THE EFFECT OF LESIONS TO THE CAUDATE NUCLEI AND CORPUS CALLOSUM ON DELAYED ALTERNATION IN THE MONKEY

THE EFFECT OF LESIONS TO THE CAUDATE NUCLEI AND CORPUS CALLOSUM ON DELAYED ALTERNATION IN THE MONKEY

by

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A. B., Brooklyn College, 1955

Submitted to the Graduate Faculty in the Division of the Natural Sciences in partial fulfillment of the requirements for the degree of Master of Science

University of Pittsburgh

1958

Foreward

The author would like to thank Dr. R. A. Patton for his guidance throughout this study and Dr. Y. D. Koskoff for the use of the facilities of the Montefiore Institute of Research, Montefiore Hospital. The author would also like to thank Melvin Rudov and Charles Vaughan, Jr. for their help during part of the study, and especially Donald Kruper for his surgical assistance.

The study was aided by a Research Grant from the U. S. Public Health Service.

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1.0. INTRODUCTION

Jacobsen, et al. (29, 30, 33) showed that monkeys deprived of their frontal lobes failed on the delayed alternation and delayed response tasks. There are two major questions which these original studies ask, and which remain unanswered today. First, what is the nature of the deficit, and second, what is the neural basis (locus) of the function? These two problems will be treated separately. All the studies reviewed here are confined to work with infrahuman organisms.

1.1. Localization of Function

This is the simpler of the two questions. This section will survey lesions made in various parts of the brain, (bilateral unless specified otherwise) usually of the monkey, and the effects on delayed response and/or delayed alternation.

The parietal lobe, excised either in part or as a whole has not, in general, been reported to produce a deficit on delayed response or delayed alternation. Jacobsen (30) removed the parietal "association" areas without producing a delayed response deficit. Removal of the postcentral gyri by Breslaw, et al. (6) produced no deficit on delayed response. Blum, et al. (5) combined postcentral gyrus (5) gave no deficit. Lashley (38), however, has reported delayed response deficit in three out of four monkeys given lesions of areas 18 and 19. These results have not been confirmed by other investigators (5, 43). Spontaneous alternation was unchanged following parietal lesions in the rat (52).

Lesions of the temporal lobe and rhinencephalon generally produce no deficit on delayed response or delayed alternation. There are two reports,

however, of deficits from these lesions. Mishkin and Pribram (48) reported that one monkey with a lesion of the ventral temporal lobe and hippocampi failed on delayed response. Three others with similar lesions succeeded, as did two others with even more extensive lesions including lateral and ventral temporal cortex, hippocampus, temporal pole, and amygdala. Two animals with lateral temporal lesions also passed the delayed response test. The second report is from Blum, et al. (5). One monkey with a lesion including hippocampus, amygdala, temporal pole and ventral cortex, failed on delayed response. There were no other animals with similar destruction in this study. Further negative results from Mishkin (46) for three animals with lesions of ventral temporal cortex including inferior temporal, fusiform, and posterior hippocampal gyri, and for three animals with lesions of hippocampal formation. Two subjects with amygdaloid lesions showed no deficit and one of these included the superior temporal convolution and supratemporal plane. Jacobsen and Elder (31) reported no deficit for one monkey with a lesion of areas 20, 21, 22. Mishkin and Pribram (49), obtained negative results on delayed alternation for three monkeys with inferior temporal lesions sparing hippocampus, amygdala and temporal pole. These same three animals also succeeded in delayed response (50). Pribram and Bagshaw (57) ablated a neuronigraphically defined, (59), frontotemporal region including posterior orbital, anterior insula, temporal polar, and periamygdaloid cortex, and failed to obtain a delayed response deficit in four monkeys. Other rhinencephalic lesions in the monkey that have failed to produce the deficit are reported for the septal area (62), and the medial frontal cortex including area 24 (61).

Two reports concerning the occipital lobes are available. Spontaneous alternation in the rat appears to be similar to the delayed alternation test

used with monkeys. Morgan and Wood (52) found that rats with lesions of the frontal areas tended to perseverate rather than alternate. Control groups with lesions of either parietal or occipital areas continued to alternate. Loucks (40) found that lesions to posterior and middle parts of the cortex of the rat did not significantly alter delayed alternation, while frontal lesions did.

Partial ablations of the frontal cortex have finally indicated the specific locus which seems to be critical for the production of the deficit on delayed response-type tests. Rosvold, et al. (61) found that neuronigraphically defined, (59), medial frontal lesions produced little or no deficit on delayed response while dorsolateral lesions produced the deficit. On the lateral surface Blum (3) found midlateral lesions more severe than either dorsal or ventrolateral areas, although the combination produced the greater deficit. Lesions of the precentral motor cortex reported by Jacobsen and Haslerud (32) and more extensively by Pribram, et al. (58) Yielded no deficit on delayed response. Two monkeys with lesions of the "frontal eye fields" are reported by Pribram (56) to show a transient deficit lasting about six months. It should be noted that these lesions partly invaded the midfrontal region. Wade (72) reported that lobectomy or lobotomy of the frontal lobes produced the usual delayed response deficit while "circumsection" of the prefrontal area gave no deficit, concluding that interruption of projections to subcortical areas rather than other cortical areas were critical. The circumsection, however, did not include the entire midfrontal region. Finally, Mishkin (47) observed that lesions extending from the inferior medial edge to the inferior lateral edge of the frontal lobes gave no deficit in two monkeys, and lesions extending from two mm. from the superior lip of the sulcus principalis to the

longitudunal fissure also gave no deficit in two monkeys. Two animals with lesions extending from the inferior lateral edge to within 2 mm. of the inferior lip of sulcus principalis also showed no deficit. All six of the above animals regained criterion in 260 or fewer trials. On the other hand, of the four additional monkeys with lesions to both lips, banks, and depths of sulcus principalis two failed to reach criterion in 1000 trials and the other two required 410 and 470 trials to reach criterion. Campbell and Harlow (8) reported recovery from the effects of frontal lesions in two animals after a prolonged recovery and retraining period. Their verbal descriptions of the lesions indicates that the sulcus principalis was left intact posteriorly. Similarly the partial deficit reported following the frontal eye field ablations (56) may possibly be explained by the intact anterior portion of sulcus principalis. The recovery that Wade (71) observed in one of two monkeys with lesions beginning "13 mm. anterior to the angle of the arcuate" may be explained similarly. The eventual recovery of two baboons with frontal lobotomies reported by Pribram (55) may be explained by the point of entrance of the lobobomy, which spared some of the sulcus principalis.

The earlier reports of deficit on delayed response following frontal lobotomy on two chimpanzees by Jacobsen, et al. (34) have not been confirmed. Blum (2) cited in (17) reports "Performance in spatial delayed response of all three (chimpanzees) was significantly above chance with delays of one minute or longer." Warren (74) has reported that cats deprived of their prefrontal areas succeed on delayed reponse. The two species should now receive caudate lesions in view of the results reported below. Summarizing these results, the critical focus seems to be the entire length of the sulcus principalis bilaterally in the monkey, and its subcortical rather than transcortical relations. These subcortical relations will now be discussed.

Ablation of the prefrontal cortex produces degeneration in the dorsomedial nucleus of the thalamus (49). The possible significance of this relationship for delayed response was investigated by Chow (13). Lesions of the pulvinar and dorsomedial nucleus, however, failed to affect delayed response in monkeys. However, these lesions may have been too small. Peters, et al. (54) using both delayed alternation and delayed response also obtained generally negative results in a large series of animals. The lesions here were larger than in the earlier study by Chow.

Lesions of the prefrontal cortex also produce degeneration in the anterior tip of the reticular nucleus, as shown by Chow (10). The effect of lesions to this area have not been reported in the literature.

Ablation of the prefrontal cortex produces cell loss in the caudate nucleus of the monkey, as shown by Harman, et al. (27). Reciprocal innervation probably exists (1). The significance of this relationship with the caudate has been investigated in the monkey by Rosvold and Delgado (62). Stimulation of the caudate via implanted electrodes during delayed alternation dropped the performance of the animals to about chance. Subsequently, lesions to the caudate in these five subjects again produced the deficit, although one animal recovered. (The experiment reported here confirms this finding.) Neither stimulation nor lesions of the putamen affected delayed alternation (62).

Lesions to the following important structures have not been reported in the literature and remain to be investigated in this function: hypothalamus; fornix; subthalamus; intralaminar nuclei of the thalamus; reticular nucleus of the thalamus; ventralis anterior and ventralis lateralis of the thalamus; globus pallidus, cerebellum; corpus callosum (reported in this study); reticular formation, and colliculi of midbrain.

In recent years the reticular formation and diffuse thalamic projection system have acquired great neurophysiological significance (15). In view of the relationship of the caudate nucleus to the reticular formation, the diffuse thalamic projection system (65) and to the frontal cortex (27, 42) this structure was selected for investigation.

1.2. Analysis of the Deficit

The analysis of the psychological deficit following frontal lesions has not been completed to date. Experimenters have administered a variety of tests and variations of the delayed response itself in an attempt to specify the factor or process which is lost. All of the interpretations presented below attempt to integrate only some of the diverse findings; none attempt to integrate all the findings. In each case it will be seen that some data cannot be incorporated into the interpretation.

The data will be ordered under two categories, (a) facilitation of delayed response, and (b) other dependent variables. Lastly, the interpretations will be presented. Although the interpretations evolved along with the experiments they are given separate treatment for the sake of clarity.

1.21. Facilitation of Delayed Response

Three studies have investigated the effect of physiological variables on monkeys already deprived of frontal cortex. Wade (71) administered Nembutal or Dial to two monkeys with delayed response deficit. Performance was significantly improved in both. After withdrawal of the drug, one animal maintained its improved performance. Pribram (55) confirmed this finding with two animals with delayed response deficits. When the Nembutal was withdrawn, performance level declined. In addition, administration of

insulin increased the level of performance very rapidly. Similarly, reduction of environmental temperature to 65 degrees farenheit improved performance while increasing the environmental temperature was ineffective (i.e., the animals would not test). Food deprivation for 48-60 hours also improved performance. However, Blum, et al. (4) were unable to obtain significant improvement on either delayed alternation or delayed response by the administration of Nembutal. The authors feel that this discrepancy may, perhaps, be explained by the difference in the time interval between the lesions and administration of the drugs. Wade (71) and Pribram (55) both began administration three months postoperatively while Blum, et al. (4) waited six months to two years.

The method of administering the delayed response test has been manipulated. These may be labeled "psychological variables". Spaet and Harlow (67) used a "matching from sample" technique. Two objects were placed on the test tray and a duplicate of one of the two (the sample) was located on the side of the test tray. S displaced the sample and obtained a food reward. After a delay interval during which the sample was removed, S was allowed to choose one of the remaining two objects. Displacement of the duplicate of the sample was reinforced. The two animals in this study solved this problem. The subjects succeeded again when only the sample was present during the predelay response. After the delay the sample was removed and the two objects placed on the tray.

Meyer, et al. (44) found that very small but significant increments could be obtained by using new objects ("trial unique") on each trial.

Finan (19) allowed his monkeys to run into one of two adjacent compartments for a bit of food before the delay interval. They were then chased out, and delayed. After the delay they were required to return to the same compartment for reinforcement. The frontal animals were able to do this.

Malmo (41) illuminated one of two panels for two seconds in a dark room. This served as the cue for his frontal animals. If, during the delay interval overhead lights were turned on for five seconds, then off, and the response permitted, chance performance occurred. (If the light was of reduced intensity the deficit was less.) If the delay was entirely in the dark there was significant improvement.

Mishkin and Pribram (49) varied the classical spatial delayed alternation task. They presented the animal with a single covered food well on the test tray. After a trial in which displacement of the cup was reinforced, the next trial was not reinforced. The correct response was leaving the cup unturned. On the following trial, a response was reinforced, etc. This is called "go-no-go" delayed alternation. Their frontal monkeys succeeded on this variation.

Mishkin and Pribram (50) also varied the delayed response procedure. They again used a single centered food well and presented over it one of two cues. After a delay, depending on which cue was presented, the frontal monkeys were required to respond or not respond. They succeeded at this. They also succeeded when the cue indicated displacement of a left versus a right cup after the delay.

Several tasks closely resembling delayed response have been used as dependent variables following frontal lesions. The common feature is the absence of external discriminative stimuli at the time of the response. Hunter (28) considered this the significant feature of delayed response.

Jacobsen, et al. (34) required their chimpanzees to push the first handle, push the second, push the third, and pull the fourth to obtain a food reward. After the frontal ablations anticipatory errors on the second and third pushes increased (in one of two chimpanzees). Carpenter (9)

trained rats on a linear maze. At four choice points along the maze the rats had to go through a left or a right door to continue on to the reinforcement at the end. The correct sequence of doors was right, right, right, left. After frontal lesions anticipatory errors on the second and third doors increased significantly over the control scores. Leary, et al. (39) reported impairment on the double alternation problem after frontal lesions in monkeys. The correct sequence of responses was RRLL and there was some improvement with training. In the study mentioned earlier by Morgan and Wood (52) spontaneous alternation in rats was observed after frontal lesions. Perseveration largely replaced alternation. Stellar, et al. (69) trained rats on a runway with six alleys leading off on the left of the main runway. The correct alley was the fourth. The experimenters attempted to eliminate all cues in the environment which the rats could use as a basis for a correct response. Again, after frontal lesions errors increase.

Two tasks which require responses to internal stimuli (at the time of response) were presented by Finan (18). Both tests require "temporal discriminations," and the frontal monkeys were successful at them. The first is the temporal maze in which two alleys of different lengths are open to the monkey, both leading to reinforcement. The correct response is traversing the shorter alley. In the second task the monkey is placed in one compartment, and this is separated from an adjoining compartment by a barrier which S can jump over. When the CS is given S must wait in his compartment for ten seconds before jumping over. The other compartment is electrified during these first ten seconds. During the next ten seconds S must jump, otherwise his compartment becomes electrified.

1.22. Other Dependent Variables

Although the delayed response-type dependent variable has been the subject of much work related to the frontal lobes, several other dependent variables have been examined. These are dealt with in this section.

Jacobsen, et al. (34) reported a "loss of experimental neurosis" in one chimpanzee after frontal lesions. In the case of monkeys he wrote (30), "The animal without its frontal areas no longer appears to 'worry' over mistakes." These findings were instrumental in the initiation of psychosurgery as a therapeutic measure for mental illness. Warden, et al. (73) reported emotional flattening after frontal extirpation in monkeys. However, these findings have not been confirmed. For the chimpanzee, Evarts and Nissen (17) observed that their two chimpanzees were, if anything, more emotional than two control animals. To complete the picture, Blum (2) found "no dimunition of emotional reactivity" in his three chimpanzees with frontal lobe ablations. The more recent reports for the monkey also oppose Jacobsens original findings. Harlow, et al. (24), with their extensive experience with frontal monkeys reported that they observed no emotional flattening or indifference to failure at their laboratory. Again, Rosvold, et al. (63) using rating methods, reported no persistent change in emotional behavior following lateral frontal lesions.

Brody and Rosvold (7) investigated the possible emotional changes following frontal lesions by a method not used by previous investigators. Six monkeys were housed in a large cage for several months. When a relatively stable dominance hierarchy had been established, the number one monkey received a bilateral frontal lobotomy. No change was observed in the dominance hierarchy. On the other hand, later lobotomies on the two most submissive monkeys, numbers five and six, produced marked changes in

the social structure. Number five moved into the number four position and competed for the number three spot. Number six also moved upward to the number five spot for several months. The results were interpreted as a loss of learned avoidance responses following frontal lobotomy. These studies and especially the last, illustrate two points concerning possible emotional changes following frontal lobotomy. First, there is a need for more accurate indexes of emotion. Second, the preoperative "personality" may be a significant variable.

Hyperactivity has been a frequent finding after frontal lesions in the monkey (4, 37, 44, 55, 61, 62, 71). The relationship between this finding and the delayed response deficit is discussed in the appropriate section.

Visual discrimination learning of patterns, objects, and colors are generally unaffected by frontal lesions (29, 30). Harlow, et al. (26) have found that although frontal monkeys are successful in learning visual discriminations they do make more errors than controls. Pribram, et al. (61) similarly found a "minimal" loss on visual discriminations. Rosvold and Delgado (62) found that during stimulation or after destruction of the caudate there was no decrement in visual discrimination although the delayed response was significantly effected. Performance on visual discriminations seems to be dependent on the temporal lobes (11, 12, 46, 48) rather than the frontal lobes.

The efficiency of the animal deprived of its frontal areas on problem boxes and multiple platform and rake problems has been investigated. Jacobsen, et al. (34) required their chimpanzees to reach through the bars for one short stick, carry this to the opposite side of the cage to draw in a second longer stick which was out of arms reach. This longer stick could

then be used to draw in food. The frontal lesions chimpanzees failed to execute this sequence. On the other hand, if the first stick was long enough to reach the food they performed well. This finding was confirmed by Warden, et al. (73) for monkeys. Problem boxes requiring usually a single manipulative response were not effected by frontal lesions in monkeys (29, 30).

Harlow and Johnson (25) used what might be called a "reaction time" test as a dependent variable. They exposed food for a variable interval randomly in a right or a left food well. After the interval if S had not picked it up, the food was withdrawn. At exposures of two seconds or longer there were no differences between frontal monkeys and controls on the number of times the food was missed. At one second exposures, the frontal monkeys failed significantly more often than controls to obtain the food.

Performance on the oddity problem has been investigated by Meyer, et al. (26). The monkey is presented with three objects, two of them are identical and the third is different. S is required to select the odd object and is reinforced for doing so. Some decrement in performance is obtained after large unilateral lesions including one frontal lobe. When the opposite frontal lobe is also removed, or the opposite PTO area, there is an additional decrement.

Warren and Harlow (75) found that the formation of learning sets with either color, form, size, or object quality as the relevant cue were unaffected by bilateral frontal lesions.

The last three dependent variables are similar in that they emphasize reversals or alternations of the ongoing responses to the opposite response. In the conditional discrimination task presented by Chow, et al. (14) two dissimilar stimulus objects are presented as in the usual visual discrimination problem. One stimulus is correct against one background and the other

is correct when the second background is present. The presentations of the two backgrounds is random. There is a decrement on this task after posterior lesions, and the decrement is increased after additional frontal lesions.

Harlow and Dagnon (23) trained their frontal animals on visual discrimination problems. When the criterion was reached the monkey was required to reverse the discrimination and select the previously incorrect stimulus object. The operated animals made significantly more errors reaching criterion on this reversal than controls.

Finally, Settlage, et al. (64) trained their monkeys on a visual discrimination. Then, using the same stimulus objects, they trained them to respond to position ~~and~~ D.S the cue, right or left. The position was correct regardless of whether the previously correct or incorrect stimulus object covered the food well. After the position discrimination was learned they switched back to the object discrimination and then back to the position discrimination, etc. The frontal monkeys made significantly more errors on this test.

1.23. Interpretations

In this section 15 interpretations will be presented which attempt to account for the deficit of the monkey with frontal lesions on delayed response-type tests. A few experiments not mentioned earlier will be introduced in this section. It will be seen that each interpretation is open to criticism.

(A) Jacobsen originally attributed the delayed response loss to a loss of immediate or recent memory, so that any activity which required integration over time cannot be carried out (29). Finan's (18) demonstration of the success of frontal monkeys on the temporal maze and shuttle box are evidence against this hypothesis. The experiments showing success

with delays in the darkness (41), predelay reinforcement (19), matching from sample (67) and the use of non-positional cues (49, 50) also indicate that recent memory per se is not lost.

(B) The hypothesis that hyperactivity may produce the delayed response deficit has been studied. The findings indicate that this is probably not true. Hyperactivity may occur without the delayed response deficit. "Hemidecorticate" monkeys are hyperactive but show no delayed response deficit (44). When the temperature is reduced to 65 degrees farenheit, frontal monkeys are still hyperactive while performance on delayed response is successful (55). On the other hand delayed response deficit may occur without hyperactivity. When Nembutal is administered there is an immediate reduction of activity in the frontal monkey, but several days of treatment are required before delayed response is improved (51). During caudate stimulation hypoactivity accompanies delayed alternation failure (62). A causal relationship between hyperactivity and delayed response deficit thus seems improbable. However, deficit is apparently always accompanied by an alteration in activity, either hyperactivity or hypoactivity, so that a common mechanism may be involved.

(C) The possibility that the failures of the frontal monkey on delayed response disturb the monkey emotionally and thus cause him to perform even more poorly was investigated by Harlow, et al. (24). Interspersed between five second delayed response trials were occasional visual discrimination and zero second delay trials. The animals usually responded successfully on these trials. This appeasement procedure, however, failed to influence the low level of performance on delayed response.

(D) The frontal eye fields are usually damaged in frontal ablations. The possibility that difficulties in eye movements and fixation may cause

the delayed response deficit was eliminated by Pribram (56). He failed to find the delayed response deficit after lesions to the frontal eye fields. The general success of frontal monkeys on visual discriminations also argues against this hypothesis.

(E) Malmo attributed the failure of frontal monkeys on delayed response to interfering stimuli during the delay interval (i.e., increased retroactive inhibition). He came to this conclusion after showing that delay in the darkness facilitated delayed response (41). However, a fan was on during the procedures acting as a partial sound screen. Presumably, therefore, the interfering stimuli must be visual. The facilitation of delayed response by the procedures described earlier (8, 19, 49, 50) in which there was normal visual stimulation during the delay interval are evidence against this hypothesis. Furthermore, the facilitation he showed may have been due not only to the delay in the darkness but to the method of presentation of the predelay cue, a single lighted panel in a dark room.

(F) Mishkin and Pribram (49) tested the possibility that frontal monkeys were unable to make frequent shifts from left to right. They presented the delayed alternation problem with one food well above the other. The animals failed this up-down alternation also.

(G) Lowered environmental temperature, administration of Nembutal and insulin all increase food intake. Since these procedures as well as prolonged food deprivation facilitated delayed response it seemed reasonable that the deficit on delayed response may be due to reduced incentive value of food (55). Miles and Rosvold (45) trained monkeys to perform delayed response where the motivation for the correct response was the termination of a shock to the feet, rather than the usual food reinforcement.

After frontal lobotomy the monkeys failed on this task. Therefore, the possible loss of food incentive value cannot be of primary importance in the production of the deficit.

(H) Several experiments have indicated a deficit in anticipatory functions. The "push-push-push-pull" test (34), and the "right-right-right-left" linear maze (9) are examples showing an increase in anticipatory errors. The goal gradient versus anticipatory gradient (16) may be taken as evidence for the opposite hypothesis, i.e., decrease of anticipatory behavior. Relating this idea to delayed response the frontal monkey would be unable to anticipate (or "plan ahead") properly. This is similar to the earlier hypothesis of deficit in "temporal integration" (29). The experiments demonstrating facilitation of delayed response all argue against this interpretation. The frontal monkey can anticipate provided that the test is varied in certain ways.

(I) The deficit in delayed response in frontal monkeys may be due in part to an increase in response perseveration. This would apply also to the observed small increase in errors on visual discrimination (23). "Perseverative interference" would also help explain the deficit on the task requiring alteration between position (place) discrimination and object discrimination (64). Harlow and Johnson (25) in their "reaction time" test randomly alternated the exposed food from left to right. Nevertheless, the frontal monkeys did not make more errors than control animals on those trials in which they were required to shift to the side opposite a previously reinforced side. Mishkin and Pribram (50) showed that a single center predelay cue could serve as an effective cue in frontal monkeys for a postdelay response to either left or right. Thus, the shifting of responses from left to right is not the source of difficulty for the frontal monkey.

(J) The difficulty frontal monkeys demonstrate on descrimination reversal (23) led to the idea that part of the deficit on delayed response may be due to "difficulty in rapidly reversing symbolic associations" rather than responses. The "matching from sample" test (67) and the single predelay cues (49, 50) showed that frontal monkeys could form associations and then rapidly reverse them on subsequent trials.

(K) Stanley and Jaynes (68) proposed that "cortical act inhibition" was lost after frontal lesions. Thus, the monkeys would be unable to inhibit their responses to the incorrect stimuli. This proposal was made in 1949. In 1939, Finan had showed in his temporal discrimination experiments (18) that frontal monkeys were able to inhibit their avoidance responses for ten seconds before jumping over the barrier into the "safe" compartment. Therefore, the proposal was inappropriate at the time it was written Additional evidence against the hypothesis comes from the demonstration of success on the "go-no-go" delayed alternation by frontal monkeys (49). Animals that had lost their "cortical act inhibition" would presumably "go-go-go."

(L) One of the most frequently cited interpretations of the delayed response deficit is that frontal monkeys suffer from reduced "attention" and as a result they fail to fixate the relevant stimuli. The correct associations, therefore, are not formed. Slight variations of this idea have been offered by several authors (8,19,24,53,71). The experimental evidence for this interpretation is abundant. Any procedure that facilitates attention facilitates delayed response performance. Facilitation by predelay cues (19), prolonged fasting (55), trial unique objects (44), drugs which reduce hyperactivity (71), matching from sample (67), nonpositional cues (49, 50), all presumably increase fixation and attention. The first criticism of this

hypothesis is Malmo's finding that "interference" during the delay interval is related to the failure of the frontal monkeys (41). A slight adjustment in the hypothesis could be made at this point to incorporate this finding. If one assumes that attention is required during the pre-delay period, and also during the delay period, and at the time of response, and at the moment of reinforcement, then the hypothesis is still intact. This leads to the second criticism. What is attention? The term is so vague that it can be applied almost anywhere as shown in the "slight adjustment" made above. After a procedure is shown to facilitate delayed response then it is explained by "increased attention". If it does not facilitate delayed response (24, 49) then it could be said that the procedure did not increase attention. The absence of any direct measure or operational definition of attention necessitates this kind of a posteriori theorizing and illustrates the relative uselessness of the term.

(M) Teuber (70) has proposed that the delayed response loss after frontal lesions may represent a loss of "memory for place". The failure of frontal monkeys on object alternation (60) which requires memory for objects rather than memory for place is evidence against this hypothesis.

(N) Mishkin and Pribram found that nonpositional cues facilitated delayed response performance, whereas positional cues were ineffective for their frontal monkeys. In their first experiment (49) they found that frontal monkeys succeeded in "go-no-go" alternation in which a single central "nonpositional" cue is used. In their second experiment (50) a single central cue indicated whether the monkey should "go-or-no" after the delay interval. A single center cue was also used to indicate a response to left or right food cups after the delay. The frontal monkeys were able to perform these tasks. "Positional cues" did not give the same results. A

single cue presented to the left of a central cup indicated "go" and the same stimulus to the right indicated "no go". This positional cue did not facilitate performance. The authors made a direct test of this hypothesis in the third experiment of the series and rejected it (60).

(0) If frontal monkeys can succeed on delayed response-type tests when the cue is "nonpositional" then they should succeed on object alternation. In this test the cue is the object, regardless of its position. Their frontal monkeys failed this test (60). The authors then revised their earlier interpretation. The "distinctiveness" of the pre-delay cue seems to be the relevant variable. This handles some of the experiments, but as the authors write, "the notion of 'distinctiveness' needs further experimental specification, however, before a conceptualization of the deficit following frontal lesions can be attempted".

Although this study was not designed to test any of the above hypotheses, the findings are related to the problem of interpretation. Specifically, the last mentioned hypothesis concerning "cue distinctiveness" received some support in this study.

2.0. STATEMENT OF THE PROBLEM

This study was designed primarily to determine the effects of bilateral lesions to the head of the caudate nuclei on delayed alternation and visual discrimination. Lesions to this structure in the manner attempted here involve cutting the corpus callosum. Therefore, it became necessary to determine separately the effects of sectioning the corpus callosum on the two tests.

3.0. METHOD

3.1. Subjects

Nine adult rhesus monkeys (macaca mulatta) served as subjects for this experiment. The subjects were randomly assigned to two groups. Subjects, sex, group assignment, and previous formal training are listed in Table I.

3.2. Apparatus

A modified Wisconsin General Test Apparatus (22) was used for testing throughout the experiment. The apparatus consists of a restraining chamber for the animal, a test tray which slides on wooden supports, an opaque (metal) screen between the restraining chamber and the test tray, and a one way mirror between the test tray and the experimenter. The tray used for this experiment measured 21 by 10 inches and was painted light gray. Near the forward edge of the tray were two circular food wells, one and one quarter inches in diameter, one half inch deep, eleven and one half inches apart on center. During the trials on both problems the one way mirror hid the experimenter's body and face from the animal, although the hands of the experimenter could be seen. (One subject, number 100, would not perform when the mirror was down during the trial and the experimenter was required to keep it up throughout training.) Between trials an opaque screen was lowered in front of the bars of the restraining chamber.

Table I

Subject Number	Sex	Group Assignment	Past Training
60	female	A	avoidance conditioning
30	male	A	avoidance conditioning
34	male	A	avoidance conditioning
94	male	A	avoidance conditioning
100	male	A	avoidance conditioning
93	male	B	avoidance conditioning
98	male	B	avoidance conditioning
103	male	B	naive
104	male	B	naive

3.3. Procedure

The nine monkeys were randomly divided into two groups; Group A consisted of five subjects and Group B consisted of four subjects. All animals were trained to displace objects from the food wells, and were adapted to the sliding doors. They were ready for testing usually within two or three weeks of adaptation. When they were ready Stage I of the experiment began. All subjects were trained on the visual pattern discrimination. A trial was given as follows: one of the two food wells in the test tray was baited and covered with the block with the plus sign, while the other food well was covered with the block with the circle; the one way mirror was lowered; the opaque screen was raised; after a delay of approximately three seconds the tray was moved forward and S was allowed one response; the opaque screen was lowered ending the trial. Thirty trials were given per day, six days per week until the criterion of two consequtive days of 26 (or more) correct responses out of thirty trials (86.6%) was reached. Training was then begun on delayed alternation and continued for thirty days. All subjects of Group A then received left caudate lesions through the corpus callosum, and after a recuperative interval they were given right caudate lesions. After another recuperative interval Stage two testing began. Group B remained in their home cages for an equivalent interval between the end of Stage I and the beginning of Stage II. In Stage II all subjects were first retested for 30 days on the delayed alternation and then tested for retention of the visual pattern discrimination until they reached the criterion. All the subjects of Group A were sacrificed and their brains removed for histological examination at the end of Stage II. Only Group B entered into Stage III. They received

one stage lesions of the corpus callosum and were retested first on delayed alternation for 30 days, then tested for retention of the visual pattern discrimination until they reached the same criterion as used in the earlier stages of the experiment. At the end of training they were sacrificed and their brains removed for histological study.

The stimuli for the visual pattern discrimination problem consisted of two blocks of wood four and one half inches long by two and three quarter inches wide, and three quarters of an inch high. They were painted flat black. A circle two and one quarter inches in diameter from the outer rim, and one quarter inch thick was painted in yellow on one of the blocks of wood. On the other a plus sign, two and one quarter inches long and wide, and one quarter inch thick was painted in yellow. The blocks were washed when they became dirty. Responses to the plus sign were always reinforced with a bit of food, usually carrots, but occasionally apple, banana, or raisin. Thirty trials were given per day. The reinforced side was randomly alternated. A non-correction procedure was used. The animals were run six days per week, until a criterion of 26 correct out of 30 trials (86.6%) on two consequtive days was reached.

The delayed alternation problem consisted of two blocks of wood four and three quarters inches long by three and one quarter inches wide, by three quarters of an inch high. They were painted flat black. The reinforcement used in this problem was the same as that used in the visual pattern discrimination. On the "opening" trial both food wells were baited and covered and the animal was reinforced for either a left or a right response. The next trial was baited on the side opposite the side the animal responded to on the opening trial. This was counted as the first trial.

After the animal responded to this side, the opposite side was baited. This was continued for a total of 30 reinforcements (actually 31, counting the "opening" trial). The animals were run six days per week for a total of 30 days. A correction technique was used in this test. Following an error the bait was not shifted, but remained in the food well until the animal made the correct response. An error on one of these correction trials is called a "repeated error" while an error following a reinforced trial is called an "error".

3.4. Surgical Technique

Following the original 30 days of training on delayed alternation in Stage I all subjects in Group A, after a rest of from ten to 12 days received a unilateral extirpation of the head of the left caudate nucleus. This was done by opening the longitudinal fissure, cutting the anterior part of the corpus callosum. This exposed the lateral ventrical and the head of the caudate nucleus. The extirpation was made by passing a small loop of wire once through the caudate in the anterior-posterior direction, and once in the dorsal-ventral direction. No severe bleeding was ever encountered by this method of producing the lesion. After a recuperative period of from 23 to 29 days a unilateral lesion of the right caudate nucleus was produced by opening the corpus callosum more posteriorly than the original corpus callosum opening, and exposing the right lateral ventricle and caudate. This lesion was made in the same way as the first lesion. After a recuperative period of from 12 to 13 days, Stage II began. The total interval between the end of testing on Stage I and the beginning of testing on Stage II was from 45 to 50 days for Group A and from 48 to 49 days for Group B. Fifty five to sixty days after the end of delayed

alternation testing in Stage II all four subjects in Group B received unilateral lesions through the corpus callosum, the cut extending as far anterior and posterior as could be seen. Subject Number 100 did not survive the surgery. Retention testing was begun 12 to 17 days following the lesion, depending upon the recovery the animal made following the lesion. The total interval between the end of delayed alternation testing in Stage II and the beginning of testing on delayed alternation in Stage III was from 69 to 72 days.

4.0. RESULTS

The results on the visual discrimination problem are presented in Table II. The Kolmogorov-Smirnov two-sample test (66) indicated that Group A was significantly superior to Group B in Stage I ($p < .01$). However, the Mann-Whitney U test (66) indicated that the difference was not significant ($p > .1$). In Stage II there was no significant difference between the two groups as shown by both the Kolmogorov-Smirnov test ($p > .05$) and the Mann-Whitney U test ($p > .3$). The results of Stage III are not readily amenable to analysis by nonparametric methods. It is apparent by inspection, however, that there is no decrement in performance of the three subjects in Stage III as compared to their performance in Stage II.

Table II

Trials to criterion on visual pattern discrimination

Subjects (No.)	Stage I	Stage II	Stage III
Group A			
34	330	30	
60	210	30	
94	180	90	
100	990	330	
102	720	150	
Group B			
93	750	120	90
98	630	120	
103	1500	90	90
104	990	0	0

Note: Data does not include criterion trials.

The total number of "errors" on delayed alternation in each stage is presented in Table III. The difference between the groups in Stage I is not significant as indicated by the Kolmogorov-Smirnov test ($p > .05$). Figure 1 presents the percent correct responses for both groups in Stage I. (Percent correct responses was calculated from the number of "errors" in thirty reinforced trials given each day.)

Table III

Total number of errors for 30 days on delayed alternation

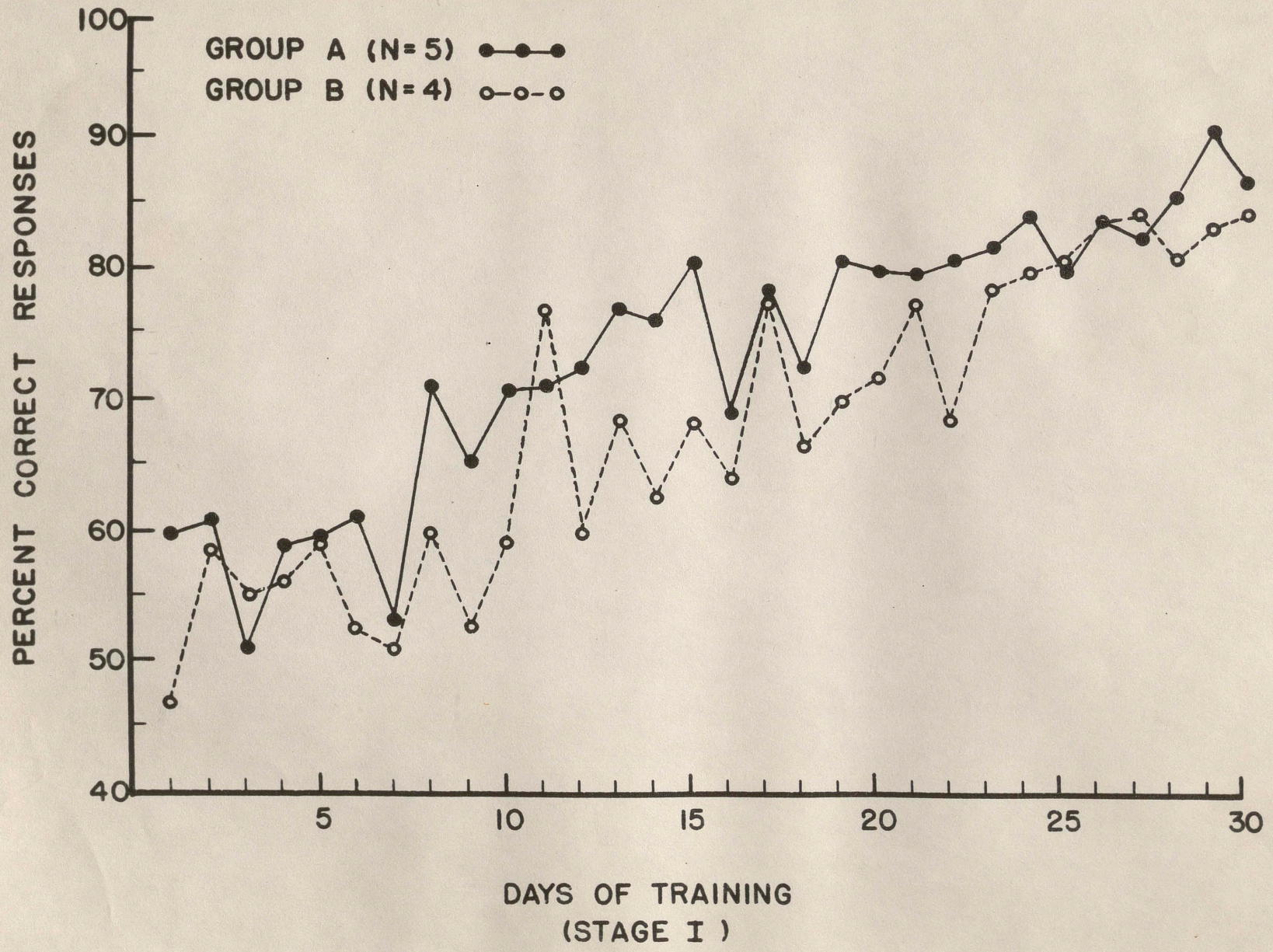
Subjects (No.)	Stage I	Stage II	Stage III
Group A			
34	280	460	
60	187	463	
94	274	453	
100	283	331	
102	176	252	
Group B			
93	217	119	75
98	223	129	
103	275	77	290
104	443	267	267

Figure 1

Percent correct responses for Group A and Group B

in Stage I

30 reinforced trials per day


GROUP A (N=5)
GROUP B (N=4)
PERCENT CORRECT RESPONSES
100
90
80
70
60
50
40
5
10
15
20
25
30
DAYS OF TRAINING
(STAGE I)

In Stage II, Group B is significantly superior to Group A (see Table III) as shown by the Kolmogorov-Smirnov two-sample test ($p < .01$). Figure 2 presents the percent correct responses for both groups in Stage II. The difference between the groups is significant for all the days in Stage II as shown by the Kolmogorov-Smirnov test ($p < .01$). The Friedman two-way analysis of variance (66) showed no significant improvement ($p > .3$) in percent correct responses during Stage II for Group A, although one subject, Number 102 did show improvement in performance as indicated in Table IV.

Table IV

Number of days at 80% correct responses or more in Stage II

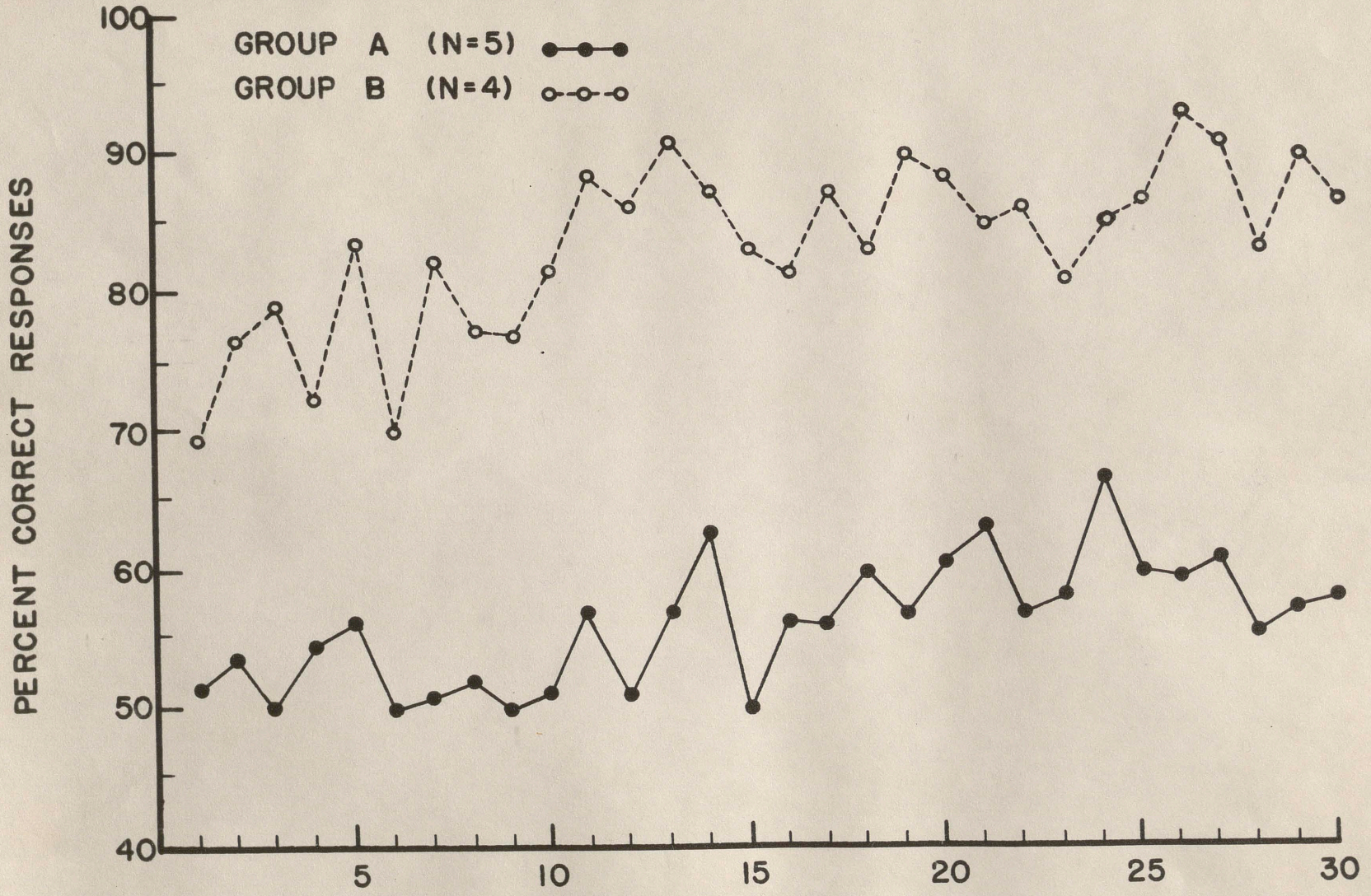
Subjects (No.)	First 15 Days	Last 15 Days
24	0	0
60	0	0
94	0	0
100	0	3
102	0	10

Figure 2

Percent correct responses for Group A and Group B

in Stage II

30 reinforced trials per day


GROUP A (N=5)
GROUP B (N=4)
PERCENT CORRECT RESPONSES
100
90
80
70
60
50
40
5
10
15
20
25
30
DAYS OF TRAINING
(STAGE II)

The total number of "repeated errors" on delayed alternation in each stage is presented in Table V. The difference between the groups in Stage I is not significant ($p > .3$) as shown by the Kolmogorov-Smirnov test. Figure 3 presents the mean number of "repeated errors" for each group in Stage I.

Table V

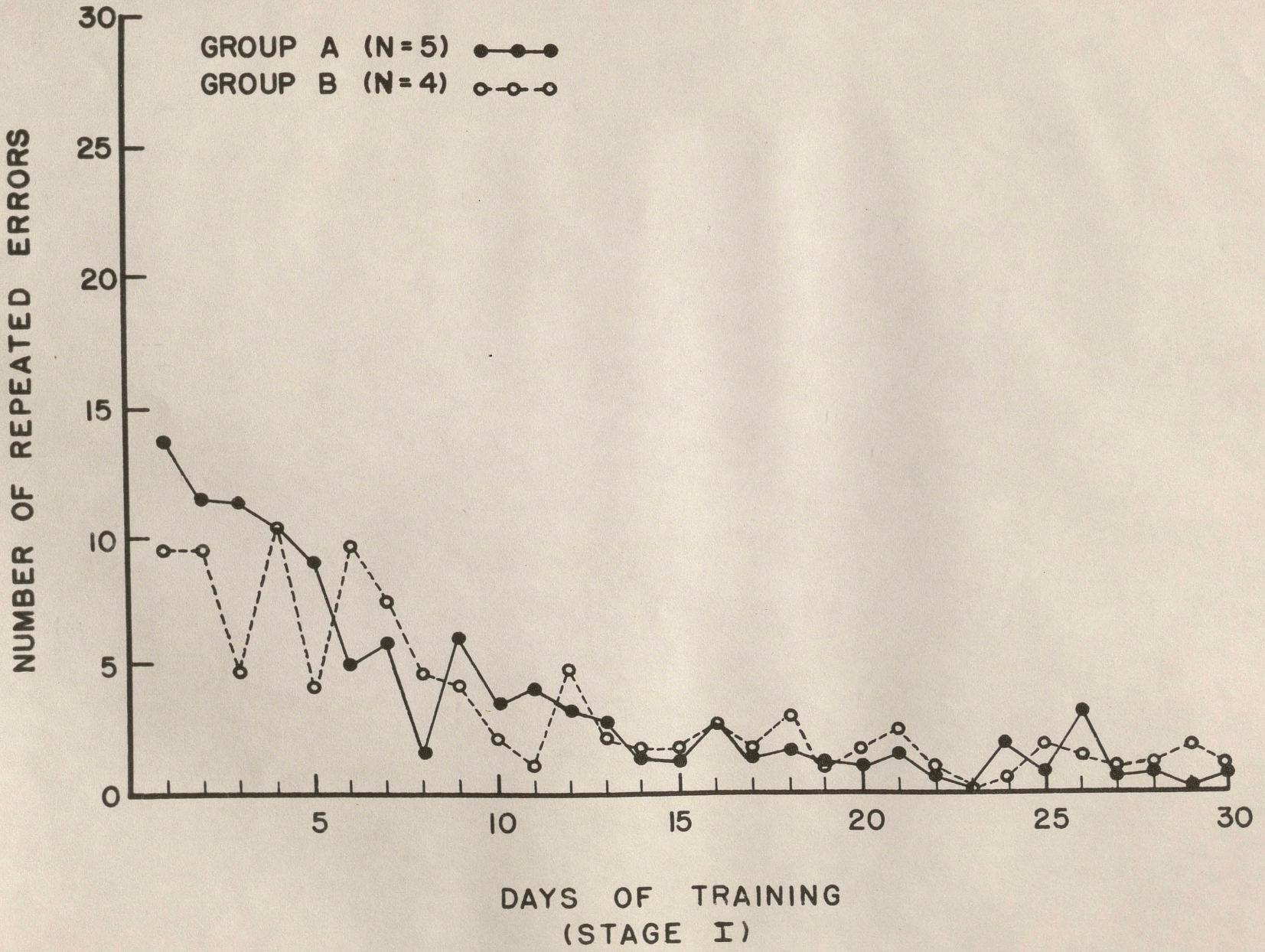
Total Number of "Repeated Errors"

For Thirty Days on Delayed Alternation

Subjects	Stage I	Stage II	Stage III
Group A			
No. 34	176	559	
No. 60	56	453	
No. 94	138	598	
No. 100	104	295	
No. 102	64	165	
Group B			
No. 93	48	14	30
No. 98	85	18	
No. 103	124	11	549
No. 104	149	57	189

Figure 3

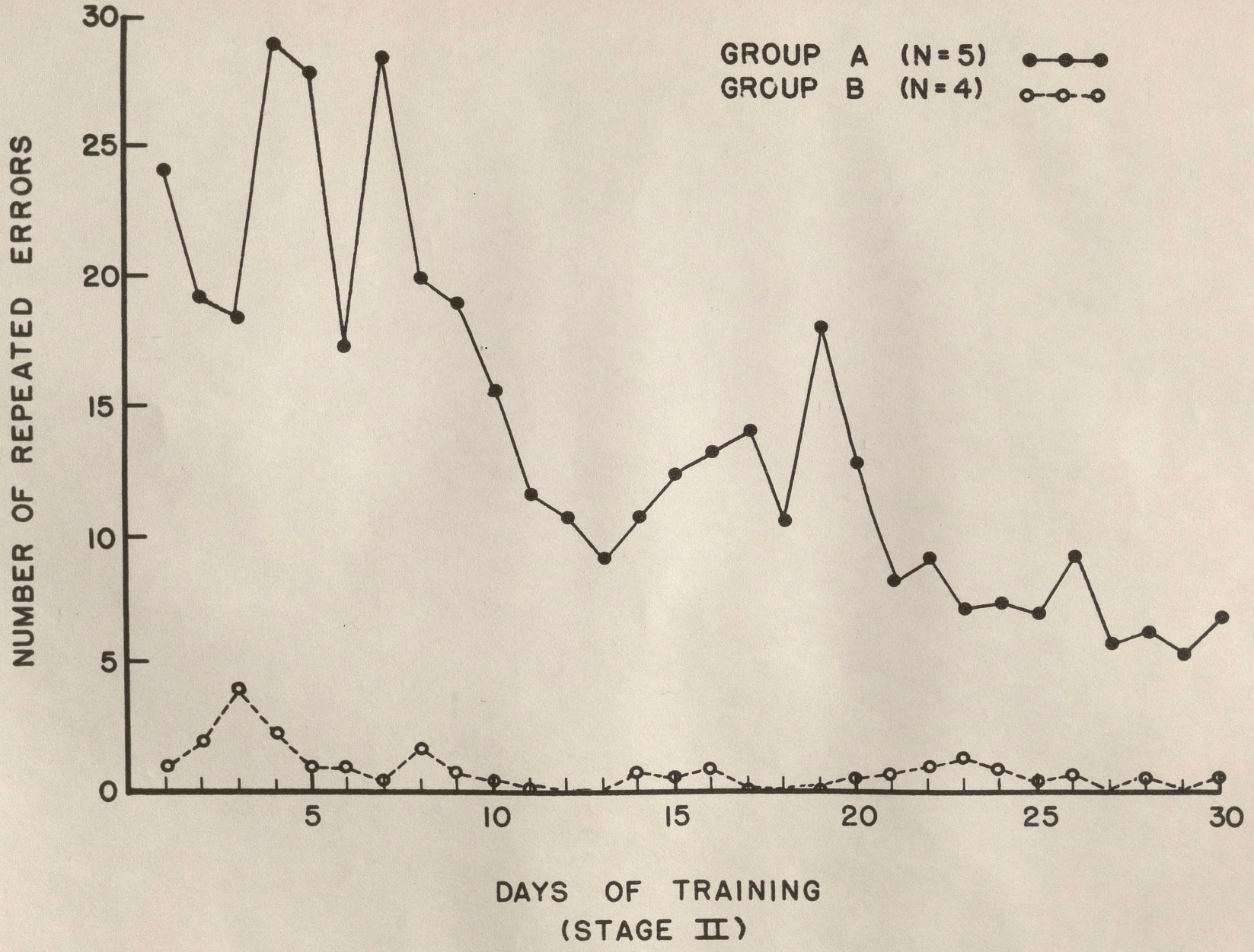
Mean number of "repeated errors" for Group A and Group B in Stage I


GROUP A (N=5)
GROUP B (N=4)
NUMBER OF REPEATED ERRORS
0
5
10
15
20
25
30
DAYS OF TRAINING
(STAGE I)

In Stage II, Group B is significantly superior to Group A (Table V) as shown by the Kolmogorov-Smirnov two-sample test ($p < .01$). Figure 4 presents the mean number of "repeated errors" for both groups in Stage II. The difference between the groups is significant for each day of Stage II as shown by the Kolmogorov-Smirnov test ($p < .01$). Group A showed a significant improvement in the number of "repeated errors" in Stage II as shown by the Friedman two-way analysis of variance ($p < .01$).

Figure 4

Mean number of "repeated errors" for Group A and Group B in Stage II


GROUP A (N=5)
GROUP B (N=4)
NUMBER OF REPEATED ERRORS
0
5
10
15
20
25
30
5
10
15
20
25
30
DAYS OF TRAINING
(STAGE III)

Only Group B participated in Stage III. Subject Number 98 died following sectioning of the corpus callosum, reducing the N to three. In view of this reduced number, the statistical analysis of the effects of sectioning the corpus callosum should be accepted with some caution. The mean percent correct responses for each stage is presented in Table VI. The Friedman two way analysis of variance was applied to the data of Table VI and showed that the difference in rank totals between the three stages was not significant ($p > .3$). In an attempt to increase the accuracy of the analysis by eliminating some of the practice effects, the analysis was repeated using the mean percent correct for the last ten days of training in each stage. The difference in rank totals for the three stages was again not significant ($p > .5$). Figure 5 presents the percent correct responses of the reduced Group B in Stages II and III.

Table VI

Mean percent correct responses

for 30 days on delayed alternation

Subjects (No.)	Stage I (percent)	Stage II (percent)	Stage III (percent)
93	75.8	86.7	91.6
	(83.6)	(87.2)	(95.3)
103	69.4	91.5	67.7
	(83.9)	(94.9)	(77.6)
104	50.9	70.3	70.3
	(65.6)	(72.3)	(75.6)

Note: Figures in parentheses indicate mean percent correct during last 10 days of each stage.

Figure 5

Percent correct responses for reduced Group B in Stages II and III

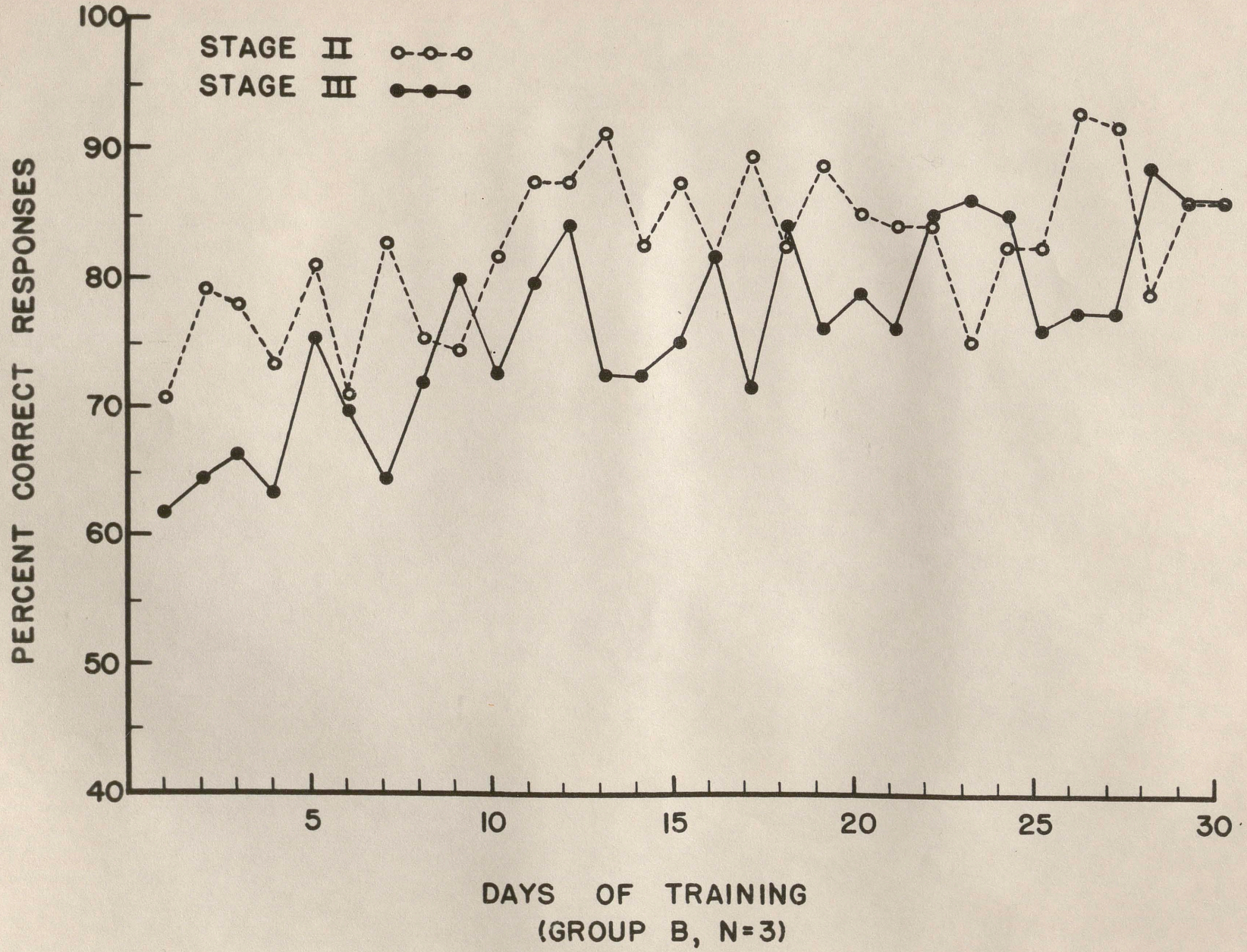

STAGE II
STAGE III
PERCENT CORRECT RESPONSES
100
90
80
70
60
50
40
5
10
15
20
25
30
DAYS OF TRAINING
(GROUP B, N=3)

Table VII presents the total number of "repeated errors" for the 30 days of each stage. The differences between the stages was not significant ($p > .1$). Repetition of the analysis of variance, using only the last ten days of each stage, also yielded nonsignificant differences ($p > .9$).

Table VII

Total Number of "repeated errors"

for 30 days on delayed alternation

Subjects (No.)	Stage I	Stage II	Stage III
93	48	14	30
	(6)	(9)	(3)
103	124	11	549
	(7)	(2)	(38)
104	149	57	189
	(38)	(16)	(24)

Note: Figures in parentheses indicate total number of "repeated errors" during last 10 days of each stage.

5.0. Discussion

The results on the visual discrimination test indicate that lesions to the caudate nuclei did not produce significant decrements in performance as compared to the unoperated controls. Since the animals with the caudate lesions also had much of the corpus callosum sectioned, the same conclusion may be reached concerning the corpus callosum. The findings on the three animals with only the corpus callosum sectioned support the conclusion that the presence of the corpus callosum is not necessary for adequate retention of visual discrimination problems. There was no test made for the adequacy of original acquisition of visual discrimination problems.

The possibly significant difference between Group A and Group B on the number of trials to criterion on the visual discrimination in Stage I must be attributed to chance factors, since the nine animals were divided into the two groups prior to Stage I by a method of random selection.

The lesions given to the animals of Group A produced different effects on the two measures of performance in delayed alternation in Stage II. The percent correct responses for the group was significantly inferior to Group B, and there was no significant improvement for the group over the 30 days of testing (although one subject did improve). However, the number of "repeated errors" was significantly greater for Group A, and there was a significant improvement on this measure of performance over the 30 days of Stage II.

It will be recalled that an incorrect response following a reinforced trial was labeled an "error". The reinforcement from the previous trial may, therefore, be considered as the cue for that response. The performance of Group A to this cue of reinforcement remained essentially

unchanged during the 30 days of Stage II. An incorrect response on the correction trials was labeled a "repeated error". The nonreinforced previous trial may be considered the cue for this incorrect response. Thus, the difference that was observed between the two measures of performance in Stage II can be thought of as the result of the difference in the nature of the cue, both of which signaled the same response, alternation.

The series of interpretations of the delayed response deficit presented earlier culminated in the hypothesis by Pribram and Mishkin (85) that "cue distinctiveness" was a significant factor. The authors indicated the need for further experimental specification of this variable. In this study it was found that the cue situation was a significant variable. The cue situation of no reinforcement was more "distinct" than the cue situation of reinforcement. This finding by no means clarifies the nature of the variable. However, the complexity of the variable is apparent, and further experimentation is certainly needed.

The effect of sectioning the corpus callosum alone, on delayed alternation should be studied further since only three animals received such lesions in this study. There is some evidence that the performance of Group B on both percent correct responses and number of "repeated errors" is deficient early in Stage III, although the statistical test indicated no significant difference between stages for the three animals with the corpus callosum sectioned. However, the performance of these animals returned to a high level of accuracy at the end of Stage III, indicating that the effect of sectioning the corpus callosum, if significant, is transient. Thus, the effects observed in Stage II for Group A on delayed alternation can be attributed primarily to the lesions of the caudate nuclei. This is in agreement with the findings of Rosvold and Delgado (62).

There is no way of knowing at present, why the lesions to the caudate nuclei produced the delayed alternation deficit. It may be that the fibers from the caudate nucleus to the frontal lobe (27, 42) facilitate the activity of the latter; therefore, when this facilitation is removed the deficit typically following frontal lesions is observed. On the other hand, the frontal cortex may facilitate the caudate nuclei, and the effects of the lesions to these structures could be explained conversely. The results reported for stimulation of the caudate (62) shed no light on this problem, since the stimulation might alter the nature of the impulses delivered to the frontal lobe, or the stimulation might distort the impulses that the caudate nucleus delivers to other parts of the brain. As a third possibility, both pathways between the caudate nuclei and frontal cortex may be involved in the behavior.

There is evidence that the frontal cortex sends fibers to the reticular formation of the brain stem (35) and that the caudate is related to both the reticular formation and diffuse thalamic projection system. Stimulation of the caudate will produce electrocortical arousal and driving of the diffuse thalamic projection nuclei (65). This data has led the author to the following suggestion for a mechanism relating the neurophysiological findings to the psychological findings.

The reciprocal circuit from the caudate to the frontal cortex and back to the caudate is tapped at one end by the fibers to the reticular formation (from the frontal cortex) and at the other end by the connections to the diffuse projection nuclei of the thalamus (from the caudate). These impulses to the reticular formation and diffuse thalamic system modulate the level of activity in the reticular formation and diffuse thalamic system. When this modulation is lost the reticular discharge that follows an incoming

stimulus to the cortex becomes distorted. Some evidence for this is given by Kennard (36) who found cortical hypersynchrony following large lesions to the caudate nucleus in the monkey. It is known that this reticular discharge is necessary for the perception of stimuli and the responses to them. The anesthetic state is characterized by the marked reduction of reticular activity (21), and lesions to the reticular formation can produce prolonged somnolence (20). In this way the support given to the specific projection system by the nonspecific projection systems of the thalamus and brain stem becomes altered and the perception of stimuli also becomes altered in some as yet unspecified manner. This hypothesis would relate the significance of the cue variable to neurophysiological data.

6.0. SUMMARY AND CONCLUSIONS

In Stage I, nine rhesus monkeys were trained to criterion on a visual pattern discrimination and then trained for 30 days on delayed alternation. Five subjects in Group A received serial bilateral lesions of the head of the caudate nuclei through the corpus callosum. The four subjects in Group B were retained as unoperated controls. Both groups were retested for 30 days on delayed alternation and retested on the visual discrimination in Stage II. In Stage III, Group B received one stage lesion of the corpus callosum. Group B was then tested for 30 days on the delayed alternation problem and retrained to criterion on the visual discrimination.

In Stage II, Group A showed significant impairment on the delayed alternation problem as compared to Group B. There was no significant change on the visual discrimination problem in Stage II.

In Stage III, there was no significant change in performance on delayed alternation, and there was no decrement in performance on the visual discrimination.

It was concluded that lesions of the caudate nuclei produce a significant impairment on delayed alternation, but not on visual discrimination retention. Sectioning the corpus callosum produced no significant impairment on delayed alternation or visual discrimination retention. The results were related to current interpretations of the nature of the deficit following frontal lesions, and a suggestion of the possible mechanism which is upset following caudate or frontal lesions was presented.

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