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Basal Ganglia: Bradykinesia Models

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Synonyms

Hypokinesia model; Slowness of movement model

Definition

Bradykinesia is the cardinal symptom of Parkinson's disease (PD). It is related to an abnormal slowness of movement. The causes of PD bradykinesia are not known largely, because there are multiple brain areas and pathways involved from the neuronal degeneration site (dopamine (DA) neurons in substantia nigra pars compacta (SNc) and ventral tegmental area (VTA)) to the muscles (see Fig. 1). Bradykinesia models are mathematical and computational constructs attempting to uncover how information is processed in the affected brain areas and what are the biophysical mechanisms giving rise to the observed slowness of movement in PD bradykinesia.

Detailed Description

Bradykinesia, the hallmark and most disabling symptom of PD, refers to an extreme slowness of movement. In early stages of the disease, PD patients have difficulties with daily activities such as walking, speaking, or getting in and out of chairs (Gibberd 1986). In the later phases of the disease, the entire movement process becomes increasingly slow and occasionally results in a complete inability to move. Patients must concentrate intensely to overcome the inertia of their limbs even when they are executing the simplest motor tasks. Movement is particularly impaired when novel movements are attempted (Connor and Abbs 1991) or when several movements are combined (Benecke et al. 1986; Lazarus and Stelmach 1992).

Anatomical Overview

Initiation and execution of voluntary movements involve brain areas and pathways. The "motor circuit" originates in the motor areas of the frontal cortex, which activate motor portions of the basal ganglia subcortical structures (striatum (STR), globus pallidus external (GPe) and internal (GPi) segments, the subthalamic nucleus (STN), the substantia nigra pars reticulata (SNr)), and the thalamus and which in turn project back to the frontal motor areas of the cortex. The basal ganglia (BG) structures are implicated in the selection of the most appropriate motor command given the current context. Motor commands from

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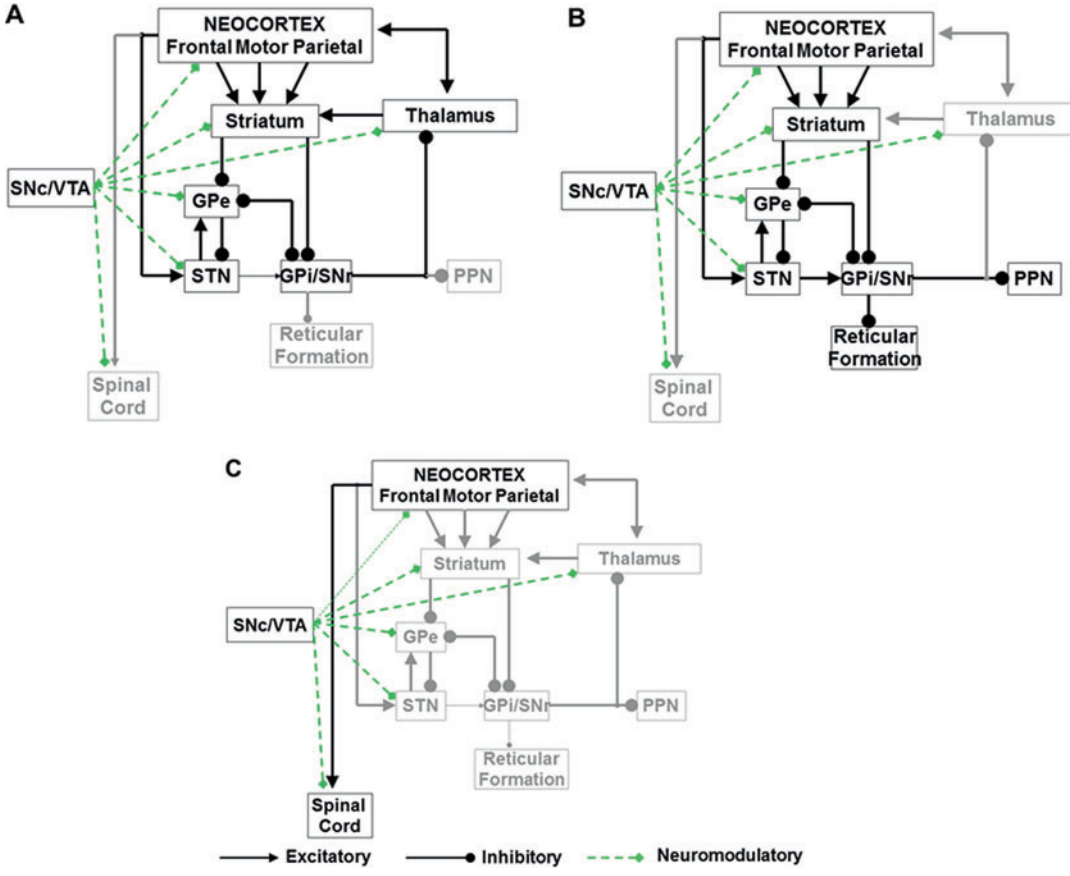


Basal Ganglia: Bradykinesia Models, Fig. 1 Brain circuits implicated in PD bradykinesia. (**a**) Pathways from the substantia nigra pars compacta (SNc) and the ventral tegmental area (VTA) to the striatum and from there to the thalamic nuclei and the frontal cortex through the substantia nigra pars reticulata (SNr) and the globus pallidus internal segment (GPi). (**b**) Pathway from the SNc and the VTA to the striatum and from there to the brainstem through the SNr and GPi. (**c**) Pathway from the SNc/VTA to cortical areas such as the supplementary motor area (SMA), the parietal cortex, and the primary motor cortex (M1) and from there to the spinal cord

the frontal motor areas of the cortex (premotor, supplementary, and primary motor areas) activate the corresponding motor spinal centers, which then activate the muscles.

Dopaminergic Pathways

A widespread DAergic innervation from SNc and VTA to BG, thalamus, cortex, and spinal cord exists (Williams and Goldman-Rakic 1998; Bjorklund and Lindvall 1984; Sanchez-Gonzalez et al. 2005; Anaya-Martinez et al. 2006). DA heavily innervates STR and modulates its activity (Gerfen et al. 1990). In addition, DA modulates other BG structures including GPe and GPi segments, STN, and SNr (Rommelfanger and Wichmann 2010).

DAergic neurons also innervate and modulate various thalamic nuclei including the ventrolateral nuclei (motor region) (Sanchez-Gonzalez et al. 2005). In rats a common DA projection exists to GP and the reticularis nucleus of the thalamus (Anaya-Martinez et al. 2006).

DA also innervates the cerebral cortex (Berger et al. 1988; Elsworth et al. 1990; Gaspar et al. 1991, 1992; Scatton et al. 1983; Lewis et al. 1988; Lidow et al. 1989; Williams and Goldman-Rakic 1998). DA afferents are densest in cortical areas 24, 4, 6, and SMA, where they display a trilaminar pattern of distribution, predominating in layers I,

IIIa, and V–VI (Berger et al. 1988; Williams and Goldman-Rakic 1998; Elsworth et al. 1990; Gaspar et al. 1991, 1992). In the granular prefrontal (areas 46, 9, 10, 11, 12), parietal (areas 1, 2, 3, 5, 7), temporal (areas 21, 22), and posterior cingulate (area 23) cortices, DA afferents are less dense and show a bilaminar pattern of distribution in the depth of layers I and V–VI (Berger et al. 1988; Gaspar et al. 1991, 1992; Scatton et al. 1983; Lewis et al. 1988; Lidow et al. 1989).

Finally, DA innervates the dorsal (sensory input) and ventral (motor output) horns of the spinal cord (Blessing and Chalmers 1979; Shirouzou et al. 1990; Weil-Fugazza and Godefroy 1993; Takada et al. 1988; Commissiong et al. 1979).

Physiological and Behavioral Phenomena

PD bradykinesia has been linked with the degeneration of dopamine neurons in SNc and VTA. Bradykinesia manifests only when 80–90% of dopamine neurons die. The degeneration of dopamine neurons leads to a number of changes relevant to bradykinesia in the neuronal, electromyographic (EMG), and movement parameters reported in parkinsonian human and animal brains:

- Increases in background activity (spontaneous firing) of STR and STN cells (Kita and Kita 2011).
- An oscillatory response to motor cortical stimulation of STR cells consisting of an excitation, a long inhibition and a slow excitation (Kita and Kita 2011).
- The latencies of the STR excitations are significantly shorter than in the controls (Kita and Kita 2011).
- An oscillatory response to STR oscillatory stimulation of GPe cells consisting of an early excitation, a short inhibition and a late excitation (Kita and Kita 2011).
- An oscillatory response to motor cortical and GPe oscillatory stimulation of STN cells consisting of either an early and late excitation or a single excitation followed by a very long inhibition (Kita and Kita 2011).
- The latency of the GPe inhibition is decreased in the DA depleted case (6-OHDA), whereas the duration and strength of the late excitation are increased (Kita and Kita 2011).
- An oscillatory pattern of GPi cells consisting of an early excitation and a long inhibition or a pattern consisting of a solo long inhibition (Kita and Kita 2011).
- The duration of the GPi excitation and long inhibition is significantly increased in the DA depleted case (Kita and Kita 2011).
- The peak GPi excitatory activity is reduced in the DA depleted case (Kita and Kita 2011).
- Reduction of peak neuronal activity and rate of development of neuronal discharge in the primary motor cortex and premotor area (Gross et al. 1983; Watts and Mandir 1992).
- Disinhibition of reciprocally tuned cells (Doudet et al. 1990). Reciprocal tuned cells are cells that discharge maximally in one movement direction but pause their activities in the opposite direction.
- Significant increase in mean duration of neuronal discharge in motor cortex preceding and following onset of movement (Gross et al. 1983; Doudet et al. 1990; Benazzouz et al. 1992).
- Multiple triphasic patterns of muscle activation (Hallett and Khoshbin 1980; Doudet et al. 1990). Triphasic pattern of muscle activation is a characteristic electromyographic (EMG) pattern characterized by alternating bursts of agonist and antagonist muscles. The first agonist burst provides the impulsive force for the movement, whereas the antagonist activity provides the braking force to halt the limb. Sometimes a second agonist burst is needed to bring the limb to the final position. In PD patients multiple such patterns are observed in order for the subjects to complete the movement.
- Reduction in the rate of development and peak amplitude of the first agonist burst of EMG activity (Godaux et al. 1992; Corcos et al. 1996; Hallett and Khoshbin 1980; Doudet et al. 1990; Watts and Mandir 1992; Berardelli et al. 1986).

- Co-contraction of muscle activation (Benazzouz et al. 1992). In PD patients the alternating agonist-antagonist-agonist muscle activation is disrupted resulting in the co-activation of opponent muscle groups.
- Increases in electromechanical delay time (time between the onset of modification of agonist EMG activity and the onset of movement) (Benazzouz et al. 1992; Doudet et al. 1985, 1990).
- Asymmetric increase in acceleration (time from movement onset to peak velocity) and deceleration (time from peak velocity till end of movement) times of a movement.
- Decrease in the peak value of the velocity trace (Godaux et al. 1992; Camarata et al. 1992; Weiss et al. 1996; Benazzouz et al. 1992; Doudet et al. 1985, 1990; Rand et al. 2000).
- Significant increases in movement time (Rand et al. 2000; Weiss et al. 1996; Doudet et al. 1985, 1990; Watts and Mandir 1992; Benazzouz et al. 1992).

Types of Theoretical Models of Bradykinesia

Theoretical models of bradykinesia fall under two major categories:

- Verbal-conceptual models: using informal and natural language, describe the brain areas, pathways, and interactions leading to parkinsonian bradykinesia.
- Mathematical and computational models: using mathematical equations as a language, describe the interactions between the various brain areas involved in movement control and execution in parkinsonian bradykinesia.

Verbal-Conceptual Models

An influential model of basal ganglia intrinsic organization was proposed by Albin and colleagues (1989). In their model, motor cortical areas drive two populations of striatal medium spiny output neurones. Neurones containing substance P and D1-type dopamine receptors comprise the "direct" pathway and make contact with the basal ganglia output nuclei. At the same time, striatal neurones containing enkephalin and D2-type dopamine receptors comprise the "indirect" pathway and contact the output nuclei via relays in the GPe and STN. Connections between the various BG components are topographically ordered (Mink 1996). Some projections such as the striatonigral projection (direct pathway) are more focused, whereas others such as the subthalamo-nigral projection (indirect pathway) are more diffuse (Mink 1996). Basal ganglia output is thought to reflect a balance between these two projections, which is disrupted when dopamine neurons die, resulting in a reduction in transmission through the direct pathway and an increase in transmission through the indirect pathway. Dominance of the indirect pathway leads to an excessive inhibition of the thalamus by the GPi, thus leading to an abnormal slowness of movement (i.e., bradykinesia).

Additional anatomical observations have suggested a more complex intrinsic organization of BG structures:

- Cortical layer V pyramidal neurons excite the striatal medium spiny neurons (MSN) giving rise to the striatopallidal projections (indirect circuit) (Lei et al. 2004).
- Cortical layer III and upper layer IV pyramidal neurons excite striatal MSN in the direct striatonigral circuit (Lei et al. 2004).
- Both populations of striatal output neurones project to the GPe, one exclusively (enkephalin/D2 neurones), the other via collaterals from the fibers innervating the output nuclei (substance P/D1 neurones) (Parent et al. 2000).
- GPe neurones make direct contact with the output nuclei as well as with the STN (Smith et al. 1998).
- GPe projects back to the striatum (Bevan et al. 1998).
- STN is driven by cortical layer V inputs (Monakow et al. 1978; Nambu et al. 1997) and subcortical ones external to the basal ganglia, now known as the "hyperdirect" pathway (Nambu et al. 2002).
- GPe is excited by the cortex-STN projection (Obeso et al. 2008; Kita 2007).

The hyperdirect pathway provides a widespread excitation of the GPi via the STN (Mink 1996) and is considered to suppress thalamic and cortical areas related to both the selection of the most appropriate motor program given the current context and competing programs before movement begins.

These experimental observations extend the original Albin and colleague model (1989) of BG information processing. Some of the mathematical and computational models of the next section attempt to explain how dysfunction of these various interconnected BG structures may lead to bradykinesia.

Mathematical and Computational Models

Cortico-Basal Ganglia-Thalamic Interactions

In line with the Albin and colleagues (1989) and Nambu et al. (2002) models, Contreras-Vidal and Stelmach (1995) introduced a detailed population-based model of basal ganglia-thalamocortical relations in normal and parkinsonian movements. The model's architecture was based on the direct, indirect, and hyperdirect pathways schema of the basal ganglia. Activation of the direct pathway resulted in activation of thalamocortical motor circuits leading to initiation and modulation of movement, whereas activation of the indirect pathway led to breaking of ongoing movement. Activation of the hyperdirect pathway facilitated rapid movement switching or the prevention of movement release. The model showed that loss of striatal DA as it occurs in PD leads to an imbalance in the neurotransmitter dynamics in the direct and indirect pathways, producing smaller than normal BG output signals. In turn these output signals activate insufficiently otherwise normally functioning motor cortical and spinal sites and produce weak and slow movements.

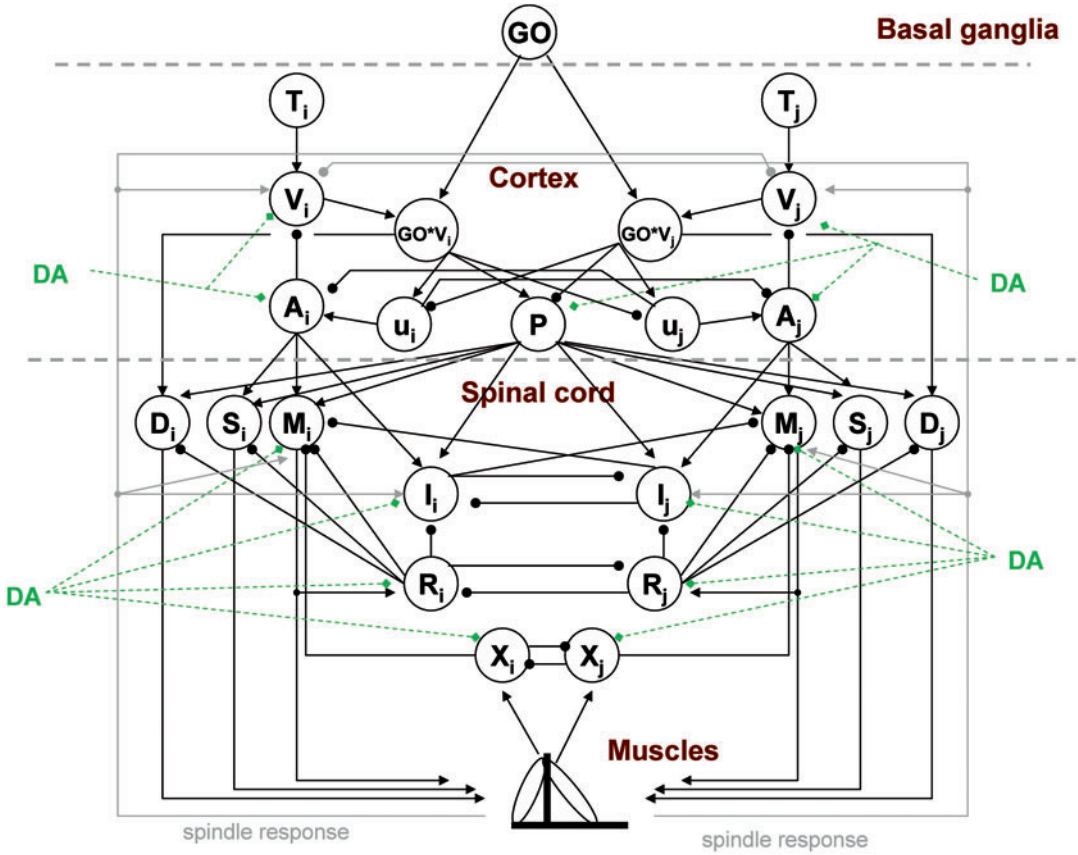
Moroney and colleagues (2008) extended the previous model to investigate the factors that contribute to the slowness of movements of PD patients when they perform simple and complex voluntary movements. Excessive dopamine depletion in the striatum and loss of spatial segregation of neuronal populations operating as functionally independent modules somatotopically mapping particular body parts contribute to a slowness of movement and to a reduced ability to suppress unwanted movements. They further showed that the therapeutic effects of deep brain stimulation (DBS) in STN result from stimulation-induced inhibition of STN, partial synaptic failure of efferent projections, or excitation of inhibitory afferent axons.

DBS is an effective treatment of PD. Chronic high frequency DBS in STN or GPi reduces motor PD symptoms including bradykinesia, although the therapeutic mechanisms of DBS are not fully understood. Recent computational studies have focused on deciphering these mechanisms on BG nuclei. Johnson et al. (2012) investigated which BG neuronal pathways when modulated with high frequency stimulation best correlated with improvement in motor symptoms (bradykinesia and rigidity). Their model predicted that stimulation of a combination of sensorimotor axons within and near the globus pallidus (specifically at the medial medullary lamina) can have the most beneficial effects on PD bradykinesia. In contrast, improvements in PD rigidity correlated more strongly with the activation of less than 10% of neuronal fibers in internal capsule (IC). Recently, Kumaravelu and colleagues (2016) computationally investigated the effectiveness of different frequencies of STN-DBS in suppressing pathological low-frequency oscillatory neural activity correlated with PD bradykinesia. The model showed that low-frequency stimulation (<40 Hz) was ineffective in suppressing the PD-related low-frequency oscillatory activity in GPi. PD low-frequency oscillatory power decreased gradually for frequencies between 50 and 130 Hz and saturated at frequencies higher than 150 Hz.

Cortico-Spino-Muscular Interactions

An alternative view to the observed abnormal slowness of movement in PD bradykinesia was proposed by Cutsuridis (Cutsuridis 2006a, b, 2007, 2010, 2013; Cutsuridis and Perantonis 2006). He suggested that the observed abnormal slowness of movement in PD bradykinesia is due to inadequately activated motor cortical and spinal cord centers because of not only dopamine

reduction in basal ganglia but also in cortical and spinal sites. His models, which were population-based models, were composed of two modules coupled together: (1) the cortical module and (2) the spino-muscular module (see Fig. 2). Both modules and their corresponding neuronal components were modulated by dopamine. The cortical module computed the motor commands sent to the spino-muscular module. The spino-muscular module was an opponent-processing control model of how spinal circuits afford independent voluntary control of joint stiffness and position. Both modules consisted of all major neuronal populations as they have been reported in the experimental literature. The model accounted for all physiological and behavioral phenomena as they have been described in a previous section. Model simulations showed that reduction of DA in cortical and subcortical motor areas disrupts, via several pathways, the rate of development and peak neuronal activity of primary motor cortical cells. These changes lead in delays in recruiting



Basal Ganglia: Bradykinesia Models, Fig. 2 Neural architecture of the dopamine modulated cortico-spinal model with muscle spindle feedback to cortex. Top: basal ganglia module (GO signal representing the opening of the thalamocortical gate via inhibition of GPi response). Middle: cortical module for trajectory formation. Bottom: opponent-processing spino-muscular module for agonist-antagonist-agonist muscle activation. Arrow black lines, excitatory projections; solid dot black lines, inhibitory projections; diamond-dotted green lines, dopamine modulation; solid arrow gray lines, excitatory feedback pathways from muscle spindles. Solid dot gray lines: inhibitory feedback pathways from muscle spindles. GO, globus pallidus internal segment (GPi) output signal; P, bidirectional co-contractive signal; T, target position command; V, difference vector (DV) activity; u, desired velocity vector (DVV) activity; A, current perceived position vector (PPV) activity; M, alpha motoneuronal activity; R, Renshaw cell activity; X, spinal type-b inhibitory interneuronal activity; I, spinal type-a inhibitory interneuronal activity; S, static γMN activity; D, dynamic γMN activity; i and j, antagonist cell pair

the appropriate level of muscle force sufficiently fast and in a reduction of the peak muscle force required to complete the movement. Repetitive and sometimes co-contractive patterns of muscle activation are needed to complete the movement. These disruptions result in an abnormal slowness of movement.

In a subsequent study, Cutsuridis (2011) investigated the origins of the co-contractive and repetitive pattern of muscle activation as observed in PD bradykinesia. Computer simulations showed that an oscillatory disrupted GPi response signal comprising at least two excitation-inhibition sequences as an input to a normally functioning cortico-spinal model of movement generation resulted in a repetitive but not co-contractive agonist-antagonist pattern of muscle activation. A repetitive and co-contractive pattern of muscle activation resulted when also dopamine was depleted in the cortex. Additional dopamine depletion in the spinal cord sites resulted in a reduction of the size, duration, and rate of change of the repetitive and co-contractive EMG bursts. These results had important consequences in the development of dopamine replacement therapies in cortex and spinal cord, which could alleviate some of the impairments of PD such as slowness of movement (bradykinesia).

Cross-References

- ▶ Basal Ganglia: Mechanisms for Action Selection
- ▶ Basal Ganglia: Overview
- ▶ Striatal Models, Cellular Detail
- ▶ Subthalamic Nucleus Cellular Models
- ▶ Subthalamopallidal Loop and Oscillations

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Further Reading

Scholarpedia

Basal Ganglia
Dopamine Anatomy
Models of Basal Ganglia
Models of Parkinson's Disease Bradykinesia
Models of Spinal Cord
Models of Thalamocortical System

Wikipedia

Hypokinesia
Motor Control
Motor System
Parkinson's Disease