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

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Introduction

Levodopa (3,4-dihydroxy-L-phenylalanine) and various D\textsubscript{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\textsubscript{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\textsubscript{2} dopamine agonists activate D\textsubscript{2} dopamine receptors, whereas antiparkinsonian dopamine agonists directly stimulate D\textsubscript{2} receptors in the BG and PFC (although some have weak affinity to D\textsubscript{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.

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\textsubscript{1} and D\textsubscript{2} dopamine receptors, whereas antiparkinsonian dopamine agonists directly stimulate D\textsubscript{2} receptors in the BG and PFC (although some have weak affinity to D\textsubscript{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.

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Dopamine D₁ and D₂ 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 D₂ receptors. However, levodopa is a dopamine precursor, taken up by dopamine cells, and converted into dopamine; thus, it acts on both D₁ and D₂ 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 D₁ and D₂ receptors, and then discuss neuropsychological studies on the effects of levodopa and D₂ 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 D₁ receptors [4–6], whereas tonic dopamine activates D₂ receptors [3, 5, 7].

Because both levodopa and dopamine agonists activate D₂ receptors, we assume that levodopa and dopamine agonists restore tonic activation of dopamine neurons, and thus activate D₂ receptors (although possibly to different degrees). However, we assume that levodopa, but not D₂ 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 D₁ and D₂ 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 D₁ receptors in the BG, is essential for learning. While large numbers of D₁ receptors are found in the BG direct pathway, D₂ receptors are more abundant in the BG indirect pathway [11]. Thus, activating D₂ 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 D₁ receptors in the PFC are important for the maintenance of information in working memory (table 2) [13, 15–17], while PFC D₂ 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 D₁ receptors in the PFC, as suggested by theoretical [16] and experimental [19] studies.

The most commonly addressed areas to investigate effects of levodopa and D₂ 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) D₂ 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 D₁ 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 D₁ receptors in the PFC.

### Table 2. Physiological and behavioral differences between phasic and tonic dopamine

<table>
<thead>
<tr>
<th>Receptor type</th>
<th>Brain region</th>
<th>PFC</th>
</tr>
</thead>
<tbody>
<tr>
<td>D₁</td>
<td>learning</td>
<td>maintenance of working memory</td>
</tr>
<tr>
<td>D₂</td>
<td>initiation of motor responses</td>
<td>motor responses based on working memory</td>
</tr>
</tbody>
</table>

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

### Table 2. Functional significance of D₁ and D₂ receptors in the striatum and PFC

<table>
<thead>
<tr>
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<td>initiation of motor responses</td>
<td>motor responses based on working memory</td>
</tr>
</tbody>
</table>

### 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.
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 D1 and D2 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 D1 receptors in the BG are key for motor learning, while D2 receptors play a role in the initiation of motor responses. In the PFC, D1 receptors are required for the maintenance of information in working memory [15, 59]. Prefrontal D2 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 3. Summary of experimental studies investigating the effects of D2 dopamine agents on learning tasks in animals and humans

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

DA = Dopamine agonist; L-DOPA = levodopa.
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 D2 agonists do not affect working memory. In our model, this is because dopamine agonists target D2 receptors, and thus do not enhance maintenance of information in working memory, a process mediated by D1 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 D2 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 D2 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-

Table 4. Summary of experimental studies investigating the effects of levodopa (L-DOPA) and D2 dopamine agents on working memory

<table>
<thead>
<tr>
<th>Study</th>
<th>Subject group</th>
<th>Medication used</th>
<th>Behavioral effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Working memory</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>1-L-DOPA monotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lange et al. [42] (1992)</td>
<td>PD patients</td>
<td>L-DOPA</td>
<td>enhancement</td>
</tr>
<tr>
<td>Lewis et al. [43] (2005)</td>
<td>PD patients</td>
<td>L-DOPA</td>
<td>enhancement</td>
</tr>
<tr>
<td>Beato et al. [44] (2008)</td>
<td>PD patients</td>
<td>L-DOPA</td>
<td>enhancement</td>
</tr>
<tr>
<td>Marini et al. [45] (2003)</td>
<td>PD patients</td>
<td>L-DOPA</td>
<td>enhancement</td>
</tr>
<tr>
<td>Brusa et al. [46] (2003)</td>
<td>PD patients</td>
<td>L-DOPA</td>
<td>–</td>
</tr>
<tr>
<td>Costa et al. [47] (2003)</td>
<td>PD patients</td>
<td>L-DOPA</td>
<td>enhancement</td>
</tr>
<tr>
<td>Pascual-Sedano et al. [48] (2008)</td>
<td>PD patients</td>
<td>L-DOPA</td>
<td>enhancement</td>
</tr>
<tr>
<td>Fernandez-Ruiz et al. [49] (1999)</td>
<td>parkinsonian monkeys</td>
<td>L-DOPA</td>
<td>enhancement</td>
</tr>
<tr>
<td>Dopamine agonist monotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Costa et al. [47] (2003)</td>
<td>PD patients</td>
<td>apomorphine</td>
<td>–</td>
</tr>
<tr>
<td>Brusa et al. [46] (2003)</td>
<td>PD patients</td>
<td>pramipexole</td>
<td>impairment</td>
</tr>
<tr>
<td>Brusa et al. [50] (2005)</td>
<td>PD patients</td>
<td>pergolide</td>
<td>enhancement</td>
</tr>
<tr>
<td>McDowell et al. [51] (1998)</td>
<td>brain injury</td>
<td>bromocriptine</td>
<td>–</td>
</tr>
</tbody>
</table>

Unlike pramipexole (which has a high affinity to D2 receptors), most studies that found that levodopa-induced dopamine and pergolide (which has a high affinity to both D1 and D2 receptors) enhance working memory performance. – = No effect.
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 (Sultzter 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 D2 dopamine agonists on cognition. Here, we have assumed that levodopa only activates D1 receptors, while both levodopa and dopamine agonists activate D2 dopamine receptors (fig. 1). Because D1-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 D1- and D2-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 D2-expressing neurons send inhibitory input to D1-expressing cells. They have found that an efferent connection from striatal D1 to D2 neurons is almost nonexistent, as we assume in our model. This unidirectional connectivity between D1- and D2-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 [18]: activation of D2-expressing neurons in the PFC inhibits D1 cells [15]. A more plausible mechanism is that tonic dopamine stimulates inhibitory D2 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 D2 to D1 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 (D2 receptors inhibit D1 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 D2 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 D2 receptors in the PFC in working memory [67, 68], arguing for a more important role for PFC D1 receptors. Experimental data, however, point to an essential role for both D1 and D2 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 D1 and D2 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 D1 and D2 receptors are based on findings of previous experimental and modeling studies. For example, several studies in animals found that D2 antagonists enhance learning [71–74]. Similarly, Eyny and Horvitz [74] found that D2 antagonists enhance learning in rats, whereas D1 antagonists impair learning. The findings that D2 antagonists enhance learning are perhaps puzzling. Our model suggests that D2 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 D1 agonists improve stimulus-response learning. In our modeling framework, D1 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 D1 antagonists block learning in the striatum, while D2 antagonists enhance learning [77]. Gurden et al. [78] also found that D1 (but not D2) 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 D1 and D2 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., D₂ and D₃) equally within our current model. This is an oversimplification because research has shown that drugs targeting D₃ receptors have some dissociable effects on behavior compared to drugs targeting D₂ 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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