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Severity of Memory Impairment in Monkeys as a Function of Locus and Extent of Damage Within the Medial Temporal Lobe Memory System

Stuart Zola-Morgan,* Larry R. Squire,*,† and Seth J. Ramus‡

*Veterans Affairs Medical Center and Departments of Psychiatry and †Neurosciences, School of Medicine and ‡Group in Neurosciences, University of California, San Diego

ABSTRACT

During the past decade, work with monkeys has helped identify the structures in the medial temporal lobe that are important for memory: the hippocampal region (including the hippocampus proper, the dentate gyrus, and the subicular complex) and adjacent cortical areas that are anatomically linked to the hippocampus, i.e., the entorhinal, perirhinal, and parahippocampal cortices. One idea that has emerged from this work is that the severity of memory impairment might increase as more components of the medial temporal lobe are damaged. We have evaluated this idea directly by examining behavioral data from 30 monkeys (ten normal monkeys and 20 monkeys with bilateral lesions involving structures within the medial temporal lobe) that have completed testing on our standard memory battery during the last 10 years. The main finding was that the severity of memory impairment depended on the locus and extent of damage to the medial temporal lobe. Specifically, damage limited to the hippocampal region produced a mild memory impairment. More severe memory impairment was produced when the damage was increased to include the adjacent entorhinal and parahippocampal cortices (the H^+ lesion). Finally, memory impairment was even more severe when the H^+ lesion was extended forward to include the anterior entorhinal cortex and the perirhinal cortex (H^{++} lesion). Taken together, these findings suggest that, whereas damage to the hippocampal region produces measurable memory impairment, a substantial part of the severe memory impairment produced by large medial temporal lobe lesions in humans and monkeys can be attributed to damage to entorhinal, perirhinal, and parahippocampal cortices adjacent to the hippocampal region. ©1994 Wiley-Liss, Inc.§

Key words: hippocampus, perirhinal cortex, entorhinal cortex, parahippocampal cortex, nonhuman primate

During the past decade, research with nonhuman primates has been successful in establishing an animal model of human amnesia and in identifying the structures in the medial temporal lobe that are essential for memory (for reviews, see Mishkin, 1982; Murray, 1992; Squire and Zola-Morgan, 1991; Zola-Morgan and Squire, 1993). The important structures are the hippocampus (together with the dentate gyrus and the subicular complex) and the adjacent perirhinal, entorhinal, and parahippocampal cortices (Fig. 1) (Squire and Zola-Morgan, 1991). The amygdala does not play an important role (Squire and Zola-Morgan, 1991; Murray, 1992). The medial temporal lobe system is necessary for establishing long-term declarative memory, i.e., the capacity for conscious recollection of facts and events (Squire, 1992).

Address correspondence and reprint requests to Stuart Zola-Morgan, Department of Psychiatry 0603, U.C.S.D. School of Medicine, La Jolla, CA 92093.

One idea that has emerged from the work with monkeys is that the severity of memory impairment might increase as more components of the medial temporal lobe memory system are damaged. For example, it has been noted that memory impairment is more severe when the perirhinal cortex is damaged together with other medial temporal lobe structures than when the perirhinal cortex is not damaged (Zola-Morgan et al., 1989c, 1993, Meunier et al., 1993).

This idea is also supported by findings from studies of human amnesia. The well-studied patient R.B. exhibited moderately severe memory impairment following bilateral damage limited to the CA1 region of the hippocampus (Zola-Morgan et al., 1986). However, patient H.M., who sustained bilateral resection of the medial temporal lobe, including the hippocampus and cortex adjacent to the hippocampus, exhibits more severe memory impairment than patient R.B. (Corkin, 1984; Scoville and Milner, 1957). Taken together, the findings from patients R.B. and H.M. make two points. First, damage to the hippocampus itself is sufficient to produce a clinically significant and long-lasting memory impairment. Second, ad-

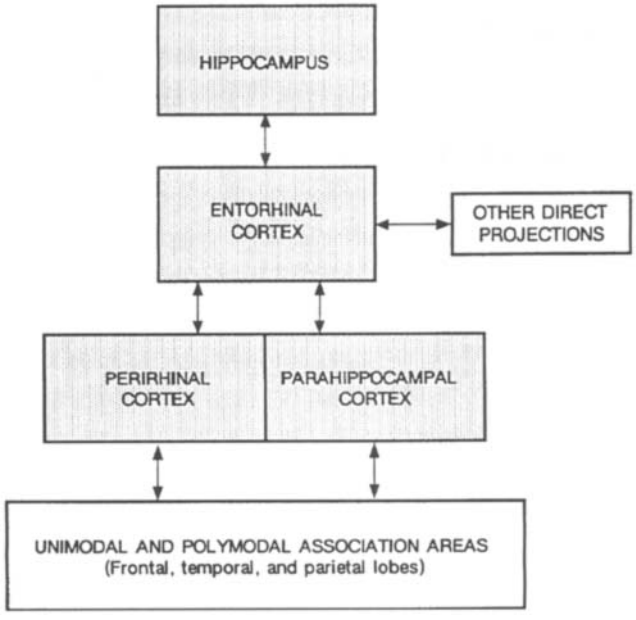

Fig. 1. A schematic view of the medial temporal lobe memory system. the entorhinal cortex is the major source of projections to the hippocampus. Nearly two-thirds of the cortical input to the entorhinal cortex originates in the adjacent perirhinal and parahippocampal cortices, which in turn receive projections from unimodal and polymodal areas in the frontal, temporal, and parietal lobes. The entorhinal cortex also receives other direct inputs from orbital frontal cortex, cingulate cortex, insular cortex, and superior temporal gyrus. All these projections are reciprocal. (From Squire and Zola-Morgan, 1991.)

ditional damage to the cortical regions adjacent to the hippocampus exacerbates the memory impairment.

The findings from monkeys and from human amnesia raise additional questions about the contribution to memory function of the structures within the medial temporal lobe. Does damage limited to the hippocampus typically produce only a modest level of memory impairment relative to larger lesions? When cortical damage is present in addition to hippocampal damage, e.g., damage to parahippocampal cortex adjacent to the hippocampus, is the memory impairment more severe? Is the memory impairment even more severe when the cortical damage is further increased to include more components of the medial temporal lobe memory system?

Individual studies can address these issues to some extent. However, in work with monkeys single studies are ordinarily limited to comparisons between two or three groups that consist of a small number of animals (usually three to five monkeys per group). In the present report, we were able to examine the behavioral data from all 42 monkeys that have completed testing on our standard memory battery during the past 10 years (ten normal monkeys and 32 monkeys with bilateral lesions involving structures within the medial temporal lobe; Table 1). These data are amenable to comparisons among groups because all 42 animals were tested using the same five tasks administered in the same order.

We first submitted the data from the 42 monkeys for each of the five tasks to a correlational analysis and a factor analysis.

Table 1. Four Sets of Monkeys Derived From Nine Previously Studied Groups*

Set	Group	n	References to behavioral and neurohistological findings
N	N	10	Zola-Morgan et al. (1992) (n = 7) Suzuki et al. (1993) (n = 3)
	A	3	Zola-Morgan et al. (1989b)
	A	4	Zola-Morgan et al. (1991)
	H	5	Unpublished
H	H	4	Clower et al. (1991); present report
	ISC	4	Zola-Morgan et al. (1992)
H⁻	H⁻	5	Zola-Morgan et al. (1989a) (n = 3) Zola-Morgan et al. (1993) (n = 2)
	H⁻A	3	Zola-Morgan et al. (1989b)
H⁻⁻	H⁻⁺	4	Zola-Morgan et al. (1993)

*Boxed groups were used only for the correlational and factor analyses (see text). Brackets show how the nine previously studied groups were arranged into one set of normal monkeys (N) and three sets of experimental monkeys (H, H⁻, and H⁻⁻) based on the locus of the lesion. These sets of monkeys were used to analyze how the severity of memory impairment was affected by variation in the extent of damage to the medial temporal lobe memory system. Nomenclature: N, normal monkeys. A, bilateral lesions of the amygdaloid complex; A⁻, bilateral incomplete lesions of the amygdaloid complex; H⁻, bilateral incomplete lesions of the hippocampus proper, the dentate gyrus, and the subicular complex; H, bilateral lesions of the hippocampus proper, the dentate gyrus, and the subicular complex; ISC, ischemia-induced lesions that resulted in significant bilateral loss of pyramidal cells in the CA1 and CA2 fields of the hippocampus proper and of somatostatin-staining cells in the dentate gyrus; H⁻, bilateral lesions that included the hippocampus proper, the dentate gyrus, the subicular complex, the posterior entorhinal cortex, and the parahippocampal cortex; H⁻A, same as H⁻ but also including the amygdaloid complex; H⁻⁺, same as H⁻ but also including the anterior entorhinal cortex and the perirhinal cortex.

With these analyses (see below), we sought to identify tasks that were strongly intercorrelated and sensitive to medial temporal lobe damage and other tasks that were intercorrelated but less sensitive or insensitive to medial temporal lobe damage. The data from the three tasks that proved to be sensitive to medial temporal lobe damage were then used to explore the relationship between the severity of memory impairment and the locus and extent of damage within the medial temporal lobe memory system. Of the 32 monkeys with lesions that contributed data to the correlational analysis and the factor analysis, the data from 20 monkeys representing five well-defined surgical groups (Table 1) were carried forward to the main analysis to consider how variations in the locus and extent of damage affected memory.

MATERIALS AND METHODS

Subjects

Forty-two cynomolgus monkeys (*Macaca fascicularis*) were used (Table 1). All monkeys weighed between 3.5 and 6 kg at the beginning of behavioral testing and were estimated to be

3–5 years old (i.e., young adults: Szabo and Cowan, 1984; Hartley et al., 1984). All but four monkeys were male.

Surgery and neurohistological analysis

The surgical procedures for all of the operated groups and detailed neurohistological analyses for all of the operated groups except the H group (see below) can be found in the corresponding references in Table 1. The lesions in three of the groups (H^+, H^{++}, and A^-; see Table 1 for nomenclature) were made by aspiration using a neurosurgical approach under direct vision. The lesions in three other groups (A, H, and H^-) were made by radiofrequency using a stereotaxic approach (see Alvarez-Royo et al., 1991) for the technique used for making H lesions). One group (H^+A) was prepared using a combination of radiofrequency (the amygdala lesion) and aspiration techniques (the hippocampal formation lesion). Finally, one group (ISC) was prepared using a noninvasive procedure that involved an inflatable neck cuff and pharmacologically induced hypotension for producing reversible cerebral ischemia. All of the 42 monkeys were given a standard battery of memory tests (see Behavioral Testing).

Analysis of the lesions in the H group

Three of the four monkeys (H1–H3) in the H group have completed behavioral testing. Their brains were processed and analyzed using standard neurohistological techniques (Zola-Morgan et al., 1993). The fourth monkey (H4), is still undergoing additional behavioral testing, and high-resolution MR images were used to estimate the extent of damage for this monkey.

Figure 2 illustrates the extent of damage in monkeys H1–H3, based on neurohistological analysis of brain tissue. Figure 3 shows photomicrographs of representative sections through the temporal lobe from monkey H1.

All the monkeys in the H group sustained substantial bilateral damage to the hippocampal region (i.e., the hippocampus proper, the dentate gyrus, and the subicular region) along most of its anteroposterior extent. The mean percent damage to the hippocampal region for the four H monkeys was 51%. It was intended that the most anterior portion and the most posterior portion of the hippocampal region be spared to insure that the amygdala and visual cortex, respectively, would not be damaged. Accordingly, these portions of the hippocampal region sustained only mild to moderate damage.

The amygdala and perirhinal cortex were spared bilaterally in all four animals. There was slight-to-moderate cell loss in layer II of the posterior portion of the entorhinal cortex in monkeys H1–H3, mainly on the left side. This cell loss presumably resulted from retrograde degeneration and it corresponds roughly to the extent of damage to the dentate gyrus. Monkey H3 sustained slight damage to the entorhinal cortex on the left side and moderate damage to the entorhinal cortex on the right side. Animal H2 sustained slight unilateral damage to the parahippocampal cortex and animal H3 sustained moderate and asymmetric damage to the parahippocampal cortex. There was also slight to moderate, and asymmetric, damage in all four of the animals to white matter subjacent to the posterior extent of the hippocampal region (Fig. 2). This damage was typically limited to the white matter in the region of the angular bundle. This region contains mainly fibers of the perforant path that originate in the entorhinal cortex and terminate in the molecular layer of the dentate gyrus (Insausti et al., 1987). In addition, this region contains afferent and efferent fibers of the adjacent subicular region. Two animals (H2 and H3) had unilateral damage to the tail of the caudate nucleus.

Behavioral testing

All behavioral testing was carried out in a Wisconsin General Testing Apparatus (Harlow and Bromer, 1938). There was no preoperative testing. Four to 8 weeks after surgery, monkeys were given four to six sessions of pretraining 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. Upon completion of pretraining, all monkeys were tested on the following tasks in the same order: 1) trial-unique delayed nonmatching to sample; 2) pattern discrimination learning; 3) delayed retention of object discriminations; 4) concurrent discrimination learning; 5) retest of trial-unique delayed nonmatching to sample. Some monkeys also received additional testing after completing these tasks.

Trial-unique delayed nonmatching to sample

On each trial, monkeys first displaced an object that covered the central food well and obtained a raisin reward (the sample phase). An opaque door was lowered for 8 s to block the monkey's view of the food wells. When the door was raised, monkeys saw two objects, the original object and a new one, which covered the two lateral food wells. They displaced the new object to obtain the raisin (the choice phase). The position of the correct object (over the left or right food well) varied pseudorandomly on each trial (Gellerman, 1933). Twenty such trials were presented daily, and each trial used a new pair of objects selected from a collection of more than 300 objects. After monkeys obtained learning criterion on the 8-s task (90 correct choices in 100 trials), they were tested at successively longer delays of 15 s, 60 s, and 10 min between the sample and choice phases of each trial. One hundred trials were given at the 15-s and 60-s delays (20 trials/day), and 50 trials were given at the 10-min delay (5 trials/day).

Pattern discrimination

Monkeys learned two different two-dimensional pattern discrimination problems. Monkeys first learned to discriminate a plus sign from a square, and then they learned to discriminate an N from a W. For each problem, the position of the correct stimulus (over the left or right food well) varied pseudorandomly on each trial (Gellerman, 1933). Thirty trials per day were given, and training continued until animals achieved a learning criterion of at least 90% correct performance on 2 consecutive days. (Nine monkeys [three in the N group, three in the H^+ group, and the three monkeys in the H^+A group] received 20 trials per day for the first discrimination problem and 30 trials per day for the second discrimination problem).

Delayed retention of object discriminations

During 2 days of training (20 trials per day), monkeys learned an easy two-choice object discrimination. After a 2-

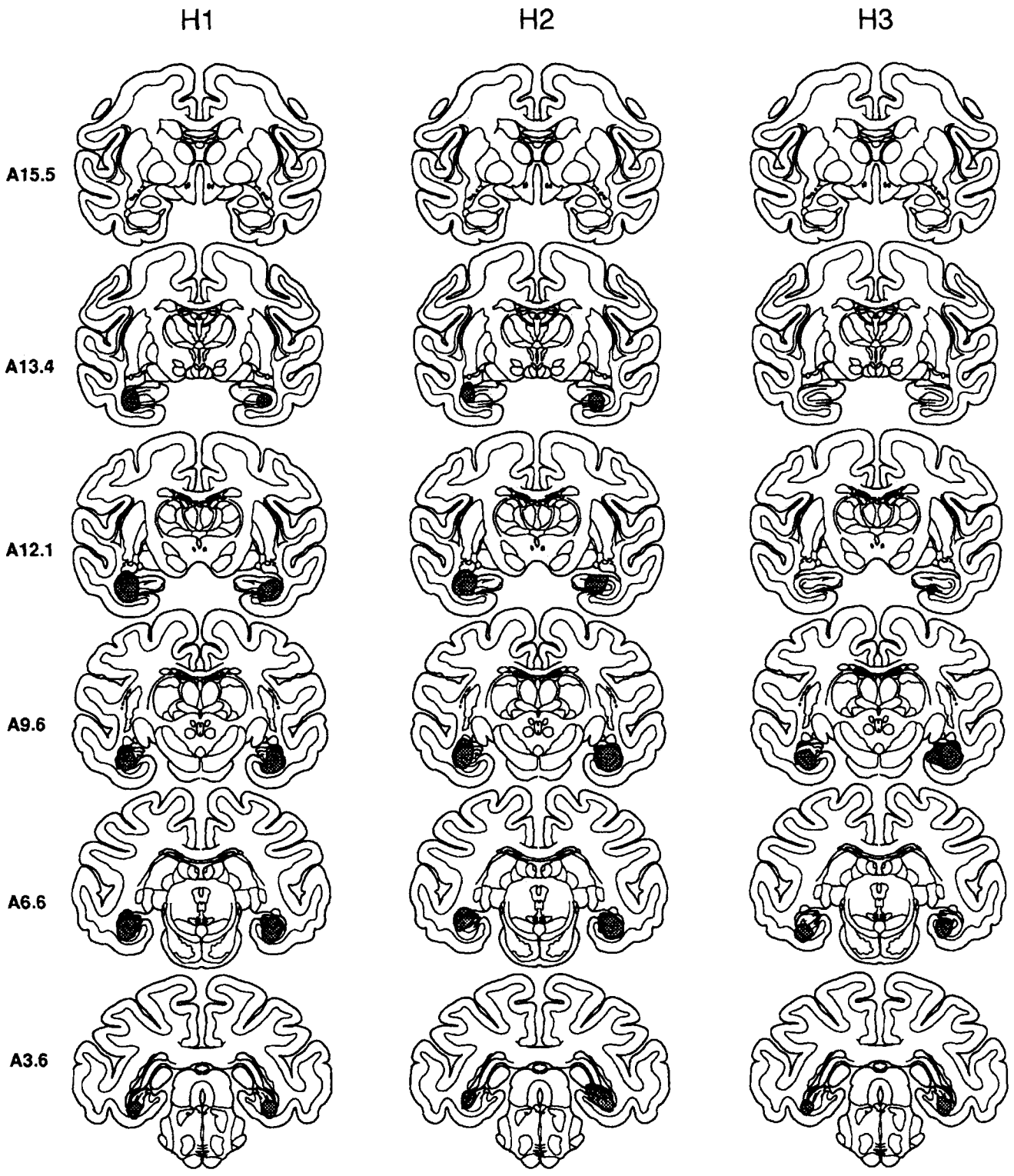

Fig. 2 Representative coronal sections through the brains of three of the four monkeys with the H lesion (H1–H3), based on neurohistological analysis of brain tissue. The anteroposterior level is indicated below each section, and the extent of damage is shown in black. Moderate bilateral damage to the entorhinal cortex was observed in one animal (H3).

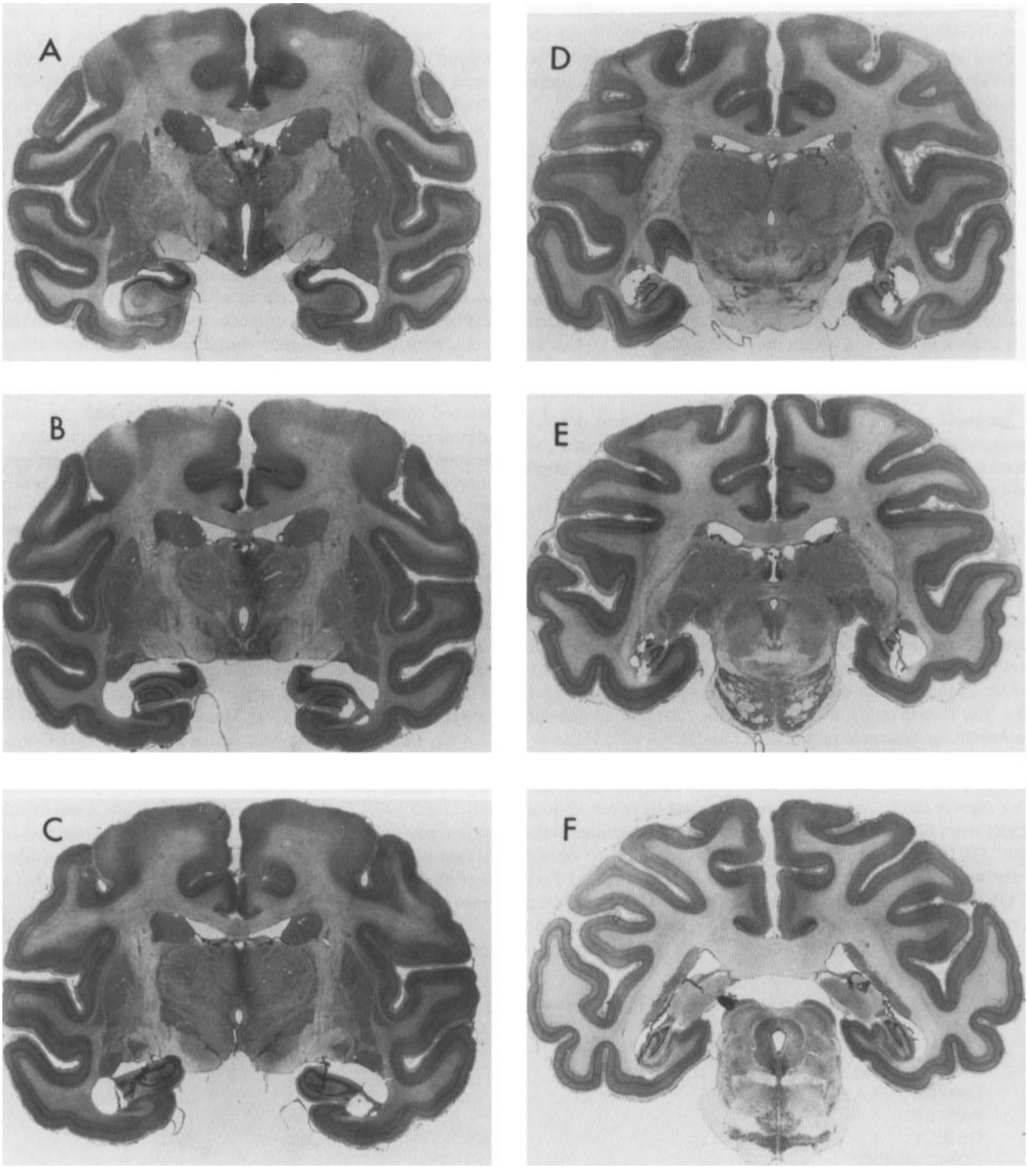

Fig. 3. Photomicrographs of representative sections through the temporal lobe of monkey H1. The sections are arranged from rostral (**A**) to caudal (**F**) and correspond approximately to anteroposterior levels A15.5–A3.6 in Figure 2. The most anterior portion of the hippocampus was intentionally spared (see text). The lesion involved much of the remaining hippocampal region bilaterally (including the dentate gyrus) throughout its anteroposterior extent. The subiculum sustained slight damage bilaterally in its anterior extent. The amygdala, perirhinal cortex, and entorhinal cortex were spared. Posteriorly, there was slight damage to the white matter subjacent to the posterior extent of the hippocampus.

day delay, memory was tested by administering another session of 20 trials. Monkeys were given four separate object-discrimination tasks. For each task, the position of the correct stimulus (over the left or right food well) varied pseudorandomly on each trial (Gellerman, 1933).

Concurrent discrimination learning

Monkeys learned eight different object discrimination pairs simultaneously. Presentation of the eight pairs was intermixed so that each pair was presented five times during the course of a single session (40 trials per day). The same object in each pair was always correct, and its position varied randomly according to a Gellerman (1933) sequence. Training continued until a learning criterion of 39 correct responses in 40 consecutive trials was achieved within one test session.

Delayed nonmatching to sample retest.

Six to 41 months after administration of the first delayed nonmatching to sample task (mean interval = 16 months), all monkeys were retested on the delayed nonmatching to sample task exactly as it had been given originally.

Correlational analysis

Six performance measures were derived from the five tasks in the test battery and analyzed using Pearson product–moment correlations: 1) the number of trials required to obtain learning criterion on the trial-unique delayed nonmatching to sample task the first time it was administered (DNMTS1-TRIALS); 2) the percent correct score averaged across the 15-s, 60-s, and 10-min delay intervals from the trial-unique delayed nonmatching to sample task (DNMTS1-DELAYS); 3) the average number of trials required to obtain learning criterion on the two-pattern discrimination tasks (PATTERN); 4) the percent correct score averaged across all 3 test days for all four object pairs of the delayed retention of object discriminations task (OBJECT); 5) the number of trials required to obtain learning criterion on the concurrent discrimination task (CONCURRENT); 6) the percent correct score averaged across the 15-s, 60-s, and 10-min delay intervals when the trial-unique delayed nonmatching to sample task was administered the second time (DNMTS2-DELAYS). (The number of trials required to obtain learning criterion when the trial-unique delayed nonmatching to sample task was readministered was not used in these analyses. More than half of the monkeys [24 of 42] obtained a score of 0 trials on this part of the task, i.e., they required no additional training beyond the 100 trials required to obtain learning criterion).

RESULTS

Correlational analysis

Table 2 shows the correlation matrix for the six performance measures. The correlational analysis indicated that the scores of four of the performance measures, drawn from three tasks, were strongly intercorrelated: the first administration of the trial-unique delayed nonmatching to sample test (whether measured by trials to criterion or performance across delays), delayed retention of object discriminations, and the second administration of the trial-unique delayed nonmatching to sample test (delay portion). These three tasks are performed poorly by amnesic patients (Squire et al., 1988; Zola-Morgan and Squire, 1990), and the tasks are sensitive to medial temporal lobe damage in monkeys (Squire and Zola-Morgan, 1991).

The correlational analysis also identified that the scores of two other tasks were strongly correlated: pattern discrimination learning and concurrent discrimination learning. Pattern discrimination learning has long been proposed to be a skill-like task for monkeys (Iversen, 1976; Squire and Zola-Morgan, 1983), and monkeys with medial temporal lobe lesions learn pattern discriminations as well as or nearly as well as normal monkeys (Orbach et al., 1960; Mahut, 1971, 1972; Correll and Scoville, 1965, 1970; Zola-Morgan and Squire, 1984). Concurrent discrimination learning can be sensitive to medial temporal lobe damage, but the results have been mixed (Zola-Morgan and Squire, 1985; Zola-Morgan et al., 1993). Thus, it was of interest that performance on the concurrent discrimination task correlated with performance on the delayed retention of object discriminations task but not with any of the other tasks that are sensitive to medial temporal lobe lesions.

These findings lead to an interesting suggestion about the concurrent discrimination learning task; namely, that it may

Table 2. Correlation Matrix for the Six Measures From the Test Battery†

	DNMTS1-DELAYS	PATTERN	OBJECT	CONCURRENT	DNMTS2-DELAYS
DNMTS1-TRIALS	−.50*	−.14	−.56*	.11	−.52*
DNMTS1-DELAYS		.28	.46*	.10	.60*
PATTERN			−.04	.43*	−.10
OBJECT				−.42*	.69*
CONCURRENT					−.18

†The Pearson product moment correlation coefficients are shown for all pairings of six measures derived from the battery of five tasks. Abbreviations: DNMTS1-TRIALS, the No. of trials required to obtain learning criterion on the trial-unique delayed nonmatching to sample task the first time it was administered; DNMTS1-DELAYS, the percent correct score averaged across the 15-s, 60-s, and 10-min delay intervals from the first administration of the trial-unique delayed nonmatching to sample task; PATTERN, the average No. of trials required to obtain learning criterion on the two pattern discrimination tasks; OBJECT, the percent correct score averaged across all 3 test days for all four object pairs of the delayed retention of object discriminations task; CONCURRENT, the No. of trials required to obtain learning criterion on the concurrent discrimination task; DNMTS2-DELAYS, the percent correct score averaged across the 15-s, 60-s, and 10-min delay intervals from the retest of the trial-unique delayed nonmatching to sample task.

*Indicates significant correlations (all $Ps < 0.01$).

be amenable to more than one learning strategy. The correlation between concurrent discrimination and the object discrimination task suggests that the concurrent discrimination task can be approached like other tasks sensitive to medial temporal lobe damage in humans and monkeys. Human amnesic patients perform poorly on the concurrent discrimination task (Squire, et al., 1988) because they attempt to memorize which object in each pair is the correct one. Several studies with rats that involved the concurrent task (using six to eight discrimination pairs) have also reported impaired performance following lesions of fimbria-fornix (Wible et al., 1992; Aggleton et al., 1992), hippocampus (Wible et al., 1992; Mumby et al., 1992), or entorhinal cortex (Rothblatt et al., 1991). Nevertheless, the concurrent discrimination task is not always sensitive to even larger medial temporal lobe lesions, whereas the object discrimination task is sensitive to such lesions (Zola-Morgan et al., 1993). We previously reviewed a large number of primate lesion studies and discrimination tasks (Squire and Zola-Morgan, 1983). The findings were that those tasks that are normally learned fastest (e.g., simple object discriminations) are more likely to depend on the integrity of the medial temporal lobe than tasks that are normally learned slowly (e.g., difficult discrimination tasks including concurrent discrimination tasks). We suggested that easier tasks are more likely to be approached as a problem for memorization, i.e., using a declarative strategy, whereas more difficult tasks, which are learned gradually, are more amenable to habit learning.

The correlation between the concurrent discrimination and the pattern discrimination task suggests that monkeys might approach the concurrent discrimination task in the same way that pattern discriminations are learned, that is, as win–stay, lose–shift habits that are acquired gradually as a set of dispositions. Studies in rats and monkeys have identified that win–stay discrimination habits can depend on the integrity of the neostriatum and can be unaffected by damage to the hippocampus or related structures (Divac et al., 1967; Packard et al., 1989; Wang et al., 1990; McDonald and White, 1993).

In summary, the results of the correlational analysis indicate that performance on three tasks are intercorrelated (trial-unique delayed nonmatching to sample, delayed retention of object discriminations, and the retest of trial-unique delayed nonmatching to sample, delay portion). In addition, the concurrent discrimination task was significantly related to only one of these three tasks (delayed retention of object discriminations), and it was also significantly related to pattern discrimination. The findings from the factor analysis, described next, reinforce these conclusions.

Factor analysis

Factor analysis was used to describe further the relationship among the task measures. Principal-components extraction from the scores of all 42 monkeys across all six measures identified two factors (Table 3). These two factors accounted for over 70% of the variance in the scores (eigenvalues: Factor 1 = 2.64, Factor 2 = 1.57). Additional factors were not substantial (Factor 3 eigenvalue = 0.653). A varimax rotation of the factors was computed, and the resulting factor loadings are reported in Table 3. Four measures loaded strongly on the first factor, i.e., DNMTS1-TRIALS, DNMTS1-DELAYS, OBJECT, and DNMTS2-DELAYS. Two measures, PATTERN and CONCURRENT, both loaded strongly on the second factor.

The results of the factor analysis make two important points. First, four measures (derived from three tasks) were closely related. Thus, performance on these three tasks appeared to be importantly influenced by a single shared factor. This factor likely reflects the dependence of all three tasks on the integrity of the medial temporal lobe.

Second, the concurrent discrimination learning task (the CONCURRENT measure) was more closely linked to pattern discrimination learning (the PATTERN measure) than to any of the other four measures of memory (Table 3). This finding was consistent with the results from the correlational analysis in which the CONCURRENT measure correlated strongly with the PATTERN measure. Thus, performance on the pattern and concurrent discrimination learning tasks depends on a factor not shared with the other learning tasks. This factor likely reflects the importance to both tasks of skill-based abilities that are independent of the medial temporal lobe.

The findings from the correlational analysis and the factor analysis, taken together, suggest that three tasks provide good measures of declarative memory. The concurrent discrimination task provides a less consistent and therefore less useful measure of this kind of memory. Accordingly, the main analysis to be described next, which explored the relationship between the severity of memory impairment and the locus and extent of damage within the medial temporal lobe memory system, was based on four measures from three tasks: the first administration of trial-unique delayed nonmatching to sample (DNMTS1-TRIALS and DNMTS1-DELAYS), delayed retention of object discrimination learning (OBJECT), and the second administration of delayed nonmatching to sample (DNMTS2-DELAYS).

Severity of memory impairment as a function of locus of damage within the medial temporal lobe memory system

The 30 monkeys whose data were used for the next analysis consisted of all the normal monkeys (n = 10) and monkeys from five previously defined surgical groups (n = 20). Of the 12 monkeys whose data were not carried forward to the next

Table 3. Factor Analysis for the Six Measures From the Test Battery*

Variable	Factor 1	Factor 2
DNMTS1-TRIALS	−.775	−.107
DNMTS1-DELAYS	.823	.255
DNMTS2-DELAYS	.827	−.136
OBJECT	.784	−.374
PATTERN	.151	.787
CONCURRENT	−.164	.855

*The factor-loadings in the two columns were based on principal-components extraction with varimax rotation from the scores of all 42 monkeys. The boxes outline the measures from the test battery that loaded strongly on each factor. Abbreviations: same as in Table 2.

analysis, three had damage limited to the amygdaloid complex (group A in Table 1) and performed normally on all the behavioral tasks. The remaining nine animals had either small and variable lesions of the hippocampal region that involved adjacent cortex (the five monkeys in group H^- in Table 1) or small lesions of the amygdala that involved adjacent cortex (the four monkeys in group A^- in Table 1). These animals exhibited a modest, significant impairment on some of the behavioral tasks, but the variable nature of the lesion made it difficult to classify the monkeys anatomically.

The five surgical groups (consisting of 20 operated monkeys) were arranged into three sets of animals based on the locus of the damage (Table 1). Set H consisted of eight monkeys with lesions limited to the hippocampus proper, the dentate gyrus, and the subicular complex, and was derived from groups H and ISC. [As reported previously, the overall performance scores for the H and ISC groups were similar (Zola-Morgan, et al., 1992)]. Set H^+ consisted of eight monkeys with lesions that included the hippocampus proper, the dentate gyrus, the subicular complex, the posterior entorhinal cortex, and the parahippocampal cortex, and was derived from groups H^+ and H^+A. ([As reported previously, the overall performance scores of the H^+ and H^+A groups were similar (Zola-Morgan, et al., 1989b)]. Set H^{++} consisted of four monkeys in which H^+ lesions were extended forward to include the anterior entorhinal cortex and the perirhinal cortex (group H^{++}). A fourth set (N) consisted of ten normal monkeys (group N).

For each of the four measures, the data from all 30 monkeys were converted to z scores. The conversion of the data to z scores permitted tasks that used different performance measures (e.g., the trials to criterion measure used for the delayed nonmatching to sample task and the percent correct measure used for the delayed retention of object discriminations task) to be compared with each other. For each monkey, an overall z score was computed by averaging the z scores obtained for the four measures. For three of the measures, DNMTS1-DELAYS, OBJECT, and DNMTS2-DELAYS, high scores represented good performance. For the DNMTS1-TRIALS measure, high scores represented poor performance. Accordingly, the z scores for the DNMTS1-TRIALS measure were multiplied by -1 to make them compatible with the other three measures.

Figure 4 shows the mean z scores obtained for the four sets of monkeys. A one-way analysis of variance revealed a significant overall effect ($F[3,29] = 45.8$, $P < 0.0001$). Individual pairwise comparisons were then carried out using the Newman-Keuls post-hoc test. These tests showed that each set of monkeys performed significantly differently from every other set ($P < 0.05$). Thus, set H performed more poorly than set N, set H^+ performed more poorly than set H, and set H^{++} performed more poorly than set H^+. Further analysis of the data indicated that the results were similar across all four task measures. A two-way analysis of variance (four groups and four task measures) revealed a significant effect of group ($F[3,29] = 45.8$, $P < 0.0001$), but no effect of task ($F[3,90] = 0.1$, $P > 0.10$) and no group $\times$ task interaction ($F[9,90] = 1.7$, $P > 0.10$).

Finally, a separate analysis using the same four sets of monkeys was carried out for the two measures (PATTERN and CONCURRENT) that loaded strongly on the second factor. A one-way analysis of variance based on the mean z scores for the four sets of monkeys revealed no significant difference ($F[3,29] = 1.3$, $P > 0.10$; N = 0.12, H = 0.20, $H^+ = -0.24$, $H^{++} = -0.21$). Thus, the performance of the monkeys on the PATTERN and CONCURRENT measures was not related to the extent of damage within the medial temporal lobe.

DISCUSSION

The important finding was that the severity of memory impairment following medial temporal lobe damage depended on the locus and extent of damage. Specifically, as measured by performance on three memory tasks (trial-unique delayed nonmatching to sample, delayed retention of object discriminations, and retest of trial-unique delayed nonmatching to sample), monkeys in set H exhibited a significant albeit mild memory impairment. When the damage was increased to include the adjacent entorhinal and parahippocampal cortex (set H^+), more severe memory impairment was observed. Finally, when damage was increased further to include the perirhinal cortex (set H^{++}), memory impairment was even more severe.

These findings make two important points. First, the finding that the damage in set H (consisting of the H and ISC groups) was sufficient to impair memory in monkeys supports the view that the hippocampus itself is critical for memory function. Figure 5 makes the point more clearly by presenting separately the findings for the H and ISC groups (mean z score: ISC group = + 0.26; H group = + .50, $P > 0.10$). Both groups performed better overall than the H^+ group (mean z score = −.50, Ps < 0.01). Thus, it seems unlikely that the ISC group had significant, widespread neuropathology in areas related to memory function beyond what was detected in the CA1 and hilar regions (Zola-Morgan et al., 1992). Moreover, both the ISC and the H groups must have less damage overall in areas related to memory function than the set of H^+ monkeys. (Work with monkeys has not yet identified the possible separate contributions of the hippocampus proper, the dentate gyrus, and the subicular complex; for further discussion, see Jarrard, 1993).

The second important point stems from the finding that the monkeys in set H^+ (consisting of the H^+ and H^+A groups) and the monkeys in set H^{++} (the H^{++} group) exhibited progressively more severe memory impairment than the monkeys in set H. This finding emphasizes the importance for memory functions of the cortical regions adjacent to the hippocampus, i.e., the entorhinal, parahippocampal, and perirhinal cortices.

Additional evidence for the importance of these cortical regions comes from work with monkeys who sustained large medial temporal lobe lesions involving the hippocampus and the amygdala (the H^+A^+ lesion; Zola-Morgan et al., 1982; Zola-Morgan and Squire, 1985) and who also sustained extensive damage to the cortical regions just described. The data from monkeys with H^+A^+ lesions (Zola-Morgan et al., 1982; Zola-Morgan and Squire, 1985) could not be used in the main analysis because the H^+A^+ group did not undergo the same version of the delayed nonmatching to sample retest as the other groups. However, a separate analysis was undertaken to compare the z scores of the H^+A^+ group to the z scores of the other groups on the three measures that all of the groups had in common (DNMTS1-TRIALS, DNMTS1-DELAYS, and

OBJECTS). The mean z score of the H^+A^+ group (−1.31) was significantly lower than the mean z scores for groups N(+ 0.79), H(+ 0.51), and H^+ (− 0.33; all Ps < 0.001) and not significantly different from the mean z score for group H^{++} (−1.11; $P > 0.10$).

Previous work has shown that the severe memory impairment associated with H^+A^+ lesions is due to the involvement of the cortical regions adjacent to the hippocampus and not to damage of the amygdala (Murray, 1992; Suzuki et al., 1993; Zola-Morgan et al., 1989b,c). The main z score analysis did not include data from the group of three monkeys with lesions limited to the amygdala (group A, Table 1). A separate analysis that included the data for group A supported the view that the amygdala does not play an important role in the kind of memory needed to perform the tasks described here. Unlike group H (mean z score, + 0.33), group A (mean z score, + 0.61) performed similarly to group N (mean z score, +0.73; $P > 0.10$) differently from groups H^+ (mean z score, −0.50; $P < 0.01$), and H^{++} (mean z score, −1.43; $P < 0.01$).

Previous data from our laboratory for monkeys with fornix lesions were also not included in the main z score analysis because (as with the H^+A^+ group) only three measures were available for the fornix group. A separate analysis was therefore undertaken to compare the z scores of the monkeys with fornix lesions to the z scores of the other groups on the three measures that all the groups had in common (DNMTS1-TRIALS, DNMTS-DELAYS, and OBJECTS). The mean z score for the fornix group (+0.45) was significantly higher than the mean z scores for groups H^+ (−0.39) and H^{++} (−1.27; Ps < 0.001), and not different from the z scores for groups N or H (Ps > 0.10).

The implication of these findings is that the cortical regions (i.e., the perirhinal, entorhinal, and parahippocampal cortices) are themselves important for memory function and that information need not reach the hippocampus itself in order for some memory storage to occur. This idea is supported by findings from several recent studies in which memory impairment occurred following damage to these cortical regions in monkeys (Gaffan and Murray, 1992; Meunier et al., 1993; Suzuki et al., 1993; Zola-Morgan et al., 1993) and rats (Otto and Eichenbaum, 1992). Indeed, the memory impairment following damage to the cortical regions alone can be quite severe. Figure 5 incorporates the data for two monkeys (PRPH 6 and PRPH 7) with conjoint bilateral damage to the perirhinal and parahippocampal cortices (the PRPH lesion). Of eight monkeys with this lesion, whose data have been reported previously (Zola-Morgan et al., 1989c; Suzuki et al., 1993), only these two monkeys completed testing on the same three tasks as all the other monkey groups. Thus, Figure 5 was constructed from the data for 32 monkeys (the original 30 monkeys from Figure 4 plus two monkeys with PRPH lesions). The addition of the two PRPH monkeys to the z score analysis had a negligible effect on the other z scores (the largest mean z score change for any set of monkeys from Figure 4 to Figure 5 was ± 0.13), and the pattern of findings reported above were unchanged. The mean z score for the two monkeys with PRPH lesions was − 0.93, a score significantly poorer than the mean z score for the H^+ animals (− 0.50, $P < 0.05$) and not significantly different from the mean z score of the H^{++} animals (−1.33, $P > 0.10$).

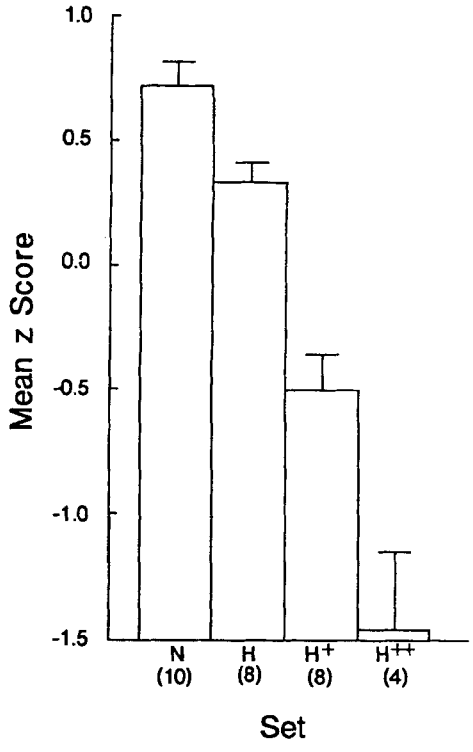

Fig. 4. Mean z scores based on the data from four measures of memory (Factor 1, Table 3) for ten normal monkeys (set N), eight monkeys with damage limited to the hippocampus proper, the dentate gyrus, and the subicular complex (set H), eight monkeys with damage that also included the adjacent entorhinal and parahippocampal cortices (set H^+), and four monkeys in which the H^+ lesion was extended forward to include the anterior entorhinal cortex and the perirhinal cortex (set H^{++}). As more components of the medial temporal lobe memory system were included in the lesion, the severity of memory impairment increased. All between-group comparisons were statistically significant. Error bars indicate standard errors of the mean.

Similar results were obtained when the data from three additional monkeys with PRPH lesions (PRPH 1–3; Zola-Morgan et al., 1989c) were included. Because these three monkeys were not administered all three tasks, the performance of all five PRPH monkeys and the monkeys in the comparison groups was evaluated by calculating a mean z score based on just three measures: DNMTS1-TRIALS, DNMTS1-DELAYS, and OBJECTS. The results were as follows: N group, + 0.80; H group, + 0.48 ; H^+ group, − 0.34; PRPH group, − 0.93; H^{++} group, −1.10. The five PRPH animals scored similarly to the H^{++} group ($P > 0.10$) and poorer than every other group (Ps < 0.01). The mean z score for the five monkeys with damage limited to the perirhinal and parahippocampal cortex was also not different from the mean z score for the H^+A^+ group described earlier (z score = − 0.99; $P > 0.10$). These data therefore provide additional support for the framework developed here; namely, damage to the cortical areas involved in the H^{++} lesion and in the H^+A^+ lesion (e.g., the perirhinal and parahippocampal cortices) is sufficient to produce severe memory impairment. Accordingly, these cortical areas them-

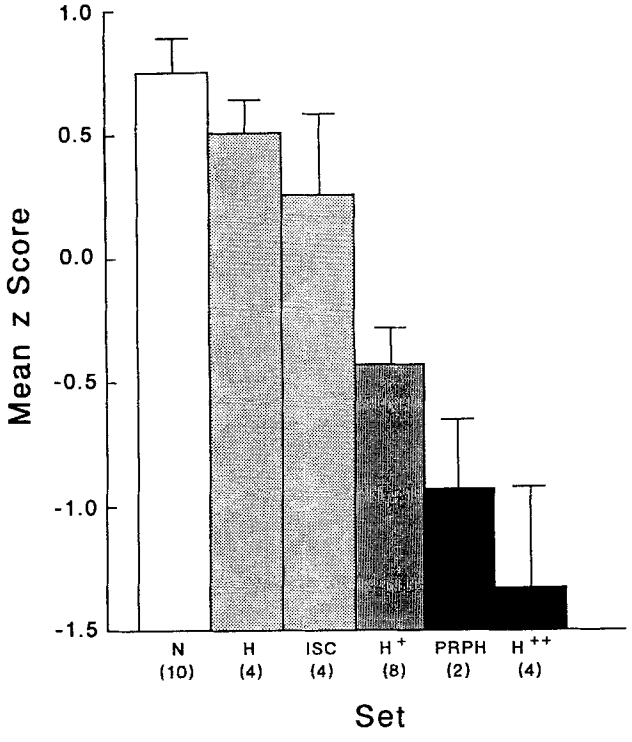

Fig. 5. Mean z scores based on the same groups of monkeys as in Figure 2 plus two monkeys with conjoint bilateral lesions of the perirhinal and parahippocampal cortices (PRPH). The two groups that constituted set H in Figure 2 are here presented separately (H and ISC). Error bars indicate standard errors of the mean.

selves, either separately or together, must contribute to memory function.

This conclusion is compatible with findings from humans. Patient R.B. exhibited moderately severe memory impairment following damage to the CA1 region of the hippocampus (Zola-Morgan et al., 1986). However, patient H.M., who sustained bilateral damage that included the hippocampus and adjacent cortex, exhibits more severe memory impairment than patient R.B. A similar point about the contribution to memory function of cortex adjacent to the hippocampus has been made in rodents based on the increasing effects on memory caused by increasing the extent of damage within the hippocampal formation (Jarrard, 1986; Morris et al., 1990).

The present findings cannot be explained by a principle like mass action (Lashley, 1929), whereby the severity of the deficit results simply from the extent of damage to medial temporal lobe tissue. When the H^+ lesion was extended forward to include the amygdala (the H^+A lesion), the memory impairment was not increased. Yet when the H^+ lesion was extended forward to include the perirhinal cortex (the H^{++} lesion), memory impairment was increased (Zola-Morgan et al., 1989b, 1993). Similarly, bilateral lesions involving the hippocampus (the H and ISC groups) impaired memory, but bilateral lesions of the amygdala did not (Clower et al., 1991; Zola-Morgan et al., 1989b, 1992). Thus what is important is which specific structures are damaged, not simply the total extent of damage.

In a recent report especially germane to the present findings, four monkeys with intended damage to the pia matter along the boundary between the parahippocampal cortex and area TE were impaired on concurrent object discrimination learning (Gaffan and Lim, 1991). It was suggested that the behavioral impairment resulted from damage to branches of the posterior cerebral artery that cross the parahippocampal gyrus en route to the area TE. In two monkeys, bilateral infarcts in area TE were apparent in histological analysis. In the other two monkeys, damage to area TE was not detected, but it was suggested that a more detailed examination of tissue might have revealed such damage. It was further argued that the standard surgical approach to the hippocampal formation, e.g., as used to produce the H^+ lesion, requires that the pia matter over the parahippocampal gyrus be damaged. Accordingly, behavioral impairment attributed to hippocampal formation lesions may be due to TE damage.

This idea requires careful evaluation because it suggests that reports of memory impairment following lesions that include the parahippocampal gyrus would need to be reinterpreted as an impairment in the processing of visual information (e.g., Mishkin, 1978; Moss et al., 1981; Mahut et al., 1981; Zola-Morgan et al., 1982; Malamut et al., 1984; Murray and Mishkin, 1984, 1986; Zola-Morgan and Squire, 1986; Zola-Morgan et al., 1989b, 1993; Overman et al., 1990; Suzuki et al., 1993). As we describe below, however, the evidence rules out the interpretation suggested by Gaffan and Lim (1991).

First, in the coronal sections presented for one monkey (Gaffan and Lim, 1991; Fig. 2), bilateral lesions appear in the perirhinal cortex. This cortex is part of the medial temporal lobe memory system (Squire and Zola-Morgan, 1991), and damage limited to this region is sufficient to impair visual recognition memory (Meunier et al., 1993). Second, monkeys with large medial temporal lobe lesions that included the parahippocampal gyrus (the H^+A^+ lesion) learned the 24-hour concurrent discrimination task about as quickly as normal animals, whereas monkeys with TE lesions were severely impaired (Phillips et al., 1988). This study provides direct evidence that bilateral damage to the parahippocampal gyrus need not produce the same behavioral effects as damage to area TE.

Finally, the effects of damage to the hippocampal formation (including the parahippocampal cortex; H^+ lesion) and damage to area TE were clearly dissociated in an earlier study of visual and tactual concurrent discrimination learning (Moss et al., 1981). In that study, monkeys with H^+ lesions were impaired on both the visual and tactual versions of the eight-pair concurrent discrimination task, whereas monkeys with TE lesions were impaired only on the visual version. Gaffan and Lim (1991) stated incorrectly that the H^+ monkeys in this study were not impaired on the tactual task. In fact, the H^+ monkeys required 996 trials and 234 errors to learn the task, whereas normal monkeys required 670 trials and 155 errors (trials: $P < .06$; errors: $P < .05$). Gaffan and Lim (1991) also suggested that the H^+ monkeys found the tactual task easier than the visual task and that the opposite was true for normal monkeys. In fact, both the H^+ monkeys and normal monkeys

required more trials to learn the tactual task (996 and 670 trials, respectively) than the visual task (810 and 370 trials, respectively). Monkeys with H^+ lesions did average somewhat fewer errors on the tactual task compared to the visual task (234 vs. 250 errors, respectively), but this difference did not approach significance.

In summary, the findings reviewed here rule out the idea that the effects of parahippocampal cortex lesions on visual learning and memory are caused by indirect damage to area TE. On the contrary, the findings show that medial temporal lobe lesions, which include cortex adjacent to the hippocampus, produce an impairment in memory that extends beyond the visual modality (Suzuki et al., 1993) and that TE lesions impair visual function.

With respect to the main findings of the present report, one additional study needs consideration. Squirrel monkeys with conjoint bilateral lesions in five different regions of the brain (the hippocampus, the amygdala, the anterior thalamic region, the mediodorsal thalamic nucleus, and the septum) were reportedly *less* impaired on the delayed nonmatching to sample task than monkeys with lesions limited to one or two of these brain regions ([the hippocampus, the hippocampus plus amygdala, or the anterior and mediodorsal thalamic regions (Irle and Markowitsch, 1990)]. If true, the findings would suggest that conjoint damage to several structures important for memory is somehow less deleterious than damage to a subset of these same structures. Such a conclusion contradicts the main finding of the present study that the severity of memory impairment increases as additional components of the medial temporal lobe memory system are damaged. However, as discussed elsewhere (Zola-Morgan and Squire, 1993), the data presented by Irle and Markowitsch (1990) are not compelling. The study involved only two monkeys in each of the single-lesion and double-lesion groups. Moreover, contrary to what was reported, the four monkeys in the five-lesion group did not perform measurably better than the monkeys with single or double lesions.

The finding that the extent of damage in the medial temporal lobe determines the severity of impairment is consistent with the possibility that structures within the medial temporal lobe make qualitatively different contributions to memory function. One sense in which this idea is plausible follows from the fact that anatomical connections from different parts of neocortex enter the medial temporal lobe memory system at different points. For example, parietal cortex projects to parahippocampal cortex, and area TE projects more strongly to perirhinal cortex than to parahippocampal cortex (Suzuki et al., 1993; Suzuki and Amaral, in press). Accordingly, it is reasonable to expect that parahippocampal and perirhinal cortical damage should produce different effects on memory. A related point follows from the observation that the hippocampus is the final site of convergence within this system. It is reasonable to expect that the hippocampus makes different contributions to memory than structures, such as the entorhinal cortex, that are placed earlier in the processing stream.

In summary, damage limited to the hippocampus proper, the dentate gyrus, and the subicular complex causes significant memory impairment, but the severity of impairment is considerably greater following damage that also includes the adjacent cortical regions, i.e., the perirhinal, entorhinal, and parahippocampal cortices. The severity of memory impairment thus depends on the extent of damage within the medial temporal lobe. Moreover, it appears that a substantial part of the severe memory impairment produced by large medial temporal lobe lesions in humans and monkeys can be attributed to damage to the cortical regions adjacent to the hippocampus.

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