Bradykinesia models of Parkinson's disease

Recommend this on Google

From Scholarpedia
Vassilis Cutsuridis (2013), Scholarpedia, 8(9):30937. doi:10.4249/scholarpedia.30937 revision #139060 [link to/cite this article]

- Dr. Vassilis Cutsuridis, School of Computer Science, University of Lincoln, Lincolnshire, U.K.

Contents

What is bradykinesia

Bradykinesia, one of the main symptoms of Parkinson's disease (PD), refers to slowness of movement. A broader definition also encompasses the inability to move (so-called 'akinesia'), where internally generated movements are no longer automatic, but increasingly require attention and concentration. 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).

The exact mechanisms causing bradykinesia are unknown. However, it is known that bradykinesia results (in some way) from the loss of dopaminergic neurons in the midbrain, the pathological hallmark of PD.

Anatomy

Brain pathways involved in motor functions

The circuit involved in voluntary movement initiation and execution originates in the motor areas of the frontal cortex. These areas project to motor portions of the basal ganglia, specifically to the striatum and the subthalamic nucleus (STN). Other basal ganglia structures, including the globus pallidus external (GPe) and internal (GPi) segments, and the substantia nigra pars reticulata (SNr), are connected to these input structures of the basal ganglia. The basal ganglia project to the thalamus, which, in turn, projects back to the frontal motor areas of the cortex (Parent and Hazrati, 1993). These partially closed loops may help to shape motor commands issued from the frontal motor areas of the cortex (premotor, supplementary and primary motor areas) to brainstem and spinal centres, which then activate muscles in appropriate patterns.

Dopaminergic pathways

A widespread dopaminergic innervation from the SNc and the ventral tegmental area (VTA) to the basal ganglia, cortex and spinal cord exists (Williams and Goldman-Rakic 1998; Bjorklund and Lindvall 1984). Dopamine heavily innervates the striatum and modulates its activity (Gerfen et al. 1990). In addition, dopamine modulates other basal ganglia structures including the globus pallidus external (GPe) and internal (GPi) segments, the subthalamic nucleus (STN) and the substantia nigra pars reticulata (SNr) (Rommelfanger and Wichmann 2010). SNc/VTA dopamine also innervates the cerebral cortex (Berger et al. 1988; Elsworth et al. 1990; Gaspar et al. 1991; Gaspar et al. 1992; Scatton et al. 1983; Lewis et al. 1988; Lidow et al. 1989; Williams and Goldman-Rakic 1998).

Dopamine also projects to 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 to the degeneration of dopamine neurons in the SNc and VTA. It becomes evident only when approximately 50% of dopamine neurons die (corresponding to > 70% dopamine loss in the striatum). Dopamine depletion in the brains of humans and animals leads to a number of changes possibly relevant to bradykinesia in neuronal, electromyographic (EMG) and movement parameters. Some of these changes include:

- 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; Pasquereau and Turner, 2011)
- Abnormal oscillatory neuronal activity in GP (external and internal) (Tremblay et al. 1989), STN and striatum. Similarly abnormal activity patterns are probably also present in the thalamus and cortex.
- 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). A 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. This finding is also found in dystonia (and may represent an element of dystonia in parkinsonian patients).
- 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 until end of movement) times of a movement.
- Decrease in the peak value of the velocity of the movement (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, defined as the time needed to complete the movement of a particular action (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, these models describe the brain areas, pathways and interactions thought to lead to parkinsonian bradykinesia.
- **Mathematical and computational models:** using mathematical equations as a language, these models describe the interactions between the various brain areas involved in movement control and execution that are relevant in parkinsonian bradykinesia.

Verbal-conceptual models

A very influential model of basal ganglia intrinsic organization was proposed by Albin and colleagues (1989). In their model, motor cortical areas drive two different populations of striatal medium spiny output neurons. Striatal medium spiny output neurons containing Substance-P (SP) and D1-type dopamine receptors comprise the "direct" pathway and make contact with the basal ganglia output nuclei (the internal pallidal segment and the substantia nigra pars reticulata), whereas striatal neurons containing enkephalin (ENK) and D2-type dopamine receptors comprise the "indirect" pathway and contact the output nuclei via the GPe and STN. The direct pathway excites the motor cortex via the thalamus in the following way: cortical cells excite the striatum, which in turn inhibits cells in the SNr/GPi complex. The SNr/GPi complex inhibits cells in the thalamus through the inhibitory ansa lenticularis pathway. The thalamus, in turn, excites the cortex via glutamatergic projections. The indirect pathway opposes the direct pathway: cortically excited striatal neurons in the indirect pathway inhibit the cells of the globus pallidus externa (GPe), which tonically inhibits the subthalamic nucleus (STN). The STN, in turn, excites the SNr/GPi complex, which inhibits the thalamus. The end result of indirect pathway activation is decreased excitatory stimulation of the motor cortex, which results in reduced muscle activity.

According to the Albin et al. model, the balance of activity of the direct and indirect pathways is disrupted when dopamine is lost in the striatum, resulting in a reduction in GABAergic (inhibitory) transmission through the direct pathway, and an increase in GABAergic transmission through the indirect pathway, resulting in excessive activity of the basal ganglia output nuclei. Projections from these nuclei are GABAergic, acting to inhibit their thalamic targets; thus, a downstream consequence of striatal dopamine loss is excessive inhibition of the thalamic targets of basal ganglia output, which, in turn, may result in reduced activity of associated cortical areas, contributing to bradykinesia.

Subsequent neuroanatomical observations painted a more complex picture of the intrinsic organization of BG structures:

- Both populations of striatal medium spiny output neurones project to the GPe, via two separate pathways: (1) one pathway directly via ENK/D2 neurones, and (2) a second pathway formed by collaterals from the SP/D1 neuronal fibres innervating the basal ganglia output nuclei (Parent et al. 2000; Durieux et al., 2009; Bateup et al., 2010);
- GPe neurons directly contact GPi and SNr, as well as the STN (Smith et al 1998);
- GPe projects back to the striatum (Bevan et al. 1998);
- Since the mid-1970s it has been known that the STN receives not only GPe inputs, but also inputs from glutamatergic sources, including the frontal cortex (Monakow et al. 1978) and the pedunculopontine nucleus. The cortex-STN-GPi/SNr route of entry of cortical information into the basal ganglia was subsequently called the "hyperdirect" pathway (e.g., Nambu et al. 2002).

The various BG components and their projections are topographically ordered (Mink, 1996). Some projections such as the striato-nigral projection may be more focused, whereas others such as the subthalamo-nigral projection are more diffuse (Parent and Hazrati, 1993; Mink 1996). The hyperdirect pathway provides a highly topographic excitation of the GPi (via the STN; Mink 1996), which then may act to suppress related thalamic and cortical areas, potentially acting to inhibit unintended movements. In contrast, the direct pathway has been speculated to do the opposite, i.e. disinhibiting thalamic and cortical areas, allowing intended movements to proceed. The opposing actions of direct and indirect pathways are said to help with the selection of the appropriate motor programs. Excessive activation of the indirect and hyperdirect pathways and under-activity of the direct pathway may lead to greater inhibition of movement in general (including intended movements). Recent optogenetic studies of the direct and indirect pathways have reported that optogenetic activation of the indirect pathway causes bradykinesia (increased freezing or reduced locomotion), whereas activation of the direct pathway causes the opposite (Kravitz et al., 2010). Repetitive optogenetic activation of the direct pathway reinforces the animal's movement, whereas repetitive activation of the indirect pathway prevents animals from moving (Kravitz et al., 2012). During normal movement both the direct and indirect pathways have been recently reported to be concurrently activated (Cui et al., 2013).

These experimental observations extend the original model of Albin and colleagues (1989). While attractive, this and other models of direct basal ganglia control of movement planning and execution are almost certainly too simplistic, because they do not take into account the fact that the activation of basal ganglia neurons is relatively late (often after the onset of EMG activity), so that their role in the selection of motor acts is doubtful. 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.

Computational models

Basal ganglia-thalamocortical interactions

In line with the models proposed by Albin and colleagues (1989) and Nambu (2002), 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 thalamo-cortical motor circuits leading to modulation of movement, whereas activation of the indirect pathway led to braking of ongoing movement. Activation of the hyperdirect pathway facilitated rapid movement switching or the prevention of movement release (Contreras-Vidal, 2005). Contreras-Vidal and Stelmach (1995) suggested that loss of striatal dopamine as it occurs in PD may lead to an imbalance in the downstream impact of the direct and indirect pathways, producing smaller-than normal basal ganglia output signals. In turn, basal ganglia output was thought to insufficiently activate 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 both contributed to slowness of movement and to a reduced ability to suppress unwanted movements. In their model, slowness of movement was the result of a reduced disinhibition of GPi, which resulted in an increased inhibition of the thalamus and a reduced activation of the agonist muscle moving the limb, whereas the reduced ability to suppress unwanted movements was the result of a decreased GPi activity that resulted in the increased facilitation of opponent thalamic centers and the co-contractions of opponent processing muscles moving the limb. They further showed that the therapeutic effects of deep brain stimulation (DBS) in STN could result from stimulation-induced inhibition of STN, partial synaptic failure of efferent projections, or excitation of inhibitory afferent axons.

Cortico-spino-muscular interactions

An alternative view to explain the observed abnormal slowness of movement in PD bradykinesia was proposed by Cutsuridis (Cutsuridis 2006a, 2006b, 2007, 2010, 2013; Cutsuridis and Perantonis 2006). These works suggested that the abnormal slowness of movement in PD bradykinesia is due to inadequately activated motor cortical and spinal cord centres because of dopamine reduction not only in basal ganglia, but also in cortical and spinal sites. These models, which were also population-based models, were composed of two modules coupled together: (1) a cortical module, and (2) a spino-muscular module. 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 incorporated all known major neuronal populations in the modeled regions. In the model, the output of the basal ganglia drove the cortical module and gated the onset, timing, and rate of change of the primary motor cortical activity (motor command), which then controlled movement parameters such as movement initiation, speed and size. The model accounted for all physiological and behavioral phenomena described above ("Physiological and behavioral phenomena"). Model simulations showed that reduction of DA in cortical and sub-cortical motor areas disrupts, via several pathways, the rate of development and peak neuronal activity of primary motor cortical cells. These changes lead to delays in recruiting the appropriate level of muscle force sufficiently fast and cause 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.

Recently, Cutsuridis (2011) extended these models by investigating the origins of the experimentally observed repetitive and co-contractive pattern of muscle activation in Parkinson's disease (see "Physiological and behavioral phenomena" section; Doudet et al., 1985, 1990; Benezzouz et al., 1992; Hallett and Khoshbin, 1980). Computer simulations showed that an oscillatory disrupted globus pallidus internal segment (GPi) response signal comprising at least two excitation–inhibition sequences as an input to a normally functioning cortico-spinal model of movement generation results in a repetitive, but not cocontractive agonist–antagonist pattern of muscle activation. A repetitive and co-contractive pattern of muscle activation results when dopamine is also depleted in the cortex. Finally, additional dopamine depletion in spinal cord sites results in a reduction of the size, duration and rate of change of the repetitive and co-contractive EMG bursts. These results have important consequences in the development of Parkinson's disease (PD) therapies such as dopamine replacement in cortex and spinal cord, which can alleviate some of the PD symptoms such as bradykinesia, rigidity and dystonia.

Conclusion

This entry describes a plethora of experimental observations from PD bradykinesia in humans and animals ranging across neuronal, electromyographic and behavioral levels and discusses related theoretical and computational models developed to reproduce and explain these findings. Some computational models of bradykinesia have focused entirely on the effects of dopamine depletion in the basal ganglio-thalamo-cortical relations, whereas others emphasize dopamine depletion in cortico-spino-muscular interactions. Future models will have to produce a more comprehensive and detailed neural model of basal ganglia-thalamo-cortico-spino-muscular interactions, in order to study more systematically the effects of dopamine depletion in these nuclei and integrate into a 'unified theory' all the known neurophysiological, EMG and behavioral observations associated with parkinsonism.

Bibliography

- Albin, R. L., Young, A. B., & Penney, J. B. (1989). The functional anatomy of basal ganglia disorders. TINS, 12, 366–375
- Bateup, H. S., Santini, E., Shen, W., Birnbaum, S., Valjent, E., Surmeier, D. J., et al. (2010). Distinct subclasses of medium spiny neurons differentially regulate striatal motor behaviors. PNAS 107, 14845-14850
- Benazzouz, A., Gross, C., Dupont, J., & Bioulac, B. (1992). MPTP induced hemiparkinsonism in monkeys: Behavioral, mechanographic, electromyographic and immunohistochemical studies. Exp Brain Res, 90, 116–120.
- Benecke, R., Rothwell, J. C., & Dick, J. P. R. (1986). Performance of simultaneous movements in patients with Parkinson's disease. Brain, 109, 739–757.
- Berardelli, A., Dick, J. P. R., Rothwell, J. C., Day, B. L., & Marsden, C. D. (1986). Scaling of the size of the first agonist EMG burst during rapid wrist movements in patients with Parkinson's disease. Journal of Neurology, Neurosurgery, and Psychiatry, 49, 1273–1279.
- Berger, B., Trottier, S., Verney, C., Gaspar, P., & Alvarez, C. (1988a). Regional and laminar distribution of dopamine and serotonin innervation in the macaque cerebral cortex: A radioautographic study. The Journal of Comparative Neurology, 273, 99–119.
- Bevan, M. D., Booth, P. A. C., Eaton, S. A. and Bolam, J. P. (1998). Selective innervation of neostriatal interneurons by a subclass of neuron in the globus pallidus of the rat. J Neurosci 18, 9438-9452
- Bjorklund, A., & Lindvall, O. (1984). Dopamine containing systems in the CNS. In A. Bjorklund, & T. Hokfelt (Vol. Eds), Handbook of chemical neuroanatomy. Classical transmitters in the CNS, Part 1 (Vol. 2) (pp. 55–121). Amsterdam: Elsevier.
- Blessing, W. W., & Chalmers, J. P. (1979). Direct projection of catecholamine (presumably dopamine)-containing neurons from the hypothalamus to spinal cord. Neuroscience Letters, 11, 35–40.
- Camarata, P. J., Parker, R. G., Park, S. K., Haines, S. J., Turner, D. A., Chae, H., et al. (1992). Effects of MPTP induced hemiparkinsonism on the kinematics of a two-dimensional, multi-joint arm movement in the rhesus monkey. Neuroscience, 48(3), 607–619.
- Commissiong, J. W., Gentleman, S., & Neff, N. H. (1979). Spinal cord dopaminergic neurons: Evidence for an uncrossed nigrostriatal pathway. Neuropharmacology, 18, 565–568.
- Connor, N. P., & Abbs, J. H. (1991). Task-dependent variations in parkinsonian motor impairments. Brain, 114, 321–332.
- Contreras-Vidal, J.L., Stelmach, G. (1995). A neural model of basal ganglia-thalamocortical relations in normal and Parkinsonian movements. Biol Cybern 73: 467-476
- Contreras-Vidal, J.L. (2005). Computer modeling in basal ganglia disorders. In: Litvan I (ed), Current Clinical Neurology: Atypical Parkinsonian Disorders, Human Press Inc: Totowa, NJ, 95-109
- Corcos, D. M., Chen, C. M., Quinn, N. P., McAuley, J., & Rothwell, J. C. (1996). Strength in Parkinson's disease: Relationship to rate of force generation and clinical status. Annals of Neurology, 39(1), 79–88.
- Cui, G., Jun, S., Jin, X., Pham, M.D., Vogel, S., Lovinger, D.M., et al. (2013). Concurrent activation of striatal direct and indirect pathways during action initiation. Nature 494, 238-242
- Cutsuridis, V. (2006a). Biologically inspired neural architectures of voluntary movement in normal and disordered states of the brain. Unpublished Ph.D. dissertation.
- Cutsuridis, V. (2006b). Neural model of dopaminergic control of arm movements in Parkinson's disease bradykinesia. In S. Kolias, A. Stafilopatis, & W. Duch (Eds.), LNCS: vol. 4131. ICANN 2006: artificial neural networks (pp. 583–591). Berlin: Springer-Verlag.
- Cutsuridis, V. (2007). Does reduced spinal reciprocal inhibition lead to cocontraction of antagonist motor units? A modeling study. International Journal of Neural Systems, 17(4), 319–327.
- Cutsuridis, V. (2010). Neural network modeling of voluntary single joint movement organization. II. Parkinson's disease. In W. A. Chaovalitwongse, P. Pardalos, & P. Xanthopoulos (Eds.), Computational neuroscience (pp. 193–212). Springer-Verlag.
- Cutsuridis, V. (2011). Origins of a repetitive and co-contractive pattern of muscle activation in Parkinson's disease. Neural Netw 24: 592-601
- Cutsuridis, V. (2013). Bradykinesia models. In: R. Jung and D. Jaeger (eds), Encyclopedia of Computational Neuroscience, Springer, USA.
- Cutsuridis, V., & Perantonis, S. (2006). A neural model of Parkinson's disease bradykinesia. Neural Netw, 19(4), 354–374.
- Doudet, D. J., Gross, C., Arluison, M., & Bioulac, B. (1990). Modifications of precentral cortex discharge and EMG activity in monkeys with MPTP induced lesions of DA nigral lesions. Exp Brain Res, 80, 177–188.
- Doudet, D. J., Gross, C., Lebrun-Grandie, P., & Bioulac, B. (1985). MPTP primate model of Parkinson's disease: A mechanographic and electromyographic study. Brain Res, 335, 194–199
- Durieux, P. F., Bearzatto, B., Guiducci, S., Buch, T., Waisman, A., Zoli, M., et al. (2009). D2R striatopallidal neurons inhibit both locomotor and drug reward processes. Nat. Neurosci. 12, 393–395.
- Elsworth, J. D., Deutch, A. Y., Redmond, D. E., Sladek, J. R., & Roth, R. H. (1990). MPTP reduces dopamine and norepinephrine concentrations in the supplementary motor area and cingulate cortex of the primate. Neurosci Lett, 114, 316–322
- Gaspar, P., Duyckaerts, C., Alvarez, C., Javoy-Agid, F., & Berger, B. (1991). Alterations of dopaminergic and noradrenergic innervations in motor cortex in Parkinson's disease. Ann Neurol, 30, 365–374.
- Gaspar, P., Stepniewska, I., & Kaas, J. H. (1992). Topography and collateralization of the dopaminergic projections to motor and lateral prefrontal cortex in owl monkeys. The Journal of Comparative Neurology, 325, 1–21
- Gerfen, C. R., Engber, T. M., Mahan, L. C., Susel, Z., Chase, T. N., Monsma, F. J. Jr., and Sibley, D. R. (1990). D1 and D2 dopamine receptor-regulated gene expression of striatonigral and striatopallidal neurons. Science 250, 1429–1432
- Godaux, E., Koulischer, D., & Jacquy, J. (1992). Parkinsonian bradykinesia is due to depression in the rate of rise of muscle activity. Annals of Neurology, 31(1), 93–100.
- Gross, C., Feger, J., Seal, J., Haramburu, P., & Bioulac, B. (1983). Neuronal activity of area 4 and movement parameters recorded in trained monkeys after unilateral lesion of the substantia nigra. Experimental Brain Research, 7, 181–193.
- Hallett, M., & Khoshbin, S. (1980). A physiological mechanism of bradykinesia. Brain, 103, 301–314.
- Kravitz, A. V., Freeze, B. S., Parker, P. R. L., Kay, K., Thwin, M. T., Deisseroth, K., et al. (2010). Regulation of parkinsonian motor behaviours by optogenetic control of basal ganglia circuitry. Nature 466, 622–626.
- Kravitz, A. V., Tye, L. D., Kreitzer, A. C. (2012). Distinct roles for direct and indirect pathway striatal neurons in reinforcement. Nat. Neurosci. 15, 816–818.
- Mink J. W. (1996). The basal ganglia: Focused selection and inhibition of competing motor programs. Prog Neurobiol 50: 381-425
- Monakow, K. H., Akert, K., Kunzle, H. (1978). Projections of the precentral motor cortex and other cortical areas of the frontal lobe to the subthalamic nucleus in the monkey. Exp Brain Res 33(3-4): 395-403
- Moroney, R., Heida, C., Geelen, J. (2008). Increased bradykinesia in Parkinson's disease with increased movement complexity: elbow flexion-extension movements. J Comput Neurosci 25: 501-519
- Lazarus, J. C., & Stelmach, G. E. (1992). Inter-limb coordination in Parkinson's disease. Movement Disorders, 7, 159–170.
- Lewis, D. A., Morrison, J. H., & Goldstein, M. (1988). Brainstem dopaminergic neurons project to monkey parietal cortex. Neuroscience Letters, 86, 11–16.
- Lidow, M. S., Goldman-Rakic, P. S., Gallager, D. W., Geschwind, D. H., & Rakic, P. (1989). Distribution of major neurotransmitter receptors in the motor and somatosensory cortex of the rhesus monkey. Neuroscience, 32(3), 609–627
- Nambu, A., Tokuno, H. and Takada, M. Functional significance of the cortico-subthalamo-pallidal 'hyperdirect' pathway. Neurosci Res 43, 111-117 (2002).
- Parent, A. et al. Organization of the basal ganglia: the importance of axonal collateralization. Trends Neurosci 23, S20-S27 (2000).
- Parent, A., Hazrati, L. N. (1993). Anatomical aspects of information processing in primate basal ganglia. TINS 16(3), 111-116
- Pasquereau, B., Turner, R. S. (2011). Primary motor cortex of parkinsonian monkey: differential effects on spontaneous activity of pyramidal tract-type neurons. Cerebral Cortex 21(6): 1362-78.

provided by University of Lincoln Institutional Repository
View metadata, citation and similar papers at core.ac.uk
brought to you by CORE

- Rand, M. K., Stelmach, G. E., & Bloedel, J. R. (2000). Movement accuracy constraints in Parkinson's disease patients. Neuropsychologia, 38, 203–212.
- Rommelfanger, K.S., Wichmann, T. (2010). Extrastriatal dopaminergic circuits of the Basal Ganglia. Front Neuroanat 4:139. doi: 10.3389/fnana.2010.00139.
- Scatton, B., Javoy-Agid, F., Rouquier, L., Dubois, B., & Agid, Y. (1983). Reduction of cortical dopamine, noradrenaline, serotonin and their metabolites in Parkinson's disease. Brain Research, 275, 321–328
- Shirouzou, M., Anraku, T., Iwashita, Y., & Yoshida, M. (1990). A new dopaminergic terminal plexus in the ventral horn of the rat spinal cord. Immunohistochemical studies at the light and the electron microscopic levels. Experientia, 46, 201–204
- Smith, Y., Bevan, M. D., Shink, E. and Bolam, J. P. Microcircuitry of the direct and indirect pathways of the basal ganglia. Neuroscience 86, 353-387 (1998).
- Takada, M., Li, Z. K., & Hattori, T. (1988). Single thalamic dopaminergic neurons project to both neocortex and spinal cord. Brain Research, 455, 346–352
- Tremblay, L., Filion, M., & Bedard, P. J. (1989). Responses of pallidal neurons to striatal stimulation in monkeys with MPTP-induced parkinsonism. Brain Research, 498(1), 17–33
- Watts, R. L., & Mandir, A. S. (1992). The role of motor cortex in the pathophysiology of voluntary movement deficits associated with parkinsonism. Neurologic Clinics, 10(2), 451–469.
- Weil-Fugazza, J., & Godefroy, F. (1993). Dorsal and ventral dopaminergic innervation of the spinal cord: Functional implications. Brain Research Bulletin, 30, 319–324
- Weiss, P., Stelmach, G. E., Adler, C. H., &Waterman, C. (1996). Parkinsonian arm movements as altered by task difficulty. Parkinsonism and Related Disorders, 2(4), 215–223
- Williams, S. M., & Goldman-Rakic, P. S. (1998). Widespread origin of the primate mesofrontal dopamine system. Cerebral Cortex, 8, 321–345

Sponsored by: Dr. Jonathan E. Rubin, University of Pittsburgh
Reviewed by (http://www.scholarpedia.org/w/index.php?title=Bradykinesia_models_of_Parkinson%27s_disease&oldid=0) : Anonymous (via Dr. Jonathan E. Rubin, University of Pittsburgh)
Reviewed by (http://www.scholarpedia.org/w/index.php?title=Bradykinesia_models_of_Parkinson%27s_disease&oldid=135358) : Anonymous (via Eugene M. Izhikevich, Editor-in-Chief of Scholarpedia, the peer-reviewed open-access encyclopedia)
Accepted on: 2013-08-05 18:22:39 GMT (http://www.scholarpedia.org/w/index.php?title=Bradykinesia_models_of_Parkinson%27s_disease&oldid=135358)
Retrieved from "http://www.scholarpedia.org/w/index.php?title=Bradykinesia_models_of_Parkinson%27s_disease&oldid=139060"
Categories: Models of brain disorders | Neuroscience | Computational neuroscience

- This page was last modified on 3 February 2014, at 21:49.
- This page has been accessed 11,040 times.
- "Bradykinesia models of Parkinson's disease" by Vassilis Cutsuridis is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 3.0 Unported License. Permissions beyond the scope of this license are described in the Terms of Use