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Group Report: Microcircuits, Molecules, and Motivated Behavior

Microcircuits in the Striatum

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ABSTRACT

The aim of this chapter is to bring together data from anatomical, neurochemical, physiological, and behavioral studies in an attempt to understand how the properties of the microcircuits of the striatum can underlie behavior in reward-related paradigms. The canonical microcircuit of the striatum in relation to corticostriatal and dopaminergic afferents is first described. Mechanisms of the selection of "appropriate assemblies of cortical neurons" for the required behavior, by the microcircuit and through the action of the neuromodulators, dopamine and acetylcholine, on corticostriatal synapses are described. The roles of dopaminergic afferents to the striatum and cholinergic neurons within the striatum in reward-related paradigm are discussed. Finally, a mechanism of how the microcircuit, at both the cellular and molecular level, can interface with global brain function in the production of reward-related behavior is discussed.

INTRODUCTION

The essential organization of the microcircuits of the striatum consists of a massive, topographic and heterogeneous input from the whole of the cortical mantle onto the striatum. This projection imparts functionality onto the striatum, which is essentially maintained throughout the cortex–basal ganglia thalamo–cortical loops. Unlike the cortex, the striatum consists of a single layer of neurons, the medium spiny neurons, which are the main targets of the afferent input to the basal ganglia, including that from the cortex, and are the output neurons of the

striatum. Information coded in striatal neurons seems to be different from that in the cortex: the response properties of close neighbors are not similar.

From a functional viewpoint, it is clear that the striatum, and indeed the basal ganglia in general, are involved in a variety of behaviors. For instance, striatal neurons in monkeys fire during memory-guided saccade paradigms (Hikosaka et al. 1989), and similarly, global activation occurs in the rat striatum during T-maze learning (Jog et al. 1999). However, a broad spatial preference of a saccade-related striatal neuron shows a marked modulation of spatial preference when reward is introduced into the paradigm. Similarly, once rats in the T-maze have learned the location of the reward, striatal neurons fire at the beginning of the maze, that is, in expectation of the reward, and in response to goal-reaching at the end of the maze. Thus, the properties of circuits in the striatum show remarkable plasticity with respect to behavioral context, reward, and learning.

A common feature of these behaviors is the *motivation* to act. These aspects of behavior and the plasticity are dependent on the dopamine input to the striatum from the substantia nigra pars compacta (SNc) and the ventral tegmental area (VTA). Thus, the striatum takes sensory, motor, cognitive, and limbic signals from the cortex; the dopamine input, which is carrying motivational or salience information (and reward-expectation error), modifies and shapes the response of the spiny neurons to these cortical signals, which then leads to the context-dependent behavior (Figure 9.1).

These observations imply a selection mechanism; we propose that the function of striatal microcircuits, as part of the cortex–basal ganglia–cortex loop, that are modified by the dopamine input, is to disregard unfavorable outcomes in favor of those that produce the reward. In this chapter, we discuss how the microcircuits of the striatum operate in this "selection" process by addressing four issues:

1. The fundamental or canonical microcircuit.
2. How "selection" can operate in this microcircuit.
3. Plasticity of this microcircuit, particularly in relation to the roles of dopamine (DA) and acetylcholine (ACh).
4. Plasticity of this microcircuit in relation to reward-related behaviors.

THE CANONICAL MICROCIRCUIT

In light of currently available anatomical and electrophysiological data, we propose that the striatal canonical microcircuit consists of two medium spiny projection neurons (MSN), one fast-spiking (FS) GABAergic interneuron, and one cholinergic neuron (Figure 9.2). The MSNs are GABAergic and receive excitatory glutamatergic inputs at the heads of their spines. An individual MSN possesses about 15,000 spines, and it is estimated that about half of these receive input from cortical terminals (Table 9.1). MSNs are also recipients of other

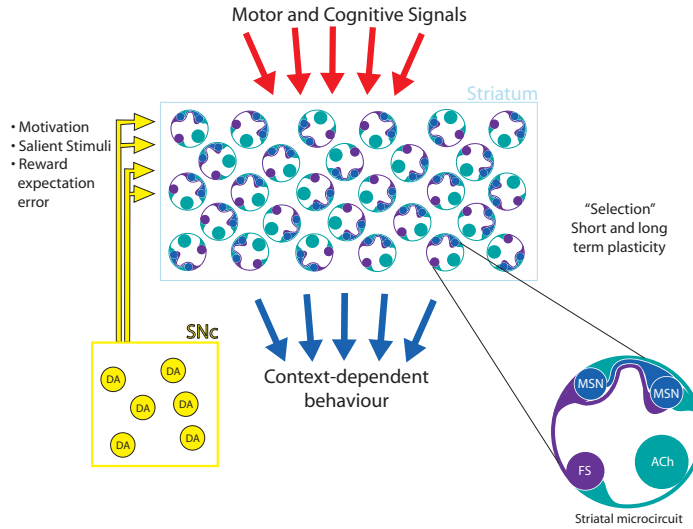

Figure 9.1 Diagrammatic representation of the functional organization of the striatum. The striatum receives motor and cognitive signals primarily from the cortex; the dopamine (DA) input, which is carrying motivational or salience information (and reward-expectation error), together with the striatal microcircuit, modifies and shapes the response of the spiny neurons to the cortical input, which then leads to the context-dependent behavior. For details of the striatal microcircuit see Figure 9.2.

afferent inputs to the striatum including the thalamus (to heads of spines and dendritic shafts; not considered further here) and, importantly for this discussion, dopaminergic input from ventral midbrain (mainly to spine necks and dendritic shafts). They also receive input from striatal interneurons, two of which are critical for the present discussion: the FS interneurons (mainly to the perikarya and proximal dendrites) and the cholinergic interneurons (similar distribution of terminals as the DA input). MSNs themselves give rise to local axon collaterals, the main targets of which are the dendritic shafts of other MSNs. The local axonal arbor is largely co-extensive with the dendritic arbor (average diameter 250 μm). MSNs give rise to the output of the striatum, one population projects to the external globus pallidus (GPe) and one projects to the output nuclei of the basal ganglia, the internal segment of the globus pallidus (GPi) and substantia nigra pars reticulata (SNr) but also providing collaterals to the GPe, and a third population (not considered in detail here) projects to the SNc.

FS GABAergic interneurons account for only a small proportion of striatal neurons, are mainly of medium size, and, like many other fast-spiking interneurons, express the calcium-binding protein, parvalbumin (PV). The main excitatory input to these neurons is also from the cortex, although they do receive

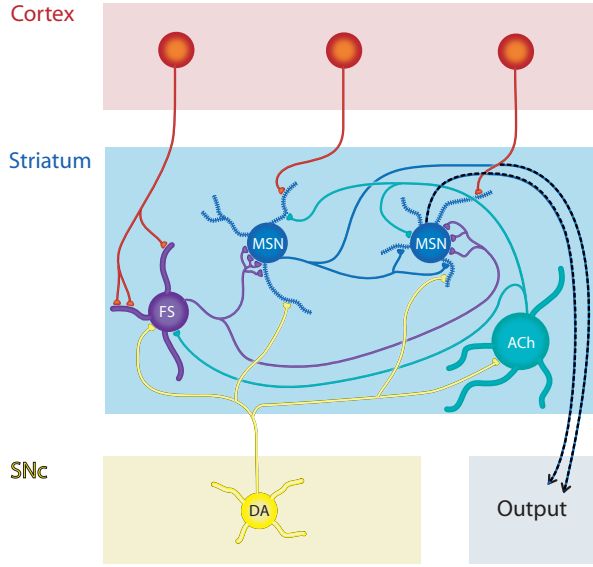

Figure 9.2 The canonical microcircuit of the striatum consists of two medium spiny projection neurons (MSN), one fast-spiking (FS) GABAergic interneuron, and one cholinergic interneuron (ACh). The MSNs are the major output neurons of the striatum and are synaptically interconnected (usually at the level of the dendritic shafts) and receive input from the other two classes of neurons: the FS GABAergic interneuron (at the level of perikarya and proximal dendrites) and ACh interneurons (on perikarya and dendrites). The ACh interneurons also innervate the FS GABAergic interneurons. Critical to the operation of the microcircuit are two afferents of the striatum: first, the corticostriatal projection that innervates the spines of MSNs and the dendrites of FS GABAergic interneurons (as well as cholinergic neurons, not illustrated), and second, the dopaminergic input from the ventral midbrain (DA) that innervates all classes of neurons in the canonical microcircuit.

input from the GPe as well as from the thalamus and cholinergic interneurons. These cells give rise to a dense axonal arbor that is again largely co-extensive with the dendritic arbor (average diameter about 250 μm**)**. The main output of FS neurons is to the perikarya and proximal dendrites of the MSN. There are a large number of PV-positive terminals innervating the proximal regions of MSNs, and it has been estimated that 4–27 PV cells converge onto an individual MSN (Koós and Tepper 1999). Furthermore, FS neurons are in a position to influence the activity of large numbers of MSNs, as their axonal arbors possess in the region of 5000 synaptic boutons, and they have been estimated to contact 135–541 MSNs (Koós and Tepper 1999).

The cholinergic neurons are the "giant" aspiny neurons of the striatum, having a dendritic diameter of up to one millimeter. They receive their afferent innervation from the thalamus, the cortex, DA terminals, and from MSNs. Their

Table 9.1 Quantitative aspects of synapses in the striatal microcircuit.

Presynaptic cell type	Total number of presynaptic cells	Number of synapses per presynaptic cell	Number of synapses per postsynaptic MSN
Corticostriatal pyramidal cell	380,000 in dendritic volume of one spiny neuron (Zheng & Wilson 2002)	40 in dendritic volume of one spiny neuron (Zheng & Wilson 2002)	7,500[a] (Zheng & Wilson 2002)
Medium spiny neuron (MSN)	2,791,000 (Oorschot 1996)	592[b] (Lee et al. 1997)	592[b] (Lee et al. 1997)
Cholinergic interneuron	12,200 (Oorschot 1997)	220,000 [c]	636[c]
GABA/PV interneuron	16,900 (Luk & Sadikot 2001)	5,000	30
Dopamine neuron	7,200 (Oorschot 1996)	370,000[d]	954[d]

[a] Assumes 50% asymmetric synapses are corticostriatal (Groves et al. 1994).
[b] Based on mean number of varicosities per striatonigral neuron (749) times fraction of varicosities with synaptophysin (0.79) (Lee et al. 1997).
[c] Assumes 6% of symmetric synapses are cholinergic (Groves et al. 1994).
[d] Assumes 9% of symmetric synapses are dopaminergic (Groves et al. 1994).

massive axonal arbor, which is far more extensive than that of the other classes, gives rise to many thousands of terminals and, possibly, even hundreds of thousands. One of the main targets of these terminals are MSNs, innervating spine necks, dendritic shafts, and perikarya.

Quantitative aspects of the cellular constituents of the striatal microcircuit provide some clues about the connectivity among them. There are an estimated 2,700,000 medium-sized spiny projection neurons (Oorschot 1996) and 16,900 aspiny GABA/PV interneurons (Luk and Sadikot 2001) in the rat striatum. Current estimates suggest each spiny projection neuron makes in the order of 600 synaptic contacts within the striatum (Oorschot et al. 2002; Wickens 2002). Estimates of the probability of connections based on realistic values of synapse density, extent of axonal and dendritic spread, and the volume of the region of overlap suggest that a pair of spiny projection neurons situated 100 μm apart, with axonal and dendritic arborizations extending up to 200 μm from the soma, would have a low probability of a synaptic contact from one cell to the other (Oorschot et al. 2002; Wickens 2002). This low probability of connections suggests that each spiny neuron probably makes synaptic contact with several

hundred others. Experimental data suggest that the average number of synapses between MSNs is 2.9 (Koós et al. 2004). Because of the low number of synapses and their dendritic location, the connection involves smaller synaptic currents and a higher failure rate than that of the FS neurons (Tunstall et al. 2002; Koós et al. 2004; Tepper and Plenz, this volume).

The FS/GABA interneurons (PV-positive) make many more synaptic contacts per neuron than the MSNs (mean of 7; Koós et al. 2004). There are an estimated 5000 boutons per interneuron. On the other hand, these interneurons constitute less than 1% of the total population of striatal neurons in the rat, and the ratio of spiny neuron to GABA interneuron is on the order of 165:1. Thus, based on these estimates, 5% of the inhibitory synaptic input to a spiny cell is from GABA interneurons and 95% from other spiny cells. These figures do not take into account extrinsic sources of GABA synapses, for example, from GP.

To gain an understanding of the functionality of the circuit, it is important to consider the quantitative aspects of the cortical inputs to both MSNs and FS neurons. It has been estimated (Kincaid et al. 1998) that, within the volume of striatum occupied by a single MSN, there are in the region of 380,000 cortical axons. Based on inter-bouton distances of filled corticostriatal axons, an individual axon gives rise to a maximum of 40 synapses in the same volume of striatum. Since there are about 2840 spiny neurons overlapping in the same volume, a single axon can then only contact less than 1.4% of MSNs. Thus, striatal spiny neurons with overlapping dendritic volumes have few cortical axons in common and cortical axons have few MSNs in common. This implies that individual spiny neurons will receive a massive convergence of individual cortical axons innervating their 15,000 spines and close neighbors will have a dramatically different complement of cortical afferents. There is thus a low degree of anatomical convergence (at the single cortical cell level) but a high degree of convergence of cortical neurons from a particular cortical region. It should be noted, however, that experimental data suggests that the pattern of cortical innervation of the PV-positive neurons (FS GABA interneurons) is different from that of MSNs, in that individual cortical axons frequently form multiple synaptic contacts with an individual PV-positive neuron (Ramanathan et al. 2002). This difference may account for the fact that FS GABA interneurons are more easily activated following cortical stimulation.

Quantitative aspects of the connectivity of the components of the "canonical microcircuit" are summarized in Table 9.1.

It is important to note that we have pared down the microcircuit to those elements that we believe are critical in the selecting and shaping of cortical inputs to the MSN. We have omitted several of the other well-established afferents of the striatum. At this stage, we also consider only those MSNs innervating basal ganglia output nuclei (GPi and SNr) and do not consider in the microcircuit the heterogeneous architecture of the striatum (striosomes and matrix as well as matrisomes located within the maxtrix.

HOW CAN "SELECTION" OPERATE IN THIS MICROCIRCUIT?

Leaving the dopaminergic and cholinergic neurons aside for the moment, the three neurons together (i.e., two MSNs and one FS neuron) form at least one feedback circuit (MSN to MSN connection) and one feedforward circuit (FS neuron to MSN). Based on the morphology, connectivity, and physiology of this microcircuit, we propose three basic methods for the "selection" of corticostriatal inputs:

1. Convergence of large numbers of cortical terminals onto an individual MSN.
2. Lateral inhibition between MSNs.
3. Feedforward inhibition of MSNs mediated by FS interneurons.

Convergence of Cortical Terminals onto an Individual Neuron

As indicated above, an individual MSN receives convergent input from about 7500 corticostriatal terminals, which probably reflects close to the same number of cortical pyramidal neurons. Given the highly hyperpolarized resting potential of MSNs (–80 mV) and the relatively small size of EPSP initiated by a single excitatory input, many corticostriatal inputs must converge almost simultaneously onto a spiny projection neuron to bring it into the sufficiently depolarized state—the UP state (see below)—to enable action potentials to be initiated. The precise number of simultaneous inputs or inputs occurring in a narrow time window to bring the neurons to the UP state is controversial and estimates vary from tens to thousands.

UP/DOWN States in Spiny Projection Neurons

Action potential firing of MSN in awake animals typically occurs in brief episodes separated by longer periods of relative quiescence (Kimura et al. 1990; Schultz and Romo 1988; Jog et al. 1999). These patterns of firing have also been demonstrated in intracellular records made from MSNs in immobilized, locally anaesthetized rats (Wilson and Groves 1981) and in urethane-anaesthetized rats (Wilson 1993). Intracellular recordings of MSNs in intact animals reveals large amplitude membrane potential fluctuations from a hyperpolarized DOWN state to a depolarized UP state (Wilson and Groves 1981; Wilson and Kawaguchi 1996; Wickens and Wilson 1998). These UP state transitions are brought about by the synaptic input from the cortex and probably also the thalamus. Thus UP state transitions do not occur after removal or deactivation of the cortex (Wilson 1993) and do not occur *in vitro* in the absence of excitatory drive, as in the brain slice at rest. On the other hand, UP states can be readily elicited in spiny projection neurons with just a minimal requirement of excitatory inputs. For example,

in cortex–striatum slice co-cultures, the spontaneous activity of the cortical culture is sufficient to drive striatal neurons into UP states (Plenz and Aertsen 1996; Plenz and Kitai 1998). Similarly, UP/DOWN state-like transitions occur in striatal slices in which at least part of the corticostriatal pathway is maintained and both cortex and striatum are exposed to excitatory agents, for example, NMDA (Vergara et al. 2003). These *in vivo* and *in vitro* results demonstrate that UP and DOWN state transitions reflect a network response of the striatum to synchronized excitatory inputs. This network response might be facilitated *in vivo* during sleep and local or general anesthesia, which are known to enhance cortical synchrony. Besides direct excitatory or generally depolarizing synaptic inputs, active properties of the dendritic membrane could contribute to UP state transitions and seem to be required to maintain the UP state under certain conditions (see below). Of the many ion channels expressed by MSNs (Table 9.2), actions on specific channels have been identified that control the generation and maintenance of the UP state in MSNs, including:

- Initiation of the UP state transition is dependent upon the interaction between inwardly rectifying (Kir2) K^+ channels and the excitatory synaptic input arising from the cortex/thalamus.
- The transition to the UP state is controlled in its initial phases by rapidly activating voltage-dependent conductances as the Kir2 channels close. The most prominent of these channels are carried by Na^+ (Nav1.1,1.6) and K^+ (Kv1.2, Kv4).

With maintained depolarization, other K^+ channels (KCNQ) enter the picture to help limit the extent of depolarization. In addition, there is evidence that other depolarizing inward conductances (Cav1.3 Ca^{2+}, Na^+) play a role in some circumstances to generate dendritic plateau potentials that help to maintain the UP state. It is important to note that these conductances are under the influence of neuromodulators and, at least in the case of Cav1.3 channels, are positioned within spines where glutamatergic inputs driving the UP state transition are placed. Thus, this is a potential key site for the control of plasticity in the striatum (see below).

Although all MSNs show UP state transitions, not all fire action potentials spontaneously (Stern et al. 1998). Action potential firing, when it occurs, happens only in the UP state. UP state transitions, however, do not necessarily lead to action potential firing and occur in silent as well as spontaneously firing cells (Wilson and Groves 1981). Thus the convergence of many cortical afferents sufficiently depolarizes the membrane to a level at which specific channels come into operation (see below) to maintain it at that level. From this UP state, then, subsequent excitatory inputs will lead to the initiation of action potentials. Therefore, the UP state is necessary, but not sufficient, for action potential firing.

In addition to the large amplitude shifts in membrane potential that occur with UP state transitions, numerous small amplitude, noise-like, fluctuations in

Table 9.2 Electrophysiologically characterized currents in spiny projection neurons.

Electrophysiologically defined current	**References**
I_{Kir} (inwardly rectifying Kir2 K^+ channel)	Hagiwara and Takahashi (1974) Leech and Stanfield (1981) Mermelstein et al. (1998) Nisenbaum and Wilson (1995) Uchimura et al. (1989)
I_{As} (slowly inactivating Kv1 K^+ channel)	Gabel and Nisenbaum (1998) Nisenbaum et al. (1998, 1994) Nisenbaum and Wilson (1995) Shen et al. (2004) Surmeier et al. (1991, 1992)
I_{Na} (Na^+ Nav1.1, 1.2, 1.6 channel)	Cepeda et al. (1995) Chao and Alzheimer (1995) Fraser et al. (1993) Hoehn et al. (1993) Ogata and Tatebayashi (1990) Schiffmann et al. (1995) Surmeier et al. (1992) Surmeier and Kitai (1997)
L (Cav1.2, Cav1.3 L-type channel)	Bargas et al. (1991, 1994) Hernandez-Lopez et al. (2000)
N, P, R (Cav 2.1, 2.2, 2.3)	Bargas et al. (1994) Mermelstein et al. (1999) Surmeier et al. (1995)
I_{Krp} (persistent KCNQ K^+ channel)	Nisenbaum et al. (1996) Shen et al. (2004)
I_{Af} (rapidly inactivating A-type, Kv4 K^+ channel)	Surmeier et al. (1988, 1989) Tkatch et al. (2000)

membrane potential appear superimposed on the UP and DOWN states. In spontaneously firing neurons, these noise-like fluctuations in membrane potential trigger action potential generation. Similar fluctuations are also observed in silent MSNs but they do not reach threshold for action potential firing, although this can occur if the membrane potential is brought closer to threshold by injection of depolarizing current (Wilson and Kawaguchi 1996).

In dual *in vivo* intracellular recordings from anaesthetized animals, transitions between UP and DOWN states are highly correlated (Stern et al. 1998). However, during a synchronized UP state, action potential firing is not synchronized. The large amplitude transitions may represent the firing of assemblies of cortical cells, while the small amplitude fluctuations represent the fine temporal structure of activity within an active assembly.

Thus, the UP state can be seen as a selection process that will enable spiny projection neurons to control basal ganglia output, but will not necessarily guarantee participation in this control.

Lateral Inhibition between Medium Spiny Projection Neurons

The classical view of the organization of the striatum is that the GABAergic lateral interaction between MSNs generates a "winner-take-all" network through mutual suppression of action potential generation at the soma. Recordings from pairs of connected neurons suggest that this is *not* the case and that the interaction can take many forms.

Current available data (see Tepper and Plenz, this volume) suggest that the GABAergic synapse between spiny projection neurons is not significantly different from other GABAergic synapses described in, for example, the cortex. Although an individual MSN receives a large number of terminals from other MSNs, because of the low probability of connections, the connections between an individual pair will be sparse. The synapse reveals a large variability in probability of release and displays short-term plasticity that is under control of neuromodulators. So far, short-term facilitation has been reported, which suggests that the transmission supports action potential bursts (Czubayko and Plenz 2002). However, short-term depression and modulation of short-term plasticity by DA has also been demonstrated (Koós et al. 2004). Taken together, these data imply that synaptic transmission between spiny projection neurons is highly variable and contributes to the temporal (short-term plasticity) and spatial (local axon collateral) dynamics of the striatal network.

The IPSC is significantly weaker at the soma than the IPSC originating from the FS interneuron (Koós et al. 2004; Tepper et al. 2004). However, the many nonlinear aspects of MSN electrophysiology provide for a rich repertoire on which this synapse could operate. First, the positive chloride reversal potential with respect to the DOWN state could allow this synapse to depolarize MSNs, thereby changing intrinsic ion channel states. Second, the predominant location of the synapse on dendrites suggests participation in the control of dendritic rather than somatic processing. For example, instead of being involved in suppressing action potential generation at the soma, MSN input to other MSN dendrites could control the temporal relationship between synaptic input and backpropagating action potentials (see below), terminate/start dendritic plateau potentials, or delay/advance action potential firing in the postsynaptic neurons.

These possible effects deviate from the classical idea that GABAergic transmission between spiny projection neurons generates a "winner-take-all" network through mutual suppression of action potential generation at the soma. It is thus clearly necessary that we characterize the nature of interaction between MSNs, not least because these synapses represent a high proportion of the

inhibitory, or rather, GABAergic, input to these cells. One possible function of the collateral synapse is discussed below.

Spike Backpropagation in MSNs (see Figure 9.3)

The strong plasticity in the corticostriatal pathway (see below) raises the question whether there is a mechanism that allows those synapses that participate in the generation of an output signal to be regulated specifically. This problem, commonly known as "credit assignment," has been suggested to be solved by a nonlinear/supralinear interaction between activated NMDA receptors in the dendrite and a backpropagating action potential into the dendrite. In this context, the NMDA receptor with bound glutamate at the active synapse provides the "flag" for which the synapse participates in an input to the neuron, whereas the backpropagation of the somatic action potentials signals back to the input that an output has been generated. The specificity occurs at the level of the intracellular calcium dynamics. In a largely simplified scheme, the backpropagating spike releases the magnesium block from NMDA receptors and those receptors that have glutamate bound allow calcium to enter the cell. This signal will control the regulation of synaptic plasticity at that synapse.

Is spike backpropagation in MSNs an important element that controls plasticity in the corticostriatal pathway? This question can be broken down into several different aspects of the problem. Experiments have been performed *in vitro* in mature cortex–striatum–substantia nigra organotypic co-cultures. In this *in vitro* system, striatal UP and DOWN states are highly comparable with UP and DOWN state fluctuations *in vivo* under urethane anesthesia with respect to, for example, spontaneous firing during UP states, UP state durations, and delay to first action potential distributions in the UP state. These similarities suggest a similarly balanced excitatory drive in the *in vitro* system compared to *in vivo*.

The results of these analyses demonstrate the following:

1. Intracellular calcium signals are not saturated in MSN dendrites despite large UP and DOWN state membrane potential fluctuations of $\sim$40 mV. Instead, the action potential number during UP states is precisely encoded in the calcium transient peak for all dendritic compartments.
2. During the DOWN state, action potentials from somatic current injections trigger strong calcium transients in higher-order dendrites. The fact that calcium transients disappear when voltage-gated sodium channels are blocked in dendrites, strongly suggests that spike backpropagation occurs in MSNs.
3. During the UP state, somatic spikes also trigger calcium transients in higher-order dendrites of MSNs. This is an important point because the UP state changes the electrotonic properties of MSNs dramatically, and it was previously questionable whether spike backpropagation could operate under these circumstances.

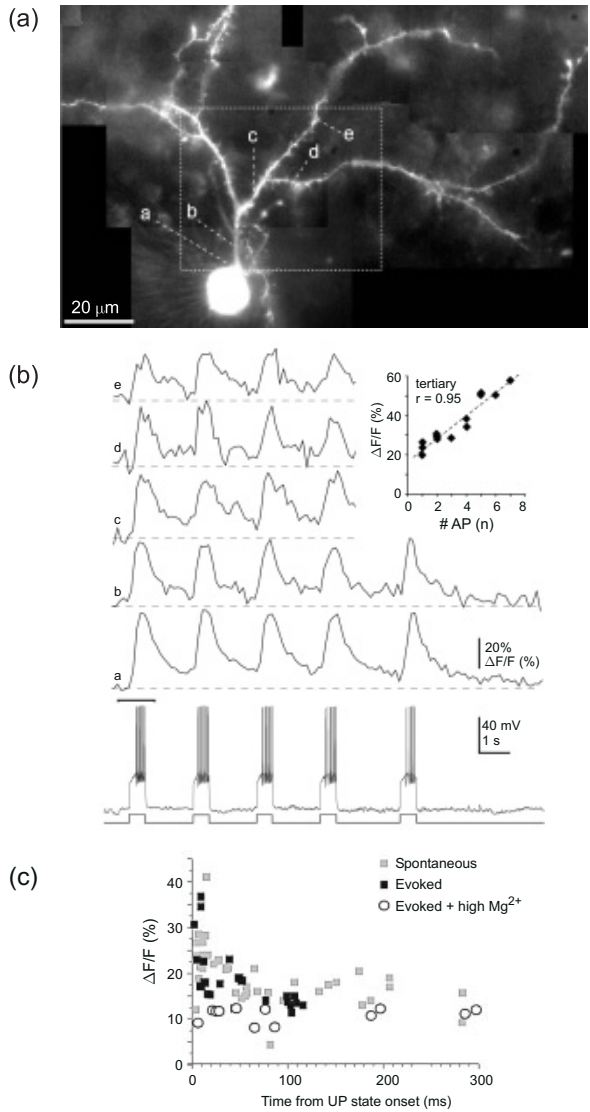

Figure 9.3 Spike backpropagation in MSNs. Through spike backpropagation, dendritic calcium transients encode the action potential (AP) bursts and action potential timing in spiny projection neurons. (a) Spiny projection neuron filled with calcium indicator Fura-2 (cortex–striatum–substantia nigra organotypic culture). (b) Repetitive action potential bursts by somatic current injection (bottom trace) elicit reliably calcium transients in soma, primary, and higher-order dendrites. The amplitude of the calcium transient is correlated linearly with the number of spontaneous somatic spikes during UP states (inset; Kerr and Plenz 2002). Characters correspond to locations in (a). (c) The dendritic calcium signal (tertiary dendrite) encodes the timing of the first single spike with respect to UP state onset through an NMDA-dependent mechanism (Kerr and Plenz 2004).

4. Calcium transients from somatic action potentials were supralinear in higher-order dendrites and could be blocked by intracellular blockade of the NMDA receptor.
5. The supralinear transients have a clear time-dependency with respect to UP state transition and spike timing. The earlier the neurons fire a somatic spike after a transition into an UP state, the stronger the resulting supralinear calcium transient in higher-order dendrites through spike backpropagation.

Taken together, all three elements that are necessary to solve the "credit assignment" problem have thus been demonstrated in MSNs in the organotypic slice preparations. First, somatic spikes backpropagate into spiny projection neuron dendrites during the UP state. Second, they interact with active synapses via the NMDA receptor. Third, this interaction is supralinear and crucial for the "credit assignment" problem.

These data open a new avenue in the control of corticostriatal input processing between spiny projection neurons. Inhibitory inputs from other spiny projection neurons by controlling the timing of spike backpropagation into the dendrite of the postsynaptic neuron might control corticostriatal plasticity in these neurons (see also below). The question that remains to be answered is whether this situation is found in MSNs *in vivo*. Differences in the synaptic environment of the organotypic culture from that found *in vivo* may alter dendritic channel and spine densities in such a way as to reduce the probability that somatic spikes are faithfully backpropagated. The advent of 2 photon laser scanning microscopy will allow resolution of this question in the near future.

Feedforward Inhibition of MSNs Mediated by FS Neurons

FS GABA interneurons innervate the proximal regions of MSNs (although the connection is not reciprocal) and an individual FS neuron will innervate probably in the region of several hundred MSNs. Paired recordings of the connections between FS neurons and MSNs reveals that FS neurons provide a strong, reliable inhibition of MSNs (see Tepper and Plenz, this volume).

Although we do not know the precise function of this inhibitory connection, it may shunt or block the cortically driven action potentials. In doing this, one of the actions may be to erase a previous constellation of spiking/nonspiking MSNs and through this may facilitate a new network configuration/selection for the future.

In light of the predominantly perisomatic targeting of the GABAergic input from FS neurons to MSNs, one of their main actions might be the timing of somatic action potentials. Because of the intense innervation of a given striatal volume by many FS interneurons, the input of FS neurons might be interpreted as setting a timing window for when spiking is allowed to occur in MSNs. In that sense, FS neurons provide a temporal framework that guides action potential

generation in the striatal microcircuit. This temporal framework could be enhanced by several mechanisms. For instance, synchronization between FS neurons might provide a spatially uniform framework that, through oscillations within the interneuron network, might set up a rhythmic framework for spiking in MSNs. Similarly, afferent control of the FS interneuron network through cortical afferents (excitatory) or inhibitory afferents (from GPe) could be interpreted as setting up unique or repetitive timing frameworks. Thus, FS interneurons operate to "select" a population of MSNs in both a spatial and temporal framework (Courtemanche et al. 2003; Parsatharathy and Graybiel 1997).

PLASTICITY OF THE MICROCIRCUIT PARTICULARLY IN RELATION TO THE ROLES OF DOPAMINE AND ACETYLCHOLINE

Plasticity of the corticostriatal and thalamostriatal pathways, brought about by reward-related input from DA neurons in the SNc and VTA, is a probable basis for the learning-related changes in striatal responses measured in single-unit studies in behaving animals. Such changes in the activity of the output neurons of the striatum may lead to changes in the probability of responses. If the rules for induction and maintenance of synaptic changes are appropriate, the resulting changes in synaptic efficacy may lead to an increased probability of behavioral responses that lead to rewards and produce an overall maximization of accumulated rewards.

The detailed requirements for induction of synaptic plasticity in the corticostriatal pathway are gradually being elucidated, but much remains to be determined before these requirements can be described with mathematical precision. Current findings support the hypothesis of a three-factor rule for synaptic modification in the striatum, in which presynaptic activity, postsynaptic depolarization, and neuromodulator activity may play a role. Each of these factors has temporal and magnitude characteristics that may influence the extent and direction of changes in synaptic efficacy.

It is well established that long-term depression (LTD) can be induced in the corticostriatal synapses by high-frequency stimulation (HFS) of the cerebral cortex. LTD is a depolarization-dependent process that requires activation of L-type calcium channels in the postsynaptic cell during the conditioning HFS and an increase in intracellular calcium concentration (Bonsi et al. 2003; Lovinger and Tyler 1996). These conditions are likely to be met in striatal cells that fire action potentials in response to excitatory synaptic input (Kerr and Plenz 2002).

Long-term potentiation (LTP) has also been reported in the striatum. Initial reports of striatal LTP were based on the effects of HFS in slices bathed in magnesium-free medium (Calabresi et al. 1992). Both DA depletion and the dopamine D_1 receptor antagonists block LTP in magnesium-free conditions (Kerr

and Wickens 2001). Dopamine, applied in a manner that mimics the natural release of DA produced by reward, is sufficient to facilitate LTP (Wickens et al. 1996). In these latter experiments, DA was applied in brief pulses coinciding with a pre- and postsynaptic conjunction of activity. The pulsatile application of DA reversed the LTD, which normally follows HFS, and potentiation of responses was induced.

Experiments *in vivo* using electrical stimulation of DA neurons in the substantia nigra have shown that endogenous release of DA evoked by behaviorally reinforcing stimulation parameters induces a potentiation of corticostriatal synapses (Reynolds et al. 2001). In addition, the degree of potentiation up to 10 min after the stimulus trains was correlated with the rate of learning of intracranial self-stimulation behavior.

Preliminary studies have indicated precise temporal requirements for the DA-dependent induction of LTP. If DA pulses that induce LTP when applied simultaneously with pre- and postsynaptic conjunction of activity are delayed by as little as 500 ms, LTD occurs instead. This strict temporal requirement argues against a cellular eligibility trace corresponding to the delay of reinforcement gradient measured behaviorally. The effectiveness of delayed reinforcers may depend on the ability of the DA system to produce a reward-prediction error in advance of the actions that lead to reward (Figure 9.4).

Plasticity of the Corticostriatal Synapse at the Molecular Level

Dopamine receptors interact with ion channels in a variety of ways (Table 9.3). One molecular mechanism proposed to underlie plasticity at the corticostriatal synapse at the level of the spine relates to modulation of the activity of L-type Ca^{2+} channels (Surmeier, this volume; Cepeda et al. 1998; Liu et al. 2004). These channels are placed strategically to a large degree in dendritic spines close to the site of glutamatergic corticostriatal and DA synapses. Activation of the D_1 type of DA receptor prolongs the UP state and increases excitability of MSNs, whereas activation of D_2 receptors reduces UP state and decreases excitability. This effect is mediated in part through phosphorylation/dephosphorylation, respectively, of L-type Ca^{2+} channels, increasing and reducing the availability of Ca^{2+} respectively. Furthermore, ACh release from the cholinergic interneurons depresses excitability at the level of the spine (but not the somatodendritic tree) by an action through M_1 muscarinic receptors and dephosphorylation of the channel. Thus, the classical view of a reciprocal relationship between DA and ACh in the striatum is reflected at the single channel level in spines. The interaction between DA and ACh is regulated by a small phosphoprotein referred to as "regulator of calmodulin signaling" (RCS). When phosphorylated by protein kinase A (PKA), RCS increases dramatically its affinity for Ca^{2+}/calmodulin, effectively blocking Ca^{2+} signaling. When D_1 receptor stimulation leads to the activation of PKA and phosphorylation of RCS, M_1 receptor suppression of

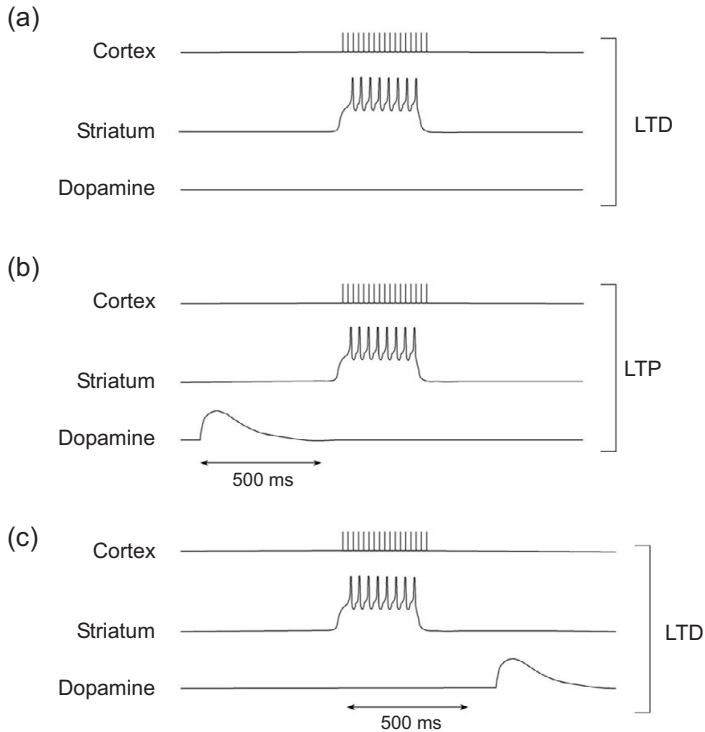

Figure 9.4 Effect of dopamine on activity-dependent synaptic plasticity in the corticostriatal pathway. (a) A conjunction of cortical presynaptic activity and striatal postsynaptic activity leads to long-term depression (LTD) in the absence of a dopamine pulse. (b) A conjunction of cortical presynaptic activity and striatal postsynaptic activity leads to long-term potentiation (LTP) if preceded by a dopamine pulse. (c) The same conjunction of cortical presynaptic activity and striatal postsynaptic activity leads to LTD if the DA pulse is delayed.

L-type Ca^{2+} channels in spines is effectively blocked. Thus, the timing of DA and ACh signals has important consequences for the regulation of Ca^{2+} dynamics in spines and possibly synaptic plasticity.

It is clear that D_1 receptor stimulation promotes excitatory events and UP-state generation in *striatonigral* MSNs. The question arises as to whether there is a corresponding signaling pathway in *striatopallidal* MSNs, that is, those neurons that predominantly express D_2 receptors. (Gerfen et al. 1995; Surmeier et al. 1996). This population of MSNs also expresses adenosine A_{2a} receptors. These receptors have the same biochemical linkages as D_1 receptors. The electrophysiological effects have not yet been investigated, but there is the potential that the cortical glutamatergic signal may be translated by 5′-nucleotidase into a "teaching" signal to these neurons, corresponding in some way to the dopaminergic signal in the D_1-expressing neurons.

Table 9.3 Dopamine receptor subtype-specific effects on ion channels.

Channel	Dopamine D_1 receptor activation	Dopamine D_2 receptor activation
I_{Kir}	Increased (Galarraga et al. 1994; Pacheco-Cano et al. 1996)	Increased* (Freedman and Weight 1988, 1989) or decreased (Uchimura and North 1990)
I_{As}	Decreased (Surmeier and Kitai 1997)	Increased (Surmeier and Kitai 1997)
I_{Na}	Reduced (Surmeier et al. 1992)	Reduced increase by D_2 (Surmeier et al. 1992)
L	Increased (Hernandez-Lopez et al. 1997; Surmeier et al. 1995)	Decreased (Hernandez-Lopez et al. 2000)
N, P	Decreased (Surmeier et al. 1995)	Decreased Surmeier et al. (1995)

* This modulation is likely to be of a Kir3 channel in a novel type of striatal neuron.

PLASTICITY OF STRIATAL MICROCIRCUITS AND REWARD-RELATED BEHAVIORS

The DA neurons of the ventral midbrain, which provide a massive and widespread innervation of the striatum (Table 9.1), respond with a brief increase or decrease in rate of firing to both the onset of *reward-predicting stimuli* and *reinforcers* as an outcome of action (decision) in classical conditioning task (Schultz et al. 1997; Fiorillo et al. 2003) or a voluntary decision task for reward (Satoh et al. 2003) (see Figure 9.5). Responses to positive and negative reinforcers precisely encode reward-expectation error. Responses to reward-predicting stimuli depend on the probability of reward. In an instrumental conditioning task with voluntary decision for reward, however, they might not encode levels of reward expectation but rather the levels of motivation, because the magnitude of responses is negatively correlated with behavioral reaction time (Action 1 in Figure 9.5). On the other hand, at the same reward-expectation level, coding reward-expectation error is positively correlated with coding motivation level (Satoh et al. 2003). This means that coding reward-expectation error by the firing rate of DA neurons is significantly modulated by motivation in such a way that gain of error coding is high when the level of motivation is high. Thus, the response of an animal to important environmental stimuli, especially a reward, is a brief increase in their firing rate and hence an increased release of DA in the striatum. Omission of expected reward (Schultz et al. 1997) and aversive stimuli (Ungless et al. 2004) induce a brief suppression in firing.

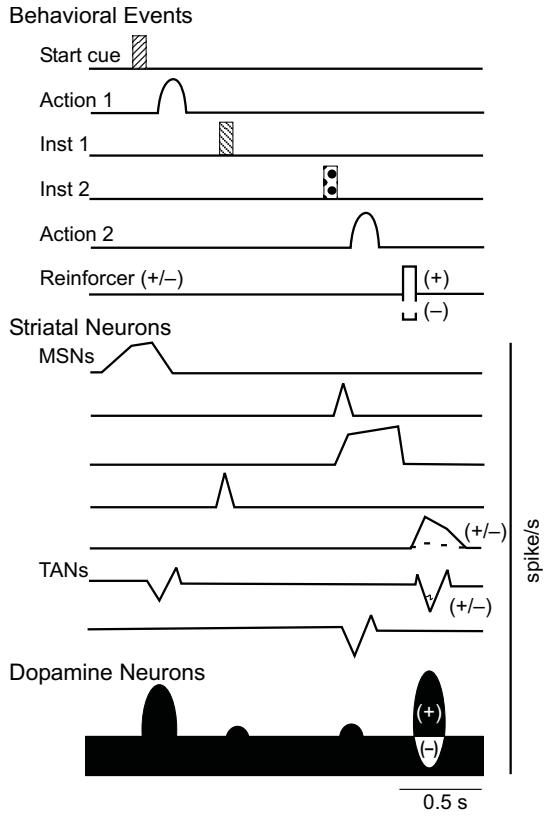

Figure 9.5 Schematic illustration of behavioral events and striatal and dopamine neuron activity during behavioral decision task for a reward in monkey. The task was initiated by illumination of the start LED on the push button as a first reward-predicting stimulus. The monkeys depressed the illuminated start button. The start LED was turned off 400 ms after the monkeys continued to hold the button. Then, the target LEDs (Inst 1) and a GO LED (Inst 2) were simultaneously activated. The monkeys were required to continue depressing the start button for variable lengths of time before the GO LED was turned off. They released the start button and depressed one of the three illuminated target buttons. If an incorrect button was depressed, a beep sound with a low tone occurred, and the next trial began by illuminating the start LED. Because the monkey remembered the incorrect button selected at the first trial, it made a choice between the two remaining buttons. If the monkey made an incorrect choice again, the third trial started after a low-tone beep and the monkey depressed the remaining, single correct button. If the correct button was depressed, a beep sound with a high tone occurred, and a small amount of reward water was delivered through the spout attached to the monkey's mouth. The high-tone and low-tone beep sounds served as positive and negative reinforcers, respectively, after the behavioral decisions. Once the monkeys found the correct button, the same button was used as the correct button in the succeeding trials. Various types of medium-size spiny neurons (MSNs) and cholinergic interneurons (TANs) show characteristic activity in relation to the behavioral events, while midbrain dopamine neurons respond to the start LED and reinforcer beep as a single group of neurons.

A population of neurons in the striatum is tonically active (TANs) and has been correlated with the large cholinergic interneurons, the fourth neuron in our canonical microcircuit. Recordings from these neurons in similar paradigms, as used above for the study of DA neurons (Yamada et al. 2004) or, indeed, simultaneous recordings of both DA neurons and TANs (Morris et al. 2004), have revealed that TANs respond selectively to sensory stimuli instructing *outcomes* of action, such as reward, aversive stimuli like air puff to an animal's face, or a sound instructing no-reward (Blazquez et al. 2002). They respond selectively to sensory stimuli instructing the motivational outcomes of action, stimuli for trigger action, and reinforcers. Reward is not necessarily special for TANs. Different groups of TANs respond more readily to reward than aversive stimuli, whereas other groups of TANs prefer aversive stimuli, and still other groups prefer a sound instructing no-reward. Thus, TANs encode the salience instructed motivational contexts, i.e., they report that an important event is about to occur (Blazquez et al. 2002). TANs in the putamen and caudate nucleus represent similar, but quantitatively different, aspects of information. The temporal response pattern of TANs in these paradigms is more or less stereotypical. There is a brief pause of tonic firing for 100 to 150 ms, followed by an increase above baseline firing. In some instances, the pause responses are preceded by a brief increase in firing.

Thus, DA neurons and TANs code events related to motivational outcomes. Additionally, DA neurons encode reward-expectation error precisely. TANs can discriminate different kinds of motivational outcomes. Therefore, information encoded by DA cells and cholinergic interneurons can work as teaching signals in different ways. The response of TANs warns the striatum about a salient event, it tells the striatum to listen. The response of DA neurons is to tell the striatum about the reinforcement.

MSNs in the striatum of awake monkeys discharge at a very low mean rate, usually less than 1 spike/s. Although their discharge properties in behavioral tasks depend on the location in the striatum, which relates to the topography of inputs from the cerebral cortex, it is common for nearby MSNs to show quite different properties, such as reward-related activity, limb or eye movement-related activity, and responses to sensory instructions. This is because of the large-scale convergence of different types of information of cortical origin onto single MSNs and the wide-scale divergence between neighboring MSNs (see above). In the behavioral task shown in Figure 9.5, MSNs are activated in relation to various aspects of task requirements. The activity of some groups of neurons increases gradually up to the start cue and Action 1. Another group of neurons show phasic activation after Instruction 1 (Inst) or Instruction 2. Still another group of neurons show burst discharges in relation to Action 2 or reinforcers. Thus, the different types of MSNs participate in encoding aspects of task requirements in a discrete manner. An important property of these different types of MSN activity is dependence on motivational state; that is, most MSNs show

stronger activation when rewarding outcomes are expected (Kawagoe et al. 1998; Lauwereyns et al. 2002; Cromwell and Schultz 2003), whereas smaller number of neurons are activated more strongly when smaller or no-reward outcome is expected (Watanabe et al. 2002).

MICROCIRCUITS, MOLECULES, AND BEHAVIOR

We have now identified a potential canonical microcircuit in the striatum, several possible ways in which the microcircuit itself can select which populations of MSNs fire and the manner in which they fire, ways in which corticostriatal synapses are plastic, and changes in the activity of DA-containung neurons in the ventral midbrain and cholinergic neurons in the striatum during specific behaviors. How can these be brought together to understand how a microcircuit can interface with global brain function in the production of behavior?

From the foregoing discussion, it is clear that one of the roles of DA in the striatum is to mediate/facilitate synaptic plasticity. Dopamine D_1 receptor stimulation is critical in the expression of LTP in the corticostriatal pathway; DA can strengthen corticostriatal synapses on the MSNs. Thus, one action of the brief increase in DA release at spines in response to reward-predicting stimuli may be to potentiate selectively the striatal synaptic inputs from the assembly of cortical neurons that are required to express the appropriate behavior. Thus striatal activity and the DA teaching signal allow the microcircuit to potentiate selectively the response to the assembly of cortical neurons for the appropriate behavior.

What then might be the role of the simultaneous depression of ACh that occurs with the increased release of DA? As indicated above, one mechanism of increasing excitability may be to influence the availability/levels of calcium through an action on the L-type Ca^{2+} channel located in spines. The decrease in ACh release and the increase in DA release would have similar net effects on the channel leading to increased probability of opening and hence increased excitability of excitatory cortical synapses. Thus the two modulators acting in concert would be in a position to provide a selective potentiation of the synapses of the "appropriate assembly of cortical neurons" related to the behavior.

Lateral interaction between MSNs will further sculpt the response of groups of MSNs to the selected group of cortical afferents and the feedforward inhibition through the FS interneurons will further "select," in both spatial and temporal domains, the group of MSNs that will fire. What the "appropriate assembly of striatal neurons" is that matches the appropriate assembly of cortical neurons is critically influenced by the divergent–convergent anatomy of corticostriatal projections (Graybiel et al. 1994). The striatum has modules, about the size of cortical columns, that organize its inputs and outputs. Striatal interneurons are also differentially represented in these compartments (called striosomes and matrisomes), and the DA–ACh modulation of striatal activity is also compartmentally selective. It thus seems likely that this architecture strongly influences

the function of striatal microcircuits. The increased or altered pattern of activity of the selected group of MSNs will then lead to the "appropriate" behavior via the basal ganglia output nuclei and their connections to subcortical premotor regions or connections with frontal cortical regions via the thalamic.

The scenario we describe here leaves many questions unanswered and raises many new questions relating to the functional organization of the striatum and the basal ganglia in general. Nevertheless, the microcircuit that we have described brings together data from anatomical, neurochemical, physiological, and behavioral studies and provides a rational basis for future studies of the basal ganglia.

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