Basal Ganglia—A Motion Perspective

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ABSTRACT

The basal ganglia represent an ancient part of the nervous system that have remained organized in a similar way over the last 500 million years and are of importance for our ability to determine which actions to choose at any given moment in time. Salient or reward stimuli act via the dopamine system and contribute to motor or procedural learning (reinforcement learning). The input stage of the basal ganglia, the striatum, is shaped by glutamatergic input from the cortex and thalamus and by the dopamine system. All intrinsic neurons of the striatum are GABAergic and inhibitory except for the cholinergic interneurons. Too little dopamine and all vertebrates show symptoms similar to that of a Parkinsonian patient, whereas too much dopamine results in hyperkinesia with involuntary movements. In this article, we discuss the detailed organization of the basal ganglia, with the different cell types, their properties, and contributions to basal ganglia functions. The striatal projection neurons represent 95% of all neurons in the striatum and are subdivided into two types, one that projects directly to the output stage, referred to as the "direct" pathway that promotes action, and the other subtype that targets the output nuclei via intercalated basal ganglia nuclei. This "indirect" pathway has an opposite effect. The striatal projection neurons express a set of ion channels that give them a high threshold for activation, whereas neurons in all other parts of the basal ganglia have a resting discharge that allows for modulation in both an increased and decreased direction. © 2020 American Physiological Society. *Compr Physiol* 10: 1241-1275, 2020.

Didactic Synopsis

Major teaching points

- The basal ganglia are evolutionarily conserved in vertebrate evolution with regard to organization, detailed connectivity, and transmitters.
- The basal ganglia with its input structure, striatum, help determine which action to select at a given moment in time.
- The cortex and thalamus provide glutamatergic input to the striatum. The responsiveness of the striatum is determined by modulatory systems, in particular, the dopamine system.
- The rodent striatum consists of 95% GABAergic striatal projection neurons (SPNs). They are subdivided into those that project directly to the output level (dSPNs), promote action and are excited by dopamine, and those that indirectly, via intrinsic basal ganglia nuclei, affect the output level (iSPNs) and inhibit action. The iSPNs are inhibited by dopamine.
- The output nuclei of the basal ganglia are tonically active at rest and inhibit different midbrain and brainstem centers for the control of eye, locomotor, and other movements, and they also convey information back to the cortex via the thalamus.
- To elicit a saccadic eye movement, for instance, the inhibitory output neurons must be inhibited by dSPNs—thus the basal ganglia promote action through disinhibition.
- The basal ganglia are central for motor (procedural) learning, also called reinforcement learning, dependent on long-term potentiation (LTP) and depression (LTD). In this process, both potentiation and depression of synaptic transmission can take place.
- The dopamine system will be activated when receiving a reward, which can facilitate synaptic plasticity and learning. Dopamine neurons are also activated by salient stimuli, and a burst of dopamine activity often precedes the initiation of a movement.
- Basal ganglia dysfunction severely affects movement, like the dopamine deficiency in Parkinson's disease that leads to hypokinesia, while degeneration of iSPNs can lead to

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involuntary movements and hyperkinesia as in Huntington's disease.

Introduction

The different roles of the cortex, basal ganglia, midbrain, and brainstem in the control of motion

The astounding ability of animals or humans to move in a graceful way is the subject of this article, whether a cheetah, a ballet dancer, or a seagull. The basal ganglia are central to this process. How is this achieved? The midbrain, brainstem, and spinal cord contain innate motor programs that coordinate basic aspects of the movement repertoire of any vertebrate species, such as eye-movements, breathing, locomotion, balance control, swallowing, and mastication. They form together a motor infrastructure (138) from which the forebrain, mainly the cortex and basal ganglia, can select the appropriate motor program at any given point in time (Figure 1). In addition, we have skilled movements, which are formed by learnt motor programs, sometimes referred to as habits when automatized. Movements adapted to a novel situation are called goal-directed movements (286). For all three types of movements, the basal ganglia have a central role. This is evident from the deleterious effects that basal ganglia dysfunction has on movement control, such as the hypokinesia of Parkinson's disease (PD) with difficulty to initiate movements or the hyperkinesia in Huntington's disease with extensive involuntary movements, as well as many other neurological and psychiatric conditions.

The cerebral cortex has a dual function in that it provides a direct input to the different brainstem motor centers in all vertebrates, and at the same time, it constitutes a major input to the basal ganglia. Different parts of the cerebral cortex target different areas of the striatum, the input stage of the basal ganglia, in a distinct topography. The striatum also receives a major input directly from the thalamus.

To deduce the role of the cerebral cortex itself in terms of motor behavior, it has in some experiments been selectively removed, leaving the basal ganglia and hypothalamus intact (35). In a variety of vertebrates, including mammals like rodents and the cat, such decorticated animals can live for

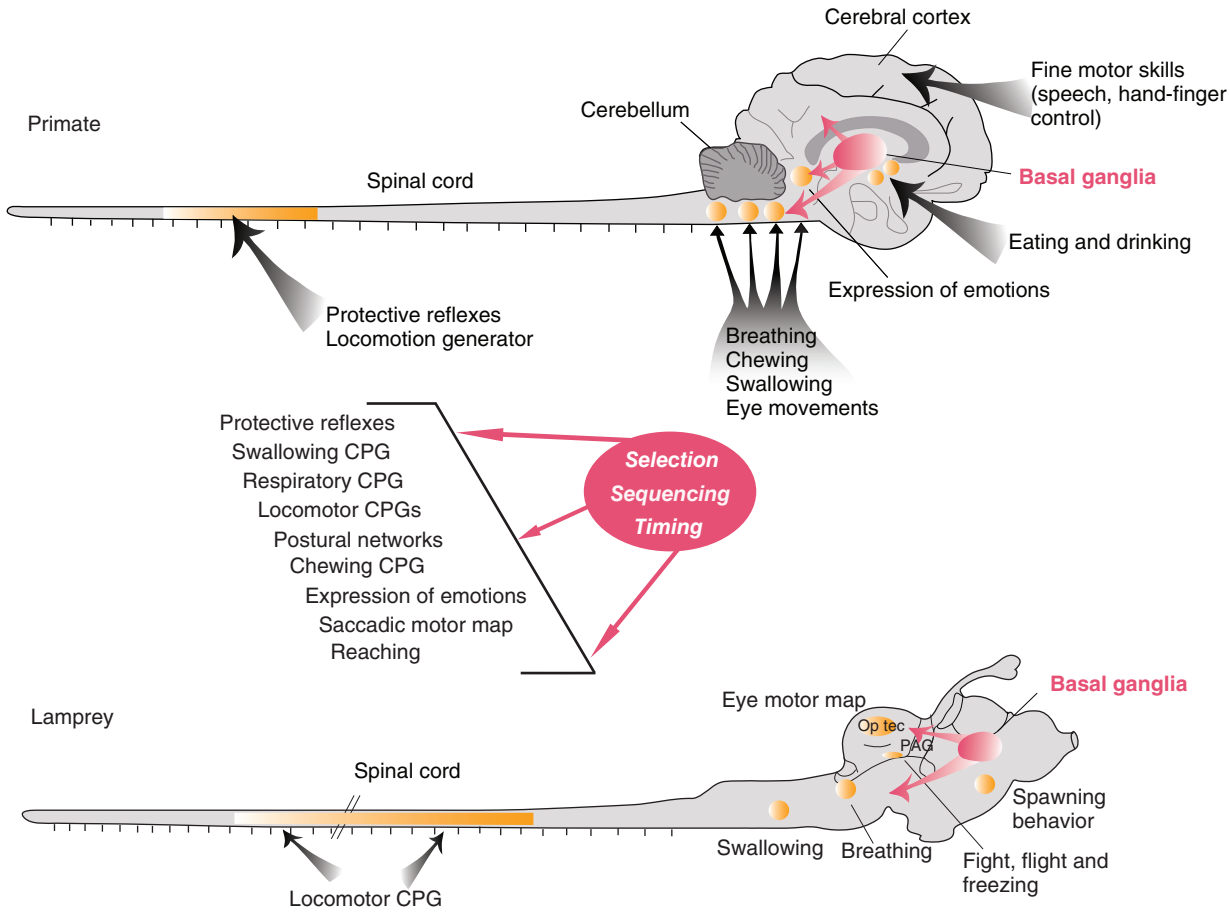


Figure 1 *Common motor infrastructure from lamprey to man*. Throughout the vertebrates, several basic motor behaviors are controlled by neuronal networks (CPGs) located in the brainstem and spinal cord. The basal ganglia play a crucial role in the selection of motor behaviors and are similarly organized in lamprey and primate. In primates, the addition of a well-developed cerebral cortex provides a locus for networks controlling fine motor skills.

years in a laboratory environment (35). They move around in a seemingly normal way, explore the environment, find their way out of simple labyrinths, get hungry, locate food and feed themselves, go through periods of sleep and maintain a diurnal rhythm. They are thus able to perform very important aspects of their normal behavioral repertoire.

In contrast, if a lesion is made leaving only the midbrain and caudal brainstem structures intact, these animals are unable to adapt to the environment, although specific motor programs can still be elicited but now performed in a stereotypic manner (136, 137). They include locomotion, eye movements, swallowing, and respiration. Thus, generation of coordinated movements adapted to the environment is entirely dependent on the integrity of the basal ganglia, as well as its input from the thalamus and other sources. The relation between the cortex and basal ganglia has been formulated by Arber and Costa (13) as *if the cortex broadcasts a wish, the basal ganglia will decide, whether the wish should be fulfilled or not*, that is if a movement should be initiated and executed or not.

The specific contributions of the cerebral cortex need careful analysis and are subtler than commonly realized. One example from Kawai et al. (179) illustrates this. They trained rodents to perform a double lever-pressing task within a fixed brief interval. This comparatively difficult task could be learnt, and they also showed that neurons in the motor cortex were activated during the task. However, if they subsequently lesioned extensive parts of the frontal cortex, including all motor areas, the rat could still, immediately after the lesion, perform the task with the same accuracy. Clearly, the cerebral cortex was not needed for the execution. However, if the cortical lesion was made before starting the training, the task could not be learnt. Thus, the cerebral cortex was not required for the execution of the learnt task, but for the learning process itself. Input from the thalamus is, however, critical to perform the learnt task (355).

In contrast, in mice, a specific part of the frontal lobe is required to perform a demanding oro-manual task of removing the crust of seeds. This task requires a dynamic sensorimotor interaction for successful execution (9, 243), something that may require continuous monitoring at the cortical level. The posterior parietal lobe may also contribute to continuously provide information regarding sensorimotor events and provide input to the striatum (168).

In monkeys, a transection of only the corticospinal tract at the brainstem level leads to specific deficits in the control of individual fingers, but other parts of the movement repertoire remain intact—the monkey could, for example, climb, move around, and grab food with no deficit (204, 205). Under these conditions, however, the cortical control of the basal ganglia, midbrain, and brainstem remains intact.

Basal Ganglia General Organization

The basal ganglia consist of an input stage, the striatum, which in primates, is composed of the caudate nucleus, with a head and a long tail (Figures 2A and 2B), and the putamen, separated by the large fiber bundles of the *capsula interna*. In rodents, the putamen is fused with the caudate nucleus. The dorsal striatum is an extensive processing center, and in rat, it contains 95 times (264) more neurons than the output stage of the basal ganglia, the substantia nigra pars reticulata (SNr), and globus pallidus interna (GPi)—a remarkable input-output ratio. In addition, there are two intrinsic nuclei, the globus pallidus externa (GPe) and the subthalamic nucleus (STN). The dopamine system substantia nigra pars compacta (SNc) is also an integrated part of the basal ganglia (Figure 2A).

The general structure of the basal ganglia is conserved throughout vertebrate evolution, as detailed below (142), and in mammals, the striatum has expanded in parallel with the neocortex. The putamen is organized in a somatotopic way, as shown in primates with different motor-related areas in cortex targeting different striatal modules to the extent that different parts of the arm, like the wrist, are represented separately (5, 149). Eye motor control is represented separately in the caudate nucleus (184).

In rodents, the striatum is subdivided into a dorsolateral part (DLS), also described as a somatomotor part that controls innate and learnt motor patterns, or habits (131, 286), and the dorsomedial part (DMS), involved in "goal-directed" movements specifically adapted to the current environmental situation. In primates, the dorsal striatum is subdivided into the caudate nucleus and putamen. The rostral part of the caudate nucleus and putamen corresponds approximately to the rodent dorsomedial striatum (DMS), while the dorsolateral striatum (DLS) corresponds to the caudal putamen and caudate tail part (184). The dorsal striatum is important for the control of motion, whereas the ventral striatum with the nucleus accumbens and its shell is linked to the limbic system (153). Our focus here will be on the control of motion and therefore the dorsal striatum.

The matrix and striosome compartments of the dorsal striatum

The striatum is subdivided into a matrix area and in striosomes (patches) representing around 20% of the striatum (Figure 2C). The matrix area represents by far the largest part of the striatum and is involved in the control of motion via the output nuclei of the basal ganglia, SNr/GPi, as detailed below. Striosomes can be identified immunohistochemically as they express the μ-opioid receptor and have a low level of acetylcholinesterase, in contrast to the matrix compartment (43, 133). Striosomes are involved in the control of dopamine neurons, and their striatal projection neurons (SPNs; see Figure 14) directly target dopamine neurons in the SNc (43, 70, 120, 129, 353). We will first consider the matrix compartment and its involvement in the control of motion. Further below, a section on striosomes will follow, considering their role in the control of dopamine activity and evaluation of motor tasks.

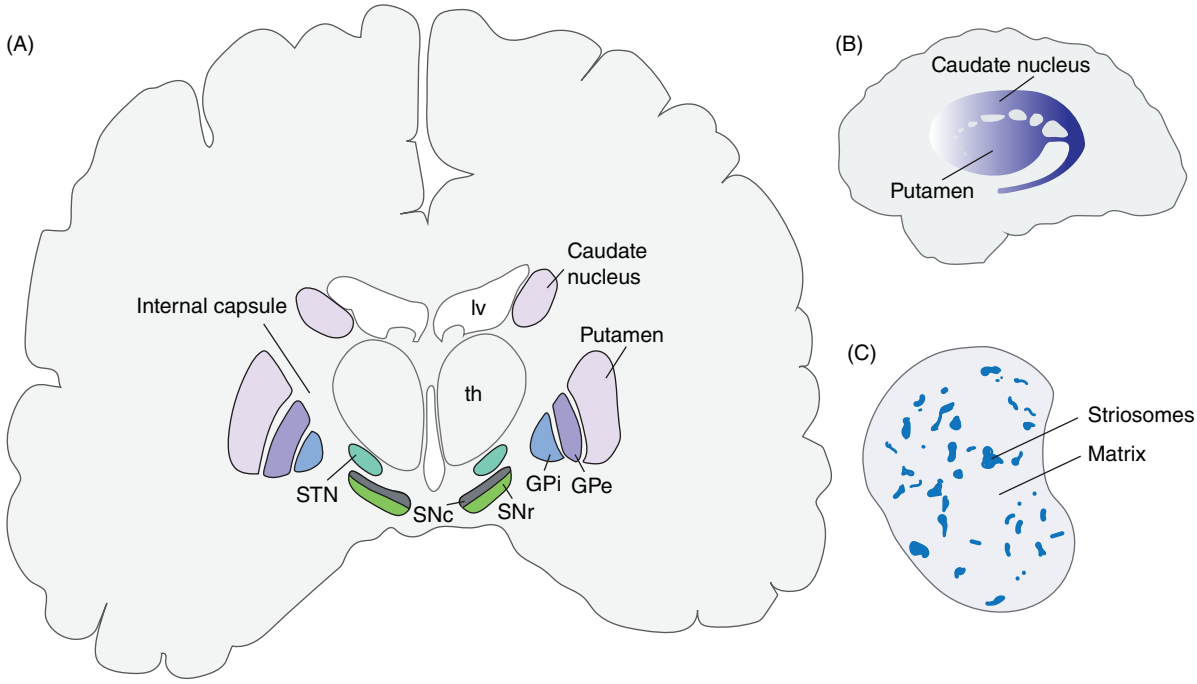


Figure 2 *The basal ganglia subnuclei in the human brain.* (A) The location of the different basal ganglia subnuclei at the level of thalamus. (B) A sagittal view of the brain showing the shape of the caudate-putamen. (C) Schematic of the striatum indicating the matrix and striosome compartments.

Connectivity within the basal ganglia and other basic characteristics

The striatum with its 2.79 million cells (rat) contains 95% projection neurons (SPNs), and approximately half project directly to the output stage (dSPNs) of the basal ganglia (SNr/GPi; direct pathway) and the other half projects instead to the GPe, which in turn projects to the SNr/GPi. The SPNs of this indirect pathway are called iSPNs (Figure 3). The SPNs are all GABAergic and inhibitory, while the STN is glutamatergic and receives input from GPe and cortex and enhances the activity of GPi and SNr. The pathway from the cerebral cortex via STN to GPi/SNr is referred to as the hyperdirect pathway. The GPe is the second-largest structure in the basal ganglia, but with its 46,000 neurons, it is still 60 times smaller than the striatum. The STN has only 13,000 neurons (215 times smaller). The net effect of dSPNs is thus to inhibit GPi/SNr, while iSPNs have the opposite effect. The dSPNs express dopamine receptors of the D1 type, which increase the excitability, if activated by dopamine, while iSPNs express D2 receptors, which instead reduce the excitability (121). Dopamine thus promotes dSPN activity, while iSPNs suppress it. Although these two subdivisions of SPNs are robust, it turns out that within each group there are further subdivisions based on RNA expression location within the striatum (227, 312).

The SPNs, dominating the striatum, are designed to be at a very negative membrane potential under resting conditions and are activated only after a sufficient excitatory drive from the cerebral cortex or thalamus (121, 324). In contrast, the

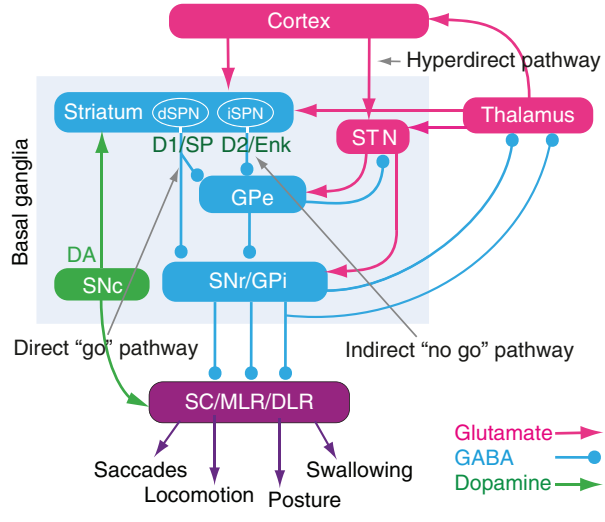


Figure 3 *The organization of the basal ganglia.* The striatum consists of GABAergic neurons, as do GPe, GPi, and SNr. SNr and GPi represent the output level of the basal ganglia, and it projects via different subpopulations of neurons to the superior colliculus (SC), the mesencephalic (MLR), and diencephalic (DLR) locomotor command regions and other brainstem motor centers, as well as back to thalamus with efference copies of information sent to the brainstem. The dSPNs that target SNr/GPi express the dopamine D1 receptor (D1) and substance P (SP), while the iSPNs express the dopamine D2 receptor (D2) and enkephalin (Enk). The indirect loop is represented by the GPe, the STN, and the output level (SNr/GPi)—the net effect being an enhancement of activity in these nuclei. Also indicated is the dopamine input from the SNc (green) to striatum and brainstem centers. Excitatory glutamatergic neurons are shown in pink and GABAergic structures in blue color.

inhibitory neurons of GPe, GPi/SNr, and the excitatory STN are all tonically active at rest due to their inherent membrane properties (127, 180, 240, 315). This means that the discharge rate of these different neurons all can be changed in an upward or a downward direction, an advantage from a control perspective. A decrease of activity in an inhibitory neuron thus results in a disinhibition of its target cells and a net excitation results in disfacilitation. Also, dopamine neurons have a tonic discharge at rest and thus can be facilitated, as in a reward situation, or reduced to zero when an anticipated reward is not provided (300).

Striatal projection neurons and connectivity in the matrix compartment

The SPNs, in general, have a very similar morphology, although the dSPNs tend to have a modestly larger dendritic tree than iSPNs, while the excitability at rest is somewhat higher in iSPNs than in dSPNs (80). Except for the proximal part of the dendrites, numerous spines are distributed throughout their dendritic tree. Practically all cortical synapses target the spines, which also applies to the input from the thalamic intralaminar central lateral (CL) nucleus. However, the intralaminar parafascicular (PF) thalamic nucleus targets to a large degree of the dendritic shafts and provides smaller EPSPs in SPNs than the CL input (99, 202). Also, the SPNs in close vicinity (100 µm) interact through inhibition acting on distal dendrites, both within each category (dSPNs and iSPNs) and between the two subtypes (276, 332).

A characteristic feature of SPNs is that they express inward rectifier K^+ channels [Kir; (260)], which are open at rest and make the membrane potential very negative and the SPNs difficult to activate (121). These Kir ion channels become inactivated if the cells are depolarized by inputs (e.g., from cortex). The cells will then become more susceptible to other excitatory inputs mediated by both NMDA and AMPA receptors. Moreover, SPNs can display plateau potentials in individual dendrites (92, 277), which is an important factor for the integration of synaptic input and plasticity (see below) and the effect of NMDA receptors and Ca^{2+} dynamics.

Striatal interneurons

In addition to the SPNs, there are 5% interneurons in the rodent striatum and seven subtypes based on single-cell RNA sequencing (249), all of which are GABAergic, except for the cholinergic interneurons (ChINs). We will consider here the three most studied (Figures 4A and 4B), which include the ChINs, the fast-spiking (FS) interneurons, and the low-threshold-spiking (LTS) interneurons. There are, however, some less well-described interneurons [see below; (335)]. Striatal types of interneurons have been considered to be conserved across mammalian species. It was, therefore, unexpected to find a new distinct type of interneuron in primates, not reported in rodents, referred to as the TAC3+ interneurons that represents 30% of the striatal interneuron (200). It is possible, however, that it does have a very rare counterpart in the mouse (J. Hjerling-Leffler, personal communication). In the marmoset, the interneuron population is larger than in rodents and represents no less than 13% of the total number of cells in the striatum compared to 5% in rodents (200).

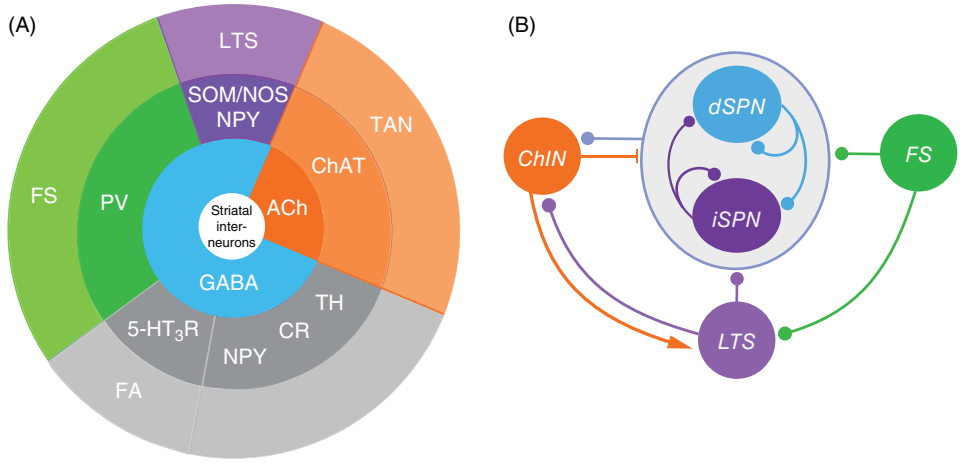


Figure 4 *Striatal interneurons and the striatal microcircuit.* (A) Each subtype of striatal interneurons identified by their neurotransmitter expression (inner circle), other molecular markers (middle circle), and electrophysiological properties (outer circle) are represented in the circular plot. Redrawn and modified, with permission, from Burke DA, et al., 2017 (50), Figure 1. (B) The striatal microcircuit with the connectivity between the striatal projection neurons (SPNs) and their input from FS, LTS and ChIN interneurons. *Abbreviations:* ACh, acetylcholine; ChAT, choline-acetyl transferase; ChIN, cholinergic interneuron; CR, calretinin; FA, fast adapting; FS, fast spiking; GABA, gamma-butyric acid; 5-HT_3R, serotonin type-3 receptor; LTS, low-threshold spiking; NOS, nitric oxide synthase; NPY, neuropeptide Y; PV, parvalbumin; SOM, somatostatin; TAN, tonically active neurons; TH, tyrosine hydroxylase.

Cholinergic interneurons

ChINs have historically been referred to as aspiny neurons (in contrast to SPNs) and have a dendritic arbor extending over approximately 200 µm, but with fewer ramifications compared to SPNs. They display a postinhibitory rebound and tend to be tonically active and have, therefore, been referred to as TANs [tonically active neurons (10, 287)]. ChINs tend to be synchronously active (285). However, other interneurons have now been found to have tonic activity, including the LTS interneurons, but they can be separated based on spike shape. The ChINs affect SPNs via muscarinic receptors (M1 for both types of SPNs and also M4 for dSPNs) and LTS interneurons via both muscarinic and nicotinic receptors (98, 232). They can also act in an unusual way by activating dopaminergic terminals directly via nicotinic receptors thereby causing a release of dopamine (52, 340), as shown with synchronous optogenetic activation of ChIN populations.

The ChINs express D2 receptors and thus become inhibited by dopamine (83). In a reward situation with a dopamine burst, ChINs thus become inhibited and are, therefore, tightly coupled in a reciprocal fashion (12, 17, 65, 245). On cortico-dSPN synapses, the combined action of a dopamine burst and simultaneous removal of the cholinergic muscarinic receptor activation (M4) promotes long-term potentiation [LTP; (87, 251, 253)], which is accomplished by an increase in dopamine combined with a decreased activation of M4 from ChINs.

In Parkinsons's disease (PD), ChINs most likely have a higher level of activity due to lack of dopamine inhibition, which may contribute to the symptoms. In the pre L-DOPA-therapy era, cholinergic (muscarinic) antagonists, like atropine or scopolamine, were used to remedy symptoms of PD (94), thereby reducing the impact of ChINs.

The ChINs receive glutamatergic input primarily from the thalamus (15, 89) and no or weak input from the cerebral cortex (16). In addition, ChINs receive input from the glutamatergic part of the pedunculopontine nucleus (PPN) that targets all striatal interneurons but not SPNs (16).

The fast-spiking (FS) interneurons

The FS interneurons provide efficient inhibition of both dSPNs and iSPNs (276), and even the same FS interneuron may activate both subtypes of SPNs. The FS interneurons target the soma and proximal dendritic area of SPNs, as well as the LTS interneurons. They tend to have short-lasting action potentials, limited spike frequency adaptation and to be electrically coupled (160, 276). A large proportion express parvalbumin [PV; (249)] and have a wide dendritic arbor (around 200 µm) with extensive axonal ramifications.

They receive strong input from the cerebral cortex, respond faster than SPNs and have, therefore, been considered to mediate feed-forward inhibition (190, 191, 207, 276). The FS interneurons also receive input from the thalamus and PPN and appear to provide little interaction with other interneurons except the LTS (16).

The low-threshold-spiking (LTS) interneurons

The LTS interneurons are GABAergic and coexpress in different combinations the peptides somatostatin (SOM), neuropeptide Y (NPY), and nitric oxide synthase (NOS). The latter secretes nitric oxide (NO) if sufficiently activated (335, 336). The LTS interneurons are spontaneously active, relatively small with a high input resistance and represent around 1% of the striatal neurons. They have three to five primary dendrites with sparse dendritic arborization and the axons can extend for up to 1 mm. The cortex provides a strong input that can elicit long-lasting plateaus and spikes (15).

In contrast to all other striatal interneurons, LTS interneurons receive no excitation from the thalamus. Instead, they receive disynaptic inhibition mediated by GABAergic tyrosine hydroxylase-expressing interneurons (THINs). The LTS interneurons provide inhibition to both SPNs and ChINs and receive nicotinic input from ChINs and inhibitory input from FS interneurons.

Additional interneurons

Other interneurons are less well described. The THINs receive input from the cerebral cortex, thalamus and PPN, and target SPNs, LTS interneurons, and ChINs. Although THINs express tyrosine hydroxylase (TH), they release gamma-butyric acid (GABA) instead of dopamine (357). There are also the CRINs (calretinin-expressing interneurons) that express 5-HT3 receptors and neuroglioform interneurons (335).

To conclude: Within the striatum, most synaptic interactions are on distal dendrites between SPNs. The FS interneurons target soma and proximal dendrites of SPNs and LTS interneurons. The latter inhibit SPNs and ChINs, which act via muscarinic receptors on SPNs and LTS interneurons (Figure 4B).

Synaptic Input to Striatum

The incentive to move is based on processed sensory information, often a combination of different senses, that reach the striatum from the cerebral cortex, thalamus, or other structures. The scent of food combined with its visual location could make you rapidly approach the food to take a bite. This requires recruiting a sequence of motor programs for locomotion, steering, grabbing the food, chewing, and finally swallowing.

The major glutamatergic input to the striatum is from different parts of the cerebral cortex, the thalamus (99, 202) and the PPN [see Figure 5B; (14, 78)]. The different modulatory systems convey another type of input, the most prominent is the dense dopaminergic input to the dorsal striatum from the SNc, while the adjacent ventral tegmental area (VTA) primarily targets the ventral striatum. Furthermore, there is a conserved 5-HT input from the raphe nucleus and a histaminergic

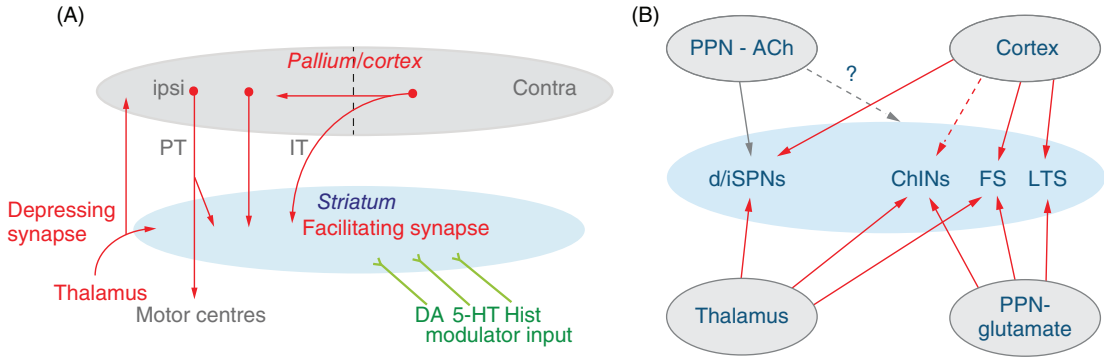


Figure 5 *Input to different neuronal subpopulations in striatum.* (A) Many cortical/pallial axons that target the brainstem and spinal cord (PT-type) give off collaterals to neurons within the striatum. There is a subset of pyramidal neurons that have intratelencephalic axons projecting to the contralateral cortex/pallium (IT-type) that also target the striatum. (B) Cortical and thalamic neurons target both direct and indirect striatal projection neurons (d/iSPNs) and the ChINs, FS, and LTS interneurons. The glutamatergic pedunculopontine (PPN) neurons only project to the interneurons, whereas the cholinergic PPN target the d/iSPNs. The red dashed arrow from cortex to ChINs indicates a variable and weak effect.

input from the ventral hypothalamus (38, 46, 99, 280, 281). In addition, there is a GABAergic inhibitory input from the GPe [(221, 222); see also below and Figure 7].

Corticostriatal projections

Cortical input to the striatum (Figure 5A) originates mainly from layer 5 and are of two types, the projection neurons to the brainstem-spinal cord [pyramidal tract (PT)-type] that give off major collaterals to the striatum, and the intratelencephalic (IT-type) neurons. The latter can excite striatal neurons and also ipsi- and contralateral cortical neurons, in particular, the motor areas (11, 19, 289, 304). Both IT- and PT-type cortical neurons target both types of SPNs, forming synapses almost exclusively on their spines, and target most interneurons although to a variable degree to ChINs (99, 202).

The cortical input to the striatum is compartmentalized in an orderly fashion (3–5). In primates, somatomotor functions are located in the putamen, which receives input from different sensory and motor areas. Oculomotor function resides in the caudate nucleus, which receives input from the temporal and frontal lobes. Likewise, the prefrontal and orbitofrontal areas project to the caudate nucleus. The limbic areas, including the anterior cingulate, however, target the ventral striatum (5, 153). In rodents, as discussed above, the DLS is a somatomotor area, whereas the DMS is involved in goal-directed movements. Whole-cell recordings from SPNs in the area that receives input from the somatosensory barrel cortex (287, 288) show that the SPNs receive input from both the ipsi- and contralateral cerebral cortex (IT-type), with excitation followed by inhibition. Moreover, the excitatory inputs to dSPNs are somewhat larger than to iSPNs (106). In the dorsolateral area, the input is exclusively somatosensory, while in the dorsomedial area, visual and somatosensory inputs converge.

One can assume that the actual cortical input to a cluster of cells in the striatum, involved in the control of a specific movement, has a very specific input from selected parts of sensorimotor microcircuits. Moreover, the projections from the different areas to the basal ganglia output nuclei are transmitted with maintained specificity to downstream motor centers, like the superior colliculus (SC), and also back to the cortex via the different thalamic relays (e.g., the ventrolateral and anterior thalamic nucleus).

The connectivity described above relates to the matrix compartment of the striatum. The smaller striosome compartment (20%) is the first to develop during ontogeny and it receives input from the orbitofrontal, cingulate, and insular cortex (70, 116), and it has direct projections to dopamine neurons in SNc/VTA (see below) and other structures involved in reward/evaluation related circuits (318, 320).

Thalamostriatal projections

The thalamic projections represent about 40% to 45% of the total cortical and thalamic projections to the striatum, but their precise role in the control of motion is far from understood. The intralaminar nuclei project to the striatum (Figure 5B) and consist of a caudal group including the PF nucleus and in primates a subdivision of PF, the centromedian (CM) nucleus. There is also a rostral intralaminar group including the CL group (118, 311, 363). In addition, there are less prominent projections from several other thalamic nuclei (6, 99, 202, 223, 231).

The importance of the thalamic input is borne out by experiments showing that when a rodent has learnt a specific task (e.g., lever-pressing with a certain interval), the motor areas in the cortex can be removed and the performance is unchanged. If, however, after learning the task, the thalamic input from PF and CL is incapacitated the task cannot be performed or learnt (179, 355).

The parafascicular (PF) nucleus/centromedian nucleus (CM)

The PF nucleus is the thalamic nucleus with the highest number of neurons projecting to the striatum. In mice, it is subdivided into three parts with transcriptionally and physiologically different neuronal properties (223). They project to the dorsolateral, medial, and central parts of the striatum, representing the somatosensory, associative, and limbic circuits, respectively. All three parts project to SPNs and ChINs, whereas FS interneurons are only activated in the dorsolateral part (107). The PF nucleus projects only to the matrix portion of the striatum. Its axons branch profusely in the striatum and form several dense plexuses (202). This suggests that PF axons may have an overall effect on the excitability of the striatal circuitry rather than targeting particular modules.

In contrast to the input from the cortex to SPNs, PF neurons synapse on both the dendritic shafts and the spines of the SPNs, being a structure involved in synaptic plasticity. The former location may imply a primary effect on dendritic excitability (99, 202). They activate both NMDA and AMPA receptors on SPNs. The three different subtypes of PF neurons differ somewhat in input resistance, capacitance, and resting potential. The PF neurons have long dendritic branches with spines and relatively few branch points. They can, therefore, be described as being of a reticular type rather than a classic thalamic relay neuron, in contrast to the neurons in CL [see below; (99)].

The PF neurons receive broad synaptic inputs from the SC, PPN, brainstem reticular formation, cortex, cerebellum, and GPi/SNr (311, 363). The PF neurons are activated by unexpected salient auditory stimuli, like beeps and clicks, and by visual and somatosensory stimuli (229). The PF activation appears to have larger impact on ChINs than on SPNs. The PF nucleus also projects to the cortex and it receives input from the same cortical area that the PF projects to. It may also involve projections from this cortical area to the same target area in the striatum that receives input from the PF nucleus (99, 202, 223).

In nonhuman primates, the rodent PF nucleus is subdivided into a CM part and a PF part, however, often treated together (118, 311, 363). Acute inactivation of the PF part disrupts attention processing and the role of CM/PF is thought to relate to attention shifting, behavioral switching, and reinforcement processes (234–236, 311, 363). The CM part receives input from the motor cortex and the other sources referred to above. Neurons in CM/PF respond with short latency to behaviorally salient stimuli (visual, somatosensory, or auditory). The CM projects primarily to the putamen, corresponding to the rodent DLS and can have a powerful effect on ChINs. If salient stimuli has been associated with reward, ChINs respond with a brief activation followed by inhibition and a postinhibitory rebound activation.

In addition to short-latency activated neurons, the CM contains neurons activated by salient stimuli with a long latency facilitation preceded by inhibition (234–236). In a situation in which the monkey under certain experimental conditions receives a large or small reward (one or several drops of juice), such long latency CM neurons respond primarily when the monkey realizes that it will receive a smaller reward than it had hoped for. Thus, when accepting this fact, these long-latency neurons were activated, and this is thought to be a behaviorally important signal for associative learning.

Intralaminar central lateral nucleus (CL)

The CL nucleus is adjacent to the PF nucleus but contains fewer neurons. CL neurons have short bushy dendrites with many branch points described as classic thalamic dendrites studded with spines (202). They display more burst firing than PF neurons. Their axon collaterals are long and smooth with synapses en passant. In contrast to PF, CL neurons synapse almost exclusively on the spines of SPNs and provide stronger depolarization, and drive dSPNs more efficiently than iSPNs (99). The NMDA/AMPA ratio is around 0.5 for CL synapses, but 2.5 for PF synapses, suggesting that PF synapses are involved in long-term plasticity and facilitating plateau potentials, more so than CL synapses.

The dopamine innervation of striatum

The dopamine innervation of the dorsal striatum originates from the SNc, whereas the nearby VTA innervates the ventral striatum. The dorsal striatum innervated by the SNc has a very high density of dopamine varicosities, it has been calculated that each spine on individual SPNs is only 1 µm away from a dopamine release site (39, 246). The rat SNc has around 12,000 neurons, and it has been estimated that each neuron has 100,000 to 370,000 synapses. For comparison, each SPN makes 300 to 500 synapses and a motoneuron even less (39). The dopamine input activates dopamine receptors of the D1 type that increase the excitability of the dSPNs, and at the same time D2 receptors, which instead reduce the excitability of iSPNs (121).

The dopaminergic SNc neurons are spontaneously active at rest, at a rate of a around 5 Hz (61), but are modulated during behavior with marked bursts or pauses (300). They used to be treated as one entity, but it now appears that dopamine neurons in different parts of the SNc differ with regard to input. In the medial part, they can be enhanced in reward situations, while dopamine neurons in the lateral part increase their activity with aversive stimuli and to salient visual or acoustic stimuli like clicks or sudden light flashes (48). Dopamine neurons that enhance their response to reward reduce their firing in a no-reward situation, while other dopamine neurons increase their firing to aversive, painful stimuli. In both cases, this can be described as a value-based motivational signal with opposite sign. Thirdly, fast alerting or salient stimuli may signal something potentially important. There are thus three dopamine populations that carry different, sometimes

overlapping messages! In line with this, different dopamine neurons project to different areas—a subpopulation of VTA neurons projects primarily to the frontal lobe, and others to the ventral striatum (28, 203). In primates, the head and tail of the caudate nucleus are supplied by different sets of dopamine neurons from the SNc, which may relate to their involvement in habitual and goal-directed aspects of behavior, respectively (184). The heterogeneity of midbrain dopamine neurons is also manifested through transcriptomics, and they can be subdivided into seven subpopulations (341).

Certain dopamine neurons in the SNc/VTA actually corelease glutamate and dopamine on striatal neurons in both rodents and lamprey (237, 322, 334, 351, 368). This is an important feature in that dopamine/glutamate neurons will be able to affect the excitability of target neurons without the inherent delay of G-protein-mediated receptors and will act in synergy with D1 receptors. Additional subpopulations of SNc/VTA neurons may also corelease GABA and dopamine (343).

Dopamine neurons in SNc/VTA receive input conveying salient and value-based information from a number of sources like the PPN and laterodorsal tegmental nucleus (LDT), the SC, the lateral habenulae, dSPN neurons of the striosomes and cerebral cortex (see further below and Figure 20). An unusual mechanism is provided by cholinergic axons (ChINs) that can activate dopaminergic terminals directly via nicotinic receptors, thereby causing a release of dopamine (52, 340), as shown with synchronous optogenetic activation of ChIN populations.

5-HT and histamine projections to striatum

Throughout vertebrate phylogeny, the raphe system provides a 5-HT innervation of the striatum (172, 281), but this is not as dense as that of the dopamine system. The 5-HT neurons are activated during the initiation of behavior and also in reward situations, but whereas the dopamine activity is in the form of short-lasting bursts, the activity of 5-HT neurons in the raphe nucleus tends to last for a longer period. In a behavioral choice situation, an enhancement of the discharge of 5-HT neurons will lead to a maintained attempt to wait for a potential reward (improved impulse control) rather than abandoning the session (112, 170, 172, 215, 241, 242, 284). The 5-HT system is clearly a significant contributor to the control of behavior both with regard to the striatum and cerebral cortex and also to other parts of the brain.

The histamine system originates from the tuberomammillary nucleus in the hypothalamus and is present in vertebrates extending from lamprey to mammals, including a conserved major projection to the striatum with a high density of histamine receptors (45, 147). Histamine neurons display a circadian activity pattern, with a low level of activity during sleep and a higher level during the awake period and greater activation during arousal (38, 147). A common experience is that antihistamines (against allergy and motion-sickness) give rise to drowsiness. The histamine terminals in the striatum do not have point-to-point synapses but the histamine is released en passant from varicosities. Histamine provides presynaptic inhibition via H3 receptors in corticostriatal and thalamostriatal glutamatergic synapses, and presynaptic inhibition of the GABAergic synapses between SPNs, but not at the FS to SPN synapse. Furthermore, they cause a decreased release of dopamine (100). Postsynaptic actions of H1 and H2 synapses involve a net depolarization of ChINs and can reduce the postspike after hyperpolarization (38, 147, 148). In PD, the level of histamine increases and an upregulation of H3 receptors occurs, while in Tourette's syndrome a reduced histamine release has been observed (147, 148).

Cholinergic projections from the pedunculopontine (PPN) and laterodorsal tegmental (LDT) nuclei to striatal SPNs

The cholinergic PPN and LDT neurons are activated in reward situations and provide part of the excitatory drive to dopamine neurons (135, 263). They also have extensive striatal projections, with the rostral part targeting the DLS, while the caudal part targets the dorsomedial and ventral striatum (77, 78). PPN and LDT neurons are also known to provide input to thalamostriatal neurons. PPN/LDT neurons can thus affect the striatum via three avenues, directly and indirectly via dopamine neurons in SNc or VTA and via the thalamus. In the striatum, the PPN targets both spines and dendritic shafts of SPNs and perhaps also interneurons, but only in the matrix region, avoiding the striosomes (77, 78).

The glutamatergic pedunculopontine (PPN) and laterodorsal tegmental (LDT) nuclei target striatal interneurons

Within the PPN, there is in addition to the cholinergic population, a glutamatergic group of PPN cells that represents an independent set of neurons and constitutes around 60% of the total number of cells (14). The glutamatergic PPN projects to the entire striatum (Figure 5), but in contrast to the cholinergic PPN neurons they do not target SPNs, only the striatal interneurons, prominently ChINs, FS interneurons and also in a smaller number of LTS interneurons and THINs recorded [(14); Figure 5]. When glutamatergic PPNs are activated optogenetically, they provide a strong excitation to these different groups of striatal interneurons, comparable to thalamic excitation. Both types of SPNs receive disynaptic inhibition due to the activation of GABAergic interneurons, without a trace of excitation. This is thus a prominent way of shutting down the entire output of the striatum. In the freely moving mouse, optogenetic activation of glutamatergic PPN neurons during movement results in an ipsiversive rotation and thus asymmetric movements. This rotating behavior stops as soon as the stimulation is terminated. It resembles the one-sided rotation produced by unilateral inactivation of the dopamine system (344).

The cerebellar–thalamic–striatal projection

Traditionally, the reciprocal relation between the cerebellum and the cerebral cortex has received considerable attention over many years (171). Recently, however, it has become evident that the different output nuclei of the cerebellum all target neurons in the intralaminar nuclei of the thalamus that in turn project to the dorsal striatum (53, 59, 165, 169, 358). Both types of SPNs and ChINs become activated. It will, therefore, be important to consider the cerebellum as a major thalamic input to the striatum, recalling that the thalamus is responsible for around 40% to 45% of the glutamatergic input to the striatum.

The amygdala and hippocampus provide input to the ventral striatum

Another source of input to parts of the striatum is from the amygdala. Emotionally tainted charged stimuli from the prefrontal and insula cortex are channeled via the glutamatergic basolateral nucleus to the ventral and DMS (63, 67). Also, the hippocampus provides input to the ventral striatum (346). When locomotion is initiated, a hippocampal theta rhythm appears, which in turn synaptically activates neurons in the ventral striatum, also in theta frequency, with repercussions in downstream motor command areas (194).

To conclude: In this section, we considered no less than ten different sources of inputs to the striatum. Clearly, the cerebral cortex and thalamus are the major players that most likely will determine whether a certain action, rather than another, is released due to the modular input to what most likely is a mosaic of striatal compartments with afference from different parts of the cerebral cortex or thalamic channels. The salient dopamine input (broadly distributed) may determine if an action takes place at all, but not which specific action (see also below). The level of histamine and 5-HT may also be important in this regard. The glutamatergic input from PPN targeting only striatal interneurons would seemingly, in isolation, turn off the striatum by activating GABA interneurons, but in reality perhaps fine tunes the level of activity within the striatal interneuron population. How the striatum processes the input from the cerebellum is not yet understood. However, to have cross-talk between the basal ganglia and cerebellum given their role in movement control should somehow be important, as are the role of the hippocampus and amygdala for the ventral striatum.

Nuclei of the Basal Ganglia—The Direct, Indirect, and Hyperdirect Pathways

As we have mentioned earlier, there are essentially three pathways from the cerebral cortex/thalamus through the basal ganglia referred to as the direct, indirect, and hyperdirect pathways [see Figure 6; (81, 255, 256)]. The direct pathway is channeled via dSPNs and targets directly the output level (SNr) to enhance the excitability in brainstem motor targets through disinhibition and thereby promote action. The indirect pathway is conveyed via iSPNs that inhibit

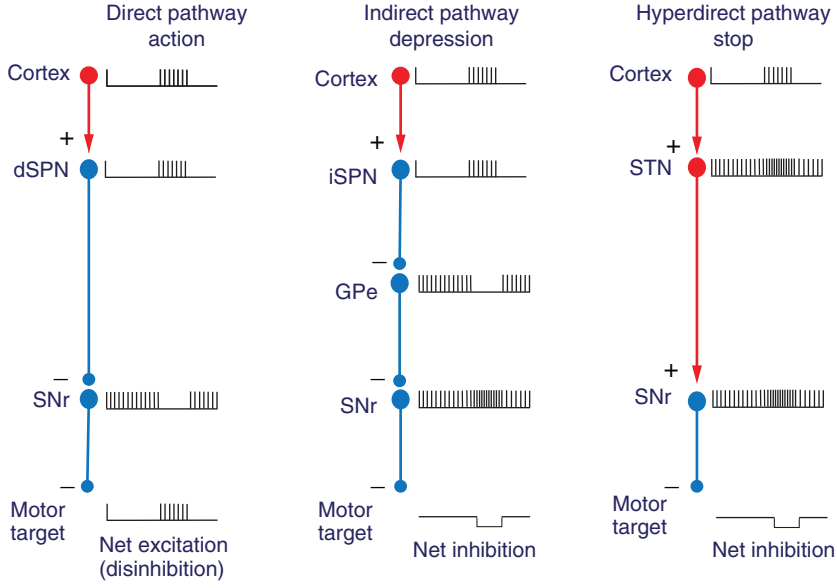


Figure 6 *The direct, indirect, and hyperdirect pathways.* Striatal projection neurons of the direct pathway (dSPNs) directly target the output level (SNr) and will enhance the excitability of brainstem motor targets through disinhibition and thus promote action. SPNs of the indirect pathway (iSPNs) will inhibit the spontaneously active GPe that in turn disinhibit SNr, thus increasing inhibition of downstream motor targets. The hyperdirect pathway projects to the glutamatergic STN that in turn targets SNr that will then inhibit the motor targets.

the spontaneously active prototypical GPe neurons that in turn disinhibit SNr and enhance SNr activity, leading to an increased inhibition of downstream motor targets. There is also cross talk between the direct pathway, in that dSPNs also inhibit the arkypallidal neurons in GPe that project massively back to the striatum [see Figure 7; (180); see below]. Finally, the hyperdirect pathway does not involve the striatum but the glutamatergic STN that in turn targets the SNr directly to enhance its activity and inhibit the motor targets (255, 256). The hyperdirect pathway is often described as a stop pathway and the indirect pathway has a depressing effect on the different motor centers.

GPi and SNr provide the output of the basal ganglia

The subdivision of the output nuclei of the basal ganglia, SNr and GPi, is present in all vertebrates. In rodents, the SNr is twice as large as GPi (or the entopeduncular nucleus as it is often referred to in rodents). They both contain GABAergic projection neurons, which have a large disc-shaped dendritic tree without spines, and the cells are arranged with the discs oriented in the same direction. The input from the striatum to GPi/SNr is orderly arranged from the different parts of striatum, and the axons of dSPNs are oriented at right angle with the dendritic discs, allowing for synapses on several neurons. Individual dSPN axons may form extensive synapses on a few selected SNr/GPi neurons, while glutamatergic synapses from STN have been reported to impinge on a large number of SNr/GPi neurons (84, 239, 240, 369). The input from GPe neurons targets the soma and proximal dendrites with large efficient IPSPs. SNr/GPi neurons are designed to be spontaneously active from 35 to 70 Hz and do not require any synaptic drive at rest, but can, of course, be modulated (e.g., from dSPNs). At rest, they keep their downstream brainstem or thalamic target cells under tonic inhibition, and if they become inhibited by dSPNs, their target cells become disinhibited. Conversely, if they become activated by the STN, inhibition of the targets will instead be enhanced.

At rest, the different SNr neurons inhibit many different motor centers at the brainstem level like the SC, for eye and orienting movements, the mesencephalic locomotor region (MLR), and centers for postural control, chewing, and swallowing (156–159, 294, 330). McElvain and Costa (230) have identified projections from SNr to the superior and inferior colliculus, midbrain, pontine, medullary reticular formation, PPN, dorsal raphe, and thalamic nuclei (ventralis lateralis, ventralis anterior, and midline nuclei, including PF). Neurons projecting to the different areas are organized in different parts of the SNr and differ both morphologically and with regard to membrane properties. The brainstem-projecting SNr neurons often send collaterals to thalamic nuclei and *vice versa* (230, 329). The same information would thus be transmitted downstream to the respective motor centers and via the thalamus back to the cerebral cortex. The thalamic relays are also compartmentalized so that information from different SNr units are fed back to the cortical area concerned with this particular type of information. Also, in the GPi/entopeduncular nucleus (352), there are projections to both brainstem centers and thalamus, but less detail is available (329).

In conclusion, it would seem that a large part of the basal ganglia's control of movement takes place through the SNr/GPi control of different brainstem centers through disinhibition of specific targets via the activation of a certain set of dSPNs. The importance of the collateral activation to the thalamus and back to the cerebral cortex could serve as an efference copy for planning the next phase of the movement at the cortical level.

The subthalamic nucleus mediates the hyperdirect pathway to stop movements

The STN is the only excitatory part of the basal ganglia. It consists of glutamatergic projection neurons with an ellipsoid dendritic tree with spines. It receives a prominent input from the cerebral cortex, which terminates on distal dendrites, whereas the extensive thalamic input (PF) synapses on proximal dendrites, in both cases on spines and shafts, utilizing both AMPA and NMDA receptors (32–34). The STN neurons are spontaneously active at rest due to inherent cellular properties, although their activity can be strongly modulated by inhibitory or excitatory synaptic inputs.

The STN consists primarily of projection neurons with few collaterals and limited interactions between them within the nucleus (315). There is in addition a smaller subpopulation with extensive collateralization (127), also clear from a transcriptomic analysis (266). Based on inputs from the cerebral cortex, the STN can be subdivided into a limbic, a cognitive and a motor compartment. In the motor part, located dorsolaterally in the STN, there is a somatotopic subdivision in the input from the different motor areas in the frontal lobe concerned with limb and eye movements (149, 152, 255, 256), whereas the limbic and cognitive areas receive input from limbic and cognitive cortical areas. The projections from the STN are in register with the downstream subdivisions of SNr concerned with different movements. The net effect of activating particular modules within the SNr is enhanced activity of the SNr neurons and increased inhibition of their related downstream motor center. The hyperdirect cortico-STN-SNr/GPi pathway can thus effectively terminate a given pattern of motor behavior. In addition to the prominent input from the cerebral cortex and thalamus, the STN receives additional inputs from the SC, cholinergic and glutamatergic PPN neurons, and dopaminergic SNc neurons (66, 186).

The STN is in addition part of the indirect pathway and receives GABAergic input from the prototypical cells of the GPe, while the STN provides excitation to the same cells (8, 186). The prototypical cells represent 70% to 80% of the GPe neurons (219), but there is specificity so that only a limited number of GPe neurons interacts with a select group of STN neurons (22). The sequence in the indirect pathway is as follows: iSPNs inhibit spontaneously active prototypical

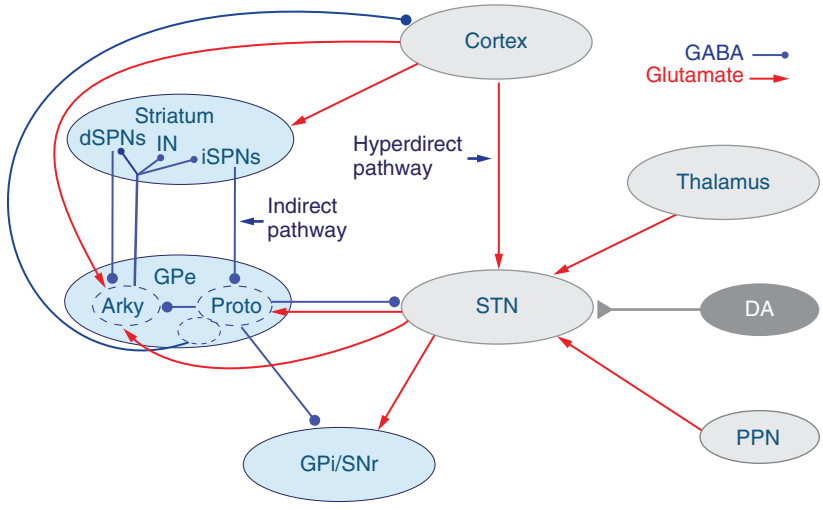


Figure 7 *Connectivity of the globus pallidus externa (GPe) and the subthalamic nucleus (STN) with target structures.* The GPe has two subpopulations of GABAergic cells, prototypical and arkypallidal cells. The prototypical cells receive input from iSPNs and STN. They project to the STN and GPi/SNr. The arkypallidal cells project back to the striatum's dSPNs, iSPNs, and interneurons, and receive input from the STN, cortex, and dSPNs. The STN receives input from the cortex, thalamus, PPN, SNc, and GPe. Like the GPe, the STN projects to the output nuclei GPi/SNr.

GPe cells, which disinhibit STN neurons and thereby enhance their activity (Figure 7). In addition, the decreased activity of the GPe neurons directly disinhibit SNr/GPi and enhance their activity.

The STN receives dopaminergic input from the SNc (113) and is thus under resting conditions subject to a low level of continuous dopamine release. During behavior, the STN is subject to the same level of dopamine drive as the striatum (e.g., reward). The STN expresses predominantly dopamine receptors of the D5 and D1 subtypes but also D2 (69, 117).

Under pathophysiological conditions with reduced dopamine innervation, oscillations at β-frequency (around 20 Hz) can occur in this reciprocal excitatory-inhibitory pathway (GPe-STN) that have been suggested to contribute to the symptoms in PD (113). In PD, the STN neurons are hyperactive (26, 27, 217, 220, 221), increasing the activity in the SNr/GPi and impairing the initiation of movements. Lesions of the STN counteract Parkinsonian symptoms by reducing the excitation of SNr/GPi (26). Clinically, large lesions of the STN have been reported to produce hyperkinesia of the appendages or the trunk [hemiballismus; (72, 314)].

It was, therefore, counterintuitive that deep brain stimulation (DBS) in the STN (25, 26) should lead to a relief of Parkinsonian symptoms, which, however, is now a well-established and successful method used clinically over several decades. Successful treatment with DBS requires high-frequency stimulation, and one possible interpretation is that it generates tonic STN activity and abolishes STN oscillations that contributes to the symptoms and thus a disconnection from the pathological STN activity (62). Moreover, high-frequency stimulation may lead to synaptic fatigue in the STN synapses, and a reduced excitatory drive onto SNr/GPi (315). The fact that the STN is subdivided into motor, cognitive, and emotional areas means that it is critical during DBS to target the motor area. The DBS is on continuously during night and day. A complication may occur when the stimulation electrode is not right on target and activates other parts of the STN, which can lead to both cognitive and emotional side effects and can even induce personality changes (24). Nevertheless, DBS has been a very successful therapy, particularly when the effect of L-DOPA becomes less effective.

In conclusion, the STN plays an important role in the operation of the basal ganglia, despite its relatively small number of neurons, by inhibiting movements in a precise manner because of the specificity of connections to the SNr.

The GPe mediates the indirect pathway from iSPN and feeds back inhibition to the striatum

The GPe in the rodent literature is sometimes referred to just as the globus pallidus, and the GPi is then called the entopeduncular nucleus. However, we use here the terminology used in primates and most species, GPe and GPi, respectively. The GPe is after the striatum the second largest structure in the basal ganglia, but with 60 times less neurons (264).

The GPe consists of two main types of GABAergic projection neurons, the prototypical and the arkypallidal (Figure 7), which are both spontaneously active at a variable rate. The prototypical GABAergic cells receive input from iSPNs and project to the STN and GPi (Figure 7) and coexpress the transcription factors Nkx2.1 and Lhx6, often PV, and represent around 60% of GPe cells. They are the essential component of the "indirect pathway". They also project back to the striatum

targeting only FS and LTS interneurons but not SPNs (299). A subgroup, the Nkx-2.1-expressing neurons, project to the cerebral cortex as part of a cortico-pallido-cortical loop (2, 60, 178, 299).

The arkypallidal cells, on the other hand, express the transcription factor FoxP2 and instead have a massive inhibitory projection back to the striatum to both SPNs and interneurons (Figure 7) with an estimate of 10,000 varicosities. The somatodendritic morphology is similar between the two types except that the prototypical cells are described as aspiny, whereas the arkypallidal cells have spines (185, 187, 219). Both types have a local collateral network within the GPe.

The input from iSPNs and STN to the prototypical GPe cells is well documented. During resting conditions, the prototypical cells are active at a higher rate than the arkypallidal cells. The latter receive inhibitory input from the prototypical cells, and excitatory from STN and tend to be rhythmically active in a reciprocal relation to the prototypical cells (1, 88, 219). Moreover, Karube et al. (178) recently showed that the arkypallidal neurons also receive strong monosynaptic input from PT-neurons in the cortical motor areas (M1 and M2) and inhibitory input from dSPNs (180). However, during movements, the arkypallidal neurons tend to be active at a higher rate. An activation of a population of arkypallidal neurons, such as from the motor areas, would very efficiently inhibit striatal neurons within their striatal target area, and they have been referred to as potential "stop cells" (219). Mallet et al. (222) showed that arkypallidal neurons were activated specifically at a stop task, in contrast to the prototypical neurons, and may thus contribute to this function together with the STN. Conversely, activity in the direct pathway inhibits the arkypallidal stop cells (180), which seems purposeful, since direct pathway activity is related to initiation of movement.

To conclude, both the STN and arkypallidal neurons receive equally strong monosynaptic input from cortical motor areas and may both contribute to "stopping" specific movements together with the glutamatergic PPN with its specific target on striatal interneurons (14). The prototypical cells will, via the indirect loop (input from iSPNs), also contribute to depressing movements. The GPe is the second-largest nucleus in the basal ganglia and with its connectivity back to both the striatum and cerebral cortex, as well as downstream to the STN and GPi/SNr, it should be considered as an important hub within the basal ganglia rather than just a relay nucleus.

The Contribution of the Direct and Indirect Pathways in the Control of Motion

Ever since the realization that the D1 receptor-expressing dSPNs project directly to the SNr and GPi, with D2 receptor-expressing iSPNs acting indirectly via GPe/STN and having an opposite effect on the neurons in SNr/GPi, the question has been asked as to their respective roles in the control of motion.

Mink (238) suggested that the dSPNs initiate movements, while iSPNs suppress competing movements. Using optogenetic techniques the Kreitzer laboratory (197, 198, 293, 294) showed that activation of dSPNs promoted the initiation of locomotion, while activating iSPNs instead had an inhibitory effect on the movements. The Costa laboratory (73, 333) showed that dSPNs and iSPNs were coactivated during the initiation and execution of locomotion and lever-pressing. Both were activated just prior to the movement and dSPNs remained active throughout the movement, while the activity in iSPNs tended to decrease earlier. This finding was further corroborated by Parker et al. (269) showing simultaneous recordings from thousands of dSPNs and iSPNs in the DMS. The two types of SPNs were coactivated in freely moving mice (73). Moreover, specific clusters of neurons within the striatum, both in the dorsomedial (269) and dorsolateral part (189, 349) were activated in relation to different aspects of the movement. This means that the striatum is subdivided into subpopulations of neurons engaged in the initiation and execution of different aspects of motor behavior. When recording the moment-to-moment changes in the activity of dSPNs and iSPNs of the DLS in freely moving animals (225), different subpopulations were activated in succession and the two types of SPNs were sometimes decorrelated. Lesioning the DLS abolished the ability to generate appropriate sequences.

In conclusion, the basis for initiating different motor actions depends on different inputs to the striatum from different parts of the cerebral cortex and thalamus that enhance the excitability in certain striatal subpopulations that via dSPNs inhibit a subset of SNr/GPi, which then release a given motor action.

The activity of dSPNs and iSPNs in reward-related tasks in rodents

In a different setting, Nonomura et al. (261) investigated the response of dorsomedial SPNs in a push/pull reward paradigm in which the reward occurred in a probabilistic way. They found that different populations were preferentially activated in the push or the pull condition. Furthermore, they reported that optogenetically and electrophysiologically identified dSPNs were activated during the execution of a pull movement, and when the reward signal occurred dSPNs continued to discharge, while a no-reward signal led to instantaneous cessation of activity (Figure 8). The iSPNs conversely were strongly activated when the no-reward signal appeared, but not when a reward occurred.

The dSPNs thus encoded reward outcomes, whereas indirect pathway neurons encoded a no-reward outcome and next-action selection. After a series of mostly no rewards, the rodent is assumed to change strategy from push to pull or *vice versa*. A continued activity in the dSPNs thus signals that a switch will not occur, while a high level of activity in the iSPNs predicts that a switch may occur. How is this achieved? The dopamine system can contribute in the following way. The dopaminergic reward signal can be expected to enhance the dSPNs through their D1 receptors, while it inhibits iSPNs

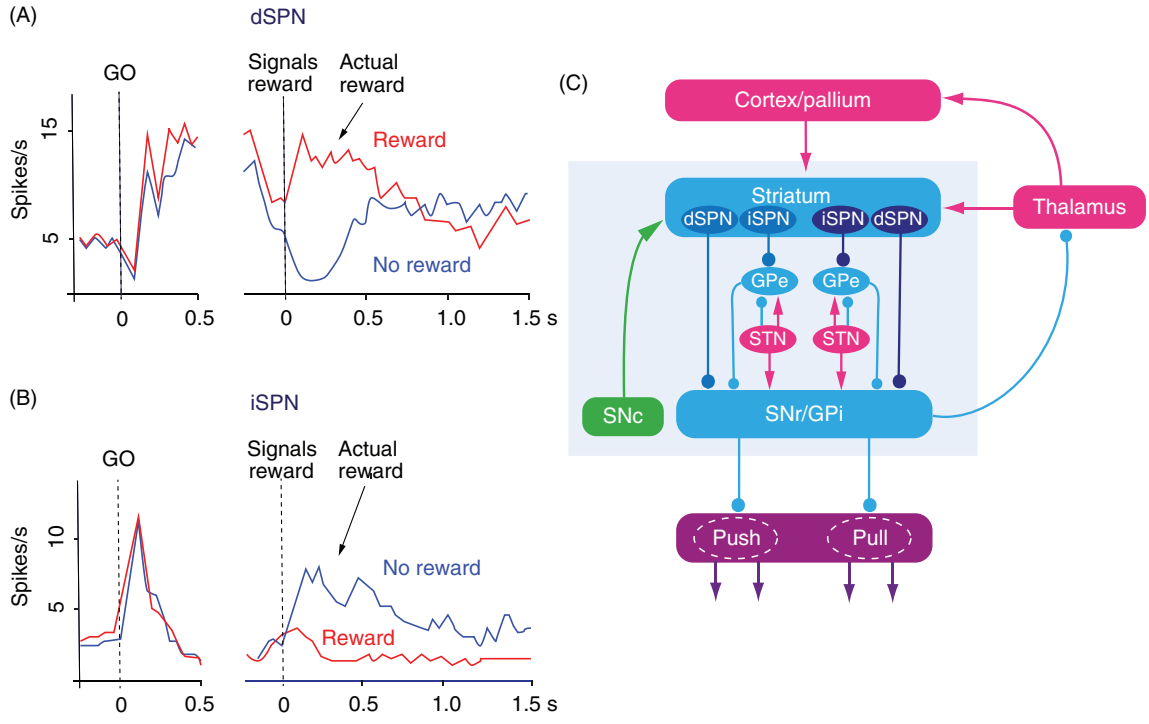


Figure 8 *The activity of striatal projection neurons of the direct and indirect pathway during a goal-directed push-pull task.* (A) Shows the activity pattern (spiking frequency) of a dSPN during a push/pull task. The red trace demonstrates a correct response (reward), and the blue trace an incorrect response (no reward). Upon the GO signal, the neuron is activated and remains active until a sound signals if the response will lead to a reward or not. The actual reward occurs with a further delay. Note that after the reward signal, the level of activity remains high, whereas with no reward the activity drops immediately. (B) The corresponding data for an indirect pathway neuron (iSPN). Note that immediately after the GO signal there is a marked increase of activity that rapidly decreases, while after the no-reward signal there is a marked increase from base-line. (C) Simplified scheme of the basal ganglia. Two separate populations of dSPNs and iSPNs control the push and the pull motion, respectively. The action is mediated by the basal ganglia output nuclei SNr and GPi to downstream motor circuits. Reused, with permission, from Grillner S, 2018 (140).

through their D2 receptors. Conversely, when there is no reward the iSPNs may become disinhibited (Figure 9).

The activity of dSPNs and iSPNs in reward-related tasks in primates

Hikosaka and colleagues have shown that the tail part of the primate caudate nucleus contains SPNs involved in the control of saccadic eye movements (182–184). By exposing the monkeys to a large panel of fractal objects, only some of which led to a reward, they were made to remember different objects over a very long time (months). Identified dSPNs were recorded while exposing the monkey to different fractal objects. The tail dSPNs (Figure 10, right part of the diagram) became activated particularly when a saccade was generated to the rewarded fractal objects—thus requiring a memory of the objects that most likely originates from the temporal lobe, which targets the tail of the caudate nucleus. The dSPNs inhibit tonically active SNr neurons that disinhibit the saccade generating neurons in the SC and thereby generate the saccade (156–159).

In contrast, iSPNs were activated when objects were presented with no reward. This was inferred from recordings of GPe neurons activated by iSPNs from the same caudate tail region and projecting to the same caudolateral part of SNr (182–184). The iSPNs thus contribute to inhibiting the saccade to nonrewarding objects. The control originates from the tail region as it does not operate after a pharmacological blockade of the tail region. Consequently, dSPNs and iSPNs in the same caudate tail region involved in the same general task appear nevertheless to respond differently to input presumably from the temporal lobe, perhaps related to the different dopamine drive in the reward and no-reward situation (Figure 9).

In contrast to the very stable long-term value assigned to a given fractal object in the tail region of the caudate nucleus, neurons in the head of the nucleus have a more flexible value relation dependent instead on short-term memory [see Figure 10 left part of the diagram; (183, 184)]. The dSPNs in the head area are also involved in the control of saccades but project to a separate medioventral region of the SNr and responds to the short-term value of an object (365). Inactivation of this region blocks the flexible response pattern in the SC and thereby generates the saccade. In contrast, iSPNs were activated when objects were presented with no connection to a reward. It should be noted that the

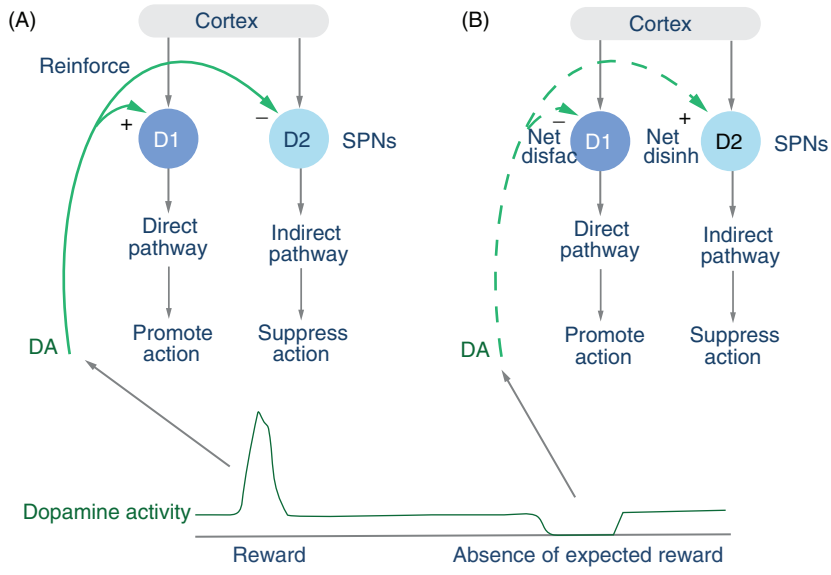


Figure 9 *The effects of enhanced or decreased dopamine activity on the direct and indirect pathways through the basal ganglia.* (A) An enhanced dopamine activity excites the striatal projection neurons of the direct pathway that express dopamine receptors of the D1 subtype, while it inhibits those of the indirect pathway through their D2 receptors. (B) Illustrates the opposite situation with decreased dopamine activity that removes excitation from the direct pathway and reduces the inhibition of the indirect pathway and thereby indirectly increase the net excitation.

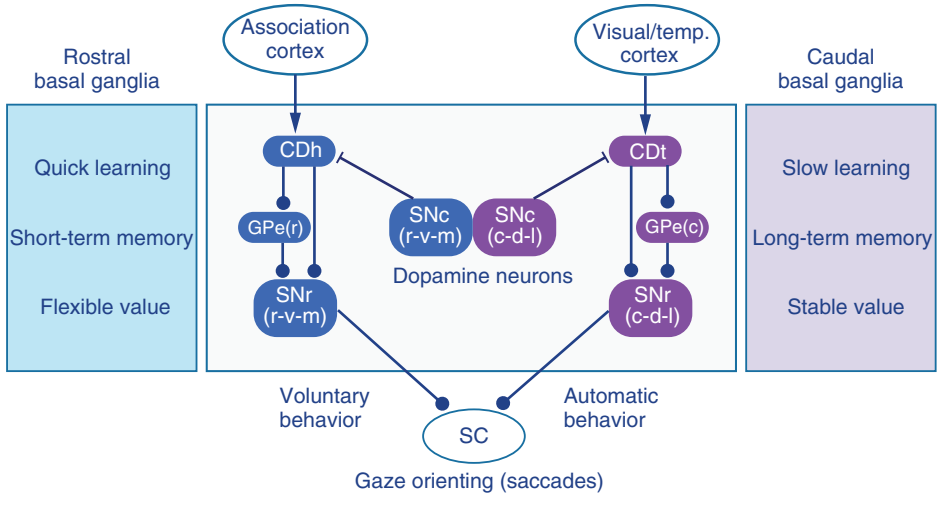


Figure 10 *Parallel pathways for goal-directed behavior conveyed via the head of the caudate nucleus (CDh) and habitual behavior produced through the tail of the caudate nucleus (CDt).* The CDt and CDh receive input from different cortical regions and both target the superior colliculus to elicit saccadic eye movements, although through separate channels and via separate output neurons of the basal ganglia in Substantia Nigra pars reticulata (SNr). Moreover, separate parts of the Substantia Nigra pars compacta (SNc) supply the two circuits. *Abbreviations:* CDh, head of the caudate nucleus; CDt, tail of the caudate nucleus; c-d-l, caudal-dorsal-lateral; GPe(c), caudal part of GPe; GPe(r), rostral part of GPe; r-v-m, rostral-ventral-medial; SC, superior colliculus. Modified and redrawn, with permission, from Kim HF and Hikosaka O, 2015 (184), Figure 6.

two circuits in Figure 10 are supplied by a separate set of dopamine neurons (228).

To conclude, the head and the tail of the caudate nucleus contains two separate circuits controlling very similar tasks requiring visual identification of specific fractal objects utilizing distinctly separate compartments of the caudate nucleus and SNr. The caudate tail part represents a hardcore habitual circuit, while the head part represents a flexible short term

memory. Moreover, they depend on separate parts of the SNc (Figure 10). In rodents, the habitual and flexible parts correspond to the DLS and DMS, respectively.

The Basal Ganglia's Downstream Control Versus Its Projections Back to the Cerebral Cortex

As we noted above, the output from SNr and GPi is subdivided into many different channels targeting different motor centers in the midbrain and brainstem to control, for example, saccadic eye movements, locomotion, steering, orofacial movements, and swallowing. All evidence suggests that disinhibition from the SNr/GPi can release different movements, perhaps combined with excitatory input from the cerebral cortex (82, 139, 141, 156–159, 331). In addition, most SNr neurons also extend a collateral to the relay nuclei in thalamus (230) that may transmit an efference copy back to the cortex or its counterpart pallium in nonmammalian vertebrates, informing about the "commands" issued by the SNr and back to the striatum. This type of information would be invaluable for planning the next move to take.

Given the extensive evidence for the downstream effect of the SNr/GPi, it is surprising and remarkable that the SNr/GPi-thalamocortical loops have dominated the basal ganglia literature over an extended time and continue to do so, although little attention has been given to its possible role for cortical processing. Loops from different parts of the striatum channeled via GPi/SNr and thalamus back to different parts of the cerebral cortex have been discussed, focused on emotional processing, motor, and cognitive functions (5). The role(s) of these SNr/GPi-thalamocortical loops are not yet clear, but as indicated above, efference copy information of the commands issued to the brainstem level seem to be one important part. It is possible that skilled movements like hand and independent finger movements are controlled from the cortical motor areas and that the SNr/GPi-thalamocortical feedback to the cortex may play a role (see below). The GPi/SNr action is via disinhibition of the thalamus thought to increase the level of excitation in the different cortical target areas, including the motor cortex that can trigger the movements. How the cognitive and emotional processes are represented is not yet understood nor is the contribution of the different loops.

In humans, unilateral lesions of the thalamic relay nucleus were performed to alleviate some of the motor symptoms of PD (93). These lesions decrease the tremor and oscillations of hand-arm movements but leave the Parkinsonian gait and posture unchanged, which presumably depend on direct downstream effects on the midbrain-brainstem. It is remarkable that no cognitive or emotional symptoms are reported as a side effect of the lesions, given the impressive attention these loops have received over many decades. It would be of considerable interest to further explore the effects of such lesions in order to better understand the possible roles of SNr/GPi-thalamocortical loops. After the lesions, when the cerebral cortex is no longer in the loop, all actions of the basal ganglia have to be exerted directly by brainstem targets.

It would also be important to consider the significance of the loops provided by thalamostriatal projections, but little information is available. One can note that the PF nucleus that projects to both striatum and cortex receives a multitude of inputs, including from the GPi/SNr. Lesions of the PF nucleus leads to deficits in attention, behavioral switching, and reinforcement processes (234–236, 311, 363).

Dopamine Neurons in the Control of Behavior, Motor Learning, and Striosomes

Dopamine neurons important for the initiation of behavior but not action-specific

How does the dopamine signals from the SNc and VTA affect striatal processing and learning? Figure 9 illustrates that an enhanced dopamine signal facilitates the dSPNs in the direct pathway through an action on D1 receptors, while the indirect pathway is depressed by inhibition of iSPNs through D2 receptors. The converse happens during the no-reward situation when dopamine neurons become silent due to lack of activation of the D1 and D2 receptors. This leads to a depolarization of the indirect pathway iSPNs, which are further promoted by the higher excitability of iSPNs, and thus a net facilitation of the indirect pathway's opposing action.

By recording from dopamine neurons of the salience category in freely moving mice using microendoscopic calcium imaging, da Silva et al. (74) showed that just before initiating self-paced movements, the dopamine neurons generated a burst. Dopamine activity was not action specific, but the degree of activity was more related to the vigor of the subsequent movement. If dopamine neurons were optogenetically activated, the likelihood that a movement would be initiated increased, and conversely, if they were inhibited, it was less likely that a movement would be initiated. On the other hand, optogenetic manipulation of dopamine activity during ongoing movements had no effect on the movement.

This gives a special and important role to the salience dopamine population that most likely exerts its action by enhancing dSPNs broadly. Thus, clusters of dSPNs that simultaneously receive excitation from a subset of cells of the motor cortex or other structures can become activated, resulting in the initiation of a specific movement. Figure 11 illustrates such a case when a module in the cerebral cortex/thalamus provides some excitation to a cluster of striatal neurons but not sufficient for a prominent activation (no action in Figure 11). However, combined with a salience burst of dopamine neurons via D1 receptors it leads to action (red cells, action A). In the set to the right, another group of cortical cells targeting another cluster of striatal cells is illustrated, which leads to another action B, provided that

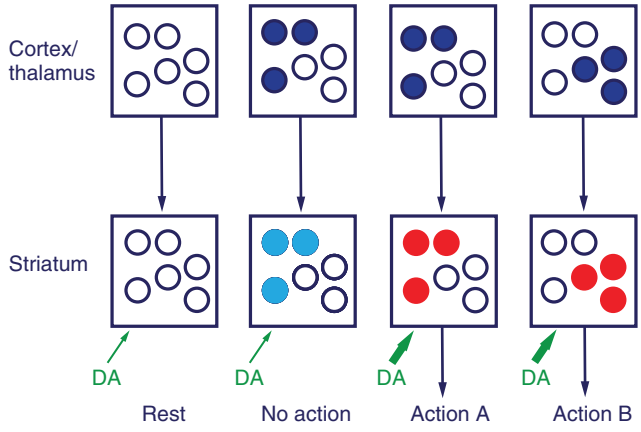


Figure 11 *Schematic representation of the effect of an increased salient dopamine (DA) burst on striatal cell populations controlling different motor acts.* When active, different cortical/thalamic cell populations (blue color) control the excitability of separate populations of striatal neurons, which are depolarized but not firing at the resting level of dopamine (2nd panel from the left). With enhanced DA activity, however, the striatal population becomes activated (3rd panel) and promotes motor action. The 4th panel shows the same condition for another population of striatal cells.

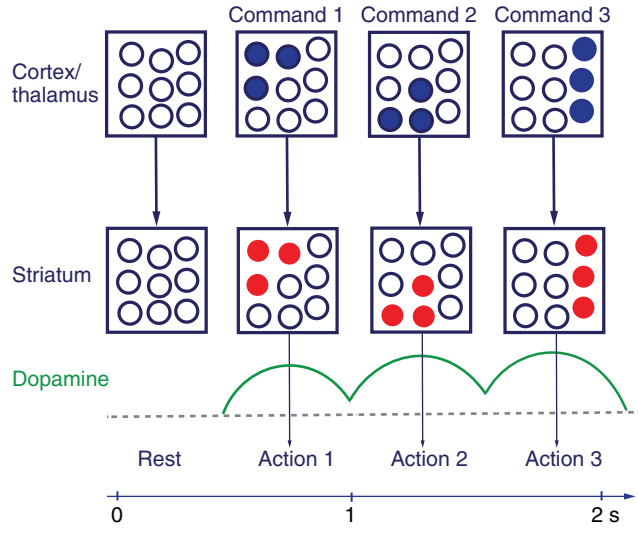


Figure 12 *A sequence of tightly coupled discrete movements combined into one integrated movement, termed chunking.* Illustration designed as in Figure 11, but with the addition of the salient dopamine burst that accompanies each discrete movement (see text).

there is also a concurrent dopamine facilitation of dSPNs. The co-activated iSPNs could act to reduce competing actions. An additional aspect is that the dopamine neurons in SNc also send collaterals to downstream motor centers in the SC and the mesencephalic locomotor center, which facilitates the initiation of behavior (271, 292, 295–297, 351).

Learning movement sequences—role of striatum and dopamine

So far, we have considered the control of single movements like a saccadic eye movement to a new target or the initiation of different motor programs, such as locomotion. In everyday life, we utilize a large number of learnt subroutines. For example, when unlocking the door of your apartment, you have to turn the key in the lock, push down the handle, and open the door—a sequence of movements that becomes automatized and turned into a habit. To learn to combine these individual movements into a well-programmed sequence of events is referred to as chunking and is also an important contribution of the basal ganglia (130, 174, 175). In rodents, habit formation is dependent on the DLS and in primates on putamen and the tail of the caudate nucleus. Patients with stroke affecting the basal ganglia have marked difficulties in learning to perform new sequences compared to healthy controls (41). Similarly, Parkinsonian patients have difficulty combining different movements into a well-coordinated sequence [(176); and see below].

It is reasonably straight forward to understand how a single motor program is selected, as discussed above. How can we combine, for instance, three distinct movements into one coordinated sequence? Each discrete movement can be elicited by a specific combination of cortical/thalamic/dopaminergic input to the striatum leading to a downstream release of a given movement. Thus, we consider three distinct inputs to the striatum leading to three distinct outputs. How can we combine them into one sequence or "chunk"? As we discussed above, the initiation of each movement is usually combined with a burst of dopamine activity (74) lasting over a second or more (Figure 12). If we elicit these three motor programs in a sequence, the dopamine activity will be combined with the concurrent inhibition of ChINs (decreased activation of M4 receptors), which would promote the development of LTP (251, 252) in the cortico-striatal synapses (dSPNs) active at this very moment. If the next movement occurs close in time when there is still residual dopamine activity related to the first movement, this would add to the dopamine activity linked to the second movement and subsequently to the third. If the different movements appear in rapid succession combined with the dopamine drive, it would thereby gradually link the three different commands into one combined sequence—chunking. This can be a potential mechanism to account for chunking and habit-formation that requires the interaction between the concurrent dopamine activity from the SNc and commands from the cerebral cortex/thalamus to SPNs. This mechanism would obviously be incapacitated after basal ganglia dysfunction, as in dopamine-deficient Parkinsonian patients or after a stroke affecting the basal ganglia (41, 176).

Striosomes, habenula, and the control of dopamine activity—evaluation of action—reinforcement learning

The matrix compartment of the striatum (80%) deals with the control of action and the dorsolateral part primarily with

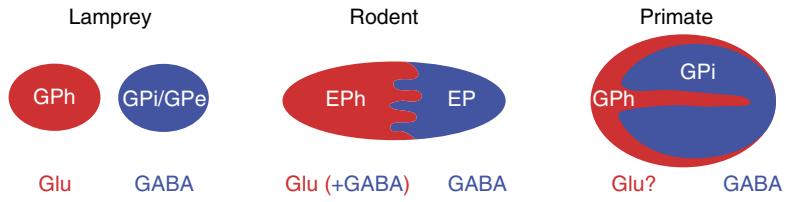


Figure 13 *Schematic representation of the excitatory globus pallidus projecting to the lateral habenulae (GPh; red), and the inhibitory compartment (GPi; blue) in lamprey, rodent, and primates.* GPh and GPi are represented in separate nuclei in lamprey but are merged into two compartments within one nucleus (entopeduncular nucleus) in rodents. In primates, the habenular projecting parts are located mostly at the periphery, also referred to as the border region of the GPi. Modified, with permission, from Stephenson-Jones M, et al., 2013 (318), Figure 7.

the control of motion. The striosomes, on the other hand, are engaged in the control of the activity of dopamine neurons in the SNc and VTA (Figure 13). They provide a value-based motivational signal (reward, aversive) or that of saliency and can serve to evaluate if an action has been successful or should be further modified or abandoned. The role of the striosome compartment appears to be to contribute to the evaluation of whether an action has been contextually appropriate for the behavior or if it should be suppressed [see above; (182–184, 261)].

The striosome compartment can be distinguished histochemically (43, 79, 133) and is distinct from the matrix section. The dendritic arbors of SPNs remain in their respective domain and an area just around the striosomes contains a large proportion of LTS interneurons and ChINs. Ontogenetically, striosomes are the first striatal compartment to develop (109, 132, 345, 348) and the cortical input to striosomes originates mainly in the limbic areas of cortex and the pregenual anterior cingulate cortex (7, 95), while the matrix area primarily receives input from neocortex. The thalamic input to striosomes originates from a restricted part of the intralaminar nucleus and does not include the PF nucleus (120).

In contrast to the matrix area, dSPNs in the striosomes target dopamine neurons in the SNc/VTA (120, 133, 353), whereas iSPNs target a subpopulation of spontaneously active glutamatergic cells adjacent to GPi, referred to as globus pallidus cells projecting to the habenulae (GPh), or border cells in primates (Figure 14), which as the name implies, project to the lateral habenulae (18, 47, 155, 163, 318, 320). This is an intricate organization conserved throughout vertebrate phylogeny. Recent data suggest that some SPNs in the matrix also target dopamine neurons (310).

In addition to striosomes, the GPh receives input from the cerebral cortex and thalamus and provides excitation to the lateral habenula (Figure 14), which in turn projects directly via a set of GABAergic interneurons to dopamine neurons. When the GPh increases in activity, the lateral habenula follows, and inhibits dopamine neurons. Conversely, if the spontaneously active GPh is inhibited, the drive to the lateral habenula decreases and dopamine neurons are disinhibited and their activity enhanced, as in a reward situation. In the mouse, it was shown by using expression of light-sensitive channel rhodopsins that a depression of GPh activity leads to a reward situation behaviorally, while an enhancement leads to a reduced motivation (320). This has also been demonstrated in primates (162). The GPh is present from lamprey to primates—in lamprey as a separate entity, in rodents as one part of the GPi (entopeduncular nucleus) and in primates, it surrounds the outer rim of the GPi with some neurons located in the center (Figure 14). In addition to the GPh, the lateral habenula receives input from the lateral hypothalamus (206) and limbic structures. If a motor action leads to an enhanced dopamine release, this may lead to a long-term facilitation of the specific cortico-striatal axons that triggered the action, reinforcing and strengthening this particular set of commands. This is the basis of reinforcement learning (see below).

Synaptic Plasticity in the Basal Ganglia

Learning and plasticity are key characteristics of all structures in the vertebrate brain, and motor learning, often referred to as reinforcement learning, is of particular importance for the function of the basal ganglia. Plasticity over different spatial and temporal scales is crucial for learning, short- and long-term memory, homeostasis, etc. (189, 214). It is what allows the different brain microcircuits to adapt over the lifetime and to recover from injuries or disease. As such, brain plasticity has far-reaching implications for understanding both the healthy and diseased basal ganglia. In line with this, impaired plasticity is implicated as a major determinant of symptoms in many brain disorders (208), including basal ganglia related disorders such as PD (275, 338), L-DOPA induced dyskinesia (40, 367), addiction (37, 350, 360), and Huntington's disease (279).

Synaptic LTP, long-term depression (LTD) and spike-time dependent potentiation (STDP), or other Hebbian-like plasticity, have been particularly studied in the corticostriatal synapses onto the two types of SPNs (85, 110, 150, 192, 193, 199, 216). This plasticity typically depends on receptor-induced $Ca^{2+}$and G-protein-dependent cascades controlled by the activity in the network, including the

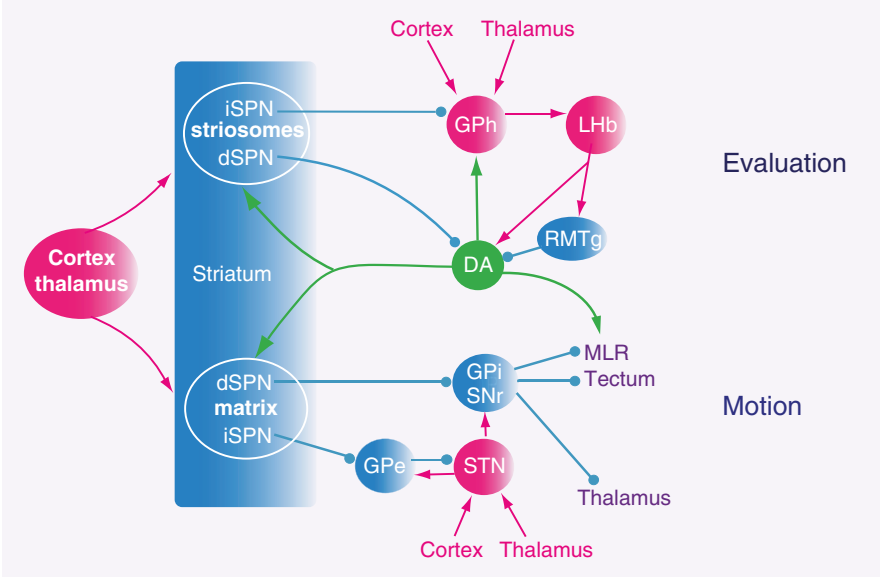


Figure 14 *Overview of the basal ganglia/habenular circuits underlying the control of motion and evaluation.* The lower motion circuit corresponds to the circuits detailed in Figure 3. The dSPNs in the matrix compartment target GPi and SNr, as well as brainstem motor centers and send a collateral back to the thalamus (the lower part of the diagram). Also indicated is the indirect pathway via the GPe and STN. The evaluation circuit, in the upper part of the diagram, shows the lateral habenula (LHb) that target the dopamine (DA) neurons both directly and indirectly via the GABAergic rostromedial tegmental nucleus (RMTg). The LHb receives input from the glutamatergic habenula-projecting globus pallidus (GPh). The GPh receives excitation from cortex and thalamus, whereas it receives inhibition from iSPNs in the striosome compartment. DA neurons are inhibited by striosomal dSPNs and send projections to the mesencephalic locomotor region (MLR) and optic tectum. The color code is blue for GABAergic, red for glutamatergic, and green for dopaminergic neurons.

neuromodulatory systems, such as dopamine and acetylcholine (ACh; Figure 15). Indeed, the striatum has one of the densest innervation by dopamine, ACh, and adenosine in the brain (314). The necessary factors involved in the induction of plasticity may vary slightly with the experimental paradigm used, most likely because calcium and the different neuromodulatory systems are recruited or balanced slightly differently (36, 111).

At the corticostriatal synapse, LTP induction needs elevation of NMDA-dependent Ca^{2+} influx (265, 302) and/or Ca^{2+} elevation due to permeable AMPA receptors (307), leading to an activation of CamKII. Ca^{2+} enhancement is, however, not sufficient for LTP to occur and requires, in addition, a parallel activation of cAMP-PKA signaling resulting from the activation of D1 receptors in the direct pathway and adenosine A2A receptor activation in the indirect pathway (253, 302). Adenosine is released during activity and originates from the dissociation of ATP (adenosine-triphosphate). Protein kinase A (PKA) will further downstream phosphorylate phosphoproteins, such as DARPP-32, in turn, inhibiting PP1 and thus delaying dephosphorylation of molecular targets, such as the phosphorylated CamKII (134, 361). Furthermore, ERK activation is crucial and protein kinase C (PKC) is also involved (150, 305). These (and other) plasticity-linked signaling molecules have several effects downstream, controlling both synaptic receptor density, spine structure, local membrane excitability, etc.

For LTD induction, other signaling pathways are involved such as Gq-dependent endocannabinoid production and activation of voltage-dependent Cav1.3 (265, 278, 306). Endocannabinoids are produced in the postsynaptic cell and induce presynaptic LTD via cannabinoid type 1 (CB1) receptors on the presynaptic terminal. For the postsynaptic induction of this type of signaling, Cav1.3 Ca^{2+} channels have been found to be crucial and postsynaptic intracellular Ca^{2+} release has been suggested to be an important component (278). Postsynaptic activation of calcium-dependent phosphatases, such as calcineurin, is likely important for promoting LTD. Interestingly, there might exist "competing" interactions between the signaling cascades leading to LTP and LTD. For instance, CaMKII inhibits the production of endocannabinoids (308) and PKA phosphorylates RGS4, which in turn decreases the Gq coupled signaling needed for LTD (210, 303). Likewise, LTD signaling cascades seem to counteract LTP initiation (302). The specific interactions are, however, not well understood, although calcineurin-dependent dephosphorylation of DARPP-32 might be one contributing factor and calcium-dependent activation of phosphodiesterases (PDEs) another (31).

Interestingly, subsecond dynamics in neuromodulatory signaling seems important in controlling not only movement

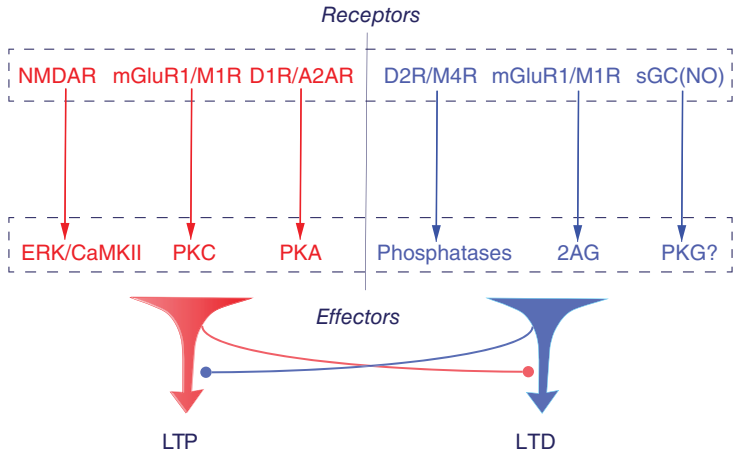


Figure 15 *Receptor-induced signaling activating downstream effectors important for long-term potentiation (LTP) or depression (LTD).* Activation of different receptors activates different protein kinases involved in LTP, whereas other sets of receptors have other downstream targets and evoke LTD. There is evidence that eliciting of LTP processes inhibit LTD, and *vice versa*. CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; PKA, protein kinase A; PKC, protein kinase C; PKG, protein kinase G; NO, nitric oxide; 2AG, 2-arachidonoylglycerol (an endocannabinoid); ERK, extracellular signal-regulated kinases; sGC, soluble guanylyl cyclase; mGluR, metabotropic glutamate receptor; A2AR, adenosine 2A receptor.

initiation (as described above) but also synaptic strength through the initiation of cAMP-PKA activation needed for LTP in both types of SPNs. Production of cAMP in the SPNs is largely dependent on adenylyl cyclase 5 (AC5), as this subtype is the dominant adenylyl cyclase in the striatum for cAMP production (359). It has been suggested that the Gi-protein inhibiting AC5 is partially activated during the resting state by tonically active ChINs that activate M4 receptors in the dSPNs (251) and in iSPNs by tonically active dopamine neurons that activate D2 receptors (364). Thus, the probability to induce LTP in the corticostriatal synapses is enhanced significantly by a transient reduction in the respective Gi-coupled branch (M4 and D2 receptors, respectively) together with a transient increase in the G_{olf} coupled branch [activating adenylyl cyclase; (49, 252, 253, 257)].

Not only is the interplay between different neuromodulatory systems in the striatum directly relevant for controlling and shaping plasticity, but because NMDA-dependent Ca^{2+} is facilitating LTP, it can be predicted that network activity leading to NMDA-dependent dendritic plateaus in the SPNs facilitate LTP in this system in a similar way to that in the hippocampus (42). This suggests an important role for a precise regulation of the localization of and activation of GABAergic inputs, especially distally located inputs, which when activated individually or in small numbers, can precisely terminate dendritic plateaus (92). In the future, the study of GABAergic synapses and plasticity will likely lead to new insights in their importance for effectively controlling the LTP/LTD balance in activated synapses.

Although most studies have focused on LTP and LTD in the corticostriatal synapses onto the two types of SPNs, experiments have shown that thalamostriatal synapses also undergo LTP and LTD (233), although here the LTD is dependent on NMDA receptors instead of endocannabinoid-signaling as thalamostriatal axons lack CB1 receptors (356). Furthermore, STDP/Hebbian activation protocols have been used to investigate the presence of LTP and LTD in interneurons (108, 259). Although plasticity at corticostriatal synapses onto the SPNs has been investigated more thoroughly than other synapses or other basal ganglia regions, it seems likely that most synapse types in the basal ganglia can undergo LTP. Plasticity in various synapse types in the striatum (108) or in other basal ganglia nuclei has been reported in different contexts (126).

In summary, multiple experimental approaches have indicated that plasticity can be induced in different synapses in the basal ganglia and causal links between LTP/LTD induction in the striatum and resulting behavioral effects are supported by data (273). Synaptic plasticity in the basal ganglia can be regarded as one crucial underlying mechanism for reward learning, goal-directed learning, and habit formation in the basal ganglia, as established experimentally (355).

Disorders of the Basal Ganglia

The basal ganglia play a very central role in many diseases that affect the control of movement. There are hypokinetic conditions like PD with difficulties to initiate movements, and conversely hyperkinetic disorders, where unintended often

well-coordinated movements occur. Hyperkinetic disorders include Huntington's disease, dystonia and hemiballismus (involuntary movements of the trunk), Tourette's syndrome with tics and vocalizations (coordinated repeated motor patterns), obsessive-compulsive disorders, and also side effects of L-DOPA therapy (57, 68, 71). Conditions like ADHD (attention deficit hyperactive disorders) affect the motor system but also attention and impulse control. Other disorders related to the ventral striatum, which include psychiatric symptoms.

In the basal ganglia, only the direct pathway promotes action (compromised by dopamine deficit in PD), whereas the indirect, hyperdirect, and cortical pathway to arkypallidal cells in GPe all stop movements, as does the glutamatergic PPN projection (see above). These pathways are in one way or another implied in hyperkinetic disorders. In the context of this article focused on the basal ganglia's control of motion, we will limit the discussion to Parkinson's and Huntington's disorders to illustrate two opposing effects of basal ganglia dysfunction. We will also include the unfortunate dyskinesias induced as a side-effect of L-DOPA therapy used for the treatment of PD.

Parkinson's disease—a hypokinetic disorder

PD (270) affects a significant portion of the aging population (1% over 60 years) and is a slowly progressive disease over one or two decades. The motor symptoms are well summarized by the classic illustration of Saint-Leger (Figure 16), a postural deficit with a bent trunk, semiflexed arms, involuntary finger movements, tremor often starting with fingers described as the "pill-rolling tremor" at 4 to 7 Hz (122) and a shuffling gait. In the later stages, mental faculties are also affected and hallucinations may occur.

The involvement of the substantia nigra in PD was reported as early as 1925 (44, 123). It was, however, only with the discovery that dopamine is a transmitter and that a blockade of dopamine action results in Parkinson-like symptoms in rats, relieved by L-DOPA, that the pathophysiology was understood (54–56, 164) and led to the L-DOPA therapy. The main motor symptoms of PD are explained by the progressive degeneration of dopamine neurons in the SNc that innervate the somatomotor part of the basal ganglia, putamen, involved in the control of motion (154, 286). These dopamine neurons are preferentially located in the lateral part of the SNc and they have an exceptionally extensive axonal arbor in the striatum, estimated to have 100,000 to 370,000 varicosities (release sites) each, which implies a very large metabolic demand on tonically active and phasically modulated SNc neurons (39, 86, 154, 246). In contrast, the SNc neurons in the medial part may have an order of magnitude fewer varicosities (154). To understand the actual reasons for the degeneration of the dopamine cells [α-synuclein misfolding, mitochondria dysfunction among others (323–325)] is of course essential for developing a therapy against the cause of the disease, rather than its many symptoms. To discuss this is, however, outside the scope of this article. The dopamine denervation also causes a reduction of the number of spines on the SPNs and degenerative effects on thalamostriatal neurons (57).

Figure 16 *The characteristic motor symptoms of Parkinson's disease.* Front and side views of a man portrayed with Parkinson's disease. These are woodcut reproductions. From Paul de Saint-Leger's 1879 doctoral thesis, *Paralysie agitante*. Fig. 145) published by Gowers (128), p. 591.

If we consider the discussion above regarding the effects of dopamine on the direct and indirect pathway, it is easy to appreciate the effect of a dopamine denervation on the basal ganglia circuitry [Figure 3; (81)]. The dSPNs will not receive support from dopamine activation of D1 receptors and will, therefore, have less excitability and be more difficult to activate from the cerebral cortex, thalamus, or other sources, and thus to initiate movements. The fact that the iSPNs receive less inhibitory effects through D2 receptors, will on the other hand make them become depolarized, further amplified by the inherently higher excitability of the iSPNs. The iSPNs will be simpler to activate from the cerebral cortex, the net result being an extra excitation of the SNr/GPi, making it more difficult for dSPNs to elicit a movement through disinhibition of downstream motor centers. As noted above, during the initiation of movement dSPNs and iSPNs can become activated in parallel but the time course will differ. Moreover, different clusters of SPNs of both types are associated with different movements. Recent recordings of large populations of dSPNs and iSPNs after dopamine depletion in rodents (269) show that dSPNs are less activated, whereas iSPNs have a higher level of activity and are more widely active. This extends and confirms the concepts of the role of dSPNs and iSPNs in PD. For the Parkinsonian brain, it will thus be more difficult to select and initiate a movement with precision.

Enhanced β-oscillations at a rate of 13 to 30 Hz occur during the normal initiation of movements and are markedly enhanced in PD (274, 313). In this context, the reciprocal interaction between STN neurons and prototypical neurons in the GPe has been considered important. Oscillations occur in this local GPe-STN circuit (Figure 7), particularly when devoid of dopamine, and become reduced by dopamine (20, 21, 220, 221). The β-oscillations in this circuit affect the downstream control of the activity in SNr and GPi. One of the benefits of DBS with tonic high-frequency stimulations is that the oscillations become blocked (see STN above). Another result of the dopamine denervation is that the sensory coding in the input to striatum from the two hemispheres is compromised (181), as well as the cortico-subthalamic connectivity (64).

The dopamine denervation affects mainly the somatomotor part of putamen, corresponding to the rodent DLS, a region involved in the control of the basic movement repertoire of trunk and limb movements. Early symptoms of PD involve a reduction in movement amplitude, a lack of coordination between the arms and legs during walking (286) and reduced amplitude of saccadic eye movements (337). The movements are in general slower, referred to as bradykinesia. The facial motor programs for expression of emotions are also affected and become more difficult to recruit. The patients may appear as if they do not react emotionally, but in reality, it is only the expression of emotions that are affected, a condition referred to as hypomimia or having a "masque face" (173).

The putamen also controls habit-forming circuits (286, 366), learnt movement sequences that can be recruited without conscious planning, like turning on the light as you enter a well-known room or pressing the clutch as you change gear in the car. As the putamen circuitry without dopamine supply becomes malfunctional, it is not surprising that Parkinsonian patients have difficulty recruiting habitual movements (286, 301). During hand-writing, the letters are reduced in size but the shape is maintained.

The more rostral part of the putamen, DMS in rodents, is concerned with goal-directed movements. These movements are slower to develop because they are adapted to new situations and are thought to be planned in some sense in more improvised or "conscious" way. As this part of the putamen is more spared from the dopamine denervation, it has been argued that the bradykinesia of Parkinsonian patients is due to the dysfunction of the somatomotor caudal putamen and the control of movement has then shifted to the more rostral less affected part of putamen. This is thought to account or contribute to the slowness of the movements, the bradykinesia.

With a well-functioning brain, it is easy to combine different movements to create a smooth, elegant, and purposeful sequence of movements. This is a very complex form of coordination, requiring perfect timing and control. For the Parkinsonian patient this is difficult, and he/she will tend to break the movement sequence into discrete separate movements. One quantitative test used in the clinic is to ask a patient to pick up an apple from the ground, a meter in front of them and take a few steps forward and put it onto a shelf. Healthy subjects will do this as a continuous sequence, but the PD patient will take one movement at a time—one step, then bend down, raise, again take a few steps and finally put the apple on the shelf (176). Essentially, patients are not able to solve the problem of coordinating the different components into one whole. This is an ability that they used to have but have lost, due to the dysfunction of the dopamine denervated putamen. In addition to the dopamine deficit, it has become clear that a number of other systems are also affected like for instance the cholinergic pedunculopontine nucleus (PPN) and locus coeruleus (41, 177).

To summarize, dopamine denervation in PD mainly affects the operation of the somatomotor part of the striatum but will broadly affect the entire basal ganglia including the STN. During the initial period of the disease, replacement therapy with L-DOPA can be quite effective, but as the degeneration proceeds, the situation deteriorates. In this phase, DBS of the STN can have remarkable effects (see above), which has benefited more than 100,000 patients world-wide. Recently, epidural stimulation of somatosensory pathways in the spinal cord has turned out to be beneficial in experimental primate and rodent models (115, 298), perhaps acting through an increased level of excitability in the striatum via thalamo-striatal and cortical pathways.

L-DOPA induced dyskinesia

Parkinsonian patients take L-DOPA as replacement therapy, which enhances dopamine levels in the striatum and reduces the symptoms. As dopamine degeneration proceeds, fluctuations in dopamine levels increase and after 4 to 5 years it is relatively common that dyskinesias develop, worsening as the disease progresses. The dyskinesias may involve facial and limb muscles and can be a very severe complication for the patients. The L-DOPA is transformed into dopamine not only in the few remaining dopamine terminals but also in the 5-HT terminals in the striatum that contribute importantly to dopamine release (57, 362).

The symptoms become worse as dopamine levels peak after L-DOPA administration, leading to an increased excitability in the dSPNs that controls what is sometimes referred to as the "Go-pathway" and inhibition of iSPNs conversely of the "NoGo-pathway". Synaptic plasticity induced in the cortico-striatal synapses, which is markedly facilitated when dopamine levels are high for an extended period, is also an important contributor. This will promote the induction of LTP. The set of cortico-striatal afferents that become facilitated by LTP induction depends on how strongly activated they are in a given situation. When LTP has been induced, the threshold for activating this particular group of dSPNs is lowered and thus the threshold for activating downstream groups of muscles. Each time the dSPNs become activated, there is a further lowering of the threshold. Finally, normally irrelevant stimuli can induce an involuntary muscle synergy, like facial tics. A number of additional factors actually contribute to the

development of dyskinesias, but it is beyond this article to detail this process and the reader is referred to Cenci (57). L-DOPA-dyskinesias represent a major problem for Parkinsonian patients, but they may also develop nonmotor symptoms that affect emotions, impulse control, and hallucinations, involving other circuits of the basal ganglia, like the ventral striatum.

Huntington's disease—a hyperkinetic disorder

Huntington's disease is a congenital and comparatively rare disease (incidence of 5 cases out of 100,000 in the US and Europe), a hyperkinetic progressive disorder due to a pathologically increased number of cytosine-adenine-guanine (CAG) repeats in the HTT-gene that codes for the protein huntingtin. The larger the number of repeats, the earlier the symptoms occur, usually in the late 30s or 40s. The disease is progressive and in the early phase, involuntary, sudden, often well-coordinated movements occur. They may include the limbs (chorea), fingers (athetos), or trunk (hemiballismus). They can involve several muscle groups often in unusual and somewhat bizarre combinations that can also include facial muscles. In the later phases of the disease, severe mental symptoms and dementia develop and akinesia may occur.

The disease is characterized by a progressive degeneration of the striatum, particularly the putamen, but also the cerebral cortex, and a certain reduction in striatal volume can be detected many years before clinical symptoms manifest (71). The initial degeneration in the striatum affects particularly the iSPNs that are at the origin of the indirect "NoGo" pathway, which results in a reduced ability to suppress movements (51, 117, 268). This can clearly contribute to the motor symptoms occurring in different parts of the body. As the degeneration continues, dSPNs also become affected, and akinetic symptoms may occur. Striatal interneurons are reported to be unaffected (51, 268). Huntington's disease, in particular, in the early phase, illustrates what happens if the neural systems that act to stop or suppress movements are damaged. It emphasizes the important challenge of the nervous system in balancing the precise initiation and termination of movement episodes.

Modeling of the Basal Ganglia

Modeling and simulation at different biological scales are very important, from subcellular level models related to plasticity and learning, over quantitatively detailed cellular level single cell- or network models to systems level models. These modeling approaches have been used to integrate and interpret the vast amount of experimental data and to generate hypotheses regarding potential mechanisms underlying phenomena observed at different levels of detail.

Subcellular level models have been useful for investigating how activation of receptor-induced signaling due to ongoing network activity and/or neuromodulation could lead to LTP or LTD. Most of the receptor-induced signaling cascades shown in Figure 15 have been investigated using simulations (36, 105, 146, 213, 250, 253, 254). For example, interesting predictions are that LTP in the corticostriatal synapse onto the dSPN are significantly facilitated if a transient increase in dopamine is paired with a pause in discharge of the ChIN, and likewise a pause in dopamine release facilitate LTP in the iSPN, which needs co-activation of adenosine A2A receptors (253, 364). In line with these predictions, molecular level simulations indeed indicate that a decrease of the inhibitory Gi-protein is needed for gating through the activation of the stimulatory G_{olf} signal (49, 347).

Models have also been used to better understand the timing requirement between the action and reward in behavioral reward learning paradigms, where the dopamine reward signal should come after the reward with a short delay. Experiments have shown that this type of timing-dependency is present at the level of dendrites and dendritic spines (307, 361). One model prediction is that while the phosphoprotein DARPP-32 is important for setting the maximal delay between reward and action, another phosphoprotein ARP21 may be a contributing factor as to why dopamine must come after the action (250).

In the above examples, transient and sufficiently large changes (up or down) in dopamine release have been found to be crucial for precise receptor-induced activations and downstream effects. Therefore, it is interesting that modeling of dopamine volume transmission in the striatum has predicted that loss of dopamine terminals (as seen in PD) affects significantly how burst activity or pauses in the dopamine neurons change the local dopamine concentration. Models at the same time predict that the basal level of dopamine-induced activity is quite robust to dopamine neuron cell death, as compensatory mechanisms exist, although the phasic regulation becomes blunted (91, 258). These types of models can help understand why synaptic plasticity is disturbed in PD for example.

Quantitatively, detailed single neurons or small network cellular level models have been built, mainly of the striatum, but also of other nuclei (75, 76, 92, 96, 97, 111, 160, 195, 212, 247, 248, 354). These models have used compartmentalized description to capture morphological features of the dendritic tree, represented membrane properties using Hodgkin–Huxley formalism and have been built in a bottom-up manner to different extents, aimed at integrating and interpreting corresponding experimental data at the cellular level and to generate predictions regarding phenomena difficult to measure today. For example, to better quantify the role of gap junctions between the striatal FS interneurons, something which is difficult to address experimentally, a network FS model neurons coupled by gap junctions was created (160), based on quantitatively-detailed models of single FS interneurons (195). It was shown that for moderate, nonsynchronized activation of individual FS neurons, the presence of gap junctions decreased spike frequency in the FS population (due to shunting) and only gave rise to a weak

spike synchronization. The presence of synchronized inputs from the cerebral cortex to neighboring FS neurons is required for gap junctions to both correlate FS spiking and counteract the decrease in spike frequency. Thus, a local FS network with gap junctions can function as a detector of transient increases in synchronous cortical inputs. When embedding such gap junction-coupled FS networks into a striatal network consisting of several 1000 SPNs, it turned out that the presence of gap junctions was important for controlling the balanced activity between the dSPNs and iSPNs (76). When a dopamine-depleted condition was simulated in the network, the presence of gap junction-coupled FS interneurons contributed significantly to conveying cortical β-oscillations into the striatal network, which are enhanced in PD (75). These observations suggest that the FS network gave rise to an entrainment effect of the SPNs when electrically coupled, in line with a study (247) showing that wide-spread FS interneuron inhibition has a stronger inhibitory effect onto SPNs than slightly synchronized FS interneuron populations. That FS interneurons convey frequency components within the striatal network is also supported by simplified spiking models (23).

Other cellular level modeling studies have focused on investigating dendritic plateau potentials in SPNs and showed that well-timed and localized inhibitory inputs can provide a precise control over the amplitude, kinetics, and duration of plateau potentials, thus directly also controlling the cell-wide synaptic integration in SPNs facilitated by plateaus (92). This sheds new light on the importance of distally located synapses, which can interrupt the plateau more effectively than proximal inhibitory synapses. As the dendritic plateau is paralleled by a significant increase in the local calcium (both NMDA- and voltage-dependent calcium), it has also been predicted, using an SPN model with enhanced calcium dynamics, that this fine control of the plateaus by GABAergic inputs can shape local calcium levels significantly and thus most likely affect plasticity (90).

Current advances in simulation- and model-building software, together with the rapid progress in generating quantitative data for constraining models of the striatal microcircuit, allow large-scale *in silico* reconstructions of the (mouse) striatum (161) considering the cellular properties and soma-dendritic morphology of large populations of iSPNs, dSPNs, ChINs, FS interneurons, and their synaptic interactions. Moreover, the simulations are based on the appropriate density of neurons (Figure 17). The basal ganglia (direct pathway) has been simulated with downstream

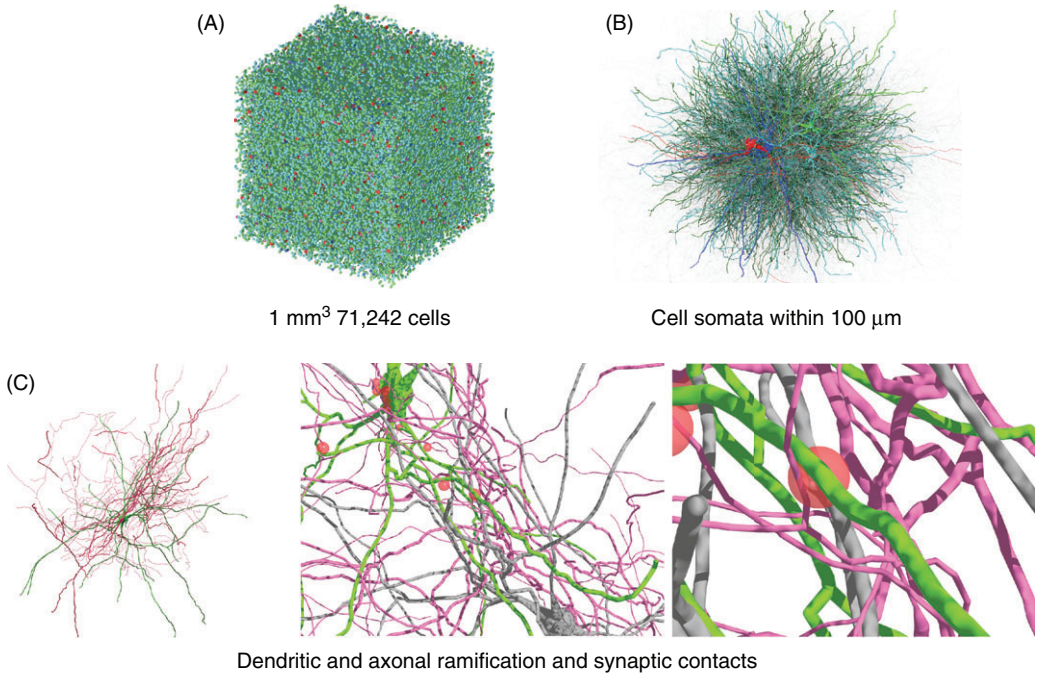


Figure 17 *Data-driven detailed simulation of striatum*. (A) Shows the somata of the number of cells (71,242) contained in 1 mm^3, distributed according to estimated densities. (B) Shows a limited number of cells with their somatodendritic arbor, based on detailed reconstruction of SPNs of both types, ChINs, and FS and LTS interneurons. The high density of dendritic and axonal branches within the tissue is evident. For each type of cell, the detailed membrane properties are simulated and validated versus their biological counterparts. (C) Simulated cells with dendrites are shown with different magnification from left to right. A touch detection algorithm is used to detect where axonal and dendritic structures come close (red circles as indicated). Depending on the pre- and postsynaptic cell types, adjusted pruning rules are applied and validated against established connectivity. In this way, the neuronal microstructure is reconstructed bottom-up in a data-driven manner. Also, optimization algorithms are used to fit electrophysiological properties to the different neuronal types. These data-driven workflows have also been used to predict cortical microcircuits (151, 226).

locomotor systems in the lamprey (196). Such large-scale models (Figure 17) are useful research tools as they can integrate and interpret a vast amount of data at a high level of granularity from the healthy or diseased brain and allow analyses of how different membrane properties, such as ion channels and plateau potentials, influence the integrated function of the simulated network.

At the systems level, several models built at different levels of detail have addressed hypotheses as to how function (e.g., action selection) can be explained based on interactions between the different basal ganglia nuclei (58, 114, 342). A sequence of models (143, 144, 167, 209) has investigated the hypothesis that the basal ganglia are performing action selection by selecting the most salient cortical command. In these models, action selection properties result from interactions between the different basal ganglia nuclei. A dSPN population is assumed to be co-activated with an iSPN population. These two populations are assumed to converge onto the same population in the output nuclei, while the interaction with the STN allows the selection threshold to adjust to ideally select one action only. In a recent model building upon this framework, both the prototypical and arkypallidal GPe neurons were represented (326) with the result that it could slightly increase the ability of the model to select an action. Also, phenomenological learning rules, extracted from experimental studies, have been implemented in this type of framework showing that the model can reproduce data describing both learning and unlearning (145). Other system level basal ganglia models have instead investigated action selection capability assuming that the co-activated iSPN population mainly influences populations in the output nuclei that belong to actions that should be prevented in a certain context (29, 30, 211), as suggested by Mink (239). The role of dSPNs and iSPNs when co-activated in different functional contexts remains unclear (188).

Several models have more specifically tried to pinpoint the control of action selection capabilities within the striatal network by exploring the role of local lateral inhibition. While the idea that lateral inhibition can underlie a winner-take-all strategy if the connectivity is strong enough, weaker connectivity more compatible with striatal experimental measurements can create transient cell ensembles of active SPNs (283).

Other system level basal ganglia models have instead identified possible mechanisms shaping network dynamics, including oscillations observed in diseased states, such as those following dopamine depletion (see Ref. 166 for an overview). While some types of oscillations may be generated or shaped as a result of changes involving the whole, or parts of, the cerebral cortex-basal ganglia-thalamic loop, the STN-GPe system has been investigated in several modeling studies. The STN-GPe system can generate oscillations under various modifications of the synaptic strengths and delays. Likewise, when changes in the balance between the activation/inhibition of GPe or STN are altered, for example when GPe activity is more inhibited due to an increased activity in the indirect pathway SPNs, the system also displays oscillations (201). Some of the models have also explored the link between functional aspects, such as action-selection capabilities and a change in dynamics/oscillations (167, 211, 326). The results predict that modifying model parameters leading to a disturbed dynamic typically also impairs action selection capabilities. However, the results also suggest that some of the factors underlying oscillations might be compensatory with regard to functions. This is, of course, also in line with that transient oscillatory activity seen in the healthy basal ganglia system. In the future, it will be important to bridge between model scales whereby the different suggested mechanisms using simplified system level models can be quantitatively mapped onto and tested in detailed cellular-level models of the various basal ganglia subnuclei.

The Basal Ganglia are Evolutionarily Conserved

A detailed comparison between the lamprey, representing the oldest group of now living vertebrates (Figure 18), and mammals (rodents and primates) have, contrary to what was anticipated, shown that the forebrain is evolutionary conserved in terms of detailed organization. This applies not only to the basal ganglia (Figure 19), the dopamine system, and the lateral and medial habenulae (142, 272, 316–319). Moreover, the dorsal pallium (cerebral cortex) has a motor area with downstream projections to midbrain and brainstem motor centers, a somatosensory area, and a visual area with retinotopic representation, as in the mammalian neocortex (262, 327, 328).

It was for a long time thought that the basal ganglia had evolved within the amniotes (267, 289, 309), an assumption that we now know is not correct. The main subnuclei of the basal ganglia have been demonstrated in different classes of vertebrates, although the knowledge is in some of the groups rather fragmented (101, 119, 124, 125, 218, 224, 244).

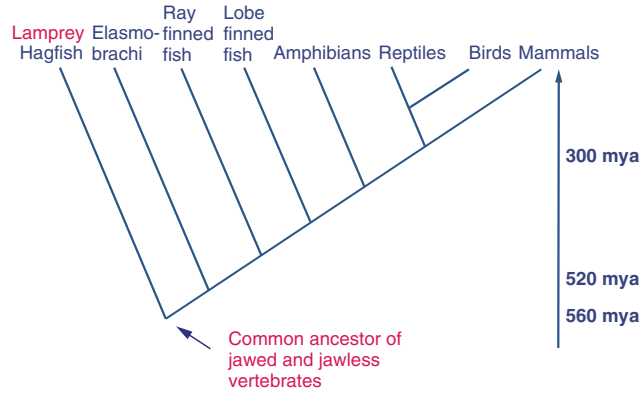
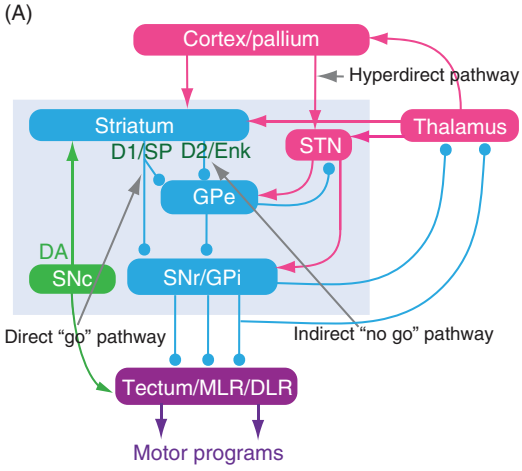


Figure 18 *Phylogenetic tree of vertebrates*. The lamprey diverged from the line to mammals around 560 million years ago (mya). Adapted, with permission, from Reiner A, et al., 1998 (290).



(B)

	Lamprey	Mammals
Input to striatum		
Cortical IT-type	+	+
Cortical PT-type	+	+
Thalamus	+	+
Dopamine	+	+
5-HT	+	+
Histamine	+	+
Striatal spiny projection neurons (SPN)		
D1R/SP	+	+
D2R/Enk	+	+
Spiny dendrites	+	+
Kir	+	+
GABA	+	+
DARPP32	+	+
Rest hyperpol.	+	+
Striatal interneurons		
Cholinergic	+	+
Fast spiking (FS)	+	+
Subtypes of INS	?	+

	Lamprey	Mammals
Output pathway SNr/GPi		
Spontaneous activity	+	+
Direct input D1R/SP SPN	+	+
GABA	+	+
Parvalbumin	+	+
Indirect loop		
GPe	+	+
Direct input from D2R/Enk SPN	+	+
GABA	+	+
Subthalamic nucleus	+	+
Glutamate	+	+
Spontanous activity	+	+
I_h	+	+

Figure 19 *From lamprey to primates—the organization of the basal ganglia is almost identical throughout vertebrate phylogeny.* (A) The striatum consists of GABAergic neurons (blue), as do the GPe, GPi, and SNr. The output level of the basal ganglia is represented by the GPi/SNr, and it projects via different subpopulations of neurons to the optic tectum (superior colliculus in mammals), the mesencephalic (MLR) and diencephalic (DLR) locomotor command regions and other brainstem motor centers, and send additional efference copies of the information back to thalamus. The indirect loop is represented by the GPe, the STN, and the output level (SNr/GPi)—the net effect is an enhancement of activity in these nuclei. The dSPNs of the direct pathway express the dopamine D1 receptor and substance P (SP), while the iSPNs express the dopamine D2 receptor and enkephalin (Enk). Excitatory glutamatergic neurons are represented by pink, GABAergic structures in blue and dopamine input from the SNc in green. (B) A table showing the key features of the basal ganglia organization that are found in mammals and lamprey. So far, subtypes of FS striatal interneurons have not been demonstrated in the lamprey.

Moreover, many aspects of the neural organization of the vertebrate basal ganglia and the corresponding structures in the arthropod (fruitfly) forebrain show some similarities (321).

Here, the focus will be on the organization of basal ganglia in the lamprey and a comparison with mammals. The lamprey striatum, the input structure of the basal ganglia, contains the two types of GABAergic SPNs, those that express the dopamine D1 receptor and substance P (SP), and those expressing the D2 receptor and encephalin (291, 319). The D1-expressing SPNs form part of the "direct pathway" that target the output nuclei, the GPi and SNr, whereas the D2 SPNs of the indirect pathway send information to the output nuclei via the GPe and STN (316–319). The lamprey striatum can, like the mammalian counterpart, be subdivided into striosomes and matriosomes by using calbindin as a marker of the matrix compartment (318). Furthermore, the striosomes also target the SNc in the lamprey and thus impact the level of dopamine released. The lamprey striatal SPNs receive a strong dopaminergic input from the SNc that excites D1 neurons and inhibits D2 neurons (102, 104, 291). As in mammals, the lamprey SPNs express inward rectifying potassium channels (Kir) that are open during resting conditions and hyperpolarize the cell. This is in sharp contrast to the spontaneously active GPi/SNr neurons. In the lamprey striatum, cholinergic (ChINs) and tyrosine hydroxylase-expressing interneurons (THINs) have been identified (281, 282), as well as a group of FS-interneurons (102). If any of the other subtypes of striatal interneurons exist in the lamprey is not yet clear. Also, the lamprey striatum receives input from the pallium/cerebral cortex and thalamus, with the palliostriatal synapses being of the facilitating type and the thalamostriatal synapses displaying activity-dependent depression (103). The pallial input to the striatum consists of both the pyramidal (PT-type) and the intratelencephalic (IT-type) tract neurons that send collaterals to the striatum [Figure 19; (328)]. The dorsal striatum in mammals, as discussed, is mainly concerned with control of motion and goal-directed behavior. The lamprey striatum most probably mainly represents the homologue of the mammalian dorsal striatum, and it is uncertain if the homologue of a ventral striatum exists in lamprey. It could well be that there is no segregation in lamprey but instead, neurons of the dorsal and ventral striatum are intermingled.

As mentioned, the output nuclei GPi/SNr in lamprey are spontaneously active, as in mammals, and keep their target nuclei, including the optic tectum, DLR, and MLR under tonic inhibition (319). Intermingled, separate pallidal subpopulations project to each motor area and can thus independently regulate their respective area. It has furthermore been demonstrated that the SNr sends an efference copy to the thalamus (316). A difference between mammals and birds with the lamprey is that GPi and GPe are intermingled in one nucleus in the lamprey. Another difference, the two mammalian cell populations of GPi neurons, the GABAergic and the glutamatergic neurons, are located in different nuclei in the lamprey. The glutamatergic cells that target the lateral habenula in a separate nucleus just dorsal to striatum, distinct from the GPi/GPe, that we have named the globus pallidus projecting to habenula [GPh; (318); see Figure 14]. As in mammals, the lateral habenula targets dopamine neurons in the SNc, either directly or via the GABAergic rostromedial tegmental nucleus (RMTg) that gives the lateral habenula

the potential to control dopamine neurons with facilitation or inhibition (Figure 13).

With respect to the intrinsic nuclei of the indirect pathway, the GPe and STN are present in lamprey and, as in mammals, the two nuclei are reciprocally connected (319). The STN is glutamatergic and their cells fire spontaneously. The STN also receives a direct projection from the pallium/cerebral cortex, representing the hyperdirect pathway (262).

The organization of the modulatory dopamine system (SNc/VTA) is well conserved from lamprey to mammals [Figure 20; (272, 292, 295, 296)]. This includes its projections to striatum, STN, GPi/SNr, and downstream motor centers, as well as the input to SNc from striatum, cortex/pallium, lateral habenula, and PPN. Recently, it was shown in the lamprey that the same dopaminergic SNc neurons that target the striatum also target the optic tectum [homologue of SC; (271)], and that glutamate and dopamine are co-released in the striatum, whereas only dopamine is released in the tectum (351). This is most probably also the situation in other vertebrates, including mammals, although it has not yet been demonstrated. With regard to dopamine projections to the MLR, they also have a complementary glutamate projection contributing to speed control (297). Like the dopamine effect on SPNs, dopamine excites tectal output neurons expressing D1 receptors and inhibits D2 neurons and are thus in a position to modulate visuomotor eye and orienting responses (271). It should be noted that if the lamprey is treated with MPTP, the animal will develop

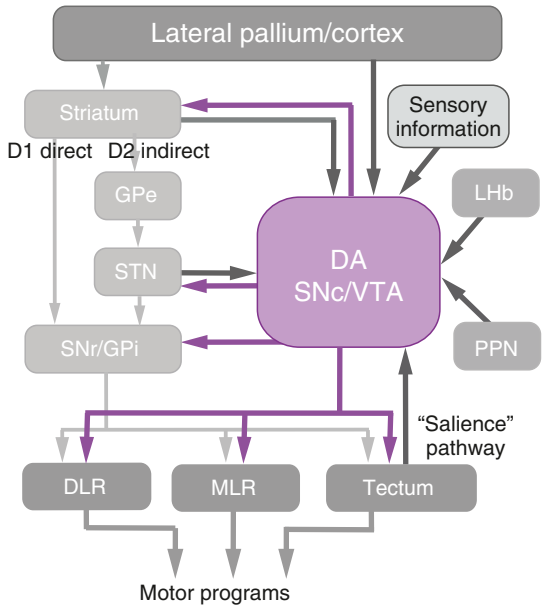


Figure 20 *The SNc connectome in lamprey and mammals.* The efferent and afferent connectivity of the SNc is virtually identical in lamprey and mammals. Thus, the dopaminergic neurons within SNc project to the same structures in the basal ganglia as in mammals and the same midbrain motor centers. The input to SNc is similarly identical from the striatum, STN, cortex/pallium, PPN, and the lateral habenulae. Reused, with permission, from Perez-Fernandez J, et al., 2014 (272).

Parkinsonian symptoms that can be rescued by apomorphine injection (339). Also, the striatal projections of the raphe 5-HT system and of the hypothalamic histamine systems are conserved [see above; (38, 45, 281)].

The fact that the detailed organization of the forebrain in lamprey and mammals is so similar implies that this organization had evolved already some 500 million years ago, when the lamprey line diverged from the evolutionary line leading to mammals (Figure 18). Of course, the number of neurons are orders of magnitude smaller in lamprey than in mammals. However, the basic organizational scheme had already evolved and has been maintained. It also implies that all vertebrates most likely have a similar organization, although adaptations to different behavioral needs may have taken place. The lamprey nervous system could be compared to a Ford Model T and that of primates to a Ferrari—the same basic functions but with much less sophistication.

Conclusion

The striatum is a main player in the control of action, however, what it, or rather the many different modules of the striatum, does is entirely dependent on the specific input they get from the cerebral cortex, thalamus, the dopamine system and the other input systems discussed above, as summarized in Figure 21. Essentially, there is the direct pathway (dSPN) that promotes action via the basal ganglia output nuclei and downstream motor centers, complemented by a direct action from the cerebral cortex. It is equally important to precisely stop a movement, as to initiate it. It is, therefore, not surprising that there are several systems designed to stop movements via different neural mechanisms, the indirect pathway via iSPNs and GPe, the arkypallidal stop cells in GPe, and the hyperdirect pathway via the STN. Together, all the components summarized in Figure 21 enable the impressive motor repertoire of a ballet dancer, an artisan, or a musician.

As should be clear from the previous pages, the basal ganglia have been at the center of interest for the neuroscience community over several years. New techniques (e.g., optogenetics, cellular imaging with endomicroscopes, RNAseq, and virus tracing) have resulted in important new insights regarding action selection. For instance, the contribution of the different types of SPNs in different forms of behavior, synaptic plasticity and motor learning have been unraveled, and it has been shown that salient stimuli activate dopamine neurons at the initiation of each movement in freely moving animals, and that new subtypes of neurons in GPe provide feedback in a remarkable way to the striatum and also that the cerebral cortex talks directly to the GPe arkypallidal neurons. We now have at least three pathways that counteract movement, the indirect, the hyperdirect, and the GPe pathway mentioned above, but only one, the direct pathway that promotes movements. From an evolutionary point of view, the surprise has been that the connectivity, cell types, transmitters, general organization, and the output level have

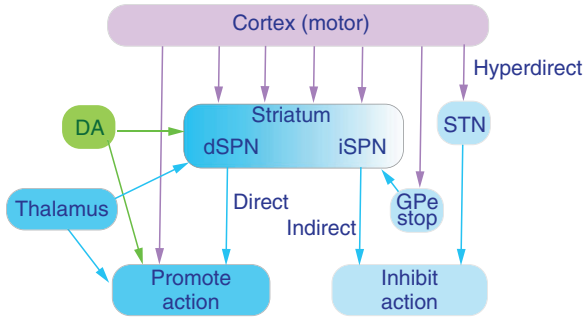


Figure 21 *Scheme summarizing the main building-blocks promoting and inhibiting action in the forebrain*. Cortical circuits can directly and via the direct pathway promote action, as can thalamic circuits and the dopamine system. The cerebral cortex can also inhibit action via the STN, the hyperdirect pathway, and via the striatum and the indirect pathway and finally via GPe inhibition of striatum. For simplicity the output nuclei of the basal ganglia are not included—only the net effect of the direct and indirect pathway.

all been conserved from early on in vertebrate evolution over some 500 million years—a very unexpected finding.

On the other hand, there are still a number of questions to resolve. We need to learn more about the detailed input from specific cortical modules in the context of different patterns of behavior, how PT- and IT-type neurons contribute to the operation of the basal ganglia and how they target modules within the striatum. Similarly, much information is needed regarding the thalamic input that represents some 40% to 45% of the glutamatergic input. Most likely, it will provide important new insights and convey important new information from brainstem centers and the output nuclei of the cerebellum with possibly detailed information about different aspects of behavior. In this article, we focused on the control of motion and the role of the dorsal striatum, an exciting new world will most likely open up when we also deepen our understanding of the ventral striatum.

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