

Cognitive Processes in Parkinson's Disease: From Dopamine to Behavior

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We present a summary of our ongoing research into the cognitive functions of the basal ganglia and their implication in Parkinson's disease (PD). Diverse cognitive functions are impaired in PD, which are sometimes enhanced, but sometimes worsened, by dopaminergic medication. Computer modeling of the basal ganglia dopamine system and its involvement in cognition has been useful for understanding these effects and for making novel predictions regarding core cognitive deficits in PD.

Introduction. Parkinson's disease (PD) is a progressive neurodegenerative disease that selectively damages dopaminergic cells that target the basal ganglia (BG). The most obvious behavioral change associated with PD is characterized by muscular rigidity, slowness of movements, and tremor. Nevertheless, a number of cognitive changes have been documented as well, which are the focus of this review. These cognitive impairments are often complex and seemingly unrelated, ranging from deficits in *reinforcement learning and decision making* (ie, choosing among multiple menu items at a restaurant and learning from the outcome of this decision) to *working memory* (holding and manipulating information in mind, as in mental arithmetic) and *attentional control* (directing attention to task-relevant versus distracting information). In the present review we present our ongoing theoretical account of these phenomena. Rather than proposing separate mechanisms for the various cognitive and motor impairments in PD, our approach unites the diverse pattern of results by adopting a mechanistic approach that attempts to decipher the underlying roles of the basal ganglia/dopamine system. We begin by describing

the general aspects of our model of this system, and then describe how cognitive impairments in PD are consistent with this model.

Relating Basal Ganglia Roles in Motor Control and Cognitive Function. In the context of motor control, various authors have suggested that the role of the BG is to selectively facilitate the execution of a single motor command, while suppressing all others.¹⁻³ Thus, the BG is thought to act as a brake on competing motor actions that are represented in motor cortex. Only the most appropriate motor command is able to release the brake and get executed at any point in time. Further, the BG does not come up with the motor responses itself, but instead modulates the execution of cortical responses by signaling "Go" or "No-Go".⁴ This functionality also helps to string simple motor commands together to form a complex motor sequence, by selecting the most appropriate command at any given portion of the sequence and inhibiting the other ones until the time is appropriate.¹ A simplified analysis of BG anatomy helps clarify the basis for this functional characterization. In brief, 2 BG pathways are



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thought to independently facilitate or suppress cortical motor commands. More specifically, 2 main projection pathways from the striatum go through different basal ganglia output structures on the way to thalamus and up to cortex (*Figure 1*). Activity in the direct pathway sends a “Go” signal to facilitate the execution of a response considered in cortex, whereas activity in the indirect pathway sends a “No-Go” signal to suppress competing responses. Dopamine modulates the relative balance of these pathways by exciting “Go” cells while inhibiting “No-Go” cells. This effect is dynamic, such that transient increases in DA leads to more “Go” and less “No-Go”, and vice versa for decreases.³ Note that in PD, motor neurons themselves are not damaged, and patients can in fact perform movements quite smoothly under some circumstances (eg, externally driven motor commands). Instead, these patients may have difficulty selecting among various competing motor actions and executing the most appropriate one. It is often suggested that depleted dopamine in PD leads to an imbalance of the direct and indirect pathways.⁵ Specifically, PD is thought to be associated with too much “No-Go” and not enough “Go”, leading to slowness of movements or *bradykinesia*. In essence, depleted DA in the BG may result in raising the threshold for facilitating a motor program while continuing to suppress competing actions.^{1,6} The observation that treatment with DA agonists and L-Dopa sometimes lead to jerking movements, or *dyskinesia*⁷ is consistent with this hypothesis by shifting the balance the other way and making the threshold for motor execution too low, rather than too high.⁸ How does the above depiction of BG involvement in motor control relate to cognition in Parkinson’s

disease? As described above, it is generally accepted that the BG acts as the motor controller by dynamically modulating activity in frontal motor cortex. Similarly, various researchers now propose a key role of parallel circuits linking the BG, thalamus, and PFC that are essentially identical to those involved in the motor circuit.⁹

Working Memory. Based on the general suggestions of basal ganglia involvement in prefrontal circuits made by Alexander and colleagues, we developed a computational model that explicitly formulated the role of the BG in working memory.² We suggested that just as the BG facilitates motor command execution in premotor cortex by disinhibiting or “releasing the brakes” it may also facilitate the updating of working memory in prefrontal cortex. For task-relevant stimuli that are suitable for working memory maintenance, the BG direct pathway may activate a “Go” signal to disinhibit the thalamus and gate the updating of PFC. In contrast, due to “No-Go” BG output, task-irrelevant information would not be robustly maintained. For example, when someone is telling you their telephone number, you have learned to activate “Go” signals to encode this into working memory, while also being able to have “No-Go” signals to ring to distracting information (eg, if your pesky friend later tries to distract you with other numbers).

Reinforcement Learning / Decision Making. When faced with a decision, such as which menu item to order at a restaurant, people often use implicit, “gut-level” strategies. They simply “know” they want to choose the steak in favor of the salmon, often without being able to explicitly state

Figure 1a and 1b

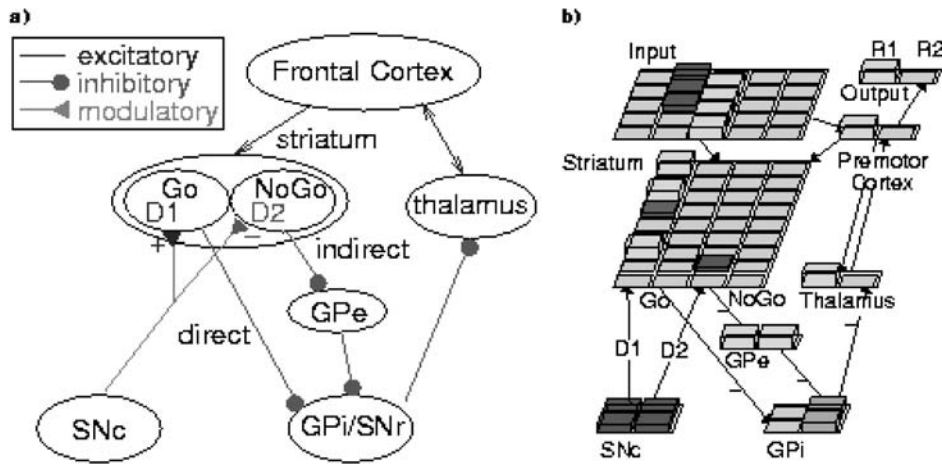


Figure 1a

The cortico-striato-thalamo-cortical loops, including the direct (“Go”) and indirect (“No-Go”) pathways of the basal ganglia. The “Go” cells disinhibit the thalamus via GPi, thereby facilitating the execution of an action represented in cortex. The “No-Go” cells have an opposing effect by increasing inhibition of the thalamus, suppressing actions from getting executed. Dopamine from the SNc projects to the dorsal striatum, causing excitation of “Go” cells via D1 receptors, and inhibition of “No-Go” via D2 receptors. GPi: internal segment of globus pallidus; GPe: external segment of globus pallidus; SNc: substantia nigra pars compacta; SNr: substantia nigra pars reticulata.

Figure 1b

The Frank (2005) neural network model of this circuit (squares represent units, with height and color reflecting neural activity; yellow = most active, red = less active, grey = not active). The Premotor Cortex selects an Output response via direct projections from the sensory Input, and is modulated by the BG projections from the Thalamus. Go units are in the left half of the Striatum layer; “No-Go” in the right half, with separate columns for the 2 responses R1 (left button), R2 (right button). In the case shown, striatum “Go” is stronger than “No-Go” for R1, inhibiting GPi, disinhibiting Thalamus, and facilitating execution of the response in cortex. A tonic level of dopamine is shown in SNc; a burst or dip ensues in a subsequent error feedback phase (not shown), causing corresponding changes in “Go”/“No-Go” unit activations, which drive learning.

the basis of their decision. In fact, in such situations, the implicit value of alternative decisions has been integrated over multiple prior experiences—your intuition is really just the integration of your experience in a very generalized way.

Given that the BG are thought to participate in selecting among various competing low-level motor responses, it is natural to extend this functionality to include higher-level decisions. The question is, how do the BG learn which decision has the highest value? Insight comes from various experiments showing that when monkeys are rewarded following a correct choice, transient increases in BG dopamine firing are observed.¹⁰ Conversely, choices that do not lead to reward are associated with dopamine dips that drop below baseline. These changes in dopamine are adaptive, and are thought to lead to the learning of rewarding behaviors. In our models, transient dopamine increases preferentially activate “Go” cells in the direct pathway via D1 receptors, while suppressing “No-Go” cells in the indirect pathway via D2 receptors.³ This change in activity

modifies synaptic plasticity, such that on subsequent trials the model is more likely to respond “Go” to a decision that has been recently rewarded. Conversely, dopamine dips lead to “No-Go” learning to avoid non-reinforced incorrect decisions. See below for a more detailed description of how this model functions, and its implications for Parkinson’s disease.

Cognitive Impairments in Parkinson’s Disease. Next, we review the evidence for cognitive deficits in PD and how it can be understood within the context of our model. We divide the cognitive deficits in PD into 2 general classes and address them in turn. The first class concerns “frontal-like” deficits, and the second is related to impairments in implicit reinforcement learning.

Frontal Deficits. Frontal-like cognitive deficits have long been attributed to patients with PD. Anecdotally, patients report difficulty with manipulating information in memory, such as counting backwards from 100. In the laboratory, PD patients are

Figure 2a
Example stimulus pairs (Hiragana characters) used in the cognitive probabilistic learning task, designed to minimize verbal encoding. One pair is presented per trial, and the participant makes a forced choice. The frequency of positive feedback for each choice is shown.

Figure 2b
Novel test pair performance in Parkinson patients on and off medication tested at the Colorado Neurological Institute (Frank, Seeberger and O'Reilly, 2004). Note that choosing A depends on having learned from positive feedback, while avoiding B depends on having learned from negative feedback.

Figure 2c
This pattern of results was predicted by the Frank (2005) model. The figure shows “Go” - “No-Go” associations for stimulus A, and “No-Go” - “Go” associations for stimulus B, recorded from the model's striatum after having been trained on the same task used with patients. Error bars reflect standard error across 25 runs of the model with random initial weights.

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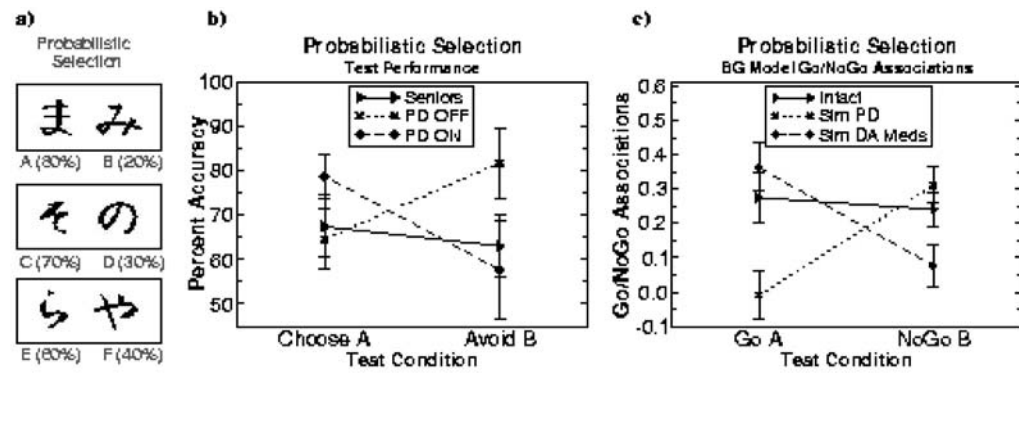
impaired at many of the same tasks as observed in patients with damage to prefrontal cortex.¹¹ The theoretical account for these observations consistently implicates a damaged BG that is interconnected in a functional circuit with prefrontal cortex.¹² Our framework holds that diminished DA in the BG results in a higher threshold for updating information in PFC, which leads to working memory impairments and rigidity, as is also observed in primates with selective striatal DA depletion. Specifically, a lack of BG DA in PD would lead to too little updating of relevant information into PFC, just as it leads to too little execution of motor commands. Conversely, too much DA in the BG would lead to excessive updating of PFC, just as it leads to L-Dopa induced motor tics and dyskinesia. Finally, a suboptimal level of DA in the PFC would lead to insufficient maintenance of task-relevant information. Any of these DA dysfunctions would lead to “frontal-like” cognitive deficits.

Implicit/Reinforcement Learning Deficits. In support of the “multiple memory system” hypothesis, researchers have found that different patient populations have different kinds of memory impairments. Amnestics with medial temporal lobe damage have impaired episodic, but intact procedural memory—that is, they cannot remember individual trials but nevertheless successfully integrate error feedback across multiple trials and perform normally in trial-and-error tasks.¹³ PD patients show the opposite pattern of results: they can remember individual experiences but have difficulty integrating error feedback across multiple trials.¹⁴⁻¹⁵ These deficits are typically studied with probabilistic classification or “cognitive

procedural learning” tasks, in which participants have to classify stimuli into different categories using trial-and-error. Patients perform as well as controls in other implicit learning tasks, such as those learned by simple observation not involving error feedback.¹⁵⁻¹⁶ In implicit categorization tasks, successful integration of information depends on both error feedback and BG integrity.¹⁷ Perhaps the most well known cognitive impairment in PD is that of the “weather prediction” categorization task in which category members are determined probabilistically and participants have to figure out statistical regularities by trial-and-error.¹⁴ Healthy participants implicitly integrate information over multiple trials, progressively improving, despite not being able to explicitly state the basis of their choices. PD patients are reliably impaired in the early stages of the task. At first glance, implicit learning deficits might appear unrelated to the frontal impairments of PD patients described above. While frontal tasks demand manipulation of information in conscious awareness, implicit learning tasks specifically measure the ability of participants to pick up on regularities that do not reach conscious awareness. The current framework provides a unified account for both classes of deficits: diminished DA in the BG causes a lack of working memory updating in PFC, but through interactions with premotor cortex it also reduces the implicit learning of stimulus-response relationships.³ Stimulus-response execution requires facilitating some responses while suppressing others, and the learning of these mappings depends on dynamic modulatory properties of DA in the BG.

A Model of Reinforcement Learning in PD. Computational modeling of the

Figure 2



dynamics of BG-cortical interactions provided an explicit formulation for how the BG is involved in cognitive reinforcement learning, and how this is impaired in PD.³

Specifically, the model (Figure 1b) addressed how phasic changes in DA during error feedback are critical for modulating “Go/No-Go” representations in the BG that facilitate or suppress the execution of motor commands. The main assumption is that during positive and negative feedback (eg, correct or incorrect), bursts and dips of DA occur that drive learning for the response. This assumption was motivated by a large amount of evidence for bursts and dips of DA during rewards or their absence in monkeys,¹⁰ which have also been inferred to occur in humans for positive and negative feedback.¹⁸ These phasic changes in DA modulate neuronal excitability, and may therefore act to reinforce the efficacy of recently active synapses, leading to the learning of rewarding behaviors. Thus in the model, “correct” responses are followed by transient increases in simulated DA that enhance synaptically driven activity in the direct/“Go” pathway, while concurrently suppressing the indirect/“No-Go” pathway. This drives “Go” learning, and enables the model to facilitate responses that on average

result in positive feedback. Conversely, after incorrect responses phasic dips in DA release the “No-Go” pathway from suppression, increasing its activity and driving “No-Go” learning. Over the course of training, this model learns how to respond in the weather prediction task, with performance levels similar to that of healthy human participants. When 75 percent of simulated dopamine neurons were removed (to model the approximate amount of damage in PD patients), the model was impaired similarly to patients.

Modeling Dopaminergic Medication Effects on Cognitive Function in PD. The same model was used to explain certain negative effects of dopaminergic medication on cognition in PD.³ While medication improves performance in task-switching, it actually tends to impair performance in probabilistic reversal.¹⁹ These authors noted that the task-dependent medication effects are likely related to the fact that different tasks recruit different parts of the striatum. Dopaminergic damage in early stage PD is restricted to the dorsal striatum, leaving the ventral striatum with normal levels of DA.²⁰ This explains why DA medication alleviates deficits in taskswitching, which relies on

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dorsal striatal interactions with dorsolateral prefrontal cortex. However, the amount of medication necessary to replenish the dorsal striatum might “overdose” the ventral striatum with DA, and is therefore detrimental to tasks that recruit it.

In order to simulate medication effects, it was hypothesized that medication increases the tonic level of DA, but that this interferes with the natural biological system's ability to dynamically regulate phasic DA changes. Specifically, phasic DA dips during negative feedback may be partially blocked by DA agonists that continue to bind to receptors. When this was simulated in the model, selective deficits were observed during probabilistic reversal, despite equivalent performance in the acquisition phase,³ mirroring the results found in medicated patients. Because increased tonic levels of DA suppressed the indirect/“No-Go” pathway, networks were unable to learn “No-Go” to override the prepotent response learned in the acquisition stage. This account is consistent with similar reversal deficits observed in healthy participants administered an acute dose of bromocriptine, a D2 agonist.²¹

Empirical Tests of the Model.

Recently, we have tested various aspects of the hypothesized roles of the basal ganglia/dopamine system across both reinforcement learning and working memory processes. First, we demonstrated striking support for a central prediction of our model regarding dopamine involvement in “Go” and “No-Go” cognitive reinforcement learning.^{3,22} We tested Parkinson's patients on and off medication, along with healthy senior control participants matched for age, education and a measure of verbal IQ. We predicted that decreased levels of dopamine in Parkinson's disease would lead to spared

“No-Go” learning, but impaired “Go” learning (which depends on DA bursts). We further predicted that dopaminergic medication should alleviate the “Go” learning deficit, but would block the effects of dopamine dips needed to support “No-Go” learning, as was simulated to account for other medication-induced cognitive deficits in Parkinson's disease.³ Results were consistent with these predictions (*Figure 2*). In a probabilistic learning task, all patients and aged-matched controls learned to make choices that were more likely to result in positive rather than negative reinforcement. The difference was in their strategy: patients taking their regular dose of dopaminergic medication implicitly learned more about the positive outcomes of their decisions (ie, they were better at “Go” learning), whereas those who had abstained from taking medication implicitly learned to avoid negative outcomes (better “No-Go” learning). Age-matched controls did not differ in their tendency to learn more from the positive/negative outcomes of their decisions.

We have also tested predictions for a more general role for BG/dopamine in cognitive function by administering low doses of dopamine agonists/antagonists to young, healthy participants.²³⁻²⁴ The drugs used (cabergoline and haloperidol) were selective for D2 receptors, which are by far most prevalent in the BG. By acting on presynaptic D2 receptors, cabergoline reduces, while haloperidol enhances, the amount of phasic dopamine that is released during dopaminergic cell bursting.²⁵ Again, results were consistent with our model.

Increases in dopamine during learning caused participants to learn more about the positive outcomes of their decisions (as in medicated Parkinson's patients), whereas decreases in dopamine caused the same participants to learn more about negative

outcomes (as in non-medicated patients).

Notably, these same effects were borne out in the context of a working memory and attentional task. Specifically, increases in dopamine by haloperidol enhanced selective working memory updating of task-relevant (ie, “positively-valenced”), but not distracting (“negatively-valenced”) information. By our model’s account, dopamine release evoked during the presentation of task-relevant information reinforces BG “Go” firing to update this information. Consistent with this analysis, increased dopamine release also caused difficulty *not* updating (ie, ignoring) this information when it subsequently became distracting in the set-shift. Finally, and perhaps most suggestive for a role of BG dopamine in working memory, participants with low baseline working memory span were most subject to the effects of increases in dopamine by haloperidol, while those with high span were most subject to decreases in dopamine by cabergoline.²³⁻²⁴ These latter results are consistent with the notion that individual differences in working memory span are partially characterized by underlying differences in dopamine levels,²⁶ but extend this hypothesis in a more mechanistic fashion consistent with our modeling.

Taken together, these results provide strong support that BG signals, under modulation by dopamine, are critical for the updating of PFC working memory representations. Further, the model’s success in capturing subtle cognitive effects in both Parkinson’s disease and controlled dopamine manipulation suggests that it can also be applied to mechanistically understand cognitive deficits in those with more complex disorders involving BG/dopamine dysfunction, such as attention deficit hyperactivity disorder (ADHD) and schizophrenia.

Conclusions and Practical Implications. In summary, we have presented a mechanistic account of how dopamine in the basal ganglia may play a functionally similar role across multiple cognitive processes. We have showed that while dopaminergic medication used to treat PD sometimes enhances cognitive function, it can also worsen or even cause cognitive deficits. At this stage it is far too preliminary to recommend changing medication prescriptions based on these results, especially considering their important benefits for treating the more profound and debilitating motor impairments associated with the disease. Nevertheless, we expect that this research will lead to a better understanding of the dopaminergic system, and ultimately better design of medications that can specifically target underlying neural dysfunction without causing unwanted side effects. Finally, because our approach is based on low-level neural mechanisms which are not specific to PD *per se*, we are hopeful that this basic science will lead to a better understanding of, and ultimately better medications to treat, other pathological conditions involving the BG/DA system, including schizophrenia, obsessive compulsive disorder, ADHD, and Huntington’s disease.

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