Chapter 3
Anatomy and Function of the Direct and Indirect Striatal Pathways

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3.1 Introduction

Several subtypes of striatal neurons were described during the 1970s and 1980s using the Golgi labeling method or electron microscopy (e.g., Kemp and Powell 1971; Fox et al. 1971; Danner and Pfister 1979; Dimova et al. 1980; Preston et al. 1980; Wilson and Groves 1980; Bishop et al. 1982; Bolam et al. 1981b; Chang and Kitai 1982; Chang et al. 1982; Tanaka 1980; DiFiglia et al. 1976; Graveland and DiFiglia 1985; Graveland et al. 1985). In a series of detailed studies carried out in the monkey, DiFiglia and co-workers identified up to six types of neurons in the striatum: type I and type II spiny neurons, type I, type II, and type III aspiny neurons, and a very small cell apparently devoid of an axon that could be a glial cell (DiFiglia et al. 1976, 1979). Type I spiny neurons were relatively small in size (20–14 μm) and exhibited four to seven dendrites forming a spherical field around the cell body. The dendrites were described as smooth near the cell body, but they became heavily covered with dendritic spines more distally. The type I neuron has been also identified as the medium-sized spiny neuron (MSN or MSPN) or medium spiny I neuron in the cat and rodent (Kemp and Powell 1971; Dimova et al. 1980; Chang et al. 1982; Bishop et al. 1982). Type I neurons were considered to account for as much as 95–96 % of all striatal neurons (Kemp and Powell 1971). The monkey type II spiny neuron has a spindle-shaped cell body, thicker dendrites, less spines, and a more extensive dendritic field than type I and represents less than 1 % of all striatal neurons. This neuronal type has also been described in cats and rodents (Kemp and Powell 1971; Dimova et al. 1980; Chang et al. 1982; Bishop et al. 1982). The function of the type II spiny neuron is still not clear, but one study found a similar neuron containing neuropeptide Y (Kubota et al. 1991). Aspiny striatal neurons

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are considered to be local interneurons (Kawaguchi et al. 1997). This chapter will focus on the phenotype and function of projection medium spiny neurons (MSN) that constitute the majority of striatal neurons.

3.2 Phenotypic Diversity of Medium Spiny Striatal Neurons

Earlier immunohistochemical studies have established that MSN contain the GABA-synthetizing enzyme glutamic acid decarboxylase (Gad) and are releasing GABA as their primary neurotransmitter (Ribak et al. 1979; Vincent et al. 1982; Nagai et al. 1983; Ottersen and Storm-Mathisen 1984; Bolam et al. 1985; Smith et al. 1987). The presence of the mRNA encoding for Gad in most striatal neurons was confirmed later on using in situ hybridization histochemistry (Chesselet et al. 1987). Although all MSN are defined as GABAergic, they can be subdivided based on their connectivity and phenotype. This chapter will review the evidence supporting the notion that striatal MSN can be subdivided into two large populations based on connectivity, morphology, chemical phenotype, and physiology. These two subtypes contribute to the so-called direct and indirect pathway of the basal ganglia and their properties play a central role in current models of basal ganglia organization (Albin et al. 1989; Crossman 1987; DeLong 1983, 1990). The chapter will also review the experimental evidence that these two pathways play distinct roles in the control of motor and cognitive functions.

3.2.1 Co-expression of Peptides

Immunohistochemical studies carried out in the 1980s and 1990s have thoroughly documented that MSN co-express GABA with one or more than one of the three peptides met-enkephalin, substance P, and dynorphin. Immunohistochemical studies combined with tract-tracing methods found that substance P and dynorphin are co-expressed in specific populations of striatal projection neurons, whereas enkephalin is present in other populations of striatal projection neurons (Anderson and Reiner 1990). Such an organization was documented in different species including pigeons, turtles, and rats (Anderson and Reiner 1990). Co-expression of substance P and dynorphin immunoreactivities was found in both the striosome and matrix striatal compartments (Besson et al. 1990). However, the percentage of substance P- and dynorphin co-localization was slightly higher in striosomes than in the matrix. Conversely, about two-thirds of all neurons were identified as enkephalin-positive in both matrix and striosomes (Besson et al. 1990). In another study comparing cats and rats, Penny and colleagues found that neurons immunoreactive for dynorphin made up about half of the neurons in rat striatum and a little less than half in the cat. Labeling for enkephalin was found in a little less than half of the neurons in the rat and about half of the neurons in the cat (Penny et al. 1986). Substance

P-immunoreactive neurons made up to 38 % of MSN in the rat and 39 % in the cat (Penny et al. 1986). An analysis using in situ hybridization histochemistry reported that the dynorphin mRNA was distributed in about half of patch and half of matrix neurons, while the enkephalin and the substance P mRNA were expressed in a little more than half of patch and about half of matrix neurons (Gerfen and Young 1988). Altogether, these immunohistochemical and in situ hybridization findings indicate that MSN can be subdivided into two major and numerically comparable populations, one that co-expresses substance P and dynorphin and one that co-expresses enkephalin. As discussed in the following paragraphs, there is evidence that a subpopulation of MSN co-expresses the three peptides, but the prevalence of these MSN remains controversial.

An earlier immunohistochemical study by Besson and colleagues (Besson et al. 1990) found that a majority of MSN expressing substance P/dynorphin also expressed enkephalin. In a more recent combined immunohistochemical and retrograde transport study in the monkey, about half of striatal neurons were found to co-express dynorphin and enkephalin (Nadjar et al. 2006). In a combined patch-clamp and PCR study, it was confirmed that some MSN co-express detectable levels of substance P and enkephalin mRNAs, but the frequency of these neurons could not be assessed (Surmeier et al. 1996). On the other hand, a more recent RT-PCR study by Wang and colleagues found that in 4-week-old rats, 11 % of MSN contained both substance P and enkephalin, while in 4-month-old rats, co-localization was only 3 % (Wang et al. 2006). In another study, the same group found that 32.3 % of MSN that contain both substance P and enkephalin are localized in the striosomal compartment (Wang et al. 2007). An immunohistochemical study in the rat nucleus accumbens found than less than 30 % of neurons co-express enkephalin and substance P, whereas more than 69 % co-express substance P and dynorphin (Furuta et al. 2002). Altogether, these findings support the likelihood that some MSN neurons co-express the three peptides, but the extent of co-localization varies between studies. Such differences could be partly explained by methodological (i.e., immunohistochemical versus gene expression studies) or species differences. As discussed above, it is also possible that the reported variability is due to developmental factors and/or differences between striatal compartments (Wang et al. 2006, 2007; Furuta et al. 2002).

3.2.2 Medium Spiny Neurons Connectivity

Early tract-tracing studies determined that the striatum contains projection neurons sending axons to the ipsilateral GP and/or to the SNr (Szabo 1967; 1970). Later on, it was reported that most striatal neurons are projection neurons (Bolam et al. 1981a, b; Graybiel and Ragsdale 1979) and combined Golgi and retrograde labeling methods identified them as MSN (Somogyi and Smith 1979). Retrograde axonal transport studies in primates further indicated that striatal projection neurons could be subdivided on the basis of their projections to the Gpe or to the Gpi and SNr (Parent

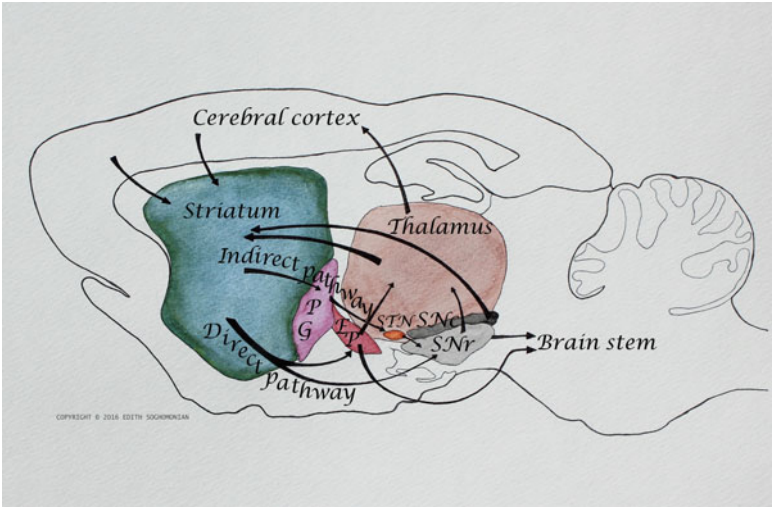

Fig. 3.1 Illustrates the major connections between basal ganglia structures and the organization of the direct and indirect pathway in a sagittal view of the rat brain. As discussed in this chapter, the subdivision into a direct and indirect pathway is a simplification since indirect pathway MSN can send axon collaterals to the SNr/EP, while direct pathway MSN can send axon collaterals to the GP. *GP* globus pallidus, *EP* entopeduncular nucleus, *STN* subthalamic nucleus, *SNc* substantia nigra pars compacta, *SNr* substantia nigra, pars reticulata

et al. 1984a, b) and at least three types of neurons were distinguished based on the fact that they projected either to the Gpe alone, to the SNr alone, or to both structures (Feger and Crossman 1984). Single cell-tracing methods provided further insights into the connectivity of striatal neurons and confirmed that MSN projected to more than one structure (Chan et al. 1981; Wilson and Phelan 1982; Parent et al. 1995a, b; Wu et al. 2000). In the primate, at least three types of striatal neurons were identified based on their target region (Parent et al. 1984a,1995a, b). One type projected to the GPe alone, a second type projected to the GPe and GPi, and a third type projected to the GPi, GPe, and SNr (Parent et al. 1995a, b). In the rat striatum, neurons were similarly subdivided into three types. Type I neurons projected to the GP only, type IIa neurons projected primarily to the SNr and EP, but also sent a small projection to the GP and type IIb neurons projected to the GP and SNr but not to the EP (Kawaguchi et al. 1990). The proportion of striatal neurons projecting to these different structures was not documented in this later study. A retrograde labeling study found that about one third of MSN that project to the GP have axon collaterals to the SNr (Castle et al. 2005).

In summary, tract-tracing combined with single-cell labeling studies have revealed that some MSN preferentially project to the GP (primate Gpe), while others preferentially project to the EP (or the primate Gpi) and to the SNr. In the literature, MSN that project to the GP (or primate GPe) are known as striatopallidal or indirect pathway neurons, while MSN that project to the SNr and/or EP (primate Gpi) are known as striatonigral or direct pathway neurons (Fig. 3.1). However, it is

apparent that this subdivision is a simplification and that some MSN do not fit this strict classification. Using viral gene transfer strategies in transgenic mice, it has been shown that the density of axon collaterals in the GP made by MSN that primarily project to the SNr (direct pathway) increases when the excitability of striatopallidal neurons is increased (Cazorla et al. 2014 and 2015). This indicates that the specificity of axonal projections from MSN can be modulated and further calls into questions the notion that striatal projections can be rigidly subdivided into a direct and indirect pathway.

As discussed in previous paragraphs, MSN can express various combinations of peptides (Besson et al. 1990; Surmeier et al. 1996; Reiner et al. 1999; Nadjar et al. 2006; Wang et al. 2006, 2007). In the rat, it was reported that striatal neurons labeled after an injection of retrograde tracer in the SNr were labeled with dynorphin and substance P, but only 1 % co-expressed enkephalin immunoreactivity (Lee et al. 1997). In contrast, neurons labeled after an injection into the GP were labeled with enkephalin, but only 17 % and 10 % were, respectively, labeled for dynorphin and substance P (Lee et al. 1997). An in situ hybridization study in the rat has shown that the majority of neurons expressing enkephalin project to the GP while a few project to the SNr, whereas neurons expressing dynorphin and substance P project mainly to the SNr but a few also project to the GP (Gerfen and Young 1988). In the monkey, 70 % and 50 % for neurons labeled after an injection of retrograde tracer, respectively, into the GPe or into the GPi co-expressed the three peptides (Nadjar et al. 2006). It is unclear if the discrepancy in co-expression between rodent and primate studies is due to species and/or methodological differences. In any case, current evidence suggests that MSN that co-express the three peptides may be those that do not fit the strict definition of direct and indirect pathway neuron.

3.2.3 Segregated Expression of Dopamine Receptors

Early neurochemical studies have shown that the dopamine D1 and D2 receptors are the two major subtypes of dopamine receptors expressed in the striatum and that they exert opposite effects on the activation of adenylyl cyclase, with D1 receptors being stimulatory and D2 receptors inhibitory (Kebabian and Calne 1979; Stoof and Kabadian 1981, 1984). Molecular cloning studies have determined that the family of dopamine D1 receptors includes the Drd1a and Drd5 receptors and that the family of dopamine D2 receptors includes the Drd2, Drd3, and Drd4 receptors (review in Beaulieu and Gainetdinov 2011). Although all dopamine receptors are expressed in the striatum (Surmeier et al. 1996), the Drd1a and the Drd2 receptors are the most abundant. The following paragraphs discuss the notion that the expression of the Drd1a and Drd2 receptors also contributes to define two different populations of MSN. This is an important notion since most studies carried out in genetically engineered mice or using viral delivery methods are based on it.

In a combined immunohistochemical and electron microscope study in the rat striatum, no co-localization of the D1 and D2 receptor was seen (Hersch et al.

1995). On the other hand, a study found that all striatal neurons co-expressed the D1 and D2 receptor (Aizman et al. 2000). However, between these two extreme outcomes, most other studies support the idea that only a subset of MSN co-expresses the D1 and D2 receptor (e.g. Meador-Woodruff et al. 1991; Weiner et al. 1991; Lester et al. 1993; Larson and Ariano 1994; Deng et al. 2006). The possibility that only some MSN co-express the Drd1a and Drd2 receptors was confirmed using PCR combined with path-clamp (Surmeier et al. 1996). The development of the Bacterial Artificial Chromosome (BAC) technology and genetically engineered mice has confirmed, at least in rodents, the limited co-expression of dopamine D1 and D2 receptors (e.g. Valjent et al. 2009). In mice expressing the marker tdTomato under the control of the Drd1a promotor and green fluorescent protein under the control of the Drd2 promotor, at embryonic day 18 only about 10 % of MSN were double-labeled. This proportion decreased at post-natal day 1 and 14 (Thibault et al. 2013). Similar evidence for limited co-expression was found in the neonatal mouse (Biezonski et al. 2015).

There is evidence that the segregation or co-expression of dopamine Drd1a and Drd2 receptors may correlate with the pattern of expression of specific peptides. Using a combination of patch-clamp and single-cell qPCR analysis, it was found that MSN having detectable levels of enkephalin, but not substance P mRNA, expressed high levels of the Drd2 receptor mRNA, while MSN with detectable levels of substance P but not enkephalin mRNA expressed high levels of the Drd1a receptor mRNA (Surmeier et al. 1996). The mRNAs for other dopamine receptor subtypes were rarely detected in MSN expressing enkephalin, but some co-expressed the D1b receptor (Surmeier et al. 1996). Conversely, the Drd3 receptor mRNA was detected in one-half of MSN expressing substance P, but other dopamine receptors were rarely detected (Surmeier et al. 1996). Finally, most MSN that co-expressed detectable levels of substance P and enkephalin mRNAs also co-expressed the Drd1a and Drd2 mRNAs (Surmeier et al. 1996).

Current evidence supports the notion that the segregation of MSN based on the expression of specific dopamine receptors and/or peptides correlates with a pattern of projection. This possibility is supported by several immunohistochemical and gene expression studies that have shown that Drd1a receptors are expressed in MSNs that primarily project to the SNr and/or the EP (or primate Gpi), while Drd2 receptors are expressed in MSNs that primarily project to the GP (or primate Gpe) (Aubert et al. 2000; Beckstead et al. 1988; Gerfen et al. 1990; Harrison et al. 1990; Le Moine et al. 1991; Harrison et al. 1992; Herve et al. 1993; Le Moine and Bloch 1995; Yung et al. 1995). Several studies in genetically engineered mice have confirmed that fluorescence induced by the activity of the Drdr1a receptor promotor in the striatum is high in the SNr, while fluorescence induced by the activity of the Drd2 receptor in the striatum is high in the GP (Gong et al. 2003; Lobo et al. 2006; Gertler et al. 2008; Bertran-Gonzalez et al. 2008; Shuen et al. 2008; Matamales et al. 2009). However, a combined confocal and retrograde labeling study in the rat found that although a large majority of neurons projecting to the SNr and EP also expressed the D1 receptor, 23 % of neurons projecting to the GP also expressed the D1 receptor (Deng et al. 2006). Conversely, although the vast majority of MSN projecting to the GP were labeled for the D2 receptor, 40 % of MSN projecting to

the SNr and EP were also labeled for the D2 receptor (Deng et al. 2006). Another study confirmed that although MSN neurons projecting to the SNr mainly express the Drd1a receptor, some also expressed the Drd2 receptor (Matamales et al. 2009). In another study, however, MSN labeled with a retrograde marker injected in the SNr did not express the D2 receptor (Gertler et al. 2008). A combined retrograde and immunohistochemical study in the monkey from Nadjar and colleagues has shown that MSN projecting to the Gpi or to the Gpe are immunolabeled for both dynorphin and enkephalin and for both the D1 or D2 receptor (Nadjar et al. 2006).

In conclusion, most experimental studies support the notion that MSN can be subdivided based on their expression of the Drd1a and Drd2 receptors, of the peptides enkephalin, substance P, and dynorphin, and on their area of projection. One consensus that emerges is that most MSN that project to the SNr and the GPi (or rodent EP) also express substance P and dynorphin and the Drd1a receptor, while most MSN that project to the GPe (or rodent GP) also express enkephalin and the Drd2 receptor. Gene expression studies support this dichotomy since drugs acting on D1 receptors or on D2 receptors differentially modulate gene expression of peptides preferentially expressed by direct or indirect pathway neurons (e.g. Bertran-Gonzalez et al. 2008; Gerfen et al. 1990; Cenci et al. 1992; Cole et al. 1992; Dragunow et al. 1990; Laprade and Soghomonian 1995; Robertson et al. 1992). However, based on the data discussed above, it is also clear that some MSN can co-express both the Drd1 and Drd2 receptors and can co-express the peptides enkephalin and substance P/dynorphin. The possibility that those MSN that co-express all markers are those that project to the SNr, EP (or Gpi), and GP (or Gpe) is supported by some studies. Interestingly, it has been recently shown that the activation of Drd2-expressing MSN in genetically modified mice increases the density of axon collaterals from direct pathway neurons to the GP (Cazorla et al. 2014). These striatonigral axon collaterals are functional and able to inhibit the firing rate of GP neurons (Cazorla et al. 2014). In contrast, the density of axon collaterals from striatonigral neurons to the GP did not change when the excitability of Drd1-expressing striatonigral neurons was modulated (Cazorla et al. 2014). This pioneering study indicates that the connectivity of MSN is not static, but can be modulated in different physiological conditions and it further emphasizes the notion that the subdivision of MSN into a direct and indirect pathway is a simplification. The possibility that MSN that do not fit the strict classification of direct and indirect pathway neuron play a distinct role in the physiology of the basal ganglia remains to be determined. With this caveat in mind, the following paragraphs will present and discuss evidence that the so-called direct and indirect MSN have different physiological properties and functional roles.

3.2.4 Membrane Properties of Direct and Indirect Pathway Neurons

The heterogeneous connectivity and chemical phenotype of striatal projection neurons are paralleled by heterogeneous electrophysiological and morphological properties. The organization of MSN into Drd1a and Drd2-expressing subsets may be

determined in part by cortical inputs because striatal neurons expressing the Drd1 receptor receive a majority of inputs from cortical neurons whose projections are restricted to the telencephalon, whereas striatal neurons expressing the Drd2 receptor receive more input from cortical neurons that contribute to the pyramidal tract (Lei et al. 2004). Using RT-PCR and confocal microscopy in slice preparations from mutant mice expressing eGFP under the activity of the dopamine Drd1 or Drd2 receptor, it was reported that Drd1-expressing striatal neurons are less excitable than Drd2-expressing neurons (Gertler et al. 2008). In addition, Drd1-expressing neurons have more primary dendrites than Drd2-expressing neurons (Gertler et al. 2008). Such a difference in excitability was also documented in another study showing that the threshold for firing action potentials is lower in Drd2-expressing than in Drd1-expressing MSN (Cepeda et al. 2008). Whole-cell and outside-out patch recordings in slices from bacterial artificial chromosome (BAC) transgenic mice were used to examine the role of $GABA_A$ receptor-mediated currents in dopamine receptor Drd1- and Drd2-expressing neurons (Ade et al. 2008). Although inhibitory synaptic currents were similar between the two neuronal populations, D2-expressing neurons had greater $GABA_A$ receptor-mediated tonic currents. Low GABA concentrations produced larger whole-cell responses and longer GABA channel openings in Drd2- than in Drd1-expressing neurons (Ade et al. 2008). It has been reported that the loss of dopamine innervation to the striatum differentially affects the excitability of Drd1- and Drd2-expressing neurons (Fieblinger et al. 2014). In parkinsonian mice, intrinsic excitability of Drd2-expressing neurons was depressed. High-dose L-DOPA treatment normalized intrinsic excitability. In contrast, the intrinsic excitability of Drd1-expressing neurons was significantly elevated and high-dose L-DOPA partially normalized this effect (Fieblinger et al. 2014). Altogether, these studies reinforce the notion that the different connectivity and chemical phenotype of Drd1 and Drd2-expressing striatal neurons is paralleled by different functional properties. The factors contributing to these differences remain unclear, but could involve cortical inputs because an electron microscopy study has shown that cortical synapses are smaller on Drd1- than on Drd2-expressing neurons (Lei et al. 2004).

3.3 Functions of the Direct and Indirect Pathway

3.3.1 Movement Control

The classical functional models of the basal ganglia are based on the notion that activation of the striatal direct pathway facilitates movement, while activation of the indirect pathway inhibits movement (Alexander et al. 1986; Alexander and Crutcher 1990; DeLong 1990). These models are supported by anatomical and physiological data and propose that paucity or loss of movement in Parkinson's disease results from an increased activation of indirect pathway neurons and a decreased activation of direct pathway neurons (Albin et al. 1989). This dual effect would result in an

increased basal ganglia output and an increased inhibition of thalamo-cortical projections to the frontal and prefrontal cortex ultimately leading to a lesser activation of cortical motor and premotor regions. Gene expression studies are consistent with an opposite role of the direct and indirect pathway on movement because in experimental models of Parkinson's disease, enkephalin gene expression in the indirect pathway is increased and preprodynorphin and preprotachykinin expression is decreased in the direct pathway (Reviewed in Soghomonian and Chesselet 2000). These changes in peptide gene expression have been considered to parallel changes in neuronal activity. A complementary role of the direct and indirect pathway in movement control was proposed in another model in which the direct pathway would contribute to the selection of motor programs, while the indirect pathway would inhibit competing motor programs (Mink 1996). The idea that the direct and indirect pathways have opposite and/or complementary roles on movement has been tested in transgenic mice models and using viral targeting methods. For instance, optogenics has been used in mice expressing channelrhodopsin-2 under the activity of the dopamine Drd1a or Drd2 receptors with the objective of independently manipulating direct or indirect pathway MSN. Using this approach, it was found that the bilateral excitation of striatal neurons expressing the dopamine Drd2 gene elicited a Parkinsonian state in mice, characterized by increased freezing, bradykinesia, and decreased locomotor initiation (Kravitz et al. 2010). In contrast, activation of striatal neurons expressing the Drd1a gene reduced freezing episodes and increased locomotion (Kravitz et al. 2010). In addition, activation of Drd1a-expressing neurons completely rescued freezing, bradykinesia, and deficits in locomotor initiation observed in a 6-hydroxydopamine-lesioned mouse model of Parkinson's disease (Kravitz et al. 2010). Conversely, other evidence has shown that the experimental ablation or disruption of the indirect pathway increases motor activity (Durieux et al. 2009; Bateup et al. 2010). Although the studies described above are consistent with the hypothesis that the direct and indirect pathways play an opposite role in the activation of movement, they do not clarify their respective role in various aspects of movement performance such as movement selection, initiation, termination, or in instrumental learning. The following paragraphs review and discuss studies that have attempted to address these questions.

Using a Cre-dependent viral expression of the genetically encoded calcium indicator GCaMP3 in Drd1a receptor- or A2a receptor-expressing (respectively direct and indirect pathway neurons) neurons in the striatum, Cui and co-workers were able to study the pattern of activation of direct and indirect pathway neurons during the execution of movement in mice performing an operant task (Cui et al. 2013). They found that both pathways were co-activated during the initiation of movement and that their concurrent activation preceded the initiation of contraversive movements and predicted the occurrence of movement (Cui et al. 2013). These findings suggest that the initiation and execution of normal movements requires a co-activation of direct and indirect striatal circuits. The finding of a co-activation of direct and indirect pathway MSN is consistent with the model proposing that these pathways could contribute to concomitantly activate selected movements and inhibit competing movements. In a study combining optogenetic identification of direct

and indirect pathway MSN with electrophysiological recordings in mice that were trained to learn a rapid motor sequence, Jin and colleagues (Jin et al. 2014) found that similar percentages of direct and indirect pathway MSN responded during the start or the end of the sequence. However, while direct pathway neurons responded similarly at the start and end of the sequence, indirect pathway neurons preferentially responded at the start of the sequence (Jin et al. 2014). Jin and colleagues interpreted this result as evidence that the direct pathway plays a preferential role in the initiation of movement, while the indirect pathway plays a preferential role in the inhibition of competing motor programs (Jin et al. 2014). The finding that the majority of changes in MSN activity occurred at the start and end of a motor sequence rather than during the sequence itself was interpreted as evidence that the basal ganglia control sequences of movements (chunking), rather than individual movements (Jin et al. 2014). In another study, genetically engineered mice were trained to execute two distinct and sequential responses to get a reward in an operant chamber (Rothwell et al. 2015). Using selective manipulations of direct and indirect pathway neurons, the study reported that serial order learning strengthened cortical synapses on direct pathway neurons (Rothwell et al. 2015).

The dual role of the direct and indirect pathways on movement is paralleled by a dual effect on neurons in the output regions of the basal ganglia. Indeed, the effectiveness of optogenetic stimulation of the direct pathway in producing movement significantly correlated with the extent of inhibition of a subpopulation of SNr neurons (Freeze et al. 2013). In contrast, motor suppression induced by activation of the indirect pathway seemed to be most strongly influenced by the population of excited SNr neurons (Freeze et al. 2013). Freeze and colleagues argued that the striatal direct and indirect pathways represent an inhibitory gate that can respectively open or close motor output from the basal ganglia (Freeze et al. 2013). This interpretation is consistent with other experimental evidence that signals through the striatopallidal indirect pathway inhibit movements through a phasic excitation of the SNr (Sano et al. 2013). In their study, Jin and colleagues found that the activity in the SNr correlated with that of direct pathway neurons, while activity in the GP correlated with that of indirect pathway neurons (Jin et al. 2014).

Most studies reviewed above are consistent with the hypothesis that activation of direct pathway neurons facilitates movement, while activation of indirect pathway neurons inhibits movement. A more complex theoretical model has been proposed in which activation of indirect pathway MSN would contribute to both the selection and concurrent inhibition of competing movements (Keeler et al. 2014). The model, which is based on evidence that dopamine D1 and D2 receptors have different biochemical properties and that their pharmacological manipulation differentially alter different phases of movement in an operant task, proposes that the direct and the indirect pathway are, respectively, involved in the preparation and the selection of movement (Keeler et al. 2014). In this model, the activation of a small subset of indirect pathway MSN would contribute to select movement and concurrently would exert a lateral inhibition on neighboring indirect pathway MSN to inhibit competing movements. In this model, the paucity of movement observed in Parkinson's disease could be explained by an abnormal activation of large popula-

tions of indirect pathway MSN so that the mechanisms leading to movement selection via lateral inhibition would be disrupted (Keeler et al. 2014). The possibility that the indirect pathway is involved in movement selection appears consistent with experimental evidence that its selective elimination impairs the accuracy of response selection in the execution of an auditory discrimination task without influencing the response time (Nishizawa et al. 2012). Conversely, selective elimination of the striatonigral pathway lengthens the response time, but does not affect the accuracy of a response selection in a two-choice reaction time task dependent on a visual stimulus (Fukabor et al. 2012). In conclusion, the exact role of the direct and indirect pathway in the control of movement remains hypothetical and future studies using more refined methods should help settle the uncertainty about the role of these pathways in movement initiation and movement selection.

3.3.2 Associative Learning, Social Behavior, and Decision Making

The basal ganglia and the striatum play an important role in learning and executing a motor performance in response to a specific sensory or environmental context (Seger and Spiering 2011). In particular, the striatum is involved in action-outcome learning and in habit learning. In action-outcome learning, the performance of a specific behavior depends on a mental representation of the outcome. In habit learning, the performance depends on a particular context. Habits are less sensitive to reward devaluation, indicating a competition between action-outcome learning and habits. The ventromedial striatum may be preferentially involved in action-outcome learning, while the dorsolateral striatum may be preferentially involved in habit learning (Balleine et al. 2007). The reader is referred to Chaps. 5, 11, 12, 18, and 19 for more detailed discussions on the role of the striatum in learning. The objective in the following paragraphs will be to discuss the respective contribution of the striatal direct and indirect pathways to learning and learning-dependent behaviors such as social behavior and decision-making.

A number of studies have used genetically engineered mice to selectively manipulate the direct or indirect pathways and assess the impact on operant learning. These studies suggest a differential role of the direct and indirect pathways in different aspects of associative and reward-based learning. In particular, these studies support the notion that the direct pathway is involved in reward-based learning, whereas the indirect pathway may be involved in avoidance behavior. For instance, in a place preference paradigm in an operant box, optogenic stimulation of Drd1a-expressing neurons induced a persistent reinforcement, whereas stimulation of Drd2-expressing neurons induced a transient punishment (Kravitz et al. 2012). Using another genetic approach to selectively inactivate with tetanus-toxin striatal neurons expressing substance P or enkephalin (direct and indirect neurons, respectively), Hikida and colleagues found that loss of the direct but not the indirect pathway impaired reward-based learning (Hikida et al. 2016). In contrast, the avoidance

aversive behavior in a dark chamber associated with an electric shock was impaired after loss of the indirect but not the direct pathway, leading the authors to conclude that the indirect pathway is critical for evoking aversive behavior (Hikida et al. 2010, 2016). Using a similar experimental approach, it was shown that Drd1a receptors in the direct pathway are critical for the acquisition, but not for the expression of appetitive reward learning (Hikida et al. 2013). In contrast, activation of Drd2 receptors in indirect pathway neurons was critical for both the acquisition and expression of aversive behavior (Hikida et al. 2013). When the transmission of either direct or indirect pathway MSN was unilaterally blocked using tetanus toxin, infusion of protein kinase A inhibitors in the accumbens core abolished passive avoidance to an electric shock when the indirect pathway was blocked (Yamaguchi et al. 2015). In addition, protein kinase A activity was increased in indirect pathway and decreased in direct pathway neurons in both aversive memory formation and retrieval (Yamaguchi et al. 2015), indicating that the second messengers systems associated with dopamine receptors are involved in these effects. In another series of experiments, mice were trained to lick a spout in response to a whisker deflection (Sippy et al. 2015). Striatal projection neurons in the dorsolateral striatum showed a strong task-related modulation and increased their activity in successful trials (Sippy et al. 2015). However, direct but not indirect pathway neurons exhibited a prominent early sensory response and optogenetic stimulation of direct pathway neurons substituted for whisker stimulation in trained mice (Sippy et al. 2015). These data support the hypothesis that direct pathway neurons are permissive for the initiation of learned reward-based action (Sippy et al. 2015). Francis and colleagues documented a dual effect of the direct and indirect pathways in mood and motivated behavior. Specifically, the activity of Drd1a-expressing neurons was decreased, while the activity of Drd2-expressing neurons was increased in mice displaying depression-like behaviors after chronic social defeat stress (Francis et al. 2015). Stimulation of Drd1a-expressing neurons increased behavioral resilience to depression, while inhibition induced depressive-like behavior after chronic social defeat stress. In contrast, the repeated activation of indirect pathway neurons in stress naïve mice induced social avoidance following a subthreshold exposure to a social defeat stress (Francis et al. 2015). Another study has shown that stimulation of Drd2-expressing neurons of the nucleus accumbens converts risk-preferring rats to risk-averse rats (Zalocusky et al. 2016). This finding is consistent with a general role of the indirect pathway in avoidance behavior.

Other studies indicate that in addition to be involved in avoidance behavior, the indirect pathway may play an important role in mediating cognitive flexibility by preventing the execution of actions that used to be rewarded but that are not anymore. Using the transmission-blocking tetanus toxin approach in the mouse, it was documented that the direct pathway in the nucleus accumbens is required for learning the association between a visually cued task and a reward (Yawata et al. 2012). In contrast, inactivation of the indirect pathway did not impair learning acquisition, but it increased perseverative behavior in response to a strategy switch in which the reward was placed in another location (Yawata et al. 2012). In this study, the administration of the D2 receptor agonist quinpirole tended to increase perse-

verative errors, particularly during the switching task, thus confirming that a decreased inhibitory action of D2 receptors on indirect pathway neurons is necessary for learning a new strategy (Yawata et al. 2012; Nakanishi et al. 2014). These data are consistent with the model of "Go" and "No Go" in which the Go signal is provided by activation of the direct pathway and the "No Go" signal by activation of the indirect pathway (Frank et al. 2004; Frank 2011). In such a case, a decreased activation of indirect pathway neurons could lead to perseveration and enhance the expression of habits. This is otherwise supported by evidence that post-synaptic plasticity of Drd2-expressing striatopallidal neurons in the dorsolateral striatum correlates with habit learning (Shan et al. 2015). In addition, habitual behavior in mice was correlated with a strengthening of direct and indirect pathway neurons in the dorsolateral striatum (O'Hare et al. 2016), but neurons in the direct pathway had a tendency to fire before the indirect pathway and habit suppression correlated with a weakened direct pathway output while habit expression correlated with indirect pathway event amplitude (O'Hare et al. 2016).

3.3.3 Addiction and Obesity

It is well-established that the striatum and dopamine are involved in reward-mediated behaviors and in addiction (Schultz 2011 and 2013; Hyman et al. 2006). On the other hand, food intake is regulated via several mechanisms, among which the reward system plays an important role. Obesity can be the result of excessive food consumption and may involve mechanisms similar to those involved in drug abuse (Kenny et al. 2013). The following paragraphs discuss evidence that the direct and indirect pathway play a dual role in addiction and in obesity.

Earlier studies have documented that pharmacological antagonists of D1 receptors block conditioned place preference for cocaine (Hiroi and White 1991; Baker et al. 1998). Using a fluorescent calcium indicator as a marker of neuronal activity, it was found that cocaine intake shifts the balance between the direct and indirect pathway towards the direct pathway (Luo et al. 2011) and loss of the direct pathway reduces locomotor activity and attenuates locomotor sensitization to repeated cocaine (Hikida et al. 2016). Similarly, decreased excitability of the direct pathway impairs persistence of amphetamine-induced behavioral sensitization (Ferguson et al. 2011). In the conditioned place preference paradigm, blockade of the direct but not indirect pathway reduces cocaine-induced place preference (Hikida et al. 2016). Optical activation of nucleus accumbens Drd1a- but not Drd2-expressing MSN enhanced morphine-conditioned place preference (Koo et al. 2014). In another study, it was found that activation of dopamine D1 receptors on the direct pathway is important for inducing cocaine-dependent sensitization and cocaine-induced addictive behavior (Hikida et al. 2013). Lobo and colleagues subsequently reported that a targeted deletion of Tropomyosin-related kinase B (TrkB), the receptor for the brain-derived neurotropic factor (BDNF), in direct pathway MSN diminished the rewarding properties of cocaine (Lobo et al. 2006). Loss of the dopamine-receptor

activated second messenger DARPP-32, in direct but not in indirect pathway MSN, prevented the stimulatory action of the psychomimetic phencyclidine on motor activity (Bonito-Oliva et al. 2016). Altogether, these findings are consistent with the notion that the activation of the direct pathway plays a key role in several addictive effects induced by psychostimulants. In contrast, activation of the indirect pathway seems to play an opposite role on several psychostimulant-induced behaviors. For instance, there is evidence that increasing the activity of the indirect pathway promotes resilience to compulsive cocaine seeking (Bock et al. 2013). Lobo and colleagues reported that the targeted deletion of the neurotrophic receptor TrkB in Drd2-expressing MSNs enhanced cocaine reward (Lobo et al. 2006). Moreover, TrkB deletion in Drd2-expressing MSN increased the excitability of indirect pathway neurons and optogenetic stimulation of these neurons decreased cocaine reward-seeking behavior (Lobo et al. 2006). Loss of the indirect pathway also leads to a delayed cocaine sensitization, although sensitization eventually re-emerges (Hikida et al. 2013). A decreased excitability of the indirect pathway facilitates behavioral sensitization (Ferguson et al. 2011). An increased synaptic strength of glutamatergic synapses on Drd2-expressing indirect pathway neurons in the nucleus accumbens was documented in mice with a history of intravenous cocaine self-administration (Bock et al. 2013). This synaptic strengthening was inversely correlated with the emergence of compulsive-like cocaine responding (Bock et al. 2013). Altogether, these data suggest that activation of the indirect pathway may oppose the addictive properties of drugs of abuse.

Adenosine A2a receptors are densely expressed in striatopallidal neurons (Svenningsson et al. 1997; Schiffmann et al. 2007). Pharmacological agonists that modulate adenosine A2a receptors and increase striatopallidal transmission reduced consumption of both highly palatable and standard chow in rats (Micioni Di Bonaventura et al. 2012) and reduced lever-pressing for food rewards (Jones-Cage et al. 2012). Conversely, pharmacological blockade of A2a receptors increased palatable food consumption when administered alone and enhanced palatable food intake triggered by intra-accumbens administration of an μ-opioid receptor agonist (DAMGO) (Pritchett et al. 2010). These findings are reminiscent of the inhibitory effects of indirect pathway stimulation on drug reward described in the previous paragraphs and suggest that Drd2-expressing indirect pathway neurons may regulate food intake in much the same way that they regulate drug rewards. A link between compulsive eating and indirect pathway neurons is supported by some studies. In particular, viral knockdown of Drd2 receptors in the striatum accelerates the development of compulsive food-seeking behavior in rats (Johnson and Kenny 2010), suggesting that the indirect pathway may control compulsive food-seeking.

3.4 Conclusions

The existence of a direct and indirect striatal pathway is supported by considerable experimental evidence, but there is also evidence that this segregation is not absolute. In addition, recent evidence indicates that both the density of MSN axonal

projections to a specific target and the expression of phenotypic markers in MSN can change during the development of the brain and/or in response to physiological challenges. Studies in genetically engineered mice have documented that the manipulation of neurons that preferentially express phenotypic markers of direct or indirect pathway neurons (i.e., dopamine Drd1a versus Drd2 receptors or enkephalin versus substance P and dynorphin) has a different impact on behavior. It should be emphasized, however, that most mice studies manipulate subsets of MSN based on their expression of specific dopamine receptors rather than on their specific area of projection. Thus, the function of MSN that do not fit the strict definition of direct or indirect pathway neuron (i.e. neurons that project to all output regions of the basal ganglia) remains unclear.

Another major outcome of recent experimental studies in mice has been to support the notion that the direct and indirect pathways play an opposite and/or complementary role in the organization of movement, in associative and in reward-based learning. In particular, current evidence supports the notion that the direct pathway is involved in the facilitation of movement and reward-associated actions, while the indirect pathway is involved in the inhibition of competing motor actions and/or the inhibition of unrewarded actions. It is important to emphasize that most studies leading to these conclusions involved experimental conditions in which the activity of large numbers of MSN was homogeneously manipulated, a situation that most likely does not occur in physiological conditions. In fact, the temporal and spatial pattern of activation or deactivation of direct and indirect pathway neurons during the preparation, initiation, execution, and termination of actions is complex. This suggests that different subsets of direct and indirect MSN code for different variables associated with an action. In order to provide a better insight into the functions of MSN, future studies should aim at activating and/or deactivating more discrete subsets of direct or indirect pathway neurons and multi-synaptic neuronal circuits associated with different subsets of direct and/or indirect pathway neurons.

References

Ade KK, Janssen MJ, Ortinski PI, Vicini S (2008) Differential tonic GABA conductances in striatal medium spiny neurons. J Neurosci 28(5):1185–1197

Aizman O, Brismar P, Uhlen E et al (2000) Anatomical and physiological evidence for D1 and D2 dopamine receptor colocalization in neostriatal neurons. Nat Neurosci 3(3):226–230

Albin RL, Young AB, Penney JB (1989) The functional anatomy of basal ganglia disorders. Trends Neurosci 12(10):366–375

Alexander GE, DeLong MR, Strick PL (1986) Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci 9:357–381

Alexander GE, Crutcher MD (1990) Functional architecture of basal ganglia circuits: neural substrates of parallel processing. Trends Neurosci 13(7):266–271

Anderson KD, Reiner A (1990) Extensive co-occurrence of substance P and dynorphin in striatal projection neurons: an evolutionarily conserved feature of basal ganglia organization. J Comp Neurol 295(3):339–369

Aubert I, Ghorayeb I, Normand E, Bloch B (2000) Phenotypical characterization of the neurons expressing the D1 and D2 dopamine receptors in the monkey striatum. J Comp Neurol 418(1):22–32

Baker DA, Fuchs RA, Specio SE, Khroyan TV, Neisewander JL (1998) Effects of intraaccumbens administration of SCH-23390 on cocaine-induced locomotion and conditioned place preference. Synapse 30(2):181–193

Balleine BW, Delgado MR, Hikosaka O (2007) The role of the dorsal striatum in reward and decision-making. J Neurosci 27(31):8161–8165

Bateup HS, Santini E, Shen W et al (2010) Distinct subclasses of medium spiny neurons differentially regulate striatal motor behaviors. Proc Natl Acad Sci U S A 107(33):14845–14850

Beaulieu JM, Gainetdinov RR (2011) The physiology, signaling, and pharmacology of dopamine receptors. Pharmacol Rev 63(1):182–217

Beckstead RM, Wooten GF, Trugman JM (1988) Distribution of D1 and D2 dopamine receptors in the basal ganglia of the cat determined by quantitative autoradiography. J Comp Neurol 268(1):131–145

Bertran-Gonzalez J, Bosch C, Maroteaux M et al (2008) Opposing patterns of signaling activation in dopamine D1 and D2 receptor-expressing striatal neurons in response to cocaine and haloperidol. J Neurosci 28(22):5671–5685

Besson MJ, Graybiel AM, Quinn B (1990) Co-expression of neuropeptides in the cat's striatum: an immunohistochemical study of substance P, dynorphin B and enkephalin. Neuroscience 39(1):33–58

Biezonski DKP, Trifilieff J, Meszaros JA et al (2015) Evidence for limited D1 and D2 receptor coexpression and colocalization within the dorsal striatum of the neonatal mouse. J Comp Neurol 523(8):1175–1189

Bishop GA, Chang HT, Kitai ST (1982) Morphological and physiological properties of neostriatal neurons: an intracellular horseradish peroxidase study in the rat. Neuroscience 7(1):179–191

Bock R, Shin JH, Kaplan AR et al (2013) Strengthening the accumbal indirect pathway promotes resilience to compulsive cocaine use. Nat Neurosci 16(5):632–638

Bolam JP, Powell JF, Totterdell S et al (1981a) The proportion of neurons in the rat neostriatum that project to the substantia nigra demonstrated using horseradish peroxidase conjugated with wheatgerm agglutinin. Brain Res 220(2):339–343

Bolam JP, Somogyi P, Totterdell S, Smith AD (1981b) A second type of striatonigral neuron: a comparison between retrogradely labelled and Golgi-stained neurons at the light and electron microscopic levels. Neuroscience 6(11):2141–2157

Bolam JP, Powell JF, Wu JY et al (1985) Glutamate decarboxylase-immunoreactive structures in the rat neostriatum: a correlated light and electron microscopic study including a combination of Golgi impregnation with immunocytochemistry. J Comp Neurol 237(1):1–20

Bonito-Oliva A, DuPont C, Madjid N et al (2016) Involvement of the striatal medium spiny neurons of the direct pathway in the motor stimulant effects of phencyclidine. Int J Neuropsychopharmacol 19(6): 1–9

Castle M, Aymerich MS, Sanchez-Esobar C et al (2005) Thalamic innervation of the direct and indirect basal ganglia pathways in the rat: ipsi- and contralateral projections. J Comp Neurol 483(2):143–153

Cazorla M, de Carvalho FD, Chohan MO et al (2014) Dopamine D2 receptors regulate the anatomical and functional balance of basal ganglia circuitry. Neuron 81(1):153–164

Cazorla M, Kang UJ, Kellendor C (2015) Balancing the basal ganglia circuitry: a possible new role for dopamine D2 receptors in health and disease. Mov Disord 30(7):895–903

Cepeda C, Andre VM, Yamazaki I et al (2008) Differential electrophysiological properties of dopamine D1 and D2 receptor-containing striatal medium-sized spiny neurons. Eur J Neurosci 27(3):671–682

Cenci MA, Campbell K, Wictorin K, Bjorklund A (1992) Striatal c-fos Induction by Cocaine or Apomorphine Occurs Preferentially in Output Neurons Projecting to the Substantia Nigra in the Rat. Eur J Neurosci 4(4):376–380

Chan HT, Wilson CJ, Kitai ST (1981) Single neostriatal efferent axons in the globus pallidus: a light and electron microscopic study. Science 213(4510):915–918

Chang HT, Kitai ST (1982) Large neostriatal neurons in the rat: an electron microscopic study of gold-toned Golgi-stained cells. Brain Res Bull 8(6):631–643
Chang HT, Wilson CJ, Kitai SJ (1982) A Golgi study of rat neostriatal neurons: light microscopic analysis. J Comp Neurol 208(2):107–126
Chesselet MF, Weiss L, Wuenschell C et al (1987) Comparative distribution of mRNAs for glutamic acid decarboxylase, tyrosine hydroxylase, and tachykinins in the basal ganglia: an in situ hybridization study in the rodent brain. J Comp Neurol 262(1):125–140
Cole AJ, Bhat RV, Patt C et al (1992) D1 dopamine receptor activation of multiple transcription factor genes in rat striatum. J Neurochem 58(4):1420–1426
Crossman AR (1987) Primate models of dyskinesia: the experimental approach to the study of basal ganglia-related involuntary movement disorders. Neuroscience 21(1):1–40
Cui G, Jun SB, Jin X et al (2013) Concurrent activation of striatal direct and indirect pathways during action initiation. Nature 494(7436):238–242
Danner H, Pfister C (1979) [Structure of the neostratum in the rat. II]. Gegenbaurs Morphol Jahrb 125(3):349–364
DeLong MR (1983) The neurophysiologic basis of abnormal movements in basal ganglia disorders. Neurobehav Toxicol Teratol 5(6):611–616
DeLong MR (1990) Primate models of movement disorders of basal ganglia origin. Trends Neurosci 13(7):281–285
Deng YP, Lei WL, Reiner A (2006) Differential perikaryal localization in rats of D1 and D2 dopamine receptors on striatal projection neuron types identified by retrograde labeling. J Chem Neuroanat 32(2–4):101–116
DiFiglia M, Pasik P, Pasik T (1976) A Golgi study of neuronal types in the neostriatum of monkeys. Brain Res 114(2):245–256
DiFiglia M, Pasik P, Pasik T (1979) Developmental aspects of neostriatal organization in monkeys. Appl Neurophysiol 42(1–2):81–83
Dimova R, Vuillet J, Seite R (1980) Study of the rat neostriatum using a combined Golgi-electron microscope technique and serial sections. Neuroscience 5(9):1581–1596
Dragunow M, Robertson GS, Faull RL et al (1990) D2 dopamine receptor antagonists induce fos and related proteins in rat striatal neurons. Neuroscience 37(2):287–294
Durieux PF, Bearzatto B, Guiducci S et al (2009) D2R striatopallidal neurons inhibit both locomotor and drug reward processes. Nat Neurosci 12(4):393–395
Feger J, Crossman AR (1984) Identification of different subpopulations of neostriatal neurones projecting to globus pallidus or substantia nigra in the monkey: a retrograde fluorescence double-labelling study. Neurosci Lett 49(1–2):7–12
Ferguson SM, Eskenazi D, Ishikawa M et al (2011) Transient neuronal inhibition reveals opposing roles of indirect and direct pathways in sensitization. Nat Neurosci 14(1):22–24
Fieblinger T, Graves SM, Sevel LE et al (2014) Cell type-specific plasticity of striatal projection neurons in parkinsonism and L-DOPA-induced dyskinesia. Nat Commun 5:5316
Fox CA, Andrade AN, Hillman DE et al (1971) The spiny neurons in the primate striatum: a Golgi and electron microscopic study. J Hirnforsch 13(3):181–201
Francis TC, Chandra R, Friend DM et al (2015) Nucleus accumbens medium spiny neuron subtypes mediate depression-related outcomes to social defeat stress. Biol Psychiatry 77(3):212–222
Frank MJ, Seeberger LC, O'Reilly RC, 2004. By carrot or by stick: cognitive reinforcement learning in parkinsonism. Science 306(5703), 1940–1943
Frank MJ (2011) Computational models of motivated action selection in corticostriatal circuits. Curr Opin Neurobiol 21(3):381–386
Freeze BS, Kravitz AV, Hammack N et al (2013) Control of basal ganglia output by direct and indirect pathway projection neurons. J Neurosci 33(47):18531–18539
Fukabor R, Okada K, Nishizawa K et al (2012) Striatal direct pathway modulates response time in execution of visual discrimination. Eur J Neurosci 35(5):784–797

Furuta T, Zhou L, Kaneko T (2002) Preprodynorphin-, preproenkephalin-, preprotachykinin A- and preprotachykinin B-immunoreactive neurons in the accumbens nucleus and olfactory tubercle: double-immunofluorescence analysis. Neuroscience 114(3):611–627

Gerfen CR, Young WS (1988) Distribution of striatonigral and striatopallidal peptidergic neurons in both patch and matrix compartments: an in situ hybridization histochemistry and fluorescent retrograde tracing study. Brain Res 460(1):161–167

Gerfen CR, Engber TM, Mahan LC et al (1990) D1 and D2 dopamine receptor-regulated gene expression of striatonigral and striatopallidal neurons. Science 250(4986):1429–1432

Gertler TS, Chan CS, Surmeier DJ (2008) Dichotomous anatomical properties of adult striatal medium spiny neurons. J Neurosci 28(43):10814–10824

Gong S, Zheng C, Doughty ML et al (2003) A gene expression atlas of the central nervous system based on bacterial artificial chromosomes. Nature 425(6961):917–925

Graveland GA, DiFiglia M (1985) The frequency and distribution of medium-sized neurons with indented nuclei in the primate and rodent neostriatum. Brain Res 327(1–2):307–311

Graveland GA, Williams RS, DiFiglia M (1985) A Golgi study of the human neostriatum: neurons and afferent fibers. J Comp Neurol 234(3):317–333

Graybiel AM, Ragsdale CW (1979) Fiber connections of the basal ganglia. Prog Brain Res 51:237–283

Harrison MB, Wiley RG, Wooten GF (1990) Selective localization of striatal D1 receptors to striatonigral neurons. Brain Res 528(2):317–322

Harrison MB, Wiley RG, Wooten GF (1992) Changes in D2 but not D1 receptor binding in the striatum following a selective lesion of striatopallidal neurons. Brain Res 590(1–2):305–310

Hersch SM, Ciliax BJ, Gutekunst CA et al (1995) Electron microscopic analysis of D1 and D2 dopamine receptor proteins in the dorsal striatum and their synaptic relationships with motor corticostriatal afferents. J Neurosci 15(7 pt 2):5222–5237

Herve D, Levi-Strauss M, Marey-Semper I et al (1993) G(olf) and Gs in rat basal ganglia: possible involvement of G(olf) in the coupling of dopamine D1 receptor with adenylyl cyclase. J Neurosci 13(5):2237–2248

Hikida T, Kimura K, Wada N et al (2010) Distinct roles of synaptic transmission in direct and indirect striatal pathways to reward and aversive behavior. Neuron 66(6):896–907

Hikida T, Yawata S, Yamaguchi T et al (2013) Pathway-specific modulation of nucleus accumbens in reward and aversive behavior via selective transmitter receptors. Proc Natl Acad Sci U S A 110(1):342–347

Hikida T, Morita M, Macpherson T (2016) Neural mechanisms of the nucleus accumbens circuit in reward and aversive learning. Neurosci Res 108:1–5

Hiroi N, White NM (1991) The amphetamine conditioned place preference: differential involvement of dopamine receptor subtypes and two dopaminergic terminal areas. Brain Res 552(1):141–152

Hyman SE, Malenka RC, Nestler EJ (2006) Neural mechanisms of addiction: the role of reward-related learning and memory. Annu Rev Neurosci 29:565–598

Jin X, Tecuapetla F, Costa RM (2014) Basal ganglia subcircuits distinctively encode the parsing and concatenation of action sequences. Nat Neurosci 17(3):423–430

Johnson PM, Kenny PJ (2010) Dopamine D2 receptors in addiction-like reward dysfunction and compulsive eating in obese rats. Nat Neurosci 13(5):635–641

Jones-Cage C, Stratford TR, Wirtshafter D (2012) Differential effects of the adenosine A(2)A agonist CGS-21680 and haloperidol on food-reinforced fixed ratio responding in the rat. Psychopharmacology (Berl) 220(1):205–213

Kawaguchi Y, Wilson CJ, Emson PC (1990) Projection subtypes of rat neostriatal matrix cells revealed by intracellular injection of biocytin. J Neurosci 10(10):3421–3438

Kawaguchi Y, Aosaki T, Kubota Y (1997) Cholinergic and GABAergic interneurons in the striatum. Nihon Shinkei Seishin Yakurigaku Zasshi 17(2):87–90

Kebabian JW, Calne DB (1979) Multiple receptors for dopamine. Nature 277(5692):93–96

Keeler JF, Pretsell DO, Robbins TW (2014) Functional implications of dopamine D1 vs. D2 receptors: a 'prepare and select' model of the striatal direct vs. indirect pathways. Neuroscience 282C:156–175

Kemp JM, Powell TP (1971) The structure of the caudate nucleus of the cat: light and electron microscopy. Philos Trans R Soc Lond B Biol Sci 262(845):383–401
Kenny PJ, Voren G, Johnson PM (2013) Dopamine D2 receptors and striatopallidal transmission in addiction and obesity. Curr Opin Neurobiol 23(4):535–538
Koo JW, Lobo MK, Chaudhury B et al (2014) Loss of BDNF signaling in D1R-expressing NAc neurons enhances morphine reward by reducing GABA inhibition. Neuropsychopharmacology 39(11):2646–2653
Kravitz AV, Freeze BS, Parker PR et al (2010) Regulation of parkinsonian motor behaviours by optogenetic control of basal ganglia circuitry. Nature 466(7306):622–626
Kravitz AV, Tye LD, Kreitzer AC (2012) Distinct roles for direct and indirect pathway striatal neurons in reinforcement. Nat Neurosci 15(6):816–818
Kubota Y, Inagaki S, Shimada S et al (1991) Spiny and aspiny types of neuropeptide Y immunoreactive neurons in the monkey neostriatum. Neurosci Lett 122(1):109–112
Laprade N, Soghomonian JJ (1995) Differential regulation of mRNA levels encoding for the two isoforms of glutamate decarboxylase (GAD65 and GAD67) by dopamine receptors in the rat striatum. Brain Res Mol Brain Res 34(1):65–74
Larson ER, Ariano MA (1994) Dopamine receptor binding on identified striatonigral neurons. Neurosci Lett 172(1–2):101–106
Le Moine C, Bloch B (1995) D1 and D2 dopamine receptor gene expression in the rat striatum: sensitive cRNA probes demonstrate prominent segregation of D1 and D2 mRNAs in distinct neuronal populations of the dorsal and ventral striatum. J Comp Neurol 355(3):418–426
Le Moine C, Normand E, Bloch B (1991) Phenotypical characterization of the rat striatal neurons expressing the D1 dopamine receptor gene. Proc Natl Acad Sci U S A 88(10):4205–4209
Lee T, Kaneko T, Taki K et al (1997) Preprodynorphin-, preproenkephalin-, and preprotachykinin-expressing neurons in the rat neostriatum: an analysis by immunocytochemistry and retrograde tracing. J Comp Neurol 386(2):229–244
Lei W, Jiao Y, Del Mar N et al (2004) Evidence for differential cortical input to direct pathway versus indirect pathway striatal projection neurons in rats. J Neurosci 24(38):8289–8299
Lester J, Fink S, Aronin N et al (1993) Colocalization of D1 and D2 dopamine receptor mRNAs in striatal neurons. Brain Res 621(1):106–110
Lobo MK, Karsten SL, Gray M et al (2006) FACS-array profiling of striatal projection neuron subtypes in juvenile and adult mouse brains. Nat Neurosci 9(3):443–452
Luo Z, Volkow ND, Heintz N, Pan Y et al (2011) Acute cocaine induces fast activation of D1 receptor and progressive deactivation of D2 receptor striatal neurons: in vivo optical microprobe [Ca2+]i imaging. J Neurosci 31(37):13180–13190
Matamales M, Bertran-Gonzalez J, Salomon L et al (2009) Striatal medium-sized spiny neurons: identification by nuclear staining and study of neuronal subpopulations in BAC transgenic mice. PLoS One 4(3), e4770
Meador-Woodruff JH, Mansour A, Healy DJ et al (1991) Comparison of the distributions of D1 and D2 dopamine receptor mRNAs in rat brain. Neuropsychopharmacology 5(4):231–242
Micioni Di Bonaventura MV, Cifani C, Lambertucci C et al (2012) A2A adenosine receptor agonists reduce both high-palatability and low-palatability food intake in female rats. Behav Pharmacol 23(5–6):567–574
Mink JW (1996) The basal ganglia: focused selection and inhibition of competing motor programs. Prog Neurobiol 50(4):381–425
Nadjar A, Brotchie JM, Guigoni C et al (2006) Phenotype of striatofugal medium spiny neurons in parkinsonian and dyskinetic nonhuman primates: a call for a reappraisal of the functional organization of the basal ganglia. J Neurosci 26(34):8653–8661
Nagai T, McGeer PL, McGeer EG (1983) Distribution of GABA-T-intensive neurons in the rat forebrain and midbrain. J Comp Neurol 218(2):220–238
Nakanishi S, Hikida T, Yawata S (2014) Distinct dopaminergic control of the direct and indirect pathways in reward-based and avoidance learning behaviors. Neuroscience 282C:49–59
Nishizawa K, Fukabori R, Okada K et al (2012) Striatal indirect pathway contributes to selection accuracy of learned motor actions. J Neurosci 32(39):13421–13432

O'Hare JK, Ade KK, Sukharnikova T et al (2016) Pathway-specific striatal substrates for habitual behavior. Neuron 89(3):472–479
Ottersen OP, Storm-Mathisen J (1984) Glutamate- and GABA-containing neurons in the mouse and rat brain, as demonstrated with a new immunocytochemical technique. J Comp Neurol 229(3):374–392
Parent A, Bouchard C, Smith Y (1984a) The striatopallidal and striatonigral projections: two distinct fiber systems in primate. Brain Res 303(2):385–390
Parent A, De Bellefeuille L, Mackey A (1984b) Organization of primate internal pallidum as revealed by fluorescent retrograde tracing of its efferent projections. Adv Neurol 40:15–20
Parent A, Charara A, Pinault D (1995a) Single striatofugal axons arborizing in both pallidal segments and in the substantia nigra in primates. Brain Res 698(1–2):280–284
Parent A, Cote PY, Lavoie B (1995b) Chemical anatomy of primate basal ganglia. Prog Neurobiol 46(2–3):131–197
Penny GR, Afsharpour S, Kitai ST (1986) The glutamate decarboxylase-, leucine enkephalin-, methionine enkephalin- and substance P-immunoreactive neurons in the neostriatum of the rat and cat: evidence for partial population overlap. Neuroscience 17(4):1011–1045
Preston RJ, Bishop GA, Kitai ST (1980) Medium spiny neuron projection from the rat striatum: an intracellular horseradish peroxidase study. Brain Res 183(2):253–263
Pritchett CE, Pardee AL, McGuirk SR et al (2010) The role of nucleus accumbens adenosine-opioid interaction in mediating palatable food intake. Brain Res 1306:85–92
Reiner A, Medina L, Haber SN (1999) The distribution of dynorphinergic terminals in striatal target regions in comparison to the distribution of substance P-containing and enkephalinergic terminals in monkeys and humans. Neuroscience 88(3):775–793
Ribak CE, Vaughn JE, Roberts E (1979) The GABA neurons and their axon terminals in rat corpus striatum as demonstrated by GAD immunocytochemistry. J Comp Neurol 187(2):261–283
Robertson GS, Vincent SR, Fibiger HC (1992) D1 and D2 dopamine receptors differentially regulate c-fos expression in striatonigral and striatopallidal neurons. Neuroscience 49(2):285–296
Rothwell PE, Hayton SJ, Sun GL et al (2015) Input- and output-specific regulation of serial order performance by corticostriatal circuits. Neuron 88(2):345–356
Sano H, Chiken S, Hikida T et al (2013) Signals through the striatopallidal indirect pathway stop movements by phasic excitation in the substantia nigra. J Neurosci 33(17):7583–7594
Schiffmann SN, Fisone G, Moresco R et al (2007) Adenosine A2A receptors and basal ganglia physiology. Prog Neurobiol 83(5):277–292
Schultz W (2011) Potential vulnerabilities of neuronal reward, risk, and decision mechanisms to addictive drugs. Neuron 69(4):603–617
Schultz W (2013) Updating dopamine reward signals. Curr Opin Neurobiol 23(2):229–238
Seger CA, Spiering BJ (2011) A critical review of habit learning and the Basal Ganglia. Front Syst Neurosci 5:66
Shan Q, Christie MJ, Balleine BW (2015) Plasticity in striatopallidal projection neurons mediates the acquisition of habitual actions. Eur J Neurosci 42(4):2097–2104
Shuen JA, Chen M, Gloss B et al (2008) Drd1a-tdTomato BAC transgenic mice for simultaneous visualization of medium spiny neurons in the direct and indirect pathways of the basal ganglia. J Neurosci 28(11):2681–2685
Sippy T, Lapray D, Crochet S et al (2015) Cell-type-specific sensorimotor processing in striatal projection neurons during goal-directed behavior. Neuron 88(2):298–305
Smith Y, Parent A, Seguela P, Descarries L (1987) Distribution of GABA-immunoreactive neurons in the basal ganglia of the squirrel monkey (Saimiri sciureus). J Comp Neurol 259(1):50–64
Soghomonian JJ, Chesselet MF (2000) GABA in the basal ganglia. In: Martin D, Olsen R (eds) GABA in the nervous system. Lippincott Williams and Wilkins, Philadelphia, pp 265–291
Somogyi P, Smith AD (1979) Projection of neostriatal spiny neurons to the substantia nigra. Application of a combined Golgi-staining and horseradish peroxidase transport procedure at both light and electron microscopic levels. Brain Res 178(1):3–15
Stoof JC, Kababian JW (1981) Opposing roles for D-1 and D-2 dopamine receptors in efflux of cyclic AMP from rat neostriatum. Nature 294(5839):366–368

Stoof JC, Kababian JW (1984) Two dopamine receptors: biochemistry, physiology and pharmacology. Life Sci 35(23):2281–2296
Surmeier DJ, Song WJ, Yan Z (1996) Coordinated expression of dopamine receptors in neostriatal medium spiny neurons. J Neurosci 16(20):6579–6591
Svenningsson P, LeMoine C, Kull B et al (1997) Cellular expression of adenosine A2A receptor messenger RNA in the rat central nervous system with special reference to dopamine innervated areas. Neuroscience 80(4):1171–1185
Szabo J (1967) The efferent projections of the putamen in the monkey. Exp Neurol 19(4):463–476
Szabo J (1970) Projections from the body of the caudate nucleus in the rhesus monkey. Exp Neurol 27(1):1–15
Tanaka D (1980) Development of spiny and aspiny neurons in the caudate nucleus of the dog during the first postnatal month. J Comp Neurol 192(2):247–263
Thibault D, Loustalot F, Fortin GM et al (2013) Evaluation of D1 and D2 dopamine receptor segregation in the developing striatum using BAC transgenic mice. PLoS One 8(7), e67219
Valjent E, Bertran-Gonzalez J, Herve D et al (2009) Looking BAC at striatal signaling: cell-specific analysis in new transgenic mice. Trends Neurosci 32(10):538–547
Vincent SR, Kimura H, McGeer EG (1982) GABA-transaminase in the basal ganglia: a pharmacohistochemical study. Brain Res 251(1):93–104
Wang HB, Laverghetta AV, Foehring R et al (2006) Single-cell RT-PCR, in situ hybridization histochemical, and immunohistochemical studies of substance P and enkephalin co-occurrence in striatal projection neurons in rats. J Chem Neuroanat 31(3):178–199
Wang HB, Deng YP, Reiner A (2007) In situ hybridization histochemical and immunohistochemical evidence that striatal projection neurons co-containing substance P and enkephalin are overrepresented in the striosomal compartment of striatum in rats. Neurosci Lett 425(3):195–199
Weiner DM, Levey AI, Sunhara RK et al (1991) D1 and D2 dopamine receptor mRNA in rat brain. Proc Natl Acad Sci U S A 88(5):1859–1863
Wilson CJ, Groves PM (1980) Fine structure and synaptic connections of the common spiny neuron of the rat neostriatum: a study employing intracellular inject of horseradish peroxidase. J Comp Neurol 194(3):599–615
Wilson CJ, Phelan KD (1982) Dual topographic representation of neostriatum in the globus pallidus of rats. Brain Res 243(2):354–359
Wu Y, Richard S, Parent A (2000) The organization of the striatal output system: a single-cell juxtacellular labeling study in the rat. Neurosci Res 38(1):49–62
Yamaguchi T, Goto A, Nakahara I et al (2015) Role of PKA signaling in D2 receptor-expressing neurons in the core of the nucleus accumbens in aversive learning. Proc Natl Acad Sci U S A 112(36):11383–11388
Yawata S, Yamaguchi T, Danjo T et al (2012) Pathway-specific control of reward learning and its flexibility via selective dopamine receptors in the nucleus accumbens. Proc Natl Acad Sci U S A 109(31):12764–12769
Yung KK, Bloam JP, Smith AD et al (1995) Immunocytochemical localization of D1 and D2 dopamine receptors in the basal ganglia of the rat: light and electron microscopy. Neuroscience 65(3):709–730
Zalocusky KA, Ramakrishnan C, Lerner TN, Davidson TJ, Knutson B, Deisseroth K (2016) Nucleus accumbens D2R cells signal prior outcomes and control risky decision-making. Nature 531(7596):642–646