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AN EXPERIMENTAL CRITIQUE OF THE EFFECTS OF ANTERIOR CINGULATE ABLATIONS IN MONKEY[1]

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Recent use of anterior cingulate ablation in the treatment of mental illness makes imperative a reinvestigation of the consequences of such ablation in sub-human primates. The operation was introduced on the grounds that behavioural changes such as "loss of fear" and "social indifference" result from bilateral removal of the anterior cingulate in monkeys. This conclusion was based on three studies involving some 14 animals (Smith, 1944; Ward, 1948; Glees, Cole, Whitty and Cairns, 1950). The experiments which lead to these conclusions were relatively short-term (two or three months), and only two of the animals in question had been trained, i.e. tested before and after operation. Histological analysis of the lesions is adequately reported in only one of the studies based on six brains (Glees *et al.*, 1950). In the present series of experiments available neurophysiological, neurosurgical, and neuroanatomical techniques were used for elucidating the basic problem of functional localization in the cingulate and medial frontal cortex.

Frontal cortex may be divided into eugranular (granular) and dysgranular (incl. agranular) portions. Specific behavioural changes have previously been correlated with ablations of all dysgranular areas (precentral motor [Lashley, 1924; Fulton and Keller, 1932; Denny-Brown, 1952] and frontotemporal [Pribram and Bagshaw, 1953]) save those abutting the corpus callosum (cingulate). In addition, selective changes in behaviour follow removal of dorsolateral granular cortex (Pribram, Mishkin, Rosvold, and Kaplan, 1952). The present report is concerned with the remaining frontal cortex: the effects of bilateral lesions of cingulate areas *per se*, and the effects of a combination of such lesions and removal of the ventromedial frontal granular cortex. The effects of anterior cingulate ablation when added to excision of the precentral

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motor cortex are reported in another study (Berman, Robinson, and Pribram, 1951).

Materials and Methods

Subjects.—Fifteen rhesus monkeys were used in this study: 5 were unoperated controls and 10 were subjected to bilateral ablations of the anterior cingulate gyrus. In addition, serving as operated controls, were 2 spider monkeys with aluminum hydroxide implantations over the cingulate cortex, one mangabey with a total anterior frontal lobectomy, and two baboons, one with a medial, the other with a lateral frontal ablation.

Behavioural observations.—A transport cage was used to move the animal from individual living quarters to an air-conditioned, sound-proofed, darkened testing room. Here the cage was moved into a dimly illuminated enclosure and secured in place, facing an opaque screen which separated the animal from the testing apparatus. When the opaque screen was raised the animal was confronted with a sliding tray to which were attached two rectangular metal cups spaced 12 in. apart. Metal cup covers, 3 in. × 4 in., served as interchangeable stimulus plaques. The animal quickly learned to displace these plaques to obtain the concealed reward (peanut). A one-way vision screen was lowered, the tray pushed forward, and the animal was permitted to make a choice. Left and right cups were baited in random order. The non-correction technique was employed. No punishment, other than withholding reward, was given for errors. Thirty trials were presented daily until the criterion of 85 correct in 100 consecutive trials was achieved. At this time, the opaque screen was interposed for delays of 0, 5, and 10 seconds after baiting; a criterion of 85 correct in 100 consecutive trials was achieved at one delay interval before the next longer interval was administered.

A visual pattern discrimination test was administered in the same apparatus. Stimulus plaques were painted bright yellow; on one a "plus," on the other a "square" was painted in flat black. The cup bearing the plaque marked "plus" was baited behind the opaque screen, the screen raised, and the animal permitted to make a choice. The position of the plaques was shifted so that the reward was located in the two cups by random order. Non-correction technique, no punishment, was used. Criterion was 85 correct choices in 100 consecutive trials. Reaction to aperiodic withholding of reward after correct choice, once the discrimination had been learned, was also observed. Duration, in seconds, of avoidance of the five trials subsequent to withholding of reward was measured. Maximum time allowed to elapse between trials was 20 seconds.

Systematic observations of the animal's activity were recorded daily. These observations included kind and degree of (1) *motility:* running, jumping, walking into and out of the transport cage, pacing, circling, sitting in the transport cage preceding, during, and following the testing session; (2) *reactivity:* pouncing, slapping or biting the cage, attempts to escape, crouching, defæcation, piloerection; and (3) *vocalization:* screaming, barking, chattering. In addition, one animal was placed in an enclosed, illuminated and ventilated sound-proofed cage, where a record of its locomotor activity was made by means of an R.C.A. Capacity Operated Relay, grounded to the cage floor and to antennæ at both ends. Changes in the antenna capacity, caused by movement of the animal in the field between the antenna and ground, activated one of 24 counters every hour (Davis, 1951). Daily food intake and basal rectal temperature were also recorded for this animal.

Social behaviour was observed in a colony of six preadolescent males by recording techniques previously described (Tinklepaugh, 1942; Warden and Galt, 1943; Brody and Rosvold, 1952). A stable dominance hierarchy became established and was observed in relation to obtaining food (one peanut at a time) and with respect to grooming behaviour. In addition, one adult male macaque was observed for a period of eighteen months living with a mature female and the resulting offspring.

Surgical procedures.—Under sodium amytal anæsthesia (0·6 c.c. 1 per cent soln. per kg. body wt.), a full osteoplastic calvarium flap was turned on the left temporal muscle. The dura was opened in a cruciate manner over the left frontal lobe. Bridging veins to the sagittal sinus were coagulated and the hemisphere retracted to expose its medial surface. A variable extent of the cortex of the anterior cingulate gyrus, precallosal and subcallosal areas, and of the medial frontal lobe was resected subpially with an 18-gauge needle sucker. A comparable excision was attempted on the right, the approach being through the falx. For the control operations, essentially the same steps were taken except that in two animals aluminium hydroxide implantations in small silver discs (4 on each anterior cingulate gyrus) were substituted for the ablations. The total lobectomy and the lateral frontal removals necessitated opening of the dura bilaterally. All subjects were observed for a minimum of three months after operation.

Anatomical methods.—Under a lethal dose of barbiturate, the animals were perfused with normal saline followed by a 10 per cent solution of formaldehyde. The brains were removed, placed in several washings of 10 per cent formaldehyde, then transferred to increasing concentrations of alcohol for dehydration. Imbedding proceeded first with 2 per cent nitrocellulose, then with 10 per cent celloidin. Serial sections at 25 mu were made, every 20th section stained with analine thionin. Tracings of every fourth stained section (2 mm. intersection intervals) were used to plot the outline of the hemisphere, the principal fissures, and the lesion on graph paper. In addition, thalamic degeneration was analysed and plotted. Criterion of degeneration in the anterior nuclei was cell loss.

Results

Behavioural results.—Six of the animals were trained both pre- and post-operatively on the visual discrimination and delayed response procedures. With one exception, all animals took fewer trials on either test to reach criterion post-operatively than pre-operatively (Table I). The

TABLE I

	Discrimination		*Delay*	
	Pre	*Post*	*Pre*	*Post*
Cin. 1	120	80	820	360
Cin. 2	400	60	600	150
Cin. 3	115	74	215	150
Cin. 4	240	140	345	180
VM	280	120	380	230
DL	120	100	240	500F

Number of trials includes criterion trials.

Results of performance on visual pattern discrimination (left) and delayed reaction tests. Pre = pre-operative, Post = post-operative scores of number of trials taken to reach criterion of 85 per cent on 100 consecutive trials. Cin. = cingulate ablation; VM = ventromedial frontal ablation; DL = dorsolateral frontal ablation. Note that all post-operative scores are lower than pre-operative except for that of DL on the delayed reaction test.

exception had received an ablation, not of the cingulate and medial frontal cortex as had the others, but of the dorsolateral frontal granular areas. These results confirm those of a more extensive study reported elsewhere (Pribram, Mishkin, Rosvold, and Kaplan, 1952).

When a reward is aperiodically withheld from a subject following correct choice in an established discrimination, one of two types of behaviour results. Either the animal ignores the episode or it shows a gross avoidance reaction characterized by retreating to the rear of the testing cage, pacing, vocalizing, or pouncing. Avoidance of subsequent trials varies from a short delay in the response to a complete refusal to test further. Of a group of 4 macaques, 2 showed the former reaction, 2 the latter. These latter animals were subjected to ablation of the anterior cingulate cortex. A definite decrease in the duration of the avoidance behaviour resulted (Table II). However, as can be seen from the table,

TABLE II.—FRUSTRATION

	Pre-op.	Post-op.
Cin. 1	—	23 sec.
Cin. 3	—	12 sec.
Cin. 5	42 sec.	3 sec.
Cin. 6	22 sec.	0·2 sec.
N 1	0·2 sec.	—
N 2	0·2 sec.	—
Lob	—	2 sec.
VM	90 sec.	53 sec.
DL	62 sec.	18 sec.

Results of performance on "frustration" trials. Seconds avoidance of trials subsequent to "frustration trial" indicated pre- and post-operatively. Cin. = cingulate ablations; N = normal; Lob = frontal lobotomy; VM = ventromedial; and DL = dorsolateral frontal ablations. Note that all frontal operations shorten the duration of the avoidance reactions.

this effect is also noted when dorsolateral frontal granular areas are ablated.

No consistent changes in the systematically observed ratings of activity (motility, reactivity, vocalization) were obtained when the pre- and post-operative scores of the tested macaques were compared. Nor was there any dramatic change in the activity measured in the activity cage. In contrast to the changes following frontotemporal ablations, no long-term changes in food intake or basal rectal temperature followed resection of the cingulate gyrus (Pribram and Bagshaw, 1953).

The social structure of a colony of immature male rhesus monkeys was unaltered by interposing extensive anterior cingulate ablations into the situation. No effect on dominance rating with respect to feeding or grooming behaviour could be observed when either the most dominant or the next to the most submissive animal in the group was operated upon

TABLE III.—SOCIAL COLONY

Pre-operative period	*Operative period*	*Post-operative period*
Cin. 7	—	Cin. 7
N 3	N 3	N 3
N 4	N 4	N 4
Cin. 8	—	Cin. 8
N 5	N 5	N 5

Dominance hierarchy is recorded from top down. Cin. = cingulate ablations; N = normal. Note no change in the structuring of the social colony subsequent to the surgical procedures performed on Cin. 7 and Cin. 8.

(Table III). These results are in marked contrast to those obtained in similar social situations following lobotomy (Brody and Rosvold, 1952) or anteromedial temporal lobectomy (Rosvold, Mirsky, and Pribram. In Press).

Lest the technique of observing the structure of a colony of immature animals of the same sex be insensitive to more subtle changes in social behaviour, a mature male was observed briefly (forty-eight hours) in relation to another adult male and also an adult female. He was then subjected to bilateral anterior cingulectomy. After two weeks he was again observed for forty-eight hours in relation to the other mature male and then placed with the mature female for eighteen months. No dramatic change in behaviour was noted toward the other male except that there appeared to be somewhat less prolonged fighting over food, the cingulectomized animal being dominant as before operation. In his relations with the female, the operated animal behaved within normal limits in all respects. A mutually protective relationship was established; the female was dominant in food situations as she had been prior to operation; grooming and sex relations were observed neither more nor less frequently than prior to operation. A baby macaque resulted from the relationship and the operated subject behaved in a most protective manner toward his family at all times: e.g. when the group was threatened with a stick, the operate would grimace, pounce, rattle the cage, and place himself between the threat and his family.

Neurological results.—The effects of ablation of the anterior cingulate cortex might be ascribed to the production of scar around the margin of the excision. In order to test the effects of such lesions 2 spider monkeys were given aluminium hydroxide cream implantations over the cingulate cortex. Weekly electrographic (animals narcotized with Nembutal) and daily behavioural observations were made. No consistent changes were noted: specifically, we observed no *petit mal*-type seizures, *grand mal* seizures, ataxia, weakness, or altered social behaviour with respect to each other or toward the experimenter. For a period of two weeks, approximately one month post-operatively, abnormal spikes referable to the right central scalp lead were recorded from one of these monkeys. This finding disappeared, however, and no other electrographic abnormalities were noted.

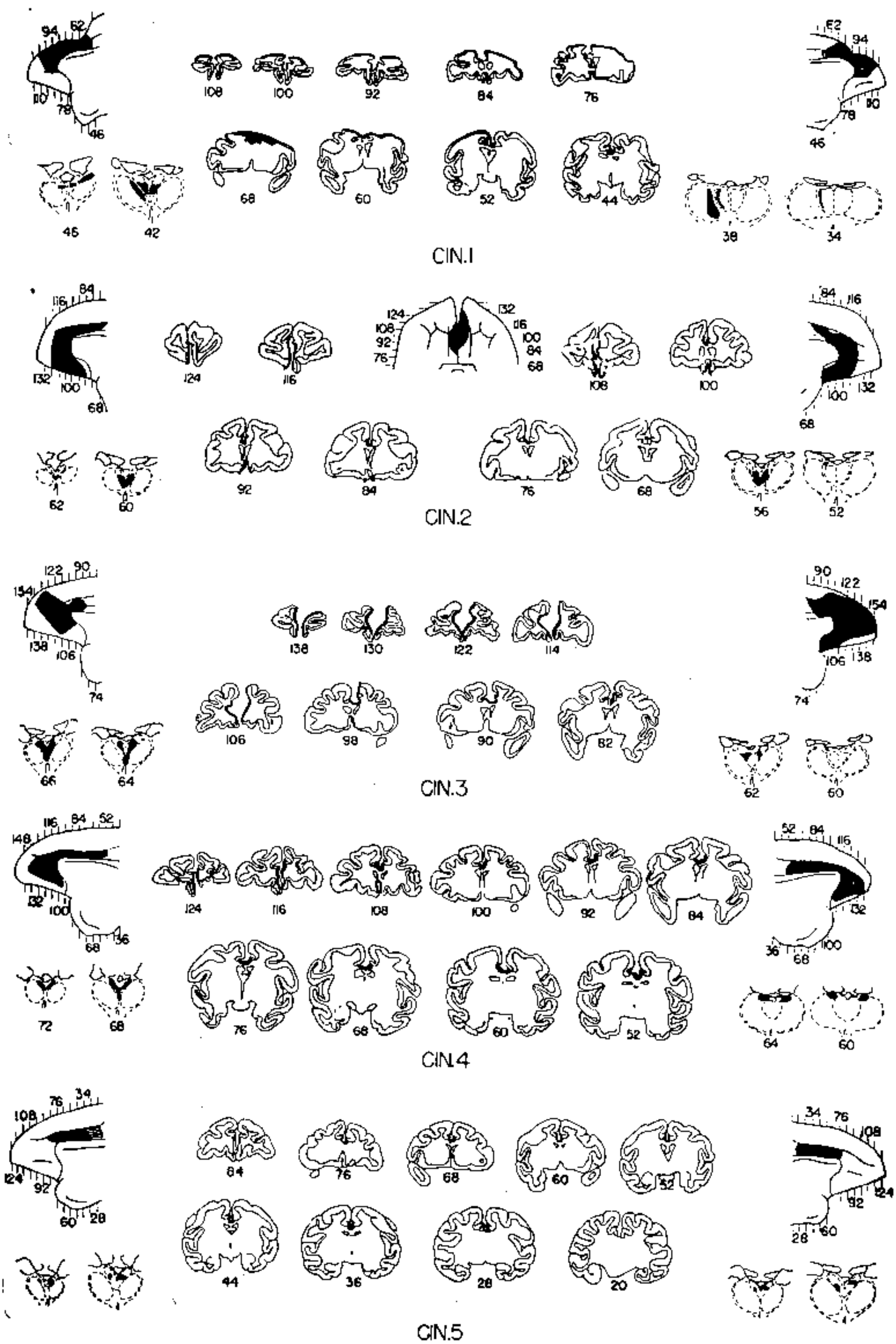
The anatomical findings are presented by means of serial reconstructions of the hemispheres with representative cross sections through resected portions (figs. 1 and 2). Retrograde degeneration in the thalamus associated with the ablations is shown diagrammatically. Whenever the resection is limited to the anterior cingulate gyrus above the corpus callosum, there is degeneration in a strip located at the junction of the n. anterior medialis and n. anterior ventralis (Cin. 5, Cin. 8, Cin. 9). More extensive invasion of the medial frontal cortex anterior to the corpus callosum leads to massive degeneration in the central portion of the n. anterior medialis (Cin. 1, 2, 3, 4, 6, 7, 10). Involvement of the subcallosal areas results in degeneration of the medial and ventral portions of this nucleus and of the n. parateniialis (Cin. 2, 3, 4, 6). Where degeneration appears in the n. anterior ventralis, the ablation extends far posteriorly in the cingulate gyrus (Cin. 4, 6, 10) or there is invasion of fibres under the anterior cingulate cortex (Cin. 2, 3, 7).

Discussion

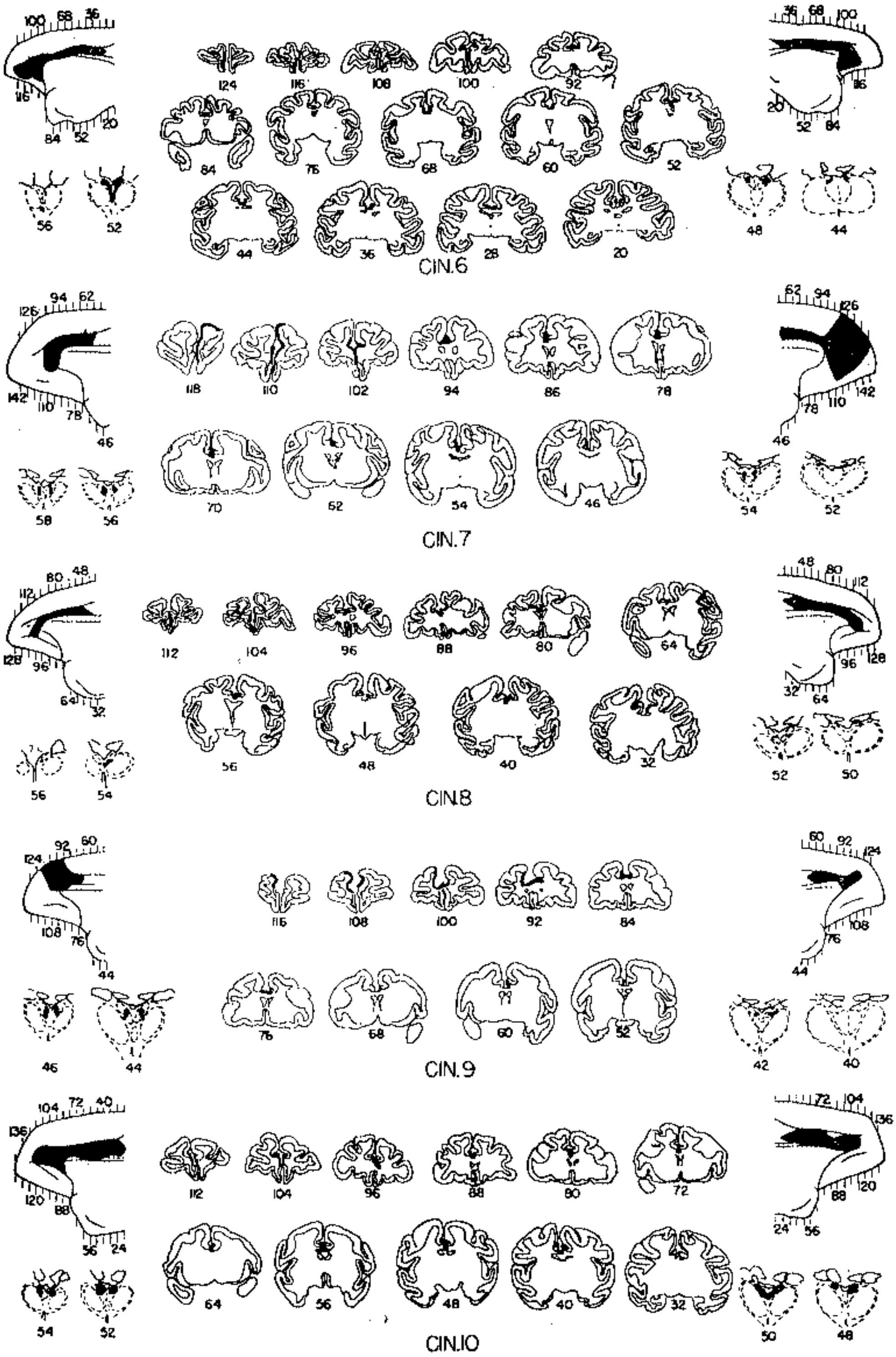
The results of these experiments indicate that resection of the cortex of the anterior cingulate gyrus, and of the pre- and subcallosal and medial frontal areas as well, does not lead to the profound and prolonged alterations in behaviour reported in earlier studies. Rather, when ablation is limited to cortex, the effects are transient, apparently minimal, and difficult to appraise. This finding is in essential agreement with that of Glees, Cole, Whitty and Cairns (1950). Since no anatomical verification appears with other reports, discrepancies with respect to the more dramatic findings cannot be resolved.

There has been considerable variability in the reported effect of frontal lesions on "emotional" behaviour of primates. On the basis of the observation that following leukotomy avoidance reactions in man are not minimized (e.g. pain threshold is unaltered) but that suffering and anxiety are reduced, we devised a measure of the duration of an avoidance reaction[1]. This measure was sensitive to the effect of anterior cingulate and medial frontal ablations. However, an effect of equal magnitude was recorded to follow lateral frontal removals. Since such lesions result

[1] Since this is a critique, certain limitations of this test technique should be mentioned. It is known that the scheduling of aperiodic reinforcement is a most important variable in determining the rate of response. No information is available on the effect of aperiodic presentation of aversive stimuli—either in determining conditioned avoidance behaviour or in extinction. Thus, the crude technique used in the present experiments must be validated with better controlled interval reinforcement and aversive scheduling. The data are reported in the hope of stirring interest in this problem.



FIGS. 1 and 2.—Cross sections and reconstructions of bilateral anterior cingulectomies and the resultant retrograde thalamic degeneration. Cin. = cingulate.



Lesion and degeneration indicated in black. Thalamus in dashed lines. Numbers refer to placement in series of cross sections.

in additional impairment (delayed response-type problems) the medial procedure appears the more selective.

The anatomical observations confirm and amplify those of previous investigations (Mettler, 1947; Rose and Woolsey, 1948; Lashley, 1941; Walker, 1938). Taken together with the findings of the present experiments, orderly arrangement of the projection of the anterior nuclei to the cortex becomes apparent. An axis drawn through the main nucleus from a dorsolateral to a ventromedial position projects to the cortex along a postero-antero-ventral arc paralleling the corpus callosum above and bending around its genu. In addition, the evidence suggests that the more medial portions of the nucleus project to the more hilar portions of the cortex, whereas no differentiation of the projection of the antero-posterior axis of the nucleus is apparent. These findings of an orderly arrangement of thalamocortical projection from the anterior nuclei may now be added to those described for the lateral geniculate, pulvinar, and mediodorsal nuclei (Lashley, 1941; Chow, 1950; Pribram, Chow and Semmes, 1953).

The anatomical findings are also of interest with respect to current theories of the neuro-anatomical correlates of emotions. The restricted connexions of the anterior cingulate gyrus *per se* with the anterior thalamic nuclei, added to the findings (Reviewed by Pribram and Kruger) that apparently only the posterior portion of the hippocampus of monkey sends fibres to the mammillary bodies, warrant a re-examination of the much publicized "hippocampus-mammillary-anterior nucleus-cingulate-hippocampus" circuit. There is, no doubt, ample evidence that such connexions exist (Lorente de Nó, 1933, 1934; Clark and Boggon, 1933; Pribram and MacLean, 1953); that they serve functions not served by other multiple chain neuronal connexions remains to be shown. In view of the paucity of behavioural changes reported in this study, the absence of any reported change after complete bilateral hippocampectomy (Mishkin. In Press), and the absence of effect of electrical stimulation of the greater portion of the hippocampus in either the anæsthetized or ambulant animal (Kaada, Pribram, and Epstein, 1949; Andy and Akert, 1952), it seems premature to decide what rôle these structures have in determining behaviour—and to base therapy on such decision.

Summary

(1) Twenty monkeys, 12 with lesions of the anterior cingulate gyrus, were used to study the effects of bilateral anterior cingulectomy.

(2) Behavioural observations consisted of testing the performance of the animals on the delayed reaction problem, a visual discrimination problem, their reaction to a "frustrating" situation, and their social behaviour. Only with respect to the reaction to "frustration" was any change in behaviour induced by the cingulectomy. Shortened duration of

avoidance behaviour resulted from ablation of the anterior cingulate cortex. Although similar changes follow other frontal lesions, these are accompanied by additional impairment—viz. of performance of the delayed reaction type of problem. Thus, medial frontal and cingulate resections have been shown to shorten selectively the duration of avoidance.

(3) Anatomical observations with respect to the projection of the anterior thalamic nuclei are of interest. The more posterior the ablation of the cingulate gyrus extends, the more degeneration is found in the n. anterior ventralis. Resection restricted to the anterior portion of the cingulate gyrus results in degeneration limited to a strip at the junction of the n. anterior ventralis and the n. anterior medialis. Invasion of the medial frontal cortex anterior to the corpus callosum is associated with massive degeneration of the n. anterior medialis. The most ventral portions of this nucleus and the n. parateniallis degenerate when the subcallosal cortex is involved. These observations establish the fact that the projection of the anterior nuclei terminate in an orderly manner in the cingulate and medial frontal cortex. An axis through the anterior thalamic nuclei extending from the dorsolateral to the ventromedial positions projects to the cortex along a postero-antero-ventral arc paralleling the corpus callosum above and bending around its genu. In addition, the evidence suggests that the more medial portions of the nucleus project to the more hilar portions of the cortex. No differentiation of the projection of the antero-posterior axis of the nucleus is apparent.

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