Part III

Models of Brain Regions and Neurotransmitters

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20

Striatum

Structure, Dynamics, and Function

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Introduction

The basal ganglia (BG) is a conglomerate of subcortical nuclei situated at the base of the forebrain that controls a variety of functions such as motor control, procedural learning, habit formation, and action selection. The BG forms multiple interacting pathways that arise in different cortical regions and terminate in the thalamic regions projecting to the brainstem (Jahanshahi, Obeso, Rothwell, & Obeso, 2015). The strategic location of the BG in the brain suggests that it serves as a hub that actively regulates and shapes the relatively abstract cortical activity before it reaches the final stage of the information processing (e.g., motor action-selection, decision making). Given its functional importance it is no surprise that BG dysfunctions result in various brain diseases such as Parkinson's disease (PD), Huntington's disease, Tourette's syndrome, and dyskinesia.

At the structural and chemical levels the BG is markedly different from other brain regions. For instance, unlike in the neocortex where networks are composed of both excitatory and inhibitory neurons, networks in the spatially segregated BG nuclei have either predominantly excitatory or inhibitory neurons. While the striatum, globus pallidus externa (GPe), globus pallidus interna (GPi), and substantia nigra compacta (SNc) are predominantly inhibitory, the subthalamic nucleus (STN) is the only excitatory nucleus. The striatum and STN are the main input nuclei, whereas the GPi and substantia nigra pars reticulata (SNr) are the principal output nuclei of BG. The SNc and the adjacent VTA (ventral tegmental area) are the seat of dopamine neurons that project and provide dopamine to the BG, primarily the striatum. There is a growing interest in understanding the functional role of the striatum given its prominent position as the main input of the BG. In this chapter we review recent progress in our understanding of the structure, electrical activity, and function of the striatum.

Architecture of the Striatal Network

Striatum is not only the main input nucleus of the BG but it is also the biggest with about 200 to 300 times more neurons than its immediate downstream nuclei (GPe and GPi) (Fig. 20.1A). Moreover, neocortical projections (Wall, De La Parra, Callaway, & Kreitzer, 2013) make it an important sensori-motor integration network (Reig & Silberberg, 2014). Recently, a number of new features of the striatal network

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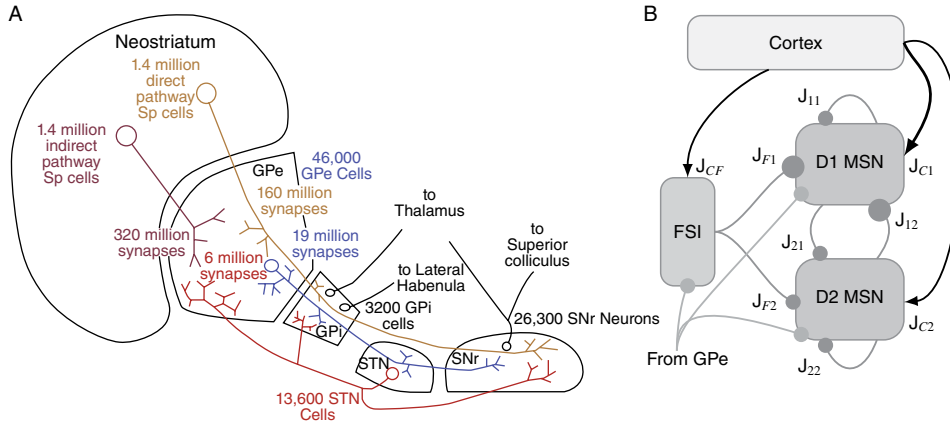

Figure 20.1 Schematic of the basal ganglia and striatum network. (A) Basal ganglia drawn to scale (figure adapted from Wilson, 2013). (B) Schematic of the striatal network. D1- and D2-MSNs receive recurrent inhibition from other MSNs (J_{11}, J_{12}, J_{21}, J_{22}—J_{xy} is the weight from *y* to *x* population), feedforward inhibition from the FSIs (J_{F1}, J_{F2}), and inhibition from the GPe via the pallidostriatal back projections (Mallet et al., 2012). The primary source of glutamatergic inputs is the cortical projections (J_{C1}, J_{C2}). The striatal circuit is inherently asymmetrical because D2-MSNs inhibit D1-MSNs more than vice versa ($J_{12} > J_{21}$) (Taverna et al., 2008; Planert et al., 2010) and FSIs inhibit D1-MSNs more than D2-MSNs ($J_{F1} > J_{F2}$) (Gittis, Nelson, Thwin, Palop, & Kreitzer, 2010). Thus, D1-MSNs experience on average higher inhibition as compared to D2-MSNs, which could be compensated via a stronger cortical input to D1-MSNs. *Source*: Bahuguna (2015). Reproduced with permission of Elsevier.

architecture have been discovered that have reinforced its role as a complex information processing system.

Striatum is a Purely Inhibitory Recurrent Network

All the different types of neurons in the striatum are inhibitory and receive multimodal excitatory and inhibitory inputs from the cortex. The medium spiny neurons (MSNs), which constitute ~95% of the striatal neurons, form a sparsely connected recurrent inhibitory network (Tepper, Koos, & Wilson, 2004) and project to the GPe and GPi/SNr. The interneurons, such as the parvalbumin, which express fast spiking interneurons (FSIs), the interneurons expressing stomatostatin or nitric oxide synthase (Tepper, Tecuapetla, Koós, & Ibáñez, 2010), and tonically active cholinergic interneurons (TANs), make up the remaining 5% of the striatal neurons. Among these, the FSIs do not receive any inhibition from other FSIs or MSNs, thereby forming a source of feedforward inhibition to the MSNs. The TANs affect the MSNs and FSI activity indirectly by modulating the excitatory synaptic strengths (Pakhotin & Bracci, 2007) and dopamine release (Threlfell, Lalic, Platt, Jennings, & Deisseroth, 2012).

Striatum is a Two-Population Network

Most MSNs express either D1 or D2 type dopamine receptors. About 20% of MSNs are known to express both D1 and D2 receptors (Perreault, Hasbi, O'Dowd, & George, 2011) but it is not clear if both types of receptors are functional simultaneously. The dopamine receptor-based classification of MSNs is motivated by at least three key differences at the level of their integrative properties and connectivity. First, D1- and D2-MSNs preferentially innervate different BG output nuclei (GPi/SNr) and GPe, respectively (Fig. 20.1). This curious anatomical arrangement led to the feedforward model of the BG in which the D1-MSNs initiate the direct or *Go* pathway and D2-MSNs initiate the indirect or *No-Go* pathway (Albin, Young, & Penney, 1995). Both these pathways are assumed to

function in an antagonistic manner (Gurney, Prescott, & Redgrave, 2001a). Recent data, however, suggest that D1-MSNs also project to the GPe, creating a partial overlap between the direct and indirect pathways (Cazorla, Carvalho, Chohan, Shegda, & Chuhma, 2014).

Second, D1- and D2-MSNs have dichotomous electrophysiological and morphological properties (Gertler, Chan, & Surmeier, 2008), for example, D1-MSNs have higher input resistance and more primary dendrites than D2-MSNs. Finally, D1- and D2-MSNs show asymmetry in their mutual and recurrent connectivity: D2-MSNs inhibit the D1-MSNs more than vice versa (Taverna, Ilijic, & Surmeier, 2008; Planert, Szydlowski, Hjorth, Grillner, & Silberberg, 2010) (Fig. 20.1B). The FSIs also contribute to this asymmetry by preferentially innervating the D1-MSNs (Gittis, Nelson, Thwin, Palop, & Kreitzer, 2010). Thus, striatum is an asymmetrically connected network of at least two different neuron populations that seem to have antagonist effects on animal behavior.

Extra Striatal Inputs to the Striatal Neurons

The striatum receives excitatory inputs from the intratelencephalic tract (IT) and pyramidal tract (PT). While the IT innervates D1- and D2-MSNs equally (Kress et al., 2013; Wall et al., 2013), the PT projections seem to make stronger connections with the D1-MSNs (Kress et al., 2013). The different cortical regions display a preference in their projection pattern for either D1- or D2-MSNs. For instance, primary sensory (S1) and limbic regions preferentially project to D1-MSNs, but the primary motor cortex (M1) projects mainly to the D2-MSNs (Wall et al., 2013). By contrast, the secondary motor cortex (M2), thalamostriatal, and dopaminergic neurons innervate the D1- and D2-MSNs equally.

The striatum receives additional inhibition from a specific GPe subpopulation that expresses proenkephalin (arkypallidal cells) (Mallet et al., 2012). The size of the arkypallidal cell population is comparable to the size of the FSI population in the striatum, therefore, the magnitude of inhibition coming from the GPe back projections to the striatum could be at least comparable to the feedforward inhibition. How does a complex network like the striatum process multi-modal cortical inputs? Modern experimental tools have started to provide a glimpse into the neuronal activity of the two types of MSNs during active behavior and in most cases these observations are challenging the prevailing notions about striatal function.

Task-related Neuronal Activity in the Striatum

The ongoing activity of the MSNs is conspicuously low (<1 Hz) (Mahon, Deniau, & Charpier, 2003). This is because of the high spiking threshold and feedforward and feedback inhibition from various sources. In the presence of an external stimulus the MSN activity could increase up to 25 Hz over short time epochs (~100 ms). The task-related changes in the average firing rate of striatal neurons are preceded by an increase in cortical rate and correlations in specific brain regions (Gage, Stoetzner, Wiltschko, & Berke, 2010; Reig & Silberberg, 2014; Seo, Lee, & Averbeck, 2012). However, the striatum does not merely "copy" the cortical activity, the convergent–divergent pattern of cortico-striatal projections can transform the cortical activity even before it is represented in the striatal activity patterns. The corticostriatal plasticity is also crucial for the acquisition of fine motors skills. Consistent with this, in N-methyl-D-aspartate receptor (NMDA) receptor knock-out animals, poor motor learning is correlated with activation of fewer neurons in the striatum and SNr during the learning phase (Jin & Costa, 2010).

Whether some aspects of the task are also encoded in the pair-wise correlations between MSNs has not been explored systematically. Low firing rates, transient responses, sparse representation of cortico-thalamic inputs, and only sparse sampling of MSNs by extracellular electrodes have severely limited the measurement of correlations between MSNs during the execution of a task. However, few

experiments have reported task-related modulation in pair-wise correlations. For instance, dorsolateral striatum shows higher correlations and a positive signal and noise correlation for reward stimuli as compared to neutral or aversive stimuli (Adler, Finkes, Katabi, Prut, & Bergman, 2013). In pathological conditions such as PD, correlations are higher than in a healthy state (Costa et al., 2006).

Balance of Go and No-Go MSN Activity

The classical model proposed by Albin (Albin et al., 1995) suggested that BG operations could be reduced to interactions among three aptly named feedforward pathways: *Go*, which initiates an action; *No-Go*, which suppresses an action; and the *Stop* pathway, which implements reactive stopping of an action. The *Go* and *No-Go* pathways originate from D1-MSNs and D2-MSNs, respectively. An action execution is also suggested to be a race between direct and hyperdirect pathways, where a *Stop* signal after the point of no return represented by STN excitation (hyperdirect pathway) is neutralized by the strong inhibitory striatonigral signal resulting in a failed *Stop* and successful *Go*. An early *Stop* signal can prevent an action execution by increasing the SNr activity before the *Go* signal (Schmidt, Leventhal, Mallet, Chen, & Berke, 2013).

Kravitz et al. (2010) provided a proof of the concept of *Go* and *No-Go* by showing that selective optogenetic activation of D1-MSN stimulation leads to increased movement, whereas D2-MSN activation leads to freezing of movements. However, this finding does not translate to natural behavior, presumably because simultaneous activation of MSNs using optogenetic means inducing excessively high synchrony. In natural behavior it is likely that only a relevant subset of D1- and D2-MSNs are concurrently activated during the action initiation creating weaker but selective recurrent inhibition, whereas stimulation of all D1- or D2-MSNs may result in a strong but nonspecific recurrent inhibition. However, it is important to note that concurrent activation of D1- and D2-MSNs as measured by calcium imaging (Cui et al., 2013) does not necessarily suggest that the two types of MSNs have comparable firing rates, and it is possible that the D1- and D2-MSNs may have different firing patterns and correlation structure to represent action initiation and action selection.

In a task where sensory stimulation (from whiskers) was coupled to a motor task (licking movement) via a reward, the membrane potential of D1-MSNs showed a fast early and slow late depolarization, while only a late depolarization was observed in D2-MSNs (Sippy, Lapray, Crochet, & Petersen, 2015). Later, when whisker stimulation was interleaved with optogenetic stimulation of D1-MSNs, both optical and sensory stimuli elicited the motor behavior, while optical stimulation of D2-MSNs blocked the motor behavior (Sippy et al., 2015). This suggests that an action preconditioned with a reward could be "summoned" by the selective activation of D1-MSNs alone. Note that when D1-MSN activity is not conditioned with a reward signal, goal-directed behavior may not be elicited by selective D1-MSN activation, though it may still increase nonspecific ambulations (Kravitz et al., 2010).

This activation to D1-MSNs could be provided by the sensory cortex (S1) (Wall et al., 2013). Consistent with this, multisensory inputs elicit a stronger depolarization in D1-MSNs (Reig & Silberberg, 2014), however this is not biphasic, as was observed by Sippy et al. (2015), presumably because the slower sensory modalities (visual and auditory) obscure the temporal dynamics of MSN activation.

The differential role of D1- and D2-MSNs becomes even more apparent in an action sequence completion task. Selective activation of M2 promotes sequence initiation, whereas its inhibition impairs it. Because M2 to D1-MSN synapses were found to be strengthened, it is reasonable to assume that M2 promotes action initiation by recruiting D1-MSNs (Rothwell et al., 2015). On the other hand, D2-MSNs are necessary for sequence completion. In fact, an imbalance in the

activity of D1- (*Go*) and D2-MSNs (*No-Go*) is required to complete sequences (Rothwell et al., 2015). Thus, both action initiation and action selection may involve a sequence of balance and imbalance of the activity of D1- and D2-MSNs over short time scales.

Striatum Activity in Brain Disorders

At the behavioral level pathologies such as PD are associated with the breakdown of reward as well as the action selection/execution dynamics in the striatum. In PD this results in an inability to initiate actions (akinesia), slowing down of an action (bradykinesia), or tremor.

Dopamine depletion-induced changes in the striatum provide better neuronal correlates of the cognitive deficits observed in PD patients. Low dopamine results in a persistent increase and decrease in the firing rate of the D2-MSNs and D1-MSNs, respectively (Mallet, Ballion, Moine, & Gonon, 2006). Moreover, the MSN activity gets entrained by the population activity and becomes more correlated even in the ongoing activity state. This implies that the striatum loses its variability and flexibility necessary to encode different stimuli and behavioral states (Costa et al., 2006). Thus, the limited behavioral repertoire of PD patients is directly correlated with the limited repertoires of the activity dynamics in the striatum (Costa, 2011). In addition, in PD, HD, and L-dopa-induced dyskinesia, MSNs lose their dendritic arbors (Cepeda, Wu, André, Cummings, & Levine et al., 2007; Fieblinger et al., 2014) and alter the structure of input correlations. Because the MSN transfer function is affected by the shared inputs and their correlations (Yim, Aertsen, & Kumar, 2011), such changes in the dendritic arbor could be sufficient to change the striatal output.

What determines the differences between the activity of D1- and D2-MSNs during natural behavior and how these differences are impaired in disease conditions? Is this governed by just the differences in the statistics of the cortical inputs, or is it shaped by interaction of cortical inputs with striatal ongoing activity, connectivity, and neuromodulators?

Computational Models of the Striatum

To understand the experimental data and computational role of the striatum a number of high-level functional and low-level network models have been proposed. High-level models ignore the details of the neuronal and synaptic properties and use the striatum as a black box to perform a high-level computation (e.g., critic in a actor–critic model of learning; Potjans, Diesmann, & Morrison, 2011). Such models are useful in developing a functional understanding of the network and designing new experiments. On the other hand, low-level network models with biophysical details of the striatal neurons and their connectivity are better suited to model the experimentally observed MSN activity and determining the function that emerges due to the low-level properties. In the following, we discuss a few key low-level models of the striatum network and the properties of the striatum dynamics that could implement high-level functions.

Striatum as a Single Population Inhibitory Network

The earliest network models of striatum focused on the inhibitory recurrent connectivity of the MSNs. Depending on the strength of the recurrent connectivity, inhibitory networks can also exhibit both asynchronous-irregular (AI) and synchronous high frequency oscillations. In the physiologically relevant AI states, inhibitory network can enhance signal-to-noise ratio of the incoming input (Yim et al., 2011). Strong recurrent inhibition can drive the network in the *Winner-Take-All* (WTA) state (Beiser & Houk, 1998; Groves, 1983; Wickens, 1990). Most high-level models of action selection implicitly or explicitly assume that the striatum operates in the WTA state (Frank, 2006). However, weak recurrent inhibition among the MSNs (Czubayko & Plenz, 2002; Jaeger, Kita, & Wilson, 1994; Tunstall et al., 2002) and their low firing rates are incompatible with the WTA dynamics.

Weak recurrent inhibition could however, support the *Winner-less Competition* (WLC) state (Rabinovich et al., 2001) in which a *winning* neuron group emerges transiently and quickly makes way for another *winner*. In such a network state an action or multimodal cortical input could be represented as a spatiotemporal pattern of multiple transient *winners* (Fukai & Tanaka, 1997; Rabinovich et al., 2001). This hypothesis suggests that striatal activity could be organized as coactivation of a small group of MSNs (striatal assemblies) in a task-dependent manner. Spiking activity of MSNs *in vitro* and *in vivo* can be clustered to reveal spatiotemporal patterns consistent with this hypothesis (Adler et al., 2012; Carrillo-Reid, Hernandez-Lopez, Tapia, Galarraga, & Bargas, 2011; Carrillo-Reid, Tecuapetla, Tapia, Herna, & Galarraga, 2008; López-Huerta et al., 2013).

A sparsely connected random network model of the striatum can be tuned to exhibit WLC states in which neuronal assemblies emerge spontaneously (Humphries, Wood, & Gurney, 2009; Ponzi & Wickens, 2010). A key requirement to have transient neuronal assemblies is to have sufficiently large group of neurons that are not mutually connected and, therefore, do not inhibit each other when activated. Such conditions could also arise due to the spatial structure of the MSN connectivity. *In vitro* experiments suggest that the MSNs in the immediate neighborhood might be sparingly connected (López-Huerta et al., 2013). Thus, neighboring MSNs could be coactivated to form a neuronal assembly (NA). This suggestion is consistent with the observation that most of the neighboring MSN pairs encode for the same stimulus selectivity (Gage et al., 2010). A recent *in vivo* imaging study in freely moving animals also suggests that indeed D1- and D2-MSNs are coactivated in compact spatial clusters (Barbera et al., 2016). A temporal sequence of NA activation could encode behavior action sequences (Adler et al., 2012).

These models, while insightful, ignore the experimental data which showed that D1- and D2-MSNs differ in their recurrent and mutual connectivity (Planert et al., 2010; Taverna et al., 2008), receive unequal cortical inputs (Wall et al., 2013) and feed-forward inhibition (Gittis et al., 2010), and have different integrative properties (Gertler et al., 2008). To understand the fine temporal dynamics of the D1- and D2-MSNs (Reig & Silberberg, 2014l Sippy et al., 2015) it is important to consider the striatum as a network of two different neuronal populations.

Striatum as a Two Population Network of D1- and D2-MSNs

During ongoing activity both D1- and D2-MSNs have low but similar firing rates. However, D1-MSNs overall receive more inhibition from D2-MSNs than vice versa. Therefore, to achieve similar firing rates D1-MSNs should either receive more cortical input or corticostriatal synapses on D1-MSNs should be stronger. In the absence of this extra cortical input, the asymmetric connectivity of D1-D2-MSNs renders the *No-Go* as the default state of the striatum (Bahuguna, Aertsen, & Kumar, 2015) (Fig. 20.2D).

The (dis)balance of D1- and D2-MSNs in the striatum is essential in action initiation or deciding a bias toward a particular action. One solution to bias a symmetric striatum would be to drive the two MSNs with different inputs (Frank, 2006; Gurney et al., 2001a; Gurney, Prescott, & Redgrave, 2001b; Humphries, Stewart, & Gurney, 2006; van Albada & Robinson, 2009). However, this would imply that the decision was solely made by the cortex, rendering the striatum as a passive transmission line.

In the case of asymmetrically connected D1-D2-MSNs as suggested by data, the two-population model suggests that low (high) inputs will favor higher activity in D1(D2)-MSNs (Fig. 20.2A). That is, the asymmetric connectivity gives rise to a decision transition threshold (DTT) and inputs below (above) the DTT result in a higher relative firing rate in D1(D2)-MSNs. Thus, the striatum acts like a threshold device that represents the level of cortical activity by changing the balance of the D1-D2-MSN firing rate (Bahuguna et al., 2015). The DTT at which

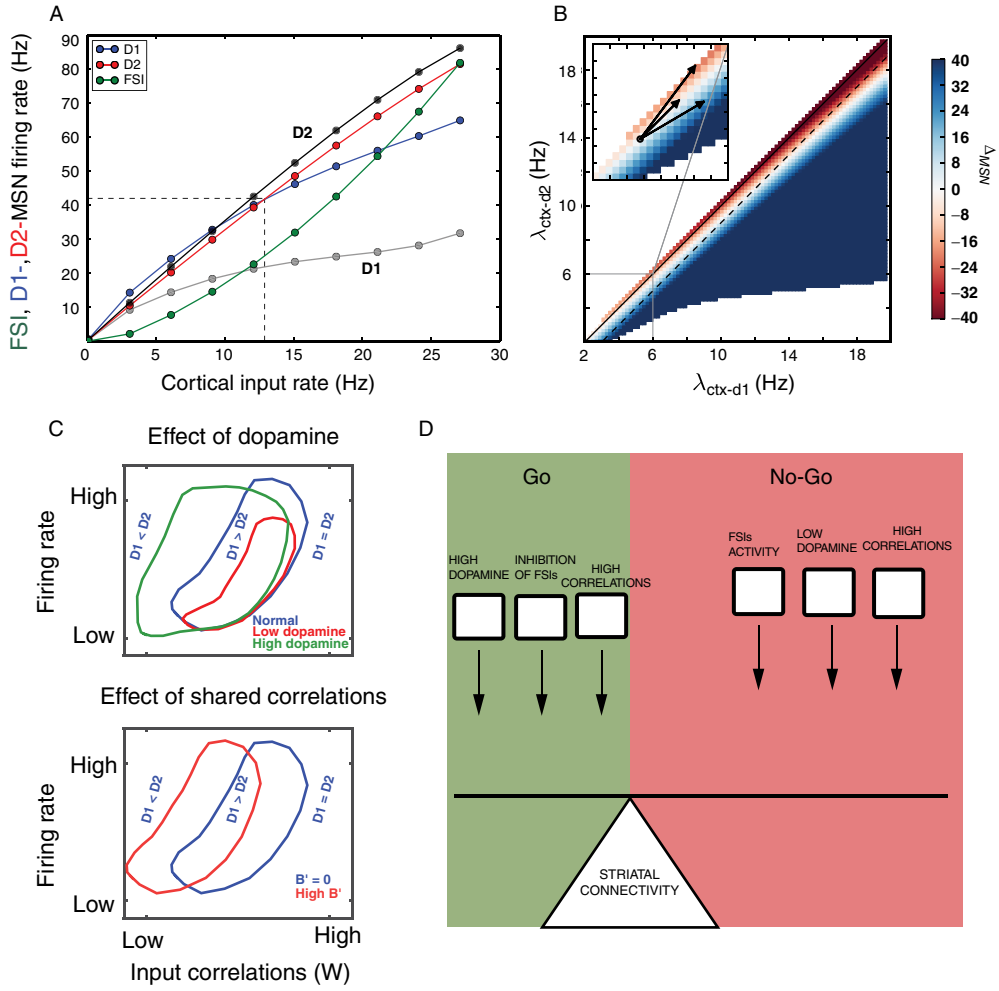

Figure 20.2 Decision transition threshold (DTT) in the striatum from Bahuguna et al. (2015). (A) Steady-state firing rates of the D1-, D2-MSNs, and FSI as a function of cortical inputs. The gray and black traces show the firing rates of the D1- and D2-MSNs when they received cortical inputs with the same strength, respectively. When D1-MSNs receive slightly extra input, for low inputs D1-MSNs have higher firing rates, but if cortical inputs are increased at some input rate/strength D2-MSN activity exceeds that of D1-MSNs (marked with the dashed line). (B) Striatal bias ($\Delta MSN = \lambda_{ctx\text{-}d1} - \lambda_{ctx\text{-}d2}$, i.e., difference between D1 and D2-MSN activity) plotted as a function of cortical input to D1 (λ_{ctx-d1}) and to D2 (λ_{ctx-d2}). The black solid line along the diagonal depicts ΔMSN for equal strength of input to D1-MSNs and D2-MSNs. The dashed black line depicts ΔMSN for a slightly higher cortical input to D1-MSNs. A DTT can be clearly seen (switching of ΔMSN from positive values to negative along the dashed line). (Inset) ΔMSN for low cortical inputs. From an operating point where ΔMSN = 0 (marked by the black circle) differential change in the cortical inputs to the D1- and D2-MSNs (e.g., by learning) could move the striatum state to a different value of ΔMSN (marked by the three arrows) and affect the behavior according to the sign of ΔMSN. (C) Schematic representation of ΔMSN as a function of input correlations and firing rates. The closed loop marks the range of input correlations and rate for which ΔMSN is positive ($\lambda_{ctx-d1} > \lambda_{ctx-d2}$). Outside the closed-loops ΔMSN could be zero or negative. High dopamine expands the region with D1-bias whereas low dopamine shrinks it. Increase in shared inputs or shared correlations has a similar effect to that of dopamine depletion. (D) Schematic description of the existence and control of striatal DTT. With the asymmetric connectivity the balance of the MSN activity is biased toward D2-MSNs. However, several input parameters and neuromodulators could tilt the balance in the favor of D1-MSNs. Figure adapted from Bahuguna et al. (2015).

the balance of MSN activity tips from D1- to D2-MSNs is determined by the degree of imbalance in the connectivity and can be modulated by inhibition from FSIs and GPe back projections, dopamine, and cortical input correlations (Fig 20.2C, D). A synchrony in the feed-forward inhibition may also cause an imbalance in D1 and D2 activity (Damodaran, Evans, & Blackwell, 2014). Flexibility in changing the DTT also makes it a good candidate to encode animal motivation and learning history. For instance, self-paced movement sequences could be initiated by reducing the DTT (e.g., by an internally generated dopamine signal) thereby making the striatum more receptive to the cortical commands, which otherwise would not have been gated by the striatum, and allowing rapid switching between *Go* and *No-Go* bias, as is required in executing action sequences (Rothwell et al., 2015).

This two-population model suggests that equal baseline firing rate of the D1- and D2-MSNs is also a convenient operating point for rapid decision making because only a small change in overall cortical input rate and/or correlations is sufficient to initiate the decision making process by biasing one MSN subpopulation over the other (Fig. 20.2B, inset).

The neocortex may provide equal inputs to the D1- and D2-MSNs in a naive state when the animal has not learned the task. After the animal has acquired the task, it is likely that inputs to the two types of task-relevant MSNs would be unequal. The model by Bahuguna and colleagues (2015) shows that even when D1- and D2-MSNs receive unequal input, DTT exists and the cortical bias for a particular decision could be overridden by various components of the BG such as the state of the striatum network and/or feedback from the GPe.

This model also helps us understand deficits in the decision making as observed in different brain diseases. The modulation of DTT by external agents such as dopamine could give a mechanistic explanation for LID (L-dopa-induced dyskinesia) and akinesia. In high (low) dopamine conditions, as a consequence of increased (decreased) strength of cortical inputs to the D1-MSNs, the DTT is observed at higher (lower) cortical inputs. That is, in high dopamine conditions a cortical input that was interpreted as *No-Go* in normal conditions would be interpreted as *Go* (characterized by increased input to D1-MSNs). Thus, the model predicts that in LID (high dopamine condition) GPi would show reduced activity. Indeed, induction of LID in MPTP-treated nonhuman primates results in a marked decrease in GPi firing rates (Boraud, Bezard, Bioulac, & Gross, 2001). Similarly, a decrease in dopamine levels leads to misinterpretation of striatal *Go* to striatal *No-Go*. The strengthening of the *No-Go* pathway might not only reduce the GPe disinhibition, but also initiate β-oscillations in the GPe–STN circuit (Kumar, Cardanobile, Rotter, & Aertsen, 2011), leading to akinetic symptoms as observed in PD. This model also predicts that increased inhibition of D2-MSNs by FSIs shortly after dopamine depletion (Gittis et al., 2011) might be a compensatory mechanism that tries to restore the bias toward D1-MSNs in the PD state. This is also strongly suggested by recent work on the balance of these pathways in asymptomatic mice (Escande et al., 2016).

Summary

Recent data on anatomy and electrophysiology of MSNs, combined with computational models show that the striatum is a far more complex network than previously assumed. The asymmetric connectivity between D1- and D2-MSNs introduces qualitatively new properties: it can function as a thresholding device to gate the cortical input and maintain a bias even when cortical inputs are ambiguous (Bahuguna et al., 2015).

However, more experimental data are required to fully understand the computations performed by the striatum. To better constrain the models data on corticostriatal synapses and relative contribution of inhibition from the GPe and FSIs are required. Available spiking activity data hint toward

formation of cell assemblies, however characterization of the differences in the spatiotemporal dynamics of the D1- and D2-MSNs would aid better understanding of the multimodal integration in the striatum and to what extent WLC is the underlying dynamical state. At this stage it also remains unclear how the thresholding behavior of the D1- and D2-MSNs network relates to the WLC type dynamics.

Already the two interacting MSN populations adorn the striatum with complex dynamics. So, it is important to further characterize the striatal neuronal diversity to determine if there are more than two function classes that differ in their connectivity and render the striatum with an even more complex dynamical repertoire. An interesting computational challenge is to adapt the high-level models of the striatum and BG based on the thresholding function of the striatum. Moreover, we need to revise the simple description of the BG based on the interacting feedforward pathways in view of the new experimental and computational work.

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