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LIMBIC LESIONS AND THE TEMPORAL STRUCTURE OF REDUNDANCY[1]

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Monkeys with dorsolateral frontal ablations have been found able to learn go no-go alternation despite a grave deficit in classical alternation. Subsequently, evidence has implicated certain limbic lesions in go-no-go types of task, e.g., passive avoidance and successive discriminations. This study was undertaken to test whether these limbic lesions would affect go-no-go more than classical alternation. The results supported the hypothesis that at least 2 classes of variables, 1 frontal and 1 limbic at the neural level, interact to make possible effective performance in alternation-type tasks.

Some years ago we were surprised to find that monkeys with dorsolateral frontal eugranular cortical lesions, while unable to perform classical delayed response and delayed alternation tasks, did learn go-no-go variations of these problems (Mishkin & Pribram, 1955, 1956).

Since these earlier studies several reports have issued which lead to the expectation that a converse effect could be produced by certain limbic system lesions. Successive go-no-go types of discrimination are more severely affected by lesions of the orbital surface of the frontal lobe than by lesions of the dorsolateral frontal cortex (Brutkowski, 1964; Mishkin, 1964; Pribram & Mishkin, 1955). These orbital lesions invade both the posterior orbital area—a part of the orbito-insulo-temporal cortex, a limbic region which includes the amygdala (Bailey, von Bonin, Gargol, & McCulloch, 1943; McCulloch, 1944; Pribram, Lennox, & Dunsmore, 1950; Pribram & MacLean, 1953)—and the medial orbital gyrus—a part of the subcallosal cingulate region (Kaada, Pribram, & Epstein, 1949; Pribram et al., 1950; Pribram & MacLean, 1953).

Another series of experimental results tends to further the expectation that some limbic system lesions, though impairing both (Pribram, Wilson, & Connors, 1962), will affect go-no-go alternation more than classical right-left alternation. Active avoidance of shock, as tested in a shuttle box, is affected by a variety of limbic system resections as well as by dorsolateral frontal resections (Pribram, 1954; Pribram & Weiskrantz, 1957). Both acquisition and extinction of conditioned avoidance are influenced, though to a different degree, by the different limbic and frontal lesions. In addition, limbic and frontal resections alter the duration over which a response is withheld in a frustrating situation (Pribram & Fulton, 1954).

More recently McCleary (1961) has extended these observations by producing differential effects of limbic lesions on active and passive (withholding) avoidance behavior. There is an apparent discrepancy in the literature between the earlier results and McCleary's. In McCleary's (1961) study, active avoidance remained unaffected by subcallosal-septal and hippocampal resections. Aside from a difference in species and perhaps in lesions, there is a difference in the procedures used in the two experiments. McCleary tested postoperatively only, while Pribram trained his *Ss* both pre- and postoperatively. McCleary's shuttle box was fitted with a door which was opened when the CS was turned on and closed shortly after the US had been given. Shock (the US) was turned on only briefly at the end of the CS-US interval. By contrast, in Pribram's situation, the shuttle box had no door (because door opening per se proved to be a sufficient cue to make monkeys jump to the other compartment), only an elevated partition dividing the two compartments; shock remained on in the

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"negative" compartment until the beginning of the following trial. Therefore *Ss* could and did jump freely between compartments during the initial trials and during extinction, and this form of avoidance conditioning partakes of both the active and passive situation used by McCleary.

In addition, the defect in avoidance obtained after cingulectomy was shown to depend on the alternation demanded in the shuttle box procedure as it is usually used (Lubar, 1964). Thus conditioned avoidance and alternation appear to have a good deal in common. Further, the no-go trials of the go–no-go alternation as it is usually given are, in essence, passive avoidance trials: *Ss* must restrain response to a stimulus which on other trials is rewarded. Therefore, it seems reasonable to suggest that those lesions (subcallosal-septal and pyriform-amygdala) which primarily influence passive avoidance (a withholding, go–no-go type of behavior) would also primarily affect go–no-go alternation.

The present experiments were undertaken to test whether two limbic system lesions, medial-frontal-cingulate (corresponding to the cat's subcallosal-septal) and orbitofrontal-insulo-temporal (corresponding to the cat's pyriform-amygdala) resections, did indeed disrupt go–no-go alternation more than right-left alternation.

Method

Subjects

One group (MFC) of four preadolescent rhesus monkeys was given a bilateral medial-frontal-cingulate ablation that encompassed the projection sector of the anterior thalamic nuclear group (Pribram & Fulton, 1954; Rose & Woolsey, 1948) and invaded the septal region. Another group (OIT) of four received a bilateral orbitofrontal-insulo-temporal resection that included all of the amygdaloid complex. This lesion is based on the sector of the forebrain that receives projections from midline thalamic components—the midline magnocellular portion of the medialis dorsalis (Pribram, Chow, & Semmes, 1953) and the midline intralaminar nuclei (McKegney, 1958; Nauta & Whitlock, 1954; Rose & Woolsey, 1948). Both lesions are also consonant with neuronographic regions delimited electrophysiologically after topical application of strychnine sulfate (Pribram et al., 1950; Pribram & MacLean, 1953).

Surgical and Histological Procedures

The MFC lesion was made in a single stage through a full calvarium flap turned on the right temporal muscle. One or two small veins extending from the saggital sinus to the frontal cortex were sacrificed on one side, the dura reflected on that side, and the interhemispheric fissure gently packed with cottonoid. Removal of the packing afforded access to the cingulate gyrus and its precallosal and subcallosal extensions into the medial frontal lobe, as well as the septal region. When the ablation in one hemisphere was completed, the limbic portions of the other hemisphere were exposed by simply incising the falx. No further such sacrifices were necessary. Symmetrical subpial removal of cortex in the second hemisphere was then made.

The OIT lesion was performed in two stages during a single surgical session. Each stage was accomplished through a myeloplastic craniotomy after removal of the zygomatic arch. A subtemporal decompression-type exposure was made of the anterior extremity of the Sylvian fissure. The middle cerebral artery was then followed downward to its origin from the circle of Willis and the exposed space gently packed with cottonoid. When the packing was removed, the orbital surface of the frontal lobe, the perisellar region, and the amygdala were plainly visualized. The amygdaloid complex and adjacent temporal cortex were removed first, then the posterior orbital area, and finally the insular cortex lying under the middle cerebral artery and between the amygdala and the frontal cortex.

All resection was done with a 19-gauge blunt needle-stock sucker; bleeding was controlled by temporary packing with cottonoid, and the wounds, including the dura, were closed in layers with silk.

After completion of behavioral testing all *Ss* were sacrificed under deep barbiturate anesthesia. Their brains were perfused with normal saline solution and 10% formalin. After removal from the skull they were frozen, sectioned, and stained as detailed in the procedure by Sherer and Pribram (1962). Reconstructions of the lesions were made from the cross sections and are shown in Figure 1.

Behavioral Testing Procedures

All *Ss* were tested both on classical right-left and go–no-go alternation in a modified Yerkes-Wisconsin hand testing apparatus prior to surgery. In the classical situation, facing *S* were two like-appearing cups with retractable lids allowing the exposure of a peanut placed alternately in one cup or the other. In the go–no-go situation, one centrally placed cup was baited on alternate trials and there was no reward on the no-go trials: *S* was expected to learn to withhold response for at least 5 sec. on unbaited trials and if *S* opened the food cup on these trials, the trial was terminated and the condition repeated until the correct (withheld) response was made. Trials in both situations

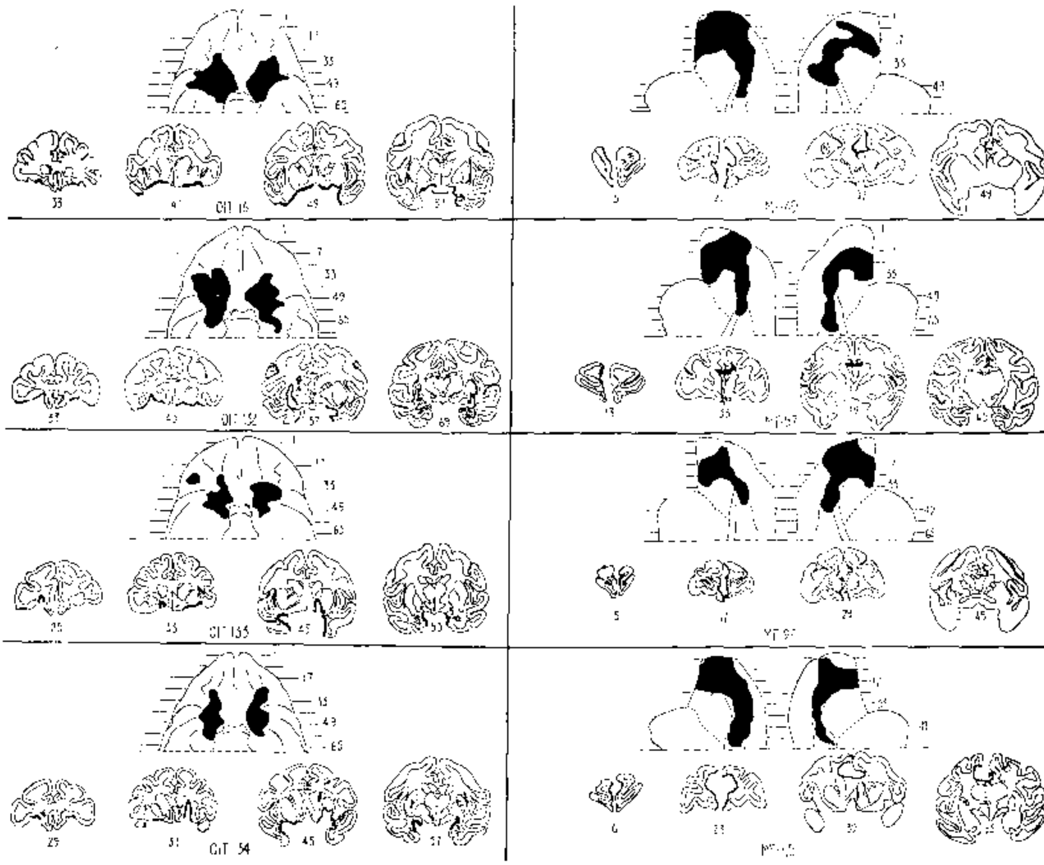

FIG. 1. Reconstructions and representative cross sections of the orbitofrontal-insulo-temporal (OIT) and medial-frontal cingulate (MFC) lesions. (There is minimal unilateral involvement of deep structures in OIT 133 and only unilateral involvement of putamen and caudate in OIT 132 and OIT 134.)

were separated by the interposition of an opaque screen between *S* and the cup(s).

Correction technique was used in both tasks. A trial included all errors made under one condition. On each testing day *Ss* were given 30 trials. Thus, there are two dependent variables used to gauge task performance: days (30 trials per day) and total errors to criterion.

Training was balanced so that half of the *Ss* received the classical and half received the go-no-go task initially. All *Ss* had to reach a criterion of 90% on 100 consecutive trials on both tests; then a 2-wk. layoff period was allowed and retention retested. Preoperative retention was always given in the order classical → go-no-go, so that all *Ss* had experienced the go-no-go task immediately prior to surgery. Postoperatively the go-no-go task was given first.

Statistical Procedures

Original learning scores were based on raw data (days or errors to criterion). Retention scores (both preoperative and postoperative) were expressed as percentage of original learning scores in order to control for the large difference in errors made during original learning of the two tasks. To give homogeneous variance across lesion groups, tasks, and time of test, individual percentage retention scores in days were transformed by $Y' = (\sqrt{Y})\,10$, and percentage retention scores in errors were transformed by $X' = [\mathrm{Log}(X+1)]\,100$.

RESULTS

An overall analysis (Task × Lesion × Test Time) of transformed retention scores yielded as the major source of variance the time (pre- vs. postoperatively) of testing ($p < .005$ for errors and $p < .025$ for days). Though none of the interactions reached statistical significance, there were consistent tendencies (for both errors and days) for the go no-go task to be affected more by both lesions and for the OIT group to suffer greater losses on both tasks.

TABLE 1

PREOPERATIVE AND POSTOPERATIVE RETENTION SCORES AS PERCENTAGES OF ORIGINAL LEARNING SCORES

S	Days				Errors			
	Go No go		Right Left		Go No-go		Right-Left	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
MFC 49	84.6	45.0	12.5	50.0	11.6	5.1	0.0	8.1
MFC 57	20.0	94.9	22.2	7.4	2.9	27.6	1.5	1.2
MFC 97	8.7	96.7	40.0	80.0	0.5	97.5	0.0	89.0
MFC 115	14.3	70.6	120.0	20.0	0.9	16.2	100.0	79.0
M	31.9	76.8	48.7	39.4	4.0	36.6	25.4	44.3
SD	27.6	21.0	42.3	28.1	4.5	36.0	43.1	39.9
OIT 116	18.2	48.5	12.5	12.5	1.0	38.7	0.0	1.8
OIT 132	20.0	73.5	26.1	95.7	0.4	46.5	1.0	213.0
OIT 133	36.4	84.3	15.4	30.8	3.2	158.0	0.0	139.0
OIT 134	11.1	97.0	20.0	40.0	0.5	129.2	1.5	20.8
M	21.4	75.8	18.5	44.7	1.3	93.1	0.6	93.6
SD	9.3	17.8	5.1	31.0	1.1	51.6	0.6	86.6

These tendencies were borne out when more restricted tests were made.

Tasks

Original learning of the two tasks (classical and go no-go alternation) can be compared in two ways. When the number of days to criterion was taken as the dependent variable, learning was shown to be about equally rapid in the two situations. When, however, total errors were considered, the go–no-go procedure was found to be about six times as difficult to acquire irrespective of whether it was the first or second test administered. Analysis of variance (Task × Group) on original learning raw scores revealed a Task effect on errors ($p < .005$).

Individual percentage scores for preoperative and postoperative retention are presented in Table 1. Comparison of pre- and postoperative retention of the basis of days by t test on transformed retention scores showed that the go–no-go task only was affected by both lesions (Group OIT, $p < .02$; Group MFC, $p < .10$). Comparison of the percentage error scores did not show this effect (Table 2).

TABLE 2

MEAN TRANSFORMED RETENTION SCORES

Group	Days						Errors					
	Go No-go			Right Left			Go No-go			Right-Left		
	Pre	Post	t^a	Pre	Post	t^a	Pre	Post	t^a	Pre	Post	t^a
MFC	51.00	86.50	2.48*	63.75	58.00	.25	53.75	137.00	1.91	60.00	128.75	1.42
OIT	45.25	86.75	4.79***	42.50	62.75	2.07	31.25	189.75	12.17****	17.50	156.75	3.35**

[a] $df = 3$; two-tailed tests.
* $p < .10$.
** $p < .05$.
*** $p < .02$.
**** $p < .01$.

Lesion Groups

Both groups originally learned both tasks equally readily whether days or errors were used as the measure. Analysis of variance (Task × Group) showed no group interactions. Comparison of pre- and postoperative transformed retention scores by t tests showed that the OIT group made more total errors postoperatively on *both* tasks (go–no-go, $p < .01$; right-left, $p < .05$). Comparison of retention in terms of days failed to separate the lesions groups (Table 2).

Discussion

The types of behavior altered by lesions of the limbic portions of the forebrain have repeatedly been shown similar to those disturbed by ablations and stimulation of the frontal eugranular cortex and different from those produced by manipulations of the cortex of the brain's dorsolateral convexity. The results reported here fit with the earlier ones and add the orbitofrontal-insulo-temporal region (including the amygdala) to the list of limbic structures involved in alternation behavior.

The hypothesis proposed in the introduction was that certain limbic lesions would affect go–no-go alternation more than they would affect right-left alternation. The postoperative behavior of the monkeys in this study tends to support the hypothesis; the go–no-go procedure was impaired by both limbic lesions though the effect of the OIT ablation was more dramatic, possibly because of more extensive invasion of subcortical structures.

In a previous study, the effect of dorsolateral frontal lesions was shown to be the converse of those produced in the present study; dorsolateral frontal lesions permanently impaired classical alternation, though the go–no-go procedure could be learned in approximately the number of trials taken by the present *Ss* before surgery. This suggests that two types of variables interact whenever alternation behavior is demanded: one type is critically related to classical alternation and the dorsolateral frontal cortex; the other is affected more by limbic lesions and becomes especially evident in the go–no-go procedure.

The mechanism of operation of these two variables remains a task for future research. Even the interpretation of the process that underlies classical alternation behavior remains controversial. An explanation in terms of the spatial nature of the task has not been completely disposed of (French, 1964; Mishkin, 1964) despite the fact that frontally lesioned monkeys fail object and operant as well as spatial alternation tasks (Pribram, 1961; Pribram & Mishkin, 1956).

Nor is interpretation of the go–no-go process any easier. Impairment of go–no-go (passive avoidance, withholding) behavior is usually attributed to an inability to inhibit responses on the no-go trials. However, as is shown in the present experiment, this inability is intrinsic to the task and must not be too readily attributed to the effect of the brain lesions. In fact, in this experiment, when the retention deficit was analyzed in terms of the percentage of total errors, the analysis failed to distinguish between the classical and the go–no-go task though it was sensitive to location of lesion. In other words, the OIT lesioned group made more repetitive errors in *both* situations. Further, our experience was that although failures to inhibit behavior were by far the most numerous occasions for error, instances of inappropriate inhibition on go trials were not rare. Indeed, even repetitive errors on go trials did occur.[2]

In summary, then, a working distinction can apparently be made between two types of behavioral process. One type occurs in

[2] On the first days of go–no-go training *Ss* might score as many as 40% of their errors on the go trials. Such errors dropped quickly, however, so that by the fifth day of testing they were recorded only occasionally. The no-go errors during this period increased in number and then decreased more slowly. Postoperatively both the go and the no-go errors showed a recrudescence, but again the go errors dropped out rapidly, the no-go errors more slowly. Postoperatively also a period of increasing no-go errors intervened before mastery, especially when impairment was great.

response to simple repetitions of events. The other takes place when the temporal patterns of redundancy with which events recur are more complex. Frontal and limbic systems are concerned with those processes which have this more complex temporal structure. The results of the present experiment support the suggestion that at least two independent classes of variables interact to make possible effective performance in the face of such complexities in temporal structure. The mechanism of operation and interaction of these two classes of variables remains to be investigated. The possibility is raised by the results of the present experiments that at the neural level, one class of variables concerns the dorsolateral frontal cortex, the other the limbic formations of the forebrain. Another possibility, however, is that alternation depending on the withholding of a response is both (relative to controls) more easily established and disrupted in brain lesioned *Ss* than is behavior in the classical task.

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