Anatomic Organization of Basoventral and Mediodorsal Visual Recipient Prefrontal Regions in the Rhesus Monkey

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ABSTRACT

The sources of ipsilateral cortical afferent projections to basoventral and mediodorsal prefrontal cortices that receive some visual input were studied with retrograde tracers (horseradish peroxidase or fluorescent dyes) in eight rhesus monkeys. The basoventral regions injected with tracers included basal (orbital) areas 11 and 12, lateral area 12, and ventral area 46. The mediodorsal regions included portions of medial area 32 and the caudal part of dorsal area 8. These sites represent areas within basoventral and mediodorsal prefrontal cortices that show a gradual increase in architectonic differentiation in a direction from the least differentiated orbital and medial limbic cortices toward the most differentiated cortices in the arcuate concavity. The results showed that the visual input to basoventral and mediodorsal prefrontal cortices originated largely in topographically distinct visual areas. Thus, basoventral sites received most of their visual cortical projections from the inferior temporal cortex. The rostral inferior temporal region was the predominant source of visual projections to orbital prefrontal sites, whereas lateral area 12 and ventral area 46 also received projections which were found more caudally. In contrast, mediodorsal prefrontal sites received most of their visual projections from dorsolateral and dorsomedial visual areas. The cells of origin were located in rostromedial visual cortices after injection of retrograde tracers in area 32 and in more caudal medial and dorsolateral visual areas after injection in caudal area 8. The latter also received substantial projections from visuomotor regions in the caudal portion of the lateral bank of the intraparietal sulcus. These results suggest that the basoventral prefrontal cortices are connected with ventral visual areas implicated in pattern recognition and discrimination, whereas the mediodorsal cortices are connected with medial and dorsolateral occipital and parietal areas associated with visuospatial functions. In addition, the prefrontal areas studied received projections from auditory and/or somatosensory cortices, from areas associated with more than one modality, and from limbic regions. Orbital area 12 seemed to be a major target of projections from somatosensory cortices and the rostral portion of medial area 32 received substantial projections from auditory cortices. The least architectonically differentiated areas (orbital area 11 and medial area 32) had more widespread corticocortical connections, including strong links with limbic cortices. In contrast, areas which showed the highest degree of architectonic differentiation within the basoventral (area 46) and the mediodorsal (area 8) prefrontal cortices had restricted corticocortical connections.

Key words: visual cortices, corticocortical connections, prefrontal architectonic differentiation, parallel visual pathways

Abbreviations

A	arcuate sulcus
AMT	anterior middle temporal dimple
C	central sulcus
Ca	calcarine fissure
CC	corpus callosum
Cg	cingulate sulcus
6DR	Dorsal rostral area 6
Ia	agranular insula
Id	dysgranular insula
Ig	granular insula
IO	inferior occipital sulcus
IP	intraparietal sulcus
IPa	rostral portion of the superior temporal sulcus
IPd	cortex in the depths of the lateral intraparietal bank
L	lunate sulcus
LF	lateral fissure
LO	lateral orbital sulcus
MO	medial orbital sulcus
MPO	medial parietooccipital sulcus
MST	middle superior temporal area
MT	visual area MT in the depths of the superior temporal sulcus
MTp	peripheral field representation in area MT
OT	occipitotemporal sulcus
P	principal sulcus
PAll	limbic periallocortex
PG	area PG within the inferior parietal lobule
PGa	cortex in the depths of the medial superior temporal bank
PMT	posterior middle temporal sulcus
PO	parietooccipital sulcus
POa-e	the superficial portion of area POa in the lateral bank of the intraparietal sulcus
POa-i	the deep portion of area POa in the lateral bank of the intraparietal sulcus
Pro	proisocortex
ProM	rostral portion of the ventral premotor cortex
R	rhinal sulcus
Ro	rostral sulcus
SII	second somatosensory area
SP	subprincipal sulcus
S.PG	area PG in the superficial portion of the lateral intraparietal bank
ST	superior temporal sulcus
TEa	visual area in the rostral part of the lateral bank of the superior temporal sulcus
TEm	inferior temporal cortex occupying the lip of the lateral superior temporal bank
TE1	the ventral portion of the rostral part of the inferior temporal gyrus
TE2	area situated dorsal and caudal to area TE1 in the inferior temporal gyrus
TE3	caudal and dorsal portion of the inferior temporal gyrus
TPO	the central portion of the medial superior temporal bank
TS1	rostral portion of auditory area in the superior temporal gyrus
TS2	auditory area within the midportion of the superior temporal gyrus and adjacent cortex in the superior temporal sulcus
TS3	auditory area within the caudal part of the superior temporal gyrus and adjacent cortex in the superior temporal sulcus
V	ventricle
6Vb	rostral portion of ventral area 6
V1	striate cortex
V2	visual area 2
V3A	visual area 3A
V3d	dorsal portion of visual area 3
V3v	ventral portion of visual area 3
V4	visual area 4
V4t	transitional part of visual area 4

There are several sites within the prefrontal cortex of macaque monkeys which receive visual input including periarcuate, periprincipalis, and orbital regions (Jones and Powell, '70; Chavis and Pandya, '76; Jacobson and Trojanowski, '77; Barbas and Mesulam, '81, '85). The visual input originates in temporal, parietal, and occipital cortices, but the precise origin of projections to each prefrontal subarea is not known. This information is important because the visual cortices form a large and diverse cortical expanse in which the visual periphery is represented several times. Recent studies have provided evidence that there may be an emphasis on different aspects of the visual environment within the various visual cortices (see Zeki, '78b; Van Essen, '79, '85; Ungerleider and Mishkin, '82; Maunsell and Newsome, '87, for reviews). Knowledge of the origin of visual projections thus may provide information on the nature of the input directed to each prefrontal subdivision.

Several lines of evidence support a hypothesis of a differential organization of visual input to subdivisions of the prefrontal cortex. Within the prefrontal cortex, which extends from the arcuate sulcus to the frontal pole, there are several functionally distinct subareas (see Rosenkilde, '79; Fuster, '80, for reviews). For example, the periarcuate cortex seems to be involved in the performance of a variety of tasks dependent on compound sensory stimuli and of complex discriminative tasks (Goldman and Rosvold, '70; Stamm, '73; Milner et al., '78; Petrides and Iversen, '78; Van Hoesen et al., '80). Anatomic findings, which show differences in the origin of visual input to subsectors of area 8, suggest that the periarcuate cortex is a heterogeneous region (Barbas and Mesulam, '81). Another subdivision of the prefrontal cortex, which includes regions along the principal sulcus, seems to be critical in delayed response tasks for which spatial factors are particularly relevant (Jacobsen, '36; Butters and Pandya, '69). Anatomic findings indicate that the cortex buried in the caudal portion of the principal sulcus receives preferential input from parietal and from medial and lateral preoccipital regions (Barbas and Mesulam, '85), which have been implicated in visual spatial tasks (Lynch, '80; Mishkin et al., '82). The anatomic evidence is, therefore, consistent with the behavioral findings. Taken together, the above data suggest that the pattern of cortical afferent connections to each visual recipient prefrontal subarea may be unique and related to their particular functional activity.

In addition to their functional heterogeneity, the various visual recipient prefrontal areas are also architectonically diverse (Vogt and Vogt, '19; Walker, '40; von Bonin and Bailey, '47; Barbas and Pandya, '82). Our recent architectonic analysis indicates that the prefrontal cortex is composed of two distinct groups of cortices: basoventral and mediodorsal. Within each group of cortices a gradual increase in laminar differentiation was observed in a direction from the least architectonically differentiated limbic cortices to the most differentiated isocortices (Barbas and Pandya, '82). Each group of cortices thus exhibits an architectonic trend within the prefrontal cortex. The basoventral axis of cortical differentiation was traced from the relatively undifferentiated limbic cortices, situated behind area 13 in the caudal orbitofrontal region, and it continued through a series of ventrolateral areas which exhibit a gradual increase in laminar differentiation. The mediodorsal axis of architectonic differentiation was traced from a medial limbic area at the rostral tip of the cingulate sulcus and proceeded dorsally and caudally through regions showing an increasing laminar differentiation toward the upper limb of the arcuate sulcus. Several loci within each group of cortices receive visual input: within the basoventral axis, in an order from the least to the most architectonically differentiated, they include orbital area 11, area 12, and ventral areas 46 and 45 of Walker ('40). Within the medio-

dorsal cortical axis, area 8 around the upper limb of the arcuate sulcus is one region that receives visual input. Earlier studies provided evidence that some medial prefrontal regions, including area 32 of Pandya et al. ('81), may receive visual input as well (Jones and Powell, '70). It seems, therefore, that within each of the two groups of prefrontal cortices visual input reaches some rather undifferentiated regions and some which show a more developed cortical architecture (Fig. 1A,B,D,E).

The purpose of the present study was to investigate the anatomic organization of visual recipient prefrontal areas within the basoventral and mediodorsal axes of prefrontal cortical differentiation. Some of the visual recipient prefrontal areas, including areas 8 and 45 in the periarcuate region, and the banks of the principal sulcus have been the focus of previous investigations (Barbas and Mesulam, '81, '85). These areas were not considered further in this study with the exception of caudal area 8 at the confluence of the upper and lower limbs of the arcuate sulcus. This region, which was shown previously to be a major target of projections from visual cortices (Barbas and Mesulam, '81), was investigated further in light of recent anatomic, physiologic, and behavioral analyses of processing in visual cortices. The anatomic organization of most other visual recipient prefrontal regions, including ventral area 46, area 12, orbital area 11 of Walker ('40), and medial area 32 of Pandya et al. ('81) hitherto have received little attention. The aim of this study was to determine whether there is a systematic topography in the origin of visual cortical projections to subdivisions within the two architectonically defined groups of prefrontal cortices. Another aim was to determine what other input reaches each of the prefrontal sites, to aid in understanding the role of these regions in behavior.

MATERIALS AND METHODS

Experiments involving horseradish peroxidase (HRP) injections were conducted on seven rhesus monkeys (*Macaca mulatta*) anesthetized with ketamine hydrochloride (10 mg/kg, i.m.) followed by sodium pentobarbital until a surgical level of anesthesia was achieved. 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 injection of additional anesthetic as needed during surgery. A bone defect was made, the dura was retracted, and the cortex was exposed.

Horseradish peroxidase (HRP) experiments

In seven animals injections of a solution containing 8% HRP conjugated to wheat germ agglutinin (Sigma) were made with a microsyringe (Hamilton, 5 μl) 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 μl) of the injectate were delivered 1.5 mm below the pial surface at each of two adjacent sites separated by 1–2 mm over a 30-minute period. The prefrontal regions injected with HRP included orbital areas 11 and 12 (n=2), lateral area 12 and ventral area 46 (n=2), medial area 32 (n=1), and caudal area 8 (n=2) (Fig. 1G–I).

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% glu-

taraldehyde, 1% paraformaldehyde in 0.1 M phosphate buffer at pH 7.4) were delivered over a 30-minute period. The fixative was followed by perfusion with 2 liters of cold (4°C) phosphate buffer (0.1 M, pH 7.4).

The brain then was removed from the skull, photographed, placed in glycerol phosphate buffer (10% glycerol and 2% DMSO in 0.1 M phosphate buffer at pH 7.4) for 1 day and in 20% glycerol phosphate buffer for another 2 days. The brain then was frozen in −75°C isopentane as described by Rosene et al. ('86), transferred to a freezing microtome, and cut in the coronal plane at 40 μm; the sections were placed in a solution of 0.1 M phosphate buffer (pH 7.4). One series of sections was treated for the visualization of HRP according to a procedure in which tetramethyl benzidine is used as the chromogen (Mesulam et al., '80): The tissue was mounted, dried, and counterstained with neutral red. Adjacent series of sections were stained for the visualization of Nissl bodies, myelin, or acetylcholinesterase to aid in delineating architectonic borders (Geneser-Jensen and Blackstad, '71; Gallyas, '79).

Experiments with callosal section

In two animals the splenium of the corpus callosum was transected to interrupt interhemispheric fibers between the visual cortices. These animals received HRP injections 5 days later in periarcuate regions (cases 7, 8) that are known to receive visual input from a variety of extrastriate cortices (Barbas and Mesulam, '81). The corpus callosum was transected to determine whether, and to what extent, visual areas receiving projections from the contralateral visual cortices project to the prefrontal cortex. In addition, the location of callosal projections aided in delineating architectonic borders within the extrastriate region, since the representation of the vertical meridian lies at the border of distinct visual cortices and receives dense callosal projections (Zeki and Sandeman, '76; Van Essen and Zeki, '78; Newsome et al., '86).

Prior to callosal transection, intravenous infusion of mannitol (Invenenx, Ohio, 25%) was given to reduce the volume of the brain and avoid traumatic edema. The splenium of the corpus callosum was surgically transected following a parasagittal craniotomy after cauterization and cutting of the midline bridging veins. After perfusion, the brains in these cases were cut in the coronal plane in series of 20 and 40 μm. Series of 40-μm-thick sections were treated for the visualization of HRP, myelin, Nissl bodies, or acetylcholinesterase. The 20-μm-thick series of sections were transferred into 10% formalin and were subsequently stained for the visualization of degenerating fibers according to a Fink-Heimer procedure modified for the primate brain by G.W. Van Hoesen.

Fluorescent dye experiment

One animal received an injection of the fluorescent dye diamidino yellow (3%, 0.5 μl) in medial prefrontal area 32 (case 6). General surgical procedures for this animal were identical to those described for the HRP experiments. After a survival period of 7 days the animal was deeply anesthetized and perfused with 6% paraformaldehyde in 0.1 M cacodylate buffer at pH 7.4. The brain was then placed in a solution of 6% paraformaldehyde with 10% glycerol and 2% DMSO for 1 day and transferred to a solution containing 20% glycerol in 2% DMSO for another 2 days. The brain was frozen, cut in the coronal plane at 40 μm, and the sections were mounted on subbed slides.
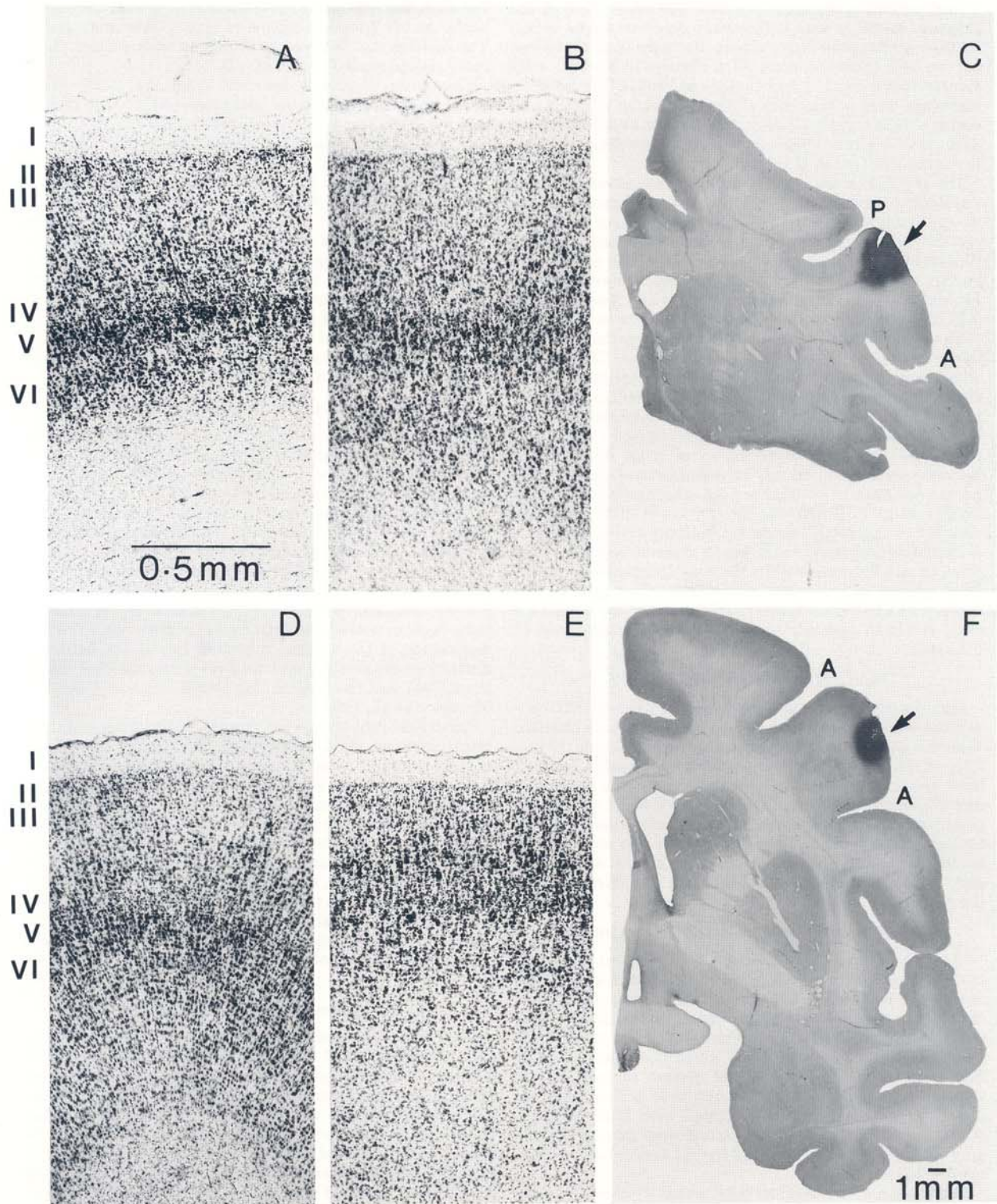
Fig. 1. (left). Brightfield photomicrographs showing the cytoarchitectonic features of some basoventral (orbital area 11, **A,** and ventral area 46, **B**) and mediodorsal regions (area 32, **D,** and area 8, **E**) which receive visual projections. HRP injection (arrow) in ventral area 46 (case 4) is shown in **C,** and is shown in **F** in area 8 (case 7). A, B, D, and E: celloidin-embedded tissue, cresyl violet stain. The relationship of the injection sites (black areas) to architectonic areas of the prefrontal cortex is shown on the medial (**G**), lateral (**H**), and basal (**I**) surfaces (right). The architectonic areas shown on the medial surface are according to the maps of Pandya et al. ('81) and Barbas and Pandya ('82); areas on the lateral and basal surfaces are according to the map of Walker ('40). Black numbers designate architectonic areas; white ones refer to cases.

Three adjacent series of sections were saved for microscopic analysis. These series were mounted and dried onto subbed slides within 4 hours after they were cut. The three series were stored in light-tight boxes with Drierite at 4°C. The first series was coverslipped with Fluoromount 7 days later and was returned to dark storage at 4°C. The second series was left uncoverslipped and was used to chart the location of retrogradely labeled cells. After the second se-

ries was charted it was stained with thionin, coverslipped, and used to determine cytoarchitectonic boundaries. Because the thionin obscured the fluorescence of series 2, further verification of the projection zones was made from the immediately adjacent sections from series 1 and 3.

Data analysis

Experimental slides prepared according to the method described above were viewed microscopically under bright-field or fluorescent illumination. Outlines of brain sections and the location of labeled neurons ipsilateral to the injection site were transferred from the slides onto paper by using an X-Y recorder (Hewlett Packard, 7044B), 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 (Fig. 1C,F). The less-densely labeled area surrounding this region was drawn as the halo of the injection site. The laminar distribution of labeled cells was also noted on the plotting.

All of the prepared slides were examined, but only representative sections (every other) among those containing labeled neurons 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.

Procedural variables, such as size of the injection site, exposure of the tissue to alcohol, etc., inadvertently differ from case to case. In order to minimize the above extrinsic factors, the relative afferent input to the injected site from a particular anatomic region was assessed by expressing the number of labeled cells in serial sections through that anatomic region as a percentage of the total number of labeled cortical cells in that case. This analysis is based on the assumption that retrograde transport and histochemical variables underlying HRP or fluorescent dye sensitivity affect all cortical regions in that case in a similar manner. It is possible then to demonstrate qualitative differences in the pattern of regional labeling among cases without making direct statistical comparisons.

Labeled cells in the immediate vicinity of the injection site (within 0.5-mm radius from the halo of the injection site, 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 thus could 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 observed also in many cortical sites but this was not charted for this study.

Reconstructions

The projection sites were serially reconstructed by using the sulci as landmarks and are 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 projection sites were also plotted on unfolded maps of the cerebral cortex. The maps were prepared by measuring the depth of sulci and exposed cortex through layer IV from
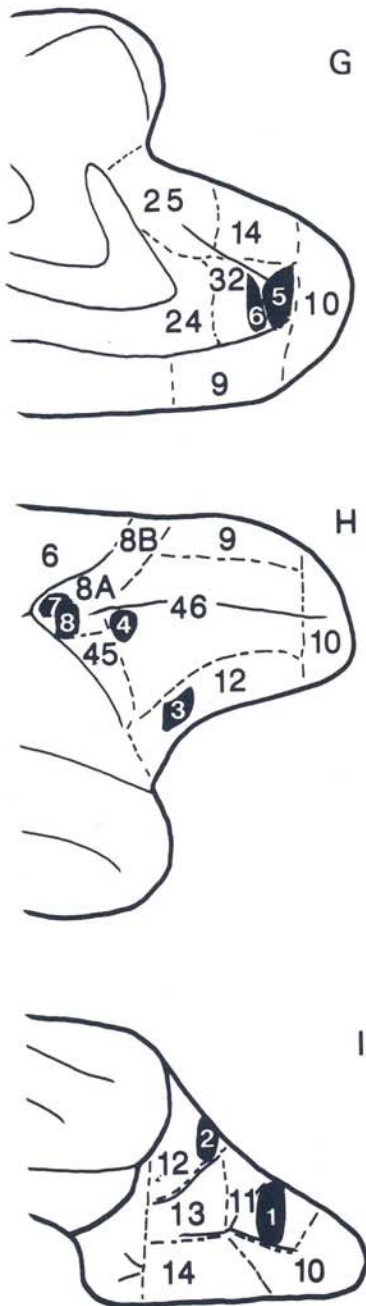

Figure 1 continued

coronal sections separated by 1.6 mm. The length of sulci and gyri for each rostrocaudal level was proportionally depicted in a straight line. The circular cortex was represented, therefore, on a flat surface by inserting an artificial cut between the medial and basal surfaces. The depth of one sulcus (the principalis, anteriorly) was used as a reference, or starting point, and is shown in the diagrams as a straight line. Another landmark was used as a starting point in more posterior levels until the entire cortex containing labeled neurons was unfolded.

The constructed map therefore contains a "fixed" axis that depicts the rostrocaudal dimension of the brain. This axis is shown from right to left in the diagrams. The dorsoventral axis shows the extent of the unfolded cortex in a series of rostrocaudal points. Because the dorsoventral axis varies in length as the extensive cortex buried in sulci is unfolded, the finished map appears elongated, and sulci that are the furthest from the reference point may appear distorted. For a better visual representation of the unfolded map, the rostrocaudal dimension was expanded by a factor of 2.5 in the diagrams. The least visually distorted regions are within the sulcal cortex whose depth is used as a reference and is shown as an arbitrary straight line. To determine whether there was areal distortion of regions that are far from the reference point, the area of several sulci was remapped separately on "ideal" diagrams in which the depth of each sulcus was depicted as a straight line. Comparisons of areas within the banks of sulci measured with a planimeter in the ideal maps and of the same sulci unfolded on the entire brain showed an average variation of 3 ± 2%. Thus it does not appear that the described method introduces a significant areal distortion.

Architectonic boundaries of regions containing HRP-labeled neurons were determined from series of matched sections stained with thionin, myelin, or acetylcholinesterase. References to architectonic areas of the prefrontal cortex situated on the lateral and basal surfaces are according to the classification of Walker ('40; Fig. 1H,I). The medial surface around the corpus callosum and the cortex rostral to it have been subdivided recently by several investigators (Pandya et al., '81; Barbas and Pandya, '82; Vogt et al., '87; Barbas and Pandya, in preparation), and references to the medial surface in this study are according to these maps (Fig. 1G).

RESULTS
Injection sites

The injection sites were situated in four basoventral (cases 1–4) and four mediodorsal (cases 5–8) prefrontal regions. The basoventral regions included two basal (orbital) sites (area 11, case 1, and the anterior portion of orbital area 12, case 2; Fig. 1I) and two ventral regions below the principal sulcus (the lateral portion of area 12, case 3, and the caudal portion of ventral area 46, case 4, Fig. 1C,H). The mediodorsal regions included area 32 of Pandya et al. ('81) situated below the rostral part of the cingulate sulcus (two cases). In one of these cases an HRP injection covered the rostral portion of area 32 (case 5), and in the other case a diamidino yellow injection was within the central portion of area 32 (case 6; Fig. 1G). In two other cases HRP injections were in area 8 in the caudal periarcuate region at the junction of the upper and lower limbs of the arcuate sulcus (Fig. 1H). One of these injections involved primarily the dorsolateral portion of area 8 (case 7, Fig. 1F); the other extended to the anterior bank of the lower limb of the arcuate sulcus and the adjacent cortex (case 8). Both of these regions are within Walker's ('40) area 8A. They were included in the dorsal category in this study on the basis of a recent architectonic study of the prefrontal cortex (Barbas and Pandya, '82; in preparation).

Intact axons in the white matter are not thought to take up HRP (LaVail, '75; Mesulam, '82). 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.

Cortical projections

Cortical regions where labeled neurons were noted following HRP or fluorescent dye injections are shown on the surface of the brain, on maps of the unfolded cortical surface, and in cross sections in Figures 2–9. The distribution of labeled neurons in the various cortices is shown in Table 1. Labeled neurons were noted in extrastriate and inferior temporal areas, in the lateral bank of the intraparietal sulcus and the inferior parietal lobule, in the superior temporal gyrus and banks of the superior temporal sulcus, in the frontal and parietal operculum, in prefrontal and premotor regions, in the insula, and in the cingulate and

TABLE 1. Distribution of Labeled Neurons in the Macaque Cortex Following Injection of Retrograde Tracers in Basoventral and Mediodorsal Prefrontal Regions[1]

| | Injection site | | | | | | | |
| | Basal | | Ventral | | Medial | | Dorsal | |
Origin	Area: 11 Case: 1	12 2	12 3	46 4	32 5	32 6	8 7	8 8
Visual	5	4	10	4	1	6	13	43
Visuomotor	—	—	<0.5	7	—	—	15	26
Auditory	<1	—	8	—	16	6	<0.5	<0.5
Somatosensory	3	31	3	1	<0.5	—	<0.5	1
Premotor	*	10	<0.5	7	—	—	13	2
Parieto-temporal	5	<1	8	1	11	*	2	4
Prefrontal	61	28	64	77	40	58	56	23
Limbic	25	25	6	2	32	29	<0.5	<0.5

[1]Data are expressed in percentages. Abbreviations here and throughout the Tables are as in list preceding Figure 1. The total number of labeled cortical cells in serial sections was: case 1, 13,445 cells in 49 sections; case 2, 9,193 cells in 43 sections; case 3, 9,452 cells in 45 sections; case 4, 12,118 cells in 51 sections; case 5, 16,487 cells in 41 sections; case 6, 2,239 cells in 40 sections; case 7, 2,452 cells in 42 sections; case 8, 1,921 cells in 49 sections.
—, No labeled neurons.
*Less than 0.1%.

retrosplenial cortex. These results are consistent with previous findings (Jones and Powell, '70; Chavis and Pandya, '76; Jacobson and Trojanowski, '77; Mesulam et al., '77; Leichnetz, '80; Barbas and Mesulam, '81; Maioli et al., '83; Petrides and Pandya, '84; Schwartz and Goldman-Rakic, '84; Andersen et al., '85; Huerta et al., '87).

The above cortical regions were classified in one of the following functional classes: visual, visuomotor, auditory, somatosensory, premotor, parietotemporal, prefrontal, or limbic. The inclusion of regions with labeled neurons in a particular category was made on the basis of two or more of the following criteria: 1) architectonic characteristics; 2) patterns of neural connections based on anatomic experiments; 3) behavioral experiments decribing deficits in various tasks following regional damage; and 4) electrophysiologic studies on the properties of neurons in specific cortical regions.

Visual

The striate cortex (area 17) and extrastriate areas 18 and 19 of Brodmann ('05), or areas OC, OB, and OA of von Bonin and Bailey ('47), and the inferior temporal cortex (areas 20, 21, or TE) have been implicated in visual function. These visual cortices have been subdivided further in recent years on the basis of physiologic and anatomic studies (for reviews see Zeki, '78a,b; Van Essen, '79, '85; Ungerleider and Mishkin; '82; Maunsell and Newsome, '87), and the newer terminology will be used wherever applicable.

In the present experiment labeled neurons were found in most visual cortices described to date. Projections from visual areas to the prefrontal cortex originated in the depths of the superior temporal sulcus, the inferior temporal gyrus, the banks of the anterior and posterior middle temporal dimples, the parietooccipital, medial parietooccipital, occipitotemporal, inferior occipital, and lunate sulci, and the calcarine fissure. The above regions are included in inferior temporal areas TE1–3, TEa, and TEm of Seltzer and Pandya, ('78) and areas MST, MT (or V5), MTp, V4, PO, V3A, V3 dorsal and ventral (the latter also known as area VP), and V2; (a list of abbreviations used and their meanings precedes Fig. 1). The delineation of borders of distinct visual cortices containing labeled neurons was made from matched sections stained for the visualization of myelin or Nissl bodies based on descriptions in recent studies (see Zeki, '78b; Van Essen, '79, '85; Maunsell and Newsome, '87, for reviews; Seltzer and Pandya, '78; Covey et al., '82; Maunsell and Van Essen, '83; Desimone and Ungerleider, '86; Colby et al., '88). In addition, areas of dense callosal projections aided in estimating the site of the vertical meridian which lies at the anterior border of area V3 and between V1 and V2 (Zeki and Sandeman, '76; Van Essen and Zeki, '78; Zeki, 78d; Newsome et al., '86). Some architectonic borders, particularly the extent of area V3A and the dorsal portion of V3, were difficult to delineate in some sections. In this study labeled neurons were assigned to the dorsal portion of area V3 on the basis of their proximity to area V2 and to an area of dense callosal projections which was taken as the position of the vertical meridian marking the anterior border of area V3. Neurons situated anterior to area V3 and caudal to area POa in the floor and lateral bank of the parietooccipital region were assigned to area V3A. The delineation of other visual cortices, including areas PO, V3 ventral (or VP), and superior temporal areas MST and MT, are based on architectonic descriptions provided in other studies (Covey et al., '82; Ungerleider and Desimone, '86; Felleman and Van Essen, '87; Colby et al., '88).

Visual cortical projections to basoventral prefrontal regions. After HRP injection in orbital area 11 and an orbital portion of area 12, labeled neurons were found in the rostral portion of the inferior temporal cortex. The labeled neurons, which accounted for 5.1% of all neurons directed to orbital area 11 and 4.1% of all those projecting to orbital area 12, were found primarily in the anterior portion of the inferior temporal gyrus, in the banks of the anterior middle temporal dimple and the anterior portion of the occipito-temporal sulcus (areas TE1 and TE2), and in the lateral bank of the superior temporal sulcus in area TEa (Table 2, cases 1, 2; Figs. 2, 3, 10A).

Injections of HRP in the lateral portion of area 12 and ventral area 46 also resulted in neuronal labeling within the inferior temporal cortex. In case 3, with an HRP injection in lateral area 12, 10.2%, and in case 4 with an HRP injection in ventral area 46, 4% of the total number of

TABLE 2. Distribution of Labeled Neurons in Visual Cortices After Injection of Retrograde Tracers in Basoventral and Mediodorsal Prefrontal Regions[1]

| | Injection site | | | | | | | |
| | Basal | | Ventral | | Medial | | Dorsal | |
Origin	Area: 11 Case: 1	12 2	12 3	46 4	32 5	32 6	8 7	8 8
Area TE1	2.8	0.4	0.7	—	—	—	—	*
Area TE2	0.7	*	1.8	*	—	—	—	—
Area TE3	—	—	0.5	0.3	—	—	0.2	1.8
Area TEa	1.6	3.7	5.9	2.9	—	—	—	—
Area TEm	—	*	1.1	0.6	—	—	—	—
MST, MTp	—	—	0.2	*	—	—	5.4	12.5
MT	—	—	—	0.2	—	—	2.5	5.4
Area PO	—	—	—	—	1.0	0.5	0.4	3.2
V4t, V4	—	—	—	*	—	—	1.3	1.7
V3A	—	—	—	—	—	—	1.6	10.6
V3d	—	—	—	—	—	—	*	2.1
V3v	—	—	—	—	—	—	1.0	3.4
V2	—	—	—	—	—	5.9	0.5	1.9
Total	5.1	4.1	10.2	4.0	1.0	6.4	12.9	42.6

[1]Data are expressed in percentages.
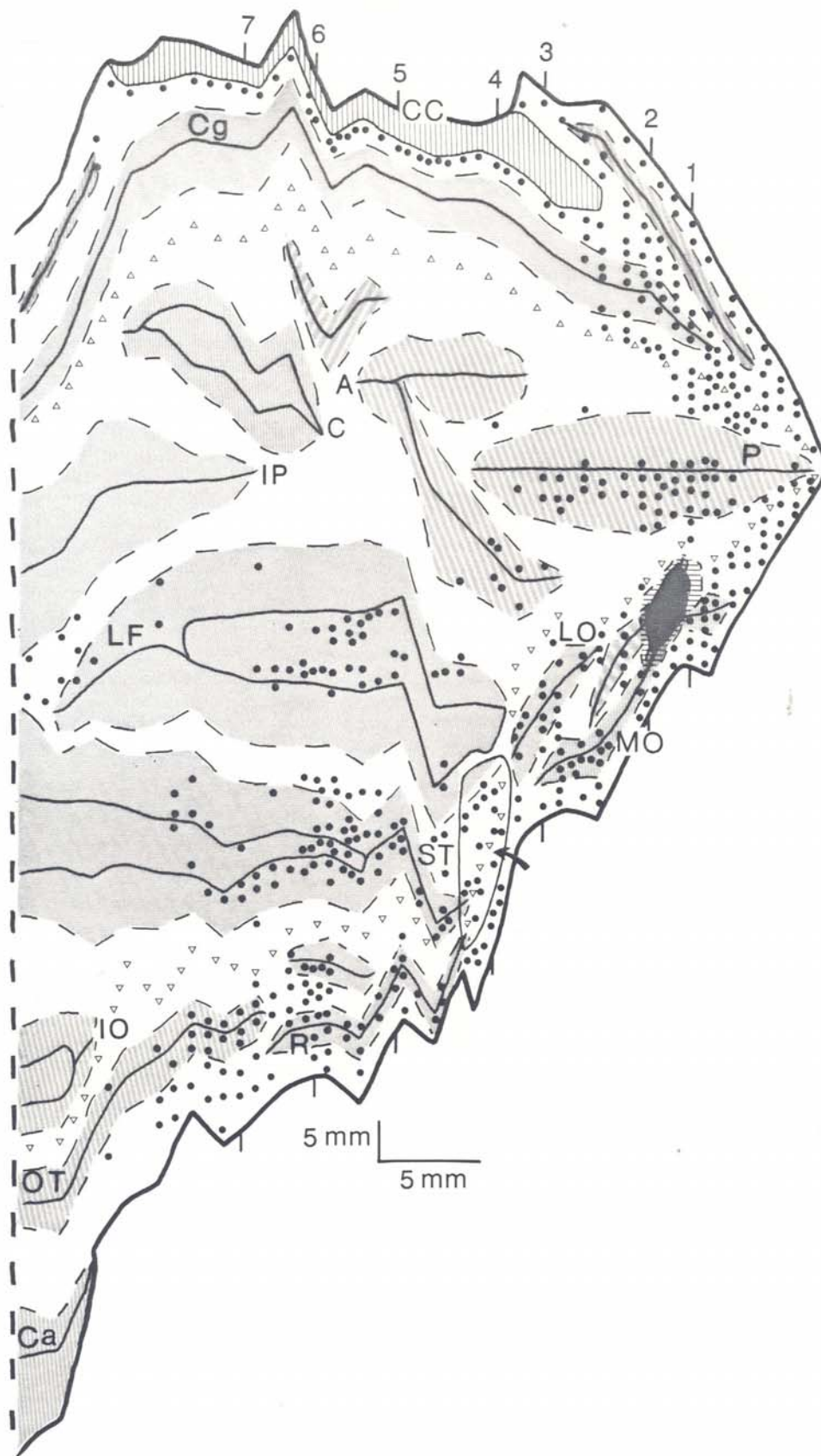—No labeled neurons.
*Less than 0.1%.

Figure 2

labeled neurons were found in the above visual areas (Table 2, cases 3, 4). Labeled neurons were noted mainly within the lateral bank of the superior temporal sulcus, the inferior temporal gyrus, and the banks of the occipitotemporal sulcus. When compared with the projections to the orbitofrontal sites, projections to lateral area 12 and ventral area 46 were found more caudally within the inferior temporal

cortex (areas TE2-3, TEa, and TEm, Figs. 4, 5). In addition, in both ventrolateral prefrontal cases there was a small number of labeled neurons in area MST or MT situated in the depths of the caudal part of the superior temporal sulcus.

Visual projections to mediodorsal prefrontal regions. Labeled neurons in visual cortices directed to area
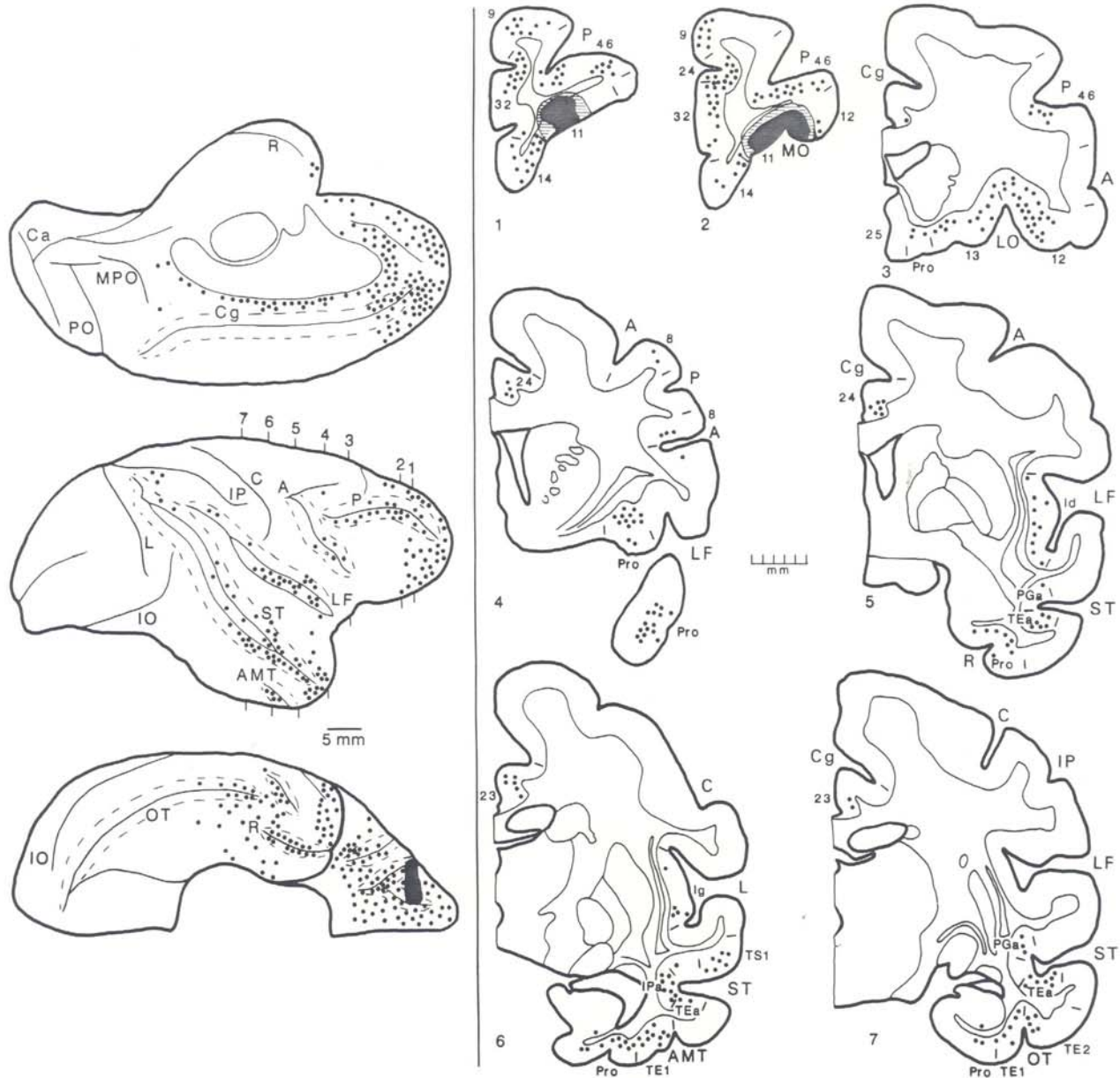

Fig. 2. The distribution of labeled neurons (represented by dots) following HRP injection (black area) in orbital area 11 (case 1) is shown on a map in which the sulci and insulae were unfolded (left, gray areas); (right) on the medial (top), lateral (center), and basal (bottom) surfaces of the cerebral hemisphere; and (far right) on coronal sections (1–7): the latter were taken at the level shown on the surface of the cortex (left). The horizontally striped area shows the halo of the injection site. The small vertical lines in the diagrams of coronal sections demarcate architectonic borders. The cortex buried in sulci is shown diagrammatically on the medial, lateral, and basal surfaces by the dotted lines (right). In the map showing the unfolded cortex the rostrocaudal dimension (right to left) was expanded by a factor of 2.5. Triangles separate the dorsolateral from the medial surface (top) and the ventrolateral from the basal surface (bottom). Heavy dotted lines indicate that cortex beyond that point was not unfolded. The corpus callosum is shown by thin vertical stripes. Curved arrow points to the portion of the temporal pole (oval within thin uninterrupted line) situated anterior to the limen insulae. The dorsomedial portion of the pole, which becomes continuous with the lower bank of the lateral fissure caudally, is shown in gray. The above conventions apply for Figures 2–9.
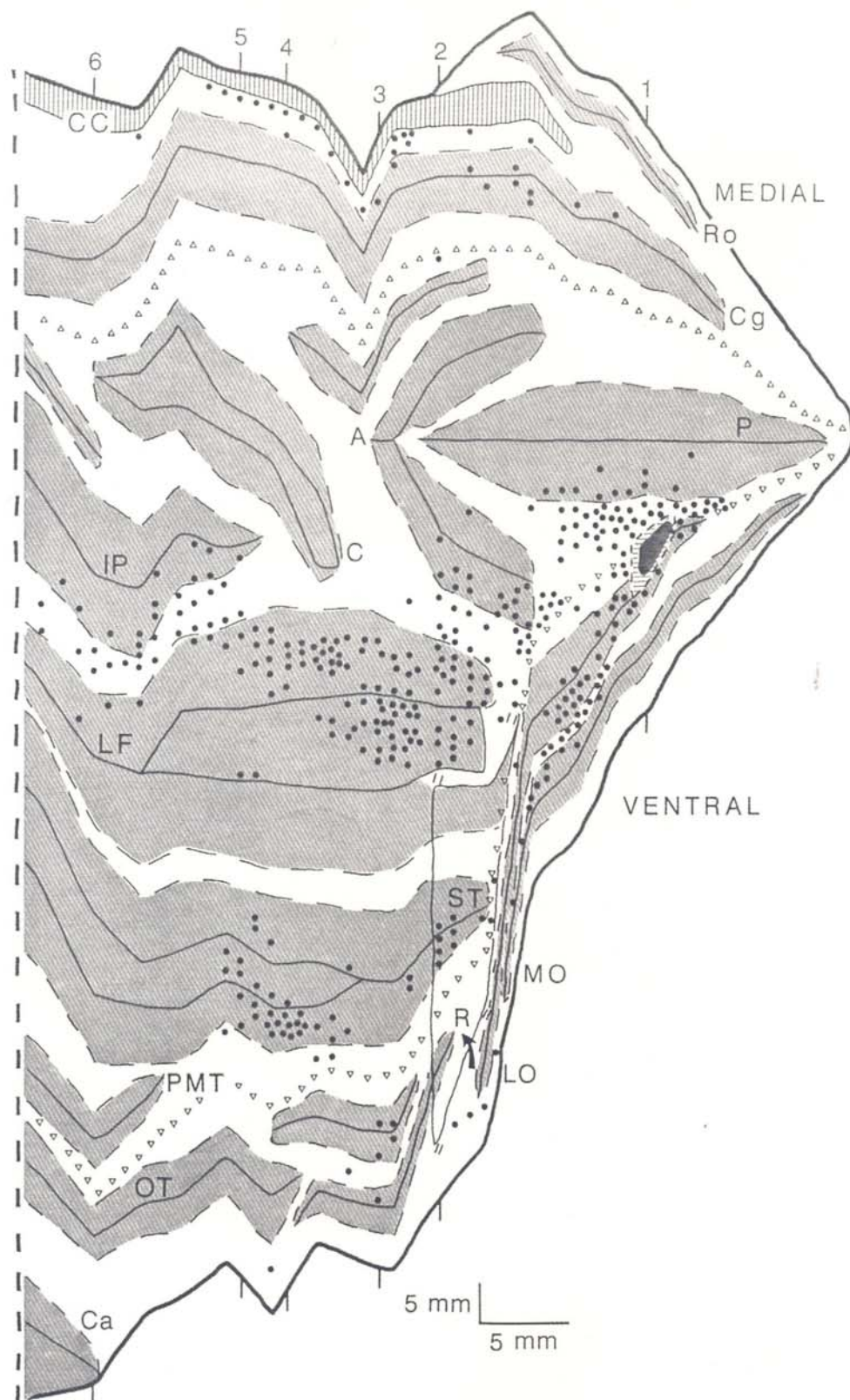
Fig. 3. The distribution of labeled neurons following HRP injection in orbital area 12 (case 2) is shown on a map where the sulci were unfolded (left) on the medial, lateral, and basal surfaces of the cerebral hemisphere (right) and on coronal sections 1–6 (far right).

32 were found exclusively in medial areas. These zones included area PO described by Covey et al. ('82) and the most rostral portion of area V2, situated within the upper bank of the calcarine fissure and the adjacent medial cortex (Figs. 6, 7). In the case with an HRP injection in rostral area 32 (case 5) 1%, and in central area 32 (case 6) 6.4% of the total number of labeled neurons were noted in medial visual cortices (Table 2, cases 5, 6).

Following HRP injection in caudal area 8 labeled neurons were found primarily in dorsomedial and dorsolateral visual cortices. Although the pattern of labeling was similar in the two cases, the proportion of labeled neurons differed (Table 2, cases 7, 8). Thus, visual cortices contained 12.9% of all labeled neurons directed to the dorsolateral portion of area 8 (case 7; Fig. 1F) and 42.6% projecting to area 8 which included a part of the anterior bank of the lower limb of the
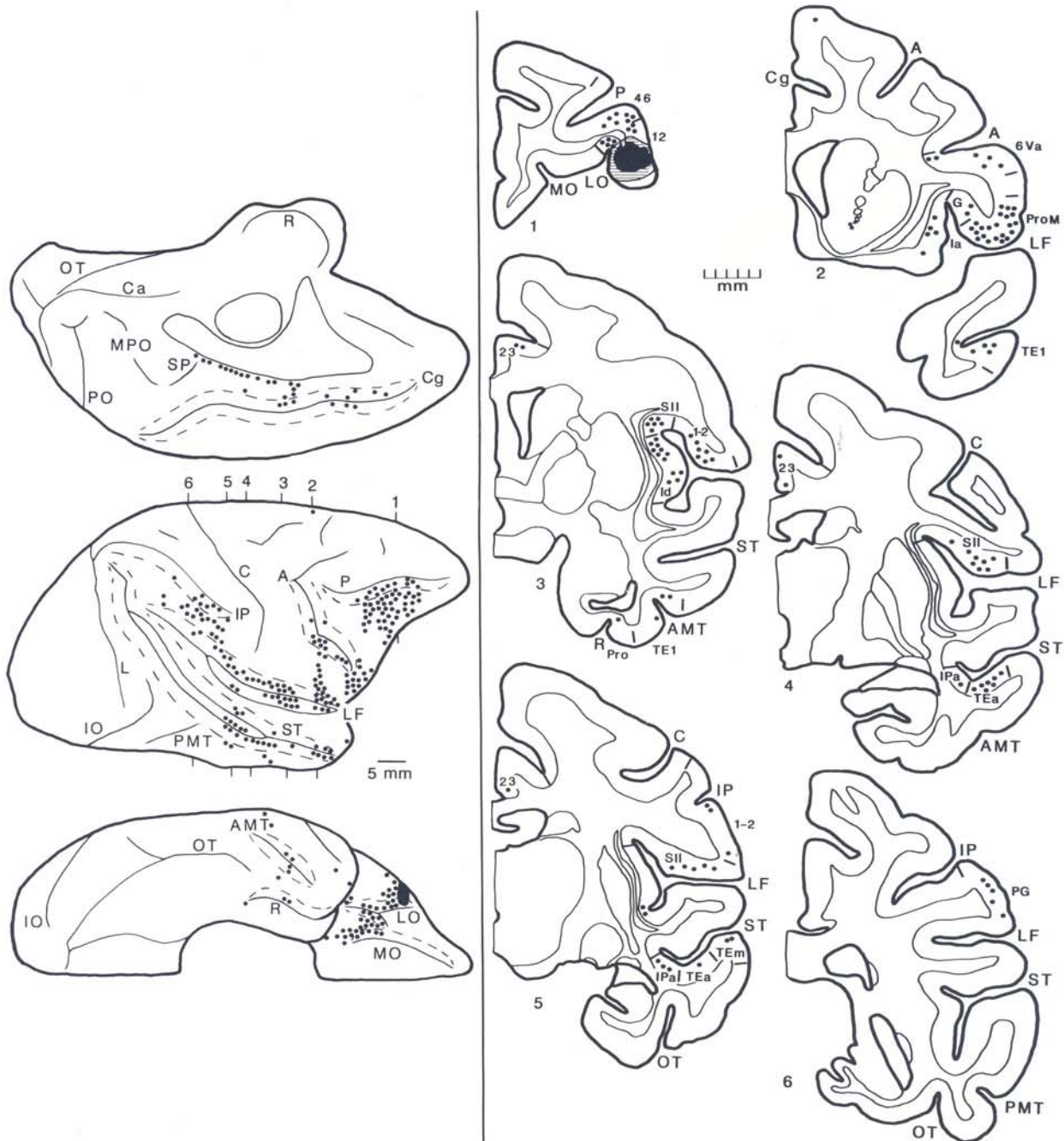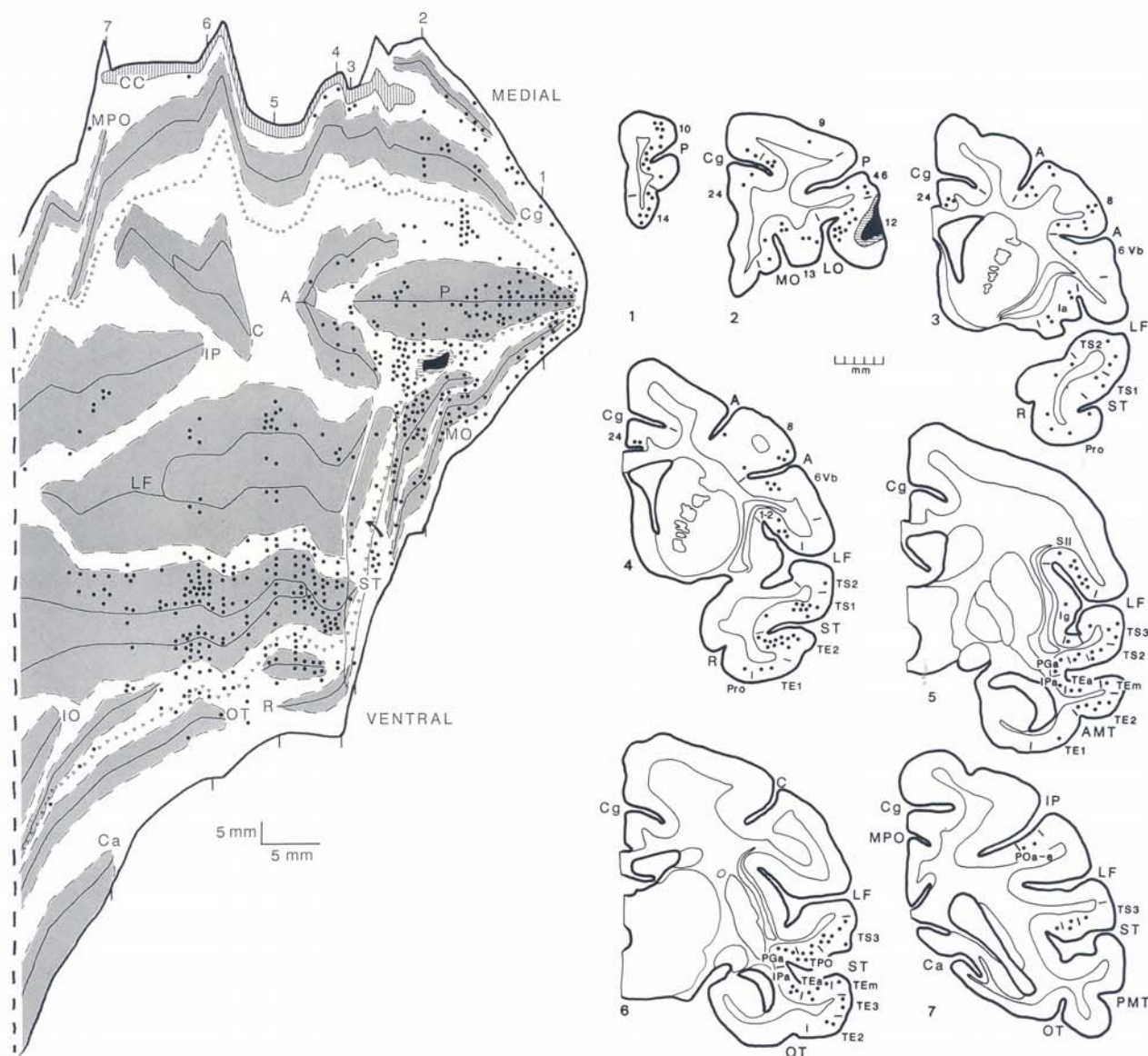

Figure 3 continued.

Fig. 4. The distribution of labeled neurons following HRP injection in lateral area 12 (case 3) is shown on a map where the sulci were unfolded (left) and on coronal section 1–7 (right).

arcuate sulcus (case 8). In both cases the labeled neurons were found within the caudal third of the floor and adjacent lateral bank of the superior temporal sulcus, in the banks of the occipitotemporal sulcus at its caudal extent, and in the banks of the parietooccipital, medial parietooccipital, inferior occipital, and lunate sulci and the rostral portion of the calcarine fissure (Figs. 8, 9, 10B).

On the basis of a combination of cytoarchitectonic and myeloarchitectonic criteria and the distribution of callosal fibers from the contralateral visual cortices, it was determined that the periarcuate cortex received input from most extrastriate areas described to date (Table 2). These included areas MST, MT, and MTp within the depths of the superior temporal sulcus, areas V3A, PO, and the dorsal portion of area V3 in the parietooccipital region, the ventral portion of area V3 (also known as area VP) in the banks of

the inferior occipital and occipitotemporal sulci, area V4 (transitional) and V4 anterior to the lunate sulcus, area V2 in the caudal portion of the occipitotemporal sulcus, and the banks of the calcarine fissure.

Site of corticocortical projections in relation to callosal terminations. The pattern of callosal terminations was similar in the two cases (Figs. 8, 9). In both periarcuate cases about one-third of all HRP-labeled neurons in visual cortices overlapped with zones which received callosal projections from the contralateral visual cortices (Fig. 10C,D). The rest of the labeled neurons were situated in extrastriate regions which received few, if any, callosal projections. There were regional variations in the overlap of corticocortical and callosal projections. For example, all labeled neurons within the lunate sulcus overlapped with sites which received callosal projections. On the other hand, most la-

beled neurons at the junction of the upper bank and the floor of the superior temporal sulcus were situated in zones which received few, if any, callosal projections.

Visuomotor

Neurons in a large parietal area, including the caudal portion of the lateral bank of the intraparietal sulcus and the adjacent inferior parietal lobule, respond to visual stimuli and in association with eye movement (see Lynch, '80; Hyvärinen, '82, for reviews). Physiologic studies have not addressed the question of functional differences between the cortex within the lateral bank of the intraparietal sulcus and the inferior parietal lobule, but architectonic studies indicate that the two regions are distinct (Seltzer and Pandya, '80; Pandya and Seltzer, '82; Seltzer and Pandya, '86). Moreover, unlike most of the cortex of the inferior parietal lobule, the sulcal parietal cortex has monosynaptic connections with neighboring visual cortices and is reciprocally connected with the superior colliculus, a pre-oculomotor center (Seltzer and Pandya, '80; Lobeck et al., '83; Lynch et al., '85). Because of the above anatomic and connectional properties, the cortex considered visuomotor in this and in previous studies is restricted to the lateral bank of the intraparietal sulcus caudally (Barbas and Mesulam, '81, '85).

The caudal portion of the lateral intraparietal bank was subdivided by Seltzer and Pandya ('80, '86) into four architectonic zones. Area IPd is situated in the depths of the intraparietal sulcus and areas POa-i, POa-e, and PG are found successively in a direction from the depth of the sulcus toward the cortical surface. Area PG occupies the superficial portion of the lateral intraparietal bank and will be referred to as sulcal area PG in this study to distinguish it from area PG within the inferior parietal lobule. Several other names have been used to describe these parietal regions as well. Area VIP of Maunsell and Van Essen ('83) corresponds to the deep portion of the lateral intraparietal bank and overlaps with areas IPd and POa-i. Area LIP of Andersen et al. ('85) is situated above area VIP and seems to overlap with area POa-e and sulcal area PG.

Labeled neurons in the lateral intraparietal bank were found in four of the cases (Table 3). In case 3 with an HRP injection in lateral area 12, fewer than 0.5%, and in case 4, with an HRP injection in ventral area 46, 6.9% of all labeled neurons were located in the lateral intraparietal bank. In both of these cases most labeled neurons were found within the upper half of the bank and were within sulcal area PG and POa-e (Table 3, cases 3, 4, Figs. 4, 5, 11A). In contrast, a higher proportion of labeled neurons in the lateral intraparietal bank was found after HRP injection in the dorsolateral (case 7, 15.3%) and in the sulcal (case 8, 26%) area 8 site. Unlike the previous cases, some of the labeled neurons in case 7 were found in the depths of the intraparietal sulcus within areas POa-i and IPd. However, like the previous two cases, most labeled neurons were found within area POa-e as well (Fig. 8). In case 8 with a sulcal area 8 HRP injection most labeled neurons were found in area POa-i, followed by areas POa-e, sulcal PG, and IPd (Figs. 9, 11B,C).

Auditory

Labeled neurons in auditory regions were found in area TA (von Bonin and Bailey, '47), or within areas TS1–3, and paAlt according to more recent classification of the auditory cortex (Galaburda and Pandya, '83). The above areas are considered auditory by virtue of their monosynaptic connections with the primary auditory cortex and on the basis of results from behavioral and electrophysiologic experiments (see Pandya and Yeterian, '85; Pandya et al., '88, for reviews). Of the two orbitofrontal cases some (0.7%) labeled neurons in auditory cortices were observed in case 1 (area 11). These labeled neurons were found in area TS1 within the rostral part of the superior temporal gyrus and the superficial part of the superior temporal sulcus (Table 4, case 1, Fig. 2). In the lateral area 12 case (case 3) 7.6% of all labeled neurons were found in auditory cortices. Most of these were seen in areas TS1–3, and a few were situated in areas paAlt, paAr, paI, and proA. There was no evidence of labeled neurons in auditory regions in case 4, which had an HRP injection in ventral area 46.

A substantial number of labeled neurons were found in auditory cortices following injection of retrograde tracers in the rostral portion of area 32 (15.9%, case 5) and in the central portion of area 32 (5.7%, case 6). Most of these labeled neurons were found in areas TS1–3 and to a lesser extent in areas paAr, paI, and proA (Figs. 6, 7, 12C). There were very few (<0.5%) labeled neurons in auditory cortices after HRP injection in area 8 (cases 7, 8).

Somatosensory

Labeled neurons in somatosensory cortices were located in the dysgranular and granular insula, in the rostral part of the lateral bank of the intraparietal sulcus, and in the adjacent cortex within area PF (von Bonin and Bailey, '47). A few labeled neurons were noted also in the floor of the central sulcus within area 3a and in area 5 at the superior

TABLE 3. Distribution of Labeled Neurons in Subdivisions of the Caudal Portion of the Lateral Intraparietal Bank After Injection of Retrograde Tracers in Basoventral and Mediodorsal Prefrontal Regions[1]

	Injection site							
	Basal		Ventral		Medial		Dorsal	
	Area: 11	12	12	46	32	32	8	8
Origin	Case: 1	2	3	4	5	6	7	8
Area IPd	—	—	—	—	—	—	0.2	2.0
Area POa-i	—	—	*	0.1	—	—	4.0	13.6
Area POa-e	—	—	0.3	2.3	—	—	11.1	6.8
Sulcal PG	—	—	—	4.5	—	—	*	3.6
Total	—	—	0.3	6.9	—	—	15.3	26.0

[1]Data are expressed in percentages.
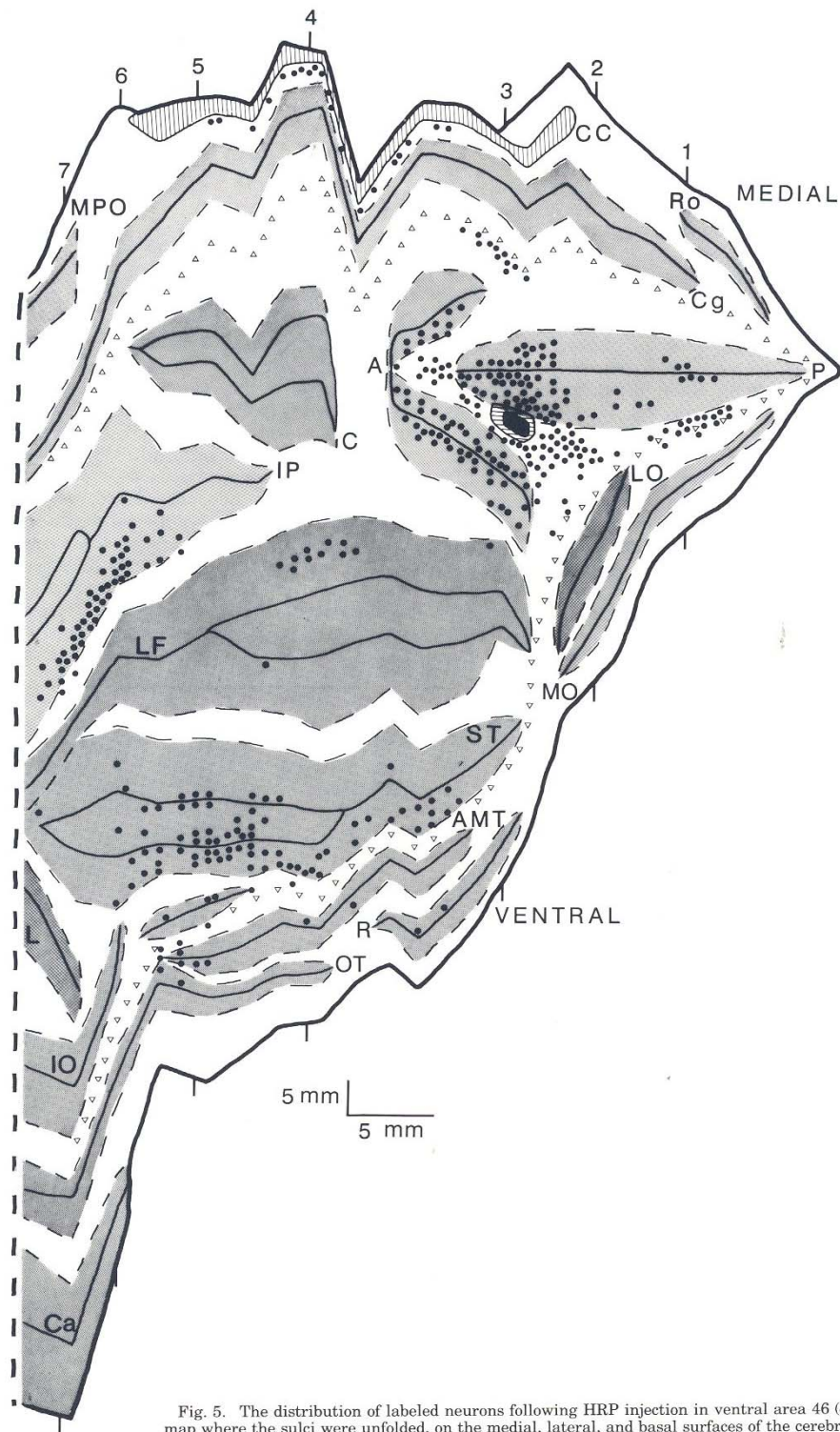— No labeled neurons.
*Less than 0.1%.

Fig. 5. The distribution of labeled neurons following HRP injection in ventral area 46 (case 4) is shown on a map where the sulci were unfolded, on the medial, lateral, and basal surfaces of the cerebral hemisphere (right) and on coronal sections 1–7 (far right).

TABLE 4. Distribution of Labeled Neurons in Auditory Cortices After Injection of Retrograde Tracers in Basoventral and Mediodorsal Prefrontal Regions[1]

	Injection site							
	Basal		Ventral		Medial		Dorsal	
Area:	11	12	12	46	32	32	8	8
Case:	1	2	3	4	5	6	7	8
Origin								
paI, proA	—	—	0.1	—	0.2	—	—	—
relt	—	—	—	—	—	—	0.3	0.4
TS2, paAr	—	—	2.4	—	1.1	1.8	—	—
TS1	0.7	—	2.0	—	10.3	2.5	—	—
TS3	—	—	3.0	—	4.3	1.4	—	—
paAlt	—	—	0.1	—	*	—	—	—
Total	0.7	—	7.6	—	15.9	5.7	0.3	0.4

[1]Data are expressed in percentages.
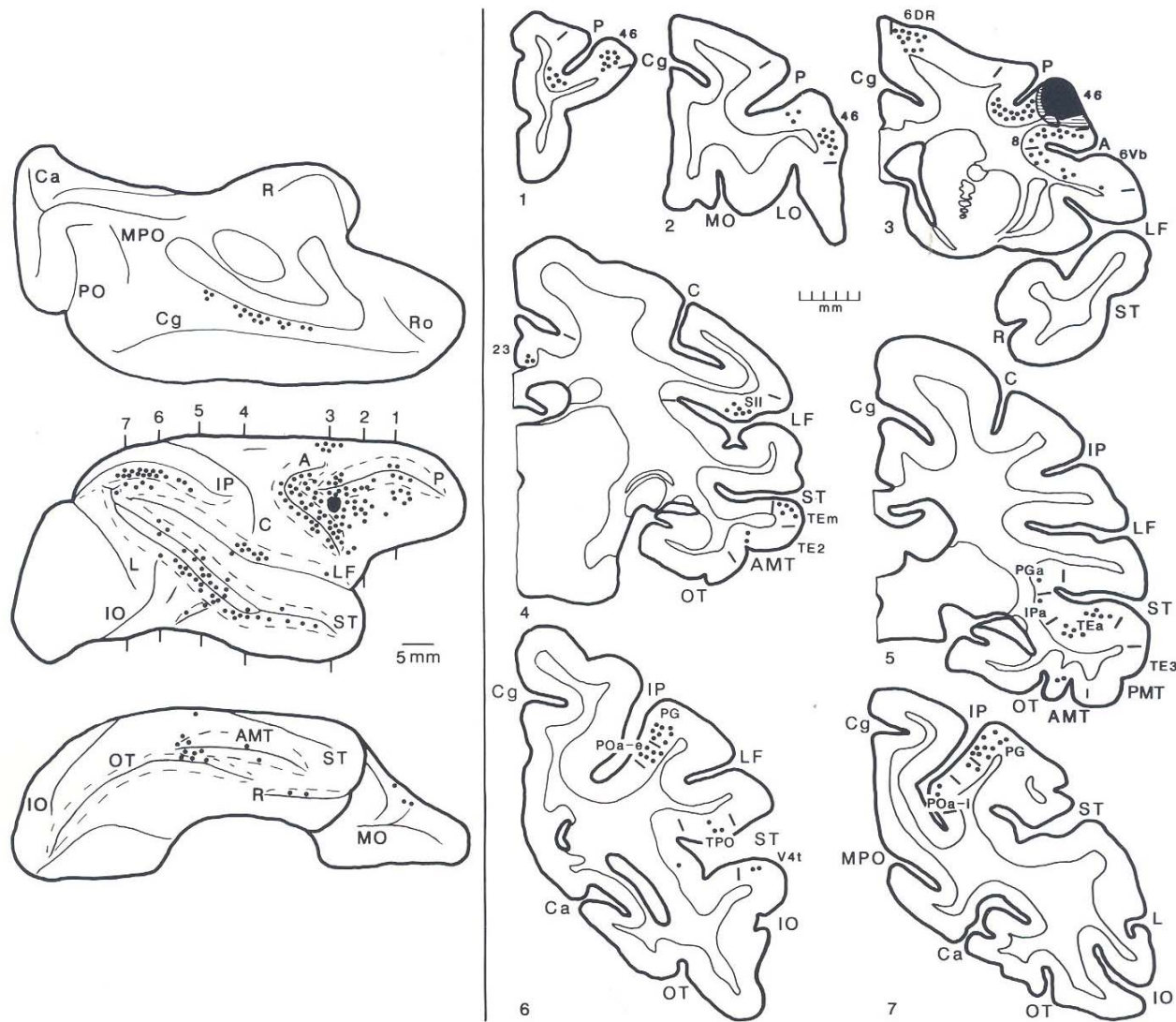— No labeled neurons.
*Less than 0.1%.

Figure 5 continued

parietal lobule. The above regions have been associated with somatic sensation on the basis of physiologic, anatomic, and behavioral experiments (see Woolsey, '81, for review; Roberts and Akert, '63; Jones and Burton, '76; Mesulam and Mufson, 82; Pandya and Seltzer, '82).

Labeled neurons in somatosensory cortices were noted in both orbitofrontal cases. After HRP injection in orbital area 11, 3% of all labeled neurons were found in areas 1 and 2 within the frontal operculum and in the dysgranular and granular insula, while fewer were seen in area SII in the parietal operculum. The orbital area 12 site (case 2, Figs. 3, 12A,B) seemed to be a major target of somatosensory projections, with 31% of its total labeled neurons found in areas 1 and 2 and SII in the frontal and pericentral operculum,

in the dysgranular and granular insula, and in area PF within the rostral third of the lateral bank of the intraparietal sulcus.

Labeled neurons in somatosensory cortices also were noted following HRP injection in lateral area 12 (3%, case 3, Fig. 4) and ventral area 46 (1%, case 4, Fig. 5). Most of these labeled neurons were found within the frontal and pericentral operculum (areas 1 and 2 and SII). The medial prefrontal and periarcuate sites had very few of their labeled neurons in somatosensory cortices (cases 5–8). These were found in the dysgranular and granular insula following a medial rostral area 32 injection (case 5, Fig. 6) and in postcentral areas 1, 3a, and 5 after injection of HRP in area 8 (cases 7–8, Figs. 8–9).
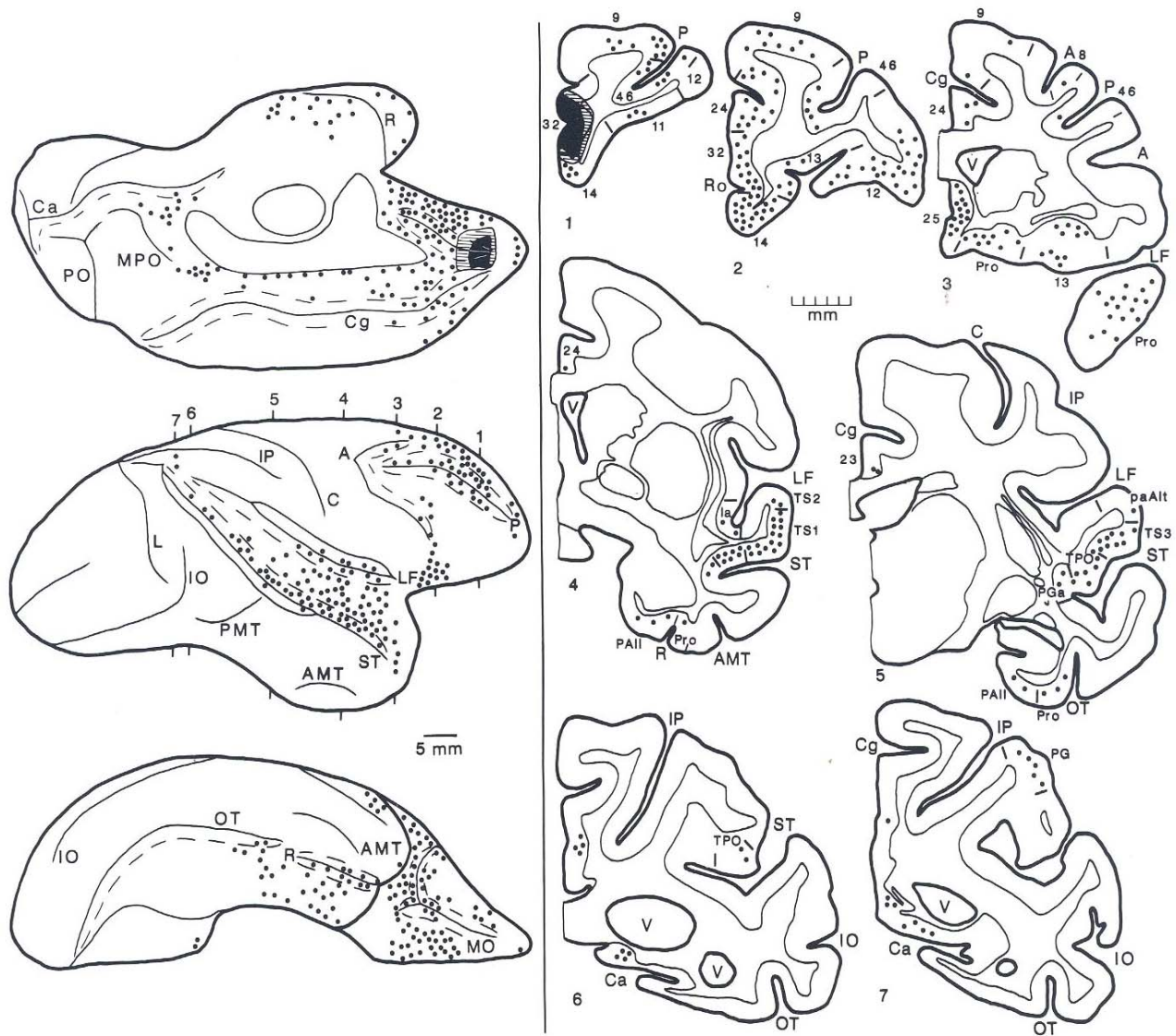

Fig. 6 The distribution of labeled neurons following HRP injection in rostral area 32 (case 5) is shown on the medial, lateral, and basal surfaces of the cerebral hemisphere (left) and on coronal sections 1–7 (right).

Premotor

Labeled neurons in premotor area 6 were located in the caudal bank of the arcuate sulcus and the adjacent cortex posteriorly and were observed mostly following HRP injection in orbital area 12 (10%, Table 1, case 2), ventral area 46 (7%, case 4), lateral area 8 (13%, case 7), and sulcal area 8 (2%, case 8). There were only a few labeled neurons in the premotor cortex following HRP injection in area 11 (case 1) or lateral area 12 (case 3), and there was no evidence of label in the area 32 cases 5 and 6.

After HRP injection in orbital area 12 (case 2) most labeled neurons were found in the rostral portion of ventral area 6 in architectonic area 6Vb (Barbas and Pandya, '87), and very few were noted in the supplementary motor area (MII) on the medial surface (Fig. 3). Similarly, after HRP injection in ventral area 46 (case 4) most labeled neurons were found in ventral area 6. These labeled neurons were

located in both the rostral (area 6Vb) and caudal (area 6Va) portion of ventral area 6. In case 4 there was also a distinct cluster of labeled cells in the rostral portion of dorsal area 6 (area 6DR, Fig. 5). In contrast to the basoventral cases, after HRP injection in subsectors of area 8 most labeled neurons were found in the rostral portion of dorsal area 6 (area 6DR, Figs. 8, 9). In one of these (case 8) some labeled neurons were seen also in area 4C at the spur of the arcuate sulcus.

Parietotemporal

Labeled neurons were seen in parietotemporal areas situated at the border of visual, somatosensory, and auditory cortices. These regions are characterized by neuronal responses and connections which are not confined to one sensory modality (Kuypers et al., '65; Jones and Powell, '70;
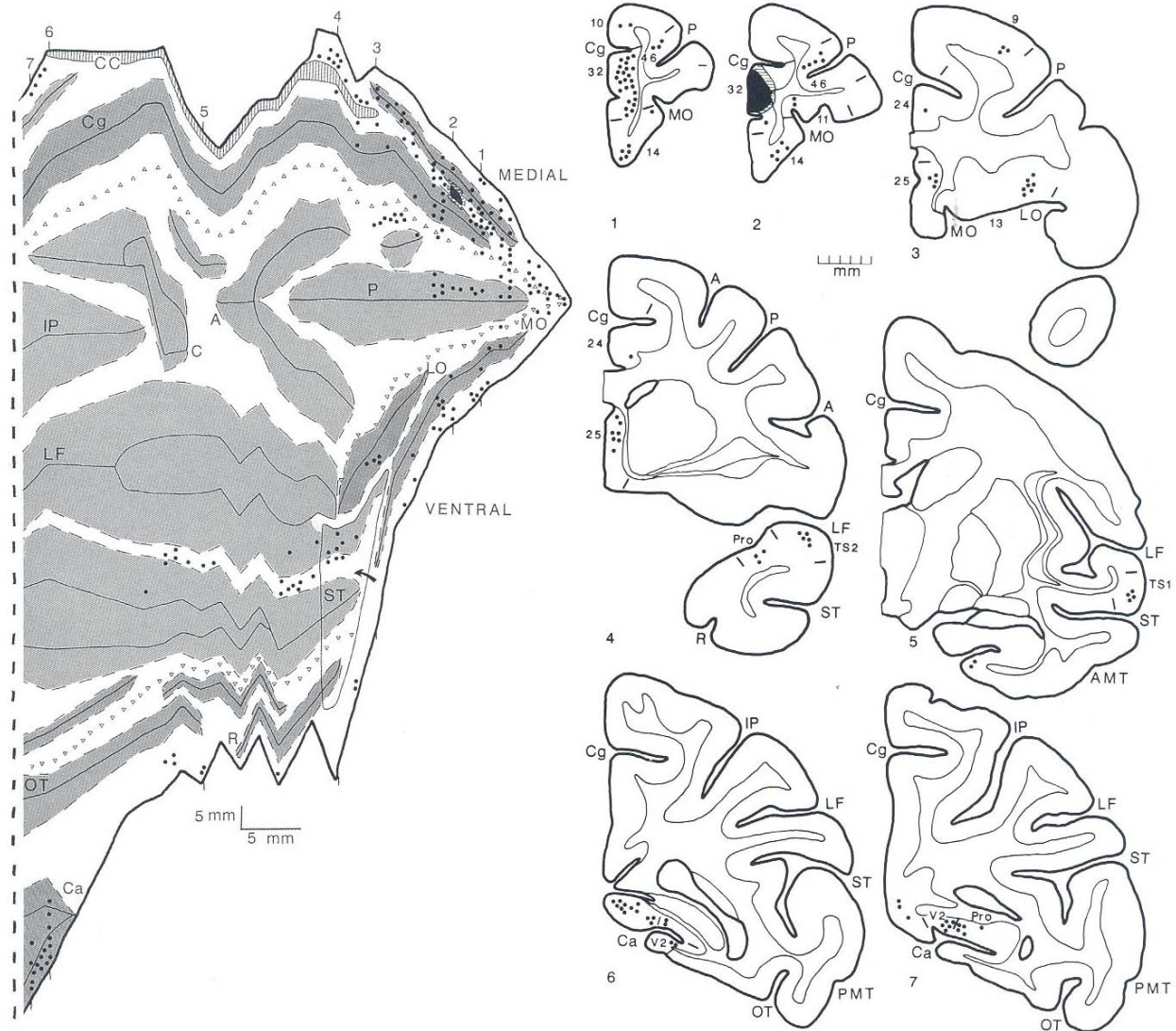
Benevento et al., '77; Divac et al., '77; Mesulam et al., '77; Seltzer and Pandya, '78; Desimone and Gross, '79; Bruce et al., '81; Baylis et al., '87). Within these cortical areas labeled neurons were found in the depths of the upper (medial) bank of the superior temporal sulcus and the inferior parietal lobule (Table 5). The architectonic nomenclature used for the superior temporal region is according to that of Seltzer and Pandya, ('78).

In the case with an HRP injection in rostral area 32 (case 5, Fig. 6) 10.9% of the labeled neurons were found in parietotemporal areas. Most of these labeled neurons were located within the central portion of the medial bank of the superior temporal sulcus (area TPO), and fewer were found in the depths of the superior temporal sulcus (area PGa) and in the medial parietal cortex. In the rest of the cases some labeled neurons (ranging from fewer than 0.6% to 8%) were found in parietotemporal regions. In the mediodorsal cases labeled neurons were noted mostly in the superior

TABLE 5. Distribution of Labeled Neurons in Parietotemporal Cortices After Injection of Retrograde Tracers in Basoventral and Mediodorsal Prefrontal Regions[1]

	Injection site							
	Basal		Ventral		Medial		Dorsal	
Area:	11	12	12	46	32	32	8	8
Case:	1	2	3	4	5	6	7	8
Origin								
Temporal								
Area TPO	2.0	0.1	4.0	*	10.0	*	2.0	2.2
Area PGa	0.5	*	2.0	*	0.3	—	*	1.2
Area IPa	2.0	0.5	2.0	0.6	—	—	—	—
Parietal								
Lateral PG	0.3	*	*	0.3	—	—	—	—
Medial PG	*	—	—	—	0.6	—	—	0.2
Total	4.8	0.6	8.0	0.9	10.9	*	2.0	3.6

[1]Data are expressed in percentages.
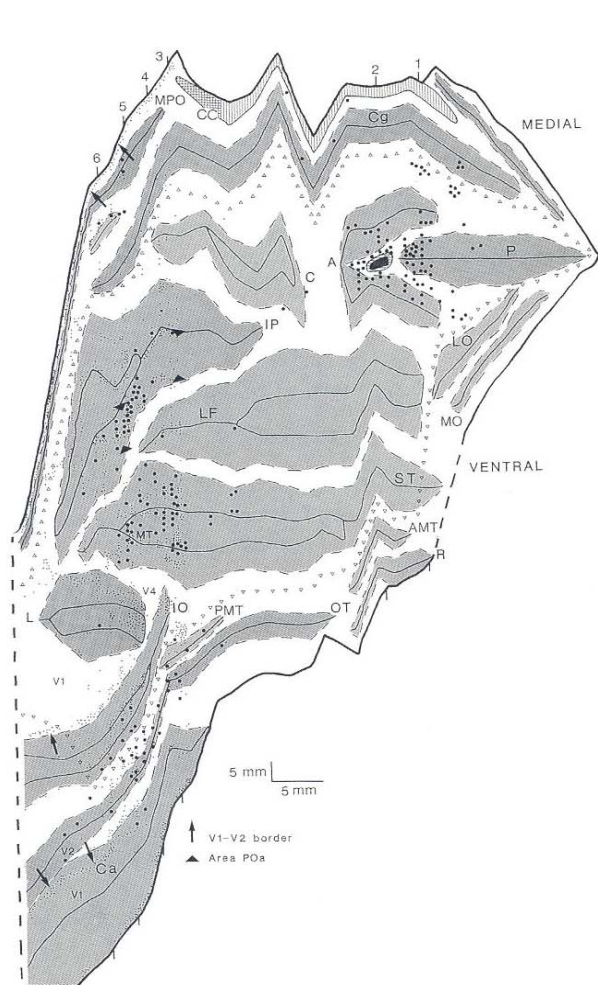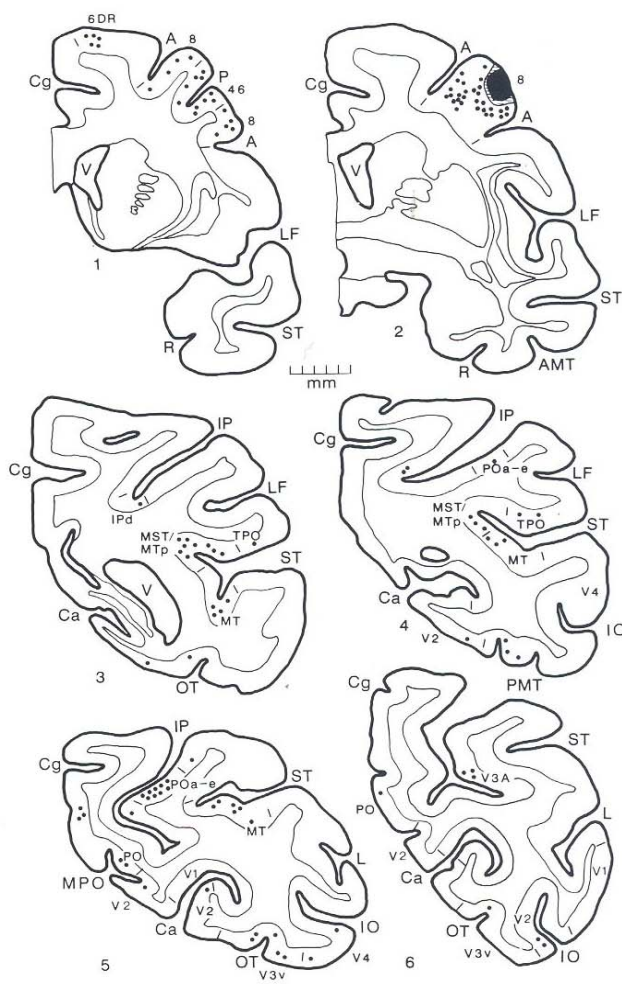*Less than 0.1%.
—No labeled neurons.

Fig. 8. The distribution of labeled neurons (large dots) following an HRP injection in the lateral portion of area 8 (case 7) is shown on a map where the sulci were unfolded (left) and on (right) coronal sections 1–6 taken at the level shown on the surface of the cortex. In the unfolded map small dots represent the areas which receive callosal projections from the contralateral visual cortices. Callosal projections were mapped by noting the sites of anterograde degeneration after sectioning of the splenium of the corpus callosum (crosshatching).

temporal areas TPO and PGa, and in the medial parietal cortex (cases 5, 7, 8, Figs. 6, 8, 9). In the basoventral cases, in addition to labeled neurons in areas TPO and PGa, some labeled neurons were seen within the floor of the rostral portion of the superior temporal sulcus (area IPa) and in the inferior parietal lobule as well (Table 5, cases 1–4, Figs. 2–5).

Prefrontal

Prefrontal cortices also are characterized by their responses to several sensory modalities and connections with multiple cortical regions (Bignall and Imbert, '69; Jones and Powell, '70; Chavis and Pandya, '76; Jacobson and Trojanowski, '77). These include prefrontal areas 8–10, 46, 11, 12 and 14 (Walker, '40; Barbas and Pandya, '82).

In all cases a substantial proportion of the total number of labeled neurons was found within prefrontal regions. In the basoventral cases most labeled neurons were found in neighboring orbital and ventral prefrontal areas (cases 1–4), and in the mediodorsal cases (cases 5–8) most labeled neurons were found in nearby medial and dorsal regions (Table 6). These labeled neurons accounted for as few as 23.3% of the total number directed to area 8 (case 8) to as many as 77.2% of all labeled cells projecting to ventral area 46 (case 4).

Limbic

Limbic cortical regions are transitional regions interposed between the allocortical areas, which have a rudimentary laminar arrangement, and isocortical areas, which are organized into six cortical laminae. Limbic areas can be readily distinguished from adjacent cortices on the basis of morphological features, including prominent deep and rarefied upper layers and a high cholinesterase and a low myelin content (Sanides and Krishnamurti, '67; Sanides, '70; Gower, '81 Barbas and Pandya, '83; Mesulam et al., '84). In architectonic terminology limbic areas are referred to as periallocortices, or, for the slightly more differentiated regions, proisocortices.

Limbic areas are situated at the foot of architectonic differentiation of each sensory system (see Sanides, '70; Gower, '81; Pandya and Yeterian, '85; Pandya et al., '88, for reviews). Thus rhinal, ventral polar, retrosplenial, and prostriate areas are continuous with the visual cortical system. The dorsal polar region and the rostral part of the ventral lateral fissure are continuous with the auditory cortex. The most rostral part of the frontal operculum, the anterior insula, and the caudal part of the cingulate (area 23) form the first step in the laminar differentiation of the somatosensory cortex. The rostral part of the cingulate (area 24) dorsomedially, and area proM of Sanides ('70) ventrolaterally, are situated at the onset of differentiation of the premotor and motor systems. In addition, prefrontal areas 32 and 25 medially, and area 13, as well as the proisocortex and periallocortex (situated behind area 13) on the orbital surface, have an incipient laminar organization and are considered limbic (Nauta, '64, '72; Barbas and Pandya, '82, Fig. 1D,G). Limbic cortices have strong connections with subcortical limbic structures (Pribram et al., '50; Nauta, '64, '72; Johnson et al., '68; Rosene and Van Hoesen, '77; Potter and Nauta, '79; Gower, '81).

In both orbitofrontal cases a substantial proportion of labeled neurons was seen in limbic cortices (Table 7, 24.8%, and 25%, cases 1, 2). Most labeled neurons directed to area 11 originated in cingulate areas 24 and 23, in basal (proisocortex and area 13, Fig. 12D,E) and medial (areas 32 and 25) prefrontal regions, and in the ventral and dorsal polar and rhinal regions (Fig. 2). Labeled neurons in limbic cortices directed to orbital area 12 were found mainly in neighboring area 13, in the rostral opercular proisocortex, in the agranular insula, and in area 23 (Fig. 3).

In the ventrolateral cases (3, 4) fewer labeled cells were seen in limbic cortices. These labeled neurons accounted for 6.2% of all neurons directed to lateral area 12 and for only 2% of those directed to ventral area 46. The labeled neurons were scattered in orbital and medial prefrontal proisocortices and in cingulate, ventral and dorsal polar, and rhinal regions (Figs. 4, 5).

TABLE 6. Distribution of Labeled Neurons in the Prefrontal Cortices Projecting to Neighboring Prefrontal Regions[1]

	Injection site							
	Basal		Ventral		Medial		Dorsal	
Area:	11	12	12	46	32	32	8	8
Case:	1	2	3	4	5	6	7	8
Origin								
Basoventral regions								
Area 11	14.8	—	3.3	—	1.4	0.4	—	—
Area 12	9.0	20.1	28.9	0.4	6.3	*	—	0.3
Ventral 10	6.3	—	12.2	—	—	—	—	0.7
Ventral 46	8.9	8.0	6.0	54.5	0.9	—	6.4	5.2
Ventral 8	0.4	—	6.0	11.2	—	—	6.4	2.3
Mediodorsal regions								
Area 14	5.9	—	1.6	—	16.6	13.7	—	—
Area 9	15.9	—	3.7	—	9.1	9.6	—	2.9
Dorsal 10	—	—	—	—	3.4	23.3	—	—
Dorsal 46	*	—	1.9	7.0	2.2	10.7	42.5	4.1
Dorsal 8	*	—	0.5	4.1	*	—	1.0	7.8
Total	61.2	28.1	64.1	77.2	39.9	57.7	56.3	23.3

[1]Data are expressed in percentages.
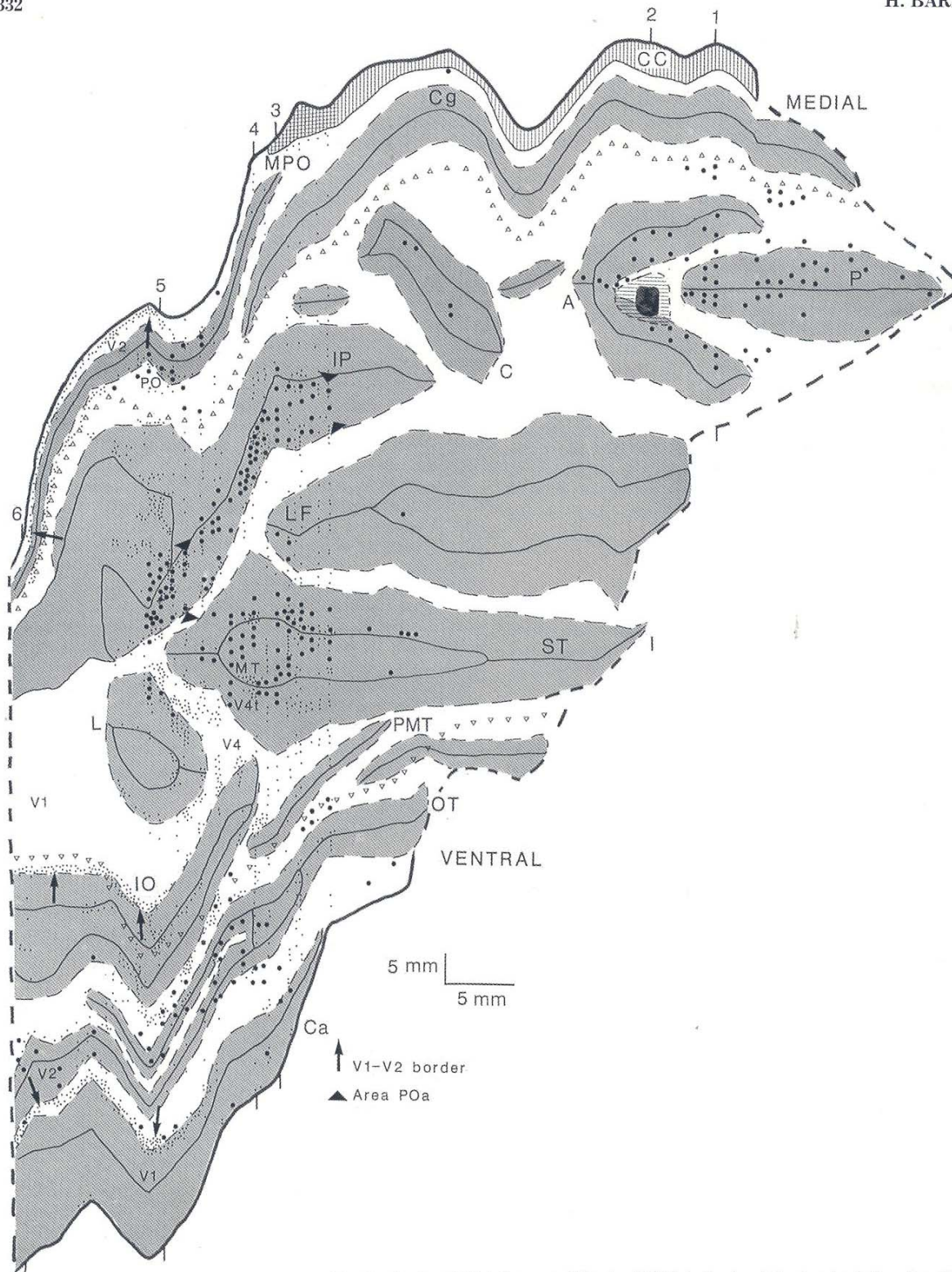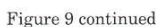— No labeled neurons.
*Less than 0.1%.

Fig. 9. The distribution of labeled neurons following HRP injection in a lateral and sulcal portion of area 8 (case 8) is shown on a map where the sulci were unfolded (left) on the medial, lateral, and basal surfaces of the cerebral hemisphere (right) and on coronal sections 1–6 (far right) taken at the level shown on the surface of the cortex (left). Small dots represent the areas of anterograde degeneration observed after sectioning the splenium of the corpus callosum (crosshatching, left).

In the medial area 32 cases approximately one-third of all labeled neurons were found in limbic cortices. Most of these labeled neurons originated in neighboring medial (areas 25 and 32; Figs. 6, 7, 12F) and orbital (proisocortex and area 13) regions. In addition, there were some labeled neurons in limbic cortices situated at the foot of visual (Fig. 10E,F), auditory, somatosensory, and premotor cortices. In the periarcuate cases (cases 7, 8) fewer than 0.5% of the total number of labeled neurons were seen in limbic cortices, and these were found primarily in area 23.

Laminar distribution of labeled neurons

The issue of the laminar origin of cortical projections to the frontal cortex was considered in detail in a previous study (Barbas, '86) and will be mentioned only briefly here. Labeled neurons were located in cortical layers III, V, and VI. The laminar origin of corticocortical projections was correlated with the architectonic differentiation of the regions giving rise to the projecting afferent fibers. Thus, prefrontally directed projections from limbic cortices, which show a rudimentary laminar organization, emanated mainly from deep layers V and VI (Fig. 12D). On the other hand, projections from increasingly more differentiated cortices arose progressively from the upper (or supragranular) layers (Fig. 12A). This pattern was observed for projections originating in visual, auditory, somatosensory, premotor, and prefrontal cortices. These results are consistent with previous findings (Barbas, '86).

The laminar origin of labeled neurons in two additional cortical zones, which were not included in a previous study (Barbas, '86), will be considered in more detail here. These include the caudal portion of the lateral bank of the intraparietal sulcus and the medial bank of the superior temporal sulcus. Most labeled neurons in the lateral intraparietal bank were found in layer III. However, relatively more labeled neurons were found in layers V and VI in the superficial portion of the sulcus (areas PG and Poa-e) when compared with the deep portions of the sulcus (areas IPd and POa-i) (Fig. 13A).

The laminar origin of labeled neurons within the medial bank of the superior temporal sulcus is shown in Figure 13B. Most labeled neurons in this region were found in
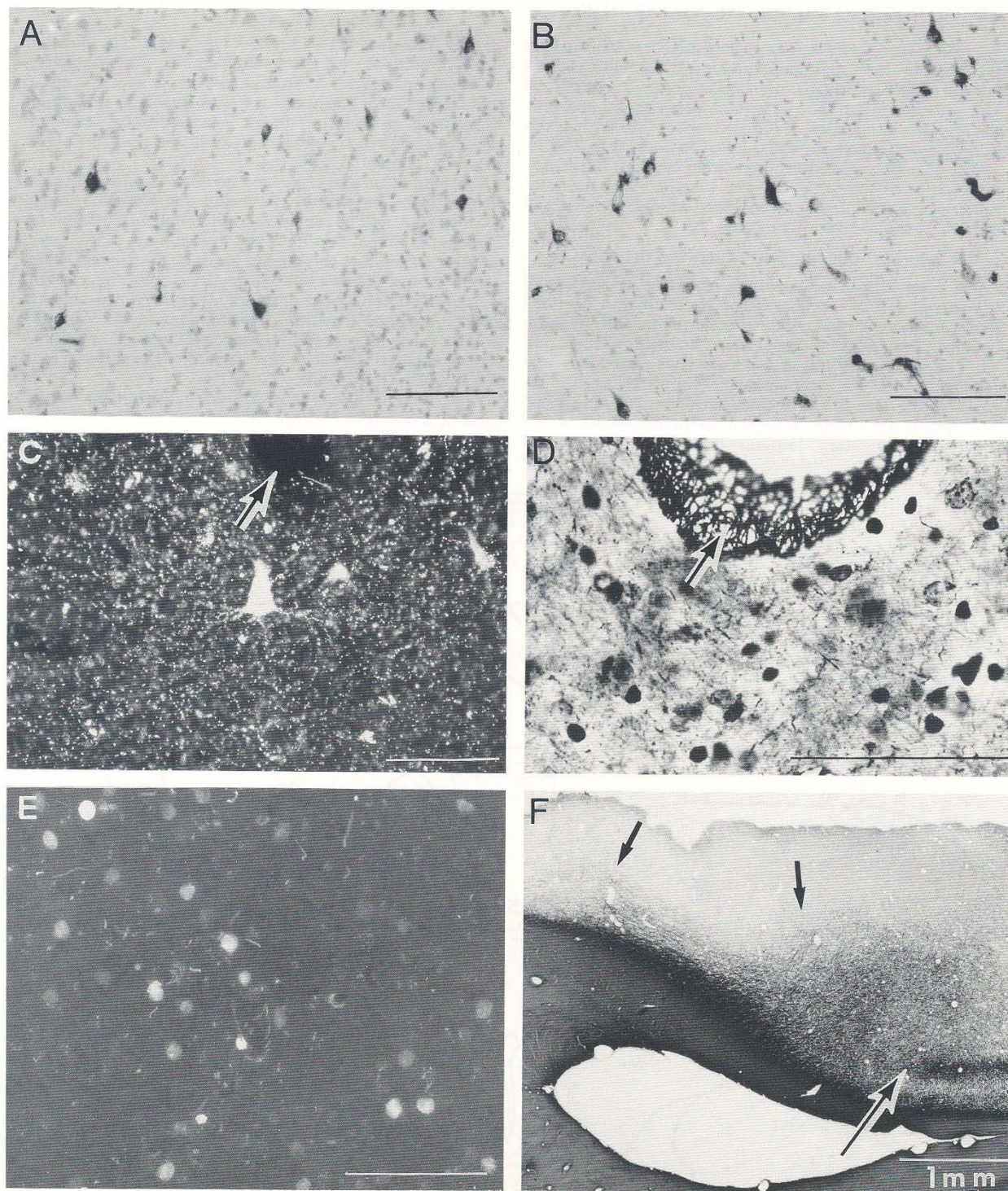

Figure 9 continued

Fig. 10. A: Brightfield photomicrograph showing labeled neurons in visual area TE1 after HRP injection in orbital area 11 (case 1) and in area V3A (**B**) after HRP injection in area 8 (case 8). C: Darkfield photomicrograph showing labeled neurons in area MT after HRP injection in area 8 (case 7); a matched section stained for the visualization of degenerating fibers after transection of the splenium of the corpus callosum (**D**) shows that the labeled neurons in C overlap with a site which receives callosal projections. Arrows in C and D point to a common blood vessel used to match the two sections. E: Fluorescent-labeled neurons in the rostral portion of the upper calcarine fissure after injection of diamidino yellow in limbic area 32 (case 6). The labeled neurons were found in an area which has a low myelin content restricted to the infragranular layers (**F**, black arrows). This cortex, which is architectonically characterized as limbic, lies at the foot of the striate area (black and white arrow). F, myelin stain (Gallyas, '79). Scale bar in A–E = 100 μm.

TABLE 7. Distribution of Labeled Neurons in Limbic Cortices After Injection of Retrograde Tracers in Basoventral and Mediodorsal Prefrontal Regions[1]

| | | Injection site | | | | | | | |
| | | Basal | | Ventral | | Medial | | Dorsal | |
Origin	Area: Case:	11 1	12 2	12 3	46 4	32 5	32 6	8 7	8 8
Visual									
Ventral polar and rhinal		2.1	0.1	0.7	*	1.8	1.3	—	0.1
Prostriate		—	—	—	—	0.2	2.2	—	*
Auditory									
Rostral ventral LF and dorsal temporal pole		1.1	—	0.2	—	1.0	0.7	—	—
Somatosensory									
Rostral opercular, insular pro		0.3	2.7	*	—	0.2	—	—	—
Area 23		2.1	1.4	*	2.0	0.2	—	0.3	0.1
Premotor									
Area 24		12.9	0.1	1.1	*	2.9	1.0	—	—
Frontal									
Orbital pro		0.8	0.2	0.6	—	0.2	—	—	—
Area 13		4.2	20.5	3.5	—	9.1	3.8	—	—
Area 25		0.4	—	—	—	15.7	8.2	—	—
Area 32		0.9	—	0.1	—	0.4	12.1	—	—
Total		24.8	25.0	6.2	2.0	31.7	29.3	0.3	0.2

[1]Data are expressed in percentages.
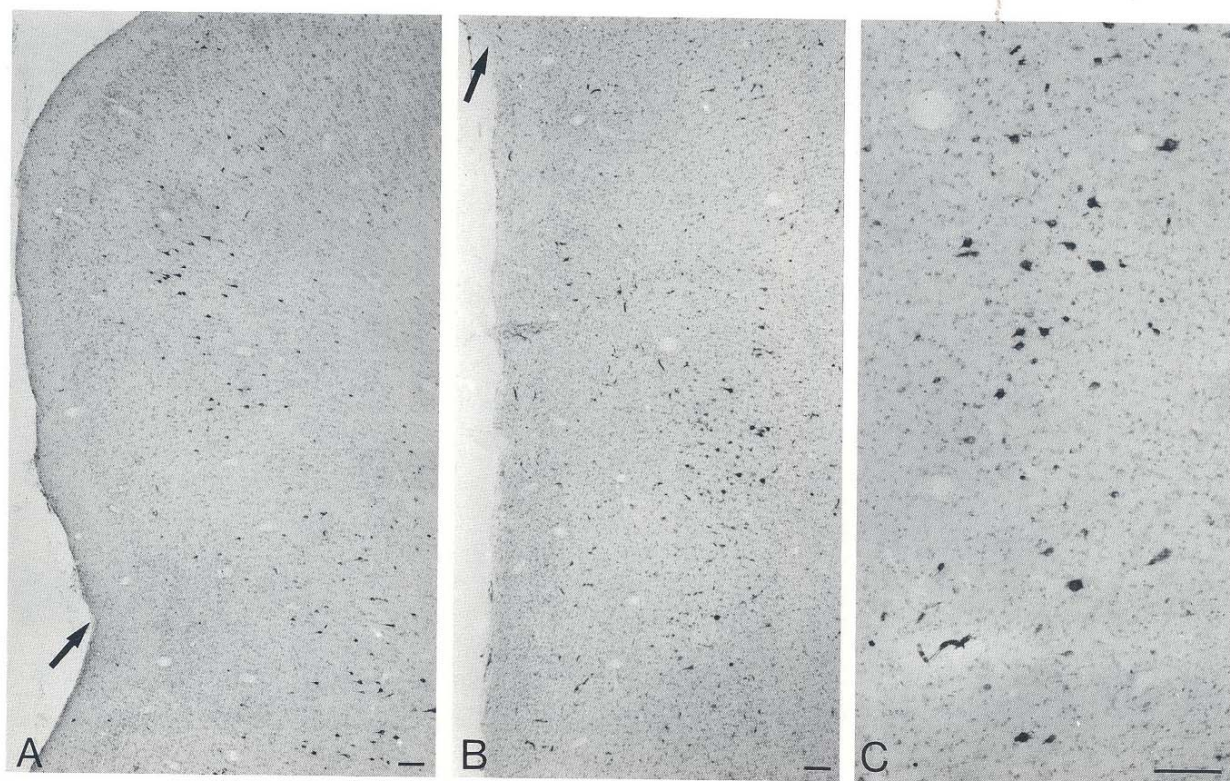*Less than 0.1%.
— No labeled neurons.

Fig. 11. A: Brightfield photomicrographs showing labeled neurons in the superficial portion of the lateral intraparietal bank (sulcal portion of area PG and area POa-e) after HRP injection in ventral area 46 (case 4) and in deeper portions of the sulcus (area POa-i, B, and IPd, C) after HRP injection in area 8 (case 8). The arrows in A and B show the site of a "pseudosulcus" within the lateral intraparietal bank, which generally marks the border between the sulcal portion of area PG and area POa-e. Scale bar = 100 μm.
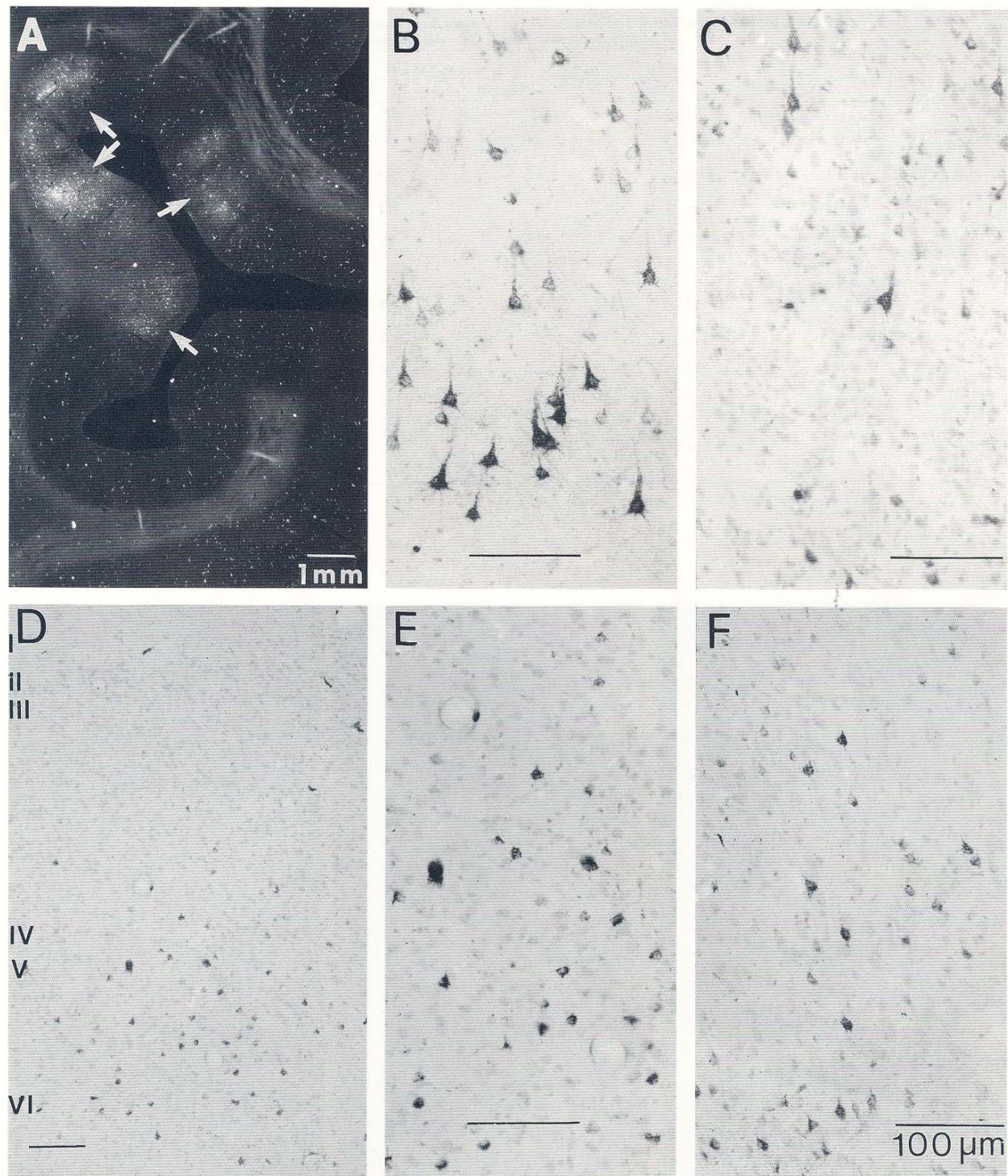
Fig. 12. A: Darkfield photomicrograph showing foci with labeled neurons in somatosensory regions within the pericentral operculum and the granular insula (white arrows) after HRP injection in orbital area 12 (case 2); some of the labeled neurons are shown in a brightfield photomicrograph in B at higher magnification. C: Brightfield photomicrograph showing labeled neurons in an auditory region in the superior temporal gyrus after HRP injection in area 32 (case 5). D: Labeled neurons concentrated in the deep layers in the orbital limbic proisocortex after HRP injection in area 11 (case 1); some of the labeled neurons are shown in E at higher magnification. F: Labeled neurons in limbic proisocortical area 25 after HRP injection in medial area 32 (case 5). Scale bar in B–F = 100 μm.
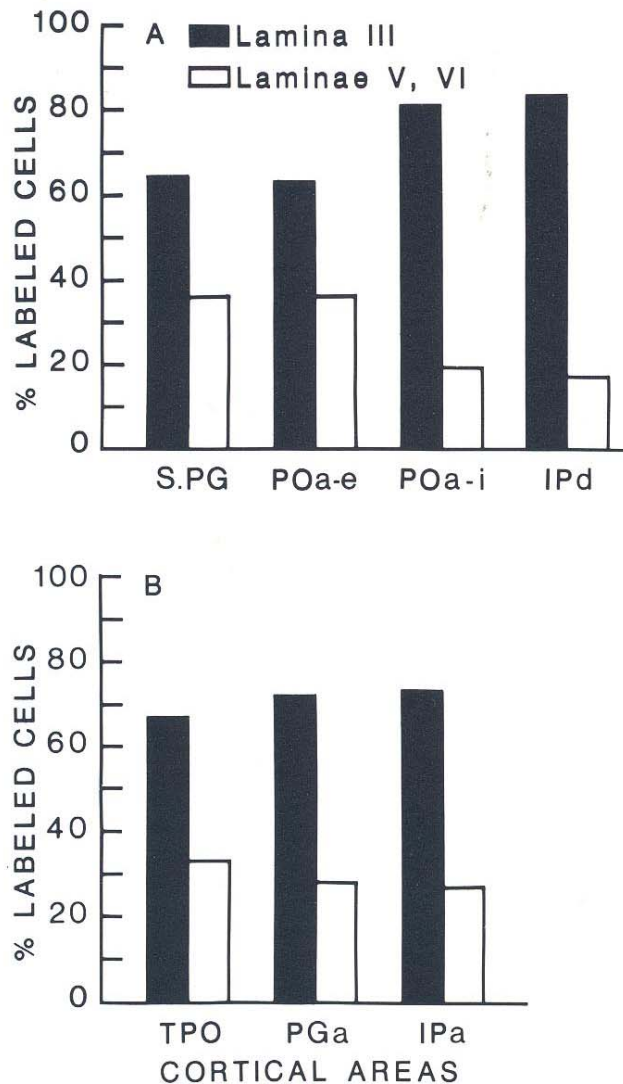
Fig. 13. Histogram showing the percentage of labeled neurons in lamina III and in laminae V and VI in subdivisions of the caudal portion of the lateral intraparietal bank (**A**) and in the medial bank of the superior temporal sulcus (**B**). The black (lamina III) and white (laminae V, VI) in each subdivision add up to 100%.

layer III as well. There were minor differences in the laminar origin of labeled neurons among the architectonic zones. Thus, area TPO, situated in the upper portion of the bank, had a somewhat higher percentage of its labeled neurons in the deep layers compared to areas PGa and IPa, which are located progressively in deeper portions of the medial superior temporal bank and the adjacent floor of the sulcus.

DISCUSSION

The origin of projections from visual cortices to basoventral and mediodorsal prefrontal regions was largely segregated. Basoventral prefrontal sites received most of their visual projections from the inferior temporal cortex. On the other hand, mediodorsal prefrontal regions received visual projections mostly from medial and dorsolateral visual cortices. These results confirm and extend previous findings in macaque monkeys (Jones and Powell, '70; Chavis and

Pandya, '76; Jacobson and Trojanowski, '77; Barbas and Mesulam, '81, '85; Huerta et al., '87) and parallel observations made in the owl monkey (Weller and Kaas, '87).

The question arises as to whether the visual projections to basoventral and mediodorsal prefrontal regions originated in functionally as well as topographically distinct cortices. There has been increasing evidence in recent years that in the primate different visual cortices may be involved in the analysis of different aspects of the visual environment. The idea of parallel processing in the visual system, originally described for subcortical visual pathways (see Stone et al., '79; Lennie, '80; Stone and Dreher, '82, for reviews), recently has been extended to processing at the cortical level. On the basis of a series of combined anatomic and behavioral studies it was suggested that there may be two parallel and functionally distinct cortical visual pathways (Ungerleider and Mishkin, '82). One of these pathways, extending from the striate area through rostroventral occipital and inferior temporal cortices, seems to be important for object recognition and discrimination. Another pathway which takes a rostrodorsal path from the striate area through dorsal occipital to caudal parietal cortices seems important for spatial functions (Ungerleider and Mishkin, '82). This view is supported by physiologic evidence. For example, neurons in the inferior temporal cortex respond to various dimensions of complex visual stimuli, and even though their receptive fields are large, they always include the fovea, a prerequisite for the detailed analysis of stimuli (Gross and Bender, '69; Desimone and Gross, '79; Fuster and Jervey, '81) On the other hand, most visually responsive lateral parietal neurons have receptive fields which exclude the fovea and respond to moving stimuli in the peripheral space (see Lynch, '80; Hyvärinen, '82, for reviews).

The segregation of function within the visual cortices is further exemplified by recent studies which described two anatomically interdigitating and functionally separate systems in the primary visual cortex of macaques. These two systems, which seem to be involved in the analysis of color or orientation, project to different subdivisions of V2 (Livingstone and Hubel, '84) and remain largely segregated in their further projection from V2 to V4 and V5 (or MT) (DeYoe and Van Essen, '85; Shipp and Zeki, '85).

The question arises as to whether projections from parallel and functionally distinct lines of visual cortices remain segregated or converge in distant regions such as the prefrontal cortex. The results showed that basoventral prefrontal sites received projections from inferior temporal cortices, where neurons respond to stimuli associated with pattern and feature analysis. In fact, damage to the inferior prefrontal convexity, which includes area 12 and parts of area 11, disrupts pattern discrimination, delayed-matching-to-sample and visual recognition, which are reminiscent of tasks supported by the inferior temporal cortex (Stamm, '73; Passingham, '75; Mishkin and Manning, '78; Voytko, '85, '86; Bachevalier and Mishkin, '86; Gaffan and Harrison, '86; Gaffan et al., '86; Horel et al., '87).

In contrast to the basoventral areas, mediodorsal prefrontal sites received most of their visual projections from medial and dorsolateral visual cortices. Medial area 32 received projections from medial area PO of Covey et al. ('82) and from the rostral part of medial area V2. There is little information concerning the response properties of neurons in area PO or the medial portion of V2, but behavioral studies suggest that these regions lie along a line of cortices

associated with visual spatial tasks (Mishkin et al., '82). Moreover, both area PO and medial area V2 contain a representation of the peripheral portion of the visual field (Gattass et al., '81; Covey et al., '82), which is not suited for pattern discrimination, but which is excellently suited for the analysis of motion and space (Motter and Mountcastle, '81; McKee and Nakayama, '84).

The periarcuate zones received a higher proportion of their projections from visual cortices when compared with most other prefrontal regions studied. In fact, an area 8 site, which included a portion of the lower limb of the arcuate sulcus, received far more projections from visual cortices than it did from its neighboring prefrontal regions. Visual cortical projections to the periarcuate zone originated in areas extending from the caudal portion of V2 at the V2-V1 border to area MST situated medial and rostral to area MT within the depths of the superior temporal sulcus (Desimone and Ungerleider, '86). The origin of visual projections to the periarcuate region is, therefore, quite diverse. But is there a functional pattern in these projections? Approximately half of the labeled neurons in visual cortices directed to area 8 were found in areas MST and MT where neurons are particularly sensitive to moving stimuli (Zeki, '74; Maunsell and Van Essen, '83; Albright et al., '84; Desimone and Ungerleider, '86). The next largest proportion of neurons in visual cortices projecting to area 8 was found in dorsal areas V3A and V3, where neurons show little selectivity for color but respond to stimulus orientation, direction, or speed. Even though there is no general agreement in the literature on the proportion of neurons responsive to each of the above visual features (Van Essen and Zeki, '78; Zeki, '78d; Baizer, '82; Felleman and Van Essen, '87), the neuronal response properties suggest a bias for spatial rather than pattern or color analysis in these visual areas (Felleman and Van Essen, '87). Most neurons in visual cortices projecting to area 8 therefore were found to lie along a line of cortices associated with the analysis of motion or space.

The relationship of the labeled neurons to the topographically organized representation of the visual field is also important in addressing the question of the type of input directed to area 8. The representation of the visual field in the cortex is difficult to assess solely on the basis of anatomic data, but several points, based on both the literature and this study, seem relevant to this issue. Combined physiologic-anatomic studies have shown that regions representing both central (2°) and peripheral (20°) parts of the upper and lower portions of the visual field of area MT project to area 8 (Ungerleider and Desimone, '86). These data and direct recordings from visually responsive neurons in area 8 (Mohler et al., '73; Suzuki, '85) suggest that area 8 may have a panoramic view of the visual field. However, the proportion of neurons directed to area 8 from visual cortices representing the center of gaze or the periphery is not known. This information is important, because even though the receptive fields of neurons in area 8 are large, their size and the relative emphasis of portions of the receptive field may change depending on the behavioral situation (Goldberg and Bushnell, '81).

The periarcuate zones examined in this study received a small proportion of their projections from area PO, an area whose physiologic characteristics and anatomic connections suggest an emphasis of the visual periphery (Covey et al., '82; Colby et al., '88). In addition, most of the projections from V2 directed to area 8 were found in the medial portion

of this topographically organized area, which also represents the peripheral visual field (Gattass et al., '81). It may be concluded, therefore, that at least these two areas send projections representing the visual periphery to area 8. With regard to other projections from visual cortices, Zeki ('80) has found that only parts of V1 representing peripheral parts of the visual field (> 30°) project directly to area V3A. Whether this is indicative of an increased emphasis of the visual periphery in area V3A, as was shown for area PO (Covey et al., '82), is not presently known.

The position of the vertical meridian, which represents the center of gaze, was estimated in this study by examining the areas of dense callosal projections after transection of the splenium of the corpus callosum. Even though this procedure is not adequate to estimate a point-to-point representation of the visual field, in combination with myeloarchitectonic and cytoarchitectonic procedures it proved useful in determining the borders of several extrastriate areas. In the two periarcuate cases (cases 7 and 8) where all of these procedures were employed, the position of the labeled neurons was superimposed on a map of the visual cortices which contained the location of callosal projections. This analysis revealed that at least some labeled neurons were found near the junction of distinct visual areas and overlapped with regions which received dense callosal projections from the contralateral visual cortices. This evidence suggests that at least some of the projections to the periarcuate zone originate in regions which may be close to the representation of the vertical meridian and thus may represent central visual fields.

However, approximately two-thirds of the labeled neurons directed to the periarcuate zone were found in areas which received few, if any, callosal projections from the contralateral visual cortices and which were far from distinct architectonic borders, suggesting that they were situated at a distance from the vertical meridian. This hypothesis is strengthened by comparing the distribution of labeled neurons with existing maps of visual cortices from other studies. The latter showed that regions in medial parietooccipital as well as those situated in medial superior temporal zones represent peripheral parts of the visual field (Covey et al., '82; Desimone and Ungerleider, '86). This evidence suggests that many of the neurons directed to area 8 originated in areas which represent peripheral parts of the visual field.

Two regions which projected to area 8, however, lie within the ventral visual cortical system associated primarily with the analysis of stimulus features. These included area V4 and the ventral portion of area V3 (or VP) (Van Essen and Zeki, '78; Zeki, '78c; Burkhalter et al., '86; Newsome et al., '86; Desimone and Schein, '87). Labeled neurons in these areas, however, accounted for fewer than one-fifth of the total number of neurons from visual cortices directed to area 8.

Further physiologic and behavioral data are necessary to ascertain whether, and to what extent, area 8 is involved primarily in spatial or discriminative analysis. The present data suggest that the periarcuate region may be continuous with a mediodorsal prefrontal line of cortices which has a role in visual spatial tasks. This line seems to include, in addition to caudal area 8, the middle and rostral tip of area 8 at the upper limb of the arcuate sulcus (Barbas and Mesulam, '81), the cortex buried in the caudal portion of the principal sulcus (Barbas and Mesulam, '85), at least part of area 9 (Mikami et al., '82; Barbas, personal obser-

vations), and medial area 32. This view is consistent with physiologic observations indicating that the periarcuate zone, which is linked with the superior colliculus, participates in eye movement tasks, involving orienting to sensory stimuli and searching the environment (Wurtz and Mohler, '76; Latto, '78; Schiller et al., '79; Goldberg and Bushnell, '81; Rizzolatti et al., '81; Goldberg and Bruce, '85). The influence of ventrolateral visual cortices, implicated in pattern recognition and discrimination, on the other hand, seemed to increase gradually from the arcuate concavity toward the orbitofrontal cortex. The present data suggest that the influences of cortices associated with feature or space and motion analysis converge, to some extent, at the level of the caudal periprincipalis-periarcuate region. This may account for the mixed discriminative and spatial deficits observed after damage to these lateral prefrontal regions (Goldman and Rosvold, '70; Latto and Cowey, '72; Latto and Iversen, '73; Latto, '78; Petrides and Iversen, '78; Van Hoesen et al., '80).

The apparent segregation in the type of projections from visual cortices to mediodorsal and basoventral prefrontal regions is further exemplified by the differential projections to these cortices from the caudal intraparietal bank, an area associated with eye movement and spatial tasks (for reviews see Lynch, '80; Hyvärinen, '82). Two of the four sites examined within the mediodorsal and basoventral prefrontal regions received some projections from the lateral intraparietal bank (Tables 1, 3). However, the periarcuate areas received a higher proportion of their projections from this visuomotor region when compared with regions below the caudal portion of the principal sulcus. Moreover, within the lateral intraparietal bank the site of labeled neurons directed to the dorsal periarcuate and the ventral periprincipalis regions differed to some extent. The periarcuate sites received a considerable proportion of their intraparietal projections from the depths of the sulcus (areas IPd and POa-i), whereas the ventral regions received projections from more superficial portions of the intraparietal bank (areas POa-e and sulcal PG, Table 3). It should be noted that only the deep portion of the lateral intraparietal bank receives projections from area MT in macaque monkeys (Maunsell and Van Essen, '83; Ungerleider and Desimone, '86). These connectional differences suggest that the lateral intraparietal bank may have distinct functional as well as architectonic subdivisions.

Does the observation of segregation of the origin of visual and visuomotor projections extend to the prefrontally directed projections from other cortical regions? The present data indicate that the origin of projections from parietotemporal and premotor regions to mediodorsal and basoventral prefrontal subdivisions differed to some extent (Table 5). For example, mediodorsal prefrontal regions received most of their superior temporal projections from the medially situated area TPO, whereas basoventral prefrontal regions received projections from the more laterally situated areas PGa and IPa as well. In addition, mediodorsal areas received projections primarily from the dorsal premotor region, and basoventral areas received projections primarily from ventral premotor regions. The same dorsoventral organization seemed to apply for the intrinsic connections of the prefrontal cortex (Table 6).

The functional significance of the segregated input from parietotemporal, premotor, and perhaps other sensory cortices is difficult to address, and the answer will ultimately lie in the realm of physiology. The dorsal and ventral pre-

motor regions have different architecture and frontal connections (Barbas and Pandya, '87). The dorsal premotor region, which contains a representation of the trunk and the lower limb, may have a role in postural mechanisms. On the other hand, the ventral premotor region, which contains a representation of the head, may be involved with movement of the head in orienting to sensory stimuli. The present data do not permit a similar analysis for the projections from auditory or somatosensory cortices because only a few of the prefrontal regions studied received projections from these cortices. However, on the basis of the present data it may be expected that mediodorsal prefrontal areas are involved in the localization of auditory and somatosensory stimuli, whereas basoventral prefrontal areas are involved in the identification of stimulus characteristics within these modalities. In fact, this hypothesis is consistent with behavioral and physiologic data supporting a discriminative role for ventral and a spatial role for dorsal prefrontal areas (Mishkin and Manning, '78; Voytko, '85; Bachevalier and Mishkin, '86; Vaadia et al., '86).

In addition to the general differences in the origin of visual projections to the basoventral and mediodorsal cortices, there were differences in the connectional organization of areas within a group of cortices as well. The mediodorsal and basoventral areas described in this study represent stages within two trends of architectonic differentiation in the prefrontal cortex (Barbas and Pandya, '82). One of these architectonic trends follows a basoventral course from a caudal orbitofrontal region, which has an incipient laminar differentiation, and proceeds radially to areas 13, 14, 11, and 12 ventral areas 10, 46, and 8, which exhibit a progressive increase in laminar differentiation. Another trend of architectonic differentiation follows a mediodorsal course from limbic areas 24, 25, and 32 and proceeds radially to area 9 and dorsal areas 10, 46, and 8. The earliest stages within each architectonic trend show the lowest, and the latest stages show the highest, degree of architectonic differentiation within the prefrontal cortex. Within the basoventral axis of architectonic differentiation the orbitofrontal cortices are the least differentiated and received visual input from the anterior parts of the inferior temporal cortex; the latter forms the first step in the caudally directed axis of architectonic differentiation of the visual cortical system (Rosene and Pandya, '83). The more architectonically differentiated areas below the principal sulcus received projections primarily from caudal inferior temporal regions. Within the mediodorsal axis of prefrontal architectonic differentiation limbic area 32 received visual input from some rather undifferentiated rostromedial preoccipital regions. On the other hand, the considerably more differentiated area 8 received projections from more caudal and similarly more differentiated visual cortices. The present data suggest that corticocortical projections exist between regions which are at a similar architectonic stage.

There are several other differences in the connectional organization of the regions studied which seem to be dependent on their stage of architectonic differentiation as well. For example, basal sites 11 and 12 are isocortical areas, but among those studied, they represent the least architectonically differentiated sites within the basoventral prefrontal cortices. Basal areas 11 and 12 showed little modality specificity in their long corticocortical projections receiving projections from regions associated with two or more modalities. Moreover, they received a substantial propor-

tion of their projections from limbic cortices. On the other hand the considerably more differentiated ventral area 46 showed a higher degree of modality specificity in its distant connections and received only a few projections from limbic cortices. Similar observations were made for regions within the mediodorsal axis of prefrontal architectonic differentiation. Thus limbic area 32 received projections from visual and auditory cortices and substantial projections from limbic cortices. On the other hand, area 8, which shows the highest degree of laminar differentiation within the prefrontal cortex, received most of its distant projections from visual and visuomotor cortices and very few from other regions. The data therefore indicate that the least architectonically differentiated areas had the most widespread and diverse cortical projections, including substantial projections from the phylogenetically older limbic cortices. On the other hand, regions which show the highest degree of architectonic differentiation had more restricted corticocortical connections and few links with limbic cortices.

It is not clear why there are so many regions within the basoventral and mediodorsal prefrontal cortex that receive projections from visual areas. The answer may lie in the architectonic differentiation of the prefrontal cortex, which may reflect ultimately on the pattern of evolution of the prefrontal cortex. The progressive architectonic differentiation observed within the prefrontal system suggests the addition of cortical areas during evolution, perhaps in response to different postural and/or environmental demands imposed on the organism. The least architectonically differentiated areas, which show little modality specificity in their corticocortical connections and have strong connections with the phylogenetically older limbic cortices, may have been among the first to develop during evolution. These cortices may have a global but integral role in the processing of visual or other sensory information. The orbitofrontal and anterior inferior temporal cortices, which are linked with corticocortical connections, thus may form the first step in the analysis of visual form. Similarly, the medial prefrontal and rostromedial visual cortices may represent the first step in the analysis of motion and space. The most architectonically differentiated areas within both mediodorsal and basoventral prefrontal cortices showed a rather high degree of modality specificity in their corticocortical connections. These areas, which had few connections with limbic cortices, may have a more specific role in the processing of sensory information. In this context it is interesting that, among the regions studied, only the periarcuate and caudal periprincipalis areas seemed to be targets of the lateral intraparietal bank. These results suggest that only the most architectonically differentiated regions within the prefrontal cortex receive projections from the intraparietal visuomotor region. This evidence suggests that these cortices may be at the same stage of architectonic differentiation and may have evolved at the same time.

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