

Memory Impairment in Monkeys Following Lesions Limited to the Hippocampus

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This study addressed the question of how severe a memory impairment is produced by a lesion limited to the hippocampus. Monkeys with circumscribed hippocampal lesions were tested on the delayed-nonmatching-to-sample task, a test of recognition memory that is sensitive to amnesia in humans. Monkeys were given no preoperative training and were given no postoperative experience prior to training on the delayed-nonmatching-to-sample task. A marked deficit was observed. The results, taken together with those from previous studies, also provided information about the role of several factors that could potentially influence the level of memory impairment following hippocampal lesions. The level of impairment does not appear to be due to any of the following factors: time of testing after surgery, prior postoperative testing, surgical techniques, species differences, or behavioral training methods. However, preoperative training experience does appear to reduce the severity of the impairment, and this factor may account for the observation that the memory impairment associated with hippocampal lesions is sometimes very mild. Finally, a recent case of human amnesia studied in this laboratory is discussed in which a bilateral lesion limited to a portion of the hippocampus produced a well-documented memory deficit.

Bilateral medial temporal lobe damage has been known for a quarter of a century to cause profound amnesia in humans (Scoville & Milner, 1957). The traditional view has been that damage to the hippocampus is responsible for the memory defect. The severity of the memory impairment that accompanies medial temporal surgery is correlated with the extent of hippocampal damage (Milner, 1974), and hippocampal damage occurs, as well, in other conditions that impair memory and that affect the medial temporal region (Benson, Marsden, & Meadows, 1974; Drachman & Adams, 1962; Gilman, 1965; Hyman, Van Hoesen, Damasio, & Barnes, 1984). In some single case studies, substantial impairments of memory have been attributed to hippocampal lesions alone (DeJong, Itabashi, & Olson, 1969; Glees & Griffith, 1952; Muramoto, Kuru, Sugishita, & Toyokura, 1979). However, the state of memory functions in these cases often is based on anecdotal reports or on incomplete histological information.

Recent successes at developing an animal model of human amnesia in the monkey (Mahut & Moss, 1984; Mishkin, Spiegler, Saunders, & Malamut, 1982; Squire & Zola-Morgan,

1983, 1985; Zola-Morgan, 1984) provide a way to identify the specific structures in the medial temporal region that when damaged caused amnesia. Work with animal models led initially to the suggestion that conjoint damage to the hippocampus and amygdala is required to produce severe memory impairment (Mishkin, 1978). Separate removal of the hippocampus or amygdala in monkeys produced very little impairment on a test of recognition memory, the trial-unique delayed-nonmatching-to-sample task (91% and 94% correct for the hippocampal and amygdala groups, respectively, at delays of 2 min; 97% correct for the normal control group). When both structures were removed conjointly, a severe impairment was observed (60% correct at delays of 2 min). These findings seem to make two important and independent points about the role of the hippocampus in memory. First, damage in addition to the hippocampus, for example, to the amygdala, can increase the severity of the memory impairment. Second, hippocampal lesions alone produce only a mild memory impairment.

The results of other studies suggested that monkeys with lesions limited to the hippocampus can be moderately or even substantially impaired. In one study in which the delayed-nonmatching-to-sample task was used, monkeys with hippocampal lesions performed at 78% correct at delays of 2 min (Mahut, Zola-Morgan, & Moss, 1982). Normal monkeys performed at 95% correct. In addition, monkeys with hippocampal lesions were substantially impaired on concurrent discrimination learning (Mahut et al., 1982; Moss, Mahut, & Zola-Morgan, 1981) and on the delayed retention of easy object discriminations (Mahut, Moss, & Zola-Morgan, 1981).

One explanation that has been offered for observed differences in the severity of the memory impairment following hippocampal lesions is that monkeys have received different

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degrees of preoperative experience (Mahut & Moss, 1984; Murray & Mishkin, 1984). In the three studies in which the delayed-nonmatching-to-sample task was used, the impairment associated with hippocampal lesions was moderately severe when no preoperative training was given (Mahut et al., 1982), it was mild when monkeys were trained preoperatively (Mishkin, 1978), and there was no impairment when extensive preoperative training was given (Murray & Mishkin, 1984).

Another possible explanation for differences in the severity of memory deficit is that monkeys in different studies have not always had the same postoperative testing histories; for example, testing on delayed nonmatching to sample sometimes occurred soon after surgery, and it sometimes occurred long after surgery, with other testing intervening. Intervening testing could establish strategies that either facilitate or compete with the strategy needed to perform delayed nonmatching to sample and thus make it difficult to compare results across studies.

A third possible explanation for differences in the severity of memory deficit is that the surgical lesions produced in different laboratories might differ in some way. On the basis of our review of the literature, we had originally suggested that hippocampal lesions might appear to produce only a mild memory impairment because the anterior portion of the hippocampus had often been spared during surgery (Squire & Zola-Morgan, 1983). Murray and Mishkin (1984) ruled out this possibility in their recent study by documenting the completeness of their lesions histologically. They found no memory impairment postoperatively in monkeys with extensive preoperative training. Thus, lesion differences based on the surgical techniques used in different laboratories probably do not account for observed differences in memory impairment. Nevertheless, at this early stage in the development of animal models, it is still important in each new study to evaluate carefully the nature of the lesion.

The present study addressed the question of how severe a memory impairment is produced by a lesion limited to the hippocampus. The delayed nonmatching task was used, because it has become a benchmark task in studies of memory impairment in the monkey. It was the first task learned after surgery, so that other postoperative experience could not affect performance. We were also able to test monkeys with hippocampal lesions that had been prepared in two different laboratories, our own and that of Mortimer Mishkin. In this way, we had an opportunity to evaluate possible contributions of any differences in surgical technique that might contribute to the severity of the memory impairment. Finally, monkeys were given no preoperative testing experience so that a reliable measure could be obtained of the ability to learn and retain new information.

Method

Subjects

Thirteen cynomolgus monkeys (*Macaca fascicularis*) were used. Five were used as normal controls (N). Eight received bilateral lesions of the hippocampus (H). Five of the operated monkeys were prepared in our surgical facility. Three others were prepared in Mishkin's laboratory at the National Institute of Mental Health (Bethesda, Maryland) and sent to us for testing. All monkeys were experimentally

naive at the start of the present study, and none of the operated monkeys had received any preoperative training.

Surgery

All surgery was performed with the monkeys under sodium pentobarbital anesthesia (30 mg/kg). Similar surgical approaches were used in both laboratories to remove the hippocampus bilaterally. The hippocampus on each side was approached by elevating the occipitotemporal convexity and entering the brain medial to the occipitotemporal sulcus and caudal to the entorhinal cortex. The hippocampus, including dentate gyrus and subicular cortex, was removed. The removal also included portions of the parahippocampal gyrus (area TF-TH of von Bonin & Bailey, 1947) and the entorhinal cortex. The upper surface of the lateral ventricle served as an identifiable dorsal boundary along the entire length of the removal. In this way it was possible to spare the temporal stem during surgical removal of the hippocampus (Zola-Morgan, Squire, & Mishkin, 1982).

Behavioral Testing

All testing was carried out in a Wisconsin General Test Apparatus (Harlow, 1944). During four to six sessions of pretraining, monkeys learned to obtain food by displacing objects that covered any of three food wells.

Trial-unique delayed nonmatching to sample. Each trial consisted of two parts: Monkeys first displaced an object that covered the central well to obtain a raisin reward; then, after 8 s they saw two objects, the original one and a new one, and they had to displace the new object to obtain the raisin. Twenty such trials were presented daily, with an intertrial interval of 20 s. In each trial we used a new pair of objects, selected randomly from a collection of more than 300 junk objects. After reaching the learning criterion of 90 correct choices in 100 trials, monkeys were tested with successively longer delays of 15 s, 60 s, and then 10 min between presentation of the sample and the choice parts of the trial. One hundred trials were given at each delay.

Pattern discrimination. Following completion of the testing described above, all monkeys were tested on two pattern discrimination tasks. In the first task, monkeys learned to discriminate a plus sign from a square, and in the second task they learned to discriminate an N from a W. In each task, monkeys saw two blue plaques (3 × 3 in.) on each of which was pasted a cutout of the pattern to be discriminated. The square (or the N) was the rewarded stimulus for half of the monkeys, and the plus sign (or the W) was rewarded for the other half of the monkeys. The position of the correct plaque varied on each trial according to a pseudorandom schedule (Geller-mann, 1933). Training continued until a learning criterion was achieved of 2 successive days of at least 90% correct performance. Twenty trials each day were administered for the first task, and 30 trials were administered each day for the second task.

Pattern discriminations can be acquired almost normally by monkeys with conjoint hippocampus-amygdala lesions (Zola-Morgan & Squire, 1984), presumably because this task depends primarily on the kind of skill learning that is spared in amnesia (Squire & Zola-Morgan, 1983). The task therefore provides a useful way to gauge the selectivity of the behavioral impairment, when lesion studies are designed to model human amnesia.

Results

Histological Findings

The brains of 5 operated monkeys were prepared for histological examination. Four of these had been operated on in

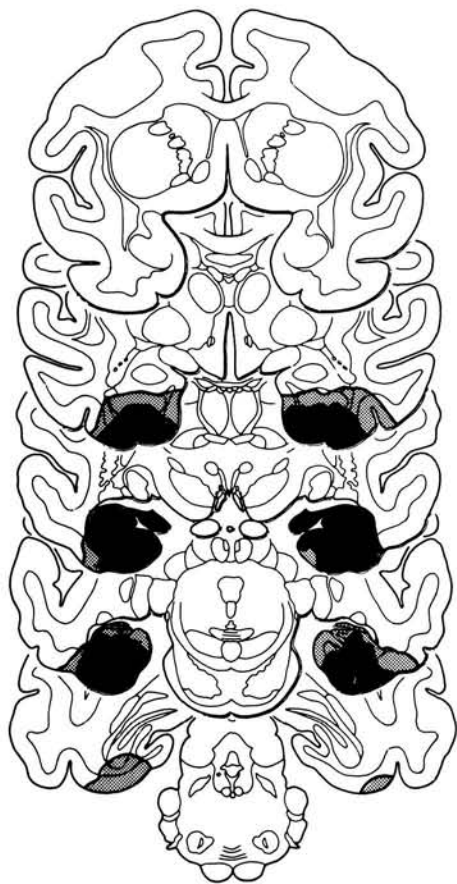


Figure 1. Representative coronal sections through the temporal lobe showing the smallest (dark) and largest (stippled) extent of damage in 5 monkeys in the hippocampal group. (The involvement of area TE was negligible in 4 monkeys, but substantial in 1 monkey. The damage to area TE in this monkey is not illustrated in the coronal sections.)

our laboratory, and 1 had been operated on in Mishkin's laboratory. The remaining 3 monkeys with H lesions, 1 from our laboratory and 2 from Mishkin's laboratory, are currently undergoing additional behavioral testing. The brains were fixed in sugar/formalin and embedded in albumin. Frozen sections were cut at 50 μ m, and every fifth section was stained with thionine for Nissl substance. All 5 monkeys sustained extensive bilateral removal of the hippocampus (Figure 1). The hippocampus was removed for its entire extent with the exception of the most anterior 2–3 mm in 2 cases. In addition to the hippocampus, the lesions in all 5 monkeys included bilaterally 30%–70% of the allocortex of the entorhinal area. In 3 monkeys, the lesion also involved more than 90% of area TF-TH bilaterally; in the other 2 monkeys the damage to area TF-TH was limited to about 20%. Inadvertent damage to area TE (von Bonin & Bailey, 1947) occurred in 4 animals, but it was less than 15% in each case. This damage probably resulted from inadvertent direct mechanical pressure applied during the elevation of the occipitotemporal convexity. The fifth monkey sustained an infarction during surgery that resulted in damage to 40%–50% of area TE; this damage was bilateral and involved mainly the ventral portion of area TE.

The caudate nuclei, the lateral geniculate nuclei, and the temporal stem did not sustain significant damage in any of the animals. The mediodorsal nucleus of the thalamus appeared normal. There was no apparent cell loss in the mammillary bodies, but there was gliosis in the medial mammillary nucleus at the site of termination of the fornix. Extensive gliosis was observed throughout the fornix.

Behavioral Findings

Delayed nonmatching to sample. Monkeys with H lesions were impaired at learning the basic task, with a delay of 8 s. Having learned the basic task, they were then impaired when the delays were extended to 15 s, 60 s, and 10 min (Figure 2). Figure 2A shows that the normal group required a mean of only 136 trials to reach learning criterion on the basic task; the H group required a mean of 430 trials, $t(11) = 2.77$, $p < .01$. As the delay was increased from 8 s to 10 min, the performance of the H group deteriorated markedly (Figure 2B). A two-way analysis of variance revealed significant effects of group, $F(1, 11) = 12.5$, $p < .01$, delay, $F(1, 3) = 51.6$, $p < .01$, and Group \times Delay interaction, $F(3, 33) = 5.8$, $p < .01$. At a delay of 10 min, the H group obtained an average score of 65% correct. This score was significantly above chance, $t(7) = 6.01$, $p < .01$, but it was distinctly lower than the average score of the normal group (78%), $t(11) = 3.65$, $p < .01$. Indeed, at the 10-min delay, only 1 operated monkey scored higher than any of the normal monkeys.

The scores of the 5 H monkeys for which histological data are available were similar to the scores of the 3 H monkeys that have not yet come to autopsy (average scores for each of the four delays for the 5 H monkeys were 91, 83, 75, 65; for the 3 H, 91, 88, 78, 64). In addition, the scores of the 5 H monkeys prepared in our laboratory were similar to the scores of the 3 H monkeys prepared by Mishkin (average scores for each of the four delays for the 5 H monkeys were: 91, 84, 77, 63; for the 3 H, 91, 87, 80, 67; also see Figure 2).

Pattern discrimination. Figure 2C shows the average number of trials required to learn the two pattern discrimination problems. The monkeys with H lesions performed normally. They required a mean of 404 trials to learn the problems, and the normal animals required a mean of 396 trials, $t(11) = 0.10$. Monkeys prepared in the two laboratories performed similarly (Figure 2).

In a previous study (Zola-Morgan & Squire, 1984), monkeys with conjoint hippocampus-amygdala lesions were not quite normal on these same two pattern discrimination tasks, and their mild impairment was due entirely to poor performance on the first five trials of each testing day. Accordingly, in the present study we analyzed separately the scores for the first five trials of each test day and the scores for the remaining trials of each test day. Despite the fact that the monkeys with H lesions performed normally overall, a small but significant impairment was present in the first five trials. The normal monkeys averaged 74% correct during the first five trials and 63% correct for the remaining trials. Monkeys with H lesions scored 64% and 62%, respectively, $t(11) = 4.6$, $p < .01$ for the first five trials, H versus N; $t(11) = 0.70$, for the remaining trials, H versus N. This impairment on the first five trials of each testing day has been studied previously and is thought

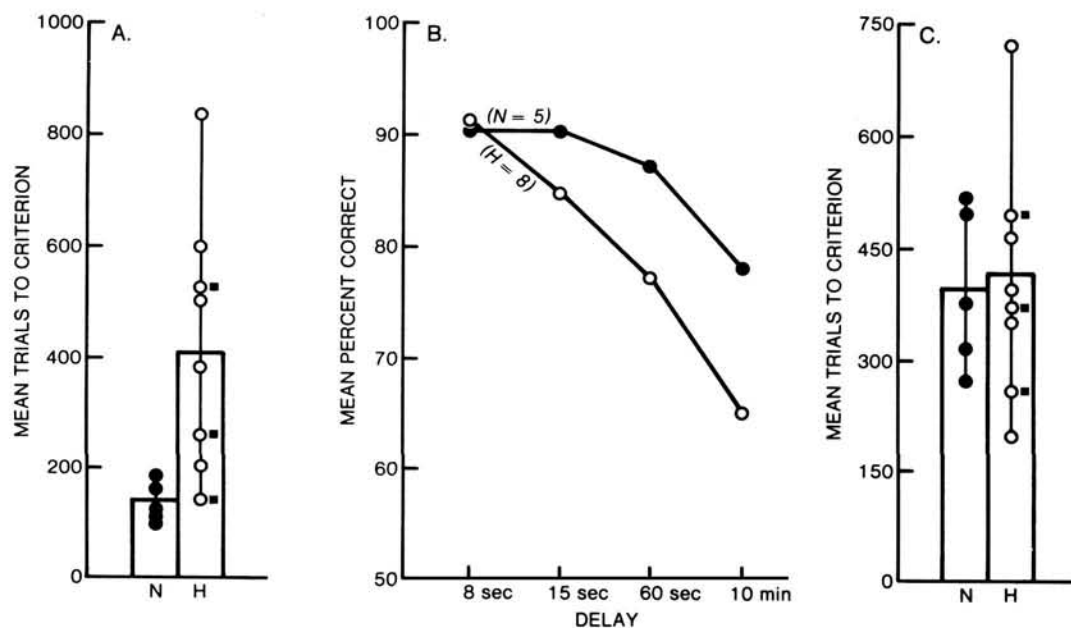


Figure 2. A: Performance of 5 normal control monkeys (N) and 8 monkeys with lesions of the hippocampus (H) on initial learning of the delayed nonmatching-to-sample task with 8-s delays. (Symbols indicate performance of individual animals in each group.) B: Performance of the N and H groups on the delay portion of the nonmatching task. C: Average scores obtained by the N and H animals for two pattern discrimination tasks. (Solid squares indicate scores of 3 monkeys prepared in Mishkin's laboratory.)

to reflect a component of this task that is not skill-like (see Zola-Morgan & Squire, 1984).

Discussion

Monkeys with bilateral lesions limited to the hippocampus exhibited a marked deficit on a behavioral test of memory that has been used in recent years to model the human amnesic syndrome. The same monkeys were normal at learning pattern discrimination problems, a finding that parallels the preserved capacity for skill learning in human amnesic patients (Zola-Morgan & Squire, 1984). These results agree with previous reports that lesions of the hippocampus can cause amnesia in the monkey (Mahut et al., 1981, 1982; Mishkin, 1978; Moss et al., 1981; see Squire & Zola-Morgan, 1983, for a review), though the severity of the reported impairment has varied considerably across studies.

In our study, monkeys were given no preoperative training, and the deficit observed postoperatively was noticeably greater than that reported when preoperative training was given (Mishkin, 1978; Murray & Mishkin, 1984). Moreover, the level of impairment was nearly identical to what was found in a different study in which training also began postoperatively (Mahut et al., 1982). Specifically, for the three delay intervals that were common to all the studies (8–10 s, 15 s, 60 s), the average postoperative score was 99% correct when there had been extensive preoperative experience (Murray & Mishkin, 1984), 93% following less extensive preoperative experience (Mishkin, 1978), 87% without any pretraining

(Mahut et al., 1982), and 85% in the present study. Together, these results support the view (Mahut & Moss, 1984; Murray & Mishkin, 1984) that preoperative testing experience is a factor in determining the level of the postoperative impairment. It might seem surprising that postoperative training can improve postoperative performance on delayed nonmatching to sample, because postoperative testing requires monkeys to remember unique test objects that they have not previously encountered. Perhaps successful preoperative experience establishes strategies (e.g., the skill of paying attention) that can facilitate postoperative performance.

Of the previous studies, the one that found the most severe impairment on delayed nonmatching to sample involved monkeys that had had 5 years of postoperative testing experience (Mahut et al., 1982). Thus, monkeys with extensive postoperative experience can nevertheless exhibit significant impairment. A recent study of monkeys with conjoint lesions of the hippocampus and the amygdala (H-A) made the same point (Zola-Morgan & Squire, 1985). A severe deficit following H-A lesions was observed shortly after surgery on delayed nonmatching to sample, and it was present to the same degree after extensive postoperative experience approximately 18 months later.

It also appears that differences in surgical technique cannot account for the variations in level of impairment found in previous studies. The 5 monkeys prepared in our facility and the 3 monkeys prepared in Mishkin's facility, and then shipped to our facility approximately 6 weeks after surgery, could not be distinguished by any of the behavioral measures

(Figure 2). In particular, it is unlikely that variability in the extent of the hippocampal removal could be responsible for differences in behavioral findings. In the 5 monkeys whose brains have thus far been examined histologically, 2 had sparing of the anterior 2–3 mm of the hippocampus. These monkeys, however, were just as impaired on the delayed nonmatching task as the 3 monkeys with complete lesions. At the 10-min delay, the 2 monkeys with slight anterior sparing of the hippocampus scored 56% and 62% correct. The 3 monkeys with complete lesions scored 60%, 64%, and 68%. These findings and other recent data (Murray & Mishkin, 1984) therefore rule out our earlier suggestion that mild impairments on the delayed nonmatching task might be explained by sparing of the anterior portion of the hippocampus (Squire & Zola-Morgan, 1983).

Two other factors also deserve mention. First, because in two studies of hippocampal lesions and the delayed-nonmatching-to-sample task rhesus monkeys were used (Mahut et al., 1982; Mishkin, 1978) and in two, cynomolgus monkeys (Murray & Mishkin, 1984; the present study), species differences could have determined the level of impairment. However, this possibility seems unlikely. In the two studies that found the least impairment, one was with rhesus monkeys (Mishkin, 1978) and the other with cynomolgus monkeys (Murray & Mishkin, 1984). Similarly, both species were used in the two studies that found the most impairment (rhesus: Mahut et al., 1982; cynomolgus: the present study).

Second, it is possible that small differences in behavioral testing methods across laboratories could influence the level of impairment. This idea also seems unlikely because the performance of normal monkeys tested in different laboratories does not vary sufficiently to account for differences in the level of impairment following hippocampal lesions; for example, in the two previous studies that included normal monkeys, the levels of impairment after hippocampal lesions were different (Mahut et al., 1982; Mishkin, 1978), but the normal monkeys performed comparably. Thus at a delay of 2 min, the normal monkeys scored 97% (Mishkin, 1978) and 95% (Mahut et al., 1982), but the operated monkeys scored 91% and 78% in the respective studies.

In summary, previously reported differences in the level of impairment following hippocampal lesions do not appear to be due to any of the following factors: time of testing after surgery, prior postoperative testing, surgical techniques, species differences, or behavioral training methods. However, preoperative training experience does appear to reduce the severity of impairment, and this factor may account for the differences reported in previous studies.

Despite the finding that a marked deficit in recognition memory can occur following circumscribed hippocampal lesions in animals without preoperative experience, it remains true that removal of the hippocampus alone results in a less severe impairment than is found following conjoint removal of the hippocampus and the amygdala (see Squire & Zola-Morgan, 1985, for comparisons across studies of the performance levels of these two operated groups). Further work is needed to determine the relative contributions to this larger deficit made by damage to the amygdala itself and by damage to entorhinal and perirhinal cortex, which are necessarily

included in the amygdala removal (Murray & Mishkin, 1983; Squire & Zola-Morgan, 1985).

Further work is also needed to know how to interpret the level of deficit that is found after hippocampal lesions in monkeys. The findings with monkeys are illuminating, but what one wants to know is whether this degree of impairment is clinically meaningful. Would a patient with such a lesion demonstrate a significant impairment in memory performance? We recently obtained clinico-pathological information relevant to this question (Zola-Morgan, Squire, & Amaral, in press). The patient was 52 years old when he developed memory impairment as the result of a hypotensive episode that followed cardiac bypass surgery. This patient survived for 5 years following the hypotensive episode, during which time he participated in our long-term studies of the neuropsychology of amnesia. His memory impairment was well documented by formal tests, and it was readily noticeable in his daily life. Complete histological analysis of his brain revealed a bilateral lesion limited to the CA1 field of the hippocampus and involving its entire anterior-posterior extent. The amygdala appeared normal and completely intact. The only other damage detected microscopically consisted of two unilateral lesions, one in the striatum and the other in somatosensory cortex.

This case shows that a circumscribed lesion limited to a portion of the hippocampal formation can produce a clinically meaningful memory impairment. Accordingly, it seems reasonable to think that the level of deficit reported here for monkeys with complete hippocampal lesions is qualitatively important and that a deficit of this magnitude on the delayed-nonmatching-to-sample task reflects considerable memory impairment. It will be important to develop additional ways to scale the impairments observed in monkeys, so that different degrees of behavioral impairment, observed on tests given to monkeys, can be related to human memory performance.

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