

Architecture and Intrinsic Connections of the Prefrontal Cortex in the Rhesus Monkey

H. BARBAS AND D.N. PANDYA

Department of Health Sciences, Boston University, Boston, Massachusetts 02215 (H.B.);
Department of Anatomy, Boston University School of Medicine (H.B., D.N.P.), and Edith
Nourse Rogers Veterans Administration Hospital (D.N.P.), Bedford, Massachusetts 01730

ABSTRACT

An investigation of the architectonic organization and intrinsic connections of the prefrontal cortex was conducted in rhesus monkeys. Cytoarchitectonic analysis indicates that in the prefrontal cortex there are two trends of gradual change in laminar characteristics that can be traced from limbic periallocortex towards isocortical areas. The stepwise change in laminar features is characterized by the emergence and gradual increase in the width of granular layer IV, by an increase in the size of pyramidal cells in layers III and V, and by a higher cell-packing density in the supragranular layers. Myeloarchitectonic analysis reveals that the limbic areas are poorly myelinated, adjacent areas have a diffuse myelin content confined to the deep layers, and in isocortices the myelinated fibers are distributed in organized horizontal bands (of Bailarger) and a vertical plexus. Using the above architectonic criteria, we observed that one of the architectonic trends takes a radial basoventral course from the periallocortex in the caudal orbitofrontal region to the adjacent proisocortex and then to area 13. The next stage of architectonic regions includes orbital areas 12, 11, and 14, which is followed by area 10, lateral area 12, and the rostral part of ventral area 46. The last group includes the caudal part of ventral area 46 and ventral area 8. The other trend takes a mediodorsal course from the periallocortex around the rostral portion of the corpus callosum to the adjacent proisocortical areas 24, 25, and 32 and then to the medially situated isocortical areas 9, 10, and 14. The next stage includes lateral areas 10 and 9 and the rostral part of dorsal area 46. The last group includes the caudal part of dorsal area 46 and dorsal area 8.

The interconnections of subdivisions of the basoventral and mediodorsal cortices were studied with the aid of anterograde and retrograde tracers. Within each trend a given area projects in two directions: to adjoining regions belonging to succeeding architectonic stages on the one hand, and to nearby regions from the preceding architectonic stage on the other. In each direction there is more than one region involved in this projection system, paralleling the radial nature of architectonic change. Periallo- and proisocortices have widespread intrinsic connections, whereas isocortices situated at a distance from limbic areas, such as area 8, have restricted connections. Most interconnections are limited to areas within the same architectonic trend. However, there are links between cortices from the two trends, and these seem to occur between areas that are at a similar stage of architectonic differentiation.

The results suggest that there are two architectonically, and perhaps functionally, distinct axes within the prefrontal cortex. The earliest stages within each axis, which have widespread connections, may have a global role in neural processing. On the other hand, the latest stages, which have restricted connections, may have a more specific role in processes associated with the frontal lobe.

Accepted April 6, 1989.

Key words: cortical architectonic differentiation, cerebral cortex, autoradiography

The prefrontal cortex has been subdivided architectonically by a number of investigators in the past. There is, however, considerable disagreement regarding the boundaries of its subdivisions (Brodman, '05; Vogt and Vogt, '19; Walker, '40; Von Bonin and Bailey, '47; Fig. 1). The most comprehensive map to date is that of Walker, who focused his study on the prefrontal cortex. In contrast, other investigators described the prefrontal architecture as part of larger surveys of the architecture of the entire cerebral cortex. In all of these studies, areal boundaries were drawn on the basis of cytoarchitectonic criteria, which rely on the gross characteristics of cells and their arrangement in cortical layers, or on the basis of myeloarchitecture, which focuses on the pattern and distribution of myelin within cortical fibers. While both procedures are useful in the study of cortical architecture, particularly when used in conjunction with each other, they individually have drawbacks. For example, cytoarchitectonic analyses suffer from the fact that boundaries at times are placed on the basis of rather subtle criteria that may not be easily recognizable by all investigators. On the other hand, myeloarchitectonic criteria are rather crude; thus subtle regional differences may be missed. The inherent difficulties of architectonic methods may be obviated if the study of cerebral architecture is considered within a theoretical framework of progressive cortical laminar differentiation. The cerebral cortical architecture can be viewed as a series of gradual changes in laminar characteristics, which can be traced from two limbic moieties: the olfactory cortex (paleocortex), and the hippocampal formation (archicortex).

Methodological advances in neuronal pathway tracing procedures have also enhanced our ability to appreciate the cerebral cortex architectonically. The usefulness of tracing procedures in the study of cortical architecture is based on observations that projections emanate from and terminate within the confines of distinct architectonic boundaries (Jones and Powell, '70; Seltzer and Pandya, '78; Pandya et al., '88).

Most previous studies have focused their analyses on the projections from several sensory and limbic areas to the prefrontal cortex (Jones and Powell, '70; Chavis and Pandya, '76; Jacobson and Trojanowski, '77; Barbas and Mesulam, '81; Petrides and Pandya, '84, '88). These studies have shown an orderly pattern in the connections between subdivisions of the prefrontal cortex and the post-Rolandic cortices. How this information may be transmitted within the subregions of the prefrontal cortex is, however, not known. In the present study our aim was twofold: first, to reexamine the architecture of the prefrontal cortex, and second, to determine the intrinsic connections of the prefrontal cortex¹ and their relationship to the regional architecture.

MATERIALS AND METHODS

The cyto- and myeloarchitecture of the prefrontal cortex were studied in four unoperated rhesus monkeys. Formalin-

perfused brains were either embedded in celloidin or frozen and sectioned in the coronal plane at 35 μ m. Sections were stained with cresyl violet for cytoarchitectonic analysis and were prepared according to the Loyez or Gallyas ('79) procedures for myeloarchitectonic analysis. The efferent intrinsic connections of the prefrontal cortex were studied with injections of tritiated amino acids, and the afferent connections were studied with the use of the retrograde transport of horseradish peroxidase (HRP) or fluorescent dyes. Surgical procedures were carried out under aseptic conditions in animals sedated with ketamine followed by sodium pentobarbital (intravenously), which was administered gradually until a surgical level of anesthesia was achieved.

In 16 rhesus monkeys tritiated amino acids (³H-leucine and ³H-proline, 0.4–1.0 μ l; specific activity 40–80 μ Ci/ μ l) were injected in different sectors of the prefrontal cortex. After a postsurgical period of 7–10 days, the monkeys were given a lethal dose of anesthetic and perfused transcardially with saline followed by 10% formalin. The brains then were removed and photographed. The hemispheres were stored in 50% ethanol, embedded in paraffin, cut in the coronal plane at 10 μ m thickness, and processed for autoradiography according to the procedure described by Cowan et al. ('72). Exposure time of radiolabeled material ranged from 3 to 6 months.

In another five animals, injections of HRP were placed in different portions of the prefrontal cortex. Injections of 8% HRP conjugated to wheat germ agglutinin (Sigma) were made with a microsyringe (Hamilton, 5 μ l). At each injection site, 0.05–0.1 μ l of HRP was delivered 1.5 mm below the pial surface. Following a 48-hour survival period, the monkeys received a lethal dose of anesthetic and were perfused according to a method described by Rosene and Mesulam ('78). The hemispheres were cut in the coronal plane at 40 μ m thickness on a freezing microtome. Sections were collected in a 0.1 M phosphate buffer (pH 7.4). Every tenth section was treated for the visualization of HRP (Mesulam et al., '80).

Abbreviations

AS	arcuate sulcus
C	caudal
CC	corpus callosum
CINGS	cingulate sulcus
CS	central sulcus
D	dorsal
L	lateral
LF	lateral fissure
M	medial
MOS	medial orbital sulcus
O	orbital
OLF	olfactory cortex
OS	orbital sulcus
PAII	limbic periallocortex
Pro	proisocortex
ProM	rostral portion of the ventral premotor cortex
PS	principal sulcus
R	rostral
STS	superior temporal sulcus
V	ventral

¹"Intrinsic connections" refers to the local connectivity between areas of the prefrontal cortex.

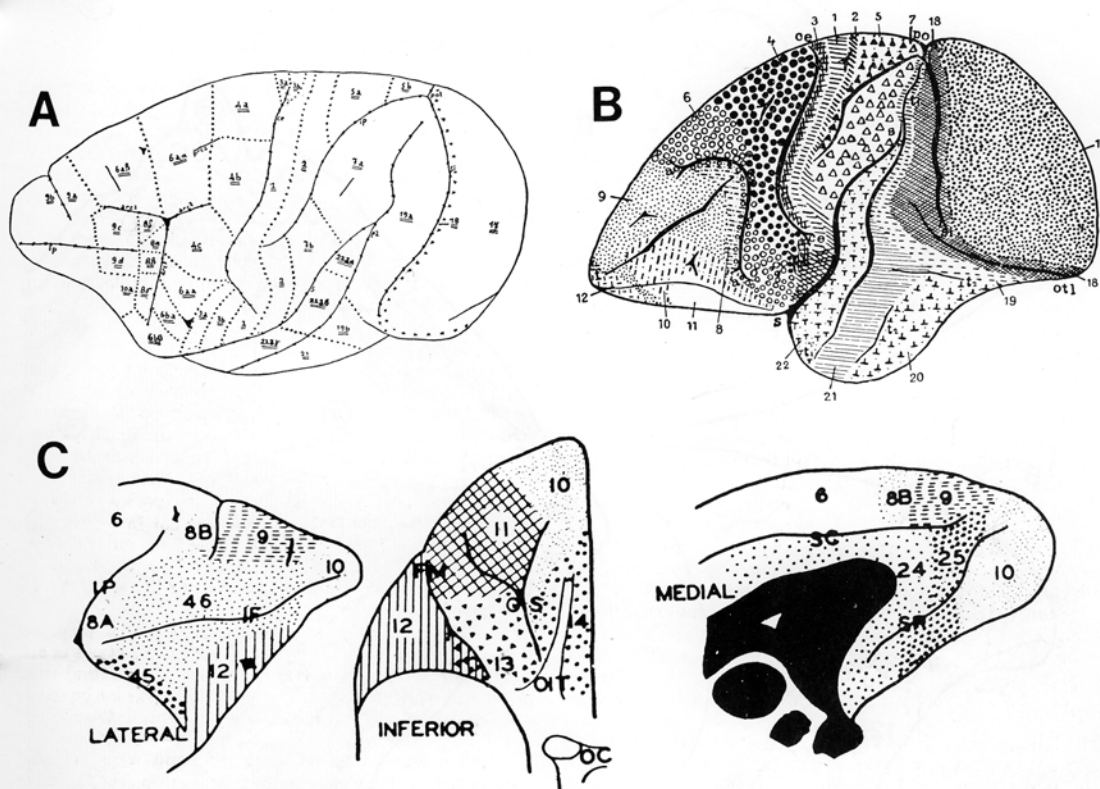


Fig. 1. Subdivisions of the prefrontal cortex according to the architectonic classification: A—Vogt and Vogt ('19); B—Brodmann ('05); and C—Walker ('40).

In one animal, an injection of the fluorescent dye diaminodimethyl yellow (3%, 0.5 μ l) was placed in medial area 32. General surgical procedures for this animal were identical to those described for the tritiated amino acids and HRP experiments. After a survival period of 7 days, the animal was given a lethal dose of anesthetic and perfused with 6% paraformaldehyde in 0.1 M cacodylate buffer at pH 7.4. The brain then was 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 μ m, and every tenth section was mounted on coated slides.

Autoradiographic tissue was viewed microscopically under darkfield, and HRP under brightfield, illumination. Outlines of brain sections and the location of the injection site, as well as the regional and laminar distribution of isotope or labeled cells ipsilateral to the injection site, were made on enlarged drawings of each brain section. The projection sites were serially reconstructed by using the sulci as landmarks and were shown on diagrams of the surface of the

cortex. The latter were drawn from photographs of each brain showing the external morphology of the experimental hemispheres. The drawings were modified to represent the relative location of cells or isotope label buried in sulci. In some cases the projection sites were also plotted on unfolded maps of the cerebral cortex as described in detail previously (Barbas and Pandya, '87; Barbas, '88). This method of unfolding the cortex results in negligible areal distortion ($3 \pm 2\%$). Architectonic areas and their borders were determined in the experimental material from sections stained with thionin (autoradiography) and with neutral red (HRP).

RESULTS

Cytoarchitecture

The different architectonic areas within the prefrontal cortex may be viewed as a series of regions showing gradual architectonic changes, as has been described for post-Rolandic cortices (Galaburda and Pandya, '83; Pandya et al., '88).

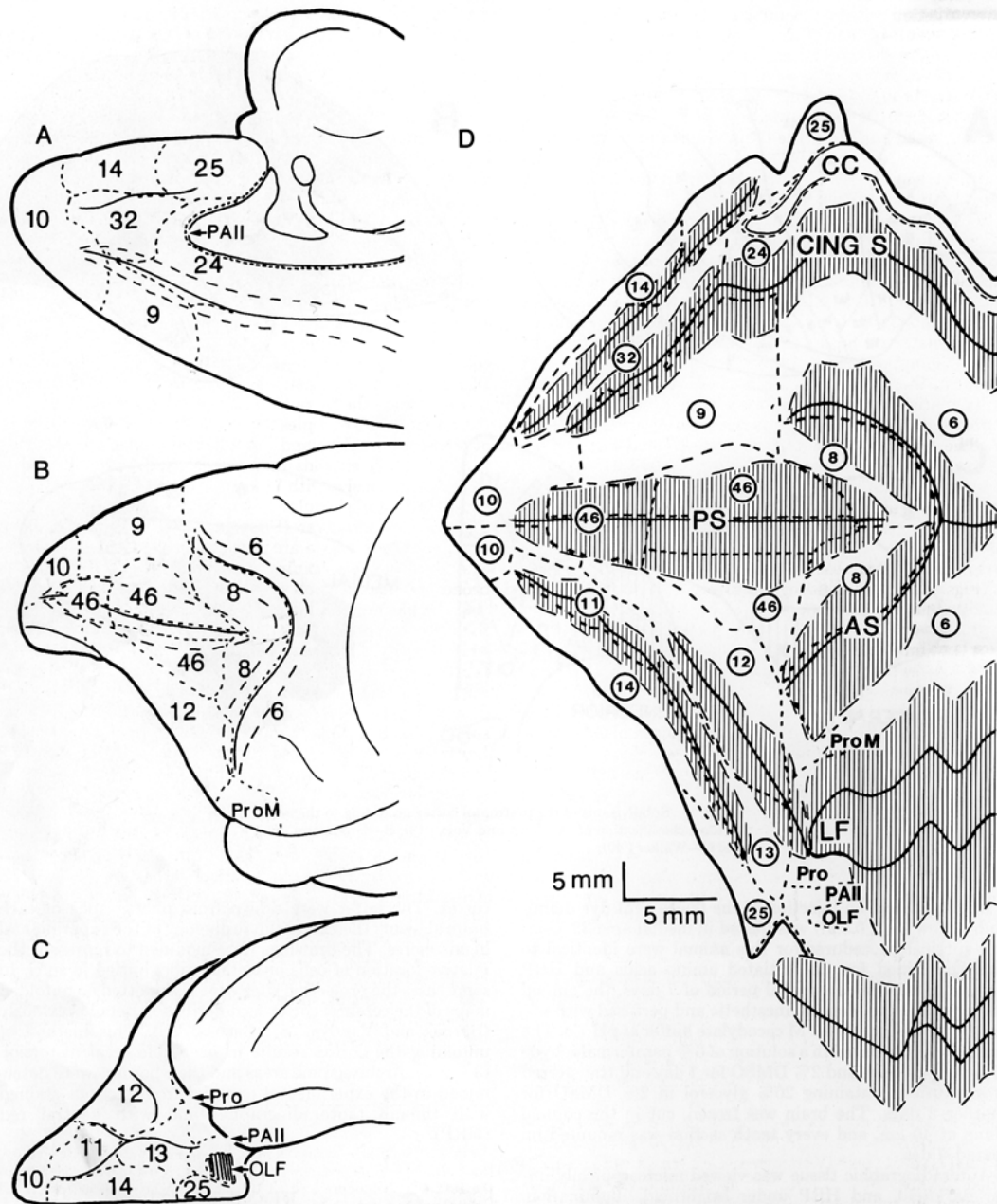


Fig. 2. The architectonic subdivisions of the prefrontal cortex, based on cytoarchitectonic criteria used in this study, are shown on the medial striped (A), lateral (B), and ventral (C) surfaces of the hemisphere and on a map where the sulci were unfolded (D). In this and in subsequent maps showing the unfolded cortex the rostrocaudal dimension (left to right) was expanded by a factor of 2.5. Small dotted lines demarcate architectonic borders; large dotted lines demarcate sulci. A map made on the basis of myeloarchitectonic criteria (not shown) was virtually identical to the one above.

According to our analysis there are two lines of architectonic differentiation within the prefrontal cortex (Fig. 2). The starting points of each of these lines are the limbic cortices, which, unlike the isocortices, do not have six layers. From these limbic cortices a stepwise increase in laminar differentiation can be identified. One of these architectonic lines can be traced from the paleocortex (olfactory tubercle) on the orbital (basal) surface of the brain (basoventral trend), and the other can be traced from archicortex (the hippocampal rudiment) on the medial surface around the genu of the corpus callosum (mediodorsal trend).

Basoventral trend. The olfactory cortex is bounded on the medial, lateral, and rostral dimensions by periallocortex which is characterized by the presence of three strata: a superficial molecular layer, a relatively sparsely populated upper layer, and a prominent deep layer (Fig. 3A). The cells in the deep part of periallocortex appear dark in Nissl-stained material and are arranged in long horizontal rows giving the appearance of multiple cell layers. Lateral and rostral to the periallocortex is proisocortex (Figs. 2C, 3B). Unlike periallocortex, proisocortex has a layer II although it is poorly demarcated. There is no apparent granular layer IV. The majority of the cells in layer III and in the deep layers are small- to medium-size pyramidal neurons. The deep layers of proisocortex have a somewhat higher cell density than the upper layers, but the contrast between the upper and lower layers is not as marked as in periallocortex.

Rostral to the proisocortex on the orbital surface is area 13 (Figs. 2C,D, 3C). This region resembles the caudally situated proisocortex but has a slightly higher cell density in layer III when compared to the proisocortex. Moreover, there is an incipient layer IV consisting of occasional granular cells. Like the proisocortex, area 13 also has slightly more prominent deep layers; layer V is the most prominent. Area 11 is situated rostral to area 13 on the orbital surface (Figs. 2C,D, 3E). In this region, layer II is composed of small cells which seem to fuse with layer III, and layer IV is still poorly developed. Compared to area 13 the cell density in the supragranular layers is higher. Layers III and V contain small- to medium-size pyramidal cells which appear in clusters.

Area 10 is situated rostral to area 11, but it extends on the medial and dorsolateral surfaces and thus occupies the entire frontal pole (Fig. 2A–D). Ventrolateral area 10 is slightly different from the mediadorsal and the latter will be described below. The ventrolateral portion of area 10 has a somewhat thicker layer II than area 11, but like area 11, there is no distinct border between layers II and III (Fig. 3F). Layer IV is somewhat better differentiated, and the infragranular layers are less prominent in area 10 than they are in area 11. Layer III contains medium-size pyramidal cells which are irregularly arranged. The overall cell density appears equal in the supragranular and the infragranular layers.

Area 12 is situated lateral to area 13 and extends to the ventrolateral surface (Fig. 2B–D). This cortex has better-defined layers II and IV than area 13. Area 12 can be subdivided further into two sectors. The orbital division is characterized by prominent infragranular layers (Fig. 3D). In this division, layer Va is more prominent and better differentiated than in area 13. The lateral portion of area 12 is further differentiated and has several characteristics which distinguish it from its orbital counterpart (Fig. 3G). For example, lateral area 12 has a better-developed layer IV, a

higher cell density in layer III, and less prominent infragranular layers than orbital area 12 (Fig. 3G).

Ventral area 46 is situated caudal to area 10 and dorsal to area 12 and extends up to the ventral bank of the principal sulcus (Fig. 2B,D). This region has a better-defined layer II than either area 10 or area 12 (Fig. 3H). Layer III contains small- to medium-size pyramidal cells which are arranged in horizontal rows. In this area the supragranular cell density is higher than the infragranular. Layer IV is distinct and clearly demarcates layers IIIc and Va. Layer VI of area 46, in general, forms a sharp boundary with the white matter.

Ventral area 46 has two divisions along its rostrocaudal axis (Fig. 2B,D). The caudal part shows a greater architectonic differentiation than the rostral. There is also a focal differentiation within caudal area 46: A medial division occupies the inner half of the lower bank of the principal sulcus, and a lateral division is located in the superficial part of the sulcus and the adjacent cortex. The latter has a columnar cellular arrangement, the pyramidal cells in layer IIIc are more prominent, and the cell density is overall higher than in the more medially situated cortex.

Ventral area 8 occupies the rostral bank of the lower limb of the arcuate sulcus and the adjacent ventrolateral cortex (Fig. 2B,D). It extends rostrally to caudal area 46 and is roughly coextensive with Walker's area 45. In this portion of area 8 the supragranular layers have a higher cell density than the infragranular (Fig. 3I). Layer III contains large pyramidal cells which are more prominent than those encountered in the adjoining portion of area 46. Layer IV is broad and distinct and contains densely packed granular cells. Unlike area 46, layer VI of area 8 does not form a distinct border, so the cells in layer VI blend gradually with the white matter. There seems to be a further focal differentiation within ventral area 8. In the sulcal part the large pyramidal cells in layer IIIc appear scattered compared to those observed in the ventrolateral portion of area 8. In addition, sulcal area 8 is less columnar than ventrolateral area 8. Layer IV is more marked in the lateral portion of area 8 when compared with the sulcal portion.

Mediodorsal trend. The mediadorsal prefrontal trend can be traced to the periallocortex situated around the corpus callosum. In this area there is no apparent laminar organization below layer I (Figs. 2A,D, 3J). The periallocortex is bounded rostrally by proisocortical areas 24, 25, and 32. Areas 24 and 25 are situated respectively above and below the genu of the corpus callosum; the latter extends into the caudal orbital surface. Area 32 is located rostral to areas 24 and 25 below the cingulate sulcus (Fig. 2A,D). In these areas layer I is broad and layer II has an irregular upper margin. There is no separation between layers II and III (Fig. 3K). The cell density is lower in the upper layers when compared with the lower layers. There is no discernible layer IV in

Fig. 3. (Overleaf) Brightfield photomicrographs of the cytoarchitectonic divisions of the prefrontal cortices. Basoventral areas are shown on the left and mediadorsal on the right. A: Orbital periallocortex. B: Orbital proisocortex. C: Area 13. D: Orbital area 12. E: Area 11. F: Ventral area 10. G: Lateral area 12. H: Ventral area 46. I: Ventral area 8. J: Medial periallocortex. K: Area 25. L: Area 32. M: Medial area 9. N: Area 14. O: Dorsal area 10. P: Lateral area 9. Q: Dorsal area 46. R: Dorsal area 8. Cortices depicted in A, B, J, K, and L lack a granular layer IV. Dash between layer designations indicates indistinct laminar borders. Celloidin-embedded tissue, cresyl violet stain. Scale bar = 1 mm.

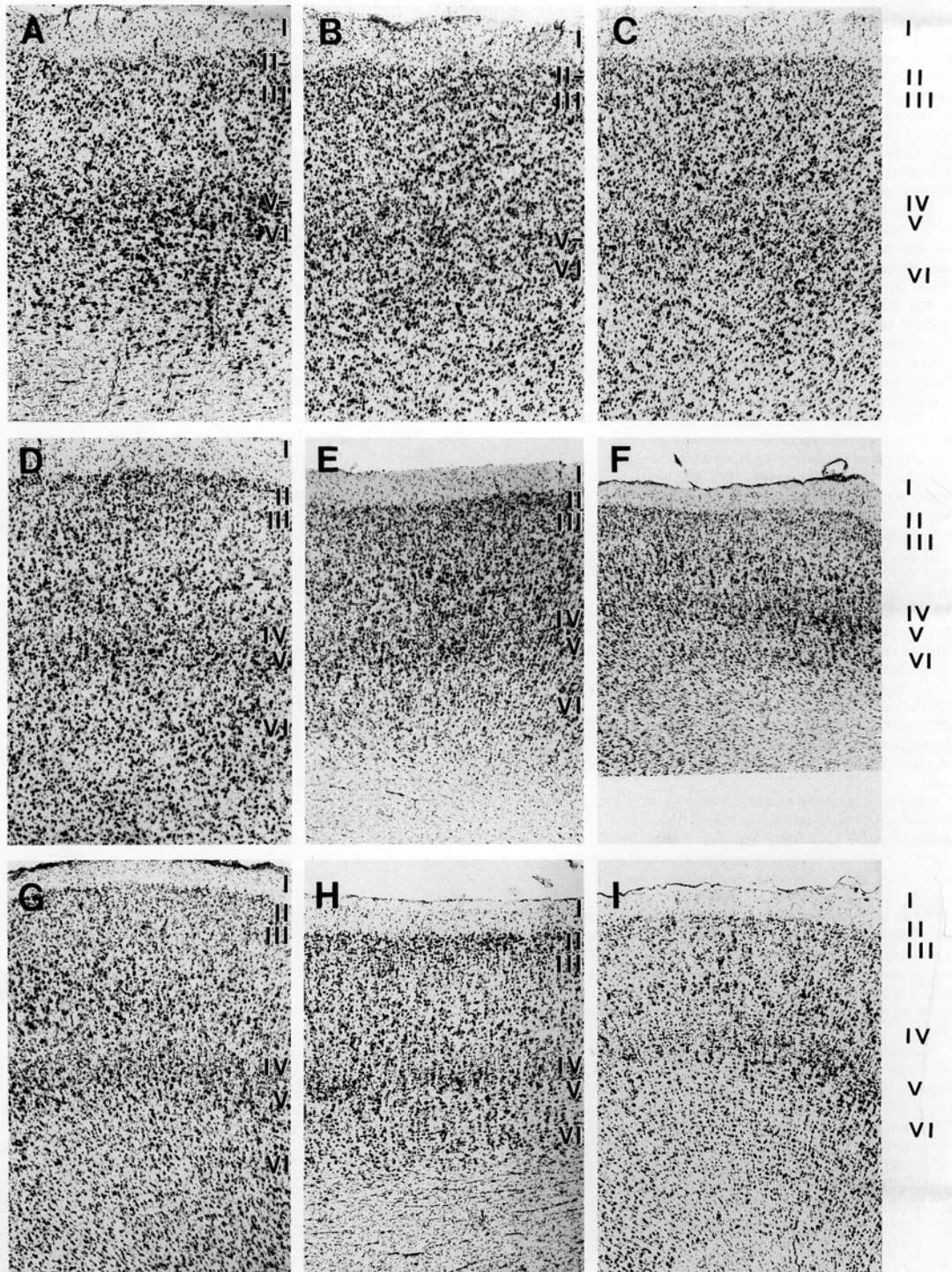


Figure 3 A-I

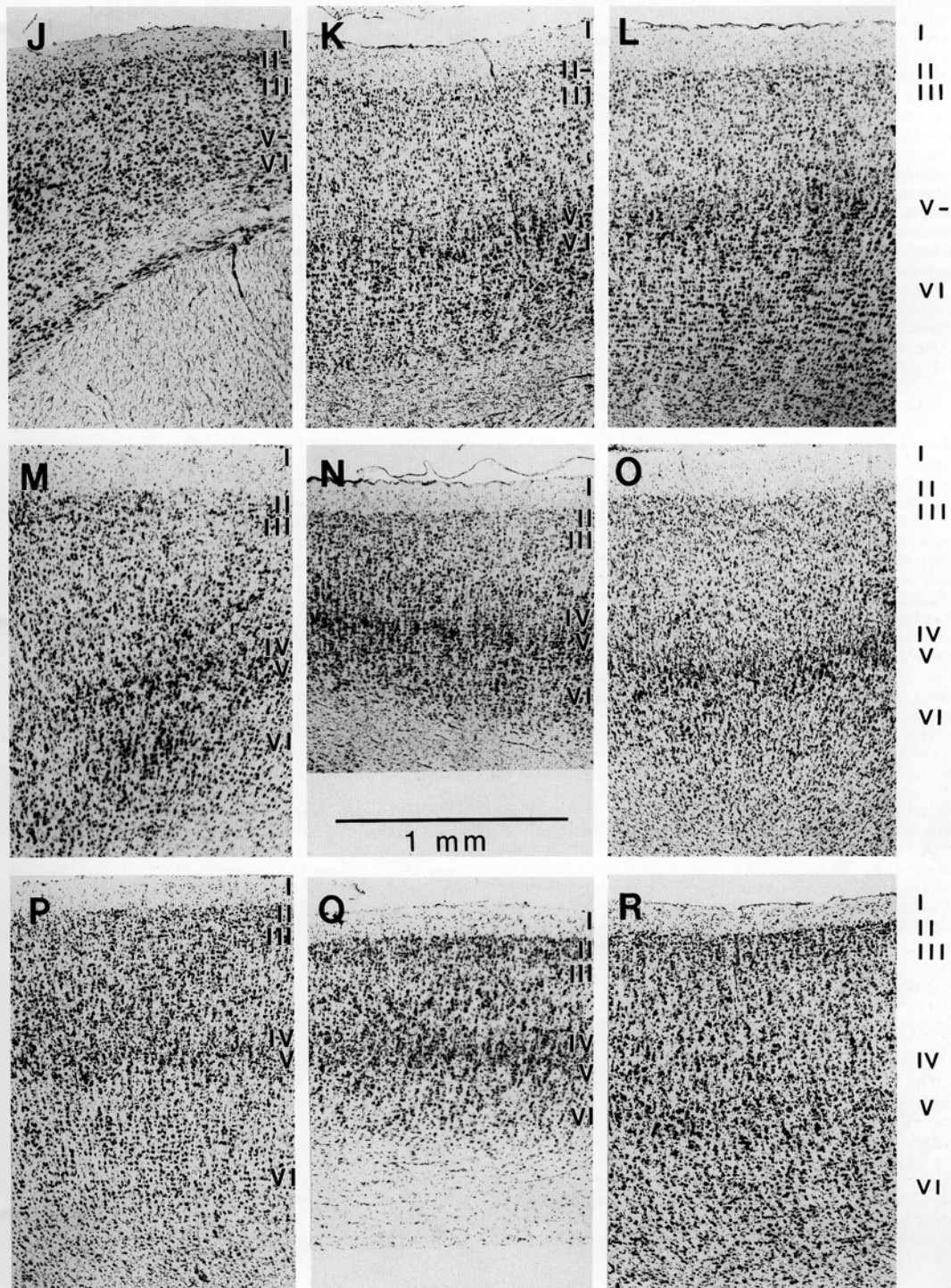


Figure 3 J-R

these regions. The neurons of layer Va appear prominent, particularly in area 24, although layer VI neurons also stain darkly (Fig. 3K,L). Compared with area 25, layer II of area 32 is slightly more discernible, and the deep layers appear somewhat lighter.

Area 14 lies below area 32 on the ventromedial surface of the prefrontal cortex and extends to the orbital surface where it joins area 11 (Figs. 2A,C,D, 3N). In area 14 layer I is narrower when compared to areas 25 and 32. Layer II is discernible but has irregular borders. In this area, layer III contains small pyramidal cells which are more densely packed than in areas 32 and 25. There is an emergence of layer IV, which is characterized by small granular cells. The neurons in layers V and VI are still more prominent than the supragranular neurons.

Area 9 occupies a position above the rostral part of the cingulate sulcus and extends dorsolaterally and caudally where it borders respectively areas 46 and 6 and dorsal area 8 (Fig. 2A,B,D). Area 9 can be subdivided into a medial and a lateral sector. The medial subdivision has a broad layer I, an indistinct layer II, and an incipient layer IV (Fig. 3M). The lateral portion of area 9 is better differentiated than its medial counterpart (Fig. 3P). For example, its layer II has a distinct upper margin, the supragranular cell density is higher than the infragranular, and its layer IV is distinguishable when compared with medial area 9.

Mediodorsal area 10 is located rostral to area 9 (Fig. 2A,B,D, 3O). The supragranular and infragranular layers seem to have an equal cell density. The size of layer IV is comparable to that seen in lateral area 9. Layer Va is prominent and contains medium-size pyramidal cells.

Dorsal area 46 is situated lateral to area 9 and caudal to area 10 and extends into the dorsal bank of the principal sulcus (Fig. 2B,D). In this region layer II is distinct and separable from layer III (Fig. 3Q). The supragranular layers are more marked than the infragranular. Layer III contains small, medium, and occasional large pyramidal cells. Compared to area 10, layer IV is well developed, and layer Va is less prominent in area 46. As area 46 extends caudally, layer II becomes increasingly more distinct and layer III contains prominent medium-size pyramidal cells. Like ventral area 46, dorsal 46 can be subdivided into a rostral and a caudal sector. The laminar borders in caudal area 46 are better delineated when compared to its rostral counterpart.

Dorsal area 8 is situated caudal to area 46 and extends into the anterior bank of the upper limb of the arcuate sulcus (Fig. 2B,D). This area has a well-defined layer II which is composed of small cells (Fig. 3R). In layer III there are distinct and regularly occurring large pyramidal cells. The neurons in the supragranular layers are more densely packed and layer IV is better developed when compared with area 46. Dorsal area 8 is characterized by the presence of a row of large pyramidal cells in layer V; this characteristic is particularly evident in the caudal portion of area 8.

Myeloarchitecture

The pattern of myelination is useful in distinguishing architectonic borders and thus may be used to confirm the boundaries of regions observed by using cytoarchitectonic criteria. The periallocortex on the orbital surface has a very low myelin content, whereas the adjacent proisocortex has a faint layer of myelinated fibers in the deep layers. Adjoining area 13 is characterized by a diffuse myelin content in the lower layers. Progressing rostrally on the orbital cortex, the myelinated fibers in area 11 are organized into a thin hori-

zontal band, which is referred to as an outer Baillarger band, set off from a more diffusely distributed myelin content in the deep layers. The orbital part of area 14 has a clear outer Baillarger band which becomes progressively less distinct medially. In contrast to areas 11 and 14, in ventral area 10 there is a relatively thick outer Baillarger band and a rather prominent vertical plexus in the deep layers. Compared to area 10, the adjacent area 12 is characterized by a thicker outer Baillarger band and vertically distributed myelinated fibers in the deep layers. Ventral area 46 has a discernible outer Baillarger band, as well as a more deeply situated horizontal band of myelinated fibers, which is referred to as the inner Baillarger band. In comparison with area 46, the adjacent ventral part of area 8 has better-defined outer and inner Baillarger bands. The inner band appears less distinct than the outer in a background of a diffuse vertical plexus.

Within the mediadorsal trend of architectonic differentiation proisocortical areas 24, 25, and 32 have a very low myelin content confined to the deep layers. Area 32 has a faint inner Baillarger band which distinguishes it from areas 24 and 25. Dorsal to proisocortical area 32, area 9 is characterized by the presence of an outer Baillarger band and a moderately thick vertical plexus. Dorsal area 10 has a very light outer Baillarger band and a diffuse vertical plexus only in the deep layers. The myelination pattern of dorsal area 46 is distinguishable from that of the surrounding areas 9 and 10 by the presence of a well-delineated outer Baillarger band. Dorsal area 8 has sharply delineated inner and outer Baillarger bands and a vertical plexus of medium density.

Intrinsic connections of the prefrontal cortex

Following injection of tritiated amino acids in different subdivisions of the prefrontal cortex labeled terminals were observed in several cortical and subcortical regions. Since our aim was to study the intrinsic organization of the prefrontal cortex, we will limit description of the distribution of labeled grains to the prefrontal cortex.

Connections of basoventral prefrontal areas. In case 1 an isotope injection was placed in the caudal orbital cortex and involved primarily the area we termed proisocortex and to a lesser extent the adjacent area 13 (Fig. 4). Labeled grains in this case were observed in the adjacent portions of proisocortex and area 13. Additionally, label was found in area 14 medially, 12 laterally, and in areas 11 and 10 rostrally on the orbital surface. On the medial surface areas 25, 32, 14, and to a lesser extent area 9 also contained label. Moreover, in this case label was noted on the lateral surface in areas 12 and 10.

In case 2 an isotope injection was placed in area 13 and there was only a minimal involvement of the adjacent orbital proisocortex (Fig. 4). On the orbital surface labeled grains were observed in the proisocortex and area 13, as well as in the adjacent areas 14, 11, and 12. Unlike the previous case, label on the medial surface was sparse and limited to proisocortical area 25.

In case 3 an isotope injection was placed in area 14 but there was involvement of adjacent area 13 (Fig. 5). On the orbital surface labeled grains were observed in portions of areas 14, 11, 10, and 12. In addition, label was seen in the lateral part of area 12 and in ventral areas 46 and 6. Small clusters of labeled grains were found on the medial surface in areas 25, 32, 14, and 9.

In case 4 an isotope injection involved the orbital portion of area 12 only (Figs. 5, 7B). In this case labeled grains were seen in the orbital proisocortex as well as in nearby areas 13,

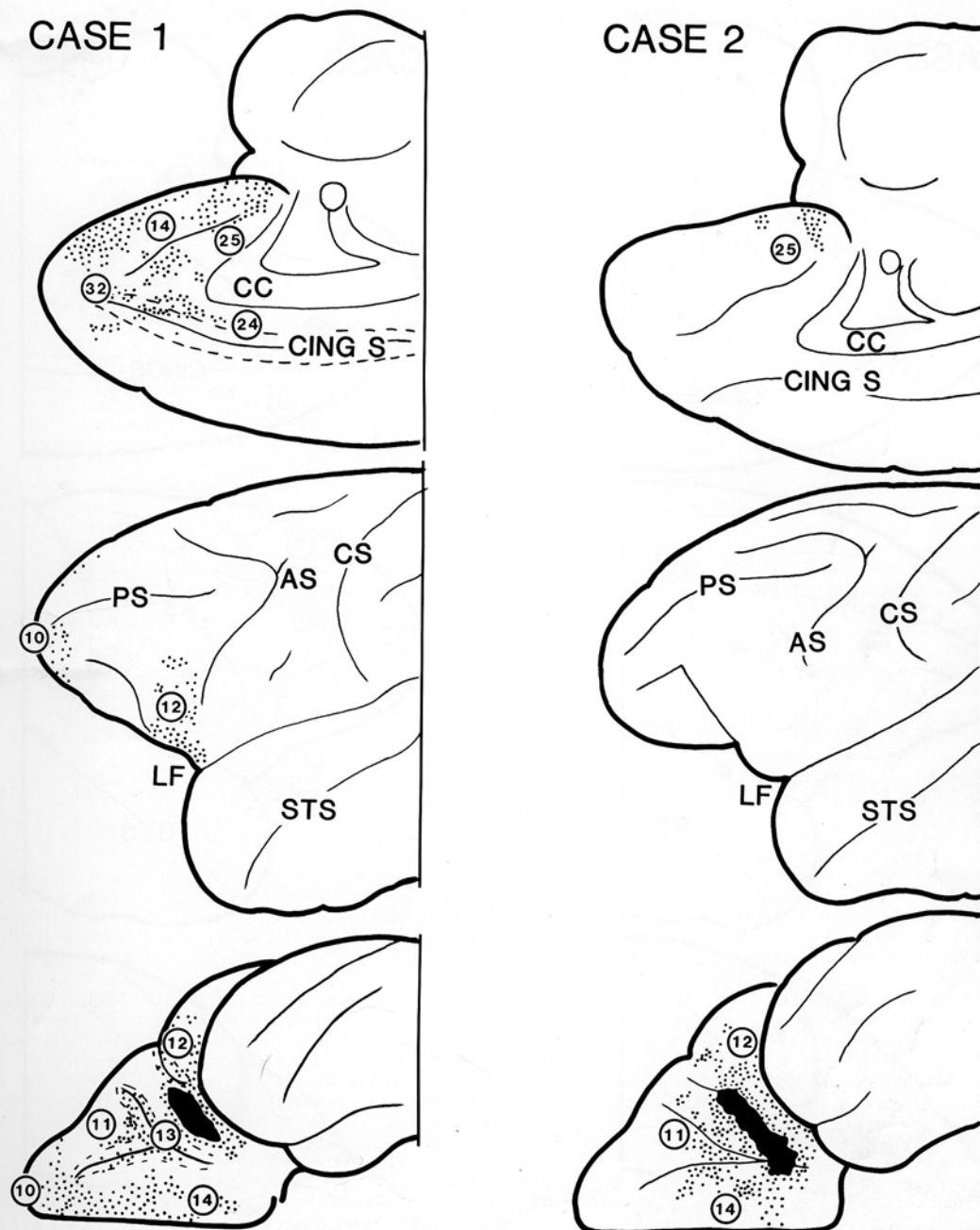


Fig. 4. The distribution of labeled grains (represented by dots) following isotope injection (represented by black area) in the orbital prefrontal cortex (case 1, left) and in area 13 (case 2, right) is shown on the medial (top), lateral (center), and basal (bottom) surfaces of the fron-

tal lobe. The dotted lines, in this and in subsequent figures, demarcate the cortex buried in sulci. The circled numbers in all figures represent architectonic areas.

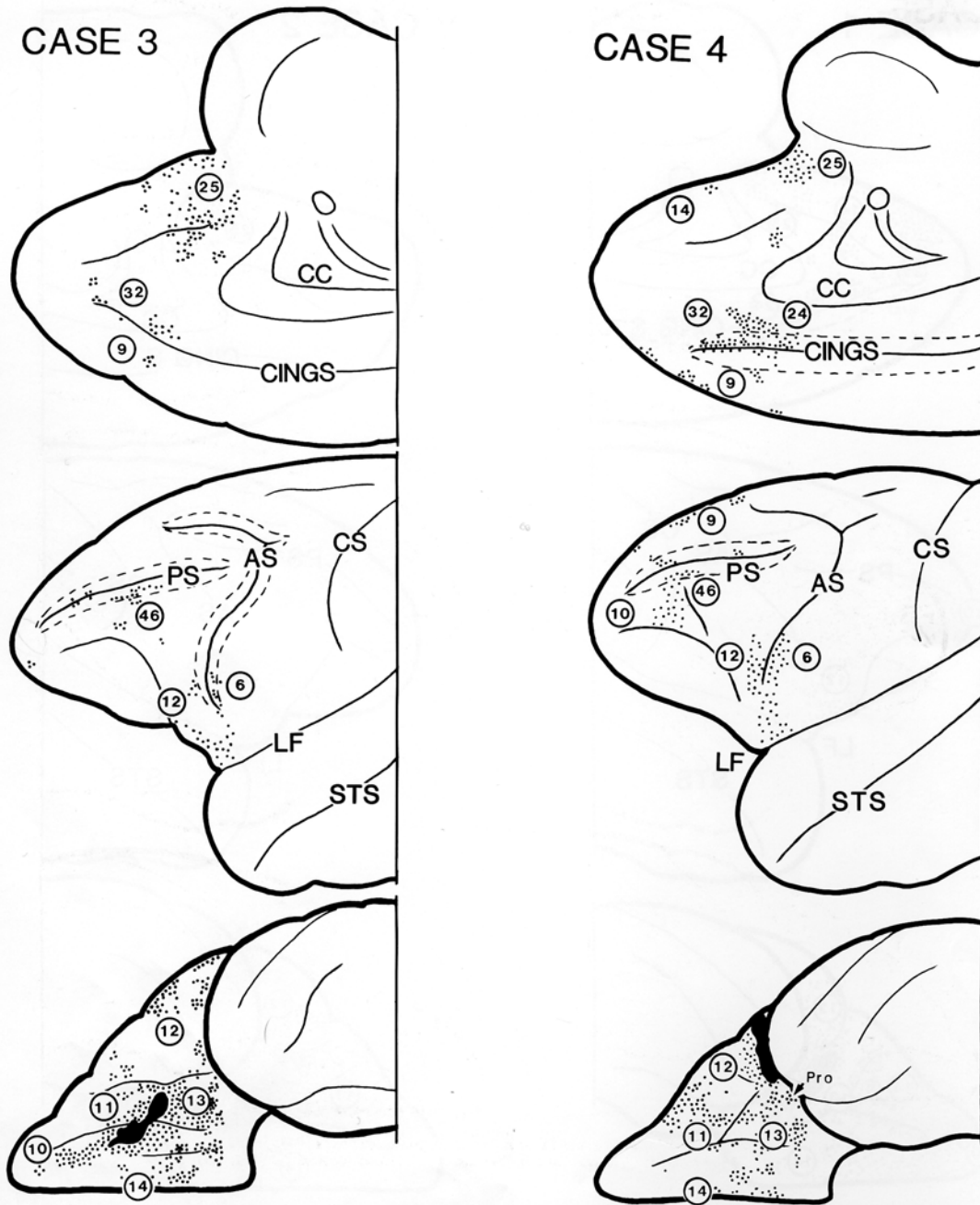


Fig. 5. The distribution of labeled grains following isotope injection in area 14 and 13 (case 3) and in orbital area 12 (case 4) is shown on the medial (top), lateral (center), and basal (bottom) surfaces of the frontal lobe.

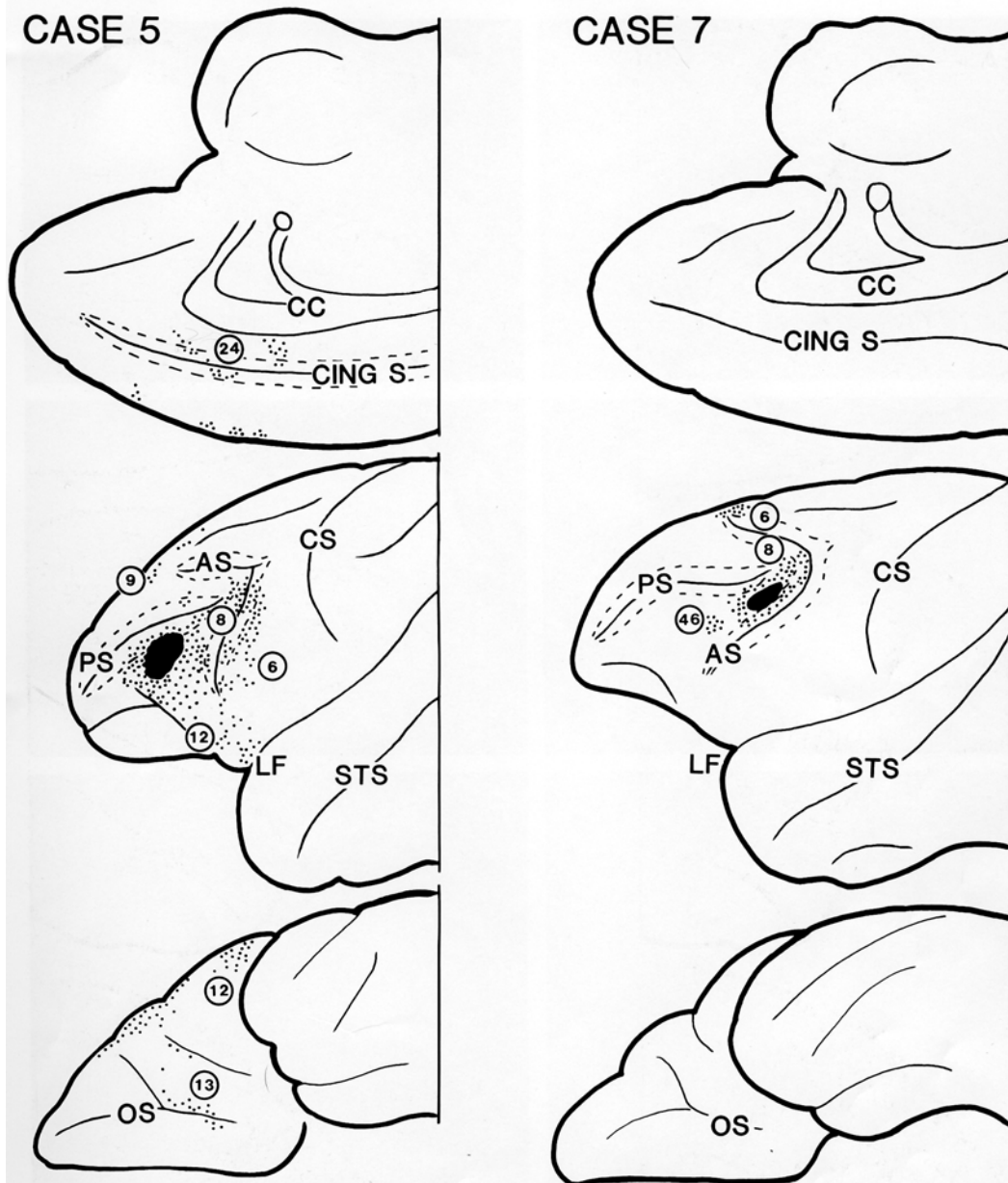


Fig. 6. The distribution of labeled grains following isotope injection in ventral area 46 (case 5) and in ventral area 8 (case 7) is shown on the medial (top), lateral (center), and basal (bottom) surfaces of the frontal lobe.

14, 11, and 12 (Fig. 7C). On the lateral surface label was found in areas 12 and 10 and the rostral portion of areas 46 (Fig. 7A) and 6. Distinct clusters of labeled grains were found on the medial surface in areas 25 (Fig. 7C), 32, 24, and 9.

In cases 5 and 6 isotope injections were placed in the central portion of ventral area 46 immediately below the principal sulcus (Figs. 6, 7E). In case 6 there was a slight involvement of dorsal area 46. Nevertheless, the pattern of label was basically similar in the two cases. Labeled grains were

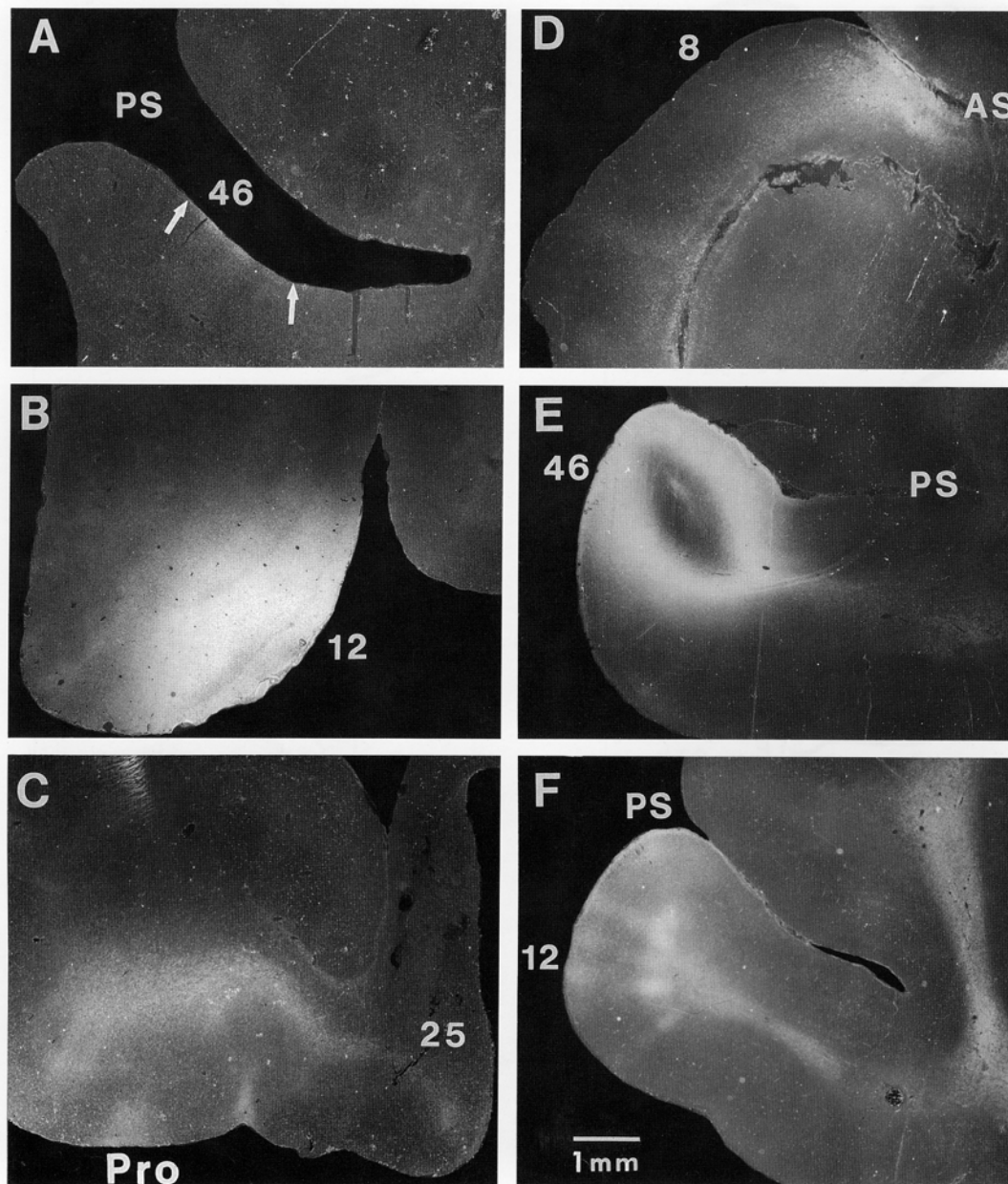


Fig. 7. Darkfield photomicrographs showing labeled grains in layer I of ventral area 46 (A) after isotope injection in orbital area 12 (B, case 4). Another projection to the orbital proisocortex and to area 25 in this case is shown in C. In this case A represents a projection directed to a more-differentiated area, and C to a less-differentiated area. Labeled grains in

area 8 (D) seen after isotope injection in ventral area 46 (E). Another projection in this case to lateral area 12 is shown in F. In this example D represents a projection directed to a more differentiated area, and F to a less-differentiated area. Scale bar = 1 mm.

TABLE 1. Distribution of Labeled Grains in the Prefrontal Cortex After Injection of Tritiated Amino Acids in Basoventral Prefrontal Areas¹

Label site	Injection site (case no.)						
	Pro,*13 (1)	13,*Pro (2)	14,*13 (3)	O12 (4)	V46 (5)	V46,*D46 (6)	V8 (7)
Basoventral							
Pro	++	++		++			
13	++	++		++	+	+	
O12	++	++	++	++	+	++	
O14	++	++	++	++			
11	++	+	++	++			
V10	++		+	+		+	
L12	++		+	+	++	++	
V46			+	+	++	++	++
V8					++	+	++
V6			+	+	++	++	
Mediodorsal ²							
25	++	+	+	++			
32	++		+	+			
24				++	+	+	
M14	++		+				
M9	+		+	+	+	+	
L9					+	+	
D10	+						
D46					+	+	
D8							+
D6					+	+	+

*+, slight involvement by ³H injection; +, light-moderate; ++, moderate-heavy label.

²In Tables 1 and 2 letters appearing before architectonic areas refer to C, caudal; D, dorsal; L, lateral; M, medial; O, orbital; R, rostral; and V, ventral.

found in the adjacent ventral areas 46 and 12 (Fig. 7F), in area 8 (Fig. 7D), in ventral area 6, and in the frontal operculum (area proM). In addition, small clusters of label were seen in dorsal areas 6, 9, and 46. On the orbital surface label was found in area 12 and in the medial portion of area 13. A few patches of labeled grains were found on the medial surface in the rostral portion of the cingulate gyrus and sulcus in areas 24 and 9.

In case 7 an isotope injection was confined to ventral area 8 (Fig. 6). In this case the distribution of labeled grains was restricted to adjacent ventral areas 8 and 46, as well as to dorsal area 8. Additionally, a distinct cluster of labeled grains was noted in dorsal area 6 above the rostral tip of the arcuate sulcus. The distribution of labeled grains in the frontal cortex after injection of tritiated amino acids in basoventral prefrontal regions is shown in Table 1.

Connections of mediodorsal prefrontal areas. In cases 8 and 9 an isotope injection was placed in area 32 on the medial surface of the prefrontal cortex (Figs. 8, 13B). The isotope injection in case 9 extended more ventrally than in case 8. Labeled grains were observed on the medial surface mainly in area 25 below the genu of the corpus callosum (Fig. 13C) and to a lesser extent in area 24 and in areas 10 and 9 (Fig. 13A). On the lateral surface label was observed in areas 9 and dorsal 10, and some was seen within the rostral portion of area 46. Clusters of labeled grains were observed in area 13, the neighboring proisocortex, and area 14 on the orbital surface. In case 9 there were some labeled grains in orbital area 12 and ventral area 10.

In case 10 an isotope injection was placed in area 9 above the rostral part of the principal sulcus (Fig. 9). The injection also involved the upper portion of the adjacent rostral area 46. On the medial surface label was found in areas 32, 24, 9, and 10. Distinct clusters of labeled grains were observed on the lateral surface in the rostral portion of dorsal areas 6 and 8 and in the rostral part of dorsal area 46 below the injection site. Small clusters of label were seen ventrally in area 12 and in the orbital portion of area 10.

CASE 8

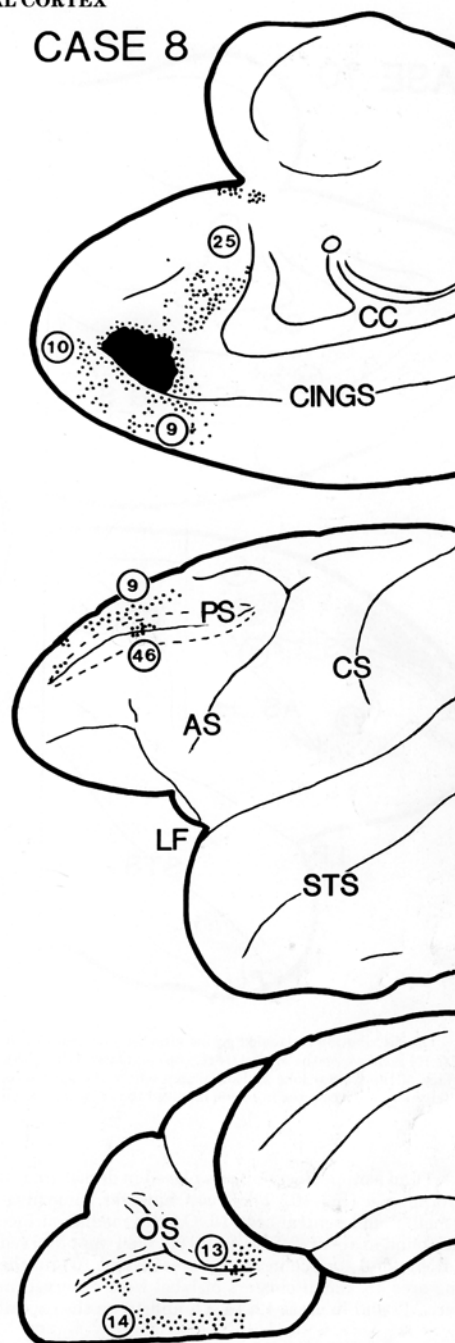


Fig. 8. The distribution of labeled grains after isotope injection in area 32 (case 8) is shown on the medial (top), lateral (center), and basal (bottom) surface of the frontal lobe.

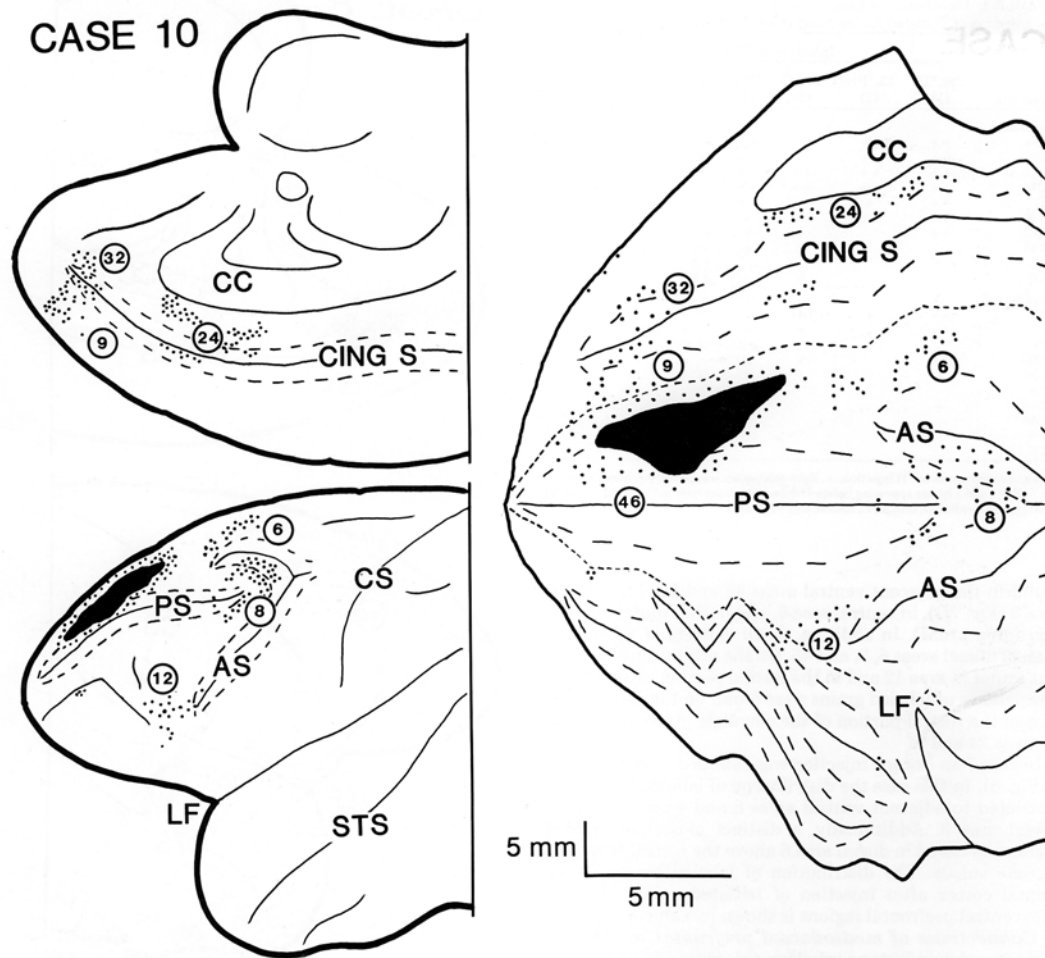


Fig. 9. The distribution of labeled grains after isotope injection in area 9 (case 10) is shown on the medial (left, top) and lateral (left, bottom) surface of the frontal lobe and on a map where the sulci were unfolded (right). In this case the injection involved the adjacent rostral

part of area 46. In the unfolded map the large dotted lines demarcate the cortex buried in sulci; the small dotted lines separate the dorsolateral from the medial surface (top) and the ventrolateral from the basal surface (bottom) in all figures.

In case 11 an isotope injection was placed in dorsal area 10 at the frontal pole (Fig. 10). There was, however, some invasion of medial and ventral area 10. On the medial surface label was found in areas 32, 24, 14, and 9. Label was observed also on the lateral surface in rostral areas 9 and 10 and the adjoining area 46. Small clusters of label were observed in lateral area 12 and in areas 12, 14, 11, and 10 on the orbital surface.

In cases 12 and 13 isotope injections were placed in dorsal area 46. In case 12 the injection involved also a small part of area 9 (Fig. 11). In case 13 the isotope involved the rostral part of dorsal 46 and slightly ventral area 46. Label was observed in rostral areas 24, 9, and 10 in both cases and in

area 32 (case 12 only) on the medial surface. On the lateral surface labeled grains were found rostral to the injection site in areas 10 and 9 and caudally in dorsal areas 46, 8, and 6. Unlike case 12, in which the isotope was restricted dorsally, in case 13, where the injection involved also ventral area 46, some label was observed in orbital areas 13, 11, 12, and ventral 46.

In cases 14–16 isotope injections were placed in dorsal area 8 (Fig. 12). Case 14 had an injection in the caudal half, and case 15 in the central portion of dorsal area 8 (Figs. 12B–D, 13D). In case 16 the isotope injection was restricted to the caudal part of dorsal area 8 at the junction of the upper and lower limbs of the arcuate sulcus (Fig. 12E). The

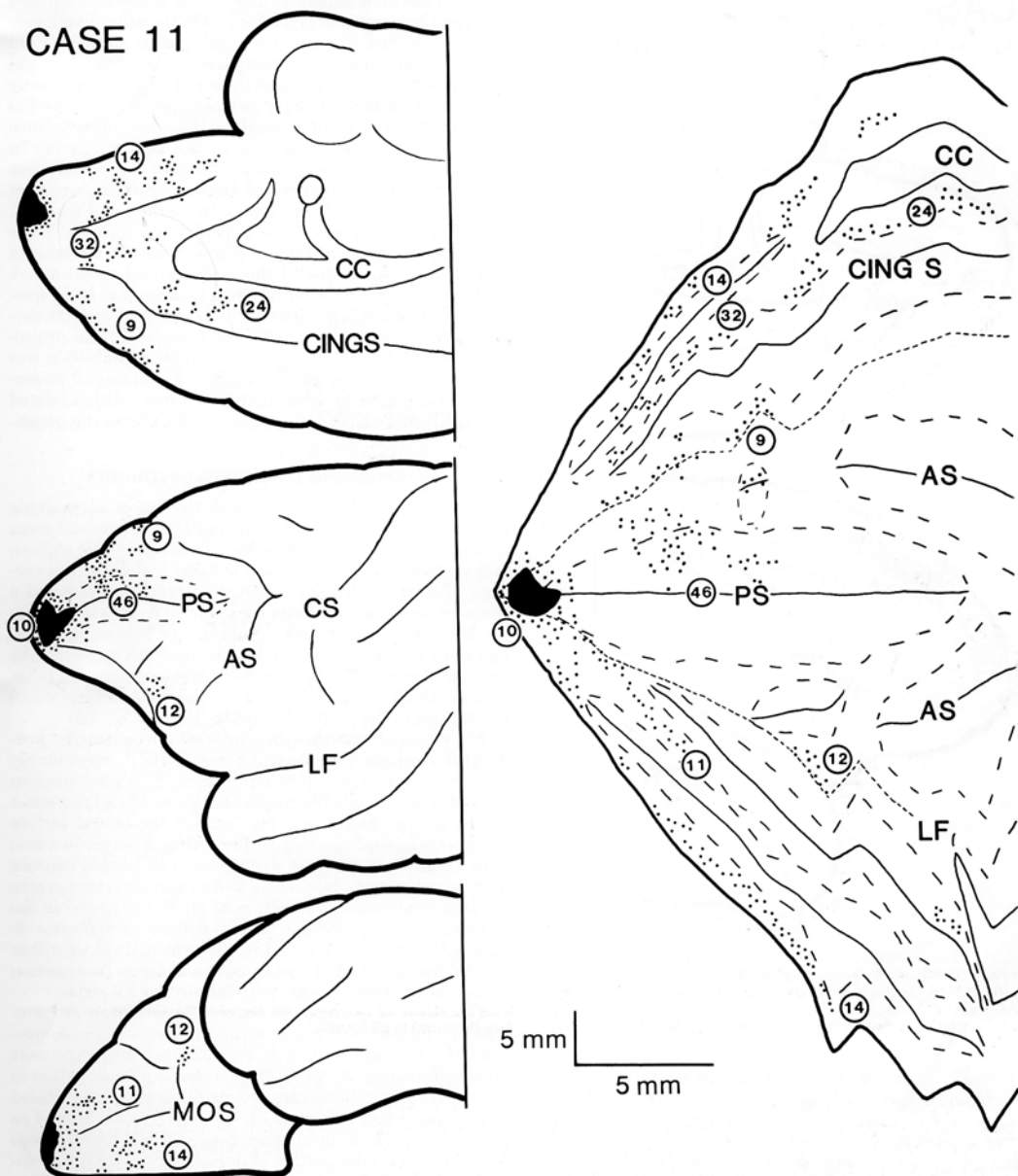


Fig. 10. The distribution of labeled grains after isotope injection in area 10 (case 11) is shown on the medial (left, top), lateral (left, center)

and basal (left, bottom) surface of the frontal lobe and on a map where the sulci were unfolded (right).

distribution of label in these cases was similar. In all cases label was observed in dorsal areas 6, 46, and 8 (Fig. 13E). In addition, clusters of label were observed in areas 9, lateral 12, and ventral 8 in all cases (Fig. 12). The distribution of labeled grains in the frontal cortex after injection of tri-

tiated amino acids in mediodorsal prefrontal regions is shown in Table 2.

Laminar distribution of label in the prefrontal cortex. The pattern of termination of the intrinsic connections of the prefrontal cortex within cortical laminae varied

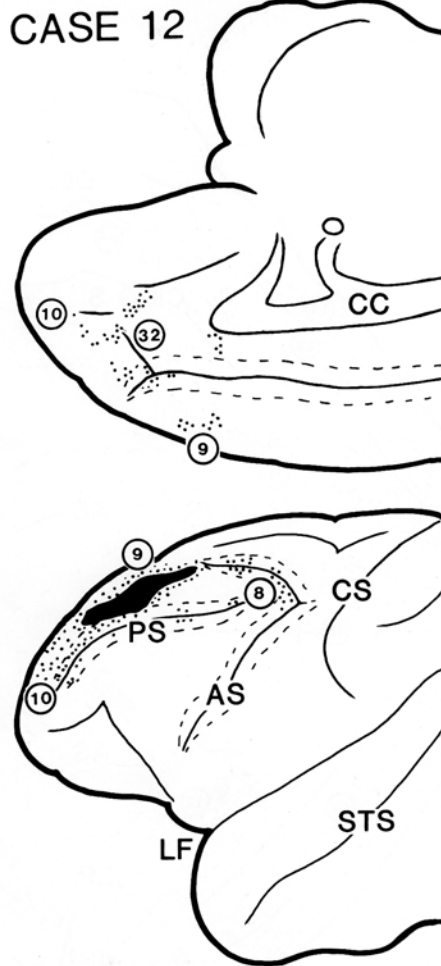


Fig. 11. The distribution of labeled grains after isotope injection in dorsal area 46 is shown on the medial (top) and lateral (bottom) surface of the frontal lobe. In this case the isotope injection invaded the adjacent area 9.

from region to region. One pattern was characterized by labeled grains organized in columns of varying widths which spanned the entire depth of the cortex (Fig. 7C). In a second pattern labeled terminals were also organized into columns with more marked label in layer I (Fig. 13C). In a third, and the least common pattern, the terminations were restricted to layer I (Fig. 7A).

To determine whether there was a consistent pattern of terminations, each projection directed to one architectonic area was recorded as belonging to one of the three patterns described above. The incidence of each pattern of terminations within an architectonic area was calculated from serial sections for each case. This analysis revealed that projections terminating in areas that had a less distinct laminar organization than the site of origin of the projections (injec-

tion site) fell predominantly into the columnar pattern, and very few terminated in layer I only. On the other hand, projections directed to areas that had a more differentiated laminar organization when compared to the cortex of origin terminated to a greater extent in layer I and less frequently into simple columns. The pattern of projections directed to areas that were at approximately the same architectonic stage as the cortex giving rise to the projections fell in between the above two extremes. Because this pattern was consistent in all cases examined, the data from all cases were pooled and the results are shown in a graph in Figure 14. Data from case 3, where the injection site included areas belonging to two architectonic stages, were not included in this analysis. In Figure 14 the category designated as -1 contains all projections terminating in areas that had a less-differentiated laminar pattern when compared with the cortices giving rise to the projections; 0 represents all projections terminating in areas whose laminar organization was similar to that of the sites of origin; +1 contains all projections terminating in areas that had a more differentiated laminar pattern than the cortices giving rise to the projections.

Retrograde tracing experiments

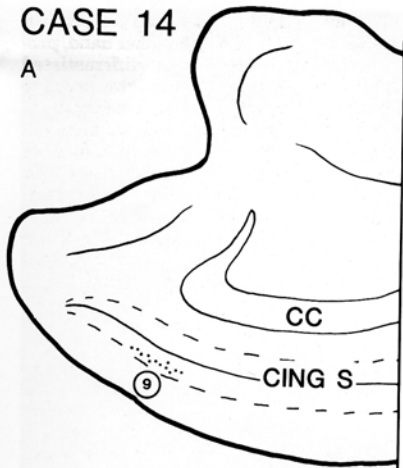
The above results obtained with the use of anterograde tracers suggested that injections in dorsal prefrontal areas resulted in label primarily within dorsal prefrontal regions, and ventral injections resulted in label within ventral cortices (Tables 1, 2). To confirm this trend we examined a series of experimental cases available to us in which retrograde tracers (horseradish peroxidase or fluorescent dyes) had been placed in distinct architectonic areas within the prefrontal cortex. These cases were previously used in other studies which examined primarily the long corticocortical projections to the prefrontal cortex (Barbas, '86, '88).

Injection of retrograde tracers in basoventral prefrontal regions. Following a small HRP injection restricted to the orbital portion of area 12, labeled neurons were observed in neighboring areas 12 and 13 and to a lesser extent in the orbital preoccipital cortex. On the lateral surface there were labeled neurons within ventral area 46. In a case with an HRP injection in ventral area 46 labeled neurons were found in areas 46, 8, and 6 and to a lesser extent in area 12. In another case an injection of HRP was placed in the concavity of the arcuate sulcus within ventral area 8. Labeled neurons were found in the principal sulcus within area 46 rostrally and in area 8 above and below the injection site. A few labeled neurons were seen in areas 9 and 6.

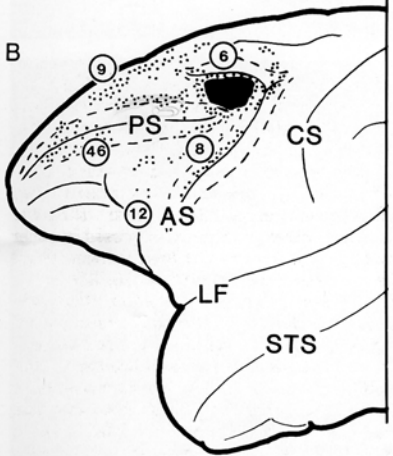
Injection of retrograde tracers in mediodorsal prefrontal regions. In a case with an injection of the fluorescent dye diamidino yellow in area 32 labeled neurons were observed in areas 25, 24, 9, and 10 and to a lesser extent in the rostral part of dorsal area 46. Additionally, some labeled neurons were found in areas 13, 12, and 11, and in area 14 on the orbital surface. In another case an HRP injection was placed in the caudal portion of dorsal area 46. On the dorso-lateral surface labeled neurons were seen in the adjoining portion of dorsal and ventral area 46, in area 8, and in dorsal area 6. An additional cluster of labeled neurons was observed in the mid-dorsal portion of area 46. In another case an HRP injection was placed in the caudal portion of area 8 within the concavity of the arcuate sulcus above the principal sulcus. Labeled neurons were found predominantly in the caudal portion of area 46, in dorsal and ventral portions of area 8, and in dorsal area 6. A few labeled neurons were found in areas 9 and 12.

CASE 14

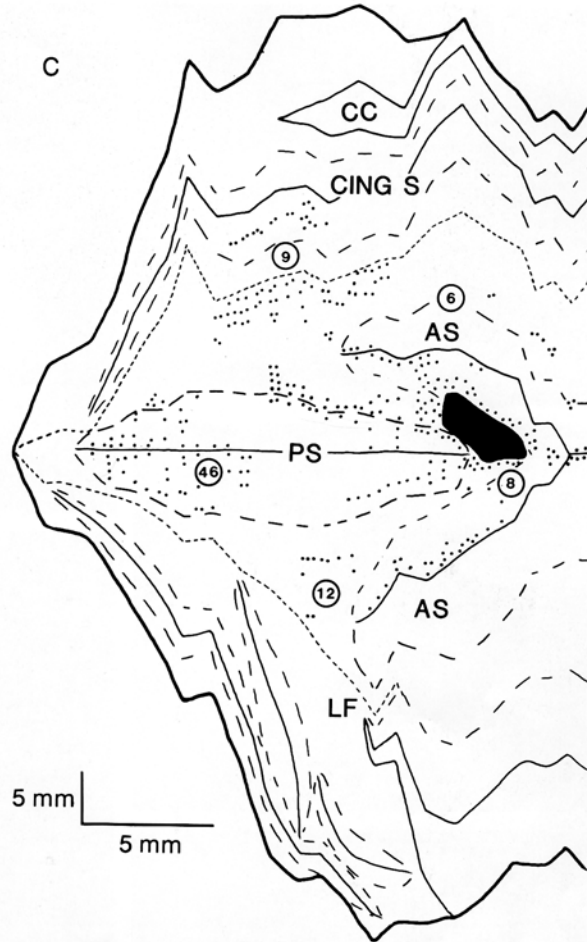
A



B

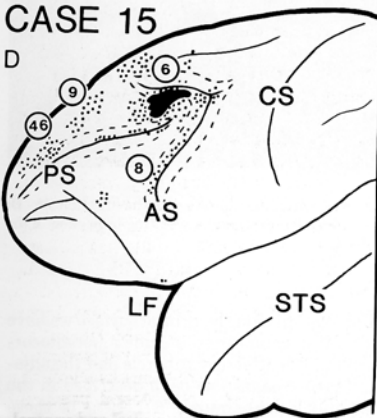


C



CASE 15

D



CASE 16

E

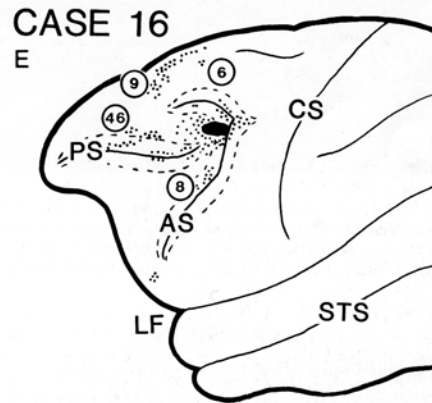


Fig. 12. Diagrams showing the distribution of labeled grains after isotope injection in area 8 in three cases. In case 14 label is shown on the medial (A) and lateral (B) surface, and on a map where the sulci were unfolded (C), and on the lateral surface in cases 15 (D) and 16 (E).

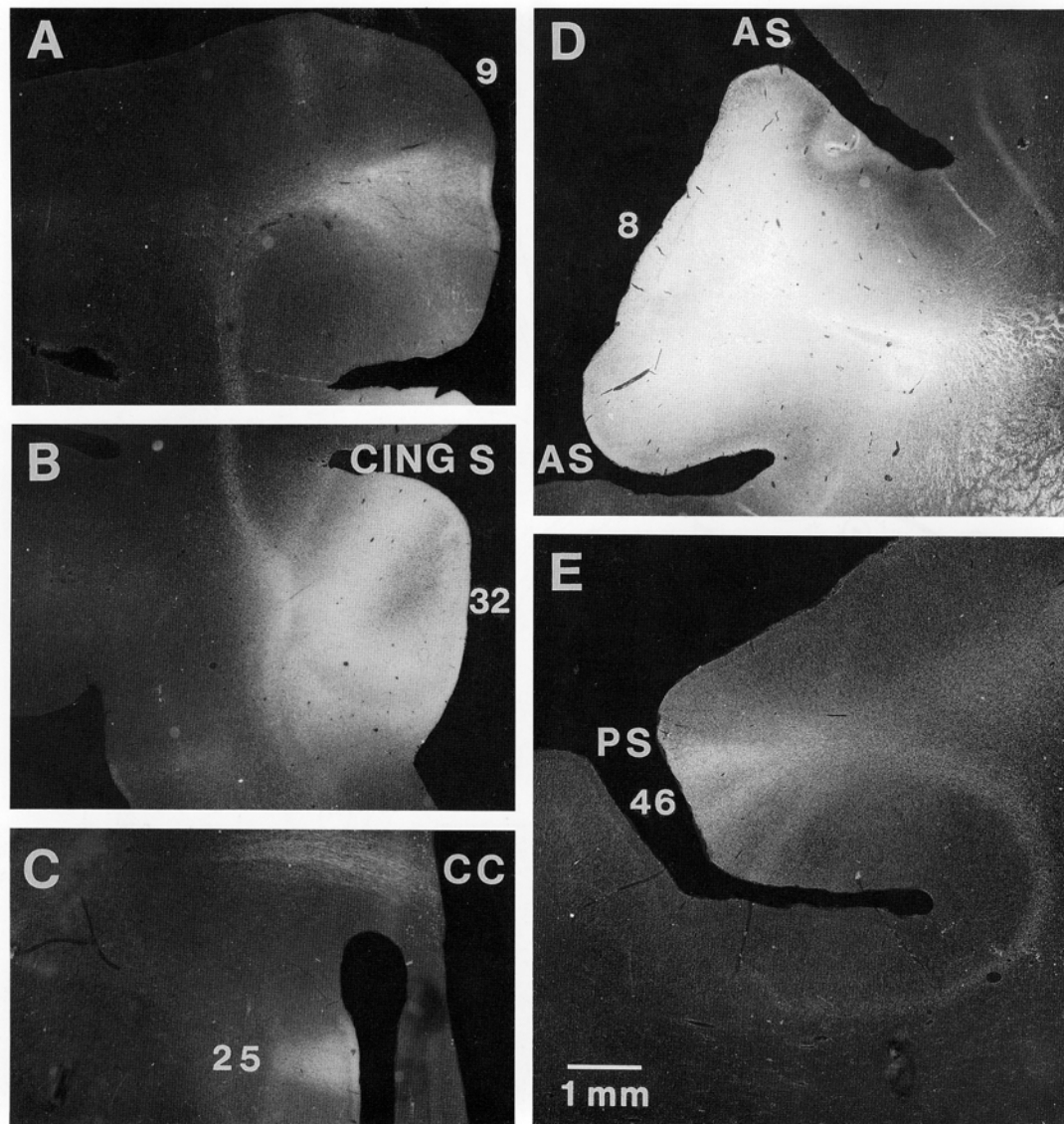


Fig. 13. Darkfield photomicrographs showing the distribution of labeled grains in area 9 (A) and in area 25 (C) after isotope injection in area 32 in case 8 (B). In this case A is an example of a projection to a more-differentiated area and C represents a projection to a region which

is at approximately the same architectonic stage as the injection site. D: An isotope injection in area 8 (case 14) and a resulting projection in the adjacent dorsal area 46 (E).

DISCUSSION

The architectonic classification of prefrontal areas that we have described in this study is in general agreement with the parcellation of Walker ('40). In fact, we have adhered to the numerical nomenclature used by Walker. There are, however, some differences between our observations and

those of Walker. For example, on the orbital surface we have extended the parcellation caudally to include a periallocortical (PAll) area around the olfactory tubercle and the adjacent proisocortical (Pro) area, as has been described in the slow loris (Sanides and Krishnamurti, '67). Both of these areas are situated caudal to area 13. In addition, there are some other differences on the orbital surface. Area 14 in the

TABLE 2. Distribution of Labeled Grains in the Prefrontal Cortex After Injection of Tritiated Amino Acids in Mediodorsal Prefrontal Areas¹

Label site	Injection site (case no.)								
	32 (8)	32 (9)	D9,*46 (10)	D10,V10 (11)	D46,*9 (12)	D46,*V46 (13)	D8 (14)	D8 (15)	D8 (16)
Basoventral									
Pro	+	+							
13	+	+				+			
O12		+		+		+			
O14	++	++		+		+			
11				+		+			
V10		+	+	+	+	+			
L12			+	+			+	+	+
V46						+			
V8							+	+	+
V6									
Mediodorsal									
25	++	++							
32			++	+	+				
24	+	+	++	++	+	+			
M14				++					
M9	++	+	+	++	+	+	+		
L9	++	++	+	++	+	+	+	++	+
D10	++	++	++	++	++	++	++	++	++
D46	+	+	+	++	++	++	++	++	++
D8			++		+	++	++	++	++
D6			++		+	+	++	++	++

¹+, slight involvement by injection; +, light-moderate; ++, moderate-heavy label.

present study extends further rostrally and area 11 is somewhat smaller than in Walker's map. In addition, we observed that area 12 has two distinct divisions: an orbital and a lateral. Area 9 extends to the border of area 6 in our map and includes a region which Walker termed 8B. Like area 12, area 9 can be subdivided into a medial and a lateral sector. We have considered the cortex in the rostral bank of the upper and lower limbs of the arcuate sulcus and the adjacent rostral cortex as area 8, in agreement with the map of Brodmann ('05). Walker divided this region into a dorsal region (area 8) and a ventral region (area 45). We also observed a difference between the dorsal and ventral sectors but we consider these regions as dorsal and ventral area 8 because of their basic similarity. On the medial surface Walker designated a region rostral to 24 as area 25. This area has been termed area 32 by Brodmann ('05), Pandya et al. ('81), and Vogt et al. ('87). Like these investigators, we also consider area 32 as a distinct region situated in front of area 24. In agreement with Vogt et al. ('87), area 25 occupies a position below the rostrum of the corpus callosum. Finally, according to our observations, area 14 extends to the medial surface where it is situated between area 25 and medial area 10.

Whereas Walker's as well as others' architectonic classifications were based on pure morphologic criteria, our analysis was guided by the hypothesis that the prefrontal cortex can be viewed as a series of areas showing gradual architectonic changes within two major cortical trends. A basoventral trend may be traced from a periallocortical area on the orbital surface, as may a mediodorsal trend from a periallocortical area on the medial cortex. These regions have an incipient laminar organization. Neighboring regions exhibit a gradual increase in laminar differentiation, spreading radially first to proisocortical, and then to isocortical areas.

Increasing architectonic differentiation is characterized by the organization of cells within cortical layers, giving a laminated appearance in progressively more differentiated areas. In the prefrontal cortex we observed a change in several architectonic features in a direction from the limbic periallocortices to isocortices in the Nissl preparation. For

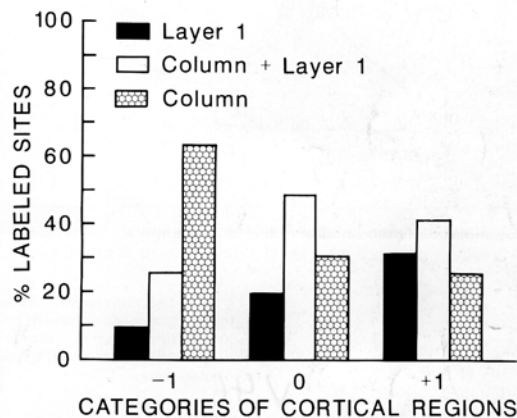


Fig. 14. Histogram showing the incidence of each of three laminar patterns of termination of projections into three cortical categories. Category -1 represents all terminations in cortices with fewer delineated laminae than the areas giving rise to the projections; 0 represents all terminations in areas whose laminar differentiation was at approximately the same stage as that of the sites of origin; +1 represents all terminations in cortices that had more delineated laminae than the regions of origin of the projections. The three bars in each cortical category add up to 100%.

example, the deep layers (V and VI) gradually lose their prominence, and the upper layers increase their cell density in a direction from the periallocortices to isocortices. Another changing feature involves layer IV, which is absent in the periallocortices and proisocortices and appears to increase gradually and become prominent in isocortical areas. In addition, the pyramidal cells in the deep and upper layers are small in the periallocortices and proisocortices but

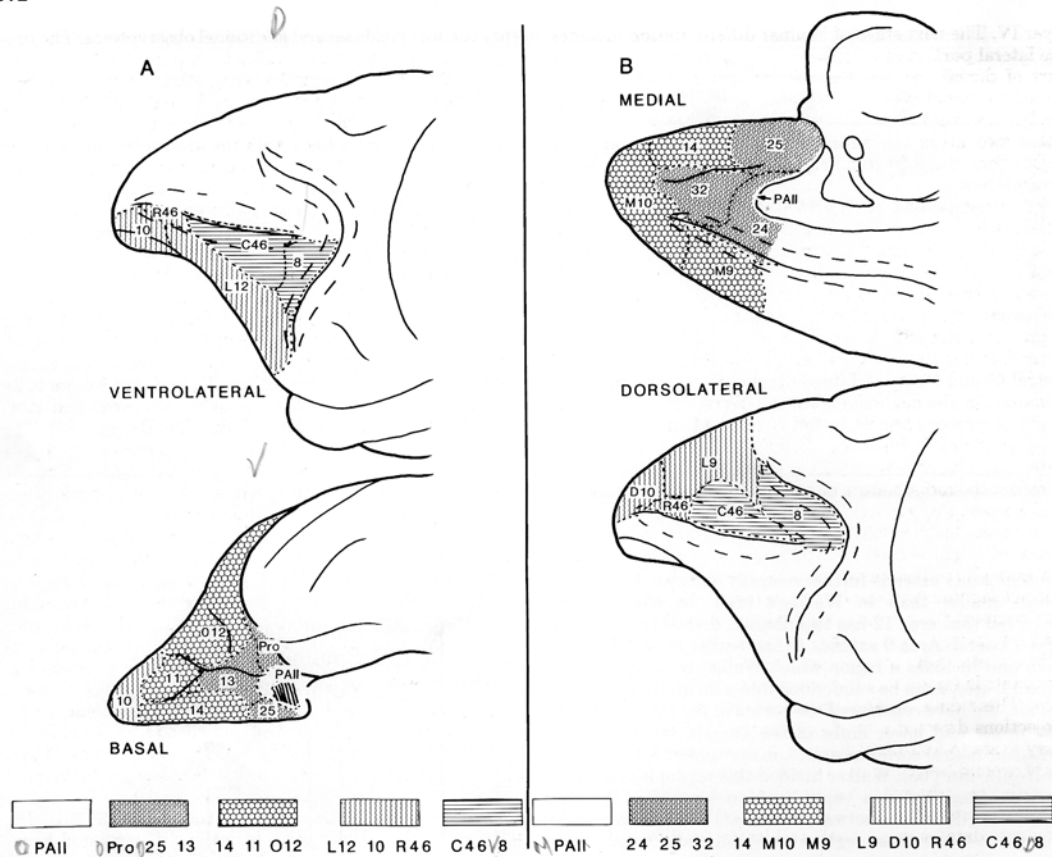


Fig. 15. Diagrams showing the architectonic stages within the basoventral (A) and mediadorsal (B) prefrontal cortices. Within each trend the axis of differentiation proceeds in a direction from the least-differentiated periallocortex (PAII) to area 8, which represents the most-differentiated cortex.

appear larger in layers III and V in areas that have a better laminar differentiation, such as areas 46 and 8. A pattern of gradual architectonic change may be observed also in material stained for myelin. There is a gradual increase in myelination from periallocortices to isocortices. Moreover, according to our observations, regions within the mediadorsal trend generally have a more prominent vertical plexus when compared with basoventral areas. A similar observation was made for the vertical plexus of dorsal and ventral area 6 (Barbas and Pandya, '87).

Because architectonic changes follow a radial pattern, it is difficult to describe cortical differentiation as a continuous line. Adjacent regions, therefore, may have slightly different architectonic features but still may be at approximately the same stage of laminar differentiation (Fig. 15). For example, areas 24, 25, and 32 are considered proisocortical on the basis of their prominent deep layers, although each has a slightly different laminar pattern. Conversely, there are gradual changes within areas considered as architectonic entities. For example, area 46 is considered as one region on

the basis of its overall architectonic features, even though its layers appear more distinct from a rostral to a caudal direction (Figs. 2, 15).

Based on architectonic criteria we observed a gradual radial differentiation within the basoventral and mediadorsal prefrontal regions as shown in Figure 15. The periallocortex in the caudal orbitofrontal region occupies the first stage in the basoventral trend. This cortex is bounded by the proisocortex, the orbital part of area 25 and area 13. The next level of laminar differentiation is observed in the adjacent areas 12, 11, and 14 on the orbital surface. Further laminar differentiation is seen in the adjoining area 10, the lateral portion of area 12, and the rostral part of ventral area 46. Caudal area 46 and ventral area 8 constitute the final stage in laminar differentiation in the basoventral trend.

The mediadorsal trend proceeds from the periallocortex, which surrounds the genu of the corpus callosum, to the proisocortical areas 24, 25, and 32. The progression of laminar differentiation proceeds to the isocortical areas 14, medial 9, and medial 10 rostrally characterized by an emerging

layer IV. The next stage of laminar differentiation includes the lateral portion of area 9, dorsal area 10, and the rostral part of dorsal area 46. Further laminar differentiation is traced to caudal area 46 and dorsal area 8, which make up the last architectonic stage in the mediodorsal trend. In the latter two areas the supragranular cell density appears higher than the infragranular, as was observed in the basoventral trend.

The progressive architectonic differentiation of prefrontal areas is reflected in their intrinsic connections. A given area projects in two directions: to more differentiated regions on the one hand and to less-differentiated regions on the other. In each direction more than one region is involved in this projection system. For example, orbital area 12 (case 4) projects to its architectonic precursors (orbital preoccipital cortex and area 13), on one hand, and to area 11, lateral area 12, rostral area 46 and 10, its architectonic successors, on the other. Likewise, in the mediodorsal trend rostral area 46 projects to the precursor areas 24, 9, and 10 on one hand and to caudal area 46 and 8, which are its architectonic successors, on the other. Thus the multiple connections of each area seem to reflect the radial nature of architectonic differentiation.

Moreover, the laminar pattern of termination of connections seems to be related to the architectonic stage of the cortex of origin and its relation to the site of termination. For example, projections directed to cortices that have a less distinct laminar organization than the site of origin terminate primarily in columns and to a lesser extent in layer I. In contrast, projections directed to cortices that have a more differentiated laminar organization than the site of origin terminate in layer I and to a lesser extent in a columnar pattern. These data parallel previous reports indicating that projections directed away from the well-differentiated primary areas to less-differentiated cortices terminate in columns around layers III and IV, whereas projections directed towards the primary areas terminate primarily in layer I (Rockland and Pandya, '79; Wong-Riley, '79). These and previous data suggest that architectonic differentiation seems to underlie the laminar pattern of corticocortical connections (Barbas, '86).

The intrinsic connections of the prefrontal cortex have several other consistent features. For example, the most-differentiated areas have restricted connections, whereas the least-differentiated areas have widespread intrinsic connections. Thus, the connections of area 8, which is highly differentiated, are largely confined to a few neighboring regions on the lateral surface of the hemisphere (Tables 1 and 2, cases 7 and 14-16). On the other hand, both orbital and medial preoccipital cortices have extensive connections which span the orbital, medial, and lateral surfaces of the hemisphere (cases 1, 8, 9). These data thus suggest that a low degree of laminar differentiation is associated with widespread connectivity, whereas a high degree of architectonic differentiation is associated with restricted connectivity. The widespread connections of the preoccipital cortices are not randomly distributed. They rather seem to respect the observed architectonic progression, projecting to several successive architectonic stages. Although most connections are limited between areas within one architectonic trend, there are some interconnections between the trends, linking areas that are at a similar architectonic stage. For example, there are connections between the orbital and medial preoccipital cortices, or area 12 and area 9, or dorsal and ventral area 8.

A comparison of the intrinsic connections of the prefrontal cortex and its long connections with post-Rolandic sen-

sory cortices yields several additional observations. The prefrontal cortex has been considered a polymodal region on the basis of its physiologic characteristics and anatomic connections (Benevento et al., '77; see Rosenkilde, '79; Fuster, '80, for reviews). However, recent anatomic analyses indicate that there are areas within the prefrontal cortex which seem to be targets of projections from one unimodal sensory area. For example, the caudal portion of area 8 and ventral area 46 seem to be targets of the visual modality (Jones and Powell, '70; Chavis and Pandya, '76; Barbas and Mesulam, '81, '85; Barbas, '88). The lateral portion of area 10, a mid-dorsal portion of area 46, area 9, dorsal area 8, medial area 32, and area 14 seem to be targets of the auditory modality (Jones and Powell, '70; Chavis and Pandya, '76; Barbas and Mesulam, '85; Petrides and Pandya, '88; Barbas, '88). In addition, regions above, below, and within the central extent of the principal sulcus, rostral area 12, and area 9 seem to be targets of the somatosensory modality (Petrides and Pandya, '84; Preuss and Goldman-Rakic, '85; Barbas, '88). The present data suggest that prefrontal areas which are the targets of one sensory modality are interconnected. Thus, the lateral portion of area 10 receives substantial projections from auditory cortices (Barbas and Mesulam, '85). Within the prefrontal cortex this portion of area 10 projects to a mid-dorsal portion of area 46, area 9, lateral area 12, and medial area 14 (case 11, Fig. 10), all of which are targets of auditory cortices. Similarly, ventral area 8 receives input from visual cortices and projects to the caudal portion of ventral area 46 (case 7), which is also a visual recipient region. It should be noted, however, that these modality-related interconnections seem to extend mainly between areas which are close in terms of their architectonic differentiation. For example, area 13, which receives visual input, is connected with neighboring visual recipient areas 12 and 11 but is not connected with the more-differentiated ventral area 46 or 8, which are also targets of visual cortices.

The question arises as to whether there is a functional distinction between the morphologically differentiated basoventral and mediodorsal trends of the prefrontal cortex. An examination of the long cortical connections of basoventral and mediodorsal prefrontal regions indicates that their sources of origin differ. For example, basoventral prefrontal areas receive projections from ventral visual, premotor, somatosensory, and auditory cortices (Jones and Powell, '70; Chavis and Pandya, '76; Preuss and Goldman-Rakic, '85; Barbas, '88). On the other hand, mediodorsal prefrontal areas receive projections from dorsal visual, dorsolateral and medial parietal and premotor, and from auditory cortices. Within the visual cortical system, a functional dichotomy has been described: Ventral visual areas have been implicated in pattern recognition and discrimination, whereas dorsal areas have been associated with spatial functions (Ungerleider and Mishkin, '82; Mishkin et al., '83). Ventral and dorsal somatosensory and premotor cortices are functionally distinct as well. For example, within the motor system, ventral areas contain the representation of the head, neck, and face (Woolsey et al., '51; Sessle and Wiesendanger, '82) and may be associated with orientation to sensory stimuli. On the other hand, the dorsal premotor area, which contains a representation of the trunk and lower limbs, may be associated with postural mechanisms. This suggests that the basoventral and mediodorsal prefrontal cortices, which are connected with functionally distinct sensory areas, may have different roles also. A functional dichotomy may exist for the prefrontally directed projections from auditory cortices as well. By analogy with prefrontally directed projec-

tions from visual cortices, input from auditory areas directed to basoventral prefrontal areas may have a role in auditory discrimination, and projections directed to mediodorsal areas may be involved in processes associated with localization of sound (Leinonen et al., '80; Hyvärinen, '82a,b).

In addition to the overall connectional differences between basoventral and mediodorsal prefrontal regions, there are also differences among subdivisions of each cortical trend and their distant cortical connections. Thus, the least-differentiated areas of both trends have the strongest links with limbic cortices, whereas the most-differentiated areas have few, if any, connections with the limbic system. In addition, the least architectonically differentiated areas of the prefrontal cortex are connected with the least-differentiated sensory cortices. For example, some of the least-architectonically differentiated orbital areas are connected with rostral superior and inferior temporal cortices, which occupy a similar position within the axis of progressive differentiation of the auditory and visual cortical systems (Chavis and Pandya, '76; Galaburda and Pandya, '83; Rosene and Pandya, '83; Barbas, '88; Petrides and Pandya, '88). Similarly, regions around the principal sulcus, which are more architectonically differentiated than orbital areas, receive projections from more caudal and similarly better-differentiated superior and inferior temporal cortices. This pattern is observed for projections directed to the prefrontal cortex from somatosensory areas as well (Jones and Powell, '70; Chavis and Pandya, '76; Petrides and Pandya, '84). Thus for each of the sensory systems there is a series of cortices exhibiting a gradual laminar differentiation, and these architectonic stages maintain connections with a series of prefrontal cortices which are at approximately the same stage of architectonic differentiation.

On the basis of behavioral studies, different functional attributes have been ascribed to orbital, ventrolateral, and periarculate prefrontal regions (see Rosenkilde, '79; Fuster, '80, for reviews). In view of the gradual architectonic differentiation described in this study, it is suggested that the differences in function among regions within one prefrontal trend may be related to their architectonic stage. Each of these architectonic stages thus may use sensory information differently. The periallocortices and proisocortices, which have strong connections with the limbic system, may be involved in functions associated with the internal state of the organism. On the other hand, the most-differentiated areas, which are not directly connected with the limbic system to a great extent, may be involved in complex discriminative and spatial functions which depend on projections from specific sensory cortices.

ACKNOWLEDGMENTS

We thank Mr. Brian Butler, Ms. Michelle Richmond, and Mr. Michael Shorr for excellent technical assistance. This work was supported by NIH grant NS24760, NSF grant BNS 8315411 (H.B.), the E.N.R.M. Veterans Administration Hospital, Bedford, MA, and NIH grant 16841 (D.N.P.).

LITERATURE CITED

- 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., and M.-M. Mesulam (1981) Organization of afferent input to subdivisions of area 8 in the rhesus monkey. *J. Comp. Neurol.* 200:407-431.
- Barbas, H., and M.-M. Mesulam (1985) Cortical afferent input to the principal region of the rhesus monkey. *Neuroscience* 15:619-637.
- Barbas, H., and D.N. Pandya (1987) Architecture and frontal cortical connections of the premotor cortex (area 6) in the rhesus monkey. *J. Comp. Neurol.* 256:211-228.
- Benevento, L.A., J. Fallon, B.J. Davis, and M. Rezak (1977) Auditory-visual interaction in single cells in the cortex of the superior temporal sulcus and the orbital frontal cortex of the macaque monkey. *Exp. Neurol.* 57:849-872.
- Brodman, K. (1905) Beiträge zur histologischen Localisation der Grosshirnrinde. III. Mitteilung: Die Rindenfelder der niederen Affen. *J. Psychol. Neurol.* 4:177-266.
- Chavis, D.A., and D.N. Pandya (1976) Further observations on corticofrontal connections in the rhesus monkey. *Brain Res.* 117:369-386.
- Cowan, W.M., D.I. Gottlieb, A.E. Hendrickson, J.L. Price, and T.A. Woolsey (1972) The autoradiographic demonstration of axonal connections in the central nervous system. *Brain Res.* 37:21-51.
- Fuster, J.M. (1980) *The Prefrontal Cortex*. New York: Raven Press.
- Galaburda, A.M., and D.N. Pandya (1983) The intrinsic, architectonic and connectional organization of the superior temporal region of the rhesus monkey. *J. Comp. Neurol.* 221:169-184.
- Gallyas, F. (1979) Silver staining of myelin by means of physical development. *Neurol. Res.* 1:203-209.
- Hyvärinen, J. (1982a) Posterior parietal lobe of the primate brain. *Physiol. Rev.* 62:1060-1129.
- Hyvärinen, J. (1982b) *The Parietal Cortex of Monkey and Man*. New York: Springer-Verlag.
- Jacobson, S., and J.Q. Trojanowski (1977) Prefrontal granular cortex of the rhesus monkey. I. Intrahemispheric cortical afferents. *Brain Res.* 132:209-233.
- Jones, E.G., and T.P.S. Powell (1970) An anatomical study of converging sensory pathways within the cerebral cortex of the monkey. *Brain* 93:793-820.
- Leinonen, L., J. Hyvärinen, and A.R.A. Sovijärvi (1980) Receptive field properties of neurons in the temporo-parietal association cortex of awake monkey. *Exp. Brain Res.* 29:203-215.
- Mesulam, M.-M., E. Hegarty, H. Barbas, K.A. Carson, E.C. Gower, A.G. Knapp, M.B. Moss, and E.J. Mufson (1980) Additional factors influencing sensitivity in the tetramethyl benzidine method for HRP neurohistochemistry. *J. Histochem. Cytochem.* 28:1255-1259.
- Mishkin, M., L.G. Ungerleider, and K.A. Macko (1983) Object vision and spatial vision: Two cortical pathways. *Trends Neurosci.* 6:414-417.
- Pandya, D.N., B. Seltzer, and H. Barbas (1988) Input-output organization of the primate cerebral cortex in the rhesus monkey. In H.D. Steklis and J. Erwin (eds): *Comparative Primate Biology*, Vol. 4: Neurosciences. New York: Alan R. Liss, Inc., pp. 39-80.
- Pandya, D.N., G.W. Van Hoesen, and M.-M. Mesulam (1981) Efferent connections of the cingulate gyrus in the rhesus monkey. *Exp. Brain Res.* 42:319-330.
- Petrides, M., and D.N. Pandya (1984) Projections to the frontal cortex from the posterior parietal region in the rhesus monkey. *J. Comp. Neurol.* 228:105-116.
- Petrides, M., and D.N. Pandya (1988) Association fiber pathways to the frontal cortex from the superior temporal region in the rhesus monkey. *J. Comp. Neurol.* 273:52-66.
- Preuss, T.M., and P.S. Goldman-Rakic (1985) Somatosensory representation in primate prefrontal cortex: Connections of the principal sulcus with S-I, S-II, and adjacent areas of the frontoparietal operculum. *Neurosci. Abstr.* 11:677.
- Rockland, K.S., and D.N. Pandya (1979) Laminar origins and terminations of cortical connections of the occipital lobe in the rhesus monkey. *Brain Res.* 179:3-20.
- Rosene, D.L., and M.-M. Mesulam (1978) Fixation variables in horseradish peroxidase neurohistochemistry. I. The effects of fixation time and perfusion procedures upon enzyme activity. *J. Histochem. Cytochem.* 26:28-39.
- Rosene, D.L., and D.N. Pandya (1983) Architectonics and connections of the posterior parahippocampal gyrus in the rhesus monkey. *Neurosci. Abstr.* 9:222.
- Rosenkilde, C.E. (1979) Functional heterogeneity of the prefrontal cortex in the monkey: A review. *Behav. Neural Biol.* 25:301-345.
- Sanides, F., and A. Krishnamurti (1967) Cytoarchitectonic subdivisions of

- sensorimotor and prefrontal regions and of bordering insular and limbic fields in slow loris (*Nycticebus coucang*). *J. Hirnforsch.* 9:225-252.
- Seltzer, B., and D.N. Pandya (1978) Afferent cortical connections and architectonics of the superior temporal sulcus and surrounding cortex in the rhesus monkey. *Brain Res.* 149:1-24.
- Sessle, B.J., and M. Wiesendanger (1982) Structural and functional definition of the motor cortex in the monkey (*Macaca fascicularis*). *J. Physiol. (Lond.)* 323:245-265.
- Ungerleider, L.G., and M. Mishkin (1982) Two cortical visual systems. In D.J. Ingle, M.A. Goodale, and R.J.W. Mansfield (eds): *Analysis of Visual Behavior*. Cambridge, MA: MIT Press, pp. 549-586.
- Vogt, B.A., D.N. Pandya, and D.L. Rosene (1987) Cingulate cortex of the rhesus monkey: I. Cytoarchitecture and thalamic afferents. *J. Comp. Neurol.* 262:256-270.
- Vogt, C., and O. Vogt (1919) Allgemeine Ergebnisse unserer Hirnforschung. *J. Psychol. Neurol.* 25:279-462.
- Von Bonin, G., and P. Bailey (1947) *The Neocortex of Macaca Mulatta*. Urbana: The University of Illinois Press.
- Walker, E. (1940) A cytoarchitectural study of the prefrontal area of the macaque monkey. *J. Comp. Neurol.* 98:59-86.
- Wong-Riley, M. (1979) Columnar cortico-cortical interconnections within the visual system of the squirrel and macaque monkeys. *Brain Res.* 162:201-217.
- Woolsey, C.N., P.H. Settlage, D.R. Meyer, W. Spencer, T. Pinto, T. Hamuy, and A.M. Travis (1951) Patterns of localization in precentral and "supplementary" motor areas and their relation to the concept of a premotor area. *Res. Publ. Assoc. Nerv. Ment. Dis.* 30:238-264.