Preface

There has been a major resurgence in stereotactic neurosurgery for the treatment of Parkinson's disease and tremor in the past several years. More recently, interest has also been rekindled in stereotactic neurosurgery for the treatment of dystonia and other movement disorders. This is based on a large number of factors, which include recognized limitations of pharmacologic therapies for these conditions, better understanding of the functional neuroanatomy and neurophysiology of the basal ganglia, use of microelectrode recording techniques for lesion localization, improved brain imaging, improved brain lesioning techniques, the rapid emergence of deep brain stimulation technology, progress in neurotransplantation, better patient selection, and improved objective methods for the evaluation of surgical results. These changes have led to increased collaboration between neurosurgeons, neurologists, clinical neurophysiologists, and neuropsychologists, all of which appear to be resulting in a better therapeutic result for patients afflicted with these disorders.

The aim of *Surgical Treatment of Parkinson's Disease and Other Movement Disorders* is to create a reference handbook that describes the methodologies we believe are necessary to carry out neurosurgical procedures for the treatment of Parkinson's disease and other movement disorders. It is directed toward neurologists who participate in these procedures or are referring patients to have them done, to neurosurgeons who are already carrying out these procedures or contemplating becoming involved, and to other health care professionals including neuropsychologists and general medical physicians seeking better familiarity with this rapidly evolving area of therapeutics. Several books concerning this subject currently exist, most of which have emerged from symposia on surgical treatment of movement disorders. We have tried here to provide a systematic and comprehensive review of the subject, which (where possible) takes a "horizontal" view of the approaches and methodologies common to more than one surgical procedure, including patient selection, patient assessment, target localization, postoperative programming methods, and positron emission tomography.

We have gathered a group of experienced and recognized authorities in the field who have provided authoritative reviews that define the current state of the art of surgical treatment of Parkinson's disease and related movement disorders. We greatly appreciate their excellent contributions as well as the work of Paul Dolgert, Craig Adams, and Mark Breaugh at Humana Press who made this work a reality. We especially thank our very patient and understanding families whose love and support helped to make this book possible. Finally we dedicate this book to our patients whose courage and persistence in the face of great adversity have allowed the work described in this book to progress toward some measure of relief of their difficult conditions.

Daniel Tarsy, *MD*
Jerrold L. Vitek, *MD, PhD*
Andres M. Lozano, *MD, PhD*

2

Basal Ganglia Circuitry and Synaptic Connectivity

Ali Charara, Mamadou Sidibé, and Yoland Smith

1. OVERALL ORGANIZATION OF THE BASAL GANGLIA

The basal ganglia are several synaptically interconnected subcortical structures that play important roles in regulating various aspects of psychomotor behaviors, and are central to the pathophysiology of common human movement disorders such as Parkinson's and Huntington's diseases (PD/HD). These structures classically include: 1) the striatum, which comprises the caudate nucleus (CD), putamen (PUT), and nucleus accumbens (Acc); 2) the globus pallidus, which includes the external (GPe; globus pallidus in nonprimates) and internal (GPi; entopeduncular nucleus [EPN] in nonprimates) segments; 3) the subthalamic nucleus (STN); and 4) the substantia nigra, which comprises the pars compacta (SNc) and pars reticulata (SNr) (Fig. 1).

The striatum, and to a lesser extent, the STN are the major receptive components of the basal ganglia. They both receive excitatory glutamatergic projections from the cerebral cortex and the thalamus. They also receive modulatory dopaminergic inputs from the SNc and ventral tegmental area (VTA) as well as serotonergic inputs from the dorsal raphe nucleus (DR). The striatum projects directly, and indirectly via the GPe and STN, to the output nuclei of the basal ganglia, the GPi, and SNr *(1–3)*. The direct and indirect striatal projections as well as the GPe projection to the STN use the inhibitory amino acid, γ-aminobutyric acid (GABA), as neurotransmitter. In contrast, the pathways from the STN to the GPi and SNr are excitatory and glutamatergic *(3)*. Thus, the basal ganglia output nuclei, GPi and SNr, receive opposite inhibitory and excitatory signals from the direct and indirect pathways. The GPi and SNr projections to the thalamus are GABAergic and tend to inhibit thalamocortical feedback which, in turn, is excitatory and glutamatergic. Furthermore, the output neurons of the GPi and SNr project to specific brainstem structures that provide descending projections to motor nuclei in the medulla and spinal cord (Fig. 1). Therefore, the major circuitry of the basal ganglia is from the cortex, through its component structures, which then convey the information to the thalamus and brainstem. The thalamus projects back upon frontal cortical areas whereas the brainstem sends feedback ascending projections to the basal ganglia or descending projections to medullary motor nuclei interconnected with the spinal cord (Fig.1).

In addition to these main basal ganglia circuits, there are additional loops and connections that may play important roles in basal ganglia functions. These include projections from the GPe to the striatum, the substantia nigra, and the reticular thalamic nucleus; projections from the STN to the GPe, tegmental pedunculopontine nucleus (PPN), striatum, and SNc; and projections from the thalamus to the striatum, the pallidum, and the STN *(3,4)* (Fig. 1). In dealing with such a complex circuitry, and because of space limitations, this review will not cover every aspects of the basal ganglia connectivity, but will

From: Contemporary Clinical Neurology:
Surgical Treatment of Parkinson's Disease and Other Movement Disorders
Edited by: D. Tarsy, J. L. Vitek, and A. M. Lozano © Humana Press Inc., Totowa, NJ

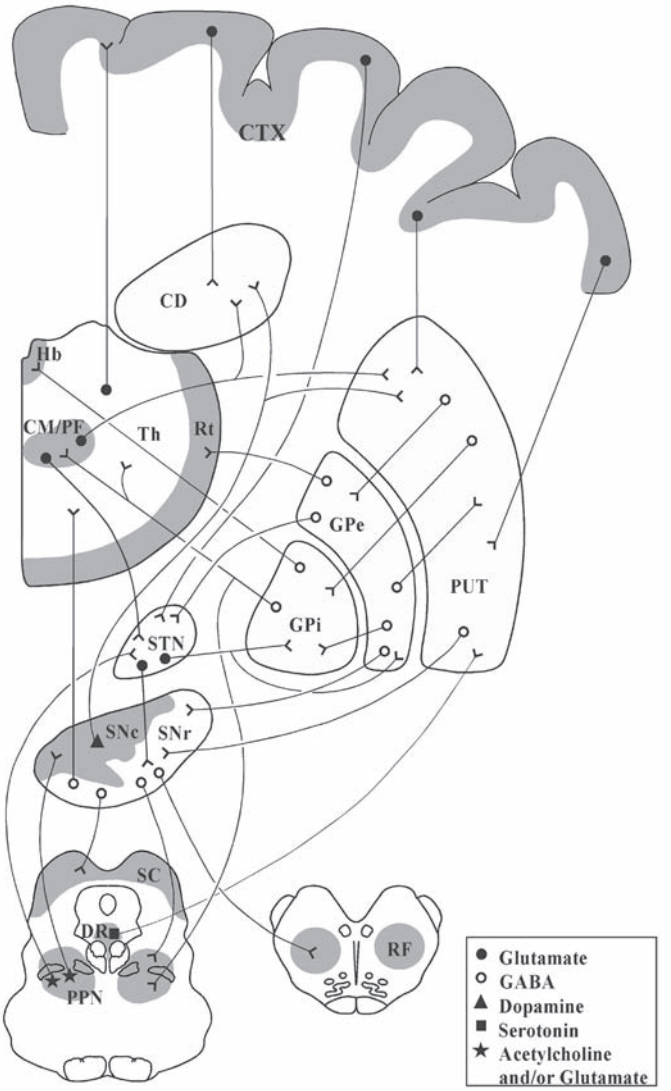

Fig. 1. Schematic diagram of major basal ganglia connections in primates. For simplification, some connections have been omitted. The main neurotransmitters are indicated by different symbols that labeled the cell bodies.

rather focus on the overall direction of information flow and highlight some recent anatomical findings that underlie novel concepts of basal ganglia organization.

2. THE STRIATUM: A MAJOR ENTRANCE TO THE BASAL GANGLIA CIRCUITRY

2.1. The Corticostriatal Projection

Nearly all regions of the cerebral cortex send topographic projections to the striatum, at varying degrees, making the cerebral cortex, by far, the strongest input to the basal ganglia; afferents from sensorimotor and associative cortices are particularly extensive, whereas those from the primary visual

and auditory cortices being much less so *(4)*. There is evidence that the striatum is subdivided into different functional territories according to its cortical inputs. In monkeys, the premotor, motor, and somatosensory cortices in the frontal lobe project mostly to the postcommissural putamen where a somatotopic representation of the leg, arm, and face occurs in the form of obliquely arranged strips *(5)*. The caudate nucleus and precommissural putamen receive projections, mostly unilateral, from association areas of the prefrontal, temporal, parietal, and cingulate cortices, and motor areas in the frontal lobe that control eye movements. The afferents from limbic cortical areas as well as from the amygdala and the hippocampus terminate preferentially in the ventral portion of the striatum *(3–8)*.

Although there is a general topographic relationship between the cerebral cortex and striatum, the integration of information from several different cortical areas is governed by convergence and divergence of corticostriatal inputs. The sensorimotor cortical areas that are functionally interconnected via corticocortical connections tend to give rise to extensively overlapping projections in the ipsilateral putamen, whereas contralateral projections from M1, except those from the face area, interdigitate with ipsilateral M1/S1 overlapping regions *(9,10)*. A similar pattern of convergence exists for the striatal projections from frontal and supplementary eye fields *(11)*. However, it appears that striatal projections from reciprocally linked areas of the association cortices are either completely segregated or interdigitated within zones of overlap in the monkey striatum *(12)*. These projections occupy longitudinal sectors that are aligned along the mediolateral axis of the striatum *(12)*.

Corticostriatal neurons are divided into at least three types, as revealed by studies using double retrograde or intracellular staining techniques in rats *(13)*. The first type, which gives rise to a relatively small component of the corticostriatal pathway, includes large pyramidal cells located in deep layer V. These cells have extensive intracortical axon arborizations, contribute to the pyramidal tract, and emit fine collaterals with very restricted arborizations in the ipsilateral striatum. The focal nature of these arborizations suggests a relatively simple and highly convergent organization of the corticostriatal pathway. A second, more common, type is located in the superficial layer V and deep layer III. These neurons give rise to bilateral corticocortical and corticostriatal projections. The axons of those cells form diffuse complexes of axon terminals that occupy a large volume of the ipsilateral and contralateral striatum. Within that volume, the density of axonal arborization is very sparse, leaving large areas uninnervated, which indicates that individual axonal branches cross the dendritic field of many striatal neurons and form mostly "en passant" synapses *(6,7,14,15)*. This pattern implies a much more complex and divergent organization of the corticostriatal pathway. A third type of corticostriatal neurons is located in the superficial layer V. These neurons project mainly to the thalamus with a collateral projection to the striatum *(6,16,17)*.

Ninety percent of neurons in the striatum are medium-sized GABAergic projection neurons, which have their distal dendrites densely covered with spines *(6,7,18)*. The remaining neurons are aspiny and comprise four main populations of chemically characterized interneurons: 1) the cholinergic neurons which partly co-express calretinin; 2) the parvalbumin-containing neurons that also contain GABA; 3) the somatostatin-immunoreactive neurons that also express neuropeptide Y, nitric oxide, and GABA; and 4) the calretinin-containing neurons that partly co-localize with choline acetyltransferase *(19,20)*. A small subset of calbindin-immunoreactive neurons also display ultrastructural features and morphological characteristics of interneurons, but the majority of calbindin-positive cells in the striatum are projection neurons *(20,21)*.

The corticostriatal afferents form asymmetric synapses principally on the head of dendritic spines of projection neurons and less frequently with dendritic shafts of projection neurons and interneurons *(18)*. The density of cortical innervation of striatal interneurons is variable depending on their chemical phenotype. For instance, parvalbumin-containing interneurons receive strong cortical inputs at the level of cell bodies and proximal dendrites *(22)*, whereas cholinergic interneurons are almost completely devoid of cortical afferents except for sparse inputs on their distal dendrites and spine-like appendages *(23–25)*. On the other hand, despite this light cortical innervation, stimulation of the cerebral cortex evokes monosynaptic excitatory postsynaptic potentials in cholinergic interneurons *(26)*.

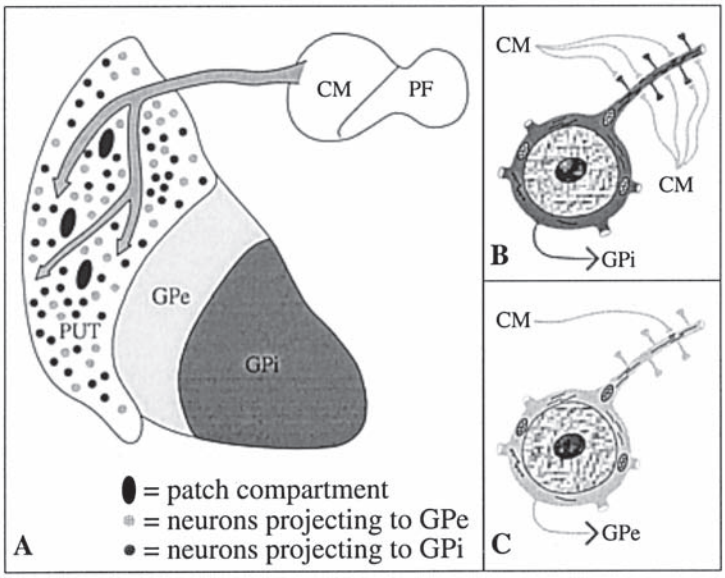

Fig. 2. Compartmental (**A**) and synaptic (**B,C**) relationships between striatopallidal neurons and thalamic afferents from the centromedian nucleus (CM) in monkeys. These data were obtained after simultaneous injections of anterograde tracers in CM and retrograde tracers in either segment of the globus pallidus. (**A**) CM inputs project mainly to the matrix striatal compartment that contains neurons projecting to GPe (light gray circles) or GPi (dark gray circles). Thalamic afferents form asymmetric synapses, frequently with striato-GPi neurons (**B**) but rarely with striato-GPe cells (**C**). (Modified with permission from ref. *29*.)

2.2. The Thalamostriatal Projection

The thalamostriatal projection, originating mostly from the centromedian (CM) and parafasicular (PF) intralaminar nuclei, is the second most prominent source of glutamatergic inputs to the striatum. Anterograde tracing studies in rats and monkeys revealed that the thalamostriatal projection is topographically organized *(8,27,28)*. In monkeys, the CM projects mainly to the sensorimotor territory of the striatum where it terminates in the form of elongated bands, whereas the PF innervates predominantly the associative territory and, to a lesser extent, the limbic territory, where it terminates in a patchy-like manner *(28,29)*. In all striatal territories, fibers from both CM and PF arborize preferentially in the matrix compartment *(28,29)* (Fig. 2). Recent evidence indicates that the precommissural putamen receives inputs from an area called dorsolateral PF (PFdl), a group of fusiform neurons that extend mediolaterally along the dorsal border of CM *(30)*. In rats and monkeys, thalamic inputs to the limbic territory arise largely from midline and rostral intralaminar nuclei *(31,32)*. Specific relay or association thalamic nuclei also project to the striatum, but to a lesser extent than intralaminar nuclei *(33–34a)*. A recent study demonstrated convergent projections from various interconnected ventral thalamic motor relay nuclei and frontal cortical motor areas to broad territories of the postcommissural putamen *(35)*. Together, these anatomical data indicate that thalamostriatal projections from intralaminar and relay nuclei are more massive and much better organized than previously thought.

Earlier electrophysiological and retrograde tracing studies suggested that thalamostriatal fibers emit collaterals to the cerebral cortex *(36–39)*. The existence of such collaterals was recently confirmed by single-cell labeling in rats *(40)*. These branched neurons were found in the parafascicular, ethmoid nucleus, posterior thalamic group, lateral posterior nucleus, mediodorsal nucleus, and anterior ventral nucleus. Collaterals of thalamostriatal fibers project to broad cortical areas and mostly arborize in layers

III, V, and VI *(40)*. It is unlikely that such collateralization is a general characteristic of thalamostriatal neurons in primates. For instance, neurons in CM that project to the primary motor cortex are largely segre-gated from thalamostriatal neurons that project to the putamen in squirrel monkeys *(33,41)*.

Both medium spiny projection neurons and aspiny interneurons are targeted by thalamostriatal afferents. In contrast to cortical boutons, that predominantly terminate on the head of dendritic spines *(18)*, thalamic terminals from caudal intralaminar nuclei form asymmetric synapses principally on dendritic shafts of medium-sized projection neurons *(28,29,42)*. However, studies in rat indicate that striatal inputs from rostral intralaminar nuclei target preferentially dendritic spines *(43)*. Thalamic inputs from CM form synapses more frequently with direct than indirect striatofugal neurons in monkeys, which indicates that the thalamus modulates differently the two major output pathways of the basal ganglia in primates *(29)* (Fig. 2). Striatal interneurons immunoreactive for choline acetyltransferase, parvalbumin and somatostatin, but not those containing calretinin, also receive substantial inputs from CM in monkeys *(44)*. In rats, cholinergic neurons are a major target of thalamic inputs from PF *(23,24)* whereas parvalbumin-containing neurons are much less innervated by thalamic afferents *(45)*. Whether this represents a species difference between primates and nonprimates regarding thalamic innervation of parvalbumin-containing interneurons or a difference in the postsynaptic targets of CM and PF inputs to the striatum remains to be established.

2.3. The Nigrostriatal Projection

The striatum receives a massive projection from midbrain dopaminergic neurons located in the SNc (cell group A9), VTA (cell group A10), and retrorubral field (RRF; cell group A8). It is largely accepted that neurons in the VTA give rise to the mesolimbocortical system, whose fibers terminate principally in the ventral striatum and frontal cortex, whereas neurons in the SNc and RRA project via the nigrostriatal pathway to the putamen and caudate nucleus. A small proportion of nigrostriatal fibers are nondopaminergic and use GABA as neurotransmitter *(46–48)*. Similarly, a GABAergic projection from the VTA to the frontal cortex has been described *(49)*. In vitro data also suggest that midbrain dopaminergic neurons may release glutamate as neurotransmitter *(50,51)*.

Various neuroanatomic studies indicate that the nigrostriatal projection is topographically organized. For instance, in rats, the sensorimotor striatum receives its main dopaminergic input from the lateral part of the SNc and dopaminergic cells in the SNr, whereas the associative striatum is mainly innervated by the medial SNc and VTA. On the other hand, the limbic striatum receives inputs from the VTA, whereas the RRA projects to all striatal territories *(52,53)*. In monkeys, attempts to outline the topographic organization of the nigrostriatal projection led to controversial results *(52)*. Some data indicate that the rostral two-thirds of the substantia nigra is connected with the head of the caudate nucleus, whereas nigral neurons projecting to the putamen are more caudally located, and display a rostrocaudal topography *(33)*. An inverse mediolateral and dorsoventral topography between the SNc and the striatum has also been proposed in monkeys *(54)*. Retrograde fluorescent double-labeling studies revealed that nigro-caudate and nigro-putamen neurons are organized in the form of interdigitated, closely intermingled clusters of various sizes distributed throughout the entire SNc in squirrel monkeys *(55)*. More recently, the organization of the nigrostriatal projection was examined in relation to the functional territories of the striatum in rhesus monkeys *(56,57)*. These studies demonstrated that the sensorimotor-related striatum receives its main input from the cell columns in the ventral tier of the SNc, whereas the limbic-related striatum is innervated preferentially by the VTA and dorsal tier of the SNc. On the other hand, the associative-related striatum receives inputs from a wide range of dopamine neurons largely localized in the densocellular part of the ventral SNc *(56,57)*.

Although some immunohistochemical data showed that the striosomes are rather poorly innervated by dopaminergic afferents compared to the extrastriosomal matrix in the striatum of adult monkeys and humans *(58,59)* most studies found that tyrosine hydroxylase- and dopamine-containing fibers terminate homogenously throughout the rat striatum *(60)*. In rats, the dopaminergic projections from

the dorsal tier of the SNc terminate mainly in the matrix compartment, whereas projections from the ventral tier of the SNc innervate preferentially the patch compartment *(47,47a)*. Dopaminergic cells of the VTA and RRA project only to the matrix *(47)*. However, attempts to delineate groups of DA neurons projecting to the matrix and/or striosomes have been less successful and failed to establish simple relations between striatal compartments and different subdivisions of the SNc in nonhuman primates *(52,53,56)*.

Ultrastructural studies revealed that dopaminergic terminals make symmetric synapses with dendritic shafts and spines of projection neurons *(18,53,61)*. In rats, the pattern of synaptic organization of dopaminergic terminals is similar in the matrix and striosomes *(48)*. In rodents, most dopaminergic synapses occur on the neck of spines whose head receives asymmetric contacts from corticostriatal fibers *(18,61)*, whereas, in monkeys, the majority of dopamine terminals form axodendritic synapses *(62)*. In contrast to cortical and dopamine terminals that often converge onto common postsynaptic targets, thalamic and dopaminergic afferents are not found in close proximity to each other in the monkey striatum *(62)*. Together, these data indicate that the dopaminergic afferents are positioned to exert a more direct and powerful modulation of cortical inputs than thalamic afferents in the striatum. Indeed, pre- and postsynaptic interactions between dopamine and cortical afferents have been shown, though the anatomical substrates for presynaptic interactions are still controversial *(63,64)*. It is worth noting that dopamine may also influence the activity of striatal projection neurons through nonjunctional appositions *(65)*, which is consistent with receptor localization studies that D1 and D2 receptors are mostly expressed extrasynaptically onto the plasma membranes of striatal neurons *(66,67)*.

It is important to keep in mind that dopamine may also influence basal ganglia functions via extrastriatal projections. Direct dopaminergic inputs to the pallidum and the subthalamic nucleus have, indeed, been described anatomically and electrophysiologically in various species *(47a,53,53a)*. The dopaminergic innervation of the thalamus is decreased in hemiparkinsonian monkeys, which suggests that this innervation largely arises from axon collaterals of the massive nigrostriatal pathway *(53a)*. Intrastriatal dopaminergic neurons also provide another route by which dopamine may influence striatal functions. These neurons are likely to be particularly important in Parkinson's disease since their number increases dramatically in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated monkeys *(53,68)*.

2.4. Other Striatal Afferents

The striatum receives many other afferent projections that, due to space limitation, will not be discussed in details in the present review. These include the serotonergic projection from the dorsal and median raphe nuclei as well as the subthalamostriatal projection. Serotonergic fibers arborize profusely throughout the entire striatum, but slightly more heavily in the ventral region *(69)*. In rats, dorsal raphe neurons projecting to the striatum send axon collaterals to the substantia nigra *(70)*. Although some serotonergic terminals form asymmetric axospinous and axodendritic synapses *(71)*, only a minor proportion of serotonergic fibers exhibit typical synaptic junctions in the rat striatum *(72)*.

In primates, subthalamic neurons that innervate the putamen are located in the sensorimotor-related dorsolateral two-thirds of the STN, whereas those projecting to the caudate nucleus are found ventrolaterally in the associative territory *(33,73)*. Other inputs to the striatum arise from the globus pallidus, pedunculopontine nucleus, and locus coeruleus *(33,74,75)*.

3. THE DIRECT AND INDIRECT STRIATOFUGAL PROJECTIONS

3.1. Original Concept

The information sent to the striatum is integrated by medium spiny projection neurons and transmitted to the output nuclei of the basal ganglia (GPi and SNr) via two pathways so-called direct and indirect pathways *(1,76)*. The direct pathway originates from a population of striatal neurons that pro-

ject directly to the GPi and SNr whereas the indirect pathway arises from striatal neurons that project to GPe. In turn, the GPe conveys the information to the STN, which then relays it to the output nuclei of the basal ganglia, the GPi, and the SNr (Fig. 1). Striatal neurons that give rise to the direct and indirect pathways are further distinguished by their expression of neuroactive peptides and dopamine receptor subtypes. Although all striatal projection neurons use GABA as their main transmitter, neurons projecting to the GPe contain enkephalin and express preferentially D2 dopamine receptors, whereas those projecting to the GPi and SNr are enriched with substance P and dynorphin and express mainly D1 dopamine receptors *(6)*.

According to functional models of basal ganglia circuits, normal basal ganglia functions require a balance between the activity of the direct and indirect pathways *(77)*. This balance is maintained, in part, by dopaminergic modulation of striatal neurons. Release of dopamine facilitates transmission through the direct pathway but reduces transmission through the indirect pathway. During normal movement, the overall effect of striatal dopamine release is to reduce the GPi/SNr inhibition of the thalamus, leading to increased activity of thalamocortical projections, which is necessary for the speed and guidance of movements. However, an imbalance of activity of these two pathways can perturb the normal degree of GPi/SNr inhibition of thalamocortical activity producing hypo- or hyperkinetic disorders *(77)*. Since the introduction of the model of direct and indirect pathways, there have been many anatomical, biochemical, and molecular studies that increased our knowledge of the organization of the basal ganglia and led to reconsider some aspects of the functional circuitry of the basal ganglia. In the following account we summarize some of these data and discuss their relevance for basal ganglia pathophysiology.

3.2. Collateralization of Striatofugal Neurons and Co-localization of Dopamine Receptors

One of the important series of data that challenged the concept of segregated direct and indirect striatofugal pathways is the demonstration that "direct" striatofugal neurons are much more collateralized than previously thought. Based on single cell filling studies, striatofugal neurons are divided into three types in rats *(78)*: 1) a first population projecting only and extensively to the GP; 2) a second type projecting to both GP and SNr; and 3) a third type projecting to GP, EP, and SNr. Similar findings were recently found in monkeys *(79)*. Although these data provide evidence for the existence of the indirect pathway, they suggest that the so-called direct striatofugal neurons display a high degree of collateralization and that none of the striatofugal neurons examined project exclusively to the GPi (or EPN) or SNr.

Another controversial issue that has been raised by various investigators over the past few years is the differential expression of D1 and D2 dopamine receptors in direct and indirect striatofugal neurons *(6)*. Although many *in situ* hybridization studies and immunohistochemical data showed that D1 and D2 receptors are largely segregated in the rat striatum, reverse transcriptase polymerase chain reaction (RT-PCR) experiments in isolated striatal neurons *(80)* and a recent double immunofluorescence study *(81)* revealed a higher level of co-localization. Furthermore, it was found that most striatal spiny neurons respond to both D1 and D2 receptor agonists, in vitro *(80,81)*. It is now apparent that this controversy is due to the differential sensitivity of RT-PCR and *in situ* hybridization methods to detect mRNAs because the relative abundance of the two receptor subtypes in direct and indirect striatofugal neurons is strikingly different. Neurons of the indirect pathway that contain enkephalin express high levels of D2 mRNA and low level of D1 mRNA, whereas direct striatofugal neurons that contain substance P express high levels of D1 mRNA but also contain low levels of D2 mRNA *(80)*. The only striatal projection neurons that express a high level of D1 and D2 receptor subtypes are a small population that contains both enkephalin and substance P *(80,82)*. Similar findings were obtained by double immunofluorescence *(81)*. These findings must be kept in mind while considering the functional significance of the direct and indirect striatofugal pathways.

3.3. Multiple Indirect Pathways

In addition to the classical indirect pathway through the GPe and STN, there is a variety of other indirect pathways and loops that process the flow of information through the basal ganglia. For instance, the GPe gives rise to GABAergic projections to basal ganglia output structures (GPi, SNr) and the reticular thalamic nucleus *(3,4,8)*. Another projection from the GPe to the striatum, which targets preferentially subpopulations of interneurons, has also been identified *(83)*. The STN projections to the GPe, SNc, striatum, and PPN *(3)* are additional indirect pathways through which cortical information flows to reach basal ganglia output structures (*see* below). Although the exact functions of these connections remain unknown, it should be kept in mind that the circuitry of the basal ganglia outlined in the original model of direct and indirect pathways is, by necessity, an oversimplification *(3)*.

3.4. Parallel Pathways through Pallido-Subthalamo-Pallidal Loops

The connections between the GPe and the STN as well as the relationships between these structures and the GPi have been the subject of many studies that aimed at elucidating how the indirect pathways influence neurons of the output structures of the basal ganglia. The GPe gives rise to a massive, topographically organized projection, which terminates throughout the entire extent of the STN in monkeys *(3,84)*. The main projection sites of the STN are the GPe, GPi, and SNr *(3,73)*. Like most other basal ganglia components, the STN comprises segregated sensorimotor, associative, and limbic territories *(85)*. However, double anterograde tracing experiments showed that there are significant zones of overlap of inputs from functionally diverse regions of the pallidal complex in rats *(86)*. In contrast to GPi/SNr neurons where GPe terminals are confined to their proximal part, the pallidosubthalamic boutons form symmetric synapses with all parts of STN neurons (Fig. 3). In many cases, the receiving STN neurons project back to the GPe indicating the reciprocal relationships between the GPe and STN *(3,8,84)*.

New insights into the connections between the GPe and the STN as well as the relationships between these structures and the GPi have recently been provided *(84)*. On one hand, the neuronal network connecting the STN, GPe, and GPi has been examined using the anterograde and retrograde transport of biotinylated dextran amine *(84)*. The findings of this study demonstrated that interconnected neurons of the GPe and the STN innervate, via axon collaterals, functionally related neurons in the GPi *(84)*. Thus, populations of neurons within the sensorimotor, cognitive, and limbic territories in the GPe are reciprocally connected with populations of neurons in the same functional territories of the STN. In turn, neurons in each of these regions innervate the same functional territory of the GPi. Additional organizational principles that do not respect the functional topography of the direct and indirect network, but rather underlie a system for integration of functionally diverse information was also reported in this and other studies *(3,8,86,87)*. It is also important to keep in mind that all GPe neurons do not project only to the STN and vice-versa. Recent single axon-tracing studies, indeed, revealed the presence of different types of neurons in GPe and STN based on their axonal projections *(88)*. GPe neurons were found to project to: 1) GPi, STN, and SNr; 2) GPi and STN; 3) STN and SNr; and 4) striatum. None of the neurons examined projects to the STN only. Similarly, five types of STN neurons have been identified: 1) neurons projecting to GPe, GPi, and SNr; 2) neurons projecting to GPe and GPi; 3) neurons projecting to GPe and SNr; 4) neurons projecting only to GPe; and 5) neurons projecting to the striatum *(88)*. Altogether, these data highlight the heterogeneity and complex patterns of projections of the GPe and STN in primates.

4. THE SUBTHALAMIC NUCLEUS: ANOTHER ENTRANCE TO THE BASAL GANGLIA CIRCUITRY

4.1. Intrinsic Organization

The STN is particularly well-developed in primates. It is a highly vascularized and densely populated structure, encapsulated by major myelinated fiber bundles, the zona incerta, and the cerebral

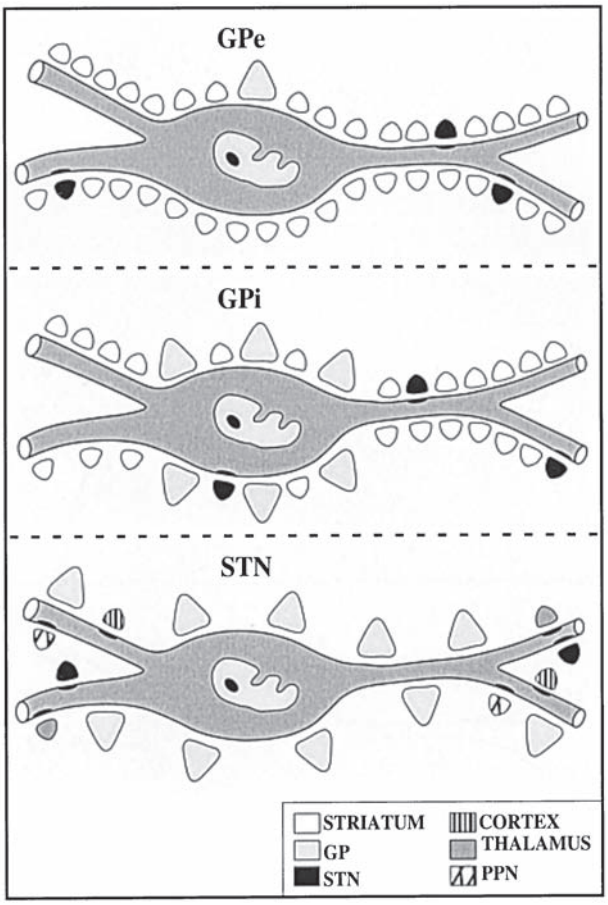

Fig. 3. Schematic drawings of the pattern of innervation of neurons in both segments of the globus pallidus and subthalamic nucleus based on data obtained in monkeys using anterograde tracers and postembedding immunogold for GABA and glutamate. The relative size and proportion of each category of terminals are represented. The major difference between GPe and GPi is that GPi neurons receive strong somatic inputs from GPe, whereas striatal and subthalamic terminals are evenly distributed on GPe and GPi neurons. (Modified with permission from ref. *3*.)

peduncle. It is noteworthy that a large number of myelinated axons, which likely convey ascending and descending information, also travel through the STN *(89,90)*. Most neurons of the STN belong to a single population of cells with spindle-shaped, pyramidal, or round perikarya *(91)*. Its principal elements are projection neurons whose dendrites can extend for more than 750 μm *(92)*. Each STN neuron gives rise to six or seven stem dendrites that branch in an ellipsoidal domain parallel to the rostrocaudal axis of the nucleus *(91)*. The existence of interneurons in the STN is controversial *(91–93)*. Although Rafols and Fox originally proposed that the monkey STN contained a population of small interneurons *(92)*, subsequent Golgi studies in cats, monkeys, and humans concluded that the STN was a relatively homogeneous structure largely composed of projection neurons *(91)*. These early findings were later supported by intracellular labeling experiments showing that the axons of all labeled STN neurons could be traced beyond the boundaries of the nucleus in rats *(94)*. Interestingly, more than half of these projection neurons had intranuclear axon collaterals that extended outside the dendritic

domains of the parent neurons suggesting that they may serve as a feedforward circuit in the STN *(94)*. Such intrinsic axon collateral systems do not seem to be as extensive in primates *(91,95)*.

4.2. The Corticosubthalamic Projection

As is the case for the striatum, the STN also receives excitatory glutamatergic projections from the cerebral cortex *(3,8,85)*. In primates, the cortico-subthalamic projection is exclusively ipsilateral and arises principally from the primary motor cortex (area 4), with a minor contribution of prefrontal and premotor cortices. The somatosensory and visual cortical areas do not project to the STN, whereas they project quite substantially to the striatum *(3,8)*. In rats, the cortico-subthalamic projection originates mainly from pyramidal layer V neurons that also project to the striatum *(96)*. In both rats and monkeys, the cortico-subthalamic projection is topographically organized: 1) afferents from the primary motor cortex (M1) are confined to the dorsolateral part of the STN; 2) the premotor (areas 8, 9, and 6), the supplementary motor area (SMA), the presupplementary motor area, and adjacent frontal cortical areas innervate mainly the medial third of the nucleus *(97)*; and 3) the prefrontal-limbic cortices project to the medialmost tip of the nucleus *(3,85)*. By virtue of its cortical inputs, the dorsolateral sector of the STN is more specifically involved in the control of skeletomotor behavior, whereas the ventromedial part is more concerned with oculomotor and associative functions *(3,85)*. Like cortical afferents to the striatum, the cortico-subthalamic projection from M1 is somatotopically organized; the face area projects laterally, the arm area centrally, and the leg area medially *(98,99)*. Interestingly, the arrangement of somatotopical representations from the SMA to the medial STN is reversed against the ordering from the M1 to the lateral STN in macaque monkeys *(98)*. Therefore, the cerebral cortex imposes a specific functional segregation not only on the striatum, but also at the level of the STN *(99)*. However, it is worth noting that STN neurons have long dendrites that may cross boundaries of functional territories imposed by cortical projections in rats *(86)*. This anatomical arrangement opens up the possibility for some functionally segregated information at the level of the cerebral cortex to converge on individual STN neurons in rodents.

4.3. The Thalamosubthalamic Projection

Another major source of excitatory inputs to the STN are the caudal intralaminar thalamic nuclei *(100)*. The thalamosubthalamic projection respects the functional organization of the STN, i.e., sensorimotor neurons in CM terminate preferentially in the dorsolateral part of the nucleus whereas limbic- and associative-related neurons in PF project almost exclusively to the medial STN *(41,100)*. In rats, the thalamosubthalamic projection is excitatory and tonically drives the activity of STN neurons *(100)*. The degree of collateralization of thalamostriatal and thalamosubthalamic neurons is controversial. A retrograde double-labeling study indicated that the thalamosubthalamic and thalamostriatal projections arise largely from segregated sets of PF neurons in rats *(96)*, whereas single-cell labeling data showed that some PF neurons that project to the striatum send axon collaterals to the STN *(101)*.

Even if cortical and thalamic inputs are relatively sparse and terminate exclusively on the distal dendrites and spines of STN neurons *(102)*, electrophysiological experiments showed that activation of these inputs results in very strong short latency monosynaptic excitatory postsynaptic potentials (EPSP) with multiple spikes in STN neurons, which in turn transmit their information to basal ganglia output structures much faster than striatofugal pathways *(103–106)*.

These observations emphasize the importance of the STN in the functional organization of the basal ganglia and strongly suggest that it may serve as another entrance for extrinsic inputs to basal ganglia circuitry. Although the exact role of these projections remains to be established, electrophysiological evidence indicates that they might be important in the formation of a center-surround organization in GPi and SNr to help focusing pertinent information during voluntary movements *(107)*.

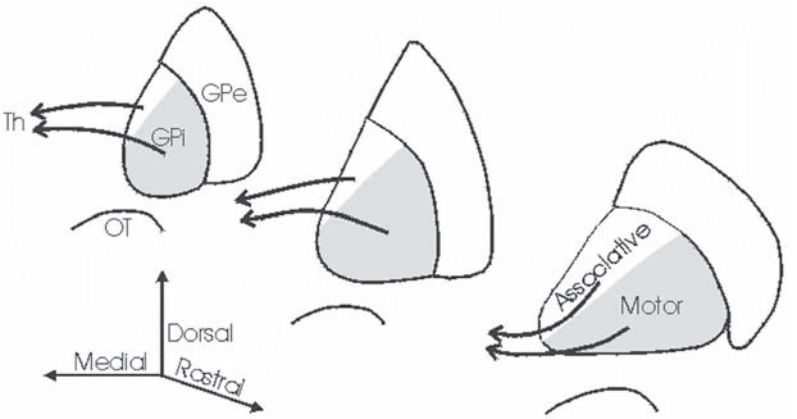

Fig. 4. Schematic diagram illustrating the course of motor and associative pallidothalamic projections originating in the caudal two-thirds of GPi (Modified with permission from ref. *110*.)

5. THE BASAL GANGLIA OUTFLOW

5.1. Pallidofugal Projections

5.1.1. The Pallidothalamic Projection

The pallidothalamic projection is topographically organized and its fibers arborize largely in the ventral anterior/ventral lateral (VA/VL) nuclei *(4,108)*. Earlier investigations of the origin of pallidothalamic fibers in the monkey, using degenerative methods, indicate that pallidothalamic fibers that travel via the ansa lenticularis and the lenticular fasciculus arise from specific portions of the GPi *(109,109a)*. According to the generally accepted scheme of pallidothalamic outflow, fibers of the ansa lenticularis arise predominantly from GPi cells located lateral to the accessory medullary laminae, which course rostrally, ventrally, and medially in the GPi. On the other hand, fibers of the lenticular fasciculus are thought to arise largely from cells in the inner part of GPi, which course dorsally and medially across the internal capsule to reach the thalamus *(109,109a)*. This scheme was recently challenged by new anatomical data obtained after injections of anterograde tracers in specific functional parts of the squirrel monkey GPi *(110)*. According to these data, the pallidothalamic fibers originating form the caudal portion of the GPi, including the motor territory, do not course ventromedially to form the ansa lenticularis, but rather, travel predominantly medially through the lenticular fasciculus en route to the thalamus. Fibers coursing below the ventral border of the pallidum in the so-called ansa lenticularis originates mostly from cells located in the rostral half of GPi *(110)* (Fig. 4). This scheme is much simpler than that currently accepted, which implies that fibers coursing through the ansa lenticularis frequently follow lengthy courses through the GPi to reach the thalamus. Therefore, the separate designation of the pallidothalamic pathways into ansa lenticularis and fasciculus lenticularis based on the location of GPi cells relative to the accessory medullary laminae is misleading and should be used with caution. This delineation is critical toward effective surgical treatment of various movement disorders *(110)*.

Efferent projections from the sensorimotor GPi remain largely segregated from the associative and limbic projections at the level of the thalamus. In squirrel monkeys, the sensorimotor GPi outputs are directed towards the posterior VL (VLp), whereas the associative and limbic GPi innervate preferentially the parvocellular VA (VApc) and the dorsal VL (VLd). The ventromedial nucleus receives inputs from the limbic GPi only *(108)*. These findings, therefore, reveal that some associative and limbic cortical information, which is largely processed in segregated cortico-striatopallidal channels,

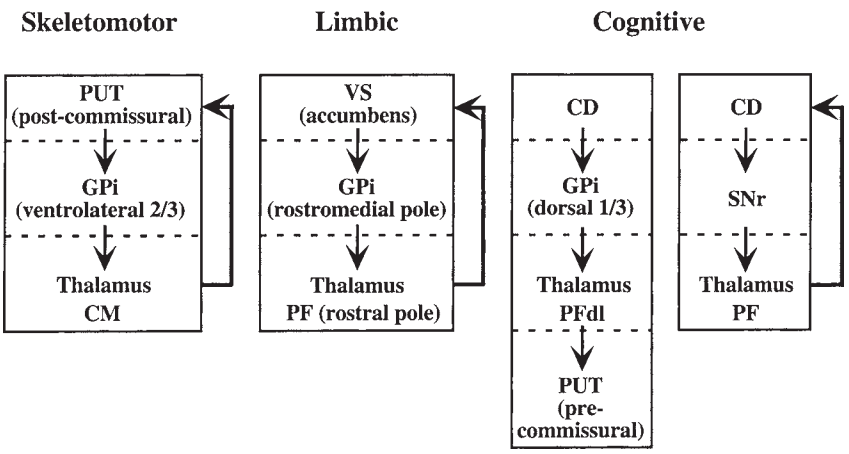

Fig. 5. Schematic diagram illustrating the synaptic interactions between basal ganglia and thalamostriatal neurons in monkeys. These data were obtained following simultaneous injections of retrograde tracers in different functional territories of the striatum and anterograde tracers in the corresponding functional regions of GPi or SNr. Note that the caudal intralaminar thalamic nuclei and the basal ganglia are interconnected by both open and closed loops.

converge to common thalamic nuclei in monkeys. It is noteworthy that about 10–20% of pallidothalamic neurons in the monkey GPi project to the contralateral VA/VL *(4,111,112)*.

Most pallidal neurons that project to thalamic motor nuclei send axon collaterals to the caudal intralaminar nuclei *(4,112,112a)*. These branched neurons are located in the central portion of GPi *(112)*. Pallidal axons arising from the sensorimotor GPi terminate in CM where they form synapses with thalamostriatal neurons projecting back to the sensorimotor territory of the striatum *(30,108)* (Fig. 5). In contrast, associative inputs from the GPi terminate massively in the dorsolateral extension of PF (PFdl), which does not project back to the caudate nucleus but rather innervates preferentially the precommissural region of the putamen (Fig. 5). Finally, the limbic GPi innervates selectively the rostrodorsal part of PF, which in turn projects back to the nucleus accumbens *(28,32)*. Therefore it appears that CM/PF is part of closed and open functional loops with the striatopallidal complex (Fig. 5).

5.1.2. The Pallidotegmental Projection

The pallidotegmental fibers terminate in the PPN, which is composed of two major subdivisions, the pars compacta and the pars diffusa *(114,118)*. Studies in monkeys indicate that more than 80% of GPi neurons projecting to the PPN send axon collaterals to the ventral thalamus *(112)*. The PPN gives rise to descending projections to the pons, medulla, and spinal cord as well as ascending projections to the thalamus and basal ganglia *(115–117)*. Thus, the pallidotegmental projection may be a route by which cortical information can reach lower motor and autonomic centers. Another possibility could be that PPN acts as an important interface between different functional territories of the GPi and sends back the processed information to the basal ganglia *(118)* (Fig. 6).

The pattern of distribution of functionally segregated pallidofugal information in the PPN has been investigated in monkeys *(118)*. The results of this study are summarized in Fig. 6. Injections of anterograde tracers in different functional territories of the GPi led to anterograde labeling, which largely converges to common regions of the pars diffusa of the PPN. The fibers that arise from the associative and limbic territories of the GPi are more widely spread than the afferents from the sensorimotor territory. Another major finding of this study was that pallidal fibers largely avoid cholinergic neurons in the pars compacta of the PPN *(118)*. These anatomical data suggest that the pars diffusa of the

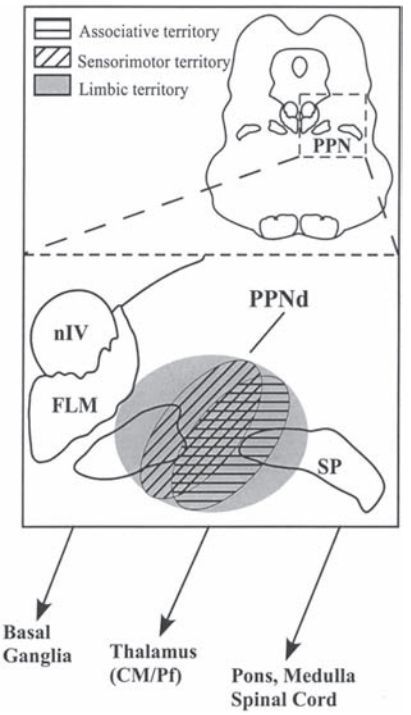

Fig. 6. Schematic drawing showing the location of anterogradely labeled fibers in the pedunculopontine tegmental nucleus (PPN) after injections of anterograde tracers in the associative, sensorimotor, and limbic terr-itories of the internal segment of the globus pallidus (GPi). Note that projections from the different functional territories of GPi largely overlap in the PPN. FLM: Medial longitudinal fasciculus; SP: Superior cerebellar peduncle. (Modified with permission from ref. *118*.)

PPN is the potential site for the integration of information arising from different functional territories of the GPi in primates (Fig. 6).

5.1.3. The Pallidohabenular Projection

In contrast to the pallidothalamic and pallidotegmental projections, which are largely collateralized, the pallidohabenular projection arises from a distinct population of neurons in the monkey GPi *(112)*. In rats, pallidohebenular neurons are located in the rostral part of the entopeduncular nucleus, whereas pallidothalamic and pallidotegmental projections arise preferentially from the caudal half of the nucleus *(119–121)*. Interestingly, pallidohabenular cells receive afferents from striatofugal neurons in the patch compartment, whereas pallidothalamic and pallidotegmental neurons are innervated by striatal neurons in the matrix compartment *(120)*. The ventral pallidum also contributes to the pallidohabenular projection in rats and cats *(122,123)*. In primates, retrograde labeling studies showed that pallidohabenular neurons are far less numerous than pallidothalamic cells and are mainly confined to a peri-GPi region, which extends medially in the lateral hypothalamus *(112,124)*. More recent studies in squirrel monkeys using sensitive anterograde labeling methods demonstrated that the pallidohabenular projection is functionally organized and more massive than previously thought *(125, 126)*. The sensorimotor GPi innervates preferentially the centrolateral part of the lateral habenular nucleus, whereas the limbic and associative GPi project massively to the medial part of the nucleus *(125)*. The pallidohabenular projection is mainly GABAergic though cholinergic neurons in the entopeduncular nucleus also contribute to this projection in rats *(125,127,128)*. Because of its prominent connections with various limbic structures, the lateral habenula is considered as a functional interface between the limbic system and basal ganglia.

5.2. Nigrofugal Projections

5.2.1. The Nigrothalamic Projection

The GPi and SNr are considered as the two main output nuclei of the basal ganglia that project massively to the ventral thalamus and brainstem nuclei. Overall, SNr and GPi afferents to the ventral thalamus are largely segregated, but in nonprimates, the ventromedial nucleus receives convergent inputs from both basal ganglia output structures and the cerebellum *(130)*. In monkeys, the nigrothalamic cells are distributed throughout the mediolateral extent of the SNr and form the largest population of nigrofugal neurons *(131)*. Inputs from the medial part of the SNr terminate mostly in the medial magnocellular division of the VA (VAmc) and the mediodorsal nucleus (MDmc) that, in turn, innervate anterior regions of the frontal lobe including the principal sulcus and the orbital cortex *(132)*. Neurons in the lateral part of the SNr project preferentially to the lateral posterior region of the VAmc and to different parts of MD mostly related to posterior regions of the frontal lobe, including the frontal eye field areas of the premotor cortex *(132)*. In rats, a lamellar organization of nigrofugal neurons has been proposed as the main constituent for the parallel processing of information flow through the SNr *(133,133a)*. According to this model, functionally segregated striatal neurons project to different lamella of SNr neurons, which in turn convey the information to different thalamic nuclei *(133,133a)*. The dendrites of individual SNr neurons largely conform to the geometry of striatonigral projections, which strongly supports the concept of a parallel architecture of striatonigral circuits *(133a)*.

SNr neurons also project to rostral and caudal intralaminar thalamic nuclei *(132–134)*. In monkeys, the nigro-intralaminar thalamic projection terminates exclusively in PF where nigral boutons form GABAergic synapses with thalamostriatal neurons that project to the caudate nucleus *(132,134)*.

5.2.2. The Nigrotegmental Projection

The nigrotegmental projection displays a dorsoventral topography and terminates preferentially on noncholinergic neurons in the medial twothirds of the PPN pars diffusa in rats *(133,135,136)*. A much smaller number of nigral fibers innervate cholinergic neurons in the PPN pars compacta *(136)*. In monkeys, the cells that give rise to the nigrotegmental projection are found throughout the mediolateral extent of the SNr and form the second largest population of SNr nigrofugal neurons *(131)*. Most nigrotegmental cells send axon collaterals to the ventral anterior thalamic nucleus *(131,133)* and receive direct inputs from the striatum *(137)*. The pattern of distribution and postsynaptic targets of nigrotegmental neurons remains to be established in primates.

5.2.3. The Nigrocollicular Projection

The SNr sends a massive and topographically organized GABAergic projection to the intermediate layer of the superior colliculus *(131,133,138)*. The nigral terminals form distinctive clusters in the deep and intermediate layers of the superior colliculus where they innervate neurons that project to the spinal cord, medulla, and periabducens area *(138–140)*. This projection plays an important role in a variety of visual and auditory responses that control saccadic eye movements toward a stimulus. This is consistent with the fact that SNr receiving neurons of the intermediate layer of the superior colliculus are targeted by visual inputs from the cortex and project to brainstem regions that control eye movements *(141)*.

5.2.4. The Nigroreticular Projection

The SNr also sends projections to the medullary reticular formation *(142,143)*. In rats, this projection arises from a population of neurons in the dorsolateral SNr and terminates in the parvicellular reticular formation *(143)*. Identified nigroreticular neurons receive GABAergic inputs from the striatum and the globus pallidus *(144)*. This projection is thought to play a role in orofacial movements because the SNr-receiving neurons of the reticular formation are directly connected with orofacial motor nuclei *(145,146)*.

6. THE PEDUNCULOPONTINE NUCLEUS: AN INTEGRAL PART OF THE BASAL GANGLIA CIRCUITRY

Many lines of anatomical and electrophysiological evidence indicate that the PPN is reciprocally connected with the basal ganglia *(155–157)*. As discussed earlier, the PPN receives substantial projections from the GPi and SNr *(118,135,136)*. An input from the STN has also been demonstrated *(73, 74)*. In turn, the PPN sends ascending projections to all basal ganglia nuclei. In rats and primates, the SNc and the STN are, by far, the most densely innervated basal ganglia structures by PPN efferents *(75,147–150)*. Both glutamate and acetylcholine are used as neurotransmitter by these projections *(150–153)*. The PPN innervation of the pallidal complex is not as dense as that of the STN and SNc, arborizes preferentially in the GPi and uses both glutamate and acetylcholine as neurotransmitters *(75,152–154)*. A light pedunculostriatal projection has also been described in rats *(147)* and monkeys *(75)*, but the chemical nature of this projection is still unknown. Taken into consideration these tight interconnections with basal ganglia structures combined with prominent descending projections to pontine, medullary, and spinal structures, the PPN is considered as a possible relay station where the striatum meets the reticular formation and the spinal cord *(115–117)*.

The PPN also sends massive cholinergic and noncholinergic projections to various thalamic nuclei *(155–158)*. These projections play a major role in mediating cortical desynchronization during waking and rapid eye movement (REM) sleep *(116,159,160)*. Cholinergic and glutamatergic PPN inputs to thalamostriatal neurons have been demonstrated *(134,161,162)*. It is interesting to note that a subpopulation of PPN neurons innervate simultaneously the basal ganglia and thalamic regions via axon collaterals *(163)*. These findings suggest that the PPN conveys information to the basal ganglia not only directly, but also indirectly via thalamostriatal neurons. Therefore, the PPN occupies a strategic position that allows modulation of neuronal activity in functional basal ganglia-thalamocortical and thalamostriatal loops. The fact that there is a significant loss of PPN neurons in parkinsonians, and that lesion of PPN results in akinesia and postural instabilities are further evidence that the PPN plays a major role in basal ganglia circuitry in both normal and pathological conditions *(117)*.

7. CONCLUDING REMARKS

Our knowledge of the basal ganglia anatomy has increased tremendously over the past 10 years, mainly owing to the introduction of highly sophisticated and sensitive tract-tracing and immunocytochemical methods suitable for light and electron microscope analysis. In this review, we highlighted recent anatomical data that has led us to reconsider some aspects of the functional circuitry of the basal ganglia.

For instance, the thalamostriatal projection, which is largely neglected in functional models of the basal ganglia connections, deserves more attention. This projection is massive and follows a highly specific pattern of functional connectivity with the striatopallidal complex. The fact that thalamic inputs are directed preferentially towards specific populations of striatal projection neurons and interneurons strongly suggests that these inputs may play a major role in the basal ganglia circuitry. The recent demonstration that thalamostriatal projections from CM/PF supply striatal neurons with information about behaviorally significant sensory events *(164)* further emphasize the importance of this projection in the functional circuitry of the basal ganglia.

Another important concern raised over the past few years relates to the validity of the direct and indirect pathways of the basal ganglia. The evidence that subpopulations of striatofugal neurons express both D1 and D2 dopamine receptors combined with the fact that striatofugal neurons are more collateralized than previously thought led to reconsider the concept that direct and indirect striatofugal pathways arise from segregated populations of striatal projection neurons. However, despite these anatomical complexities of the basal ganglia circuitry, it is clear that the "relatively simple" functional model of direct and indirect pathways still remains the most appropriate working framework

for understanding changes in the basal ganglia circuitry and develop novel therapeutic strategies for movement disorders.

Another critical aspect that should deserve attention in the future is the relative importance of the STN and the striatum as major entrances of cortical information to the basal ganglia. Although the striatum receives much more massive inputs from the cerebral cortex and thalamus than the STN, the fact that the information flowing through the corticosubthalamic projection reach the output structures of the basal ganglia faster than that traveling through the striatum deserves consideration.

Finally, more attention should definitely be paid at the PPN as an integral component of the basal ganglia and a potential target for the development of new therapies for Parkinson's disease.

ACKNOWLEDGMENTS

The authors acknowledge Jean-François Paré for his skilfull technical assistance. This work was supported by NIH grants R01-37423, R01-37948 and RR 00165.

REFERENCES

1. Albin, R. L., Young, A. B., and Penney, J. B. (1989) The functional anatomy of basal ganglia disorders. *Trends Neurosci.* **12,** 366–375.
2. DeLong, M. R. (1990) Primate models of movement disorders of basal ganglia origin. *Trends Neurosci.* **13,** 281–285.
3. Smith, Y., Bevan, M. D., Shink, E., and Bolam, J. P. (1998) Microcircuitry of the direct and indirect pathways of the basal ganglia. *Neuroscience* **86,** 353–387.
4. Parent, A. and Hazrati, L.-N. (1995) Functional anatomy of the basal ganglia. I. The cortico-basal ganglia-thalamocortical loop. *Brain Res. Rev.* **20,** 91–127.
5. Alexander, G. E. and DeLong, M. R. (1985) Microstimulation of the primate neostriatum. II. Somatotopic of striatal microexcitable zones and their relations to neuronal response properties. *J. Neurophysiol.* **53,** 1417–1430.
6. Gerfen, C. R. and Wilson, C. J. (1996) The basal ganglia. In: *Handbook of Chemical Neuroanatomy, Integrated Systems of the CNS, Part III* (Björklund, A., Hökfelt, T., and Swanson, L., eds.), Elsevier, Amsterdam, pp. 369–466.
7. Wilson, C. J. (1998) Basal Ganglia. In: *The Synaptic Organization of the Brain* (Shepherd, G. M., ed.), Oxford University Press, New York, NY, pp. 329–375.
8. Smith, Y., Shink E., and Sidibé M. (1998) Neuronal circuitry and synaptic connectivity of the basal ganglia. In: *Neurosurgery Clinics of North America* (Bakay, A. E., ed.), W.B. Saunders, Philadelphia, PA, pp. 203–222.
9. Flaherty, A. W. and Graybiel, A. M. (1991) Corticostriatal transformation in the primate somatosensory system. Projections from physiologically mapped body-part representations. *J. Neurophysiol.* **66,** 1249–1263.
10. Flaherty, A. W. and Graybiel, A. M. (1993) Two input systems for body representations in the primate striatal matrix: experimental evidence in the squirrel monkey. *J. Neurosci.* **13,** 1120–1137.
11. Parthasarathy, H. B., Schall, J. D., and Graybiel, A. M. (1992) Distributed but convergent ordering of corticostriatal projections: analysis of the frontal eye field and the supplementary eye field in the macaque monkey. *J. Neurosci*. **12,** 4468–4488.
12. Selemon, L. D. and Goldman-Rakic, P. S. (1990) Longitudinal topography and interdigitation of corticostriatal projections in the rhesus monkey. *J. Neurosci.* **5,** 776–794.
13. Cowan, R. L. and Wilson, C.J. (1994) Spontaneous firing patterns and axonal projections of single corticostriatal neurons in the rat medial agranular cortex. *J. Neurophysiol.* **71,** 17–32.
14. Kincaid, A. E., Zheng, T., and Wilson, C. J. (1998) Connectivity and convergence of single corticostriatal axons. *J. Neurosci.* **18,** 4722–4731.
15. Wilson, C. J. (1995) The contribution of cortical neurons to the firing pattern of striatal spiny neurons. In: *Models of Information Processing in the Basal Ganglia* (Houk, J. C., Davis, J. L., and Beiser, D. G., eds.), The MIT Press, Cambridge, MA, pp. 29–50.
16. Paré, D. and Smith, Y. (1996) Thalamic collaterals of corticostriatal axons: their termination field and synaptic targets in cats. *J. Comp. Neurol.* **372,** 551–567.
17. Lévesque, M., Gagnon, S., Parent, A., and Deschênes, M. (1996) Axonal arborizations of corticostriatal and corticothalamic fibers arising from the second somatosensory area in the rat. *Cereb. Cortex* **6,** 759–770.
18. Smith, A. D. and Bolam, J. P. (1990) The neural network of the basal ganglia as revealed by the study of synaptic connections of identified neurons. *Trends Neurosci.* **13,** 259–265.
19. Kawaguchi, Y., Wilson, C. J., Augood, S. J., and Emson, P. C. (1995) Striatal interneurons: chemical, physiological and morphological characterization. *Trends Neurosci.* **18,** 527–535.
20. Cicchetti, F., Prensa, L., Wu, Y., and Parent, A. (2001) Chemical anatomy of striatal interneurons in normal individuals and in patients with Huntington's disease. *Brain Res. Rev.* **34,** 80–101.
21. Bennett, B. D. and Bolam, J. P. (1993) Two populations of calbindin D28k-immunoreactive neurons in the striatum of the rat. *Brain Res.* **610,** 305–310.

22. Lapper, S. R., Smith, Y., Sadikot, A. F., Parent, A., and Bolam, J. P. (1992) Cortical input to parvalbumin-immunoreactive neurons in the putamen of the squirrel monkey. *Brain Res.* **580,** 215–224.
23. Lapper, S. R. and Bolam, J. P. (1992) Input from the frontal cortex and the parafascicular nucleus to cholinergic interneurons in the dorsal striatum of the rat. *Neuroscience* **51,** 533–545.
24. Meredith, G. E. and Wouterlood, F. G. (1990) Hippocampal and midline thalamic fibers and terminals in relation to the choline acetyltransferase-immunoreactive neurons in nucleus accumbens of the rat: a light and electron microscopic study. *J. Comp. Neurol.* **296,** 204–221.
25. Thomas, T. M, Smith, Y., Levey, A. I., and Hersch, S. M. (2000) Cortical inputs to m2-immunoreactive striatal interneurons in rat and monkey. *Synapse* **37,** 252–261.
26. Wilson, C. J., Chang, H. T., and Kitai, S. T. (1990) Firing patterns and synaptic potentials of identified giant aspiny interneurons in the rat neostriatum. *J. Neurosci.* **10,** 508–519.
27. Groenewegen, H. J. and Berendse, H. W. (1994) The specificity of the nonspecific midline and intralaminar thalamic nuclei. *Trends Neurosci.* **17,** 52–57.
28. Sadikot, A. F., Parent, A., Smith, Y., and Bolam, J. P. (1992) Efferent connections of the centromedian and parafascicular nuclei in the squirrel monkey: a light and electron microscopic study of the thalamostriatal projection in relation to striatal heterogeneity. *J. Comp. Neurol.* **320,** 228–242.
29. Sidibé, M. and Smith, Y. (1996) Differential synaptic innervation of striatofugal neurons projecting to the internal or external segments of the globus pallidus by thalamic afferents in the squirrel monkey. *J. Comp. Neurol.* **365,** 445–465.
30. Sidibé, M., Pare, J.-L., and Smith, Y. (2002) Nigral and pallidal inputs to functionally segregated thalamostriatal neurons in the centromedian/parafascicular intralaminar nuclear complex in monkey. *J. Comp Neurol.* **447(3),** 286–299.
31. Groenewegen, H. J. and Berendse, H. W. (1994) The specificity of the nonspecific midline and intralaminar thalamic nuclei. *Trends Neurosci.* **17,** 52–57.
32. Giménez-Amaya, J. M., McFarland, N. R., De Las Heras, S., and Haber, S. N. (1995) Organization of thalamic projections to the ventral striatum in the primate. *J. Comp. Neurol.* **354,** 127–149.
33. Smith, Y. and Parent, A. (1986) Differential connections of the caudate nucleus and putamen in squirrel monkeys (*Saimiri sciureus*). *Neuroscience* **18,** 347–371.
34. McFarland, N. R. and Haber, S. N. (2001) Organization of thalamostriatal terminals from the ventral motor nuclei in the macaque. *J. Comp. Neurol.* **429,** 321–336.

34a. Lin, C.-S., May, P. J., and Hall, W. C. (1984) Nonintralaminar thalamostriatal projection sin the gray squirrel (*Sciureus carolinensis*) and tree shrew (*Tupaia glis*). *J. Comp. Neurol.* **230,** 33–46.

35. McFarland, N. R. and Haber, S. N. (2000) Convergent inputs from thalamic motor nuclei and frontal cortical areas to the dorsal striatum in the primate. *J. Neurosci.* **20,** 3798–3813.
36. Rasminsky, M., Mauro, A., and Albe-fessard, D. (1973) Projections of medial thalamic nuclei to the putamen and frontal cerebral cortex in the cat. *Brain Res.* **61,** 69–77.
37. Jinnai, K. and Matsuda, Y. (1979) Neurons of the motor cortex projecting commonly on the caudate nucleus and the lower brain stem in the cat. *Neurosci. Lett.* **26,** 95–99.
38. Royce, G. J. (1983) Single thalamic neurons which project to both the rostral cortex and caudate nucleus studied with the fluorescent double labeling method. *Exp. Neurol.* **79,** 773–784.
39. Macchi, G., Bentivoglio, M., Molinari, M., and Minciacchi, D. (1984) The thalamo-caudate versus thalamo-cortical projections as studied in the cat with fluorescent retrograde double labeling. *Exp. Brain Res.* **54,** 225–239.
40. Deschênes, M., Bourassa, J., and Parent, A. (1996) Striatal and cortical projections of single neurons from the central lateral thalamic nucleus in the rat. *Neuroscience* **72,** 679–687.
41. Sadikot, A. F., Parent, A., and François, C. (1992) Efferent connections of the centromedian and parafascicular thalamic nuclei in the squirrel monkey: a PHA-L study of subcortical projections. *J. Comp. Neurol.* **315,** 137–159.
42. Dubé, L., Smith, A. D., and Bolam, J. P. (1988) Identification of synaptic terminals of thalamic and cortical origin in contact with distinct medium-sized spiny neurons in the rat neostriatum. *J Comp. Neurol.* **267,** 455–471.
43. Xu, Z. C., Wilson, C. J., and Emson, P. C. (1991) Restoration of thalamostriatal projections in rat neostriatal grafts: an electron microscopic analysis. *J. Comp. Neurol.* **303,** 22–34.
44. Sidibé, M. and Smith, Y. (1999) Thalamic inputs to striatal interneurons in monkeys: synaptic organization and co-localization of calcium binding proteins. *Neuroscience* **89,** 1189–1208.
45. Rudkin, T. M. and Sadikot, A. F. (1999) Thalamic inputs to parvalbumin-immunoreactive GABAergic interneurons: Organization in normal striatum and effect of neonatal decortication. *Neuroscience* **88,** 1165–1175.
46. Rodríguez, M. and González-Hernández, T. (1999) Electrophysiological and morphological evidence for a GABAergic projection nigrostriatal pathway. *J. Neurosci.* **19,** 4682–4694.
47. Gerfen, C. R., Herkenham, M., and Thibault, J. (1987) The neostriatal mosaic: II. Patch- and matrix-directed mesostriatal dopaminergic and non-dopaminergic systems. *J. Neurosci.* **7,** 3915–3934.

47a. Prensa, L. and Parent, A. (2001) The nigrostriatal pathway in the rat: a single-axon study of the relationship between dorsal and ventral tier nigral neurons and the striosome/matrix striatal compartments. *J. Neurosci.* **21,** 7247–7260.

48. Hanley, J. J. and Bolam, J. P. (1997) Synaptology of the nigrostriatal projection in relation to the compartmental organization of the neostriatum in the rat. *Neuroscience* **81,** 353–370.
49. Steffensen, S. C., Svingos, A. L., Pickel, V. M., and Henriksen, S. J. (1998) Electrophysiological characterization of GABAergic neurons in the ventral tegmental area. *J. Neurosci.* **18,** 8003–8015.
50. Sulzer, D., Joyce, M. P., Lin, L., Geldwert, D., Haber, S. N., Hattori, T., and Rayport, S. (1998) Dopamine neurons make glutamatergic synapses in vitro. *J. Neurosci.* **18,** 4588–4602.

51. Joyce, M. P. and Rayport, S. (2000) Mesoaccumbens dopamine neuron synapses reconstructed in vitro are glutamatergic. *Neuroscience* **99,** 445–456.
52. Joel, D. and Weiner, I. (2000) The connections of the dopaminergic system with the striatum in rats and primates: an analysis with respect to the functional and compartmental organization of the striatum. *Neuroscience* **96,** 451–474.
53. Smith, Y. and Kieval, J. Z. (2000) Anatomy of the dopamine system in the basal ganglia. *Trends Neurosci.* **23,** S28–S33.
53a. Freeman, A., Ciliax, B., Bakay, R., Daley, J., Miller, R. D., Keating, G., Levey, A., and Rye, D. (2001) Nigrostriatal collaterals to thalamus degenerate in parkinsonian animal models. *Ann. Neurol.* **50,** 321–329.
54. Szabo, J. (1980) Organization of the ascending striatal afferents in monkeys. *J. Comp. Neurol.* **189,** 307–321.
55. Parent, A., Mackey, A., and De Bellefeuille, L. (1983) The subcortical afferents to caudate nucleus and putamen in primate: a fluorescence retrograde double labeling study. *Neuroscience* **10,** 1137–1150.
56. Lynd-Balta, E. and Haber, S. N. (1994) The organization of midbrain projections to the striatum in the primate: sensorimotor-related striatum versus ventral striatum. *Neuroscience* **59,** 625–640.
57. Lynd-Balta, E. and Haber, S. N. (1994) The organization of midbrain projections to the ventral striatum in the primate. *Neuroscience* **59,** 609–623.
58. Lavoie, B., Smith, Y., and Parent, A. (1989) Dopaminergic innervation of the basal ganglia in the squirrel monkey as revealed by tyrosine hydroxylase immunohistochemistry *J. Comp. Neurol.* **289,** 36–52.
59. Graybiel, A. M., Hirsch, E. C., and Agid, Y. A. (1987) Differences in tyrosine hydroxylase-like immunoreactivity characterize the mesostriatal innervation of striosomes and extrastriosomal matrix at maturity. *Proc. Natl. Acad. Sci. USA* **84,** 303–307.
60. Hökfelt, T., Martensson, R., Björklund, A., Kleinau, S., and Goldstein M. (1984) Distributional maps of tyrosine hydroxylase-immunoreactive neurons in the rat brain. In: *Handbook of Chemical Neuroanatomy. Vol. 2. Classical Transmitters in the CNS Part 1,* (Björklund, A. and Hökfelt T., eds.), Elsevier, Amsterdam, Netherlands, pp. 277–379.
61. Freund, T. F., Powell, J. F., and Smith, A. D. (1984) Tyrosine hydroxylase-immunoreactive boutons in synaptic contact with identified striatonigral neurons, with particular reference to dendritic spines. *Neuroscience* **13,** 1189–1215.
62. Smith, Y., Bennett, B. D., Bolam, J. P., Parent, A., and Sadikot, A. F. (1994) Synaptic relationships between dopaminergic afferents and cortical or thalamic input in the sensorimotor territory of the striatum in monkey. *J. Comp. Neurol.* **344,** 1–19.
63. Calabresi, P., Pisani, A., Mercuri, N. B., and Bernardi, G. (1996) The corticostriatal projection: from synaptic plasticity to dysfunctions of the basal ganglia. *Trends Neurosci.* **19,** 19–24.
64. Calabresi, P., De Murtas, M., and Bernardi, G. (1997) The neostriatum beyond the motor function: experimental and clinical evidence. *Neuroscience* **78,** 39–60.
65. Descarries, L., Watkins, K. C., Garcia, S., Bosler, O., and Doucet, G. (1996) Dual character, asynaptic and synaptic, of the dopamine innervation in adult rat neostriatum: a quantitative autoradiographic and immunocytochemical analysis. *J. Comp. Neurol.* **375,** 167–186.
66. Yung, K. K. L., Bolam, J. P., Smith, A. D., Hersch, S. M., Ciliax, B. J., and Levey, A. I. (1995) Immunocytochemical localization of D1 and D2 dopamine receptors in the basal ganglia of the rat: light and electron microscopy. *Neuroscience* **65,** 709–730.
67. Caillé, I., Dumartin, B., and Bloch, B. (1996) Ultrastructural localization of D1 dopamine receptor immunoreactivity in rat striatonigral neurons and its relation with dopaminergic innervation. *Brain Res.* **730,** 17–31.
68. Betarbet, R., Turner, R., Chockkan, V., DeLong, M. R., Allers, K. A., Walters, J., Levey, A. I., and Greenamyre, J. T. (1997) Dopaminergic neurons intrinsic to the primate striatum. *J. Neurosci.* **17,** 6761–6768.
69. Lavoie, B. and Parent, A. (1990) Immunohistochemical study of the serotoninergic innervation of the basal ganglia in the squirrel monkey. *J. Comp. Neurol.* **299,** 1–16.
70. Van der Kooy, D. and Hattori, T. (1980) Dorsal raphe cells with collateral projections to the caudate-putamen and substantia nigra: a fluorescent retrograde double labeling study in the rat. *Brain Res.* **186,** 1–7.
71. Pasik, P., Pasik, T., Holstein, G. R., and Pecci-Saavedra, J. (1984) Serotoninergic innervation of the monkey basal ganglia: an immunocytochemical study. In: *The Basal Ganglia: Structures and Function* (McKenzie, J. S., Kemm, R. E., and Wilcock, L.N., eds.), Plenum Press, New York, pp. 115–129.
72. Soghomonian, J. J., Descarries, L., and Watkins, K. C. (1989) Serotonin innervation in adult rat neostriatum. II. Ultrastructural features: a radioautographic and immunocytochemical study. *Brain Res.* **481,** 67–86.
73. Parent, A. and Smith, Y. (1987) Organization of efferent projections of the subthalamic nucleus in the squirrel monkey as revealed by retrograde labeling methods. *Brain Res.* **436,** 296–310.
74. Jackson, A. and Crossman, A. R. (1983) Nucleus tegmenti pedunculopontinus: Efferent connections with special reference to the basal ganglia, studied in the rat by anterograde and retrograde transport of horseradish peroxidase. *Neuroscience* **10,** 725–765.
75. Lavoie, B. and Parent, A. (1994) Pedunculopontine nucleus in the squirrel monkey: projections to the basal ganglia as revealed by anterograde tract-tracing methods. *J. Comp. Neurol.* **344,** 210–231.
76. Bergman, H., Wichmann, T., and DeLong, M. R. (1990) Reversal of experimental parkinsonism by lesions of the subthalamic nucleus. *Science* **249,** 1436–1438.
77. DeLong, M. R. (1990) Primate models of movement disorders of basal ganglia origin. *Trends Neurosci.* **13,** 281–285.
78. Kawaguchi, Y., Wilson, C. J., and Emson, P. C. (1990) Projection subtypes of rat neostriatal matrix cells revealed by intracellular injection of biocytin. *J. Neurosci.* **10,** 3421–3438.
79. Parent, A., Charara, A., and Pinault, D. (1995) Single striatofugal axons arborizing in both pallidal segments and in the substantia nigra in primate. *Brain Res.* **698,** 280–284.

80. Surmeier, D. J., Eberwine, J., Wilson, C. J., Cao, Y., Stefani, A., and Kitai, S. T. (1992) Dopamine receptor subtypes colocalize in rat striatonigral neurons. *Proc. Natl. Acad. Sci. USA* **89,** 10,178–10,182.
81. Aizman, O., Brismar, H., Uhlen, P., Zettergren, E., Levey, A. I., Forssberg, H., et al. (2000) Anatomical and physiological evidence for D1 and D2 dopamine receptor colocalization in neostriatal neurons. *Nat. Neurosci.* **3,** 226–230.
82. Surmeier, D. J., Song, W. J., and Yan, Z. (1996) Coordinated expression of dopamine receptors in neostriatal medium spiny neurons. *J. Neurosci.* **16,** 6579–6591.
83. Bevan, M. D., Booth, P. A., Eaton, S. A., and Bolam J. P. (1998) Selective innervation of neostriatal interneurons by a subclass of neurons in the globus pallidus of the rat. *J. Neurosci.* **18,** 9438–9452.
84. Shink, E., Bevan, M. D., Bolam, J. P., and Smith, Y. (1996) The subthalamic nucleus and the external pallidum: two tightly interconnected structures that control the output of the basal ganglia in the monkey. *Neuroscience* **73,** 335–357.
85. Parent, A. (1990) Extrinsic connections of the basal ganglia. *Trends Neurosci.* **13,** 254–258.
86. Bevan, M. D., Clarke, N. P., and Bolam, J. P. (1997) Synaptic integration of functionally diverse pallidal information in the entopeduncular nucleus and subthalamic nucleus in the rat. *J. Neurosci.* **17,** 308–324.
87. Joel, D. and Weiner, I. (1997) The connections of the primate subthalamic nucleus: indirect pathways and the open-interconnected scheme of basal ganglia-thalamocortical circuitry. *Brain Res. Rev.* **23,** 62–78.
88. Parent, A., Sato, F., Wu, Y., Gauthier, J., Lévesque, M., and Parent M. (2000) Organization of the basal ganglia: the importance of axonal collateralization. *Trends Neurosci.* **23,** S20–S27.
89. Hassler, R., Usunoff, K. G., Romansky, K. V., and Christ, J. F. (1982) Electron microscopy of the subthalamic nucleus in the baboon. I. Synaptic organization of the subthalamic nucleus in the baboon. *J. Hirnforsch.* **23,** 597–611.
90. Smith, Y., Bolam, J. P., and Von Krosigk, M. (1990) Topographical and synaptic organization of the GABA-containing pallidosubthalamic projection in the rat. *Eur. J. Neurosci.* **2,** 500–511.
91. Yelnik, J. and Percheron, G. (1979) Subthalamic neurons in primates: a quantitative and comparative analysis. *Neuroscience* **4,** 1717–1773.
92. Rafols, J. A. and Fox, C. A. (1976) The neurons in the primate subthalamic nucleus: a Golgi and electron microscopic study. *J. Comp. Neurol.* **168,** 75–111.
93. Iwahori, N. (1978) A Golgi study on the subthalamic nucleus of the cat. *J. Comp. Neurol.* **182,** 383–397.
94. Kita, H., Chang, H. T., and Kitai, S. T. (1983) The morphology of intracellularly labeled rat subthalamic neurons: a light microscopic analysis. *J. Comp. Neurol.* **215,** 245–257.
95. Sato, F., Parent, M., Levesque, M., and Parent, A. (2000) Axonal branching pattern of neurons of the subthalamic nucleus in primates. *J. Comp. Neurol.* **424,** 142–152.
96. Féger, J., Bevan, M., and Crossman, A. R. (1994) The projections from the parafascicular thalamic nucleus to the subthalamic nucleus and the striatum arise from separate neuronal populations: a comparison with the corticostriatal and corticosubthalamic efferents in a retrograde fluorescent double-labelling study. *Neuroscience* **60,** 125–132.
97. Inase, M., Tokuno, H., Nambu, A., Akazawa, T., and Takada, M. (1999) Corticostriatal and corticosubthalamic input zones from the presupplementary area in the macaque monkey: comparison with the input zones from the supplementary motor area. *Brain Res.* **833,** 191–201.
98. Nambu, A., Takada, M., Inase, M., and Tokuno, H. (1996) Dual somatotopical representations of the primate subthalamic nucleus: Evidence for ordered but reversed body-map transformations from the primary motor cortex and the supplementary motor area. *J. Neurosci.* **16,** 2671–2683.
99. Wichmann, T., Bergman, H., and DeLong, M. R. (1994) The primate subthalamic nucleus. I. Functional properties in intact animals. *J. Neurophysiol.* **72,** 494–506.
100. Féger, J., Hassani, O. K., and Mouroux, M. (1997) The subthalamic nucleus and its connections: New electrophysiological and pharmacological data. *Adv. Neurol.* **74,** 31–43.
101. Deschênes, M., Bourassa, J., Doan, V. D., and Parent, A. (1996) A single-cell study of the axonal projections arising from the posterior intralaminar nuclei in the rat. *Eur. J. Neurosci.* **8,** 329–343.
102. Bevan, M. D., Francis, C. M., and Bolam, J. P. (1995) The glutamate-enriched cortical and thalamic input to neurons in the subthalamic nucleus of the rat: convergence with GABA-positive terminals. *J. Comp. Neurol.* **361,** 491–511.
103. Kita, H. (1994) Physiology of two disynaptic pathways from the sensorimotor cortex to the basal ganglia output nuclei. In: *The Basal Ganglia IV, New Ideas and Data on Structure and Function* (Percheron, G., Mckenzie, J. S., and Féger, J., eds.), Plenum Press, New York, pp. 263–276.
104. Maurice, N., Deniau, J. M., Glowinski, J., and Thierry, A. M. (1998) Relationships between the prefrontal cortex and the basal ganglia in the rat: physiology of the corticosubthalamic circuits. *J. Neurosci.* **18,** 9539–9546.
105. Mouroux, M. and Féger, J. (1993) Evidence that the parafascicular projection to the subthalamic nucleus is glutamatergic. *Neuroreport* **4,** 613–615.
106. Nambu, A., Tokuno, H., Hamada, I., Kita, H., Imanishi, M., Akazawa, T., et al. (2000) Excitatory cortical inputs to pallidal neurons via the subthalamic nucleus in the monkey. *J. Neurophysiol.* **84,** 289–300.
107. Mink, J. W. (1996) The basal ganglia: focused selection and inhibition of competing programs. *Prog, Neurobiol.* **50,** 381–425.
108. Sidibé, M., Bevan, M. D., Bolam, J. P., and Smith Y. (1997) Efferent connections of the internal globus pallidus in the squirrel monkey: I. Topography and synaptic organization of the pallidothalamic projection. *J. Comp. Neurol.* **382,** 323–347.
109. Kuo, J. S. and Carpenter, M. B. (1973) Organization of pallidothalamic projections in the rhesus monkey. *J. Comp. Neurol.* **151,** 201–236.

109a. Parent, A. (1996) *Carpenter's Human Neuroanatomy*, 9th ed. Williams and Wilkins, Philadelphia, PA.
110. Baron, M. S., Sidibé, M., DeLong, M. R., and Smith, Y. (2001) Course of motor and associative pallidothalamic projections in monkeys. *J. Comp. Neurol.* **429,** 490–501.
111. Hazrati, L.-N. and Parent, A. (1991) Contralateral pallidothalamic and pallidotegmental projections in primates: an anterograde and retrograde labeling study. *Brain Res.* **567,** 212–223.
112. Parent, M., Lévesque, M., and Parent, A. (1999) The pallidofugal projection system in primates: evidence for neurons branching ipsilaterally and contralaterally to the thalamus and brainstem. *J. Chem. Neuroanat.* **16,** 153–165.
112a. Parent, M., Levesque, M., and Parent, A. (2001). Two types of projection neurons in the internal pallidum of primates: single-axon tracing and three-dimensional reconstruction. *J. Comp. Neurol.* **439(2),** 162–175.
113. Spann, B. M. and Grofova, I. (1992) Cholinergic and non-cholinergic neurons in the rat pedunculopontine tegmental nucleus. *Anat. Embryol.* **186,** 215–227.
114. Lavoie, B. and Parent, A. (1994b) Pedunculopontine nucleus in the squirrel monkey: distribution of cholinergic and monoaminergic neurons in the mesopontine tegmentum with evidence for the presence of glutamate in cholinergic neurons. *J. Comp. Neurol.* **344,** 190–209.
115. Inglis, W. L. and Winn, P. (1995) The pedunculopontine tegmental nucleus: where the striatum meets the reticular formation. *Prog. Neurobiol.* **47,** 1–29.
116. Rye, D. B. (1997) Contributions of the pedunculopontine region to normal and altered REM sleep. *Sleep* **20,** 757–788.
117. Pahapill, P. A. and Lozano, A. M. (2000) The pedunculopontine nucleus and Parkinson's disease. *Brain* **123,** 1767–1783.
118. Shink E, Sidibé, M., and Smith, Y. (1997) Efferent connections of the internal globus pallidus in the squirrel monkey: I. Topography and synaptic organization of the pallidal efferents to the pedunculopontine nucleus. *J. Comp. Neurol.* **382,** 348–363.
119. Larsen, K. D. and McBride, R. L. (1979) The organization of feline entopeduncular nucleus projections: anatomical studies. *J. Comp. Neurol.* **184,** 293–308.
120. Rajakumar, N., Elisevich, K., and Flumerfelt, B. A. (1993) Compartmental origin of the striato-entopeduncular projection in the rat. *J. Comp. Neurol.* **331,** 286–296.
121. Van der Kooy, D. and Carter, D. A. (1981) The organization of the efferent projections and striatal afferents of the entopeduncular nucleus and adjacent areas in the rat. *Brain Res.* **211,** 15–36.
122. Groenewegen, H. J., Berendse, H. W., and Haber, S. N. (1993) Organization of the output of the ventral striatopallidal system in the rat: ventral pallidal efferents. *Neuroscience* **57,** 113–142.
123. Spooren, W. P. M. J., Haber, S. N., Veening, J. G., and Cools, A. R. (1995) Descending efferent connections of the sub-pallidal areas in the cat: projections to the lateral habenula. *Neuroreport* **6,** 977–980.
124. Parent, A. and DeBellefeuille, L. (1982) Organization of efferent projections from the internal segment of the globus pallidus in primates as revealed by fluorescence retrograde labeling method. *Brain Res.* **245,** 201–213.
125. Shink, E., Sidibé, M., Bouffard, J.-F., and Smith, Y. (1996) Efferent projections of different functional territories of the internal pallidum in monleys. *Soc. Neurosci.* **22,** 411.
126. Parent, M., Lévesque, M., and Parent, A. (2000) Single-axon tracing study of the internal pallidum. *Soc. Neurosci.* **26,** 964.
127. Araki, M., McGeer, P. L., and McGeer, E. G. (1984) Retrograde HRP tracing combined with a pharmacohistochemical method for GABA transaminase for the identification of presumptive GABAergic projections to the habenula. *Brain Res.* **304,** 271–277.
128. Moriizumi, T. and Hattori, T. (1992) Choline acetyltransferase-immunoreactive neurons in the rat entopeduncular nucleus. *Neuroscience* **46,** 721–728.
129. Ilinsky, I. A., Tourtelotte, W. G., and Kultas-Ilinsky, K. (1993) Anatomical distinctions between the two basal ganglia afferent territories in the primate motor thalamus. *Stereotact. Funct. Neurosurg.* **60,** 62–69.
130. Sakai, S. T. and Patton, K. (1993) Distribution of cerebellothalamic and nigrothalamic projections in the dog: A double anterograde tracing study. *J. Comp. Neurol.* **330,** 183–194.
131. Parent, A., Mackey, A., Smith, Y., and Boucher R. (1983) The output organization of the substantia nigra in primate as revealed by a retrograde double labeling method. *Brain Res. Bull.* **10,** 529–537.
132. Ilinsky, I. A., Jouandet, M. L., and Goldman-Rakic, P. S. (1985) Organization of the nigrothalamocortical system in the rhesus monkey. *J. Comp. Neurol.* **236,** 315–330.
133. Deniau, J.-M. and Thierry, A.-M. (1997) Anatomical segregation processing in the rat substantia nigra pars reticulata. In: *Adv. Neurol. The Basal Ganglia and New Surgical Approaches for Parkinson's Disease* (Obeso, J. A., DeLong, M. R., Ohye, C., and Marsden, C. D., eds.), Lippinscott-Raven Publishers, Philadelphia, PA, pp. 83–96.
133a. Mailly, P., Charpier, S., Mahon, S., Menetrey, A., Thierry, A. M., Glowinsky, J., and Deniau, J.-M. (2001) Dendritic arborizations of the rat substantia nigra pars reticulata neurons: spatial organization and relation to the lamellar compartmentation of straito-nigral projections. *J. Neurosci.* **21,** 6874–6888.
134. Smith, Y., Sidibé, M., and Paré, J.-F. (2000) Synaptic inputs from the substantia nigra and the pedunculopontine nucleus to thalamostriatal neurons in monkeys. *Soc. Neurosci. Abstr.* **26,** 965.
135. Spann, B. M. and Grofova, I. (1991) Nigropedunculopontine projection in the rat: an anterograde tracing study with *phaseolus vulgaris-leucoagglutinin* (PHA-L). *J. Comp. Neurol.* **311,** 375–388.
136. Grofova, I. and Zhou, M. (1998) Nigral innervation of cholinergic and glutamatergic cells in the rat mesopontine tegmentum: light and electron microscopic anterograde tracing and immunohistochemical studies. *J. Comp. Neurol.* **395,** 359–379.

137. Tokuno, H., Moriizumi, T., Kudo, M., Kitao, Y., and Nakamura, Y. (1989) Monosynaptic striatal inputs to the nigrotegmental neurons: an electron microscopic study in the cat. *Brain Res.* **485,** 189–192.
138. Redgrave, P., Marrow, L., and Dean, P. (1992) Topographical organization of the nigrotectal projection in rat: Evidence for segregated channels. *Neuroscience* **50,** 571–595.
139. Tokuno, H. and Nakamura Y. (1987) Organization of the nigrotectospinal pathway in the cat: a light and electron microscopic study. *Brain Res.* **436,** 76–84.
140. Williams, M. N. and Faull, R. L. M. (1988) The nigrotectal projection and tectospinal neurons in the rat. A light and electron microscopic study demonstrating a monosynaptic nigral input to identified tectospinal neurons. *Neuroscience* **25,** 533–562.
141. Hikosaka, O., Takikawa, Y., and Kawagoe, R. (2000) Role of basal ganglia in the control of purposive saccadic eye movements. *Physiol. Rev.* **80,** 953–978.
142. Chronister, R. B., Walding, J. S., Aldes, L. D., and Marco, L. A. (1988) Interconnections between substantia nigra reticulata and medullary reticular formation. *Brain Res. Bull.* **21,** 313–317.
143. von Krosigk, M. and Smith, A. D. (1990) Descending projections from the substantia nigra and retrorubral field to the medullary and pontomedullary reticular formation. *Eur. J. Neurosci.* **3,** 260–273.
144. Von Krosigk, M., Smith, Y., Bolam, J. P., and Smith, A. D. (1992) Synaptic organization of GABAergic inputs from the striatum and the globus pallidus onto neurons in the substantia nigra and retrorubral field which project to the medullary reticular formation. *Neuroscience* **50,** 531–549.
145. Chandler, S. H., Turman, J. Jr., Salem, L., and Goldberg, L. J. (1990) The effects of nanoliter ejections of lidocaine into the pontomedullary reticular formation on cortically induced rhythmical jaw movements in the guinea pig. *Brain Res.* **526,** 54–64.
146. Travers, J. B. and Norgren, R. (1983) Afferent projections to the oral motor nuclei in the rat. *J. Comp. Neurol.* **220,** 280–298.
147. Rye, D. B., Saper, C. B., Lee, H. J., and Wainer, B. H. (1987) Pedunculopontine tegmental nucleus of the rat: cytoarchitecture, cytochemistry, and some extrapyramidal connections of the mesopontine tegmentum. *J. Comp. Neurol.* **259,** 483–528.
148. Moon Edley, S. and Graybiel, A. M. (1983) The afferent and efferent connections of the feline nucleus tegmenti pedunculopontinus, pars compacta. *J. Comp. Neurol.* **217,** 187–215.
149. Lee, H. J., Rye, D. B., Hallanger, A. E., Levey, A. I., and Wainer, B. H. (1988) Cholinergic vs noncholinergic efferents from the mesopontine tegmentum to the extrapyramidal motor system nuclei. *J. Comp. Neurol.* **275,** 469–492.
150. Charara, A., Smith, Y., and Parent, A. (1996) Glutamatergic inputs from the pedunculopontine nucleus to midbrain dopaminergic neurons in primates: *Phaseolus vulgaris*-leucoagglutinin anterograde labeling combined with postembedding glutamate and GABA immunohistochemistry. *J. Comp. Neurol.* **364,** 254–266.
151. Bevan, M. D. and Bolam, J. P. (1995) Cholinergic, GABAergic, and glutamate-enriched inputs from the mesopontine tegmentum to the subthalamic nucleus in the rat. *J. Neurosci.* **15,** 7105–7120.
152. Clarke, N. P., Bevan, M. D., Cozzari, C., Hartman, B. K., and Bolam, J. P. (1997) Glutamate-enriched cholinergic synaptic terminals in the entopeduncular nucleus and subthalamic nucleus of the rat. *Neuroscience* **81,** 371–385.
153. Clarke, N. P., Bolam, J. P., and Bevan, M. D. (1996) Glutamate-enriched inputs from the mesopontine tegmentum to the entopeduncular nucleus in the rat. *Eur. J. Neurosci.* **8,** 1363–1376.
154. Charara, A. and Parent, A. (1994) Brainstem dopaminergic, cholinergic and serotoninergic afferents to the pallidum in the squirrel monkey. *Brain Res.* **640,** 155–170.
155. Woolf, N. J. and Butcher, L. L. (1986) Cholinergic systems in the rat brain: III. Projections from the pontomesencephalic tegmentum to the thalamus, tectum, basal ganglia, and basal forebrain. *Brain Res. Bull.* **16,** 603–637.
156. Hallanger, A. E., Levey, A. I., Lee, H. J., Rye, D. B., and Wainer, B. H. (1987) The origins of cholinergic and other subcortical afferents to the thalamus in the rat. *J. Comp. Neurol.* **262,** 105–124.
157. Paré, D., Smith, Y., Parent, A., and Stériade, M. (1988) Projections of brainstem core cholinergic and non-cholinergic neurons of cat to intralaminar and reticular thalamic nuclei. *Neuroscience* **25,** 69–86.
158. Stériade, M., Paré, D., Parent, A., and Smith, Y. (1988) Projections of cholinergic and non-cholinergic neurons of the brainstem core to relay and associational thalamic nuclei in the cat and macaque monkey. *Neuroscience* **25,** 47–67.
159. Steriade, M., Datta, S., Paré, D., Oakson, G., and Curro Dossi, R. C. (1990) Neuronal activities in brain-stem cholinergic nuclei related to tonic activation processes in thalamocortical systems. *J. Neurosci.* **10,** 2541–2559.
160. Reese, N. B., Garcia-Rill, E., and Skinner, R. D. (1995) The pedunculopontine nucleus-auditory input, arousal and pathophysiology. *Prog. Neurobiol.* **47,** 105–133.
161. Erro, E., Lanciego, J. L., and Giménez-Amaya, J. M. (1999) Relationships between thalamostriatal neurons and pedunculopontine projections to the thalamus: a neuroanatomical tract-tracing study in the rat. *Exp. Brain Res.* **127,** 162–170.
162. Isaacson, L. G. and Tanaka, D. Jr. (1988) Cholinergic innervation of canine thalamostriatal projection neurons: an ultrastructural study combining choline acetyltransferase immunocytochemistry and WGA-HRP retrograde labeling. *J. Comp. Neurol.* **277,** 529–540.
163. Takakusaki, K., Shiroyama, T., Yamamoto, T., and Kitai S. T. (1996) Cholinergic and noncholinergic tegmental pedunculopontine projection neurons in rats revealed by intracellular labeling. *J. Comp. Neurol.* **371,** 345–361.
164. Matsumoto, N., Minamimoto, T., Graybiel, A. M., and Kimura, M. (2001) Neurons in the thalamic CM-Pf complex supply striatal neurons with information about behaviorally significant sensory events. *J. Neurophysiol.* **85,** 960–976.