1963 ✓ (98)

Journal of Comparative and Physiological Psychology
1963, Vol. 56, No. 1, 11–18

DELAYED-RESPONSE PERFORMANCE FOLLOWING OPTIC TRACT SECTION, UNILATERAL FRONTAL LESION, AND COMMISSUROTOMY[1]

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Serial operations were performed on 9 Macaca mulatta to transect optic tract on one side, to ablate one frontal area, and to transect the corpus callosum, psalterium and anterior commissure. Delayed-response performance in Ss with visual input ipsilateral to normal frontal area was superior to that in those with visual input contralateral to normal cortex. Subsequent commissurotomy virtually ended correct delayed-response performance in Ss with contralateral lesions, but had far less effect on those with ipsilateral lesions. Hyperactivity was not correlated with impairment of delayed-response performance. Corticocortical connections between occipital and anterior frontal cortex via cortical association fibers are probably crucial for successful delayed-response performance. Moreover, interhemispheric connections are capable of sustaining psychological functions dependent on corticocortical connections.

Bilateral lesions of the frontal granular cortex impair the monkey's ability to perform a variety of delayed-response type tasks (Jacobsen, 1935; Meyer, Harlow, & Settlage, 1951). The critical locus appears to be the dorsolateral frontal cortex, especially the region in and around *sulcus principalis* (Blum, 1952; Mishkin, 1957; Pribram, Mishkin, Rosvold, & Kaplan, 1952). As lobotomy is also followed by impairment of delayed response (Orbach, 1956; Wade, 1952), connections of frontal cortex with other brain structures apparently are necessary for delayed-response performance. Thalamocortical projections seem to be not essential, since massive lesions of the dorsomedial nucleus do not affect delayed response (Chow, 1954; Peters, Rosvold, & Mirsky, 1956). Lesions of the caudate nucleus, on the other hand, do impair such performance (Dean & Davis, 1959; Rosvold & Delgado, 1956). These authors have suggested that the loss following lobotomy may result from the severance of fiber connections between the frontal lobes and caudate nucleus. The role of corticocortical circuits in the delayed response remains unclear. In a direct study of the functions of corticocortical connections, Wade (1952) found that circumsection of the dorsolateral frontal lobes to the depth of the gray matter did not impair delayed response performance and concluded that connections with subcortical structures via the white matter must therefore account for the deficits following lobotomy. However, her circumsections were rather far anterior and did not cut through the cortex within the *sulcus principalis*, an area which Mishkin's (1957) study showed to be of great importance. By contrast, Wade's two lobotomies, which apparently did pass through the cortex within this region, led to a marked deficit in delayed response.

The present study was designed to investigate the role of corticocortical pathways in delayed response. Specifically, it is argued that if vision is restricted to one hemisphere by transection of one optic

[1] This investigation was initiated during tenure by the senior author of a Postdoctoral Fellowship from the National Institute of Mental Health, United States Public Health Service Grant No. M-3372. The research was also supported by a grant from the National Science Foundation, by the National Institute of Mental Health Grant No. MH-06722, and by the F. P. Hixon Fund of the California Institute of Technology. We are grateful to Janet Chapple, who assisted in all phases of the training.

tract, and if the anterior frontal lobe contralateral to the visual input is then ablated, the only remaining completely corticocortical connections between occipital and frontal areas pass via the commissural system (presumably via a prestriate or an inferotemporal relay). If subsequent commissural section impairs delayed response, the role of corticocortical pathways in successful performance is evident. Neocortical commissural connections appear to be predominantly homotopic (Bremer, Brihaye, & André-Balisaux, 1956); therefore, an ipsilateral occipitofrontal circuit should be more efficient than a contralateral one, since the contralateral circuit would contain at least one more (commissural) neuron. In a comparable study Blum (1949) obtained results somewhat different from those reported here. These differences will be analyzed in the Discussion.

Methods

Subjects

Nine *Macaca mulatta*, each weighing about 8 lb., were used. All were adolescent and experimentally naive.

Apparatus

The *S*s were trained in a modified Wisconsin apparatus, equipped in front with a transparent and an opaque screen. With these screens *E* could allow or prevent vision during the delay interval. The test cage contained a movable barrier so that the position of either side wall could be changed independently. Monkeys could thus be restricted to a specific side of the cage in order to facilitate the training necessary to overcome the effects of hemianopia on performance.

Delayed-Response Tests

In transparent screen training *S* was shown a raisin through the plastic screen. The raisin was then placed in one of two wells, both of which were then covered with black wooden blocks. After a specified delay, the screen was raised, so that *S* could choose one well or the other. Opaque screen training was identical, except that a fiberboard screen was lowered after the raisin was placed and remained down throughout the delay interval. Correction of errors was not permitted.

Table 1 summarizes the testing sequences for all nine *S*s. With either screen, *S* worked 50 trials a day on gradually increasing delays. Initially, no delay was imposed. When *S* made 9 correct responses in any block of 10 successive trials, a 1-sec. delay was initiated. When the same score was made with this delay, the interval was increased to 2 sec. Similarly, at each delay interval, as soon as *S* made 9 correct responses in any block of 10 trials, the interval was increased by 1 sec. The criterion performance was 9 correct trials out of 10 with a 15-sec. delay. To prevent attainment of the criterion by random successes, the initial delay interval for each day's testing was set at 1 sec. shorter than the maximum delay for the preceding day. This procedure imposed a minimum of 240 trials for reaching the 15-sec. criterion, i.e., if an

TABLE 1

Summary of Surgical Procedures and Test Sequences

Monkey	Testing Screen[b]	Operation[a]	Testing Screen[b]	Operation[a]	Testing Screen[b]	Operation[a]	Testing Screen[b]
			Ipsilateral Group				
ABR		L-Op.tr.sec.	T	L-Pf.abl.	T	Comm.	T; O
FRD				L-Op.tr.sec. & L-Pf.abl.	O		
IRV	T	L-Op.tr.sec.	T	L-Pf.abl.	T	Comm.	T; O
WLC		R-Op.tr.sec.		Comm.	T	R-Pf.abl.	T; O
			Contralateral Group				
DNY	O			R-Op.tr.sec. & L-Pf.abl.	T		
GRG	O			L-Op.tr.sec. & R-Pf.abl.	O		
GLT	T	L-Op.tr.sec.	T	R-Pf.abl.	T		
JCB	T	L-Op.tr.sec.	T	R-Pf.abl.	T	Comm.	T; O
ULY		R-Op.tr.sec.	T	L-Pf.abl.	T	Comm.	T; O

[a] Symbols used: L(left) or R(right) indicates side of lesion; Op.tr.sec. = Optic tract section; Pf. abl. = Prefrontal ablation.
[b] T = transparent; O = opaque.

animal was correct on all trials, it would reach criterion performance on the fourth day, in 240 trials.

In addition to delayed response reported here, most of the *S*s were tested concurrently on visuomotor coordination and a simple visual discrimination habit in another apparatus.

Operative Technique

To minimize damage to the hemisphere which was to remain intact, all operations were carried out from the same side, even in the three-stage operations. Initially a large skull plate was removed, exposing much of the lateral surface of the hemispheres from the orbital ridge to the posterior part of the parietal lobe. This plate extended about 4 mm. across the midline and laterally well below the insertion of the temporal muscle. The optic tract was approached by gently retracting one frontal lobe, while the head was tilted backwards, to expose the optic chiasma and the desired optic tract. The contralateral or ipsilateral tract was then sectioned about 2–3 mm. caudal to the chiasm. Frontal lobes were ablated by subpial suction with a glass cannula, and in general, the ablation extended from the anterior bank of the arcuate sulcus to the frontal pole. All of the dorsolateral cortex within these boundaries was removed, including that within the *sulcus principalis*. The *corpus callosum*, *psalterium*, and *anterior commissure* were exposed by gentle retraction of the exposed hemispheres and sectioned in the midline. All surgery was carried out with the aid of a dissecting microscope. The locations of the lesions and the order in which they were placed in each animal are given in Table 1.

Histology

After testing seven of the *S*s were perfused intraventricularly with 10% formalin, and their brains removed. Three of these were embedded in celloidon and four were frozen for sectioning. Sections were cut coronally at 30 or 40 μ. Every thirty-second and thirty-third of the 30 μ sections and every twenty-fourth and twenty-fifth of the 40 μ sections were stained, one set of sections with Weil stain for fibers and the other with cresyl violet for verification and reconstruction of the frontal lesions. FRD died during the experiment, and his brain was not sectioned; GRG was assigned to a subsequent study.

Results

Delayed Response

All *S*s tested preoperatively rapidly reached the criterion of 9 correct choices in 10 trials at 15 sec. delay. The five *S*s tested after unilateral optic tract section also reached this criterion after an initial difficulty due to the effects of tract section and its attendant hemianopia. The effect of

TABLE 2

Delayed-Response Performance after Unilateral Optic Tract and Prefrontal Lesions

Monkey	Transparent Screen		Opaque Screen	
	No. of Trials to Criterion[a]	Maximum Delay (sec.)	No. of Trials to Criterion[a]	Maximum Delay (sec.)
Ipsilateral Group				
ABR	310	15		
IRV	340	15		
FRD			490	15
Contralateral Group				
JCB	1390	15		
ULY	540	15		
DNY	3000[b]	12		
GLT	3000[b]	10		
GRG			3000[b]	12

[a] Nine correct choices in 10 trials at 15 sec. delay.
[b] Training discontinued

subsequent unilateral cortical ablation on delayed-response performance depended upon whether the frontal area removed was ipsilateral or contralateral to the visual input remaining intact (Table 2). Regardless of the type of screen used, *S*s with ipsilateral lesions of the optic tract and frontal cortex rapidly reached the criterion performance at 15 sec. delay. In contrast, three of the five *S*s with contralaterally placed lesions did not reach criterion level after 3000 trials. WLC reached criterion performance rapidly after optic tract section and commissurotomy, with both frontal cortices intact. His performance was thus similar to that of the three *S*s with ipsilateral lesions of the optic tract and frontal cortex.

The performance of *S*s with three lesions —optic tract section, cortical ablation, and commissurotomy—is shown in Table 3. Even though both *S*s with contralaterally placed optic tract and cortical lesions had reached criterion on the transparent screen problem before being subjected to commissurotomy (see Table 2), they now performed very poorly in this test. These two *S*s exhibited even more marked disruption of delayed-response performance when tested with the opaque screen. At no time

TABLE 3
DELAYED-RESPONSE PERFORMANCE AFTER COMMISSUROTOMY PLUS UNILATERAL OPTIC TRACT AND PREFRONTAL LESIONS

Monkey	Transparent Screen		Opaque Screen	
	No. of Trials to Criterion[a]	Maximum Delay (sec.)	No. of Trials to Criterion[a]	Maximum Delay (sec.)
Ipsilateral Group				
ABR	830	15	2040	15
IRV	390	15	1470	15
WLC	330	15	350	15
Contralateral Group				
JCB	2540	15	3000[b]	3
ULY	3000[b]	12	3000[b]	4

[a] Nine correct choices in 10 trials at 15 sec. delay.
[b] Training discontinued.

during the 3,000 trials on this test did their performance appear to be much better than chance. Although maximum delays of 3 and 4 sec. are given in Table 3, these *S*s seldom performed better than chance even at 1 sec. delays. In contrast, the ipsilateral group was able to reach criterion on both tests. Although these *S*s showed some decrement in performance when the opaque screen was used, all achieved criterion within 60 days of testing.

Hyperactivity

Tendencies toward hyperactivity during training were observed and recorded. Two of the nine *S*s were rated as slightly hyperactive, two moderately hyperactive, and two markedly hyperactive. However, there was no correlation between hyperactivity and impairment of delayed response. Despite a severe impairment of delayed-response performance after the third operation, monkeys JCB and ULY showed little or no hyperactivity. On the other hand, FRD performed very well on the delayed response despite his marked hyperactivity following optic tract section and prefrontal ablation. In general, the instances of hyperactivity also seemed independent of the laterality of the lesions.

Mnemonics

Any obvious devices of movement or positioning, such as picking at the floor of the test cage near the baited well, that *S* appeared to use during the tests were noted. Such behavior was not observed after optic tract section alone. After cortical ablation, however, *S*s with frontal lesions contralateral to the optic tract section appeared to use mnemonic devices, but those with ipsilateral lesions did not. The two groups differed in this respect most clearly after the third-stage operation. Both *S*s with contralateral lesions, in addition to commissurotomy, performed well at times with the transparent screen, and both appeared to be using a mnemonic device closely related to successful performance. JCB picked at the floor near the positive well, and frequently glanced at it during the delay interval. When he discontinued this stereotyped behavior, his accuracy dropped to a chance level. ULY adopted a habit of intermittently grasping the cage bar nearest the positive well throughout the delay interval. Successful performance was contingent on maintaining this directive behavior. The three *S*s with ipsilateral lesions in addition to commissurotomy initially tended to position themselves near the positive well, but soon began to move freely about the test cage during the delay interval. These *S*s were eventually able to reach criterion performance without an observable reliance on such devices.

Visual Field Defects

After optic tract section, the performance of all *S*s was disrupted owing to the hemianopia produced by interruption of the visual fibers from one homonymous field. However, all *S*s overcame this difficulty during training and soon reached their preoperative level of delayed-response performance. In three of the four *S*s that underwent commissurotomy as their final operation, some difficulties of the type initially associated with tract section temporarily reappeared. This reinstatement of field defect seemed to be independent of the locus of the frontal lesion. All *S*s overcame this added difficulty as they had the effects of the original tract section.

Anatomical Verification

In six of the seven *S*s for which histological sections were available, the intended optic tract had been completely transected. In WLC, residual undegenerated fibers, comprising an estimated 5% of the total fibers in a normal tract, were present. Figure 1 shows a representative Weil-stained coronal section at a level between the chiasma and the lateral geniculate bodies. Note the well myelinated, normal-appearing optic tract on the left. Most of the right optic tract is missing, and the few fibers remaining visible are completely degenerate. Such total degeneration was evident in six *S*s. Weil stain also revealed that the *corpus callosum* and the anterior and hippocampal commissures were completely transected in two (ABR, IRV) of the five *S*s subjected to commissurotomy. The remaining three *S*s (JCB, WLC, ULY) had a small portion of the callosal tip, ventral to the genu, intact. Calculations show that these uncut anterior fibers constituted a maximum of 3–4% of the total number of callosal fibers. In all five *S*s the remaining genual fibers, the body, and the *splenium* were completely transected. Note the cut and degenerate *corpus callosum* in Figure 1.

All frontal lesions were substantially alike, and, as intended, included most of the dorsolateral cortex between the arcuate sulcus and the frontal pole. In all seven *S*s there was considerable unilateral degeneration of the dorsomedial nucleus of the thalamus ipsilateral to the ablated frontal area. Figure 2 is a reconstruction of the frontal lesion in the brain of ULY, with a representative series through the thalamus.

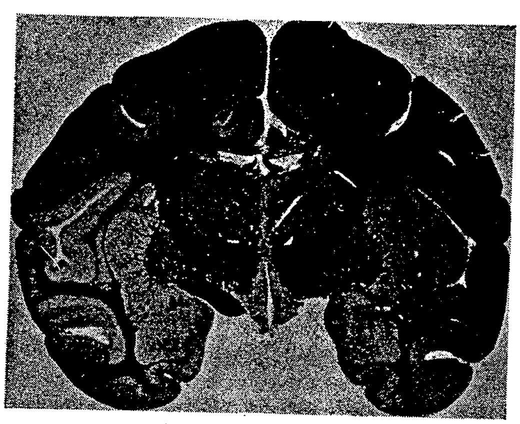

Fig. 1. Monkey ULY: Weil-stained coronal section at level of optic tracts.

Discussion

The foregoing results point to the importance of integration between occipital and frontal areas for successful delayed-response performance. Evidence in respect to the position of the connection, however, is not conclusive. It is clear (Table 2) that ipsilateral connections between the two cortical areas are more efficient than contralateral ones, but the *S*s with contralateral lesions were not completely impaired in delayed-response performance. Two of them reached the difficult criterion of 15-sec. delay. After commissural section, however, the performance of these *S*s was profoundly deficient. Thus, the commissural connections between the hemispheres appear to have served as a surviving route in a circuit between visual and frontal areas, the interruption of which led to a severe deficit in delayed response. Since the commissural sections involved neocortical fibers almost entirely, it is probable that at least one relay within this circuit is within the cortex. This relay is very likely via the prestriate cortex, since anatomical evidence suggests that there are few or no direct commissural connections of Area 17 (Bremer et al., 1956). Further evidence is required, however, to specify the other relays in such a circuit. For example, it is not clear from the present study whether the pathways are entirely corticocortical, or whether subcortical (e.g., tectal) relays are also involved.

The performance of the *S*s with contralateral lesions after commissurotomy closely paralleled that of monkeys with bilateral frontal lesions. According to Battig, Rosvold, and Mishkin (1960), monkeys with bilateral lesions achieved successful performance at moderate delay intervals under just the conditions described in this study. That is, they could perform successfully if the discriminanda were visible

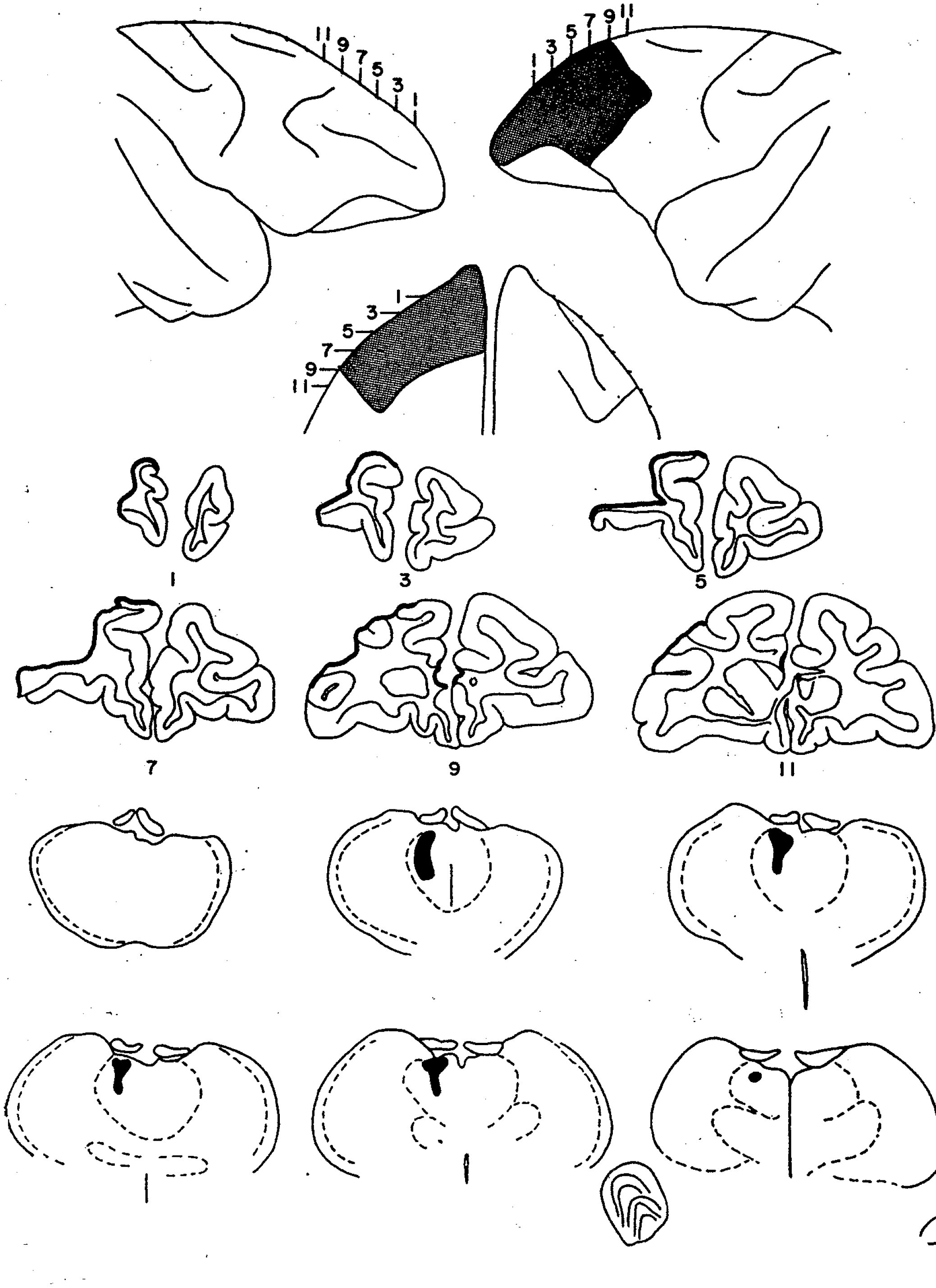

FIG. 2. Monkey ULY: Reconstruction of frontal lesion and representative cross sections through cortex and thalamus. (Black indicates lesion in cortex and degeneration in thalamus.)

throughout the delay period and if this interval was very gradually increased. When the discriminanda were not visible during the delay, however, their *S*s, like the contralateral group in the present series, could not perform at much better than a chance level.

At first glance, the present results appear to contradict Blum's (1949) work. He found a decrement in delayed response in only one of four animals that had undergone unilateral occipital lobectomy, contralateral frontal ablation, and section of the *corpus callosum*. However, it appears that the differences in the lesions are sufficient to explain the differences in experimental results. In Blum's study the frontal lesions were confined to the region of the anterior bank of the arcuate sulcus, the "frontal eye fields." Although performance of delayed response is impaired by such lesions (Pribram, 1955), the deficit is not so severe as that following removal of more anterior cortical areas, especially the region within the *sulcus principalis*. Second, occipital ablation is probably less reliable than optic tract section as a means of restricting visual input. Since very little precise pattern vision is required for delayed response, even a small residual portion of visual cortex ipsilateral to the intact frontal cortex might be sufficient for successful performance of this task. Finally, the only interhemispheric connections severed by Blum were the *corpus callosum* and, presumably, the *psalterium*, whereas not only these structures but also the anterior commissure was transected in the present experiments.

The observation that successful delayed-response performance seems to depend on the preservation of some connection between the occipital and the frontal cortex is reminiscent of recent findings on the role of commissural connections between occipital and inferotemporal areas (Ettlinger, 1959; Mishkin, 1958). By a series of unilateral lesions Ettlinger showed that commissurotomy impairs visual discrimination performance in animals previously subjected to unilateral optic tract section and contralateral ablation of temporal neocortex. Mishkin used unilateral occipital ablation rather than optic tract section to restrict vision to one hemisphere. His findings were identical to those of Ettlinger. Commissurotomy produced a far greater impairment of visual discrimination performance in animals with contralaterally placed occipital and temporal lesions than in those with ipsilateral lesions. These observations are supplemented by those of Chow (1961), who showed that cross-hatching of the inferotemporal cortex may produce impairment of visual discrimination similar to that following bilateral lesions. He attributes this effect to interruption of short intracortical association fibers. His work indicates that the temporal neocortex functions in visual learning via a corticocortical input from the occipital lobe. The present data suggest that the anterior frontal cortex functions in an analogous manner in delayed-response performance.

The lack of correlation between the degree of delayed-response decrement and the occurrence of hyperactivity in the *S*s of the present series suggests that these phenomena, the two most frequently reported effects of frontal lesions, may be dissociable. Further, the changes in activity observed after frontal ablations probably result from interaction of the cortex with subcortical structures and do not appear regularly in monkeys with unilateral lesions. Our experience confirms Blum's (1949) observation that no consistent change in activity follows unilateral visual deficits combined with contralateral frontal ablation and transection of the *corpus callosum*.

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(Received January 18, 1962)