Modular Organization of Projection Neurons in the Matrix Compartment of the Primate Striatum

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It is well known that the striatum has a chemical architecture dividing it into striosomes and matrix, and that these compartments have different input–output connections. However, striatal afferent-fiber systems also form vividly patchy terminal fields in the matrix, and studies in the past year have uncovered instances of nonstriosomal clustering of striatal output neurons. In the experiments reported here, we systematically investigated this output-neuron clustering in the primate, using the striatopallidal system as a model. Our goals were to determine whether the modular organization is a general characteristic of projection neurons in the striatal matrix, whether the modularity occurs independent of striosomal boundaries, and whether the output modules are systematically organized.

We studied the distribution of striatopallidal projection neurons in 9 adult squirrel monkeys by centering deposits of the retrograde tracer HRP-WGA in either the external segment or the internal segment of the globus pallidus. Following injections of each type, many retrogradely labeled neurons appeared in the striatal matrix in clusters and bands having cross-sectional diameters of 0.2–0.8 mm. Comparisons with adjoining sections stained to demonstrate striosomes established that the local groups of striatal output neurons sometimes abutted striosomes but often did not. The retrogradely labeled clusters and bands appeared both in the caudate nucleus and in the putamen. Their arrangements were regular and often periodic.

These findings suggest that the large matrix compartment of the primate striatum, which is the primary site of origin of striatal outputs to the pallidum and the reticular part of the substantia nigra, contains systematic mosaics of projection neurons. We propose that this output-neuron modularity of the striatal matrix in the primate could serve as the template for redistribution of the massive afferent-fiber systems of the striatum into specialized striatopallidal output channels.

The neurochemical anatomy of the striatum suggests a two-compartment mosaicism of striatal tissue in which a smaller striosomal compartment is embedded in a much larger body of extrastriosomal tissue referred to as the matrix (Graybiel and Ragsdale, 1978, 1983; Herkenham and Pert, 1981; Gerfen, 1984, 1985; Gerfen et al., 1985; Chesselet and Graybiel, 1986; Graybiel et al., 1986; Joyce et al., 1986; Besson et al., 1988; Groves et al., 1988; Desban et al., 1989; Graybiel, 1989). The striosomes and matrix, in addition to being chemically distinct from one another, have different input–output connections and different developmental histories (Graybiel et al., 1979; Ragsdale and Graybiel, 1981, 1988a,b, 1990; Kent et al., 1982; Gerfen, 1984, 1985, 1989; Graybiel, 1984; Murrin and Ferrer, 1984; Donoghue and Herkenham, 1986; Gerfen et al., 1987; Jiménez-Castellanos and Graybiel, 1987, 1989; van der Kooy and Fishell, 1987; Langer and Graybiel, 1989; Giménez-Amaya and Graybiel, 1990; Lowenstein et al., 1990). The borders of striosomes are also specialized, particularly in the primate (Graybiel and Ragsdale, 1978, 1983; Beach and McGeer, 1984; Faull et al., 1989). Although the distributions of neurotransmitter and receptor markers are not uniform in the matrix (Joyce et al., 1986; Besson et al., 1988), no sharply delimited neurochemical inhomogeneities comparable to striosomes have yet been found in the matrix.

There is growing evidence, however, that many afferent-fiber systems terminating in identified matrix have patchy distributions (Malach and Graybiel, 1986; Alexander et al., 1988; Ragsdale and Graybiel, 1988b; Flaherty et al., 1989; Sadikot et al., 1990). This patchiness, documented in both the cat and the monkey, suggests that the input–output organization of the matrix is modular. Moreover, recent findings in the cat suggest that output neurons of the matrix also form clusters, some projecting to the pallidum and some to the substantia nigra (Desban et al., 1989; Jiménez-Castellanos and Graybiel, 1989). Retrogradely labeled cell clusters have been noted in the primate in our own and others' studies of the striatopallidal and striatonigral connections (Giménez-Amaya and Graybiel, 1988, 1989a,b, 1990; Koliatsos et al., 1988; Selemon and Goldman-Rakic, 1989), but no systematic study of this phenomenon has yet been reported. In the work presented here, we made a detailed study of neuronal clustering in the matrix of the squirrel monkey. With the striatopallidal system as a model, we focused on three key issues: (1) whether the clumping of projection neurons is a general characteristic of matrix in the caudate nucleus and putamen or a property only of part of the primate striatum, (2) whether the clumping is independent of the striosomal system or mainly a striosome-avoidance pattern that gives the appearance of independent aggregation of matrix neurons, and (3) whether the

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modularity is systematic and periodic in nature, as though reflecting a basic macroscopic plan of cellular organization of the primate striatum as a whole. Understanding such cellular modularity clearly would be essential for any account of the input-output organization of the primate striatum, and also could be helpful in interpreting patterns of striatal degeneration occurring as a consequence of extrapyramidal disorders in the human.

Our findings strongly suggest that modularity of cellular composition is a general phenomenon in the primate striatum, encompassing not only the neurochemically distinct striosomes, but also systematically arranged groups of projection neurons within the matrix. Thus, like the cerebral cortex, the entire striatum appears divisible into local neuronal sets distinguishable on the basis of their specialized efferent connections.

Materials and Methods

Deposits of horseradish peroxidase conjugated with wheat germ agglutinin (HRP-WGA; 10% in saline; Sigma Chemical Co.; Gonatas et al., 1979) were made unilaterally or bilaterally in the pallidal complex or striatum of 9 adult squirrel monkeys (*Saimiri sciureus*) first tranquilized with ketamine hydrochloride (25 mg/kg) and then anesthetized with sodium pentobarbital (Nembutal; 12.5 mg/kg). The tracer deposits were made under stereotaxic guidance (Gergen and MacLean, 1962; Emmers and Akert, 1963) with vertically or obliquely held glass micropipettes through which brief puffs of air were applied by means of a Pneumatic Pico Pump (PV800, World Precision Instruments). Volumes injected ranged from 10 to 80 nl. For the pallidal injections, the tracer deposits were centered in either the internal segment (cases SMHP 5L, SMHP 5R, SMHRF 2L, and SMHRP 1L) or the external segment (cases SMRHNP 1L, SMHP 12L, and SMHP 4L). Striatal injection sites were in the caudate nucleus (SMHPNT 1L), putamen (SMRHN 1L), or both (SMHP 1R). Survival times after surgery ranged from 44 to 48 hr. Experiments described elsewhere (Giménez-Amaya and Graybiel, 1990) provided controls in which HRP-WGA was injected at different levels of the internal capsule, cerebral peduncle, and substantia nigra. In addition, some of the animals used in that study were reanalyzed for this report.

Animals were perfused under deep sodium pentobarbital (Nembutal) anesthesia with (1) 0.5–1 liter of saline (0.9% NaCl), (2) 2 liters of 4% paraformaldehyde in 0.1 M dibasic phosphate buffer containing 0.9% saline (PBS; pH, 7.4) and 5% sucrose, and (3) 1.5 liters of the sucrose-PBS solution containing 5% sucrose. The brains were then blocked, soaked overnight in 30% sucrose-PBS solution, and cut in the coronal plane at 40 μ m on a freezing microtome. Sections were processed to demonstrate HRP-WGA, butyrylcholinesterase (BuChE), acetylcholinesterase (AChE), and enkephalin-like immunoreactivity. For HRP-WGA histochemistry, sections were reacted according to the tetramethylbenzidine (TMB) protocol of Mesulam (Mesulam, 1978; Mesulam et al., 1980), with frequent changes of incubation solution and concentrations of H_2O_2 (0.006–0.015%) determined by trials. AChE and BuChE staining was carried out by a slightly modified Geneser-Jensen and Blackstad protocol as described elsewhere (Geneser-Jensen and Blackstad, 1971; Langer and Graybiel, 1989). For enkephalin-like immunohistochemistry, sections were processed by the peroxidase-antiperoxidase method (Sternberger, 1979; protocol B of Graybiel and Chesselet, 1984) with anti-met-enkephalin antiserum kindly provided by Dr. R. P. Elde and diluted 1:1000.

Sections stained by the TMB method were studied with bright- and dark-field illumination and with crossed polarizers placed in the light path (Illing and Wässle, 1979). The sizes of the effective injection sites were estimated by eye and are shown in illustrations at their maximum estimated size including their less densely labeled peripheries. Retrogradely labeled neurons in selected sections from each case were charted with the aid of a drawing tube. Patterns of retrograde cell labeling in the striatum were compared to patterns of BuChE and AChE staining and enkephalin-like immunoreactivity visible in adjacent sections. As often as possible, reliance was placed on interstain consistency of identification of the striosomes (usually three stains in the caudate nucleus and usually two, but occasionally one or all three, in the putamen). Where the staining patterns were blurred, such scoring was not attempted.

Results

Three characteristic patterns of retrograde cell labeling were observed in the striatum following tracer injections affecting predominantly the internal (GPi) or external (GPe) segment of the globus pallidus. These patterns are illustrated for the putamen in Figure 1, which shows a cross-section from a case in which the HRP-WGA injection site principally involved the GPi (see Fig. 8, case SMHP 5L). First, there were fields of retrograde labeling containing gaps in which labeled neurons were relatively sparse. As described in our previous report (Giménez-Amaya and Graybiel, 1990), many of the sparsely labeled gaps corresponded to striosomes identified in serially adjoining sections. Second, even in zones in which there was abundant retrograde labeling, it was often possible to identify clusters of strongly labeled cells and other clusters of less strongly labeled cells alternating with one another. Third, there were usually clusters and bands of labeled neurons that were not connected with the main field of labeling in the planes of sections in which they occurred. Both the clusters and the bands in the main field and those at a distance from it were about the size of striosomes (ca. 0.2–0.8 mm wide in transverse sections).

General occurrence of bands and clusters of cell labeling in the matrix compartment and their independence of striosomal boundaries

The cases illustrated in Figures 2 and 3 establish that circumscribed groupings of retrogradely labeled projection neurons are features of the extrastriosomal matrix of both the putamen and the caudate nucleus. Furthermore, the cases show that these clusters and bands are not necessarily bordered by striosomes and thus are entities within the matrix itself.

Figure 2A shows three nearly horizontal bands of retrogradely labeled neurons (a–c) in the putamen of a monkey in which the injection site was placed in the rostral pole of the GPe (see Fig. 8, case SMRHNP 1L). The deposit extended caudally to involve the dorsal part of both pallidal segments. The labeled bands in the putamen and the gaps between them are about 0.3–0.4 mm wide. In the near-serial sections stained for BuChE activity (Fig. 2B) and for enkephalin-like immunoreactivity (Fig. 2C), striosomes with about the same or slightly greater dimensions are visible within the same district of the putamen.

Comparisons among the three patterns of staining demonstrate that the bands of retrogradely labeled matrix cells are not simply formed as a result of labeled neurons avoiding striosomes in the field of labeling. As shown in the consecutive panels in Figure 2, the upper two bands of cell labeling (a, b) are in the matrix, and the sparsely labeled gap between them corresponds to a well-delineated striosome. However, the gap between the two lower bands of retrograde cell labeling (b, c) does not correspond to a histochemically identifiable striosome. It thus appears to represent a band of *unlabeled* matrix neurons intervening between two parallel bands of labeled matrix neurons.

Striking bands and clusters of retrogradely labeled matrix neurons were also found in the caudate nucleus. An example of such arrangements of labeled neurons is shown in Figure 3. Retrogradely labeled neurons are collected into diagonally oriented bands, all of which lie within the matrix. Some of these contain strongly labeled neurons; others, weakly labeled neurons. Each band is surrounded by unlabeled matrix tissue. The injection site in this case was situated quite rostrally in the GPe and the adjoining dorsolateral corner of the GPi (see Fig. 8, case

Figure 1. Characteristic patterns of retrograde cell labeling in the striatum elicited by injections of HRP-WGA centered in the internal segment of the globus pallidus, from case SMHP 5L; see Figures 7B and 8 for drawings of the injection site. Abundant cell labeling is evident in the dorsal putamen, and clusters of retrogradely labeled neurons appear ventrally. Note that, in the main dorsal field of labeling, clusters of strongly labeled and weakly labeled neurons alternate with one another. There are prominent gaps in the labeling, including 2 dorsal gaps (asterisk) that were identified as striosomes by reference to serially adjoining sections stained for BuChE. Elsewhere, the histochemistry was uninformative with respect to scoring striosomes. There is a thin unlabeled "peripallidal strip" next to the GPe; in all cases, this zone was nearly devoid of cell labeling. The photograph also illustrates labeled neurons in the globus pallidus. CN, caudate nucleus; IC, internal capsule; GPe, external segment of the globus pallidus; P, putamen. Scale bar, 1 mm.

SMHP 12L). The injection tract also involved the caudal head of the caudate nucleus, but this would not affect labeling at the rostral levels shown in Figure 3, because the striatum does not have long-distance association connections and labeling around striatal injection sites was limited to a 1–2 mm radius.

Systematic organization of neuronal modules in the striatal matrix

Two patterns of cellular labeling pointed to a high degree of order in the modules of retrogradely labeled matrix neurons. First, circumscribed zones of strong and weak cell labeling frequently alternated with one another in the matrix. Figure 4 illustrates this pattern of labeling in case SMHP 4L, in which the HRP-WGA deposit was centered in the ventral part of the GPe and extended into the outer margin of the GPi (see Fig. 8). As shown at low magnification in Figure 4A, nearly the entire

ventrolateral part of the putamen contained prominent retrograde labeling distributed in a series of broad bands (a–d) separated by narrower bands with few labeled neurons.

Close inspection of the bands showed that they were made up of pairs (or even triplets) of weakly and strongly labeled subbands (see b1 and b2 in Fig. 4B). In the section illustrated, the widths of the subbands were about the same as those of the intervening interband zones containing few retrogradely labeled neurons (ca. 0.3–0.4 mm). Each of these interbands could be shown to correspond to a striosome by reference to near-serial sections stained for BuChE activity (Fig. 4C) or for enkephalin-like immunoreactivity (Fig. 4D). The macroscopic banding pattern thus reflected the presence of bands of strongly labeled and weakly labeled matrix cells alternating with one another and with striosomes.

Second, there was a marked tendency toward periodic ar-

Figure 2. *A*, Illustration of regularly spaced bands of striatal neurons in the putamen (*a–c*), retrogradely labeled by a pallidal injection centered in the rostral GPe (case SMRHNP 1L; see Figs. 7*B*, 8). The bands of labeled cells alternate with bands of very sparse labeling. The upper 2 weakly labeled bands (marked by single asterisks) correspond to striosomes, as identified in adjoining BuChE-stained (*B*) and enkephalin-immunostained

Figure 3. Banding of retrogradely labeled neurons in the matrix of the caudate nucleus (CN) in case SMHP 12L, illustrated in a section stained by the TMB method (A). An adjacent section, stained for AChE activity, is shown in B. The injection site (see Figs. 7B, 8) was centered in the GPe. In A, 2 weakly labeled cell bands (a, c) and 2 intensely labeled cell bands (b, d) appear in a field of retrograde labeling. Three AChE-poor striosomes in the region are marked by asterisks in B, and the corresponding zones are illustrated by the same symbols in A. By reference to the AChE staining, it can be seen that the bands of labeled cells appear in the matrix, and that their aggregation into bands is not forced by the presence of striosomal tissue everywhere flanking the bands. IC, internal capsule; P, putamen. Scale bar, 1 mm for A and B.

rangement of the nonadjacent clusters of labeled neurons in the matrix. The schematic chartings in Figure 5 were drawn to illustrate the spacing of retrogradely labeled clusters and bands for the entire region of retrograde labeling in one case of GPi injection (SMHRF 2L). Both in the zones of prominent banding and in the main field made up of adjoining weakly and strongly labeled clusters, the aggregates of labeled neurons tended to line up along curved lines with a periodicity of about 0.25–0.3 mm. The photomicrographs in Figure 6, from another case of GPi injection (SMHRP 1L), demonstrate that, in a single case, the individual modules of retrogradely labeled neurons can have the form of elongated bands (3–4 mm long) or rounded elliptical clusters (0.2–0.3 mm wide) at different transverse levels. The aggregates thus do not have the simple shape of anteroposteriorly elongated cylinders, but instead, have more complex forms subtending large transverse dimensions at some levels.

Internal and external pallidal placement of injection sites as a predictor of projection-neuron clustering

The possibility that different clumps of neurons project to the external or internal pallidum was the leading hypothesis

prompted by our initial study of the striatopallidal connection (Giménez-Amaya and Graybiel, 1988, 1990) and by that of Koliatsos et al. (1988). For technical reasons, however, it was not possible to be sure of this. First, no cases of double retrograde labeling of the two pallidal segments had sufficiently well-matched injection sites to permit adequate two-tracer analysis of the problem. Second, injection sites large enough to elicit the widespread labeling in which such macroscopic clusters can be identified tended to extend beyond the confines of a single pallidal segment. Third, all injections of GPe involved fibers *en route* to GPi, and injections in either pallidal segment could involve *en passant* striatonigral fibers. Finally, there was an unexplained pattern of extensive “main fields” of cell labeling in some regions of the striatum, with more isolated clusters and bands of cell labeling in other regions. This latter property of the labeling left open the possibility that the clustering was a sporadic phenomenon, related to randomly occurring unevenness in the distribution of tracer at the injection sites, rather than an organized systematic modularity intrinsic to the striatum.

As another approach to this problem, we tried to determine whether the degree of patchiness of the retrograde striatal la-

(C) sections (see matched single asterisks). The TMB and enkephalin-immunostained sections are serially adjoining; 1 section is missing between the TMB and BuChE sections. The ventral band of sparse labeling, however, does not correspond to an identifiable striosome (see photomicrographs in D and E of regions bracketed in A and C). Arrow in A points to a cell cluster adjoining a striosome marked by double asterisks in A–C. CN, caudate nucleus; IC, internal capsule; P, putamen; bv, blood vessel. Scale bar, 1 mm for A–C.

Figure 4. Banding of strongly and weakly labeled matrix neurons in the putamen elicited by an HRP-WGA deposit centered in ventral GPe (see case SMHP 4L in Figs. 7B, 8). The low-power photograph in *A* illustrates 3 broad bands of HRP-WGA-positive neurons (*a–c*) and a fourth smaller band (*d*) visible with TMB histochemistry; band *b* can be further subdivided in 2 retrogradely labeled subbands running from dorsal and medial to ventral and lateral. The edge of the pipette track is at upper left-hand corner. Gaps between the bands of cell labeling correspond to striosomes identifiable in nearby BuChE-stained (*C*) and enkephalin-immunostained (*D*) sections lying on either side of the TMB-stained section; some corresponding regions in the 3 panels are marked by arrows. Note the U-shaped striosome visible in *A* and *C* (1 section apart), only part of which appears in *D* (separated from *A* by 3 sections). The higher-magnification photomicrograph in *B* (see rectangle in *A*) spans the dark (*b1*) and light (*b2*) subbands of band *b*, the striosome (*S*) between bands *b* and *c*, and the dark region of band *c* on the bottom. Both the neuropil and the cell bodies in the densely stained subbands are more strongly stained than the neuropil and cell bodies of the more weakly labeled subbands. Scale bar, 1 mm for *A*, *C*, and *D*.

Figure 5. Schematic chartings for case SMHRF 2L, illustrating the entire striatal region containing retrograde cell labeling (stippling). Within the main field of retrograde labeling, distinguishable clusters of stronger and weaker cell labeling are indicated (see also Fig. 1). The disjunct clusters tend to have a regular periodic arrangement along axes parallel to the sides of the putamen (indicated schematically in 2 chartings). The injection site (shading) was centered in GPi rostrally and invaded both segments dorsally and caudally (see Fig. 7A). The extensive tracer deposit along the pipette's track through the internal capsule is also shown. An arrow marks the level of the center of the pallidal injection site. CN, caudate nucleus; AC, anterior commissure; IC, internal capsule; P, putamen; GPe, external segment of the globus pallidus; GPi, internal segment of the globus pallidus.

being could be interpreted in terms of the known geometry of the striatopallidal projection. We first studied the distribution of anterogradely labeled striatopallidal fibers within the pallidum (experiments not illustrated). We confirmed the general "spokes-in-a-wheel" radial pattern for the striatopallidal, wherein the caudate nucleus projects dorsally within the pallidum at midpallidal levels, and successively more ventrolateral parts of the striatum (within the putamen) project to progressively more ventral wedges of pallidal tissue (Voneida, 1960; Szabo, 1962; Cowan and Powell, 1966; Kemp and Powell, 1971; Percheron et al., 1984b; Parent, 1986; Smith and Parent, 1986). This organization allowed us to assess the patterns of retrograde labeling in relation to the radial positions of the deposits (Fig. 7). According to this radial geometry, injections centered in the GPe should lead to some fiber-of-passage labeling of fibers *en route* to radially matched parts of GPi, but if separate striatal cell clusters do project, respectively, to the GPe and the GPi, then the degree of patchiness in striatal labeling should be roughly predictable by the relative involvement of corresponding wedge-shaped sectors of the two pallidal segments at different anteroposterior levels.

The cases studied support this prediction. In Figure 1, the main field of labeling (containing weakly and strongly labeled cell clusters) appears dorsally, whereas isolated bands and clusters of labeled cells appear ventrally. In the pallidum, the injection site was confined to the GPi except at its dorsal periphery, which extended into the GPe (Fig. 8). According to the hypothesis that there are separate GPi-targeted and GPe-targeted neuronal clusters in the matrix, the dorsal intermixing of weakly and strongly labeled clusters could represent peripherally labeled GPe-projecting neurons (weakly labeled) alternating with intensely labeled GPi-projecting neurons. The more isolated ventral patches could correspond to neurons projecting to the region in which the deposit infiltrated only one pallidal segment (GPi). A similar analysis could account for the pattern of labeling in the GPi case illustrated in Figure 6.

Of the GPe injections, the most restricted was that illustrated in Figure 4; only the extreme outer margin of GPi was affected

in addition to GPe. This placement is compatible with the finding of alternating bands of strongly and weakly labeled neurons in the putamen, the weakly labeled groups reflecting fiber-of-passage labeling of axons *en route* to GPi and/or direct labeling of axons projecting to the outer part of GPi. In the cases shown in Figures 2 and 3, the injection sites were confined to GPe rostrally and extended into both segments farther caudally (Fig. 8). In apparent accord, the zones in which labeling in the matrix was in the form of relatively isolated bands and clusters of neurons occurred rostrally, and the fields with extensive labeling occurred caudally. Finally, in the case illustrated in Figure 5, the injection site strongly involved both pallidal segments, except in a rostral and rostroventral zone where GPi was injected without associated involvement of the GPe. Correspondingly, there was widespread labeling in the matrix at caudal levels of the putamen, but at the rostral end of the field of putamenal labeling, and also rostroventrally, there were discrete bands and clusters of retrogradely labeled neurons.

Discussion

The matrix compartment makes up over 80% of the volume of the caudate nucleus and putamen and is the main source of striatal fibers projecting to the pallidum and the substantia nigra pars reticulata. The findings described here demonstrate that, in the primate, the striatal projection neurons of the matrix are organized into a systematic series of macroscopic clusters and bands with about the same size as striosomes. The initial evidence for sorting of striatal projection neurons into compartments was confined to distinguishing striosomes and matrix as separate efferent entities (Graybiel et al., 1979; Gerfen, 1984). The implication of the findings reported here is that output-neuron modularity is a general characteristic of striatal tissue in the primate and thus could serve as a template for input-output channeling in the striatum.

Widespread cellular modularity in the matrix compartment

Our evidence clearly indicates that the clumpy character of the matrix is not specific to one functional (or anatomical) subdi-

Figure 6. Regularly spaced bands and clusters of retrogradely labeled neurons in 2 sections through the putamen of case SMHRP 1L, for which the injection site (shown in *C*) was centered in GPe but invaded dorsal GPe. The sections are 2.24 mm apart. The HRP-positive pipette track skirted the dorsomedial edge of the putamen, shown in *A* and *B* in exaggerated form because of the contrast needed to make retrogradely labeled neurons in the adjoining putamen visible at low magnification. At the more rostral level illustrated (*A*), there is a main field of retrograde cell labeling dorsally, comprised of very strongly and less strongly labeled cell clusters interrupted by sparsely labeled gaps. Ventrally, there are long bands comprised of weakly and strongly labeled cells. The more medial band (*short arrows*) extends 3–4 mm in a curve parallel to the medial face of the putamen. The lateral band (*long arrows*) extends for about 3 mm along the lateral edge of the putamen. Along the lengths of the 2 bands, there are intervals of denser cell labeling and intervals of weaker cell labeling. The 2 bands merge ventrally. In the more caudal section (*B*), there also is a main dorsal field of retrograde labeling, but nearly all of the other cell labeling is in the form of clusters of labeled neurons (examples at *arrowheads*). Many labeled neurons appear also in the globus pallidus in both sections. *GPe*, external segment of the globus pallidus; *GPe*, internal segment of the globus pallidus; *P*, putamen. Scale bar, 1 mm for *A* and *B*.

vision of the striatum, for example, the putamen with its dominant inputs from sensory-motor cortex. Projection neurons (1) were found at nearly all levels of the striatum, (2) appeared in every case, (3) tended to be regularly spaced whether in the main field or dispersed sets, (4) occurred whether the pallidal injection site was rostral, caudal, dorsal, or ventral, and (5) could be found, in individual cases, in regions extending for millimeters. Our findings further suggest that, at least for matrix neurons labeled by GPi injections, the aggregates of efferent cells, though appearing patchy in cross-sections, can be extended three-dimensionally and branched. Interestingly, these are characteristic hallmarks of the striosomal system (Graybiel and Ragsdale, 1978; Graybiel et al., 1981a; Groves et al., 1988; Desban et al., 1989).

Many neurons in the primate's caudate nucleus project to the substantia nigra (Parent et al., 1984; Parent, 1986; Smith and Parent, 1986), and there is also a considerable putamenonigral projection in the primate (Jiménez-Castellanos and Graybiel, 1989; Selemon and Goldman-Rakic, 1989). Some striatonigral neurons may have been labeled by infiltration of striatonigral fibers in transit (see Giménez-Amaya and Graybiel, 1990), though little striatal cell labeling was observed with control injections made at different levels of the internal capsule or in the cerebral peduncle (see Giménez-Amaya and Graybiel, 1990). Desban et al. (1989) and Jiménez-Castellanos and Graybiel (1989) have presented evidence that there are striatonigral cell clusters in the matrix of the cat's caudate nucleus, and the brief report by Selemon and Goldman-Rakic (1989) suggests that these occur also in the primate. Thus, the modular arrangements of projection neurons demonstrated here following pallidal injections might represent only part of the cellular mosaic in the matrix compartment of the primate's striatum.

Modules in the matrix have nonstriosomal as well as striosomal boundaries

Two observations prompted our conclusion that there are sets of cell clusters in the matrix whose boundaries are not solely determined by striosomal borders. First, isolated clusters and bands of retrogradely labeled cells were found that were surrounded by unlabeled matrix tissue, not by striosomes. Second, in zones where there were alternating bands of cell labeling, some of the labeled bands alternated with sparsely labeled gaps that were *not* striosomes, as well as with gaps that did correspond to striosomes. Reliable identification of striosomes was crucial to accurate interpretation of these retrograde labeling patterns. If the presence of clusters and bands of retrogradely labeled neurons simply resulted from the intervention of sparsely labeled striosomes into fields of more heavily labeled matrix neurons, modularity of the matrix would not be indicated. Similarly, if adjoining weakly and strongly labeled clusters and bands could not be identified as belonging to the matrix, again, striosome/matrix modularity could account for the clustered arrangements observed. Identifying striosomes posed no special problem in the caudate nucleus, but achieving comparably clear images of striosomes was difficult in parts of the putamen. By staining many sections, however, and by choosing cases in which these stains seemed particularly well differentiated, we obtained images of striosomes in a considerable part of the putamen as well as in the caudate nucleus. We conclude on this basis that both the evidence for nonstriosomal gaps in matrix cell labeling and the evidence for clustering in identified matrix point to true

Figure 7. *A*, Examples of radial analysis of the injection sites (shading) shown for cases SMHP 5R and SMHRF 2L. In both cases, the injection site was centered in a ventral sector of GPi, but GPe was contaminated dorsally. Maximum extents of the injection sites are shown. Broken lines indicate radial sectors parallel to striatopallidal afferents. The relative overlap of the injection sites with the external and internal halves of these pallidal sectors was used to interpret the patterns of retrograde striatal labeling observed (see text). *B*, Schematic horizontal view of the caudate and lenticular nuclei with reconstructions of the centers of the injection sites (shading) in the pallidum of the cases illustrated in Figure 8. A radial analysis similar to that shown in *A* can be used to analyze the anteroposterior locations of the deposits relative to the locations of retrogradely labeled striatal cells organized into cluster formations. IC, internal capsule; GPe, external segment of the globus pallidus; GPi, internal segment of the globus pallidus; P, putamen; R, rostral; L, lateral.

modularity in the organization of projection neurons in the matrix compartment.

Modules in the matrix have regular arrangements

A systematic spacing of retrogradely labeled cell clusters and bands was one of the most striking findings in this study. Regular

Figure 8. Schematic diagrams illustrating the pallidal injection sites (*shading*) in the cases illustrated photographically in Figure 1 (case *SMHP 5L*), Figure 2 (case *SMRHNP 1L*), Figure 3 (case *SMHP 12L*), and Figure 4 (case *SMHP 4L*). The maximum extent of the deposits is indicated. For each case, an *arrow* marks the level of the center of the injection site, and sections shown are about 0.4 mm apart. *AC*, anterior commissure; *CN*, caudate nucleus; *IC*, internal capsule; *GPe*, external segment of the globus pallidus; *GPi*, internal segment of the globus pallidus; *P*, putamen; *Th*, thalamus.

spacing of alternating weak and strong labeling was a common finding in the main fields of labeling, as well. The fact that weakly and strongly labeled bands, clusters, and gaps in the matrix alternated with each other (and with identifiable striosomes) points to the presence of multiple systems of projection neurons in the matrix and suggests that the different modular systems can abut each other as well as striosomes. Striosomes are themselves quite regularly spaced through the matrix and may impose systematicity on the adjoining matrix. The regular spacing of individual sets of retrogradely labeled cell clusters that we observed may thus represent a general multicompartiment periodicity rather than a singular pattern referable to matrix projection neurons alone.

Pallidal targets of the projection-neuron modules in the matrix

Although our experiments indicate widespread modularity in the organization of projection neurons in the striatal matrix and strongly support the view that the modularity is a property of striatopallidal neurons, they do not settle the question of whether the modules are comprised of neurons projecting to one or

the other segment of the globus pallidus, or neurons projecting to different subdivisions within each segment, or some mixture of neurons of these types. The highly ordered cellular architecture of the pallidum (Fox et al., 1974; Percheron et al., 1984a), the bands and disks formed by the radially oriented afferent fibers terminating there (Parent, 1986; Smith et al., 1990; J.-M. Giménez-Amaya and A. M. Graybiel, unpublished observations), and the subdivision of the internal segment into inner and outer halves (Carpenter, 1981, 1989; Haber and Elde, 1981) all suggest that the pallidum has a complex internal structure not probed by our experiments. Such pallidal subdivisions, rather than the better-known internal and external pallidal segments, clearly could be the targets of the striatal output modules described here. Interestingly, however, we were unable to reject the hypothesis that the labeled neurons in the cell clusters might have axons preferentially directed toward either GPe or GPi. First, by taking into account the radial organization of striatopallidal fibers, the degree and location of patchiness of the labeled matrix-cell distributions could usually be predicted quite readily from the injection site placements in the two segments.

Retrogradely labeled clusters and bands were particularly striking when the segment injected was GPi, avoiding the fiber-of-passage problem attending GPe injections. By contrast, when the injection sites were mainly confined to GPe, we often observed regions of abundant but heterogeneous matrix-neuron labeling in which strongly labeled and weakly labeled cellular clusters alternated with or abutted each other. Finally, a combination of patterns was present in cases in which both pallidal segments were heavily infiltrated by the injected tracer. To take into account the finer-scale geometry of striatopallidal fibers, however, further refinement of single and multiple retrograde tracer methods for intrapallidal injections will be needed, and ultimately, anterograde tracer injections confined to individual projection-neuron clusters will be required to identify with certainty the intrapallidal compartments corresponding to the clusters of striatopallidal neurons.

Multicompartment model of striatal organization and its functional implications

The output modules described here for the primate's matrix compartment bear a striking resemblance to modular distributions of corticostriatal and thalamostriatal afferent fibers that have been explicitly identified as terminating in the striatal matrix in primates (Ragsdale and Graybiel, 1988b; Flaherty et al., 1989; Sadikot et al., 1990). The generality of the projection-neuron clustering also parallels the generality of modularity in the organization of striatal afferent connections (Künzle, 1975; Goldman and Nauta, 1977; Jones et al., 1977; Yeterian and Van Hoesen, 1978; Herkenham and Pert, 1981; Ragsdale and Graybiel, 1981, 1984, 1988a,b, 1990; Reale and Imig, 1983; Selemon and Goldman-Rakic, 1985, 1989; Jiménez-Castellanos and Graybiel, 1987; Sadikot et al., 1990). The relationship between these input and output clusters of the matrix remains to be explored. The findings presented here suggest, however, that projection neurons of the striatal matrix are sufficiently organized at the macroscopic level to permit modular input-output conduction through the striatum and specialized processing within individual modules. An anatomical basis for modular intrinsic processing in the striatum has already been demonstrated for striosomes (Graybiel et al., 1981; Gerfen, 1984; Graybiel and Chesselet, 1984; Chesselet and Graybiel, 1986; Sandell et al., 1986; Besson et al., 1988; Bolam et al., 1988; Kawaguchi et al., 1989).

Finally, from a functional viewpoint, clumping of matrix neurons is of particular interest in two respects: First, a number of electrophysiological studies have demonstrated distinct subtypes of striatal neurons (Kimura et al., 1984; Kimura, 1986; Niesenbaum et al., 1988; Alexander and Crutcher, 1989; Hikosaka et al., 1989a-c), and these could be differentially represented in different anatomical clusters. Clusters of units sharing somatosensory receptive fields (Crutcher and DeLong, 1984; Liles and Updyke, 1985) and small "microexcitable zones" in which stimulation elicits movements (Alexander and DeLong, 1985) have already been identified in the monkey. Second, our evidence supports the view that the modularity may reflect specific targeting of the subdivisions within the globus pallidus. Accordingly, the modularity could ultimately contribute to the functional specializations of the pallido-subthalamic (GPe-based) and pallido-thalamic (GPi-based) systems of the basal ganglia, including subsystems that may lie within them (Schell and Strick, 1984; Alexander et al., 1986; Crossman, 1987; Reiner et al., 1988; Graybiel, 1989; Young et al., 1989).

References

- Alexander GE, Crutcher MD (1989) Coding in spatial rather than joint coordinates of putamen and motor cortex preparatory activity preceding planned limb movements. In: *Neural mechanisms in disorders of movement* (Crossman AR, Sambrook MA, eds), pp 55-62. London: Libbey.
- Alexander GE, DeLong MR (1985) Microstimulation of the primate striatum: I. Physiological properties of striatal microexcitable zones. *J Neurophysiol* 53:1417-1432.
- Alexander GE, DeLong MR, Strick PL (1986) Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu Rev Neurosci* 9:357-381.
- Alexander GE, Koliatsos VE, Martin LJ, Hedreen J, Hamada I, DeLong MR (1988) Organization of the primate basal ganglia "motor circuit": I. Motor cortex (MC) and supplementary motor area (SMA) project to complementary regions within the matrix compartment of putamen. *Soc Neurosci Abstr* 14:720.
- Beach TG, McGeer EG (1984) The distribution of substance P in the primate basal ganglia: an immunohistochemical study of the baboon and human brain. *Neuroscience* 13:29-52.
- Besson MJ, Graybiel AM, Nastuk M (1988) SCH 23390 ligand binding to D1 dopamine receptors in the basal ganglia of the cat and primate: delineation of striosomal compartments and pallidal and nigral subdivisions. *Neuroscience* 26:101-119.
- Bolam JP, Izzo PN, Graybiel AM (1988) Cellular substrates of the histochemically-defined striosome/matrix system of the caudate nucleus: a combined Golgi and immunohistochemical study in rat and ferret. *Neuroscience* 24:853-875.
- Carpenter MB (1981) Anatomy of the corpus striatum and brain stem integrating systems. In: *Handbook of physiology*, Vol 2, The nervous system (Brooks VB, ed), pp 947-995. Bethesda, MD: American Physiological Society.
- Carpenter MB (1989) Connectivity patterns of thalamic nuclei implicated in dyskinesia. *Stereotact Funct Neurosurg* 52:79-119.
- Chesselet MF, Graybiel AM (1986) Striatal neurons expressing somatostatin-like immunoreactivity: evidence for a peptidergic interneuronal system in the cat. *Neuroscience* 17:547-571.
- Cowan WM, Powell TPS (1966) Strio-pallidal projections in the monkey. *J Neurol Neurosurg* 29:426-439.
- Crossman AR (1987) Primate models of dyskinesia: an experimental approach to the study of the basal ganglia-related involuntary movement disorders. *Neuroscience* 21:1-40.
- Crutcher MD, DeLong MR (1984) Single cell studies of the primate putamen. I. Functional organization. *Exp Brain Res* 53:233-243.
- Desban M, Gauchy C, Kemel ML, Besson MJ, Glowinski J (1989) Three-dimensional organization of striosomal compartments and patchy distribution of striatonigral projections in the matrix of the cat caudate nucleus. *Neuroscience* 29:551-566.
- Donoghue JP, Herkenham M (1986) Neostriatal projections from individual cortical fields conform to histochemically distinct striatal compartments in the rat. *Brain Res* 365:397-403.
- Emmers R, Akert K (1963) A stereotaxic atlas of the brain of the squirrel monkey (*Saimiri sciureus*). Madison: University of Wisconsin.
- Faull RLM, Dragunow M, Villiger JW (1989) The distribution of neurotensin receptors and acetylcholinesterase in the human caudate nucleus: evidence for the existence of a third neurochemical compartment. *Brain Res* 488:381-386.
- Flaherty AW, Graybiel AM, Sur M, Garraghty P (1989) Distinctive patterns of projections to striatum from physiologically-mapped somatosensory representations in primate cortex. *Soc Neurosci Abstr* 15:659.
- Fox CA, Andrade AN, LuQui JJ, Ralfols JA (1974) The primate globus pallidus: a Golgi and electron microscopic study. *J Hirnforsch* 15:75-93.
- Geneser-Jensen FA, Blackstad JW (1971) Distribution of acetylcholinesterase in the hippocampal region of the guinea pig. *Z Zellforsch Mikrosk Anat* 114:460-481.
- Gerfen CR (1984) The neostriatal mosaic: compartmentalization of corticostriatal input and striatonigral output systems. *Nature* 311:461-464.
- Gerfen CR (1985) The neostriatal mosaic. I. Compartmental organization of projections from the striatum to the substantia nigra in the rat. *J Comp Neurol* 236:454-476.

- Gerfen CR (1989) The neostriatal mosaic: striatal patch-matrix organization is related to cortical lamination. *Science* 246:385–388.
- Gerfen CR, Baimbridge KG, Miller JJ (1985) The neostriatal mosaic: compartmental distribution of calcium-binding protein and parvalbumin in the basal ganglia of the rat and monkey. *Proc Natl Acad Sci USA* 82:8780–8784.
- Gerfen CR, Herkenham M, Thibault J (1987) The neostriatal mosaic: II. Patch- and matrix-directed mesostriatal dopaminergic and non-dopaminergic systems. *J Neurosci* 7:3915–3934.
- Gergen JA, MacLean PD (1962) A stereotaxic atlas of the squirrel monkey's brain (*Saimiri sciureus*). Bethesda, MD: National Institutes of Health.
- Giménez-Amaya JM, Graybiel AM (1988) Compartmental origins of the striatopallidal projection in the primate. *Soc Neurosci Abstr* 14:156.
- Giménez-Amaya JM, Graybiel AM (1989a) Two types of compartmental ordering of striatopallidal projection neurons in the primate. *Abstr IBAGS Meeting* 3:72.
- Giménez-Amaya JM, Graybiel AM (1989b) Evidence that the extra-striosomal matrix of the primate striatum contains a mosaic of neuronal cell-clusters preferentially projecting to the external and to the internal pallidum. *Soc Neurosci Abstr* 15:907.
- Giménez-Amaya JM, Graybiel AM (1990) Compartmental origins of the striatopallidal projection in the primate. *Neuroscience* 34:111–126.
- Goldman PS, Nauta WJH (1977) An intricately patterned prefronto-caudate projection in the rhesus monkey. *J Comp Neurol* 171:369–386.
- Gonatas NK, Harper C, Mizutani T, Gonatas JO (1979) Superior sensitivity of conjugates of horseradish peroxidase with wheat germ agglutinin for studies of retrograde axonal transport. *J Histochem Cytochem* 27:728–734.
- Graybiel AM (1984) Correspondence between the dopamine islands and striosomes in the mammalian striatum. *Neuroscience* 13:1157–1187.
- Graybiel AM (1989) Dopaminergic and cholinergic systems in the striatum. In: *Neural mechanisms in disorders of movement* (Crossman AR, Sambrook MA, eds), pp 3–15. London: Libbey.
- Graybiel AM, Chesselet MF (1984) Compartmental distribution of striatal cell bodies expressing met-enkephalin-like immunoreactivity. *Proc Natl Acad Sci USA* 81:7980–7984.
- Graybiel AM, Ragsdale CW (1978) Histochemically distinct compartments in the striatum of human, monkey and cat demonstrated by acetylcholinesterase staining. *Proc Natl Acad Sci USA* 75:5723–5726.
- Graybiel AM, Ragsdale CW (1983) Biochemical anatomy of the striatum. In: *Chemical neuroanatomy* (Emson PC, ed), pp 427–504. New York: Raven.
- Graybiel AM, Ragsdale CW, Moon-Edley S (1979) Compartments in the striatum of the cat observed by retrograde cell labeling. *Exp Brain Res* 34:189–195.
- Graybiel AM, Ragsdale CW, Yoneoka ES, Elde RP (1981) An immunohistochemical study of enkephalins and other neuropeptides in the striatum of the cat with evidence that the peptides are arranged to form mosaic patterns in register with striosomal compartments visible by acetylcholinesterase. *Neuroscience* 6:377–397.
- Graybiel AM, Baughman RW, Eckenstein F (1986) Cholinergic neuropil of the striatum observes striosomal boundaries. *Nature* 323:625–627.
- Groves PM, Martone M, Young SJ, Armstrong DM (1988) Three-dimensional pattern of enkephalin-like immunoreactivity in the caudate nucleus of the cat. *J Neurosci* 8:892–900.
- Haber SN, Elde RP (1981) Correlation between met-enkephalin and substance P immunoreactivity in the primate globus pallidus. *Neuroscience* 6:1291–1297.
- Herkenham M, Pert CB (1981) Mosaic distribution of opiate receptors, parafascicular projections and acetylcholinesterase in rat striatum. *Nature* 291:415–418.
- 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.
- Illing RB, Wässle H (1979) Visualization of the HRP reaction product using the polarization microscope. *Neurosci Lett* 13:7–11.
- Jiménez-Castellanos J, Graybiel AM (1987) Subdivisions of dopamine-containing A8-A9-A10 complex identified by their differential mesostriatal innervation of striosomes and extrastriosomal matrix. *Neuroscience* 23:223–242.
- Jiménez-Castellanos J, Graybiel AM (1989) Compartmental origins of striatal efferent projections in the cat. *Neuroscience* 32:297–321.
- Jones EG, Culter JD, Burton H, Porter R (1977) Cells of origin and terminal distribution of corticostriatal fibers arising in the sensory-motor cortex of monkeys. *J Comp Neurol* 173:53–80.
- Joyce JN, Sapp DW, Marshall JF (1986) Human striatal dopamine receptors are organized in compartments. *Proc Natl Acad Sci USA* 83:8002–8006.
- Kawaguchi Y, Wilson CJ, Emson PC (1989) Intracellular recording of identified neostriatal patch and matrix spiny cells in a slice preparation preserving cortical inputs. *J Neurophysiol* 62:1052–1068.
- Kemp JA, Powell TPS (1971) The connections of the striatum and globus pallidus: synthesis and speculations. *Philos Trans R Soc Lond [Biol]* 262:441–457.
- Kent JL, Pert CB, Herkenham M (1982) Ontogeny of opiate receptors in rat forebrain: visualization by *in vitro* autoradiography. *Dev Brain Res* 2:487–504.
- Kimura M (1986) The role of primate putamen neurons in the association of sensory stimuli with movement. *Neurosci Res* 3:436–443.
- Kimura M, Rajkowski J, Evarts E (1984) Tonicity discharging putamen neurons exhibit set dependent responses. *Proc Natl Acad Sci USA* 81:4998–5001.
- Koliatsos VE, Martin LJ, Hedreen J, Alexander GE, Hamada I, Price DL, DeLong MR (1988) Organization of the primate basal ganglia “motor circuit”: 2. Putaminal projections to internal (GPi) and external (GPe) globus pallidus originate in distinct neuronal populations within the matrix compartment. *Soc Neurosci Abstr* 14:720.
- Künzle H (1975) Bilateral projections from precentral motor cortex to the putamen and other parts of the basal ganglia. *Brain Res* 88:195–210.
- Langer LF, Graybiel AM (1989) Distinct nigrostriatal projection systems innervate striosomes and matrix in the primate striatum. *Brain Res* 498:344–350.
- Liles SL, Updyke BV (1985) Projection of the digit and wrist area of precentral gyrus to the putamen: relation between topography and physiological properties of neurons in the putamen. *Brain Res* 339:245–255.
- Lowenstein PR, Joyce JN, Coyle JT, Marshall JF (1990) Striosomal organization of cholinergic and dopaminergic uptake sites and cholinergic M1 receptors in the adult human striatum: a quantitative receptor autoradiographic study. *Brain Res* 510:122–126.
- Malach R, Graybiel AM (1986) Mosaic architecture of the somatic sensory-recipient sector of the cat's striatum. *J Neurosci* 6:3436–3458.
- Mesulam MM (1978) Tetramethyl benzidine for horseradish-peroxidase neurohistochemistry: a non-carcinogenic blue reaction-product with superior sensitivity for visualizing neural afferents and efferents. *J Histochem Cytochem* 26:106–117.
- Mesulam MM, Hegarty E, Barbas H, Carson KA, Gower EC, Knapp AG, Moss MB, Mufson EJ (1980) Additional factors influencing sensitivity in the tetramethyl benzidine method for horseradish peroxidase neurohistochemistry. *J Histochem Cytochem* 28:1255–1259.
- Murrin LC, Ferrer JR (1984) Ontogeny of the rat striatum: correspondence of dopamine terminals, opiate receptors and acetylcholinesterase. *Neurosci Lett* 47:155–160.
- Niesenbaum AU, Orr W-B, Berger T-W (1988) Evidence for two distinct subpopulations of neurons within the rat striatum. *J Neurosci* 8:4138–4150.
- Parent A (1986) *Comparative neurobiology of the basal ganglia*. New York: Wiley.
- Parent A, Bouchard C, Smith Y (1984) The striatopallidal and striatonigral projections: two distinct fiber systems in primate. *Brain Res* 303:385–390.
- Percheron G, Yelnik J, François C (1984a) A Golgi analysis of the primate globus pallidus. III. Spatial organization of the striato-pallidal complex. *J Comp Neurol* 227:214–227.
- Percheron G, Yelnik J, François C (1984b) The primate striato-pal-

- lido-nigral system: an integrative system for cortical information. In: *The basal ganglia: structure and function* (McKenzie JS, Kemm RE, Wilcock LN, eds), pp 87–105. New York: Plenum.
- Ragsdale CW, Graybiel AM (1981) The fronto-striatal projection in the cat and monkey and its relationship to inhomogeneities established by acetylcholinesterase histochemistry. *Brain Res* 208:259–266.
- Ragsdale CW, Graybiel AM (1984) Further observations on the striosomal organization of frontostriatal projections in cats and monkeys. *Soc Neurosci Abstr* 10:514.
- Ragsdale CW, Graybiel AM (1988a) Fibers from the basolateral nucleus of the amygdala selectively innervate striosomes in the caudate nucleus of the cat. *J Comp Neurol* 269:506–522.
- Ragsdale CW, Graybiel AM (1988b) Multiple patterns of thalamostriatal innervation in the cat. In: *Cellular thalamic mechanisms* (Bentivoglio M, Spreafico R, eds), pp 261–267. Amsterdam: Excerpta Medica.
- Ragsdale CW, Graybiel AM (1990) A simple ordering of neocortical areas established by the compartmental organization of their striatal projections. *Proc Natl Acad Sci USA* 87:6196–6199.
- Reale RA, Imig TJ (1983) Auditory cortical field projections to the basal ganglia of the cat. *Neuroscience* 8:67–86.
- Reiner A, Albin RL, Anderson KD, D'Amato CJ, Penney JB, Young AB (1988) Differential loss of striatal projection neurons in Huntington disease. *Proc Natl Acad Sci USA* 85:5733–5737.
- Sadikot AF, Parent A, François C (1990) The centre median and parafascicular thalamic nuclei project respectively to the sensorimotor and associative-limbic striatal territories in the squirrel monkey. *Brain Res* 510:161–165.
- Sandell JH, Graybiel AM, Chesselet MF (1986) A new enzyme marker for striatal compartmentalization: NADPH diaphorase activity in the caudate nucleus and putamen of the cat. *J Comp Neurol* 243:326–334.
- Schell GR, Strick PL (1984) The origin of thalamic inputs to the arcuate premotor and supplementary motor areas. *J Neurosci* 4:539–560.
- 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 (1989) Retrograde labeling of striatonigral and striatopallidal neurons in the rhesus monkey. *Soc Neurosci Abstr* 15:659.
- Smith Y, Parent A (1986) Differential connections of caudate nucleus and putamen in the squirrel monkey (*Saimiri sciureus*). *Neuroscience* 18:347–371.
- Smith Y, Hazrati L-N, Parent A (1990) Efferent projections of the subthalamic nucleus in the squirrel monkey as studied by the PHA-L anterograde tracing method. *J Comp Neurol* 294:306–323.
- Sternberger LA (1979) *Immunocytochemistry*. New York: Wiley.
- Szabo J (1962) Topical distribution of the striatal efferents in the monkey. *Exp Neurol* 5:21–36.
- van der Kooy D, Fishell G (1987) Neuronal birthdate underlies the development of striatal compartments. *Brain Res* 401:155–161.
- Voneida TJ (1960) An experimental study of the course and destination of fibers arising in the head of the caudate nucleus in the cat and monkey. *J Comp Neurol* 115:75–87.
- 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.
- Young AB, Albin RL, Penney JB (1989) Neuropharmacology of basal ganglia functions: relationship to pathophysiology of movement disorders. In: *Neural mechanisms in disorders of movement* (Crossman AR, Sambrook MA, eds), pp 17–28. London: Libbey.