Reprinted from Science, March 1, 1963, Vol. 139, No. 3557, pages 824-825

D-45

A-45

Hippocampectomy and Behavior Sequences

Abstract. *Four monkeys with bilateral hippocampal lesions were trained to respond sequentially to visual stimuli, presented with an automated discrimination apparatus. Two different sequential tasks were presented. The experimental animals were significantly inferior on both problems to six control animals. Since no impairment appeared on simple visual discriminations presented with intertrial intervals from 5 seconds to 6 minutes, simple sensory deficits and "short-term" memory impairments appear unlikely. The results strengthen the interpretation that bilateral hippocampal lesions interfere with the acquisition of those behaviors which involve the execution of sequential responses.*

Experiments which involve limbic system lesions have generally been relevant to one of two apparently separate hypotheses concerning the functions of the limbic system in behavior. Milner and Penfield (*1*), Scoville (*2*), and Walker (*3*) have reported that hippocampal damage in humans results in serious "short-term" memory deficits. The other major hypothesis stems from Klüver and Bucy's work on the "temporal lobe syndrome" (*4*) coupled with Papez' idea that the limbic system is critically involved in emotional behaviors (*5*).

The majority of limbic lesions reported above have included damage to the amygdala as well as the hippocampus. Conclusions concerning the functions of the hippocampus per se are therefore difficult. It has been suggested by Pribram that a common element running through these studies is that limbic system lesions in fact disrupt the execution of complex sequences of action (*6*). The hippocampus (Ammon's horn) was selected as the limbic system structure to be ablated. The purpose of this experiment was to test directly the effect of bilateral hippocampal damage on behavior sequences.

The apparatus used was an automated discrimination apparatus (DADTA) (*7*). This machine can present 1 to 12 different stimuli on 2.5- by 1.5-inch Lucite panels. The subject makes his choice by depressing these panels. The presentation of the stimulus patterns and reinforcements are pre-programmed and responses recorded for processing by a general-purpose computer. For this experiment, the stimuli were presented in random positions across the 16 possible panels. Reinforcement consisted of one peanut kernel.

The subjects were ten experimentally naive, immature rhesus monkeys, six females and four males. After initial familiarization with the apparatus, all subjects were trained to discriminate a numeral "6" from a "4" to a 90-percent criterion of 45 correct out of 50 responses. Matched pairs were then formed among eight of the monkeys on the basis of their performance on the initial discrimination.

All animals were retrained to criterion 2 weeks after the initial acquisition. One member of each of the four matched pairs then received a one-stage bilateral hippocampal ablation. Two additional animals were given control lesions to the hippocampal gyrus, but with the hippocampus itself spared. These lesions were approximately the same size as the hippocampal lesions.

Anatomical reconstructions of the brains of monkeys previously operated in the same manner as in the present study have been published elsewhere (*8*). The surgical procedures are outlined in the same publication. The subjects in the present study are currently being used in further experiments.

Two weeks postoperatively, the subjects were retrained to the 90-percent criterion on the "6"-"4" discrimination. The sequential problems were then presented to the subjects. In the first of these, which we have termed the "self-ordered" sequence, the subjects were required to press two numeral "1"s which were displayed randomly among the 16 possible panels. Both panels had to be pressed in order to obtain the reinforcement. This could be done in either order, but repetitive pressing of the same stimulus was counted as an error. We have used the term "self-ordered" because once a panel is selected, the sequence is determined and the other panel must then be selected in order to obtain the peanut. Subjects were given 50 trials per day until they had either reached a criterion of 10 consecutive correct responses or had completed 1200 trials.

The other sequential task we have called the "externally ordered" sequence. In this situation, the subjects were required to depress a numeral "1" and then a numeral "5," *in that order*. All other sequences of responding were counted as errors. The stimuli were again displayed in random positions. All monkeys were given 50 trials per day until they reached a criterion of ten consecutive correct responses or until they had completed 3000 trials. If a monkey had not reached criterion after 1200 trials, added feedback was instituted: the houselight within the experimental box blinked off for ½ second after each response. In both problems, the intertrial interval was 6 seconds.

Although the animals with lesions of the hippocampus demonstrated a slight transient impairment of the preoperatively learned discrimination, all experimental subjects showed great retention, and no significant difference occurred between the groups ($t = < 1$).

On the "self-ordered" sequence, however, three of the four hippocampal animals showed no indication of learning, failing to reach criterion in 1200 trials. One hippocampal subject did reach criterion in 130 trials, which is within the normal range. With regard to the control groups, separate analysis revealed no significant differences between the operated and unoperated, and they were combined into a single group. The average number of trials to criterion for this control group was 298. The difference between this performance and that of the subjects with hippocampal lesions is significant at $< .05$ (Fisher's exact probability test).

The subjects with hippocampal lesions also demonstrated a significant deficit on the "externally ordered" sequential problem. All of the control subjects learned the problem in an average of 1216 trials, while the average for subjects with hippocampal lesions was 1897. The difference between the two

Table 1. Number of trials (and errors) to criterion for subjects with the hippocampus resected and for control subjects, on the "self-ordered" and "externally ordered" sequence tasks and discrimination tasks with varying intertrial intervals.

Task	Trials to criterion (errors)	
	Resected subjects (N = 4)	Control subjects (N = 6)
Ordered sequences		
"Self"	932* (574)	298 (133)
"External"	1897† (1476)	1216 (728)
Discrimination trial spacing		
5 seconds	108 (38)	100 (39)
30 seconds	66 (23)	76 (22)
3 minutes	42 (18)	49 (21)
6 minutes	27 (7)	26 (6)

* Three of four did not reach criterion in 1200 trials. † One of four did not reach criterion in 3000 trials.

groups was significant at $<.01$. Moreover, no hippocampal subject reached criterion before the added feedback light was instituted, as did three of the six control animals. The added feedback improved the performance of all animals.

The performance of the hippocampectomized subjects was further analyzed to determine if simple response perseveration could account for their inferior performance in the sequential tasks. One could be led to this conclusion from the results of the "self-ordered" task, where this was the only possible type of error. The data from the "externally ordered" task, however, do not support a perseveration hypothesis. Perseveratory errors (responding to the same panel) either within or across trials were not significantly more prominent in either group. Individual monkeys in both groups did on occasion display stretches of perseveratory behavior, but no consistent result obtained. It is of course possible that a breakdown of sequential responding could be manifested as perseveration in some situations (as in the "self-ordered" task); but it appears that this is only one of possible alternative behaviors.

Following completion of the two sequential tasks, two of the previously unoperated control monkeys received bilateral hippocampectomies. All animals were then retrained to criterion on both problems 2 weeks after these operations. For these retention tests, the "self-ordered" sequence was tested first, followed by the "externally ordered" task.

The retention results were rather ambiguous. Clear differences occurred between the two newly hippocampectomized subjects and the other monkeys. On the "self-ordered" problem, these two animals took 160 and 346 trials to re-reach criterion. In contrast, the other four hippocampectomized subjects retrained in an average of 48 trials. However, this result was reversed for the "externally ordered" sequence. The two "retention" hippocampectomized subjects retrained in only 73 and 33 trials, as compared with an average of 147 for the other hippocampectomized subjects and 168 trials for the control subjects. A deficit in retention occurred in the "self-ordered" task, while on the "externally ordered" problem, these same subjects retrained in fewer trials than the other animals. One possible explanation for this result is that the hippocampectomized "retention" subjects benefited from the extra practice on the first task, this benefit showing up on the second task.

Following these retention tests, the "short-term" memory hypothesis was investigated. All subjects were trained to a criterion of ten consecutive correct choices on each of four different visual discriminations. The DADTA apparatus was again used to present the four different pairs of numerals which served as stimuli. One of the stimuli of each pair was consistently reinforced, and the position of the two stimuli was varied randomly across the 16 panels.

On these four problems, each discrimination was presented with a different intertrial interval (5 seconds, 30 seconds, 3 minutes, 6 minutes). The order of the presentation of the four tasks was balanced.

It was assumed that if any short-term memory impairment occurred, it would be more apparent on the discriminations with the longer intertrial intervals. No impairment occurred among the hippocampectomized animals on any of the discriminations. Both groups took, on the average, fewer trials to criterion on the problems with longer intertrial intervals. Since the order of presentation of the problems was balanced, transfer effects from one discrimination to another cannot be a factor in this result. It is of course possible that the discriminations were easier at the longer intertrial intervals, although there was no a priori reason to suspect this. Table 1 summarizes the data of this experiment with regard to "self-ordered," "externally ordered," and varying intertrial interval discriminations.

Our conclusion is that bilateral hippocampal lesions interfere selectively with the acquisition of behaviors which involve the execution of sequential responses. We found no indication of "short-term" memory deficits with two-choice visual discriminations over intertrial intervals up to 6 minutes. This result is similar to that of Orbach *et al.* (9), who found no retardation of learning a simple visual discrimination in widely separated trials by monkeys with primarily amygdala and hippocampal lesions.

No emotional changes were noted in these animals, although further tests utilizing the galvanic skin response are in progress to investigate this possibility (*10*).

DANIEL P. KIMBLE
KARL H. PRIBRAM
Stanford University, Medical Center, Palo Alto, California

References and Notes

1. B. Milner and W. Penfield, *Trans. Am. Neurol. Assoc.* 80, 42 (1955).
2. W. B. Scoville, *J. Neurosurg.* 11, 64 (1954).
3. A. E. Walker, *A.M.A. Arch. Neurol. Psychiat.* 78, 543 (1957).
4. H. Klüver and P. C. Bucy, *J. Psychol.* 5, 33 (1938).
5. J. W. Papez, *A.M.A. Arch. Neurol. Psychiat.* 38, 725 (1937).
6. K. H. Pribram, *Ann. Rev. Psychol.* 11, 1 (1960).
7. ———, K. W. Gardner, G. L. Pressman, M. Bagshaw, *Psychol. Repts.* 11, 247 (1962).
8. K. H. Pribram and L. Weiskrantz, *J. Comp. Physiol. Psychol.* 50, 74 (1957).
9. J. Orbach, B. Milner, T. Rasmussen, *Arch. Neurol.* 3, 230 (1960).
10. Supported by grants from the U.S. Public Health Service (MF-17,131; MY-3732-C2) and the Department of the Army (MD-2073). A preliminary report was presented at the American Psychological Association meetings in St. Louis, Mo., on 5 September 1962.

14 January 1963