The Persistent Mystery of the Basal Ganglia's Contribution to Motor Control

Pietro Mazzoni

Pietro Mazzoni is Associate Professor of Neurology and Director of the Motor Performance Laboratory at Columbia University in New York. He obtained a medical degree at Harvard and a PhD in Neuroscience at MIT, and he trained in Neurology, Movement Disorders, and Human Motor Control at Columbia. His research interests include the role of the basal ganglia in motor control and motor learning. He steadfastly maintains that becoming bald whilst working with his coauthor during his PhD studies was pure coincidence.

Martyn Bracewell

is Senior Lecturer in Neurology and Neuroscience at Bangor University, and honorary consultant neurologist to the Walton Centre in Liverpool and the Betsi Cadwaladhr University Health Board in North Wales. He trained in neurology at Oxford, Queen Square and Birmingham, and did a PhD in neuroscience at MIT. His research interests include sensorimotor integration, non-invasive brain stimulation and novel approaches to neuro-rehabilitation.

Correspondence to:
Pietro Mazzoni, MD PhD
710 W. 168th St, Box NI-175
The Neurological Institute
New York, NY, USA.

In the second article in our series on motor control, we turn our attention to the persistent mystery of what the basal ganglia actually do. We present an update on the canonical 'circuit diagram' of Alexander and colleagues, and discuss some new ideas on the role of the basal ganglia in selection of the parameters of action.

Martyn Bracewell, Series editor

The role of the basal ganglia (BG) in motor control has long been mysterious. These nuclei were always at a disadvantage, relative to other motor structures, with regards to hypotheses about their functions. Consider, for example, the primary motor cortex. It has direct projections to spinal motor neurones; electrical stimulation elicits movement; and lesions cause weakness. It was thus natural to hypothesise that the motor cortex encodes motor commands.

For the BG, on the other hand, a simple intuition is elusive. These nuclei receive information from many brain regions and project to brain structures that drive actions, suggesting a role in motor control. However, the clinical symptoms caused by BG disorders, such as rigidity, reduction of movement speed and amplitude, involuntary movements, and abnormal postures, are so varied and complex that a simple motor hypothesis is difficult to formulate.

Marsden synthesised a vast body of knowledge regarding motor abnormalities due to BG disorders, and hypothesised that the BG "are responsible for the automatic execution of learned motor tasks."[1] This hypothesis embodied the fundamental idea that the BG do not simply make movement possible, but rather that they make it possible to move in a certain manner. Indeed, early neurophysiologic studies found neural activity that was frustratingly difficult to relate to simple movement parameters, such as amplitude and direction, and was greatly affected by non-motor factors. Only years later did evidence emerge of how neural activity might encode whether a movement is executed automatically[2] and whether it is executed as a "learned" motor task.[3]

A canonical circuit for the BG

These conceptual difficulties did not dissuade researchers from a painstaking effort to establish the anatomical, chemical, and physiological connectivity of the BG. This "bottom-up" approach identified a circuit (the motor loop; Figure 1A) connecting the BG and the motor cortical areas, which became the working model for hypotheses about BG function. In addition, this circuit was found to be one of several parallel circuits linking different parts of the basal ganglia to different cortical regions. Alexander and colleagues' review[4] introduced two ideas that have fundamentally influenced our notions of BG function: the BG's circuitry is specifically suited to a particular type of computation (processing signals from multiple brain structures to influence behaviour), and this computation is carried out over multiple functional domains (motor, oculomotor, cognitive, and emotional).

The motor circuit is a loop in which motor and other cortical areas project to the BG, which in turn project back to motor cortical areas by way of the thalamus. In early formulations of this loop[5] (Figure 1A), the striatum is the sole input nucleus, receiving information from motor cortical areas. The striatum projects to the internal segment of the globus pallidum (GPi) by the "direct pathway". GPi is the output nucleus, projecting to thalamus, and thence to motor cortical areas. The remaining nuclei (external segment of the globus pallidum, GPe, and subthalamic nucleus, STN) are part of the BG's internal circuitry, forming the "indirect pathway." The substantia nigra pars compacta (SNc) has a modulatory role, via its dopaminergic projection to the striatum.

Major features of this circuit are that the striatum inhibits GPi (via the direct pathway), and GPi, in turn, inhibits motor cortical areas. These features suggested that the BG tonically inhibit movement, and that when a movement is to occur, an excitatory signal from motor cortical areas causes the striatum to briefly inhibit GPi.

Figure 1: Schematic diagram of the motor cortico-BG loop.
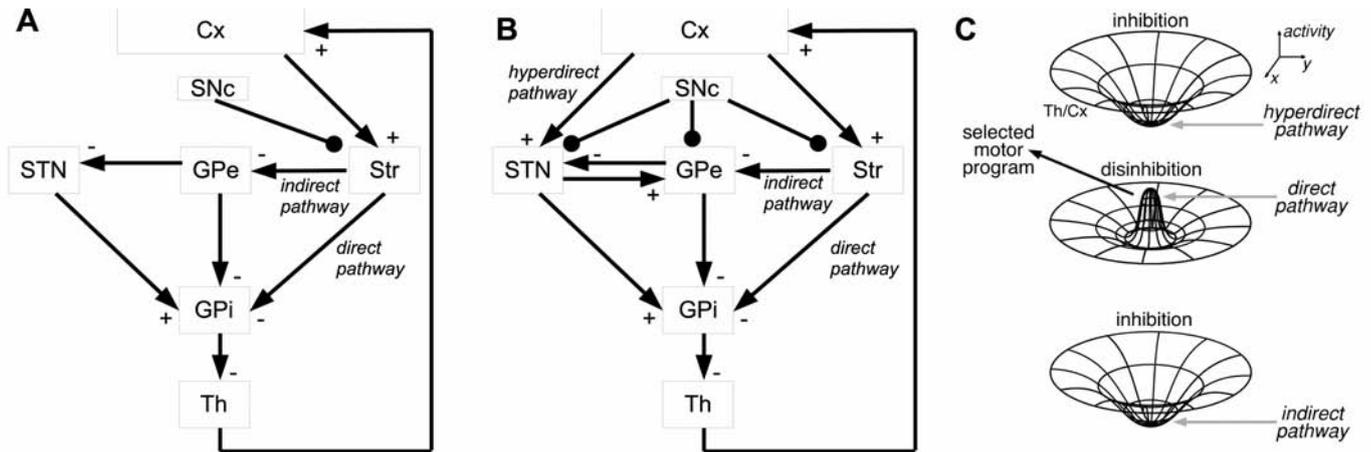
A. Early version of the model circuit.[5] The striatum receives cortical signals related to a desired movement, and projects to GPi via direct and indirect pathways. The GPi projects to thalamus, which in turn projects to motor cortical areas. Projections to brainstem structures are not shown. Excitatory (glutamatergic) synapses are indicated as arrows with "+", inhibitory (GABAergic) synapses as arrows with "-". Dopaminergic synapses (from the SNc) are indicated as filled circles. Cx, cortex; GPe, external segment of globus pallidum; GPi, internal segment of globus pallidum; SNc, substantia nigra pas compacta; STN, subthalamic nucleus; Str, striatum; Th, thalamus.

B. Updated version of the cortico-BG loop. In addition to the connections shown in (A), there is an excitatory connection from cortex to STN (hyperdirect pathway) and an excitatory connection from STN to GPe.

C. Dynamic model of basal ganglia function explaining activity changes in thalamus and/or cortex (Th/Cx) caused by sequential inputs through the hyperdirect (top), direct (middle), and indirect (bottom) pathways. Time (t) proceeds from top to bottom. (Adapted, from Nambu et al.,[9] with permission from Elsevier).

Thus inhibition of motor cortex is temporarily removed (disinhibition) and the desired action can occur. The indirect pathway (striatum to GPe to STN to GPi) balances the inhibitory effect of the direct pathway. Dopamine from SNc to striatum plays a modulatory role by setting the excitability of direct and indirect pathways.

Dysregulation of this circuit successfully explains certain motor abnormalities in Parkinson's disease (PD) and other motor disorders.[5,6] In PD, for example, dopamine depletion in the SNc results in reduced activation of the direct pathway. This pathway is therefore less effective in overcoming the GPi's tonic inhibition of motor cortex, and movements thus become more difficult to initiate. In Huntington's disease, degeneration of neurons in the indirect pathway leads to a reduction of the GPi's tonic inhibition of motor cortex, and thus to the occurrence of involuntary movements. These descriptions became the basis for novel, circuit-based symptomatic treatments for PD and other movement disorders, namely, focal lesions and deep-brain stimulation of the BG.[7]

The discovery of the cortico-BG loop set the stage for a further major conceptual advance. Mink and Thach proposed that the BG "filter" motor plans, so that neural signals for desired movements are enhanced and those for similar but undesired movements are suppressed.[8] They posited a "centre-surround" organisation of projections from striatum to GPi, which refines a cortical motor command so that the desired movement is enabled and other competing motor programs are inhibited.

A "hyperdirect" pathway
In the last two decades, there have been several advances in our understanding of anatomy and physiology of this "canonical" BG circuitry. In this updated description,[9,10] the STN joins the striatum as an input nucleus receiving cortical projections (Figure 1B). The STN is now considered part of a "hyperdirect" pathway that contributes to the filtering action of direct and indirect pathways, helping to facilitate desired movements and inhibit competing motor programs. Recordings from these structures suggest a temporal evolution of this process.[9] The first event associated with a cortical motor signal is activation of the STN via the "hyperdirect" pathway (cortex-STN-GPi), which causes global excitation of GPi and momentary suppression of all movements. Activation of the direct pathway (cortex-striatum-GPi), a few milliseconds later, inhibits only GPi neurons encoding the desired movement, and thus activates the desired motor program through disinhibition of selected thalamic targets. Finally, a signal through the indirect pathway (cortex-striatum-GPe-STN-GPi) puts an end to the motor command and terminates the movement.

This updated model of the motor circuit introduced temporal dynamics to signal processing in the BG. The pathophysiology of akinesia in a primate model of PD can now be described in temporal and spatial terms: when a movement is triggered by the cortex, abnormally large signals through hyperdirect and indirect pathways suppress larger-than-normal areas of thalamus/cortex, and signals through the direct pathway are reduced in amplitude and duration. Smaller areas of the thalamus/cortex are thus disinhibited for a shorter period of time than normal, and the desired motor program cannot be released.[11]

Action selection and reinforcement learning
Our current understanding of BG circuits offers a substrate on which to map hypotheses about action selection, reward-driven behaviour, and reinforcement learning. Theoretical and behavioural studies of learning had long predicted the existence of mechanisms for selecting an optimal action among several choices, and for learning to do so based on reward and penalty. The convergence of cortical signals onto the BG, and the adaptive temporal relationship of striatal dopamine signals to reward prediction, are ideal candidates for implementing reinforcement learning algorithms.[12,13] At the synaptic level, dopaminergic projections from SNc to striatum and STN have the power to adjust the strength of cortical projections to these nuclei, allowing the possibility of precisely fine-tuning the effect of BG processing of cortical signals.[14] These mechanisms for synaptic adjustments are well suited to the modification of action selection mechanisms based on reinforcement learning, and thus to the development of automatic, habit-based behavioural patterns.[3]

Can such computations help explain clinical movement abnormalities? Certain deficits, such as increased delays in movement onset in PD and abnormal postures of dystonia, can be related, respectively, to inadequate flow of signals through the direct pathway and to

abnormal balance between GPi excitation and inhibition.[5,8] It is not obvious, on the other hand, how symptoms such as reduced movement speed and amplitude in PD might result from abnormal movement selection. Moreover, it is not clear how to relate changes in dopamine-dependent habit-learning mechanisms to the motor symptoms of PD. While certain types of learning are impaired in PD,[15] this disorder's clinical symptoms affect quotidian, well-rehearsed movements that are not thought to require new learning.

Part of this difficulty may lie in limitations in our understanding of normal motor control, which has traditionally considered kinematic and kinetic parameters, such as speed and force, to be outside the domain of action selection. Recent work, however, suggests that movement speed may be subject to selection processes analogous to those observed in motivation-driven action selection, and that bradykinesia in PD results from faulty speed selection policies, rather than from an inability to move at normal speeds.[16] This interpretation suggests that movement kinematics are governed by selection processes with their own optimality policies, response to reinforcement, and susceptibility to habit development. Thus the initiation, speed, amplitude, and time course of movements may require circuitry specialised for optimal selection of parameters, similar to the mechanisms that guide action selection and habit learning. The reinforcement signals and optimality policies relevant to motor control may be distinct from those that guide action selection and more complex behaviour, but there may be computational analogies between the selection of *how* to perform a movement (e.g., how soon, how fast, how long) and the selection of *what* movement to perform. Such considerations may extend our understanding of clinical motor symptoms of BG disease that are not explained by current models, and may provide new insights into the BG's more mysterious motor functions. ◆

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