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J. Neurophysiol. 1960, *23*
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EFFECTS OF EPILEPTOGENIC LESIONS IN FRONTAL CORTEX ON LEARNING AND RETENTION IN MONKEYS[1]

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(Received for publication April 20, 1960)

ALUMINUM HYDROXIDE CREAM placed on the surface or injected into the layers of the cerebral cortex results in chronic focal epileptoid discharges (4). The discharges are registered in the electroencephalogram or are behaviorally demonstrated by seizures. These effects are generally first observed about eight weeks after implantation and persist for the remaining life of the animal. A number of investigators (2, 3, 9) have assessed the effects of such irritative lesions on monkeys' ability to retain tasks which they had learned before placement of the material. When monkeys were given periodic retention tests before and after placement of aluminum hydroxide over frontal, inferotemporal, occipital (3), or preoccipital cortex (2), no appreciable deficits were found on visual discrimination or on alternation tasks. However, when monkeys with occipital implants were first trained on visual discrimination tasks after the onset of epileptoid discharges, they showed marked deficits in the rate of learning (5). When trained on the alternation task, these monkeys attained criterion as rapidly as did normal monkeys. These results suggest that learning rates, but not retention ability, might be affected by epileptoid discharges from those cortical areas which, on the basis of ablation studies (10), have been found selectively related to specific behavioral tasks. Frontally lobectomized monkeys have been shown deficient in the learning and in the retention of delayed alternation tasks. In the present experiments aluminum hydroxide paste was placed over lateral frontal cortex in different groups of monkeys before and after they were trained on alternation tasks.

METHOD

Subjects. Immature monkeys with no prior testing experience were used. The experimental animals were subjected to surgery, performed aseptically under Nembutal anaesthesia. Commercial Amphojel was boiled to the consistency of thick paste and packed in silver disks, 9 mm. in diameter. Disks were placed bilaterally on the pial surfaces of lateral frontal cortex, medial and lateral to the principal sulcus and anterior to the arcuate sulcus. In Experiment I three disks, and in Experiment II four disks, were placed on each cortical surface. The dura was closed by sutures over the disks.

[1] This research was supported in part by Grant G-4422, National Science Foundation, and Grant M-545 (C6), National Institute of Mental Health, U. S. Public Health Service, Bethesda, Md.

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EEG recordings. Electroencephalographic recordings were taken from all experimental animals preoperatively and then at monthly intervals. During these recordings the monkey was placed supinely in a tight wooden box and seven electrodes (wound clips) were attached to selected points of the scalp. Subjects were in a quiet, electrically shielded room and EEGs were obtained while they were awake or during drowsiness. An Offner six-channel Dynograph Recorder was used. In one monkey (#532) the disks on the right side were removed after four months and chronic cortical recording electrodes were implanted. The electrode assembly consisted of a thin polyethylene sheet which supported five stainless steel points (0.5 mm. in diameter) placed in a line, 7 mm. between adjacent points. Wires from the electrode points, brought together in a cable, were soldered to a small female transistor plug. The assembly was placed on cortex so that the electrodes were near the principal sulcus with the posterior point just behind the arcuate sulcus. The dura was sutured over the electrode assembly and the connecting plug was tied to the posterior skull.

Anatomy. After termination of the experiment, the experimental animals were sacrificed, the metal disks were removed, and the brains were processed according to procedures described by Mishkin (6).

Experiment I

Apparatus. Monkeys were trained in a Wisconsin General Test Apparatus. For the alternation task a subject in a portable cage faced a testing tray consisting of two rectangular boxes 12 inches apart, each covered with an unpainted aluminum slide. By pushing the slide forward, the monkey would find a peanut in the container. Between trials a sliding opaque panel was interposed between the monkey and the testing tray. A one-way vision panel concealed the experimenter from the animal's view. For the object discrimination task the two food wells were covered by a black dome-shaped wooden block and a white triangular block (each 7 cm. wide at the base and 17 cm. high). The monkey pushed the objects aside in order to expose the food wells. The dome-shaped block, which was the rewarded cue, was placed over the left or the right well according to a random sequence.

Procedure. During preliminary training subjects learned to jump into the testing cage, pick the peanut from a food well, and finally push back blank covers. Training on the delayed alternation task was then given, consisting of 50 trials daily, generally six days per week. Both boxes were baited on the first (free) trial of each session and on subsequent trials the peanut was placed in the cup opposite to the one which had been previously rewarded. A correct response was made when the monkey shifted to the opposite cup after obtaining a reward. After an error response, the reward remained in the same cup until the monkey opened the correct box. Each subject was trained to alternate between the two cups until it attained the learning criterion of 90 correct responses in 100 consecutive trials.

Eight rhesus monkeys in three experimental groups were tested. Three subjects in the *Retention Group* (Group *R*) were trained to criterion performance on the alternation task and were then given retention tests at intervals of three weeks. On each retention series the monkey was tested until it made 45 correct responses in 50 consecutive trials. During the week following the second retention series, the Amphojel paste was implanted. On the following week retention tests were resumed and then repeated at three-week intervals until a total of nine retention series had been given.

Three monkeys in the *Learning Group* (Group *L*) were operated upon before training was started. After the electroencephalograms revealed paroxysmal spike discharges from frontal cortex, they were trained on the alternation task to the learning criterion. One monkey (#510) died shortly thereafter. (The autopsy showed peritoneal infection.) The two remaining subjects were given two series of retention tests at intervals of three weeks. Between these tests they were trained on the visual object discrimination task to the criterion of 90 correct responses in 100 trials.

Two monkeys in the *Control Group* (Group *D*) were operated upon and tested according to the same schedule as those in Group *L*, except that empty disks were placed over frontal cortex and the object discrimination task was not given.

Experiment II

Apparatus. Monkeys were tested on the alternation task in an automatic apparatus. A subject was seated in a restraining chair with one wrist attached by a chain to the chair,

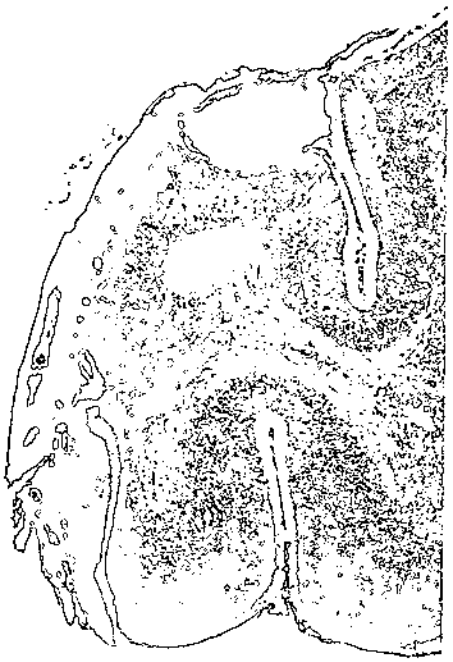

FIG. 1. Low-power photomicrograph of section through frontal cortex (Monkey #492, Experiment II) after removal of disks. (Thionine stain.)

facing a diffusely lighted panel. Two levers, 6 inches apart horizontally, protruded 0.5 inch in front of the panel and food cups were underneath each lever. When the monkey pressed on either lever with its free hand, both levers retracted behind the panel for a period of 8 sec. The first press during each session was rewarded with a 50 mg. sugar pellet which dropped into the cup beneath the lever while the cup was illuminated for 2 sec. Subsequently, the subject was rewarded if it pressed on the lever opposite to the one which had been previously rewarded. The control panel contained counters for the presses on the left and on the right lever, rewarded presses, and initial errors (the second consecutive presses on the same lever). Responses were also recorded on an Esterline Operations Recorder.

Procedure. Four experimental and five unoperated cynomolgus monkeys were used. The experimental subjects started training after their EEGs showed clear-cut patterns of paroxysmal discharges from frontal cortex. Subjects were adapted to the restraining chair and learned to manipulate the levers of the automatic apparatus and to pick pellets from the cups. The testing schedule was then started, during which 120–150 rewarded trials were given daily, generally six days per week. Testing of the normal animals was stopped after the criterion of 85 correct alternations in 100 consecutive trials had been attained. Testing of the experimental animals which did not attain this criterion was terminated after 2,400 trials.

After an interval of several weeks, the subjects were trained in the apparatus used in Experiment I on a visual pattern discrimination. On this task the slides over the food cups had yellow patterns painted on black backgrounds. The rewarded pattern formed a cross and the unrewarded one the sides of a square, all lines being 4.5 cm. long and 1 cm. wide. The rewarded pattern was on the left or right box on successive trials according to a chance sequence. Fifty trials were given daily until criterion of 90 correct responses in 100 trials was attained. Finally, the control animals were trained on the object discrimination task described in Experiment I. (Only four controls were used on these tests.)

RESULTS

Anatomy. The disks were found to be entirely encapsulated by connective tissue. The anatomical picture of cortex underneath the disks and the forma-

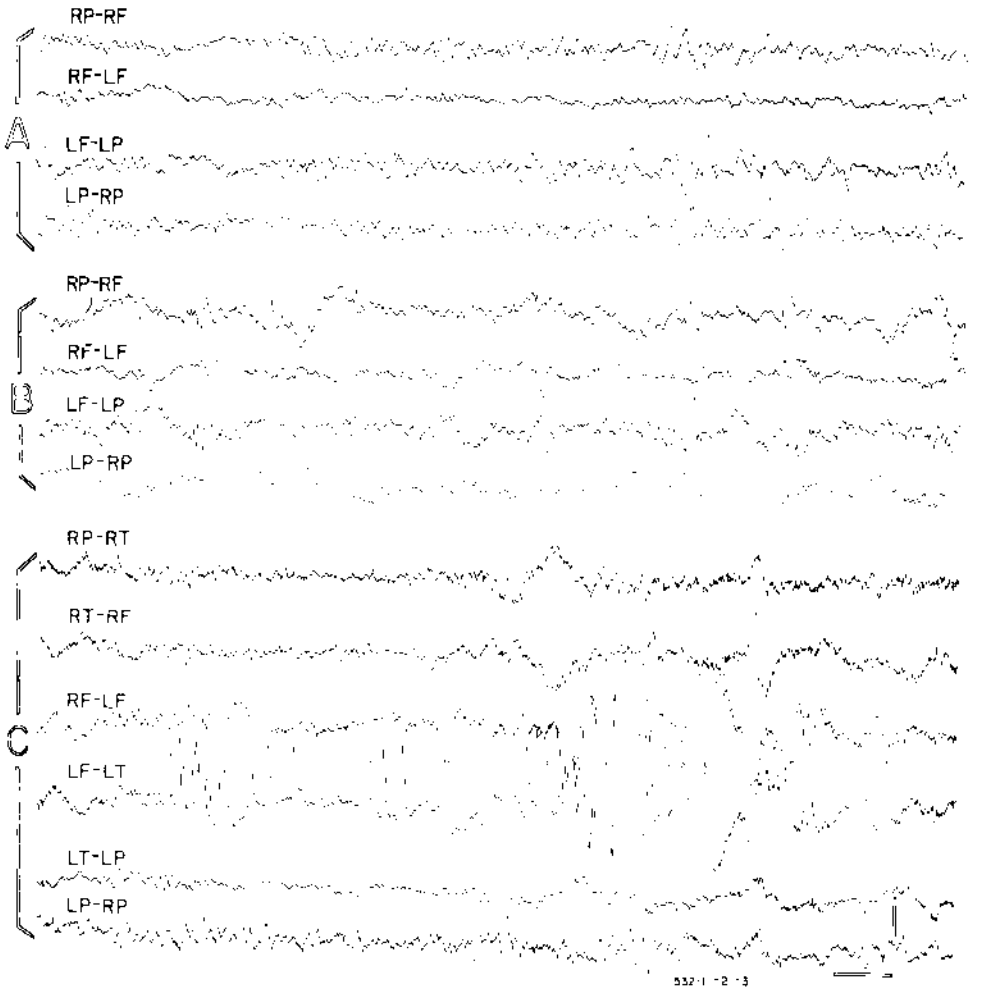

FIG. 2. Sample of EEG of Monkey #532 (Experiment II, Group *R*). A, preoperatively; B, 4 weeks; C, 8 weeks after implantation of aluminum hydroxide. Bipolar scalp recordings between locations indicated: L, left; R, right hemisphere; F, frontal; T, anterior temporal; P, posterior parietal; V, vertex. Calibration: horizontal line, 1 sec.; vertical line, 100 μV.

tion of scar tissue, as seen in Fig. 1, are in agreement with the descriptions given by previous investigators (1, 2). The thalamus was examined for retrograde degeneration. Small areas of gliosis were observed in the nucleus medialis dorsalis in some of the brains with frontal implants. However, in other brains there were no noticeable zones of thalamic degeneration. Thus, damage to cortical neurons was never extensive and in some cases could not be demonstrated.

Electroencephalography. During the recording sessions the animals were generally awake with occasional brief periods of drowsiness. In all but two of the experimental monkeys recordings taken eight to ten weeks postopera-

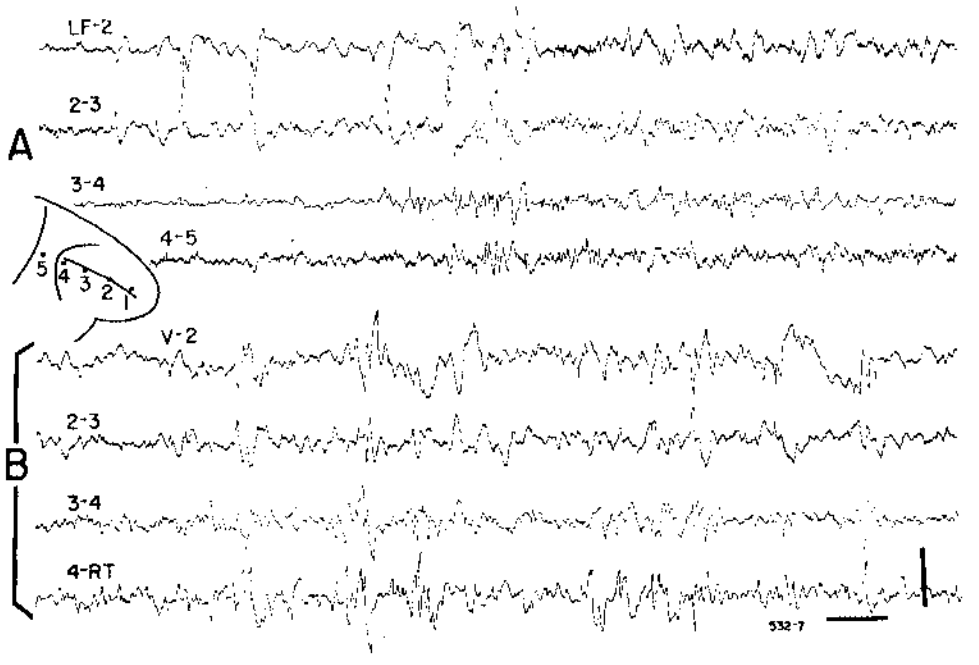

FIG. 3. Samples of electrocorticogram of Monkey #532, taken 10 weeks postoperatively. Bipolar recordings between electrode points indicated (see Fig. 2). Calibration: horizontal line, 1 sec.; vertical line, 300 μV. A and B are different samples from same recording session.

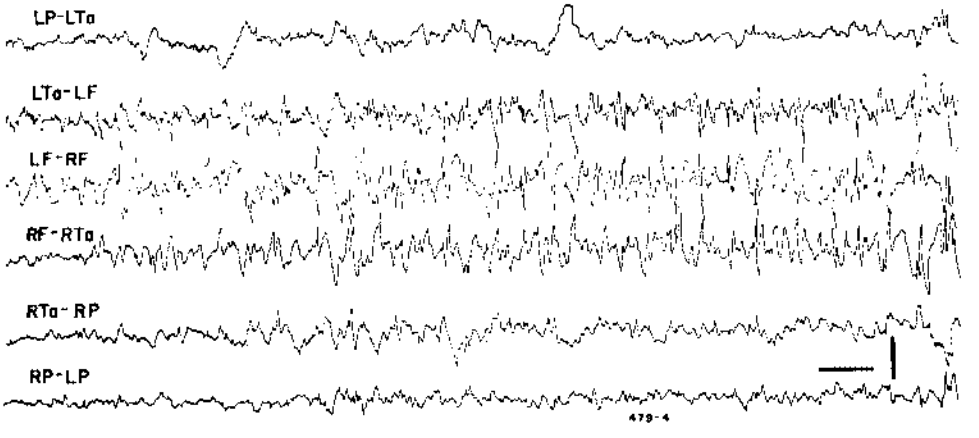

FIG. 4. Sample of EEG of Monkey #479 (Experiment II), taken 12 weeks postoperatively. Bipolar scalp recordings between electrode points indicated (see Fig. 2). Calibration: horizontal line, 1 sec.; vertical line, 100 μV.

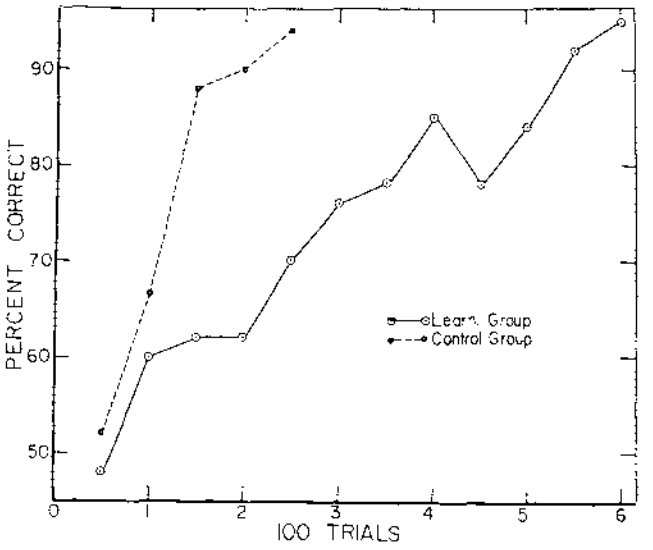

FIG. 5. Learning curves on alternation task (Experiment I) for epileptoid monkeys (Group *L*) and control groups (Groups *R* and *D*) combined. Group medians for successive blocks of 50 trials.

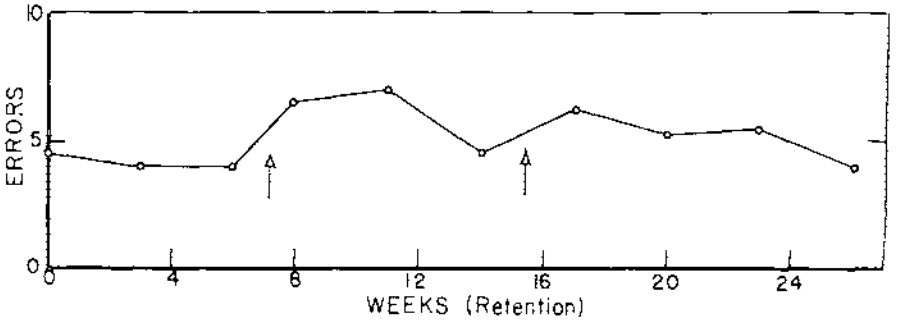

FIG. 6. Retention curve for Group *R* on alternation task. Scores are group medians of number of errors during first 50 trials of each retention series. Abscissa represents number of weeks after learning series. (Score for week "0" is for last 50 trials of learning series.) First arrow: period of implantation of disks; second arrow: first signs of paroxysmal EEG discharges.

tively showed paroxysmal spike discharges from frontal cortex. In subject #492 these patterns were first observed 14 weeks postoperatively and subject #557 responded to Metrazol activation (three spaced i.m. injections of 5 mg./kg. body weight) by localized frontal discharges. Frontal spiking was observed in recordings taken during subsequent months in every one of the ten experimental monkeys. All recordings from the two monkeys with empty implanted disks were essentially normal, showing no patterns of frontal discharges or other pathological signs.

Figure 2 shows the recordings of a monkey in Group *R*, Experiment I,

taken preoperatively and four and eight weeks after implantation. In the first postoperative EEG occasional isolated spike discharges from frontal cortex may be observed, but these never built up to paroxysmal episodes and were not considered pathological. In the subsequent recording (Fig. 2c) clear-cut spike discharges were seen, originating from left frontal cortex. Recordings taken during the subsequent month showed independent focal discharges from left and right frontal areas. The localization of discharging foci may be seen in Fig. 3, taken with cortical electrodes (7 mm. apart) ten weeks after implantation and four weeks after removal of the disks. Figure 3A

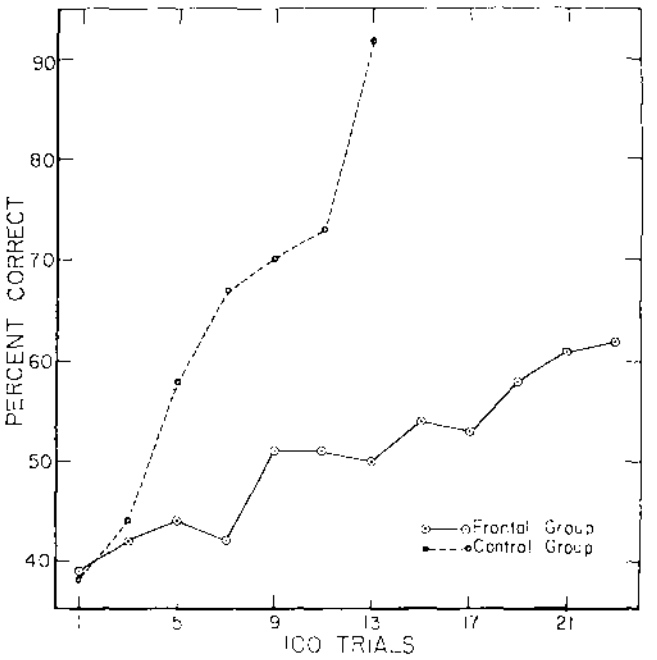

FIG. 7. Learning curves on delayed alternation (Experiment II) for epileptoid monkeys (frontal group) and normal animals (control group). Group medians of per cent correct responses for alternate blocks of 100 trials.

shows isolated spikes from electrode 2, which do not appear to spread to adjacent electrodes. In Fig. 3B the discharging focus is near electrode 4 with some spread to adjacent points. In other portions of this recording simultaneous paroxysmal activity was seen over larger portions of left frontal cortex, but no spread to motor or temporal cortex was observed. Figure 4 shows the EEG from a subject in Experiment II, taken 12 weeks postoperatively. High-voltage spike discharges may be seen over both frontal areas with considerable synchronization from left and right hemispheres. The discharging foci were restricted to frontal cortex with essentially normal tracings from other scalp electrodes.

During episodes of electrical paroxysmal discharges, rolling movements of the eyes and occasional head shaking by the monkey were sometimes ob-

served, but these did not generally elaborate to convulsive movements. Occasional major convulsions were seen while monkeys were in home cages or during behavioral testing. In other animals, from all experimental groups, motor signs indicative of convulsions were never observed.

BEHAVIORAL TESTING

Experiment I

Learning. On the alternation task the unoperated monkeys in Group *R* attained the learning criterion after 100, 110, and 180 trials, respectively, and the subjects with implanted empty disks after 80 and 130 trials. The three epileptoid animals (Group *L*), however, needed 430, 490, and 510 trials, respectively, until they reached criterion per-

Table 1. Summary of results—Experiment II

Monkey	Delayed alternation (highest score)		Visual discrimination (trials to criterion)	
	% correct	Trials*	Pattern	Object
		Normal group		
473	88	1,650	360	10
488	89	1,120	530	0
490	86	1,920	380	10
536	87	770	380	10
537	91	990	—†	—
		Epileptoid group		
474	66	2,420	550	—
479	77	2,970	320	—
492	79	2,780	190	—
518	58	2,440	140	—

* Normals: number of trials to 85% correct in 100 trials. Epileptoids: total number of training trials.

† Not tested.

formance. On the object discrimination task both subjects in Group *L* responded at criterion level after ten trials. The slower learning rate of the epileptoid monkeys on the alternation task is shown by Fig. 5, which represents learning curves for Group *L* and for the combined Groups *R* and *D*. Both curves increase approximately linearly from chance to the 85% correct performance level. The slopes of straight lines fitted to the curves are 36.4% increase per 100 trials for the control group and 9.2% per 100 trials for Group *L*. Consequently, the learning deficit of the epileptoid monkeys may be expressed by a decrease in rate to approximately one-fourth the learning rate for normal monkeys.

Retention. The median error scores for Group *R* on successive retention series are represented in Fig. 6. Small increases in error scores are seen on the first postoperative test and again after the onset of epileptoid discharges. On both of these tests the subjects reached the retention criterion after a maximum of ten relearning trials, and on the final three retention series the error scores for the group were within the limits of normal monkeys. The effects of epileptoid discharges on retention ability may also be evaluated by comparing retention scores for "normal" monkeys (Group *D* and Group *R* before implantation) with the scores for epileptoid monkeys (Group *L* and Group *R* after onset of discharges). The median error score for the group of five normal monkeys was 4.2 errors on the first and 6.0 errors on the second retention series, while the group of five epileptoid monkeys obtained 7.6 and 6.0 errors, respectively, on the two postepileptogenic series. These data suggest a

slight retention deficit on the first postepileptogenic series, with scores returning to normal limits during subsequent tests. The low score on the first retention series for the normal monkeys may be a consequence of the additional training during the learning tests (100 criterion trials). Consequently, scores on the second series (median of 6.0 errors) may be the most representative for retention by normal monkeys. Differences in retention scores between the two groups were found to be statistically not significant ($p = .200$ on Mann-Whitney *U*-test).

Experiment II

The results from this experiment are summarized in Table 1. On the delayed alternation task the unoperated monkeys responded at criterion level after 770 to 1,920 learning trials, whereas none of the experimental animals reached this level after 2,420 or more trials, when training was terminated. However, the performance of these monkeys showed improvement during training, as seen by the group's learning curve (Fig. 7), which rose from an initial 39% correct responses to 62% at the end of testing. Improved performance was seen by every monkey in this group, subject #479 reaching the highest maximum of 79% correct responses. In contrast to their deficit on the alternation task, the frontal subjects attained criterion on visual discrimination problems within the range of learning trials required by normal monkeys (see Table 1). The learning curves in Fig. 7 rise at approximately linear rates (straight line fit) of 40% increase per 1,000 trials for the control group and 9.5% increase per 1,000 trials for the epileptoid group. The slower learning rate by the experimental group of approximately one-fourth the rate of normals corresponds to the deficit in learning rate obtained in Experiment I. Thus the two experiments, in which different apparatus were employed, resulted in approximately equal reduction in learning rates by epileptoid monkeys compared to normals.

Discussion

The results from the present investigation support earlier findings (3, 9) that cortical implantation of aluminum hydroxide paste and subsequent development of epileptogenic discharges do not interfere with the monkey's *retention* ability for tasks learned either before or after placement of the substance. None of the five epileptoid monkeys tested for retention on the alternation task (Experiment I) showed consistent memory loss during any of the test series. Similarly, Henry and Pribram (3), using a somewhat different testing schedule with two frontally epileptoid monkeys, found a high degree of retention ability on the alternation task during a postoperative period of six months, although clinical seizures were reported in both subjects.

Learning of the alternation task, however, proceeded at retarded rates by the epileptoid monkeys in the two experiments. In Experiment II a newly developed automatic apparatus was used, in which normal monkeys require about ten times the number of trials to reach criterion as is needed in the manual testing apparatus. The results of the two experiments with different apparatus are, however, consistent in revealing comparable learning deficits by epileptoid monkeys to approximately one-fourth the rate of normal animals. The deficit appears restricted to tasks associated with the frontal lobes, since the epileptoid subjects learned visual discrimination problems at normal rates. Moreover, the two monkeys with implanted empty disks learned at the same rates as those of unoperated animals.

Since ablation of frontal cortex results in severe disruption of alternation behavior, the deficits found in the present investigation may be the conse-

quence of damage to cortex. Destruction of cortical tissue was, however, always much less extensive than that obtained from even incomplete ablations; and in several subjects, which showed marked impairment in learning, no retrograde degeneration in the thalamus could be found. Cortical damage to the frontal lobes was restricted to the dorsal and lateral surfaces and did not affect neurons in the depth of the principal sulcus, the region found by Mishkin (7) to be crucial to delayed alternation tasks. Consequently, it seems unlikely that gross anatomical damage to cortical neurons was responsible for the behavioral deficits which were observed.

Placement of the disks always resulted in the growth of considerable scar tissue around the disks. It may be possible that the learning deficit was related to the formation of this tissue, which starts forming shortly after placement of the foreign material. The lack of consistent impairment during retention tests and the normal learning rates of monkeys with empty disks would argue against this hypothesis. Examination of the brains of the monkeys with implanted empty disks showed similar growth of scar tissue surrounding the disks as was seen in the brains where the disks had been filled with aluminum hydroxide paste.

Finally, the observed learning deficit might be related to the occurrence of epileptogenic discharges throughout the period of training. Morrell *et al.* (8), in an investigation of the effects of aluminum hydroxide implants on conditioned blocking of the cortical alpha rhythm, found that conditioned blocking was markedly impaired after the onset of epileptogenic discharges. The deficit was specific to the sensory modality explored; for example, discharges in auditory cortex disrupted blocking previously conditioned to auditory stimuli but not conditioned responses to visual or somesthetic stimuli. Moreover, when the discharging foci were subsequently excised, marked improvement in the elicitation of conditioned responses were observed.

Epileptogenic discharges are indicative of disturbances in normal ongoing patterns of electrical cortical activity. Electroencephalograms in which these discharges appear also contain many patterns of normal electrical activity. The patterns of normal EEG activity may indicate a sufficient amount of healthy neuronal function to account for intact memory for previously learned habits. The efficient learning of new tasks, however, may require a higher degree of stability of cortical organization than is available to the epileptogenic discharging brain. Consequently, retardation in the learning process is observed.

Summary

Experimental epileptiform discharges were induced in monkeys by placement of aluminum hydroxide paste, packed in small silver disks, bilaterally over lateral frontal cortex. Scalp electroencephalograms were taken preoperatively and then at monthly intervals. Focal paroxysmal discharges

from frontal cortex were first seen in the EEGs during the second month after implantation. These patterns were recorded from all subjects during the remainder of their lives.

Two experiments were conducted. In Experiment I untrained rhesus monkeys were trained in a manual apparatus on a delayed alternation task to the criterion of 90 correct alternations in 100 successive trials. Three subjects, which started training after the onset of epileptoid discharges, required 420, 490 and 510 trials to the criterion; whereas subjects with empty implanted disks reached criterion after 80 and 130 trials, and unoperated monkeys after 100, 110, and 180 trials. Comparisons of learning curves indicated that the performance level of the normal group increased at a rate approximately four times the rate for the epileptoid monkeys. The latter subjects learned a visual discrimination task without deficit. The three unoperated monkeys were given nine series of retention tests (to 45 correct responses in 50 trials) at intervals of three weeks. Aluminum hydroxide paste was implanted after the second retention series. The scores of these tests showed no appreciable impairment either postoperatively or after the onset of epileptoid discharges.

In Experiment II untrained cynomolgus monkeys were first tested on an automatic alternation task. Five normal monkeys attained the criterion of 85 correct alternations in 100 trials after 770 to 1,920 trials. The four experimental subjects, which started training after the onset of paroxysmal discharges, did not attain this criterion after 2,400 trials, although their performance improved during training. The learning curve for the normal group rose at a rate approximately four times the rate for the epileptoid group. When the subjects were then tested on a visual discrimination task, the epileptoid group attained criterion without deficit.

The present results, taken together with those from earlier investigations on behavioral consequences of focal epileptoid discharges, indicate marked differences in impairment between retention of previously learned problems and acquisition of new tasks. Retention tests reveal no appreciable memory loss, but there is marked impairment in learning rates. The deficit appears to be restricted to those tasks which are correlated with the cortical structures from which discharges are recorded.

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