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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 neurons in substantia nigra pars compacta (SNc) and ventral tegmental area (VTA)) to the muscles. 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

Q2 Initiation and execution of voluntary movements involves 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, globus pallidus external (GPe) and internal (GPi) segments, subthalamic nucleus (STN), 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 structures are implicated in the selection of the most appropriate motor command given the current context. Motor commands from the frontal motor areas of the cortex (premotor, supplementary, and

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primary motor areas) activate the corresponding motor spinal centers, which then activate the muscles.

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. All motor cortical and subcortical areas are innervated by SNc and VTA dopamine neurons (Williams and Goldman-Rakic 1998; Bjorklund and Lindvall 1984; Gerfen et al. 1990). 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:

- 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).
- Abnormal oscillatory GP (external and internal) neuronal responses (Tremblay et al. 1989).
- Disinhibition of reciprocally tuned cells (Doudet et al. 1990). Reciprocally 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 coactivation 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).

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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 neurons. Neurons 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 neurons containing enkephalin and D2-type dopamine receptors comprise the "indirect" pathway and contact the output nuclei via relays in the GPe and STN. Basal ganglia output was 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:

- Both populations of striatal output neurons project to the GPe, one exclusively (enkephalin/D2 neurons) and the other via collaterals from the fibers innervating the output nuclei (substance P/D1 neurons) (Parent et al. 2000).
- GP neurons make direct contact with the output nuclei as well as with the STN (Smith et al. 1998).
- The GP also projects back to the striatum (Bevan et al. 1998).
- The STN is driven by both cortical and subcortical structures external to the basal ganglia, now known as the "hyperdirect" pathway (Nambu et al. 2002).

Connections between the various BG components are topographically ordered (Mink 1996). Some projections such as the striatonigral projection are more focused, whereas others such as the subthalamo-nigral projection are more diffuse (Mink 1996). The hyperdirect pathway provides a widespread excitation of the GPi (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. On the other hand, the direct pathway facilitates movement via a more focused disinhibition of the thalamus, while the indirect pathway brakes this facilitation (Alexander and Crutcher 1990).

These experimental observations extend the original Albin and colleagues model (1989) of BG information processing. Some of the mathematical and computational models of the next section

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attempt to explain how dysfunction of these various interconnected BG structures may lead to bradykinesia.

Mathematical and Computational Models

Basal Ganglia-Thalamocortical 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. Contreras-Vidal and Stelmach 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.

Cortico-spinomuscular Interactions

An alternative view to the observed abnormal slowness of movement in PD bradykinesia was proposed by Cutsuridis (Cutsuridis 2006a, b, 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 dopamine reduction not only in the 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 spinomuscular module. Both modules and their corresponding neuronal components were modulated by dopamine. The cortical module computed the motor commands sent to the spinomuscular module. The spinomuscular 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 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

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activation are needed to complete the movement. These disruptions result in an abnormal slowness of movement.

Cross-References

- Basal Ganglia: Mechanisms for Action Selection
- Basal Ganglia: Overview
- Striatal Models: Spiny Neuron Network Interactions
- Subthalamic Nucleus Cellular Models
- Subthalamopallidal Loop and Oscillations

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Models of Parkinson's Disease Bradykinesia
Models of Spinal Cord
Models of Thalamocortical System
Wikipedia
Hypokinesia
Motor Control
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