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SUBCORTICAL MECHANISMS IN THE "SEARCHING" OR "ATTENTION" RESPONSE ELICITED BY PREFRONTAL CORTICAL STIMULATION IN UNANESTHETIZED CATS§

In a previous paper the authors have described a characteristic "searching" or "attention" response which can be elicited by electrical stimulation of cortical regions of the medial surface of the hemisphere as well as from the hippocampus of unanesthetized cats.[13] Quite a similar type of response may be obtained on stimulation of the phylogenetically younger basolateral division of the amygdaloid nuclear complex, but not from its phylogenetically older anteromedial part.[12]

The response is a rather typical one (Fig. 1). Immediately at the onset of stimulation all spontaneous pre-occupation such as walking or licking ceases; the facial expression changes to one of "attention," perhaps associated with some surprise, bewilderment, or anxiety: the animal raises its head, the eyes open and the pupils dilate; there are slight pricking movements of the ears and quick anxious glancing or searching movements of the eyes and head, almost invariably to one side, contralateral to that of stimulation. This searching may result in circling movements to the opposite side of that stimulated. The reaction to external stimuli seems to be decreased, the animal's attention being intensely fixed on "something imaginary" in the environment.

In some animals, particularly with low-intensity stimulation, the quick glancing movements were directed towards both sides, sometimes predominantly to the ipsilateral side. By slightly increasing the stimulus intensity, however, the glancing changed to the contralateral side.

In Fig. 2A the filled squares indicate the points on the medial aspect of the hemisphere from which this "searching" or "attention" response has

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been elicited. The responsive sites appear to be located mainly within the prefrontal cortex and the limbic (cingular) gyrus (including the anterior and posterior limbic areas and the retrosplenial region). Finally, some points are located within the medial portion of the hippocampal gyrus.

The present investigation is concerned with the subcortical structures involved in this "searching" response obtained by stimulation of the medial

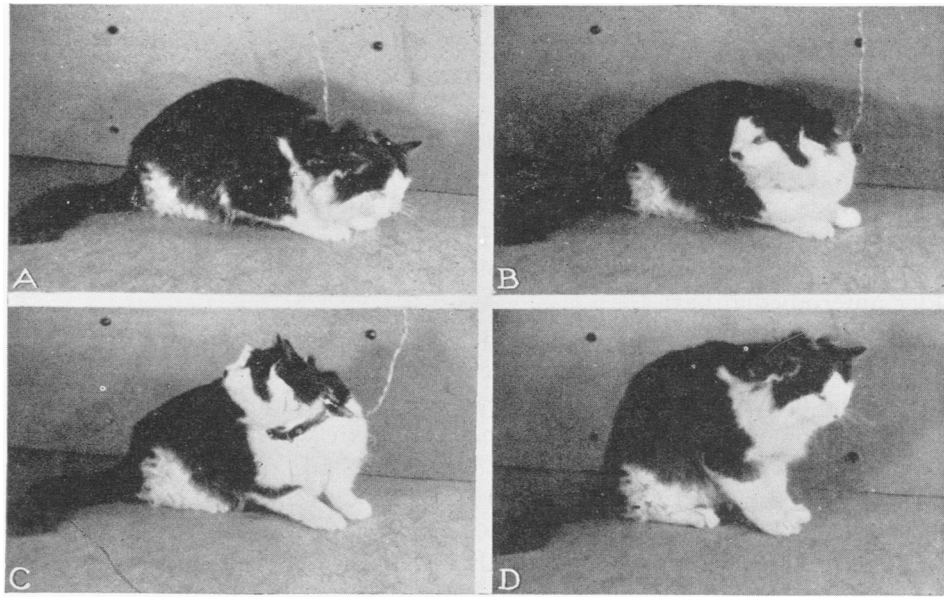

FIG. 1. The "searching" or "attention" response elicted by electrical stimulation of the medial surface of the left prefrontal region. A. Before stimulation. B and C. A few seconds after onset of stimulation; quick glancing movements towards the right side. D. A few seconds after end of stimulation.

prefrontal cortex. The method employed has been to implant needle electrodes in the responsive cortical field and, on the following days, to make various subcortical lesions followed by repeated cortical stimulation. By this combined stimulation-ablation technique subcortical structures whose integrity are necessary for the elicitation of the response have been determined.

MATERIAL AND METHODS

In a series of 30 cats a total of 60 bipolar needle electrodes, insulated except for the tips, were implanted in the medial prefrontal areas of cats under Nembutal anesthesia. The following day, when the effect of the anesthesia had worn off, stimulation was carried out while the animal was freely moving on a platform. In the animals yielding

the "searching" response (45 of the 60 electrodes) various subcortical structures were destroyed electrolytically, the electrodes being oriented by the Horsley-Clarke instrument. After a second complete recovery from the anesthesia the prefrontal stimulation was repeated. In some animals in which the subcortical lesion left the prefrontal "searching" response intact, one or two additional lesions were made. After a few days the cats were killed and the sites of the stimulating electrodes and the extent of the subcortical lesions were identified in histological sections. For further details of the method the reader is referred to a previous communication.[18]

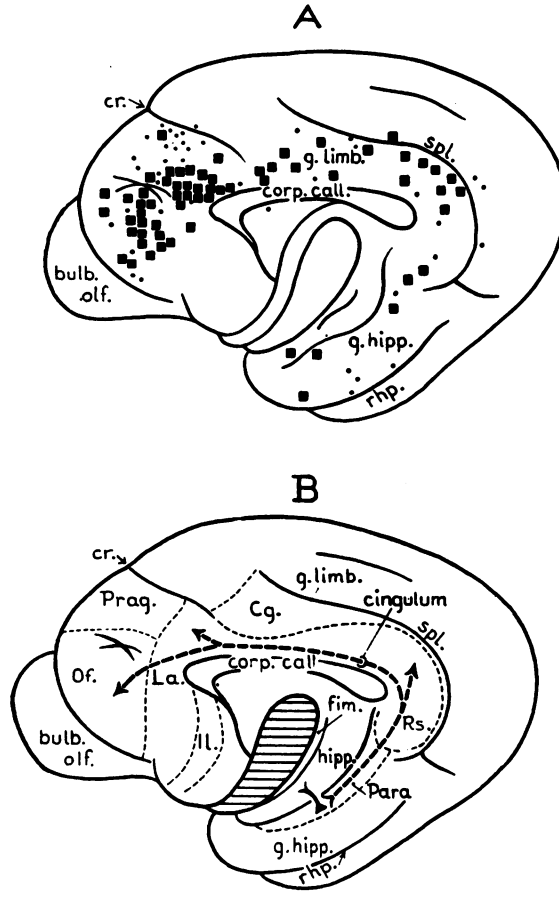

FIG. 2. A. Medial aspect of the cat's hemisphere indicating points (squares) from which the "searching" response has been produced on electrical stimulation. Dots, no such response. B. Area subdivision of the medial surface, mainly according to Rose and Woolsey.[14] Origin and course of the fibers of the cingulum bundle according to current concept (cf. text).

RESULTS

A. Lesions of the cingulum bundle. According to the recent study of Adey and Meyer[1] a conspicuous portion of the cingulum bundle of monkeys originates in the granular prefrontal cortex, mainly from its medial division. Further contributions to the cingulum bundle come from the anterior and posterior limbic (cingular) gyrus. These fibers appear to terminate in the pre- and parasubiculum of the hippocampal formation and possibly in the hippocampus itself.[1]

Because of the similarities between the distribution of the sites yielding the "searching" response, and the origin, course, and termination of the cingulum bundle (Fig. 2) our interest was first focused on this bundle as the possible mediator of the response from the prefrontal region.

However, complete bilateral section of this bundle in four cats at a trans-

verse plane corresponding to the middle or posterior portion of the corpus callosum did not influence the "searching" response elicited from the prefrontal cortex (Fig. 3). The response could be induced just as readily after this section as in the intact animal. In the experiment illustrated in Figure 3, both fornices were included in the lesion, indicating that the prefrontal "searching" response is independent of this structure as well.

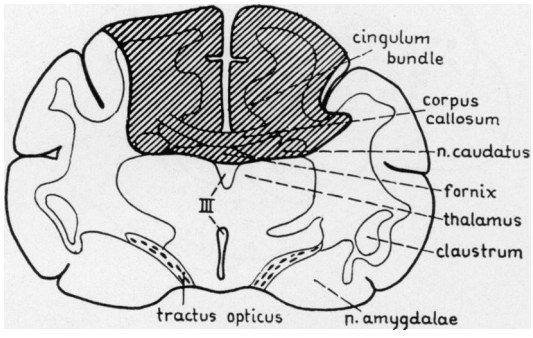

FIG. 3. Diagram of transverse section through an electrolytic lesion severing the cingulum bundle and the fornix on both sides. The "searching" response elicited by stimulating the medial prefrontal cortex on the right side remained entirely unaltered after this lesion.

B. Amygdala, septal nuclei, hypothalamus, stria medullaris, and habenula. Extensive bilateral lesions of these structures were without noticeable influence on the prefrontal "searching" response. The lesions of the amygdala usually included part of the internal capsule (Fig. 4), but in other experiments the amygdala was destroyed more selectively. In one cat the hypothalamic lesion extended from the mammillary bodies posteriorly to the optic chiasma rostrally and included the anterior portion of the posterior hypothalamic nucleus, the greater portion of the dorsal and anterior hypothalamic area, and the ventromedial nucleus, mainly on the ipsilateral side.

C. Thalamus. Following lesions of various parts of the thalamic nuclear complex in 10 cats the prefrontal "searching" response was either eliminated, altered in character, or left intact. Description of a few experiments will best serve as illustration.

Cat 52. Typical contralateral "searching" responses were obtained by stimulating through two electrodes implanted in the medial prefrontal cortex on the *right* side. An extensive lesion was then made of the *ipsilateral* medial half of the thalamus (Fig. 5, right side). The lesion included the stria medullaris and the greater part of the habenula, the entire dorsomedial and most of the anterior nucleus, the medial part of the n. lateralis posterior and n. lateralis anterior, and almost the entire n. centralis medialis, n. paracentralis, and n. centralis lateralis on the same side.

Following this lesion the prefrontal "searching" response was less pronounced and changed in character from a typical contralateral searching to a predominantly ipsilateral response.

A second lesion involving the septal nuclei on both sides had no effect. However, following a third lesion of the medial part of the thalamus on the *left* side the "searching" response elicited from the right prefrontal cortex was completely abolished. This lesion included, as is seen from Figure 5 (left), the stria medullaris, the greater part of the dorsomedial nucleus and of n. centralis medialis, n. paracentralis, and n. centralis lateralis, and, finally, the medial portion of the nuclei lateralis anterior and posterior.

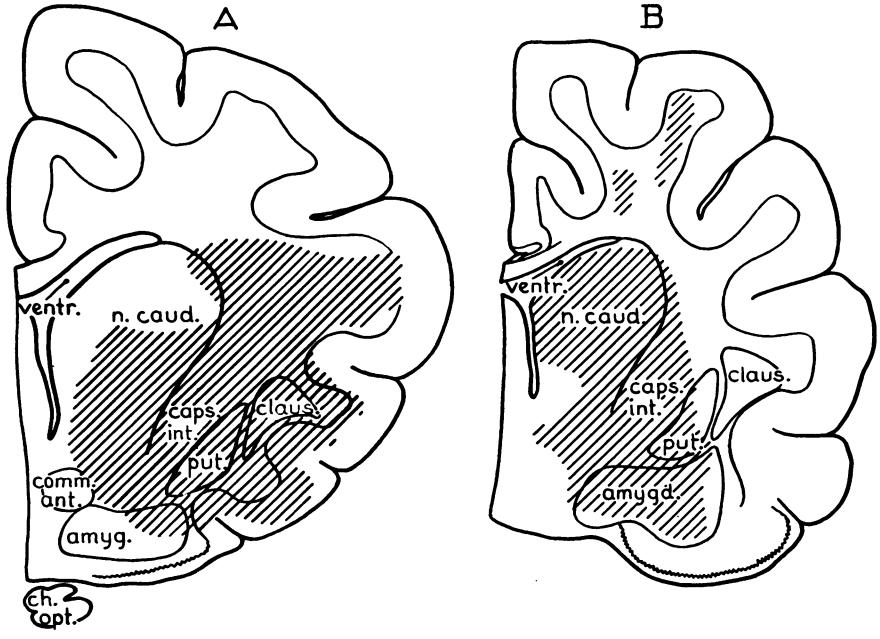

FIG. 4. Diagram of transverse sections through the right hemisphere in two cats with extensive lesions of the internal capsule and adjacent grey nuclear masses (cf. text).

It may be concluded from this experiment that the prefrontal "searching" response is abolished by a bilateral lesion of the medial portion of the thalamus.

Further experiments with smaller lesions of the medial thalamus led to the following generalization: The prefrontal "searching" response disappeared only following lesions of the greater part of the cells of the n. centralis medialis, n. paracentralis, and n. centralis lateralis on both sides. On the other hand, rather extensive lesions of the medial thalamus sparing these nuclei did not significantly influence the response. Thus, the lesion illustrated in Figure 6, leaving the n. centralis medialis, n. paracentralis, and n. centralis lateralis intact, but including on both sides the greater part of the dorsomedial nuclei and habenulae, the medial portion of the nucleus

lateralis posterior and the centrum medianum, and, further, the rostral portion of tectum mesencephali and the peri-aqueductal grey did not alter the prefrontal "searching" response.

From these and a number of similar experiments it was *concluded* that bilateral lesions of the following thalamic nuclei seemed to be of no influence on the prefrontal "searching" response: the lateral, the dorsomedial and the anterior nuclei, the centrum medianum, and the n. reuniens. The same was true for rather extensive lesions of the rostral parts of the tectum mesencephali. *Ipsilateral* lesions of the n. paracentralis and n. centralis lateralis were followed by some reduction of the response and sometimes in a reversal of the searching from the contralateral to the ipsilateral side. On the other hand, lesions of these nuclei confined to the contralateral side appeared to be without any effect.

D. Lesions of the white matter between the prefrontal cortex and the diencephalon. Electrolytic lesions involving the anterior basal portion of the ipsilateral internal capsule just below and lateral to the head of the caudate nucleus in three cats completely abolished the "searching" response which could be readily obtained in these animals pre-operatively on stimulating the prefrontal cortex on the same side (Fig. 4). In these experiments various portions of the neighboring amygdaloid nuclei, caudate, putamen, claustrum, and the fibers of the lateral part of the internal capsule were included in the lesion, but the results obtained in other animals with lesions of these structures permit one to conclude that the "searching" response elicited from the prefrontal cortex is dependent on the fibers running through the anterior basal portion of the internal capsule. This portion, then, most likely contains the fibers interconnecting the medial prefrontal cortex and those thalamic midline nuclei responsible for the stimulation effect.

DISCUSSION

The subcortical structures of importance for the elicitation of the "searching" or "attention" response from the medial prefrontal cortex appear to be the n. centralis medialis, n. paracentralis, and n. centralis lateralis, which are parts of the intralaminar nuclei of the thalamus. It is of considerable interest that Akert,[2] working in Hess' laboratory, has reported briefly on a similar type of behavioral change (consisting of a slow turning of the head to the contralateral side) on stimulating the intralaminar nuclei and of the adjacent dorsomedial and anterior thalamic nuclei. Thus, a cortico-thalamic rather than a cortico-cingulo-hippocampal mechanism seems to be involved. It seems likely, although not yet proven, that the

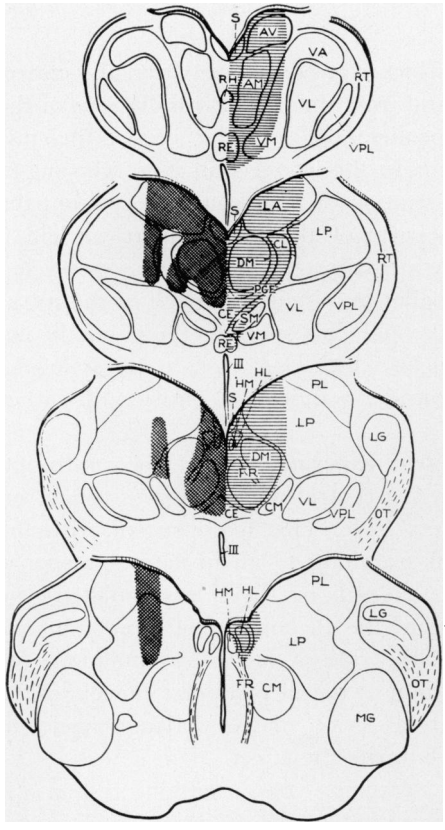

FIG. 5. Drawings of serial sections through two electrolytically produced lesions of the thalamus; the first on the right side (horizontally shaded), the second on the left side (cross-hatched). Cf. text.

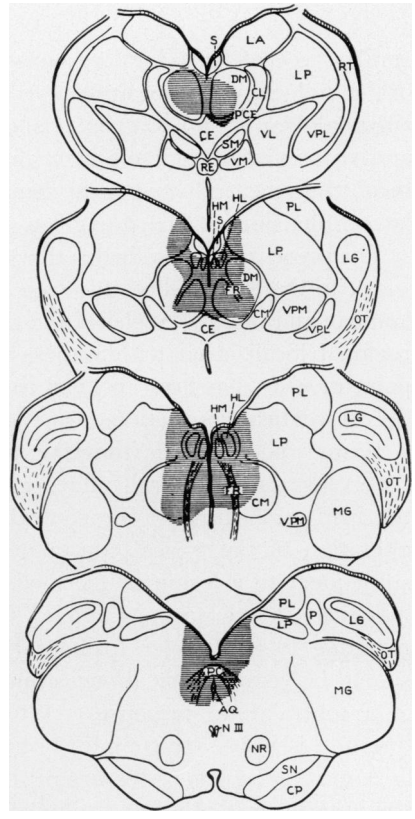

FIG. 6. Drawings of serial sections through a rather extensive lesion of the medial thalamus, but sparing the n. centralis medialis (CE), n. paracentralis (PCE), and n. centralis lateralis (CL). This lesion was without any influence on the prefrontal "searching" response.

ABBREVIATIONS FOR FIGURE 5 AND FIGURE 6 (ACCORDING TO JIMENEZ-CASTELLANOS[10]):

AM	n. anteromedialis	OT	optic tract
AQ	aqueduct	P	n. posterior
AV	n. anteroventralis	PC	posterior commissure
CE	n. centralis medialis	PCE	n. paracentralis
CL	n. centralis lateralis	PL	pulvinar
CM	n. centrum medianum	RE	n. reuniens
CP	cerebral peduncle	RH	n. rhomboidalis
DM	n. dorsomedialis	RT	n. reticularis
FR	fasciculus retroflexus	S	stria medullaris
HL	n. habenularis lateralis	SM	n. submedius
HM	n. habenularis medialis	SN	substantia nigra
LA	n. lateralis, pars anterior	VA	n. ventralis, pars anterior
LG	lateral geniculate body	VL	n. ventralis, pars lateralis
LP	n. lateralis, pars posterior	VM	n. ventralis, pars medialis
MG	medial geniculate body	VPL	n. ventralis, pars posterolateralis
NR	n. ruber	VPM	n. ventralis, pars posteromedialis

similar type of behavioral response which can be induced from the cortex of the limbic and hippocampal gyri[13] and from the basolateral division of the amygdaloid nuclear complex[12] is dependent on a similar cortico-thalamic and an amygdalo-thalamic mechanism. In this connection it is relevant to recall the recent physiological demonstration of fiber connections from the lateral division of the amygdala to parts of the intralaminar nuclei.[3, 5, 9]

The present study indicates that the medial prefrontal cortex is connected —not to the entire—but only to a smaller and limited portion of the intralaminar and midline nuclei of the thalamus. This suggests the possibility of regional localization within these nuclei which one, from a physiological point of view, has been inclined to consider a functional entity with rather diffuse cortical connections.

It may be inferred from the present experiments that the prefrontal cortex exerts a bilateral influence on the central nuclei, more strongly on the ipsilateral than on the contralateral side. This is consistent with the alteration of the typical contralateral searching to an ipsilateral response subsequent to a lesion of the medial thalamus on the side stimulated; the influence on the opposite, intact side of the thalamus now predominates, resulting in a response ipsilateral to the side of cortical stimulation. (It should be recalled that direct stimulation of the intralaminar nuclei results in a contralateral response.) A bilateral lesion of the thalamic nuclei in question is necessary completely to eliminate the effect.

A most conspicuous feature of the "searching" or "attention" response is the initial arrest of all pre-stimulatory activities, the cessation of all movements in execution, including respiration, without any appreciable loss of muscular tone. It is most likely that this quieting effect on movements represents the same phenomenon as that previously observed by Tower[15] in anesthetized cats on stimulating in the medial hemisphere the same cortical areas which are dealt with in this communication. Tower's findings have been confirmed and the inhibitory effects on somato-motor activities studied in greater detail by one of us.[11, p. 98]

The functional significance of the "searching" or "attention" response is not clear. The term "attention" merely refers to the outward manifestation of the behavior change. Extreme caution must be exercised in any attempt to interpret the real nature of the response. This particularly applies to animal experiments in which we lack any information concerning the animal's subjective experience and level of consciousness during the stimulation. A few suggestions, however, might be ventured:

As discussed previously,[13] we are inclined to consider the "attention" response as secondary to some kind of sensation or physical experience. The animals are undoubtedly conscious, but their attention appears to be

attracted and intensely fixed on "something" which they seem to experience. As a consequence there is frequently an impairment of the animal's usual alertness with decreased reactions to external, visual, auditory, and tactile stimuli. On the other hand, one should not forget that we are dealing with an artificial type of stimulation which might interfere with the normal functioning of the subcortical structures in question.

According to the current concept the intralaminar nuclei are included in the brain stem activating system. They have been shown to yield an arousal effect of the electrocortical activity on high-frequency stimulation and have also been considered to increase the animal's general alertness. An immediate inhibition of pre-stimulatory somato-motor activities is also a characteristic of intralaminar stimulation and possibly represents an integrative part of the arousal or attention response. In this connection it is relevant to recall that high-frequency stimulation of the medial cortical areas under consideration may also result in a widespread desynchronization or arousal effect of the electrocortical activity similar to that obtained on intralaminar stimulation (for references cf. Kaada,[11, pp. 200 and 237]). It has previously been suggested that this cortically induced effect on the electrocortical activity similarly is most likely mediated through the brain stem activating system.[11, p. 238]

Taken together, quite similar behavioral, somato-motor and electrocorticographic effects may be obtained on electrical stimulation of the intralaminar nuclei and of the medial cortical areas in question; this seems to indicate a close functional relationship.

A similar, but weaker, quieting influence on spontaneous movements has also been obtained from an area of the middle and posterior parts of the first temporal convolution of the monkey[6, 11] and from the corresponding area of the cat.[15, 11] Quite recently Huertas, O'Doherty, and Forster[8] have observed a desynchronization or flattening of the EEG record (termed by them "suppression") which from their description appears to be identical with the effects obtained on intralaminar and medial cortical stimulation. Also, the change in the animal's behavior, when it is stimulated in the waking state,[7] bears some resemblance to that obtained in the present study. Finally, French, Hernãndez-Peón, and Livingston[4] have demonstrated connections from this temporal area to the brain stem activating system.

It appears not unlikely, therefore, that there exists a temporal area of functional significance similar to that of the frontal, limbic, and amygdaloid areas.

The present study possibly has some bearing on prefrontal leucotomy in mental diseases. According to the current concept, the beneficial effects of this operation are considered to be due to the interruption of fibers interconnecting the prefrontal cortex and the dorsomedial thalamic nucleus. Our experiments indicate a second prefrontal-thalamic system which undoubtedly is interfered with in most instances in the usual leucotomy, particularly

when the lower medial quadrant of the white matter is included. Also, in thalamectomies intending to destroy the dorsomedial nucleus it seems almost inevitable not to encroach upon the adjoining n. centralis medialis, n. paracentralis, and n. centralis lateralis. It remains for future research to decide whether interruption of this second prefrontal-thalamic system has anything to do with the effects obtained in leucotomized patients. It will prove a difficult task, however, to destroy selectively in human patients the central nuclei with their laminar shape and their relatively great extent.

SUMMARY

1. Stimulation of the medial prefrontal cortical region through implanted electrodes in unanesthetized freely moving cats results in a typical "attention" or "searching" response characterized by dilatation of the pupils, pricking of the ears, quick glancing or searching movements to the contralateral side associated with raising of the head and foretrunk.

2. Attempts have been made by combined stimulation-ablation techniques to determine which subcortical structures are necessary for the elicitation of this response.

3. The "searching" response was abolished by lesions which included the anterior basal part of the internal capsule on the same side, or when part of the intralaminar nuclei of the thalamus (notably n. centralis medialis, n. paracentralis, and n. centralis lateralis) were destroyed bilaterally. Destruction of part of the central nuclei reduced the "searching" reaction, but complete disappearance of the response required a bilateral and total destruction of the same nuclei.

4. The "searching" response still persisted after the following lesions: bilateral destruction of the cingulum bundle, the fornices, the dorsomedial nuclei or the centre median of thalamus, the habenulae and striae medullares thalami. Also without effect were fairly extensive lesions of the anterior group of the thalamic nuclei, the caudate nuclei, the hypothalamus, and the tegmentum mesencephali on both sides.

5. The nature of the response, and the possible bearing of the described second prefrontal-thalamic system on prefrontal leucotomy in mental diseases, are discussed.

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