

Functional Neuroanatomy of the Basal Ganglia

José L. Lanciego, Natasha Luquin, and José A. Obeso

Department of Neuroscience, Center for Applied Medical Research (CIMA & CIBERNED), University of Navarra Medical College, Pamplona, Spain

Correspondence: jobeso@unav.es



The “basal ganglia” refers to a group of subcortical nuclei responsible primarily for motor control, as well as other roles such as motor learning, executive functions and behaviors, and emotions. Proposed more than two decades ago, the classical basal ganglia model shows how information flows through the basal ganglia back to the cortex through two pathways with opposing effects for the proper execution of movement. Although much of the model has remained, the model has been modified and amplified with the emergence of new data. Furthermore, parallel circuits subserve the other functions of the basal ganglia engaging associative and limbic territories. Disruption of the basal ganglia network forms the basis for several movement disorders. This article provides a comprehensive account of basal ganglia functional anatomy and chemistry and the major pathophysiological changes underlying disorders of movement. We try to answer three key questions related to the basal ganglia, as follows: What are the basal ganglia? What are they made of? How do they work? Some insight on the canonical basal ganglia model is provided, together with a selection of paradoxes and some views over the horizon in the field.

The basal ganglia and related nuclei consist of a variety of subcortical cell groups engaged primarily in motor control, together with a wider variety of roles such as motor learning, executive functions and behavior, and emotions. The term *basal ganglia* in the strictest sense refers to nuclei embedded deep in the brain hemispheres (striatum or caudate-putamen and globus pallidus), whereas *related nuclei* consist of structures located in the diencephalon (subthalamic nucleus), mesencephalon (substantia nigra), and pons (pedunculopontine nucleus). Ideas and concepts regarding the functions of the basal ganglia were strongly influenced by clinical observations during the 20th

century, which showed that lesions of the lenticular nucleus (putamen and globus pallidus) and the subthalamic nucleus (STN) were associated with parkinsonian signs, dystonia, and hemiballismus (Wilson 1925; Purdon-Martin 1927). Thus, the terms *extra-pyramidal system* and *extra-pyramidal syndrome* were frequently used in the past to refer to the pathological basis of movement disorders in an attempt to make a clear distinction from the *pyramidal system* (corticofugal neurons that give rise to corticospinal projections). At present, these terms and distinctions are considered obsolete and misleading and, therefore, will not be used in this article.

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The basal ganglia and related nuclei can be broadly categorized as (1) input nuclei, (2) output nuclei, and (3) intrinsic nuclei. Input nuclei are those structures receiving incoming information from different sources, mainly cortical, thalamic, and nigral in origin. The caudate nucleus (CN), the putamen (Put), and the accumbens nucleus (Acb) are all considered input nuclei. The output nuclei are those structures that send basal ganglia information to the thalamus and consist of the internal segment of the globus pallidus (GPi) and the substantia nigra pars reticulata (SNr). Finally, intrinsic nuclei such as the external segment of the globus pallidus (GPe), the STN and the substantia nigra pars compacta (SNc) are located between the input and output nuclei in the relay of information. Cortical and thalamic efferent information enters the striatum (CN, Put, and Acb) to be processed further within the basal ganglia system. The output nuclei (GPi and SNr) project mainly to the thalamus (ventral nuclei), which, in turn, project back to the cerebral cortex (mainly frontal lobe). The appropriate functioning of the basal ganglia system requires dopamine to be released at the input nuclei. Dopamine dysfunction is associated with several basal ganglia movement disorders such as the parkinsonian syndrome (i.e., Parkinson's disease), dystonia, chorea, and tics. All major basal ganglia components are illustrated in Figure 1.

BASAL GANGLIA NUCLEI

Input Nuclei: The Striatum

The striatum is by far the largest subcortical brain structure in the mammalian brain, with an estimated volume of 10 cm³ in the human brain (Schröder et al. 1975). It is a heterogeneous structure that receives afferents from several cortical and subcortical structures and projects to various basal ganglia nuclei.

Striatal Neurons: Projection Neurons and Interneurons

The striatum contains two different types of neurons: projection neurons and interneurons (90% and 10% of striatal neurons, respectively). Projection or striatofugal neurons are also called medium-sized spiny neurons (MSNs) because these multipolar neurons have small to medium cellular somata (20 μm in diameter), and their dendritic processes are covered by postsynaptic specializations called dendritic spines (Fig. 2). All striatal MSNs are inhibitory neurons that use GABA as the neurotransmitter. Striatofugal MSNs could be divided further, according to their projection targets, into those innervating the GPe nucleus and those projecting to the output nuclei GPi and SNr. Striatal MSNs innervating the GPe nucleus express the dopamine receptor subtype 2 (D₂R), which

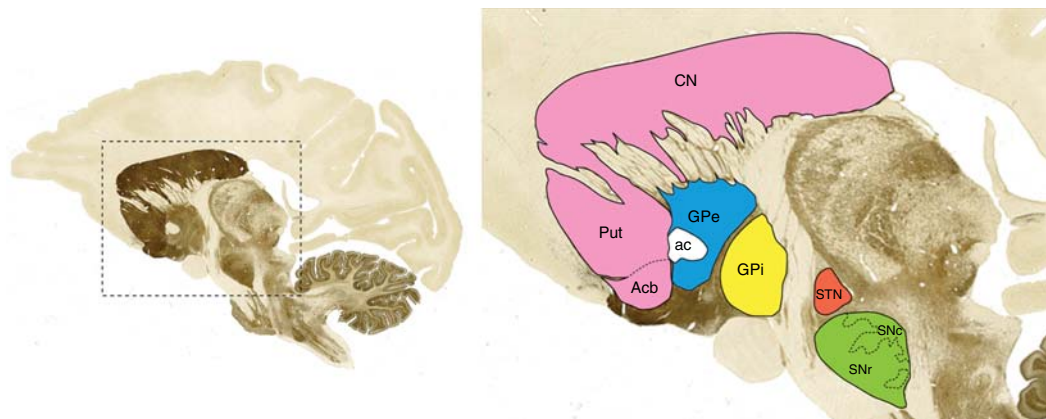


Figure 1. Basal ganglia nuclei. Parasagittal section through the monkey brain (stained with the acetylcholinesterase method) showing the localization and boundaries of all major components of the basal ganglia system.

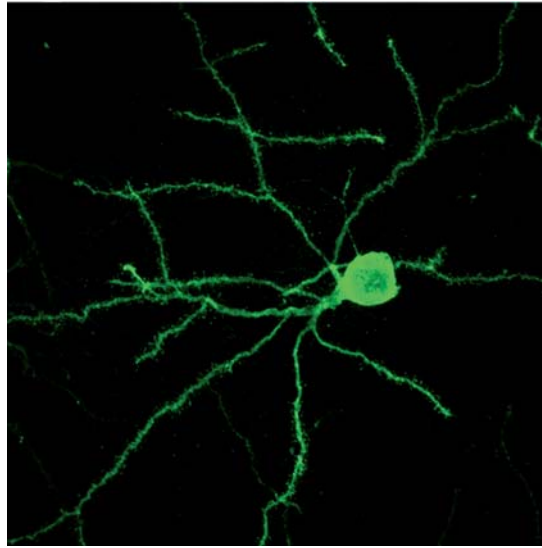


Figure 2. Striatal medium-sized spiny neurons (MSNs). Striatal MSNs are the most abundant neuronal phenotype in the striatum (representing up to 95% of the total number of striatal neurons). These medium-sized neurons (20 μm in diameter) are multipolar stellate cells with radially oriented dendrites. These dendrites are covered by small postsynaptic specializations called dendritic spines. Photomicrograph taken from a striato-nigral-projecting MSN, retrogradely labeled following the delivery of rabies virus into the substantia nigra pars reticulata.

inhibits intracellular adenylyl-cyclase through G-protein signaling, and give rise to the indirect pathway (striato-GPe-STN-GPi/SNr). On the other hand, striatal MSNs projecting directly to GPi and SNr contain dopamine receptor subtype 1 receptors (D_1R), which activate adenylyl-cyclase signaling (D_1 -containing neurons), and give rise to the direct striatopallidal pathway. Furthermore, striatal MSNs projecting through the indirect pathway are known to contain the neuropeptide enkephalin, whereas the neuropeptides substance P and dynorphin are expressed in those MSNs projecting directly to the GPi and SNr.

In addition to these spiny projection neurons, the striatum also contains several different classes of local-circuit neurons (interneurons), all of which show smooth dendrites. Interneurons in the striatum are often classified into four groups depending on their neurochemical profiles and morphological characteristics (for review, see Kawaguchi et al. 1995). The most abundant group of interneurons consists of large

aspiry cholinergic neurons that use acetylcholine as neurotransmitter. Electrophysiologically, these neurons show a rather continuous and constant firing pattern of activity and are therefore also known as tonically active neurons (TANs). Another type of striatal interneuron is GABAergic and also contains the calcium-binding protein parvalbumin. Based on their electrophysiological fingerprint, these neurons are also called fast-spiking interneurons (FSIs). Another group of GABAergic interneurons with a different phenotype is those containing the calcium-binding protein calretinin. In addition to parvalbumin and calretinin, a third type of GABAergic interneuron, known as nitroergic interneuron, uses nitric oxide as the neurotransmitter. Both TAN and FSI interneurons modulate the activity of striatofugal neurons and are, in turn, under dopaminergic control, forming a complex intrastriatal microcircuit, which is discussed below (see section “Classic Basal Ganglia Model”). Calretinin-positive and nitroergic interneurons innervate TAN and FSI interneurons.

Striatal Compartments: Striosomes and Matrix

The striatum appears as a rather homogeneous structure when viewed with cytoarchitectural techniques; however, the use of some specific immunohistochemical markers highlights two subdivisions: striosomes and matrix compartments. The first evidence for these striatal compartments, shown using the histochemical detection of the enzyme acetylcholinesterase (AChE), was published in the late 1970s by Graybiel and Ragsdale (1978). The pattern of AChE staining revealed the presence of several patchy areas showing weak AChE activity (striosomes, sometimes also called patches) immersed within a background of more intense AChE staining (matrix). Moreover, the immunocytochemical detection of the μ opioid receptor revealed an enriched expression of this receptor within the striosomes, together with a weaker expression in the matrix (Perth et al. 1976; Desban et al. 1995). From a neurochemical perspective, striosomes are characterized by strong immunoreactivity against enkephalin,

substance P, GABA, and neurotensin (Graybiel et al. 1981; Gerfen 1984), whereas the matrix compartment is enriched with calcium-binding proteins such as parvalbumin (Prensa et al. 1999) and calbindin (Fig. 3) (Gerfen et al. 1985).

In terms of striatal afferent and efferent systems, striosomes and the matrix could be viewed as isolated compartments. Although striatal MSNs show profuse arborization throughout the striatum (Fig. 2), their dendritic domains and local axon collaterals remain restricted within the striatal compartment in which they are located. In other words, dendrites from MSNs located in a striosomal compartment never enter the matrix, and the same holds true for matrix MSNs. Such a distinct compartmental segregation of MSNs was first reported by Penny et al. (1988) and Kawaguchi et al. (1989) and more recently confirmed by Fujiyama et al. (2011). Furthermore, matrix MSNs innervate the GPe, GPi, and SNr, whereas MSNs located in striosomes preferentially project to the SNC, also giving rise to axon collaterals targeting the GPe, GPi, and SNr (Gerfen

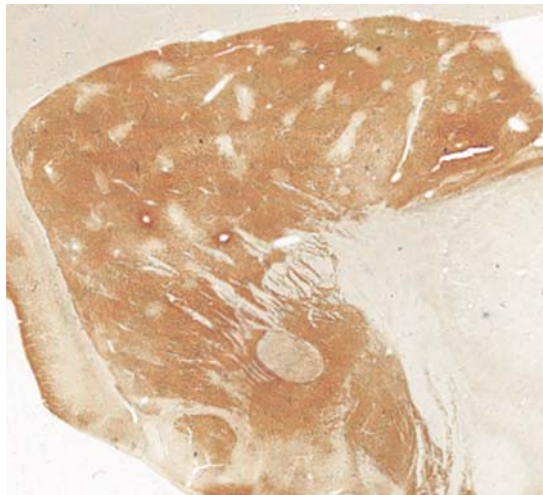


Figure 3. Striatal compartments. Although the striatum appears as a rather homogeneous structure, several histochemical and immunohistochemical stains evidence the presence of two compartments named striosomes and matrix. The photomicrograph is taken from a parasagittal section through the primate striatum. The immunohistochemical detection of the calcium-binding protein calbindin reveals the presence of a number of patchy areas with weak calbindin stain (striosomes) immersed within a background showing higher calbindin stain (matrix).



1984; Bolam et al. 1988; Kawaguchi et al. 1989; Giménez-Amaya and Graybiel 1990; Fujiyama et al. 2011).

Striatal glutamatergic afferents originating from the cerebral cortex, thalamus, and amygdala, as well as dopaminergic afferents arising from SNc are heterogeneously distributed throughout the striosome/matrix compartments. Motor and sensory areas of the cerebral cortex, together with thalamostriatal projections and dopaminergic neurons from the SNc, mainly innervate the matrix compartment, whereas cortical limbic areas, the basolateral amygdala, and ventral parts of the SNc preferentially target striosomes (Graybiel 1984, 1990; Donoghue and Herkenham 1986; Ragsdale and Graybiel 1988; Gerfen 1992; Sadikot et al. 1992a,b; Kincaid and Wilson 1996). At present, an accurate explanation of the functional correlate underlying this striosome/matrix compartmental organization is still lacking.

Striatal Afferents: Cortex, Thalamus, Substantia Nigra, and Raphe

The entire cerebral cortex projects to the striatum. Both ipsilateral and contralateral cortices send glutamatergic projections that make asymmetric synaptic contacts mainly with dendritic spines of striatal MSNs. In addition to cortical limbic areas innervating the striosomal compartment (Gerfen 1984; Donoghue and Herkenham 1986), the bulk of corticostriatal projections spread through the matrix compartment, and these projections are topographically organized (Selemon and Goldman-Rakic 1985). Pyramidal neurons located in cortical layers III and Va innervate the matrix, whereas cortical input from prefrontal cortices originating from pyramidal neurons in deeper layer V reaches the striosomal compartment. Up to two different types of layer V pyramidal neurons innervating the striatum have been described: the so-called pyramidal tract neurons (PT-type), which consist of striatal collaterals that project through the cortico-pyramidal tract, and the intratelencephalic neurons (IT-type). PT-type neurons provide ipsilateral input to the striatum, whereas IT-type neurons innervate the striatum bilaterally

(Reiner et al. 2003; for review, see Reiner et al. 2010). Furthermore, IT-type neurons mainly innervate striatal MSNs giving rise to the direct pathway, whereas PT-type neurons mainly contact striatal MSNs in the indirect circuit (Lei et al. 2004). More recently, such a selective pattern of striatal innervation from IT-type neurons has been challenged by Baillon et al. (2008), who show that IT-type neurons equally excite striatonigral and striatopallidal neurons (direct and indirect pathway neurons in rodents). However, this is not completely inconsistent with preferential IT-type input to MSNs of the direct pathway and PT-type innervation of striato-GPe neurons (Lei et al. 2004).

In addition to the corticostriatal system, thalamostriatal projections are a major source of glutamatergic afferents reaching the striatum. Initial descriptions of the thalamostriatal system were made by Vogt and Vogt (1941) as well as by Powell and Cowan (1956) in the mid-20th century. Although this pathway has been properly characterized anatomically, very little is known regarding the role it plays in basal ganglia function and dysfunction. Until recently, the thalamostriatal pathway had been largely neglected in most modern models summarizing basal ganglia circuits. Virtually all types of striatal neurons are contacted by thalamostriatal afferents, which include projection neurons (Dubé et al. 1988; Sidibé and Smith 1999; Gonzalo et al. 2002; Bacci et al. 2004; Lanciego et al. 2004; Smith et al. 2004; Castle et al. 2005) and striatal interneurons (Meredith and Wouterlood 1990; Lapper and Bolam 1992; Lapper et al. 1992; Bennet and Bolam 1993; Rudkin and Sadikot 1999; Sidibé and Smith 1999; Thomas et al. 2000). It has been generally considered that thalamostriatal axons preferentially contact the dendritic shafts of striatal MSNs (Sadikot et al. 1990; Smith and Bolam 1990; Sidibé and Smith 1996; Smith et al. 2004), whereas corticostriatal afferents mainly synapse with dendritic spines. This distinct segregation of postsynaptic structures has been challenged by recent studies showing that thalamostriatal afferents originating from the centromedian-parafascicular (CM-Pf) thalamic complex only target dendritic



shafts, whereas thalamic inputs arising from nuclei other than the CM-Pf complex contact dendritic spines (Raju et al. 2006). Furthermore, although the midline and intralaminar thalamic nuclei are often considered the main source of the thalamostriatal system (Berendse and Groenewegen 1990; Groenewegen and Berendse 1994), it is worth noting that the ventral thalamic motor nuclei also contribute to thalamostriatal projections (McFarland and Haber 2001).

The corticostriatal and thalamostriatal projections can be differentiated based on the type of vesicular glutamate transporter expressed. The vesicular glutamate transporter isoform 1 (vGlut1) has been commonly used as a marker for corticostriatal projections, whereas the vesicular glutamate transporter isoform 2 (vGlut2) typically characterizes thalamostriatal terminals (Kaneko et al. 2002; Fujiyama et al. 2004, 2006; Raju and Smith 2005; Raju et al. 2006). Despite this apparent segregation of glutamate transporters, vGlut1 transcripts have been found in ventral relay and associative thalamic nuclei (Barroso-Chinea et al. 2007), which contribute substantially to the thalamostriatal system (Beckstead 1984a,b; Smith and Parent 1986; Berendse and Groenewegen 1990; Erro et al. 2001, 2002; McFarland and Haber 2001; Van der Werf et al. 2002). In this regard, recent data from our group have shown coexpression of vGlut1 and vGlut2 transcripts within single thalamostriatal-projection neurons located in thalamic territories other than the midline and intralaminar nuclei (Barroso-Chinea et al. 2008).

In summary, the thalamostriatal system is currently viewed as a dual system, consisting of a projection originating from midline and intralaminar thalamic nuclei (vGlut2-positive projections), together with another projection that arises from ventral and associative relay nuclei that uses both isoforms of the vesicular glutamate transporter.

The nigrostriatal system originates from the SNc (A9 group from Dahlström and Fuxe 1964) and provides the major source of dopaminergic innervation reaching the striatum. The retrorubral field (A8) and the ventral tegmental area (A10) also participate in the mesostriatal and

mesolimbic dopaminergic projections. At least two different territories have been described within the SNc: dorsal and ventral tiers. Dopaminergic neurons in the ventral tier are organized in columns, enter the SNr, and give rise to a topographically organized nigrostriatal projection (Lynd-Balta and Haber 1994a,b; Haber et al. 2000). Dopaminergic terminals densely innervate the striatal matrix compartment, whereas striosomes display different densities of nigrostriatal innervation (Prensa and Parent 2001). Nigrostriatal axons synapse with both types of striatal MSNs. It has been generally accepted that dopaminergic input exerts a facilitatory effect on D₁R-containing MSNs (direct pathway neurons) and an inhibitory effect on D₂R-containing MSNs (indirect pathway neurons). Such a dichotomous effect on striatal projection neuron activity represents one of the foundations of the basal ganglia model, as explained below; however, it should not be taken for granted in physiological terms. An important morphological feature of the nigrostriatal projection is the very large number of axonal arborizations it expresses. In the rat, one dopaminergic axon is estimated to innervate some 75,000 MSNs, and one MSN is under the influence of 95–194 dopaminergic neurons on average (Matsuda et al. 2009). These figures are thought to be much higher in the primate, where one dopaminergic neuron may make up to 1 million synaptic contacts onto striatal neurons. This huge profusion of dopaminergic connectivity implies a wide modulatory effect of dopamine by the nigrostriatal projection.

Finally, other sources of glutamatergic inputs to the striatum arise from the amygdaloid complex reaching striosomes (Ragsdale and Graybiel 1988) and serotonergic projections originating from the raphe nuclei, with a preponderant role for the dorsal raphe nuclei. The presence of serotonergic projections has long been characterized (Andén et al. 1966; Bobillier et al. 1976; Szabo 1980), and its functional correlate remains unknown. More recently, this projection has gained increasing attention because serotonergic axons have been suggested to underlie graft-induced dyskinesias and by extension levodopa-induced dyskinesias (López

et al. 2001, López-Real et al. 2003; Carta et al. 2007, 2008a,b, 2010).

Striatal Efferents: Striatum-GPe and Striatum-GPi/SNr

Two main routes for striatofugal projections have been properly characterized: D₂R-expressing striatal MSNs innervating the GPe and D₁R-expressing striatal MSNs projecting downstream to the GPi and SNr. It has been formerly considered that striatal fibers reaching GPe and GPi were, in fact, collaterals of striatonigral projections (Fox and Rafols 1975), although the current view of the striatofugal system describes three different types of striatofugal MSNs, innervating the GPe, GPi, or SNr (Beckstead and Cruz 1986). However, it is well known that efferent striatal neurons interact with different target structures through axon collaterals (for review, see Parent et al. 2000), and, indeed, modern dual retrograde tract-tracing studies have shown that a substantial proportion of striatonigral-projecting MSNs send collaterals to GPe (Castle et al. 2005). Although much anatomical, neurochemical, and electrophysiological evidence has supported the complementary distribution of D₁R and D₂R within different types of striatofugal neurons (Beckstead et al. 1988; Gerfen et al. 1990; for review, see Bertrán-González et al. 2010), such a sharp degree of D₁R/D₂R complementary expression still remains controversial. In this regard, two fundamental questions remain unanswered: whether the segregation of striatofugal MSNs is matched by the differential expression of dopamine receptors and whether the two populations of striatofugal MSNs are fully segregated from each other. The recent implementation of BAC-transgenic mice has shown that only a small number of striatal efferent neurons (<6% in the dorsolateral striatum) coexpress D₁R and D₂R (Bertrán-González et al. 2008). These newly available data challenge earlier indications that roughly half of striatal MSNs coexpress both dopamine receptors (for review, see Bertrán-González et al. 2010). When considering anatomical data gathered from juxtacellular tract-tracing studies and single axon reconstruction, approximately half of striatal

MSNs innervating the GPi and SNr also send axon collaterals to the GPe, whereas most striatal MSNs were found to innervate GPe directly (Kawaguchi et al. 1990; Parent et al. 2000; Wu et al. 2000). It is also worth noting that these types of anatomical data have their own limitations, including a limited number of axons being reconstructed and the lack of information on the relative importance of each axon collateral when compared with the main axonal terminal field.

Output Nuclei: Globus Pallidus, Internal Segment, and Substantia Nigra Pars Reticulata

The GPi, also known as the medial division of the globus pallidus, and the SNr are often grouped together as basal ganglia output nuclei because they share a number of cyto- and chemoarchitectural characteristics and to some extent similar types of afferent and efferent systems. Both nuclei consist of inhibitory GABAergic neurons with a high rate of discharge that fire tonically to inhibit their targets. In comparison with the striatum, the GPi shows a smaller cellular density. This feature, together with the presence of a large number of myelinated striatofugal fibers crossing the GPi nucleus, provides the GPi with a paler appearance when compared with the striatum.

As discussed above, the GPi and SNr receive two different types of inputs. D₁R-containing striatal MSNs that give rise to the direct pathway are a major source of inhibition to the GPi and SNr. The STN provides an excitatory glutamatergic projection to the GPi and SNr, part of the indirect pathway. The subthalamopallidal and subthalamonigral projections are highly collateralized (simultaneously reaching GPi and SNr neurons) and can be easily characterized immunohistochemically using antibodies against vGlut2. Both types of afferent systems (GABAergic and glutamatergic) converge onto basal ganglia output neurons, which, in turn, innervate thalamic targets and brainstem (i.e., superior colliculus, PPN). Thalamic-recipient areas of basal ganglia output neurons differ slightly when considering pallidothalamic versus nigrothalamic projections, differences that paved the way for introducing an accurate parcellation of

the ventral thalamic nuclei based on hodological criteria (Ilinsky and Kultas-Ilinsky 1987; Percheron et al. 1996). In this respect, pallidothalamic projections innervate the densicellular and parvicellular territories of the ventral anterior motor thalamus (VAdc and VApC, respectively), whereas nigrothalamic projections mainly target the magnocellular division of the ventral anterior motor thalamus (VAmc). Moreover, thalamic intralaminar nuclei (mainly the CM-Pf complex) are also known to be innervated by basal ganglia output. There are two routes by which pallidothalamic projections can gain access to their respective thalamic targets: (1) projections that arise from neurons located in lateral GPi territories form the ansa lenticularis that course around the internal capsule finally entering the so-called field H of Forel (also known as the prerubral field); and (2) axons from more medially located GPi neurons that course through the internal capsule to form the lenticular fasciculus (Forel's field H2) located between the STN and the zona incerta. The lenticular fasciculus merges with the ansa lenticularis at the level of field H of Forel to enter the thalamic fasciculus (H1 of Forel), the latter finally reaching ventral and intralaminar thalamic nuclei.

INTRINSIC NUCLEI

Globus Pallidus, External Segment

The GPe (also known as the lateral division of the globus pallidus) is part of the pallidal complex together with GPi and the ventral pallidum. The GPe is surrounded laterally by the putamen, from which it is separated by the lateral medullary lamina. The boundary between the GPe and GPi is made of another thin layer of myelinated fibers named the medial medullary lamina. The GPe shares with the GPi several cyto- and chemoarchitectural features, because both nuclei are made of sparsely distributed GABAergic neurons with large somas. All GPi and GPe neurons are also characterized by an enriched expression of the calcium-binding protein parvalbumin.

Two principal afferent systems innervate GPe neurons. The GPe receives a GABAergic

projection from D₂R-containing striatal MSNs, an inhibitory projection that represents the first synaptic relay station of the indirect pathway as is discussed below. Moreover, striatal projections innervating GPe neurons also show an enriched expression of adenosine type 2A receptors (A_{2A}-Rs), and thus antibodies against A_{2A}-Rs have been used to define the boundaries of the GPe nucleus accurately (Rosin et al. 1988; Bogenpohl et al. 2012). GPe neurons are also reciprocally connected with STN neurons from which they receive strong glutamatergic excitatory projections (vGlut2-positive). The existence of such a close interrelationship between the GPe and STN has provided the foundation for no longer considering the GPe as simply a relay station between the striatum and the STN (Shink et al. 1996; Joel and Weiner 1997; Nambu 2004). Furthermore, it has long been known that both segments of the globus pallidus (GPe and GPi) are also reciprocally interconnected. Finally, another minor source of glutamatergic afferents is represented by inputs received from the caudal intralaminar nuclei (Kincaid et al. 1991; Marini et al. 1999; Yashukawa et al. 2004).

Subthalamic Nucleus

Extensive research has been performed in the last few decades focused on the subthalamic nucleus of Luys. This small subcortical nucleus, with densely packed neurons, is located immediately ventral to the zona incerta and rostral to the substantia nigra. It has become very relevant and well known over the last decade because it is the best surgical target for electrode placement during deep brain stimulation (STN-DBS). The canonical basal ganglia model (Albin et al. 1989; DeLong 1990) provided an oversimplified view of afferent and efferent STN connectivity. This simplistic view, which only considered GABAergic input from the GPe and STN efferents targeting basal ganglia output nuclei, has been superseded by much experimental evidence that emerged shortly after the model was first introduced (see section, "Pathophysiology: A Summary," below). Besides the classical GABAergic projection from GPe neurons (second relay station of the indirect pathway), the STN



also receives glutamatergic projections from the cerebral cortex (known as the hyperdirect pathway) (see Nambu et al. 2002; Nambu 2004, 2005) and the ipsilateral thalamic caudal intralaminar nuclei (Sugimoto and Hattori 1983; Sugimoto et al. 1983; Royce and Mourey 1985; Sadikot et al. 1992a,b; Sidibé and Smith 1996; Marini et al. 1999; Gonzalo et al. 2002; Lanciego et al. 2004, 2009; Castle et al. 2005), as well as a minor projection from the contralateral caudal intralaminar nuclei (Gerfen et al. 1982; Castle et al. 2005). Finally, it is also worth noting that the STN also receives a sparse dopaminergic projection from the SNc, as a part of the so-called nigro-extrastriatal projection system (for review, see Rommelfanger and Wichmann 2010).

The cerebral cortex sends direct projections to the STN, which, in turn, innervates the output nuclei, thus providing a way for motor-related cortical areas to access the output nuclei directly, bypassing the input nuclei. This pathway is characterized by shorter conduction times than those funneled through direct and indirect basal ganglia pathways and therefore exerts powerful excitation onto basal ganglia output. Furthermore, cortical inputs arising from the primary motor cortex, the supplementary motor area, premotor cortices, frontal eye field area, and supplementary eye field area are conveyed through the cortico-subthalamic hyperdirect pathway, somatotopically organized at the level of the STN (Nambu et al. 1996, 2002). The direct projection arising from the caudal intralaminar nuclei is another important source of glutamatergic activation, described in rodents, cats, and primates (Sugimoto and Hattori 1983; Sugimoto et al. 1983; Royce and Mourey 1985; Sadikot et al. 1992; Sidibé and Smith 1996; Marini et al. 1999; Gonzalo et al. 2002; Lanciego et al. 2004, 2009; Castle et al. 2005). Thalamo-subthalamic projections are topographically organized (Sadikot et al. 1992; Lanciego et al. 2004), reaching STN efferent neurons innervating the GPe and SNr/GPi (Castle et al. 2005). Furthermore, thalamo-subthalamic projections are bilateral, albeit with an ipsilateral predominance (Castle et al. 2005). Indeed, opposite changes in STN activity have been found following drug-induced stimula-

tion or inhibition of the caudal intralaminar nuclei (Mouroux et al. 1995).

The bulk of STN efferent projections are directed toward the basal ganglia nuclei, a projection typically characterized by highly branched neuronal processes. It has been postulated that most STN efferent neurons send axons that simultaneously innervate the GPi, GPe, and SNr (Van der Kooy and Hattori 1980; Kita et al. 1983; Kita and Kitai 1987; Plenz and Kitai 1999; Castle et al. 2005). The pattern of axonal collateralization has served to identify up to five distinct types of STN efferent neurons (Parent et al. 2000; Sato et al. 2000). In addition to STN projections to the GPi, GPe, and SNr, efferent STN neurons also innervate thalamic targets: those projecting ipsilaterally to ventral thalamic motor nuclei (Nauta and Cole 1978; Rico et al. 2010) and a smaller contralateral projection linking the STN with the parafascicular nucleus (Gerfen et al. 1982; Castle et al. 2005). Furthermore, dual retrograde tract-tracing studies have shown that subthalamic projections reaching the GPi and ventral thalamic nuclei largely arise from different subpopulations of STN neurons (Rico et al. 2010).

Substantia Nigra Pars Compacta

Deep in the ventral midbrain, several groups of tyrosine-positive neurons supplying the basal ganglia nuclei with dopamine can be found. According to Dahlström and Fuxe (1964), these dopaminergic neurons could be classified in up to three main groups: A10 neurons (ventral tegmental area), A9 neurons (SNc), and A8 neurons (retrosubthalamic field). Neurons from the A10 field mainly innervate the accumbens nucleus as well as several limbic-related areas, whereas the nigrostriatal projection mainly arises from the A9 and A8 dopaminergic groups. In the past few years, efforts were made to subdivide the SNc into several clusters or cell groups. Because this issue is beyond the scope of this article, this will not be addressed here. However, more information can be found elsewhere (González-Hernández and Rodríguez 2000; Fu et al. 2012). In humans, dopaminergic neurons located in the SNc contain the dopamine precursor

neuromelanin, a pigment that produces the black color inherent to SNc territories as seen in freshly extracted brains in human necropsies. Interestingly, this black pigment of the SNc is still maintained in human albinism, because the gene coding cutaneous melanin is different from the one coding neuromelanin. Dopaminergic neurons in the SNc degenerate progressively in Parkinson's disease (PD), leading to severe dopamine deficiency and the appearance of the cardinal features of the disease. Neurons still alive often display intracellular aggregates of misfolded proteins, from which α -synuclein is the most prominent, giving rise to circular shape aggregates known as Lewy bodies (Fig. 4), which represent the histopathological hallmark of PD.

FUNCTIONAL ORGANIZATION OF THE BASAL GANGLIA: THE CANONICAL MODEL

Classic Basal Ganglia Model

The functional organization of the basal ganglia formulated in the 1980s was based on the concept that neuronal signals from the cortex flow to the striatum, through the GPi and SNr, and project back to the cortex via the thalamus, forming parallel cortico–basal ganglia–thalamo–cortical loops. Although the model was primarily formulated to understand the patho-

physiology of movement, the existence of parallel circuits subserving oculo-motor control, executive functions, and emotions was also recognized.

The basis of the model resides in the striatopallidal connections via the direct and the indirect projections (Fig. 5), which have an opposite functional effect on basal ganglia output (Albin et al 1989; DeLong 1990). Activation of GABAergic MSNs that give rise to the direct pathway inhibits GPi/SNr tonic activity, inducing a pause of neuronal firing. At the same time, activation of MSNs of the indirect pathway first inhibits GPe neurons, followed by disinhibition of the STN, which then excites GPi/SNr neurons. Because pauses of neuronal firing in the basal ganglia output are associated with the occurrence of an action (e.g., an eye movement saccade), and discharges are associated with stopping or halting movement, the direct and indirect pathways are viewed as opposite functional projection systems that facilitate and inhibit movements and behaviors, respectively. As previously mentioned, the nigrostriatal projection exerts a differential effect on D_1R/D_2R MSNs, facilitating and inhibiting the direct and indirect circuits, respectively (Gerfen et al. 1990). Accordingly, dopaminergic depletion reduces the facilitation of MSNs in the direct pathway and increases the activation of indirect circuit neurons, which leads to increased

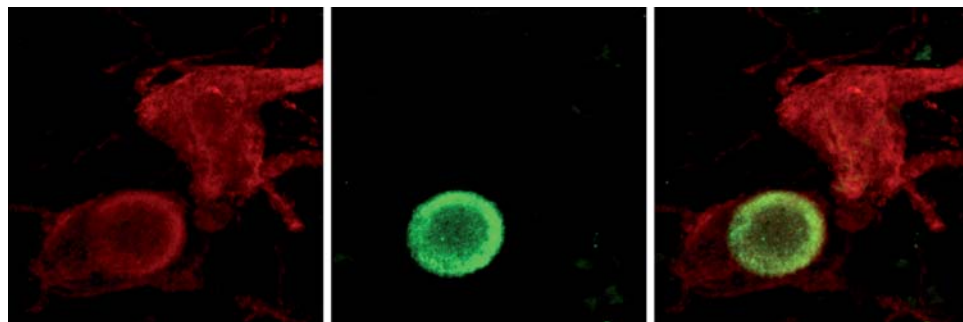


Figure 4. Lewy bodies in dopaminergic neurons from the substantia nigra pars compacta. In humans suffering from Parkinson's disease, dopaminergic neurons accumulate intracytoplasmic aggregates of misfolded α -synuclein. These aggregates often adopt a circular shape and form the so-called Lewy bodies, which represent the pathological hallmark of this disease. Dual immunofluorescent detection of tyrosine hydroxylase (red channel) and α -synuclein (green channel), identifying two dopaminergic neurons from a PD patient, one of them showing a typical intracytoplasmic Lewy body.

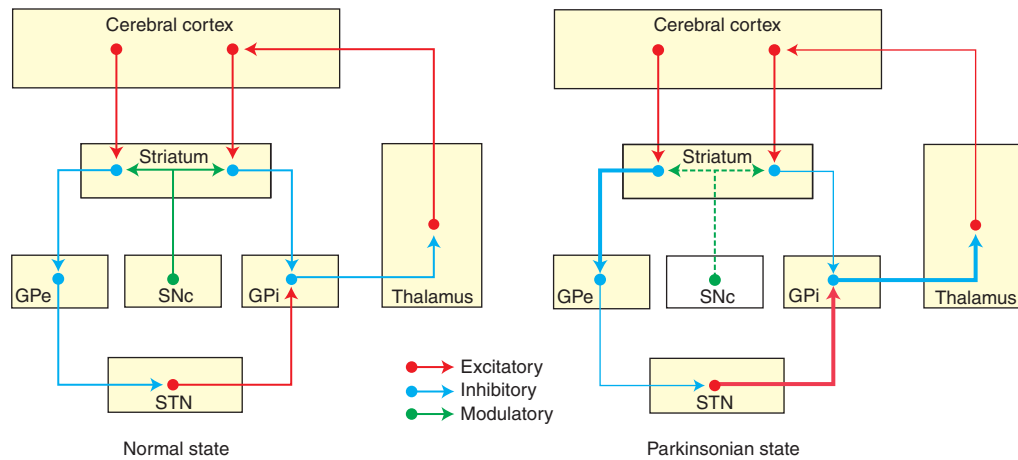


Figure 5. Schematic summary of the original basal ganglia model. The motor circuit is composed of a cortico-striatal (putaminal) projection, two major striatofugal projection systems giving rise to the direct and indirect pathways, and the efferent pallido–thalamo–cortical projections to close the motor loop. The thickness of arrows represents the functional state of a given circuit. Thicker arrows illustrate hyperactive pathways, whereas thinner arrows represent hypoactive circuits.

activity of the STN, which, in turn, overactivates inhibitory output neurons in the GPi/SNr, such that the reduction of GABAergic inhibition of direct MSNs combined with an increased glutamatergic driving force from the disinhibited STN increases activity in the GPi/SNr. This effectively reduces the likelihood of phasic inhibitory activity in these output neurons, thus impeding movement initiation and execution. Seminal studies in the monkey by Crossman (1987) led to a similar understanding of the dyskinetic state (i.e., hemichorea-ballism and levodopa-induced dyskinesias), essentially considered to result from decreased GPi output and, therefore, functionally opposed to the parkinsonian state (Obeso et al. 2000, 2008).

This dual concept of the classic basal ganglia model gained considerable support from many different experimental and clinical sources. Over the years, quite a few difficulties were encountered in trying to fit together new findings with the classical model, creating paradoxes that have been hotly discussed. Among these, the two best recognized and puzzling paradoxes are the following: (1) Lesion of the basal ganglia output should provoke a marked reduction in inhibition of the thalamocortical projection

and therefore facilitate or disinhibit movements. However, in monkeys and patients, pallidotomy does not induce involuntary movements, but on the contrary, it abolishes dyskinesias (Carpenter et al. 1950; Lozano et al. 1995). (2) Lesion of the STN, GPi, or motor thalamus singly or in combination does not deteriorate motor function (Marsden and Obeso 1994), but it is actually associated with marked improvement in PD patients (Obeso et al. 2009).

Nevertheless, the model served to stimulate considerable advances in the understanding of basal ganglia organization and, importantly, paved the way for the resurgence of functional neurosurgery for Parkinson's disease (see below). Interestingly, two recent studies in the rat using optogenetics have provided strong support for the classical model. Kravitz et al. (2010) showed that selective stimulation of MSNs expressing D_2R (indirect circuit) provoked movement arrest, whereas activation of MSNs expressing D_1R led to movement activation. This essentially confirmed the notion that the indirect and direct circuits are in functional equilibrium, inhibiting and facilitating movement, respectively. Bateup et al. (2010) found that the loss of DARPP-32 in the "direct"

striatonigral projection abolished levodopa-induced dyskinesias, whereas in striatopallidal neurons produced a robust increase in locomotor activity and reduced cataleptic response to haloperidol. These two elegant studies selectively activating or inhibiting the direct and indirect striatopallidal circuits corroborated the functional balance of both projection systems.

Current Concepts

The original functional organization of the basal ganglia was conceived as a loop, in which cortical afferent activity is dispatched to and modulated by the basal ganglia, which subsequently sends back a signal to the cortex to facilitate (or inhibit) motor activity. Accordingly, the basal ganglia were featured as a “go through” station within the motor loop. Current thinking has modified this functional model on several fronts and in fundamental aspects. It is now known that the basal ganglia has several loops, where cortical and subcortical projections interact with internal reentry loops (Fig. 6) forming a complex network, ideally designed for se-

lecting and inhibiting simultaneously occurring events and signals.

Functional Subdivisions: Basal Ganglia Domains

The basal ganglia are functionally subdivided into motor, associative, and limbic/emotional domains based on their relationship with relevant cortical projection areas and the engagement of these regions. Thus, in addition to the well-known role of the basal ganglia in motor control, there is now a better appreciation for other functions such as attention and time estimation, implicit learning and habit formation, and reward-related behavior and emotions, all of which are associated with the activation of cortical loops that connect with the CN, the anterior putamen, or the ventral putamen (Hikosaka et al. 2002; Buhusi and Meck 2005; Yin and Knowlton 2006). Important evidence for this concept has arisen from studies in non-human and human primates.

In monkeys, bicuculline injections in the motor putamen elicited focal, brief muscle jerks

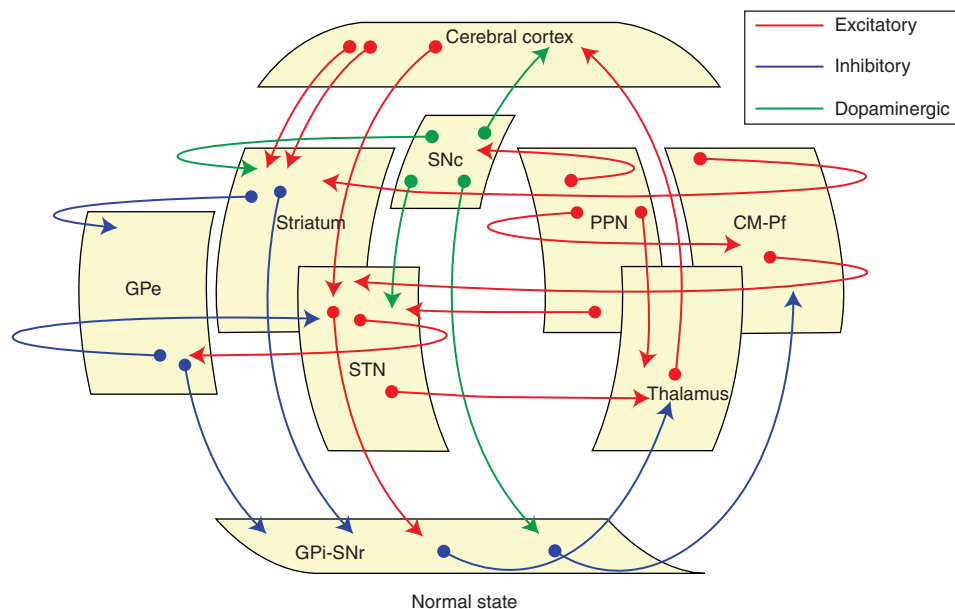


Figure 6. Basal ganglia circuits. Cartoon showing the main circuits linking the basal ganglia nuclei. Besides traditional cortico-basal ganglia-thalamocortical circuits, several transverse loops have been described in the last few years, most of them with a putative modulatory role.

(tic-like) that were accompanied by increased neuronal activity in the GPe, marked reduction in the GPi, and increased firing in the primary motor cortex (M1) time-locked to the jerks (McCairn et al. 2009). This is a firm indication that movement release is punctually associated with a reduction of GPi output activity. Moreover, focal bicuculline injections, to block specific subregions of the striatum, GPe, and STN produced dyskinesias, stereotopies, and hyperactivity among other behavioral abnormalities when injected into the postero-lateral (motor) segment, associative and limbic regions (François et al. 2004; Karachi et al. 2009). Injections in the ventral striatum also elicited sexual behaviors (erection and ejaculation) and vomiting (Worbe et al. 2009).

Human activation studies using functional magnetic resonance imaging (fMRI) and positron emission tomography (15-0 H₂O-PET) showed topographical segregation according to the requested task and underlying functions. Thus, activation in the posterior (i.e., sensorimotor) putamen was consistently encountered for movements and presented a somatotopical organization, with the leg lying dorsal, face ventral, and arm in between, as expected (Lehéricy et al. 2005). Preparatory activation as well as finger movement sequencing was located more rostrally in the anterior putamen, whereas activation of the associative territory was observed during tasks such as motor internal representation selection and planning of sequential actions (Monchi et al. 2006), whereas tasks evoking emotional responses typically activate the region of the ventral striatum, where the accumbens nucleus is recognized.

Functional Anatomy

Corticostriatal Connections. GABAergic MSNs receive profuse glutamatergic inputs from most cortical regions and the thalamus, which predominantly form asymmetric contacts with the heads of dendritic spines. Input to MSNs also comes from dopaminergic, cholinergic, and GABAergic neurons, which tend to form symmetric synaptic contacts. In the rat, approximately 5000 glutamatergic afferents

project to each striatal MSN, and 100 MSNs project onto each pallidal neuron. This arrangement is probably the anatomical basis for fundamental striatal function, that is, selection and filtering of incoming/outgoing signals. The capacity of the striatum to filter massive incoming signals is facilitated by several mechanisms, among which the nigrostriatal dopaminergic projection plays a paramount role. Thus, dopamine exerts a dual effect on MSNs (Onn et al. 2000), inhibiting striatal D₂R-containing neurons and exciting striatal neurons that express D₁Rs through L-type calcium channels. Activation of selected nigrostriatal projections leads to dopamine elevation in innervated striatal regions in parallel with a marked dopamine reduction in adjacent zones. This is supported by experimental evidence indicating that dopamine enhances synchronous corticostriatal afferent volleys while simultaneously inhibiting other inputs (Bamford et al. 2004). The creation of a gradient or salient pattern of activity is thought to govern dopaminergic signaling, probably underlying the responses to reward (and addiction), habit formation, and motor learning. Another important component of striatal internal functioning is provided by striatal cholinergic TANs and GABAergic FISs interneurons. Phasic release of dopamine induces firing pauses in TANs that facilitate corticostriatal transmission (Bonsi et al. 2011). GABAergic interneurons, which are also modulated by dopamine, along with axon collaterals from MSNs, mediate a powerful intrastriatal inhibition (Tepper et al. 2004). Together, interneurons modulate striatal excitability providing a mechanism to facilitate a given pool of MSNs excited from the cortex, while competing stimuli are canceled.

Corticosubthalamic Connections. The STN is subdivided into a motor, associative, and limbic region. The dorsolateral STN corresponds with the motor region. STN neurons in the healthy monkey fire at 20–30 Hz and provide tonic excitatory input to both segments of the globus pallidus. Lesion or blockade of the STN is associated with a significant reduction in the mean firing rate of pallidal neurons.

Initial studies recording STN activity in awake monkeys performing a task indicated that neuronal firing occurred after or coinciding with movement initiation (DeLong et al. 1985). This suggested that the STN was not involved with signals associated with movement onset, in keeping with the prevailing idea that the STN was mainly related to movement inhibition. However, recent studies recording single cell activity and local field potentials in patients with Parkinson's disease have shown clear evidence of activation up to 1 sec before initiation of movement (Rodriguez-Oroz et al. 2001; Alegre et al. 2005). Thus, when a voluntary movement is going to be performed, the same cortical volley that arrives to the putamen is dispatched to the STN. Indeed, studies in monkeys have shown that the cortico-STN-GPe/GPi projection is a fast-conducting system, well placed to modulate basal ganglia output (Nambu 2004).

Subcortical Connections. Thalamo-Basal Ganglia Loops and Brainstem Circuits. The role and importance of projections and feedback loops between the basal ganglia and several subcortical regions were not well considered in the initial basal ganglia model, but have been extensively documented in the last decade (McHaffie et al. 2005). Interestingly, it is now acknowledged that re-entrant loops involving the neocortex are neither novel nor the first evolutionary example of closed-loop architecture involving the basal ganglia. Thus, there are phylogenetically older subcortical loops between the basal ganglia and brainstem motor structures, including the superior and inferior colliculi, periaqueductal gray, pedunculopontine nucleus, cuneiform area and parabrachial complex, and various pontine and medullary reticular nuclei. The interested reader may consult recent excellent reviews on this subject (Redgrave et al. 2010, 2011; Smith et al. 2011).

Pathophysiology: A Summary

Movement disorders comprise a variety of motor problems, not all of which are associated with dysfunction of the basal ganglia. Those that have a clearly established pathological basis

and are caused by pathophysiological mechanisms directly involving the basal ganglia are the following: (1) the parkinsonian syndrome composed of rigidity, akinesia/bradykinesia, and resting tremor; (2) dystonia characterized by prolonged muscle spasms and abnormal postures; and (3) chorea-ballism, in which fragments of movements flow irregularly from one body segment to another, to cause a dance-like appearance. When the amplitude of the movement is very large, the term *ballism* is applied. From a practical point of view, levodopa-induced dyskinesias in PD patients, which are by and large choreic in nature, represent the most frequent cause of choreic dyskinesias in the general population.

The Parkinsonian Syndrome

The best known cause and example of the parkinsonian syndrome is Parkinson's disease, which is mainly characterized by poverty of spontaneous movements (hypokinesia) and slowness of voluntary movement (bradykinesia), as well as increased muscle tone (rigidity) and tremor at rest. Dopamine striatal depletion secondary to cell loss in the SNc is the cause of the major clinical features of Parkinson's disease. A large bulk of evidence has been accumulated from both experimental models and patients with Parkinson's disease to show that dopamine depletion shifts the balance of basal ganglia activity toward the indirect circuit, leading to excessive activity of the STN that overstimulates the GPi/SNr. Increased output from the GPi/SNr overinhibits the thalamocortical projection, reducing cortical neuronal activation associated with movement initiation (DeLong 1990; Obeso et al. 2000).

The way in which the basal ganglia modulate and respond to external input is also distorted in the parkinsonian state. The putamen, STN, and GPi show augmented neuronal responses to peripheral stimulation, which impairs physiological selection or filtering of incoming signals discussed above. Overall, the basal ganglia are shifted toward inhibiting cortically aided movements by an increased activation of the STN–GPi network and reduced

excitability in the direct cortico-putaminal-GPi projection (Obeso et al. 2008).

Remarkably, our current understanding of basal ganglia pathophysiology does not provide an adequate explanation for the two other cardinal features of Parkinson's disease, namely, rigidity and tremor. Regarding the latter, studies in PD patients during surgery and in the monkey MPTP model have started to unravel some interesting features (Heimer et al. 2002). Nevertheless, it is fascinating to realize that when nearly reaching 200 years after James Parkinson described the "Shaking Palsy," and therefore, the parkinsonian tremor, its origin remains a mystery.

Pathophysiology of Dyskinesias

Chorea-ballism is the abnormal release of fragments of normal movement. In simple terms, the pathophysiology of dyskinetic movements may be seen as the opposite of parkinsonism. Chorea is mainly caused by drugs, such as levodopa in Parkinson's disease, in neurodegenerative diseases such as Huntington's disease and secondary to systemic conditions like hyperthyroidism or lupus erythematosus.

According to the basal ganglia model, dyskinesias (i.e., chorea or ballism) result from reduced activity in the STN-GPi projection leading to decreased firing in GPi output (Crossman 1987; DeLong 1990). Choreatic or ballistic movements can occur secondary to focal lesion in the basal ganglia, such as the STN. In the 1980s, fundamental work performed in control monkeys showed that local administration of bicuculline to block the striato-GPe projection induced chorea-ballism in the contralateral hemibody. This was associated with increased 2-deoxyglucose uptake in the STN as seen with autoradiography (Mitchell et al. 1989), indicating excessive inhibition from the GPe onto the STN, consequently decreasing glutamatergic excitatory activity directed to the GPi. Neuronal recording of extracellular activity in the GPi of control monkeys with chorea induced by an injection of bicuculline into the GPe showed a reduction in neuronal firing rate and an abnormal pattern of neuronal synchronization (Filion

2000). The initial evidence, therefore, supported a major role for the indirect pathway for the induction of dyskinesias. Subsequently, recording of neuronal activity in the GPe and GPi in MPTP-treated monkeys and PD patients during surgery, although showing levodopa-induced dyskinesias, further showed the increase and reduction of GPe and GPi neuronal activity, respectively, as a basic pathophysiological feature of choreic dyskinesias (Papa et al. 1999). More recently, evidence has accumulated for increased and extra-synaptic shifting of NMDA glutamatergic receptors (Gardoni et al. 2006) and abnormal D₁R receptor activation in the striatum of dyskinetic animals (Berthet et al. 2009), suggesting a paramount role of the direct circuit as a mediator of levodopa-induced dyskinesias (Bateup et al. 2010).

CONCLUSIONS

The basal ganglia network may be viewed as multiple parallel loops and re-entering circuits whereby motor, associative, and limbic territories are engaged mainly in the control of movement, behavior, and emotions. This is likely to be sustained by the same basic architectural and functional organization, differentially applied to (1) selection and facilitation of pre-frontal-striatopallidal activity during the performance and acquisition of new activities and task (goal-directed system); (2) reinforcement learning to create habitual responses automatically performed by the motor circuit (habit system); and (3) stopping an ongoing activity and switching to a new one if necessary, which is mainly mediated by the inferior frontal cortex/STN-cortical circuit. Abnormalities in these domains and functions lead to movement disorders such as parkinsonism and dyskinesias, obsessive compulsive disorders, and alterations of mood (i.e., apathy, euphoria).

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