11

Microcircuits of the Striatum

J. Paul Bolam

The striatum (or caudate-putamen, or caudate nucleus and putamen in those species in which they are divided by the internal capsule) is the major division of the basal ganglia, a group of structures involved in a variety of processes, including movement and cognitive and mnemonic functions. The striatum consists of a population of principal neurons, the medium-sized densely spiny neurons (MSNs; up to 97% of all neurons depending on species), which are the projection neurons of the striatum, several populations of GABAergic interneurons, and a population of cholinergic interneurons. The principal afferents of the striatum are glutamatergic, are derived from the cortex and thalamus, and mainly innervate the spines of MSNs. The essential computation performed by the striatum is the selection of which MSNs will fire, the consequence of which is altered firing of basal ganglia output neurons and hence the selection of the basal ganglia–associated behavior.

The essential aspects of the microcircuitry of the striatum are summarized as follows (also see Figs. 11.1– 11.3):

1. Under resting conditions the large population of MSNs is in a quiescent relatively hyperpolarized state, and selected MSNs or groups of MSNs are activated by afferent excitatory input/drive originating in the cortex and thalamus (Fig. 11.1).
2. The response of MSNs to excitatory drive from the cortex and thalamus is modified by the local collaterals of the MSNs (feedback inhibition) and the activity of GABAergic interneurons (feedforward inhibition; Fig. 11.2).
3. Short- and long-term plasticity of the excitatory transmission is under the control of modulatory inputs to the striatum, principally the dopaminergic nigrostriatal projection, but also possibly serotonergic and histaminergic afferents, and by the activity of cholinergic interneurons (Fig. 11.3).

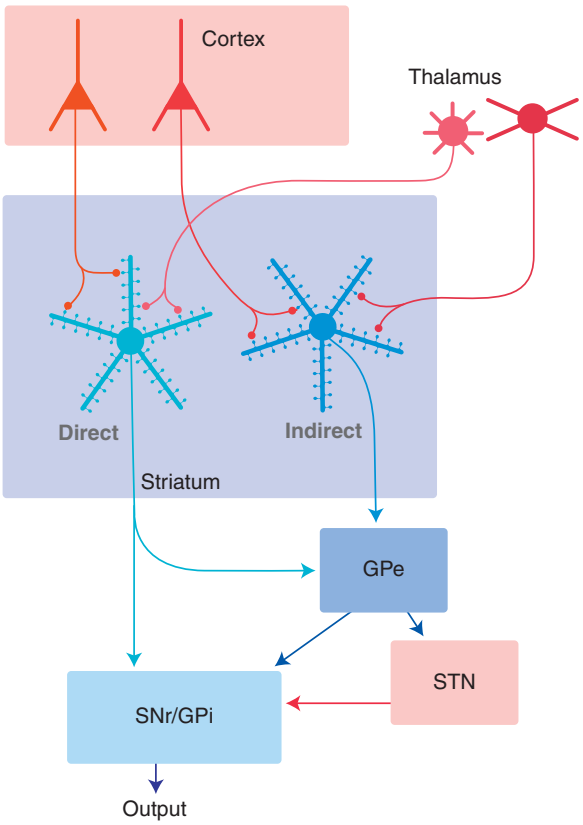

FIGURE 11–1. Microcircuit of the striatum. The majority of neurons in the striatum are the GABAergic output neurons, the medium-size densely spiny neurons (MSNs). MSNs are of two main types; on the left is an MSN of the direct pathway. These neurons *directly* innervate the output nuclei of the basal ganglia, the internal segment of the globus pallidus (GPi), and the substantia nigra pars reticulata (SNr), and they also send a collateral to the external segment of the globus pallidus (GPe). On the right is an MSN of the indirect pathway. These neurons *indirectly* innervate the output nuclei of the basal ganglia by innervating the GPe and then the output nuclei, and by innervation of the subthalamic nucleus (STN). Under resting conditions the MSNs are quiescent. They are activated by their main afferents, the excitatory, glutamatergic input originating in the cortex (CTX) and thalamus (THAL). Sufficient excitatory input to their 10–15,000 spines raises them to a depolarized "up-state" from which action potentials can be driven that then influence the activity of the output neurons of the basal ganglia via the direct and indirect pathways. The expression of basal ganglia function is thus a consequence of which MSNs are "selected," ultimately leading to the selection of the behavior. It is unknown as yet, whether individual MSNs receive input from both the cortex and the thalamus or whether individual cortical or thalamic axons innervate both direct and indirect pathways neurons. Red indicates glutamatergic structures; blue indicates GABAergic structures.

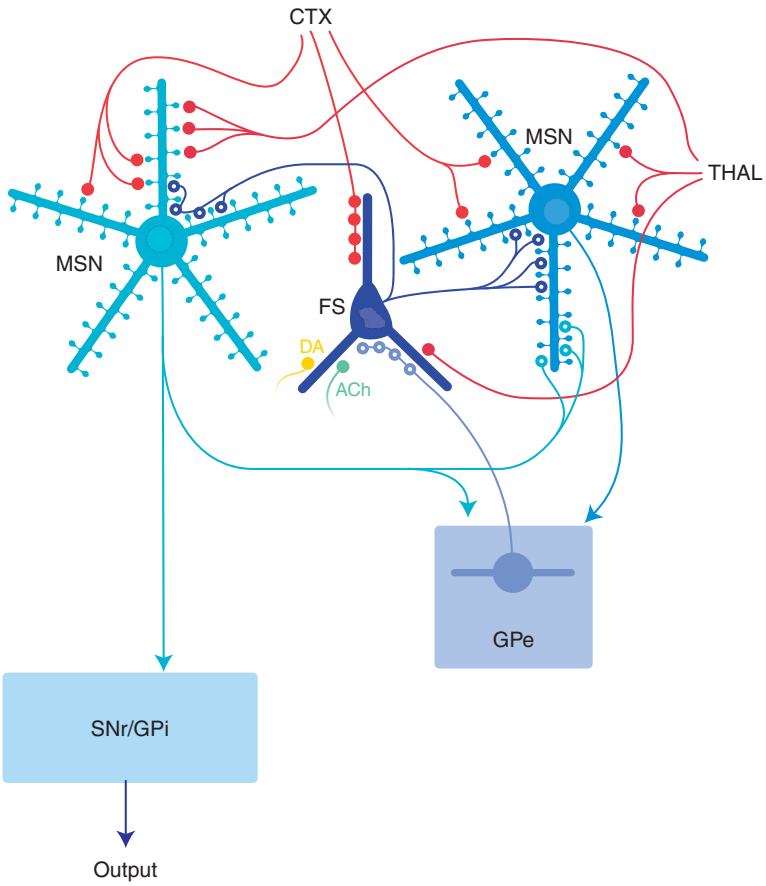

FIGURE 11–2. GABAergic inputs sculpt the response of medium-size densely spiny neurons (MSNs) to cortical and thalamic afferents. MSNs receive both feedback and feedforward GABAergic inhibition. Feedback inhibition is subserved by the axons of MSNs, which, in addition to giving rise to the output of the striatum, also give rise to local axon collaterals. The main synaptic target of the local collaterals is the dendrites (mainly distal) of other MSNs (only a connection between a direct pathway MSN and an indirect pathway MSN is illustrated here). In comparison to the interneurons, the response to MSN collateral activation is relatively weak when measured at the level of the soma. Feedback inhibition may thus involve dendritic processing rather than controlling the output of MSNs. Feedforward inhibition is mediated by GABAergic interneurons of which there are at least three types. Only one is illustrated here, the parvalbumin-positive fast-spiking GABAergic interneuron (FS). These neurons receive both cortical and thalamic input and in turn provide a powerful feedforward inhibition in the proximal regions of MSNs, which can prevent or delay the initiation of action potentials. The FS interneurons, as well as those that express NOS, also receive a prominent input to their cell bodies and proximal dendrites from the tonically active GABAergic neurons of the external globus pallidus (GPe). Thus, by virtue of their large axonal arbor, GABAergic interneurons are in a position to select which populations of MSNs will fire; they in turn are under the control of neurons of the GPe. Since the major input to neurons of the GPe are MSNs, the network involving the "indirect pathway" is critically involved in the selection of individual of groups of MSNs. GABAergic interneurons also receive input from dopaminergic terminals (DA, yellow) and cholinergic terminals (ACh, green). It is unknown as yet whether individual GABAergic interneurons receive input from both the cortex and the thalamus or whether the same cortical or thalamic axons innervate both MSNs and their connected GABAergic interneurons. Red indicates glutamatergic structures; blue indicates GABAergic structures.

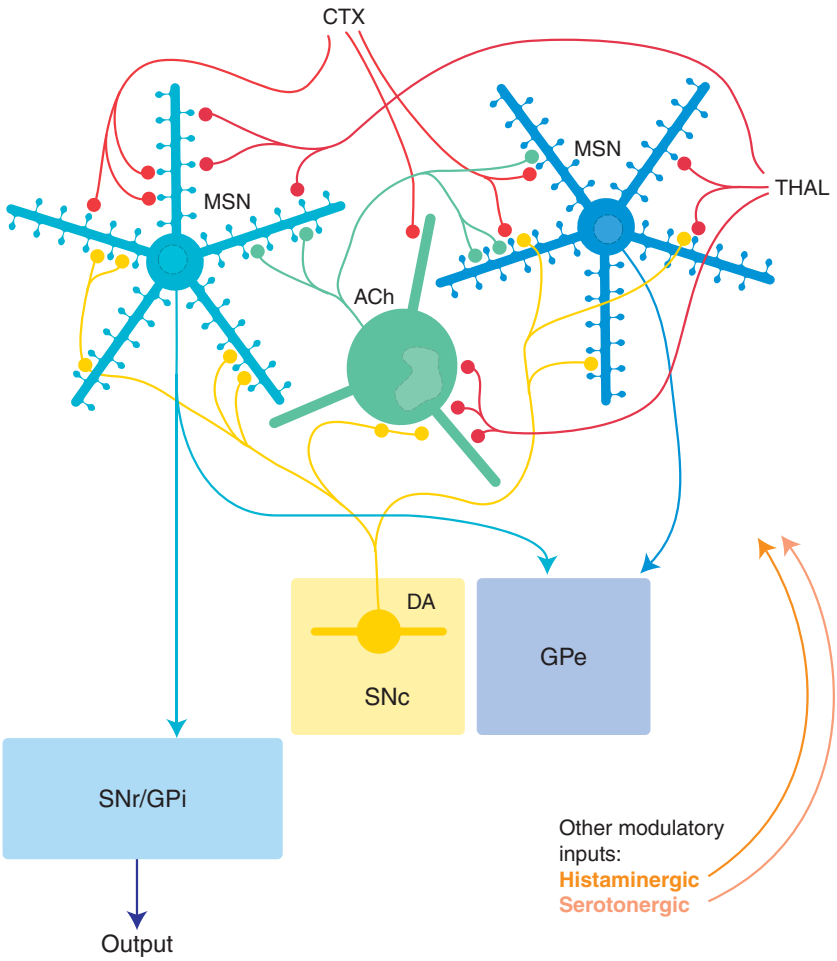

FIGURE 11–3. Modulatory control of the activity of medium-size densely spiny neurons (MSNs). The dopaminergic nigrostriatal projection (DA, yellow) provides a dense innervation of the striatum. Synaptically released dopamine, or dopamine spill-over from the synapse, modulates the responses of MSNs to the excitatory input at both pre- and postsynaptic sites. The net effect of dopamine is the long- or short-term enhancement or attenuation of glutamatergic transmission. Cholinergic neurons (ACh, green) also underlie a modulatory control of MSNs. Released acetylcholine acting upon both muscarinic and nicotine receptors modulates the release of glutamate presynaptically and the responsiveness of MSNs to other afferents by a variety of mechanisms. Cholinergic interneurons, like other classes of interneurons in the striatum, are a site of interaction of neuromodulators within the striatum. The striatum also receives "modulatory input" from serotonergic-containing afferents originating in the dorsal raphé and histaminergic afferents from the tuberomammillary nucleus. Little is known of their connections and functional properties. It is unknown as yet whether individual cholinergic interneurons receive input from both the cortex and the thalamus or whether the same cortical or thalamic axons innervate both MSNs and their connected cholinergic interneurons. Red indicates glutamatergic structures; blue indicates GABAergic structures.

Medium-Sized Densely Spiny Neurons and Their Excitatory Afferents

Medium-sized densely spiny neurons give rise to several dendrites that are initially spine free but then become densely laden with spines after the first bifurcation. They utilize GABA as their major neurotransmitter and are subdivided into two major subpopulations on the basis of their projection region, pattern of axonal collateralization, and their neurochemical content. One subpopulation gives rise to the "direct pathway," that is, they preferentially project *directly* to the output nuclei of the basal ganglia, the internal segment of the globus pallidus (GPi or entopeduncular nucleus in some species), and the substantia nigra pars reticulata (SNr) (but also sending a collateral to the external segment of the globus pallidus; GPe). They selectively express (among other molecular markers) the neuropeptides substance P and dynorphin, and the D1 subtype of dopamine receptor. The second subpopulation gives rise to the "indirect pathway"; they exclusively project to the GPe, which in turn projects to the output nuclei directly and via the subthalamic nucleus, that is, they thus *indirectly* innervate the output nuclei. They selectively express (among other molecular markers) enkephalin and the D2 subtype of dopamine receptors.

Under resting conditions, most neurons in the striatum (with the exception of cholinergic interneurons) are quiescent. The principal "driver" inputs to the striatum, and the basal ganglia in general, are the excitatory glutamatergic afferents from the cortex and the thalamus (mainly the intralaminar thalamic nuclei). The massive excitatory input from the cortex is derived from virtually the whole cortical mantle and provides motor, cognitive, and limbic information. Two main classes of pyramidal neurons give rise to the projection: pyramidal tract neurons (lower layer V) that give off collaterals within the ipsilateral striatum and pyramidal neurons that bilaterally innervate the cortex and striatum only (layer III and upper layer V). The main synaptic targets of the corticostriatal projection are the spines of both direct and indirect pathway MSNs. The two types of neurons seem to show selectivity for the different classes of MSNs (Lei et al., 2004). Corticostriatal terminals also make synaptic contact with the dendritic shafts of interneurons. Individual corticostriatal axons are likely to give rise to only a small number of synapses with an individual MSN, which, since MSNs possess 10,000–15,000 spines, implies a massive convergence of cortical input (Wilson, 2007).

The excitatory input from the thalamus is of the same order of magnitude as the cortical input when considering the number of synapses within the striatum (Lacey et al., 2005; Raju et al., 2008). The thalamostriatal projection mainly originates in the intralaminar nuclei, providing information about the external world and the state of arousal and wakefulness, however, many other thalamic nuclei also innervate the striatum. The main synaptic targets are the spines of both direct and indirect pathway MSNs, but they also

innervate the dendritic shafts of MSNs and interneurons. Thalamostriatal neurons are of *at least* two markedly distinct types with respect to their somatodendritic morphology, their firing characteristics, and their synaptic targets within the striatum (Lacey et al., 2007). Those originating in the central lateral nucleus have a bushy dendritic arbor typical of thalamic neurons, give rise to low-threshold Ca^{2+} spike bursts, and innervate exclusively the spines of MSNs (presumably giving rise to both the direct and indirect pathways). In contrast, those in the parafascicular nucleus have long, infrequently branching dendrites, have a lower firing frequency, are less bursty, and mainly innervate dendritic shafts of striatal interneurons although the spines of MSNs are also targets. The precise distribution of postsynaptic targets is highly variable among individual parafascicular neurons. As with the cortical input, it is likely that there is a massive convergence of thalamic afferents onto individual MSNs. It is also likely that there is convergence of both cortical and thalamic inputs at the level of individual MSNs.

Both of these excitatory afferents are highly topographically organized. Corresponding functional territories of cortex and thalamus innervate similar regions of the striatum; thus, they impart the functionality upon the striatum and the basal ganglia in general. However, it should be noted that there are many sites and mechanisms in the striatum and other regions of the basal ganglia that underlie the integration of functionally diverse information.

Principles of Operation of the Microcircuits of the Striatum

Alterations in the firing of the output neurons of the basal ganglia (GABAergic, tonically active neurons in the SNr and GPi) underlie the expression of basal ganglia function. The principal players in the control of their activity are MSNs, either through their direct innervation of the output neurons or their indirect innervation of the output neurons through the "indirect pathway," or rather, the complex networks underlying the "indirect pathway." The role of the microcircuits of the striatum is the selection of individual, or groups, of MSNs to fire action potentials and thereby influence the activity of the output neurons of the basal ganglia and hence the selection, learning, and reinforcing of the appropriate behavior. Under resting conditions, MSNs are held at a relatively hyperpolarized and quiescent state as a consequence of the profile of ion channels they express. The excitatory drive to the MSNs carried by the glutamatergic corticostriatal and thalamostriatal pathways leads to depolarization of MSNs, bringing them to a so-called up-state. It is in this state that additional excitatory inputs, an alteration in the strengths of the synapses, or an alteration in the balance of excitatory and inhibitory inputs, leads to the firing of action potentials. Which individual MSNs or ensembles of MSNs fire at a given moment of time will depend on which afferent fibers are active, the pattern of innervation of individual MSNs by individual afferent axons, and the degree of convergence at the level of individual MSNs, the feedback and

feedforward inhibition (via their local collaterals and via interneurons) and modulation of the excitatory transmission. According to the classical "direct/indirect pathway model," the firing of the selected population of MSNs will lead to the inhibition of a selected group of basal ganglia output neurons, which will then lead to the selection of the basal ganglia behavior. Simultaneous activation of MSNs of the indirect pathway is considered to temporally and/or spatially inhibit/attenuate or focus the basal ganglia behavior. However, the role of the "indirect" pathway is likely to be more complex and involve the selection process at every level of the basal ganglia.

Sculpting of the Response of Medium-Sized Densely Spiny Neurons by GABA Transmission

Feedback Inhibition

In addition to providing the output of the striatum, MSNs give rise to local axon collaterals, the main synaptic targets of which are the dendritic shafts of other MSNs. Direct pathway MSNs innervate other direct pathway neurons as do indirect pathway MSNs. Similarly, MSNs of the two pathways are synaptically interconnected. Synapses are located principally on the dendritic shafts in the more distal regions, that is, the spiny regions of the dendrites. The responses of spiking in a single presynaptic spiny neuron on postsynaptic MSNs are weak when measured at the level of the soma (particularly compared to the response to GABA interneurons; see Feedforward Inhibition) and do not significantly affect spike timing or generation (Tepper et al., 2008). This presumably relates to the location of the synapses on distal dendrites. Feedback inhibition may thus be involved in dendritic processing; however, sufficient convergent and simultaneous activation of MSN collaterals may influence the firing of the target MSNs (Wilson, 2007).

Feedforward Inhibition

The striatum also contains at least three populations of GABAergic interneurons, which account for ~3%–10% of striatal neurons depending on species: *(1)* Fast-spiking, parvalbumin-positive interneurons (FS-PV); *(2)* those that express nitric oxide synthase (NOS), neuropeptide Y, and somatostatin; and *(3)* those that express calretinin. The connections of GABAergic interneurons are summarized in Figure 11.2; most of the data are derived from the FS-PV neurons and to some extent the NOS-positive neurons. The GABAergic interneurons mainly innervate the dendritic shafts of MSNs and, at least in the case of FS-PV GABAergic interneurons, mainly in their proximal regions, including the perikaryon. They receive prominent input from terminals forming asymmetrical synapses derived from the cortex and thalamus. Unlike the

feedback inhibition, feedforward inhibition is powerful and widespread. Spiking in a single interneuron leads to profound inhibitory postsynaptic potentials (IPSPs) in MSNs that are capable of blocking the generation of spikes in a large number of postsynaptic MSNs (Tepper et al., 2008). Although it is not known whether GABAergic interneurons receive the same cortical and thalamic input as do their target MSNs, it is clear that fast-spiking interneurons do provide a feedforward inhibition *in vivo* (Mallet et al., 2005). One of the roles of FS-PV interneurons may be to synchronize the activity of large populations of MSNs because their activation can lead to a brief delay in the firing of MSNs and their extensive axonal arborization (about 5000 synapses) means they are in contact with many (possibly hundreds) of MSNs (Koos and Tepper, 1999).

The FS-PV GABAergic interneurons, as well as the NOS-expressing GABAergic interneurons, receive a prominent innervation of their cell bodies and proximal dendrites from tonically active GABAergic neurons of the GPe (Bevan et al., 1998), which will presumably shunt excitatory cortical and thalamic drive. Firing of GABAergic interneurons will presumably only occur with the release or altered pattern of this inhibitory control. This will occur when MSNs of the indirect pathway are activated. Thus, GABAergic interneurons are involved in the spatiotemporal selection of which individual and ensembles of MSNs fire; in turn, they are under the control of the activity of neurons of the GPe and ultimately the activity of MSNs that give rise to the indirect pathway.

Modulatory Control of the Activity of Medium-Sized Densely Spiny Neurons

Modulatory Afferents

The activity of MSNs and excitatory afferents are under the *modulatory* control (short- and long-term plasticity) of several afferents to the striatum, including the histaminergic input from the tuberomammillary nucleus (providing information on wakefulness), serotonergic input originating in the dorsal raphé (providing information on basic physiological functions such as sleep, arousal, and satiety, as well as mood and emotion), and dopaminergic input from the substantia nigra pars compacta (SNc; providing information on motivation, reward, and stimulus salience). The density of the histaminergic and serotonergic innervation is relatively low compared to the dopaminergic innervation, and both seem to give rise to only few synapses; however, there little is known about their connections.

The dopaminergic innervation of the dorsal striatum originates in the SNc and a group of dopamine neurons located more ventrally in the SNr. Those dopaminergic neurons of the ventral tegmental area provide the main

dopaminergic innervation of the ventral striatum and the prefrontal cortex. Dopamine neurons are heterogeneous with respect to their activity during reward-related activity (Bromberg-Martin and Hikosaka, 2009; Brown et al., 2009), but clearly their activities relate to reward, reward prediction error, and salience of an event and, as such, play a role in reinforcement-based learning.

Individual dopamine neurons provide a phenomenal innervation of the dorsal striatum. In the rat, the average total length of the axon of an individual dopamine neuron in the striatum is in the region of 47 cm and the arborization can occupy up to 5.7% of the volume of the striatum (Matsuda et al., 2009). This implies a large degree of convergence but similarly a large degree of divergence. Based on the numbers of neurons in the SNc and the striatum, and the known synaptic organization of the dopaminergic nigrostriatal projection, it is estimated that an individual dopaminergic neuron gives rise to between 170,00 and 408,000 synapses in the dorsal striatum (Moss and Bolam, 2010). The synapses are small and symmetrical (Gray's type 2) and are formed with dendritic spines, shafts, and perikarya of MSNs and interneurons. About 20% of those spines of MSNs that receive input from the *cortex* are apposed by a dopamine axon and about half make synaptic contact. Similarly, about 20% of those spines of MSNs that receive input from the *thalamus* are apposed by a dopamine axon and about half make synaptic contact. The association of the dopaminergic axons and synapses with spines and dendrites of MSNs, however, is unlikely to be a selective or targeted phenomenon as, when corrected for size, all structures in the striatum have an equal probability of being apposed by or in synaptic contact with dopaminergic axons (Moss and Bolam, 2008). Furthermore, the dopaminergic innervation is so dense that every point within the striatum is within 1 μm of a dopaminergic synapse. Since it has been proposed that synaptically released dopamine can diffuse up to 2–8 μm in a sufficient concentration to stimulate both high- and low-affinity dopamine receptors (Rice and Cragg, 2008), then every structure in the striatum is under the influence of dopamine.

Dopamine released at synapses located on structures postsynaptic to the excitatory cortical or thalamic synapses (and presumably dopamine that has diffused from synapses) modulates the response of MSNs to the excitatory input. Modulation of excitatory transmission can also occur at the level of the presynaptic terminal. There are many forms of dopamine-dependent plasticity or modulation of excitatory input to MSNs, including long-term potentiation, long-term depression, and changes in excitability and interactions at the level of receptors, signaling pathways, and gene regulation. Many factors influence the dopamine-dependent plasticity, including spike timing, the subclass of dopamine receptors involved, as well as the activation of NMDA receptors, the release of endocannabinoids, and the action of cholinergic interneurons (Wickens, 2009). The net effect is the long- or short-term enhancement or attenuation of glutamatergic transmission and the selection of which

neurons reach or are prevented from reaching firing threshold, thus playing a role in reinforcement learning.

Cholinergic Interneurons

In addition to the GABAergic interneurons, the striatum also contains a population of large cholinergic interneurons (giant aspiny neurons) that give rise to a massive axonal arbor (the striatum contains the highest density of cholinergic markers in the brain). They innervate MSNs (in a similar manner to the dopaminergic innervation) and receive major inputs from the parafascicular nucleus of the thalamus (and presumably other thalamic nuclei), the cortex (seemingly mostly in their distal regions), and MSNs of both the direct and indirect pathway. They are considered to be the so-called tonically active neurons (TANs), whose activity is intimately related to the activity of dopamine neurons; a pause in their firing during reward-related paradigms is associated with the burst in activity in dopamine neurons and is considered to code the salience of an event. However, as with dopamine neurons the functional properties of cholinergic neurons are heterogeneous (Apicella et al., 2009). Released acetylcholine acting upon both muscarinic and nicotine receptors modulates the release of glutamate presynaptically and the responsiveness of MSNs to other afferents by a variety of mechanisms (Pisani et al., 2007). The effects of changes in the firing of cholinergic neurons, as with the dopamine input, thus plays a role in the selection of which individual MSNs or groups of MSNs are raised to firing threshold. It should be noted also that cholinergic interneurons, like other classes of interneurons in the striatum, are a site of interaction of neuromodulators within the striatum (Koos and Tepper, 2002).

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12

Templates for Neural Dynamics in the Striatum: Striosomes and Matrisomes

Ann M. Graybiel

The striatum appears to be a relatively simple forebrain region, when compared to the overlying neocortex with its horizontal layers and vertical columns. In fact, however, the striatum in mammals has a sophisticated architecture of its own. This large subcortical region is now suspected of having a major influence on how the neocortex carries out its own functions—even functions related to human language (Graybiel, 2008; Enard et al., 2009). Furthermore, abnormalities in the striatum are increasingly being discovered in human disorders affecting cognitive as well as motor functions. It is, as a consequence, increasingly difficult to see the neocortex as a "higher structure" and the striatum as a "lower structure" in ranking their influence on behavior. In this chapter, I suggest that the functional architecture of the striatum provides a physical template for dynamic plasticity in striatal networks. I then propose that this dynamic plasticity may be key to understanding how the basal ganglia influence the neocortex as well as downstream action systems of the brain: first, by promoting adaptive behavioral flexibility, and second, by allowing the forebrain to create, as a result, chunked cognitive and motor action patterns.

The Striatum Has a Modular Neurochemical Organization: Striosomes

The first clue to the modularity of the striatum came from the early application of methods for studying the distributions of neurotransmitter-related substances in the brain. For example, the striatum stands out sharply among forebrain regions as having very strong expression of markers for cholinergic

and dopaminergic transmission, and these turn out not to be uniform. Nor are the distributions of other neurotransmitters, neuromodulators, receptors, and even second messenger molecules uniform. Nearly every one of these has a striking distribution, in which widely dispersed, relatively small zones stand out as being enriched or impoverished in the substance being analyzed. We called these zones "striosomes" (striatal bodies) to distinguish them from the much larger extrastriosomal striatal tissue, which we called the "matrix" (Graybiel and Ragsdale, 1978; Graybiel, 1990). Striosomal organization of striatal transmitter systems is present from quite early in embryonic development. In some instances, there are dramatic shifts in striosome/matrix expression patterns across development (e.g., for substances related to dopaminergic and cholinergic transmission), while for other substances the compartmental distributions are relatively stable.

The Striatum Has a Modular Input-Output Organization: Striosomes and Matrisomes

The modular organization of the striatum extends beyond a simple striosome/matrix organization, because the inputs to the matrix also are largely organized into modules. For example, the somatosensory cortex projects to the striatum in such a way that regions representing particular parts of the body map project to widely dispersed patchy regions in the matrix. Moreover, somatotopically matched parts of the somatosensory and motor cortex send overlapping patchy inputs to the striatum. This suggests that information about a given functional domain is collected into dispersed, but organized, convergence zones. This organization holds also for striatal inputs from the oculomotor cortex. It further has been shown that the dispersed matrisomes receiving inputs from corresponding somatosensory and motor cortex themselves can send convergent outputs to the basal ganglia output nuclei (Fig. 12.1A). Thus, there is a divergent-reconvergent architecture for the cortex-to-striatum-to-output nuclei of the basal ganglia (Flaherty and Graybiel, 1994). The entire map of striatal input-output organization has not been established. However, there is enough evidence to suggest highly principled connectivity between most areas of the neocortex and the striatum (Ragsdale and Graybiel, 1990).

Striosomes and Matrisomes as Templates for Plasticity

The divergent-reconvergent architecture of matrisomes seems ideal for allowing new combinations of inputs and outputs to be flexibly coordinated. For example, somatosensory input matrisomes receive inputs related to a given part of the body from corresponding parts of several somatosensory

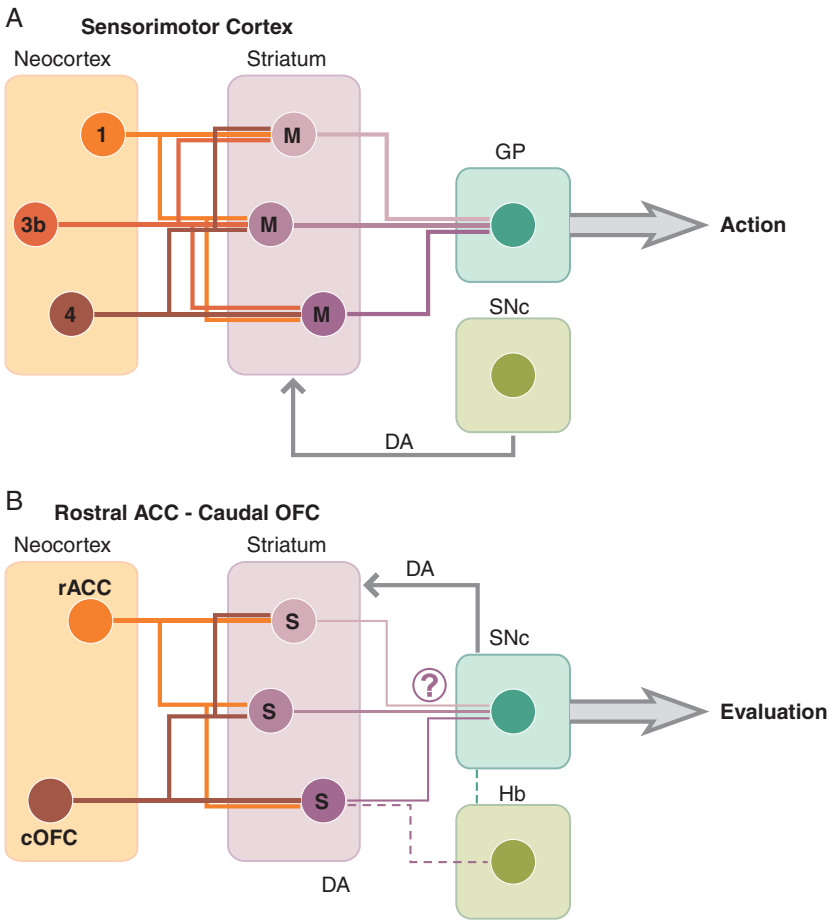

FIGURE 12–1. Schematic diagram of cortico-basal ganglia circuits leading through the striatum. (*A*) Sensorimotor circuits channeled through sensorimotor matrisomes. (*B*) Limbic-affective circuits channeled through striosomes. 1, 3b, 4, areas 1 and 3b of somatosensory cortex and area 4 of motor cortex; cOFC, caudal orbitofrontal cortex; DA, dopamine; GP, globus pallidus; Hb, habenula; M, matrisome; rACC, rostral (pregenual) anterior cingulate cortex; S, striosome; SNc, substantia nigra pars compacta.

areas and from the motor cortex. By having these different inputs converge, the modularity increases the chance for spatially local activation of striatal neurons. This convergence allows timing to become critical: when the inputs are convergent, they could differentially activate the matrisomes if the inputs were temporally correlated. This idea is supported by evidence that when somatosensory or motor cortex are stimulated to provide briefly simultaneous activation of cortical sites with matching somatotopy, striatal neurons in the corresponding matrisomes are stimulated to express early response

genes (Parthasarathy and Graybiel, 1997). Thus matrisomes provide a way for information from different functionally related cortical regions to be recombined flexibly, rapidly, and selectively.

The striosomal system might be a comparable system to allow dynamic modulation of high-order circuits related to emotion, motivation, and evaluation (Fig. 12.1B). For example, striosomes in the anterior striatum receive converging inputs from the anterior cingulate cortex and the caudal orbitofrontal cortex, regions important for neural monitoring and control of motivation and emotion (Eblen and Graybiel, 1995). Moreover, neurons in striosomes project to the immediate vicinity of the dopamine-containing neurons of the substantia nigra, and they can also probably influence nigral activity via the lateral habenula (Rajakumar et al., 1993). This pattern suggests that the striosomes could have a powerful influence over what is learned through the action of basal ganglia-based circuits related to reinforcement-based learning (Eblen and Graybiel, 1995; Graybiel, 2008). Striosomes could also be related to the registration of salient stimuli and the reactions made to them, regardless of whether learning occurs. Far more needs to be learned about the connections of these striatal modules, and their physiology is still not known. Indirect evidence, however, some from physiology, supports the idea that striosomes might be related to processing salient stimuli, either rewarding or aversive (Aosaki et al., 1995; White and Hiroi, 1998; Blazquez et al., 2002).

Local and Distributed Processing by Striosomes and Matrisomes

Striosomes and matrisomes are three-dimensionally extended labyrinthine structures spread out widely within the striatum, not local patches or spheres (Graybiel and Ragsdale, 1978; Mikula et al., 2009). Moreover, the striosomes have distributions suggesting that they could provide nearly complete coverage of the part of the striatum in which they lie (Graybiel, 1984). This means that they could serve to coordinate, in space and time, the activity of many striatal neurons within their resident regions. This idea suggests that these modules could be important not only for local coordination of striatal processing—within individual striosomes or matrisomes—but also for coordination of more distributed striatal domains.

Striatal Compartments and State-Level Dynamic Processing

Coherent local field potential (LFP) activity is present in the striatum, even though only a small percentage of the single units in the striatum show coherent spike activity. For example, in monkeys performing oculomotor tasks, the LFP activity in the striatum exhibits high levels of beta-band coherence.

However, localized task-activated regions can exit from this general coherence in relation to task demands. These localized regions could represent matrisomes with task-related activity (Courtemanche et al., 2003). If so, the compartmentalization of the striatum would be important for organizing patterns of synchrony there, and thus for organizing global patterns of information flow.

A puzzle still to be addressed is how such broad synchrony of LFP activity, present even across regions that are parts of functionally distinct cortico-basal ganglia loops, is related to the distinctly different spike activity patterns that can be recorded in these different regions of the striatum. One idea is that the LFP coherence acts as a thresholding device, and that the pop-out of task-related activity represents supra-threshold activity (Courtemanche et al., 2003). The interneurons of the striatum are likely critical in setting these patterns of coherent activity and in organizing such dynamic filtering; all appear to have compartmentalized distributions, with most being more concentrated in the matrix or near striosome-matrix borders (Aosaki et al., 1995). The striosome and matrix compartments could thus be important for setting temporal patterns of activity in the striatum.

Striosomes and Repetitive Behaviors

The transmitter-related specializations of striosomes relative to the surrounding matrix are impressive, suggesting that striosomes are likely to have particular functional effects due to their molecular expression patterns. The functional significance of this neurochemical specialization of the striosomes is still not understood. However, it is known that striosomes and matrix respond differently to treatments with dopamine receptor agonists. These differential responses likely have important functional implications. For example, the ratio of activity in striosomes and matrix in some parts of the striatum is highly correlated with the level of repetitive behavior induced by drugs such as amphetamine (Saka et al., 2004). The levels of levodopa-induced dyskinesias in models of parkinsonism are also correlated with differential striosome/matrix gene expression (Crittenden et al., 2009). One possibility raised by these findings is that differential activity in striosomes produces differential reinforcement-related signals leading to repetitive behaviors. Striosomes could be critical in influencing the balance between positive and negative reinforcement contexts and expectations (Graybiel, 2008). This suggestion is especially interesting given the differentially strong inputs to part of the striosomal system from the pregenual anterior cingulate cortex and the posterior orbitofrontal cortex. There is a pressing need to identify striosomes in electrophysiological recordings, and work in our laboratory is focused on this goal.

Striosomes and Human Neurologic and Neuropsychiatric Disorders

We and colleagues have identified differential effects on striosomes in primate and rodent models of addiction, parkinsonism, repetitive movement and thought disorders, and dopa-responsive dystonia. Moreover, in postmortem human brains, striosomes have been found to be differentially affected in subgroups of Huntington disease patients who in life suffered mood disorders as major symptoms (Tippett et al., 2007), and in patients with X-linked dystonia-parkinsonism (Goto et al., 2005). These findings raise the possibility that the compartmental organization of the striatum will prove to be important for understanding the etiology of some neurologic and neuropsychiatric disorders.

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