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Dissociating the Cognitive Effects of Levodopa versus Dopamine Agonists in a Neurocomputational Model of Learning in Parkinson's Disease

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Key Words

Basal ganglia · Dopamine agonists · Levodopa · Parkinson's disease · Prefrontal cortex · Reinforcement · Stimulus-response learning · Working memory

Abstract

Background/Aims: Levodopa and dopamine agonists have different effects on the motor, cognitive, and psychiatric aspects of Parkinson's disease (PD). ***Methods:*** Using a computational model of basal ganglia (BG) and prefrontal cortex (PFC) dopamine, we provide a theoretical synthesis of the dissociable effects of these dopaminergic medications on brain and cognition. Our model incorporates the findings that levodopa is converted by dopamine cells into dopamine, and thus activates prefrontal and striatal D_1 and D_2 dopamine receptors, whereas antiparkinsonian dopamine agonists directly stimulate D_2 receptors in the BG and PFC (although some have weak affinity to D_1 receptors). ***Results:*** In agreement with prior neuropsychological studies, our model explains how levodopa enhances, but dopamine agonists impair or have no effect on, stimulus-response learning and working memory. ***Conclusion:*** Our model explains how levodopa and dopamine agonists have differential effects on motor and cognitive processes in PD.

Introduction

Levodopa (3,4-dihydroxy-L-phenylalanine) and various D_2 dopamine agonists such as pramipexole and ropinirole are the primary dopamine replacement therapies for Parkinson's disease (PD) patients. Although there are many clinical studies of differential effects of levodopa versus D_2 dopamine agonists on PD motor symptoms, including motor complications and dyskinesia, there are few cognitive assessments and no computational studies dissociating their effects on cognition. We provide here a computational model that differentiates the role of levodopa versus dopamine agonists on cognition using our prior circuit level model of the basal ganglia (BG) and prefrontal cortex (PFC; fig. 1a). In our model, we incorporate the simplified assumption that dopamine produced from levodopa and D_2 dopamine agonists activate D_2 dopamine receptors, while levodopa is converted to dopamine, which binds to D_1 receptors (fig. 1b) [1–3]. Because D_1 receptors are associated with learning, working memory, and dyskinesia (see Discussion below), our model provides a mechanistic account for how levodopa (but not dopamine agonists) enhances learning and working memory, particularly in early stages of PD. We start by describing the neural mechanism of levodopa and dopamine agonists.

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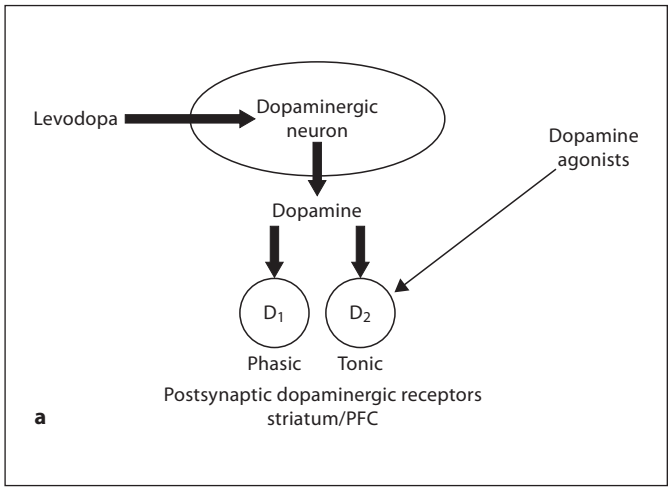

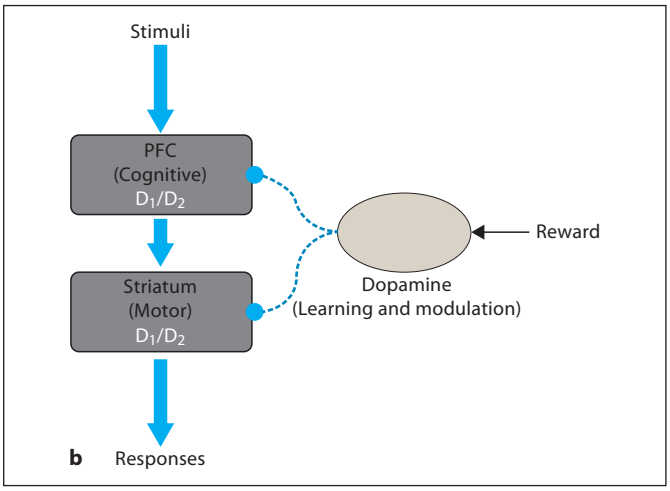

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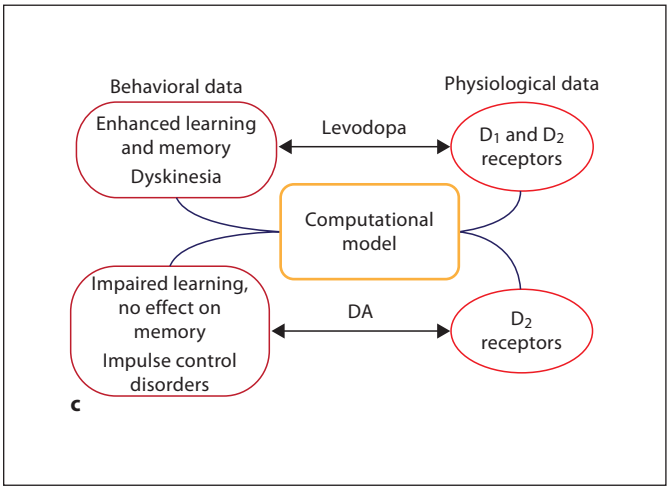


Fig. 1. a Schematic of the differential effects of levodopa versus dopamine agonists on D_1/D_2 receptors and phasic and tonic dopamine in the striatum/PFC. **b** Model architecture. The striatum is important for learning motor responses, whereas the PFC is key for higher cognitive functions, such as working memory. Dopamine modulates learning, motor, and cognitive processes in the striatum and PFC. **c** Physiological data show that dopamine converted from levodopa binds to D_1 and D_2 receptors, and commonly used non-ergot dopamine agonists (DA) to treat Parkinson's disease have a large affinity to D_2 receptors. Behavioral studies show that levodopa (unlike many D_2 dopamine agonists) enhances learning and working memory, but can lead to dyskinesia. Our computational model bridges the gap between these physiological and behavioral data.

Dopamine D_1 and D_2 receptors are abundant in the PFC and BG. Physiological and behavioral studies have demonstrated that levodopa and dopamine agonists work differently on dopamine receptors. Most of the commonly used non-ergot dopamine agonists, such as pramipexole and ropinirole, have a high affinity for D_2 receptors. However, levodopa is a dopamine precursor, taken up by dopamine cells, and converted into dopamine; thus, it acts on both D_1 and D_2 dopamine receptors [1–3]. Based on these findings, we will show here how levodopa and dopamine agonists may have different effects on cognition. We first review experimental studies on the physiological and behavioral function of D_1 and D_2 receptors, and then discuss neuropsychological studies on the effects of levodopa and D_2 dopamine agonists on motor and cognitive processes. Both behavioral and physiological studies provided constraints for our simulation model (fig. 1a).

Dopamine projections to the BG and PFC fluctuate between two different modes of firing patterns: phasic and tonic. The phasic mode is fast acting and spans milliseconds, while the tonic mode is long acting and can span minutes (table 1). Experimental studies have shown that phasic dopamine activates D_1 receptors [4–6], whereas tonic dopamine activates D_2 receptors [3, 5, 7].

Because both levodopa and dopamine agonists activate D_2 receptors, we assume that levodopa and dopamine agonists restore tonic activation of dopamine neurons, and thus activate D_2 receptors (although possibly to different degrees). However, we assume that levodopa, but not D_2 dopamine agonists, increases dopamine levels, and thus restores phasic activity of dopamine neurons. The assumption that repeated levodopa administration enhances both phasic and tonic signals is, indeed, in agreement with a physiological study of Harden and

Grace [8], one of the few studies that recorded dopamine activity from parkinsonian rats, and showed that repeated levodopa administration resulted in an increase in dopamine release following spontaneous activation of a greater proportion of nigral dopaminergic cells.

We next discuss the role of D_1 and D_2 receptors in the BG and PFC, how they impact motor and cognitive functions, and how these relate to learning and working memory. In the BG, phasic and tonic dopamine is key for learning and the initiation of motor responses [9]. For example, using optogenetic methods, Tsai et al. [10] found that phasic firing of dopamine cells, which stimulates D_1 receptors in the BG, is essential for learning. While large numbers of D_1 receptors are found in the BG direct pathway, D_2 receptors are more abundant in the BG indirect pathway [11]. Thus, activating D_2 receptors attenuates the inhibitory function of the BG indirect pathway, which in turn facilitates the initiation of motor responses.

Dopamine receptors in the PFC are essential for higher cognitive functions such as working memory and executive control [12–14]. An extensive body of experimental data shows that D_1 receptors in the PFC are important for the maintenance of information in working memory (table 2) [13, 15–17], while PFC D_2 receptors are key for motor responses based on information maintained in working memory, a process known as memory-guided motor responses (table 2) [18]. Our model hypothesizes that learning to maintain information in working memory is mediated by D_1 receptors in the PFC, as suggested by theoretical [16] and experimental [19] studies.

The most commonly addressed areas to investigate effects of levodopa and D_2 dopamine agonists on cognition are learning and working memory. Experimental studies have consistently shown that the administration of levodopa to healthy subjects and PD patients enhances learning (table 3). Unlike levodopa, most (but not all) D_2 dopamine agonists were consistently found to impair learning in PD patients and healthy subjects (table 3). Our model assumes that levodopa enhances learning because it increases the levels of dopamine which binds to D_1 receptors in the BG. Similarly, most (but not all) studies have found that the administration of levodopa to PD patients enhances working memory (table 4). As shown in table 4, some studies show that dopamine agonists have no effect on working memory, though others found that some dopamine agonists, such as pramipexole, could impair working memory. Our model hypothesizes that levodopa enhances working memory because it activates D_1 receptors in the PFC.

Table 1. Physiological and behavioral differences between phasic and tonic dopamine

	Phasic	Tonic
Acting	fast-acting	long-acting
Measured by	voltammetry	microdialysis
Modulated by	glutamate	GABA
Behavioral effect	learning	motor responses
Model	learning rate	activation function

See recent work by Grace [3] for elaboration on differences between phasic and tonic dopamine firing modes.

Table 2. Functional significance of D_1 and D_2 receptors in the striatum and PFC

Receptor type	Brain region	
	striatum	PFC
D_1	learning	maintenance of working memory
D_2	initiation of motor responses	motor responses based on working memory

Model and Tasks

Model architecture and learning rules are the same as in our previous model of frontostriatal interactions during multicue category learning in PD, where we utilize the actor-critic architecture, in which the critic is important for feedback-based learning, while the actor is essential for action-selection learning. The critic sends a teaching signal to the actor to strengthen or weaken action-selection learning. However, the critic is not informed about the action that the actor selects, but is informed about whether the selected action culminated in a rewarding consequence or not. The temporal difference model is utilized to train the model [52].

The model has four modules: PFC/cognitive, striatum/motor response, dopamine, and input (not shown; fig. 1). The PFC/cognitive layer is fully connected to the striatum/motor layer. The input (not shown) and PFC modules have the same number of nodes. Each unit in the input module represents a cue presented to the network. The striatum/motor module has three nodes, each representing a different motor response. Input patterns presented to the network activate their corresponding units in the input module. The input module sends topographic projections to the PFC layer. We use a winner-take-all network to simulate inhibitory connectivity among PFC neurons. Here, we argue that competitive dynamics among PFC neurons is the brain mechanism underlying limited working memory processes.

Table 3. Summary of experimental studies investigating the effects of D_2 dopamine agents on learning tasks in animals and humans

Study	Subject group	Medication used	Behavioral effects
Stimulus-response learning			
L-DOPA monotherapy			
Knecht et al. [20] (2004)	healthy subjects	L-DOPA	enhancement
Pavlis et al. [21] (2006)	rats	L-DOPA	enhancement
Gotham et al. [22] (1988)	PD patients	L-DOPA	impairment
Scheidtmann et al. [23] (2001)	stroke patients	L-DOPA	enhancement
Rosser et al. [24] (2008)	stroke patients	L-DOPA	enhancement
Pleger et al. [25] (2009)	healthy subjects	L-DOPA	enhancement
Robinson et al. [26] (2007)	parkinsonian mice	L-DOPA	enhancement
Graef et al. [27] (2010)	PD patients	L-DOPA	enhancement
Floel et al. [28] (2008)	healthy subjects	L-DOPA	enhancement
Pessiglione et al. [29] (2006)	healthy subjects	L-DOPA	enhancement
Beeler et al. [30] (2010)	PD patients	L-DOPA	enhancement
de Vries et al. [31] (2010)	PD patients	L-DOPA	enhancement
DA monotherapy			
Breitenstein et al. [32] (2006)	healthy subjects	pergolide	impairment
Pizzagalli et al. [33] (2007)	healthy subjects	pramipexole	impairment
Frank et al. [34] (2006)	healthy subjects	cabergoline	impairment
Santesso et al. [35] (2009)	healthy subjects	pramipexole	impairment
McClure et al. [36] (2010)	schizotypal personality disorder	pergolide	enhancement
DA + L-DOPA			
Feigin et al. [37] (2003)	PD patients	DA + L-DOPA	impairment
Shohamy et al. [38] (2006)	PD patients	DA + L-DOPA	impairment
Jahanshahi et al. [39] (2009)	PD patients	DA + L-DOPA	impairment
Housden et al. [40] (2010)	PD patients	DA + L-DOPA	impairment
Mongeon et al. [41]	PD patients	DA + L-DOPA	impairment

DA = Dopamine agonist; L-DOPA = levodopa.

The simulated striatum in the model learns to map input stimuli to responses [for similar ideas see 53–55]. Like the PFC module, we use a winner-take-all network to simulate inhibitory connectivity among simulated striatal neurons. At the cognitive level, the winning node represents the selected motor response. Unlike most existing BG models [54–58], the BG in our model learns to map representations of selected stimuli and working memory information to motor responses.

Unlike prior models, which assume that the effects of levodopa and dopamine agonists on cognition are similar, our new model simulates the functional contribution of dopamine D_1 and D_2 receptors in the PFC and BG (fig. 1). In this new model, the striatum is important for learning motor responses, whereas the PFC is essential for working memory. Specifically, this model assumes that D_1 receptors in the BG are key for motor learning, while D_2 receptors play a role in the initiation of motor responses. In the PFC, D_1 receptors are required for the maintenance of information in working memory [15, 59]. Prefrontal D_2 receptors, on the other hand, are important for memory-guided responses [18] (fig. 1). We simulated the effects of phasic dopamine by manipulating the learning rate parameter in the PFC and striatal modules. We also simulated the effects of tonic dopamine by manipulating the effects of gain parameter in sigmoidal activation in the simulated brain region [52].

The model simulates performance in stimulus-response learning and working memory. The stimulus-response learning task is a two-alternative, forced-choice response task in which the subject (in our case the subject is a single run of the simulation model) learns to associate different stimuli with different responses, based on corrective feedback. The working memory task is also a forced-choice response task, in which, besides a stimulus representation and response phases, it also includes delay and probe phases. During the delay phase, the model learns to maintain the previously presented cue in working memory. The probe stimulus triggers the subject to make a motor response based on which cue was presented before the delay. The model is rewarded if it makes the correct motor response [60].

Table 4. Summary of experimental studies investigating the effects of levodopa (L-DOPA) and D_2 dopamine agents on working memory

Study	Subject group	Medication used	Behavioral effects
Working memory			
L-DOPA monotherapy			
Lange et al. [42] (1992)	PD patients	L-DOPA	enhancement
Lewis et al. [43] (2005)	PD patients	L-DOPA	enhancement
Beato et al. [44] (2008)	PD patients	L-DOPA	enhancement
Marini et al. [45] (2003)	PD patients	L-DOPA	enhancement
Brusa et al. [46] (2003)	PD patients	L-DOPA	–
Costa et al. [47] (2003)	PD patients	L-DOPA	enhancement
Pascual-Sedano et al. [48] (2008)	PD patients	L-DOPA	enhancement
Fernandez-Ruiz et al. [49] (1999)	parkinsonian monkeys	L-DOPA	enhancement
Dopamine agonist monotherapy			
Costa et al. [47] (2003)	PD patients	apomorphine	–
Brusa et al. [46] (2003)	PD patients	pramipexole	impairment
Brusa et al. [50] (2005)	PD patients	pergolide	enhancement
McDowell et al. [51] (1998)	brain injury	bromocriptine	–

Unlike pramipexole (which has a high affinity to D_2 receptors), most studies that found that levodopa-induced dopamine and pergolide (which has a high affinity to both D_1 and D_2 receptors) enhance working memory performance. – = No effect.

Results

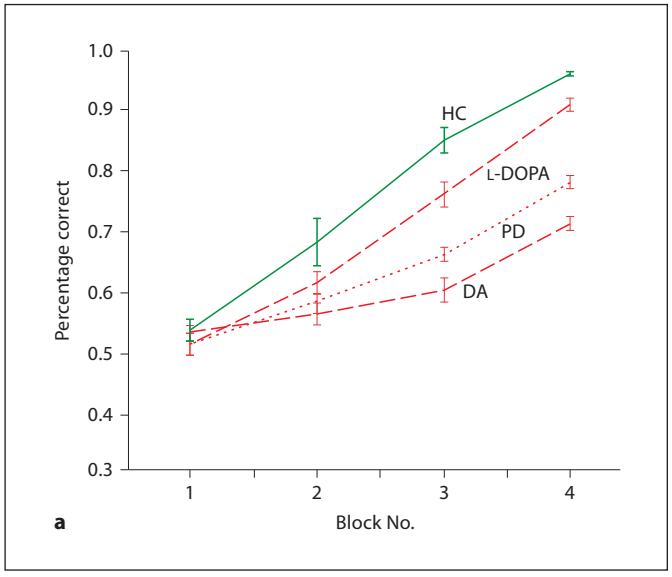
We first present our simulation results of the effects of levodopa and dopamine agonists on cognition in PD patients. We then present our simulation results of the dose-dependent effects of dopamine agonists on cognition in healthy subjects.

Simulation of Effects of Levodopa and Dopamine Agonists on Cognition in PD Patients

Simulation results show that PD patients are more impaired than controls at stimulus-response learning tasks (fig. 2a). In agreement with experimental results (table 3), our simulation results show that levodopa enhances stimulus-response learning, while dopamine agonists impair this learning. Similarly, our simulation results show that levodopa enhances working memory (fig. 2b), as reported in many neuropsychological studies. Model simulations also show that D_2 agonists do not affect working memory. In our model, this is because dopamine agonists target D_2 receptors, and thus do not enhance maintenance of information in working memory, a process mediated by D_1 receptors in the PFC.

Simulation of Dose-Dependent Effects of Dopamine Agonists on Cognition in Healthy Subjects

Our model of the cognitive effects of levodopa and dopamine agonists in PD patients can also be applied to pharmacological studies of healthy individuals. Experimental studies have shown that the effects of D_2 dopamine agonists on cognition depend on the exact dose administered to the subjects. For example, studies found that in healthy subjects, a low dose (1.25 mg) of the dopamine agonist bromocriptine has no effect or impairs working memory [61], while a high dose (2.5 mg) of bromocriptine enhances working memory [51, 62]. This is in agreement with neuropsychological studies in which a low dose of dopamine agonists was found to either impair or have no effect on working memory in PD patients (table 4). We assume that different doses of D_2 dopamine agonists affect tonic firing of dopamine cells, such that the higher the dose, the higher the tonic activity of dopamine neurons. Our model shows that a low dose of agonists slightly impairs working memory in simulated healthy subjects, while a high dose enhances working memory in the model (fig. 3b). In the working memory simulation, 2 of 100 simulation runs did not learn the task, so we removed them from analysis, as is the practice in experimental studies. Furthermore, simulation results show that a low dose of dopamine ago-



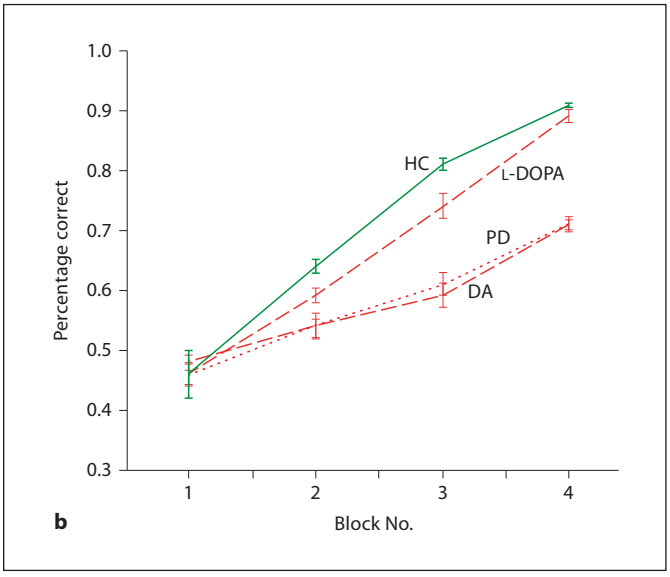
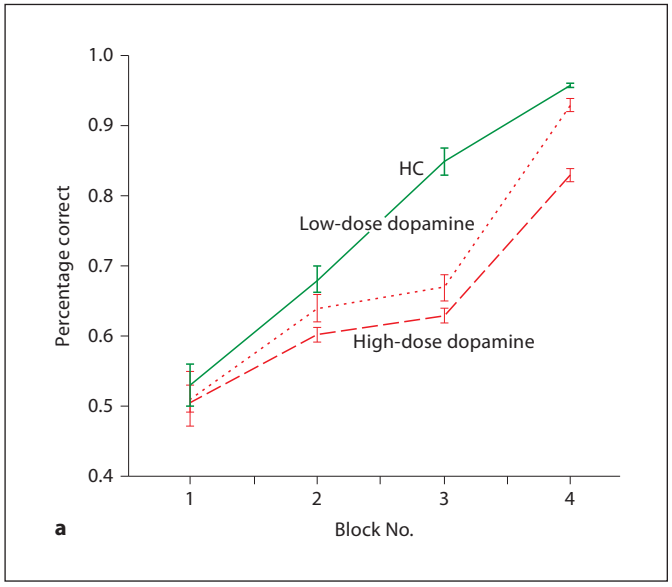


Fig. 2. Simulation results of the effects of levodopa and dopamine agonists on: stimulus-response learning (**a**) and working memory (**b**) in PD patients. Levodopa enhances performance in stimulus-response and working memory tasks, while dopamine agonists impair stimulus-response learning and have no effect on working memory. HC = Healthy controls; PD = unmedicated PD patients; L-DOPA = PD subjects on levodopa; DA = PD patients on dopamine agonists. Error bars indicate SE.



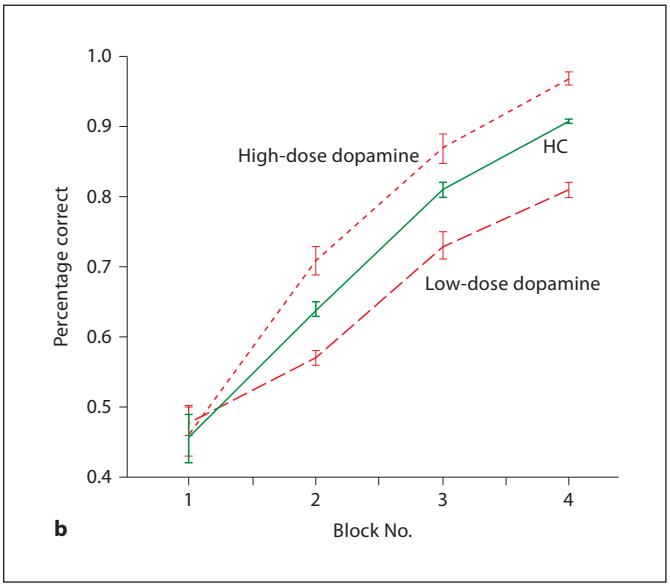


Fig. 3. Simulation results of effects of different doses of dopamine agonists on stimulus-response learning (**a**) and working memory performance (**b**) in healthy subjects. **a** Simulation results of different effects of doses of dopamine agonists on stimulus-response learning in healthy subjects. A low-dose of dopamine agonists impairs learning, in agreement with experimental results (Santesso et al. [35]), and a large dose of dopamine agonists further impairs learning, which is a new prediction of our model. **b** A low dose of dopamine agonists impairs working memory [62], while a large dose of dopamine agonists enhances working memory, in agreement with experimental results [61]. Low-dose dopamine here refers to low-dose dopamine agonist (Sultzer et al. [63]). Error bars indicate SE.

nists impairs stimulus-response learning (fig. 3a) while a higher dose further impairs stimulus-response learning.

Discussion

Our neurocomputational model simulates the differential effects of levodopa versus D_2 dopamine agonists on cognition. Here, we have assumed that levodopa only activates D_1 receptors, while both levodopa and dopamine agonists activate D_2 dopamine receptors (fig. 1). Because D_1-receptor activation is associated with learning, working memory, and dyskinesia, our model provides an account for how levodopa enhances learning and working memory, but is associated with dyskinesia.

Interactions between D_1- and D_2-Expressing Neurons

What is the neural mechanism by which an increase in tonic dopamine leads to a decrease in phasic signaling? In a recent in vitro study, Taverna et al. [64] have shown that striatal D_2-expressing neurons send inhibitory input to D_1-expressing cells. They have found that an efferent connection from striatal D_1 to D_2 neurons is almost nonexistent, as we assume in our model. This unidirectional connectivity between D_1- and D_2-expressing cells might explain how an increase in tonic dopamine leads to a decrease in phasic signaling. Experimental data show that a similar neural mechanism exists in the PFC [65]: activation of D_2-expressing neurons in the PFC [18] inhibits D_1 cells [15]. A more plausible mechanism is that tonic dopamine stimulates inhibitory D_2 autoreceptors, thereby decreasing phasic dopamine responses [66]. A working hypothesis to provide an explanation for the function would be that this connectivity in the PFC (not simulated in our model) discontinues the maintenance of information in working memory once a motor response is made. The existence of inhibitory connectivity from D_2 to D_1 neurons in the BG and PFC suggests the utilization of an existing neural mechanism from motor performance to be applicable as well to cognitive performance (D_2 receptors inhibit D_1 receptors in the PFC to discontinue maintenance of information in working memory once a response is made), which would explain the differential effects of levodopa and D_2 dopamine agonists.

Comparison to Prior Theoretical Models

The current model addresses important clinical data not simulated by prior models of PD and dopamine medications. For example, prior models do not simulate dissociable effects of different PD medications on brain and cognition [52, 67]. Most past models have also ignored any potential function of D_2 receptors in the PFC in working memory [67, 68], arguing for a more important role for PFC D_1 receptors. Experimental data, however, point to an essential role for both D_1 and D_2 receptors in PFC for working memory [18, 69]. Like our model, a prior model by Helie et al. [70] also assumes that PD affects prefrontal dopamine. Our model simulates the functional contribution of D_1 and D_2 receptors in both the BG and PFC in learning and working memory.

Experimental Data Accounted for by the Model

Our computational hypotheses about the different functions of D_1 and D_2 receptors are based on findings of previous experimental and modeling studies. For example, several studies in animals found that D_2 antagonists enhance learning [71–74]. Similarly, Eyny and Horvitz [74] found that D_2 antagonists enhance learning in rats, whereas D_1 antagonists impair learning. The findings that D_2 antagonists enhance learning are perhaps puzzling. Our model suggests that D_2 antagonists decrease the effects of tonic dopamine levels, and thus increase the scope of phasic firing of dopamine neurons, which in turn enhance learning. Similarly, Smith-Roe and Kelley [75] found that D_1 agonists improve stimulus-response learning. In our modeling framework, D_1 agonists might enhance the effect of phasic signaling of dopamine cells, which is essential for synaptic modification and learning in the corticostriatal pathway [76]. In agreement with our model, physiological studies found that D_1 antagonists block learning in the striatum, while D_2 antagonists enhance learning [77]. Gurden et al. [78] also found that D_1 (but not D_2) receptors in PFC are important for NMDA-dependent long-term potentiation (but for different results, see Xu and Yao [79]). Overall, many behavioral and physiological data point to specific roles of D_1 and D_2 receptors in the striatum in learning and initiation of motor responses, which are, to a large extent, in agreement with our model.

Limitations and Future Directions for Modeling

The limitations of our model suggest several possible future directions for theoretical development and computational modeling, which, in turn, would inform future experimental and clinical studies. First, our model does not simulate the effects of the combination of both levodopa and dopamine agonists on cognition, though the two medications are commonly used together to treat PD symptoms. Our model, however, suggests that adding

levodopa to dopamine agonists to treat PD symptoms may result in the best of both treatments: although levodopa has a shorter half-life than most dopamine agonists, levodopa perhaps enhances phasic firing of dopamine cells, and thus enhances learning and focused attention. These processes are probably not enhanced with dopamine agonists [80]. Second, we treated dopamine receptors in the same family (e.g., D_2 and D_3) equally within our current model. This is an oversimplification because research has shown that drugs targeting D_3 receptors have some dissociable effects on behavior compared to drugs targeting D_2 receptors, such as methamphetamine and quinpirole.

In recent years, neurocomputational modeling has become an increasingly useful tool for understanding the diverse and complex linkages between brain and behavior; we illustrate here how such modeling can also be applied to creating a closer rapprochement between theoretical neuroscience and practical issues in clinical neurology and psychiatry.

Disclosure Statement

The authors report no conflict of interest regarding the content of this article.

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