6 Neurophysiology of the Basal Ganglia and Deep Brain Stimulation

Boran Urfalı, Yasin Temel, and Hagai Bergman

Abstract

Our understanding of the physiology of the basal ganglia and deep brain stimulation (DBS) has evolved and has been shaped by decades of studies of the basal ganglia in experimental animal models and human patients.

The classical models of the basal ganglia describe direct, indirect, and hyper-direct pathways connecting the cortex with the striatum and the basal ganglia output structures. The basal ganglia output nuclei modulate the excitability of the motor cortex. In Parkinson's disease, dopamine depletion leads to reduced excitability of the motor cortex and akinesia. This model predicted increased activity in the subthalamic nucleus (STN) following dopamine depletion and suggested that the therapeutic effects of DBS are achieved through the restoration of normal STN discharge rate.

More recent computational models of the basal ganglia depict these as an actor/critic reinforcement learning network. The actor is the main axis of the basal ganglia connecting between all cortical areas encoding current state and the brain motor centers. The critic, or the teacher, is composed of midbrain dopaminergic neurons encoding the mismatch between predictions and reality. In this model, the main effect of dopamine is to modulate the efficacy of the cortico-striatal synapse. The efficacy of the cortico-striatal synapse dedicates the behavioral policy that is the coupling between state and action.

Finally, the recently formulated computational model of the basal ganglia combines the main features of the classical direct/indirect pathways and modern reinforcement learning models. The basal ganglia critics (neuromodulators, including the dopaminergic, cholinergic, serotonergic, and histaminergic projections to the striatum) modulate both the excitability of striatal neurons and the efficacy of the cortico-striatal synapses. The model

B. Urfalı
Department of Neurosurgery, Hatay Mustafa Kemal University-Tayfur Ata Sökmen Faculty of Medicine, Hatay, Turkey

Department of Medical Neurobiology (Physiology), Institute of Medical Research—Israel-Canada (IMRIC), The Hebrew University-Hadassah Medical School, Jerusalem, Israel

Y. Temel
Department of Neurosurgery, Maastricht University Medical Center, Maastricht, The Netherlands

Maastricht University-MHeNS School for Mental Health and Neuroscience, Maastricht, The Netherlands
e-mail: y.temel@maastrichtuniversity.nl

H. Bergman (✉)
Department of Medical Neurobiology (Physiology), Institute of Medical Research—Israel-Canada (IMRIC), The Hebrew University-Hadassah Medical School, Jerusalem, Israel

The Edmond and Lily Safra Center for Brain Research (ELSC), The Hebrew University, Jerusalem, Israel
e-mail: hagaibe@ekmd.huji.ac.il

Y. Temel et al. (eds.), *Fundamentals and Clinics of Deep Brain Stimulation*,
https://doi.org/10.1007/978-3-030-36346-8_6

further suggests that the basal ganglia networks are the default connection between the brain structures encoding state and actions.

Degeneration or abnormal activity of basal ganglia neuromodulators leads to abnormal activity of neurons in the main axis of the basal ganglia. Since the basal ganglia networks are the default connection between state and actions, the other neural networks (e.g., cortico-cortical networks) cannot compensate for the abnormal basal ganglia activity. Therapy of basal ganglia-related neurological and psychiatric disorders can be therefore achieved by inactivation of the basal ganglia main axis. Functional inactivation (information lesion) of the basal ganglia networks is achieved by lesion or DBS paradigms and enables compensation by other neuronal networks and restoration of normal behavioral policy.

Introduction

The neurophysiology of the basal ganglia described in this chapter is illustrated with Parkinson's disease (PD) as example. This choice was made because PD is the most common disorder of the basal ganglia, and because the intensive research is done on animal models of PD. Nowadays, further physiological information on the basal ganglia is achieved during physiological navigation toward targets of deep brain stimulation (DBS) therapy.

Neurophysiological Models of the Basal Ganglia

The Classical Direct/Indirect D1/D2 Model of the Basal Ganglia Networks

Today, most textbooks of Neurology depict the basal ganglia as part of a closed loop connecting all cortical areas through the direct and indirect pathways of the basal ganglia to the motor cortex (Albin et al. 1989; Bergman et al. 1990). The motor cortex projects to the spinal level through the cortico-spinal (or: pyramidal) pathway and controls muscle activation and movements (Fig. 6.1).

This model of the basal ganglia emphasizes the structure of the two segregated basal ganglia pathways. Both basal ganglia pathways start in the

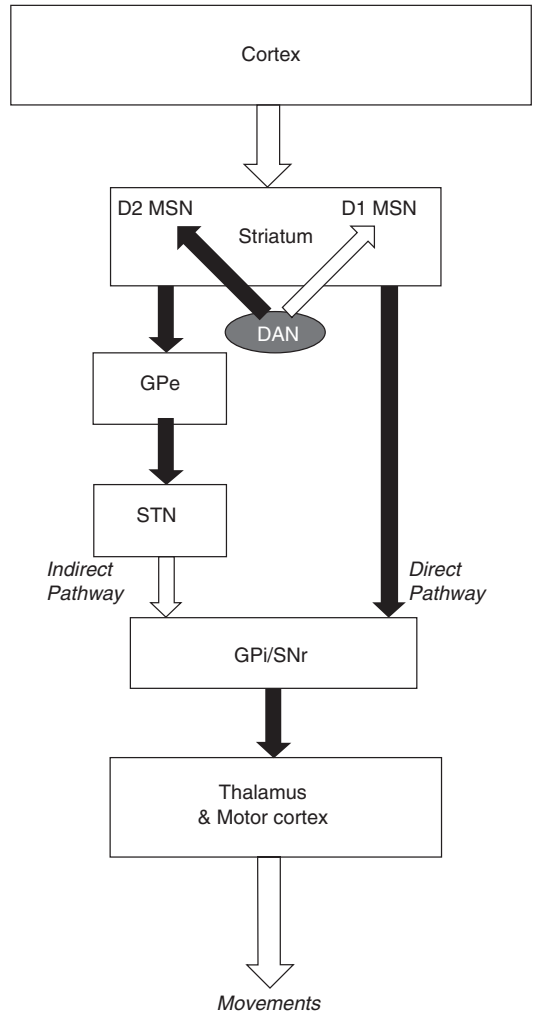

Fig. 6.1 The classical Direct/Indirect D1/D2 model of the basal ganglia. White arrows represent excitatory, that is, glutaminergic, dopamine affecting D1 MSN connections. Black arrows represent inhibitory, that is, GABAergic, dopamine affecting D2 MSN connections. *DAN* midbrain dopaminergic neurons, *GPe* external globus paalidus, *GPi* internal globus pallidus, *MSN* striatal medium spiny (projection) neurons, *SNr* Substantia nigra pars reticulata, *STN* subthalamic nucleus

projection neurons (medium spiny neurons, MSNs) of the striatum and converge on the output structures of the basal ganglia—the internal segment of the globus pallidus (GPi) and the substantia nigra pars reticulata (SNr). The striatal projection neurons express two types of G-protein-coupled dopamine receptors. The "direct" pathway starts with MSNs that express D1 dopamine receptors and lead to (direct) mono-synaptic GABAergic inhibition of the GPi/SNr. The "indirect pathway" projection starts with D2 MSNs is poly-synaptic and dis-inhibitory, providing net excitation to the GPi/SNr through the external segment of the external globus pallidus (GPe) and the glutamatergic (excitatory) subthalamic nucleus (STN). Dopamine has differential effects on the two basal ganglia pathways. Dopamine excites D1 MSNs and facilitates transmission along the direct pathway. Dopamine inhibits D2 MSNs and dis-facilitates transmission along the indirect pathway.

This classical D1/D2 direct/indirect basal ganglia rate model has changed the history of clinical physiology and neuroscience. It provides a general framework for the major finding of physiological studies of parkinsonian MPTP-treated monkeys (Fig. 6.2). These studies reported that, following dopamine depletion, there was a decrease in the average discharge rate of GPe neurons. On the other hand, they reported an increase in discharge rate in the GPi (Miller and DeLong 1987; Filion and Tremblay 1991) and STN (Bergman et al. 1994). Reverse trends of pallidal discharge rates in response to dopamine replacement therapy have been reported in both primates (Filion et al. 1991; Papa et al. 1999; Heimer et al. 2006) and human patients (Hutchinson et al. 1997; Merello et al. 1999; Lee et al. 2007).

The classical D1/D2 direct/indirect model can also explain the physiological mechanisms of dopamine replacement therapy for PD. Dopamine precursors and post-synaptic agonists enable the restoration of the normal dopamine tone to the striatum and therefore raise the level of excitability of the motor cortex and ameliorate parkinsonian akinesia. Similarly, STN and GPi inactivation, for example, by gamma aminobutyric acid (GABA) agonists (Wichmann et al. 1994), lesions (Bergman et al. 1990; Wichmann et al. 1994), or DBS (under the assumption that DBS mimics inactivation, see below), leads to a reduction in the over-activation of the inhibitory output of the basal ganglia to the motor thalamocortical networks.

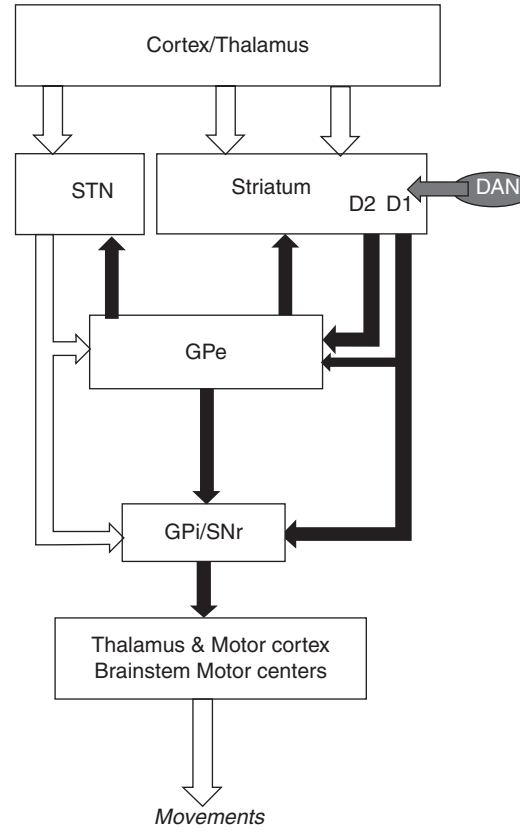

Fig. 6.2 Up-to-date box and arrow model of the basal ganglia. White and black arrows represent excitatory (glutamate), inhibitory (GABA), and dopaminergic (mode of action depends on post-synaptic dopamine receptors) connections, respectively. *DAN* midbrain dopaminergic neurons, *GPe* external globus paalidus, *GPi* internal globus pallidus, *D1*, *D2* striatal medium spiny (projection) neurons, *SNr* Substantia nigra pars reticulata, *STN* subthalamic nucleus

However, recent anatomical studies have revealed that the connectivity between the basal ganglia is much more complex than the simple connectivity depicted by the classical D1/D2 direct/indirect model. Figure 6.2 depicts our current box and arrow model of the basal ganglia

network (Deffains et al. 2016). Moreover, the box and arrow models (Figs. 6.1 and 6.2) are falling short in explaining the dynamic patterns of basal ganglia activity and PD. A common finding of physiological recording of spiking and field potential activity in MPTP-treated monkeys (Miller and DeLong 1987; Filion and Tremblay 1991; Bergman et al. 1994) and human patients with PD undergoing DBS procedures (Levy et al. 2002a, b; Weinberger et al. 2009; Zaidel et al. 2010) is an increase in the fraction of basal ganglia neurons that discharge in periodic bursts at the tremor, or theta frequency (3–7 Hz) and at the beta range frequency (13–30 Hz in humans, 8–20 Hz in the MPTP-treated African green monkey). Finally, these box and arrow models (Figs. 6.1 and 6.2) neglect the emerging roles of the basal ganglia in reinforcement learning (see below) and behavioral adaptions to the changing environment.

The Reinforcement Learning Model of the Basal Ganglia

More modern computational models treat the basal ganglia as an actor/critic reinforcement learning network (Schultz et al. 1997). The main axis or the actor part connects between cortical areas encoding the current state of the agent, for example, what the agent sees, hears, and remembers. The main axis implements the mapping between states and actions, for example, the behavioral policy. The midbrain dopaminergic neurons play the role of the critic or the teacher. They calculate the mismatch between pleasure predictions and reality, that is, the prediction error. The prediction error is used to update the predictions for the future and for optimization of the behavioral policy by reinforcing those actions that led to a state that is better than predictions, and by weakening the associations between state and actions that led to a state worse than predictions. Pleasure can be either positive or negative in these models, and the computational goal of the basal ganglia is to maximize the future-discounted cumulative pleasure.

In terms of basal ganglia anatomy (Fig. 6.3), the neural networks of the basal ganglia main axis (actor) connect the state-encoding cortical and thalamic neurons with the cortical and brainstem motor centers. The midbrain dopaminergic neurons are the critics of the basal ganglia network. Their normal background activity (around 4–5 spikes/s) encodes a match between predictions and reality. Positive prediction errors (reality better than predictions) are encoded by bursts of the discharge of dopamine neurons. On the other hand, omission of the expected reward, prediction of aversive events, and other cases of negative prediction error (reality worse than predictions) are encoded by depression of the spiking activity (Schultz 2001; Tobler et al. 2005). These changes in dopamine activity, and the coinciding cortical and striatal discharge, lead to plastic changes in the efficacy of the cortico-striatal synapses (e.g., long-term potentiation) and therefore to modulation of the association between states, as encoded by the cortical activity, and action.

This reinforcement actor/critic model of the basal ganglia has revolutionized current understanding of physiological mechanisms of model-free, or procedural, implicit, learning. The model also provides insights into certain basal ganglia-related disorders such as the slow development of levodopa-induced dyskinesia. However, as for the classical direct/indirect D1/D2 model, this model has its own pitfalls. For example, the reinforcement learning model basal of the ganglia fails to provide a mechanism for the ultra-fast action of dopamine agonists and antagonists, such as apomorphine or haloperidol. Moreover, the model assumes a single final currency, pleasure or punishment, to control behavior and thus probably does not fully describe the multidimensional emotional repertoire of humans and animals.

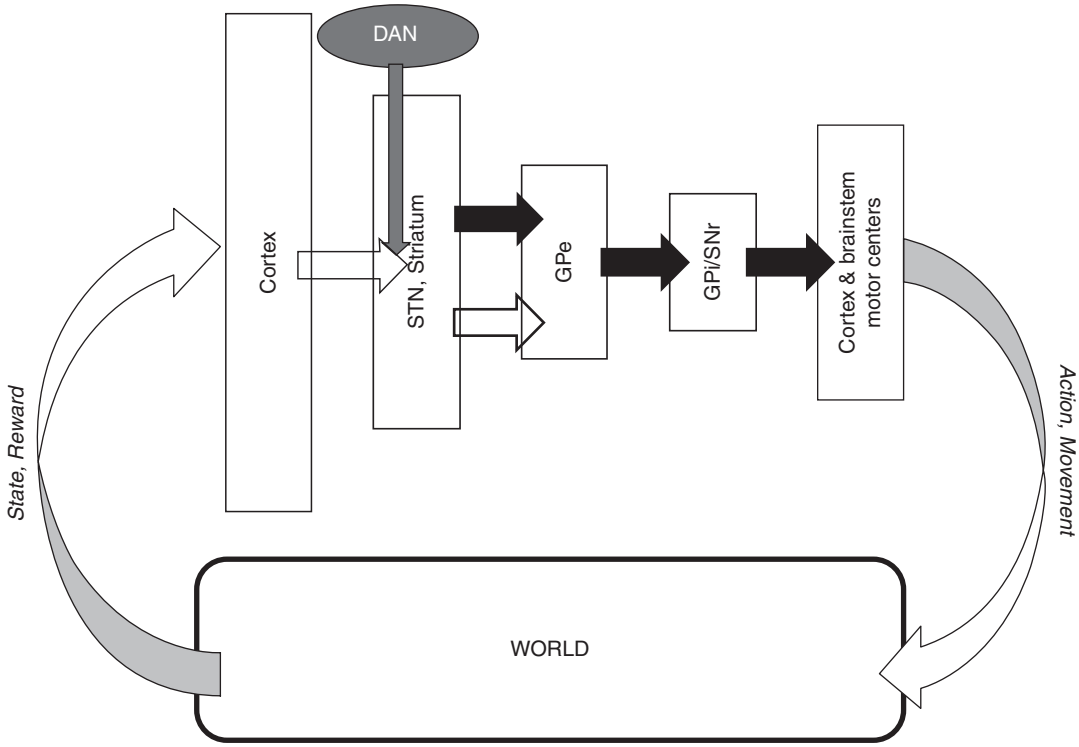

Fig. 6.3 Anatomical description of the actor/critic reinforcement model of the basal ganglia. The actor is the main axis of the basal ganglia connecting between cortical area encoding the current state and the brain motor centers. The critic or the teacher is represented by the midbrain dopaminergic neurons. The critic encodes the pleasure prediction error and modulates the coupling between state and action. *DAN* midbrain dopaminergic neurons, *GPe* external globus paalidus, *GPi* internal globus pallidus, *SNr* Substantia nigra pars reticulata, *STN* subthalamic nucleus

The Multi-objective Optimization Model of the Basal Ganglia

The midbrain dopaminergic neurons are not the only modulators of the basal ganglia. Sriatal cholinergic interneurons, dorsal raphe serotonin (5-HT) neurons, and tubero-mamillary histamine neurons also modulate basal ganglia activity and therefore should be considered part of the basal ganglia critic system (Fig. 6.4). In this multi-critic model, the basal ganglia computational goal is to optimize the tradeoff between the goals of maximizing future cumulative gain and minimizing the behavioral, or information, cost. Thus, this model offers multiple (i.e., two or more—rather than one single) objective optimization (Parush et al. 2011). This multi-objective optimization goal naturally leads to a model where each of the basal ganglia critics plays a dual role. First, similar to the reinforcement model described above, the basal ganglia critics affect the efficacy of the cortico-striatal synapses. Second, the basal ganglia critics also affect the excitability of the striatal projection neurons (as in the classical D1/D2 direct/indirect basal ganglia model) and therefore control the tradeoff between gain and cost and the continuum between exploratory (gambling) and greedy (akinetic) behavioral policies (the motor vigor).

The multiple-critic, multi-objective optimization model (Fig. 6.4) captures the complex organization of the basal ganglia actor/critic network better. The combined effects of the critics on striatal excitability and on cortico-striatal synaptic efficacy enable the model to account for both ultra-fast effects (e.g., apomorphine) and slow

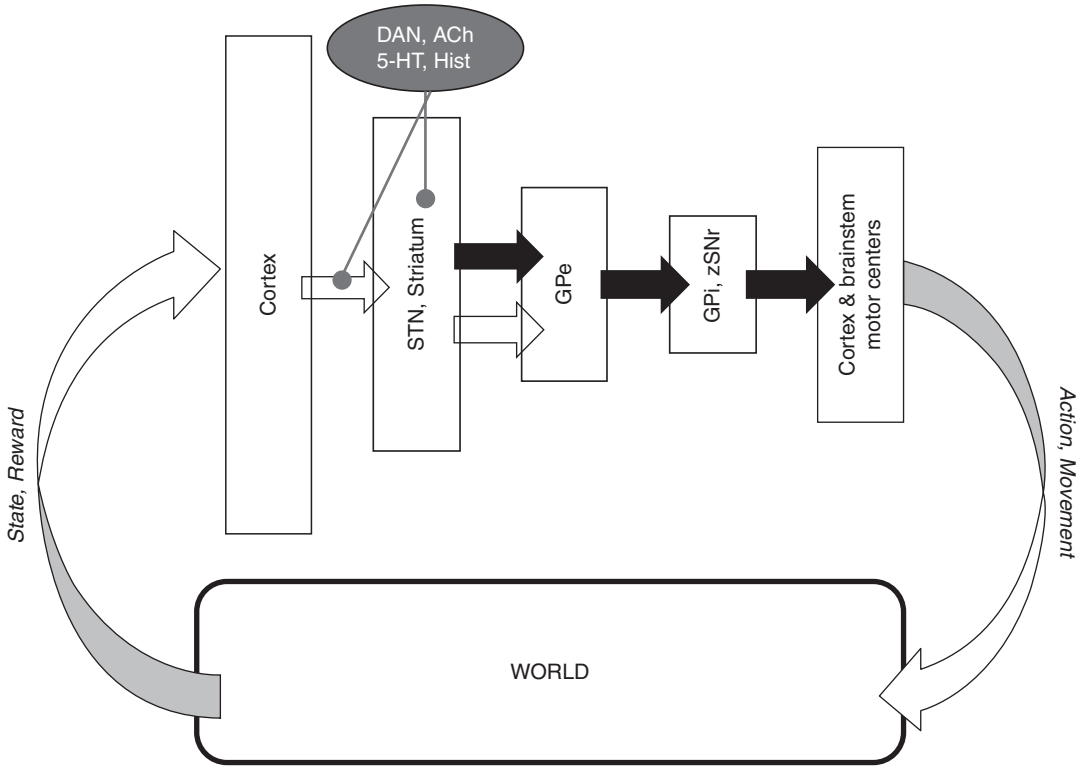

Fig. 6.4 Anatomical description of the multi-objective optimization model of the basal ganglia. Multiple and differential effects of basal ganglia critics on the excitability of the main axis of the basal ganglia, through modulation of the excitability of striatal projection neurons, and on state-to-action coupling, through modulation of the efficacy of cortico-striatal synapses. *5-HT* serotonin, *ACh* cholinergic interneurons of the striatum, *DAN* midbrain dopaminergic neurons, *GPe* external globus paalidus, *GPi* internal globus pallidus, *Hist* histamine, *SNr* Substantia nigra pars reticulata, *STN* subthalamic nucleus

procedural learning kinetics. Furthermore, the model provides insights into the role of the non-dopaminergic critics in the physiology and pathophysiology of the basal ganglia including the dopamine-acetylcholine motor balance and serotonin-related depression in PD.

The Neurophysiology of Deep Brain Stimulation

The first step in the treatment of PD is dopamine replacement therapy (DRT) with levodopa or post-synaptic dopamine agonists. The goal of DRT is to restore the full dynamic range of dopamine physiology, including phasic bursts and tonic level. However, the increased sprouting of dopaminergic axons, the over-sensitization of dopamine receptors, and other pathophysiological changes occurring over the many years of DRT lead to abnormal dynamics of dopamine in the striatum. After a number of years of treatment with DRT, PD patients no longer experience great benefits of DRT, and side effects such as levodopa-induced dyskinesias significantly affect quality of life.

The classical direct/indirect D1/D2 model and the physiological recordings in the MPTP primate model of PD have led to a shift in the focus of therapy from the critic (DRT) to the actor part of the basal ganglia (DBS of the STN or GPi). Physiological studies have revealed changes in the discharge rate, firing pattern, and synchronization of neurons in the main axis if the basal

ganglia in MPTP-treated monkeys. Inactivation of these over-active basal ganglia nuclei in monkeys and humans leads to an amelioration of parkinsonian symptoms and to new therapeutic methods that can be applied after failure of DRT. The mechanism of DBS is still debated; however, most people would agree that the fast effects of DBS mimic the effects of inactivation (the information lesion hypothesis). This is in line with the notion that the basal ganglia network is the default, fast, and unconscious link between the neural structures encoding the current state and action, for example, the default system of Kahneman's Thinking Fast and Slow (2011). However, there are many additional networks, for example, the cortico-cortical and cerebellum centered networks. These networks provide parallel connectivity between state and action (Fig. 6.5); however, since the basal ganglia are the default connection between state and action, the other networks cannot compensate for abnormal basal ganglia activity. Silencing the basal ganglia abnormal activity enables the other networks to compensate and to reestablish close to normal state-to-action coupling.

The unique features of convergence along the main axis of the basal ganglia increase the efficacy of basal ganglia inactivation (Bar-Gad et al. 2003). This funneling structure enables the normal basal ganglia to extract the features of the current state (probably related to motor behavior) that are important for the ongoing and future movements. On the other hand, when the basal ganglia "misbehave," one can use this funneling structure to achieve major effects on the cortex and brainstem by inactivation of small basal ganglia structures. The recent demonstration that the STN is the "driving force" of both basal ganglia physiology

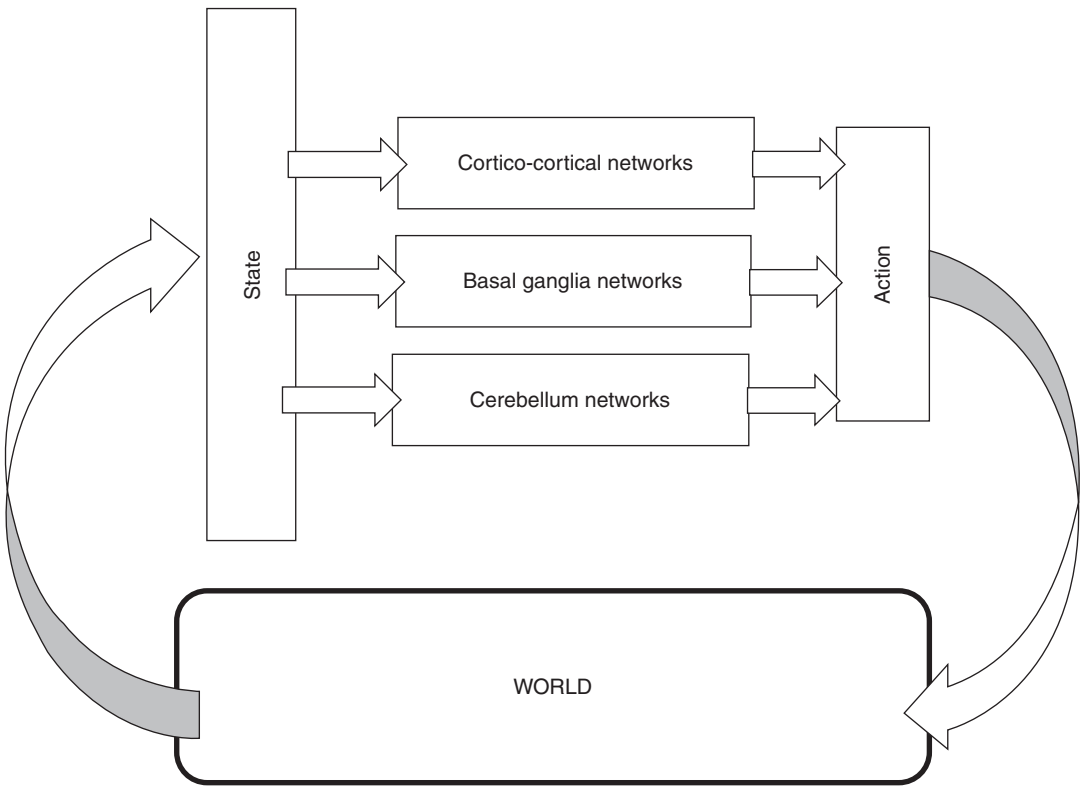

Fig. 6.5 The basal ganglia network is one of many neural networks connecting state to action in the nervous system. The basal ganglia network is the default system for connecting between state and action. However, other networks, like the cortico-cortical and the cerebellum, as well as many other, connect also between state and action

and pathophysiology gives another support to the common use of the STN as the most optimal DBS target, at least for PD (Deffains et al. 2016).

However, permanent inactivation of a basal ganglia target is only achieved by lesioning and hence is not recommended as a therapy of choice. DBS is a reversible and adjustable procedure and thus better suits current demands for efficient and ethical therapy. Thus, the modern therapy of PD and other basal ganglia disorders has shifted from chemical manipulation at the neurotransmitter level of the basal ganglia critic to manipulation of spiking activity in the basal ganglia actor. DBS treatments are also effective in other basal ganglia-related movement disorders such as dystonia and essential tremor, and DBS is currently being tested for psychiatric disorders in which the basal ganglia play a role, such as obsessive-compulsive disorder and major depressive disorder.

Conclusions

Our understanding of the basal ganglia networks and basal ganglia-related disorders, such as PD, has been shaped by the computational models of the basal ganglia. The classical D1/D2 direct indirect models assumed that the role of dopamine and the basal ganglia lies in modulating the excitability of the motor cortex. The actor/critic reinforcement models assume that the role of dopamine is to modulate the synaptic efficacy of the cortico-striatal synapse and the behavioral policy. Finally, the third-generation models, the multiple critics, multiple objective optimization models, assume that there is more than one dopaminergic critic, or teacher, in the basal ganglia. The basal ganglia critics modulate both the excitability and synaptic efficacy in the striatum, and enable multi-objective optimization of the ongoing and future behavior.

Basal ganglia actor/critic multi-objective optimization algorithms can be used to improve next-generation DBS devices. These next-generation DBS devices will exploit basal ganglia actor/critic multi-objective optimization algorithms and will provide even better therapy for human patients. Today, DBS adjustments must be made by a physician every 2–10 weeks. However, the dynamic and complex nature of PD calls for more frequent and more sophisticated adjustment of the DBS parameters. This can be achieved by closed-loop DBS methods (Rosin et al. 2011; see also Chap. 5). Thus, future closed-loop DBS devices will be aiming at achievement of multi-objective optimization of the patient's motor and non-motor symptoms, along with minimization of the side effects of DBS therapy.

Acknowledgments This work was supported by the Simone and Bernard Guttman chair of Brain Research, and by the Rosetrees and Vorst foundations (to HB).

References

Albin RL, Young AB, Penney JB. The functional anatomy of basal ganglia disorders. Trends Neurosci. 1989;12:366–75.

Bar-Gad I, Morris G, Bergman H. Information processing, dimensionality reduction and reinforcement learning in the basal ganglia. Prog Neurobiol. 2003;71:439–73.

Bergman H, Wichmann T, DeLong MR. Reversal of experimental parkinsonism by lesions of the subthalamic nucleus. Science. 1990;249:1436–8.

Bergman H, Wichmann T, Karmon B, DeLong MR. The primate subthalamic nucleus. II. Neuronal activity in the MPTP model of parkinsonism. J Neurophysiol. 1994;72:507–20.

Deffains M, Iskhakova L, Katabi S, Israel Z, Bergman H. Subthalamic, not striatal, activity correlates to basal ganglia downstream activity in normal and parkinsonian monkeys. Elife. 2016;5. pii: e16443. https://doi.org/10.7554/eLife.16443.

Filion M, Tremblay L. Abnormal spontaneous activity of globus pallidus neurons in monkeys with MPTP-induced parkinsonism. Brain Res. 1991;547:142–51.

Filion M, Tremblay L, Bedard PJ. Effects of dopamine agonists on the spontaneous activity of globus pallidus neurons in monkeys with MPTP-induced parkinsonism. Brain Res. 1991;547:152–61.

Heimer G, Rivlin-Etzion M, Bar-Gad I, Goldberg JA, Haber SN, Bergman H. Dopamine replacement therapy does not restore the full spectrum of normal pallidal activity in the 1-methyl-4-phenyl-1,2,3,6-tetra-hydropyridine primate model of parkinsonism. J Neurosci. 2006;26:8101–14.

Hutchinson WD, Levy R, Dostrovsky JO, Lozano AM, Lang AE. Effects of apomorphine on globus pallidus neurons in parkinsonian patients. Ann Neurol. 1997;42:767–75.

Lee JI, Verhagen ML, Ohara S, Dougherty PM, Kim JH, Lenz FA. Internal pallidal neuronal activity during

mild drug-related dyskinesias in Parkinson's disease: decreased firing rates and altered firing patterns. J Neurophysiol. 2007;97:2627–41.

Levy R, Hutchison WD, Lozano AM, Dostrovsky JO. Synchronized neuronal discharge in the basal ganglia of parkinsonian patients is limited to oscillatory activity. J Neurosci. 2002a;22:2855–61.

Levy R, Ashby P, Hutchison WD, Lang AE, Lozano AM, Dostrovsky JO. Dependence of subthalamic nucleus oscillations on movement and dopamine in Parkinson's disease. Brain. 2002b;125:1196–209.

Merello M, Balej J, Delfino M, Cammarota A, Betti O, Leiguarda R. Apomorphine induces changes in GPi spontaneous outflow in patients with Parkinson's disease. Mov Disord. 1999;14:45–9.

Miller WC, DeLong MR. Altered tonic activity of neurons in the globus pallidus and subthalamic nucleus in the primate MPTP model of parkinsonism. In: Carpenter MB, Jayaraman A, editors. The basal ganglia II. New York: Plenum Press; 1987. p. 415–27.

Papa SM, DeSimone R, Fiorani M, Oldfield EH. Internal globus pallidus discharge is nearly suppressed during levodopa-induced dyskinesias. Ann Neurol. 1999;46:732–8.

Parush N, Tishby N, Bergman H. Dopaminergic balance between reward maximization and policy complexity. Front Syst Neurosci. 2011;5:22.

Rosin B, Slovik M, Mitelman R, Rivlin-Etzion M, Haber SN, Israel Z, Vaadia E, Bergman H. Closed-loop deep brain stimulation is superior in ameliorating parkinsonism. Neuron. 2011;72:370–84.

Schultz W. Reward signaling by dopamine neurons. Neuroscientist. 2001;7:293–302.

Schultz W, Dayan P, Montague PR. A neural substrate of prediction and reward. Science. 1997;275:1593–9.

Tobler PN, Fiorillo CD, Schultz W. Adaptive coding of reward value by dopamine neurons. Science. 2005;307:1642–5.

Weinberger M, Hutchison WD, Lozano AM, Hodaie M, Dostrovsky JO. Increased gamma oscillatory activity in the subthalamic nucleus during tremor in Parkinson's disease patients. J Neurophysiol. 2009;101:789–802.

Wichmann T, Soares J. Neuronal firing before and after burst discharges in the monkey Basal Ganglia is predictably patterned in the normal state and altered in parkinsonism. J Neurophysiol. 2016;95:2120–33.

Wichmann T, Bergman H, DeLong MR. The primate subthalamic nucleus. III. Changes in motor behavior and neuronal activity in the internal pallidum induced by subthalamic inactivation in the MPTP model of parkinsonism. J Neurophysiol. 1994;72:521–30.

Zaidel A, Spivak A, Grieb B, Bergman H, Israel Z. Subthalamic span of beta oscillations predicts deep brain stimulation efficacy for patients with Parkinson's disease. Brain. 2010;133:2007–21.