ORIGINAL PAPER

E. H. Yeterian · D. N. Pandya

Laminar origin of striatal and thalamic projections of the prefrontal cortex in rhesus monkeys

Abstract Prefrontostriatal and prefrontothalamic connections in rhesus monkeys have been shown to be organized in a topographic manner. These projections originate largely from infragranular layers V and VI. To examine whether the striatal and thalamic connections from the prefrontal cortex arise from separate neuronal populations or are collateralized, two different fluorescent retrograde tracers (diamidino yellow and fast blue) were injected into topographically similar regions of the head of the caudate nucleus and the mediodorsal nucleus in the same animal. The results show that although prefrontostriatal and prefrontothalamic projections arise from similar topographic regions, their laminar origins are distinctive. The connections to the head of the caudate nucleus originate mainly from layer Va, to a lesser extent from layer Vb, with a minor contribution from layers III and VI. In contrast, the projections to the mediodorsal nucleus emanate largely from layer VI, and also from layer Vb. Only occasional double-labeled neurons were observed, indicating that prefrontostriatal and prefrontothalamic connections originate from separate neuronal populations. The differential laminar distributions of neurons projecting to the head of the caudate nucleus and the mediodorsal nucleus suggest that these structures may receive independent types of information from the prefrontal cortex.

E. H. Yeterian (✉)
Department of Psychology, Colby College, Waterville,
ME 04901, USA

E. H. Yeterian · D. N. Pandya
Edith Nourse Rogers Memorial Veterans Hospital,
200 Springs Road, Bedford, MA 01730, USA

D. N. Pandya
Departments of Anatomy and Neurology, Boston University
School of Medicine, Boston, MA 02118, USA

D. N. Pandya
Harvard Neurological Unit, Beth Israel Hospital, Boston,
MA 02215, USA

Introduction

It is well known that the prefrontal cortex in the rhesus monkey projects to both the striatum, in particular the head of the caudate nucleus (HCN), and the mediodorsal (MD) nucleus of the thalamus. The cells of origin of these connections have been reported to be located predominantly in infragranular cortical layers. According to Arikuni and Kubota (1986) corticostriatal projection neurons are located in layers II-VI, with layer V containing the greatest concentration of cells. Saint-Cyr et al. (1990) have reported that corticostriatal projections stem mainly from layer V, and to a lesser extent from layers III and VI. With respect to corticothalamic projections, it has been reported that the cells of origin are located predominantly in layer VI and to a lesser extent in layer V (Arikuni et al. 1983; Jones 1985; Russchen et al. 1987; Giguere and Goldman-Rakic 1988; Siwek and Pandya 1992). Recently, it has been shown that specific architectonic regions of the prefrontal cortex in the rhesus monkey project to topographically similar portions of the HCN and of the MD nucleus (Russchen et al. 1987; Giguere and Goldman-Rakic 1988; Siwek and Pandya 1991; Yeterian and Pandya 1991). For example, medial and orbital prefrontal areas project to the medial sector of both nuclei, whereas caudal and lateral prefrontal regions tend to project more laterally. In view of the fact that both corticostriatal and corticothalamic projections originate largely from infragranular layers, it is of interest to know the precise laminar and topographic relationships of these two cortical efferent cell populations in greater detail.

The laminar origins of prefrontal projections to the HCN and the MD nucleus in monkeys have been investigated separately for these two subcortical structures. The availability of multiple fluorescent retrograde tracers (FRTs) allows for the simultaneous visualization of

corticostriatal and corticothalamic cells of origin in a single animal, which permits an examination of the precise nature of their laminar organization. Specific issues that can be addressed with multiple tracers include whether the cells of origin of corticostriatal and corticothalamic projections are organized in an overlapping or interdigitating manner, and whether these projections originate from common neurons, i.e., are collateralized. To our knowledge, no study has examined these issues with regard to the HCN and the MD nucleus in primates.

Recent formulations of connectivity within the primate brain have emphasized the existence of parallel distributed circuitry originating in specific cortical regions, and involving corticocortical as well as cortico-subcortical systems (Alexander et al. 1986; Selemon and Goldman-Rakic 1988; Alexander and Crutcher 1990; Cavada and Goldman-Rakic 1991; Yeterian and Pandya 1991). The existence of collateral pathways from specific prefrontal regions to the striatum and the thalamus might allow for the parallel activation of these nuclei. Our findings provide information on the topographic distribution as well as the laminar organization of cells of origin of prefrontal projections to topographically similar portions of the head of the caudate and the mediodorsal nuclei using FRTs.

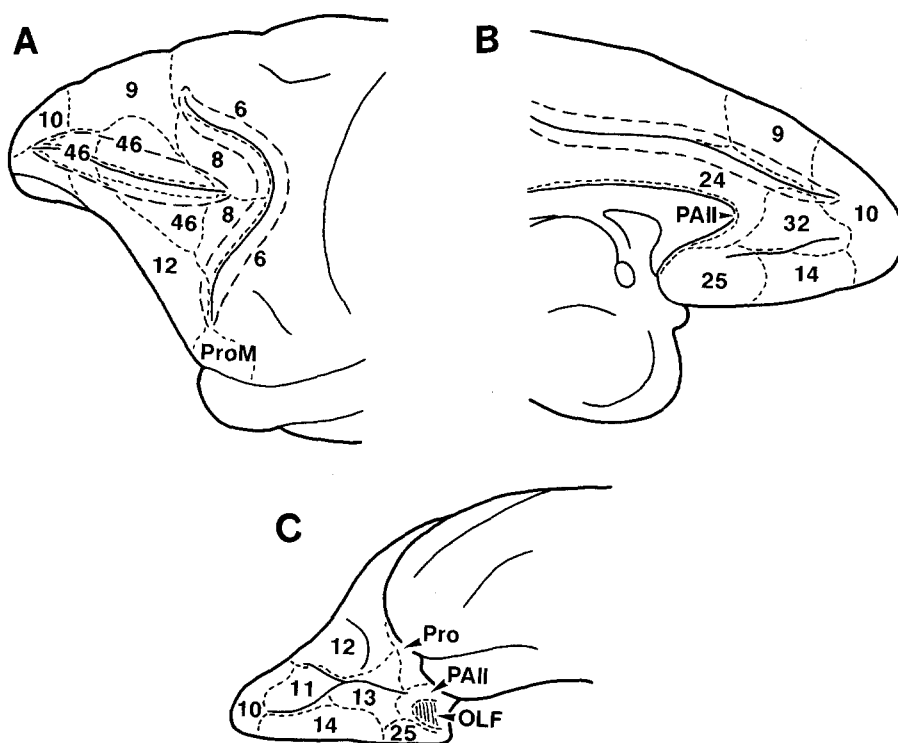A preliminary report of these data has been presented (Yeterian and Pandya 1992).

Fig. 1 *Upper diagrams* show the architectonic subdivisions of the lateral (**A**), medial (**B**), and orbital (**C**) prefrontal regions of the rhesus monkey according to Barbas and Pandya (1989). *Lower diagrams* depict the architectonic subdivisions of the prefrontal cortex of the rhesus monkey according to Walker (1940) (*ProM* promotor cortex, *PAll* periallocortex, *Pro* proisocortex, *OLF* olfactory cortex)
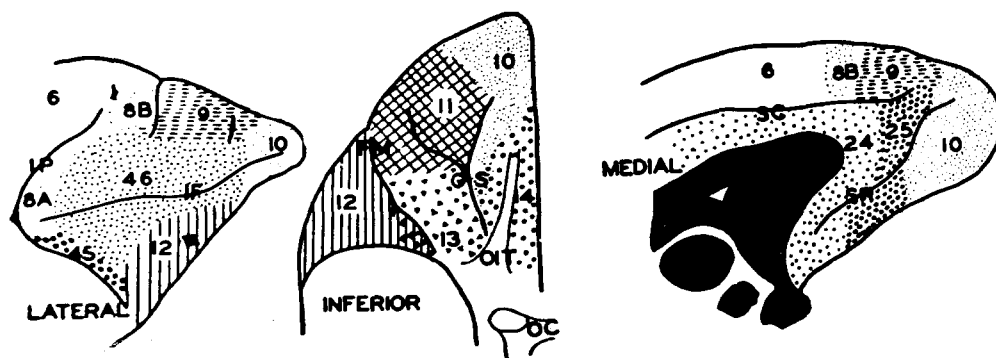
Materials and methods

Surgical procedures

Under pentobarbital sodium anesthesia, a midline craniotomy was performed in three rhesus monkeys. The interhemispheric space was exposed following a paramedian dural flap and by coagulating the bridging veins. Each animal received 50–100 ml of 25% mannitol intravenously during the surgery, which facilitated shrinkage of the cerebral hemispheres and thereby permitted the visualization of midline structures. The rostral half of the corpus callosum was sectioned slightly lateral to the midline, using micropipette suctioning, to allow entry into the third ventricle. Visualization of the head of the caudate nucleus as well as the mediodorsal thalamic nucleus was achieved with the aid of an operating microscope. Each animal received two separate FRT injections under direct visualization, one in the HCN (e.g., fast blue, FB) and another in the MD nucleus (e.g., diamidino yellow, DY). In each intended target area of the HCN and the MD nucleus, two penetrations were made with a Hamilton microsyringe attached to a micromanipulator. Each injection consisted of 0.5 μl of FRT (0.3% dilution). After a postsurgery survival period of 8–10 days, animals received a lethal dose of pentobarbital sodium and were perfused transcardially with 300–400 ml of normal saline followed by 2 l of 4% paraformaldehyde in cacodylate buffer. The brains were removed, photographed, and stored in buffer with graded glycerin solutions (10% for 1 day and 20% for 2 days). Following cryoprotection according to the metod of Rosene et al. (1986), the injected hemisphere was sectioned at 30-μm thickness in the coronal plane. Animal care was provided in accordance with the *NIH Guide for Care and Use of Laboratory Animals*.
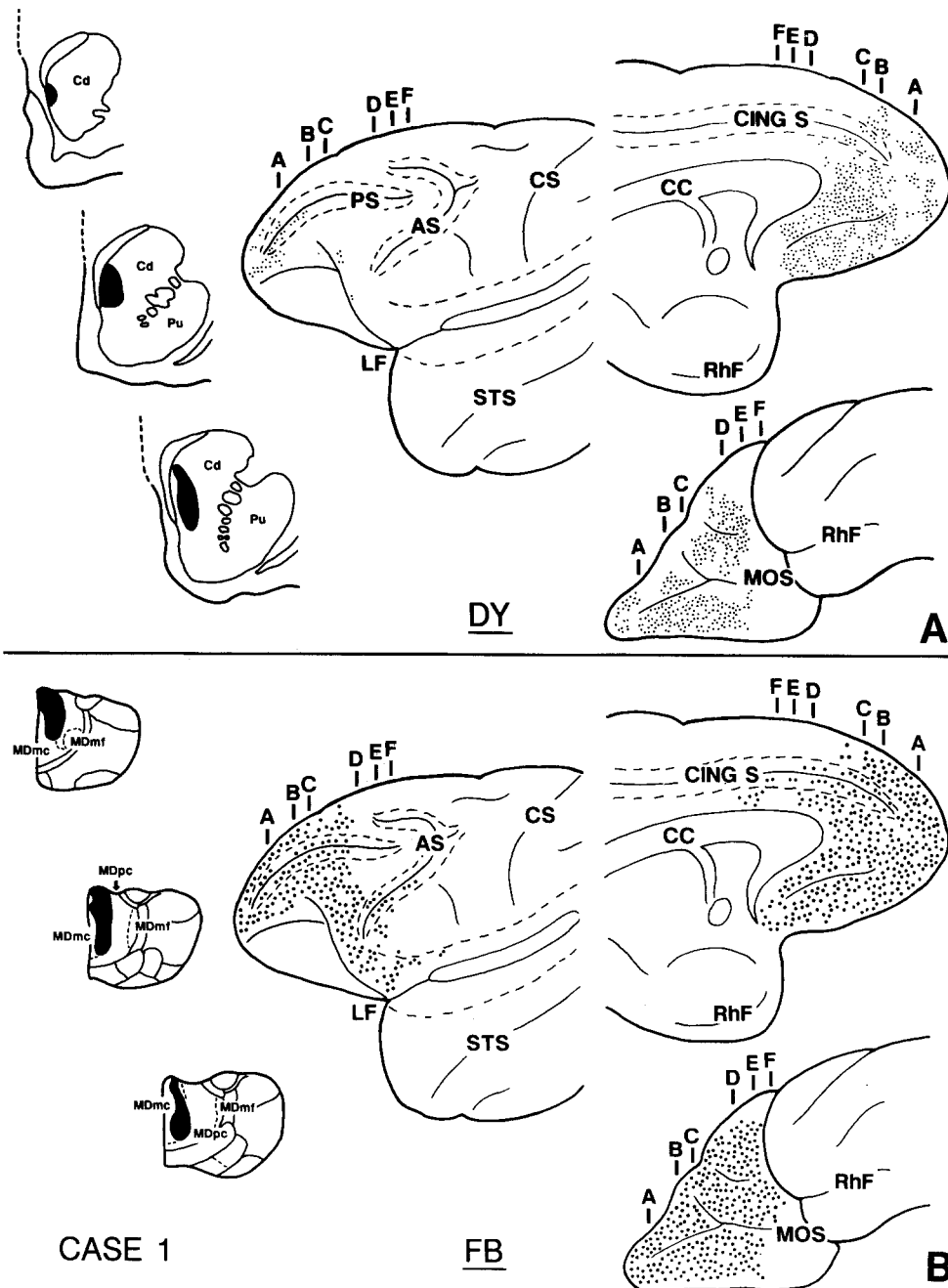

Fig. 2 A Diagrammatic representations of the diamidino yellow (DY) injection site in the ventromedial portion of the head of the caudate nucleus (*Cd*) in case 1 (shown in *black* in three rostral-to-caudal sections, *left*), and the distribution of retrogradely labeled cells (*small dots*) in the lateral, medial, and orbital prefrontal cortices. B Diagrammatic representations of the fast blue (FB) injection site in the medial portion of the mediodorsal nucleus (*MD*) in case 1 (shown in *black* in three rostral-to-caudal sections, *left*), and the distribution of retrogradely labeled cells (*large dots*) in the lateral, medial, and orbital prefrontal cortices. (*AS* arcuate sulcus, *CC* corpus callosum, *CING S* cingulate sulcus, *CS* central sulcus, *LF* lateral fissure, *MDmc* magnocellular division of MD, *MDmf* multiform division of MD, *MDpc* parvocellular division of MD, *MOS* medial orbital sulcus, *PS* principal sulcus, *Pu* putamen, *RhF* rhinal fissure, *STS* superior temporal sulcus)

Data analysis

Representative sections through the prefrontal cortex were examined under fluorescent illumination, and the laminar distribution of labeled neurons was recorded using an X-Y plotter. Subsequently, each charted section was stained with cresyl violet. This allowed the precise determination of the laminar distribution of labeled cells, as well as permitting the delineation of the FRT injection sites in the HCN and the MD nucleus. The architectonic parcellations of prefrontal cortical areas used in this study are those of Walker (1940) and Barbas and Pandya (1989; Fig. 1). Although labeled neurons were observed in each of these cases in the frontal cortex as well as in other parts of the cerebral hemi-

sphere, the present description is focused only on the neuronal distribution in the prefrontal cortex.

Results

In case 1, the DY injection was placed in the HCN, and FB in the MD nucleus. The injection in the HCN was confined to the medial portion of the rostral half of the nucleus (Fig. 2A). The resulting DY-labeled cells were observed predominantly in medial and orbital prefron-
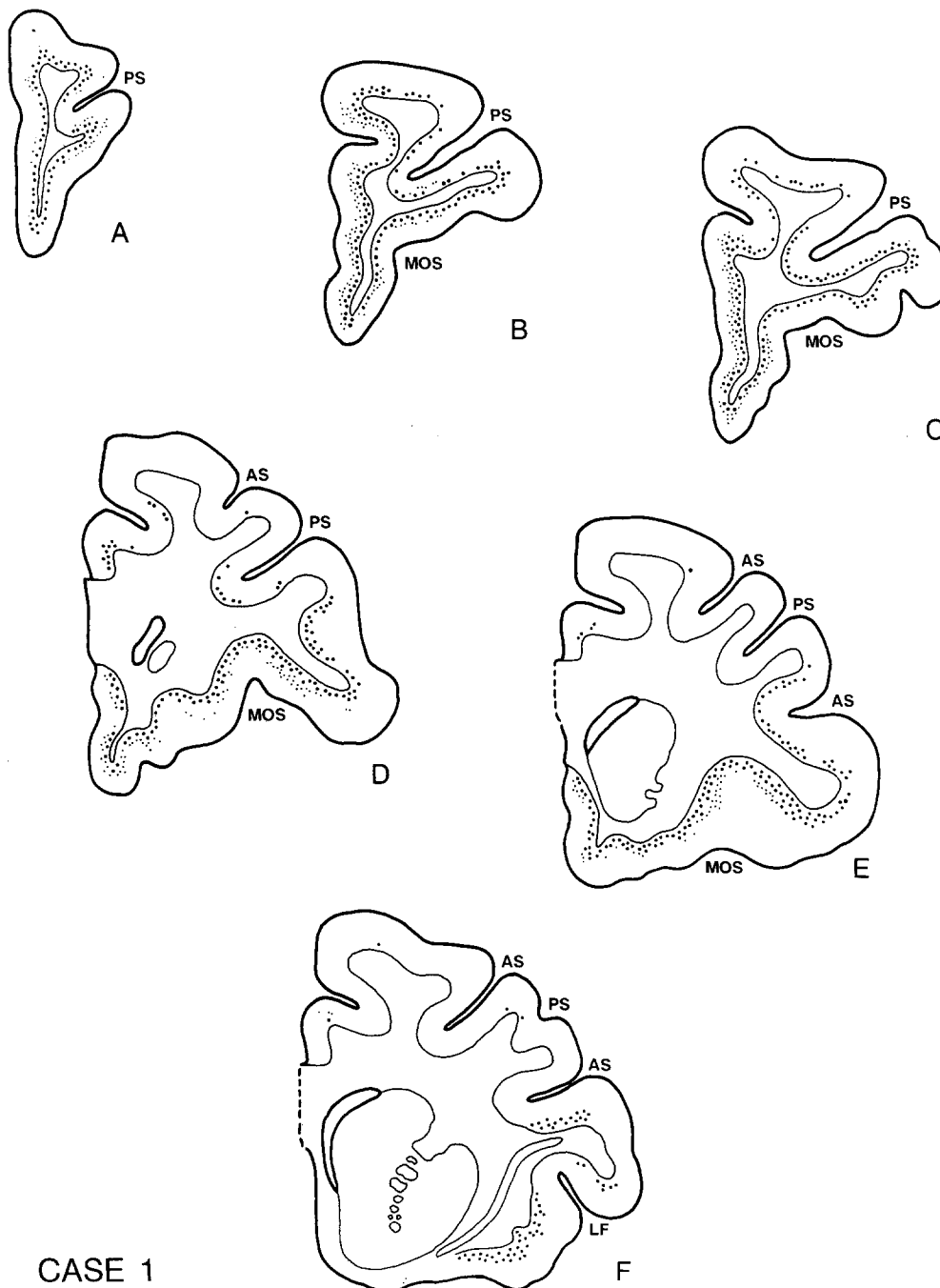

Fig. 3A–F Diagrams of six representative rostral-to-caudal coronal sections (taken from the levels shown in the preceding figure) through the prefrontal cortex depicting the laminar distribution of di-amidino yellow-labeled (corticostriatal, *small dots*) and fast blue-labeled (corticothalamic, *large dots*) cells in case 1. (*PS* principal sulcus, *MOS* medial orbital sulcus, *AS* arcuate sulcus, *LF* lateral fissure)

CASE 1

tal cortices. On the medial surface, labeled neurons occurred in clusters within areas 25, 32, 10, and 14, with a few in area 24. On the orbital surface, neurons were concentrated within areas 10, 11, 12, 13, and 14. Some labeled cells were noted in the rostral part of the lower bank of the principal sulcus (areas 10 and 46) and in adjoining area 10 (Fig. 2A).

The injection in the MD nucleus was located in the medial portion of the rostral half of the structure (Fig. 2B) involving mainly the magnocellular division (MDmc) and extending laterally to the medial border of the parvocellular division (MDpc). The resulting FB-labeled neurons were observed in lateral, medial, and orbital prefrontal regions. On the medial surface, heavy accumulations of labeled cells occurred in almost all architectonic subdivisions, including areas 24, 25, 32, 10, and 14. Likewise, on the orbital surface, neurons were observed in areas 10, 11, 12, 13, 14, and in the orbital proisocortex. Compared with the medial and orbital prefrontal cortices, the distribution of labeled neurons on the lateral surface was relatively less extensive and avoided the caudodorsal sector. These cells were noted in areas 10, 9, 12, and in the rostral part of area 46 (Fig. 2B). In addition, labeled neurons were observed in ventral area 6 and in the gustatory area in the rostral frontal operculum. In certain architectonic subregions, DY- and FB-labeled neurons occurred together. This was noted especially in medial and orbital regions, areas 32, 14, 25, 13, and 12. It should be pointed out that although DY- (corticostriatal) and FB-labeled (corticothalamic) cells were observed in similar architectonic areas, they were not necessarily located in identical parts of a given region.

In regard to the laminar distribution in case 1, the DY-labeled (corticostriatal) neurons occurred predominantly in layer Va and to a lesser extent in layer Vb. Occasional DY-labeled neurons were noted in layer VI and in supragranular layers (mainly in layer III). The FB-labeled (corticothalamic) neurons, in contrast, were found primarily in layer VI, with some also noted in layer Vb. Only a few neurons were noted in layer Va (Figs. 3, 4, 11A, B). In certain subregions, the corticostriatal and corticothalamic projection neurons occurred together in adjacent sectors of layers V and VI, notably in medial and orbital prefrontal cortices (see Fig. 3B–E). Figure 4 depicts the differential laminar pattern of DY- and FB-labeled cells in area 32 in this case and shows the presence of some overlap in the distribution of DY- and FB-labeled cells in layer Vb. Despite the comingling of corticostriatal and corticothalamic projection neurons in infragranular layers, only occasional double-labeled neurons were observed.

In case 2, the FRT injections were reversed, i.e., FB was placed in the HCN and DY in the MD nucleus. The HCN injection was located somewhat more caudally and dorsally than that of the preceding case, with the bulk of the injectate located in the central portion of the nucleus (Fig. 5A). The resulting FB-labeled neurons occurred in distinct clusters in lateral, medial, and orbital prefrontal regions. On the lateral surface, the main bulk of labeled cells was located in the rostral prefrontal cortex, involving area 10, and in both banks of the principal sulcus, area 46. A few labeled neurons were located in areas 9, 12, and 8, and in the gustatory region of the rostral frontal operculum. On the medial surface, labeled cells were observed in areas 24, 25, 32, 10, and 14,
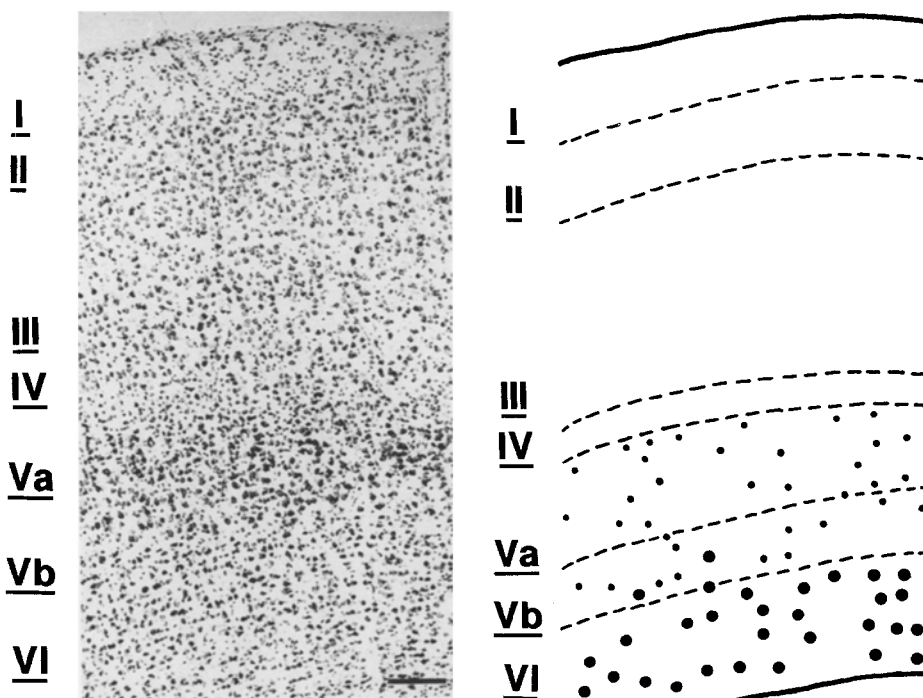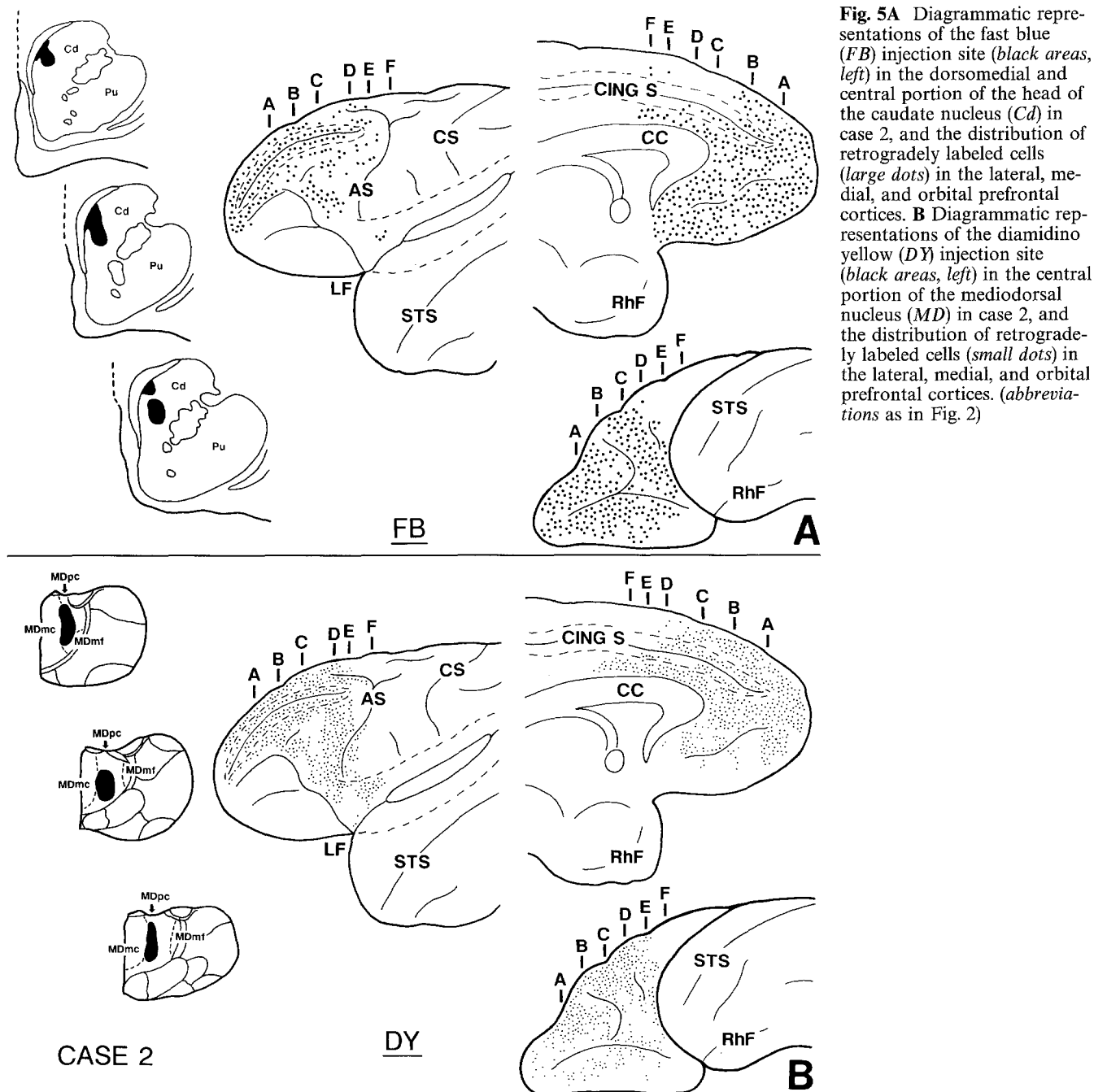

Fig. 4 On the *left* is a photomicrograph of a Nissl-stained section from area 32 in case 1. On the *right* is a diagrammatic representation of the cortical laminae in the same area depicting the distribution of diamidino yellow-labeled (corticostriatal, *small dots*) and fast blue-labeled (corticothalamic, *large dots*) neurons. *Scale bar* 150 μm

and those on the orbital surface, in areas 10, 11, 12, 13, 14, and in the orbital proisocortex.

The injection in the MD nucleus also was more caudal and lateral than in the preceding case, involving mainly the MDpc, but also encroaching to a small extent on the MDmc. The resulting DY-labeled cells were observed in the central portion of the dorsolateral surface of the prefrontal cortex, avoiding the extreme rostral and caudal sectors. A substantial number of labeled neurons were noted in area 9, in area 46 including both banks of the principal sulcus, in area 12, and in the gustatory region of the frontal operculum. Only a few

labeled cells were seen rostrally in area 10, caudally in area 8, as well as in ventral area 6. On the medial surface, the distribution of labeled neurons involved mainly areas 24, 32, 9, and 10. In contrast to case 1, there were a limited number of cells in areas 25 and 14. On the orbital surface, the bulk of labeled neurons was found in lateral area 10, area 12, and to a lesser extent in areas 13, 14, and in the orbital proisocortex (Fig. 5B).

With respect to laminar distribution in case 2, the FB-labeled (corticostriatal) neurons were located mainly in layer Va, with some in layer Vb. Occasional neurons were noted in layer VI and in layer III. DY-labeled

Fig. 5A Diagrammatic representations of the fast blue (FB) injection site (black areas, left) in the dorsomedial and central portion of the head of the caudate nucleus (Cd) in case 2, and the distribution of retrogradely labeled cells (large dots) in the lateral, medial, and orbital prefrontal cortices. B Diagrammatic representations of the diamidino yellow (DY) injection site (black areas, left) in the central portion of the mediodorsal nucleus (MD) in case 2, and the distribution of retrogradely labeled cells (small dots) in the lateral, medial, and orbital prefrontal cortices. (abbreviations as in Fig. 2)

(corticothalamic) neurons, in contrast, were observed mainly in layer VI and to a lesser extent in layer Vb (Figs. 6, 7, 11C, D). Like the preceding case, within certain architectonic regions, FB- and DY-labeled neurons occurred together. This was noted predominantly in areas 10, 11, 32, 24, 46, and 9, and to a lesser extent in areas 13 and 14 (see Fig. 6A–E). Figure 7 shows the differential laminar distribution of FB- and DY-labeled neurons in area 10. As in case 1, although there was some overlap of the distributions of corticostriatal and corticothalamic cells of origin in infragranular layers, very few double-labeled neurons were observed.

In the preceding two cases, the FRT injections involved mainly the medial and central sectors of the HCN and the MD nucleus. In case 3, FB was injected into the dorsal and lateral portions of the HCN (Fig. 8A). Unlike cases 1 and 2, labeled neurons were found primarily in dorsomedial (areas 9, 10, and 24) and dorsolateral (area 9, and dorsal areas 46 and 8) prefrontal cortex. Only a few labeled cells were observed in areas 32, 14, and in the ventrolateral prefrontal cortex (areas 10, 12, and 46). Likewise, the orbital frontal cortex displayed only scattered labeled neurons in areas 10, 11, 12, 13, and 14 (Fig. 8A).
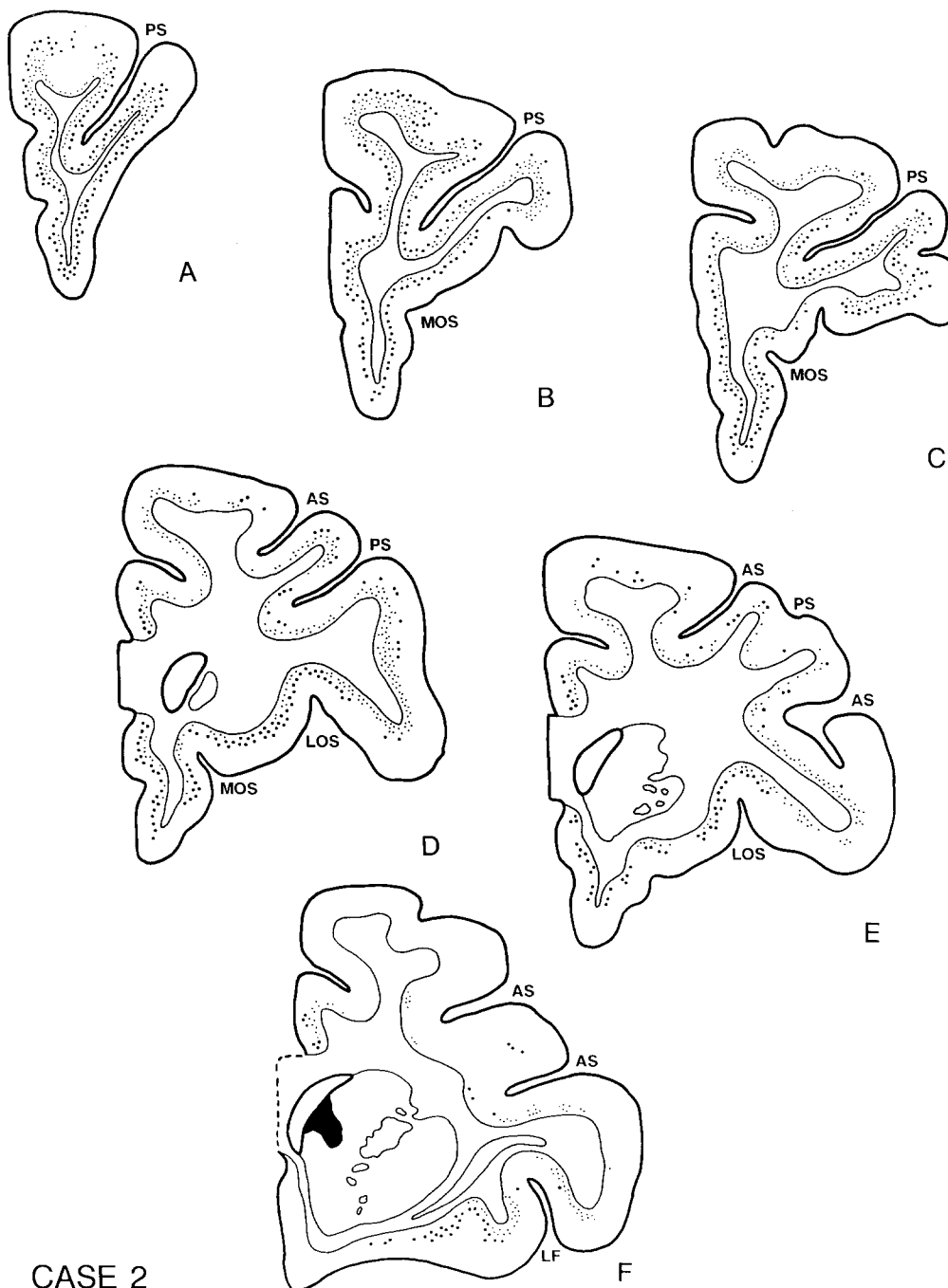

Fig. 6A–F Diagrams of six representative rostral-to-caudal coronal sections (taken from the levels shown in the preceding figure) through the prefrontal cortex depicting the laminar distribution of fast blue-labeled (corticostriatal, *large dots*) and diamidino yellow-labeled (corticothalamic, *small dots*) cells in case 2. (*LOS* lateral orbital sulcus; *other abbreviations* as in Fig. 3)
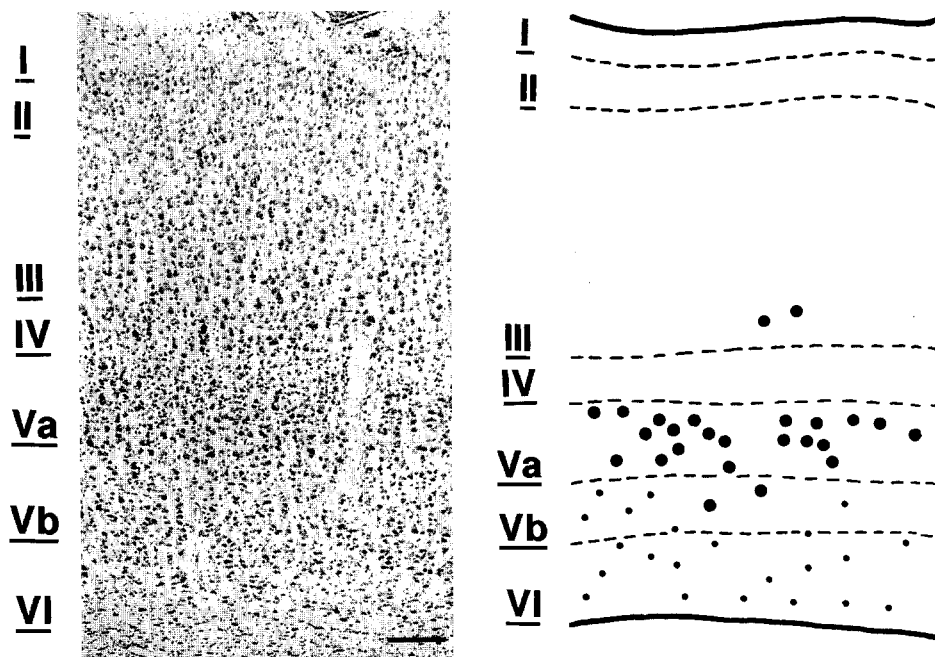
CASE 2

Fig. 7 On the *left* is a photomicrograph of a Nissl-stained section from area 10 in case 2. On the *right* is a diagrammatic representation of the cortical laminae in the same area depicting the distribution of fast blue-labeled (corticostriatal, *large dots*) and diamidino yellow-labeled (corticothalamic, *small dots*) neurons. *Scale bar* 150 μm

The DY injections were located in the lateral part of the MD nucleus, involving the lateral portion of MDpc and extending into the medial portion of the multiform division, MDmf (Fig. 8B). The resulting labeled neurons occurred predominantly in the dorsolateral (dorsal area 46, area 9, and dorsal area 8) and dorsomedial (medial area 9) prefrontal cortex. Relatively few labeled cells were seen in ventral areas 46 and 8, area 12, medial area 10, and in the orbital frontal cortex (areas 11 and 12; Fig. 8B).

As in the preceding two cases, in case 3 the FB-labeled (corticostriatal) neurons were located mainly in layer Va, with some neurons in layer Vb. Only occasional labeled cells were discerned in layer VI and in the deeper portion of layer III. DY-labeled (corticothalamic) neurons, in contrast, were observed mainly in layer VI, with a few noted in layer Vb. There were scattered labeled cells observed in layer Va (Figs. 9, 10). Figure 10 depicts the specific laminar distributions of FB- and DY-labeled neurons in area 8. Like the cases described above, within certain architectonic zones, the FB- and DY-labeled neurons occurred together. This pattern was seen predominantly in medial and lateral area 9, dorsal area 46, and in dorsal area 8 (see Fig. 9B–F). As in cases 1 and 2, despite the coexistence of large numbers of FB- and DY-labeled neurons within specific architectonic regions, only occasional double-labeled cells were noted.

Discussion

Laminar organization of the cells of origin of prefrontostriatal and prefrontothalamic connections

The major focus of the present investigation was to determine whether there are collateralized projections from the prefrontal cortex to the caudate and the MD nuclei. It is known that projections to the striatum and the thalamus originate predominantly from infragranular cortical layers (Jones et al. 1977; Arikuni et al. 1983; Jones 1985; Arikuni and Kubota 1986; Russchen et al. 1987; Giguere and Goldman-Rakic 1988; Saint-Cyr et al. 1990; Siwek and Pandya 1992). According to Jones et al. (1977), corticostriatal projections originate in layer V, primarily in the superficial portion of the lamina. Arikuni and Kubota (1986) reported that corticostriatal projections arise from layers II–VI, with the highest density of cells in layer Va. Saint-Cyr et al. (1990), using FRT as well as horseradish peroxidase techniques, demonstrated that corticostriatal projection neurons arise from supra- as well as infragranular layers, with the majority of cells in layer V. With respect to corticothalamic connections of the prefrontal cortex in monkeys, Arikuni et al. (1983) reported that projections to the MD nucleus from medial, orbital, and dorsolateral cortical regions arise from layers V and VI. Russchen et al. (1987) observed that prefrontal cortical neurons that give rise to projections to the MD nucleus are concentrated in layer VI. Giguere and Goldman-Rakic (1988) have shown that thalamic (MD nucleus) projection neurons in the prefrontal cortex are located mainly in the superficial part of layer VI and that relatively few neurons are found in the superficial part of layer V. Si-
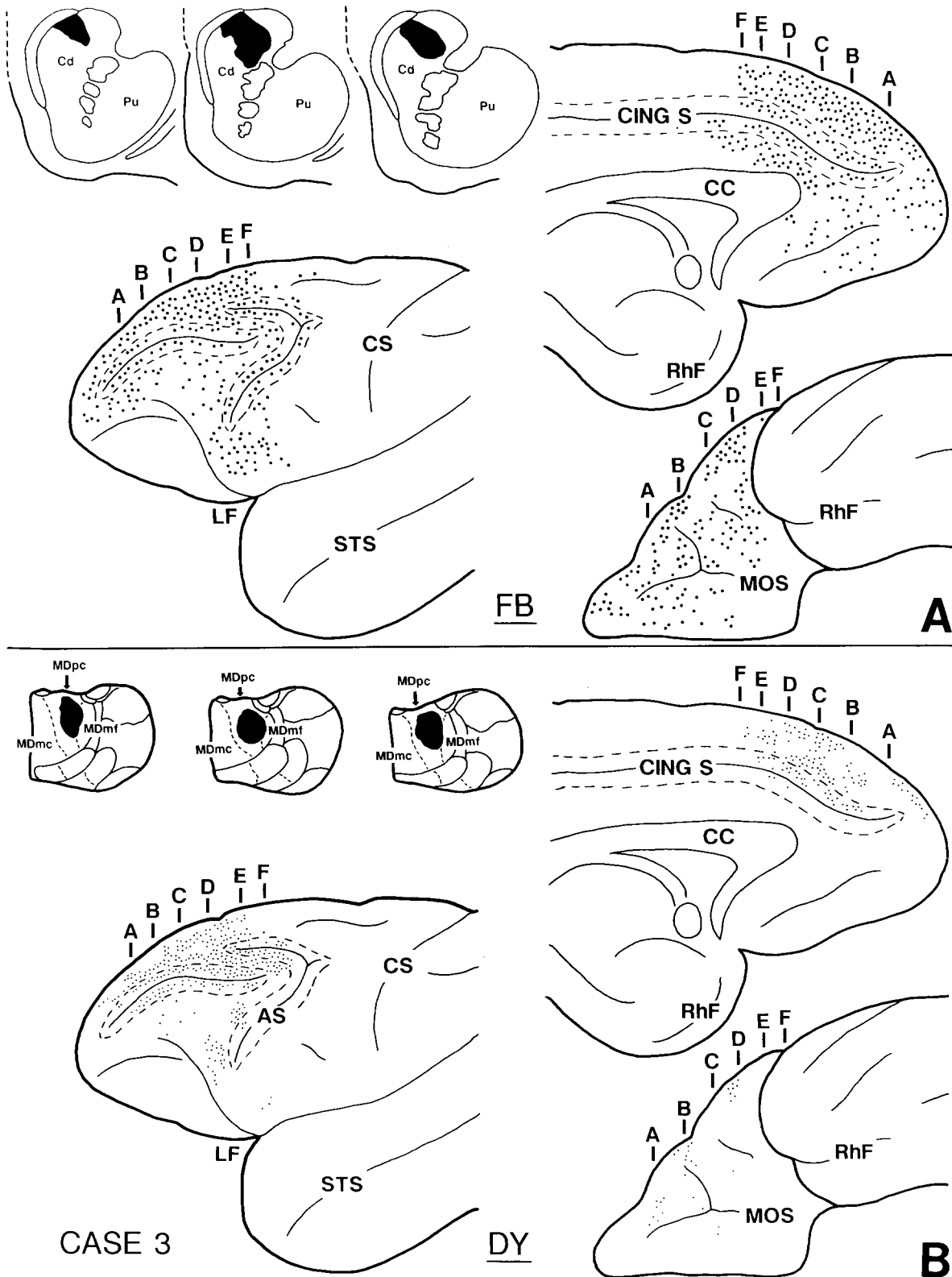
Fig. 8A Diagrammatic representations of the fast blue (*FB*) injection site (*black areas, top left*) in the dorsal and lateral sectors of the head of the caudate nucleus in case 3, and the distribution of retrogradely labeled cells (*large dots*) in the lateral, medial, and orbital prefrontal cortices. **B** Diagrammatic representations of the diamidino yellow (*DY*) injection site (*black areas, top left*) in the medial portion of the mediodorsal nucleus in case 3, and the distribution of retrogradely labeled cells (*small dots*) in the lateral, medial, and orbital prefrontal cortices. (*Abbreviations* as in Fig. 2)
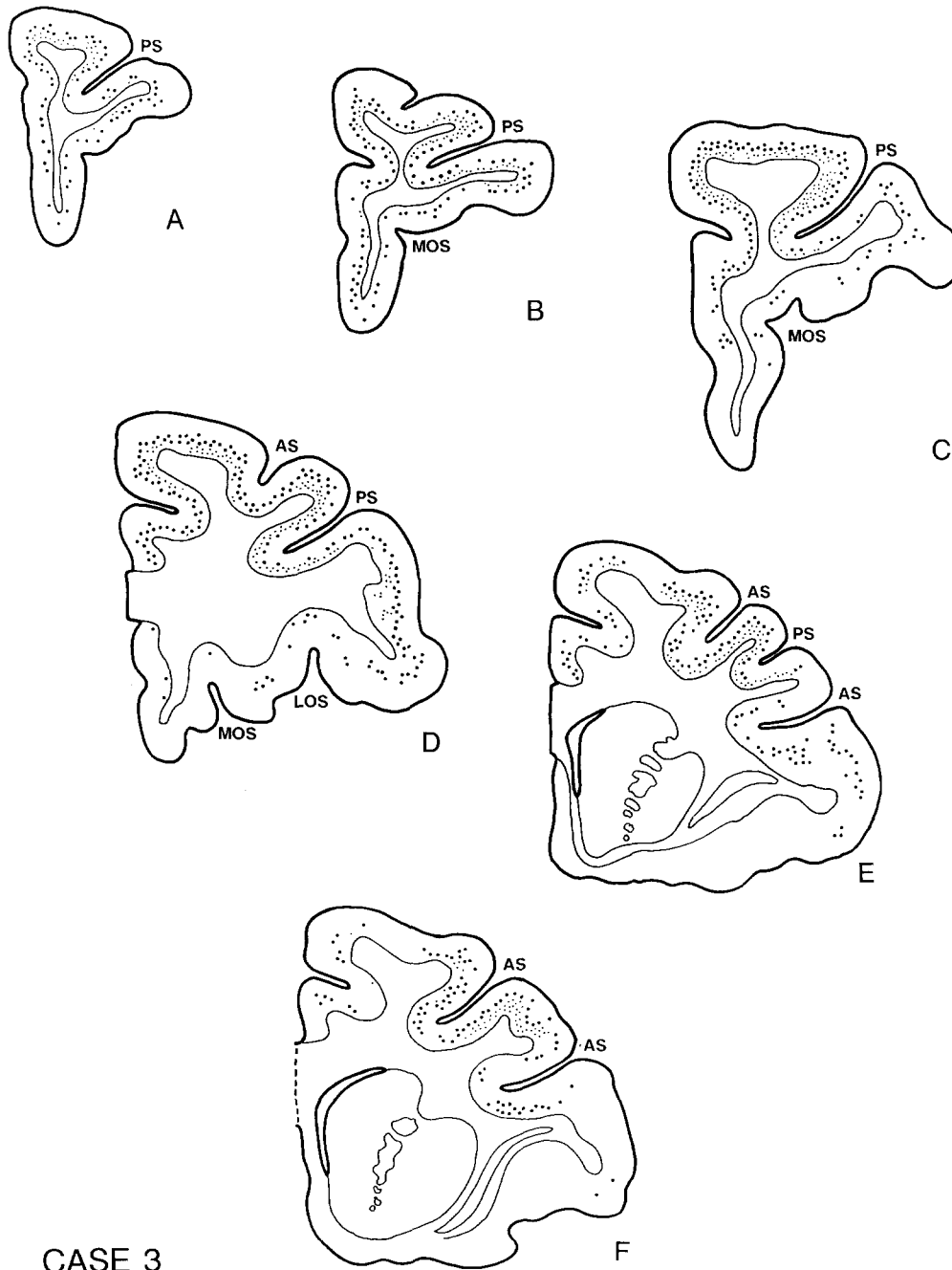
Fig. 9A–F Diagrams of six representative rostral-to-caudal coronal sections (taken from the levels shown in the preceding figure) through the prefrontal cortex depicting the laminar distribution of fast blue-labeled (corticostriatal, *large dots*) and diamidino yellow-labeled (corticothalamic, *small dots*) cells in case 3. (*Abbreviations* as in Fig. 3)

CASE 3

wek and Pandya (1992) also have demonstrated that prefrontothalamic projections stem predominantly from layer VI and to a lesser extent from layer V.

The use of simultaneous injections of two different FRTs has permitted the comparison of the cells of origin of two corticosubcortical systems in single animals. According to our observations, despite the comingling of significant numbers of DY- and FB-labeled cells in the infragranular layers of certain prefrontal regions, there is very little evidence to suggest that the corticostriatal and corticothalamic pathways are collateralized. Our findings indicate that striatal projections are

derived mainly from layer Va and also from layer Vb. In contrast, projections to the MD nucleus originate predominantly from layer VI and also from layer Vb. Thus, it appears that, although prefrontostriatal and prefrontothalamic projections have similar topographic distributions within the HCN and the MD nucleus, these connections arise from virtually separate neuronal populations within the infragranular layers of the prefrontal cortex.
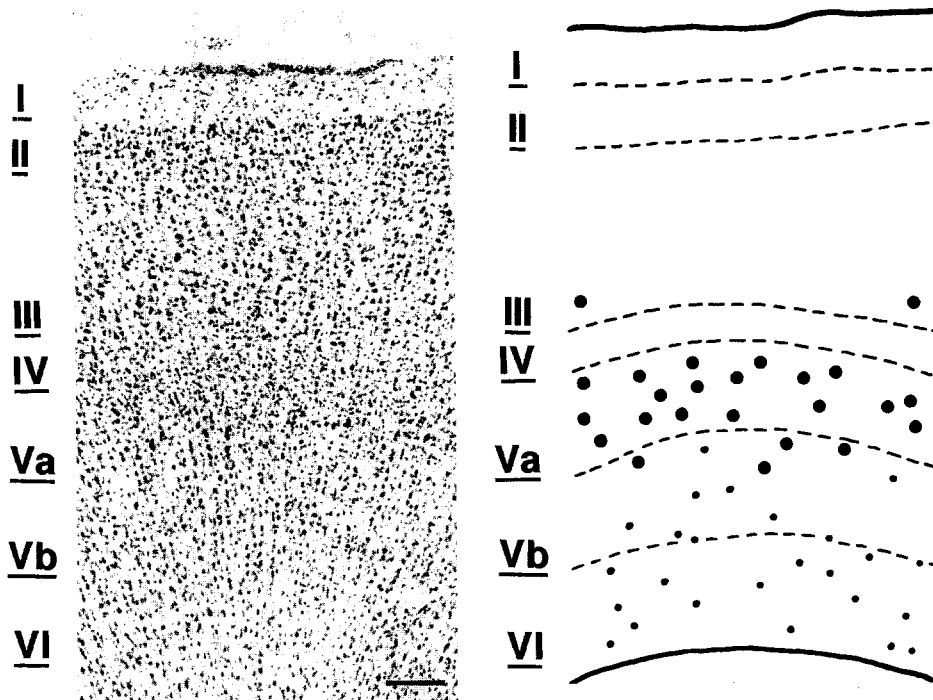
Fig. 10 On the *left* is a photomicrograph of a Nissl-stained section from area 8 in case 3. On the *right* is a diagrammatic representation of the cortical laminae in the same area depicting the distribution of fast blue-labeled (corticostriatal, *large dots*) and diamidino yellow-labeled (corticothalamic, *small dots*) neurons. *Scale bar* 150 μm

Topography of prefrontostriatal and prefrontothalamic cells of origin

In addition to delineating the laminar origins of corticostriatal and corticothalamic connectivity, our results provide information on the topographic relationships between the prefrontal cortex and the caudate and the MD nuclei. According to the present findings, more medial portions of the HCN are related mainly to the orbital (areas 10–14) and medial (areas 32, 25, 10, and 14) surfaces, whereas the central portion also receives substantial input from the rostrolateral prefrontal cortex (areas 10, 46, 9, and 12). Similar relationships have been shown for the medialmost portion of the HCN by Arikuni and Kubota (1986) using the horseradish peroxidase tracing technique, and by Saint-Cyr et al. (1990) using fluorescent retrograde tracers, and for the central portion of the HCN by Arikuni and Kubota (1986). The lateral portion of the HCN receives input predominantly from the dorsomedial and dorsolateral prefrontal cortices (area 9, and dorsal areas 46 and 8). These observations also confirm and complement recent descriptions of corticostriatal relationships based on autoradiographic tracing techniques (Selemon and Goldman-Rakic 1985; Yeterian and Pandya 1991).

In regard to corticothalamic connections, the present results show that, like the HCN, the medial portion of the MD nucleus (MDmc and the medial sector of MDpc) receives input from medial (areas 24, 25, 32, 10, and 14), orbital (areas 10–14), rostrolateral (areas 10, 9, and 46), and ventrolateral (areas 12, 6, and the opercular gustatory region) cortices. The central portion (MDpc and the lateral sector of MDmc) is related strongly to the dorsomedial, lateral orbital, and lateral prefrontal

regions, and also to the caudal prefrontal cortex including the caudal part of area 46, rostral area 8, the lateral and medial portions of area 9, ventral area 6, and the opercular gustatory region. However, this portion of the MD nucleus lacks connections from the ventromedial prefrontal cortex and has minor connections from the medial orbital cortex. In contrast, the lateral sector of the MD nucleus (the lateral portion of MDpc and the medial sector of MDmf) is heavily connected with the dorsomedial and dorsolateral prefrontal cortex (area 9, and the dorsal and caudal portions of areas 46 and 8), but has only minor connections from the ventrolateral and orbital prefrontal cortices, and lacks connections from the ventromedial prefrontal cortex. The present results regarding the cortical relationships of different subdivisions of the MD nucleus are in agreement with those of Russchen et al. (1987) and Giguere and Goldman-Rakic (1988). Arikuni et al. (1983), however, have shown only limited projection neurons in the medial and orbital cortices and heavy projection neurons in the dorsolateral and caudal prefrontal regions following an HRP injection involving all subdivisions of the MD nucleus at its mid-level in the rostrocaudal dimension. The present findings nevertheless are consistent with recent reports of corticothalamic connectivity in which similar topographic relationships between the prefrontal cortex and the subdivisions of the MD nucleus have been shown using anterograde tracing methods (Russchen et al. 1987; Siwek and Pandya 1991).

In recent years, a number of organizational principles have been proposed with regard to corticostriatal connectivity in monkeys (e.g., Yeterian and Van Hoesen 1978; Selemon and Goldman-Rakic 1985; Alexander et al. 1986; Yeterian and Pandya 1991; Parthasarathy
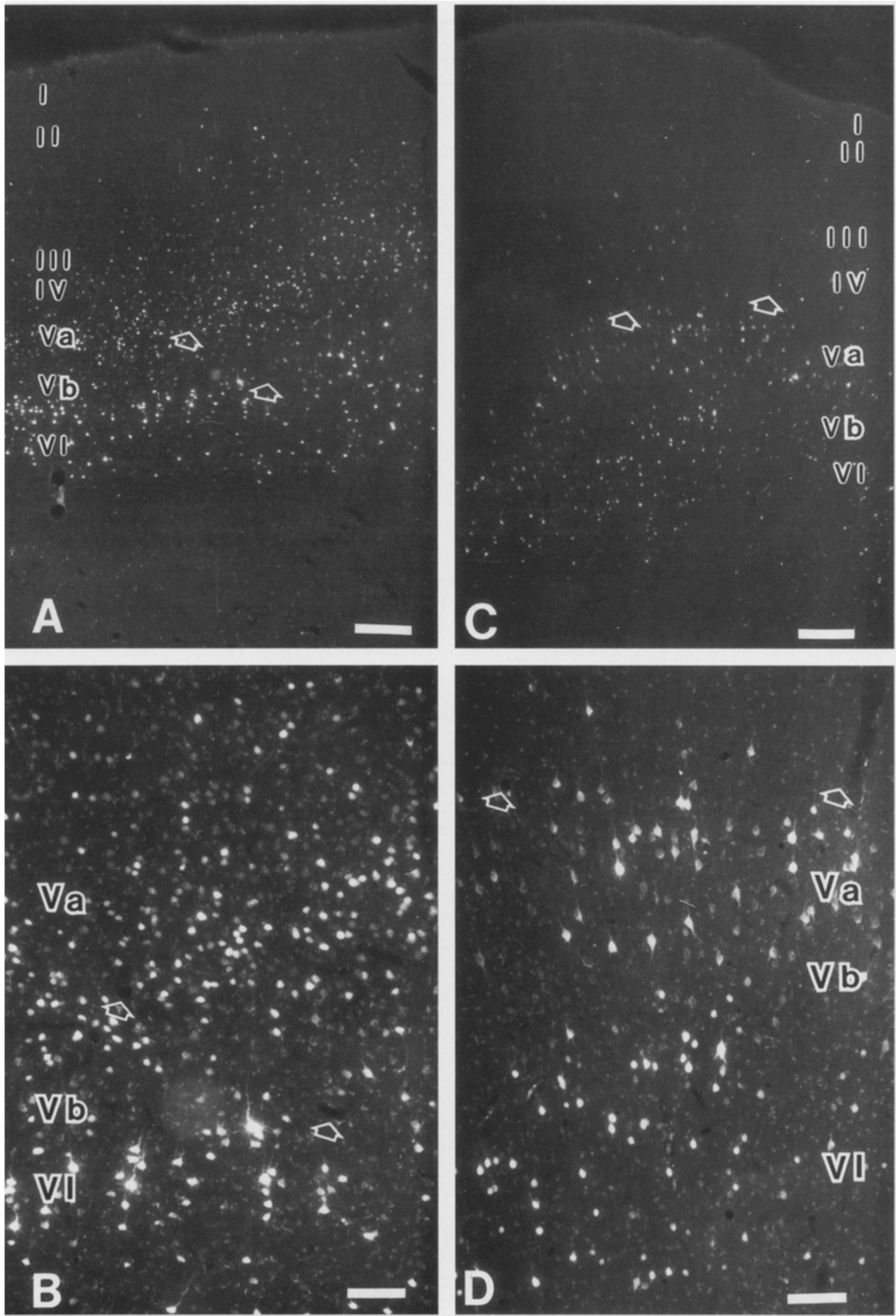
et al. 1992). One specific dimension of prefrontal corti-costriatal organization concerns the relationship between architectonic differentiation at the cortical level and the distribution of prefrontostriatal connections (Yeterian and Pandya 1991). According to this principle based on data from anterograde tracing experiments, less differentiated prefrontal regions, which occupy the medial and orbital surfaces, project heavily to the medial portion of the HCN. In contrast, highly differentiated caudal prefrontal regions project mainly to the lateral portion of the HCN. Intermediate areas located in the dorsolateral and ventrolateral prefrontal sectors are related strongly to the central portion of the nucleus. The present findings, obtained from FRT injections in medial as well as lateral sectors of the HCN, appear to follow this principle.

It is interesting to note that a similar architectonic-connectional relationship has been shown for the projections from various prefrontal cortical regions to the MD nucleus (Russchen et al. 1987; Siwek and Pandya 1991, 1992). The results described above regarding corticothalamic connections also appear to be consistent with this principle. Thus, the medial sector of the MD nucleus is related mainly to the medial and orbital prefrontal cortices. The central portion is related more strongly to dorsal and lateral prefrontal regions than to medial and orbital regions. The lateral division of the MD nucleus, in contrast, is related preferentially to the dorsolateral and caudalmost portion of the prefrontal cortex, and has limited connections with ventromedial and orbital regions.

Functional implications

According to the present results, it seems that specific sectors of the prefrontal cortex are related to topographically similar areas of the HCN and the MD nucleus. There is a sizable literature regarding the physiology and the behavioral roles of specific prefrontal cortical regions. However, there have been relatively few functional studies focusing on specific sectors of the caudate and the MD nuclei. It should be pointed out that a

given cortical region may project to more than one sector of these subcortical nuclei and hence could play a role in more than one process. Nevertheless, a comparison of available observations pertaining to specific prefrontal regions and the portions of the HCN and the MD nucleus with which they are preferentially connected indicates that these related structures have some commonality of function.

The ventromedial prefrontal cortex has been implicated in visceral-autonomic (e.g., Nakano et al. 1984), olfactory and gustatory (e.g., Tanabe et al. 1975; Rolls et al. 1990), and social-emotional (Butter et al. 1968; Butter and Snyder 1972; Raleigh and Steklis 1981) processes, as well as in object-reinforcement relationships (Rosenkilde et al. 1981). In comparison with the ventromedial sector of the prefrontal cortex, only a few studies have examined specifically the functional roles of the medial portions of the HCN and of the MD nucleus. With regard to the HCN, it has been shown that the medial and ventral sectors are related to visceral-autonomic, ingestive, gustatory, and reinforcement-related processes (Rubinstein and Delgado 1963; Rolls et al. 1983; Nishino et al. 1984; Schultz et al. 1992). Likewise, it has been suggested that the medial subdivision of the MD nucleus, MDmc, has a role in autonomic regulation, olfactory processes, and object-reinforcement associations (Benjamin and Jackson 1974; Motokizawa 1974; Hallowitz and MacLean 1977; Yarita et al. 1980; Isseroff et al. 1982; Aggleton and Mishkin 1983; Russchen et al. 1987; Gaffan and Murray 1990). Thus, there appears to be some similarity in the functions of the medial sectors of the HCN and the MD nucleus, both of which receive strong input from the ventromedial prefrontal region.

The dorsolateral prefrontal cortex, including the periprincipalis region, has been shown to have a role in spatial processes and in working or representational memory (e.g., Passingham 1975, 1985; Bauer and Fuster 1976; Niki and Watanabe 1976; Kojima and Goldman-Rakic 1984; Quintana et al. 1988; Gaffan and Harrison 1989; Di Pellegrino and Wise 1991; Funahashi et al. 1993; Tanila et al. 1993; Wilson et al. 1993). In contrast, the ventrolateral prefrontal cortex is involved in response inhibition, but not autonomic or emotional functions (Iversen and Mishkin 1970, 1973), and in memory for objects (Stamm 1973; Passingham 1975; Kowalska et al. 1991; Wilson et al. 1993). It has been shown that neurons in the central portion of the HCN are activated during cognitive tasks involving expectancy of a cue or target (Hikosaka et al. 1989c). Additionally, the central and dorsal portion of the HCN appears to be involved preferentially in spatial functions (e.g., Divac 1972; Rosvold 1972). In the case of the MD nucleus, its central portion has been shown to have a role in tasks involving temporal delay and short-term memory (Alexander and Fuster 1973; Fuster and Alexander 1973). Thus, like the dorsolateral prefrontal cortex, the central sectors of the HCN and of the MD nucleus both appear to have a role in mnemonic processes.

Fig. 11A–D Photomicrographs showing the laminar distribution of retrogradely labeled cells in area 14 in case 1, and in area 32 in case 2. In case 1 (**A** low magnification, **B** high magnification), note the predominance of labeled neurons (evident as labeled nuclei) in layer Va following a diamidino yellow (DY) injection in the head of the caudate nucleus, and labeled neurons (evident as *filled cells*) mainly in layer VI following a fast blue (FB) injection in the mediodorsal nucleus. Also seen is a degree of intermingling of DY- and FB-labeled cells in layer Vb. In case 2 (**C** low magnification, **D** high magnification), note the presence of FB-labeled neurons mainly in layer Va and also in layer Vb following an injection in the head of the caudate nucleus, and DY-labeled neurons mainly in layer VI and also in layer Vb following an injection in the mediodorsal nucleus. Th *arrows* indicate corresponding blood vessels as landmarks. *Scale bars*: **A, C** 210 μm; **B, D** 120 μm

Finally, the cortex in and around the arcuate sulcus has been shown to subserve visual attentional and orientation processes (e.g., Welch and Stuteville 1958; Rizzolatti et al. 1981; Collin et al. 1982; Goldberg and Bruce 1985; Vaadia et al. 1986; Lawler and Cowey 1987; Lynch 1987; Azuma et al. 1988; Funahashi et al. 1991; MacAvoy et al. 1991; Schall 1991; Dassonville et al. 1992). With regard to the caudate nucleus, neurons in the central and lateral sector have been shown to be involved in the initiation of saccadic eye movements (Hikosaka et al. 1989a, b). Similarly, the lateral division of the MD nucleus, MDmf, has been suggested to subserve oculomotor function (Schlag and Schlag-Rey 1984, 1986; Schlag-Rey and Schlag 1984; Huerta and Kaas 1990). It therefore appears that the lateral portions of the HCN and the MD nucleus are involved in functions relating to eye movements.

Thus, it seems that, as one moves from medial to lateral sectors of both the HCN and the MD nucleus, there is a functional shift that reflects the differential roles of the prefrontal regions that provide the predominant input to these specific sectors. Recent conceptualizations of the overall functional organization of the primate brain have emphasized the existence of parallel distributed circuitry at both the cortical and the subcortical level (e.g., Alexander et al. 1986; Selemon and Goldman-Rakic 1988; Yeterian and Pandya 1991). With respect to corticosubcortical relationships, it has been proposed that a given cortical region is related, via its efferent projections, to numerous subcortical structures. The present observations, when viewed in the light of physiological and behavioral studies of prefrontal, striatal, and thalamic subregions, indicate that there are functional similarities between specific cortical regions and the subcortical nuclei to which they project.

One of the findings in this study is the presence of a projection specifically from the frontal operculum to the medial and ventral sectors of the MD nucleus. According to physiological and behavioral studies, this region has a role in gustatory processes (e.g., Benjamin and Burton 1968; Scott et al. 1986; Rolls et al. 1988; Ogawa et al. 1989; Plata-Salamán and Scott 1992). Previous anatomical investigations have demonstrated that the gustatory area is connected with a number of thalamic nuclei: the parvocellular portion of the ventroposteromedial nucleus; the ventroposteroinferior nucleus; the ventral sector of the central lateral nucleus; and the ventralmost portion of the MD nucleus (Roberts and Akert 1963; Ganchrow and Erickson 1972; Wirth 1973; Jones and Burton 1976; Kusama et al. 1985; Pritchard et al. 1986). Our observations support the notion that the frontal opercular gustatory region has a reciprocal relationship with the MD nucleus. The functional significance of this connectivity remains to be determined.

A key observation of the present study is that projections from particular prefrontal cortical regions to topographically similar sectors of the HCN and the MD nucleus originate from distinct cell populations. It may be that the discrete pathways emanating from specific

laminae within a given prefrontal region and directed toward the HCN and the MD nucleus are conveying somewhat different types of information.

The major output of prefrontal regions to the HCN and the MD nucleus originates from layers V and VI. Several investigations have shown that infragranular cortical laminae give rise to reciprocal, or feedback, projections from relatively less differentiated to more differentiated cortical areas (e.g., Spatz 1977; Rockland and Pandya 1979; Van Essen and Maunsell 1983). It is not known whether the neurons of layers V and VI of the prefrontal cortex, which provide feedback at the cortical level, are the same cells that project to the HCN and the MD nucleus in primates. In other species, however, it has been shown that certain corticocortical and corticostriatal connections emanate from the same neurons (Fisher et al. 1986; Ferino et al. 1987). If a similar pattern of collateralization for prefrontal connectivity exists in primates, this would imply that the projections from layers V and VI are providing modulation of cortical input to a specific prefrontal region (via reciprocal corticocortical connections), while also influencing the subcortical structures associated with that cortical region.

References

Aggleton JP, Mishkin M (1983) Visual recognition impairment following medial thalamic lesions in monkeys. Neuropsychologia 21:189–197

Alexander GE, Crutcher MD (1990) Functional architecture of basal ganglia circuits: neural substrates of parallel processing. Trends Neurosci 13:266–271

Alexander GE, Fuster JM (1973) Effects of cooling prefrontal cortex on cell firing in the nucleus medialis dorsalis. Brain Res 61:93–105

Alexander GE, DeLong MR, Strick PL (1986) Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci 9:357–381

Arikuni T, Kubota K (1986) The organization of prefrontocaudate projections and their laminar origin in the macaque monkey: a retrograde study using HRP-gel. J Comp Neurol 244:492–510

Arikuni T, Sakai M, Kubota K (1983) Columnar aggregation of prefrontal and anterior cingulate cortical cells projecting to the thalamic mediodorsal nucleus in the monkey. J Comp Neurol 220:116–125

Azuma M, Nakayama H, Sasaki Y, Suzuki H (1988) Relation between visual input and motor outflow for eye movements in monkey frontal eye field. Behav Brain Res 27:93–98

Barbas H, Pandya DN (1989) Architecture and intrinsic connections of the prefrontal cortex in the rhesus monkey. J Comp Neurol 286:353–375

Bauer RH, Fuster JM (1976) Delayed-matching and delayed-response deficit from cooling dorsolateral prefrontal cortex in monkeys. J Comp Physiol Psychol 90:293–302

Benjamin RM, Burton H (1968) Projection of taste nerve afferents to anterior opercular-insular cortex in squirrel monkey (*Saimiri sciureus*). Brain Res 7:221–231

Benjamin RM, Jackson JC (1974) Unit discharge in the mediodorsal nucleus of the squirrel monkey evoked by electrical stimulation of the olfactory bulb. Brain Res 75:181–191

Butter CM, Snyder DR (1972) Alterations in aversive and aggressive behaviors following orbital frontal lesions in rhesus monkeys. Acta Neurobiol Exp 32:525–565

Butter CM, Mishkin M, Mirsky AF (1968) Emotional responses toward humans in monkeys with selective frontal lesions. Physiol Behav 3:213–215

Cavada C, Goldman-Rakic PS (1991) Topographic segregation of corticostriatal projections from posterior parietal subdivisions in the macaque monkey. Neuroscience 42:683–696

Collin NG, Cowey A, Latto R, Marzi C (1982) The role of frontal eye-fields and superior colliculi in visual search and non-visual search in rhesus monkeys. Behav Brain Res 4:177–193

Dassonville P, Schlag J, Schlag-Rey M (1992) The frontal eye field provides the goal of saccadic eye movement. Exp Brain Res 89:300–310

DiPellegrino G, Wise SP (1991) A neurophysiological comparison of three distinct regions of the primate frontal lobe. Brain 114:951–978

Divac I (1972) Neostriatum and functions of prefrontal cortex. Acta Neurobiol Exp 32:461–477

Ferino F, Thierry AM, Saffroy M, Glowinski J (1987) Interhemispheric and subcortical collaterals of medial prefrontal cortical neurons in the rat. Brain Res 417:257–266

Fisher RS, Boylan MK, Hull CD, Buchwald NA, Levine MS (1986) Branched projections of cat sensorimotor cortex: multiple retrograde labeling via commissural corticocortical, decussated corticostriatal and undecussated corticostriatal axons. Brain Res 384:395–400

Funahashi S, Bruce CJ, Goldman-Rakic PS (1991) Neuronal activity related to saccadic eye movements in the monkey's dorsolateral prefrontal cortex. J Neurophysiol 65:1464–1483

Funahashi S, Bruce CJ, Goldman-Rakic PS (1993) Dorsolateral prefrontal lesions and oculomotor delayed-response performance: evidence for mnemonic "scotomas". J Neurosci 13:1479–1497

Fuster JM, Alexander GE (1973) Firing changes in cells of the nucleus medialis dorsalis associated with delayed response behavior. Brain Res 61:79–91

Gaffan D, Harrison S (1989) A comparison of the effects of fornix transection and sulcus principalis ablation upon spatial learning by monkeys. Behav Brain Res 31:207–220

Gaffan D, Murray EA (1990) Amygdalar interaction with the mediodorsal nucleus of the thalamus and the ventromedial prefrontal cortex in stimulus-reward associative learning in the monkey. J Neurosci 10:3479–3493

Ganchrow D, Erickson RP (1972) Thalamocortical relations in gustation. Brain Res 36:289–305

Giguere M, Goldman-Rakic PS (1988) Mediodorsal nucleus: areal, laminar, and tangential distribution of afferents and efferents in the frontal lobe of rhesus monkeys. J Comp Neurol 277:195–213

Goldberg ME, Bruce CJ (1985) Cerebral cortical activity associated with the orientation of visual attention in the rhesus monkey. Vision Res 25:471–481

Hallowitz RA, MacLean PD (1977) Effects of vagal volleys on units of intralaminar and juxtalaminar thalamic nuclei in monkeys. Brain Res 130:271–286

Hikosaka O, Sakamoto M, Usui S (1989a) Functional properties of monkey caudate neurons. I. Activities related to saccadic eye movements. J Neurophysiol 61:780–798

Hikosaka O, Sakamoto M, Usui S (1989b) Functional properties of monkey caudate neurons. II. Visual and auditory responses. J Neurophysiol 61:799–813

Hikosaka O, Sakamoto M, Usui S (1989c) Functional properties of monkey caudate neurons. III. Activities related to expectation of target and reward. J Neurophysiol 61:814–832

Huerta MF, Kaas JH (1990) Supplementary eye field as defined by intracortical microstimulation: connections in macaques. J Comp Neurol 293:299–330

Isseroff A, Rosvold HE, Galkin TW, Goldman-Rakic PS (1982) Spatial memory impairments following damage to the mediodorsal nucleus of the thalamus in rhesus monkeys. Brain Res 232:97–113

Iversen SD, Mishkin M (1970) Perseverative interference in monkeys following selective lesions of the inferior prefrontal covexity. Exp Brain Res 11:376–386

Iversen SD, Mishkin M (1973) Comparison of superior temporal and inferior prefrontal lesions on auditory and non-auditory tasks in rhesus monkeys. Brain Res 55:355–367

Jones EG (1985) The thalamus. Plenum, New York

Jones EG, Burton H (1976) Areal differences in the laminar distribution of thalamic afferents in cortical fields of the insular, parietal and temporal regions of primates. J Comp Neurol 168:197–248

Jones EG, Coulter JD, Burton H, Porter R (1977) Cells of origin and terminaldistribution of corticostriatal fibers arising in the sensory-motor cortex of monkeys. J Comp Neurol 173:53–80

Kojima S, Goldman-Rakic PS (1984) Functional analysis of spatially discriminative neurons in prefrontal cortex of rhesus monkey. Brain Res 291:229–240

Kowalska DM, Bachevalier J, Mishkin M (1991) The role of the inferior prefrontal convexity in performance of delayed nonmatching-to-sample. Neuropsychologia 29:583–600

Kusama T, Fujioka M, Miyakawa Y, Fujii M (1985) Connections of the fronto-parietal operculum with the posterior ventral thalamic nucleus, especially its medial nucleus, in monkeys. J Hirnforsch 26:317–331

Lawler KA, Cowey A (1987) On the role of posterior parietal and prefrontal cortex in visuospatial perception and attention. Exp Brain Res 65:695–698

Lynch JC (1987) Frontal eye field lesions in monkeys disrupt visual pursuit. Exp Brain Res 68:437–441

MacAvoy MG, Gottlieb JP, Bruce CJ (1991) Smooth-pursuit eye movement representation in the primate frontal eye field. Cereb Cortex 1:95–102

Motokizawa F (1974) Olfactory input to the thalamus: electrophysiological evidence. Brain Res 67:334–337

Nakano Y, Oomura Y, Nishino H, Aou S, Yamamoto T, Nemoto S (1984) Neuronal activity in the medial orbitofrontal cortex of the behaving monkey: modulation by glucose and satiety. Brain Res Bull 12:381–385

Niki H, Watanabe M (1976) Prefrontal unit activity and delayed response: relation to cue location versus direction of response. Brain Res 105:79–88

Nishino H, Ono T, Sasaki K, Fukuda M, Muramoto KI (1984) Caudate unit activity during operant feeding behavior in monkeys and modulation by cooling prefrontal cortex. Behav Brain Res 11:21–33

Ogawa H, Ito S-I, Nomura T (1989) Oral cavity representation at the frontal operculum of macaque monkeys. Neurosci Res 6:283–298

Parthasarathy HB, Schall JD, Graybiel AM (1992) Distributed but convergent ordering of corticostriatal projections: analysis of the frontal eye field and the supplementary eye field in the macaque monkey. J Neurosci 12:4468–4488

Passingham RE (1975) Delayed matching after selective prefrontal lesions in monkeys (*Macaca mulatta*). Brain Res 92:89–102

Passingham RE (1985) Memory of monkeys (*Macaca mulatta*) with lesions in prefrontal cortex. Behav Neurosci 99:3–21

Plata-Salamán CR, Scott TR (1992) Taste neurons in the cortex of the alert cynomolgus monkey. Brain Res Bull 28:333–336

Pritchard TC, Hamilton RB, Morse JR, Norgren R (1986) Projections of thalamic gustatory and lingual areas in the monkey, *Macaca fascicularis*. J Comp Neurol 244:213–228

Quintana J, Yajeya J, Fuster JM (1988) Prefrontal representation of stimulus attributes during delay tasks. I. Unit activity in cross-temporal integration of sensory and sensory-motor information. Brain Res 474:211–221

Raleigh MJ, Steklis HD (1981) Effects of orbitofrontal and temporal neocortical lesions on the affiliative behavior of vervet monkeys (Cercopithecus aethiops sabaeus). Exp Neurol 73:378–389

Rizzolatti G, Scandolara C, Matelli M, Gentilucci M (1981) Afferent properties of periarcuate neurons in macaque monkeys. II. Visual responses. Behav Brain Res 2:147–163

Roberts TS, Akert K (1963) Insular and opercular cortex and its thalamic projection in Macaca mulatta. Schweiz Arch Neurol Psychiatr 92:1–43

Rockland KR, Pandya DN (1979) Laminar origins and terminations of cortical connections of the occipital lobe in the rhesus monkey. Brain Res 179:3–20

Rolls ET, Thorpe SJ, Maddison SP (1983) Responses of striatal neurons in the behaving monkey. 1. Head of the caudate nucleus. Behav Brain Res 7:179–210

Rolls ET, Scott TR, Sienkiewicz ZJ, Yaxley S (1988) The responsiveness of neurones in the frontal opercular gustatory cortex of the macaque monkey is independent of hunger. J Physiol (Lond) 397:1–12

Rolls ET, Yaxley S, Sienkiewicz ZJ (1990) Gustatory responses of single neurons in the caudolateral orbitofrontal cortex of the macaque monkey. J Neurophysiol 64:1055–1066

Rosene DL, Roy NJ, Davis BJ (1986) A cryoprotection method that facilitates cutting frozen sections of whole monkey brains for histological and histochemical processing without freezing artifact. J Histochem Cytochem 34:1301–1315

Rosenkilde CE, Bauer RH, Fuster JM (1981) Single cell activity in ventral prefrontal cortex of behaving monkeys. Brain Res 209:375–394

Rosvold HE (1972) The frontal lobe system: Cortical-subcortical interrelationships. Acta Neurobiol Exp 32:439–460

Rubinstein EH, Delgado JMR (1963) Inhibition induced by forebrain stimulation in the monkey. Am J Physiol 205:941–948

Russchen FT, Amaral DG, Price JL (1987) The afferent input to the magnocellular division of the mediodorsal thalamic nucleus in the monkey, Macaca fascicularis. J Comp Neurol 256:175–210

Saint-Cyr JA, Ungerleider LG, Desimone R (1990) Organization of visual cortical inputs to the striatum and subsequent outputs to the pallido-nigral complex in the monkey. J Comp Neurol 298:129–156

Schall JD (1991) Neuronal activity related to visually guided saccades in the frontal eye fields of rhesus monkeys: comparison with supplementary eye fields. J Neurophysiol 66:559–579

Schlag J, Schlag-Rey M (1984) Visuomotor functions of central thalamus in monkey. II. Unit activity related to visual events, targeting, and fixation. J Neurophysiol 51:1175–1195

Schlag J, Schlag-Rey M (1986) Role of the central thalamus in gaze control. In: Freund HJ, Büttner U, Cohen B, Noth J (eds) The oculomotor and skeletalmotor system: differences and similarities. Prog Brain Res 64:191–201

Schlag-Rey M, Schlag J (1984) Visuomotor functions of central thalamus in monkey. I. Unit activity related to spontaneous eye movements. J Neurophysiol 51:1149–1174

Schultz W, Apicella P, Scarnati E, Ljungberg T (1992) Neuronal activity in monkey ventral striatum related to the expectation of reward. J Neurosci 12:4595–4610

Scott TR, Yaxley S, Sienkiewicz ZJ, Rolls ET (1986) Gustatory responses in the frontal opercular cortex of the alert cynomolgus monkey. J Neurophysiol 56:876–890

Selemon LD, Goldman-Rakic PS (1985) Longitudinal topography and interdigitation of corticostriatal projections in the rhesus monkey. J Neurosci 5:776–794

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

Siwek DF, Pandya DN (1991) Prefrontal projections to the mediodorsal nucleus of the thalamus in the rhesus monkey. J Comp Neurol 31:509–524

Siwek DF, Pandya DN (1992) The differential laminar distribution of cells in prefrontal cortex projecting to the mediodorsal nucleus. Soc Neurosci Abstr 18:304

Spatz WB (1977) Topographically organized reciprocal connections between areas 17 and MT (visual area of superior temporal sulcus) in the marmoset Callithrix jacchus. Exp Brain Res 27:559–572

Stamm JS (1973) Functional dissociation between the inferior and arcuate segments of dorsolateral prefrontal cortex in the monkey. Neuropsychologia 11:181–190

Tanabe T, Yarita H, Iino M, Ooshima Y, Takagi SF (1975) Olfactory projection area in orbitofrontal cortex of the monkey. J Neurophysiol 38:1269–1283

Tanila H, Carlson S, Linnankoski I, Kahila H (1993) Regional distribution of functions in dorsolateral prefrontal cortex of the monkey. Behav Brain Res 53:63–72

Vaadia E, Benson DA, Heinz RD, Goldstein MH Jr (1986) Unit study of monkey frontal cortex: active localization of auditory and visual stimuli. J Neurophysiol 56:934–952

Van Essen DC, Maunsell JHR (1983) Hierarchical organization and functional streams in the visual cortex. Trends Neurosci 6:370–375

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

Welch K, Stuteville P (1958) Experimental production of unilateral neglect in monkeys. Brain 81:341–347

Wilson FAW, Scalaidhe SPO, Goldman-Rakic PS (1993) Dissociation of object and spatial processing domains in the primate prefrontal cortex. Science 260:1955–1958

Wirth FP (1973) Insular-diencephalic connections in the macaque. J Comp Neurol 150:361–392

Yarita H, Iino M, Kogure S, Takagi SF (1980) A transthalamic olfactory pathway to orbitofrontal cortex in the monkey. J Neurophysiol 43:69–85

Yeterian EH, Pandya DN (1991) Prefrontostriatal connections in relation to cortical architectonic organization in rhesus monkeys. J Comp Neurol 312:43–67

Yeterian EH, Pandya DN (1992) Laminar origin of striatal and thalamic projections of the prefrontal cortex in rhesus monkeys. Soc Neurosci Abstr 18:305

Yeterian EH, Van Hoesen GW (1978) Cortico-striate projections in the rhesus monkey: the organization of certain cortico-caudate connections. Brain Res 139:43–63