

Highly Restricted Origin of Prefrontal Cortical Inputs to Striosomes in the Macaque Monkey

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The prefrontal cortex is made up of neocortical areas thought to mediate aspects of the temporal and spatial organization of behavior. One of the prime output targets of the prefrontal cortex is the striatum, which is thought to operate in series with the prefrontal cortex in some neural computations. We have analyzed this prefronto-striatal projection in cynomolgus monkeys by combining anterograde neuronal tract tracing methods with neurochemical markers for the striosome and matrix compartments of the striatum. Our results single out two parts of the frontal cortex as projecting densely to the striosome compartment of the striatum: the posterior orbitofrontal/anterior insular cortex and the mediodorsal prefrontal/ventromedial striatum. These areas jointly innervated striosomes in the anterior and ventromedial striatum, mainly in the caudate nucleus. Striosomes in the dorsolateral striatum were never labeled. Thus, the anatomical subsystem defined by striosome affiliation includes three cortical and striatal regions that, in humans, have been implicated in obsessive–compulsive disorder. Nearly all of the remaining parts of the prefrontal cortex studied projected preferentially to the matrix compartment. Most of these prefrontal inputs were also patchy, and many of the patches (matrisomes) were selectively paired with nearby striosomes. The highly fractionated organization of prefrontal inputs to striosomes and matrisomes could form a template for computational networks in the striatum that redistribute prefrontal corticostriatal inputs to serve in context-dependent behavioral planning.

[Key words: frontal lobe, caudate nucleus, orbitofrontal cortex, anterior cingulate cortex, obsessive-compulsive disorder, basal ganglia]

Clinical, neurobehavioral, and imaging studies have established broad functional subdivisions within the prefrontal cortex. Parts of the lateral convexity cortex are selectively activated during tasks engaging spatial working memory and behavioral planning (Frith et al., 1991; Sawaguchi and Goldman-Rakic, 1991; Fu-

nahashi et al., 1993; Petrides et al., 1993; for review, see Fuster, 1989). By contrast, medial prefrontal/anterior cingulate cortex and orbitofrontal cortex can be selectively activated in paradigms evoking emotional responsivity, response selection or suppression, and attention shifts (Rosenkilde et al., 1981; Yamamoto et al., 1984; MacLean and Newman, 1988; Posner et al., 1988; Pardo et al., 1990, 1991, 1993; George et al., 1993; Paus et al., 1993). Regionally selective metabolic dysfunctions of the prefrontal cortex have also been found in major psychiatric disorders. In schizophrenic patients, tasks engaging the dorsolateral prefrontal cortex do not lead to increased activation of this area, as they do in normal subjects (Berman and Weinberger, 1990; Park and Holzman, 1992). Abnormalities in metabolic activity in the orbitofrontal cortex, medial prefrontal cortex, or both, have been found in major depression (Drevets et al., 1992), depression associated with Parkinson's and Huntington's diseases (Mayberg et al., 1990, 1992), obsessive–compulsive disorder (OCD; Baxter et al., 1988, 1992; Swedo et al., 1989, 1992; Benkelfat et al., 1990; Sawle et al., 1991; Rubin et al., 1992), Gilles de la Tourette syndrome (Baxter et al., 1990), and schizophrenia (Andreason et al., 1992).

Imaging studies of the basal ganglia have raised the possibility that in such neuropsychiatric illnesses, and also in the course of normal behavior, the prefrontal cortex operates in conjunction with the caudate nucleus (Baxter et al., 1988, 1992; Swedo et al., 1989; Drevets et al., 1992; Cummings, 1993; Rauch et al., 1994). This new evidence supports the concept developed from earlier anatomical and lesion studies that different areas of the prefrontal cortex interact with different parts of the caudate nucleus to form high-level functional subsystems within the forebrain (Teuber and Proctor, 1964; Iversen and Mishkin, 1970; Divac, 1972; Rosvold 1972; Iversen, 1979).

How are these proposed functional subsystems organized? The known connectivity between the prefrontal cortex and the caudate nucleus in primate already indicates that they have three interesting characteristics. First, the direct connections are one way, from the frontal cortex to the caudate nucleus. The caudate nucleus (and, more generally, the striatum) must project through several synaptic stations before its information is sent to the cortex (Graybiel, 1990; Parent, 1990). Second, the connections from the prefrontal cortex to the caudate nucleus, although broadly topographic, are “distributed” in the sense that any one small part of the cortex projects to a considerable extent of the caudate nucleus (Künzle, 1975; Goldman and Nauta, 1977; Yeterian and van Hoesen, 1978; Selemon and Goldman-Rakic, 1985). Finally, the prefrontal inputs to the caudate nucleus are organized in patchy patterns (Kün-

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Table 1. Summary of cases

Case	Cortical site	Area	Tracer	Amount	Predominant compartment		
					Strio	Matrix	Mixed
1A	Frontal pole	10	met	210 nl			+
1B	Principal/arcuate	46	WGA-HRP	180 nl		+	
2A	Posterior orbitofrontal	13/Ia	met	150 nl	+		
3A ^a	Principal sulcus	8/46	met	200 nl		+	
5A	Lateral orbitofrontal	11	met	370 nl		+	
6A	Posterior orbitofrontal	13/Ia	met	140 nl	+		
6B	Orbitofrontal	12/13	WGA-HRP	280 nl			+
7A	Posterior orbitofrontal	13	met	†	+		
7B	Orbitofrontal	13	WGA-HRP	†			+
8A	Lateral orbitofrontal	12	met	120 nl		+	
9B	Medial prefrontal	14	WGA-HRP	180 nl		+	
12A	Anterior cingulate	24/32	met	180 nl	+		
12B	Prelimbic/ant. cingulate	10/32	WGA-HRP	200 nl		+	
13A	Dorsolateral convexity	9/46	met	300 nl		+	
13B	Inferior convexity	12/46	WGA-HRP	260 nl		+	
14A	Prelimbic/ant. cingulate	32	met	160 nl	+		
14B	Prelimbic/ant. cingulate	32	WGA-HRP	120 nl		+	
15A	Gyrus rectus	14/25	met	100 nl		+	
16B	Gyrus rectus	14	WGA-HRP	160 nl		+	

See text and figures for further description of the cortical areas injected. met, L-[³⁵S]-methionine; WGA-HRP, wheat germ agglutinin-conjugated horseradish peroxidase.

^a *Macaca mulatta*.

† Values uncertain.

zle, 1975; Goldman and Nauta, 1977; Ragsdale and Graybiel, 1981). These three characteristics have led to the notion that there are multiple prefrontal and premotor circuits in the basal ganglia (Graybiel, 1984; Alexander et al., 1986; Hoover and Strick, 1993), and to the idea that the modularity of input connections may be related to the intrinsic neurochemical compartments of the caudate nucleus, striosomes and matrix (Graybiel and Ragsdale, 1978, Graybiel et al., 1981), or to compartments within the matrix (Parthasarathy et al., 1992; Flaherty and Graybiel, 1994). In the experiments reported here and briefly in Eblen and Graybiel (1992, 1993), we directly tested these ideas by analyzing the connections of different sites in the prefrontal cortex with the striosomes and matrix of the caudate nucleus.

Materials and Methods

The distinguishable anterograde tracer substances, L-[³⁵S]-methionine (DuPont New England Nuclear, Boston; 200 μ Ci/ μ l in sterile saline) and a wheatgerm agglutinin-horseradish peroxidase conjugate (WGA-HRP, Sigma, St. Louis, MO; 15% in sterile saline), were placed in orbital, medial, or lateral sites in the left prefrontal cortex of 10 adult female and 2 male cynomolgus monkeys (*Macaca fascicularis*). One lateral injection was made in an adult male rhesus monkey (*Macaca mulatta*) that had been used previously in chronic microelectrode recording studies (Tehovnik and Lee, 1990). Successful injections are listed in Table 1.

Injection protocols. Anesthesia was induced with ketamine hydrochloride i.m. and was maintained with a mixture of ketamine hydrochloride and xylazine i.m. Fluids (lactated Ringer's solution) were delivered during surgery by an intravenous catheter, and anesthetic levels were determined by monitoring heart rate, respiratory rate, and reflexes. Surgeries were performed under sterile conditions with the animal's head in a Kopf stereotaxic headholder. Bone and dural flaps were turned over the intended injection sites, tracers were injected with hand-held 1 μ l Hamilton syringes, and the surgical opening was closed in layers.

A total of 0.08–0.18 μ l of tracer was delivered in 0.01–0.02 μ l aliquots over a period of several minutes at two or more closely spaced locations for each injection site (see Table 1).

Tissue preparation and histology. Brains were perfused after 48–72 hour survival periods by transcardial perfusion with the animals deeply anesthetized with ketamine hydrochloride (10 mg/kg i.m.) and Nembutal (10–15 mg/kg i.p.). Perfusion solutions given were, in sequence, heparinized saline, 4% paraformaldehyde in 0.1 M phosphate-buffered saline (PBS) containing 5% sucrose, and PBS containing 5% sucrose. The brains were cut coronally at 40 μ m on a freezing microtome, and the sections were stained or processed for autoradiography as described earlier (Flaherty and Graybiel, 1991; Parthasarathy et al., 1992). For autoradiography, every sixth section was slide mounted, dipped in NTB-2 liquid emulsion (Kodak), and exposed for 10 d to 6 weeks, developed in Kodak D-19 at 15°C, and counterstained with cresylecht violet. WGA-HRP staining was carried out on other series of sections by the tetramethylbenzidine (TMB) protocol of Mesulam (1978) with slight modifications (Parthasarathy et al., 1992). Sections serially adjoining those prepared to demonstrate the transported label were stained for acetylthiocholinesterase (AChE; Geneser-Jensen and Blackstad, 1971; Graybiel and Ragsdale, 1978) or for Met-enkephalin-like immunoreactivity (Parthasarathy et al., 1992). Striosomes were identified as circumscribed zones with low AChE activity, differentially low enkephalin immunostaining of cell bodies (Graybiel and Chesselet, 1984), or their distinctive neuropil enkephalin immunostaining.

Data analysis. Sections were studied under bright-field and dark-field illumination and, for WGA-HRP reaction product, with cross-polarized dark-field illumination (Illing and Wässle, 1979). The injection sites were reconstructed in serial sections with sulci and gyri visible on the brain photographs serving as landmarks. Borders of the effective injection sites were estimated by eye, as described by Parthasarathy et al. (1992), following the maps of Walker (1940), Mesulam and Mufson (1982), Morecraft et al. (1992), Ray and Price (1993), and Carmichael and Price (1994). Distributions of transported label in the striatum were charted with the aid of a dissecting microscope coupled to a drawing tube. Scoring of the labeled corticostriatal fiber distributions as lying in striosomes or in matrix or in both was done by comparing the experimentally labeled distributions with the patterns of staining visible in

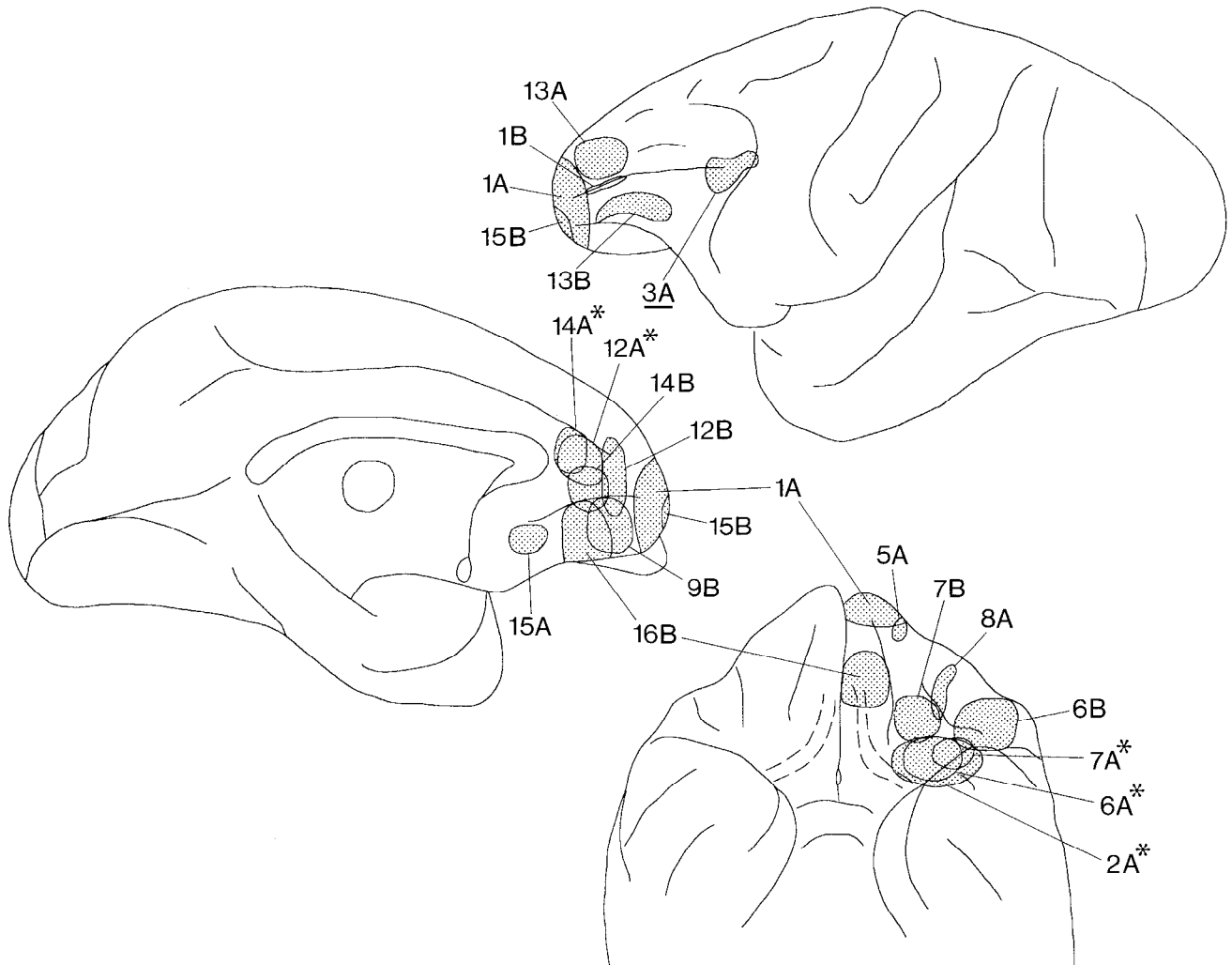


Figure 1. The locations of anterograde tracer injection sites shown in semischematic lateral, medial, and ventral views of the left hemisphere of a cynomolgus macaque monkey brain. Case numbers ending with *A* indicate sites at which injections of L-³⁵S-methionine were made. Case numbers ending with *B* indicate cases with WGA-HRP injection sites. Case numbers with * indicate cases with strong projections to striosomes. Case 3A was a *Macaca mulatta*.

adjacent sections processed either for AChE activity or for enkephalin-like immunoreactivity. Striosomes detected by the two markers were coincident in regions in which both stains were successful, but there were variations from monkey to monkey in the quality of the two stains, and there were regional variations in the staining patterns as well as heterogeneous staining of the matrix, especially in the enkephalin-immunostained sections. In the ventral parts of the caudoputamen, both marker distributions were complex and, when possible, both were studied to evaluate the compartmentalization of tracer labeling (Graybiel and Chesselet, 1984; Martin et al., 1991). All identifications of striosomes and matrix reported were made with these technical limitations and qualifications.

Results

General plan of the prefrontostriatal projection in the macaque

Figure 1 illustrates the locations of the three groups of injection sites made: six injections in the medial, lateral, and posterior periallocortical orbital cortex; seven injections in the medial prefrontal cortex, except in its most dorsal part; two injections in the frontal pole; and four injections in the lateral convexity cortex that were, respectively, dorsal, ventral, posterior to the principal sulcus, and within it. The deposits extended through all cortical layers but did not always infiltrate them equally. Thus,

most of the prefrontal cortex was included in the present study, exceptions being the dorsal part of the medial prefrontal cortex including area 9 and the ventral cortex stretching between the orbital and medial prefrontal areas.

Regardless of the placement of the cortical injection sites, the labeled prefrontostriatal projections extended through a considerable volume of the striatum, always including the head of the caudate nucleus. Viewed in cross-section, they were distributed within discontinuous, diagonally oriented fields. The most intense and most patchy labeling was in the head of the ipsilateral caudate nucleus. The putamen also was labeled in all cases, usually less strongly (Fig. 2). All injected cortical sites also projected contralaterally, but the contralateral striatal labeling was weaker than that on the ipsilateral side and usually was visible only at anterior-posterior levels at which the strongest ipsilateral labeling occurred. Our analysis was restricted to the ipsilateral side.

The prefrontal projections to the striatum were invariably most broadly distributed in the anterior part of the striatum, and farther caudally became progressively restricted to fields stretching from the medial and dorsomedial caudate nucleus to the

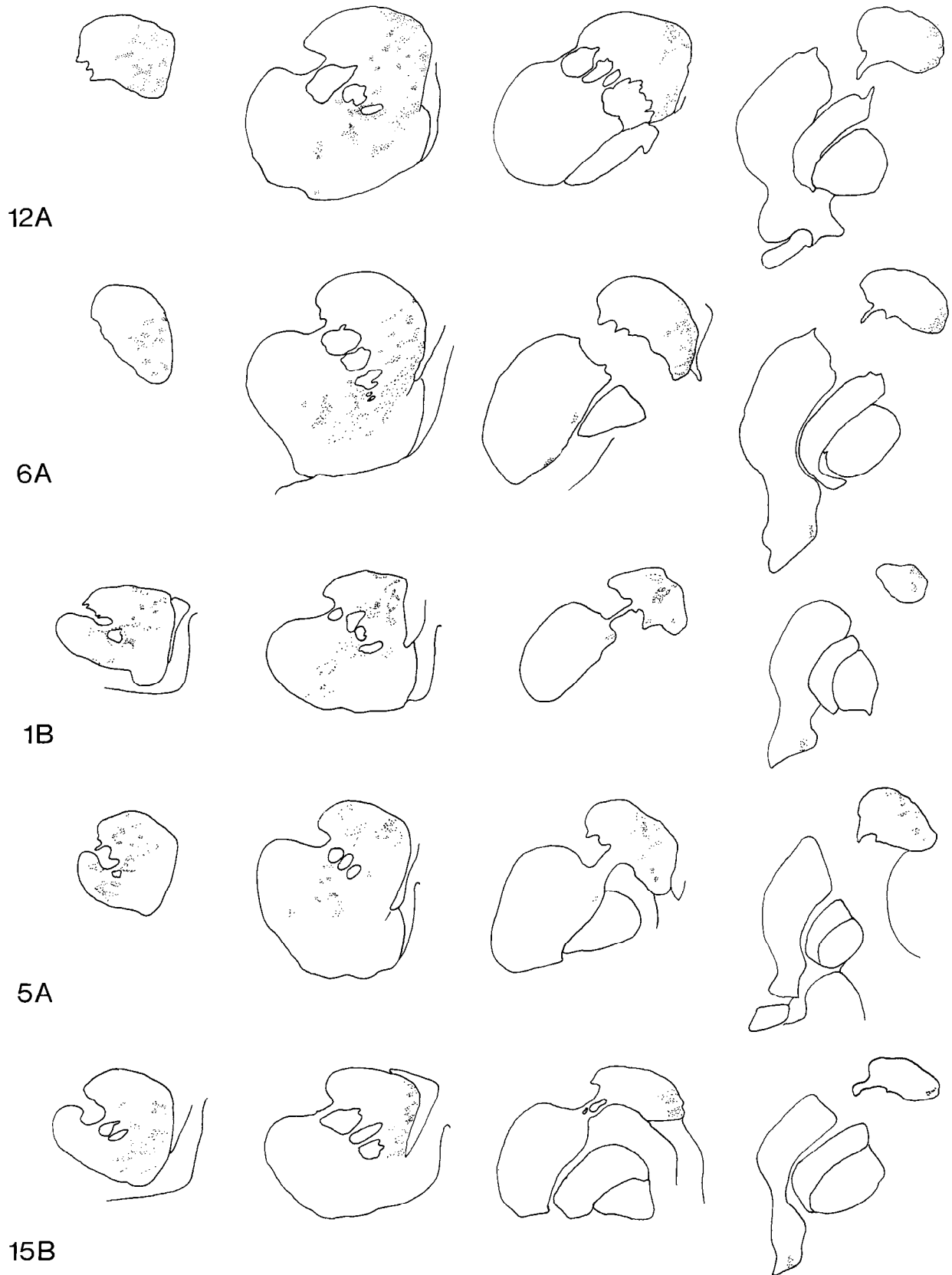


Figure 2. The topography of the prefrontostriatal projection. Each series of semischematic drawings shows four coronal sections through the striatum illustrating, from left to right, the level of the head of the caudate nucleus, the level of the nucleus accumbens, the level of the anterior commissure, and the level of the globus pallidus. *Case 12A*: injection of medial prefrontal cortex; *case 6A*, injection of posterior orbital cortex; *case 1B*, injection of principal sulcal cortex; *case 5A*, injection of lateral orbital cortex; *case 15B*, injection of frontal pole. See also Figure 1.

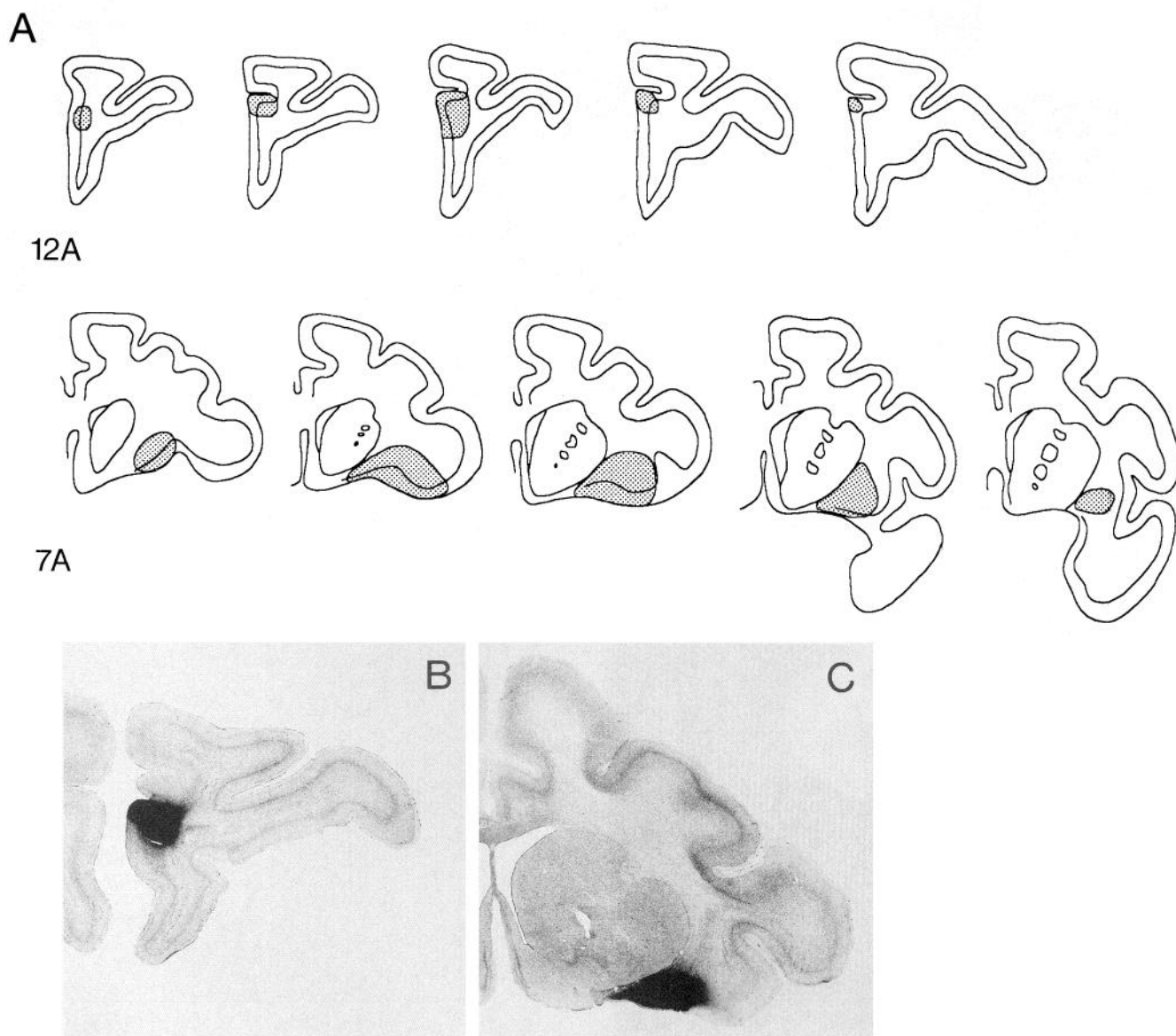


Figure 3. Examples of prefrontal cortical injection sites that led to selective corticostriatal labeling of striosomes. **A**, Schematic drawings of coronal sections display the anteroposterior extents of the injection sites of medial prefrontal/anterior cingulate case 12A and posterior orbitofrontal/anterior insula case 7A. Photographs of the injection sites are shown in **B** for case 12A and in **C** for case 7A.

medial and ventromedial putamen. It was also in the anterior sections that compartmentalization of the labeled projections was most pronounced and consistent. In more caudal sections, the labeling pattern changed, becoming more diffuse and shifting toward the ventral margins of the body and tail of the caudate nucleus and the posterior putamen.

A general topography of the prefrontostriatal projection was apparent in that inputs from the lateral prefrontal regions (such as cortex associated with the principal sulcus and the lateral orbitofrontal cortex) reached farther laterally and dorsally in the caudate nucleus than did more inputs from caudal and medial parts of the prefrontal cortex (Fig. 2). However, it was striking that the fiber systems traced from posterior orbitofrontal cortex and from the medial prefrontal/anterior cingulate cortex had overlapping distributions (Fig. 2). The frontal pole projected predominantly to a medial sector of the caudate nucleus lying along the ventricular wall (Fig. 2).

Selective targeting of striatal compartments by fibers from the macaque prefrontal cortex

The compartmental analysis yielded four clear-cut results. First, nearly all of the sites in the prefrontal cortex injected, whether orbital, medial, or lateral, preferentially innervated the matrix compartment of the caudate nucleus. The only exceptions were sites in the posterior orbital and posterior medial prefrontal cortex, which preferentially innervated sets of striosomes in the caudate nucleus (Figs. 1, 3; Table 1). Second, even with injections at these striosome-projecting cortical sites, many striosomes in the lateral and caudal parts of the caudate nucleus were never detectably labeled, and there was little labeling of striosomes in the putamen except ventromedially. Thus, the prefrontal corticostriatal system does not innervate all striosomes in the macaque striatum. Third, even in cases with robust and selective labeling of striosomes, there were

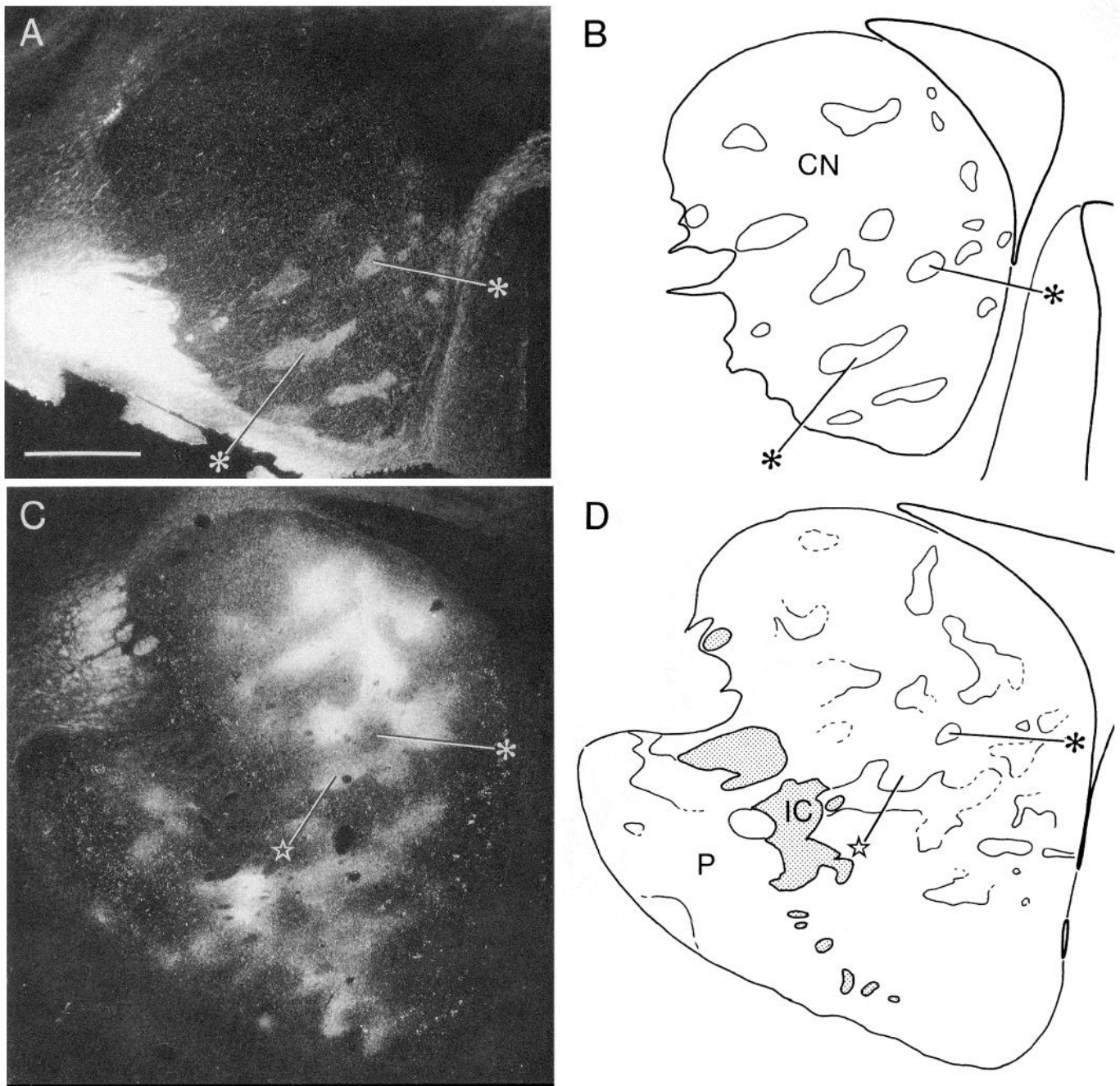


Figure 4. Different regions of the macaque prefrontal cortex target striosomes and matrix. *A* and *B*, Serial sections illustrating predominant projection to striosomes in case 7A labeled by an injection of ^{35}S -methionine into the posterior orbital cortex (see Fig. 3 for injection site). *A* shows dark-field micrograph of a coronal section through the rostral part of the caudate nucleus. Labeling, which appears white, is mainly in discrete patchy foci. *B* shows drawing of a section adjacent to that illustrated in *A* and displays striosomes as detected by AChE histochemistry (fine outlines, examples at asterisks). Corresponding locations in *A* are similarly marked. Note that the labeled input patches in *A* match precisely the striosomes shown in *B*. *C* and *D*, A pair of serial sections through the left anterior caudate nucleus of case 13A, in which the injection site was in the dorsolateral prefrontal cortex (see Fig. 1). The autoradiogram in *C* illustrates the distribution of labeled corticostriatal fibers. *D* shows drawing of the adjoining section, stained for enkephalin-like immunoreactivity to indicate striosomes (fine outlines, example at asterisk). Note that this prefrontal projection largely avoids striosomes: when a patch of label is visible, it is in the matrix (example at star). Stipple indicates internal capsule (*IC*). *CN*—caudate nucleus, *P*—putamen. Scale bar in *A* indicates 2 mm.

variable amounts of accompanying labeling of the ventromedial matrix. These innervation patterns took the form of obliquely oriented fields of dorsal innervation with preferential striosomal labeling and a ventromedial region in which striosomes (insofar as they could be identified with confidence) were not selectively targeted. Thus, striosome-selective fields

of prefrontal innervation were accompanied by a generally more ventromedial labeling in the matrix. Finally, the much more broadly derived prefrontal inputs to the matrix compartment of the striatum were themselves heterogeneously distributed, and in some cases, such compartments were at least partially coincident with zones of enhanced enkephalin-like im-

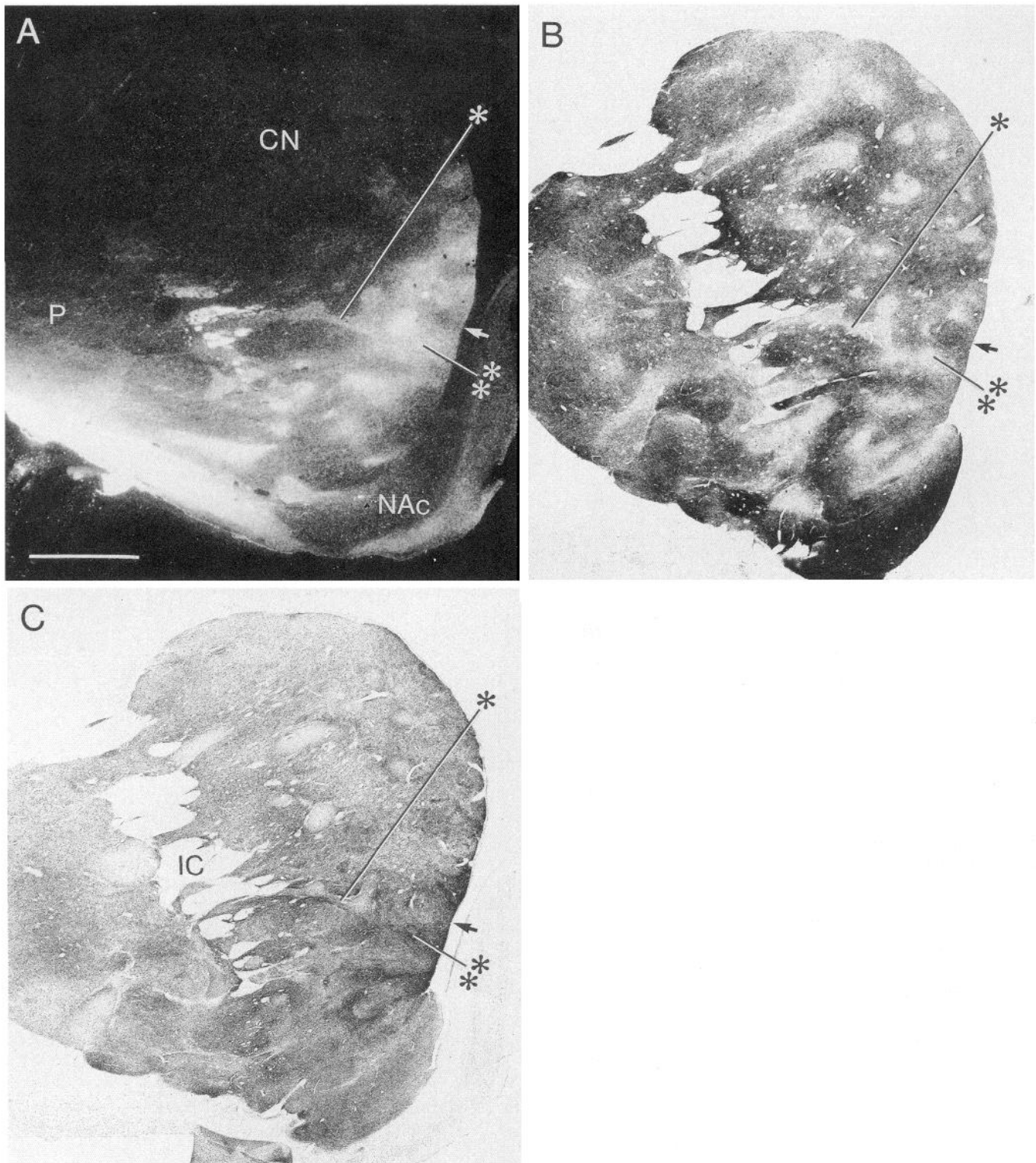


Figure 5. Posterior orbital cortex has a striatal projection that is only partly selective for striosomes. *A*, Distribution of autoradiographic labeling in the caudate nucleus of case 7A, illustrated at a level slightly more caudal level than that shown in Figure 4A. *B* and *C*, Photomicrographs of sections adjacent to the one shown in *A* stained, respectively, for AChE activity (*B*) and for enkephalin-like immunoreactivity (*C*). Note that dorsally and laterally (and anteriorly, see Fig. 4A), the label fills AChE-poor striosomes (see asterisks). Ventromedially, the label is also heterogeneously distributed but occurs both in striosomes and in matrix. *Single and double asterisks in B* indicate two AChE-poor striosomes that are innervated by labeled fibers. The more dorsal one (*single asterisk*) is enkephalin-poor, but the lower more ventral striosome has enkephalin-rich neuropil (*double asterisks*); cf. Graybiel et al. (1981); Martin et al. (1991). The dorsal striosome is illustrated at higher magnification in Figure 6. Note that discrete parts of the matrix are avoided by the input label (example at *arrow*). The nucleus accumbens (*NAc*) is devoid of label. *CN*—caudate nucleus, *P*—putamen. Scale bar in *A* indicates 2 mm.

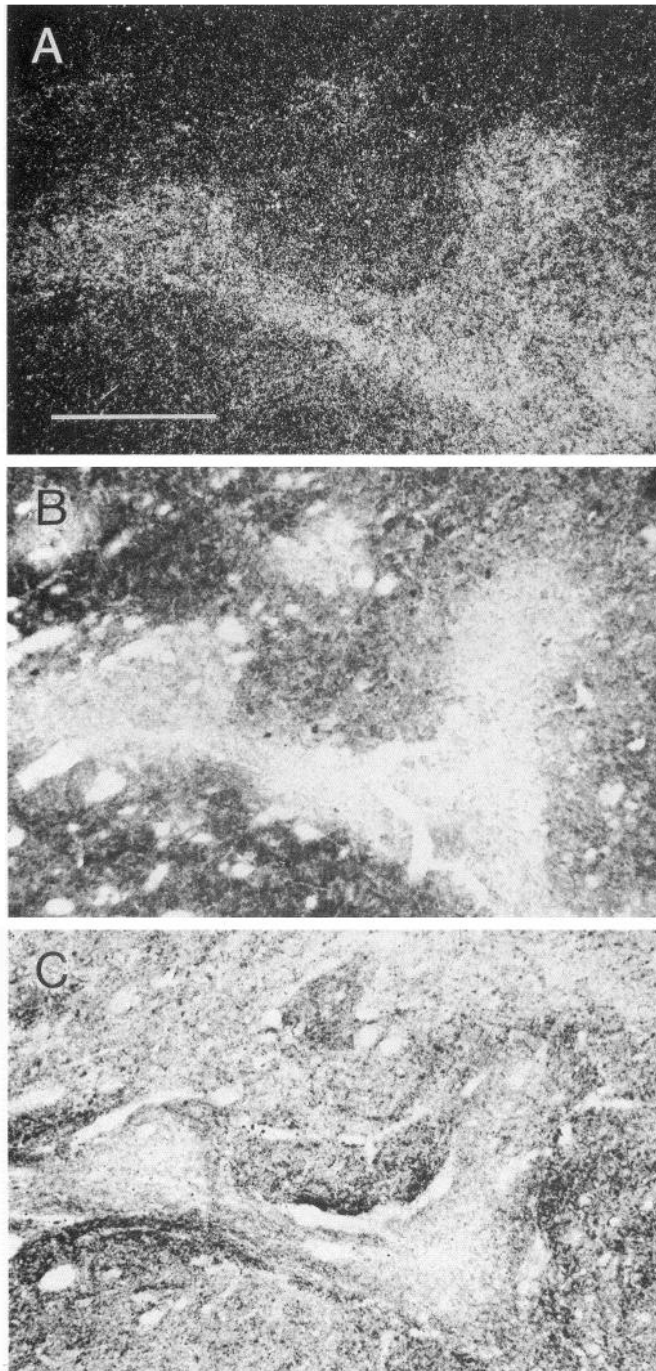


Figure 6. Posterior orbitofrontal input to histochemically identified striosome. Photomicrographs of the striosome shown by single asterisk in Figure 5, illustrating enhanced ^{35}S -methionine labeling of the striosome (A), identified both by its AChE-poor neuropil (B) and by its relatively low enkephalin-like immunoreactivity (C). Scale bar indicates 0.5 mm.

munoreactivity. Thus, both striosome-directed and matrix-directed prefrontostriatal projections are compartmentalized. These points are documented below, together with the topographies of the prefrontal input systems identified.

Restricted origins of prefrontal projections to striosomes

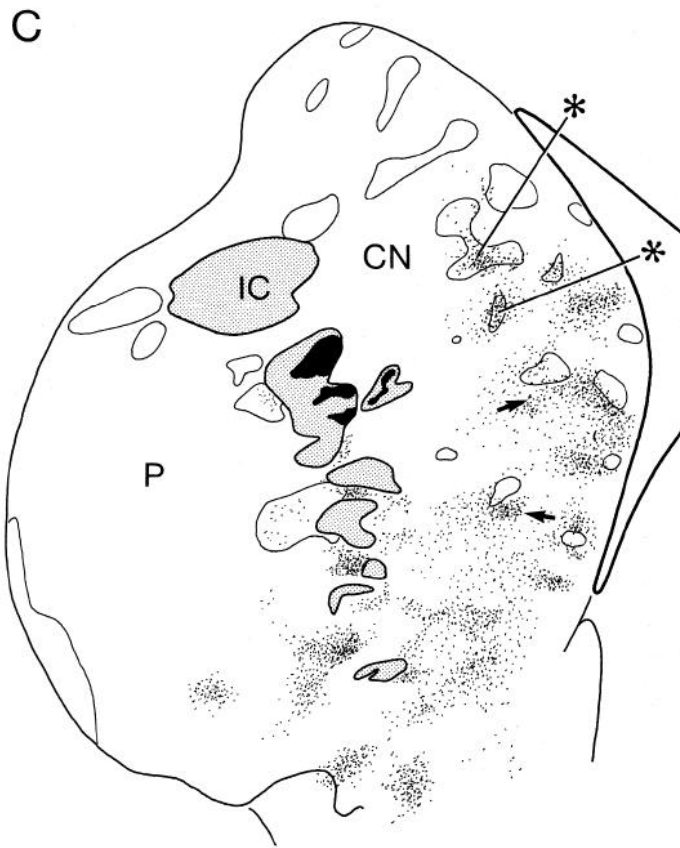
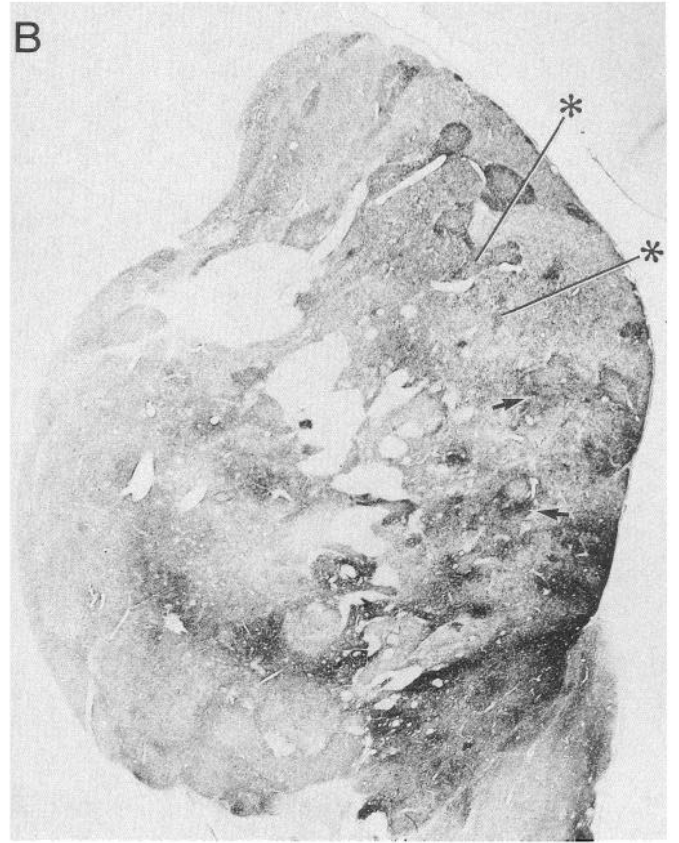
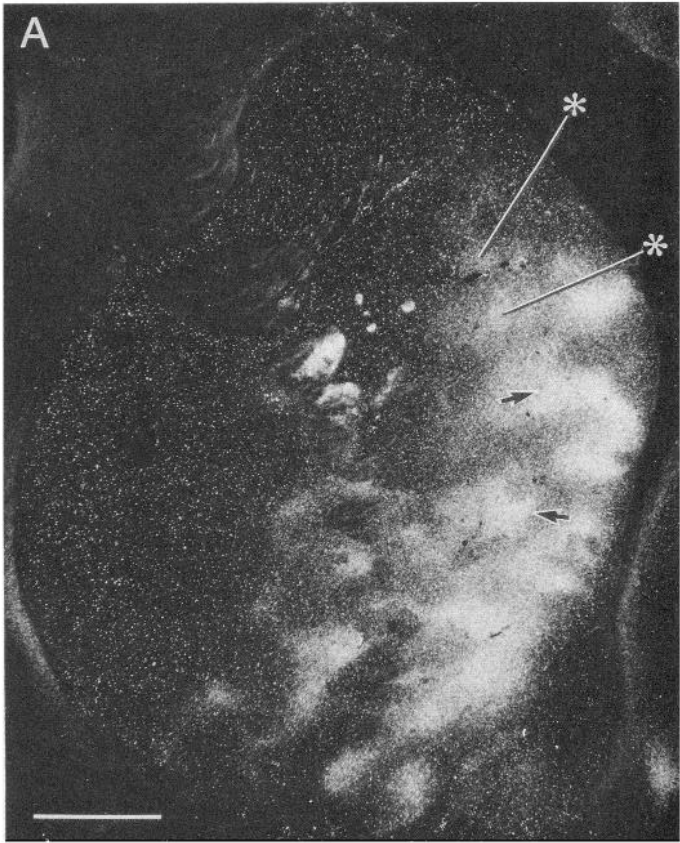
Selective innervation of striosomes was found for only 5 of the 20 cortical injections made. Three of the injection sites involved the posterior orbital cortex, and the other two were centered in the medial prelimbic cortex at its border with the anterior cingulate cortex.

The injection sites in the posterior orbitofrontal cortex involved posterior area 13 as well as the anterior insula and parts of the underlying claustrum (Fig. 3). The patterns of corticostriatal projection in these cases were similar and are illustrated by case 7A in Figures 4–6. Strongly labeled clusters of orbitofrontal fibers appeared ventrally in the head of the caudate nucleus and, farther caudally, in a diagonally oriented zone that extended from the medial border of the caudate nucleus to the ventrolateral putamen. The labeled input clusters corresponded to striosomes identified in adjacent sections.

In contrast to this pronounced orbitofrontal innervation of striosomes, labeling in the matrix surrounding the innervated striosomes was at or near baseline levels of intensity rostrally. However, at slightly more caudal levels, as the field of predominant striosomal labeling became weaker (Fig. 5), strong label began to appear in the medial part of the caudate nucleus, and this was mainly in the matrix compartment. Thus, rostrally and dorsally within the distribution field of the orbitofrontal fibers, striosomes were selectively labeled, but medially and ventrally the striosomes were not. The fields of differential striosome and matrix labeling were connected with one another at the level shown in Figure 5 by fingers of labeling matching striosomes that stretched laterally toward the zone of weaker striosome labeling. The periventricular band of matrix labeling was itself heterogeneous. There were zones of weaker labeling in its ventral part, and these zones, like the associated band of labeling, were within the matrix compartment. At caudal levels, the weak, diffuse labeling still visible was confined to the ventral tip of the body and tail of the caudate nucleus, and could not be assigned to either striosome or matrix compartments. As shown in Figure 5, the nucleus accumbens was not detectably labeled.

The characteristic pattern of labeling found in the cases of medial prelimbic injection is illustrated in Figure 7. The injection sites in these cases were situated in the cortex immediately anteriorly to the rostral tip of the corpus callosum. They appeared to involve area 32 and caudally area 24. Labeling at rostral levels of the striatum appeared in crisp patches identified as striosomes (data not shown). At more caudal levels, a clear change in the labeling pattern occurred, so that there was a marked distinction between the dorsal, central, and ventral parts of the projection field. Dorsally, the labeling was weak but co-

Figure 7. Dorsal and ventral caudoputamen are differently innervated by a single prefrontal cortical region in relation to enkephalin-immunostained compartments. A, Dark-field micrograph demonstrating the patchy autoradiographic labeling in the caudate nucleus following injection of the posterior medial prefrontal cortex (case 14A). B, Section adjacent to A, stained for enkephalin-like immunoreactivity. C, Overlay charting of sections shown in A and B, with striosomes shown by fine outlines and densely labeled projections shown by dots. The internal capsule (IC) is shown in stipple, with jet black to indicate densely labeled capsular fiber bundles. In the most dorsal part of the projection field, striosomes appear to be faintly labeled (examples at asterisks). Most of the labeling in the medial caudoputamen is in the matrix. In the ventromedial striatum, there are patches of labeled input fibers. Some of these correspond to enkephalin-rich zones next to enkephalin-poor striosomes (examples at arrows). CN—caudate nucleus, P—putamen. Scale bar in A indicates 2 mm.



incided with striosomes (Fig. 7A and 7B). Centrally, the strongest label was found outside striosomes, and the labeled zones actually interdigitated with striosomes detected by either AChE activity or enkephalin-like immunoreactivity (Fig. 7C). Finally, in the ventromedial sector, no association with enkephalin-poor zones was obvious, but some of the labeling was found to coincide with or to occupy parts of zones of strong enkephalin-like immunoreactivity (Fig. 7C). Thus, for the medial prefrontal/anterior cingulate cortex injected, we found evidence for a general projection pattern similar to the one observed in the posterior orbitofrontal cases.

Prefrontal projection systems innervating the matrix

Even in the posterior orbitofrontal and medial prefrontal/anterior cingulate cases, there was at least some labeling of fibers innervating the striatal matrix medially and ventrally. However, in all other cases except one, the matrix was the principal target of the prefrontal input when the injection sites did not overlap the orbitofrontal or posterior mediofrontal sites.

In monkeys in which the dorsolateral prefrontal cortex or cortex in and near the principal sulcus was injected, there was dense and apparently nearly uniform labeling of the matrix within the striatal projection fields (Fig. 2). There were pockets of very low, near-background levels of labeling within these fields, and every such zone that we could score corresponded to a striosome. This projection pattern is shown in Figure 2 for case 1B, in which a large tracer deposit was placed in the dorsal and ventral banks of the principal sulcus. A similar projection pattern was seen in case 13A, in which a large injection of tracer was made in the dorsolateral prefrontal cortex (Fig. 4B). It was notable that within the main projection fields labeled in these cases, the labeled innervation appeared nearly to fill the matrix; the borders of the field were themselves irregular with some outlying patches of label, but the main field was strongly labeled throughout.

In a second group of cases, with injection sites in the lateral convexity (case 13B), the lateral orbitofrontal cortex (cases 5A and 8A), and in the anterior arcuate cortex (case 3A), the labeled corticostriatal projections were also predominantly distributed within the matrix, but they differed from the first group by having definitely patchy distributions within the matrix. An example of such a heterogeneous matrix-input system is shown in Figure 8. The distribution of the labeled input patches in some of these cases seemed to be nonrandom: many lay adjacent to striosomes, and some interdigitated with striosomes within the field of innervation.

In a third group of three cases, the corticostriatal labeling was not selective to either the matrix or the striosome compartment. In two of the cases (6B and 7B), the injection sites partly overlapped the caudal orbitofrontal cortex identified as having projections to striosomes and partly included more rostral orbitofrontal cortex which, in other cases, was shown to innervate primarily matrix (Fig. 1). Thus, the lack of clear differential labeling of striosomes or matrix was to be expected. However, this explanation does not account for the results in case 1A, in which the injection site was in the frontal pole (Fig. 1). In this case of mixed innervation, most of the labeling was in the matrix and was distinctly patchy. When compared to striosomes in serially adjoining sections, the patches of label mostly fell in the matrix. However, in every section studied, there was, nevertheless, some association between the labeled patches and striosomes. Most frequently, the input patches were situated next to striosomes, but overlapped them partially. In other instances, a

striosome was found within a much larger patch of input labeling. The rare examples in which labeled patches and striosomes were strictly adjacent were nearly all in the dorsomedial part of the caudate nucleus.

Discussion

Frontostriatal circuits interconnecting the prefrontal cortex and the caudate nucleus are thought to participate in the neural activity underlying cognitive and affect-driven behaviors, and to be disordered in corresponding neuropsychiatric disorders. The experiments we report here establish that these circuits can be divided into two major sets in the macaque monkey. One originates in highly restricted regions of the posterior orbital/anterior insular cortex and the posterior medial prefrontal/anterior cingulate cortex, which preferentially innervate part of the striosomal system of the caudate nucleus. The second, much larger set of connections arises in the dorsolateral and ventrolateral prefrontal cortex and anterior frontal and anterior orbital cortex and preferentially innervates the matrix. These prefrontal inputs often form patches in the matrix (matrisomes), some of which systematically abut striosomes. These modular patterns of prefrontal projection suggest that in the primate, several mechanisms may exist for integration of corticostriatal inputs within the prefrontostriatal system as a whole.

Selective inputs to striosomes from the primate prefrontal cortex

It is striking that the posterior orbital and posterior mediofrontal sites that project to striosomes, besides the similar compartmental affiliation of their striatal projections, share anatomical connections with core structures of the limbic system such as the amygdala, the hippocampus, the medial part of the medio-dorsal thalamic nucleus, the habenula, the central gray substance, and the hypothalamus (Morecraft et al., 1992). These cortical areas are also among the regions of the macaque cortex receiving both serotonergic and dopaminergic innervation (Lewis, 1992), and are transcortically interconnected (Barbas and Pandya, 1989; Ray and Price, 1993; Carmichael and Price, 1994). According to cytoarchitectural analyses, these posterior orbital and medial regions represent the least differentiated "limbic" cortex of the frontal lobe (Sanides, 1970; Barbas and Pandya, 1989). The posterior orbital cortex, in fact, receives direct connections from olfactory cortex (Takagi, 1986; Barbas, 1993). These characteristics suggest that the major functional specializations of the striosome-projecting prefrontal cortex are tightly linked to those of the subcortical limbic system; these range from control of visceral responses and of emotions, such as the fear response for the amygdaloid complex, to the memory-related functions posited for the hippocampal formation (see, e.g., Davis, 1992; Zola-Morgan and Squire, 1993).

In humans, the orbitofrontal and the medial prefrontal-anterior cingulate areas have been implicated in behavioral and emotional responsivity and initiative (Fuster 1989; Cummings, 1993; see, e.g., Pardo et al., 1993). Moreover, the orbitofrontal and anterior cingulate cortex are the two cortical areas that, along with the head of the caudate nucleus, show differential blood flow patterns in patients suffering from obsessive-compulsive disorder (Baxter et al., 1988; Swedo et al., 1989; Insel, 1992; Rauch et al., 1994). Insofar as comparisons can be made between cortical regions in human and macaque, the neurologic and neuropsychiatric findings suggest that there may be true functional specialization of striosome-projecting prefrontal cor-

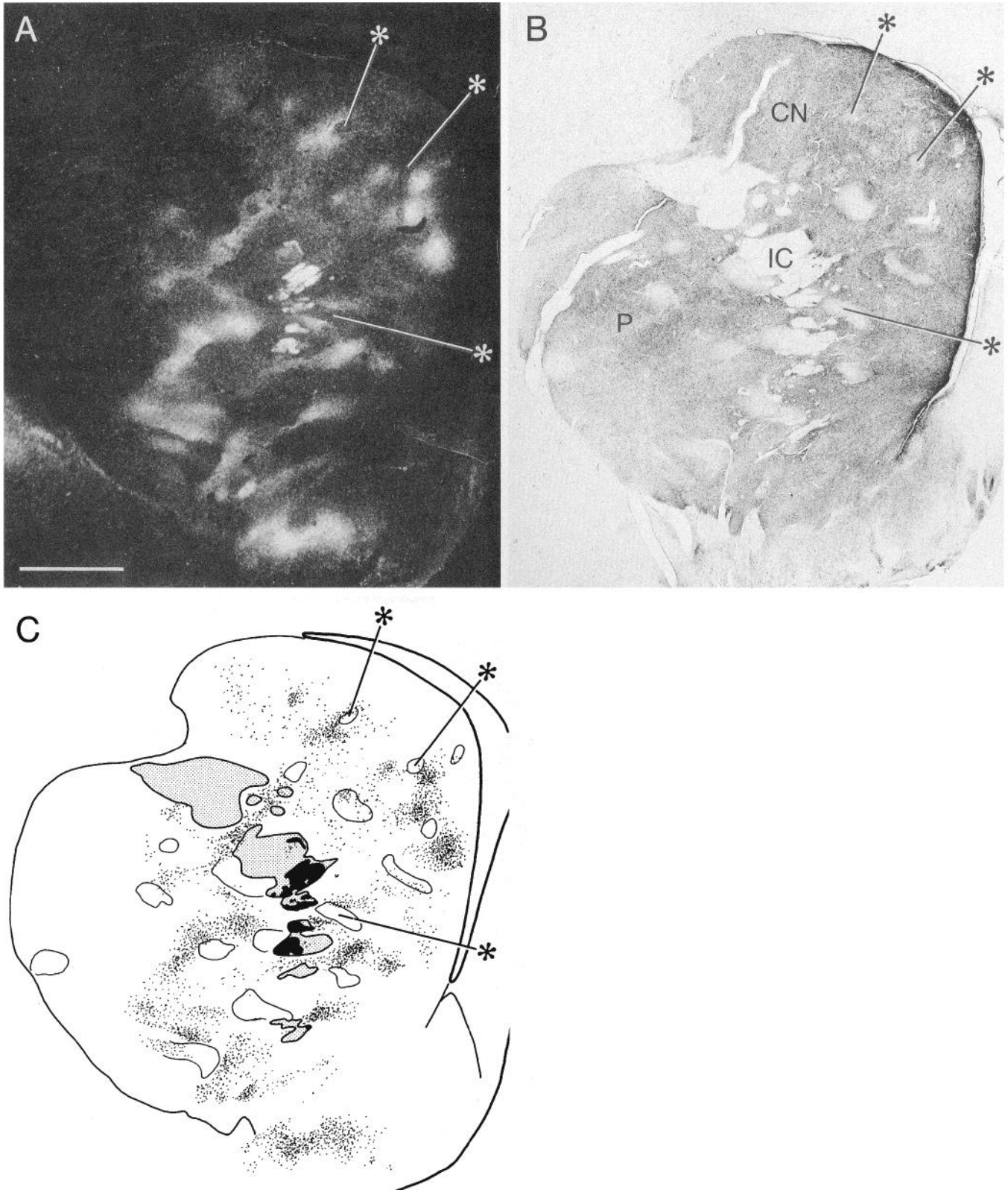


Figure 8. Some prefrontal inputs to the matrix form patches in the matrix (matrisomes) that are close to striosomes. **A**, Dark-field micrograph illustrating patchy autoradiographic labeling in the caudate nucleus and putamen in case 5A, in which the injection site was in the anterior lateral orbital cortex. **B**, Adjacent section stained for enkephalin-like immunoreactivity. **C**, Composite overlay charting of sections shown in **A** and **B**. Striosomes are shown by *fine outlines* (examples at *asterisks*), the heavily labeled inputs by *dots*. The internal capsule is shown in *stipple* (**IC**), with *jet black* showing regions of intense capsular labeling. Note that the patches of labeling are in the matrix, and that most lie adjacent to a striosome. **CN**—caudate nucleus, **P**—putamen. Scale bar in **A** indicates 2 mm.

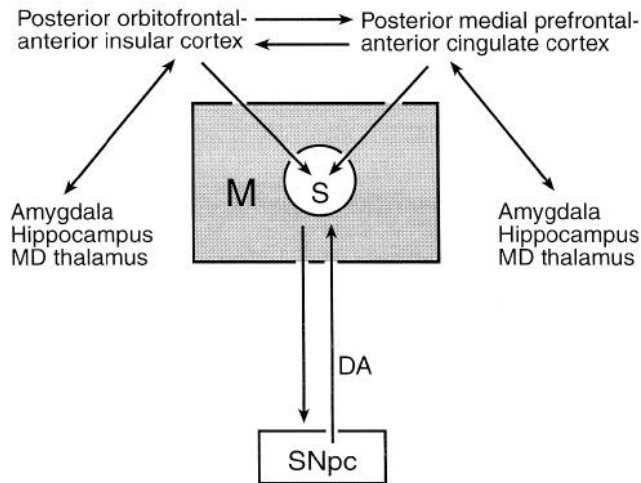


Figure 9. Prefrontal subsystems targeting striosomes in the macaque monkey caudate nucleus have reciprocal connections with structures of the limbic system, and striosomes target the substantia nigra, pars compacta. Diagram summarizes main prefrontal inputs to anterior striosomal compartment (*S*) identified in the experiments described. *MD*—mediodorsal nucleus (of thalamus); *M*—matrix compartment of striatum; *SNpc*—pars compacta of substantia nigra; *DA*—dopamine.

text for aspects of behavior ultimately related to behavioral drive. However, at least 22 cortical areas have been distinguished within the medial and prefrontal orbital cortex of the macaque (Carmichael and Price, 1994), and the human prefrontal cortex has been finely subdivided as well. We have identified only broad regional origins of the striosome-selective prefrontal inputs in the present study.

In such functional terms, it is particularly interesting that striosomes, unlike the matrix, are thought to send direct projections to the dopamine-containing neurons of the substantia nigra pars compacta or to their immediate vicinity (Graybiel 1990; Gerfen, 1992). Many of these dopamine-containing neurons become activated in relation to rewards and to stimuli representing rewards in behaving macaque monkeys (Schultz, et al., 1993). The present results suggest that the dopamine-containing nigral system receives a highly selective prefrontostriatal input, conveyed through striosomes, and that this input could be part of the neural mechanism related to underlying selective behavioral drive. In humans, orbitofrontal and anterior cingulate/medial prefrontal cortical areas have been suggested to collaborate in the production of neuropsychiatric symptoms found in obsessive-compulsive disorder (Baxter et al., 1988, 1992; Swedo et al., 1989; Machlin et al., 1991; Insel, 1992; Rauch et al., 1994; Schwartz et al., 1995). Our results suggest the speculation that iterative interactions between these cortical regions and the dopamine-containing nigral neurons, conveyed via the striosomal system, might function in producing or maintaining such perseverative behavioral states (see also Damasio et al., 1990).

Although the medial prefrontal and orbitofrontal cortices were the only prefrontal sites we found to have preferential projections to striosomes, they did not innervate all of them. If the other striosomes do receive cortical inputs, they could come from the stretches of prefrontal cortex we did not inject, for example, the posterior medial orbital cortex between the medial prefrontal and the posterior orbital sites, or the dorsoanterior medial prefrontal cortex. We did see labeling of striosomes (usually with adjoining matrix) with a large polar cortical injection, but we were unable to pinpoint the origin of the striosomal input.

An interesting possibility is that other, nonfrontal areas of neocortex may project to striosomes in the monkey.

We were unable to detect dense prefrontal inputs to the nucleus accumbens, or at least to its medial part. This negative finding separates the type of “limbic” input in the prefrontostriatal system from “limbic” input carried by the direct hippocampal-accumbens pathway (Kelley and Domesick, 1982; Russchen et al., 1985). We did note, however, pronounced labeling just dorsal to the nucleus accumbens in the posterior orbitofrontal and prelimbic cases. This ventromedial labeling in the caudate nucleus and putamen appeared to be in the matrix, insofar as the compartments could be recognized. Thus, a transition zone or “prelimbic striatum” between the dorsal caudate-putamen and the nucleus accumbens could be identified on the basis of its prefrontal inputs from the cortical areas that, farther dorsally, project selectively to striosomes. This projection system resembles that showing dense autoradiographic labeling for serotonin uptake sites (Insel et al., 1992) and 5-HT receptor sites (Waeber and Palacios, 1994).

Systems of prefrontal inputs to the matrix compartment of the primate striatum

Our findings demonstrate that in the macaque monkey, as in the rat (Donoghue and Herkenham, 1986) and the cat (Ragsdale and Graybiel, 1981, 1990), much of the prefrontal cortex projects to the matrix compartment. What is striking in the monkey, with its large prefrontal cortex, is how extensive this predominantly matrix-projecting territory is. Dorsolateral, ventrolateral, anterior medial, and even lateral and anterior orbital cortex primarily target the matrix, as do the more posterior premotor areas so far investigated (Parthasarathy et al., 1992). Even the striosome-projecting posterior orbitofrontal and prelimbic cortical areas project to ventral matrix-like tissue, as noted above.

The distributions of these matrix input systems were notable in a second respect. All of the relatively small injection sites labeled relatively discrete, patchy zones in the matrix representing the matrixes identified in earlier experiments on inputs to the striatum from sensorimotor cortex (Flaherty and Graybiel, 1991, 1994). Only with large tracer deposits in the dorsolateral prefrontal cortex and the anterior principal sulcus was labeling distributed more broadly. We were unable to determine whether this more widespread matrix labeling resulted from the high background labeling, or to true terminal labeling. However, patchy labeling in the caudate nucleus has been observed in previous studies following dorsolateral prefrontal tracer injections (Ragsdale and Graybiel, 1981; Selemon and Goldman-Rakic, 1985).

Mosaic arrangement of striosomes and matrixes innervated by different prefrontostriatal areas

The fact that some prefrontal input matrixes were consistently found in close spatial relationship to striosomes is of particular interest, for it suggests that although the posterior orbitofrontal and posterior medial prefrontal inputs to striosomes are spatially separated from the other prefrontal input systems, interactions among these systems might, nevertheless, occur across striosomal borders. This could be important functionally, for at least some striatal neurons at striosome-matrix borders undergo reward-related plastic changes during behavioral conditioning in the macaque (Aosaki et al., 1994, 1995; Graybiel et al., 1994). Striosome/matrix pairs were common in cases with injections in the anterior and lateral orbital cortex. Thus, cross-com-

partment interactions could conditionally integrate functions of anterior and posterior orbital prefrontal systems, among others. In humans, anterior and posterior orbitofrontal areas have been shown to be differently active during symptomatic episodes in obsessive-compulsive disorder (Rauch et al., 1994).

Finally, we found evidence in a few cases that some of the striosome-adjacent input patterns may even be associated with neurochemical specializations of the matrix. It has been noted repeatedly that in cats (Graybiel and Ragsdale, 1978; Graybiel et al., 1981; Graybiel and Chesselet, 1984), monkeys (Graybiel and Ragsdale, 1978; Martin et al., 1991), and humans (Graybiel and Ragsdale, 1978; Nastuk and Graybiel, 1985; Manley et al., 1994), the ventral part of the caudate nucleus (and, in the primate, the ventral putamen) is neurochemically complex; that there are several kinds of "patches" in addition to AChE-poor striosomes; and that some neurochemical distributions switch from a pattern of patches dorsally to holes ventrally. We found clear instances in which prefrontal fibers appeared to have a dorsal-fill but ventromedial-avoid pattern (cf. Ragsdale and Graybiel, 1990), and some of the ventrally situated fiber patches sat in enkephalin-rich zones adjacent to enkephalin-poor striosomes. Although our evidence is preliminary, it suggests that in some regions, at least, neurochemical correlates may be found for some matrixesomes (cf. Aosaki et al., 1995).

Associative neural processing in the caudate nucleus

A major conceptual issue in the analysis of forebrain organization in primates is how information from the large and highly differentiated neocortex is conveyed to the much smaller subcortical targets of these inputs. Our evidence suggests that the prefrontal cortex can divide up its corticostriatal inputs into subsystems, many of which are patchy, so that different sets of input patches can overlap, abut, or be distributed with interspaces between them. This diversity of input-arrangements could provide the basis for highly effective redistribution within an associative network allowing novel combinations or dissociations of inputs so that different input-output linkages could be selected. This suggestion extends arguments made previously in relation to sensorimotor processing in the striatum (Malach and Graybiel, 1985; Flaherty and Graybiel, 1991, 1994; Brown, 1992; Parthasarathy et al., 1992; Graybiel et al., 1994). In the sensorimotor striatum, such novel associations could assist in the selection of context-dependent motor sequences and implementation strategies. Our evidence for similar heterogeneity of prefrontal cortical inputs to the matrix suggests that compartmentalization in the striatum may also permit selective interactions among cortical systems thought to carry out different cognitive tasks. Perhaps such activity in striatal networks of the caudate nucleus could be a source of the "cognitive functions" imputed to the striatum.

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