THE JOURNAL OF COMPARATIVE NEUROLOGY 242:535-560 (1985)

The Primate Mediodorsal (MD) Nucleus and Its Projection to the Frontal Lobe

PATRICIA S. GOLDMAN-RAKIC AND LINDA J. PORRINO
Section of Neuroanatomy, Yale University School of Medicine, New Haven, Connecticut 06510 (P.S.G.-R.); Laboratory of Cerebral Metabolism, National Institutes of Mental Health, Bethesda, Maryland 20205 (L.J.P.)

ABSTRACT

The frontal lobe projections of the mediodorsal (MD) nucleus of the thalamus were examined in rhesus monkey by transport of retrograde markers injected into one of nine cytoarchitectonic regions (Walker's areas 6, 8A, 9, 10, 11, 12, 13, 46, and Brodmann's area 4) located in the rostral third of the cerebrum. Each area of prefrontal, premotor, or motor cortex injected was found to receive a topographically unique thalamic input from clusters of cells in specific subdivisions within MD. All of the prefrontal areas examined also receive topographically organized inputs from other thalamic nuclei including, most prominently, the ventral anterior (VA) and medial pulvinar nuclei. Conversely, and in agreement with previous findings, MD projects to areas of the frontal lobe beyond the traditional borders of prefrontal cortex, such as the anterior cingulate and supplementary motor cortex. The topography of thalamocortical neurons revealed in coronal sections through VA, MD, and pulvinar is circumferential. In the medial part of MD, for example, thalamocortical neurons shift from a dorsal to a ventral position for cortical targets lying medial to lateral along the ventral surface of the lobe; neurons in the lateral MD move from a ventral to a dorsal position, for cortical areas situated lateral to medial on the convexity of the hemisphere. The aggregate evidence for topographic specificity is supported further by experiments in which different fluorescent dyes were placed in multiple areas of the frontal lobe in each of three cases. The results show that very few, if any, thalamic neurons project to more than one area of cortex. The widespread cortical targets of MD neurons together with evidence for multiple thalamic inputs to prefrontal areas support a revision of the classical hodological definition of prefrontal cortex as the exclusive cortical recipient of MD projections. Rather, the prefrontal cortex is defined by multiple specific relationships with the thalamus.

Key words: medial pulvinar nucleus, mediodorsal nucleus, prefrontal cortex, ventral anterior nucleus, rhesus monkey

A role for the mediodorsal (MD) nucleus of the thalamus in the cognitive and emotional life of the individual was suggested nearly a century ago (Monakow, 1895) and is increasingly supported by contemporary evidence of the MD's specific participation in the memory systems of the human brain (Shulman, '57; Victor et al., '71; McEntee et al., '76; Squire and Moore, '79). In keeping with both its affective and cognitive functions, the mediodorsal nucleus reaches its peak dimensions and cytoarchitectonic complexity in the human brain in parallel with the expansion of the prefrontal cortex to which it projects (Filimonov, '49; Yakovlev, '69; Van Buren and Borke, '72). However, unlike most other major thalamic nuclei, such as the lateral geniculate nucleus, which have been extensively analyzed, the subnuclear organization of the MD has not been worked out in detail in primates and the exact limits of its cortical targets remain unclear. Such information is crucial if we

Accepted October 1, 1985.

Address reprint requests to P.S. Goldman-Rakic, Section of Neuroanatomy, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06510.

are ever to understand the functions of the MD and its contribution to human memory.

Another important reason for studying MD-cortical relationships is that this connection has been heavily relied upon to define prefrontal cortex in a wide spectrum of mammalian species (e.g., Akert, '64; Krettek and Price, '77; Leonard, '69, '79; Markowitsch and Pritzel, '79), ever since Rose and Woolsey ('48) first suggested that the prefrontal cortex (called "orbitofrontal") could "be defined as the projection area of the mediodorsal nucleus." This hodological definition has been extremely important for studies of nonprimate orders, all of which lack an internal granular layer that is the denotative cytoarchitectonic feature of prefrontal cortex in primates. However, the criteria for comparative analysis need to be reexamined in light of recent reports that prefrontal cortex receives projections from thalamic nuclei other than the MD (Baleydier and Mauguiere, '80; Jacobson et al., '78; Kievit and Kuypers, '77) and conversely, that the mediodorsal nucleus projects to cortical regions beyond the traditional boundaries of the prefrontal granular cortex such as the cingulate (Vogt et al., '79; Baleydier and Mauguiere, '80), insular (Mufson and Mesulam, '84), premotor (Schell and Strick, '84; Ilinsky et al., '85), and parietal (Kasdon and Jacobson, '78) cortices.

The present study employed the retrograde transport of HRP and fluorescent dyes, singly and in combination, to clarify the issue of thalamocortical specificity in primates. The goal was to obtain a finer-grained map of topographic relationships between major nuclear subdivisions of the MD and major cytoarchitectonic zones in the frontal lobe. We reasoned that more precise mapping of these connections is necessary for evaluating the functional relationships between these structures, for assessing the significance of clinical findings in which one or another portion of the mediodorsal nucleus is damaged, and for comparative anatomic investigations that seek to establish homologies between areas of prefrontal cortex in monkeys and those in other species.

METHODS

Horseradish peroxidase histochemistry

Nine 2–4-kg macaque monkeys received closely spaced, multiple injections of 20–50% horseradish peroxidase (HRP) or gel implants of HRP or injections of 1.5–2.0% wheat germ agglutinin conjugated to HRP (WGA-HRP). Injections or implants were placed in a variety of granular cortical areas that were intended to correspond to the major cytoarchitectonic areas of prefrontal association cortex as defined by Walker, ('40a) as well as in two adjacent nongranular cortical areas (Fig. 1, left panel). For each area injected, a craniectomy was made large enough to expose all sulcal landmarks in the area of interest and injections were placed within this region. As illustrated in the right panel of Figure 1, the HRP injection sites or cases were arbitrarily numbered as follows: (1) the anterior orbital cortex at the cortex at the frontal pole (Walker's area 10); (2) the posterior medial orbital cortex (Walker's area 13); (3) the lateral inferior convexity (Walker's area 12); (4) the ventral and (5) dorsal bank of the principal sulcus (Walker's area 46); (6) the superior prefrontal gyrus on the dorsomedial wall of the hemisphere and adjacent dorsal convexity (Walkers area 8B and 9); (7) the anterior cingulate gyrus (Walker's area 24); (8) the anterior bank of the arcuate sulcus (Walker's area 8A and 45); (9) the medial premotor cortex (Walker's area 6) corresponding to the anterior supplementary motor (SMA) cortex (Muakkassa and Strick, '79); and (10) both banks of the principal sulcus and adjacent cortex (not shown). It should be noted that the injections in cases #7 and #9 lay outside the boundaries of frontal granular cortex.

Animals were prepared for surgery with ketamine (10 mg/kg) and operated on under sodium pentobarbital (40 mg/kg) anesthesia. The injections were made under direct visual guidance at depths between 1 and 3 mm in one of the cortical areas described above. Pressure injections were made by using a Hamilton microliter syringe in volumes varying from 0.2 to 0.3 μl per injection. In one monkey, injections were placed in the dorsal bank of the principal sulcus in one hemisphere and in the ventral bank of the same sulcus in the other (for convenience, referred to as

Abbreviations

AM	anterior medial nucleus
A	arcuate sulcus
AV	anterior ventral nucleus
C	cingulate sulcus
Ce	centrum medianum
CE	central sulcus
CL	central lateral nucleus
Cif	central inferior nucleus
DY	Diamidino Yellow
FB	Fast Blue
FEF	frontal eye field
GM	medial geniculate nucleus
GMmc	medial geniculate nucleus, pars magnocellularis
GMpc	medial geniculate nucleus, pars parvicellularis
HM	medial habenular nucleus
HL	lateral habenula nucleus
IA	inferior arcuate sulcus
IC	inferior convexity
LD	lateral dorsal nucleus
Li	nucleus limitans
Lme	external medullary lamina
LP	lateral posterior nucleus
LO	lateral orbital sulcus
MD	mediodorsal nucleus
MDde or MDd	mediodorsal nucleus, pars densocellularis
MDmc	mediodorsal nucleus, pars magnocellularis
MDmf	mediodorsal nucleus, pars multiformis
MDpc	mediodorsal nucleus, pars parvicellularis
ML	medial lemniscus
MO	medial orbital cortex
PC	posterior commissures
Pcn	paracentral nucleus
Pf	parafascicular nucleus
PI	Propidium Iodide
PI	inferior pulvinar subnucleus
PM-	medial pulvinar subnucleus
PL	lateral pulvinar subnucleus
PS	principal sulcus
R	reticular thalamic nucleus
Re	nucleus reuniens
Sm	stria medullaris
SMA	supplementary motor area
STN	subthalamic nucleus
THI	habenulo-interpedunuclar tract
VA	ventral anterior nucleus
VAmc	ventral anterior nucleus, pars magnocellularis
VApc	ventral anterior nucleus, pars parvicellularis
VLc	ventral lateral nucleus, pars caudalis
VLo	ventral lateral nucleus, pars oralis
VLm	ventral lateral nucleus, pars medialis
VLps	ventral lateral nucleus, pars postrema
VPM	ventral posterior medial nucleus
VPLo	ventral posterior lateral nucleus, pars oralis
VPLc	ventral posterior lateral nucleus, pars caudalis
VPMpc	ventral posterior medial nucleus, pars parvicellularis
X	area X

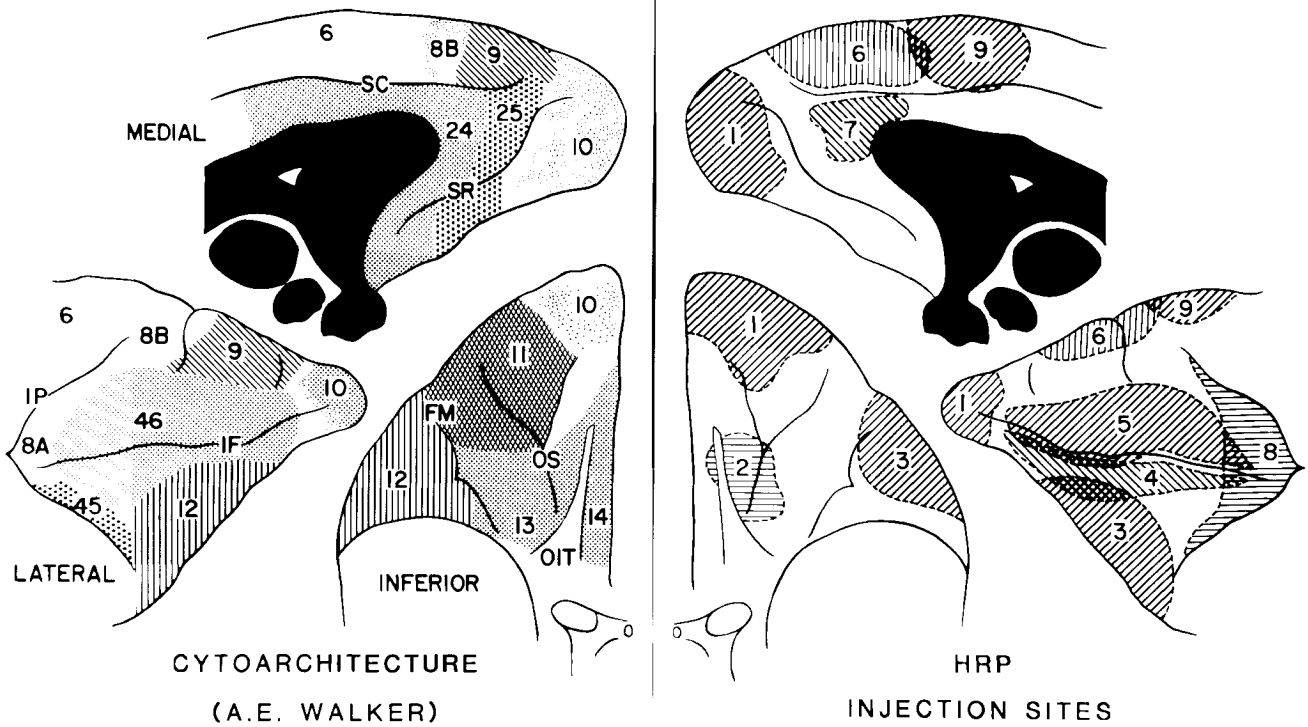


Fig. 1. A.E. Walker's cytoarchitectonic map of macaque prefrontal cortex is shown on the left (Walker, '40a); HRP injection sites are represented on a mirror-image diagram of the Walker map to illustrate the degree of correspondence between the areas injected and specific cytoarchitectonic subdivisions of prefrontal, premotor and cingulate cortex. The abbreviations, SC (callosal marginal sulcus), IF (inferior frontal sulcus), IP (inferior premotor sulcus), FM (medial frontal sulcus), and OS (orbital sulcus) are no longer used and have long since been replaced by cingulate, principal, superior arcuate, medial orbital, and lateral orbital sulci. The numbering of the HRP injection sites is arbitrary for demonstration of topographic relationships. The anterior orbital injection (case #1) covered Walker's area 10 at the frontal pole and extend caudally into area 11 on the ventrolateral surface of the hemisphere. A small area of cortex on the outermost dorsolateral surface including the anterior tip of the principal sulcus (PS) was also included in this injection site. The smallest injection (case #2) was that made in the medial orbital cortex (Walker's area 13) straddling the posterior orbital sulcus (Figs. 1, 4E). The injection of the inferior convexity in case #3 extended from the inferior frontal gyrus to the lateral orbital sulcus on the ventral surface of the lobe and was coextensive with Walker's area 12 (Figs. 1, 4D). The injection in the ventral bank of the principal sulcus (case #4) extended along the entire rostral-caudal limits of the sulcus and slightly encroached upon Walker's area 12 (Figs. 1, 4C) but did not spread to the dorsal bank of the PS. However, in the same animal's opposite hemisphere, the injection in the dorsal bank of the principal sulcus (case #5) labeled the rim and depth of the dorsal PS and spread both to a portion of the ventral bank of the principal sulcus along most of its anterior half and to adjacent dorsal cortex encompassed by Walker's area 46 (Fig. 1, 4B). The dorsomedial injection (case #6) was confined to the superior prefrontal gyrus on the dorsomedial aspect of the hemisphere bordering the dorsal margin of the cingulate sulcus (callosal marginal sulcus of Walker) (Figs. 1, 4A). Rostrally it encompassed the medial part of Walker's area 9, which begins at the anterior limit of the cingulate sulcus. Caudally the injection extended slightly into Walker's area 8B and the anterior portion of area 6 behind the genu of the corpus callosum. In case #7, the anterior fifth of the cingulate gyrus was labeled beginning rostral to the genu of the corpus callosum; this region mainly corresponds to Walker's area 24 with some slight encroachment on area 25 (Figs. 1, 4F). The injection into the frontal eye fields, case #8, labeled the anterior bank of the arcuate sulcus, both its superior and inferior rami, as well as some tissue in the caudal portion of the principal sulcus (Fig. 1). The injection in case #9 covered the superior medial gyrus from the level of the perpendicular extension of the superior limb of the arcuate to the level of the precentral dimple (Fig. 1). Based on direct anatomical connections with the motor cortex (Muakkassa and Strick, '79), this area corresponds largely to the head area of the supplementary motor cortex.

cases #4 and #5). In all other cases, injections were unilateral and confined to only one cytoarchitectonic area.

After a survival period of 48 hours, each animal was deeply anesthetized with sodium pentobarbital, injected with sodium heparin (1,000 units/kg), and flushed intracardially with normal saline at room temperature, followed by 1–2 liters of fixative containing 1% paraformaldehyde and 1.25–2.5% gluteraldehyde in 0.1 M phosphate buffer (pH 7.4) at 37°C. The perfusion was continued with 2 liters of 10% sucrose in 0.1 M phosphate buffer (pH 7.4) at 4°C, followed in most cases by 2 liters of 20% sucrose in the same buffer. The brain was removed immediately, blocked, and kept in either 20% or 30% sucrose buffer at 4°C. After 24–72 hours, 40-μm frozen sections were cut in the frontal plane and treated according to the benzidine dihydrochloride or tetramethylbenzidine protocols of Mesulam ('76, '78).

Slides were examined for HRP-positive cells under bright- and darkfield illumination up to 400×. Injection sites were reconstructed and selected areas were charted with the aid of an overhead projector. The distribution of labeled perikarya was charted in each section through the thalamus. To facilitate comparison of topography among cases and achieve standardization of the results, the data for each animal were then transferred to a common set of drawings of the thalamus based on Olzewski's ('52) atlas.

Fluorescent tracers

Three additional monkeys (cases #11, #12, and #13) were injected with fluorescent tracers in multiple labeling experiments. Injections of three fluorescent dyes, Fast Blue (FB), Diamidino Yellow (DY), and Propidium Iodide (PI), were made in different cortical areas and processed as described

previously (Schwartz and Goldman-Rakic, '84). In one monkey, case #11, FB was injected into the orbital cortex and DY was injected into the dorsal bank of the principal sulcus in the same hemisphere; in the other hemisphere, FB was injected into the frontal eye fields and DY was injected into the ventral bank of the principal sulcus. Given the homolateral organization of thalamocortical projections, the use of both hemispheres allowed unambiguous boundaries for topographic distributions of adjacent projection systems as well as economical use of the valuable rhesus monkey. In two other animals, PI was injected into the principal sulcus. In case #12, the injections were placed along the caudal two-thirds of the dorsal bank while in the other monkey, case #13, both banks were injected over approximately the same length. Both of these animals had second and third dye injections, respectively, in the supplementary motor cortex (Walker's area 6) and forelimb area of the primary motor cortex (Walker's area 4).

The perfusion was initiated with heparanized saline followed by 4% paraformaldlehyde in 0.1 M phosphate buffer, pH 7.4, and then followed with the same fixative containing increasing concentrations of sucrose up to 30%. Two of the brains were cut into 40-um-thick sections in the sagittal plane; one was sectioned at the same thickness but in the coronal plane.

Distributions of the thalamocortical neurons labeled with fluorescent dyes were charted by a semiautomatic computer (Leitz Dialux-20 fluorescent microscope stage equipped with Minnesota Datametrics readout heads connected via amplifiers to an X-Y plotter). The FB- and DY-labeled neurons were visualized through a 360-nm wavelength filter, and the PI-labeled cells through a 550-nm wavelength filter. The sections were charted at a magnification of 22.5×. After plotting, the sections were counterstained with cresyl violet for identification of thalamic nuclei. Selected sections were also photographed.

Photomicrographs of cresyl-violet-stained sections from sagittally sectioned brains containing fluorescent tracers were printed at a final magnification that matched that of charts of distributions of thalamocortical neurons. Transparent acetate film sheets were overlaid on photomicrographs of these sections and the boundaries of thalamic nuclei were outlined on them.

RESULTS

Cytoarchitecture of the mediodorsal nucleus

In the rhesus monkey, as in humans, the MD occupies most of the area between the internal medullary laminae and the periventricular gray in the middle third of the thalamus. Following Olszewski's ('52) cytoarchitectonic atlas of the macaque thalamus, four subdivisions of the MD are recognized (Figs. 2, 3). A magnocellular portion (MDmc) is located rostrally and medially, and consists of fairly large, deeply staining multipolar cells (Fig. 2A,B, 3A). This portion lies more dorsally at anterior levels and disappears at the more caudal extent of this nucleus (Fig. 3B). The parvicellular (MDpc) portion contains clusters of smaller, paler-staining cells and is situated lateral to the MDmc and extends into the most caudal portions of the mediodorsal nucleus. The multiformis portion (MDmf), also referred to as "pars paralamellaris," occupies the most lateral part of the nucleus and forms a narrow band of darkly staining, large cells just adjacent to the internal medullary lamina (Fig. 2A,B, 3A). Caudally, at the level of the habenula, a fourth subdivision, the densocellular portion (MDde), consisting of medium-sized, darkly staining cells, lies medial to the medial pulvinar and lateral posterior nuclei and lateral to the MDpc and the habenula (Fig. 3B).

Localization of HRP injection sites

The extent of selected HRP cortical injection sites is shown in Figures 1 and 4 and all injection sites are fully described in the legend to Figure 1. The area of labeling in all cases was mainly confined to one cytoarchitectonic region of the cortex, with limited encroachment on adjacent cortical areas and some involvement also of white matter in the larger injection fields. However, in no case was there spread of label to any subcortical structures.

Retrograde labeling in MD

The magnocellular subnucleus of the MD was the principal site of dense neuronal labeling in three cases with injections in ventral prefrontal areas. Following injections in the anterior cortex surrounding the frontal pole (case #1), the medial orbital cortex (case #2), and the inferior convexity (case #3), labeled somata were present in the MDmc throughout most of its rostral-caudal extent. With injections in the medial orbital cortex, HRP-positive cells were concentrated primarily in the most dorsal part of the MDmc (Figs. 5, 8A) while neurons labeled after injections in the inferior convexity were located ventrally in the MDmc and extended further caudally (Fig. 6). The pattern of labeling in case #1 with injections in the anterior orbital cortex at the frontal pole was intermediate—occupying a central location in anterior sections and a more dorsal and lateral position in the most posterior sections (Figs. 7, 8B). In cases #1 and #3, some clusters of labeled neurons were present in other moieties of MD, particularly in central portions of the nucleus (+6.9, +5.7 in Figs. 6, 7).

Cases with injections in the dorsolateral prefrontal cortex received their major thalamic innervation from the parvicellular portion of the mediodorsal nucleus (Figs. 9–13). In case #4 with injections placed into the ventral bank of the principal sulcus, labeled cells were located in the ventral half of the parvicellular subdivision (Fig. 9). At rostral levels of the MD, the labeled neurons were located in the center of the MD; at intermediate A-P levels, labeled neurons occupied the entire ventral half of the MDpc and in the more caudal part of the MD occupied a medial ventral strip adjacent ot the MDmc. Following injections in the dorsal bank of the principal sulcus in the dorsal bank of the principal sulcus in case #5, neurons shifted dorsolaterally in the MDpc (Fig. 10). In line with the previous observations of Jacobson, Butters, and Tovsky ('76), isolated labeled neurons were also found in the magnocellular moiety of the MD, particularly in midregions of the thalamus where this portion of the MD reaches its widest extent (see level +6.9 in Fig. 10). Overlap in the position of labeled cells following the separate tracer injections in the ventral and dorsal banks of the principal sulcus (cases #4 and #5, respectively) was slight, confined to central regions of the nucleus, and probably largely due to the involvement of the ventral bank in case #4. In this case, a labeling pattern characterized by aggregations or clusters of labeled cells surrounding circular or elliptical areas containing unlabeled cells was particularly striking in sections processed by the DAB method, in which the superimposition of anterograde labeling of corticothalamic fibers was reduced to a minimum (Fig. 11).

The retrograde labeling in case #10, with the largest HRP injection in both banks of the principal sulcus, was vir-

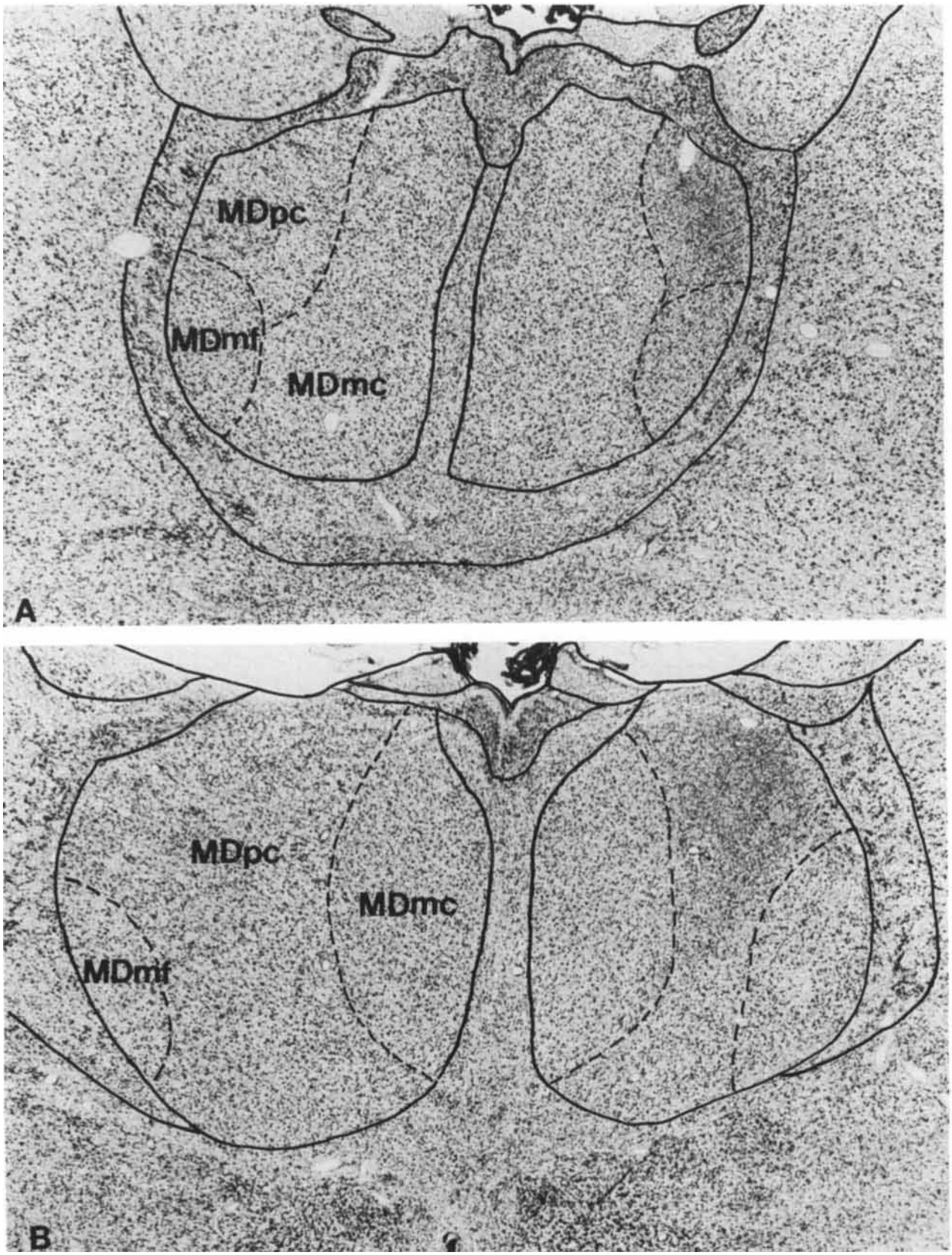


Fig. 2. Low-power photographs of cresyl-violet-stained sections through the mediodorsal nucleus at anterior-posterior levels corresponding to Horsley-Clark coordinates +7.5 (A) and +6.9 (B), showing MDmf, MDpc, and MDmc subnuclear divisions. In this and the next figure, gliosis is present in and helps to delineate MDpc on the right because the animal had been given a resection of the principal sulcus in the right hemisphere several months before death.

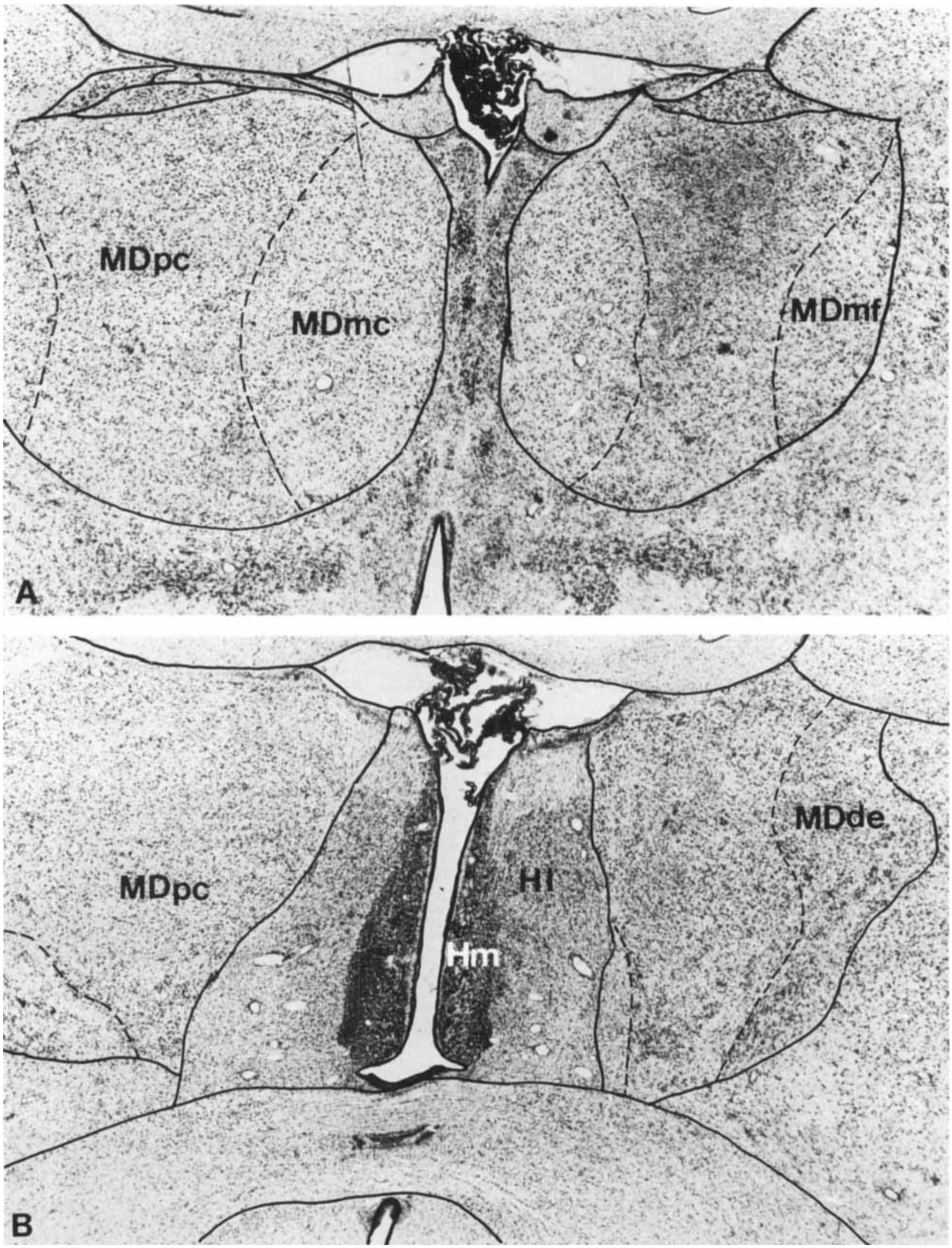


Fig. 3. Photographs of cresyl-violet-stained sections from the posterior MD of the same monkey shown in Figure 2. A is at +5.7 and B is at around +3.3, where the medial (Hm) and lateral (Hl) habenula are present and MDde becomes prominent.

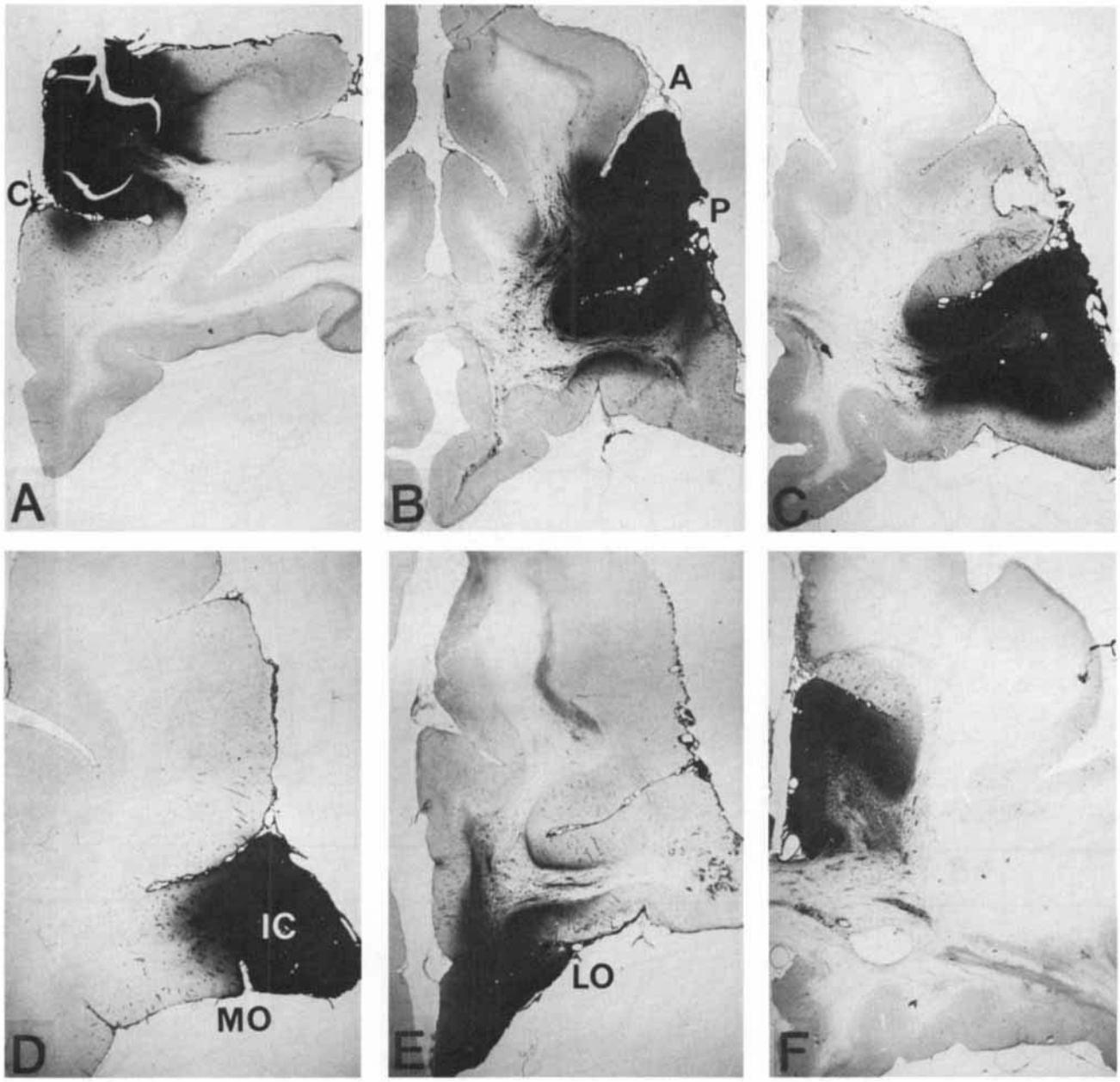


Fig. 4. Photomicrographs of selected HRP injection sites in (A) the dorsomedial cortex; (B) the dorsal and ventral banks of the principal sulcus; (C) the ventral bank of the principal sulcus; (D) the inferior convexity; (E) the medial orbital; and (F) the cingulate gyrus. Full descriptions of the anterior-posterior and mediolateral extent of these and all other injection sites are provided in the legend to Figure 1 and in the text. Abbreviations: C, cingulate sulcus; A, arcuate sulcus; P, principal sulcus; IC, inferior convexity; MO, medial orbital sulcus, and; LO, lateral orbital sulcus.

tually a composite of the two partial PS injections (Fig. 12A). In this case, processed exclusively by the TMB method, anterograde as well as retrograde transport was extensive. Nevertheless, oval territories of unlabeled neurons were still present (Fig. 12A), indicating that a given moiety of the MD is a mosaic of cell clusters most of which project to a primary target, and some of which project to other cortical or perhaps subcortical targets.

The MDpc was also the site of origin for thalamocortical projections to the dorsomedial prefrontal cortex (case #6). After injections in this cortical area, labeled neurons were confined to the most posterior part of the MDpc and were also present in the densocellular subdivision, MDde (Fig. 13). In the posterior MDpc, the HRP-positive cells occupied a dorsal position and therefore appeared to overlap to some extent with neurons projecting to the dorsal bank of the principal sulcus (compare Figs. 10, 13). Similarly, HRP injections in the supplementary motor cortex (case #9) resulted in dense concentrations of labeled cells in the caudal half of the MDpc, in its dorsal and particularly its ventral portion. In this particular case, we were not able to determine whether cells in the MDde were also positive because

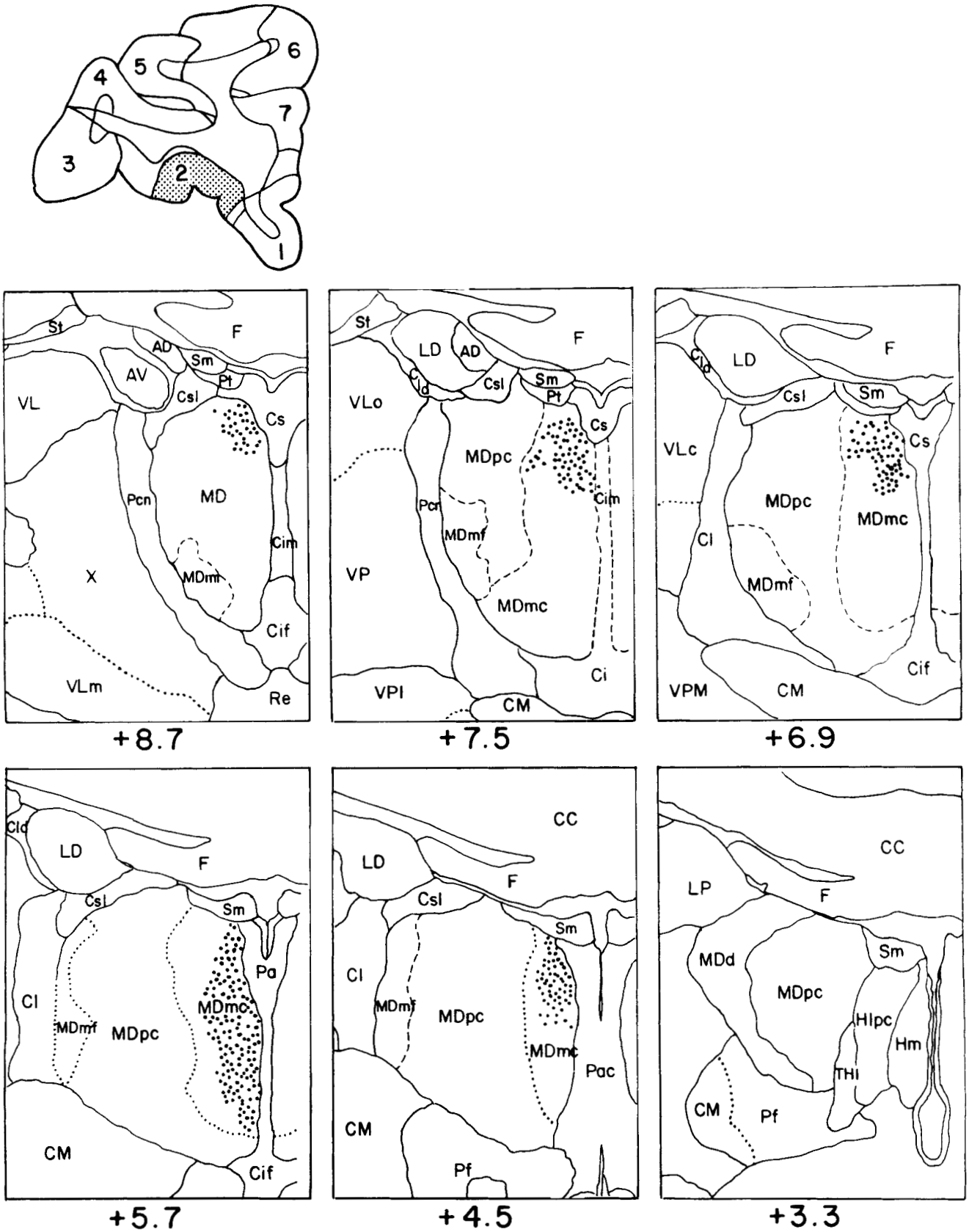


Fig. 5. Diagrammatic illustration of the pattern of cell labeling following injection into the medial orbital cortex (case #2) at six A-P levels through the mediodorsal nucleus, as depicted in Olszewski's atlas through the macaque thalamus (Olszewski, '50). The injection site in this and subsequent figures is shaded in a coronal section through the middle of prefrontal cortex, illustrated at the top of each figure.

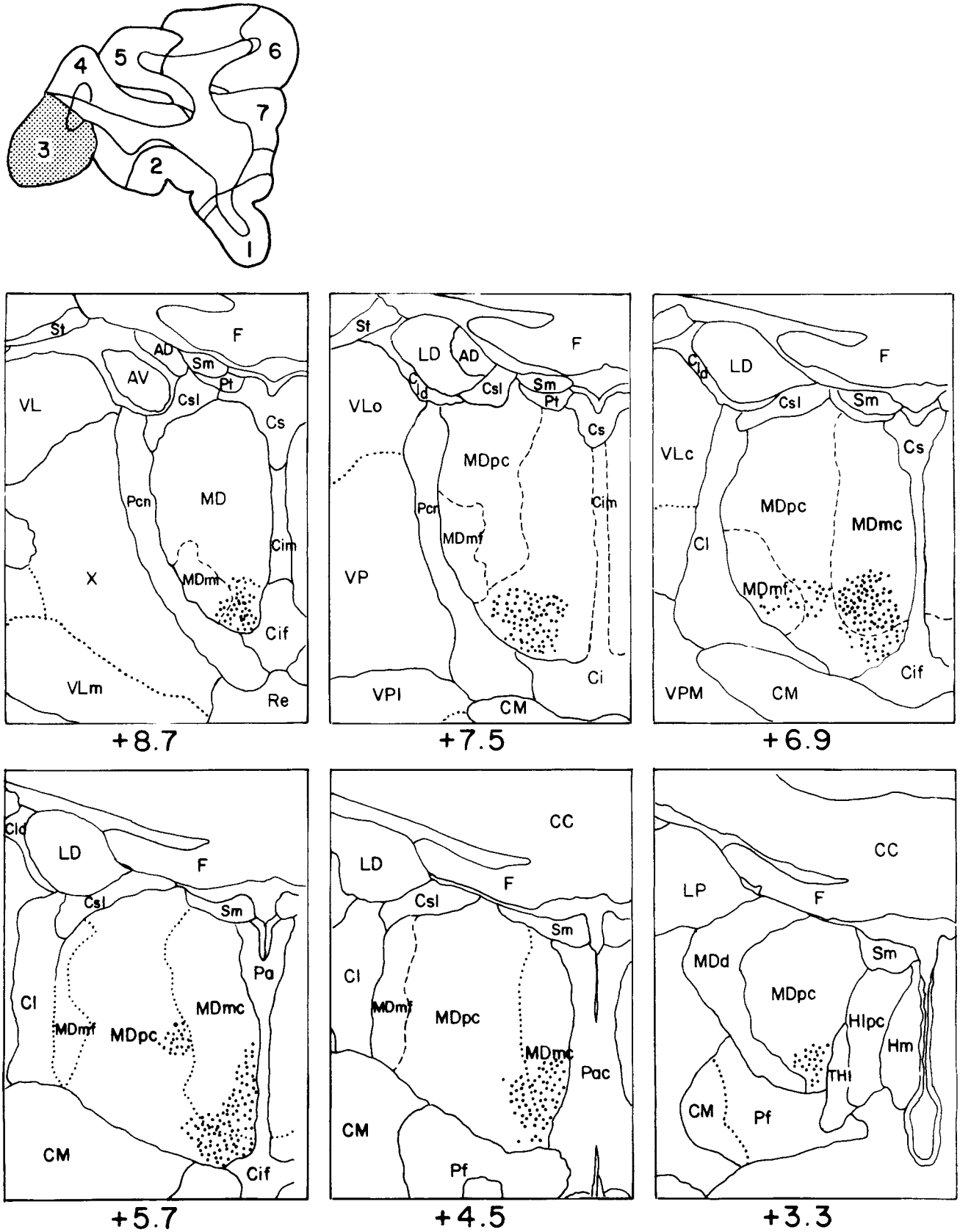


Fig. 6. Diagram illustrating pattern of cell labeling following injection of HRP into the inferior convexity cortex in case #3. Explanation as in Figure 5.

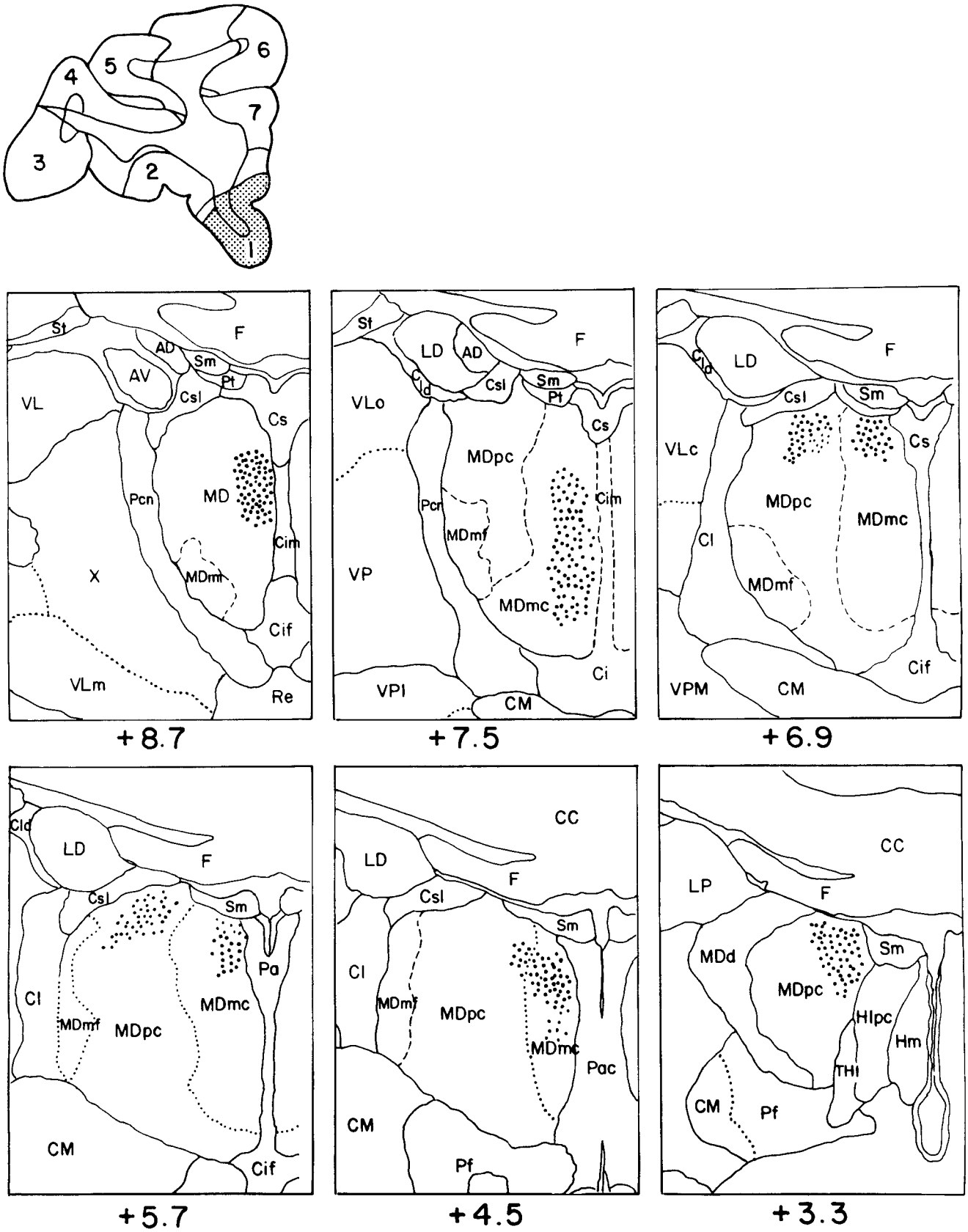


Fig. 7. Pattern of retrograde labeling in the various subdivisions of MD after an HRP injection into the anterior orbital cortex as the frontal pole (case #1).

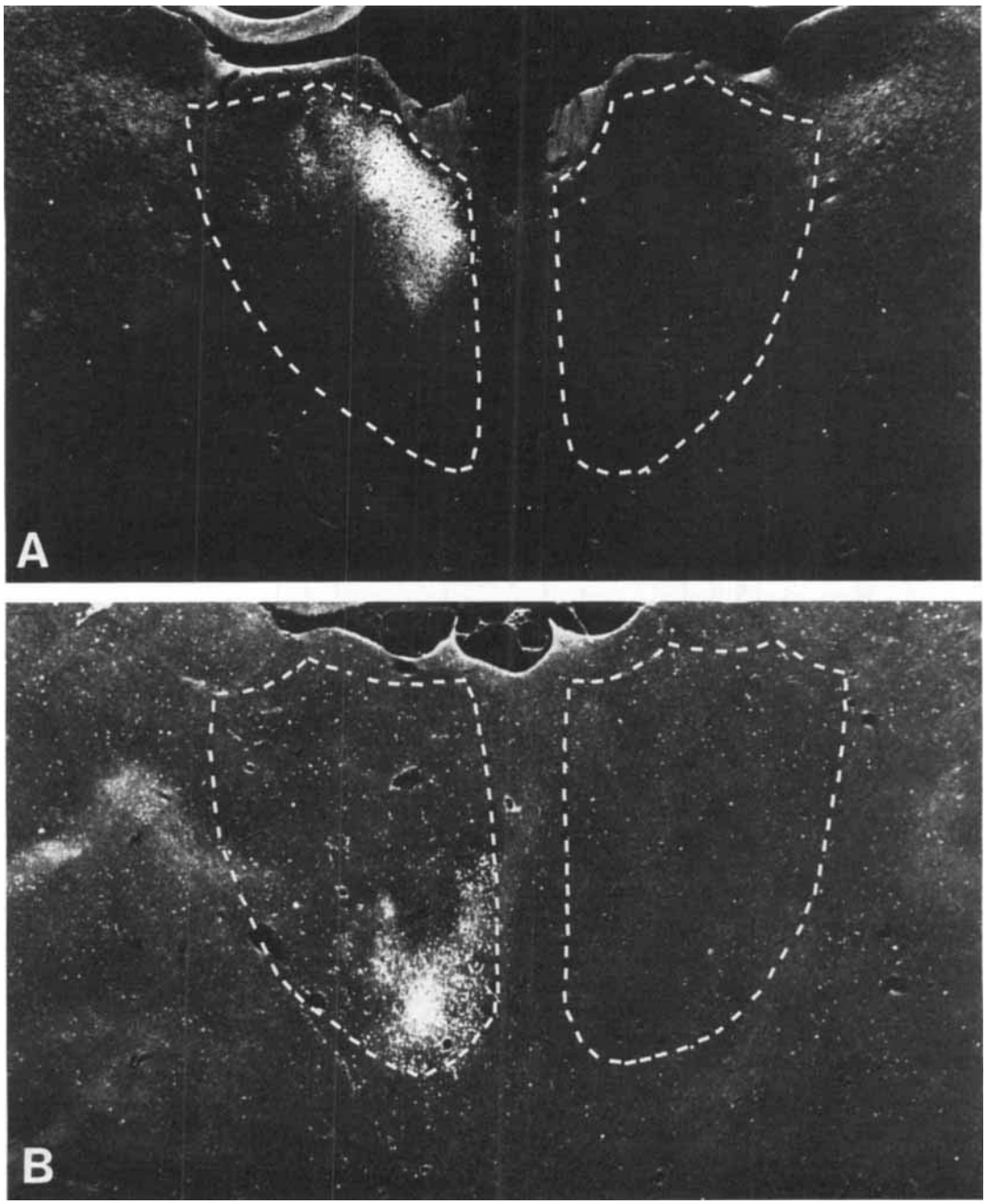


Fig. 8. Darkfield photomicrograph of retrogradely labeled areas in the medial part of MD (MDmc) after injection into the medial orbital (A) and inferior convexity (B) cortex of the prefrontal cortex. Note the distinctly different locations of these two groups of projection neurons.

the posterior thalamus in this case suffered cutting artifacts. However, the MDde was very heavily labeled in the cases with dye injections in the SMA (see below, Fig. 15).

As expected, the most lateral paralamellar division (MDmf of Olszewski) projected selectively to the anterior bank of the arcuate sulcus, in case #8. In this area, which corresponds to the area of the frontal eye field, HRP pellets labeled cells throughout the entire MDmf (Fig. 12B). Only scattered labeled cells were present in this nucleus in cases with injections in the ventral principal sulcus (Fig. 9), inferior convexity (Fig. 7), and supplementary motor cortex (see below), possibly from minor spread of label to the nearest portion of the anterior arcuate sulcus in each of these cases.

The lowest density of labeled cells in the MD was observed in case #7 with an injection of the anterior cingulate gyrus. HRP-filled cells were confined to central portions of the nucleus at its most posterior limit. A moderate number of cells were concentrated in a dorsal position at the boundary between the MDmc and MDpc (Fig. 14). The small number of MD labeled neurons is unlikely to be due to the size of the injected area since in the same case, brainstem nuclei were more heavily labeled than after equivalent

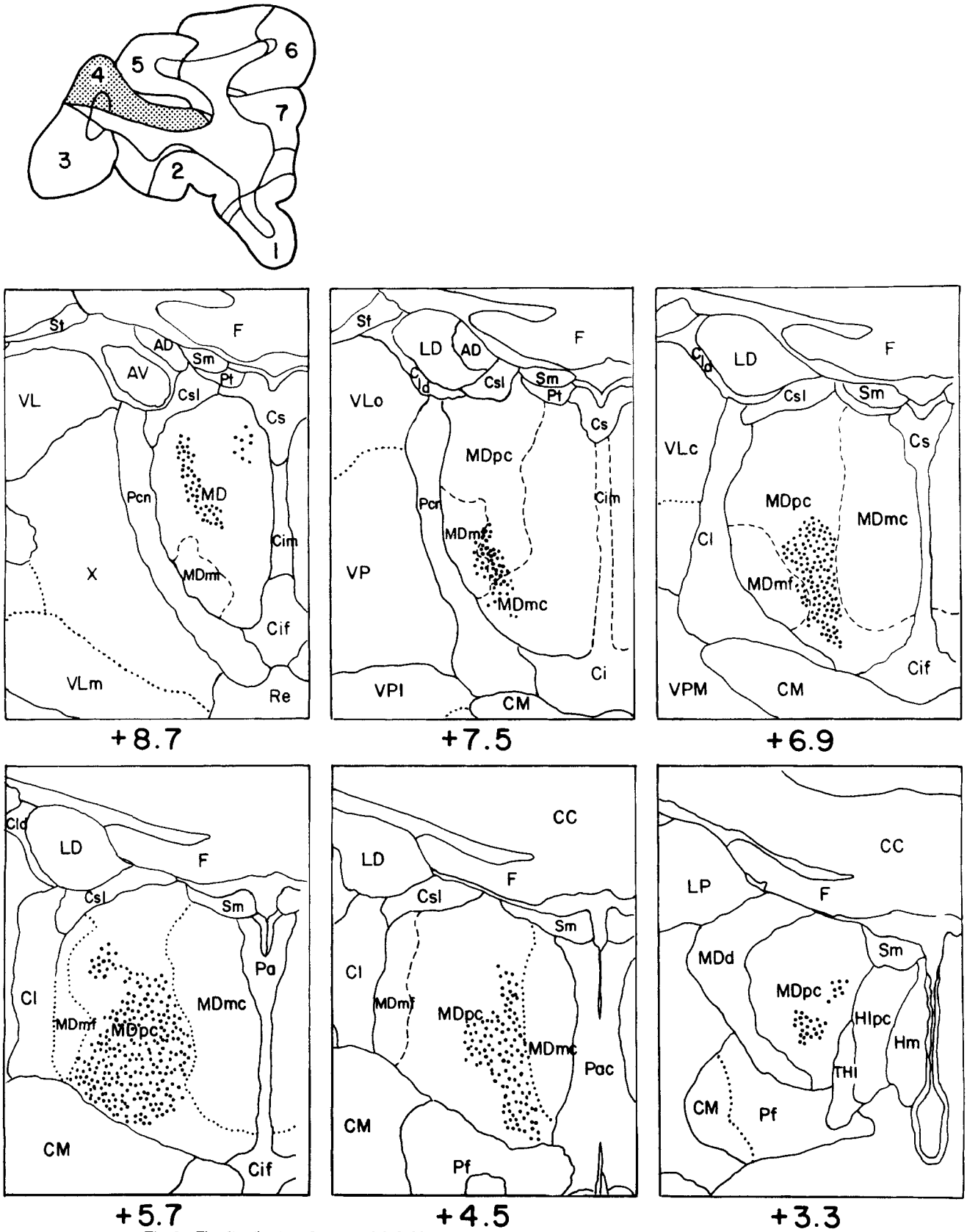


Fig. 9. The distribution of neurons labeled by an injection in the ventral principal sulcus is shown at various levels of MD on standard diagrams. The main source of projections is from the parvicellular moeity of MD at all levels.

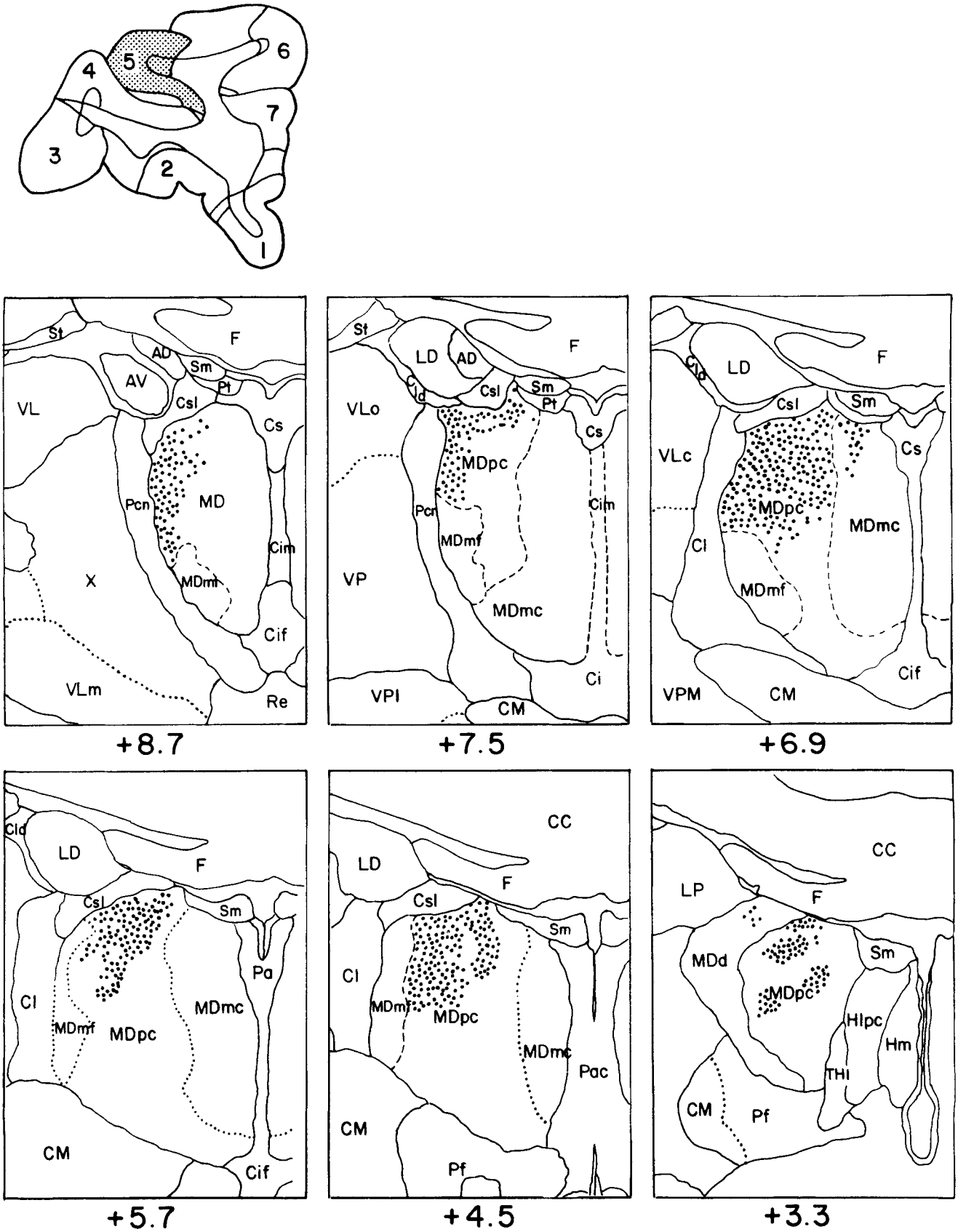


Fig. 10. Pattern of labeled neurons in MD following HRP injections into the dorsal bank of the principal sulcus. In comparison to ventral bank injections, the location of HRP-positive neurons is located preferentially in the dorsal half of the MDpc.

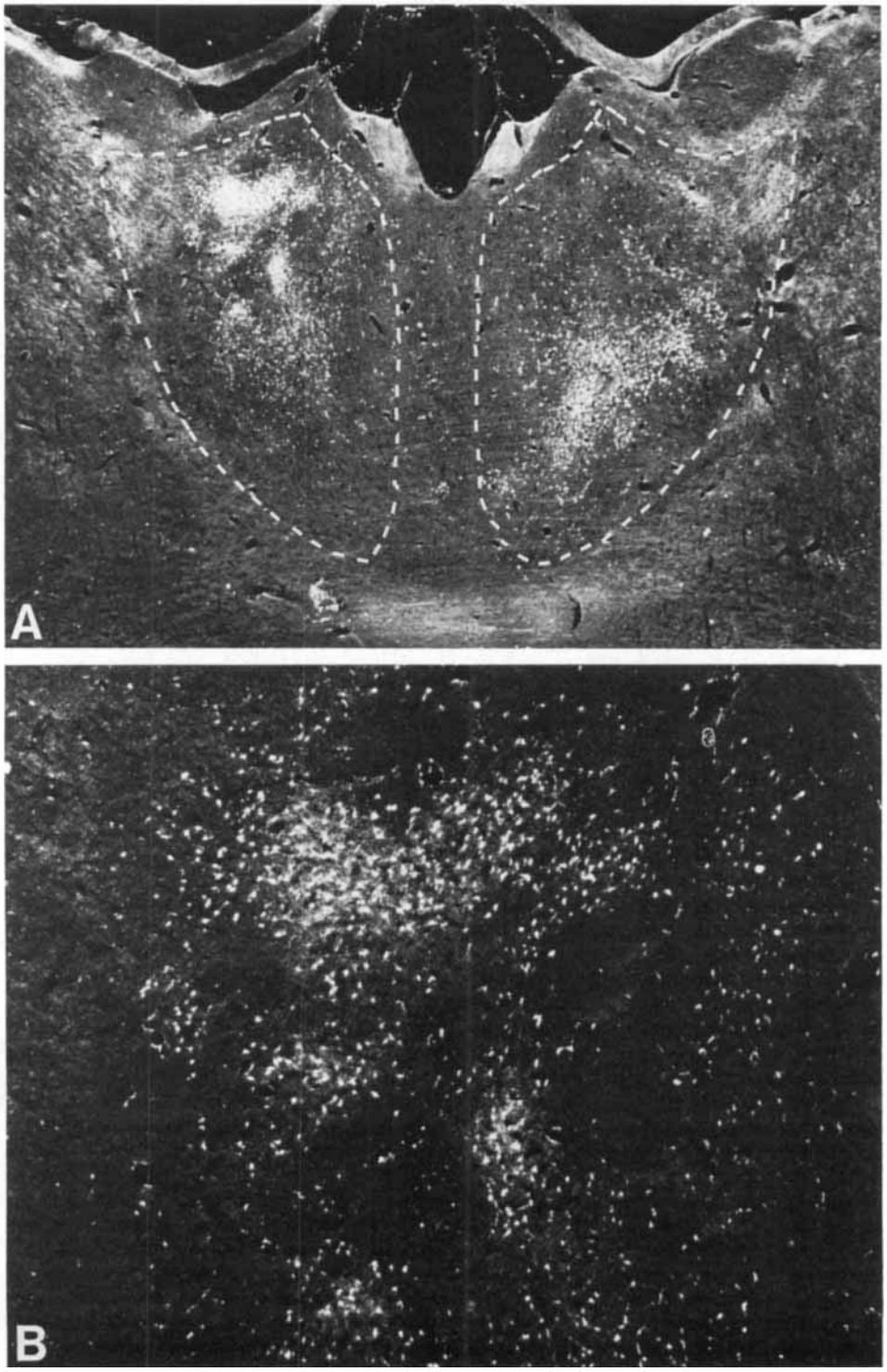


Fig. 11. A. Darkfield photomicrographs illustrating the pattern of labeling found in the dorsal part of MDpc when HRP was injected in the dorsal bank of the left hemisphere and in the ventral part of MDpc when the ventral bank of the principal sulcus was injected in the right hemisphere in the same monkey. Because of the relative absence of heavy anterograde labeling in this case the clustering of retrogradely labeled cells was particularly evident. B. Higher magnification of the area shown in the left MD above to reveal thalamocortical clusters.

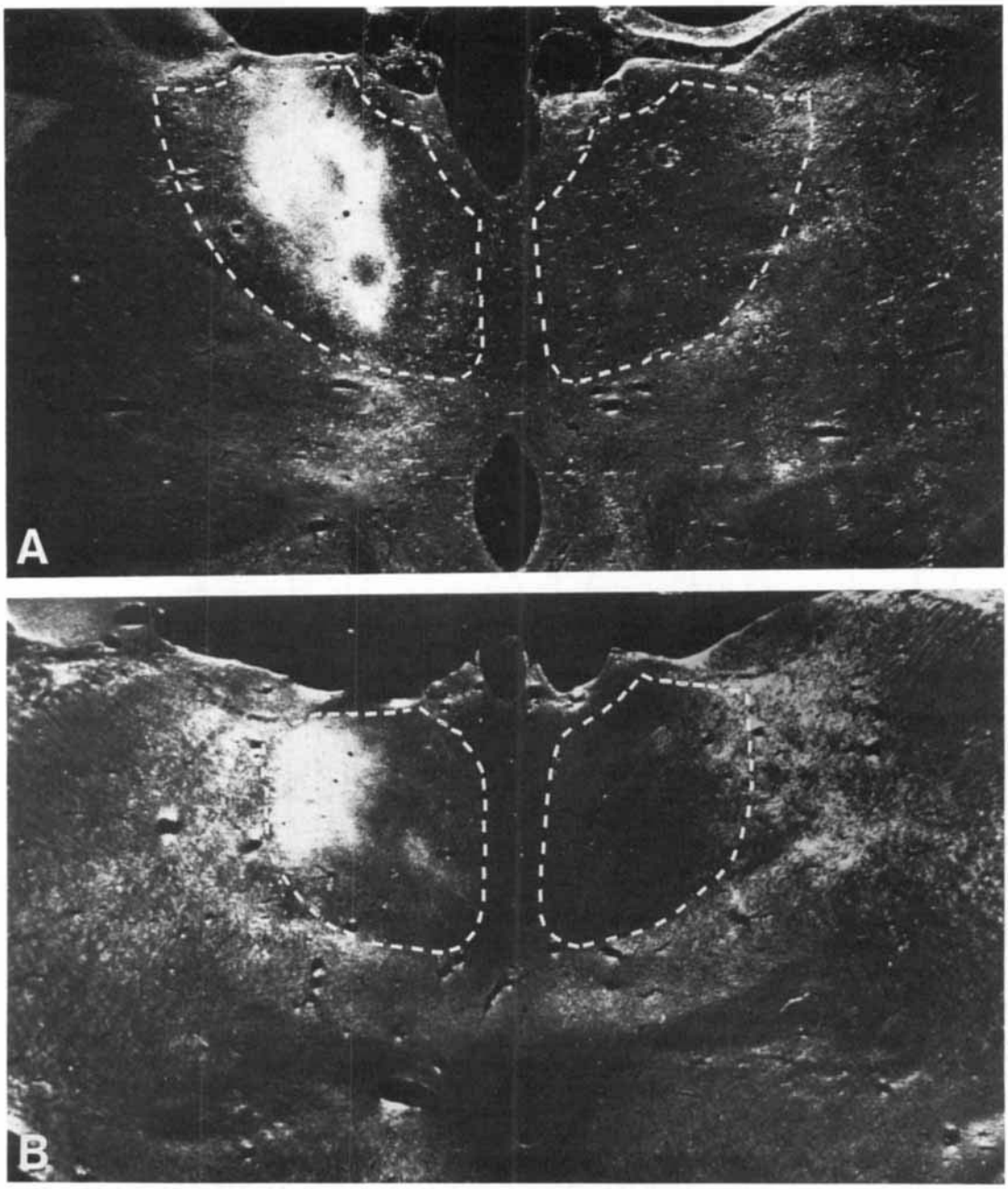


Fig. 12. Darkfield photographs of the MD demonstrating (A) location of combined anterograde and retrograde labeling in MDpc following a large injection of both banks of the principal sulcus and (B) following a large injection of the frontal eye field. Note that the frontal eye field labeling is located more laterally in MD (in MDmf) than is label from the principal sulcus, which is confined to MDpc. Also note the round or elliptical areas of unlabeled cells surrounded by dense fibers and cells labeled from the principal sulcus.

injections in prefrontal areas (Porrino and Goldman-Rakic, '82).

Localization of fluorescent dye injection sites

In all cases, the injection sites spanned a 2–4-mm^2 area consisting of dense extracellular and intracellular labeling, surrounding small lesions caused by the needle tracks. These areas of concentrated dyes were usually themselves surrounded by a halo zone containing densely labeled somata. The degree to which individual penetrations coalesced into an uninterrupted injection zone varied with the placement as well as the type of dye. In case #11, the DY injection sites were confined to the dorsal bank of the principal sulcus, remaining in limited spots on the rim of the sulcus along most of its length (Fig. 9 in Ilinsky et al., '85). The FB orbital injection was roughly coextensive with Walker's area 11. In the opposite hemisphere, FB was limited to the rostral rim of the arcuate sulcus primarily along the superior ramus and central arch of this sulcus, corresponding to the area of the frontal eye field. NY injections

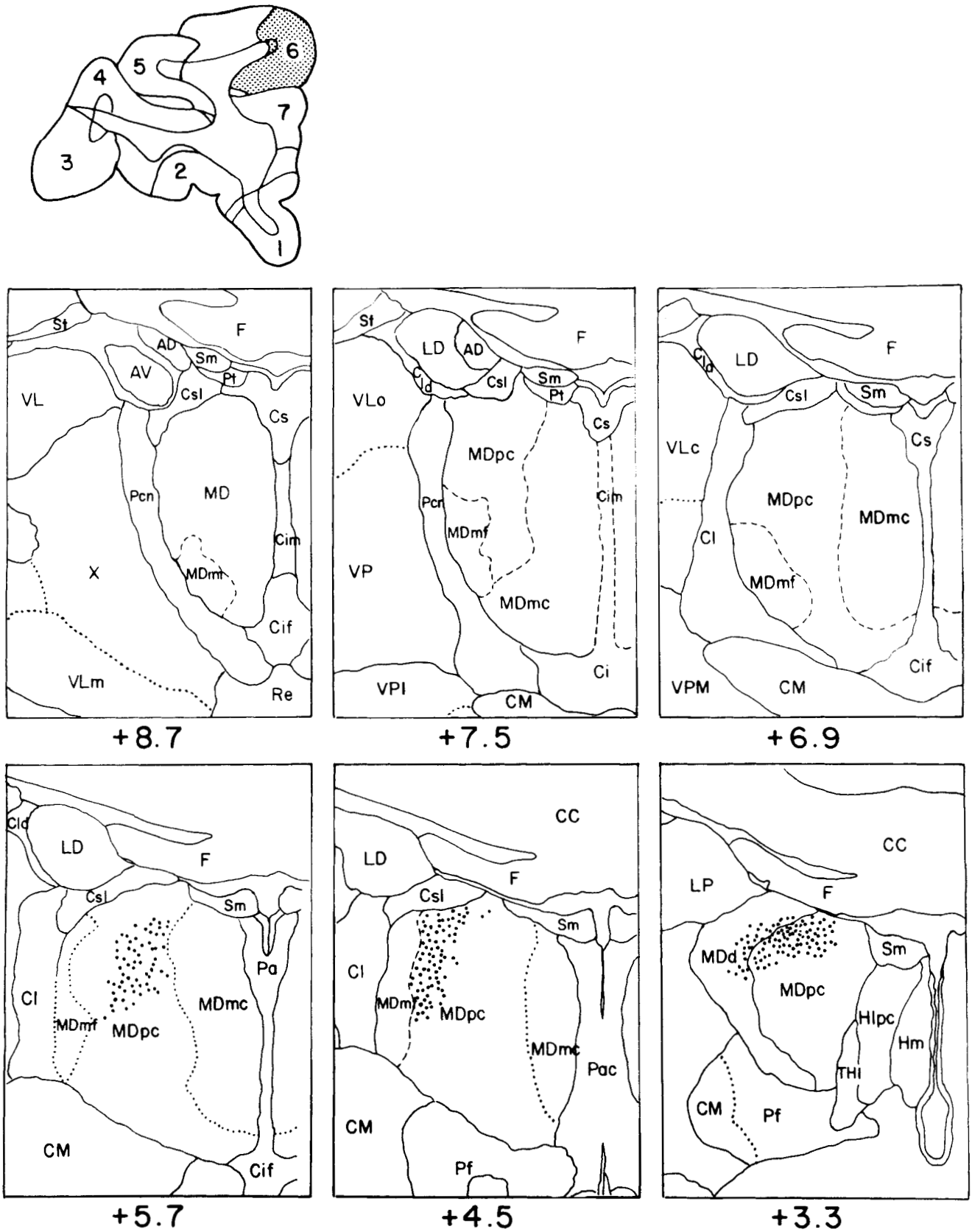


Fig. 13. The pattern of retrograde label in MDpc after an injection of HRP into the dorsomedial cortex. The distribution of retrogradely labeled neurons is skewed more posteriorally compared to most other injections, which labeled MD throughout its anterior-posterior extent.

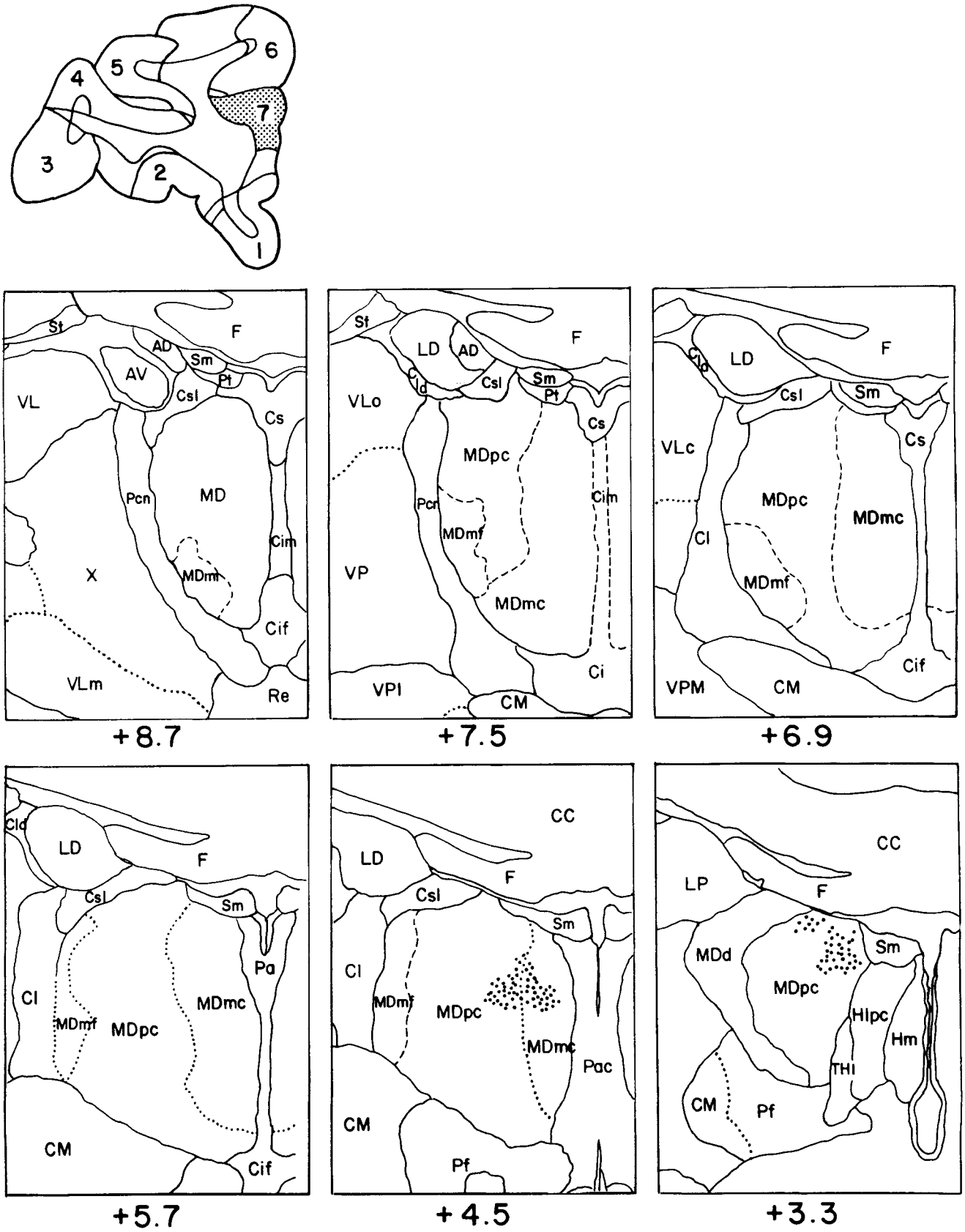


Fig. 14. The distribution of HRP-positive neurons in MD after an injection of the anterior cingulate cortex. The retrogradely labeled cells occupy a restricted posterior zone straddling MDpc and MDmc.

in the ventral bank of the principal sulcus extended along the rim of the sulcus over virtually its entire length.

In cases #12 and #13, injections were made in the principal sulcus, the supplementary motor cortex, and the motor cortex (Fig. 15). In case #12, the PI label was largely confined to the caudal half of the principal sulcus with some spread to the ventral bank anteriorally (Fig. 15). The injection sites in the supplementary motor area and motor cortex were restricted to their intended sites. The anterior limit of the SMA injection was at the approximate point that a perpendicular extension of the superior ramus of the arcuate sulcus would transect the midline and extended as far posterior as the caudal edge of the precentral dimple. The motor cortex injections occupied an irregularly shaped small surface area along the middle third of the precentral gyrus and extended into the anterior bank of the central sulcus. In case #13 with the same three injection targets, the spread of label in the SMA and motor cortex was very similar to the animal just described except that in this case the PI injection into both banks of the principal sulcal cortex spread to the inferior convexity.

Pattern or retrograde transport of fluorescent dyes in MD

The purpose of combining injections of two or three distinct fluorescent tracers in different cytoarchitectonic areas of the same hemisphere was to assess whether single thalamic neurons send collateral axons to more than one cortical area. In all cases, the vast majority of cells were single-labeled and cells labeled by more than one dye were virtually nonexistent. In case #11, in line with findings in the single-labeled case, DY in the dorsal bank of the principal sulcus labeled neurons concentrated in the dorsal MDpc while FB in the orbital cortex labeled neurons primarily in the ventral MDmc with only a scattering of FB-positive cells in other subnuclei such as in the MDmf. In the right hemisphere of the same case, DY in the ventral bank of the principal sulcus labeled neurons in the ventral part of the MDpc and FB in the anterior bank of the arcuate sulcus resulted in a dense concentration of retrogradely labeled cells restricted to the lateral portion of the MDmf throughout its entire anterior-posterior extent. Again, even though virtually every section examined contained both types of labeled neurons, few, if any, were double-labeled.

In cases #12 and #13, with simultaneous injections in the principal sulcus, the SMA, and motor cortex, the MD contained numerous labeled neurons, mostly in the parvicellular moiety but also in the MDmc in the case in which the PI injection covered both dorsolateral and ventral convexity cortex. The disposition of labeled neurons after injections of FB into the SMA were found mainly in the posterior part of the MDpc and MDde and did not overlap the PI-positive cells projecting to the principal sulcus (Fig. 15). No FB-labeled neurons were observed in the MDmc, and only a very few were observed in the MDmf. Consistent with the report of Schell and Strick ('84), the MD was found to contain some labeled cells after injections into the motor cortex (D–F, Fig. 15). These were found only in the very most posterior and lateral parts of the MDpc and almost appeared to be dorsal extensions of cell populations labeled in the nuclei centralis lateralis (CL) and centre medianum (CM). Again, although every section examined and/or charted on the X-Y plotter contained numerous PI- and FB-labeled cells, none were double-labeled.

Other thalamic projections to prefrontal cortex

In all cases with injections in the prefrontal cortex, HRP-positive cells were present in the anterior (AV and AM) and/or ventral anterior (VA) nuclei, in addition to the MD (Figs. 16, 18A). The AV-AM complex contained a medial to lateral representation of neurons projecting to the dorsal principal sulcus, the ventral principal sulcus, and the inferior convexity, respectively (Fig. 16). In the VA proper, the most substantial projection was to the dorsomedial convexity. Smaller projections to the other prefrontal areas were topographically organized in the VAmc and, in coronal section, the entire VA projection had a circumferential organization such that for cases #1-7, the location of labeled cells changed in a counterclockwise direction (Fig. 16).

Among the midline and intralaminar nuclei, the paracentral and densocellular nuclei contained labeled cells in all cases as did the centre median and parafascicular nuclei and nucleus limitans. With the notable exception of the anterior cingulate case, HRP-positive cells were observed in every animal in the posterior thalamus where they were most concentrated in the medial pulvinar (Figs. 17, 18B). The principal sulcus had the largest relative representation in the medial pulvinar (Fig. 18). Again, topographic organization was circumferential but in an opposite direction to that of the VA (Fig. 16).

DISCUSSION

Topography of MD-prefrontal projection

Our present understanding of the organization of the MD in primates is based for the most part on experimental studies in macaque monkeys that were carried out in the middle of the present century with the method of retrograde chromatolysis (e.g., Clark and Boggen, '35; Walker, '40a; Bonin and Green, '49; Pribram et al., '53) and on comparable postmortem observations on the thalamus of patients that had undergone prefrontal lobotomy (Freeman and Watts, '47, '48; McLardy, '50; Meyer et al., '47; Angevine, et al., '64). The general conclusions from these early studies was that the mediodorsal nucleus projects solely to the prefrontal cortex and the prefrontal cortex, in turn, is the sole projection target of the mediodorsal nucleus. Further, a rather strict mediolateral organization of the MD was recognized in which lateral moieties of the nucleus projected to the dorsal convexity cortex while the medial subdivision projected to the ventral surface of the frontal lobe (Walker '40b, Mettler, '47; Pribram et al., '53; Akert, '64). The present results using retrograde transport are in essential agreement with this major division of the MD. However, the use of more sensitive tracing methods and placement of tracers into distinct cytoarchitectonic subdivisions of prefrontal cortex in the present study has provided a new level of precision in the topographic map. As shown in a summary diagram representing an intermediate anteroposterior level through the MD, the thalamocortical system of connectivity has a circumferential organization (Fig. 19). In cross section through the nucleus, the dorsomedial cortex and dorsal principal sulcus is represented predominantly in the lateral and dorsal half of the

Fig. 15. Tricolored overlays that illustrate the independence of projections from the thalamus to the principal sulcus (PI, red), the anterior supplementary motor cortex (FB, blue), and the hand and arm areas of the primary motor cortex (DY, black). These data were charted with a semicomputerized X-Y plotter so that every dot represents a single-labeled neuron. No double- or triple-labeled neurons were found. In this figure and in Fig. 17, the densocellular subnucleus of MD is labeled MDdc; all other abbreviations are as in other figures.

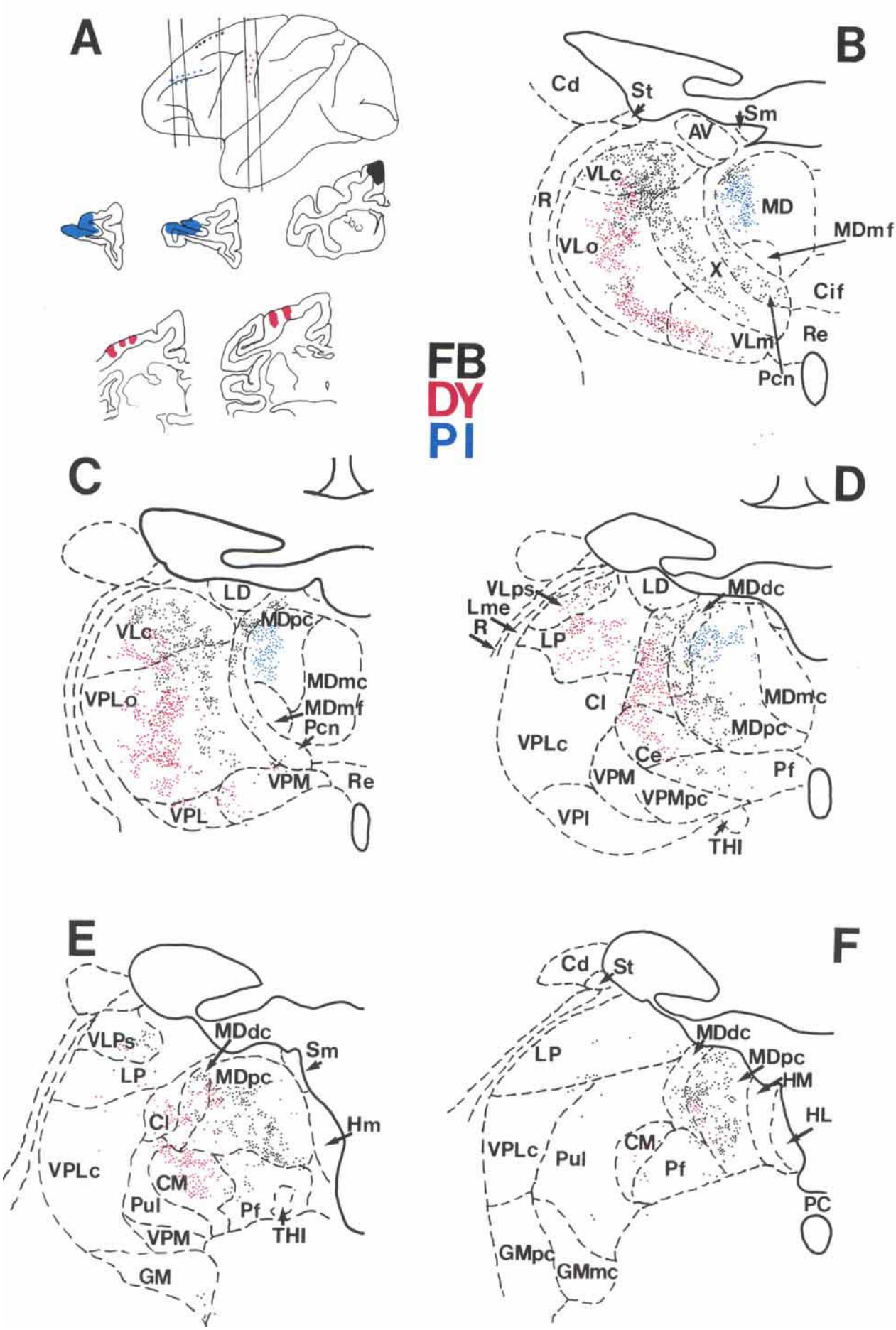
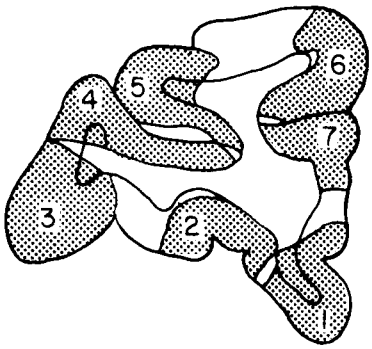
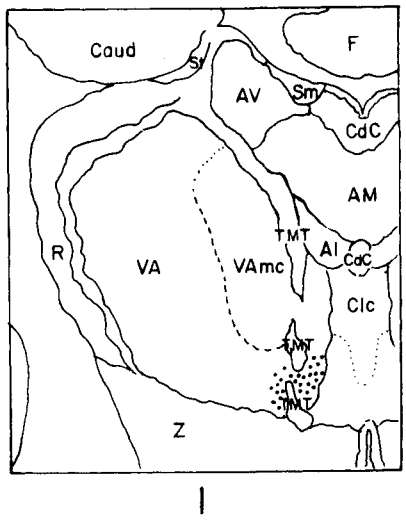
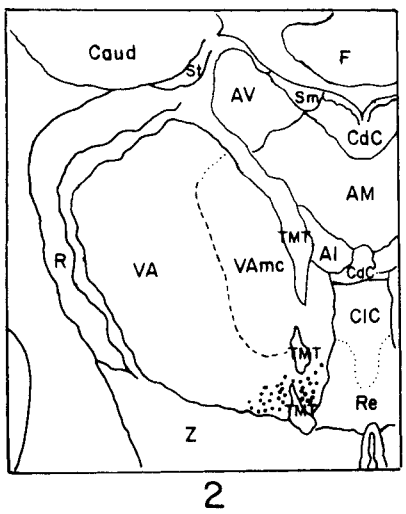
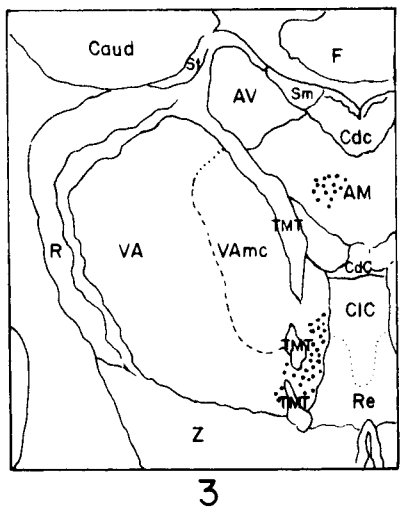

A
B
Cd
St
Sm
AV
VLc
R
MD
MDmf
VLo
X
Cif
VLm
Re
Pcn
FB
DY
PI
C
LD
MDpc
VLc
MDmc
VPLo
MDmf
Pcn
VPM
Re
VPL
D
VLps
LD
MDdc
Lme
R
LP
CI
MDmc
MDpc
VPLc
Ce
Pf
VPM
VPMpc
VPI
THI
E
VLPs
MDdc
Sm
LP
MDpc
CI
Hm
VPLc
CM
Pul
Pf
VPM
THI
GM
F
Cd
St
MDdc
LP
MDpc
HM
HL
VPLc
Pul
CM
Pf
PC
GMpc
GMmc

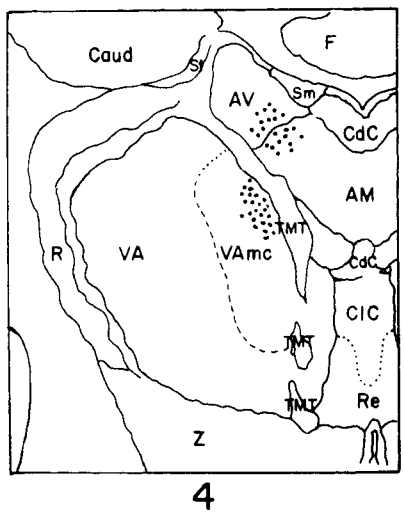
Figure 15

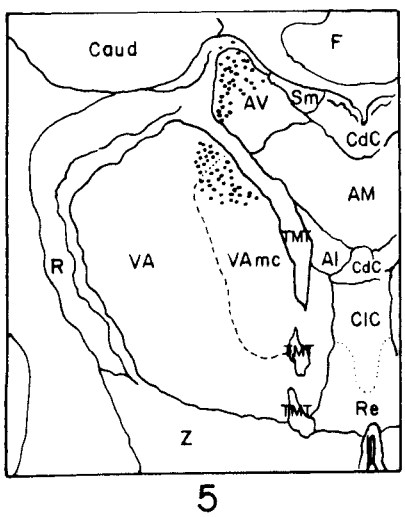


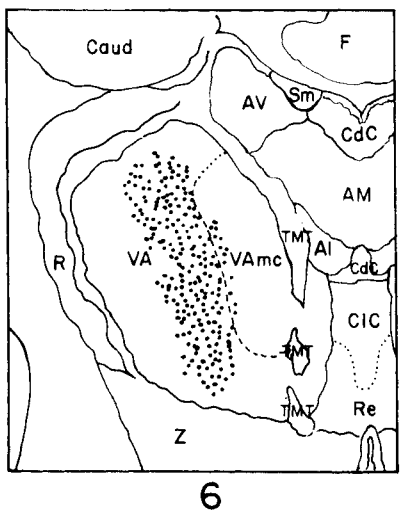












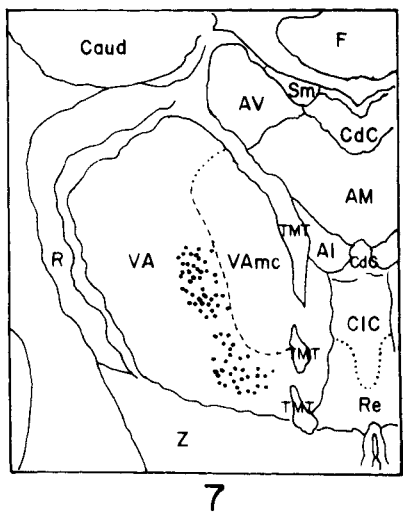


Fig. 16. A composite diagram illustrating seven selected injections sites and the topographic order of projections from the anteroventral (AV), the anteromedial (AM), and the ventral (VA) nuclei of the thalamus at a single A-P level through the thalamus. Note that the largest projection from VA is to the dorsomedial cortex. The numbers correspond to injections sites in the drawing and are the same as the case numbers used in the text.

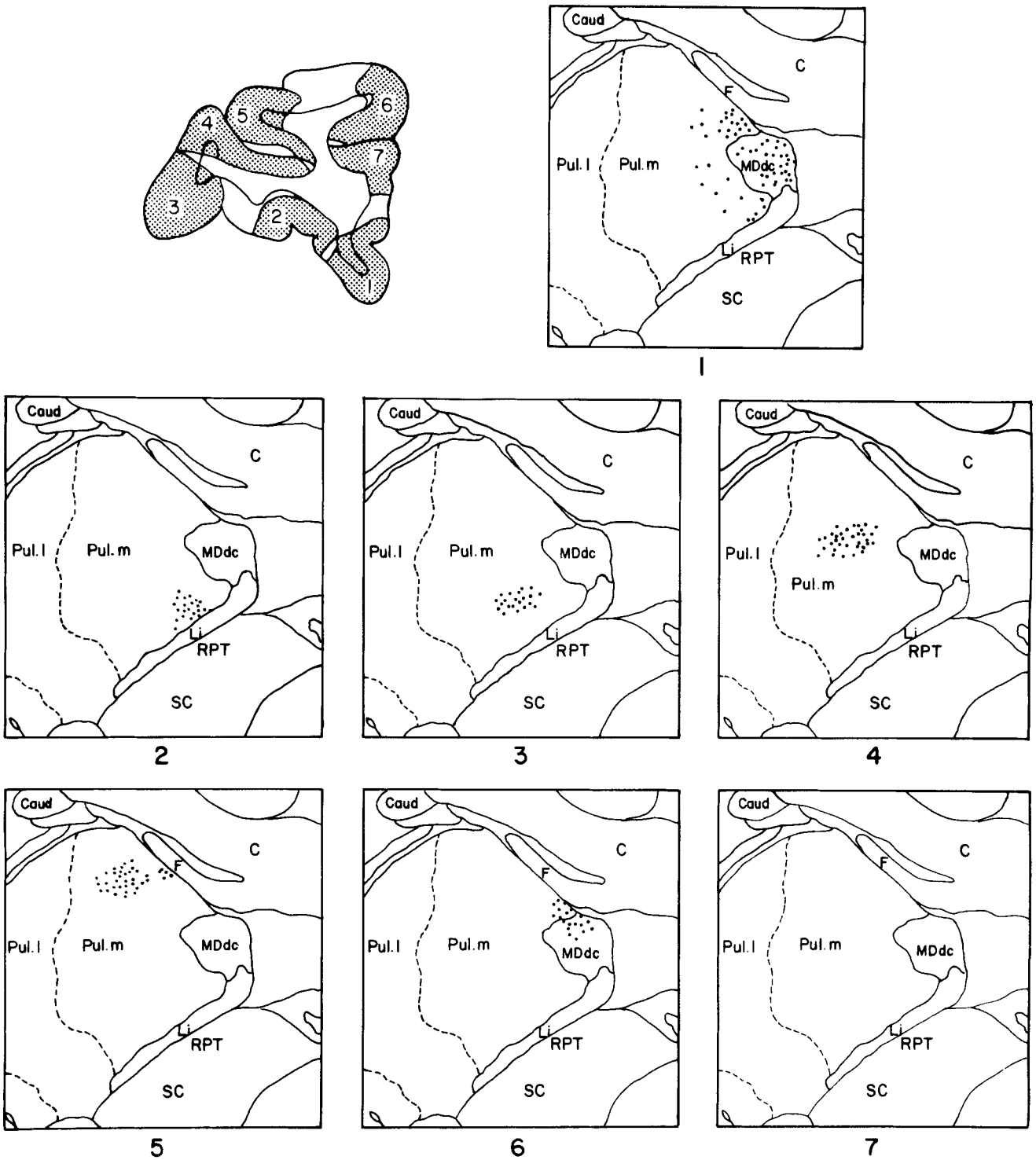


Fig. 17. Medial pulvinar projections to seven selected areas of the prefrontal cortex. The dorsal and orbital areas appear to receive the heaviest projections whereas the medial cortical areas are poorly represented (dorsomedial, case #6) or lacking in representation (cingulate, case #7).

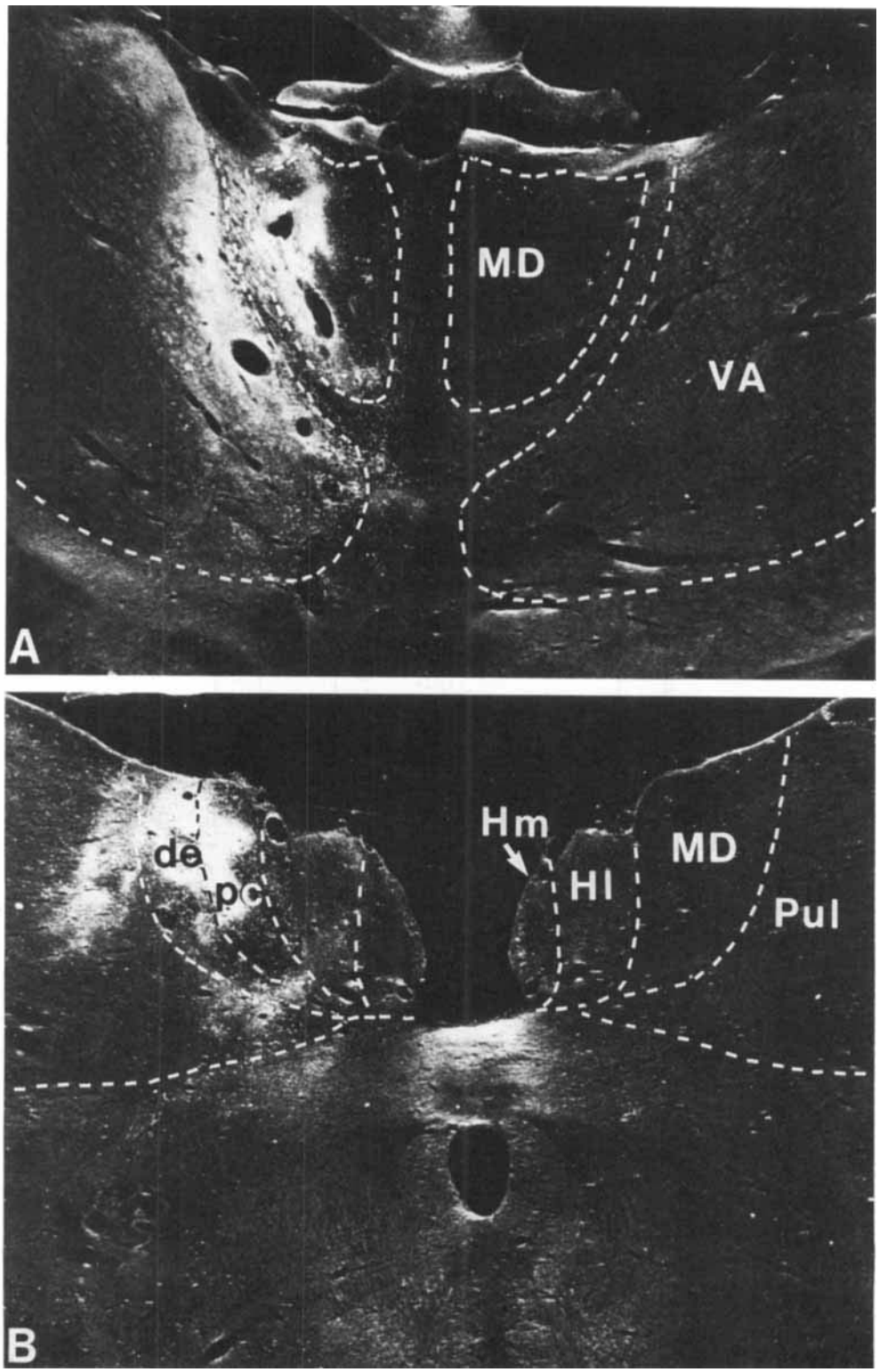


Fig. 18. Photomicrographs through the VA (A) and pulvinar (B) documenting the size and location of thalamocortical projections to the principal sulcal cortex from these thalamic nuclei. The MD labeling in the same monkey is shown in Figure 12A.

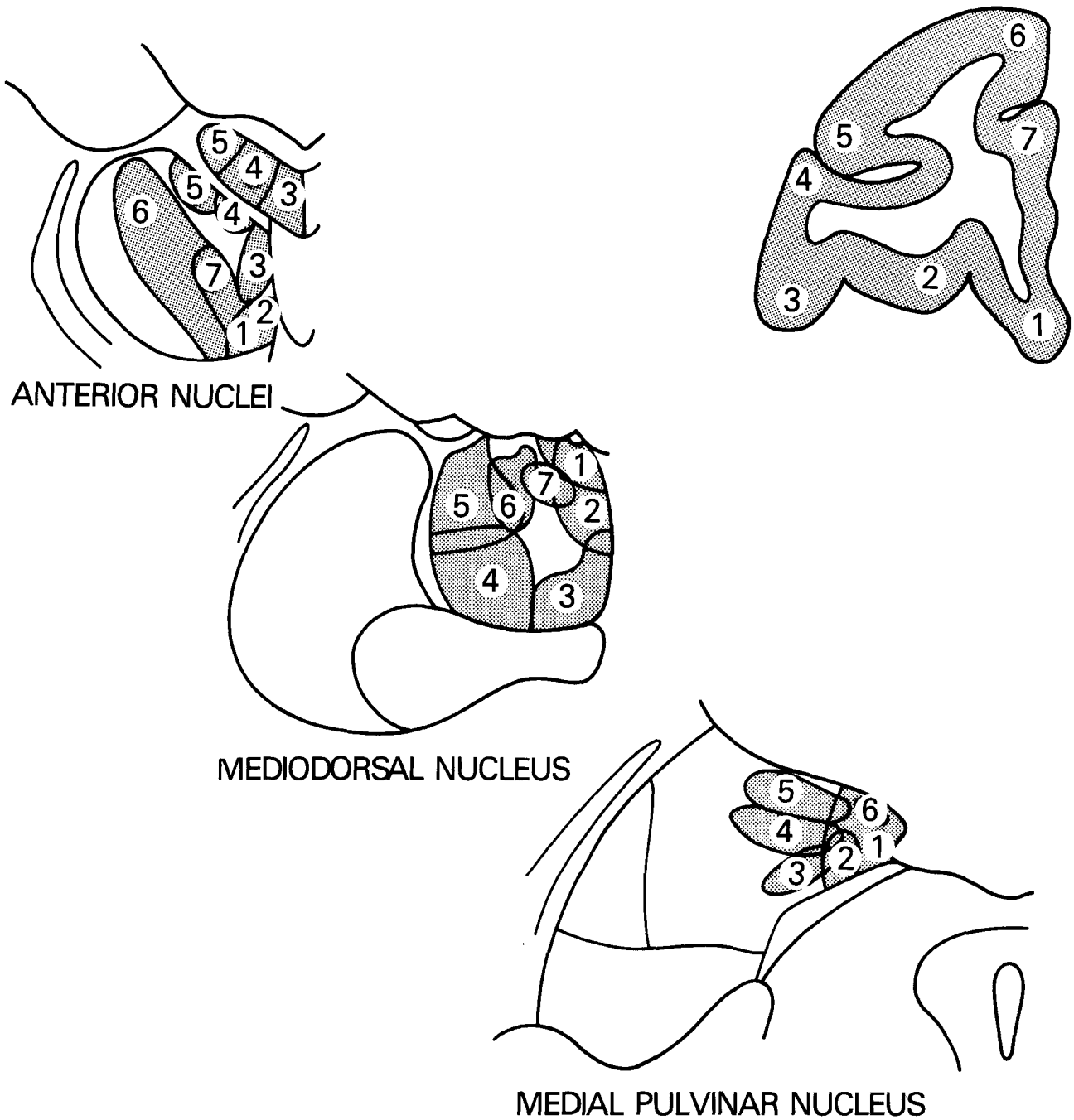


Fig. 19. Summary diagram of topographic relationships between VA (upper left), MD (middle), and pulvinar (lower left) and selected cytoarchitectonic subdivisions of prefrontal cortex. It is interesting that all three nuclei have a circumferential organization, and unexplained that this organization is counterclockwise for the VA and clockwise for MD and medial pulvinar. This diagram shows clearly that each subdivision of these major thalamic nuclei projects to one and only one cytoarchitectonic area of cortex such that each of the cortical areas receives a unique thalamic input.

parvicellular subnucleus while the ventral PS is represented in ventral MDpc. The inferior convexity extending on the lateral portion of the ventral surface of the frontal lobe is innervated by neurons concentrated in the ventral half of the MDmc, while the medial cortical areas on the ventral surface receive thalamic innervation from the dorsal half of the MDmc. The cingulate thalamocortical representation is located dorsally, wedged between that of the orbital and dorsomedial cortices. From this analysis it may be concluded that the thalamic innervation of association and limbic cortex is topographically organized in an area-to-area and presumably a finer-grained, perhaps point-to-point, representation analagous to that described in the sensory systems.

Multiple cortical targets of MD

In agreement with previous studies, the present findings show that MD neurons project to cortical targets outside the formal boundaries of the prefrontal granular cortex,

most notably the premotor (Schell and Strick, '84; Ilinsky et al., '85) but also the primary motor (Schell and Strick, '84) and anterior cingulate (Vogt et al., '79; Baleydier and Mauguiere, '80) cortical areas. Most of these nonprefrontal projections are relatively sparse. For example, relatively few neurons were labeled in the MD by injections placed in anterior cingulate cortex and these were confined to a shorter anterior-posterior expanse of the MD, as was the case in earlier studies of anterior and posterior cingulate areas (Vogt et al., '79; Baleydier and Mauguiere, '80). Likewise the projection to motor cortex is from a very small number of cells situated in the most posterior part of the MDde. In contrast, and in agreement with other recent findings (Schell and Strick, '84; Ilinsky et al., '85), the SMA, like the principal sulcus, has a substantial innervation from neurons concentrated in the caudal part of the MDpc and also from the MDde. It may be of interest that damage to the posterior part of the MD including MDde has been particularly associated with memory loss both in patients with Wernicke-Korsakoff disease (Victor et al., '71) and in monkeys with experimentally induced lesions of the MD (Isseroff et al., '82).

Multiple thalamic inputs to prefrontal cortex

In agreement with many previous reports in monkey (e.g., Bos and Benevento, '75; Kievit and Kuypers, '77; Trojanowski and Jacobson, '76; Baleydier and Mauguiere, '80) and other mammals (Beckstead, '76; Krettek and Price, '77; Benjamin et al., '78), prefrontal granular cortex receives major afferents from a number of thalamic nuclei other than the MD, including the anterior group, VA, and medial pulvinar. The present findings extend these earlier reports by drawing attention to the fact that thalamic nuclei other than the MD issue topographically organized projections to widespread areas of the prefrontal cortex.

The multiple, topographically organized thalamic inputs to prefrontal cortex seem to fit fairly well the scheme proposed by Kievit and Kuypers ('77) of longitudinally extensive bands of thalamocortical projections that span nuclear boundaries throughout the thalamus. It is important to remember, however, that this organization is descriptive only for broad expanses of cortex and any given cytoarchitectonic subdivision of cortex may not be represented by a continuous band of cells throughout the entire length of the thalamus. For example, in the case of the anterior cingulate injection, labeled cells were present in the VApc and posterior MD but not in the anterior MD, which lay in between these two locations. Similarly, projections to the medial orbital cortex were present in the VA, anterior MDmc, and medial pulvinar but not in the posterior MDmc. Thus, in both instances, there is a gap in the continuity of A-P representation across nuclear borders.

The nuclear and subnuclear compartmentalization of thalamocortical afferents described here appears to provide a mechanism for the channeling of distinct information arriving at the thalamus from lower centers (see also Velayos and Reinoso-Suarez, '82). Thus, the primate MDmc receives a major innervation from the amygdala (Porrino et al., '81) while the MDmf and MDpc are targets of both the superior colliculus (Benevento and Fallon, '75; Harting et al., '80) and medial substantia nigra (Ilinsky et al., '85). The VAmc also connects the medial substantia nigra with the prefrontal cortex (Ilinsky et al., '85). The connections of the anteroventral and anteromedial nuclei with the prefrontal cortex are noteworthy because of the latter's traditional association with the hippocampus and limbic cortex (Domesick, '72; Niimi, '78). Finally, the medial pulvinar receives sparse projections from the retina (Itaya and Van Hoesen, '83) and more substantial input from the deep layers of the colliculus (Benevento and Fallon '75) as well as from diverse areas of limbic, sensory, and sensory association cortex (Benevento and Fallon, '75; Baleydier and Mauguiere, '85). It is thus a potential thalamic source of visuomotor information to prefrontal regions. Altogether, these findings indicate that the intrinsic, "association" subnuclei of the thalamus are organized as a number of parallel pathways connecting brainstem, basal ganglia, limbic, and sensorimotor centers with the anterior cortex of the frontal lobe.

Implications for comparative studies

The multiplicity of topographically organized projections from thalamic nuclei to frontal granular cortex, as well as to the nongranular cortical targets of the MD, leads to the conclusion that each discrete cytoarchitectonic subdivision of the primate frontal cortex receives a unique pattern of thalamic connections that can be distinguished from all others not only in terms of topographic location, but also in terms of size and number. A similar conclusion was reached earlier in careful mapping of the MD projection in the rat (Kreitek and Price, '77) and rabbit (Benjamin et al., '78). With regard to areal distribution within the primate thalamus, it is of interest that the principal sulcus is represented in the entire lateral half of the MD (MDpc), while all the remaining areas composing the ventral and medial surfaces of the prefrontal cortex receive their entire MD innervation from the MDmc. Likewise, in the pulvinar, the largest representation appears to be the principal sulcus (cases #4,5) relative to other areas (Fig. 19). This may be contrasted to the topography of projections from the VA where the principal sulcus has only a small representation in the VAmc relative to that of the dorsomedial cortex, which originates from a quite large territory of this nucleus (Fig. 19). Thus, the precise relationships between various specific nuclear subdivisions of the dorsal thalamus and specific cytoarchitectonic subdivisions of the prefrontal cortex provide a basis for defining the prefrontal cortex by its connections to the thalamus in the tradition of Rose and Woolsey ('48), although with a greatly increased degree of anatomical detail. Based on the pattern of results obtained in the present study, it would now be possible, for example, to define principal sulcal cortex (Walker's area 46) as that cortex which receives innervation from the dorsal MDpc, the VAmc, and the medial pulvinar. More generally, granular prefrontal areas may all have in common a nontrivial input from the medial VA, MD, and medial pulvinar, a pattern of innervation that is shared by neither the anterior cingulate, the supplementary motor, nor the motor cortex nor other areas such as the posterior cingulate cortex (Baleydier and Mauguiere, '80; Schell and Streck, '84; Vogt et al., '79).

The implications of the present findings for comparative studies is that the establishment of homologies between different species will require a greater specification of both the cortical and thalamic subdivisions being compared. As pointed out by Markowitsch and Pritzel ('79), definition of prefrontal cortex in various species has been based on the presence of an MD innervation, generally without consideration of different MD subnuclei or thalamic projections in addition to those arising from the MD. These classifica-

tions may need to be reconsidered in light of the present and previous findings that MD afferents can target cingulate and premotor as well as prefrontal cortex.

Intrinsic organization of MD

Following cortical injections, neurons in the MD tended to be labeled in cell aggregates, reminiscent of the cytoarchitectonic and anatomical parcellation in the neostriatum (Goldman-Rakic, '82; Selemon and Goldman-Rakic, '85) and prefrontal cortex (Schwartz and Goldman-Rakic, '84). Moreover, the results of double- and triple-labeling experiments provide the most direct evidence that each projection from the MD originates in separate and distinct clusters of neurons and that little if any collateralization exists among thalamic neurons that innervate different cytoarchitectonic areas of frontal neocortex. A possible exception is the apparent common location in the dorsal MDpc of projections to Walker's areas 46 and 9. This could be due to some overlap in injection sites, to imprecision in matching between sections from different animals, or to genuine thalamic collateralization. This specific pair of cortical areas was unfortunately not included in our fluorescent dye experiments and thus the issue of collateralization of their thalamic input needs further study. However, the most parsimonious prediction for such an experiment would be that neurons projecting to areas 46 and 9 will exhibit topographic overlap but not collateralization. Segregation of projections seems to be a general rule governing the organization of thalamocortical connectivity in virtually all areas of the cortex that have been studied to date (e.g., Jones, '83; Ilinsky et al., '85). However, we cannot be sure that some thalamic neurons might not have widespread collaterals perhaps even to different lobes. An explanation still is wanting for the fact that there is little detectable retrograde degeneration in the medial pulvinar, for example, following large prefrontal cortex lesions (e.g., Walker, '40b; Akert, '64; Goldman, '71).

The clustered configuration of thalamocortical neurons is related to the finding of a certain degree of "cross-innervation" between major nuclear subdivisions of the MD and a given cortical subdivision. For example, following both HRP and fluorescent dye injections in the dorsal bank of the principal sulcus (case #5), we found some labeled cells in the MDmc even though the MDpc was the principal source of the thalamic projection to this cortical area (see also Jacobson et al., '76). We cannot rule out that some of this labeling was due to spread of label between adjacent cortical areas, e.g., to the frontal pole or inferior convexity. Alternatively, it is possible that some of the "displaced" clusters of labeled cells could be filling in the "holes" left in the main line projection. Possibly there are clusters of MDpc cells within the boundary of the MDmc, just as there are "fingers" of the VAmc intruding within the VA proper (e.g., Olszewski, '52; Ilinsky et al., '85) that would be revealed by more detailed cytoarchitectonic study. Recent findings that the projections of the medial substantia nigra (Ilinsky et al., '85) and amygdala (Aggleton and Mishkin, '84) terminate in small dense patches in the MDmc and/or MDpc indicate that cellular groups in the mediodorsal nucleus can be differentiated by their inputs as well as their atypical pattern of cortical projection. Thus, the labeled and unlabeled cellular clusters and "holes" observed in the present study are not likely to be artifacts of incomplete target labeling or spread of label between adjacent cortical territories. Rather, they may be further expressions of the high degree of compartmentalization that characterizes the organization of connections in the primate brain (see Goldman-Rakic, '84). Possibly cell clusters in MD innervate particular columns of cortical neurons much as layers of the lateral geniculate nucleus are preferentially related to ocular dominance columns.

ACKNOWLEDGMENTS

This work was supported by MH 00298 and MH 38546.

LITERATURE CITED

Aggelton, J.P., and M. Mishkin (1984) Projections of the amygdala to the thalamus in cynomolgus monkey. J. Comp. Neurol. *222*:56–68.

Akert, K. (1964) Comparative anatomy of the frontal cortex and thalamocortical connections. In: The Frontal Granular Cortex and Behavior. J.M. Warren and K. Akert (eds): New York: McGraw-Hill, pp. 372–396.

Angevine, J.B., S. Locke, and P.I. Yakovlev (1964) Limbic nuclei of thalamus and connections of limbic cortex. IV. Thalamocortical projection of the magnocellular medial dorsal nucleus in man. Arch. Neurol. *10*:165–180.

Baleydier, C., and F. Mauguiere (1980) The duality of the cingulate gyrus in monkey; neuroanatomical study and functional hypothesis. Brain *103*:525–554.

Baleydier, C., and F. Mauguiere (1985) Anatomical evidence for medial pulvinar connections with the posterior cingulate cortex, the retrosplenial area, and the posterior parahippocampal gyrus in monkeys. J. Comp. Neurol. *232*:219–228.

Beckstead, R.M. (1976) Convergent thalamic and mesencephalic projections to the anterior medial cortex in the rat. J. Comp. Neurol. *166*:403–416.

Benevento, L.A., and J.H. Fallon (1975) The ascending projections of the superior colliculus in the rhesus monkey (Macaca mulatta). J. Comp. Neurol. *160*:339–362.

Benjamin, R.M., J.C. Jackson, and G.T. Golden (1978) Cortical projections of the thalamic mediodorsal nucleus in the rat. Brain Res. *141*:251–265.

Bonin, von G., and J.R. Green (1949) Connections between orbital cortex and diencephalon in the macaque. J. Comp. Neurol. *90*:243–254.

Bos, J., and L.A. Benevento (1975) Projections of the medial pulvinar to orbital cortex and frontal eye fields in the rhesus monkey. Exp. Neurol. *49*:487–496.

Clark, W.E. LeG., and R.H. Boggon (1935) The thalamic connections of the parietal and frontal lobes of the brain in the monkey. Philos. Trans. R. Soc. Lond. [Biol.] *224*:313–359.

Domesick, V.B. (1972) Thalamic relations of the medial cortex in the rat. Brain Behav. Evol. *6*:457–487.

Filimonov, I.N. (1949) Cortical cytoarchitecture—general concepts. Classification of the architectonic formations. In: Cytoarchitecture of the Cerebral Cortex in Man. S.A. Sarkisov, I.N.F. Filimonov, and N.S. Preobrazhenskaya (eds): Moscow, Medgiz.

Freeman, W., and J.W. Watts (1947) Retrograde degeneration of the thalamus following prefrontal lobotomy. J. Comp. Neurol. *86*:65–93.

Freeman, W., and J.W. Watts (1948) The thalamic projection to the frontal lobe. Res. Publ. Ass. Nerv. Ment. Dis. *27*:200–209.

Goldman, P.S. (1971) Functional development of the prefrontal cortex in early life and the problem of neuronal plasticity. Exp. Neurol. *32*:366–287.

Goldman-Rakic, P.S. (1982) Cytoarchitectonic heterogeneity of the primate neostriatum: Subdivision into island and matrix cellular compartments. J. Comp. Neurol. *205*:398–413.

Goldman-Rakic, P.S. (1984) Modular organization of prefrontal cortex. Trends Neurosci. *7*:419–424.

Harting, J.K., M.F. Huerta, A.J. Frankfurter, N.L. Strominger, and G.J. Royce (1980) Ascending pathways from the monkey superior colliculus: An autoradiographic analysis. J. Comp. Neurol. *192*:853–882.

Ilinsky, I., M. Jouandet, and P.S. Goldman-Rakic (1985) Organization of the nigrothalamocortical system in rhesus monkey. J. Comp. Neurol. *236*:315–330.

Isseroff, A., H.E. Rosvold, T.W. Galkin, and P.S. Goldman-Rakic (1982) Spatial memory impairments following damage to the mediodorsal nucleus of the thalamus in rhesus monkeys. Brain Res. *232*:97–113.

Itaya, S.K., and G.W. Van Hoesen (1983) Retinal projections to the inferior and medial pulvinar nuclei in the Old-World monkey. Brain Res. *269*:223–230.

Jacobson, S., N. Butters, and N.J. Tovsky (1978) Afferent and efferent subcortical projections of behaviorally defined sectors of prefrontal granular cortex. Brain Res. *159:*279–296.

Jones, E.G. (1983) Lack of collateral thalamocortical projections to fields of the first somatic sensory cortex in monkeys. Exp. Brain Res. *52:*375–384.

Kasdon, D.L., and S. Jacobson (1978) The thalamic afferents to the inferior parietal lobule of the rhesus monkey. J. Comp. Neurol. *177:*685–705.

Kievet, J., and H.G.J.M. Kuypers (1977) Organization of the thalamocortical connections to the frontal lobe in the rhesus monkey. Exp. Brain Res. *29:*299–322.

Krettek, J.E., and J.L. Price (1977) The cortical projections of the medial dorsal nucleus and adjacent nuclei in the rat. J. Comp. Neurol. *171:*157–192.

Leonard, C.M. (1969) The prefrontal cortex of the rat. I. Cortical projections of the mediodorsal nucleus. II. Efferent connections. Brain Res. *12:*321–343.

Leonard, C.M. (1972) The connections of the dorsomedial nuclei. Brain Behav. Evol. *6:*524–541.

Markowitsch, J.J., and M. Pritzel (1979) The prefrontal cortex: projection area of the thalamic mediodorsal nucleus. Physiol. Psychol. *1:*1–6.

McEntee, W.J., M.P. Biber, D.P. Perl, and D.F. Benson (1976) Diencephalic amnesia: a reappraisal. J. Neurol. Neurosurg. Psychiatr. *39:*436–441.

McLardy, T. (1950) Thalamic projection to frontal cortex in man. J. Neurol. Neurosurg. Psychiatr. *13:*198–202.

Mesulam, M.-M. (1976) The blue reaction product in horseradish peroxidase neurohistochemistry: Incubation parameters and visiability. J. Histochem. Cytochem. *24:*1273–1280.

Mesulam, M.-M. (1978) Tetramethyl benzidine for horseradish peroxidase neurohistochemistry: A non-carcinogenic blue reaction product with superior sensitivity for visualizing neural afferents and efferents. J. Histochem. Cytochem. *26:*106–117.

Mettler, F.A. (1947) Extracortical connections of the primate cerebral cortex. J. Comp. Neurol. *86:*95–117.

Meyer, A., E. Beck, and T. McLardy (1947) Prefrontal leucotomy: A neuroanatomical report. Brain *70:*18–49.

Monakow, C. (1895) Experimentelle und pathologisch-anatomische Untersuchungen über die Haubenregion, den Sehhügl und die Regio subthalamica, nebst Beitragen zue Kenntniss früh erworbenes Gross und Kleinhirndefect. Arch. Psychiat. Nervenkr. *27:*1–128, 386–479.

Muakkassa, K.F., and P.L. Strick (1979) Frontal lobe inputs to primate motor cortex:evidence for four somatotopically organized 'premotor' areas. Brain Res. *177:*176–182.

Mufson, E.J., and M.M. Mesulam (1984) Thalamic connections of the insula in the rhesus monkey and comments on the paralimbic connectivity of the medial pulvinar nucleus. J. Comp. Neurol. *227:*109–120.

Niimi, M. (1978) Cortical projections of the anterior thalamic nuclei in the cat. Exp. Brain Res. *31:*403–416.

Olzewski, J. (1952) The Thalamus of Macaca Mulatta. New York: S. Basel, Karger (ed) 93pp.

Porrino, L.J., A.M. Crane, and P.S. Goldman-Rakic (1981) Direct and indirect pathways from the amygdala to the frontal lobe in rhesus monkey. J. Comp. Neurol. *198:*121–136.

Porrino, L.J., and P.S. Goldman-Rakic (1982) Brain stem innervation of prefrontal and anterior cingulate cortex in the rhesus monkey revealed by retrograde transport of HRP. J. Comp. Neurol. *205:*63–76.

Pribram, K.H., K.L. Chow, and J. Semmes (1953) Limit and organization of the cortical projections from the medial thalamic nucleus in monkey. J. Comp. Neurol. *98:*433–448.

Rose, J.E., and C.N. Woolsey (1948) The orbitofrontal cortex and its connections with the mediodorsal nucleus in rabbit, sheep and cat. Res. Publ. Ass. Nerv. Ment. Dis. *27:*210–232.

Schell, G.R., and P.L. Strick (1984) The origin of thalamic inputs to the arcuate, premotor and supplementary areas. J. Neurosci. *4:*539–560.

Schwartz, M.L., and P.S. Goldman-Rakic (1984) Callosal and intrahemispheric connectivity of the prefrontal association cortex in rhesus monkey: Relation between intraparietal and principal sulcal cortex. J. Comp. Neurol. *226:*403–420.

Selemon, L.D., and P.S. Goldman-Rakic (1985) Longitudinal topography and interdigitation of cortico-striatal projections in the rhesus monkey. J. Neurosci. *00:*000–000.

Shulman, S. (1957) Bilateral symmetrical degeneration of the thalamus: A clinico-pathological study. J. Neuropathol. Exp. Neurol. *16:*446–470.

Squire, L.R., and R.Y. Moore (1979) Dorsal thalamic lesion in a noted case of human memory dysfunction. Ann. Neurol. *6:*503–506.

Trojanowski, J.Q., and J. Jacobson (1976) Medial pulvinar afferents to frontal eye fields in rhesus monkey demonstrated by horseradish peroxidase. Brain Res. *80:*395–411.

Van Buren, J.M., and R.C. Borke (1972) Variations and Connections of the Human Thalamus. 1. The nuclei and Cerebral Connections of the Human Thalamus. New York: Springer-Verlag, pp. 66–75.

Velayos, J.L., and F. Reinoso-Suarez (1982) Topographic organization of the brainstem afferents to the mediodorsal thalamic nucleus. J. Comp. Neurol. *206:*17–27.

Victor, M., R. Adams, and G. Collins (1971) The Wernicke-Korsakoff Syndrome. F.A. Davis (ed): Philadelphia.

Vogt, B.A., D.L. Rosene, and D.N. Pandya (1979) Thalamic and cortical afferents differentiate anterior from posterior cingulate cortex in the monkey. Science *204:*205–207.

Walker, A.E. (1940a) A cytoarchitectural study of the prefrontal area of the macaque monkey. J. Comp. Neurol. *73:*59–86.

Walker, A.E. (1940b) The medial thalamic nucleus: Comparative anatomical physiological and clinical study of nucleus medialis dorsalis thalami. J. Comp. Neurol. *73:*87–115.

Yakovlev, P.I. (1969) Development of the nuclei of the dorsal thalamus and the cerebral cortex. Morphogenetic and tectogenetic correlation. In S. Locke (ed): Modern Neurology. Boston: Little, Brown and Company, pp. 15–53.