

LESIONS OF "FRONTAL EYE FIELDS" AND DELAYED RESPONSE OF BABOONS¹

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IN MAN THE "superior midfrontal zone" has been considered to be of prime significance in the intellectual deficit resulting from frontal lobe removals (8), a consideration which has received some experimental confirmation (7). In monkey, homologous cortex has been shown to be critically related to the performance disability in delayed response and delayed alternation problems (1, 12). Lashley has suggested that, since the performance of classical delay problems depends in part on vision, the decrement in performance following frontal lesions might be related to the invasion of the posterior portion of the superior midfrontal zone: "the frontal eye fields." This suggestion received some support from the results of selective partial ablations of frontal cortex in man which indicated that while excision of no one cortical area of those sampled influenced intellectual functions permanently, those involving the frontal eye fields produced "the most pronounced of the transient effects noted" (7).

In addition to locus, the type of injury may be important in relating changes in behavior to frontal lobe lesions. Stated explicitly, maximum behavioral change is expected to result from pathologically functioning tissue rather than from lack of tissue *per se* (5). With regard to the relationship between frontal lesions and delayed response performance, support for this hypothesis has been adduced. One study has shown that an animal with severe impairment of delayed response performance following frontal resection was susceptible to Jacksonian seizures when benzedrine was administered in doses too small to affect unoperated animals (3). Another study reported the effects on delayed response performance of implantation of aluminum hydroxide cream over the anterior frontal cortex. Marked, although inconsistent, impairment of performance resulted from such lesions in spite of the fact that only minimal anatomical damage to cerebral tissue could be observed (9).

The present study was undertaken to answer specifically the questions posed by the previous experiments. (i) Can the decrement in delayed re-

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sponse problem solving performance be selectively related to injury of the "frontal eye fields"? (ii) Is the decrement in delayed response performance related to dysfunction of this cortex rather than absence of tissue?

MATERIALS AND METHODS

Four *Chlorocebus* baboons, immature females, were trained to a criterion of 90 per cent correct responses in 100 consecutive trials in a visual pattern discrimination and in the delayed response problem. Apparatus, testing procedures, and preoperative testing schedule were identical with those described in detail by Pribram *et al.* (12). In addition, visual fields and visual pursuit were examined by the method described by Pribram and Bagshaw (10).

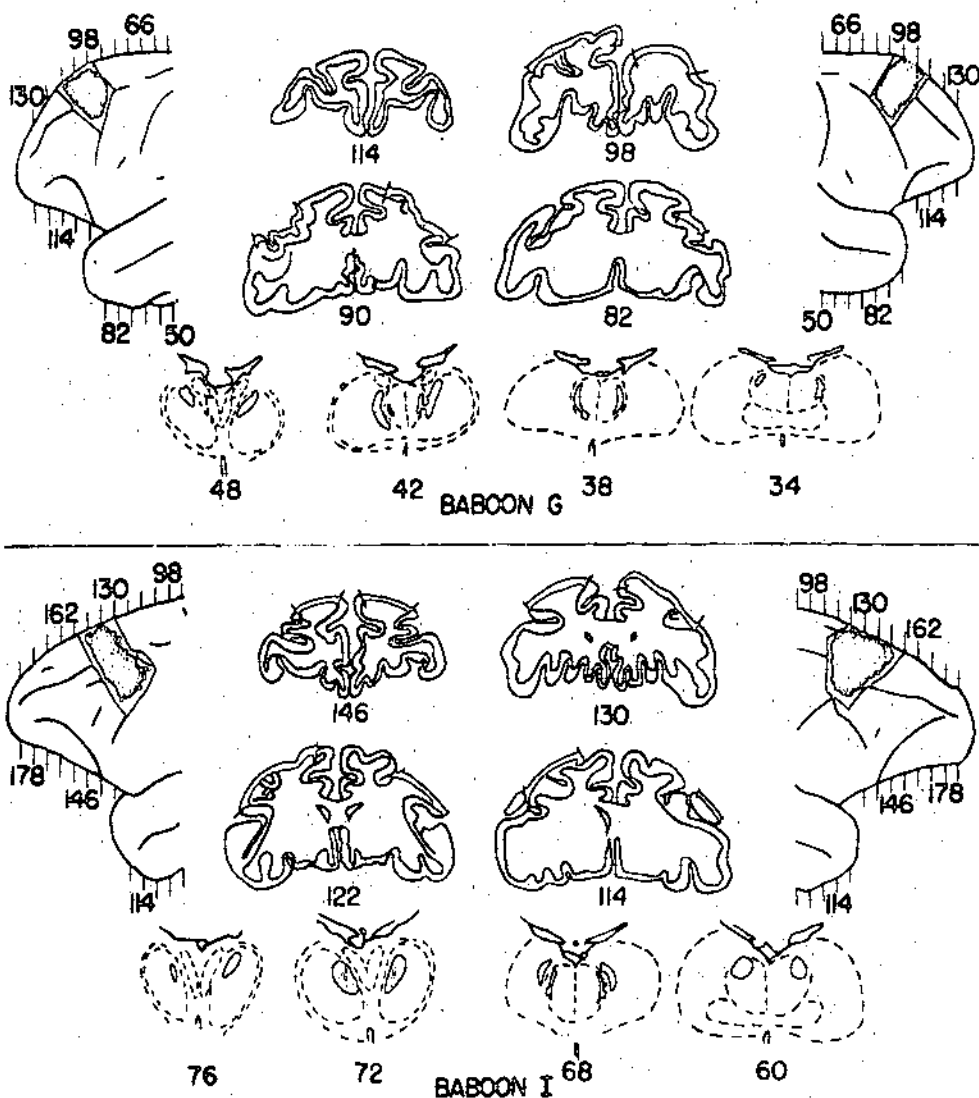


FIG. 1. Reconstruction, representative cross sections through lesions and thalamus of brains of baboons G and I who received resections of "frontal eye fields." Black indicates lesion in cortex and degeneration in thalamus.

Two animals were angle and superior r third animal had imp aluminum hydroxide superior ramus, and served as an unoper through a full calvari cream was prepared to a workable consist minutes.

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riterion of 90 per cent discrimination and in the operative testing schedule (12). In addition, visual d by Pribram and Bag-

Two animals were subjected to bilateral, one-stage resections of both banks of the angle and superior ramus of the arcuate sulcus and the surrounding exposed cortex. A third animal had implanted on each hemisphere four 1 cm. diameter silver discs filled with aluminum hydroxide cream, two within the limbs of the arcuate sulcus, one above the superior ramus, and one on the medial surface above the cingulate gyrus. The fourth animal served as an unoperated control. All surgical procedures were performed aseptically through a full calvarium flap hinged on the left temporal muscle. The aluminum hydroxide cream was prepared from commercial Amphogel by dilution with normal saline solution to a workable consistency and sterilized by immersion in a bath of boiling water for 20 minutes.

During the first postoperative month all four animals were tested weekly in the visual field and pursuit tasks and given 100 trials of visual discrimination. Also during the first postoperative month 150 trials (50 trials per day) of delayed response were given and this number of trials repeated each month for six months, and thereafter every three months for the remainder of the first postoperative year. During the tenth postoperative month all were trained to perform the delayed alternation problem in the manner described by Pribram *et al.* (12).

In addition to the other procedures, the animal with the aluminum hydroxide cream implantation and the unoperated control were subjected, during the eighth postoperative month, to intravenous injections of metrazol sufficient to produce generalized convulsive seizures. Delayed response testing was resumed within 15 minutes following the end of the seizures and continued for 350 trials (at 50 trials per day) distributed over the week following the injection. Subsequently, 1 mg./kg. per day of orally administered benzedrine was given all four animals daily for one week. Testing continued during this period. Electroencephalograms were obtained once preoperatively and once each postoperative month for 12 months. Animals were anesthetized with sodium pentobarbital (30 mg./kg.) for this procedure. No waking records were made lest such a procedure interfere with behavioral testing.

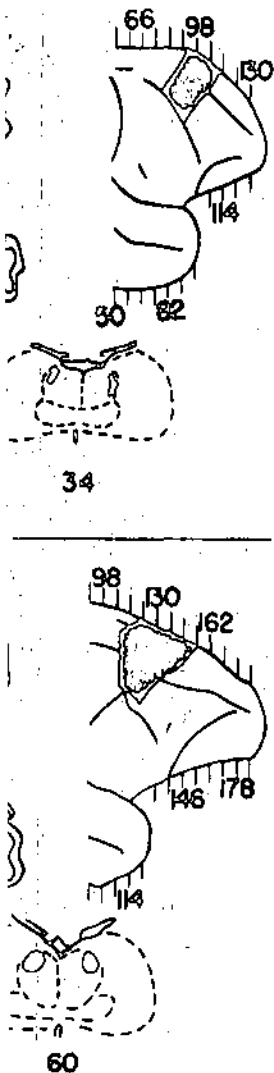
Following completion of the testing program all operates were sacrificed. Their brains were perfused with saline solution and with 10 per cent formalin. They were then fixed, dehydrated in alcohols, imbedded in celloidin, serially sectioned and stained with thionine. From these sections, the cortical extent of the lesions was reconstructed.

Reconstructions, representative cross sections and thalamic degeneration are shown in Fig. 1. The lesions are approximately bilaterally symmetrical and involve the anterior dorsal agranular and the posterior dorsal granular frontal cortex. The resection extends to include the depths of the arcuate sulcus, especially that of the superior limb. The posterior extremity of the principal sulcus is also involved. Retrograde thalamic degeneration is limited to the lateral portion of the n. medialis dorsalis, especially the paralamellar portion, the medial portions of the n. ventralis anterior, and the n. ventralis lateralis. These observations confirm those obtained in the macaque monkey regarding the thalamo-cortical relationship of this portion of the brain (4, 11).

The discs filled with aluminum hydroxide cream had outlined, in the frontal cortex adjacent, anterior and dorsal to the arcuate sulcus, round areas which were compressed and which had lost the laminar arrangement of nerve cells. Throughout and around the margins of each of these areas was a moderate amount of glial proliferation. The cortex surrounding each lesion stained poorly with thionine for as far as 2 mm. although no chromatolysis, pyknosis, or other abnormality was apparent. Serial analysis of the thalamus failed to reveal any cellular abnormality.

RESULTS

1. *Seizures.* All electroencephalographic records fell within normal limits except those obtained postoperatively from the animal with aluminum hydroxide cream implantations. These records showed abnormal, relatively high voltage slow waves (3-4/sec.). These slow waves were first observed in the second postoperative month and reached a maximum amplitude of 100 μ V. in the sixth postoperative month. They were still present but of approximately half this amplitude in the twelfth postoperative month. The slow activity was approximately equal bilaterally and though obtained from



h lesions and thalamus e fields." Black indicates

all leads was maximal in the frontal and central recordings. In addition, occasional bizarre spikes were observed in the left frontal recording during the second, third, fourth, sixth, and seventh postoperative months. No other abnormalities were observed.

Except after metrazol injections, convulsions were observed only in the animal with aluminum hydroxide cream implantation. They were seen for the first time two months postoperatively, were Jacksonian in type, and consisted in a nystagmoid jerking of the eyes which spread to involve the head and occasionally the upper extremities. They lasted 2 minutes each; no generalized convulsions ensued. The seizures appeared to be bilaterally symmetrical at this time. One or two seizures were observed daily - some during the period of behavioral testing. No immediate effect of seizure on test performance was seen: The animal would usually continue to respond, and respond correctly, even during the period of an observable seizure. These convulsive episodes continued in this manner during the next month, but increased in frequency and duration. Approximately three and one-half months postoperatively the seizure pattern spread to involve the trunk musculature. Turning of eyes and head was followed by body rotation and then by circular running in ever tightening spirals. These running seizures were observed to be in either a clockwise or in a counterclockwise direction; occasionally, the running would abruptly change direction. At this time, the seizures could be initiated by threatening the animal with a stick, or by presenting him with food. Seizures were often terminated by clonic-tonic generalized convulsions accompanied by complete unresponsiveness. Four months postoperatively the seizures became less frequent, though when they occurred they were as severe as before. By the end of the fourth postoperative month convulsive episodes were no longer observed and could not be induced by threatening gestures or by presentation of food.

Convulsions were produced by intravenous injections of metrazol in the animal with aluminum hydroxide cream implantation and in the control animal. However, the dose necessary to produce convulsions was one-half as great for the former as compared with the latter animal. Oral administration of benzedrine did not result in convulsions in any operate or in the control animal.

2. *Behavior.* There was no gross limitation of eye movements in any animal even during the first postoperative week. No change in eye movements was noted whether the observations were made while the animal was "spontaneously" searching or during the testing of visual pursuit. Nor was there any impairment of the visual field in these animals.²

² There has been considerable controversy regarding a "pseudohemianopia" alleged to follow unilateral frontal resections; as the ablations in the current experiments were made bilaterally in one stage, no information regarding this problem was obtained. The author has seen a transient change in performance lasting about one week following a unilateral procedure when two objects are brought simultaneously into both temporal fields of the animal (double simultaneous stimulation). During this period, animals fail to respond to objects in the visual field contralateral to the lesions even when such objects are "preferred" food (banana) or "threatening" (stick) and the paired object is "neutral" (peanut). In such animals a visual field defect was not detected when other methods were used.

Table 1. Del.

Post-operative month	B	L
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2		
3		
4		
5		
6		
9		
12		

* Jacksonian seizure
 † Convulsions general
 ‡ Delayed response fields" (baboons G and eye fields" (baboon H 150 consecutive trials response performance

Finally, there was a decrease in performance. The animals operated preoperatively (ran within 10 trials. In performance, the animal again gave criterion

Scores obtained be noted are the first month in performance six months postoperative in performance (to five months) of the did not coincide with and to fourth month performance decrease (see Table 3). Operates and on the completed. These were are compared with

Scores of original presented in Table 2. Operates presented animals with resection controls have performed animals with resection open until data on

Table 1. Delayed response. Preoperative mean 310 (range 130-410) trials to 90% in 100 consecutive trials

Post-operative month	Baboon G Resection	Baboon H Aluminum cream	Baboon I Resection	Baboon J Control
1	77	88	71	80
2	70	91*	66	88
3	72	88	68	93
4	74	63†	73	87
5	78	65†	75	88
6	81	87	88	91
9	87	95	87	93
12	92	93	86	96

* Jacksonian seizures observed daily.

† Convulsions generalized; more frequent and severe at this time.

Delayed response performance scores of animals with (i) resections of the "frontal eye fields" (baboons G and I) and (ii) aluminum hydroxide cream implants over the "frontal eye fields" (baboon H) and of a control animal (baboon J). Scores are per cent correct of 150 consecutive trials. Note lag between onset of convulsions and decrement in delayed response performance in baboon H.

Finally, there was no impairment of visual pattern discrimination performance. The animals had learned this discrimination with a mean of 240 trials preoperatively (range 120-410); all animals reached criterion postoperatively within 10 trials. During the periods of decrement in delayed response performance, the animal with the aluminum hydroxide cream implantation again gave criterion visual discrimination performance without further training.

Scores obtained in the delayed response test are detailed in Table 1. To be noted are the findings that (i) the animals with resections showed a decrement in performance (70 per cent level) which persisted for approximately six months postoperatively, and (ii) the onset and termination of decrement in performance (to a 65 per cent level during the fourth and fifth postoperative months) of the animal with aluminum hydroxide cream implantation did not coincide with the onset and termination of convulsive seizures (second to fourth month). Temporal dissociation between convulsions and performance decrement is also observed to follow metrazol induced seizures (see Table 3). Oral administration of benzedrine had the same effect on all operates and on the control animal: only 10-15 trials per day were completed. These were performed without any noticeable decrement when scores are compared with the immediately preceding performance of the animal.

Scores of original learning of the delayed alternation problem are presented in Table 2. These are to be compared with the scores of other frontal operates presented by Pribram *et al.* (12). Although performance of the animals with resections is below that of the control animal in this study, other controls have performed at the lower level. The question of whether the animals with resections performed within normal limits must therefore be left open until data on more animals are available.

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Table 2. Delayed alternation. (10-11 postoperative months)

Week	Baboon G Resection	Baboon H Aluminum cream	Baboon I Resection	Baboon J Control
1	77	76	83	100
2	79	74	86	98
3	83	77	86	---
4	77	84	88	---
5	77	81	91	---

Delayed alternation performance scores of the animals used in this study. Scores are per cent correct of 250 consecutive trials. These results are to be compared with those obtained under similar conditions in baboons with dorsolateral or ventromedial frontal granular cortex resections reported by Pribram *et al.* (12).

3. *Summary of results.* Resection of the "frontal eye fields" interferes with delayed response performance; however, this interference is not as drastic as that resulting from lesions which also include the dorsolateral frontal granular cortex (12). Immediate postoperative scores of 70-75 per cent are attained when the resection is limited to the frontal eye fields and improvement of performance occurs with time and practice—a stable performance level comparable to preoperative performance may be attained within a year. Postoperative initial learning of delayed alternation compares favorably with that of other frontal operates and one control animal (C3 reported by Pribram *et al.*) although two other nonoperate controls (C1 and baboon J) performed at a higher level.

Aluminum hydroxide cream implantations result in Jacksonian seizures beginning with eye and head movements and in sporadic decrement in delayed response performance level. Seizures and performance decrement are not necessarily associated; seizures may be present without concomitant decrement in performance (*viz.*, Table 2, 2nd and 3rd month); onset of the decrement in performance does not follow metrazol-induced seizures immediately but is delayed for a day and persists for four days although no

Table 3. Metrazol in 8th postoperative month

Days	Baboon H (Irritative) 3 IV injections of 0.75 cc. metrazol each	Baboon J (Control) 3 IV injections of 1.5 cc. metrazol each
1	92	90
2-3	44	91
4-5	80	92
6-7	95	92

Comparison of the effects of metrazol-induced convulsions on the performance of delayed response by an animal with aluminum hydroxide cream implantation over the "frontal eye fields" (baboon H) and a control animal (baboon J). Numbers indicate performance scores on 100 consecutive trials except on day 1. The score for this day is based on 50 trials given within 15 minutes following the last induced convulsion.

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further seizures are noted; metrazol-induced seizures in the nonoperate control animal are not followed by any decrement of performance (Table 3).

DISCUSSION

The findings of the current study indicate that lesions of the frontal eye fields do not impair delayed response performance as drastically as lesions which also invade the dorsolateral frontal granular cortex (12); this result makes it unlikely that the decrement in performance can be related to the central mechanisms regulating eye movements. This contention is further supported by the partial dissociation between convulsive episodes and change in performance. Since, in a study by Blum (1), impaired delayed response performance followed frontal lesions whether the predelay cue was auditory or visual, that author concluded that "decrement in postoperative performance is unrelated to the modality through which the differentiating cue is received." Thus it appears that the involvement of frontal cortex in delayed response performance cannot be selectively related to the visual modality, no matter whether a "sensory" or a "motor" mechanism is hypothesized.

The dissociation between decrement in performance resulting from the aluminum hydroxide cream implantation and the electrical evidence of dysfunction casts some doubt on the conception that the effects of frontal resections are primarily due to the effects of scars produced at the borders of the ablation. The dissociation between change in performance and convulsive episodes, as well as the delay in onset of performance decrement following metrazol seizures, makes it necessary to modify current hypotheses concerning the mechanism of the production of deficit: neither the idea that "irritative" lesions cause dysfunction as measured by the electroencephalogram, nor the conception that "loss" of the tissue presumed to provide the locus of "immediate-memory traces," account, by themselves, for all the data. Apparently the cerebral mechanism implicated in delayed response performance is susceptible to disruption either by resection or by aluminum hydroxide cream implantation. As yet this mechanism defies precise specification.

SUMMARY

1. Four Chacma baboons were trained to a criterion of 90 per cent correct responses in 100 consecutive trials in a visual pattern discrimination and in the delayed response problem.

2. Two animals were subjected to bilateral, one-stage resections of both banks of the angle and superior ramus of the arcuate sulcus and surrounding exposed cortex. A third animal had implanted on each hemisphere four 1 cm. diameter silver discs filled with aluminum hydroxide cream, two within the limbs of the arcuate sulcus, one above the superior ramus, and one on the medial surface above the cingulate gyrus. The fourth animal served as an unoperated control.

months)

Baboon J Control
100
98

in this study. Scores are compared with those of ventromedial frontal

fields" interferes with performance is not as drastic as bilateral frontal granular cortex. 75 per cent are attained and improvement in performance level is maintained within a year. Performance compares favorably with that reported by Prioleo and baboon J) performance

Jacksonian seizures and a 50 per cent decrement in performance decrement are noted without concomitant seizures (within a month); onset of the metrazol-induced seizures immediately after days although no

Baboon J (Control)
3 IV injections of 5 cc. metrazol each
90
91
92
92

the performance of delayed response after implantation over the control. Numbers indicate performance for this day is based on the number of correct responses.

3. Decrement in performance was restricted to the delayed response situation in those animals given resections of the frontal eye fields. Performance ranged around the 70 per cent level for six months postoperatively.

4. The animal with the aluminum hydroxide cream implantation suffered from seizures, both electrical and behavioral. In addition, this animal showed a decrement in delayed response performance for a period of two months. This decrement was partially dissociated in time from the occurrence of seizures.

5. Metrazol-induced seizures resulted in decrement or delayed response performance in the animal with aluminum hydroxide cream implantation, but not in the unoperated control. Decrement in performance was delayed, however; immediately after seizures the animal performed at criterion, but performance fell to chance during the following two days.

6. It is concluded that frontal eye fields, although implicated in delayed response performance, are not *critically* related to this behavior since more anteriorly placed lesions result in a more profound deficit in performance. It is also concluded that the effect of such anteriorly placed lesions cannot be ascribed to scarring of the frontal eye fields since aluminum hydroxide cream lesions have only a temporary effect on performance. Finally, an interesting and yet unexplained phenomenon has been described: the temporal dissociation between convulsive episodes and performance decrement.

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