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KARL H. PRIBRAM, WILLIAM A. WILSON, JR., AND JANE CONNORS

*Stanford University, Palo Alto, California, and Bryn Mawr College, Bryn Mawr, Pennsylvania*

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# Effects of Lesions of the Medial Forebrain on Alternation Behavior of Rhesus Monkeys

KARL H. PRIBRAM, WILLIAM A. WILSON, JR., AND JANE CONNORS[1]

*Stanford University, Palo Alto, California, and Bryn Mawr College, Bryn Mawr, Pennsylvania*

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In two experiments involving the delayed alternation task, monkeys with lesions of the hippocampal formation and monkeys with lesions of cingulate cortex were compared with controls. Either of these lesions caused impairment in original postoperative learning of delayed alternation; the hippocampal formation resections also produced a deficit in the retention of preoperatively acquired delayed alternation. The findings support the suggestion that these medial forebrain areas are related to cerebral systems which include the anterior frontal cortex, and that these areas are necessary to more than "emotional" behavior.

## Introduction

There is still considerable confusion as to the basis of the behavioral changes that follow lesions of the medial portions of the forebrain. Some authors focus on the control by these structures of the autonomic nervous system, and therefore, of the visceral functions of the body (5). They see as basic the effects of medial forebrain lesions on "emotional behavior." To test this conception, monkeys (14), cats (1, 3), and rats (2) have been studied in shuttle-box situations, and changes have been shown in avoidance behavior.

An alternate approach has come from the neurosurgical clinic. When large portions of the medial surface of the temporal lobe are removed, patients show a marked change in their capacity to remember events that occur after the surgery has taken place (6). Changes in emotion are minimal in such patients. The question arises, therefore, whether the

[1] These experiments were performed at the Institute of Living, Hartford, and were supported in part by generous grants from the National Institutes of Health and the Department of the Army. A report of the results preliminary to the completion of histological verification of lesion was presented at the American Psychological Association Convention in 1958 (15).

observed effects on avoidance behavior in animals are secondary to some other, more basic, change.

There is a system of connections of the medial forebrain which provides a method for formulating and testing such an hypothesis: The anterior, central, and medial nuclei form a core group within the dorsal thalamus which can be distinguished from an external portion, composed of the ventral, posterior, and geniculate nuclei (9). The medial nucleus of this core projects to the anterior frontal isocortex (10); the anterior nuclei and midline parts of the central group project to the medial forebrain (4). Destruction of the anterior frontal isocortex of monkeys is followed by inability to perform delayed reaction and delayed alternation tasks (8). The question can therefore be asked whether lesions of the medial forebrain would not lead to a similar defect in behavior.

Delayed reaction has been tested on many occasions in monkeys with medial forebrain lesions and these animals have, in general, performed as well as their controls on this task (7, 13). Alternation, on the other hand, has been reported to be defective after extensive lesions of the medial part of the temporal lobe (7). The aim of the present study is to confirm and extend these results by examining systematically the effects of medial forebrain lesions made in accord with anatomically identifiable criteria.

The structures of the medial forebrain can be divided into three main systems (12). The first of these is intimately connected with the olfactory bulb; the second consists of the basolateral group of nuclei of the amygdaloid complex and the structures of the septal region. It is the third system, however, which is the special focus of this particular study. This system includes the hippocampal formation and the cingulate cortex. Studies of the effect of cingulate lesions have shown behavior to be minimally affected (11). The effects of lesions of the hippocampal formation have proved even more resistant to behavioral analysis.

## Procedures and Results

### Experiment I

*Subjects.* Nine immature experimentally naive rhesus monkeys were used. After preoperative testing they were divided into groups of three. One group was subjected to lesions of the hippocampal formation, another group was given cingulate resections, and the remaining animals served as unoperated controls.

*Surgical and Anatomical Procedures.* All surgical operations were single-stage bilateral procedures performed by subpial aspiration under Nembutal anesthesia. The cingulate lesions were designed to remove the pre-, sub-, and supracallosal cingulate cortex—the projections of the

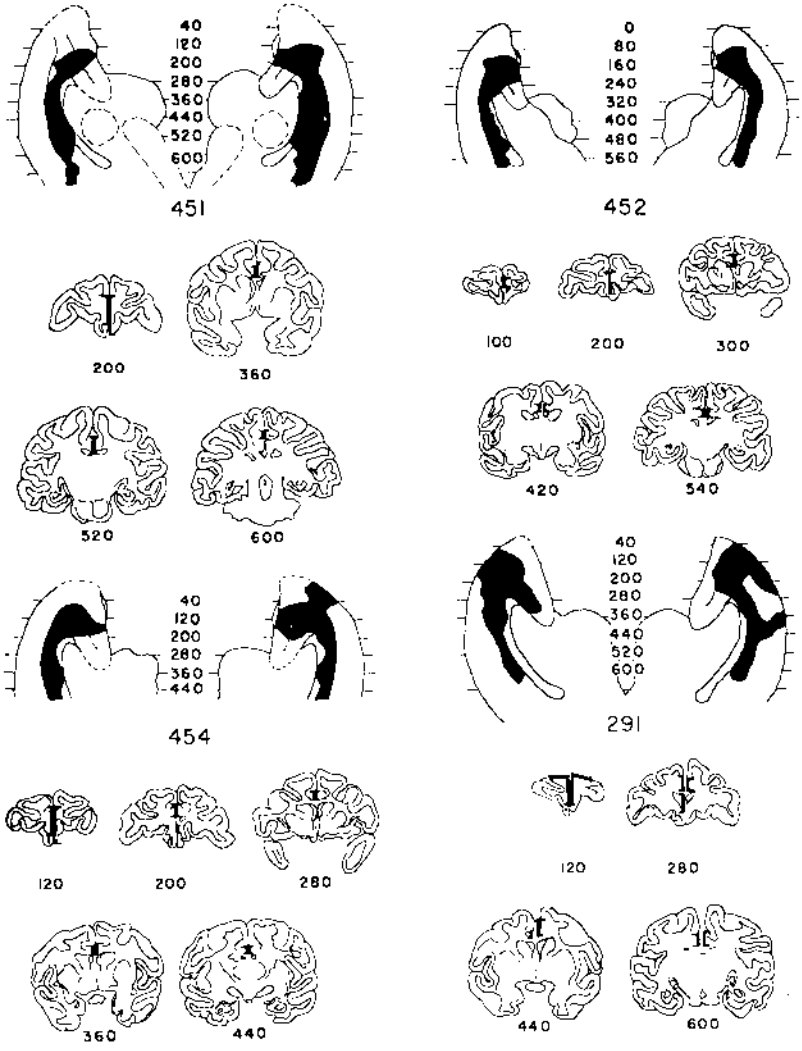



FIG. 1. Reconstructions of extent, and sample cross sections of depth, of cingulate and inferotemporal resections. Lesion indicated in black.

anterior nuclear group of the dorsal thalamus; lesions of the hippocampal formation were intended to include the subicular complex and entorhinal cortex as well as the hippocampus proper. For cingulate cortex removals, an osteoplastic craniotomy was performed. A few parasagittal veins were

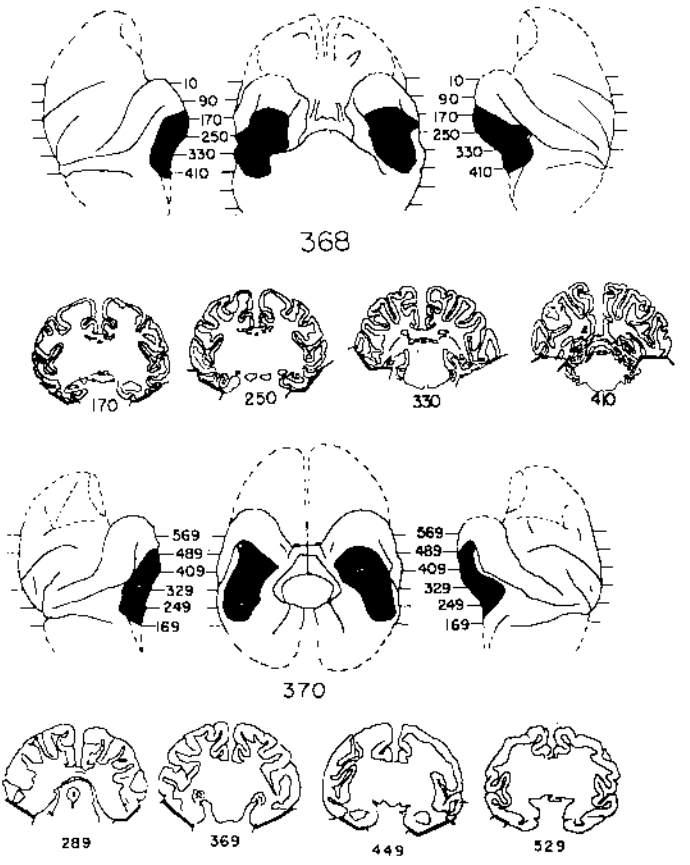
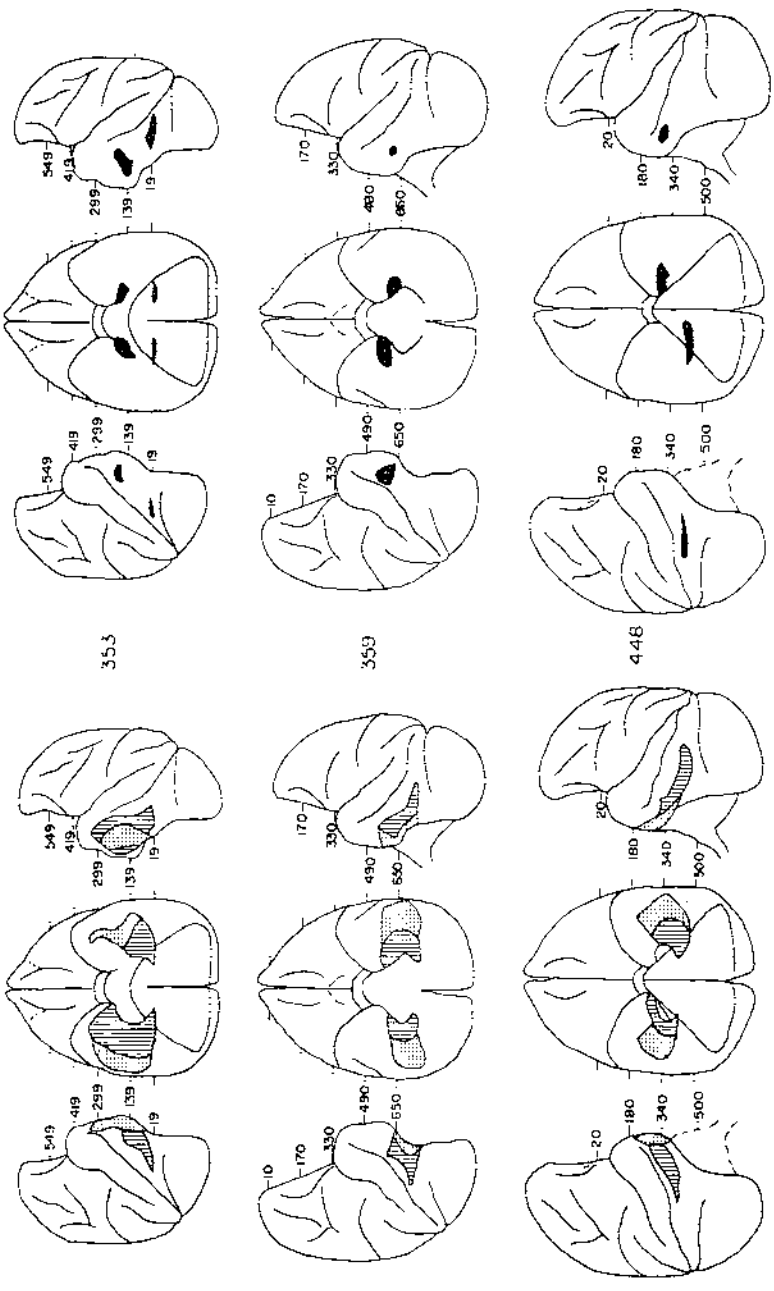



FIG. 1 (*continued*)

sacrificed to expose the medial surface of the hemisphere on one side through an incision in the dura. The cingulate cortex of the other side was approached through the falx. For the lesion of the hippocampal formation, a myoplastic flap was performed in the temporal region, the temporal bone removed, and the ventral surface of the temporal lobe exposed. Incision was then made just medial to the hippocampal-fusiform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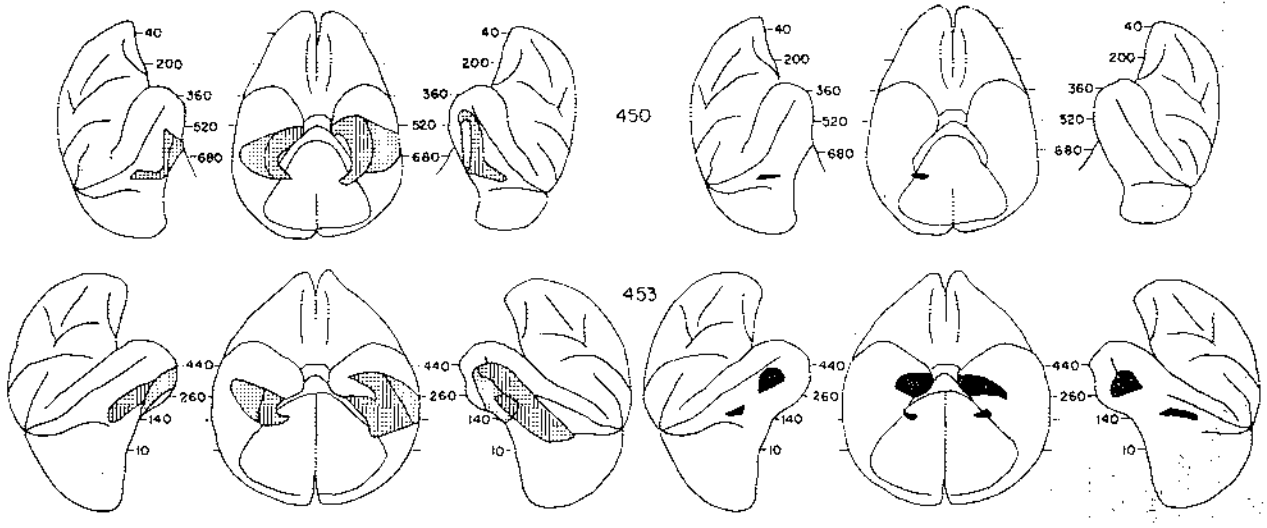


FIG. 2. Reconstructions of the extent of lesion (left), and the extent of remnants (right), after bilateral resections of the hippocampal formation. Stippled area indicates damage to superficial cortex; striped area indicates resection in depth. The remnants of spared portions of the hippocampal formation appear in black.

sulcus, and all of the hippocampus and the overlying cortex of the hippocampal gyrus was removed. After testing was completed the animals were killed, their brains were perfused with formalin, fixed, dehydrated, and embedded in celloidin. Serial sections at 50 μ were made and stained with analine thionine. These were used to prepare the reconstructions of the lesions which appear in Figs. 1 and 2.

Reconstruction shows that cingulectomies of the pre-, sub-, and supracallosal areas were effected (451, 452, 454 in Fig. 1). The lesions extended well into the posterior parietal regions. In some brains there was minimal invasion of the corpus callosum. In two subjects the lesion extended dorsally on one hemisphere to include some of the anterior frontal cortex. Except for minimal degeneration in the dorsal portion of the dorsomedial nucleus in these brains, thalamic degeneration was restricted to the anterior nuclear group. The anteromedial and anteroventral nuclei were totally degenerated in all hemispheres; the anterodorsal showed only occasional patches of degeneration. The hippocampal formation was almost totally removed in the brains of the other monkeys (448, 450, 453 in Fig. 2). A remnant of the hippocampal formation remained anteriorly and posteriorly in most but not all hemispheres. There was in addition, in all hemispheres, considerable inadvertent damage to the inferotemporal isocortex with some concommittant retrograde degeneration in the posterior portions of the inferior pulvinar.

*Preoperative Testing*. The animals were tested in a modified Wisconsin General Testing Apparatus, in which the only source of light was in the monkey's compartment. One-way vision screens separated the monkey from the testing compartment, and the testing compartment from the experimenter, permitting the animal to be observed at all times.

On each test trial the subject was presented with a testing tray containing two shallow boxes 30.5 cm apart. Preliminary to formal testing the animals were taught to obtain a peanut reward by displacing unpainted aluminum lids which covered on successive trials more and more of the interior of the boxes. After this was completed, alternation training began. Fifty trials a day were given on the alternation task to a criterion of 90 correct in 100 consecutive trials. On the first trial of each day both boxes were baited; subsequently on each trial the box other than the one to which the animal had last responded was baited. The delay interval between trials was approximately 5 sec. Two weeks after initial learning, a measure of preoperative retention was obtained for each animal (except

unoperated control 449) by retesting on delayed alternation to the same criterion.

*Postoperative Testing.* Two weeks after operation the animals were once again tested in delayed alternation to the same criterion or to a maximum of 1,250 trials. The animals were then tested on visual discrim-

TABLE 1
EXPERIMENT I. NUMBER OF TRIALS AND (IN PARENTHESES) TOTAL ERRORS TO CRITERION

| Animal | Alternation Preop. learning | Alternation Preop. retention | Operation | Alternation Postop. retention | Visual discrim. Postop. learning |
|---|---|---|---|---|---|
| 430 | 540 (224) | 0 (9) | None | 0 (8) | 140 (68) |
| 444 | 595 (237) | 210 (54) | None | 0 (9) | 170 (77) |
| 449 | 305 (129) | — | None | 0 (10) | 290 (140) |
| 451 | 370 (162) | 105 (26) | Cingulate | 0 (8) | 290 (156) |
| 452 | 445 (146) | 50 (15) | Cingulate | 0 (4) | 230 (115) |
| 454 | 700 (323) | 0 (6) | Cingulate | 0 (9) | 350 (167) |
| 448 | 580 (186) | 210 (50) | Hippocampal | 1250 F (301)[a] | 1250 F (578)[a] |
| 450 | 240 (101) | 0 (10) | Hippocampal | 125 (39) | 380 (180) |
| 453 | 575 (270) | 0 (7) | Hippocampal | 880 (317) | 1250 F (650)[a] |

[a] 1250 F indicates that the subject did not reach criterion within 1250 trials.

ination: Stimulus figures consisted of a plus sign (+) with bars 47.6 mm long and 11.1 mm wide, and an outline square 43 mm in outside measurement with sides 9.5 mm in width. These stimuli were applied with yellow paint to the surface of aluminum covers, which were placed on the boxes which had been used in delayed alternation. The positive cover (the +) and the peanut reward appeared on the right or the left box in accordance with a predetermined balanced order. Correction was not allowed after an error. Fifty trials a day were given to each animal to the criterion of 90 correct out of 100 trials.

*Results.* Trials to criterion and total errors are presented in Table 1 for all animals on all problems. On original preoperative learning of delayed alternation the animals reached criterion in a mean of 483.3 trials with 197.6 total errors; criterion on preoperative retention testing was reached in a mean of 71.9 trials with 22.1 errors. In postoperative testing of alternation, all normal controls and all animals with cingulate lesions showed complete retention. All three with lesions of the hippocampal formation showed large deficits in retention of the alternation

habit, although one did exhibit some savings relative to the original preoperative learning. On the visual discrimination problem all of the subjects with resections of the hippocampal formation required more trials and errors than the normal controls or those with cingulate lesions; two of them failed to learn within 1,250 trials. The scores of those with cingulate lesions are not grossly different from those of the normal monkeys, but the subjects with cingulate lesions did require, on the average, more trials and errors than the normals; two made more errors than all three of the normals; and the third made more errors than two of the normals.

## Experiment 2

*Subjects.* Six monkeys were used. Prior to this experiment the two with cingulate lesions had been trained to perform a temperature discrimination; the other animals had participated in a study in which they learned to press levers to obtain food and to avoid shock.

TABLE 2
Experiment 2. Number of Trials and (in Parentheses) Total Errors to Criterion

| Animal | Operation | Alternation Postop. learning |
|---|---|---|
| 368 | Inferotemporal | 445 (150) |
| 370 | Inferotemporal | 505 (171) |
| 291 | Cingulate | 1250 F (449)[a] |
| Y 65 | Cingulate | 1095 (322) |
| 353 | Hippocampal | 1250 F (589)[a] |
| 359 | Hippocampal | 880 (328) |

[a] 1250 F indicates that the subject did not reach criterion within 1250 trials.

*Surgical and Anatomical Procedures.* All of these animals underwent surgical procedures approximately 6 months before the beginning of this study. The general surgical and histological procedures were the same as those described for experiment 1. Two were given cingulate lesions and two were subjected to lesions of the hippocampal formation. Two others had resections of the inferotemporal cortical region, consisting of the inferotemporal and fusiform gyri. The approach for this operation was the same as that for resection of the hippocampal formation.

Representative reconstructions of the brains are shown in Figs. 1 and 2. The lesions are similar to those reported in experiment 1; the resections

intended to include inferotemporal isocortex spared the hippocampal formation completely.

*Testing.* The subjects in this experiment were tested on initial learning of delayed alternation postoperatively. The same procedure was followed as outlined for experiment 1 to the same criterion of learning.

*Results.* The results are shown in Table 2. The scores of the inferotemporally operated animals are well within the range of performance of normal animals, as exemplified by the preoperative scores of experiment 1. All of the four others showed a deficit relative to the behavior of normals. Two animals, 291 and 353, were actually tested over 1,800 and 2,000 trials, respectively, without reaching criterion. Errors to 1,250 trials are presented in the table to facilitate comparison.

## Discussion

The results with respect to the behavioral deficit on the alternation task are clear-cut. Resections of the hippocampal formation markedly impair the retention of a preoperatively learned delayed alternation performance. Such resections also interfere with the original learning of this task. This defect in the performance of delayed alternation that follows such medial temporal lesions differs markedly from the entirely negative results obtained when isocortical temporal lesions are made.

The results of resection of the cingulate cortex are also clear-cut. Retention of a preoperatively learned alternation performance is unimpaired. On the other hand, original learning of alternation is markedly retarded by cingulectomy. This finding is hitherto unreported in the literature, but fits in general with the results obtained in an earlier study that analyzed the differences in the effects of medial vs. lateral frontal lesions (13).

The effects of medial forebrain ablations on visual discrimination are not so easily interpreted. Original learning of the visual discrimination task appears to be very slightly retarded after cingulate ablations and is markedly retarded after the resections of the hippocampal formation. However, the retardation in learning that follows cingulate ablations is not statistically significant. Furthermore, as can be seen from Fig. 2, the lesions made to remove the hippocampal formation invaded the inferotemporal cortex. Such lesions disrupt markedly visual discrimination performances. It would be foolhardy, therefore, to reach any positive conclusion from this study concerning the effect of medial and basal cortical lesions on visual discrimination performances.

In conclusion, the results of these experiments demonstrate that alternation learning and performance are affected by medial forebrain lesions. These findings support the view that medial and basal forebrain structures are in some way related to the same cerebral systems to which the anterior frontal cortex belongs—a view derived from electrophysiological and comparative neuroanatomical data. The results also suggest that the effects of medial and basal forebrain lesions are not restricted to behavior within the category "emotion."

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