

## Organization of Afferent Input to Subdivisions of Area 8 in the Rhesus Monkey

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**ABSTRACT** The sources of ipsilateral afferents to subdivisions of one frontal eye field (Walker, '40a area 8) were studied with horseradish peroxidase (HRP) in macaque monkeys. There were major differences in the distribution of cells projecting to the caudal and rostral parts of area 8. The majority (53%) of labeled cortical cells projecting to caudal regions were in visual association areas, and an additional 23% were in the ventral bank of the intraparietal sulcus, where neurons may have predominantly visual and visuomotor properties. In contrast, rostral area 8 had a much lower percentage of its cortical input originating in visual association areas (5%) or in the ventral bank of the intraparietal sulcus (8%). After HRP injection in this rostral part, 21% of labeled cells were in auditory association areas and 13% in paralimbic regions, whereas labeling in these two types of cortex was negligible after HRP administration to caudal parts of area 8. The percentage of cells in other association regions (portions of the banks of the superior temporal sulcus, dorsolateral parietal, medial parietal, and prefrontal cortices) was higher in the rostral (53%) than in the caudal case (21%). The results suggest that caudal area 8 may be involved in head and eye movements in response to visual stimuli, while its anterior subdivisions may be involved in directing the head and eyes in response to auditory stimuli. Furthermore, limbic input may also be relevant to the neural processing occurring in rostral frontal eye fields, perhaps by directing attention toward motivationally relevant stimuli.

Frontal cortical regions, situated rostral to the premotor cortex, have been associated with eye movements for over a century, because their electrical stimulation has been shown to elicit eye movements in various species, including humans and monkeys (Bender, '55; Brucher, '66; Clark and Lashley, '47; Crosby et al., '52; Ferrier, 1874; Foerster, '31; Grunbaum and Sherrington, '01; Marrocco, '78; Penfield and Boldrey, '37; Risien-Russell, 1894; Robinson and Fuchs, '69; Sherrington, 1893; Wagman et al., '61). These cortical regions, which in the monkey include the cortex anterior to the arcuate sulcus, have been referred to as the frontal eye fields (Brucher, '66; Crosby et al., '52). The involvement of these frontal cortical regions in the initiation of eye movements in the behaving monkey has been disputed because they are neither necessary nor sufficient for the response (Pasik and Pasik, '64). However, when the superior colliculus is destroyed, damage to the frontal eye fields seriously disrupts saccadic eye movements in monkeys

(Schiller et al., '79), thus suggesting that these regions may constitute one component of a complex neural network subserving eye movements.

In several species including humans, monkeys, and cats, damage in the region of the frontal eye fields results in transient disturbances in locomotor and orienting behaviors and in inefficient search of the environment (Bianchi, 1895; Brucher, '66; Dreher and Zernicki, '69; Heilman and Valenstein, '72; Jeannerod et al., '68; Kennard, '39; Latto, '78; Latto and Cowey, '72; Latto and Iversen, '73; Schlag-Rey and Lindsley, '70; Silberpfennig, '41 '42; Walker and Fulton, '38; Welch and Stuteville, '58). More lasting deficits are observed in monkeys with frontal eye field lesions when the animals are tested on complex discrimination tasks, such as those requiring a right or left response based on the appearance of one of two central stimuli (Goldman and Rosvold, '70; Milner et al., '78; Stamm, '73). Similarly, monkeys with frontal eye field lesions

perform poorly on tasks requiring responses to compound sensory stimuli, while they can master tasks requiring responses to the component sensory stimuli (Petrides and Iversen, '78; Van Hoesen et al., '80).

The frontal eye fields in the primate have thus been implicated in a variety of complex behaviors, including head and eye movements, orientation to sensory stimuli, and complex discrimination tasks which require integration of sensory input (Kennard, '39; Petrides and Iversen, '78; Van Hoesen et al., '80). Anatomical and electrophysiological studies are in general agreement with the nature of the behavioral consequences following destruction of these cortical regions. Visual and auditory association areas project to the frontal eye fields in monkeys (Chavis and Pandya, '76; Jacobson and Trojanowski, '77; Jones and Powell, '70; Pandya and Kuypers, '69), and neurons in these regions fire in association with eye and/or head movements (Bizzi and Schiller, '70; Bushnell and Goldberg, '79), and respond to visual and/or auditory stimuli (Mohler et al., '73; Nelson and Bignall, '73).

Notwithstanding the multiplicity of input to the frontal eye fields and the complexity of the behavioral consequences following their destruction, these regions have generally been regarded as a homogeneous region, an assumption which may not be justified. For example, there is considerable disagreement on the architectonic boundaries and subdivisions of area 8 (Brodmann, '05; Vogt and Vogt, '19; Walker, '40a), which in the primate is considered to be coextensive with the frontal eye fields. Moreover, there are conflicting physiological data concerning the temporal relationship of neuronal firing activity and eye movements in the frontal eye fields in monkeys (Bizzi, '67, '68; Bizzi and Schiller, '70; Bushnell and Goldberg, '79; Kurtzberg and Vaughan, '77). It is likely that the frontal eye fields comprise a heterogeneous set of cortical regions, each characterized by distinct anatomic features and subserving different behavioral functions. The apparent disagreement concerning the functions of the frontal eye fields may thus reflect the possibility that different subsectors were investigated.

The pattern of afferent input to subsectors of the frontal eye fields remains incompletely understood at the anatomical level, largely because of methodological limitations. For example, ablation-degeneration techniques, which have been widely used to trace neural projections to the frontal eye fields, are limited by inadvertent damage to fibers of passage, as well

as by the difficulty of studying projections originating in sulci which are generally inaccessible to direct surgical approach. On the other hand, studies based on the retrograde transport of neural tracers, such as horseradish peroxidase (HRP), enable the evaluation of the total afferent input to a particular region by injection of the enzyme to the area of interest. However, previous studies which have included injections of HRP into the frontal eye fields in monkeys have also involved regions extending beyond this region or included the entire area 8 (Jacobson and Trojanowski, '77; Leichnetz and Astruc, '78, '79). The question of the regional organization of afferent input to subsectors of area 8 has, therefore, not been addressed.

The purpose of the present study was to investigate the organization of afferent input to subdivisions of one frontal eye field in macaque monkeys with small injections of HRP. The region investigated corresponds to Walker's ('40a) cytoarchitectonic area 8 and is the one frontal eye field that has recently been re-examined in considerable detail with respect to eye movements (Robinson and Fuchs, '69).<sup>1</sup> In the analysis of results, emphasis was placed on the cortical afferent projections with a brief description of thalamic and other subcortical afferents. Results indicate that the cortical input to subdivisions of the frontal eye field investigated is not homogeneous. Instead, it shows an orderly organization whereby afferents from visual association areas project to caudal parts of the field and afferents originating in auditory association, polymodal, and paralimbic regions project to its more rostral segments.<sup>2</sup>

#### METHODS

Experiments involving HRP injections were conducted on three rhesus monkeys (*Macaca mulatta*), anesthetized with sodium pentobarbital (35 mg/kg intraperitoneally). Surgery was performed under aseptic conditions. The monkey's head was firmly positioned in a holder which left the cranium unobstructed for surgical approach. The femoral vein was catheterized for infusion of mannitol (Invenex, Ohio, 25%) to reduce the volume of the brain and avoid traumatic edema. A bone defect was made, the dura was retracted, and the cortex exposed.

Injections of HRP (Miles, 20% aqueous solution) were made with a microsyringe (Hamil-

<sup>1</sup>The second frontal eye field is situated rostral to the lower limb of the arcuate sulcus and corresponds to Walker's ('40a) area 45.

<sup>2</sup>A preliminary report has been published as an abstract (Barbas and Mesulam, '80).

*Abbreviations*

A	Arcuate sulcus	MD dc	Nucleus medialis dorsalis pars densocellularis
AM	Nucleus anterior medialis	MO	Medial orbital sulcus
AV	Nucleus anterior ventralis	MPO	Medial parieto-occipital sulcus
C	Central sulcus	NB	Nucleus basalis
Ca	Calcarine fissure	OT	Occipitotemporal sulcus
Cau	Caudate	P	Principal sulcus
Cg	Cingulate sulcus	Pc	Nucleus paracentralis
CL	Nucleus centralis lateralis	Pf	Nucleus parafascicularis
cl	Clastrum	Pi	Nucleus pulvinaris inferior
CM	Nucleus centrum medianum	Pm	Nucleus pulvinaris medialis
CSL	Nucleus centralis superior lateralis	PMT	Posterior middle temporal sulcus
GC	Griseum centrale	PO	Parieto-occipital sulcus
GLD	Nucleus geniculatus lateralis	Pu	Nucleus putamen
GM	Nucleus geniculatus medialis	R	Rhinal sulcus
GP	Globus pallidus	Re	Nucleus reunions
H	Hypothalamus	Ret	Nucleus reticularis
Ha	Nucleus habenularis	SM	Stria medullaris
IO	Inferior occipital sulcus	SN	Substantia nigra
IP	Intraparietal sulcus	SP	Subparietal sulcus
L	Lunate sulcus	ST	Superior temporal sulcus
LD	Nucleus lateralis dorsalis	V	Ventricle
LF	Lateral fissure	VA	Nucleus ventralis anterior
Li	Nucleus limitans	VL	Nucleus ventralis lateralis
LO	Lateral orbital sulcus	VPL	Nucleus ventralis posterior lateralis
LP	Nucleus lateralis posterior	VPM	Nucleus ventralis posterior medialis
MD	Nucleus medialis dorsalis		

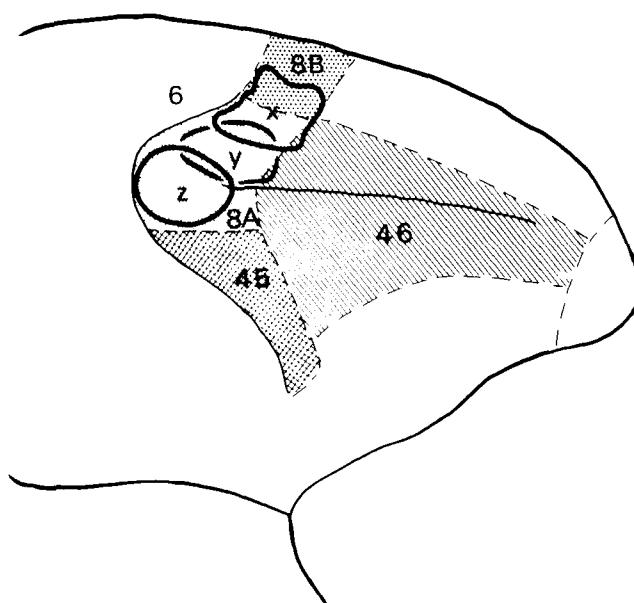


Fig. 1. Diagram of the monkey frontal cortex showing the extent of Walker's (40a) cytoarchitectonic area 8 on the dorsolateral surface and the approximate location of the HRP injection sites anterior to the arcuate sulcus in the rostral (x), intermediate (y), and caudal (z) cases. The full extent of the injection sites, including involvement of the cortex buried in the arcuate sulcus and the halo of the injection sites is shown in Figures 6-8.

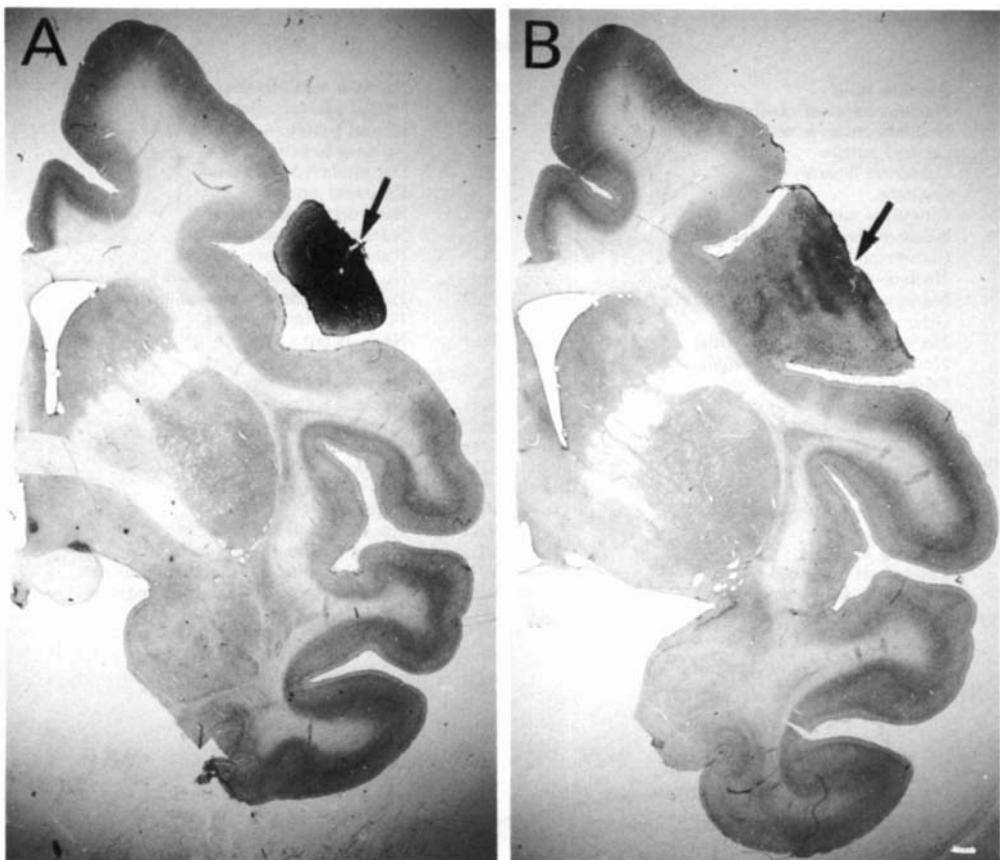


Fig. 2. A. Brightfield photomicrograph of coronal section through the core of the injection site in a case where the caudal part of area 8 was injected with HRP. (Arrow shows the needle mark.) Note that the injection does not involve the adjacent area 6. B. Brightfield photomicrograph of another coronal section 1.6 mm anterior to that in A, showing the rapid attenuation of the injection site. Regions like those in B (arrow) were considered as the halo of the injection site. Calibration bar 1 mm.

ton, 75N, 5  $\mu$ l) mounted on a microdrive which was attached to a carrier (Kopf). The needle was lowered to the desired site under microscopic guidance. Small amounts (0.05  $\mu$ l) of the injectate were delivered 1.5 mm below the pial surface at each of two to three adjacent sites separated by 1–2 mm over a 30-minute period. The frontal regions injected with HRP extended along the rostral bank and adjoining cortex of the upper limb of the arcuate sulcus (Walker's area 8). The injection in each of the three monkeys covered approximately one-third of Walker's area 8 (Fig. 1). Because there are inter-animal differences in the shape of the arcuate sulcus and in the size of the gap between the principal sulcus and the arcuate sulcus (Falk, '78), monkeys with similarly shaped arcuate sulci were assigned to the study at the time of surgery.

Following a 40–48-hour survival period the monkeys were reanesthetized and perfused through the heart with saline until the blood was cleared. A timed fixation procedure then followed, during which 2 liters of fixative (1.25% glutaraldehyde and 1% paraformaldehyde in 0.1 M phosphate buffer, pH 7.4) were delivered over a 30-minute period. The fixative was followed by perfusion with 2 liters of cold (4°C) sucrose phosphate buffer (10% sucrose in 0.1 M phosphate buffer, pH 7.4). The latter was used to wash excess, unbound fixative from the tissue. This procedure allows regulation of the duration of fixation and prevents loss of HRP activity as a result of excessive exposure to aldehydes (Rosene and Mesulam, '78).

The brain was then removed from the skull, photographed, placed in sucrose buffer, and transferred to a freezing microtome, where it

was cut at 40  $\mu\text{m}$ . Sections were collected in a 0.1 M phosphate buffer (pH 7.4). Every tenth section was treated for the visualization of HRP according to a procedure in which tetramethyl benzidine is used as the chromogen (Mesulam, '78; Mesulam et al., '80).

### Data analysis

Experimental slides prepared according to the method described above were viewed microscopically under brightfield illumination. Outlines of brain sections and the location of labeled cells ipsilateral to the injection site were transferred from the slides on to paper with the aid of an X-Y plotter (Hewlett Packard, 7044 A) which was electronically coupled to the stage of the microscope. The extent of the injection site was outlined on the same paper. The area containing dark reaction product, where neither cells nor axons were distinguishable, was considered as the injection core. The less densely labeled area surrounding this region was drawn as the halo of the injection site (Fig. 2). The laminar distribution of labeled cells was also noted on the plot.

All of the prepared slides were examined, but only representative sections (usually every other) among those containing labeled neurons were charted. If adjacent sections differed in the distribution of labeled neurons, then both sections were charted. Labeled neurons (represented as dots on the charted hemisphere which was drawn 8.5 times its actual size) were counted directly from the charted material in serial sections. The relative afferent input to the injected site from a particular anatomical region was assessed by expressing the number of labeled cortical cells in serial sections through that region as a percentage of the total number of labeled cortical cells in that case.

Intact axons in the white matter are not thought to take up HRP (LaVail, '75; Mesulam, in press). In all cases in this study the needle tracts were restricted to the cortical mantle, and there was no apparent damage to the underlying white matter. Thus, although some reaction product was noted to extend to the intact white matter underlying the injection site, it is not likely to have contributed to the final pattern of transport.

Labeled cells in the immediate vicinity of the injection site (within 0.5 mm radius from the halo of the injection, and extending up to 1.6 mm anterior to the rostral, and 1.6 mm posterior to the caudal limits of the injection site) were not included in the calculation of the total number of labeled cortical cells for each case.

Although neurons in this vicinity might have been labeled through retrograde transport of HRP and could thus constitute local projections, the presence of a background saturated with reaction-product raised the possibility of labeling through direct spread of HRP from the injection site. Anterogradely transported enzyme was also observed in many cortical sites but this was not charted for the purpose of this study.

The projection sites were serially reconstructed with the sulci as landmarks and were shown on diagrams of the surface of the cortex. The latter were drawn from photographs of each brain showing the external morphology of the experimental hemispheres. The drawings were modified to represent the relative location of cells buried in sulci.

The determination of cytoarchitectonic boundaries of regions containing labeled neurons was facilitated by viewing the experimental sections with a green filter. To determine the cytoarchitecture of the segment of area 8 injected with HRP, a series of matching sections through the injection site was stained with cresyl violet. The results were compared with those obtained by examining the cytoarchitectonic features of two normal monkey cerebra embedded in celloidin, cut in 40- $\mu\text{m}$  sections, and stained with cresyl violet.

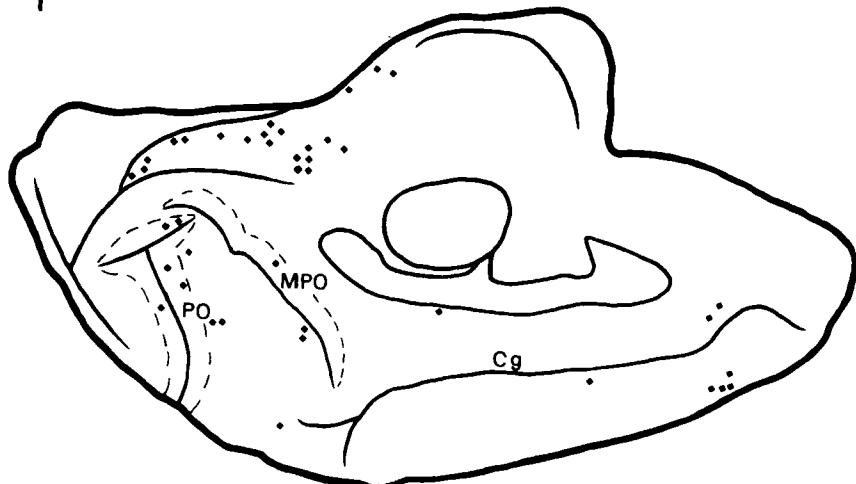
Labeled neurons in thalamic and other subcortical regions (amygdala, nucleus basalis) were also charted. The boundaries of these nuclei were determined by comparing the experimental sections with matched sections processed for the visualization of acetylcholinesterase (AChE) (Mesulam and Van Hoesen, '76), which reliably demarcates subcortical nuclei (Olivier et al., '70).

## RESULTS

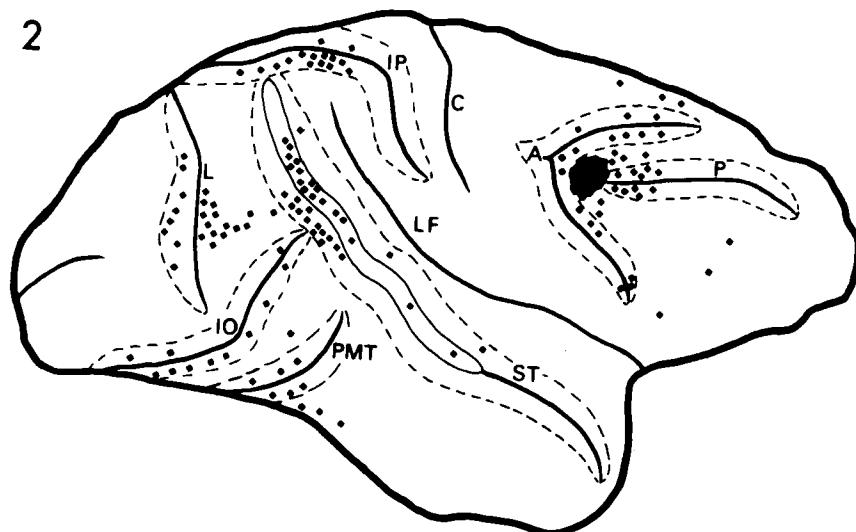
### Cortical projections

The cortical regions where labeled neurons were noted after HRP injections in area 8 are shown on the surfaces of the brain in the three cases in Figures 3-5. Labeled cortical cells were noted in peristriate and inferior temporal cortex; in the inferior parietal lobule and medial parietal cortex; in the superior temporal gyrus and banks of the superior temporal sulcus; in the banks of the lateral (Sylvian) fissure; in prefrontal regions; and cingulate and retrosplenial cortex. These results are consistent with those of Jacobson and Trojanowski ('77) and Leichnetz and Astruc ('78, '79), which were also obtained following HRP injections in area 8.

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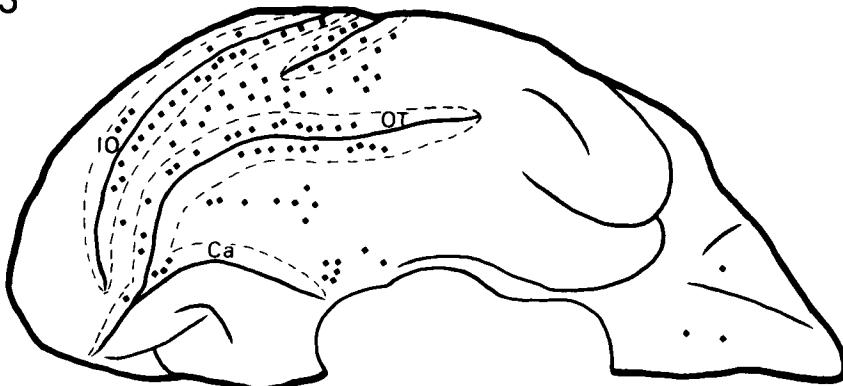


Fig. 3. 1—Medial, 2—lateral, and 3—ventral view of a brain in which the caudal part of the frontal eye field was injected with HRP. The core of the injection site is shown in black on the lateral view and the labeled neurons as black diamonds on the three brain surfaces. The dotted lines represent the banks of sulci, and the island drawn in uninterrupted line represents the cortex in the depths of the superior temporal sulcus. The density of the black diamonds represents the relative distribution of labeled neurons in each cortical region. These conventions apply for Figures 3–5. For quantitative distribution of labeled neurons by region, see note on Table 1. Note the predominance of neurons in occipital visual association regions and in the depths and ventral bank of the superior temporal sulcus (ST).

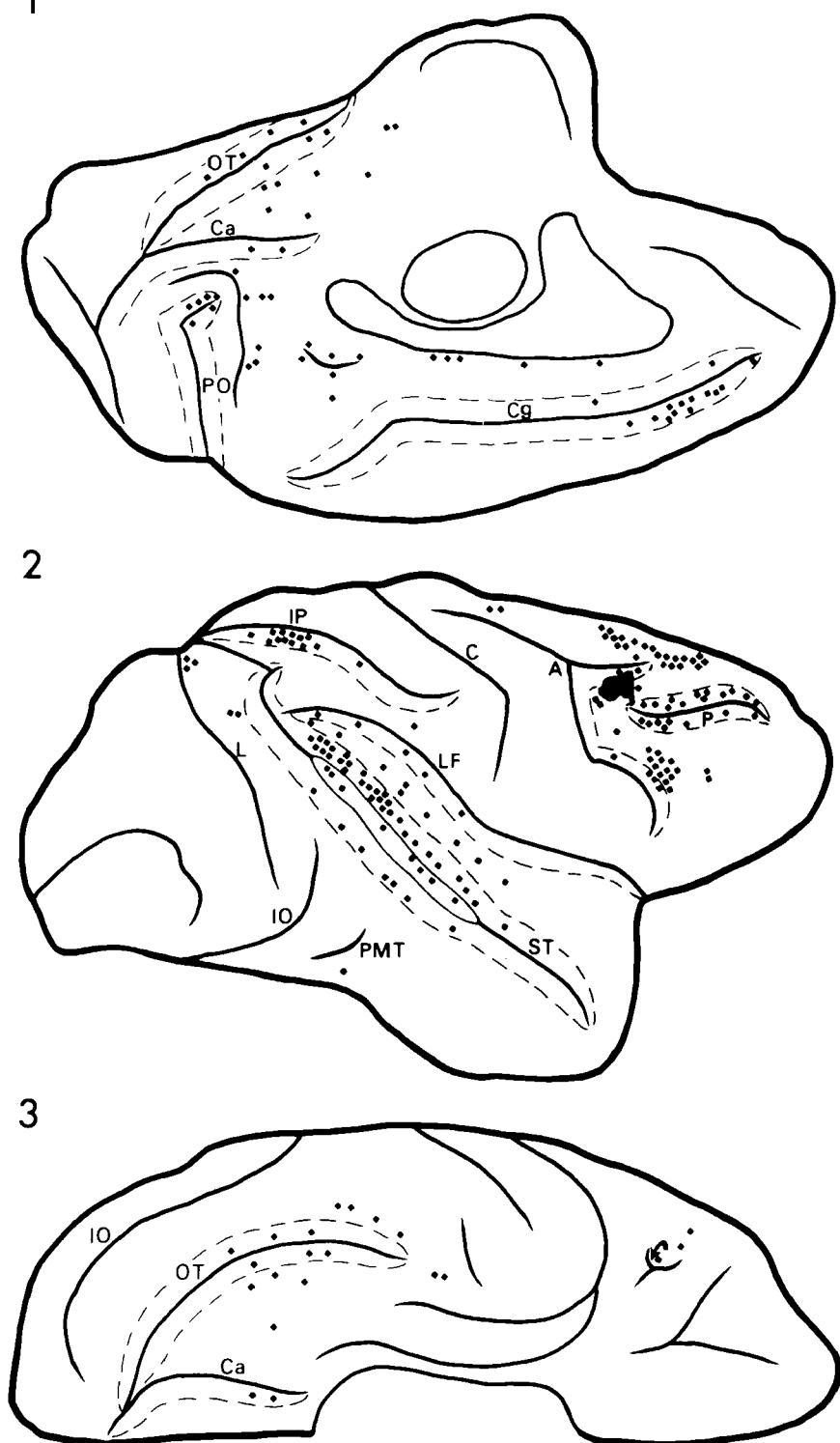


Fig. 4. 1—Medial, 2—lateral, and 3—ventral view of a brain in which the middle part of the frontal eye field was injected with HRP. The majority of labeled neurons were in frontal high-order association and premotor cortical regions, while there were fewer neurons in visual and auditory association regions.

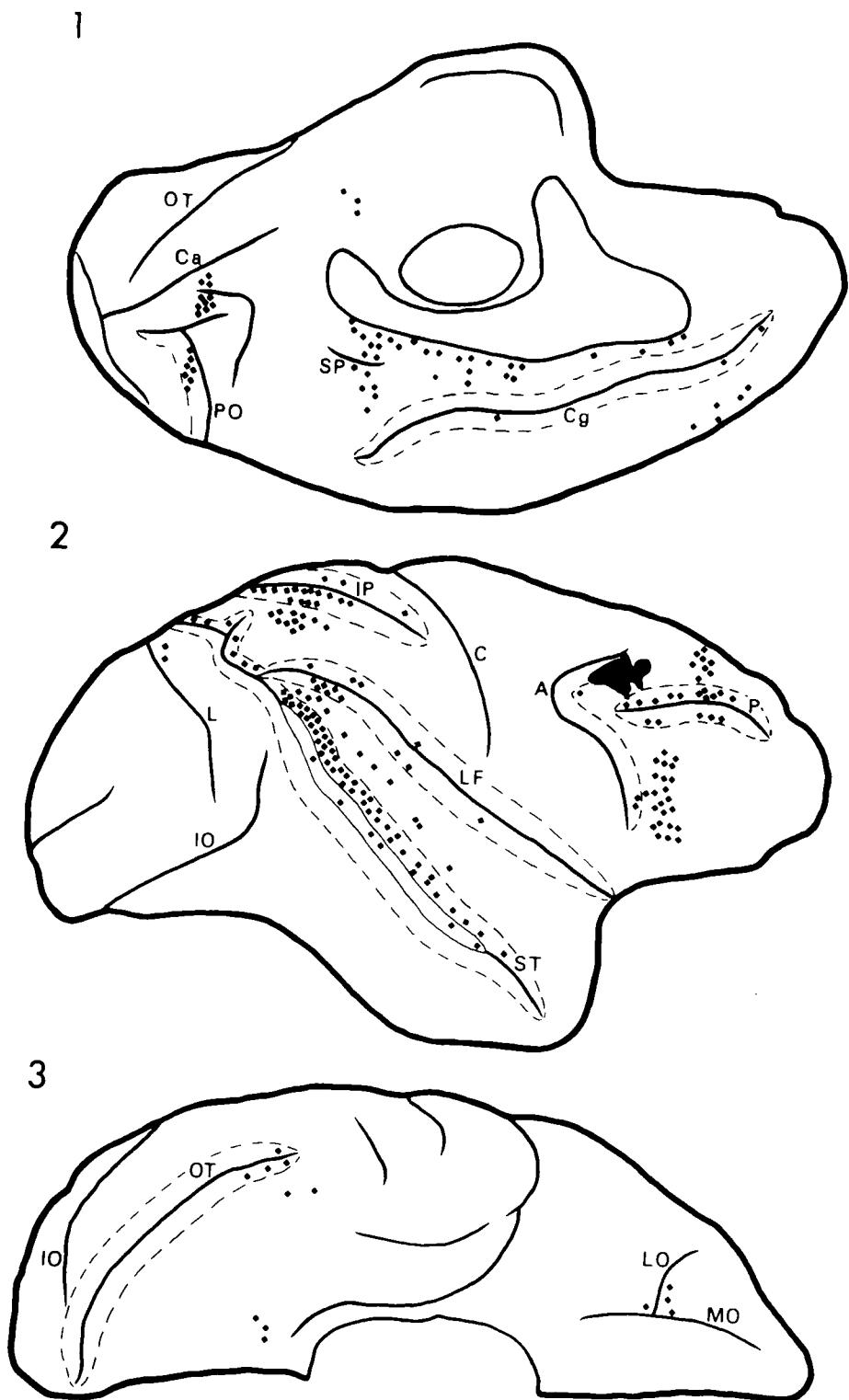


Fig. 5. 1—Medial, 2—lateral, and 3—ventral view of a brain in which the rostral part of the frontal eye field was injected with HRP. The majority of labeled neurons in this case were in posterior and anterior high-order association regions. In this case, there were more labeled neurons in auditory association and paralimbic regions and fewer in visual association regions than in the other two.

The above cortical regions may be included in one of the following functional classes: 1—visual association; 2—auditory association; 3—high-order association<sup>3</sup>; 4— premotor; and 5—paralimbic. The inclusion of regions with labeled neurons in one of these categories was made on the basis of one or more of the following criteria: 1—cytoarchitectonic characteristics<sup>4</sup>; 2—patterns of neural connectivity based on anatomical experiments; 3—behavioral experiments describing deficits in various tasks following regional damage; and 4—electrophysiological studies on the properties of neurons in specific cortical regions.

There were marked differences in the distribution of cells projecting to the three sites of area 8. The majority of neurons projecting to caudal area 8 were in visual association areas. In contrast, rostral parts of area 8 received projections from cells that were mostly in high-order association areas, but also from those in auditory association and paralimbic regions. In a case with an injection in the middle part of area 8, the relative distribution of neurons in visual, auditory, and paralimbic regions fell in between that of the rostral and caudal cases. To show the similarities and differences in the projection pattern in the three cases, direct comparisons will be made among the three cases for each region below.

#### *Visual association*

Visual association regions containing labeled neurons included the peristriate area (areas OA, OB of Von Bonin and Bailey, '47; or 19 and 18 of Brodmann, '05) and the inferior temporal cortex (area TE of Von Bonin and Bailey, or 20 and 21 of Brodmann).<sup>4</sup> Peristriate regions have been implicated in visual function on the basis of behavioral (Ades, '46; Ades and Raab, '49; Mishkin, '66), anatomical (Cragg and Ainsworth, '69; Jones and Powell, '70; Kuypers et al., '65; Pandya and Kuypers, '69), and electrophysiological (Cowey, '64; Hubel and Wiesel, '70; Zeki, '78c; Zeki and Sandeman, '76) experiments, as have also been inferior temporal regions (Blum et al., '50; Dean, '76; Desimone and Gross, '79; Gross and Bender, '69; Iwai and Mishkin, '69; Mishkin, '66). Peristriate regions where labeled neurons were noted included both banks of the occipitotemporal, inferior occipital, lunate, and parieto-occipital sulci, the dorsal bank of the calcarine fissure, and portions of the depths and ventral bank of the superior temporal sulcus.<sup>4</sup> Labeled neurons within the inferior temporal cortex were caudally situated and extended

into the ventral bank and depths of the superior temporal sulcus.

In a case with HRP injections in the caudal part of area 8 a large number of labeled cells (45%) were in peristriate areas, and an additional 8% of the cells were in the inferior temporal cortex. In sharp contrast, when HRP injections were made in a rostral region of area 8 the percentage of cells in peristriate (3%) and inferior temporal cortex (2%) was lower. In the case with an intermediate area 8 HRP injection, the percentage of cells in peristriate regions was 4%, and in the inferior temporal cortex it was 7% (Figs. 3–8, Table 1).

#### *Visuomotor*

The cortex limited to the posterior part of the ventral bank of the intraparietal sulcus has properties which distinguish it from its neighboring regions: It has direct connections with area OA (Seltzer and Pandya, '80), and neurons in this region respond to visual stimuli and in association with eye movement (Lynch et al., '77; Mountcastle et al., '75; Robinson et al., '78; Yin and Mountcastle, '77). In its caudal extent this cortex is contiguous with the cytoarchitectonically distinguishable area OA. Because of its special properties and direct connections with area OA, this intrasulcal portion of Von Bonin and Bailey's ('47) PG cortex will be con-

<sup>3</sup>High-order association regions include those that are not confined to one sensory modality as shown by electrophysiological, behavioral, or anatomical studies. These include the polymodal and supramodal types of cortex which have been described in another context (Mesulam et al., '77).

<sup>4</sup>The boundaries of many architectonic regions are formed by sulci. However, there are no natural boundaries for other cortical regions, and cytoarchitectonic criteria alone must be applied to delineate them from surrounding regions. A brief cytoarchitectonic profile will be given below only for those regions whose boundaries are not easily distinguishable by topographic landmarks and where the cytoarchitectonic differences between adjacent regions were used to specify the location of labeled neurons in these experiments.

There are no natural boundaries between Von Bonin and Bailey's ('47) area OA and the inferior parietal lobule (area PG). However, the cytoarchitecture of these regions differs. Area OA has a differentiated layer II, a dense granular layer IV, and a clear separation between layers V and VI. Area PG, on the other hand, has less well-differentiated layers II and IV, and there is no separation between layers V and VI. Area OA is similarly contiguous with parts of the inferior temporal cortex (area TE) within the ventral bank of the superior temporal sulcus. Area OA and TE have a similar architecture but their distinction is facilitated by the more accentuated columnar arrangement of neurons in area TE.

Another region where no natural boundaries exist is between the superficial part of the dorsal limb of the superior temporal sulcus, which is an auditory association region, and the ventral part of the same sulcus, which has polymodal features. The former region has been called area TAA (Seltzer and Pandya, '78) and is characterized by a predominance of the supragranular layers, prominent IIIc and Va pyramids, and a clear separation between layers V and VI. Area TAA is contiguous ventromedially with area TPO. The latter is distinguished from TAA by the less prominent pyramids in layer V, and a wider space between layers V and VI (Seltzer and Pandya, '78).

TABLE 1. Distribution of labeled cortical neurons in the macaque cortex following HRP injection in subdivisions of Area 8<sup>1</sup>

Cortical regions	Injection site		
	Caudal	Middle percentage of labeled cells	Rostral
Visual association	53%	11%	5%
Visuomotor (ventral bank of caudal intra- parietal sulcus)	23%	7%	8%
Auditory association	--	10%	21%
Somatosensory association	<1%	--	<1%
Posterior high- order association	3%	12%	23%
Frontal high- order association	18%	47%	30%
Premotor (area 6)	2%	11%	--
Paralimbic	<1%	2%	13%

<sup>1</sup>The total number of cortical cells in serial coronal sections in the three cases was: caudal case—2,109 cells in 67 sections; middle case—2,824 cells in 53 sections; rostral case—5,641 cells in 47 sections.

sidered separately with the assumption that it has a visuomotor function.<sup>5</sup>

In the case with a caudal area 8 HRP injection 23% of the labeled cortical neurons were in the intrasulcal PG cortex. In contrast, the cases with middle and rostral area 8 HRP injections had respectively only 7% and 8% of their labeled cortical cells in this region. The location of labeled neurons within the ventral bank of the sulcus also differed in the three cases. The labeled neurons in the caudal case were concentrated in the deepest half of the bank, whereas in the middle case they were in the middle one-third of the bank. In the most rostral case, the labeled neurons were both in the superficial and deepest one-third of the bank, leaving a relatively free region within the middle third of the bank (Figs. 6–9).

#### Auditory association

These regions included the ventral bank of the lateral (Sylvian) fissure, the adjacent superior temporal gyrus, and part of the dorsal bank of the superior temporal sulcus. On cytoarchitectonic grounds these regions include area TA of Von Bonin and Bailey ('47) and areas Tpt and TAa of Pandya and Sanides ('73) and Seltzer and Pandya ('78).<sup>4</sup> These regions constitute auditory association regions by virtue of their monosynaptic connections with the primary auditory cortex demonstrated anatomically (Pandya et al., '69; Pandya and Sanides, '73; Seltzer and Pandya, '78), and on the basis of behavioral (Massopust et al., '65; Wegener, '64) and electrophysiological experiments (Ades and Felder, '42; Hocherman et al., '76; Leino-

nen et al., '80; Merzenich and Brugge, '73; Miller et al., '72; Pribram et al., '54; Walzl and Woolsey, '43).

In the case with HRP injections in the caudal part of area 8, there were no labeled neurons in auditory association regions. However, labeled neurons were observed when the middle part of area 8 was injected and these constituted 10% of all labeled cortical cells in this case; in the most rostral area 8 case, 21% of the labeled cortical cells were in auditory association regions (Figs. 3–8, Table 1).

#### Somatosensory association

There were very few labeled cells in somatosensory association regions in any of the three cases studied with HRP. These labeled cells were in the dorsal bank of the intraparietal sulcus (area PE of Von Bonin and Bailey, '47) and on the dorsal bank of the lateral fissure. In the case with a caudal HRP injection, labeled neurons in these regions amounted to 0.5% of the total and in the most rostral case they were 0.8%. In the middle case the percentage of cells in somatosensory association regions was less than 0.5%.

#### Premotor

The only case with a significant proportion of labeled cells (11%) in area 6 (Brodmann, '05)

<sup>4</sup>Even though the cortex along the ventral bank of the intraparietal sulcus and the dorsolateral surface of the inferior parietal lobule have been considered as a unit in architectonic (area PG of Von Bonin and Bailey, '47) and physiological (Mountcastle et al., '75) studies, they will be considered separately here because of the differences in connectivity in the two areas (Mesulam et al., '77; Seltzer and Pandya, '80).

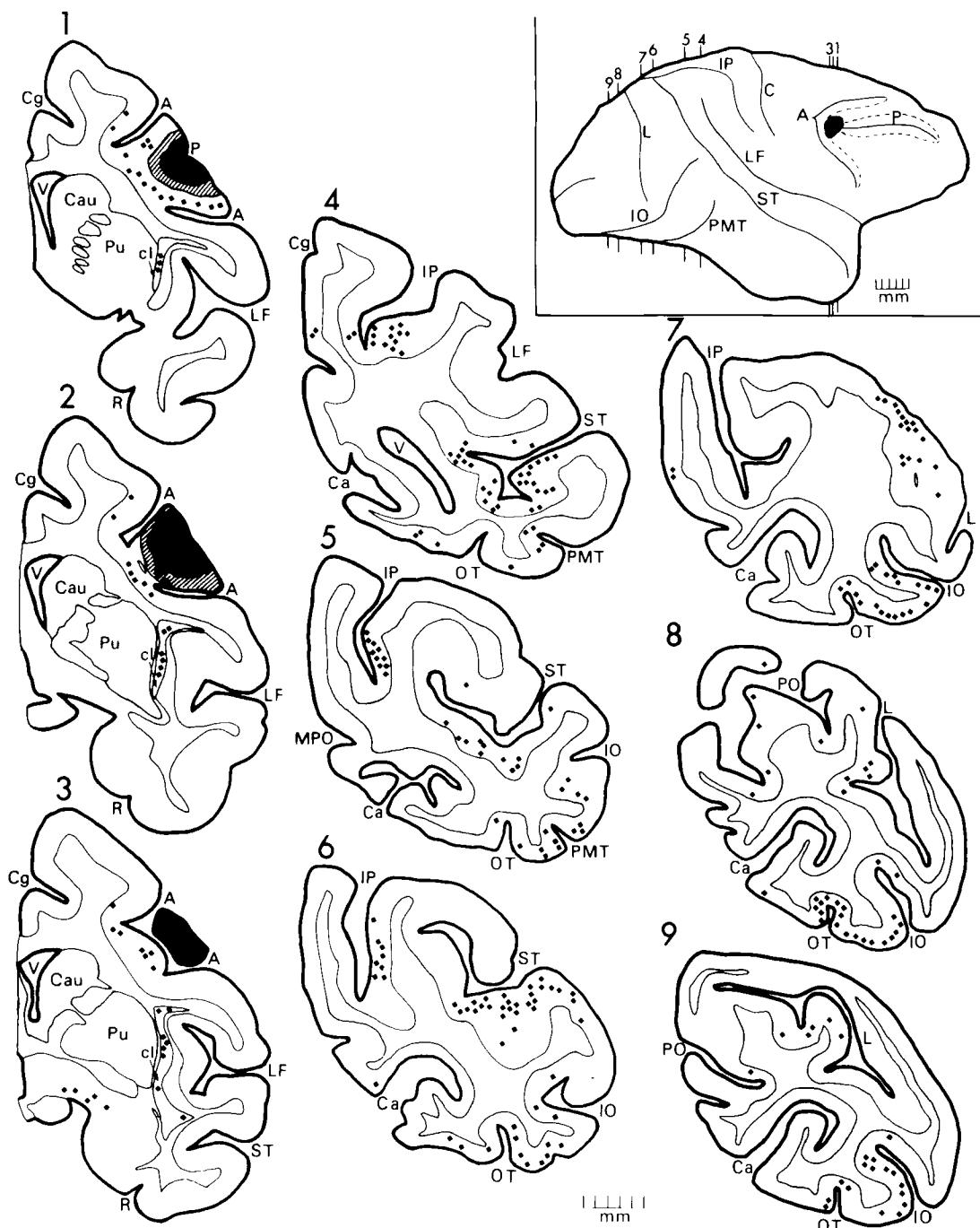


Fig. 6. Coronal sections taken at the level indicated on the dorsolateral view of the brain (insert) showing the distribution of labeled neurons (black diamonds) following HRP injection in the caudal part of the frontal eye field. The core of the injection site is shown in black on the dorsolateral surface of the brain, and in the coronal sections 1-3. The striped area shows the extent of HRP spread from the injection site. Note the predominance of labeled neurons in peristriate cortex and inferior temporal regions and in the ventral bank of the intraparietal sulcus.

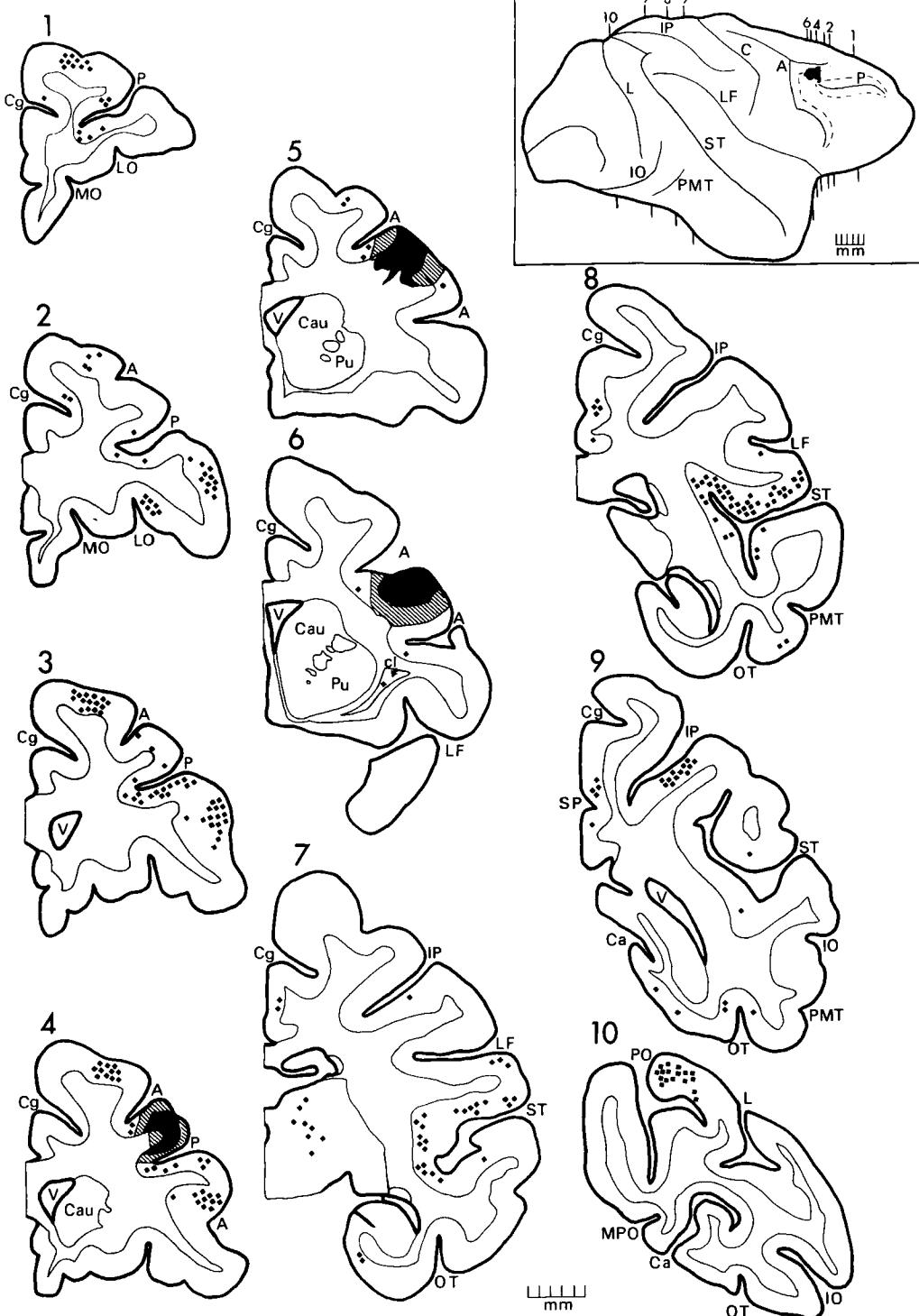


Fig. 7. Coronal sections taken at the level indicated on the dorsolateral view of the brain (insert) showing the distribution of labeled neurons (black diamonds) following HRP injection in the middle part of the frontal eye field. The core of the injection site is shown in black on the dorsolateral surface of the brain and in the coronal sections 4–6. Note the predominance of labeled neurons in frontal high-order association and in premotor regions. Labeled neurons were also in posterior high-order association, as well as in visual and auditory association regions.

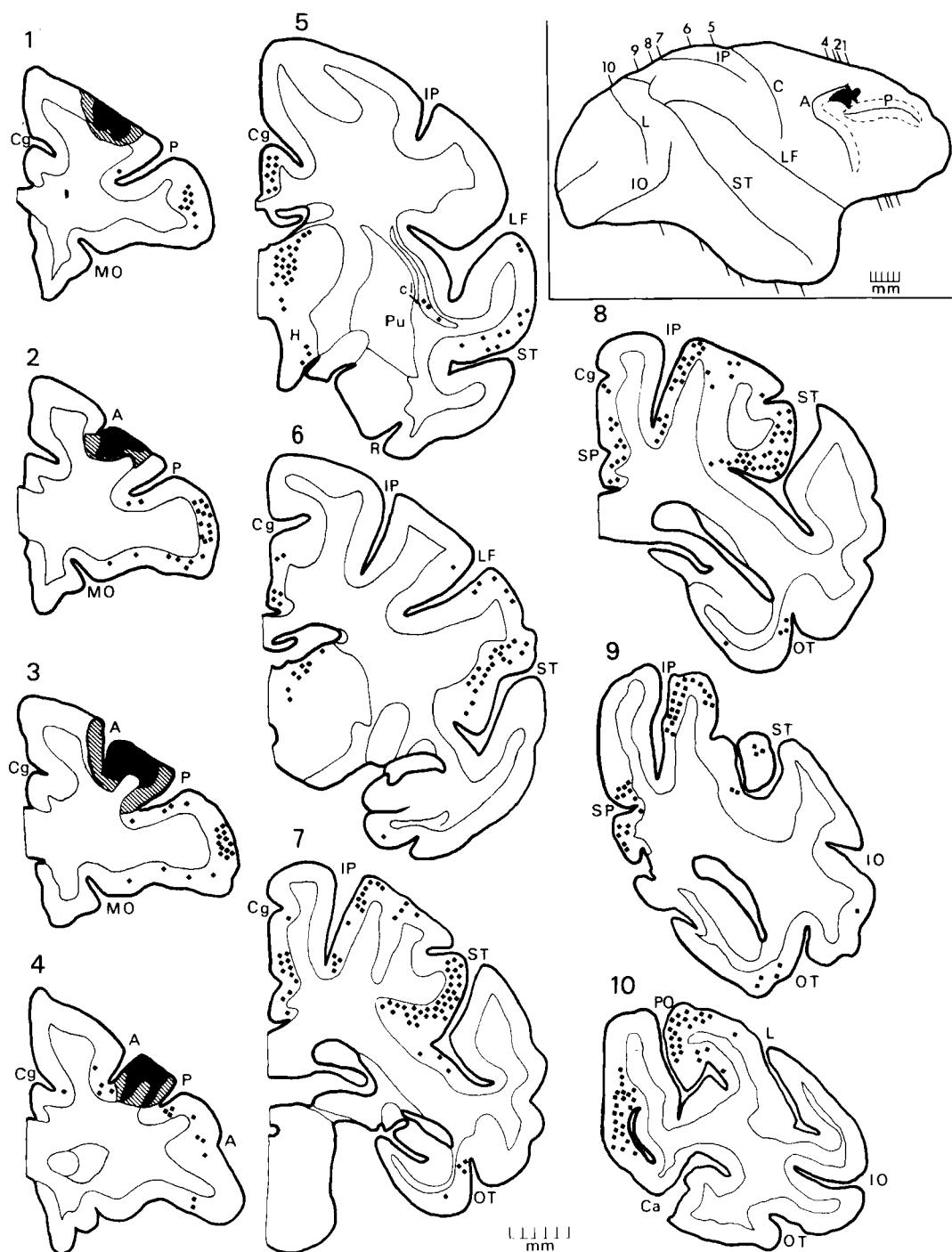


Fig. 8. Coronal sections taken at the level indicated on the dorsolateral view of the brain (insert) showing the distribution of labeled neurons (black diamonds) following HRP injection in the rostral part of the frontal eye field. The core of the injection site is shown in black on the dorsolateral surface of the brain, and in the coronal sections 1-4. The majority of labeled neurons in this case were in posterior and anterior high-order association regions and in auditory association and paralimbic regions.

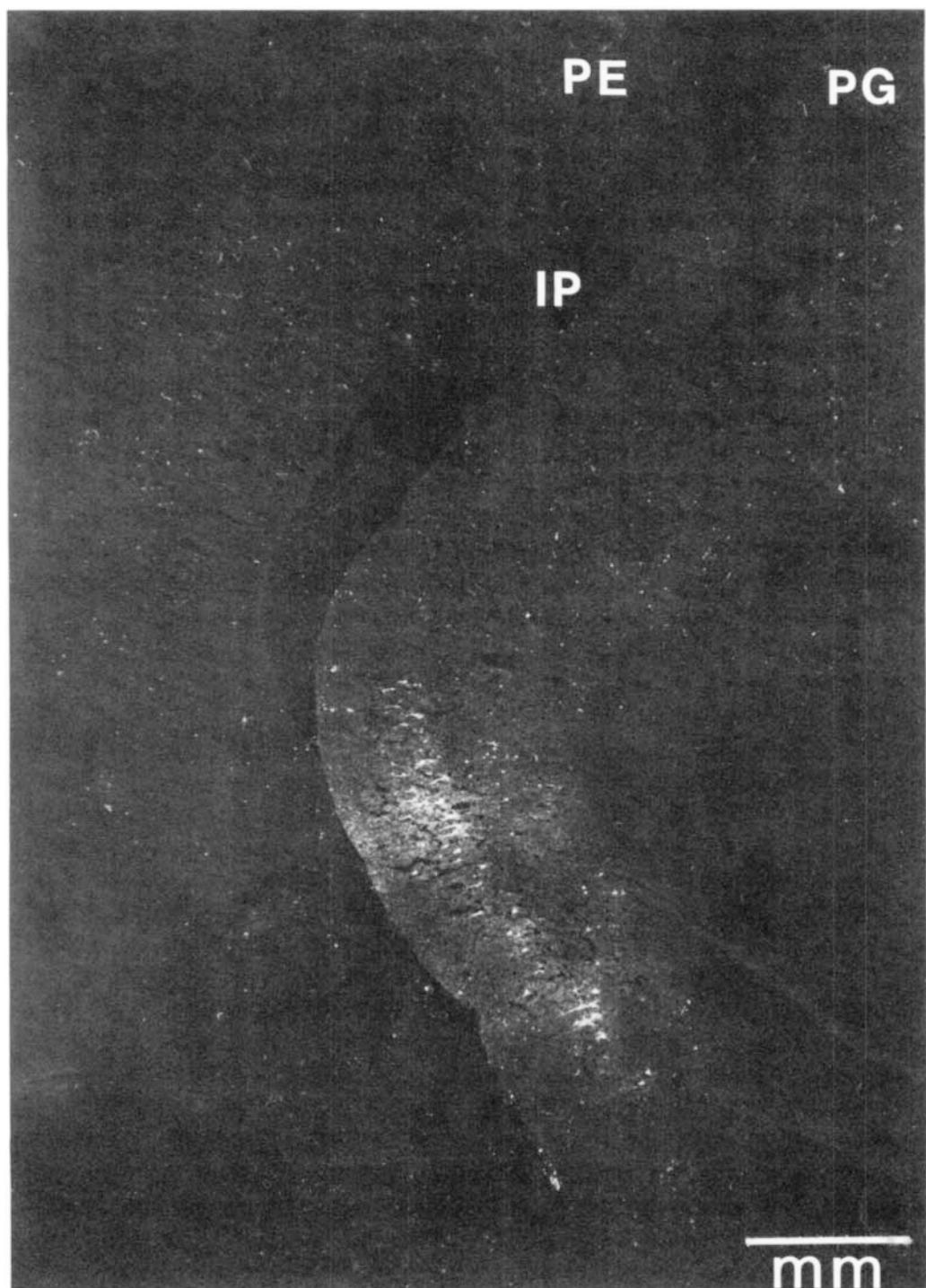


Fig. 9. Darkfield photomicrograph of coronal section through the intraparietal sulcus showing the restricted distribution of labeled neurons in the ventral bank of the intraparietal sulcus following injection of HRP in the caudal part of the frontal eye field.

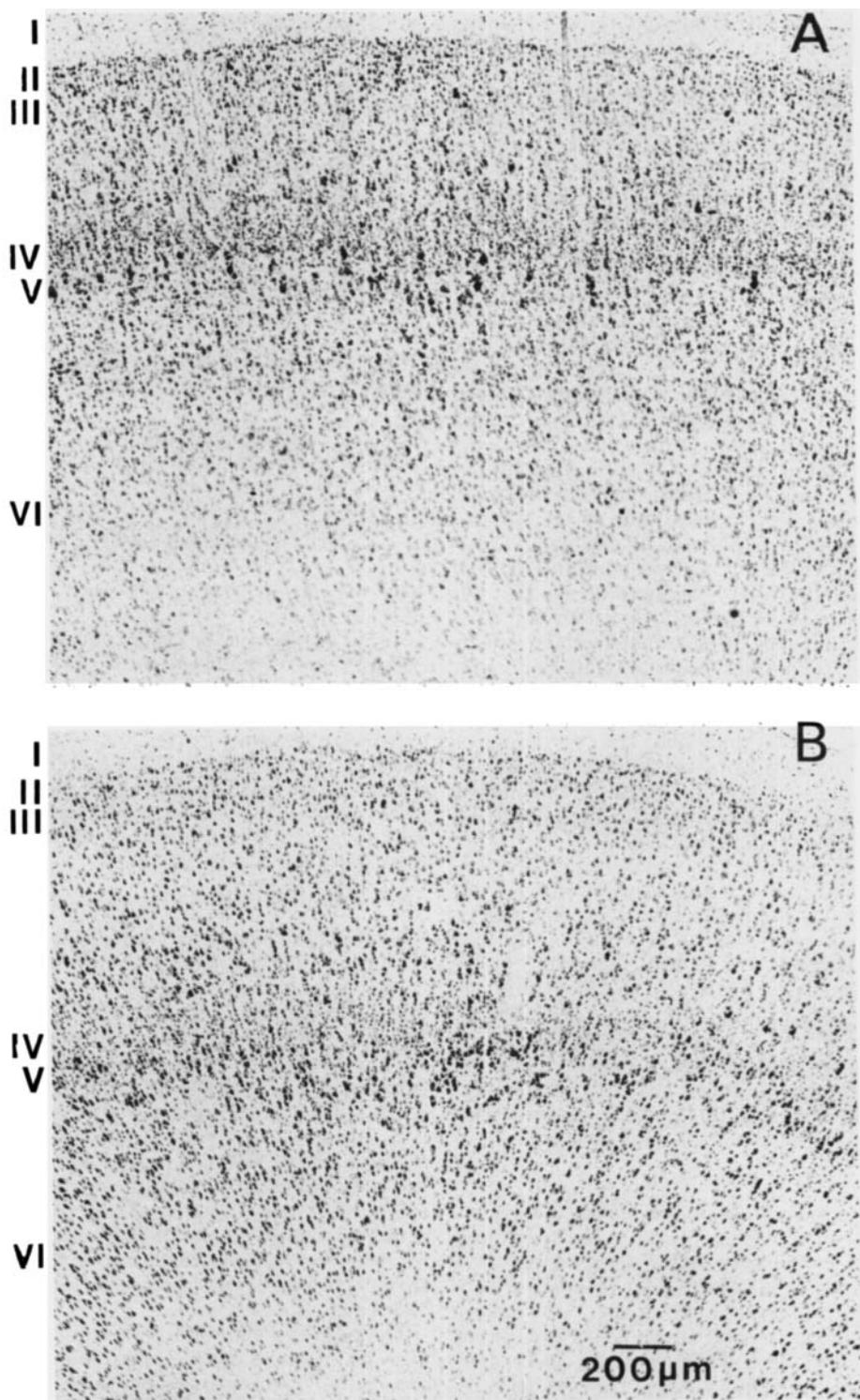


Fig. 10. Brightfield photomicrograph showing the cytoarchitectonic features of a caudal (A) and a rostral (B) periarcuate region. Note the difference in the size of the pyramids in laminae III and V, in the density of the granular layer IV, and in the depth and density of lamina III between the two regions. Celloidin-embedded tissue, cresyl violet stain.

was the middle case. The caudal case had fewer cells in area 6 (2%), and the rostral had none.

#### *High-order association regions*

Labeled neurons were also seen in regions where the connectivity and physiological characteristics of neurons are not confined to one sensory modality. These areas will be referred to as high-order association regions in this study.

Regions in the posterior high-order association category included the deepest two-thirds of the dorsal bank of the superior temporal sulcus (a region which is cytoarchitectonically different from the more superficially situated TAa area on the same bank) (Seltzer and Pandya, '78)<sup>4</sup>, the medial parietal cortex, and the dorsolateral part of area PG. The inclusion of these regions in the high-order association category is based on their neuronal response properties (Benevento et al., '77; Desimone and Gross, '79) and on anatomical connectional studies (Chavis and Pandya, '76; Jones and Powell, '70; Kuypers et al., '65; Mesulam et al., '77; Seltzer and Pandya, '78).

The lowest percentage of labeled neurons in posterior high-order association regions was noted in the case with the most caudal (3%), and the highest in the case with the most rostral (23%) area 8 HRP injection. The percentage of neurons projecting to the middle site fell in between these two cases with 12% of the labeled cortical cells being in posterior high-order association regions in this case.

Labeled neurons in anterior high-order association areas were seen in parts of areas 46, 12, 9, 10, 45, and 8 (Walker, '40a). Neurons in these regions respond to several sensory modalities (Bignall and Imbert, '69), and receive afferents from multiple cortical regions (Chavis and Pandya, '76; Jones and Powell, '70). The caudal part of area 8 had the lowest percentage (18%), the middle case the highest (47%), and the anterior case an intermediate (30%) percentage of the labeled cells in frontal high-order association regions (Table 1).

#### *Paralimbic*

Paralimbic regions where labeled neurons were seen included cingulate and retrosplenial cortex and the banks and regions between the medial and lateral orbital sulci. A few cells were in the parahippocampal gyrus, in regions which may correspond to area TH of Von Bonin and Bailey ('47). These regions have connections with limbic structures (Jones and Powell, '70; Johnson et al., '68; Nauta, '64; Pan-

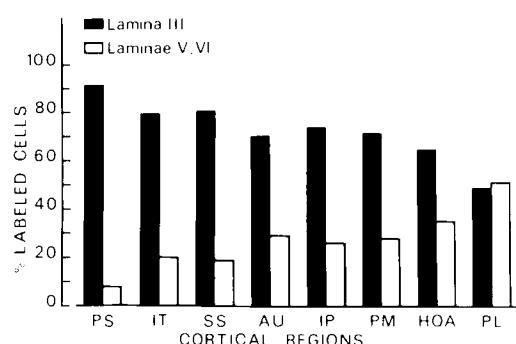


Fig. 11. Histogram showing the percentage of labeled neurons in lamina III, and in laminae V and VI in peristriate (PS), inferior temporal (IT), somatosensory (SS), auditory (AU), ventral bank of intraparietal sulcus (IP), premotor (PM), high-order association (HOA), and paralimbic (PL) cortical regions. The black (lamina III) and white (laminae V, VI) bars in each region add up to 100%. Note that the percentage of neurons in layer III decreases from peristriate to high-order association to paralimbic regions. For list of regions included in each category see text.

dya and Kuypers, '69; Potter and Nauta, '79; Pribram et al., '50; Rose and Van Hoesen, '77; Van Hoesen, '80; Van Hoesen and Pandya, '75).

The highest percentage of labeled cells in paralimbic regions occurred following the most rostral injection of HRP (13%). A small number of labeled neurons (2%) were noted in the middle case, whereas in the caudal case labeled cells in paralimbic regions amounted to less than 1% (Figs. 3–8, Table 1).

#### *Cytoarchitectonic characteristics*

Having observed the striking differences between the projection patterns of the caudal and rostral parts of the frontal eye field, we decided to see whether there are cytoarchitectonic differences between these two regions as well. Area 8 as a whole can be easily distinguished from the adjoining areas 46 and 6. Unlike area 8, area 6 lacks a granular layer IV, and the large pyramids in layers III and V form a central band. Area 46 has a greater cell density in the supragranular layers than in the infragranular layers, there is a discernible separation between layers V and VI, and the neurons show a columnar organization throughout the six cortical layers; area 8 lacks the latter two features.

The posterior half of area 8 is characterized by rows of large pyramids in layers III and, especially, V, which are close to a well-differentiated granular layer IV (Fig. 10A). In pro-

gressively more rostral regions, the pyramids in layers III and V are less prominent, while the granular layer IV is thinner than in posterior regions. Moreover, lamina III is 60% thicker but less compact in anterior than in posterior regions (Fig. 10B). This distinction between anterior and posterior regions may well parallel the distinction that Walker ('40a) made between area 8A (caudal) and area 8B (rostral). It is clear, however, that the differences in connectivity within subsectors of the region known as area 8 are underlain by cytoarchitectonic differences.

#### *Laminar distribution of labeled neurons*

Labeled cortical neurons were restricted to cortical layers III and V with a few observed in VI. The distribution of labeled neurons in these layers differed from one cortical region to the other in a manner consistent from case to case. Because of the similar trends in the distribution of labeled cells by layer in each functional category in the three HRP cases, the results were pooled, and are shown graphically in Figure 11. Because of the difficulty in determining the border between layers V and VI, labeled neurons in the infragranular layers were considered together.

Most labeled neurons were in cortical layer III. The supragranular preponderance of labeling was generally most pronounced in the parakoniocortical unimodal association areas (92% of labeled neurons in peristriate visual association regions were in layer III), and less marked in high-order association areas (72%), while a reverse trend was noted in paralimbic areas, where the majority (51%) of neurons were in layers V and VI.

#### *Subcortical projections*

The nomenclature for the thalamus is according to that of Olszewski ('52) and Burton and Jones ('76). The delineation of nuclear boundaries was aided by comparing the experimental sections with matched sections processed for the visualization of AChE (Fig. 12A).

The distribution of labeled neurons in various thalamic nuclei varied somewhat from case to case but they were generally similar. All three area 8 subdivisions received thalamic afferents from the magnocellular, parvocellular, densocellular, and pars multiformis divisions of the nucleus medialis dorsalis. Most labeled cells were in the parvocellular and pars multiformis parts of the medialis dorsalis, and these cells occupied a crescent on the lateral extent of the nucleus. Through the focus of the

projection within the nucleus all cells appeared to be labeled against a background of heavy anterograde labeling (Fig. 12B), in agreement with previous studies (Astruc, '71; Künzle and Akert, '77). Other nuclei where labeled neurons were observed (in descending order with respect to the density of labeled cell clusters) included: nucleus paracentralis, ventralis lateralis, ventralis anterior, limitans, pulvinar medialis, centralis lateralis, centralis superior lateralis, and reunions (Figs. 13, 14).

In all cases there were labeled neurons in the claustrum and in other limbic structures within the basal forebrain (nucleus basalis and hypothalamic region). A few labeled neurons (two to three per section) were also seen in the lateral basal nucleus of the amygdala, but not in other amygdaloid nuclei. The thalamic and other subcortical results are consistent with previous findings (Akert, '64; Bos and Ben-vento, '75; Jacobson and Trojanowski, '75; Kievit and Kuypers, '74, '75, '77; Leichnetz and Astruc, '78, '79; Mettler, '47; Scollo-Lavizzari and Akert, '63; Trojanowski and Jacobson, '74; Walker, '40b). Labeled neurons were also present in the brainstem, but were not examined for the present study.

#### DISCUSSION

There were marked differences in the distribution of labeled cells in the various cortical regions following HRP injection into subsectors of Walker's ('40a) area 8. The major source of input to the caudal part of area 8 was the visual association regions. In sharp contrast, neurons in visual association regions constituted only a small proportion of the number of cortical cells projecting to the most rostral part of area 8. The differences were also qualitative, for projections from visual areas to the two segments of the frontal eye field originated in different sectors of visual association cortex. Peristriate neurons projecting to the caudal part of area 8 were in the anterior bank and depths of the lunate sulcus, in parts of the ventral bank of the superior temporal sulcus, and in the banks of the inferior occipital sulcus. Most of these regions overlap with those that represent central parts of the visual field, including possibly the fovea, while others represent more peripheral parts of the visual field (Van Essen and Zeki, '78; Zeki, '69, '77, 78a,b; Zeki and Sandeman, '76). On the other hand, most of the visual association neurons projecting to the rostral part of area 8 were in the caudal bank of the parieto-occipital sulcus, in regions corre-

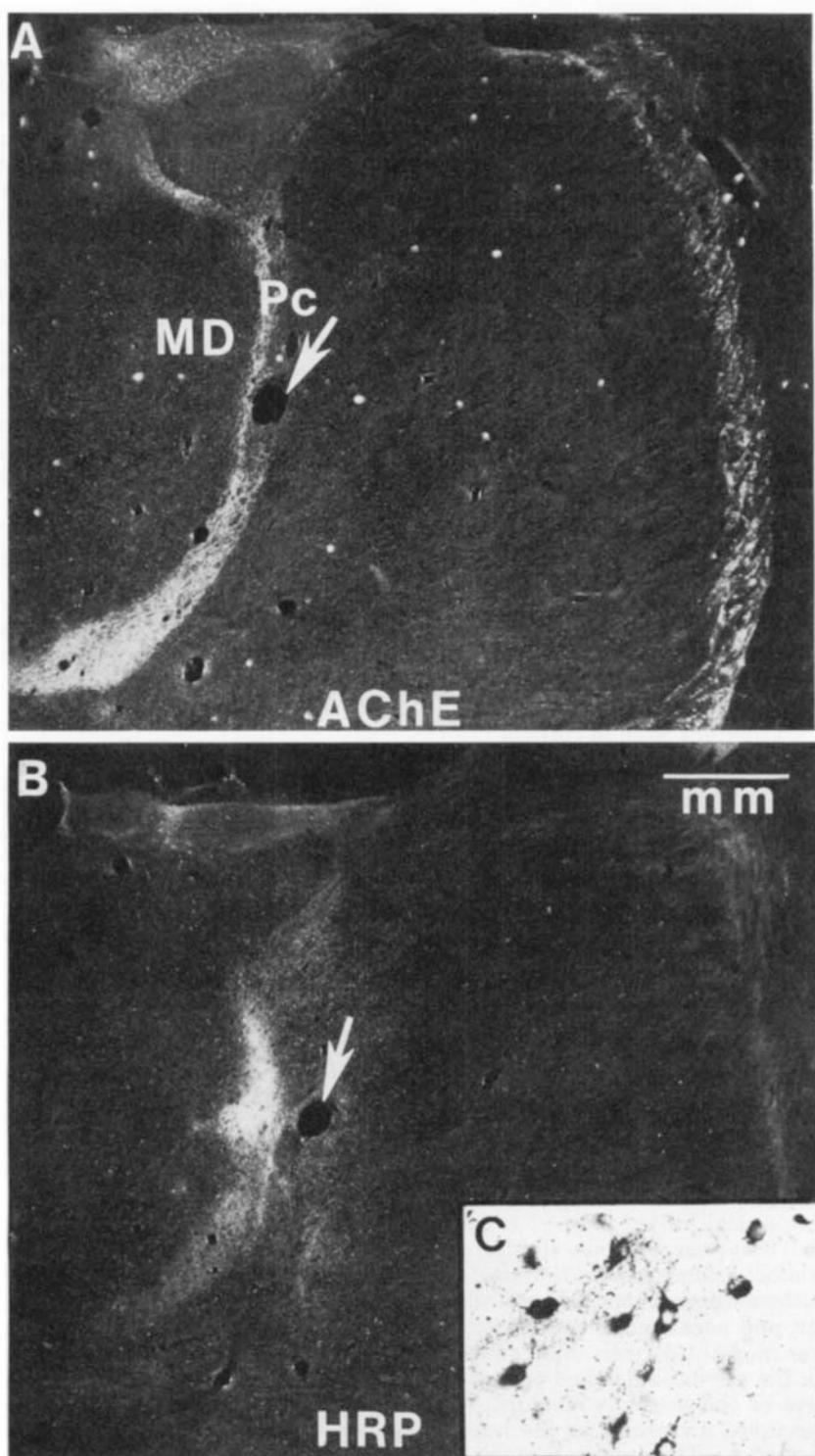


Figure 12

sponding to the representation of more peripheral parts of the visual field (Zeki, '77, '78b). Moreover, neurons in regions which may be concerned with binocular depth perception, in the depths of the lunate sulcus (Hubel and Wiesel, '70), and with movement, in the ventral bank of the superior temporal sulcus (Zeki, '74), appeared to be preferentially directed to the more caudal parts of area 8.

The extensive visual input from various peri-striate and inferior temporal regions to caudal frontal eye field regions is consistent with the physiological response properties of neurons in these regions, since neurons most easily driven by conventional visual stimuli are confined to posterior parts of the frontal eye field (Pigarev et al., '79; Wurtz and Mohler, '76). The visual receptive fields of neurons in area 8 are large, and a few include the fovea (Mohler et al., '73), a situation consistent with the type of input that the neurons receive from visual association areas.

The present study also showed that the proportion of neurons from auditory association regions projecting to the most rostral part of area 8 was higher than that projecting to the middle site, while no cells from auditory association regions projected to the caudal segment. In this respect, the input from auditory association regions to the frontal eye field under study followed a trend opposite to that from visual association regions. These data are consistent with studies based on ablation-degeneration experiments which showed that visual association regions project to Walker's ('40a)area 8A, which is situated caudally within the frontal eye field, while auditory association regions project more rostrally to area 8B (Jones, '69; Jones and Powell, '70).

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Fig. 12. A. Darkfield photomicrograph showing AChE-stained section through the nucleus medialis dorsalis of the thalamus of the caudal case. Note the boundaries of thalamic nuclei formed by the differential AChE stain of the various nuclei. B. Darkfield photomicrograph of section adjacent to that in A which was processed for the visualization of HRP label following injection in the caudal part of the frontal eye field. The heaviest HRP label is medial to the blood vessel (arrow) which runs through the AChE-staining nucleus paracentralis (Pc) in A. The HRP label forms a crescent in the lateral part of the nucleus medialis dorsalis (MD) situated just medial to the nucleus paracentralis. Some HRP label is also seen in the nucleus paracentralis. C. Brightfield photomicrograph of a portion of the nucleus medialis dorsalis shown in B at higher magnification where labeled neurons are seen. The extraperikaryal reaction product around the labeled neurons indicates the presence of intradendritic or anterogradely transported HRP. Original magnification in C,  $\times 320$ .

Although neurons in periarculate regions respond to both visual and auditory stimuli in the macaque and squirrel monkeys (Mohler et al., '73; Nelson and Bignall, '73; Schechter and Murphy, '75), no systematic electrophysiological study of the topographical organization of these modalities has been made. However, regional variations with respect to saccadic eye movement have been reported for the frontal eye field. Stimulation of posterior regions (which correspond to our caudal site) elicits small ( $1^\circ$ – $5^\circ$ ) and medium size ( $5^\circ$ – $15^\circ$ ) horizontal, and to a lesser degree vertical saccadic eye movements, while stimulation of the anterior part (which corresponds to our rostral site) elicits large ( $20^\circ$ – $60^\circ$ ) horizontal saccades (Robinson and Fuchs, '69). There may be a functional connection between the differences in the size of saccadic eye movement elicited with electrical cortical stimulation and the differential pattern of afferent input into subsectors of area 8. Taken together this evidence suggests that the caudal region may be involved in orienting the eyes and head to visual stimuli which appear near the center of the visual field, while the rostral region may be involved in directing the eyes and head to more peripheral visual stimuli, and also to auditory stimuli. Orientation to stimuli within central and para-central parts of the visual field can be accomplished with small and medium size saccades, but orientation toward stimuli in the peripheral field would require saccades and head movements of a greater magnitude. It should also be noted that auditory stimuli can reach the animal from all directions, and that their localization may be relatively more difficult. Thus, large head and eye movements may be necessary for orienting to auditory stimuli. It is therefore interesting that the part of the frontal eye field stimulation of which elicits large saccades is also the part that receives input from auditory association regions.

Following damage to the frontal eye fields monkeys neglect sensory stimuli contralateral to the damaged side (Bianchi, 1895; Brucher, '66; Clark and Lashley, '47; Kennard, '39; Welch and Stuteville, '58), and they also show deficits in visual search (Latto and Cowey, '72). Sensory neglect has been described following damage to two other regions of the cerebral cortex of the monkey, namely the cingulate cortex, and the inferior parietal lobule (Heilman et al., '71; Watson et al., '73). Since both of these areas project preferentially to the rostral part of the frontal eye field, loss of this region may be primarily responsible for the sensory neglect



Fig. 13. Coronal sections through the thalamus and hypothalamus showing the distribution of labeled subcortical neurons following HRP injection in the caudal part of the frontal eye field.

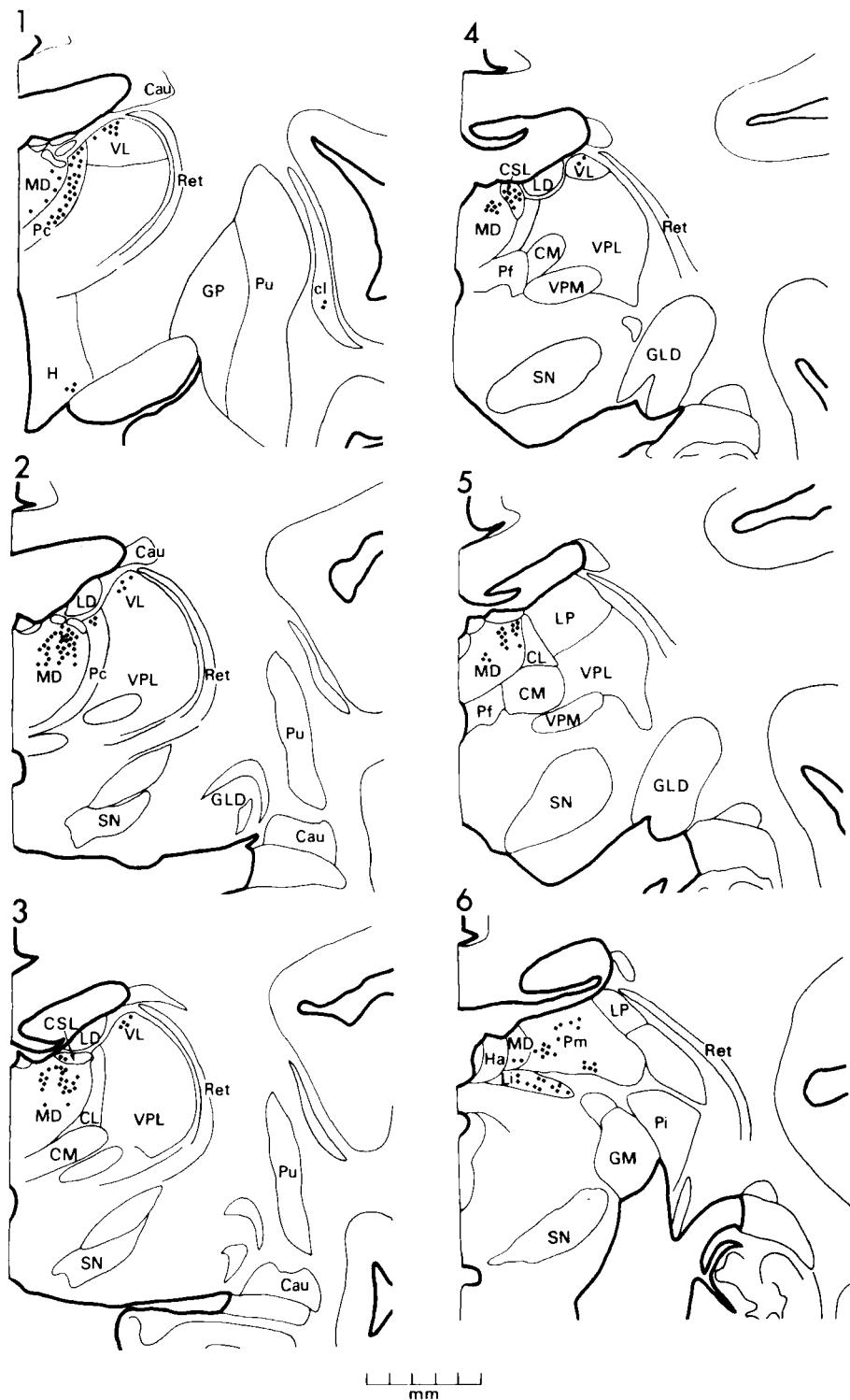


Fig. 14. Coronal sections through the thalamus and hypothalamus showing the distribution of labeled subcortical neurons following HPR injection in the rostral part of the frontal eye field.

observed following periarcuate damage. A common feature of all three cortices is a strong input from other limbic and paralimbic regions (Mesulam et al., '77; Rosene and Van Hoesen, '77). It is tempting to speculate that sensory neglect may be due to removal of high-order association regions where sensory and limbic input is integrated, since this integration may be necessary for directing attention toward motivationally relevant stimuli in the extra-personal space.<sup>6</sup>

Neurons in the frontal eye fields fire in association with eye movements (Bizzi, '67, '68; Bushnell and Goldberg, '79) and respond to visual stimuli (Mohler et al., '73), characteristics which they share with neurons in the inferior parietal lobule (Mountcastle et al., '75; Yin and Mountcastle, '77). Studies in awake monkeys further suggest that neurons in the inferior parietal lobule fire while the monkeys are attending to stimuli which have motivational significance for them (Hyvärinen and Poranen, '74; Lynch et al., '77; Mountcastle et al., '75; Robinson et al., '78). This behavior may depend on the presence of limbic and paralimbic input, which has been shown to reach the dorsolateral part of the inferior parietal lobule (PG) (Mesulam et al., '77). It would be interesting to know whether there are neurons with parallel properties in the rostral part of area 8, a region which receives input from paralimbic cortices as well as from the inferior parietal lobule.

The intermediate frontal eye field site in the present study showed a pattern of afferent connections which fell somewhere between that of the other two cases with respect to the proportion of cells in visual, auditory, and paralimbic regions, but it differed in one aspect: This intermediate region received a greater proportion of its afferent input from neighboring prefrontal cortical regions and from other parts of the frontal eye field than the other two. Moreover, it was the only part of the frontal eye field that received any significant input from the premotor (area 6) region posterior to the arcuate sulcus. It is not known if this region may also be preferentially involved in projections to other parts of the frontal eye fields and could thus participate in the coordination of incoming sensory and motor impulses among subsectors of the frontal eye field.

The distribution of labeled cells in the cortical layers displayed regional variation. Projections from neurons in unimodal sensory association regions arose mostly in lamina III, whereas this predominance was less marked in high-order association areas, and was absent in paralimbic regions, where the labeling was

equally distributed in infragranular and supragranular layers. The laminar distribution of the labeled cells could potentially specify more precisely the type of signals that one cortical region sends to another.

The present study demonstrated an orderly pattern in the organization of input to sub-sectors of the frontal eye field investigated (Walker's area 8). Input from visual areas was predominantly directed to the caudal parts whereas input from auditory areas, high-order association areas, and paralimbic cortices reached the more rostral parts. Marked cytoarchitectonic differences within area 8 appeared to parallel these differences in connectivity. The caudal part of area 8 may be involved in orienting toward visual stimuli while more rostral parts of this region may also be involved in orienting toward auditory stimuli. Furthermore, the paralimbic input into the rostral portion of area 8 may provide a mechanism for directing attention toward motivationally relevant stimuli in the extra-personal space. However, further architectonic, physiological, and behavioral analyses are necessary to determine whether independent criteria, other than connectivity, will also confirm the existence and significance of these topographical subdivisions in this part of the frontal eye fields.

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<sup>6</sup>The anatomical observations indicate that auditory and paralimbic areas preferentially project to more rostral parts of area 8. However, on the basis of the present results it cannot be determined whether the two types of projections overlap or whether they are merely close to each other.

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