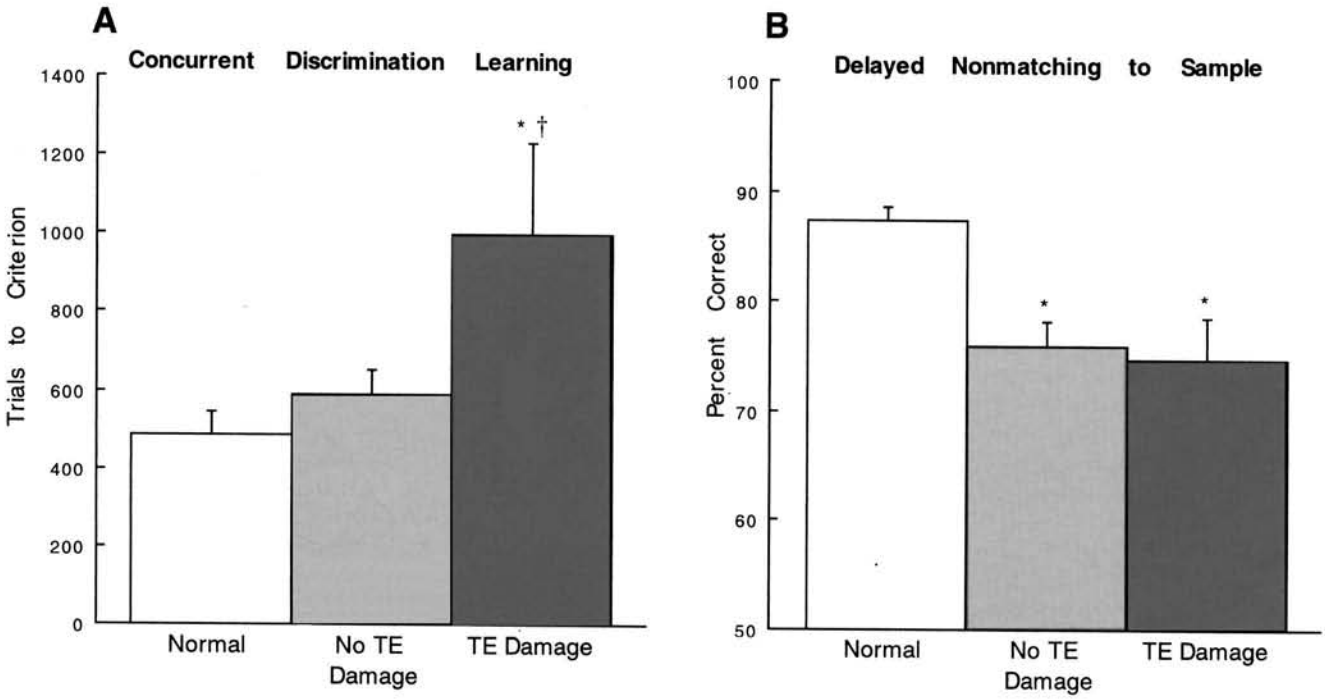


*Figure 6.* The bars in A represent the performance on the concurrent discrimination learning task by normal monkeys (Normal; $n = 10$), monkeys with medial temporal lobe lesions that did not include damage to area TE (No TE Damage; $n = 18$), and monkeys with medial temporal lobe lesions that did include damage to area TE (TE Damage; $n = 5$). A higher score on trials to criterion represents worse performance. $*p < .01$ relative to the normal group; $\dagger p < .01$ relative to the no TE damage group. The bars in B represent the performance on the delayed nonmatching to sample task by normal monkeys (Normal; $n = 10$), monkeys with medial temporal lobe lesions that did not include damage to area TE (No TE Damage; $n = 18$), and monkeys with medial temporal lobe lesions that did include damage to area TE (TE Damage; $n = 5$). A higher score on percentage correct represents better performance. $*p < .01$ relative to the normal group.

between the amount of damage to the structures that were measured and performance on the two behavioral tasks, $\chi^2(10, N = 23) = 60.92, p < .001$. Two canonical variates were significant in describing these data sets. Because the second and weaker of the two canonical variates was significant, $\chi^2(4, N = 23) = 18.35, p < .005$, both canonical variates could be interpreted. As shown in Table 4, Canonical Variate 1 weighted heavily on the amount of damage to area TE (0.672) and on performance on the concurrent discrimination learning task (0.841). The other canonical variate weighted heavily on the amount of damage to each of the medial temporal lobe structures measured: the PR cortex (−0.696), PH cortex (−0.733), ER cortex (−0.963), and the hippocampal region (−0.677) and on performance on the DNMS task (0.974). The second variate also weighted to a lesser extent on the amount of area TE damage (−0.377). These findings indicate that area TE is relatively more important for performance on the concurrent discrimination learning task than is any medial temporal lobe structure. By contrast, medial temporal lobe structures and to some extent area TE are all important for performance of the DNMS task.

Table 4
*Canonical Correlation Analyses for Two Behavioral Tasks*

| Area and task | Canonical variate 1 | Canonical variate 2 |
|---|---|---|
| Area TE | 0.672 | −0.377 |
| PR cortex | −0.028 | −0.696 |
| PH cortex | 0.457 | −0.733 |
| ER cortex | 0.103 | −0.963 |
| H | 0.287 | −0.677 |
| Concurrent discrimination | 0.841 | −0.541 |
| Delayed nonmatching to sample | 0.225 | 0.974 |

*Note.* PR = perirhinal; PH = parahippocampal; ER = entorhinal; H = hippocampal region.

## Discussion

In monkeys with medial temporal lobe lesions ($n = 23$), the amount of inadvertent damage to area TE was predictive of performance on the concurrent discrimination learning task. Specifically, as the amount of damage to area TE increased, the monkeys' performance on this task worsened (see Figure 5A). In contrast, whereas inadvertent damage to area TE caused an impairment on the concurrent discrimination learning task, no impairment was observed at all when there was no damage to area TE (see Figure 6A). In particular, the amount of damage to the PR cortex bore no relationship to performance on the concurrent discrimination learning task (Figure 5B). For example, 2 monkeys had

lesions that damaged approximately 85 and 90% of the PR cortex, respectively, and these monkeys performed normally on the concurrent discrimination learning task (trials to criterion = 360 and 400, respectively). Thus, area TE was more important than any medial temporal lobe structure for performance of the concurrent discrimination learning task.

We suggest that previous inconsistent findings regarding the concurrent discrimination learning task and medial temporal lobe lesions in monkeys can be resolved by understanding the impact on performance of unintended damage to area TE. Both in our own earlier work and in other studies, impaired concurrent discrimination learning following lesions of medial temporal lobe structures appears to have been due to inadvertent damage to area TE. Indeed, inadvertent damage to area TE was evident even in the first published reports of medial temporal lobe lesions and concurrent discrimination learning (Correll & Scoville, 1965, 1970).

Most previous studies that investigated the effects of area TE lesions, rather than medial temporal lobe lesions, were based on earlier interpretations of the border between area TE and the PR cortex (Iwai & Mishkin, 1968; Moss et al., 1981; Phillips et al., 1988). Therefore, these earlier studies left open the possibility that behavioral impairments attributed to area TE damage were actually due to the involvement of PR cortex. In the present study, analysis of the amount of damage to area TE and the PR cortex was based on the more recent understanding of the border between these two cortical regions. We found that damage to area TE, and not damage to the PR cortex, is the cause of impaired concurrent discrimination learning.

This conclusion is strengthened by preliminary findings from monkeys with circumscribed lesions of area TE who were given the concurrent discrimination learning task (Buffalo et al., 1995). Five monkeys were prepared with intended bilateral circumscribed lesions of area TE, using the revised neuroanatomical criteria of Suzuki and Amaral (1994a). The performance of this group was compared to that of 7 unoperated control monkeys and 5 monkeys with intended bilateral lesions of the PR cortex, also prepared using the revised neuroanatomical criteria of Suzuki and Amaral (1994a). The TE group was impaired on the concurrent discrimination learning task (normal group = 488 trials to criterion; TE = 933 trials to criterion; $p < .05$). By contrast, the PR group was unimpaired on this task (normal group = 488 trials to criterion; PR = 639 trials to criterion; $p > .1$). These findings are preliminary, because histological material is thus far available for only 1 monkey in the TE group (monkey TE 1, presented in the present study).

It is important to note that the monkeys' poor performance on the concurrent discrimination learning task was due to the amount of damage they sustained to area TE and not simply to the amount of overall tissue damage. We identified all the lesioned monkeys in this study that sustained moderate-to-extensive damage to medial temporal lobe structures accompanied by minimal damage to area TE, that is, a score of .5 or less (monkeys $H^+A^+$ 3, $H^+$ 1, $H^+$ 2; see Table 2). By contrast, monkey TE 1 sustained no damage to medial temporal lobe structures but sustained extensive damage to area TE. We determined the amount of overall tissue damage in these 4 monkeys in the following way. First, using unfolded maps of the temporal lobes of 5 normal monkeys (Suzuki & Amaral, 1994a; Figure 11), we determined the volume of each of the medial temporal lobe structures as well as area TE. We then used the amount of damage each monkey sustained to each structure (see Table 2) to compute the amount of overall tissue damage for each monkey. Monkeys $H^+A^+$ 3, $H^+$ 1, and $H^+$ 2 had approximately 198%, 93%, and 96% more overall tissue damage respectively than monkey TE 1, yet their scores on the concurrent discrimination learning task were lower than that of monkey TE 1 (trials to criterion: $H^+A^+$ 3 = 760; $H^+$ 1 = 760; $H^+$ 2 = 720; TE 1 = 1,040). These data confirm that poor performance on this task is due specifically to area TE damage and cannot be attributed to a mass action effect.

We suggest that the concurrent discrimination learning task can be accomplished as a task of habit learning. An earlier factor analysis of tasks used to measure memory in the monkey suggested that the concurrent discrimination learning task shares features with pattern discrimination learning (Zola-Morgan et al., 1994). Like pattern discrimination learning, concurrent discrimination learning in monkeys exhibits characteristics of skill or habit learning. Both of these tasks are acquired gradually across several hundred trials and could depend on acquiring a set of object-reward dispositions. The present findings provide additional support for this idea by showing that the concurrent discrimination learning task, like the pattern discrimination task, can be acquired normally despite medial temporal lobe damage.

It is interesting to note that humans acquire the concurrent discrimination learning task, as well as the pattern discrimination task, declaratively, not as habits (Oscar-Berman & Zola-Morgan, 1980; Squire et al., 1988). Although monkeys acquire both tasks incrementally, humans approach these tasks as problems of memorization, in the same way that they approach the learning of items, lists, and facts. That is, humans explicitly attempt to memorize the correct stimulus in each pair. Human amnesic patients are impaired at concurrent discrimination learning, and their success at the task correlates with their ability to describe the objects used in the test (Squire et al., 1988). Clearly, two factors that have impeded analyses of the concurrent discrimination learning task are that (a) some memory tasks can in principle be solved either declaratively or nondeclaratively; and that (b) humans and monkeys may use fundamentally different strategies to learn the same task.

The current findings provide evidence, within the visual modality, of a distinction between the functions of area TE and the PR cortex. PR cortex is a component of the medial temporal lobe memory system important for declarative memory. Area TE is important for performance on the concurrent discrimination learning task. Phillips et al. (1988) proposed that area TE may be part of a corticostriatal system that associates cortical sensory inputs with extrapyramidally generated motor outputs, thus yielding the simulus–response bonds that constitute habits. However, as Phillips et al. (1988) emphasized, area TE is also part of a corticolimbic system that translates visual perception into visual declara-

tive memories. Area TE originates a major input to the PR cortex (Suzuki et al., 1994a) and is well situated to play a critical role in visual declarative memory. Indeed, damage to area TE impairs visual recognition memory performance as measured by the DNMS task (Buffalo, Zola-Morgan, & Squire, 1994; Malkova et al., 1995, Mishkin, 1982). Thus, cortical area TE participates in both visual declarative memory and visual habit memory. The PR cortex is a component of the medial temporal lobe memory system and an anatomical target of area TE. It is important for forming visual declarative memories but not visual habit memories.

In a recent report (Buckley & Gaffan, 1997), 3 monkeys with lesions of the PR cortex were mildly impaired at relearning a preoperatively acquired concurrent discrimination learning set using 20 pairs of objects and a 24-hr intertrial interval. However, in this report, all of the monkeys with lesions of the PR cortex also sustained inadvertent damage to area TE. Additionally, the monkey who obtained the most impaired score on relearning the preoperatively acquired concurrent discrimination learning set was the monkey who sustained the most damage to area TE. Accordingly, the findings from this study are wholly consistent with the idea that performance on concurrent discrimination learning is dependent on the integrity of area TE.

The stimuli used in the concurrent discrimination learning task and the visual DNMS task were three-dimensional, multicolored junk objects. These are the kind of stimuli that should normally be processed by visual area TE (Gross, Rocha-Miranda, & Bender, 1972; Tanaka, 1996). It is, therefore, not surprising that damage to area TE impairs performance on both tasks. At the same time, it should be possible to demonstrate normal performance by monkeys with area TE damage on visual discrimination tasks involving simpler stimuli, which could be processed by visual areas upstream from area TE (e.g., area TEO). The present study, therefore, provides a clue to how a complete double dissociation between area TE and the PR cortex might be demonstrated. Specifically, on a declarative memory task using simple, easily discriminable visual stimuli (Zola-Morgan & Squire, 1984), monkeys with PR cortex damage should be impaired whereas monkeys with area TE damage might be unimpaired. By contrast, on a task involving complex visual stimuli that can be acquired as a habit, monkeys with PR damage should be unimpaired while monkeys with area TE damage should be impaired. The present findings provide evidence supporting the second component of this double dissociation. Performance on the concurrent discrimination learning task with complex visual stimuli, which we suggest is a task of habit memory, depends on area TE and not on the PR cortex.

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