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EFFECTS OF SMALL FRONTAL LESIONS ON DELAYED ALTERNATION IN MONKEYS[1]

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THIS EXPERIMENT attempts to define the minimal cortical lesion which will disrupt a monkey's performance on a delayed-response type of problem. If such a cortical focus can be precisely located, data from neuroanatomy and electrophysiology relating this cortical area to other cerebral structures might then be used to suggest the larger cerebral network, and, hence, the neural mechanism, which mediates this class of problem-solving behavior. Of more immediate concern, neural mechanisms already proposed could be more accurately evaluated against the touchstone provided by a description of the cortical focus. A series of studies by Pribram and his associates (13, 15, 16, 18) has demonstrated that the cortical area focally concerned in delayed-response types of functions must be limited at least to the lateral surface of the frontal lobes anterior to the arcuate sulcus. The purpose of the present experiment is to determine whether results obtained by Blum (1) implying an even more limited focus—namely, the mid-lateral cortex—could be substantiated.

Subjects. Ten immature *Macaca mulatta* (*Rhesus*) monkeys, without previous training, were used as subjects.

Apparatus. All animals were trained in a Wisconsin General-Testing Apparatus. The essential features of the apparatus are: an enclosure divided into two sections—an animal chamber and a section for the testing tray; a sliding panel which can be lowered between the two sections to conceal the testing tray from the animal during the baiting and delay periods; a one-way-vision screen which conceals the experimenter when the sliding panel is raised.

METHODS

All animals were trained on delayed-alternation, a delayed-response type of problem that consistently reveals impairment in monkeys with large anterior frontal lesions (8, 18). The animal's task was to displace alternately the lids of two cups, placed 18 in. apart on the sliding tray, for food reward concealed in the cups. Each daily session was introduced by one preliminary trial in which both cups were baited. On the first scored trial the cup not chosen on the preliminary trial was baited. After each correct choice the alternate cup was baited. After an error the concealed food was left in place until, on a subsequent trial, the animal chose correctly. Thus, the animal was trained to alternate be-

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tween the two cups whether or not its previous response was rewarded. Approximately 5 sec. intervened between the end of the response on one trial (sliding panel was lowered) and the opportunity for response on the next (sliding panel was raised). The cups were baited during this interval while they were concealed from the animal's view. Training was continued for 30 trials a day until the animals reached the criterion of 90 correct in 100 consecutive trials. After learning the task each subject received one of four different single-stage bilaterally symmetrical lesions. Ten days after operation the animals were retrained on the alternation problem to the preoperative criterion or for a maximum of 1000 trials.

Operations. The general surgical techniques have been described elsewhere (18). Two animals (VF-7, VF-10) received ventral frontal control lesions, extending from the ventromedial to the ventrolateral edge of the lobe. Similar lesions had been investigated in previous studies (13, 18) and had been found to produce little if any effect on delayed-response or delayed-alternation performance. The lateral surface was then subdivided into three regions. Two animals (IF-273, IF-274) received inferior frontal lesions, extending from the ventrolateral edge of the lobe to the inferior lip of the sulcus principalis. Four animals (MF-11, -19, -47, -87) received midlateral frontal lesions, which included the lips and banks of the sulcus principalis. Finally, two animals (SF-8, SF-50) received superior frontal lesions, extending from the superior lip of the sulcus principalis to the longitudinal fissure.

As can be seen from the reconstructions and cross-sections in Figs. 1 and 2, adjacent lesions—arranged in the order ventral, inferior, midlateral, and superior—overlapped at their boundaries. In general, the lesions extended from the level of the limbs of sulcus arcuatus forward to the pole.

Results

Midlateral lesions. Preoperative and postoperative trial and error scores are shown in Table 1. Of the ten animals, the poorest postoperatively were the four animals with midlateral lesions. Of these four, two animals failed to reach criterion in 1000 trials and the two others attained criterion only after 400 trials. The two animals that failed in 1000 trials were punished with a mild shock each time they touched the incorrect cup in the last 500 trials. Despite this added incentive their performance during the second half of training was little better than their performance during the first half (see Table 1).

A comparison of the lesions *within* the midlateral frontal group does not seem to yield any consistent relationship between locus or extent of cortical damage and magnitude of the alternation deficit. Of the two animals with the most complete resection of the *banks* and *depths* of the sulcus principalis, one did relearn the alternation (MF-19) and one did not (MF-87). Of the two animals with the most complete resection of the *lips* and *surface* surrounding the sulcus principalis, one relearned the problem (MF-47) and one did not (MF-11). With respect to overall extent of damage the two animals that succeeded in reacquiring the alternation habit seem to have had at least as much damage to the midlateral region as the two animals that failed. There is, however, one anatomical finding which does appear to correlate with the behavioral deficits of the midlateral animals. As may be seen in Figs. 1 and 2, the extent of retrograde degeneration in nucleus medialis dorsalis is considerably greater in the two animals which failed than in the two which relearned. It cannot be determined whether the greater degeneration resulted from greater damage to a small critical area of the midlateral frontal cortex

or whether it was due instead to greater damage to the projection fibers below the cortex. At any rate, as will be pointed out shortly, the retrograde degeneration, itself, would seem to be of doubtful significance for the behavior studied.

Inferior lesions. The only other operated animals which showed evidence of impairment were the two animals with inferior frontal lesions. Both required a larger number of trials to achieve criterion than they had required before operation. It is of interest, however, that on the first two or three days of postoperative testing the performance of these two animals averaged 88–90 per cent correct. Only on the third day of training in the case of IF-274 and the fourth day for IF-273 (for both, approximately two weeks postoperatively) did performance fall, but then, abruptly, to chance. Within a

Table 1. Delayed alternation

Scores are trials and errors preceding criterion of 90 correct in 100 consecutive trials. A score of 1000 trials denotes inability to attain criterion; error scores in such cases are divided into those for first and second 500-trial blocks. (VF, IF, MF, SF = ventral, inferior, midlateral, superior frontal lesions respectively.)

	Preoperative		Postoperative	
	Trials	Errors	Trials	Errors
VF-7	660	234	170	39
VF-10	240	100	60	15
IF-273	210	89	240	43
IF-274	180	60	260	93
MF-11	330	128	1000	506 (271–235)
MF-19	930	326	410	129
MF-47	510	161	470	140
MF-87	60	14	1000	264 (137–127)
SF-8	190	75	0	0
SF-50	340	150	100	19

week of further training the performance of both animals returned to their final preoperative and initial postoperative level. One month later these animals were again tested to determine whether a disruption in performance would reoccur, but both animals achieved criterion immediately and remained at this level for 200 trials.

Other lesions. All four animals with ventral frontal or superior frontal lesions reattained criterion quickly in the postoperative testing. They required an average of 75 per cent fewer trials and 85 per cent fewer errors than they had required for learning the task initially.

In summary, the results suggest (i) that damage limited to the region of the sulcus principalis will always produce at least some impairment in delayed alternation, and, on occasion, may produce marked and sustained impairment; (ii) that damage limited to the inferior lateral surface may also produce impairment but that it is considerably less severe; and finally, (iii)

that damage limited either to the superior lateral surface or to the ventral surface probably produces no impairment. It does not seem likely that these differences in the effects of the various lesions can be ascribed to differences in the extent of the removals. The damage in all four types of lesion, as can be seen from the reconstructions and cross sections in Fig. 1, are of roughly equal extent.

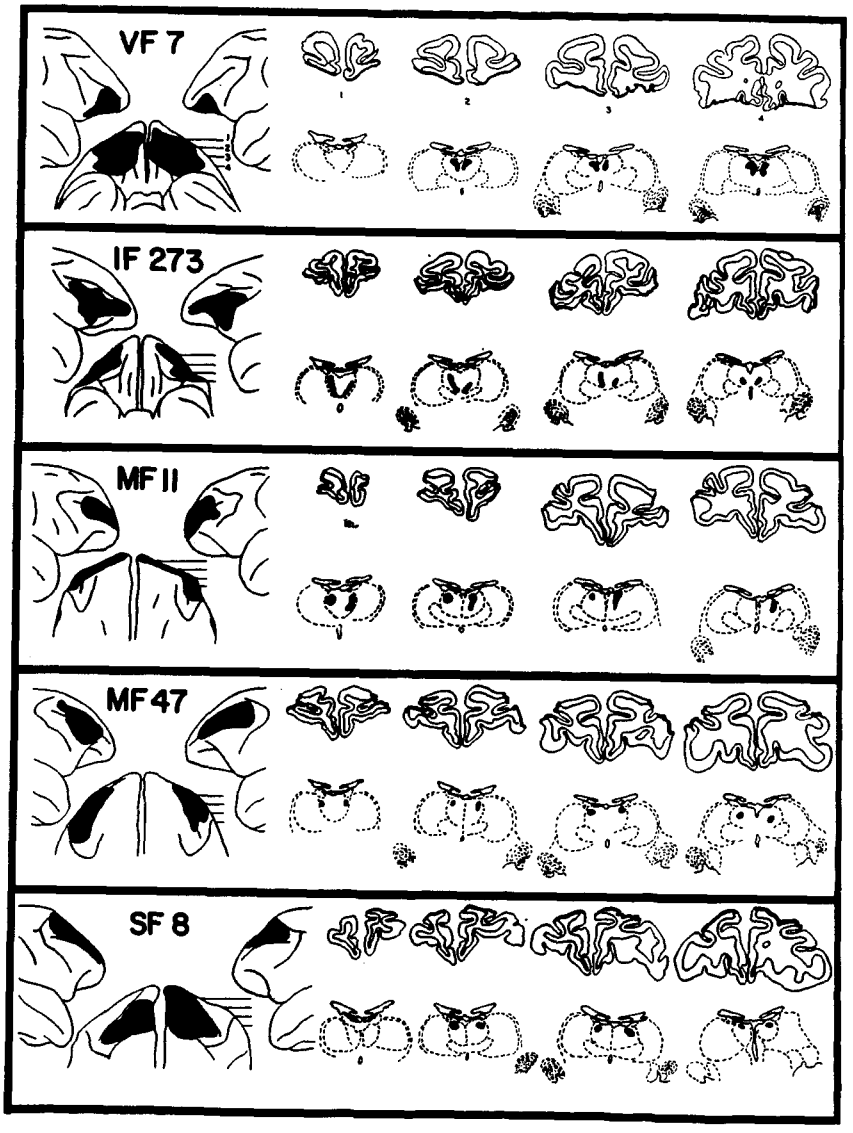

FIG. 1. Diagrams of lesions. Black in reconstructions and cross sections indicates area of ablation. Black in thalamus indicates area of retrograde degeneration. For each animal the four cerebral frontal sections correspond to four anterior-posterior levels as indicated for animal VF-7.

COMMENT

The results of this experiment substantiate the conclusion reached by Blum (1) that the midlateral frontal cortex may be considered to be the focal cortical area serving delayed-response types of behavior in the monkey. This conclusion is not necessarily contradicted by Pribram's recent finding (12) that lesions of the "frontal eye-fields" (*i.e.*, in and around the sulcus arcuatus) may also produce delayed-response deficit, since the posterior portion of the midlateral region was included in Pribram's lesions. It should be

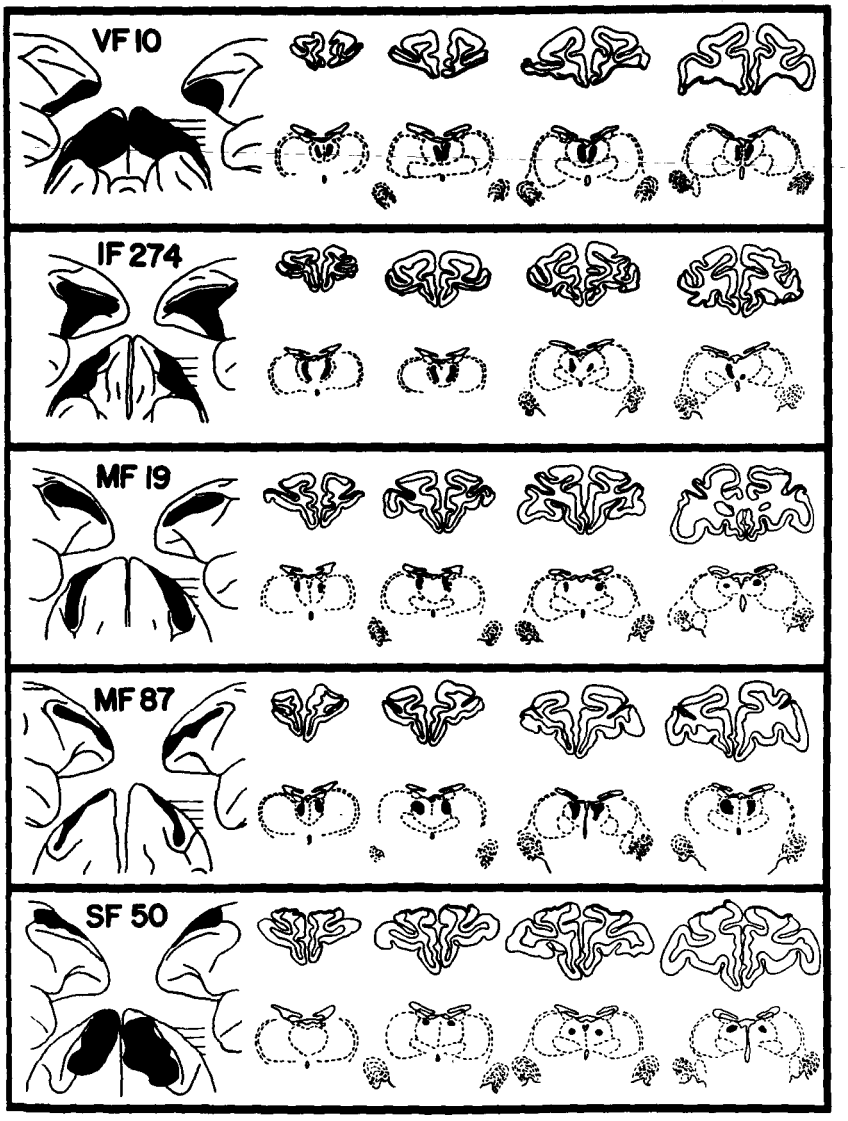

FIG. 2. See legend to Fig. 1.

noted, further, that in the present experiment and in Blum's invasion of the "frontal eye fields" above the midlateral region did not seem to interfere with performance on delayed-response types of tasks.

The severity and irreversibility of the deficit that can be produced by a lesion limited to midlateral frontal cortex is demonstrated by the history of MF-11. This animal was studied intensively on a variety of delayed-response types of tasks for more than a year following operation (8, 9, 17). Throughout this period MF-11 continued to perform as poorly as did animals with total destruction of the lateral granular cortex of the frontal lobes. Other animals in the present experiment with midlateral lesions of the same size as that in MF-11 did not sustain nearly as severe deficit. This variability in performance among the midlateral animals is probably related to the particular size of lesion which was studied—that is, midlateral lesions larger than the ones studied would probably always result in severe deficit; smaller midlateral lesions might not ever produce a severe deficit.

The delayed behavioral effect found in the animals with *inferior* frontal lesions could be related to the proximity of the damage to the proposed focal cortical area. The phenomenon of delayed behavioral disturbance has raised the possibility that deficits following brain damage are only indirectly related to the cortical removal (3, 4). However, a recent study (10) designed to investigate delayed effects in monkeys failed to demonstrate the phenomenon, and such effects were not observed in any of the animals with midlateral lesions. When delayed disturbance does occur it may be due, perhaps as it was in the present experiment, to a lesion which borders a critical area, affecting it by the development of pathological tissue at the borders of the lesion. Such an explanation fails to account, however, for the alck of effect in animals with superior lateral surface lesions which also bordered the proposed critical area.

Wade (20) has provided evidence that the essential connections of any focal frontal area which mediates delayed-response must be with subcortical structures via projection fibers, and not with other cortical areas via short association fibers. This conclusion was based on a comparison between the effects of lobotomy and of circumsection of the frontal lobes, the former lesions producing severe impairment on delayed response, and the latter, none.

At least two subcortical structures, the thalamic nucleus medialis dorsalis and the caudate nucleus, have projections to the frontal cortex. With respect to the thalamic nucleus, data from retrograde degeneration studies indicate that the central parvicellular portion of n. medialis dorsalis projects to the cortex along the sulcus principalis (14). However, Chow (2), investigating the effects of stereotaxic lesions in this portion of the nucleus, failed to find any evidence of delayed-response impairment. This negative result has since been confirmed by Peters *et al.* (11).

With respect to a second subcortical-frontal projection system, Mettler and others (6, 7) have recently succeeded in recording activity in frontal cortex on stimulation of the caudate nucleus. They have described the re-

sponsive area as corresponding to areas 10 and possibly 11 of Brodmann. This evidence for a caudate-frontal projection is supported by the findings by Mettler *et al.* (6, 7) and Harman *et al.* (5) of shrinkage and loss of cells in the caudate nucleus following ablation of the active frontal region. Evidence that the caudate nucleus may, indeed, play an important role in delayed-response behavior has been obtained by Rosvold and Delgado (19) in a study of the effects of intracerebral stimulation during performance on an alternation task. Analysis of the placement of electrodes in these experiments showed that both electrical stimulation and subsequent electrocoagulation of points in the head of the caudate nucleus interfered with the animal's performance. The present results and those of Blum, however, have shown that lesions which damage the proposed caudate projection field (the ventrolateral edge of the frontal lobes) do not produce as severe impairment as do lesions above this projection field (the midlateral frontal region).

For the present, then, the evidence suggesting that midlateral frontal cortex constitutes a critical focus for delayed-responses does not correlate well with other neural data. Further work aimed at resolving the discrepancies, particularly with respect to a possible caudate-frontal mechanism, is certainly indicated. However, it would also seem profitable at this time to search for other subcortical structures which could conceivably interact with the proposed frontal focus in the mediation of delayed-response types of behavior.

Summary

To help define the cortical area focally concerned in delayed-response types of functions in the monkey, ten animals were given various subtotal lesions of frontal granular cortex and tested for the retention of a delayed-alternation habit. The four animals that received lesions of the midlateral cortex performed more poorly than the animals with other lesions. In one instance a midlateral lesion produced a deficit that was as severe and as long-lasting as that following total anterior frontal ablation. The results are discussed in relation to possible neural mechanisms for the mediation of delayed-responses in the monkey.

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