

# Medial Prefrontal Cortices Are Unified by Common Connections With Superior Temporal Cortices and Distinguished by Input From Memory-Related Areas in the Rhesus Monkey

H. BARBAS,<sup>1,2\*</sup> H. GHASHGHAELI,<sup>1</sup> S.M. DOMBROWSKI,<sup>3</sup> AND N.L. REMPEL-CLOWER<sup>1</sup>

<sup>1</sup>Department of Health Sciences, Boston University, Boston, Massachusetts 02215

<sup>2</sup>Department of Anatomy and Neurobiology, Boston University School of Medicine, Boston, Massachusetts 02218

<sup>3</sup>Department of Behavioral Neuroscience, Boston University School of Medicine, Boston, Massachusetts 02218

---

---

## ABSTRACT

Medial prefrontal cortices in primates have been associated with emotion, memory, and complex cognitive processes. Here we investigated whether the pattern of cortical connections could indicate whether the medial prefrontal cortex constitutes a homogeneous region, or if it can be parceled into distinct sectors. Projections from medial temporal memory-related cortices subdivided medial cortices into different sectors, by targeting preferentially caudal medial areas (area 24, caudal 32 and 25), to a lesser extent rostral medial areas (rostral area 32, areas 14 and 10), and sparsely area 9. Area 9 was distinguished by its strong connections with premotor cortices. Projections from unimodal sensory cortices reached preferentially specific medial cortices, including a projection from visual cortices to area 32/24, from somatosensory cortices to area 9, and from olfactory cortices to area 14. Medial cortices were robustly interconnected, suggesting that local circuits are important in the neural processing in this region. Medial prefrontal cortices were unified by bidirectional connections with superior temporal cortices, including auditory areas. Auditory pathways may have a role in the specialization of medial prefrontal cortices in species-specific communication in non-human primates and language functions in humans. *J. Comp. Neurol.* 410:343-367, 1999.

© 1999 Wiley-Liss, Inc.

**Indexing terms:** auditory connections; working memory; long-term memory; vocalization; schizophrenia

---

---

The medial sector of the prefrontal cortex in primates encompasses a set of architectonically diverse areas, extending from areas surrounding the rostral part of the corpus callosum to the medial frontal pole. The caudal medial prefrontal cortices, which form a crescent around the rostral part of the corpus callosum, are included in the classic Papez (1937) circuit for emotion. This region encompasses architectonic areas 32, 25, and 24, which have in common a number of functional, connectional, and structural features. For example, caudal medial cortices have a common role in vocalization, emitted in response to emotional stimuli (for review see Vogt and Barbas, 1988). These medial cortices are enriched in opiate receptors, a feature that is consistent with their involvement in the affective aspect of pain (Vogt et al., 1979, 1993, 1995;

Rainville et al., 1997). In addition, posterior medial areas have a set of connections with subcortical limbic structures including the hippocampus (for review see Barbas, 1997), suggesting that they may have a role in mnemonic processing. Finally, all caudal medial cortices lack a well-delineated granular layer 4 and are considered dysgranu-

---

Grant sponsor: National Institutes of Health; Grant number: NS24760; Grant sponsor: National Institutes of Mental Health; Grant number: F32MH11151.

\*Correspondence to: Helen Barbas, Department of Health Sciences, Boston University, 635 Commonwealth Avenue, Room 431, Boston, MA 02215. E-mail: barbas@bu.edu

Received 14 August 1998; Revised 27 January 1999; Accepted 4 March 1999

lar (Barbas and Pandya, 1989; Morecraft et al., 1992). The above characteristics apply to posterior medial areas, which collectively make up the limbic component of the medial prefrontal region (Barbas and Pandya, 1989).

There are several additional cortices situated anteriorly within the medial prefrontal region, including area 9 dorsally, area 14 rostroventrally, and area 10, which caps the frontal pole. There is comparatively less information on the functions or connections of anterior medial areas, although recent studies have provided evidence that area 9 has an important role in the selection of appropriate responses in complex cognitive tasks (e.g., Petrides, 1995). Unlike the posterior cortices, areas 9, 10, and 14 have six cortical layers, including a granular layer 4, and thus are considered eulaminar areas.

The question arises on whether medial cortices can be considered a functional unit, or if subareas have specialized characteristics. In this article, we addressed this issue from the perspective of their cortical connections. Previous studies have provided information on the connections of some medial areas, most of which focused on specific posterior areas (Vogt et al., 1979; Baleyrier and Mauguier, 1980; Pandya et al., 1981; Vogt and Pandya, 1987; Barbas, 1988; Morecraft et al., 1992; Carmichael and Price, 1995; for reviews see Pandya et al., 1988; Barbas, 1995a, 1997), but there is little information on the cortical connections of the anterior medial areas, and in particular areas 10 and 9. Here we studied the cortical connections of all medial areas with a goal to determine whether specific sets of connections could define distinct domains within the medial prefrontal region. We addressed the following questions: Do cortical areas associated with mnemonic

processes target specific sectors within the medial prefrontal region? Which are the common and unique inputs from sensory and other cortices to these areas? Finally, do these areas have direct access to cortical motor control systems for executive functions?

## MATERIALS AND METHODS

### Cases

Experiments were conducted on 10 rhesus monkeys (*Macaca mulatta*) according to the NIH Guide for the Care and Use of Laboratory Animals (NIH publication 80-22, 1987). The detailed topography of intrinsic and distant corticocortical connections of the cases in this study has not been previously described. Some of these cases were used to study the connections of prefrontal cortices with subcortical structures, including the amygdala, the hippocampus, the thalamus, and the hypothalamus (Barbas and De Olmos, 1990; Barbas et al., 1991; Dermon and Barbas, 1994; Barbas and Blatt, 1995; Rempel-Clower and Barbas, 1998). The use of some of these cases in corticocortical studies was limited to analysis of the distribution of a small number of double-labeled neurons (~1% of all cortical neurons; Barbas, 1995b), or the patterns of the laminar origin and termination of intrinsic connections within the prefrontal cortex (Barbas and Rempel-Clower, 1997). Case AE, with an injection of wheat germ agglutinin conjugated to horseradish peroxidase (WGA-HRP) in area 32, was previously used to study the distribution of retrogradely labeled neurons in the cortex (Barbas, 1988; case 5), and our analysis here is restricted to anterograde label. In

### Abbreviations

3a	somatosensory area	PaAr	rostral para-auditory cortex
8 D	dorsal area 8	PaI	rostromedial auditory association area
8 V	ventral area 8	PAll	periallocortex (agranular cortex)
A	arcuate sulcus	PE	parietal association area
AMT	anterior middle temporal dimple	PGa	polymodal area in the depths of the upper bank of superior temporal sulcus
AON	anterior olfactory nucleus (olfactory area)	Pir	piriform (olfactory) cortex
C	central sulcus	PMT	posterior middle temporal dimple
Ca	calcarine fissure	PO	medial visual association area
CC	corpus callosum	ProA	medial auditory association area
Cg	cingulate sulcus	R46 D	rostral part of dorsal area 46
D6	dorsal area 6	R46 V	rostral part of ventral area 46
D9	dorsal area 9	r	rhodamine-labeled latex microspheres
DLP	dorsolateral temporal pole (dysgranular cortex)	R	rhinal sulcus
DMP	dorsomedial temporal pole (agranular and dysgranular cortex)	RM	rostromedial region
dy	diamidino yellow	Ro	rostral sulcus
fb	fast blue	RP	rostral auditory parabelt
G	gustatory area	RT	rostrottemporal
HRP	horseradish peroxidase	RTL	lateral rostrottemporal auditory belt
Iag	agranular insula	RTM	medial rostrottemporal auditory belt
Idg	dysgranular insula	SII	somatosensory association area
Ig	granular insula	ST	superior temporal sulcus
IO	inferior occipital sulcus	TE1-2	temporal visual association areas
IP	intraparietal sulcus	TEa	temporal visual association area in the lower bank of the superior temporal sulcus
L12	lateral part of area 12	TF	lateral and rostral parahippocampal cortex
LF	lateral fissure	TH	medial and caudal parahippocampal cortex
LO	lateral orbital sulcus	TPO	polymodal area in the upper bank of the superior temporal sulcus
M7	medial area 7	TS1-3	temporal auditory association areas
M9	medial area 9	V2	visual association area
MII	supplementary motor area	V6	ventral area 6
MO	medial orbital sulcus	VMP	ventromedial pole
O12	orbital part of area 12	WGA	wheat germ agglutinin
OLF	olfactory area	wm	white matter
OPro	orbital proisocortex (dysgranular cortex)		
OT	occipitotemporal sulcus		
P	principal sulcus		

TABLE 1. Injection Sites in Prefrontal Cortices and Types of Analyses Conducted

Area injected	Case	Tracer type
25	AH	WGA-HRP <sup>1,2</sup>
32/24	Alb	Fast blue <sup>3</sup>
32	AKy	Diamidino yellow <sup>3</sup>
32	AE	WGA-HRP <sup>2</sup>
32	MDQ	[ <sup>3</sup> H] amino acids <sup>2</sup>
14	AKb	Fast blue <sup>3</sup>
14	DLb	Fast blue <sup>3</sup>
M9 (rostral)	AO	WGA-HRP <sup>2,3</sup>
M9 (rostral)	AKr	Rhodamine microspheres <sup>4</sup>
M9 (caudal)	AQy	Diamidino yellow <sup>3</sup>
D9 (caudal)	AQb	Fast blue <sup>3</sup>
M10	ARb	Fast blue <sup>3</sup>
10	AP	WGA-HRP <sup>4</sup>

<sup>1</sup>Quantitative analysis of projection neurons outside prefrontal cortices.

<sup>2</sup>Analysis of anterograde label in temporal auditory and some adjacent cortices.

<sup>3</sup>Quantitative analysis of projection neurons in all cortical areas.

<sup>4</sup>Qualitative analysis only; confirmatory cases.

recent articles, cases used to study different connections have been identified by the same codes for direct reference (Dermon and Barbas, 1994; Barbas, 1995b; Barbas and Blatt, 1995; Rempel-Clower and Barbas, 1998).

### Surgical procedures

The monkeys were anesthetized with ketamine hydrochloride (10 mg/kg, intramuscularly) followed by sodium pentobarbital administered intravenously through a femoral catheter until a surgical level of anesthesia was achieved. Additional anesthetic was administered during surgery as needed. Surgery was performed under aseptic conditions. The monkey's head was firmly positioned in a holder, which left the cranium unobstructed for surgical approach. A craniotomy was made, the dura was retracted, and the cortex was exposed.

Table 1 shows the number of cases, number of sites, and types of dyes injected. Injections of WGA-HRP (Sigma, St. Louis, MO) were placed in prefrontal cortices in four animals and fluorescent dyes (fast blue, diamidino yellow, or rhodamine-labeled latex microspheres) were injected in five animals. Another case available for study of anterograde label had been injected with [<sup>3</sup>H] amino acids. All injections were made with a microsyringe (5  $\mu$ l; Hamilton, Reno, NV) mounted on a microdrive. The needle was lowered to the desired site under microscopic guidance. In each case, small amounts (0.05  $\mu$ l, 8% WGA-HRP; 0.3  $\mu$ l, 3% diamidino yellow, fast blue, or rhodamine-labeled latex microspheres; 0.5  $\mu$ l [<sup>3</sup>H] leucine and [<sup>3</sup>H] proline, specific activity 40–80 Ci/mmol) 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. In cases with fluorescent dyes, 1–3 different sites were injected with distinct tracers in each animal.

In the HRP experiments, 40–48 hours after injection the monkeys were anesthetized deeply and perfused through the heart with saline followed by 2 liters of fixative (1.25% glutaraldehyde, 1% paraformaldehyde in 0.1 M phosphate buffer, pH 7.4), followed by 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% dimethyl sulfoxide [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 (Rosene et al., 1986), transferred to a freezing microtome, and cut in the coronal plane at 40  $\mu$ m in 10 series. One series of sections was

treated to visualize HRP (Mesulam et al., 1980). The tissue was mounted, dried, and counterstained with neutral red.

In animals injected with fluorescent dyes or [<sup>3</sup>H] amino acids, the survival period was 10 days. The animals then were anesthetized deeply and perfused with 4% or 6% paraformaldehyde in 0.1 M cacodylate buffer (pH 7.4). The brains in the fluorescent dye experiments were post-fixed in a solution of 4% or 6% paraformaldehyde with glycerol and 2% DMSO, frozen, and cut as described above. Two adjacent series of sections were saved for microscopic analysis. These series were mounted and dried onto gelatin-coated slides and stored in light-tight boxes with Drierite at 4°C. The first series was coverslipped with Fluoromount 7 days later and returned to dark storage at 4°C. The second series was left uncoverslipped and used to chart the location of retrogradely labeled neurons. After the second series was charted it was stained with cresyl violet, coverslipped, and used to determine cytoarchitectonic boundaries. The brain of the animal injected with [<sup>3</sup>H] amino acids was embedded in paraffin, cut in the coronal plane at 10  $\mu$ m, and processed for autoradiography according to the procedure described by Cowan et al. (1972).

In all experiments, series of sections adjacent to those prepared to visualize retrograde tracer labeling were stained for Nissl bodies and acetylcholinesterase (AChE), or myelin (or both), to aid in delineating architectonic borders (Geneser-Jensen and Blackstad, 1971; Gallyas, 1979).

### Data analysis

**Retrograde label.** Brain sections prepared according to the methods described above were viewed microscopically under brightfield and darkfield illuminations for HRP cases, or fluorescence illumination in experiments with dyes. Drawings of cortical areas, the location of labeled neurons ipsilateral to the injection site, and the site of blood vessels used as landmarks were transferred from the slides onto paper by means of a digital plotter (Hewlett Packard 7475A, Palo Alto, CA) electronically coupled to the stage of the microscope and to a computer (Austin 486, Austin, TX). In this system, the analog signals are converted to digital signals via an analog-to-digital converter (Data Translation, Marlboro, MA) in the computer. Software developed for this purpose ensured that each labeled neuron noted by the experimenter was recorded only once, as described previously (Barbas and De Olmos, 1990). Movement of the stage of the microscope was recorded via linear potentiometers (Vernitec, Deer Park, NY) mounted on the X and Y axes of the stage of the microscope and coupled to a power supply. This procedure allows accurate topographic presentation of labeled neurons within the cortex.

Every other section through the entire cortex in one series was examined and charted. Labeled neurons were counted by outlining the region of interest (e.g., one area) by moving the X and Y axes of the stage of the microscope. The number of labeled neurons within the enclosed region was calculated by an algorithm written for this purpose.

**Anterograde label.** We examined anterograde label in 4 WGA-HRP or autoradiographic cases under darkfield illumination by using a fiber optic illuminator to ensure even lighting conditions at low and high magnifications (Optical Analysis Corp., Nashua, NH). The density of anterograde label was evaluated qualitatively on a scale of 1–6, with ratings of 1–2 assigned for light, 3–4 for moderate, and 5–6 for dense label for layers 1, 2–3, 4, and 5–6 for each area in

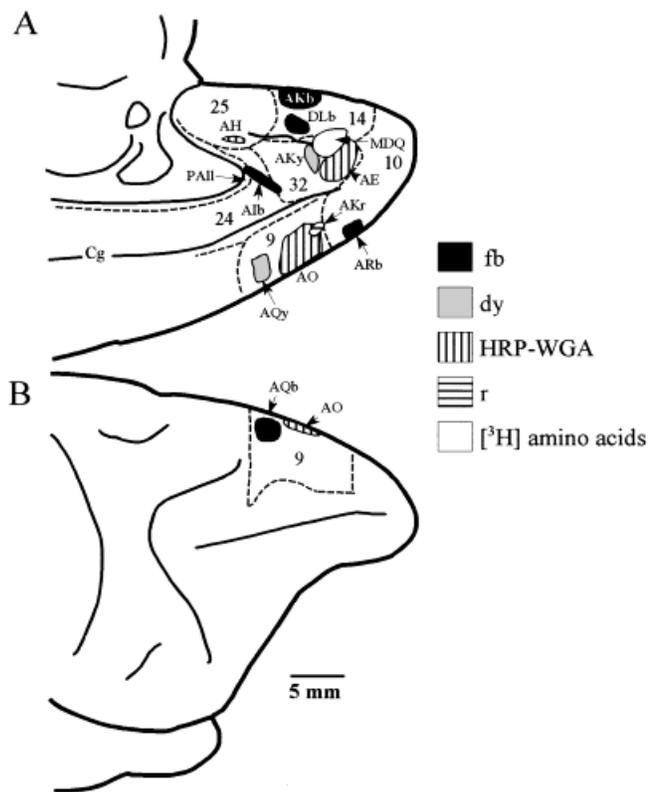


Fig. 1. Composite of injection sites shown on the medial (A) and lateral (B) surfaces of the frontal lobe. The injection sites are superimposed on an architectonic map of the prefrontal cortex (Barbas and Pandya, 1989). Dotted lines demarcate architectonic areas indicated by numbers. Pall, medial periallocortex; Cg, cingulate sulcus; fb, fast blue; dy, diamidino yellow; r, rhodamine-labeled latex microspheres. All other letter combinations refer to cases.

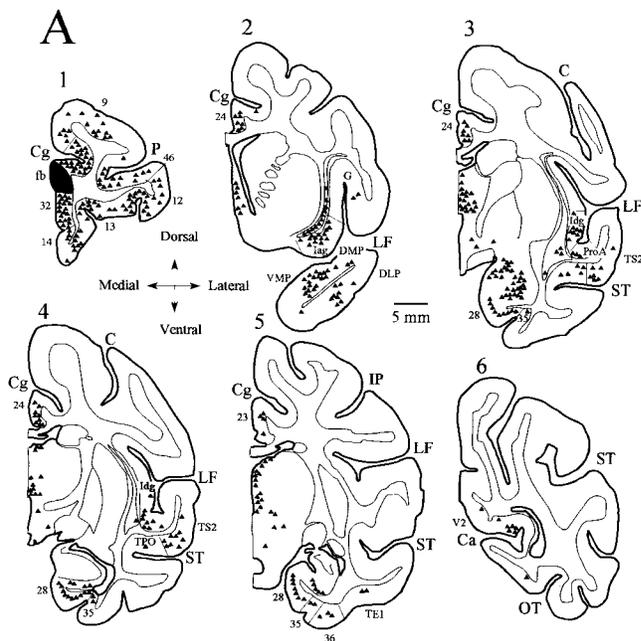


Fig. 2. Case A1b. A: The distribution of labeled neurons (black triangles) in coronal sections in rostral to caudal (1–6) cortical areas after injection of fast blue (fb) in medial prefrontal area 32/24. B: The topography of all labeled neurons in case A1b is shown on an unfolded map of the cortex. Dotted lines (top) separate the medial from the lateral surface (center). The dotted lines below the principal sulcus (P) and through the temporal pole demarcate the lateral from the basal surface (bottom). In this and in other maps of the unfolded cortex, large numbers on top correspond to the levels of the coronal sections shown in A in each case. In all unfolded maps, a straight line coursing from the top to the bottom of the figure represents the unfolded cortex in any given coronal section, and the cortex represented at the top and bottom of this line is continuous. The cortex buried in sulci is shaded; some sulci [e.g., the central sulcus (C) in this figure] were not unfolded but their relative location with respect to anatomic landmarks is preserved. Small numbers in the diagrams indicate architectonic areas. The number of dots in the diagrams represents the relative density of labeled neurons; for the exact number of labeled neurons in each area, see Tables 2–4. The above conventions apply for all maps with labeled neurons. For abbreviations, see list.

TABLE 2. Distribution of Labeled Neurons in Prefrontal Cortices Projecting to Medial Prefrontal Cortices<sup>1</sup>

Origin	Injection site								
	Area Case	32/24 Alb	32 AKy	14 AKb	14 DLb	M9 AO	M9 AQy	L9 AQb	M10 ARb
Area Pall		1.3	0.2	0.3	— <sup>2</sup>	— <sup>3</sup>	—	—	—
Area OPro		8.1	3.4	5.6	1.6	0.9	—	—	0.7
Area 25		10.7	12.5	26.8	13.1	1.1	—	0.2	1.4
Area 13		2.6	3.3	6.9	7.1	0.4	0.1	0.2	0.1
Area 24		25.0	9.5	2.2	0.2	18.3	18.2	20.9	14.9
Area 32		13.9	25.4	7.1	11.8	6.2	4.8	6.6	8.2
Area 14		0.5	21.4	36.2	33.9	7.8	0.2	2.0	7.2
Area 11		2.4	3.1	1.5	0.3	11.1	—	—	5.4
Area O12		8.1	0.7	0.8	1.7	2.6	5.2	2.9	9.5
Area L12		2.2	—	—	0.9	1.0	0.2	0.5	—
Area 10		11.3	14.9	11.8	27.6	2.3	2.1	1.4	22.5
Area 9		5.7	3.2	0.2	1.2	34.8	68.2	57.2	12.5
Area R46 D		1.6	1.3	0	0.1	4.0	—	1.2	11.5
Area R46 V		6.7	1.3	0.5	0.8	8.2	—	3.2	4.6
Area 8 D		—	—	—	—	0.9	0.7	3.7	1.4
Area 8 V		—	—	—	—	0.1	0.2	—	—

<sup>1</sup>Data are expressed in percentages; total percent in each column = 100; the total number of labeled neurons in the prefrontal cortices was: case Akb, 10,002 neurons; case DLb, 3,930 neurons; case AKy, 18,670 neurons; case A1b, 20,969 neurons; case AO, 12,426 neurons; case AQy, 1,900 neurons; case AQb, 1,201 neurons; case ARb, 3,211 neurons.

<sup>2</sup>—, no labeled neurons. In cases AO and A1b, some neurons in area 24 were found in a rostral cingulate motor area.

<sup>3</sup>—, less than 0.1%.

each section. If more than one site contained label within a single architectonic area, then each site was rated separately. In addition, density values were obtained with an image analysis system (MetaMorph, Universal Imaging, West Chester, PA). This high resolution system uses a CCD camera mounted on the microscope and captures images directly from brain sections. Measurements were made under darkfield illumination at a magnification of 100×. An initial density measure in each section was taken in an area with no anterograde label to determine the level of background. The background density was subtracted from subsequent density measures to determine the density of anterograde label. Measurements of density of anterograde label represented the mean density taken from samples distributed throughout each area to avoid retrogradely labeled neurons. The cumulative density of label within the entire extent of each architectonic area was calculated from serial coronal sections for layers 1, 2–3, 4, and 5–6, which were subsequently collapsed into upper (1–3) and deep (4–6) layers. To determine the laminar pattern of anterograde label, data were normalized so that the density in the upper and lower layers was expressed

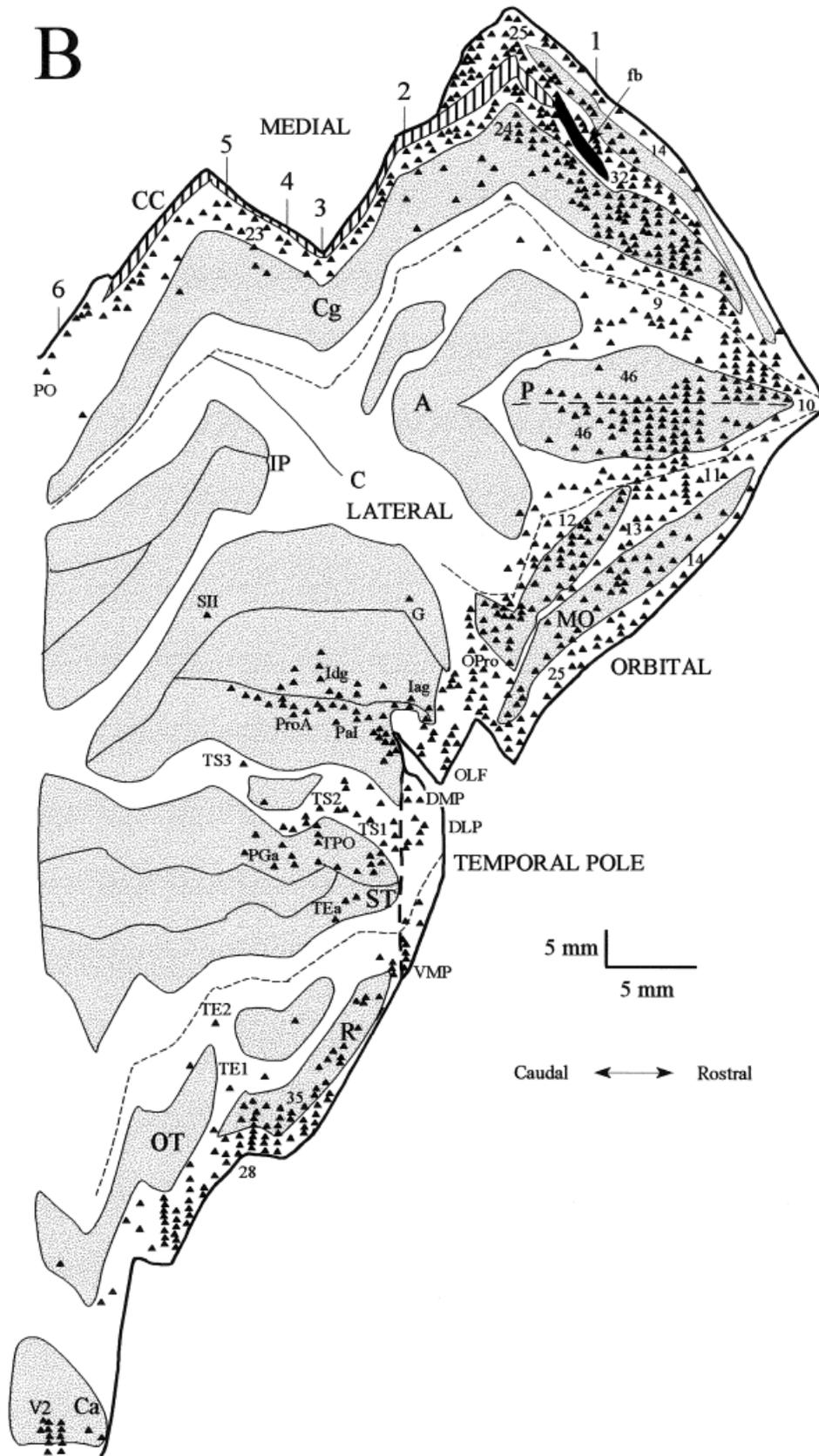


Figure 2 (Continued)

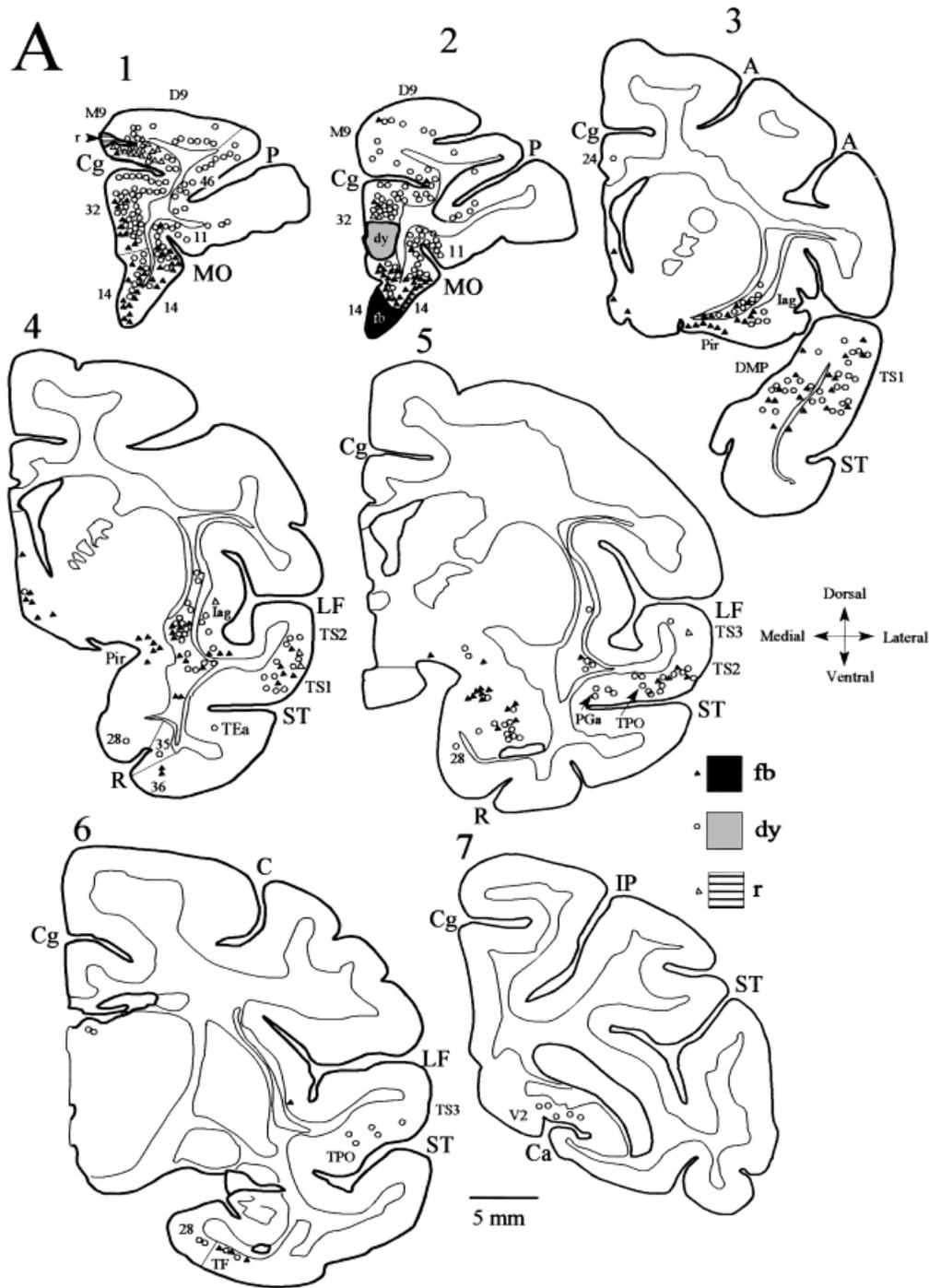


Fig. 3. Case AK. **A:** The distribution of cortical labeled neurons in diagrams of coronal sections in rostral to caudal (1–7) cortical areas after injection of diamidino yellow (dy) in area 32 (open circles; injection site is shown in 2, stippled); fast blue (fb) in area 14 (black triangles; injection site is shown in 2, black); rhodamine-labeled microspheres (r) in medial area 9 (open triangles; injection site is shown in 1, stripes). **B–D:** An unfolded map of the cortex in case AK shows the distribution of all labeled neurons in the cortex for the 3 injection sites separately. **B:** The distribution of labeled neurons (open circles) on the unfolded surface of the cortex which project to area 32 (the injection site, dy, is shown on the medial surface, top). **C:** (page 350) The distribution of labeled neurons (black triangles) projecting to

area 14 (injection site, fb, is shown on the medial surface, top, arrow, and the basal surface, bottom, arrow). These surfaces are continuous on the unfolded cortex, as shown in a cross section (A, 2). **D:** (page 351) The distribution of labeled neurons (open triangles) projecting to medial area 9 (injection site, r, is shown on the medial surface, top). In this case, the medial, orbital, and basal temporal surfaces were unfolded separately, using as a starting point the cingulate sulcus to unfold the medial surface (top), the principalis for the lateral cortex, the medial orbital for the orbitofrontal cortex, and the occipitotemporal for the basal temporal surface. Double dashed lines in D indicate that the cortex beyond that point was not opened. For abbreviations, see list.

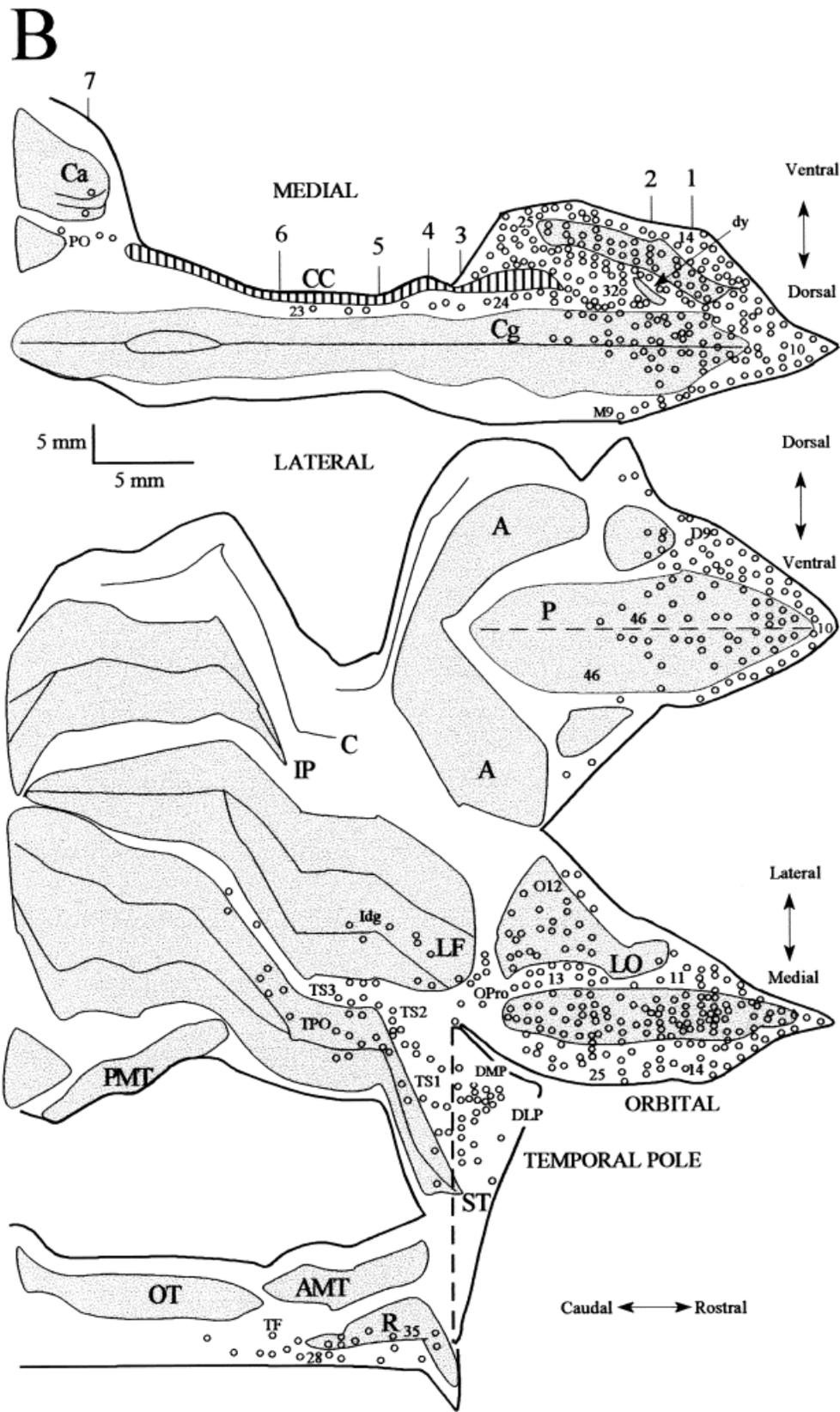


Figure 3 (Continued)



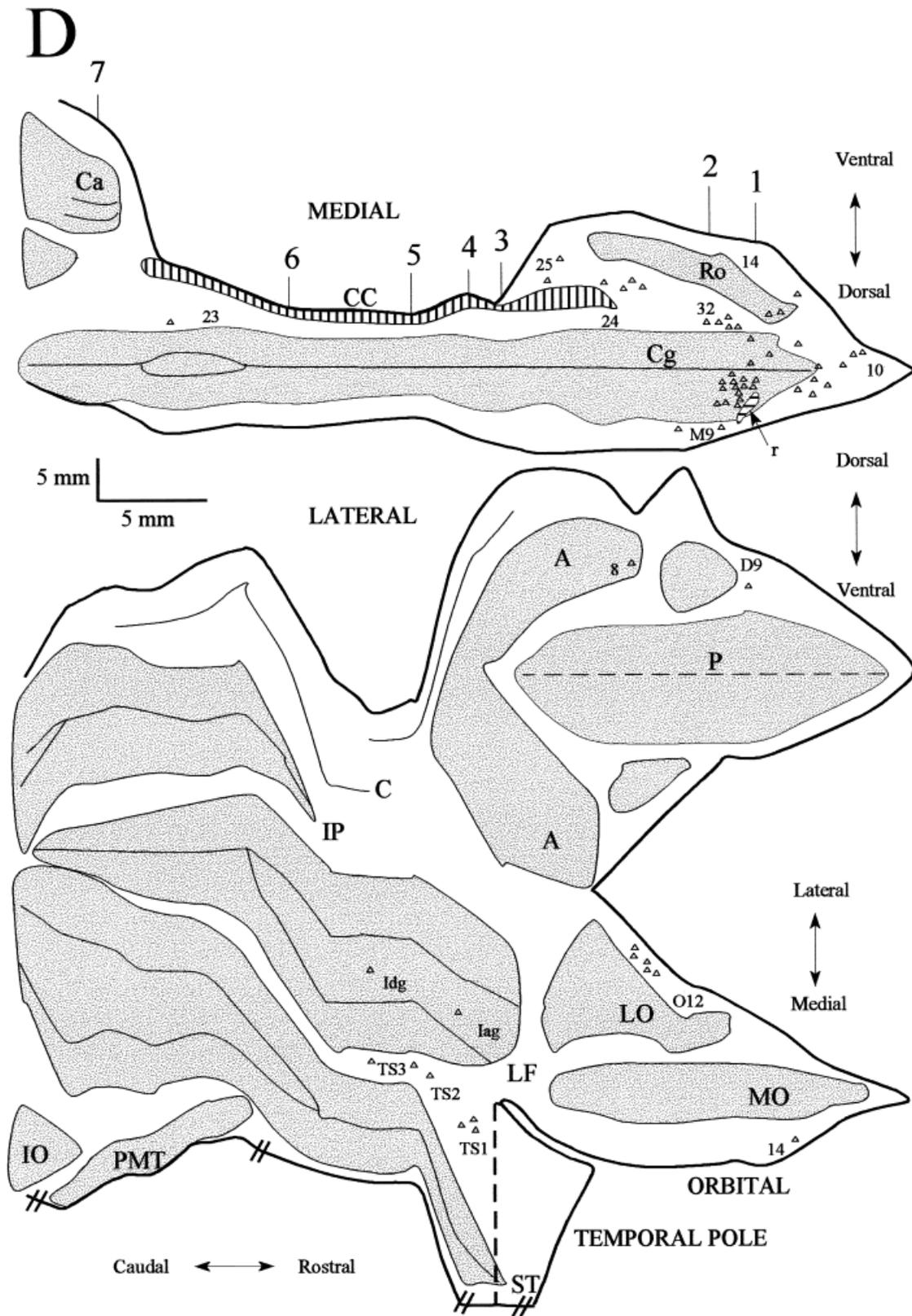


Figure 3 (Continued)

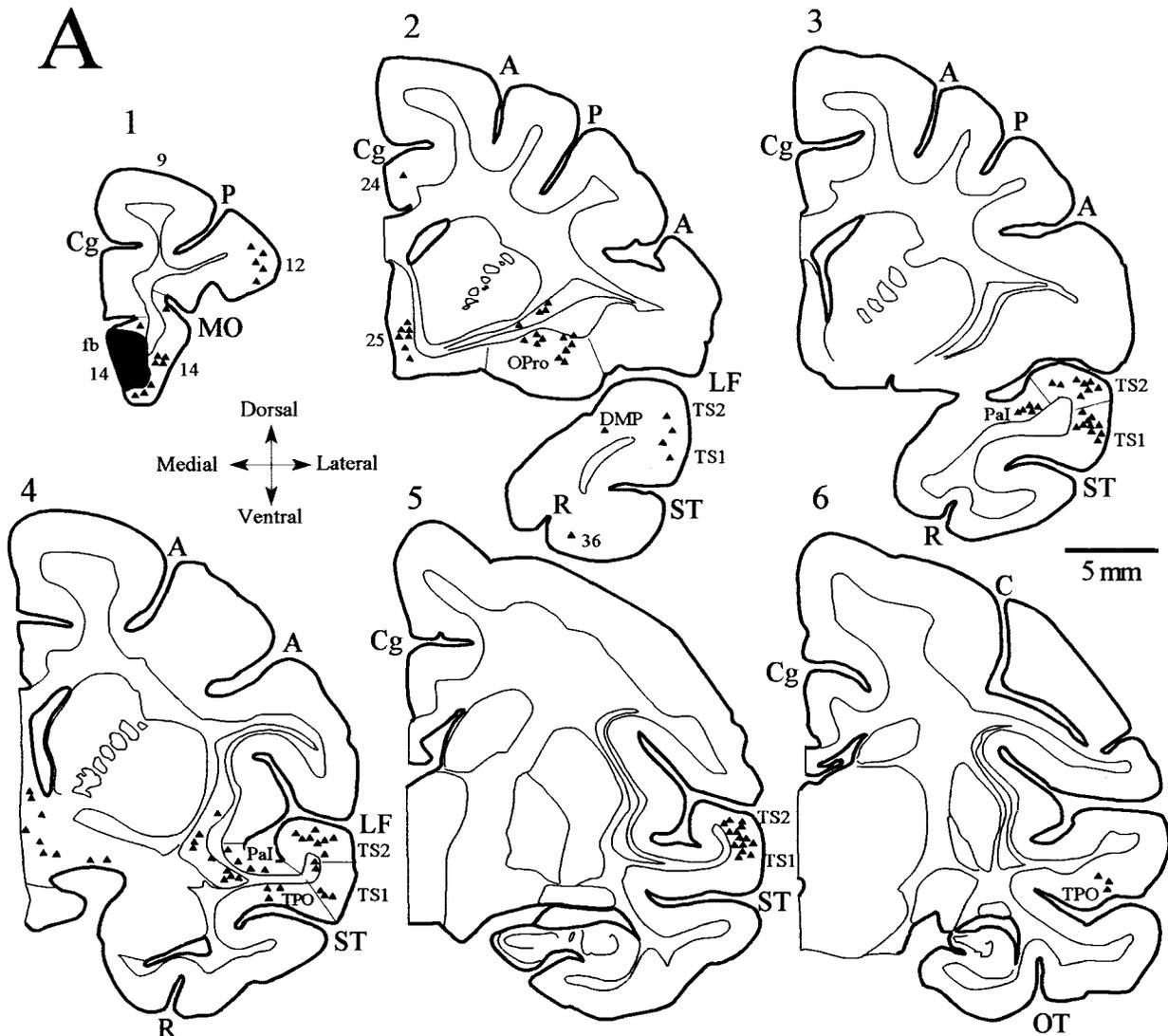


Fig. 4. Case DLb. **A:** The distribution of cortical labeled neurons (black triangles) in diagrams of coronal sections in rostral to caudal (1-6) cortical areas after injection of fast blue (fb) in area 14. **B:** The

topography of all labeled neurons in case DLb is shown on an unfolded map of the cortex; the arrow (top) points to the injection site (fb). For abbreviations, see list.

as a percentage of the total in that area (total density = density in upper layers + density in deep layers).

### Reconstruction of cortical injection sites and projection zones

The cortical regions containing the injection sites were reconstructed serially by using the sulci as landmarks, as described previously (Barbas, 1988), and are shown on diagrams of the surface of the cortex (Fig. 1). The latter were drawn from photographs of each brain showing the external morphology of the experimental hemispheres. Projection areas were shown on representative coronal sections and on maps of the unfolded cortex, constructed as described previously (Barbas, 1988). References to architectonic areas of the prefrontal cortex are according to a previous study (Barbas and Pandya, 1989) modified from the map of Walker (1940).

### RESULTS Injection sites

The medial prefrontal cortex is composed of architectonic area 25, the rostral extent of area 24, area 32, area 14, and the medial parts of areas 9 and 10. Table 1 shows the areas injected with tracers and the types of tracers injected in each case, which are also shown in a composite diagram on the map of the prefrontal cortex in Figure 1.

Intact axons in the white matter are not thought to take up HRP, though there is less information about fluorescent dyes in this regard (LaVail, 1975; Mesulam, 1982). In one of these cases (case ALb), with an injection in area 24 and the caudal part of area 32, the dye spread to the adjacent tip of the corpus callosum. In case AP, with an injection in the frontal pole in area 10, the needle mark extended to the adjacent white matter. In case AKr, a small injection of rhodamine-labeled microspheres in medial area 9 was

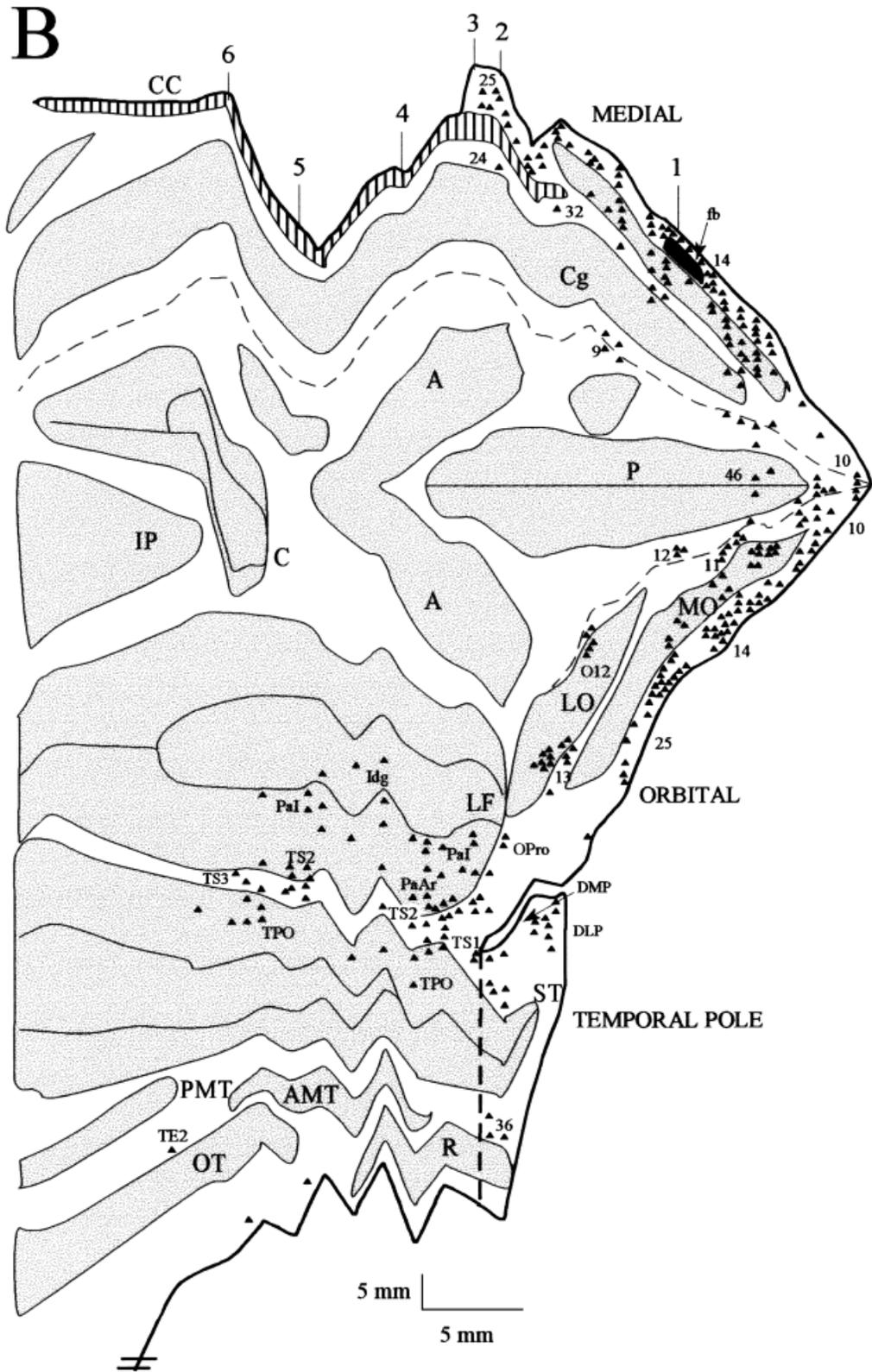


Figure 4 (Continued)

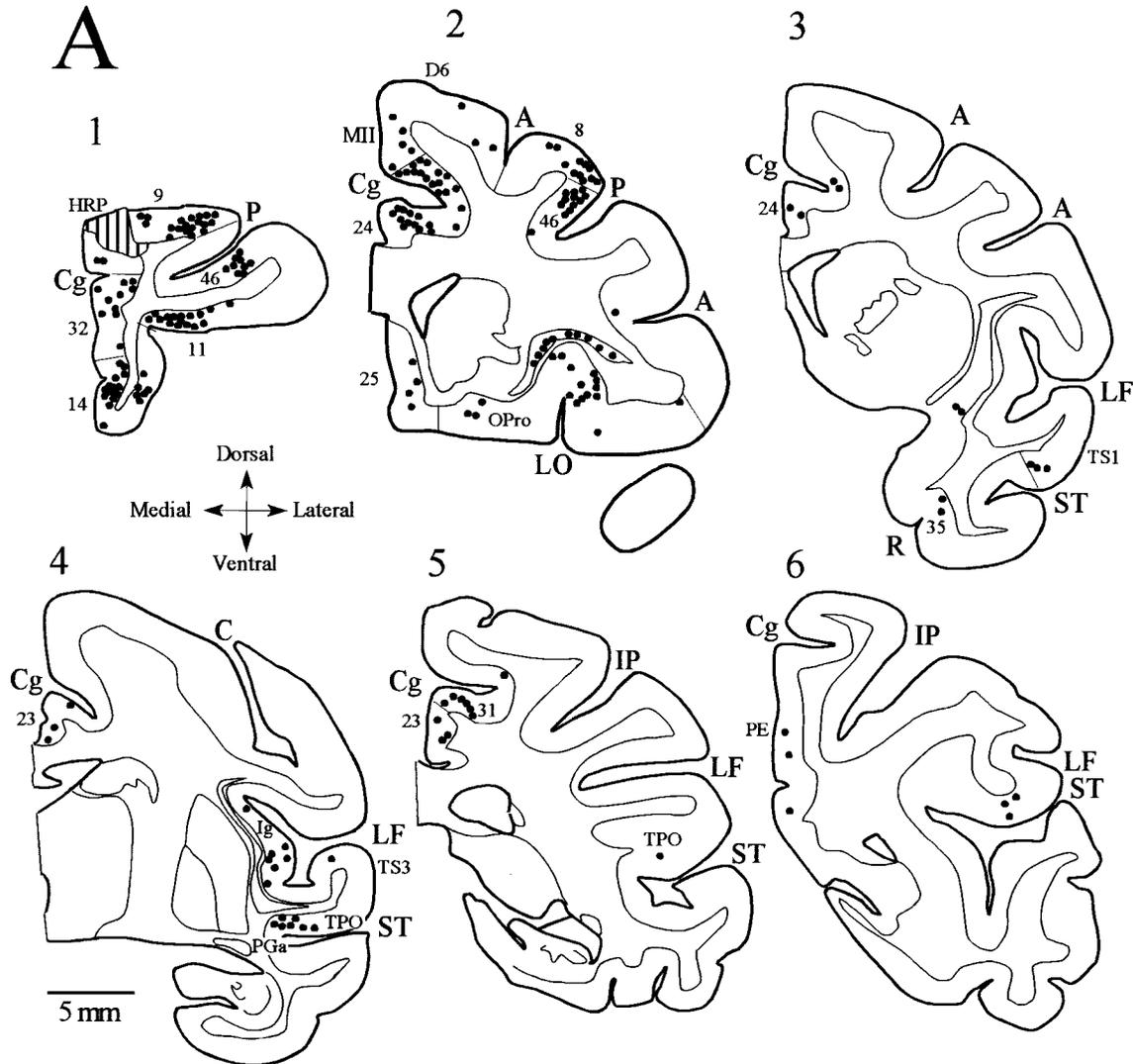


Fig. 5. Case AO. **A:** The distribution of cortical labeled neurons (dots) in diagrams of coronal sections in rostral to caudal (1–6) cortical areas after injection of WGA-HRP in the rostral part of medial area 9 (shown in 1). **B:** The topography of all labeled neurons in case AO on an

unfolded map of the cortex. In this figure, the medial surface was opened separately with the cingulate sulcus serving as the reference point. For abbreviations, see list.

restricted to cortical layers 1–5. Cases AP and AKr were used for general observations but are not included in the quantitative analyses. In the rest of the cases, the needle marks and the core of the injection sites were restricted to the cortical mantle.

### Connections: Retrograde label

**Distribution of labeled neurons in prefrontal cortices.** Detailed quantitative analyses of projection neurons in prefrontal cortices were conducted in six cases (eight injection sites; Table 2). The majority of labeled neurons were found within the prefrontal cortex. On average 85% of projection neurons were found in prefrontal cortices, and of these about one-third were intrinsic, i.e., they were found in the same area as the injection site. Moreover, the majority of labeled neurons came from neighboring prefrontal areas that shared a border with the injected site (~50–90%).

**Area 32/24.** In two cases with injections in area 32 (case AKy) or 32/24 (case A1b), numerous labeled neurons were noted in area 32, area 25, area 24, area 10, OPro, area 13, and area 9. The main differences in these two cases were a higher preponderance of labeled neurons in area 46 in case A1b (Fig. 2A,B) than in case AKy, and a very robust distribution of labeled neurons in area 14 directed to the central part of area 32 (case AKy; Fig. 3A) but not to its caudal part and area 24 (Table 2). In addition, labeled neurons were noted in medial area Pall in case A1b. Finally, in case A1b, labeled neurons were noted in area 12, particularly in its orbital component (Fig. 2B), whereas only a few labeled neurons were noted in area 12 in case AKy (Fig. 3B).

**Area 14.** The prefrontal connections of cases with injections in area 14 are shown topographically on maps in Figures 3A, C and 4A, B, and quantitatively in Table 2. In

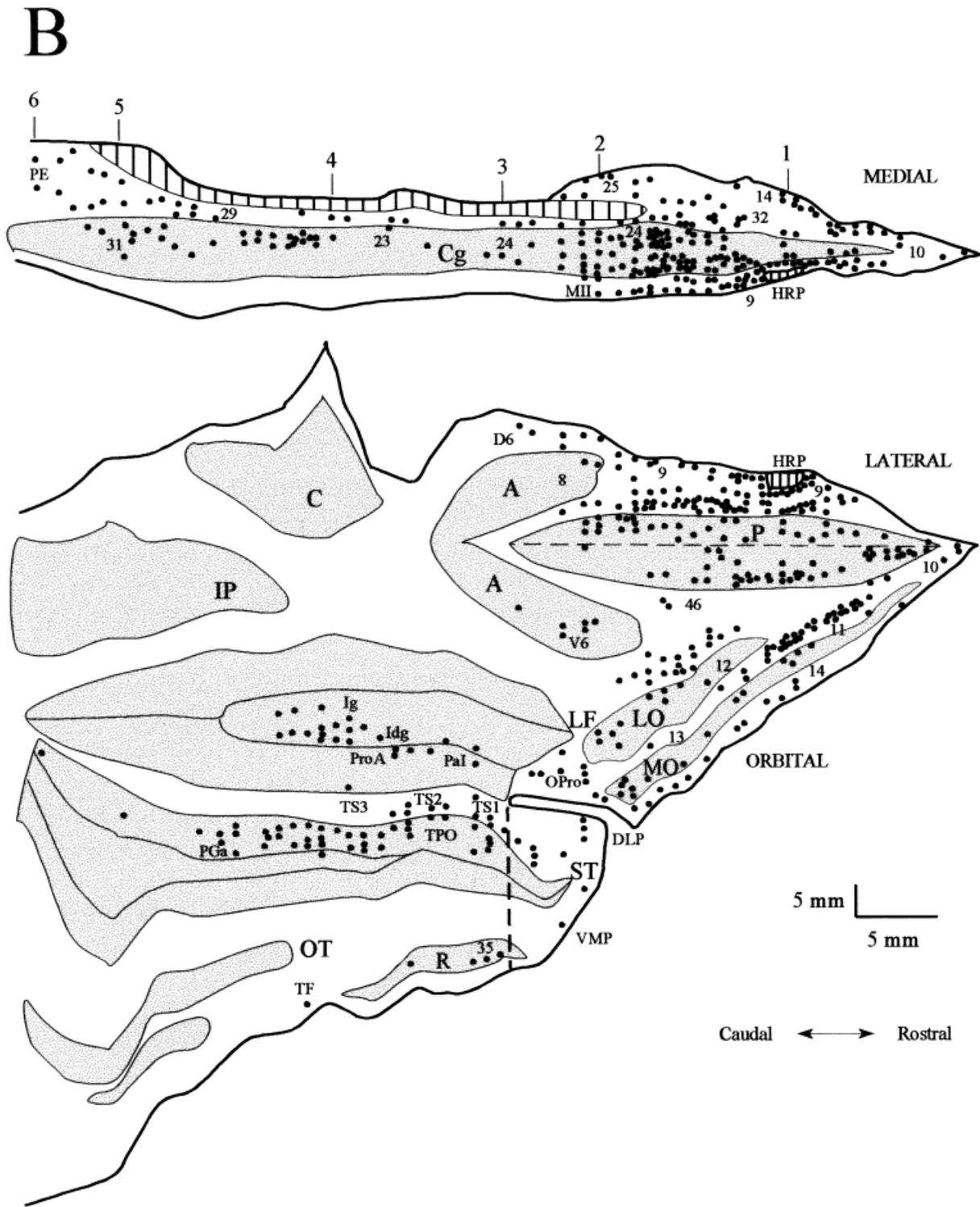


Figure 5 (Continued)

addition to a robust and quantitatively comparable intrinsic projection from the non-injected parts of area 14 in these cases, labeled neurons were found mostly in neighboring areas 25, 32, and 10 and in orbitofrontal areas 13 and OPro. In both cases, a small proportion of the labeled

neurons was noted in area 24, the rostral part of area 46, area 11, and area 12.

**Area 9.** The distribution of labeled neurons in prefrontal cortices was similar in cases with injections in area 9 (Figs. 3D, 5A,B, 6). In addition to the preponderance of

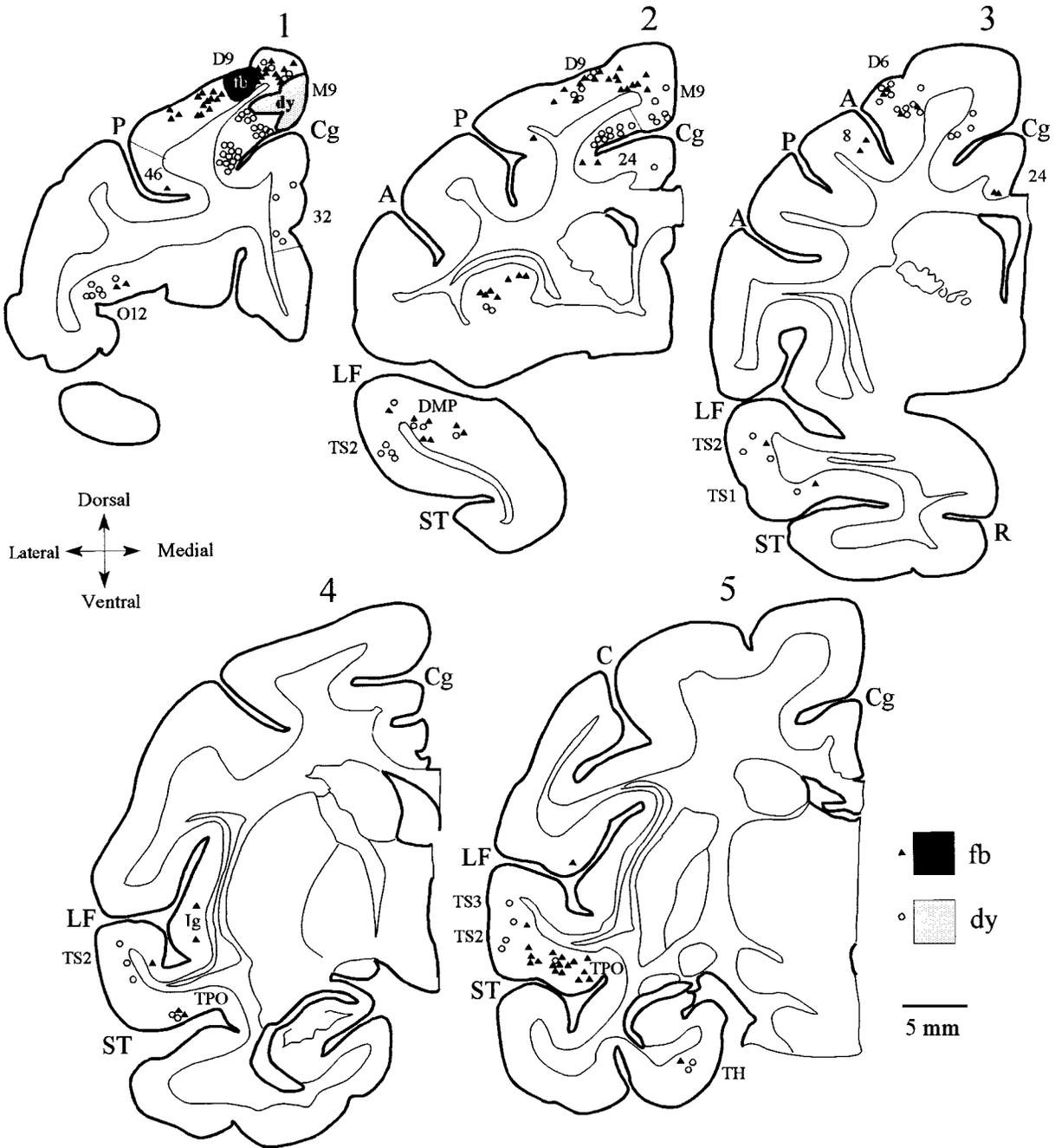


Fig. 6. Case AQ. The distribution of cortical labeled neurons in diagrams of coronal sections in rostral to caudal (1-5) cortical areas after injection of diamidino yellow (dy; open circles) in medial area 9 (M9; injection site is shown in 1); fast blue (fb; black triangles) in dorsal area 9 (D9; injection site is shown in 1). For abbreviations, see list.

labeled neurons in the non-injected parts of area 9, labeled neurons were noted in the adjacent areas 24, 32, 10, 14, and 12 in all cases. Only a few labeled neurons were found in area 13 and in area 8. In cases AO and AQb, there were labeled neurons in the rostral part of area 46. In addition, significant numbers of labeled neurons in area 11 were noted only in case AO, with the most rostral injection in area 9 (Fig. 5A). A similar distribution of labeled neurons

was noted in case AKr, with a small injection of rhodamine in the rostral and medial part of area 9 (Fig. 3D).

**Area 10.** Like other prefrontal cortices, in a case with an injection in medial area 10, the most robust connections were intrinsic, emanating from the adjacent parts of area 10 (Fig. 7A,B). In addition, many labeled neurons were seen in adjacent area 9, the rostral and central parts of area 46, and particularly its dorsal component. A substan-

tial proportion of labeled neurons was found in areas 24, 32, 12, 14, and 11. Finally, a few labeled neurons were noted in area 25, area 8, area 13, and area OPro (Fig. 7B).

### Distant connections of medial prefrontal cortices

Labeled neurons in cortices beyond the prefrontal were mapped and detailed quantitative analyses were conducted for 9 of the 11 sites injected with tracers (Tables 3, 4). Additional observations were made for another two sites, which were used as confirmatory cases, as shown in Table 1. Data in Tables 3 and 4 are expressed as a percentage of the total number of labeled neurons in post-arcuate areas.

**Terminology of areas in the anterior superior temporal region.** In most cases, the highest incidence of labeled neurons outside the prefrontal cortex was noted in superior temporal cortices. These cortices, which include auditory association areas, have been mapped using architectonic procedures (Galaburda and Pandya, 1983). In recent studies, several investigators have modified earlier maps with the aid of chemoarchitectonic markers, physiological, and connectational studies (Morel et al., 1993; Jones et al., 1995; Molinari et al., 1995; Kosaki et al., 1997; Hackett et al., 1998). References to the terminology of earlier and recent studies are included wherever possible. Below we include a brief review of the varied terminology used in the literature for approximately the rostral half of the superior temporal region, which included the heaviest projections to medial prefrontal cortices.

The most rostral parts of the superior temporal region within the temporal pole belong to the limbic system by virtue of their structure and connections. These areas are positive for calbindin and relatively devoid of parvalbumin immunoreactivity (Kondo et al., 1994; Jones et al., 1995). The terms dorsolateral pole (DLP) and dorsomedial pole (DMP) used in this study refer to the agranular and dysgranular cortex of the dorsal part of the temporal pole. In previous studies, this portion of the temporal pole has been referred to as area 38 (Brodmann, 1909), area TG (Von Bonin and Bailey, 1947), area Pro (Pandya and Sanides, 1973; Galaburda and Pandya, 1983), the agranular and dysgranular component of the temporal pole (TPa-p, TPDg; Mesulam and Mufson, 1982; Moran et al., 1987), the periallocortical and dorsal proisocortical division of the temporal pole (TPpAll, TPproD; Gower, 1989), and dorsal area 36 (36d; Suzuki and Amaral, 1994b). The dorsal dysgranular portion of the temporal pole is continuous caudally with areas TS1 and TS2, and is connected with them (Galaburda and Pandya, 1983).

The temporal pole, all of area TS1, and most of area TS2 lie anterior to regions considered to be part of the auditory association region in a recent study (Hackett et al., 1998). Approximately half of the caudal gyral part of TS2 overlaps with auditory parabelt area RP of Hackett et al. (1998). Areas TS1 and TS2 have connections with auditory association areas (Galaburda and Pandya, 1983; Jones et al., 1995), even though their strength diminishes in increasingly rostral superior temporal areas (Hackett et al., 1998). Bidirectional thalamic connections of TS1 and TS2 involve several thalamic nuclei, including the medial pulvinar, the suprageniculata, and the magnocellular sector of the medial geniculate nucleus (MGmc) (Pandya et al., 1994; for review see Jones, 1985). MGmc has neuronal

responses that are primarily auditory and broadly tuned and projects diffusely to all auditory cortices (Burton and Jones, 1976; Morel et al., 1993; Molinari et al., 1995; for review see Jones, 1985). The above connections suggest that TS1 and TS2 may have a role in auditory processes, and a recent study suggested that these areas along with areas TS3 and Tpt may have a role in auditory memory (Colombo et al., 1996). However, in view of the paucity of detailed physiologic studies in anterior superior temporal cortices, it is not possible to ascertain the functional attributes of TS1 and TS2 at this time.

Area TS3 of Galaburda and Pandya (1983) is situated caudal to area TS2 and overlaps extensively with auditory association areas RP and RTL of Hackett et al. (1998). Area PaI and ProA (Galaburda and Pandya, 1983) appear to overlap with area M of Kosaki et al. (1997). Area PaI overlaps with area RTM and area ProA with area RM of Hackett et al. (1998). Area PaAr of Galaburda and Pandya (1983) overlaps with core area RT of Hackett et al. (1998).

In this study, we have used the descriptive terminology DLP and DMP to refer to the temporal pole (area Pro in the map of Galaburda and Pandya, 1983). The terminology used for superior temporal regions beyond the temporal pole is based largely on the map of Galaburda and Pandya (1983) and Hackett et al. (1998).

**Projections from auditory and adjacent superior temporal cortices.** Table 3 shows the detailed distribution of labeled neurons in superior temporal and dorsolateral and dorsomedial temporal polar areas after injection of tracers in medial prefrontal cortices. Projection neurons were found in several auditory association areas. Using the terminology of a recent study (Hackett et al., 1998), a small number of projection neurons were found in a rostral part of the auditory core (area RT), and to a greater extent in surrounding auditory belt (areas RTM, RM, and RTL) and parabelt (area RP) areas which correspond to areas PaAr, PaI, ProA, and TS3 of Galaburda and Pandya (1983). In addition, many labeled neurons were found in the rostrally adjacent areas TS2 and TS1 of Galaburda and Pandya (1983), and in the dorsal part of the temporal pole. There were no labeled neurons in posterior auditory association areas beyond area TS3.

**Areas 32, 24, and 25.** A substantial proportion of labeled neurons in auditory association and adjacent superior temporal cortices projected to area 32 (case AKy; Fig. 3A,B), area 25 (case AH; Fig. 8), and area 32/24 (case AlB; Fig. 2A,B). With regard to topography, most of the labeled neurons projecting to area 25 were found in TS1, those directed to area 32 were distributed in TS2 and TS1, and a smaller number were found in TS3 (case AKy; Table 3). Labeled neurons projecting to area 32/24 were found mostly in TS2, followed by TS1, and a few scattered labeled neurons were seen in TS3 (RP) (Fig. 2A,B). Some labeled neurons were noted in area ProA (RM) (case AlB; Fig. 2B) and in area PaAr (RT) (case AH). In all cases, labeled neurons were also seen in adjacent dorsolateral and dorsomedial temporal polar regions, and these were most numerous in case AKy (Figs. 2A,B, 3A,B, 8).

**Area 14.** In cases with injection in area 14, substantial numbers of projection neurons were noted in auditory and anterior superior temporal association cortices (Table 3). Case DLb, with an injection in the upper part of area 14, had a substantial number of labeled neurons in auditory areas PaI (RTM), PaAr (RT), TS3 (RP), as well as in rostral

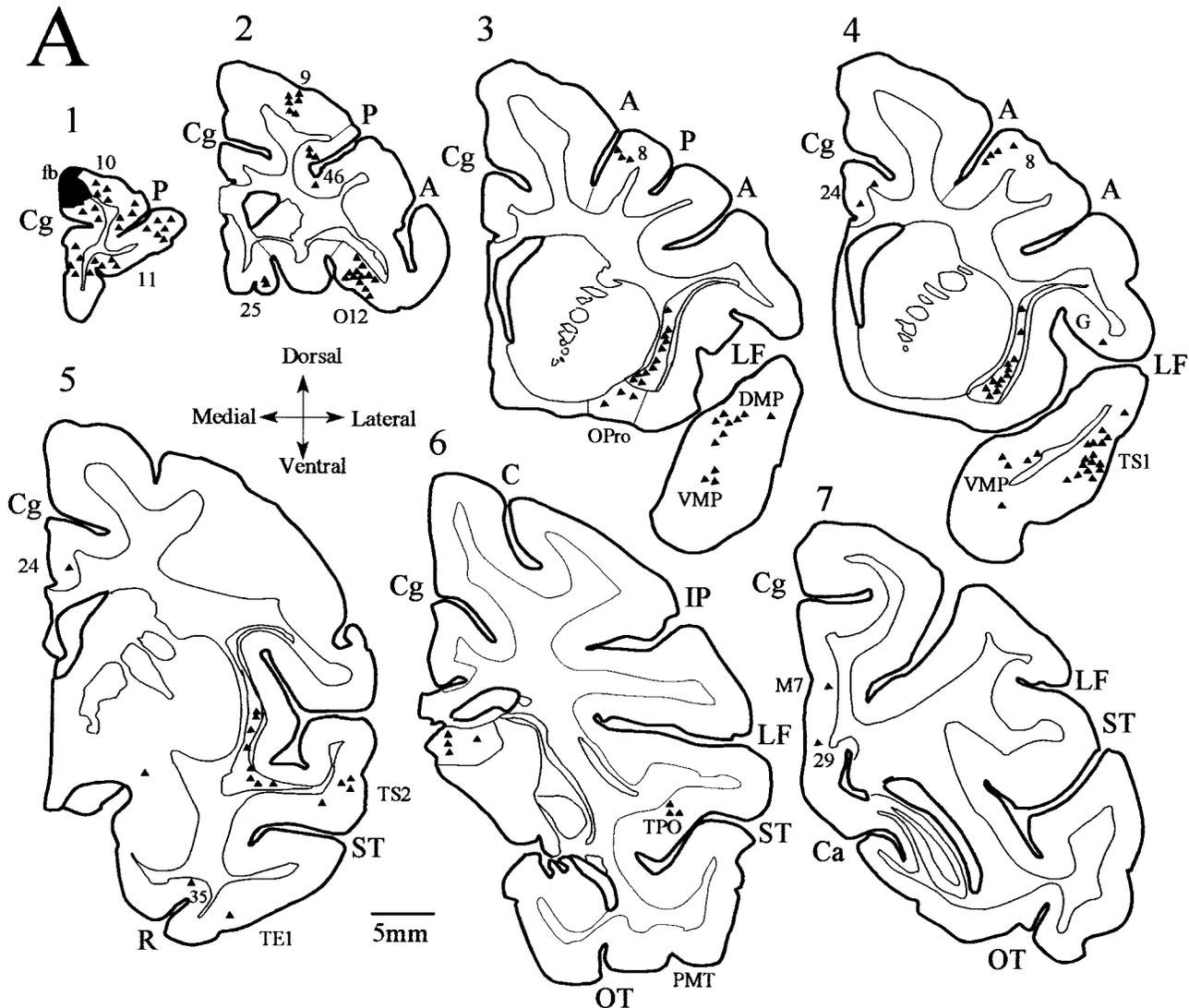


Fig. 7. Case ARb. **A:** The distribution of labeled neurons (black triangles) in diagrams of coronal sections in rostral to caudal (1–7) cortical areas after injection of fast blue (fb) in area 10 (shown in 1). **B:** The topography of all labeled neurons in case ARb on an unfolded

map of the cortex. The medial and orbitofrontal surfaces were unfolded separately but are otherwise in precise register with respect to rostrocaudal position. For abbreviations, see list.

superior temporal cortices TS1 and TS2 (Fig. 4A,B). In another case, with an injection in the lower portion of area 14 (AKb), labeled neurons in superior temporal cortices were most prevalent in areas TS1 and TS2, and sparsely distributed in areas TS3 (RP) and PaI (RTM) (case AKb; Fig. 3A,C). In addition, substantial numbers of labeled neurons were found in dorsolateral and dorsomedial temporal polar regions, particularly in case AKb (Table 3, Fig. 3A,C), and to a lesser extent in case DLb (Fig. 4A,B).

**Area 9.** A substantial number of labeled neurons in anterior superior temporal and auditory association areas projected to area 9 (Table 3). In all cases, most of the labeled neurons were found in area TS2, followed by area TS1 and TS3 (RP) (Figs. 5A,B, 6). In case AKr, with a small injection in medial area 9, most labeled neurons were found in TS2 followed by area TS3 (Fig. 3A,D). In case AO, some labeled neurons were noted in area PaI (RTM) and ProA (RM); Fig. 5B). In all of these cases, labeled neurons

were found also in adjacent dorsomedial and dorsolateral temporal polar cortices (Figs. 5B, 6).

**Area 10.** In case ARb, with an injection in medial area 10, a large number of labeled neurons were found in superior temporal cortices, most of which were distributed in TS1 and to a smaller extent in TS2 (Table 3, Fig. 7A,B). This case differed from the rest in that it did not have labeled neurons in superior temporal cortices beyond area TS2. In addition, labeled neurons were found in dorsolateral and dorsomedial temporal polar regions. Similar observations with regard to the topography of connections in auditory and temporal polar areas were made in case AP, with a small injection in the rostral part of area 10 (not shown).

**Projections from parietotemporal polymodal cortices.** In all cases, there were labeled neurons in polymodal temporal cortices, including areas TPO and PGa, situated in the depths and the upper bank of the superior

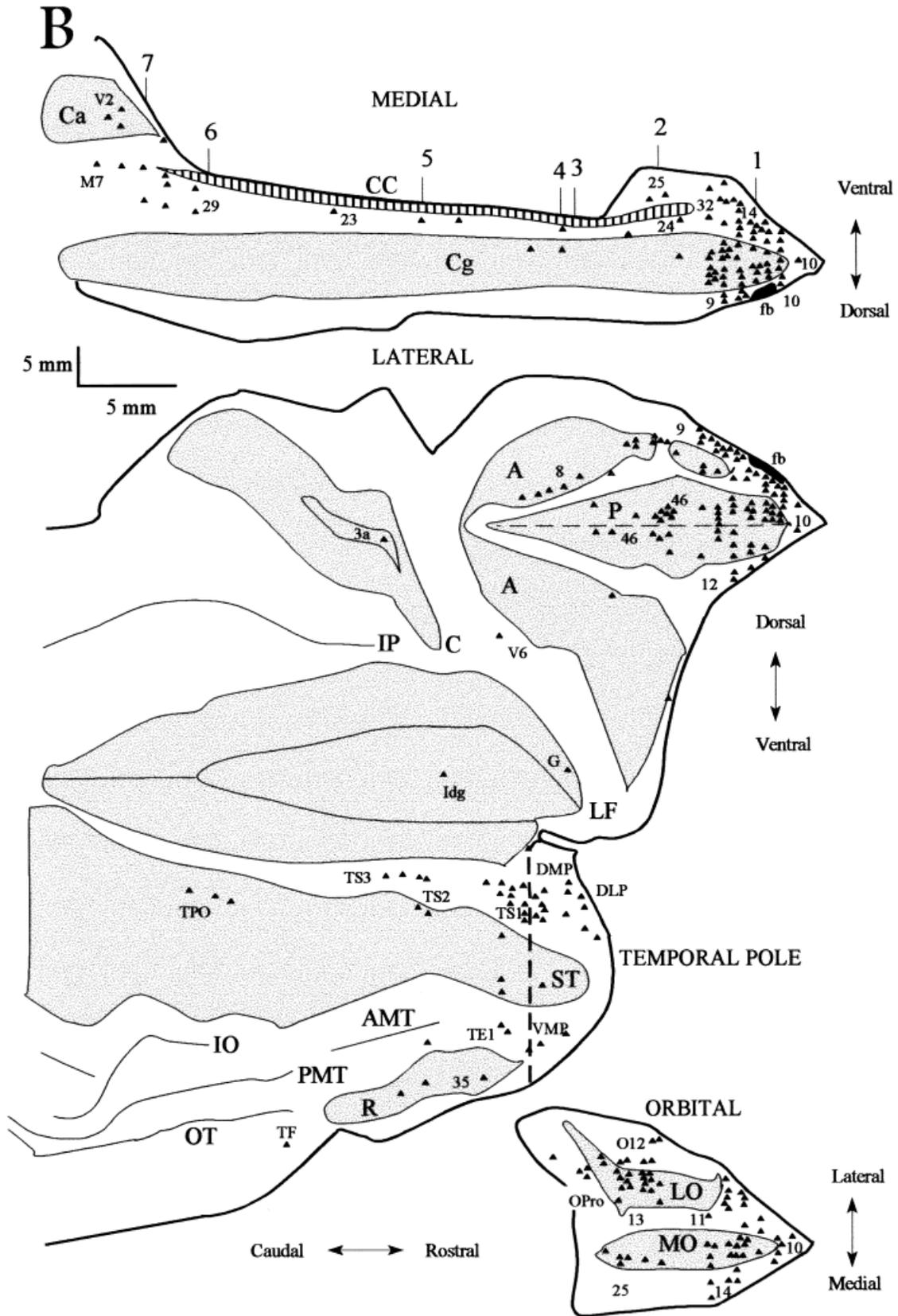


Figure 7 (Continued)

TABLE 3. Distribution of Labeled Neurons in Auditory and Adjacent Superior Temporal Cortices Projecting to Medial Prefrontal Cortices<sup>1</sup>

Origin	Area Case	Injection site								
		25 AH	32/24 AIB	32 AKy	14 AKb	14 DLb	M9 AO	M9 AQy	L9 AQb	M10 ARb
Auditory association and anterior superior temporal gyrus										
PaAr (~RT)		1.6	–	–	–	3.5	–	–	0.4	–
ProA (*RM)		–	1.6	–	–	–	1.1	–	–	–
PaI (*RTM)		–	1.1	0.3	0.7	15.7	1.1	–	–	–
TS3 (#RP, *RTL)		–	0.2	4.3	0.6	3.5	3.2	3.9	0.3	–
TS2		0.8	4.9	18.8	4.6	28.4	11.8	29.5	23.1	10.2
TS1		16.5	1.9	13.1	8.1	31.1	7.6	4.1	4.2	51.7
Para-auditory limbic										
Dorsolateral pole		2.0	5.1	7.0	3.9	5.6	3.8	0.8	1.1	0.8
Dorsomedial pole		2.3	5.0	27.2	39.9	5.6	1.5	6.9	9.1	10.2

<sup>1</sup>Data are expressed in percentages of the total number of labeled neurons in post-arcuate areas (for details of total number of labeled neurons in each case see Table 4). Architectonic designations (in parentheses) are according to Galaburda and Pandya (1983) and Hackett et al. (1998). Areas PaI and ProA appear to overlap with area M of Kosaki et al. (1997). Approximately half of the caudal gyral portion of area TS2 overlaps with parabelt area RP of Hackett et al. (1998). The rostral part of area TS2 and all of TS1 are found rostral to the auditory parabelt region of Hackett et al. (1998). Symbols: –, core; \*, belt; and #, parabelt areas in the map of Hackett et al. (1998). –, no labeled neurons.

TABLE 4. Distribution of Labeled Neurons in Post-Arcuate Cortices Projecting to Medial Prefrontal Cortices<sup>1</sup>

Origin	Area Case	Injection site								
		25 AH	32/24 AIB	32 AKy	14 AKb	14 DLb	M9 AO	M9 AQy	L9 AQb	M10 ARb
Auditory and anterior superior temporal <sup>2</sup>		18.9	9.7	36.5	14.0	82.2	24.8	37.5	28.0	61.9
Para-auditory limbic <sup>2</sup>		4.3	10.1	34.2	43.8	11.2	5.3	7.7	10.2	11.0
Parietotemporal		0.8	2.2	12.2	1.5	3.8	19.1	1.8	46.6	5.2
Visual		–	9.3	0.9	0.2	0.1	0.1	–	0.4	3.0
Entorhinal (area 28)		58.3	32.8	3.9	0.2	–	0.3	–	–	0.6
Perirhinal (areas 35, 36)		11.8	11.2	5.7	17.3	1.1	0.8	0.4	–	8.3
Parahippocampal		5.9	–	–	–	–	0.2	2.4	0.4	–
Prostriate		–	1.7	1.5	–	–	–	–	–	0.6
Somatosensory		–	0.1	–	–	–	9.8	–	2.2	1.1
Iag, Idg		–	12.6	4.0	1.9	1.5	0.9	–	–	0.3
Areas 23, 31, 29		–	7.5	0.7	0.1	–	31.4	–	–	7.7
Gustatory		–	0.1	–	–	–	–	–	–	–
Olfactory		–	2.7	0.3	21.0	–	–	–	–	–
Premotor		–	–	–	–	–	7.2	50.1	12.1	0.3

<sup>1</sup>Data are expressed in percentages of the total number of neurons in post-arcuate areas, which amounted to: case AH, 254 neurons; case AKb, 1,153 neurons; case DLb, 717 neurons; case AKy, 670 neurons; case AIB, 3,174; case AO, 1,234 neurons; case AQy, 491 neurons; case AQb, 264 neurons; case ARb, 362 neurons. Total percent in each column = 100. In cases AIB and AO, some neurons in area 24 were found in a rostral cingulate premotor region according to the map of He et al. (1995).

<sup>2</sup>Detailed parcelling of auditory, anterior superior temporal, and dorsal temporal polar cortices is shown in Table 3. –, no labeled neurons.

temporal sulcus. In case AQb, with an injection in the dorsal part of area 9, labeled neurons in parietotemporal cortices predominated (case AQb, 46.6%; Fig. 6) and included a substantial proportion of the projection neurons directed to rostral area 9 (case AO, 19.1%; Fig. 5A,B, Table 4). A substantial proportion of labeled neurons were also noted in parietotemporal cortices after injection in area 32 (case AKy, 12.2%; Table 4, Fig. 3A,B). A small number of labeled neurons in parietotemporal cortices were noted after injection in medial area 10 (case ARb, 5.2%; Fig. 7A,B), area 32/24 (case AIB; Fig. 2B), area 14 (cases AKb, DLb; Figs. 3C, 4A,B), the caudal part of medial area 9 (case AQy; Fig. 6), and area 25 (case AH; Fig. 8).

**Projections from visual cortices.** A significant number of labeled neurons in visual association cortices were noted only in one case, with an injection in area 32/24 (case AIB, 9.3%), and to a lesser extent in a case with an injection in medial area 10 (case ARb; Table 4). In case AIB, the labeled neurons were found mostly in the medial part of area V2 within the medial bank of the calcarine fissure and the adjacent dorsolateral cortex, followed by medial visual area PO, in areas representing the peripheral visual field (Gattass et al., 1981; Colby et al., 1988). Only a few labeled neurons were noted in ventrolateral cortices TE1, TE2, and TEa (Figs. 2A,B, 7A,B). In cases with injection in area 14, 32, or 9, only a few, if any, scattered labeled neurons were seen in visual association cortices.

**Projections from entorhinal, perirhinal, and parahippocampal cortices.** The terminology and borders for the entorhinal and perirhinal cortices are according to the maps of Amaral et al. (1987) and Suzuki and Amaral (1994a), which are based on the classic studies of Brodmann (1909) rostrally and Von Bonin and Bailey (1947) caudally. Labeled neurons were noted in entorhinal (area 28), in perirhinal (areas 35 and 36), and to a lesser extent in parahippocampal areas (areas TF, TH). A particularly robust projection from the above cortices was seen in case AH, with an injection in area 25, which accounted for three-fourths of all labeled neurons in the post-arcuate cortices (Fig. 8). Many labeled neurons were also seen in the entorhinal and perirhinal cortices in case AIB, with an injection in area 32/24, which accounted for about half of all labeled neurons in post-arcuate areas in this case (Table 4, Fig. 2A,B). In both cases, most of the labeled neurons were found in entorhinal area 28. Labeled neurons in the above cortices were also noted after injection in area 32 (case AKy), and these were found mostly in area 35, followed by area 28 (Fig. 3A,B). A significant number of labeled neurons were mapped in perirhinal cortices in one of the cases with injection in area 14 (case AKb; Fig. 3C), and in case ARb with an injection in medial area 10 (Fig. 7A,B). In cases with injection in area 9, only a few labeled neurons were seen in the above areas (Table 4).

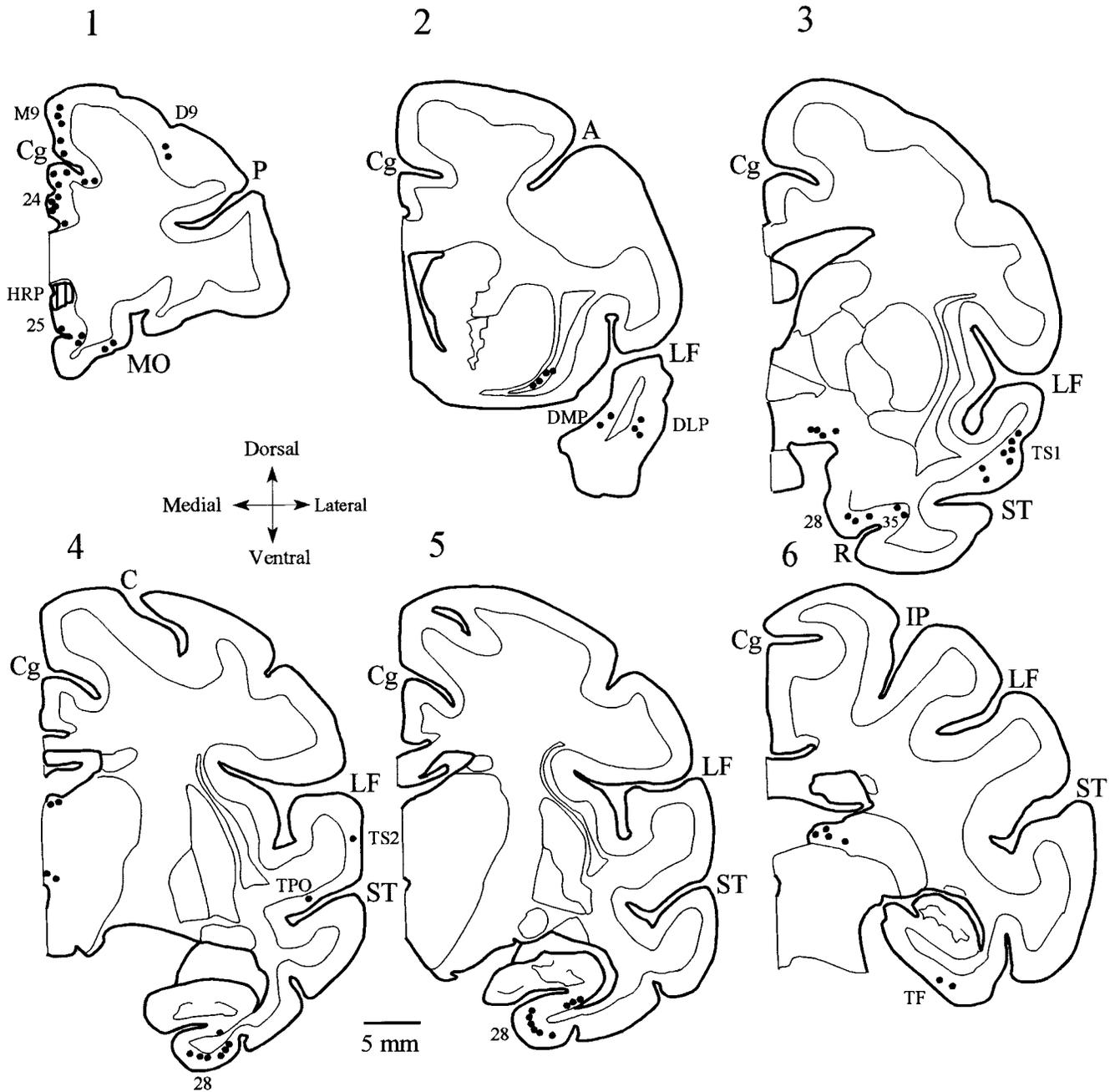


Fig. 8. Case AH. The distribution of labeled neurons (dots) in diagrams of coronal sections in rostral to caudal (1–6) cortical areas after injection of HRP in area 25 (shown in 1). For abbreviations, see list.

**Projections from somatosensory cortices.** Projection neurons in somatosensory association cortices were noted mainly in case AO, with an injection in rostral area 9 (case AO, 9.8%; Table 4, Fig. 5A,B), to a lesser extent in a case with injection in caudomedial area 9 (case AQB; Fig. 6), and the adjacent dorsomedial part of area 10 (case ARB). In case AO, most labeled neurons were found in the granular part of the insula (Ig), and to a lesser extent in parietal association area (PE) and the parietal operculum (Fig. 5A,B). In cases AQY and ARB, labeled neurons were distributed in Ig and in the parietal operculum (areas S1,

S2), in medial area PE, and in area 3a (case ARB; Fig. 7A,B).

**Projections from caudal cingulate and insular limbic cortices.** Substantial numbers of labeled neurons were also found in the dysgranular (Idg) and agranular (Iag) parts of the insula, which are contiguous with lateral somatosensory areas, and in cingulate areas 23, 29, and 31, which lie adjacent to the medial parietal somatosensory cortices. The highest proportion of labeled neurons in these areas was found in case AO, with an injection in the rostral part of medial area 9 (Table 4, Fig. 5B). In this case,

the labeled neurons were distributed mostly in cingulate areas 23, 31, 29 (31.4%), and only a few were found in the Idg. The adjacent dorsomedial area 10 also received projections from these cortices (case ARb), and these were found mostly in the above cingulate areas as well (7.7%; Fig. 7B) and fewer were seen in Idg. The caudal part of area 32 and the adjacent area 24 (case AIb) received projections from a substantial proportion of labeled neurons from the above areas (Table 4). Unlike area 9 and medial area 10, labeled neurons in case AIb were found in substantial numbers in insular areas Idg and Iag (12.6%; Fig. 2A,B). Labeled neurons were also directed to area 32 from insular areas Iag and Idg and to a lesser extent from area 23 (case AKy; Fig. 3B, Table 4). Only a few labeled neurons were seen after area 14 injections and they were distributed mostly in insular areas Iag and Idg (cases AKb, DLb; Table 4). Scattered labeled neurons in the gustatory area were found only in case AIb.

**Projections from olfactory cortices.** Substantial numbers of projection neurons in olfactory cortices, including the prepiriform cortex, the anterior olfactory nucleus, and the olfactory tubercle, were directed mainly to area 14 (case AKb, 21%; Fig. 3A,C) and to a lesser extent to the caudal part of area 32/24 (case AIb; Fig. 2B).

**Projections from premotor cortices.** Only cases with injections in area 9 had a substantial proportion of labeled neurons in lateral and supplementary premotor cortices (case AQy, 50.1%; case AQB, 12.1%; Fig. 6; case AO, 7.2%, Fig. 5A,B). In cases with injections in caudal area 9 (cases AQy and AQB), the labeled neurons were found mostly in the dorsal part of area 6 (Fig. 6). In a case with a rostral area 9 injection (case AO), the labeled neurons were distributed in dorsal area 6, the supplementary motor area (MII), and to a lesser extent in ventral area 6 (Fig. 5A,B). In addition, in all cases with injection in area 9, some labeled neurons in area 24 were found in the rostral cingulate motor area CMAr of He et al. (1995). These neurons are included under area 24 in Table 2, and accounted for 25% of labeled neurons in area 24 in case AQy, 14% in case AO, and 3% in AQB (Figs. 3B, 5A,B, 6). Neurons in motor cingulate areas within area 24 were seen in only one other case (case AIb, area 32/24), and these accounted for 12% of the neurons listed under area 24 in this case (Fig. 2A,B). Most neurons seen in area 24 in all other cases were found anterior to the cingulate motor areas described in several recent studies (e.g., He et al., 1995).

**Laminar origin of projection neurons.** Labeled neurons were found in the upper layers (2–3) as well as in the deep layers (5–6). The laminar pattern of connections within prefrontal cortices, or from sensory, motor, and polymodal areas to prefrontal cortices was the focus of previous studies (Barbas, 1986; Barbas and Rempel-Clover, 1997) and will not be described in detail here. Our observations are consistent with previous findings that projection neurons in eulaminate cortices with well-delineated layers were found predominantly, though not exclusively, in the upper layers, particularly when their destination in prefrontal cortices was a limbic area, characterized by having fewer than 6 layers (e.g., area 25). This pattern of connection suggests a predominant role in feedforward communication. In contrast, projection neurons in temporoparietal limbic cortices originated predominantly in the deep layers, particularly when their prefrontal destination was a eulaminate area (e.g., area 9),

TABLE 5. Mean Density of Anterograde Label by Layers in Superior Temporal Cortices After Injection of Anterograde Tracers in Prefrontal Cortices<sup>1</sup>

Cortical area	Layer 1	Layers 2–3	Layer 4	Layers 5–6
Case AH (area 25)				
Dorsolateral pole	3.4 (9)	7.1 (19)	9.9 (27)	16.9 (45)
TS1	12.6 (23)	14.3 (26)	12.5 (23)	15.2 (28)
TS2	4.6 (15)	5.7 (18)	6.7 (22)	14.1 (45)
TPO	12.3 (49)	4.3 (18)	4.0 (16)	4.2 (17)
Case AE (area 32)				
TS1	37.6 (24)	49.9 (31)	36.5 (23)	35.9 (22)
TS2	15.1 (19)	25.5 (33)	17.5 (22)	20.4 (26)
TS3 (RP)	16.1 (23)	29.2 (42)	11.2 (16)	13.6 (19)
TPO	35.1 (25)	49.1 (34)	27.7 (19)	30.8 (22)
Case MDQ (area 32)				
Dorsolateral pole	11.5 (16)	20.3 (29)	26.1 (37)	12.4 (18)
TS1	30.2 (37)	18.8 (23)	20.1 (25)	12.4 (15)
TS2	33.2 (62)	8.0 (15)	7.1 (13)	5.4 (10)
TS3 (RP)	17.6 (63)	4.8 (17)	5.0 (18)	0.7 (2)
Case AO (area M9)				
TS2	24.9 (59)	5.1 (12)	4.7 (11)	7.5 (18)
TPO	24.4 (41)	13.6 (23)	11.3 (19)	10.3 (17)

<sup>1</sup>Numbers indicate the mean density of anterograde label measured for all sites in each cortical area. Numbers in parentheses indicate the percentage of total anterograde label in each layer for the cortical area. Area TS3 overlaps with parabelt area RP of Hackett et al. (1998).

suggesting a predominant role in feedback communication.

### Anterograde label: Regional and laminar distribution of efferent terminals from prefrontal to auditory and adjacent cortices

Medial prefrontal cortices as a group were distinguished by their connection with superior temporal association cortices. To determine the bidirectional relationship of prefrontal cortices with superior temporal areas, we examined the termination of efferent fibers in temporal cortices after injection of anterograde tracers in prefrontal areas 25, 32, and 9 in 4 cases by using a qualitative scale of 1–6 or by measuring density of label with the aid of an imaging analysis system (as described in Materials and Methods). Values obtained using the two independent measures were highly correlated (Pearson  $r = 0.924$ ,  $P < 0.001$ ).

The termination of efferent fibers in superior temporal cortices is shown in Table 5 for layers 1, 2–3, 4, and 5–6. Moderate to heavy anterograde label was seen in temporal areas TS1 and TS2 in all cases examined. In addition, moderate anterograde labeling was noted in TS3 (RP) in two cases with injections in area 32. Efferent fibers terminated in both the deep (4–6) and upper (1–3) cortical layers in all cases, albeit to a different degree. Efferent fibers emanating from area 25 (case AH) terminated in the deep and superficial layers of TS1 (in a ratio of about 1:1) and TS2 (in a ratio of about 7:3). Efferent fibers from area 32 (cases MDQ and AE) terminated within the upper and deep layers of temporal area TS2, and their density was somewhat higher in the upper layers, particularly for case MDQ (Table 5). When the destination was a dorsolateral temporal polar region, efferent fibers terminated most densely in the deep layers (layers 4 and 5–6; Table 5, cases AH, MDQ; Fig. 9A). In contrast, in both cases with area 32 injection, efferent fibers terminated predominantly in the upper layers of temporal area TS3 (Table 5, Fig. 9B).

In two of the WGA-HRP cases, we compared the distribution of projection neurons in temporal auditory cortices that projected to prefrontal cortices. In all projection sites, when the density of efferent fibers in the temporal cortices was higher in the upper than in the lower layers, projec-

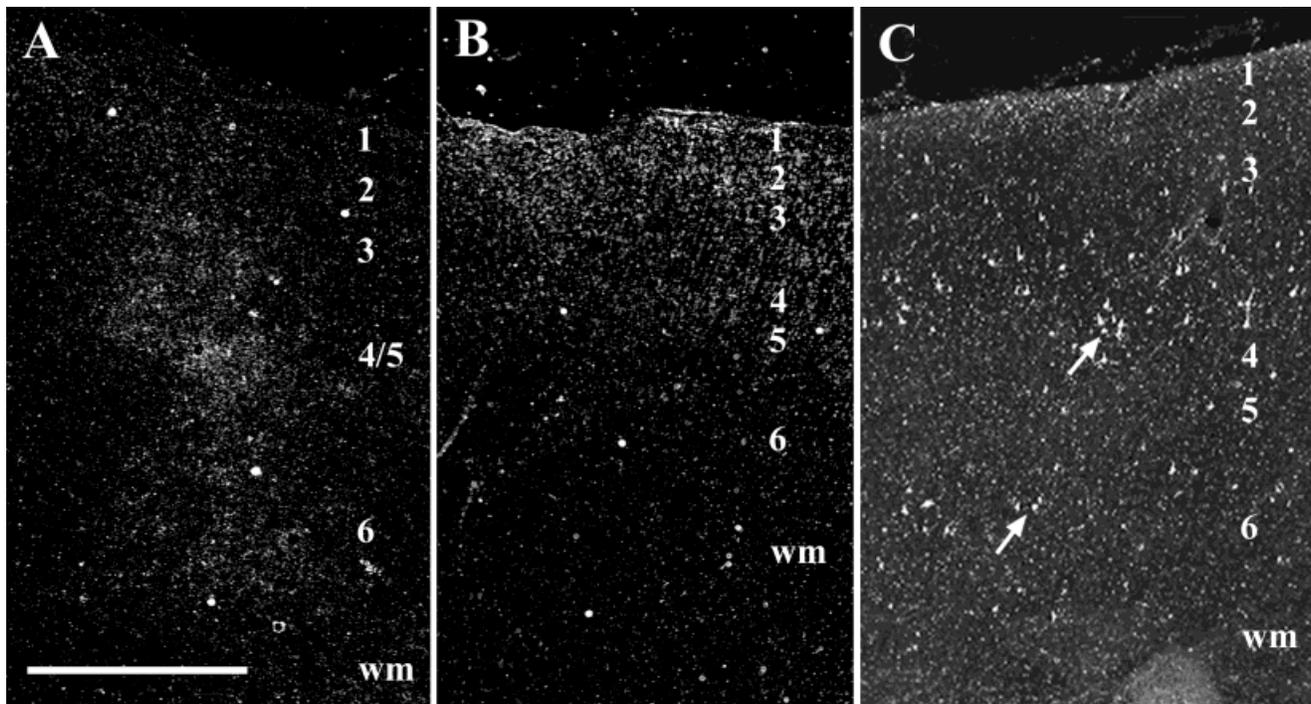


Fig. 9. **A:** Darkfield image of a coronal section showing anterograde label (white grain, most dense in layers 3–5) in the dorsolateral temporal polar cortex after injection of [ $^3\text{H}$ ] amino acids in area 32 (case MDQ). **B:** Anterograde label in cortical area TS3 is most dense in layer 1 in case MDQ. **C:** Both labeled terminals (heaviest in layer 1) and labeled neurons (especially in layer 3, white arrows indicate

clusters of neurons) are shown in area TS2 after an injection of WGA-HRP in medial area 9 (case AO). Numbers indicate cortical layer. Frames were captured directly from histological brain slides using a CCD camera and were imported into Adobe Photoshop for assembly and labeling but were not retouched. wm, white matter. Scale bar = 1 mm.

tion neurons in temporal cortices were found in higher numbers in the upper than in the deep layers (Fig. 9C). For comparison, we measured anterograde label in polymodal area TPO, situated in the depths of the upper bank of the superior temporal sulcus (Seltzer and Pandya, 1978). In all cases, the density was higher in the upper (1–3) than in the deep (4–6) layers (Table 5).

## DISCUSSION

### Memory-related structures issue robust projections to medial prefrontal cortices

Medial prefrontal areas received input from the rhinal region, confirming and extending previous findings (e.g., Vogt and Pandya, 1987; Barbas, 1988; Carmichael and Price, 1995; Bachevalier et al., 1997). A direct comparison of the connections of all architectonically distinct medial prefrontal cortices in this study suggests that they can be separated into different tiers. Medial prefrontal areas found caudally, including areas 25 and 24/32, were distinguished for their strong connections with the entorhinal (area 28) and perirhinal cortices (areas 35, 36). In contrast, a much lower number of projection neurons from rhinal cortices projected to rostral areas 32, 10, and 14. Area 9 stood apart from other medial prefrontal areas, in that it received few, if any, projections from perirhinal cortices.

The profile of connections of caudal medial prefrontal cortices suggests that they may be part of neural circuits involved in long-term mnemonic processing. Along with their robust linkage with memory-related rhinal cortices

shown here, the same medial prefrontal areas are robustly connected with the hippocampal formation (Barbas and Blatt, 1995), limbic thalamic nuclei, including the midline, the magnocellular sector of the mediodorsal nucleus (MDmc), and the caudal part of parvocellular MD (MDpc) (Baleydier and Mauguier, 1980; Goldman-Rakic and Porrino, 1985; Barbas et al., 1991; Morecraft et al., 1992; Ray and Price, 1993; Dermon and Barbas, 1994). All of the above structures have been implicated in long-term memory and their damage leads to inability to recall information acquired after the lesion (for reviews see Markowitsch, 1982; Squire and Zola-Morgan, 1988; Amaral et al., 1990; Squire, 1992; Zola-Morgan and Squire, 1993). Consistent with their connections, damage to medial prefrontal cortices in non-human primates results in visual recognition deficits (Voytko, 1985; Bachevalier and Mishkin, 1986) comparable to the classic amnesic syndrome seen after hippocampal lesions (Talland et al., 1967; Alexander and Freedman, 1984). In humans, mnemonic deficits are often evidenced after vascular lesions of the anterior communicating artery, which supplies the ventromedial prefrontal areas (Crowell and Morawetz, 1977; D'Esposito et al., 1996), including Brodmann's (1909) areas 25, 24, and 32 around the rostrum of the corpus callosum.

In contrast, anteriorly situated medial prefrontal areas received fewer, if any, projections from the above memory-related structures. Previous studies indicate that area 9, like adjacent lateral prefrontal cortices, receives thalamic projections from MDpc and only a sparse projection from

the hippocampal formation (Dermon and Barbas, 1994; Barbas and Blatt, 1995). However, like lateral prefrontal cortices, such as area 46, rostral area 9 and area 10 receive a substantial projection from posterior cingulate areas 29a-c, 23, and 31, as well as from anterior cingulate area 24. Input from these cingulate areas may have a role in attentional processes (Mesulam, 1981, 1990; Vogt et al., 1992), consistent with the involvement of lateral prefrontal cortices in cognitive tasks where attention is critical in keeping stimuli and responses in temporary memory in order to perform a sequential task (for reviews see Goldman-Rakic, 1988; Petrides, 1989; Fuster, 1993). Thus, whereas lesions of lateral prefrontal cortices do not render non-human primates or humans amnesic (Milner and Petrides, 1984; Janowsky et al., 1989; Petrides, 1989), their damage impairs performance when a stimulus must be remembered after a short delay in working memory tasks (Jacobsen, 1936; Fuster, 1973; Bauer and Fuster, 1976; Kubota et al., 1980; Kojima and Goldman-Rakic, 1982; Sawaguchi et al., 1988; Funahashi et al., 1989; Kubota and Niki, 1990; Sawaguchi and Goldman-Rakic, 1991; for reviews see Goldman-Rakic, 1988; Fuster, 1989). It is possible that this type of mnemonic processing is supported, in part, by a pathway linking lateral prefrontal areas with cingulate areas.

### **Auditory association and anterior superior temporal cortices target medial prefrontal cortices**

In contrast to their segregation into distinct domains with regard to specific aspects of mnemonic processing, all medial prefrontal cortices received projections from anterior superior temporal and neighboring auditory association cortices. These data confirm and extend previous findings (Jones, 1969; Jacobson and Trojanowski, 1977; Müller-Preuss et al., 1980; Vogt and Pandya, 1987; Barbas, 1988; Petrides and Pandya, 1988). A particularly robust projection from auditory cortices reached the upper part of area 14. Medial area 10 was distinguished from all other medial prefrontal areas by robust projections from anterior superior temporal areas TS1 and TS2, which for the most part lie outside the auditory parabelt area (Hackett et al., 1998).

The functional significance of projections from auditory and anterior superior temporal cortices to medial prefrontal cortices is not known. The auditory parabelt and belt areas, which included most neurons from auditory areas projecting to the medial prefrontal cortices, do not respond to pure auditory tones, but rather are broadly tuned (Kosaki et al., 1997) and appear to respond best to complex species-specific vocalizations in macaque monkeys (Rauschecker et al., 1995; Rauschecker, 1998). In fact, cingulate areas situated around the rostrum of the corpus callosum have a role in vocalization (Smith, 1945; Sutton et al., 1974; Jürgens, 1976; Müller-Preuss and Jürgens, 1976; Müller-Preuss et al., 1980; Sutton et al., 1985; for review see Vogt and Barbas, 1988). Although these medial prefrontal cortices are not considered speech areas, imaging studies suggest that they are involved in speech production, a role consistent with the classic findings of akinetic mutism after anterior cingulate lesions in humans (e.g., Barris and Schuman, 1953; Nielsen and Jacobs, 1951; Buge et al., 1975). Electrical stimulation of the cingulate vocalization cortices decreases the auditory evoked activity in superior temporal auditory cortices (Müller-Preuss

et al., 1980; Müller-Preuss and Ploog, 1981). Parallel evidence from imaging studies in humans indicates that cognitive tasks involving verbal fluency activate the anterior cingulate region and result in reduction of activity in superior temporal auditory cortices (Dolan et al., 1995; Frith and Dolan, 1996). This evidence suggests that when areas with a role in vocalization or verbal fluency are active, auditory association areas show a reduction in activity. These inhibitory effects on auditory cortices may be exercised by other prefrontal areas as well, because damage centered in lateral prefrontal areas 9 and 46 in humans results in an increase in the magnitude of auditory evoked responses in temporal auditory cortices (Knight et al., 1989). The above evidence suggests that lateral as well as medial prefrontal cortices exercise inhibitory control on auditory cortices.

Moreover, there appears to be a functional distinction in the activity of medial prefrontal and auditory cortices during monitoring of actual versus inner speech, and these relationships are altered specifically in those schizophrenic patients who experience auditory hallucinations (McGuire et al., 1995, 1996; Frith and Dolan, 1997). Medial prefrontal and auditory cortices thus may function in concert to distinguish external auditory stimuli from internal auditory representations. The altered pattern of activity in patients who hallucinate may be due to a functional breakdown of a feedback pathway from medial prefrontal to auditory cortices. Our data indicated that medial prefrontal cortices issued primarily feedback projections terminating most densely, though not exclusively, in the upper layers of auditory cortices. The function of this input may be modulatory, since layer 1, in particular, is enriched in GABAergic receptors (for review see Vogt, 1991). In contrast to the pattern of termination in auditory cortices, medial prefrontal cortices issued feedforward projections to dorsal temporal polar cortices terminating predominantly in layer 4 and the deep layers, and received predominantly feedback projections originating mostly from the deep layers (5-6) of temporal polar cortices. These specific interactions of medial prefrontal cortices with dorsal superior temporal polar cortices may encode the emotional significance of auditory stimuli and may help explain why auditory hallucinations are generally emotionally charged (for review see Frith, 1996).

### **Sporadic projections from sensory cortices to medial prefrontal cortices**

Projections from sensory association cortices outside the auditory were not particularly prominent, and reached preferentially specific medial prefrontal cortices. The sporadic distribution of input from sensory cortices to medial prefrontal cortices is in sharp contrast to the pattern of sensory input reaching the orbitofrontal cortices, which is both rich and diverse (Morecraft et al., 1992; Barbas, 1993). This evidence suggests that the use of sensory information by any given medial prefrontal area is indirect. Medial prefrontal cortices may share information from unimodal sensory cortices through their rich interconnections with each other and with orbitofrontal cortices (e.g., Barbas and Mesulam, 1981, 1985; Barbas, 1988, 1993). The strong interconnections linking medial prefrontal cortices suggest that local circuits have a major role in the neural processing in this region.

### Preferential linkage of area 9 with motor cortices

Among medial prefrontal cortices, area 9 was distinguished by its robust connections with lateral and supplementary premotor areas, as well as with cingulate premotor area CMAr of He et al. (1995). Besides area 9, only area 24/32 had connections with the rostral cingulate motor area. While afferent neurons from area 24 projected to the rest of the medial prefrontal areas investigated, most were found in areas lying anterior to cingulate motor areas described in macaque monkeys (e.g., Muakkassa and Strick, 1979; Hutchins et al., 1988; Dum and Strick, 1991; Luppino et al., 1991; Shima et al., 1991; Morecraft and Van Hoesen, 1992; Galea and Darian-Smith, 1994; He et al., 1995). Moreover, the connections of area 9 with premotor cortices are reciprocal (e.g., Pandya and Kuypers, 1969; Jones and Powell, 1970; Pandya and Vignolo, 1971; Pandya et al., 1971, 1981; Barbas and Pandya, 1987; Selemon and Goldman-Rakic, 1988; McGuire et al., 1991; Bates and Goldman-Rakic, 1993), which may explain, in part, the prominent role of area 9 in monitoring self-generated responses in cognitive tasks (Petrides, 1995). Area 9 received projections from all other medial prefrontal cortices, suggesting that signals from other medial prefrontal cortices may be transmitted to the premotor cortical system through area 9.

### CONCLUSIONS

Anatomic and behavioral evidence suggests that the medial prefrontal region has functionally distinct sectors. A caudal sector is connected with medial temporal cortices, the hippocampus, and limbic thalamic nuclei, and may participate in networks involved in long-term memory. In contrast, a rostral sector is affiliated with caudal cingulate areas associated with attentional processes, and appears to be aligned with lateral prefrontal cortices that have a role in working memory. Medial prefrontal areas have common and reciprocal connections with anterior superior temporal and auditory cortices. These pathways appear to be important in species-specific vocalizations and may mediate the process of distinguishing external auditory stimuli from internal auditory representations.

### LITERATURE CITED

- Alexander MP, Freedman M. 1984. Amnesia after anterior communicating artery aneurysm rupture. *Neurology* 34:752-757.
- Amaral DG, Insausti R, Cowan WM. 1987. The entorhinal cortex of the monkey. I. Cytoarchitectonic organization. *J Comp Neurol* 264:326-355.
- Amaral DG, Insausti R, Zola-Morgan S, Squire LR, Suzuki WA. 1990. The perirhinal and parahippocampal cortices and medial temporal lobe memory function. In: Vision, memory, and the temporal lobe. New York: Elsevier. p. 149-161.
- Bachevalier J, Mishkin M. 1986. Visual recognition impairment follows ventromedial but not dorsolateral prefrontal lesions in monkeys. *Behav Brain Res* 20:249-261.
- Bachevalier J, Meunier M, Lu MX, Ungerleider LG. 1997. Thalamic and temporal cortex input to medial prefrontal cortex in rhesus monkeys. *Exp Brain Res* 115:430-444.
- Baleydier C, Mauguier F. 1980. The duality of the cingulate gyrus in monkey. Neuroanatomical study and functional hypothesis. *Brain* 103:525-554.
- Barbas H. 1986. Pattern in the laminar origin of corticocortical connections. *J Comp Neurol* 252:415-422.
- Barbas H. 1988. Anatomic organization of basoventral and mediodorsal visual recipient prefrontal regions in the rhesus monkey. *J Comp Neurol* 276:313-342.
- Barbas H. 1993. Organization of cortical afferent input to orbitofrontal areas in the rhesus monkey. *Neuroscience* 56:841-864.
- Barbas H. 1995a. Anatomic basis of cognitive-emotional interactions in the primate prefrontal cortex. *Neurosci Behav Rev* 19:499-510.
- Barbas H. 1995b. Pattern in the cortical distribution of prefrontally directed neurons with divergent axons in the rhesus monkey. *Cereb Cortex* 5:158-165.
- Barbas H. 1997. Two prefrontal limbic systems: their common and unique features. In: Sakata H, Mikami A, Fuster JM, editors. The association cortex: structure and function. Amsterdam: Harwood. 99-115.
- Barbas H, Blatt GJ. 1995. Topographically specific hippocampal projections target functionally distinct prefrontal areas in the rhesus monkey. *Hippocampus* 5:511-533.
- Barbas H, De Olmos J. 1990. Projections from the amygdala to basoventral and mediodorsal prefrontal regions in the rhesus monkey. *J Comp Neurol* 301:1-23.
- Barbas H, Mesulam M-M. 1981. Organization of afferent input to subdivisions of area 8 in the rhesus monkey. *J Comp Neurol* 200:407-431.
- Barbas H, Mesulam M-M. 1985. Cortical afferent input to the principalis region of the rhesus monkey. *Neuroscience* 15:619-637.
- Barbas H, Pandya DN. 1987. Architecture and frontal cortical connections of the premotor cortex (area 6) in the rhesus monkey. *J Comp Neurol* 256:211-218.
- Barbas H, Pandya DN. 1989. Architecture and intrinsic connections of the prefrontal cortex in the rhesus monkey. *J Comp Neurol* 286:353-375.
- Barbas H, Rempel-Clower N. 1997. Cortical structure predicts the pattern of corticocortical connections. *Cereb Cortex* 7:635-646.
- Barbas H, Henion TH, Dermon CR. 1991. Diverse thalamic projections to the prefrontal cortex in the rhesus monkey. *J Comp Neurol* 313:65-94.
- Barris RW, Schuman HR. 1953. Bilateral anterior cingulate gyrus lesions. Syndrome of the anterior cingulate gyri. *Neurology* 3:44-52.
- Bates JF, Goldman-Rakic PS. 1993. Prefrontal connections of medial motor areas in the rhesus monkey. *J Comp Neurol* 336:211-228.
- Bauer RH, Fuster JM. 1976. Delayed-matching and delayed-response deficit from cooling dorsolateral prefrontal cortex in monkeys. *J Comp Physiol Psychol* 90:299-302.
- Brodmann K. 1909. Vergleichende Lokalisationslehre der Grosshirnrinde in ihren Prinzipien dargestellt auf Grund der Zellenbaues. Leipzig: Barth.
- Buge A, Escourolle R, Rancurel G, Poisson M. 1975. Akinetic mutism and bicingular softening. Three anatomo-clinical cases. *Rev Neurol (Paris)* 131:121-131.
- Burton H, Jones EG. 1976. The posterior thalamic region and its cortical projection in new world and old world monkeys. *J Comp Neurol* 168:249-302.
- Carmichael ST, Price JL. 1995. Limbic connections of the orbital and medial prefrontal cortex in macaque monkeys. *J Comp Neurol* 363:615-641.
- Colby CL, Gattass R, Olson CR, Gross CG. 1988. Topographical organization of cortical afferents to extrastriate visual area PO in the macaque: a dual tracer study. *J Comp Neurol* 269:392-413.
- Colombo M, Rodman HR, Gross CG. 1996. The effects of superior temporal cortex lesions on the processing and retention of auditory information in monkeys (*Cebus apella*). *J Neurosci* 15:4501-4517.
- Cowan WM, Gottlieb DI, Hendrickson AE, Price JL, Woolsey TA. 1972. The autoradiographic demonstration of axonal connections in the central nervous system. *Brain Res* 37:21-51.
- Crowell RM, Morawetz RB. 1977. The anterior communicating artery has significant branches. *Stroke* 8:272-273.
- Dermon CR, Barbas H. 1994. Contralateral thalamic projections predominantly reach transitional cortices in the rhesus monkey. *J Comp Neurol* 344:508-531.
- D'Esposito M, Alexander MP, Fischer R, McClinchey-Bertho R, O'Connor M. 1996. Recovery of memory and executive function following anterior communicating artery aneurysm rupture. *J Int Neuropsychol Soc* 2:565-570.
- Dolan RJ, Fletcher P, Frith CD, Friston KJ, Frackowiak RSJ, Grasby PM. 1995. Dopaminergic modulation of impaired cognitive activation in the anterior cingulate cortex in schizophrenia. *Nature* 378:180-182.
- Dum RP, Strick PL. 1991. The origin of corticospinal projections from the premotor areas in the frontal lobe. *J Neurosci* 11:667-689.
- Frith C. 1996. The role of the prefrontal cortex in self-consciousness: the

- case of auditory hallucinations. *Philos Trans R Soc Lond Ser B* 351:1505–1512.
- Frith C, Dolan R. 1996. The role of the prefrontal cortex in higher cognitive functions. *Cog Brain Res* 5:175–181.
- Frith C, Dolan RJ. 1997. Brain mechanisms associated with top-down processes in perception. *Philos Trans R Soc Lond Ser B* 352:1221–1230.
- Funahashi S, Bruce CJ, Goldman-Rakic PS. 1989. Mnemonic coding of visual space in the monkey's dorsolateral prefrontal cortex. *J Neurophysiol* 61:331–349.
- Fuster JM. 1973. Unit activity in prefrontal cortex during delayed-response performance: neuronal correlates of transient memory. *J Neurophysiol* 36:61–78.
- Fuster JM. 1989. *The prefrontal cortex: anatomy, physiology and neuropsychology of the frontal lobe*. 2nd edition. New York: Raven Press. 255 p.
- Fuster JM. 1993. Frontal lobes. *Curr Opin Neurobiol* 3:160–165.
- Galaburda AM, Pandya DN. 1983. The intrinsic architectonic and connective organization of the superior temporal region of the rhesus monkey. *J Comp Neurol* 221:169–184.
- Galea MP, Darian-Smith I. 1994. Multiple corticospinal neuron populations in the macaque monkey are specified by their unique cortical origins, spinal terminations, and connections. *Cereb Cortex* 4:166–194.
- Gallyas F. 1979. Silver staining of myelin by means of physical development. *Neurol Res* 1:203–209.
- Gattass R, Gross CG, Sandell JH. 1981. Visual topography of V2 in the macaque. *J Comp Neurol* 201:519–539.
- Geneser-Jensen FA, Blackstad TW. 1971. Distribution of acetyl cholinesterase in the hippocampal region of the guinea pig. *Z Zellforsch Mikrosk Anat* 114:460–481.
- Goldman-Rakic PS. 1988. Topography of cognition: parallel distributed networks in primate association cortex. *Annu Rev Neurosci* 11:137–156.
- Goldman-Rakic PS, Porrino LJ. 1985. The primate mediodorsal (MD) nucleus and its projection to the frontal lobe. *J Comp Neurol* 242:535–560.
- Gower EC. 1989. Efferent projections from limbic cortex of the temporal pole to the magnocellular medial dorsal nucleus in the rhesus monkey. *J Comp Neurol* 280:343–358.
- Hackett TA, Stepniowska I, Kaas JH. 1998. Subdivisions of auditory cortex and ipsilateral cortical connections of the parabelt auditory cortex in macaque monkeys. *J Comp Neurol* 394:475–495.
- He S-Q, Dunn RP, Strick PL. 1995. Topographic organization of corticospinal projections from the frontal lobe: motor areas on the medial surface of the hemisphere. *J Neurosci* 15:3284–3306.
- Hutchins KD, Martino AM, Strick PL. 1988. Corticospinal projections from the medial wall of the hemisphere. *Exp Brain Res* 71:667–672.
- Jacobsen CF. 1936. Studies of cerebral function in primates. I. The functions of the frontal association area in monkeys. *Comp Psychol Monogr* 13:3–60.
- Jacobson S, Trojanowski LQ. 1977. Prefrontal granular cortex of the rhesus monkey. I. Intra-hemispheric cortical afferents. *Brain Res* 132:209–233.
- Janowsky JS, Shimamura AP, Kritchevsky M, Squire LR. 1989. Cognitive impairment following frontal lobe damage and its relevance to human amnesia. *Behav Neurosci* 103:548–560.
- Jones EG. 1969. Interrelationships of parieto-temporal and frontal cortex in the rhesus monkey. *Brain Res* 13:412–415.
- Jones EG. 1985. *The thalamus*. New York: Plenum Press. 935 p.
- Jones EG, Powell TPS. 1970. An anatomical study of converging sensory pathways within the cerebral cortex. *Brain* 93:793–820.
- Jones EG, Dell'Anna ME, Molinari M, Rausell E, Hashikawa T. 1995. Subdivisions of macaque monkey auditory cortex revealed by calcium-binding protein immunoreactivity. *J Comp Neurol* 362:153–170.
- Jürgens U. 1976. Projections from the cortical larynx area in the squirrel monkey. *Exp Brain Res* 25:401–411.
- Knight RT, Scabini D, Woods DL. 1989. Prefrontal cortex gating of auditory transmission in humans. *Brain Res* 504:338–342.
- Kojima S, Goldman-Rakic PS. 1982. Delay-related activity of prefrontal neurons in rhesus monkeys performing delayed response. *Brain Res* 248:43–49.
- Kondo H, Hashikawa T, Tanaka K, Jones EG. 1994. Neurochemical gradient along the monkey occipito-temporal cortical pathway. *NeuroReport* 5:613–616.
- Kosaki H, Hashikawa T, He J, Jones EG. 1997. Tonotopic organization of auditory cortical fields delineated by parvalbumin immunoreactivity in macaque monkeys. *J Comp Neurol* 386:304–316.
- Kubota K, Niki H. 1990. Prefrontal cortical unit activity and delayed alternation performance in monkeys. *J Neurophysiol* 34:337–347.
- Kubota K, Tonoike M, Mikami A. 1980. Neuronal activity in the monkey dorsolateral prefrontal cortex during a discrimination task with delay. *Brain Res* 183:29–42.
- LaVail JH. 1975. Retrograde cell degeneration and retrograde transport techniques. In: Cowan WM, Cuenod M, editors. *The use of axonal transport for studies of neuronal connectivity*. New York: Elsevier. p 217–248.
- Luppino G, Matelli M, Camarda RM, Gallese V, Rizzolatti G. 1991. Multiple representations of body movements in mesial area 6 and the adjacent cingulate cortex: an intracortical microstimulation study in the macaque monkey. *J Comp Neurol* 311:463–482.
- Markowitsch HJ. 1982. Thalamic mediodorsal nucleus and memory: a critical evaluation of studies in animals and man. *Neurosci Biobehav Rev* 6:351–380.
- McGuire PK, Bates JF, Goldman-Rakic PS. 1991. Interhemispheric integration. I. Symmetry and convergence of the corticocortical connections of the left and the right principal sulcus (PS) and the left and the right supplementary motor area (SMA) in the rhesus monkey. *Cereb Cortex* 1:390–407.
- McGuire PK, Silbersweig DA, Wright I, Murray RM, David AS, Frackowiak RSJ, Frith CD. 1995. Abnormal monitoring of inner speech: a physiological basis for auditory hallucinations. *Lancet* 346:596–600.
- McGuire PK, Silbersweig DA, Wright I, Murray RM, Frackowiak RSJ, Frith CD. 1996. The neural correlates of inner speech and auditory verbal imagery in schizophrenia: relationship to auditory verbal hallucinations. *Br J Psychiatry* 169:148–159.
- Mesulam M-M. 1981. A cortical network for directed attention and unilateral neglect. *Ann Neurol* 10:309–325.
- Mesulam M-M. 1982. Principles of horseradish peroxidase neurohistochemistry and their applications for tracing neural pathways—axonal transport, enzyme histochemistry and light microscopic analysis. In: Mesulam M-M, editor. *Tracing neuronal connections with horseradish peroxidase*. Chichester: John Wiley. p 1–151.
- Mesulam M-M. 1990. Large-scale neurocognitive networks and distributed processing for attention, language, and memory. *Ann Neurol* 28:597–613.
- Mesulam M-M, Mufson EJ. 1982. Insula of the old world monkey. I. Architectonics in the insulo-orbito-temporal component of the paralimbic brain. *J Comp Neurol* 212:1–22.
- Mesulam M-M, Hegarty E, Barbas H, Carson KA, Gower EC, Knapp AG, Moss MB, Mufson EJ. 1980. Additional factors influencing sensitivity in the tetramethyl benzidine method for horseradish peroxidase neurohistochemistry. *J Histochem Cytochem* 28:1255–1259.
- Milner B, Petrides M. 1984. Behavioural effects of frontal-lobe lesions in man. *Trends Neurosci* 7:403–407.
- Molinari M, Dell'Anna ME, Rausell E, Leggio MG, Hashikawa T, Jones EG. 1995. Auditory thalamocortical pathways defined in monkeys by calcium-binding protein immunoreactivity. *J Comp Neurol* 362:171–194.
- Moran MA, Mufson EJ, Mesulam MM. 1987. Neural inputs into the temporopolar cortex of the rhesus monkey. *J Comp Neurol* 256:88–103.
- Morecraft RJ, Van Hoesen GW. 1992. Cingulate input to the primary and supplementary motor cortices in the rhesus monkey: evidence for somatotopy in areas 24c and 23c. *J Comp Neurol* 322:471–489.
- Morecraft RJ, Geula C, Mesulam M-M. 1992. Cytoarchitecture and neural afferents of orbitofrontal cortex in the brain of the monkey. *J Comp Neurol* 323:341–358.
- Morel A, Garraghty PE, Kaas JH. 1993. Tonotopic organization, architectonic fields, and connections of auditory cortex in macaque monkeys. *J Comp Neurol* 335:437–459.
- Muakkassa KF, Strick PL. 1979. Frontal lobe inputs to primate motor cortex: evidence for four somatotopically organized premotor areas. *Brain Res* 177:176–182.
- Müller-Preuss P, Jürgens U. 1976. Projections from the “cingular” vocalization area in the squirrel monkey. *Brain Res* 103:29–43.
- Müller-Preuss P, Ploog D. 1981. Inhibition of auditory cortical neurons during phonation. *Brain Res* 215:61–76.
- Müller-Preuss JD, Newman JD, Jürgens U. 1980. Anatomical and physiological evidence for a relationship between the cingular vocalization area and the auditory cortex in the squirrel monkey. *Brain Res* 202:307–315.
- Nielsen JM, Jacobs LL. 1951. Bilateral lesions of the anterior cingulate gyri. *Bull Los Angeles Neurol Soc* 16:231–234.

- Pandya DN, Kuypers HGJM. 1969. Cortico-cortical connections in the rhesus monkey. *Brain Res* 13:13–36.
- Pandya DN, Sanides F. 1973. Architectonic parcellation of the temporal operculum in rhesus monkey and its projection pattern. *Z Anat Entwicklungsgesch* 139:127–161.
- Pandya DN, Vignolo LA. 1971. Intra- and interhemispheric projections of the precentral, premotor and arcuate areas in the rhesus monkey. *Brain Res* 26:217–233.
- Pandya DN, Dye P, Butters N. 1971. Efferent cortico-cortical projections of the prefrontal cortex in the rhesus monkey. *Brain Res* 31:35–46.
- Pandya DN, Van Hoesen GW, Mesulam M-M. 1981. Efferent connections of the cingulate gyrus in the rhesus monkey. *Exp Brain Res* 42:319–330.
- Pandya DN, Seltzer B, Barbas H. 1988. Input-output organization of the primate cerebral cortex. In: Steklis HD, Erwin J, editors. *Comparative primate biology*. Volume 4. Neurosciences. New York: Alan R. Liss. 39–80.
- Pandya DN, Rosene DL, Doolittle AM. 1994. Corticothalamic connections of auditory-related areas of the temporal lobe in the rhesus monkey. *J Comp Neurol* 345:447–471.
- Papez JW. 1937. A proposed mechanism of emotion. *AMA Arch Neurol Psychiatr* 38:725–743.
- Petrides M. 1989. Frontal lobes and memory. In: Boller F, Grafman J, editors. *Handbook of neuropsychology*. Volume 3. New York: Elsevier Science Publishers B.V. (Biomedical Division). p 75–90.
- Petrides M. 1995. Impairments on nonspatial self-ordered and externally ordered working memory tasks after lesions of the mid-dorsal part of the lateral frontal cortex in the monkey. *J Neurosci* 15:359–375.
- Petrides M, Pandya DN. 1988. Association fiber pathways to the frontal cortex from the superior temporal region in the rhesus monkey. *J Comp Neurol* 273:52–66.
- Rainville P, Duncan GH, Price DD, Carrier B, Bushnell MC. 1997. Pain affect encoded in human anterior cingulate but not somatosensory cortex. *Science* 277:968–971.
- Rauschecker JP. 1998. Parallel processing in the auditory cortex of primates. *Audiol Neurootol* 3:86–103.
- Rauschecker JP, Tian B, Hauser M. 1995. Processing of complex sounds in the macaque nonprimary auditory cortex. *Science* 268:111–114.
- Ray JP, Price JL. 1993. The organization of projections from the mediodorsal nucleus of the thalamus to orbital and medial prefrontal cortex in macaque monkeys. *J Comp Neurol* 337:1–31.
- Rempel-Clower N, Barbas H. 1998. Topographic organization of connections between the hypothalamus and prefrontal cortex in the rhesus monkey. *J Comp Neurol* 398:393–419.
- Rosene DL, Roy NJ, Davis BJ. 1986. A cryoprotection method that facilitates cutting frozen sections of whole monkey brains from histological and histochemical processing without freezing artifact. *J Histochem Cytochem* 34:1301–1315.
- Sawaguchi T, Goldman-Rakic PS. 1991. D1 dopamine receptors in prefrontal cortex: involvement in working memory. *Science* 251:947–950.
- Sawaguchi T, Matsumura M, Kubota K. 1988. Dopamine enhances the neuronal activity of spatial short-term memory task in the primate prefrontal cortex. *Neurosci Res* 5:465–473.
- Selemon LD, Goldman-Rakic PS. 1988. Common cortical and subcortical targets of the dorsolateral prefrontal and posterior parietal cortices in the rhesus monkey: evidence for a distributed neural network subserving spatially guided behavior. *J Neurosci* 8:4049–4068.
- Seltzer B, Pandya DN. 1978. Afferent cortical connections and architectonics of the superior temporal sulcus and surrounding cortex in the rhesus monkey. *Brain Res* 149:1–24.
- Shima K, Aya K, Mushiake H, Inase M, Aizawa H, Tanji J. 1991. Two movement-related foci in the primate cingulate cortex observed in signal-triggered and self-paced forelimb movements. *J Neurophysiol* 65:188–202.
- Smith WK. 1945. The functional significance of the rostral cingulate cortex as revealed by its responses to electrical excitation. *J Neurophysiol* 8:241–255.
- Squire LR. 1992. Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. *Psychol Rev* 99:195–231.
- Squire LR, Zola-Morgan S. 1988. Memory: brain systems and behavior. *Trends Neurosci* 11:170–175.
- Sutton D, Larson C, Lindeman RC. 1974. Neocortical and limbic lesion effects on primate phonation. *Brain Res* 71:61–75.
- Sutton D, Trachy RE, Lindeman RC. 1985. Discriminative phonation in macaques: effects of anterior mesial cortex damage. *Exp Brain Res* 59:410–413.
- Suzuki WA, Amaral DG. 1994a. Perirhinal and parahippocampal cortices of the macaque monkey: cortical afferents. *J Comp Neurol* 350:497–533.
- Suzuki WA, Amaral DG. 1994b. Topographic organization of the reciprocal connections between the monkey entorhinal cortex and the perirhinal and parahippocampal cortices. *J Neurosci* 14:1856–1877.
- Talland GA, Sweet WH, Ballantine T. 1967. Amnesic syndrome with anterior communicating artery aneurysm. *J Nerv Ment Dis* 145:179–192.
- Vogt BA. 1991. The role of layer I in cortical function. In: Peters A, editor. *Cerebral cortex*. Volume 9. New York: Plenum Press. p 49–79.
- Vogt BA, Barbas H. 1988. Structure and connections of the cingulate vocalization region in the rhesus monkey. In: Newman JD, editor. *The physiological control of mammalian vocalization*. New York: Plenum Press. p 203–225.
- Vogt BA, Pandya DN. 1987. Cingulate cortex of the rhesus monkey. II. Cortical afferents. *J Comp Neurol* 262:271–289.
- Vogt BA, Rosene DL, Pandya DN. 1979. Thalamic and cortical afferents differentiate anterior from posterior cingulate cortex in the monkey. *Science* 204:205–207.
- Vogt BA, Finch DM, Olson CR. 1992. Functional heterogeneity in cingulate cortex: the anterior executive and posterior evaluative regions. *Cereb Cortex* 2:435–443.
- Vogt BA, Sikes RW, Vogt LJ. 1993. Anterior cingulate cortex and the medial pain system. In: Vogt BA, Gabriel M, editors. *Neurobiology of cingulate cortex and limbic thalamus: a comprehensive handbook*. Boston: Birkhauser. 313–344.
- Vogt BA, Wiley RG, Jensen EL. 1995. Localization of mu and delta opioid receptors to anterior cingulate afferents and projection neurons and input/output model of mu regulation. *Exp Neurol* 135:83–92.
- Von Bonin G, Bailey P. 1947. *The neocortex of Macaca mulatta*. Urbana: University of Illinois Press. 168 p.
- Voytko ML. 1985. Cooling orbital frontal cortex disrupts matching-to-sample and visual discrimination learning in monkeys. *Physiol Psychol* 13:219–229.
- Walker C. 1940. A cytoarchitectural study of the prefrontal area of the macaque monkey. *J Comp Neurol* 98:59–86.
- Zola-Morgan S, Squire LR. 1993. Neuroanatomy of memory. *Annu Rev Neurosci* 16:547–563.