

## Cortical Area 8 and its Thalamic Projection in *Macaca mulatta*<sup>1</sup>

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The frontal eye fields were discovered in 1874 by Ferrier and though considerable research has subsequently been done on physiological, anatomical and clinical aspects of this area in man and monkey (Smith, '49), the specific role of the frontal cortex in the complex organization of oculomotor activity is still virtually unknown. Even the elucidation of anatomical problems has made little progress since Brodmann ('05) characterized the area of the frontal eye field as a specific cortical area (area 8), though histological maps were repeatedly challenged by electro-physiological localization charts. Uncertainty also exists about the thalamic nucleus of origin of afferent projections to area 8. Yet, thalamo-cortical relationship is of fundamental importance for the understanding of the anatomical and functional organization of a given cortical field, and they have proved to be uniquely suited for comparative studies of mammalian cortex (Akert, '63). For example the orbitofrontal region (i.e. frontal granular cortex) has been defined as the receiving area of the nucleus medialis dorsalis in several species (Rose and Woolsey, '48), and the precentral motor cortex (Brodmann's area 4) has been shown to receive essential thalamic afferents from nucleus ventralis lateralis (Akert and Woolsey, '53). Since area 8 is situated between the precentral motor and the orbitofrontal regions its thalamic counterpart could not have been predicted with certainty. To Hassler ('49) it seemed more reasonable to assume that area 8 receives afferents from nucleus ventralis lateralis (the most medial portion) because he considered the eye fields primarily a motor cortex comparable to the fields of origin of the pyramidal system. Seemingly, there is supporting evidence for this

hypothesis from human cases with lesions of the frontal eye fields (Stern, '42; Norman, '45; Freeman and Watts, '47). On the other hand, there are experimental observations in the Rhesus monkey by Walker ('40b) and Mettler ('47) as well as by Pribram, Chow and Semmes ('53) who have found that the afferents to area 8 arise from nucleus medialis dorsalis (the most lateral portion).

A decision in this dilemma with the aid of ablation-degeneration techniques is difficult because in the higher primates a considerable portion of area 8 is situated in the depth of a sulcus. In the species *Macaca mulatta*, area 8 is partially situated in the depth of sulcus arcuatus, and its surgical removal may entail unintended damage to subcortical fiber systems which innervate cortical areas other than area 8. The same source of errors exists in most if not all human cases with damage to area 8. This can lead to errors in the interpretation of retrograde thalamic changes and contrasting conclusions may be drawn by different investigators. In order to eliminate error factors of this kind control cases have been included in this study in which the areas rostrally as well as caudally to area 8 were ablated without injuring area 8 itself. The results of the test and control series in respect to retrograde thalamic degeneration were consistent and have shown that area 8 receives projections from the paralamellar portion of nucleus medialis dorsalis.

### MATERIAL AND METHODS

Thirteen young Rhesus monkeys (*Macaca mulatta*) were used. These animals weighed approximately two and one-half — three and one-half kilograms; they

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were operated under deep sodium pentobarbital anesthesia. The cerebral cortex was exposed by first turning a bone flap and then fenestrating the dura mater. The cortical areas were removed by careful aspiration with the aid of micropipettes. Particular care was taken to preserve the pial circulation. All operations were performed under aseptic conditions. After about 30–50 days the animals were sacrificed, the brains were perfused *in vivo* with 10% neutral formalin and after fixation in the same solution they were embedded in celloidin. Coronal sections, 30  $\mu$  in thickness, were prepared and every second section was mounted and stained with thionin. The outlines of individual brain sections were drawn with the aid of a photographic projection apparatus and the lesions were projected from these individual sections upon a standard brain diagram of *Macaca mulatta* by rectilinear reconstruction. The extent of the lesions

was determined in great detail by projecting the cortex in and around the arcuate sulcus onto a simple plane. Figure 1 illustrates the surface of area 8 within and around the banks of the arcuate sulcus in a standard diagram to be used to map the extent of all experimental ablations. Microscopic studies of the lesions and particularly of the surrounding cortex were made in order to assert and identify more accurately the extent of cortical damage in terms of ablation or preservation of area 8. In all cases, with the exception of experiment 5 it was found that cortical tissue had been removed exclusively. In experiment 5 there was a small subcortical injury.

The retrograde degeneration in the thalamus was determined microscopically on the basis of (1) cell loss, (2) cell atrophy and (3) gliosis. Mild degrees of degeneration were ignored. India ink outlines of representative thalamic sections were

*Abbreviations to figures and plates*

CC, Corpus callosum	MD, Nucleus medialis dorsalis thalami
CL, Nucleus centralis lateralis thalami	s.a., Sulcus arcuatus
F, Fornix	s.p., Sulcus principalis
I.D., Nucleus lateralis dorsalis thalami	

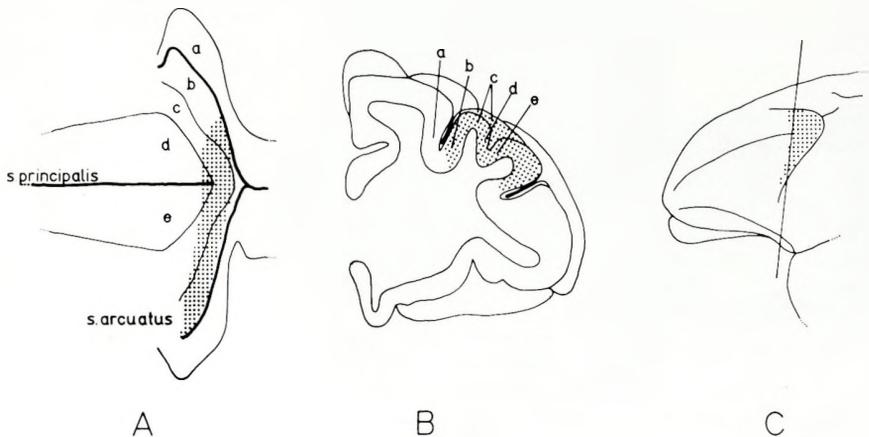


Fig. 1 Cytoarchitectural map of area 8 (dotted area).

A — Two dimensional reconstruction of the cortical surfaces in and around sulcus arcuatus.

B — Three dimensional view of area 8 situated in a coronal brain slice of the left hemisphere at the level of sulcus arcuatus.

C — Extent of area 8 on the lateral surface of the left hemisphere. The vertical line indicates the level of figure 1 B. a = caudal bank, b = depth, c = rostral bank of sulcus arcuatus. d = dorsal bank, e = ventral bank of sulcus principalis.

drawn for each case and the extent and intensity of retrograde degeneration were indicated with symbols.

### RESULTS

First, an attempt was made to obtain histological criteria towards a definition of area 8 in the Rhesus monkey. There is incomplete agreement between Brodmann ('05), von Bonin and Bailey ('47), C. and O. Vogt ('19) and Walker ('40a) in this respect. Our own findings are briefly as follows: The cortex of area 8 can be defined as having a relatively well developed granular layer IV and large pyramidal cells in layers III and V. These three features are unequivocal and their combination in area 8 is unique. The cortex so defined is limited to the ventral limb of the rostral bank of sulcus arcuatus and figure 1 illustrates the topographical details obtained in the reconstruction of an individual hemisphere that was cut coronally in serial sections. There is individual variation mainly in respect to the dorsal and ventral extent of this narrow zone. In no case was there a crossing over onto

the caudal bank of arcuate sulcus, and the histological picture of the dorsal limb of the rostral bank of sulcus arcuatus differs markedly. For histological documentation the reader is referred to plate XII (pg. 113) of von Bonin and Bailey's atlas ('47).

Secondly, the fine architecture of nucleus medialis dorsalis (MD) was surveyed microscopically in normal material and again compared with the results of previous investigators. The three MD subdivisions of Olszewski ('52) were adopted; his pars multiformis is designated pars paralamellaris dorsalis in this paper.

#### 1. Experimental ablations of area 8

Unilateral ablations of area 8 were performed in five monkeys. The results of reconstruction of the cortical lesions and the retrograde thalamic degenerations are illustrated in figures 2-7. A short verbal description is given in the following paragraphs:

*Experiment 1 (285 R).* The cortical ablation (fig. 2) involves a small dorsal portion of area 8 adjacent to the caudal tip

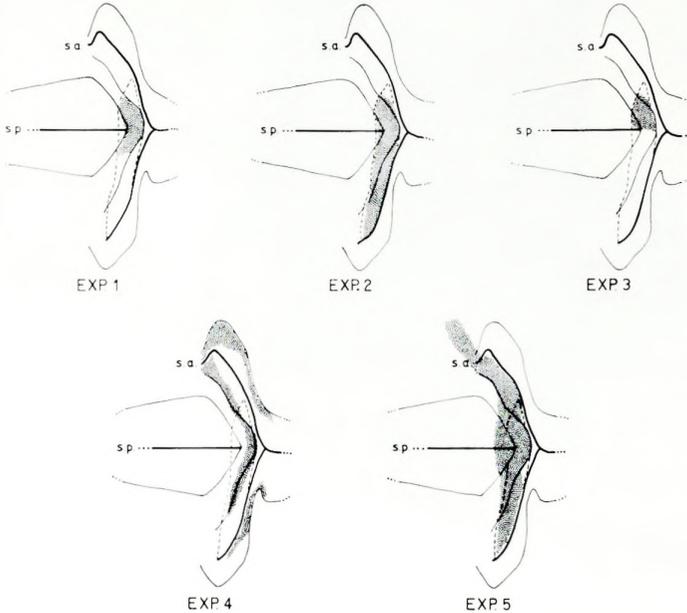


Fig. 2 Reconstruction of cortical lesions in 5 experiments in which area 8 was destroyed by subpial aspiration technique. The extent (dotted area) was verified histologically and plotted in the diagram presented in figure 1. Dashed line — extent of area 8.

of sulcus principalis. The lesion is restricted to rostral bank of sulcus arcuatus. There is no undercutting of the depths of this sulcus. The thalamic degeneration is depicted in figure 3. Pars paralamellaris dorsalis of MD is degenerated. There is no degeneration in the nucleus centralis lateralis or in nucleus ventralis lateralis.

*Experiment 2 (59-18 L).* The cortical ablation (fig. 2) involves almost the entire area 8 sparing but a minimal portion at the dorsal tip. The ablation includes the

rostral bank of sulcus arcuatus as well as cortical tissue at the depth of the sulcus sparing the caudal bank. Retrograde thalamic degeneration is pictured in figure 4. Pars paralamellaris dorsalis of MD is heavily degenerated in its complete extent. No degeneration is found in nucleus ventralis lateralis, while scattered neurons in nucleus centralis lateralis seem atrophied (see photomicrograph in fig. 11).

*Experiment 3 (52-47 R).* The cortical ablation depicted in figure 2 is the smallest

Figs. 3, 4, 5, 6, 7 Retrograde degeneration in the thalamus in experiment 1 to 5; for extent and localization of cortical lesions see figure 2. The cellular changes are confined to MD in all but one case (experiment 4) in which the cortical ablation includes the caudal bank of sulcus arcuatus.

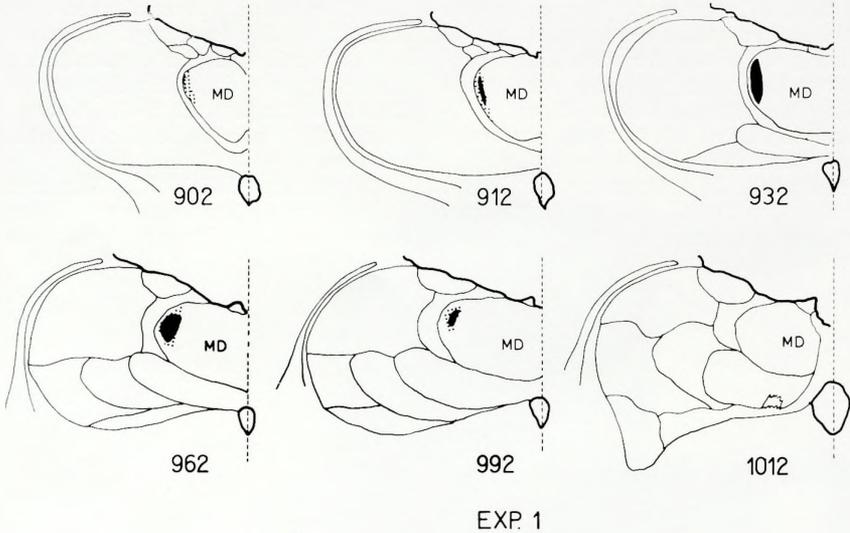


Figure 3

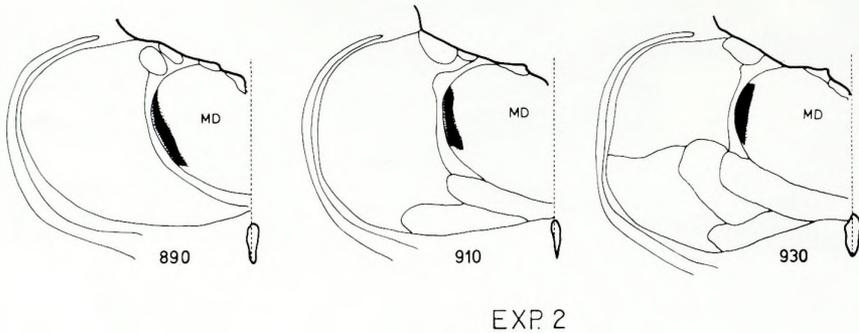
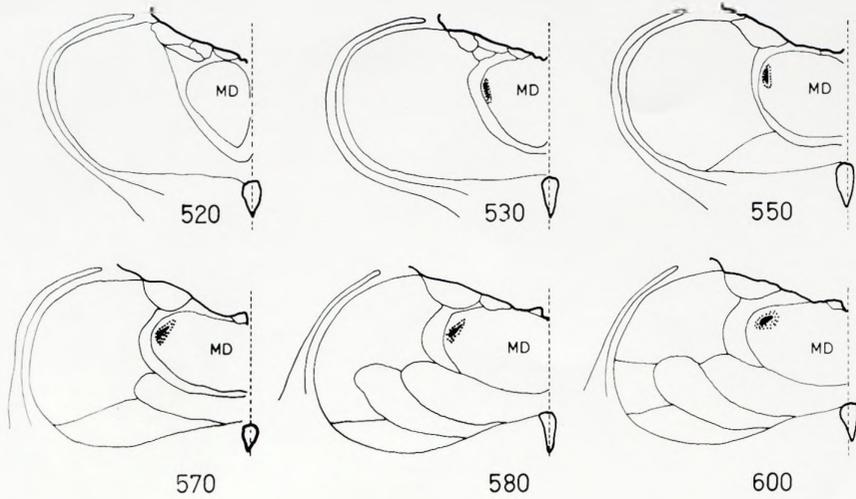
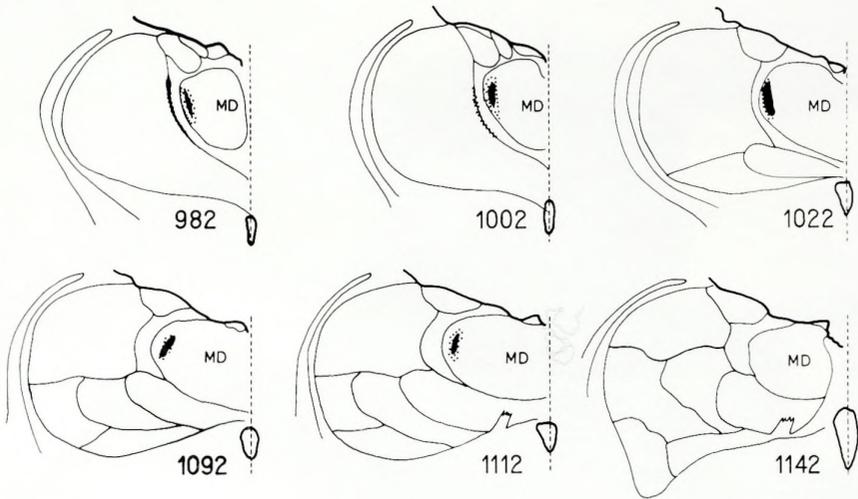


Figure 4



## EXP. 3

Figure 5

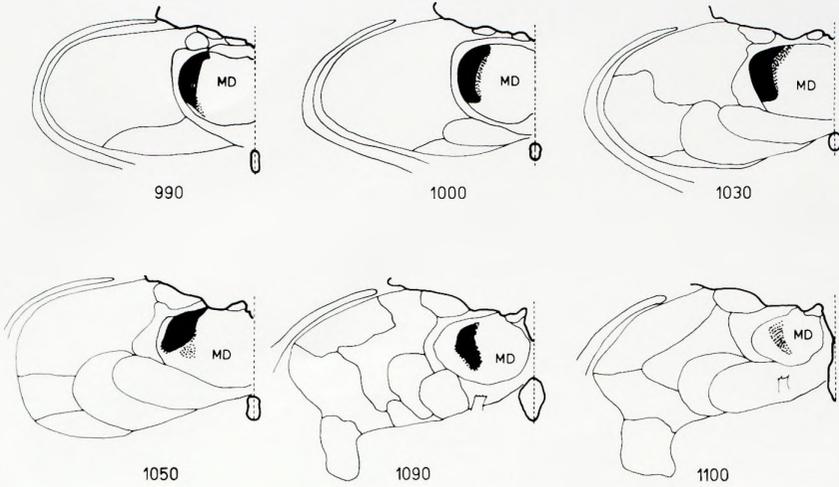


## EXP. 4

Figure 6

of the group. It is situated dorsally in area 8 above the level of sulcus principalis. The cellular changes in the thalamus illustrated in figure 5 are rather minimal and limited to the dorsal portions of pars paramellaris dorsalis of MD. There are no changes in the neighboring areas of the thalamus.

*Experiment 4 (275 R).* The cortical ablation as seen in figures 2 and 9 involves the superficial tissues of the rostral and caudal banks of sulcus arcuatus leaving the deeper portions intact. The thalamic changes are illustrated in figure 6. Retrograde degeneration is seen in the dorsal paramellar portion of MD as well as in



## EXP 5

Figure 7

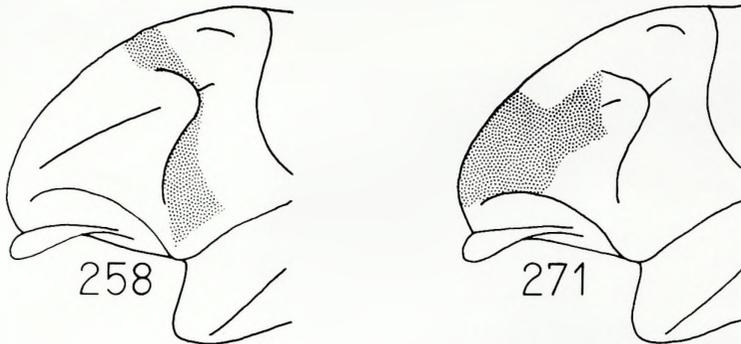


Fig. 8 Control lesions in Brodmann's area 6 (case 258) and 9 (case 271) which fail to produce retrograde degeneration in the dorsal paralamellar portion of MD.

the paralamellar portion of VL. In addition, there are scattered atrophic cells in nucleus centralis lateralis.

*Experiment 5 (266 L).* The cortical removal (fig. 2) is the largest of the group. All of area 8 is destroyed; in addition, the lesion extends rostrally and dorsally beyond the histological boundaries of area 8. The thalamic degeneration as shown in figure 7 is very marked. Pars paralamellaris dorsalis of MD is completely atrophied and replaced by gliotic scar tissue. The area of degeneration also includes adjacent portions of pars parvocellularis of MD. No changes are found in nucleus ventralis lateralis.

## 2. Experimental ablations of areas 6 and 9 of Brodmann

Two control groups of four monkeys each had bilateral ablations of Brodmann's areas 6 and 9 respectively. The data will be dealt with in detail in another paper. The extent of these lesions is shown in figure 8. Ablation of Brodmann's area 6 leads to degeneration of the paralamellar portions of VL, and removal of Brodmann's area 9 causes retrograde changes of the parvocellular portion of MD (fig. 12). The dorsal paralamellar portion of MD is spared in both series.

## DISCUSSION

These experiments demonstrate that the ablation of cortical area 8 in the Rhesus monkey leads to retrograde degeneration of the dorsal paralamellar portion of nucleus medialis dorsalis thalami. This conclusion is supported by the results of control experiments involving the ablation of Brodmann's areas 6 and 9 in which the dorsal paralamellar portion of MD remains intact and the adjacent areas of VL and MD respectively undergo retrograde changes. Specifically, area 6 lesions cause degenerations in the paralamellar portion of VL (called area X by Olszewski, '52), and area 9 lesions affect the parvocellular portion of MD. Thus, it appears that there is the following orderly arrangement of thalamo-cortical projections upon the region of sulcus arcuatus: Areas 9, 8 and 6 of Brodmann are arranged in a rostro-caudal sequence on the lateral surface of the frontal lobe and receive afferents from adjacent thalamic nuclei grouped together in a lateral-medial order. The topological relationship is slightly disrupted, however, by the fact that the intralaminar nuclei which separate MD and VL fail to participate in this system. According to topography, one would expect nucleus centralis lateralis and nucleus paracentralis to project upon cortex in the depth of the arcuate sulcus, but the data of the present study fail to support this hypothesis. At best, there is minimal atrophy of the neurons of intralaminar nuclei when a relatively large lesion of areas 8 and 6 is present. Furthermore, the experiments of Powell and Cowan ('56) suggest that nucleus centralis lateralis and nucleus paracentralis project upon the head of the caudate nucleus. Thus, connections of intralaminar nuclei with frontal cortex are more likely to be sustaining collaterals or indirect.

The thalamic area reacting to removal of area 8 represents a well defined nuclear subunit of MD which is clearly shown in the atlas of Olszewski ('52). Walker ('40b) was the first to draw attention to this paralamellar area and suggest its relation to area 8. Work in this laboratory made it necessary to differentiate between a dorsal and ventral portion of the paralamellar zone. While the dorsal portion

depends on the integrity of area 8, the ventral degenerates after removal of a circumscribed segment of opercular cortex subjacent to the ventral tip of area 8 (Roberts and Akert, '63). The dorsal portion is further characterized by relatively large polygonal cells which bear greater resemblance to the neurons of paralamellar VL than to those of the other subdivisions of MD, even though topographically these cells are members of the MD population. This situation is somewhat analogous to the intermediary position held by cortical area 8 which shares morphological characteristics with the precentral agranular and with the frontal granular regions.

The fact that such a typical thalamic region degenerates in toto after removal of cortical area 8 is significant in two ways. First, it lends strong support to the cytoarchitectural concept of cortical area 8 presented in this paper. Secondly, it establishes an anatomical relationship which may help to elucidate the functional role of this region. Hess ('48) stimulated the paralamellar region of MD in waking cats and noted contraversive turning of eyes and head. He suggested that this effect was comparable to that seen when the frontal eye field was stimulated in monkeys. The present results seem to support this comparison. Unfortunately, little is known about the afferent pathways which convey physiological signals to the paralamellar portion of MD.

The cytoarchitectural map of area 8 presented in this paper seems to be quite similar to that of previous investigators. It seems important to point out that the three principal histological features (see Results) of area 8 are to be found only in the cortex of the ventral limb of the rostral bank of sulcus arcuatus. The same conclusion was reached by C. and O. Vogt ('19) and by von Bonin and Bailey ('47). The latter designated the cortex of the ventral limb of the rostral bank of sulcus arcuatus: "FDI." Walker's ('40a) "area 45" is also limited to the ventral limb. Crosby, Yoss and Henderson ('52) studied the frontal eye fields with electrical stimulation method and found the entire rostral bank of sulcus arcuatus excitable. They demonstrated two oculomotor systems,

one situated in the dorsal half and the second, a mirror-image of the first, in the ventral half. It is the ventral system which corresponds exactly to the localization of area 8 as defined cytoarchitecturally and by thalamocortical studies in this paper. Since efferent pathways to the region of oculomotor nuclei and to the tegmental reticular formation were found by Crosby, Yoss and Henderson ('52) to emanate predominantly from their ventral oculomotor system, the identification of area 8 with the latter is now supported by three lines of evidence: (a) cytoarchitectural, (b) afferent projections from the thalamus, (c) efferent projections to motor outflows.

The finding of two motor representations arranged in mirror-image fashion brings to mind Woolsey's concept of cortical motor systems (Woolsey, '58). The ventral oculomotor system of Crosby and coworkers may be compared with Woolsey's precentral motor cortex. Although the analogy is incomplete, there are comparable cytoarchitectural features, and similarities clearly exist between thalamic afferents and corticofugal projection patterns. Unfortunately, the analogy between the dorsal oculomotor system of Crosby and coworkers and the supplementary motor cortex of Woolsey, attractive as it might appear, suffers from the lack of precise anatomical information on both areas and only future research can determine its merits.

#### SUMMARY

1. A cytoarchitectural map of area 8 in *Macaca mulatta* is presented which is based on unequivocal criteria: very large pyramidal cells in layers III and V in the presence of a well developed granular layer IV. The area so defined is limited to the ventral limb of the rostral bank of sulcus arcuatus. This concept of area 8 is consistent with earlier findings by the Vogts and by von Bonin and Bailey.

2. Circumscribed removal of this area in five animals leads to retrograde degeneration of pars paralamellaris dorsalis of nucleus medialis dorsalis (MD) thalami. This finding of a specific thalamo-cortical projection lends strong support to the present concept of area 8.

3. Ablations of the adjacent cortical areas 6 and 9 of Brodmann in eight animals fail to cause any changes in pars paralamellaris dorsalis of MD but affect the paralamellar portion of nucleus ventralis lateralis (VL) and the parvocellular portion of MD respectively. The topological order of thalamic nuclei projecting upon areas 6, 8 and 9 is discussed.

4. An almost identical cortical area has been located ventrally in the rostral limb of sulcus arcuatus by Crosby and coworkers on the basis of electrical stimulation experiments and the study of secondary degeneration of efferent pathways. The correspondence between the two sets of data is consistent with Woolsey's concept of cortical motor systems: The existence of two frontal oculomotor fields, the first situated ventrally and the second, a mirror-image, located dorsally in the rostral bank of sulcus arcuatus. The ventral system can be compared with the precentral motor cortex, while the dorsal system may represent the analogue of the supplementary motor cortex.

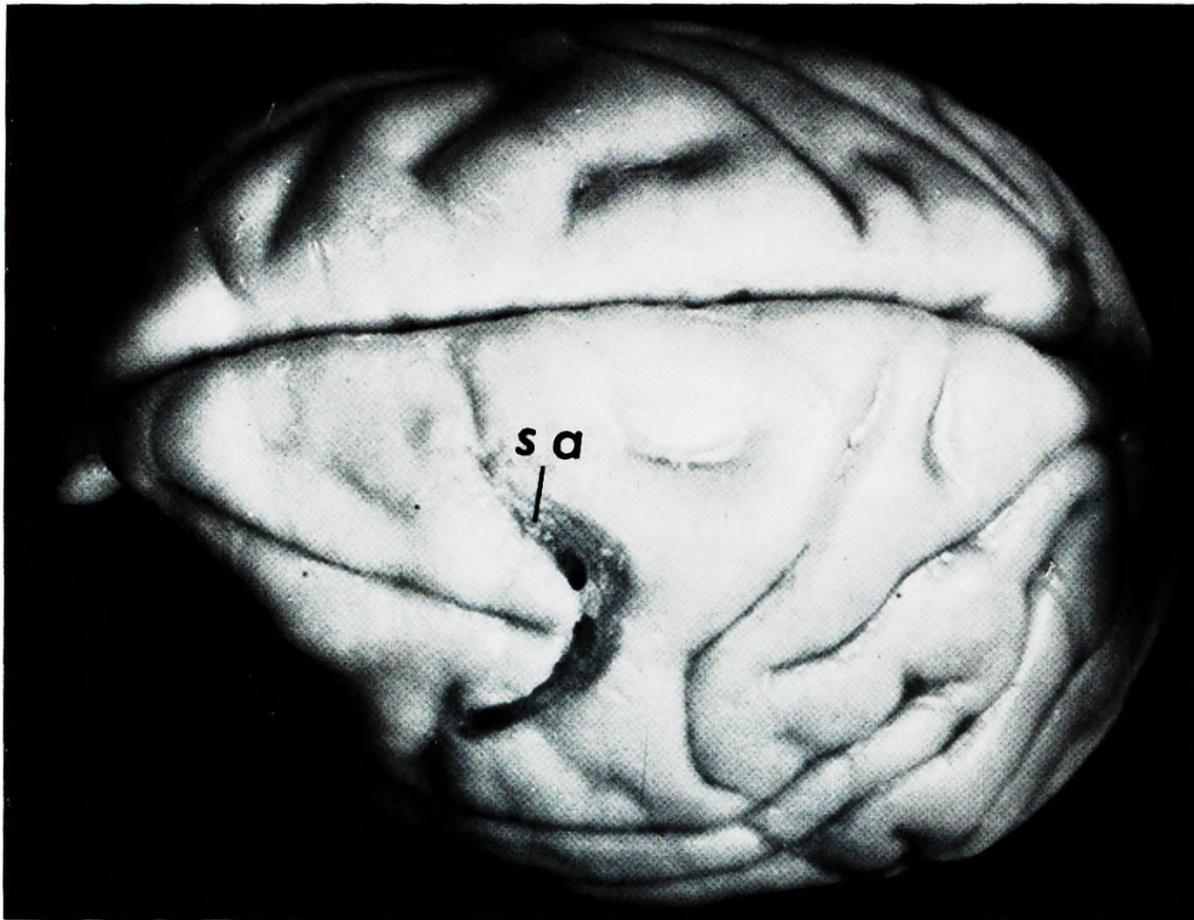
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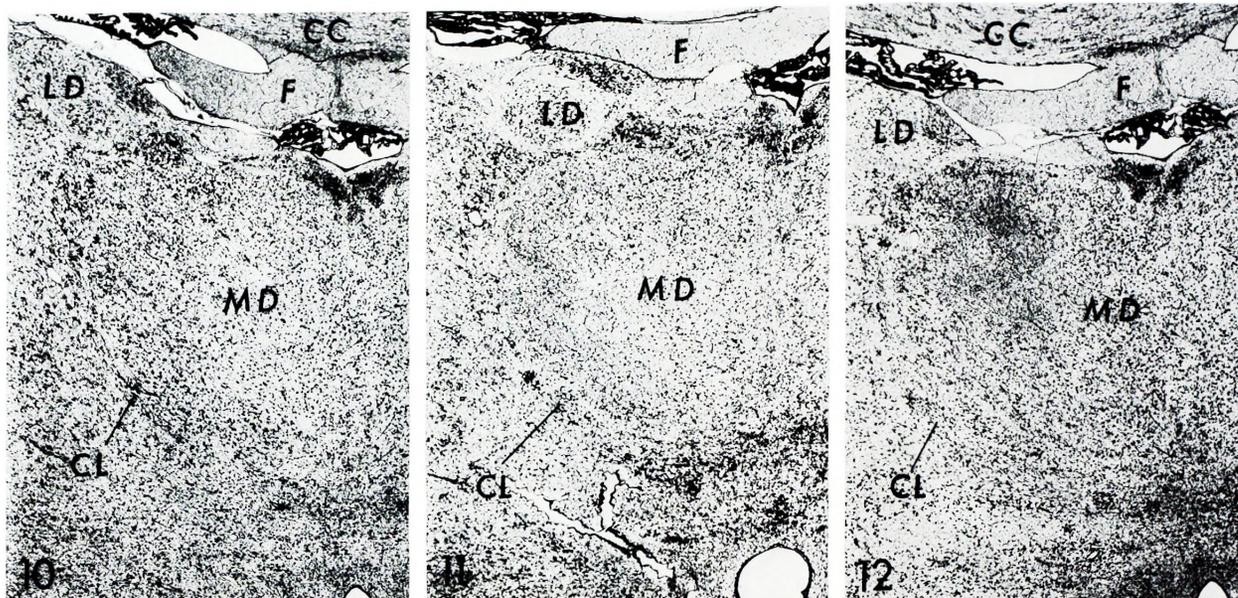
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9 Experiment 4 (275 R): Rostral and caudal bank of sulcus arcuatus are removed (see reconstructions fig. 2 and fig. 6).



Nucleus medialis dorsalis thalami. Coronal sections from three individual monkey brains taken at approximately the same level. (Nissl stain,  $30 \mu$ ,  $\times 18$ ).

10 Normal section.

11 Retrograde degeneration in pars paralamellaris dorsalis MD (case 59-18 L) after complete removal of area 8.

12 Retrograde degeneration in pars parvocellularis MD (case 271 L) after removal of Brodmann's area 9. Note the sparing in this case of pars paralamellaris dorsalis.