# Stepping out of the box: information processing in the neural networks of the basal ganglia

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The Albin-DeLong 'box and arrow' model has long been the accepted standard model for the basal ganglia network. However, advances in physiological and anatomical research have enabled a more detailed neural network approach. Recent computational models hold that the basal ganglia use reinforcement signals and local competitive learning rules to reduce the dimensionality of sparse cortical information. These models predict a steady-state situation with diminished efficacy of lateral inhibition and low synchronization. In this framework, Parkinson's disease can be characterized as a persistent state of negative reinforcement, inefficient dimensionality reduction, and abnormally synchronized basal ganglia activity.

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**Abbreviations**

| | |
|---|---|
| **BG** | basal ganglia |
| **CM-Pf** | centro–median parafascicular complex |
| **GABA** | γ-amino butyric acid |
| **GPi** | globus pallidus, internal segment |
| **GPe** | globus pallidus, external segment |
| **LTP** | long-term potentiation |
| **MPTP** | 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride |
| **PD** | Parkinson's disease |
| **SNc** | substantia nigra pars compacta |
| **SNr** | substantia nigra pars reticulata |
| **STN** | subthalamic nucleus |
| **TANs** | tonically active neurons |

## Introduction

The basal ganglia (BG) are a complicated interconnected network of neuronal elements that process motor, cognitive and motivational (limbic) cortical information [1,2•]. The clinical manifestations of neuronal disorders of the BG, including hypokinetic movement disorders such as Parkinson's disease (PD) and hyperkinetic movement disorders, such as Hemiballismus and Huntington's disease, suggest that the BG use this multi-dimensional cortical information to generate, or to control, action. Many computational models of the BG function have been developed (see reviews in [3,4]). These models have generated testable hypotheses, and enable greater insights into the physiology and pathophysiology of the BG and human diseases. In this review, we use this background to construct a better understanding of normal and pathological information processing in the BG cortical circuits.

## The classical 'box and arrow' view of the BG

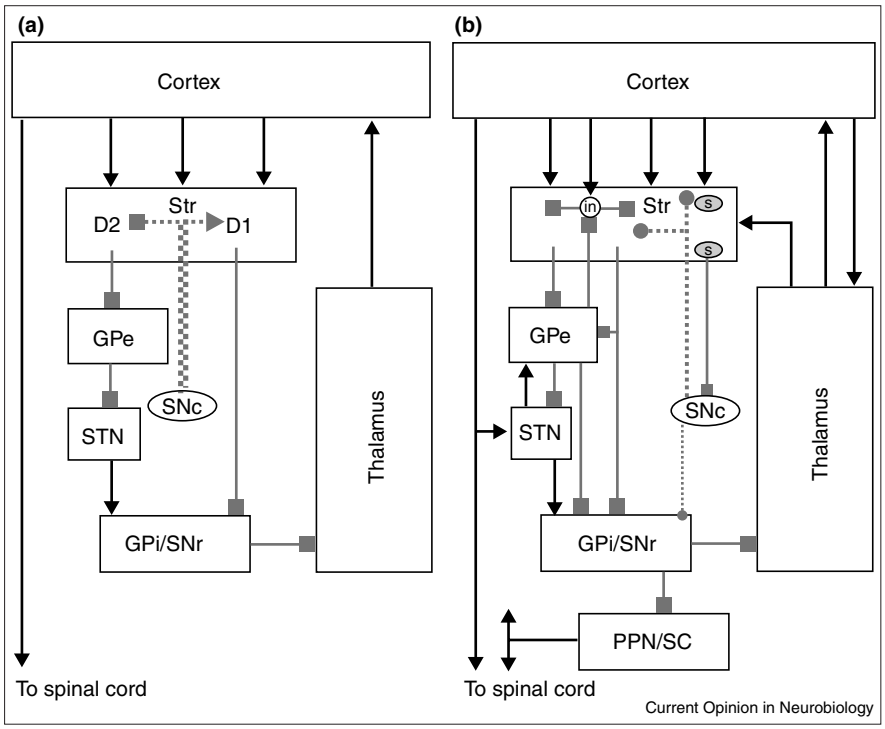
Information processing in any neuronal system is bound by the underlying anatomical substrate. One of the first modern models (the Albin-DeLong model [5,6]) of BG function was inspired by the dominant anatomical connections of BG nuclei and their neurochemistry. A major pathway in the BG circuitry leads from most cortical areas to the striatum. Subsequent projections link striatal neurons to the BG output stage (i.e. the globus pallidus, internal segment [GPi] and the substantia nigra, pars reticulata [SNr], for simplicity referred to hereafter as GPi). The BG control — via γ-amino butyric acid (GABA)ergic inhibitory projections of GPi neurons — the activity of the excitatory thalamo–cortical networks (Figure 1a). The Albin-DeLong model assumes two segregated feed-forward pathways from the striatum to the GPi. The direct pathway is made up of direct GABAergic projections to the GPi. The indirect pathway connects a different population of striatal neurons to the GPi, via the globus pallidus, external segment (GPe) and the subthalamic nucleus (STN). The net effect of the striatum over the GPi is inhibitory for the direct pathway, and excitatory (due to double inhibition) for the indirect pathway. Because of the inhibitory pallido–thalamic projections, the direct pathway is part of a positive feedback loop connecting the cortex–striatum–GPi back to the frontal cortex, whereas the indirect pathway is part of a negative feedback loop. Finally, dopamine modulates the activity of striatal neurons that give rise to the direct and indirect pathways, by D1-receptor-mediated excitation and D2-receptor-mediated inhibition, respectively (Figure 1a). Thus, dopamine increases the gain of the positive trans-cortical BG loop and decreases the gain of the negative loop, eventually promoting activation of the frontal cortex and action.

Most students of BG anatomy agree that the BG circuitry can be divided into three partially overlapping anatomical domains: the somato–motor domain, the associative–cognitive domain and the limbic domain. However, the degree of overlap and convergence in the BG is still under discussion [7,8]. The above description of direct and indirect pathways can therefore be applied to a segregated (e.g. motor) basal ganglia loop [7] or to the entire network [8].

## The action–selection paradigm and lateral inhibition models of the basal ganglia

The assumption of separate direct–inhibitory and indirect–excitatory striato–pallidal pathways leads to two different views of the BG. The first assumes that the two pathways converge on the same pallidal neurons, therefore enabling temporal scaling of their activity. The second view assumes that the two pathways project to different

**Figure 1**




The 'box and arrow' models of BG circuitry. **(a)** The Albin-DeLong model of BG circuitry. The figure provides a schematic outline of the basic circuitry and the transmitters in the BG. Black lines represent glutamatergic connections, gray lines represent GABAergic connections and dashed gray lines represent dopaminergic connections. Lines ending in squares represent inhibitory connections (GABA, D2 receptors), and lines ending in triangles show excitatory connections (glutamate, D1 receptors). **(b)** Less schematic 'box and arrow' diagram of BG circuitry. Lines ending in circles represent modulatory dopaminergic connections. Str, striatum; s, striosomes; PPN, pedunculopontine nucleus; SC, superior colliculus; in: parvalbumin positive GABAergic interneurons.

populations of pallidal neurons. When actions or voluntary movements are generated by cortical mechanisms, the indirect pathway acts broadly, mainly through the divergent STN–GPi projections [9], to inhibit competing motor programs. Simultaneously, the direct pathway focally removes the inhibition from the desired movement or action [10,11].

The BG also uses surround or lateral inhibition to generate focal activation. Most BG neurons form extensive collateral connections within their nuclei of origin [12•]. Because both striatal and GPi neurons use GABA as their main neurotransmitter, the collateral system serves as a lateral inhibition network. Moreover, the inhibitory parvalbumin positive GABAergic interneurons provide another efficient substrate for lateral inhibition in the striatum [2•,13]. Indeed, many models of BG function have been influenced by this strong anatomical lateral connectivity, and assume strong functional mutual inhibition between striatal neurons or domains [14••].

## Alterations in discharge rate of BG neurons and pathophysiology of movement disorders

Despite the arguments regarding the precise nature of BG processing, the Albin-DeLong 'box and arrow' model has generally been accepted as the core model for BG function. The main achievement of this model lies in accounting for pathophysiological mechanisms of both hypokinetic and hyperkinetic movement disorders. The model predicts an enhanced tonic inhibition of the thalamo–cortical circuitry in hypokinetic disorders and a diminished amount of inhibition of these circuits in hyperkinetic disorders [6]. The scaling versus the focusing schools of thought are usually incorporated into the model, which suggests that hypokinetic and hyperkinetic movement disorders represent over- or under-activity of neuronal circuits performing more or less scaling or focusing, respectively [15••]. The model has received apparent support from the findings that STN and GPi firing rates are increased in PD [6]. Moreover, it has been shown that inactivation of these nuclei can ameliorate the motor symptoms in Parkinsonian animals [16] and human patients [17].

## The BG network is more complicated than the BG models

Although many experimental findings are in agreement with the Albin-DeLong model, accumulating evidence challenges this classical view in several respects. First, neurons in the BG show extensive collateral connectivity [12•] and additional internal and external (e.g. to brainstem nuclei) projections [2•] that are incompatible with the simplified classical view. Second, recent studies indicate that: D1 and D2 receptors co-localize on striatal neurons [18••]; all striatal neurons projecting to GPi also project to GPe [2•,19]; and D1/D2 activation cannot simply be described as purely excitatory or inhibitory, respectively [20•]. Third, lesions of the GPi not only ameliorate the hypokinetic clinical characteristics of PD, but also alleviate hyperkinetic disturbances; and lesions in the thalamus do not lead to PD-like motor symptoms [21]. Fourth and finally, physiological studies do not reveal strong inhibition between BG

neighboring neurons [22,23••] as predicted by recent expansions of the Albin-DeLong model (e.g. action–selection or lateral inhibition models).

A possible solution to the accumulating new physiological and anatomical data is to incorporate these new findings into a more complex model with more boxes and arrows (Figure 1b). However, the complex anatomical and physiological structure of each of the neurons in the BG network calls for a new approach that will use the recent advances of neural computation methods.

## Sparse information is transmitted from the cortex to the BG

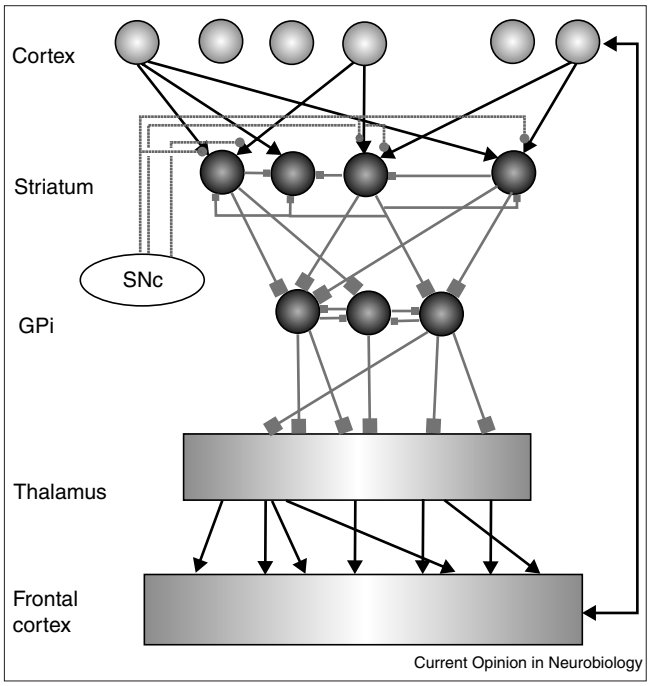
The mutual inhibition models and the focusing (action–selection) models predict strong lateral inhibitory interactions between BG neurons. These inhibitory processes should be characterized by inhibitory postsynaptic potentials, and by negative correlation or suppression of firing of one neuron by the firing of another neuron in multiple neuron recordings. This prediction, however, has not been borne out by physiological intracellular studies. No evidence has been found for functional synaptic interactions between striatal projection neurons ([22], but see also [24]). Similarly, multiple neuron recordings have failed to reveal correlations between the spiking activity of simultaneously recorded pallidal neurons [23••].

A possible reason for the lack of BG correlation is sparse cortico–BG connectivity. The cortico–striatal–pallidal pathway is anatomically characterized by a high degree of numerical reduction. The number of striatal neurons is two orders of magnitude less than the number of cortical neurons projecting to the striatum, and an additional reduction of the same magnitude occurs from the striatum to the GPi [8,25]. Recent studies indicate that the anatomy of the cortico–striatal pathways is heterogeneous and discontinuous, and that individual cortical foci give rise to multiple and separate sites of striatal innervation [26–28]. Quantitative analysis of single neuron tracing reveals a low degree of cortical input sharing by nearby striatal neurons [29,30••]. Moreover, the cortico–striatal physiological message is not a simple read-out of the cortical state [31••]. Finally, many recent anatomical and physiological studies concur that the main circuits passing through the BG remain separate under normal conditions [7,23••,32]. Thus, despite the huge numerical reduction from the cortex to the GPi, GPi activity probably represents an optimally compressed (uncorrelated) version of distinctive features of cortical information.

## Reinforcement learning models of the BG

Most brain dopamine is generated by midbrain dopaminergic neurons, projecting to the striatum. The central role of dopamine in controlling motivation and learning has been known for many years [33], however, most 'box and arrow' models of the BG have overlooked the relationships between dopamine and learning in normal BG function. The outstanding series of physiological experiments by

**Figure 2**




The reinforcement driven dimensionality reduction neural network model of the main axis of the BG. The model is composed of a three-layered feed-forward network simulating the cortico–striato–pallidal circuit with lateral inhibitory connections at the intermediate (striatum) and output (pallidum) layers. Neuronal layers that are not included in the current model are shown as boxes. A reinforcement (dopaminergic) signal is provided at the intermediate (striatal) layer. Arrowhead black connections represent glutamatergic excitatory synapses, square-head gray connections represent GABAergic inhibitory synapses and round-head broken-line connections represent dopaminergic modulatory synapses.

Schultz (see [34]) revealed that the dopaminergic signal is best characterized as relating to the differences between the animal's predictions and reality. Thus, dopaminergic neurons respond to perceived differences between predictions and reality with an enhanced firing rate, which is shifted to the earliest prediction of future reward. Furthermore, a suppression of firing occurs when a predicted reward fails to occur. Tonically active neurons (TANs), probably the cholinergic interneurons of the striatum, show similar responses for predicted and unpredicted rewards [27]. This behavior resembles that of the 'critic' in reinforcement temporal delay learning models [35]. The temporal delay learning models are based on the actor–critic architecture. The actor (controller) provides a control signal to the environment (controlled system) that provides a feedback signal to the actor. The critic produces evaluative or reinforcement feedback to the actor by observing the consequences of the actor's behavior on the environment. In a learning process, the critic adjusts the actor's behavior so as to maximize the total amount of future rewards (reinforcements). The cortex–BG–cortex axis is therefore modeled as the 'actor' and the dopaminergic (and cholinergic) neurons as the 'critic' or the provider of the teaching signal (henceforth the reinforcement signal) [34,36].

**Table 1**

**Hebbian and anti-Hebbian learning rules.**

| Presynaptic and post-synaptic activity | Synaptic efficacy | |
|---|---|---|
| | Hebbian learning | Anti-Hebbian learning |
| Synchronous | Increase | Decrease |
| Asynchronous | Decrease | Increase |

The table represents Stent's modification of Hebb's rule: synchronous (or conjunctive) firing of the presynaptic and postsynaptic neurons (within a 100–500 ms time window) increases the efficacy of the synapse between these neurons in Hebbian learning and decreases the efficacy of that synapse in anti-Hebbian learning. Non-simultaneous (asynchronous) firing has opposite effects. In mathematical terms, Hebb's rule can be expressed as $\Delta w_{ij} = \eta \bullet [x_i \bullet y_j]$, where $x$ and $y$ are the differences between the presynaptic and postsynaptic activity and their respective averages, $i$ and $j$ are indexes of the presynaptic and postsynaptic neurons, $w$ is the synaptic efficacy (i.e. the probability of the presynaptic neuron to induce action potentials in the postsynaptic cell), $w_{ij} \geq 0$ for excitatory synapses and $w_{ij} \leq 0$ for inhibitory synapses, and $\eta$ is a scaling factor that regulates the learning rate. Physiologically speaking, Hebbian learning 'rewards a job well done' and vice versa. In an excitatory synapse, the desired effect is activation of the postsynaptic cell by the presynaptic cell. Thus, a synchronous activation causes an increase in synaptic efficacy. However, for an inhibitory synapse the desired effect is a suppression of the activity of the postsynaptic cell by the presynaptic activity. Therefore, conjunctive activity of the presynaptic and postsynaptic neurons represents a 'failure' of the inhibitory synapse and the Hebbian learning rule causes a mathematical increase in synaptic efficacy (e.g. from −100 to −50 arbitrary units of synaptic efficacy) that is equivalent to a physiological decrease in the efficacy of the inhibitory synapse. Anti-Hebbian learning causes a mathematical decrease (equal to a physiological increase) in the efficacy of the inhibitory synapse following synchronous activation. This increased physiological efficacy of inhibitory synapses can lead to decorrelation of presynaptic and postsynaptic activity.

**Table 2**

**Reinforcement-driven Hebbian learning rules.**

| Reinforcement signal | Presynaptic and post-synaptic activity | Synaptic efficacy |
|---|---|---|
| Positive | Synchronous | Increase |
| Positive | Asynchronous | Decrease |
| Zero | Synchronous | No change |
| Zero | Asynchronous | No change |
| Negative | Synchronous | Decrease |
| Negative | Asynchronous | Increase |

In a triple synapse (e.g. the cortico–dopaminergic–striatal synapse) the changes in synaptic efficacy are influenced by both the reinforcement signal and the presynaptic and postsynaptic activity. Mathematically, the learning rule is expressed as $\Delta w_{ij} = \eta \bullet [x_i \bullet y_j]$, where $x$ and $y$ are the cortex (presynaptic) and striatal (postsynaptic) activity (related to mean activity), $w$ is the synaptic efficacy of the cortico-striatal synapse ($w_{ij} \geq 0$), $\eta$ is a scaling factor that regulates the learning rate and $r$ is the reinforcement signal. The reinforcement control signal is positive, enabling Hebbian learning, for reward-related events and zero, clamping the efficacies of BG synapses, for non reward-related events (baseline dopamine levels). Reduction of dopamine levels below background level is reflected by negative reinforcement values and reversal of the learning rules in the cortico–striatal synapses. Finally, in the triple synapses the learning rates are proportional to the absolute value of the reinforcement signal.

Actor–critic models predict that the reinforcement signal will modulate synaptic transmission in the actor. Indeed, plastic changes in the morphology of BG synapses occur after dopamine depletion [37]. Physiological studies show that both the dopaminergic [38,39••] and the cholinergic [40] signals modulate the access of cortical input to striatal projection neurons. Moreover, as predicted by reinforcement learning models, BG neurons significantly change their discharge as a function of the prediction of future reward [41,42•,43] and during different phases of learning [44].

## Dimensionality reduction neural networks

Reinforcement learning models emphasize the position of the BG in normal behavior; however, the role of the BG in the pathophysiology of movement disorders has been overlooked. A model that combines most of the anatomical, physiological and computational approaches cited above has recently been suggested [45••] (Figure 2, and see [14,46•] for related approaches). The model assumes that the BG perform efficient dimensionality reduction [47,48] and decorrelation of the large information space spanned by the activity of the cortico–striatal neurons. Theoretical studies demonstrate that neural networks can perform such efficient coding using local cellular competitive learning rules [47]. In the BG case, inter-layer (cortico–striatal and striatal–GPi) feed-forward connectivity is controlled by Hebbian rules whereas lateral intra-layer inhibitory connectivity is controlled by anti-Hebbian rules (Table 1).

According to this model, the BG dimensionality reduction is affected not only by the statistical properties of the cortical patterns but also by their behavioral significance. This is achieved by a triple striatal synapse, in which the reinforcement (dopaminergic or cholinergic) signal controls the feed-forward cortico–striatal Hebbian learning (Table 2). Following presentation of novel input patterns or a change in the reinforcement signal, the network (Figure 2) performs sub-optimal information compression and the activity of the GPi neurons becomes correlated. This correlation causes an increase in the physiological efficacies of the inhibitory lateral synapses (Table 1, anti-Hebbian learning rule) and changes in the efficacies of the feed-forward connections. These changes, in turn, result in decorrelation of neuronal activity within the GPi. Thus, decorrelation of BG activity is achieved by a dynamic process and not by fixed sparse cortico–BG connectivity. Moreover, the reinforcement signal causes the extraction to become discriminative, performing better for reward related inputs but not for unrelated events. Finally, dopamine depletion — a negative reinforcement signal from the perspective of striatal neurons — as in PD, substantially impairs the dimensionality reduction process. The consequential modifications of the BG synapses results in increased synchronization among BG neurons [23••,49,50]. Conventional dopamine replacement therapy

restores the background level of dopamine. However, the intermittent pulsatile nature of the treatment causes inevitable fluctuations in striatal dopamine [51]. These fluctuations are randomly timed relative to the environment and therefore may result in the generation of random encoding and the development of dyskinesia.

## Closing the loop, sequential behavior and conclusions

The output of the BG is directed mainly towards the thalamus. Most models of the BG network assume that the thalamus acts as a simple relay station between the GPi and the frontal cortex. However, the projections from GPi to several thalamic nuclei, the heavy back projections from the cortex to the thalamus and to the reticular nucleus, the thalamo-striatal projections [52•,53••], and finally the complex thalamic network, suggest that the thalamus serves a more complicated role. In any case, at least part of the BG output is fed back through the thalamus to the frontal cortex and the striatum. Although it is not yet clear whether the system is a complete closed system or an open interconnected system [54,55], the gross anatomy of the BG is one of a semi-closed loop. This semi-closed loop allows the BG to play a key role in sequential behavior [56,57].

In conclusion, computational models have been instrumental in advancing our understanding of the BG in normal and pathological behavior. The reinforcement dimensionality reduction model of the BG circuitry uses the main features of many of these models, and provides insights into some of the mysteries of the BG. It explains the role of the anatomical numerical reduction and lateral connections in the BG, the tonic, background level of the neuronal reinforcement signal, and the physiological finding of independent and synchronized pallidal activity in normal and Parkinsonian states, respectively. Further studies of the predictions of this and other models should enable us to better shape realistic models of the BG, and to gain a better understanding of the role of the BG in health and disease.

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This study investigates the role of D1/D2 dopamine receptors in long-term potentiation (LTP) in the cortico–striatal pathway, using intracellular recording from striatal neurons in a slice preparation. LTP was blocked by dopamine depletion and by a D1 antagonist but was not blocked by a D2 antagonist. In dopamine-depleted slices, the ability to induce LTP could be restored by bath application of the dopamine D1 receptor agonist. These results show that activation of D1 receptors by either endogenous dopamine or exogenous dopamine agonists is a requirement for the induction of LTP in the cortico–striatal pathway.

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multi-dimensional encoding. Thus, in a case of N binary units, an action–selection process can encode only N states, whereas a dimensionality–reduction model could conceivably encode $2^N$ states. The authors propose that by using a reinforcement-driven dimensionality reduction process, the BG achieve efficient extraction of salient cortical information that may then be used by the frontal cortex for execution and planning of upcoming actions.

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