

Dopamine Overdose Hypothesis: Evidence and Clinical Implications

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ABSTRACT: About a half a century has passed since dopamine was identified as a neurotransmitter, and it has been several decades since it was established that people with Parkinson's disease receive motor symptom relief from oral levodopa. Despite the evidence that levodopa can reduce motor symptoms, there has been a developing body of literature that dopaminergic therapy can improve cognitive functions in some patients but make them worse in others. Over the past two decades, several laboratories have shown that dopaminergic medications can impair the action of intact neural structures and impair the behaviors associated with these structures. In this review, we consider the evidence that has accumulated in the areas of reversal learning, motor sequence learning, and other cognitive tasks. The purported inverted-U shaped relationship between dopamine levels and performance is complex and includes many contributory factors. The regional striatal topography of nigrostriatal denervation

is a critical factor, as supported by multimodal neuroimaging studies. A patient's individual genotype will determine the relative baseline position on this inverted-U curve. Dopaminergic pharmacotherapy and individual gene polymorphisms can affect the mesolimbic and prefrontal cortical dopaminergic functions in a comparable, inverted-U dose-response relationship. Depending on these factors, a patient can respond positively or negatively to levodopa when performing reversal learning and motor sequence learning tasks. These tasks may continue to be relevant as our society moves to increased technological demands of a digital world that requires newly learned motor sequences and adaptive behaviors to manage daily life activities. © 2013 International Parkinson and Movement Disorder Society

Key Words: dopamine; ventral striatum; dorsal striatum; prefrontal cortex; learning

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A little over half a century has passed since dopamine was identified as a neurotransmitter and it was recognized that depleting monoamines in the brain through the administration of reserpine caused hunched immobility in rodents.¹ This finding led to the hypothesis of a dopaminergic depletion disorder as the pathophysiological basis of Parkinson's disease. Since then, dopamine substitution using (L-3,4-dihydroxyphenylalanine [L-dopa]) has been the most widely used pharmacotherapy for Parkinson's disease. Despite reducing symptom manifestation, a majority of patients chronically exposed to dopamine therapy will eventually develop motor complications, including

response fluctuations and drug-induced dyskinesias (abnormal, involuntary movements), such as choreic and dystonic limb or truncal movements.² In addition, while restoring cognitive functions associated with dopamine-depleted brain regions, dopamine substitution can also impair certain cognitive functions, such as probabilistic reversal learning, motor sequence learning, and other cognitive tasks, that are associated with intact dopamine-dependent brain regions.^{3–5} Dopamine overstimulation has been studied for over a decade since the work of Gotham and colleagues,⁶ and the articles by Swainson and colleagues⁷ and Cools and colleagues³ initially proposed the dopamine overdose hypothesis.

Fronto-executive cognitive deficits can be observed even in early Parkinson's disease in the areas that include executive function, learning, memory, motor inhibition, impulse control, and visuospatial processing.⁸ These cognitive deficits may be related to mesocortical, mesolimbic, and nigrostriatal dopaminergic pathways as well as other pathways associated with acetylcholine and norepinephrine.⁸ Cognitive deterioration after dopaminergic therapy can occur in several tasks. In this review of the dopamine overdose hypothesis, we characterize the specific evidence supporting this hypothesis by reviewing the relevant literature in the areas of reversal learning, motor sequence learning, and other cognitive tasks. Issues related to impulsivity and reward processing are not addressed in this review, because these issues have been addressed previously.^{9,10} First, we discuss the physiology of the dopamine overdose hypothesis. Next, we discuss evidence for the negative effects of dopaminergic medication on probabilistic reversal learning, followed by the evidence for the negative effects of dopaminergic medication on motor sequence learning. We then discuss the evidence that other cognitive tasks can be negatively affected by L-dopa when patients with Parkinson's disease carry specific genetic polymorphisms. Finally, we discuss the clinical implications of the hypothesis as they apply to the treatment and management of patients with Parkinson's disease.

Physiological Basis for the Dopamine Overdose Hypothesis

There are two major subtypes of dopaminergic neurons in the brain: the neurons of the substantia nigra pars compacta (A9 neurons)¹¹, which give rise to the nigrostriatal pathway, and the A10 neurons of the ventral tegmental area (VTA), which give rise to the mesolimbic and mesocortical pathways that innervate parts of the limbic system and the neocortex.¹² The regional pattern of degeneration within the substantia nigra in patients with Parkinson's disease appears to be specific, such that a loss of pigmented neurons is greatest in the ventral lateral tier, followed by the dorsal tier, which is different to the patterns identified

with healthy aging.¹³ In vivo diffusion magnetic resonance imaging (MRI) has provided evidence in support of this selective pattern of degeneration by showing that measures of structural integrity within the ventral and lateral substantia nigra are most affected in early Parkinson's disease compared with control subjects,^{14,15} whereas the dorsal substantia nigra is affected more in older adults than in young adults.¹⁶

The ventral lateral tier of the substantia nigra sends dopaminergic projections primarily to the dorsal putamen, whereas the dorsal tier of the substantia nigra sends dopaminergic projections primarily to the ventral striatum. The ventral striatum also receives projections from the VTA.¹¹ Studies using ¹⁸F-dopa positron emission tomography (PET) have demonstrated that patients with unilateral Parkinson's disease who are in Hoehn and Yahr stage 1 have reduced dopamine storage primarily within the dorsal putamen contralateral to motor symptoms.¹⁷ In a cross-sectional study, it was demonstrated that, in early Parkinson's disease, ¹⁸F-dopa metabolism was reduced by almost 50% in the dorsal rostral putamen and dorsal caudal putamen, whereas the ventral putamen was unaffected.¹⁸ With the progression of disease symptoms, there is a loss of ¹⁸F-dopa metabolism in the ventral putamen. Longitudinal multitracer PET studies have demonstrated that the posterior-dorsal to anterior-ventral striatal gradient of nigrostriatal denervation is maintained, whereas the asymmetry gradient becomes less prominent with progressive Parkinson's disease.¹⁹ Figure 1A illustrates the posterior-dorsal to anterior-ventral gradient of nigrostriatal denervation in Parkinson's disease across different stages of disease severity (from mild to severe, left to right). Early and most severe loss of nerve terminals is in the dorsal and posterior putamen. Anterior and ventral striatal regions are relatively spared, at least in the early stage of disease. This pattern of striatal degeneration from dorsal to ventral segments with the progression of Parkinson's disease provides a fundamental basis for the dopamine overdose hypothesis. That is, regions that are less affected early in the disease could be over stimulated by exogenous dopamine administration.

It has been several decades since Cotzias and colleagues²⁰ demonstrated the striking efficacy of oral L-dopa for relieving motor symptoms of Parkinson's disease. Since that time, L-dopa has remained the gold standard for antiparkinsonian therapy. Nonetheless, because the dorsal putamen is mostly affected in early Parkinson's disease, whereas the ventral striatum remains relatively intact,¹⁸ a given dose of L-dopa that has beneficial effects for most motor tasks that rely upon the dorsal putamen can also have deleterious effects on specific cognitive and motor tasks that specifically rely upon the ventral striatum.⁵ The administration of L-dopa is thought to decarboxylase in

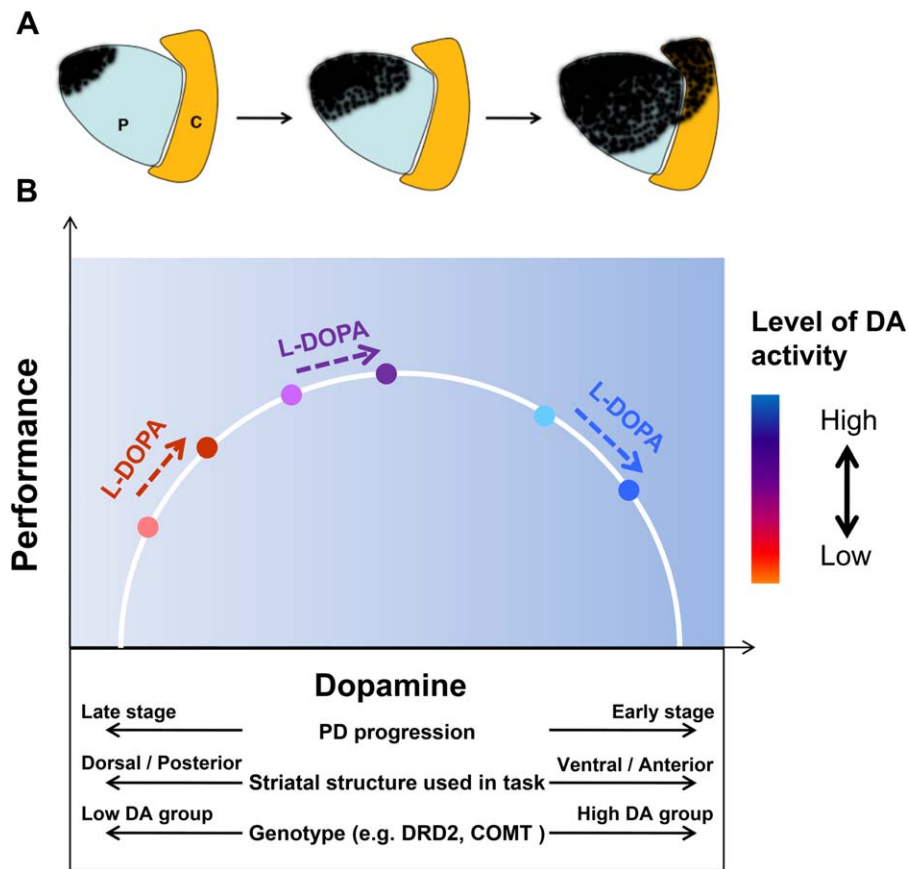


FIG. 1. (A) The posterior-dorsal to anterior-ventral gradient of nigrostriatal denervation is illustrated in Parkinson's disease (PD) across different stages of severity of disease (from mild to severe; left to right). Early and most severe loss of nerve terminals is in the dorsal and posterior putamen (P). Anterior and ventral striatal regions are relatively spared, at least in early stage of disease. C indicates caudate. (B) Individual patients can experience differing performance effects in response to levodopa (L-DOPA) administration because of a combination of factors, including stage of disease, striatal structure used in the task, and genotype for genetic polymorphisms that play a role in dopaminergic metabolism in the striatum and prefrontal cortex (Cools 2006⁵). These factors collectively determine each patient's starting location on the inverted-U shaped function describing the association between dopamine (DA) and performance, which, in turn determines whether performance will worsen, improve, or show no change with dopaminergic medications. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

remaining dopaminergic neurons; thus, the lack of specificity of dopamine therapy can lead to a possible over stimulation of ventral striatal areas that remain intact. Figure 1B illustrates the many factors that can modulate the effects of dopaminergic medication on performance, including disease stage, striatal structure engaged by the task, and genotype for genes that regulate endogenous dopamine availability. The dopamine overdose hypothesis proposes that, when patients with Parkinson's disease are off L-dopa or other dopaminergic medications, their performance on tasks like probabilistic reversal learning is optimal, whereas their performance on cognitive tasks like set-switching is impaired. Because reversal learning and set-switching implicate the ventral and dorsal striatum, respectively,^{21,22} these tasks have provided excellent paradigms to investigate dopaminergic effects on different striatal regions. Furthermore, when L-dopa or other dopaminergic medications are given to the patient, the proposal is that performance on probabilistic reversal learning will worsen, but set-switching performance

improves. Whereas set-switching requires flexible swapping or switching between tasks, reversal learning requires an adaptation to a previously learned stimulus-reward contingency. The central tenet of the dopamine overdose hypothesis is that tasks that rely on the ventral striatum will be impaired by dopaminergic medications in early Parkinson's disease because of overstimulation of the structure.

In addition to the effects of dopamine on the ventral and dorsal striatum, there is also evidence that dopamine overdose effects can occur in prefrontal cortex.⁸ The mesocortical dopaminergic pathway projects from the VTA to the frontal cortex, and this pathway regulates numerous cognitive functions, including set-shifting, working memory, and planning. As reviewed in subsequent sections, the studies in the literature collectively point to a cortical and subcortical role for dopamine overdose effects. In the next sections, we review the specific evidence in support of the dopamine overdose hypothesis in several domains of learning and cognitive performance.

TABLE 1. Summary of studies in which probabilistic learning and motor sequence learning paradigms have been investigated in patients with Parkinson's disease off and on L-dopa

Study	Outcome Measure	Results
Swainson et al. 2000 ⁷ Cools et al. 2001 ³ Shohamy et al. 2006 ³¹	Probabilistic reversal learning Probabilistic reversal learning Probabilistic category learning	Medicated PD groups showed impairments on reversal learning tasks Dopamine medication induced impairment in reversal stage of learning task Impairment in initial learning, but not transfer, of association between stimuli and rewards
Cools et al. 2006 ⁶⁴	Deterministic reversal learning	Dopaminergic medication-induced deficits on reversal shifting were restricted to reversals signaled by unexpected punishment but not by unexpected reward
Funkiewiez et al 2006 ⁶⁵ Cools et al. 2007 ⁶⁶	Probabilistic reversal learning Probabilistic reversal learning	L-Dopa impaired performance on the extinction phase of reversal learning task L-Dopa disrupted activity in the nucleus accumbens but not in the dorsal striatum or prefrontal cortex during reversal learning
Graef et al. 2010 ²⁷	Probabilistic reversal learning	Reward based reversal learning with changing reward contingencies was impaired with dopamine medication
Feigin et al 2003 ⁴⁹ Carbon and Eidelberg 2006 ⁴⁸	Motor sequence learning Motor sequence learning	L-Dopa infusion had no effect on motor sequence learning L-Dopa decreased measures of network activity and learning task performance in PD patients
Ghilardi et al 2007 ⁵¹	Motor sequence learning	L-Dopa improved scores on simple motor tasks and movement speed but had no effect on motor sequence learning
Argyelan et al. 2008 ⁵²	Motor sequence learning	In de novo patients, L-dopa suppressed learning-related deactivation of the ventromedial prefrontal cortex
Kwak et al. 2010 ⁴ Kwak et al. 2012 ⁴⁴	Motor sequence learning Motor sequence learning	Dopamine medication selectively impaired early-phase motor sequence learning L-Dopa decreased ventral striatum activation during the early learning phase; extent was correlated with L-dopa-associated reductions in motor sequence learning
Kwak et al. 2013 ⁴³	Motor sequence learning	Improved sequence learning only for patients carrying the minor T allele for a DRD2 polymorphism
Kwak et al. 2013 ⁵³	Motor sequence learning	Spatial pattern of nigrostriatal dopaminergic denervation predicted L-dopa-associated impairments in motor sequence learning

PD, Parkinson's disease; L-dopa, levodopa; DRD2, dopamine receptor D2.

Reversal Learning and Dopamine in Parkinson's Disease

Table 1 provides a summary of the studies that have investigated reversal learning paradigms in patients with Parkinson's disease off and on L-dopa. The consistent empirical finding has been that, when patients are on L-dopa, reversal learning performance is impaired compared with their performance off L-dopa. Initial evidence in support of this finding was from a study by Swainson and colleagues.⁷ Those authors studied three groups of patients with Parkinson's disease, including mild/unmedicated, mild/medicated, and severe/medicated patients. The reversal learning task required patients to choose between a red pattern and a green pattern, with one pattern rewarded over the other on a probabilistic schedule. The participants were asked to learn the task and figure out which pattern was correct; and, after a series of trials, the correct pattern was reversed. This was not immediately detectable, given that rewards were assigned probabilistically (eg, 80:20 ratio). When the reversal occurred, patients in the mild/medicated and severe/medicated groups had difficulty adapting to the new pattern; however, patients in the mild/unmedicated group had no difficulty adapting in the reversal learning task. In a subsequent study by the same laboratory,³ set-

switching performance and reversal learning were compared in two groups of patients with Parkinson's disease while either off or on dopaminergic therapy. The set-switch task required patients to identify the correct letter or number in a well learned sequence and did not require them to adapt to a new condition as in the reversal learning task. The authors observed that reaction time during the set-switch task was reduced with dopaminergic medication. During the reversal learning task, patients with Parkinson's disease in the off and on medication groups made more errors than control participants at the reversal learning stage, but the patients with Parkinson's disease who were off medication were able to adapt to the reversal. Patients on dopaminergic medication had more difficulty shifting their performance when the reward stimuli reversed. Although the between-group design used in those studies may have made interpretations difficult, they did provide a critical advance in identifying which type(s) of task is detrimentally affected by dopaminergic medication in mild to moderate Parkinson's disease.

Subsequent studies by the same laboratory and others have used within-subjects designs to test patients with Parkinson's disease off and on L-dopa. Fifteen patients with Parkinson's were tested off and

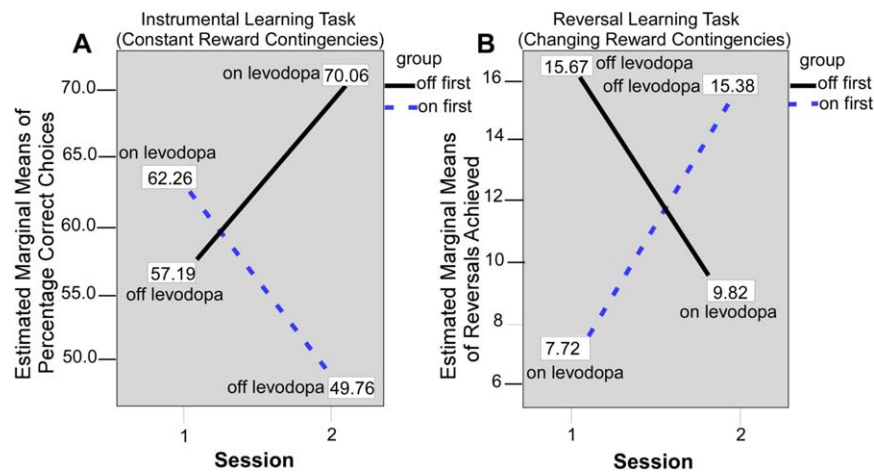


FIG. 2. (A) Performance in the on-beginner (“on first”) and off-beginner (“off first”) subgroups is illustrated across sessions on the reversal learning task. Covariate-corrected estimated means of the number of reversals achieved are shown in boxes. **(B)** Performance in the on-beginner (“on first”) and off-beginner subgroups (“off first”) is illustrated across sessions on the instrumental learning task. Covariate-corrected estimated means of percentage of correct choices are shown in boxes (adapted from Graef and colleagues 2010²⁷). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

on L-dopa monotherapy using an instrumental learning task with constant stimulus-reward associations and a reversal learning task that had changing reward contingencies. The study counterbalanced whether patients were tested in the on or off state first. A simple instrumental learning task was used, because it has been linked mainly with dorsal striatum and frontal circuits,^{23,24} whereas the reversal learning task has been linked with ventral striatum and frontal circuits.^{21,25,26} The prediction was that dopaminergic medication would have opposite effects on performance during these two tasks. Figure 2 illustrates experimental findings from the study during the instrumental learning task and the reversal learning task.²⁷ During the instrumental learning task (Fig. 2A), which had constant reward contingencies, patients on L-dopa produced a greater percentage of correct choices compared with when they were off L-dopa. Figure 2B illustrates the opposite pattern for the reversal learning task. Here, patients on L-dopa produced fewer reversal errors than when they were off medication. These findings controlled for the testing order and tested the same patients, and the results provide compelling evidence that reversal learning is impaired when patients with Parkinson’s disease are on medication.

Another probabilistic learning task, which was developed by Gluck and colleagues, is the weather prediction task.²⁸ In this task, four *cards* have independent and probabilistic relationships to two possible outcomes: *sun* and *rain*. Patients with Parkinson’s disease exhibit impaired learning on this task when they are on dopaminergic medication, but they learn at a rate similar to that of controls when off medication.^{29,30} In a similar paradigm, Parkinson’s patients and a group of controls were asked to learn which of

two stimuli was associated with a reward.³¹ The stimuli varied in shape and color, with only dimension predicting reward. The patients with Parkinson’s disease were impaired at learning the initial association when on medications, but not when they were off medications. In the next phase of the study, the relevant dimension of each stimulus was held constant, whereas the irrelevant feature changed. The control group, the on-medication Parkinson’s group, and the off-medication Parkinson’s group all performed equally well during this transfer phase. Because it has been shown that the weather prediction task relies on the head caudate nucleus³² (a more anterior striatal structure that exhibits dopaminergic denervation later in Parkinson’s disease than the putamen), these findings provide additional support that the dopamine overdose hypothesis plays a role in the behavior of patients with Parkinson’s disease when they are on L-dopa.

Dopamine stimulates receptors in the basal ganglia and prefrontal cortex, and there is an important distinction for D1 and D2 receptors in these brain regions. The dopamine overdose hypothesis is also supported from studies of dopamine synthesis in animals and pharmacological studies in healthy adults. In animal models, stimulating D1 receptors with dopaminergic medication in the prefrontal cortex has revealed changes in the firing of neurons during the delay period of delayed-response tasks.^{33–35} Computational models have provided insight into how dopamine enhances D1 receptor stimulation such that dopamine can increase the resistance to distracting stimuli.^{36,37} D2 receptors are more abundant in the basal ganglia than in the prefrontal cortex, and it has been suggested that the basal ganglia may serve as a gating mechanism for updating the prefrontal cortex.³⁸ D2

receptor stimulation has been tested in healthy adults using the D2 receptor agonist bromocriptine relative to their baseline dopamine synthesis capacity as determined by ^{18}F -fluoro-L-meta-tyrosine PET tracer.³⁹ Individuals performed a reward-based reversal learning task with deterministic stimulus-outcome contingencies that required a button press to predict whether the face or scene stimulus would lead to a reward or punishment. The authors observed that, in a placebo test, striatal dopamine synthesis was positively related to reversal learning performance. Individuals with low striatal dopamine synthesis performed poorly on the reversal learning task, whereas high striatal dopamine synthesis was associated with high reversal learning performance. The participants with low striatal dopamine synthesis responded positively to bromocriptine. In contrast, participants with high baseline striatal dopamine synthesis were over stimulated by bromocriptine and exhibited impaired reversal learning performance when on the drug.

In a study using event-related functional MRI (fMRI), it was observed that, in healthy adults performing a probabilistic reversal learning task, the ventral striatum and ventrolateral prefrontal cortex were specifically activated when individuals committed reversal errors.²¹ A recent study evaluated the effects of bromocriptine versus sulpiride (a D2 receptor antagonist) and the combination of both drugs on reward and punishment reversal learning.⁴⁰ It was found that improved reward relative to punishment reversal learning performance occurred with the administration of sulpiride compared with bromocriptine. These findings provide additional insight into the specificity of the D1 and D2 receptors related to reward and punishment during reversal learning.⁴⁰ Next, we discuss the pertinent findings for the dopamine overdose hypothesis in relation to motor sequence learning.

Motor Sequence Learning and Dopamine in Parkinson's Disease

Both probabilistic reversal learning and category learning rely on more ventral subcortical structures, such as the nucleus accumbens and caudate nucleus, which remain relatively intact in mild to moderate Parkinson's disease. Thus, the dopamine overdose hypothesis provides a plausible framework from which to interpret the finding that patients perform these tasks better when off medication. There is a gradient of dopaminergic denervation within the caudate and putamen as well, with the more ventral and anterior portions of these structures affected later in the disease.^{41,42} The Seidler laboratory has conducted a series of experiments to investigate interactions between this gradient of denervation and anti-

parkinsonian medications working with a motor sequence learning task.^{4,43,44}

Motor sequence learning refers to the capacity to combine individual elements of action into one smooth, cohesive movement. For example, patients moving into an assisted-living facility may need to learn an action sequence to navigate their new surroundings. Sequential behavior is also important for skills like driving and playing a musical instrument, and motor sequence learning plays an important role in many physical rehabilitation protocols. In healthy individuals, it is known that the process of motor sequence learning relies on the striatum.⁴⁵⁻⁴⁷ In particular, it has been demonstrated that, early in sequence learning, the more ventral and anterior portions of the striatum (ie, associative striatum) are engaged⁴⁷; whereas, once a sequence becomes well learned, it is represented in the more dorsal and posterior aspects of the striatum (ie, sensorimotor striatum). Previous studies investigating the effects of medication on sequence learning in Parkinson's patients have yielded mixed results. Table 1 includes the study by Carbon and Eidelberg,⁴⁸ which references data from two prior studies from the same laboratory indicating that motor sequence learning was impaired by L-dopa. The initial article by Feigin and colleagues⁴⁹ indicated that L-dopa reduced sequence learning in Parkinson's patients for a subjective measure of self-reported learning. When comparing objective measures, those investigators reported nonsignificant differences in sequence learning for patients on versus off L-dopa.^{50,51} Although not significant for objective measures of learning, the direction of change was an indication that L-dopa may be impairing sequencing learning for some individuals—the opposite of the effects observed with deep brain stimulation, which improved sequencing learning.^{48,49} This line of work averaged performance across time rather than examining performance changes in the context of learning. Based on the purported inverted-U-shaped relationship between dopamine levels and performance and the established changes in associative and sensorimotor striatum with learning, it is possible that Parkinson's patients learned new motor sequences faster in the early stages of learning when they were off medication compared with their speed of learning on medication. In contrast, once sequences become well learned, patients may be able to perform them better when on medication as opposed to off medication.

In an initial experiment,⁴ 14 patients with mild to moderate Parkinson's disease and 11 healthy controls within the same age range were evaluated for their ability to learn a sequence of finger movements. Patients were tested on two separate occasions: once on their anti-parkinsonian medications, which included various combinations of medications across the participants of

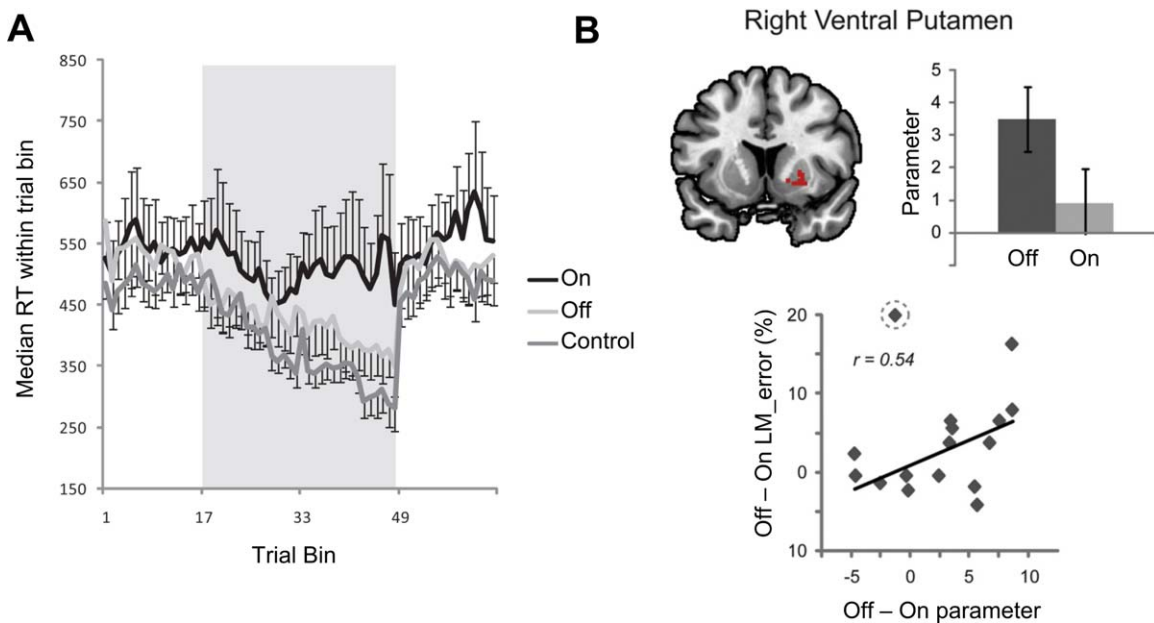


FIG. 3. (A) Patients off their medication learn new sequences of action at the same rate as healthy controls, whereas patients on medication are impaired. For trials 1 through 16 and 49 through 64, participants pressed buttons in response to randomly cued stimuli; trials 17 through 48 were sequence practice trials (from Kwak et al. 2010⁴). (B) A region in the right ventral putamen is illustrated that is more active when patients learn a motor sequence off medication than when they are on medication. This differential activation is correlated with off-medication improvements in sequence learning (from Kwak et al. 2013⁴³). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

L-dopa and/or dopamine agonists; and, on the second occasion, patients were tested in the functional off state 12 to 18 hours after taking their last dose of dopaminergic medications. Testing occurred in a counterbalanced fashion across medication states. As predicted by the dopamine overdose hypothesis, patients off medication exhibited early learning improvements that were equivalent to those of control participants for the early phase of learning (see Fig. 3A). As learning progressed, performance of the patients on medication began to catch up to that of their off-medication performance.

In a follow up study,⁴⁴ new cohorts of 17 Parkinson's patients and 21 healthy controls were studied to evaluate brain networks after being recruited during sequence learning with fMRI. Again, patients were tested across two different days. For this study, a single-blind, placebo-controlled medication design was used, and patients were given either L-dopa plus carbidopa or placebo plus carbidopa after arriving for the study in the functional off state. The order of drug versus placebo testing was counterbalanced across testing days. It was observed that L-dopa was associated with decreased recruitment of the ventral putamen during the early phase of sequence learning. Moreover, the difference in activation levels in this structure between on-medication and off-medication testing days was correlated with differences in sequence learning performance between on and off days across individual patients. That is, patients who had the largest decrease in ventral putamen activation when on medication versus off medication exhibited

the largest decrease in sequence learning abilities when on medication versus off medication, as illustrated in Figure 3B. A PET investigation by another group reported reduced brain deactivation when Parkinson's patients were learning a sequence of actions on versus off L-dopa.⁵² Taken together, these findings suggest that both task-relevant and default network activation can be negatively impacted by the administration of L-dopa in mild to moderate stage Parkinson's disease.

Another study measured dopaminergic denervation in 18 Parkinson's patients using ¹¹C-dihydrotetrabenazine PET scans.⁵³ Patients acquired new motor sequences on two testing days in a counterbalanced within-subjects design on either placebo or L-dopa plus carbidopa. The ratio of denervation in the anterior putamen versus the posterior dorsal putamen predicted the level of L-dopa-associated impairments in motor sequence learning. That is, patients who had relatively less denervation in the anterior putamen exhibited greater on-medication sequence learning decrements. Thus, individual differences in the magnitude of motor sequence learning dopamine overdose effects can be predicted by the spatial pattern of dopaminergic denervation across the striatum.

Genotype and Dopaminergic Medication Interact to Influence Cognitive Function

Another set of studies indicates that dopaminergic medication may lead to deleterious performance on specific cognitive tasks, depending on the genotype of

the patient (Fig. 1B). A common polymorphism in the catechol O-methyltransferase (COMT) gene has a strong influence on performance on tests of working memory, attention, and planning.^{54–56} COMT is an important regulator of dopamine levels, and it is believed that its activity primarily influences dopamine levels in the prefrontal cortex.^{57,58} In healthy individuals,⁵⁹ low-activity COMT genotypes are associated with improved performance on the Wisconsin Card Sorting Test, and fMRI studies have confirmed that prefrontal cortex activity is influenced by the COMT genotype. However, performance on a Tower of London cognitive test in a large cohort of 288 patients with Parkinson's disease indicated that low COMT activity was associated with impaired performance, and the effect was more pronounced in those patients who were taking dopaminergic medications.⁵⁴ Using fMRI, it was observed that patients with Parkinson's disease who were homozygous for valine (val/val; high COMT activity) performed better and had greater activity in the frontal-parietal cortex compared with patients with Parkinson's disease who were homozygous for methionine (met/met; low COMT activity).⁵⁶ The authors did not find clear fMRI differences in the putamen or caudate nucleus.

In a task of attention control,⁵⁵ a group of patients with Parkinson's disease who tested positive for the high COMT genotype (val/val) adopted a more optimal attention shifting strategy compared with a group who had Parkinson's disease with the low COMT genotype (met/met). The low-COMT genotype group failed to adopt the attention shifting strategy. The authors also observed that the fronto-parietal network typically associated with attention was less active in the low-COMT genotype group compared with the high-COMT genotype group. There were no differences observed in the putamen or caudate nucleus.

Another gene that may interact with medication effects in Parkinson's patients is the DRD2 gene, which codes for dopamine D2 receptors in the striatum. A recent study⁴³ evaluated whether a particular DRD2 polymorphism (reference single nucleotide polymorphism rs1076560; G > T) was associated with the on-medication versus off-medication sequence learning effects that were previously reported in patients with Parkinson's disease. DRD2 T allele carriers of this polymorphism have reduced D2S expression (short isoform of the D2 receptor) compared with G allele carriers, who have higher D2 receptor availability. It was predicted that patients with Parkinson's disease who were minor T allele carriers would exhibit a greater benefit of L-dopa on early stage sequence learning. This hypothesis was evaluated in a behavioral study with 45 patients who had Parkinson's disease, including 1 patient who had the TT genotype (grouped together with GT patients), 10 who had the

GT genotype, and 34 who had the GG genotype. Patients were tested on two days according to a single-blind, placebo-controlled design. L-Dopa improved early sequence learning over the level of placebo pill only for the TT and GT patients, whereas GG patients did not learn better on L-dopa. In contrast, L-dopa improved performance on the grooved pegboard test, a simple motor execution test that should rely predominately on the sensorimotor striatum, for all patients regardless of genotype.

These findings suggest that endogenous dopamine-modulating factors and exogenous dopamine interact to result in dopamine overdose effects in patients with Parkinson's disease. That is, disease, genetics, and medication status can all influence an individual's location on the inverted-U-shaped function relating dopamine to performance. Moreover, these studies suggest that the viewpoint that the dopamine overdose hypothesis occurs only because of the ventral and dorsal striatum is too narrow and that other factors, including the prefrontal and parietal cortices, also play a role. In addition, these findings further demonstrate that it is important to consider the genotype of the patient when interpreting the effects of dopamine on cognitive functions.

Clinical Implications and Conclusions

The clear consensus of a large body of literature is that dopaminergic therapy can improve cognitive functions in some patients but makes them worse in others (for an in-depth review, see Cools⁵). The dopamine overdose hypothesis provides a conceptual framework to better understand patients' individual cognitive responses to dopaminergic pharmacotherapy in Parkinson's disease. The purported inverted-U-shaped relationship between dopamine levels and performance is complex and includes many contributory factors. As discussed in this review, the regional striatal topography of nigrostriatal denervation is a critical factor, as supported by fMRI and dopaminergic PET studies. Second, a patient's individual genotype will determine the relative baseline position on this inverted-U curve. Third, dopaminergic pharmacotherapy and individual gene polymorphisms, such as COMT, can also affect the mesolimbic and prefrontal cortical dopaminergic functions in a comparable inverted-U dose-response relationship, similar to what has been proposed for the striatum. Therefore, currently, a patient's individual cognitive response to dopaminergic pharmacotherapy cannot be predicted by a simple formula. However, several clinical implications may be inferred based on the available literature and experience in clinical movement disorders practice.

Striatal dopamine overdose effects have been identified for probabilistic reversal learning and motor sequence learning tasks. Implications for instrumental activities of daily living are clearly apparent. Current

technological advances in society will affect individuals who are living with Parkinson's disease. Exposure to new electronic gadgets for daily communication, financial management, bill paying, receiving health care, and even medication management are essentially unavoidable and will challenge patients' learning skill abilities. This will include sequential motor behaviors like fine and precise finger movements when using these new gadgets. Navigation in new environments, whether it is driving a car in new surroundings or moving into a new place to live, will be equally challenging.

A key predictor for adverse cognitive learning effects of dopaminergic therapy is the presence of early stage and/or mild severity of disease, in which overdose effects of dopaminergic medications are predicted to be most prominent. Practical implications of the dopamine overdose hypothesis in the management of the individual patient with Parkinson's disease will depend first on the identification of a dopaminergic dose-related cognitive or behavioral problem. If such a problem is present, then a simple pointer will be to implement a new motor learning challenge, such as using a new device, when in a relative medication *off* state (assuming preservation of critical motor abilities). Apart from learning new motor behaviors in an *off* state, a rational pharmacological therapy approach based on the principle of the lowest effective dose also may help to prevent or ameliorate dopaminergic *on* overdose cognitive adverse effects. Most of all, clinicians need to consider a broader range of symptoms and individual patient priorities in adjusting medication dosages by suggesting medication strategies that strike a better balance between motor and cognitive symptoms.⁶⁰ It is also important to consider premorbid personality and psychiatric history when making clinical decisions. Future clinical treatment algorithms may include information about specific gene polymorphisms that affect the dopamine system (so-called "personalized medicine"). It may also be prudent to consider exercise as an adjunct to dopamine therapy to reduce motor symptoms to also minimize the overdose, because recent studies have shown promise using balance training over six months⁶¹ and progressive resistance exercise over two years.⁶²

Cognitive functions, including reward-based learning, have been the major focus of research of the dopamine overdose hypothesis.⁶⁰ However, much less is known about the neurobehavioral correlates of these impairments and how they affect the instrumental activities of daily living. Dopamine dysregulation syndrome is a dysfunction of the reward system in patients with Parkinson's disease who are on dopaminergic drugs: particularly dopamine agonists. Patients with dopamine dysregulation syndrome exhibit evidence of impulse control disorders.⁶³ Further research is needed to determine whether an excess of exogenous dopamine release within the anteroventral

striatum and related cortical projections may be a mechanistic factor underlying impulsive and/or risk-taking behaviors in susceptible patients. ■

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