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SOME PHYSICAL AND PHARMACOLOGICAL FACTORS AFFECTING DELAYED RESPONSE PERFORMANCE OF BABOONS FOLLOWING FRONTAL LOBOTOMY*

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INTRODUCTION

HUNTER (13) devised the delayed response test as a method to evaluate, in animals, the variables intervening between the exposure of the subject to a stimulus configuration and that response of the subject which alters the stimulus configuration. Essentially, the method interposes a time interval between exposure and opportunity for such response. The investigations of Jacobsen and co-workers (15) demonstrated that the ability to perform adequately on delayed response can be used as an index of frontal lobe function in monkeys. These studies were interpreted as indicating that the frontal cortex is essential to bridging the temporal gap interposed in the test situation.

On the other hand, Nissen (29) and his co-workers interpreted their studies to indicate that delayed response performance is difficult for operated animals because of some failure which occurred at the time of stimulus presentation. Support of this viewpoint comes from Lashley (23) who, in describing the conditional reaction, pointed out that performance of this test depends on the animal's ability to take cognizance of the context in which the discriminanda appear. The failure of animals with frontal lesions to perform this test (34) adds credence to the view that such lesions limit an animal's ability to perform any test whenever performance depends on the animal's reaction† to an element in the stimulus configuration which is not immediately altered by this reaction. Malmo (28) tested these alternative suggestions as to the temporal locus of the failure, and, using the indirect technique, demonstrated that if distractions are kept at a minimum during the test procedure, performance of the delayed response test is possible for frontal lobectomized animals. When distractions were interposed during the delay period the animals failed.

These experiments again shifted attention to the delay period as the critical one for interpretation of frontal lobe function. Wade (32) sought to reduce distractibility by pharmacological means. She used barbiturates to

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† The term "reaction" is used hereafter to denote acts which are initiated by specific stimulus configurations. Acts refer to serially sequential behavior, implying central neural activity. "Response" is used to denote observable motor behavior.

test the hypothesis that the resultant reduction in activity lowers the lobectomized animal's distractibility and so improves its capacity for delayed response. Her results confirmed the expectation as to improved performance. However, the persistence of the ability to perform the test after withdrawal of the drug in the face of recurring hyperactivity in one of her animals threw some doubt on the mechanism supposedly involved. Nevertheless, as Wade points out, increased quadrupedal pacing and inability to perform the delayed response reaction are two consistently observed changes in monkeys following frontal ablations. It is logical to inquire, therefore, whether any consistent relation between activity and performance of the delayed reaction can be determined.

Increased quadrupedal pacing or hyperactivity has followed frontal lesions in a variety of animals (2, 20, 22, 30, 31). Brobeck has called attention to the fact that over a 24-hour period a change in a normal rat's food intake inversely affects activity in such a manner that another variable of energy metabolism— temperature regulation– is maintained constant. Food plays a major role in the direct method delayed reponse test. Barbiturates are well-known antihyperthermics (3) and have been shown temporarily to increase food intake in rats (7, 17). The present experiments were undertaken to determine whether other pharmacological agents and physical changes would affect delayed response performance in accordance with their known effects on energy relationships.

MATERIALS AND METHODS

Two immature female Chacma baboons (*Papio porcarius*) were trained to perform the spatial delayed response test at 15 seconds' delay. The test was performed in the usual manner: within view of the animal but beyond his reach, food was placed in one of two identical trays covered by identical sliding lids; a screen was lowered for 15 seconds, raised, the tray pushed up to the animal after a brief hesitation, and the animal given his choice between the trays. The food was alternated between the two trays in random order. The animals received the food immediately when they chose the correct tray; if an error was made the reward was withheld for 10 seconds, when response to the other tray was permitted. Twenty to forty trials were given daily. Criterion of adequate performance was 150 consecutive trials at 85 per cent or better. The animals were simultaneously trained to perform a simple color discrimination. Observations of general behavior were made throughout the testing period.

Under amytal anesthesia the baboons were subjected to a limited bilateral frontal lobotomy. In an attempt to make this operation homologous with that performed on humans, care was taken to remain anterior to the frontal eyefields and to spare the fibres connecting the posterior orbital and anterior cingulate areas with subcortical structures. The animals were sacrificed during the tenth postoperative month. Anatomical verification of the lesions is reported in Figures 1 and 2, together with analysis of the resultant thalamic degeneration.

Drugs were administered as follows: Nembutal intramuscularly in from half to three-quarters the anesthetic intraperitoneal dose. Criterion for effectiveness was a staggering animal which could still perform the manipulations demanded by the test. Insulin was given in doses of 0.25 to 0.50 unit per kg. body weight intramuscularly. Benzedrine was given orally in 5 mg. doses. Testing was begun one-half to one hour after the administration of each of the drugs. Temperature effects were also tested. These were produced in air-conditioned rooms. The animals were kept at the test temperature (65° F. and 100° F.) for three hours before testing. The temperature in their home cage was approximately 80° F. The animals' food intake was kept constant at approximately 350 calories per day during the months of testing.

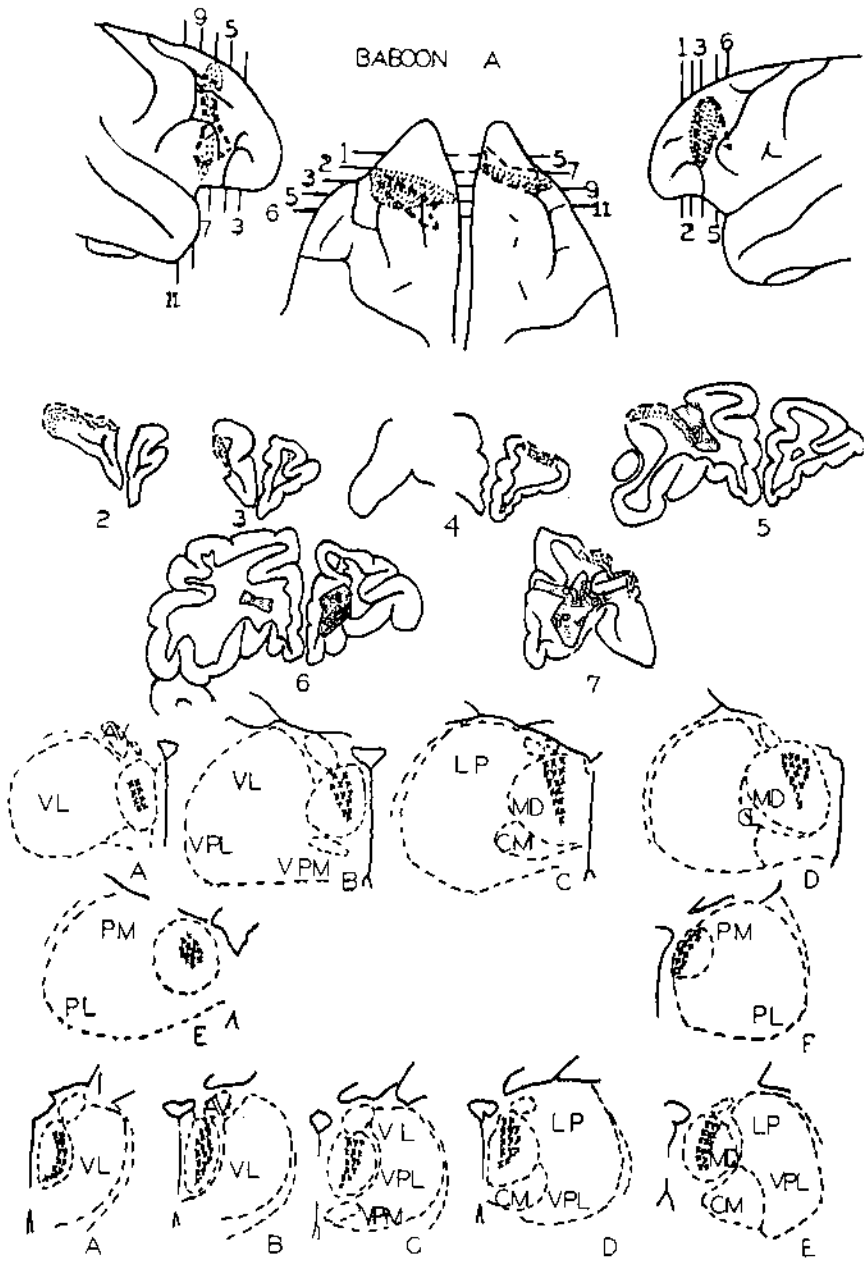

FIG. 1. Lesion of baboon A giving lateral and dorsal reconstructions of frontal cortex. Stippled areas indicate cortical damage. Broken lines outline extent of leukotomy. Representative sections demonstrate depth of lesion. Degeneration in mediodorsal nucleus indicated in thalamic cross-sections by x. Nomenclature of the thalamic nuclei according to Walker (33) (MD, mediodorsal; CM, centromedian; VL, ventrolateral; CL, centrolateral; VPL, ventroposterolateral; VPM, ventroposteromedial; PM, medial pulvinar; PL, lateral pulvinar)

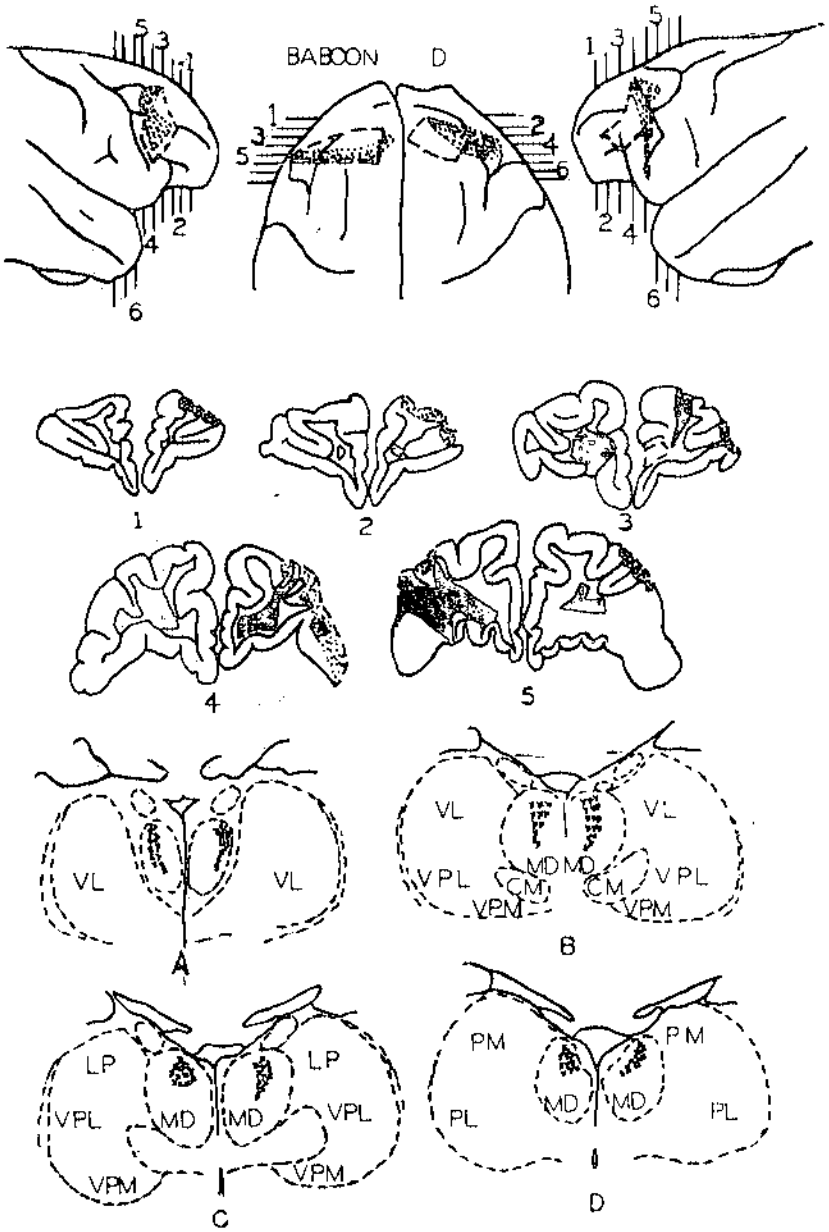

FIG. 2. Lesion of baboon D. See Fig. 1 for nomenclature.

RESULTS

These observations were made during the first six months after operation. The animals were unable to perform the delayed response test immediately after operation (tests were begun 3–24 hours postoperatively). They were also unable to perform the color discrimination for the first week to 10 days

after operation but recovered this ability after 30–60 trials within two weeks of operation. During the first month following operation 400 trials were given each animal in the delayed response situation. The animals failed to achieve the criterion even for short delays of 5 seconds (although they could perform at 1–2 second delays). They were tested for two more weeks to a total of 650 consecutive trials with no improvement. Forced pacing was present in the test situation at all times.

Nembutal. Under the influence of Nembutal no immediate improvement was noted in the ability of the lobotomized animals to perform the delayed response test although there was a marked diminution of the forced pacing. During approximately 400 trials given during the second and third postoperative month, however, these animals gradually improved their performance at 5 seconds' delay and were given longer delays very gradually. In the third and fourth postoperative months they attained approximately 80 per cent correct performance at 15 seconds' delay on 150 consecutive trials when the drug was used. The drug was then discontinued and the animals tested again at the 15 seconds' delay. They returned to their previous postoperative low level of performance.

Benzedrine. During the third and fourth postoperative months after administration of benzedrine in doses of 5 mg. the lobotomized animals refused to test. Three to six separate attempts were made with each animal—occasionally 2 or 3 random trials would result. The animals showed a marked increase in the forced pacing which appeared in the test situation following operation. After withdrawal of the drug the animals returned to their previous postoperative performance level.

Insulin. One to two hours after the intramuscular administration of 0.25-0.50 units of insulin per kg. body weight the lobotomized baboons performed between the 80 and 90 per cent levels on 100 consecutive trials at 15 seconds' delay in spite of an increase in the stereotyped forced pacing. (This was late in the fifth or early in the sixth postoperative month.) After withdrawal of the drugs both animals returned to their previous postoperative low level of performance.

Change in temperature. A 15-degree reduction of the environmental temperature (to approximately 65°F.) for three hours prior to and during testing caused dramatic improvement in the ability of the lobotomized animals to perform the delayed response test. Correct responses in almost 80–90 per cent of 100 consecutive trials (15 seconds) were achieved early in the fourth and fifth postoperative months in spite of the continuation of forced pacing in the test situation. When the tests were repeated without any temperature alteration the animals reverted to previous postoperative behavior. Exposure to an increase in environmental temperature of 15°–20° (to approximately 100°F.) for three hours prior to and during the testing period resulted in no significant change in level of performance, but the animals would test for only 5–10 trials per session.

Changes in feeding. The animals were routinely fed once in 24 hours.

After fasting for 48–60 hours the performance of the baboons improved slowly. After several unsuccessful attempts a 75–80 per cent level of performance was obtained on 50 consecutive trials with a 15 seconds' delay in the fourth and fifth postoperative months. Repetition of the tests under normal feeding conditions resulted in a return to the previous postoperative scores.

Table I

(Baboon A)

Conditions	Date (1948–1949)	Delay (sec.)	No. Consec. Trials	No. of Errors	% Correct
Preoperative Learning	6/15– 8/11	0–15	350	105	
Preoperative Critical	8/24– 9/15	15	150	20	87
Operation	9/21/48				
Postoperative Learning	9/22–11/16	0–5	400	130	
Postoperative Critical	11/17–11/24	5	150	65	57
Nembutal Learning	11/30–12/20	5–15	400	93	
Nembutal Critical	12/20–12/22	15	100	18	82
Normal Conditions	1/5 –1/6	15	50	26	48
Benzedrine 5 mg.	1/7 – 1/12	15	3	2	refused to test
Normal Conditions	1/14– 1/15	15	50	26	48
65°F. for 3 hours	1/24– 1/27	15	100	12	88
Normal Conditions	1/28– 1/29	15	50	20	60
Heat	1/30– 2/1	15	10	5	refused to test
Normal Conditions	2/2 – 2/3	15	50	21	58
Fasting (48–60 hours)	2/5 – 2/10	15	50	10	80
Normal Conditions	2/11– 2/12	15	50	24	52
Prefeeding	2/14– 2/16	15	10	4	refused to test
Normal Conditions	2/17– 2/18	15	50	22	56
Insulin (2 units)	2/22– 2/25	15	100	14	86
Normal Conditions	3/1 – 3/2	15	50	24	52
Nembutal	3/3 – 3/4	15	50	10	80
Normal Conditions	3/5 – 3/6	15	50	16	68
Normal Conditions	3/23– 4/12	15	100	15	85

Discussion

The results of the present experiments show that the effects on test performance of the physical changes and pharmacological agents used are consistent with their known short-term effects on energy relationships. Exposure to cooling (5) and insulin (16) are known to stimulate appetite and food intake in man. A 15°–20° drop in environmental temperature will temporarily increase the food intake of rats (20). Exposure to heat, on the other hand, will temporarily diminish the food intake in rats (4). Benzedrine (9, 11) is known to diminish appetite and so reduce obesity. As indicated before, Nembutal (3) is a well-known antihyperthermic and has also been shown temporarily to increase food intake in rats (17). It appears therefore that those physical changes and pharmacological agents which tend temporarily to increase food intake increased effective test performance in the present experiments whereas those that temporarily decrease food intake

lowered performance scores. It has been suggested (10, 16) that the alterations in blood sugar level secondary to insulin administration directly affect central mechanisms regulating food intake. This view is reenforced by the fact that in the present experiments insulin and cooling were dramatically more effective in the rapidity with which they altered performance level than was food deprivation. It is thus likely that both the improved test

Table II

(Baboon D)

Conditions	Date (1948–1949)	Delay (sec.)	No. Consec. Trials	No. of Errors	% Correct
Preoperative Learning	6/24– 9/1	0–15	400	103	
Preoperative Critical	9/3 –10/19	15	150	28	88
Operation	10/20/48				
Postoperative Learning	10/20–11/22	0– 5	400	227	
Postoperative Critical	11/23–12/1	5	150	60	53
Nembutal Learning	12/1 –12/22	5–15	400	108	
Nembutal Critical	1/5 – 1/11	15	100	21	79
Normal Conditions	1/14– 1/15	15	50	21	58
Benzedrine	1/17– 1/19	15	0		refused to test
Normal Conditions	1/21– 1/22	15	50	22	56
65°F. for 3 hours	1/24– 1/27	15	100	24	76
Normal Conditions	1/28– 1/29	15	50	24	52
Heat	1/30– 2/1	15	10	7	refused to test
Normal Conditions	2/2 – 2/3	15	50	22	56
Fasting (48–60 hours)	2/5 – 2/10	15	50	13	74
Normal Conditions	2/11– 2/12	15	50	23	54
Prefeeding	2/14– 2/16	15	12	7	refused to test
Normal Conditions	2/17– 2/18	15	50	24	52
Insulin (2 units)	2/22– 2/24	15	100	10	90
Normal Conditions	3/1 – 3/2	15	50	19	62
Nembutal	3/3 – 3/4	15	50	10	80
Normal Conditions	3/5 – 3/6	15	50	10	80
Normal Conditions	3/22– 4/12	15	100	9	91

performance and augmented food intake were due to the same basic alteration in central mechanisms of the organism by the factors investigated.

Little is known as to the nature of this change (18) in central mechanisms. Laidlaw and Kennard (21) have demonstrated a differential effect of barbiturates on the paraventricular and supraoptic nuclei of the hypothalamus and have reviewed the evidence of others for such an effect. This structure has, of course, also been implicated in the regulation of body temperature (19, 26) and blood sugar (1, 6, 8, 12, 14, 24). Whether the effect of the physical changes and pharmacological agents used in the present experiments is mediated through hypothalamic mechanisms remains a problem for further investigation.

The result of this alteration in central mechanisms is to increase the stimulus value of food in the delayed response situation. When subject to the conditions which have been shown temporarily to increase food intake,

the animals who finally succeed in performing in the delay situation invariably give some evidence of a selective response to the stimulus presentation. In different animals the following responses have been observed: a twist of the head toward the correct side which gradually was replaced by a definite and peculiar roll of the eyes; a tapping of the correct side of the cage; a change, if necessary, in the direction of forced pacing so that the correct side was always approached first. Under those conditions in which delayed response performance remained at or near the chance level such selective responses were not observed. Conversely, when the lobotomized animals were performing adequately, as during exposure to cold or under insulin, performance was unaffected once such a response had been made, no matter what distractions were interposed (*e.g.*, noise, another baboon eating peanuts while sitting on tester's lap). This confirms the impression that when failure occurs, the deficit is due to factors operating at or near the time of stimulus presentation. On the other hand, since the lobotomized animals were able to perform the test whenever no delay was interposed between the stimulus presentation and the opportunity for a response which terminates the stimulus configuration (as with all other "frontal" animals), the deficit is present only when the animal's reaction is prevented from becoming complete—i.e., it does not result in terminating the stimulus configuration. This is confirmed by the fact that the animals showed no deficit on visual discrimination tests. Malmo's experiments (28) demonstrated that interference factors during the delay period can prevent appropriate completion. Since in all of Malmo's experiments the stimulus value of the test object was maximal for the indirect method, the differences in the effect of interference factors in the two experiments must be ascribed to differences in severity of deficit. This explanation is borne out by the fact that the lobotomized baboons reached the 80 per cent level of performance under normal conditions six months postoperatively. The difference between performance of Malmo's animals and the baboons may be due to differences in extent of lesion, differences in the amount of postoperative training, species differences or a combination of these effects. Whatever the explanation for these differences, the behavior of the lobotomized baboons indicates that the reaction of the animal at or near the time of stimulus presentation must be considered in any interpretation of failure in delayed response performance. However, there still remains the problem of characterizing that reaction which will resist interference factors.

The results of the present experiments indicate, therefore, that the physical and pharmacological factors which facilitate performance in the delayed response situation are effective in increasing the stimulus value of the test object. These physical and pharmacological factors presumably affect central neural mechanisms (hypothalamic?). Frontal lesions (also obviously central neural) have been shown to interfere with such performance by lessening the animal's ability to react selectively to a stimulus configuration (or part thereof) in the absence of opportunity for altering that stimulus configuration. It remains for further experiment to determine the relation

between the central mechanisms involved and the implications of the behavioral manifestations of these relations. Such experiments should help to clarify the neurophysiological basis for such concepts as "appetite," "motivation," "anticipation" and "abstraction" which play a major role in describing the effects of frontal lesions in man.

Summary

1. Two immature female Chacma baboons (*Papio porcarius*) were trained in the delayed response situation, subjected to bilateral frontal lobotomy, and retested under various physical and pharmacological conditions.

2. The animals showed a low level of performance in the delayed response situation for six months postoperatively under normal conditions (food intake approximately 350 calories per day, temperature approximately 80°).

3. The following conditions significantly improved test performance: intramuscular injection of Nembutal in approximately half the anesthetic dose; the intramuscular injection of 0.25–0.50 unit of insulin per kg. body weight; a reduction of the environmental temperature by 15°–20° for three hours before testing; fasting for 48–60 hours before testing.

4. Benzedrine (5 mg.), elevation of the environmental temperature for three hours before testing, and prefeeding immediately before testing, resulted in a few chance trials or complete refusal to test.

5. The relationship of these physical and pharmacological changes to energy metabolism is discussed: those alterations in conditions which temporarily increase food intake increase test scores; those which temporarily decrease food intake impair performance.

6. The nature of the impairment in delayed response performance following frontal lesions is discussed.

7. The physical changes and pharmacological agents used have been shown to affect central neural mechanisms. The significance of the relation between these mechanisms and frontal lesions and their behavioral implications are pointed out.

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