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A model of reversal learning and working memory in medicated and unmedicated patients with Parkinson's disease

Ahmed A. Moustafa [a,b,*], Mohammed M. Herzallah [c,d], Mark A. Gluck [c]

[a] School of Social Sciences and Psychology & Marcs Institute for Brain and Behaviour, University of Western Sydney, Sydney, New South Wales, Australia
[b] Department of Veterans Affairs, New Jersey Health Care System, East Orange, NJ, USA
[c] Center for Molecular and Behavioral Neuroscience, Rutgers University—Newark, 197 University Avenue, Newark, NJ 07102, USA
[d] Al-Quds Cognitive Neuroscience Lab, Faculty of Medicine, Al-Quds University, Abu Dis, Palestine

HIGHLIGHTS

- Neural network model of cognition in Parkinson's disease.
- Model presents a framework to explain results from three different cognitive tasks.
- The focus of the model is learning and reversal, as well as working memory.
- Model explains functional interactions between basal ganglia and prefrontal cortex.
- Model suggests a new approach to remediate Parkinson's deficits in learning.

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ABSTRACT

We present a neural network model of cognition in medicated and unmedicated patients with Parkinson's disease (PD) in various learning and memory tasks. The model extends our prior models of the basal ganglia and PD with further modeling of the role of prefrontal cortex (PFC) dopamine in stimulus–response learning, reversal, and working memory. In our model, PD is associated with decreased dopamine levels in the basal ganglia and PFC, whereas dopamine medications increase dopamine levels in both brain structures. Simulation results suggest that dopamine medications impair stimulus–response learning in agreement with experimental data (Breitenstein et al., 2006; Gotham, Brown, & Marsden, 1988). We show how decreased dopamine levels in the PFC in unmedicated PD patients are associated with impaired working memory performance, as seen experimentally (Costa et al., 2003; Lange et al., 1992; Moustafa, Sherman, & Frank, 2008; Owen, Sahakian, Hodges, Summers, & Polkey, 1995). Further, our model simulations illustrate how increases in tonic dopamine levels in the PFC due to dopamine medications will enhance working memory, in accord with previous modeling and experimental results (Cohen, Braver, & Brown, 2002; Durstewitz, Seamans, & Sejnowski, 2000; Wang, Vijayraghavan, & Goldman-Rakic, 2004). The model is also consistent with data reported in Cools, Barker, Sahakian, and Robbins (2001), who showed that dopamine medications impair reversal learning. In addition, our model shows that extended training of the reversal phase leads to enhanced reversal performance in medicated PD patients, which is a new, and as yet untested, prediction of the model. Overall, our model provides a unified account for performance in various behavioral tasks using common computational principles.

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1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder associated with reduced dopamine levels in the basal ganglia, particularly the dorsal striatum (Kish, Shannak, & Hornykiewicz, 1988; Rinne et al., 2000). In addition to motor dysfunction, PD patients show impairment performing various cognitive tasks such as planning (Dagher, Owen, Boecker, & Brooks, 1999; Owen, Doyon, Dagher, Sadikot, & Evans, 1998) and cognitive set shifting (Hayes, Davidson, Keele, & Rafal, 1998). PD patients also show impairment performing various working memory tasks, including delayed-response tasks (Partiot et al., 1996), the Wisconsin Card Sorting Task (Amos, 2000; Cooper, Sagar, Jordan, Harvey, & Sullivan, 1991; Lees & Smith, 1983; Owen et al., 1993; Pickett, Kuniholm, Protopapas, Friedman, & Lieberman, 1998), object and spatial span tasks

* Corresponding author at: School of Social Sciences and Psychology & Marcs Institute for Brain and Behaviour, University of Western Sydney, Sydney, New South Wales, Australia.
E-mail addresses: ahmedhalimo@gmail.com, a.moustafa@uws.edu.au (A.A. Moustafa).

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(Gabrieli, Singh, Stebbins, & Goetz, 1996), as well as other working memory tasks (Lewis et al., 2003).

In reversal learning, subjects initially learn to associate different stimuli with different responses (stimulus–response learning), and subsequently learn to associate the same stimuli with the opposite responses (i.e., reversal). Experimental studies show that dopamine agonists, such as pergolide and bromocriptine, impair reversal learning in monkeys, PD patients, and healthy subjects (Cools et al., 2001; Jentsch, Olausson, De La Garza, & Taylor, 2002; Swainson et al., 2000). Cools et al. (2001) found that medicated PD patients on dopamine agonists are more impaired at reversal learning than unmedicated patients (also see Swainson et al., 2000). Jentsch et al. (2002) found that the administration of cocaine (dopamine reuptake inhibitor) to monkeys lead to impairment in reversal learning. Similar results were found with administering quinpirole (dopamine agonist) to rats (Boulougouris, Castane, & Robbins, 2009). It is hypothesized that dopamine medications might overdose the PFC and thus impair performance in reversal tasks (Cools et al., 2001). In line with this hypothesis, we show how simulating this dopamine 'overdosing' of the PFC due to the administration of dopaminergic medications impairs reversal performance in our model (see Experimental Procedures section for more details).

Dopamine medications (both precursors and agonists) are used to treat motor symptoms of PD (tremor, rigidity, and bradykinesia), but can either enhance or impair cognitive function (Cools et al., 2001; Feigin et al., 2003; Frank, Seeberger, & O'Reilly R, 2004; Swainson et al., 2000). For example, various studies show that dopamine medications impair stimulus–response learning in both PD patients (Gotham, Brown, & Marsden, 1988; Jahanshahi, Wilkinson, Gahir, Dharmaindra, & Lagnado, 2010) and healthy subjects (Breitenstein et al., 2006; Pizzagalli et al., 2007). In stimulus–response learning tasks, subjects learn to associate the presentation of different stimuli with different responses based on corrective feedback. Unlike stimulus–response learning, many studies found that dopamine medications enhance working memory performance in PD patients as well as in Parkinsonian animal models (Costa et al., 2003; Lange et al., 1992; Lewis, Slabosz, Robbins, Barker, & Owen, 2005; Owen, Sahakian, Hodges, Summers, & Polkey, 1995). It was also found that dopamine agonists enhance working memory performance in healthy subjects (Mehta, Swainson, Ogilvie, Sahakian, & Robbins, 2001).

The model we present here builds on our earlier models (Moustafa & Gluck, 2011; Moustafa & Maida, 2007), and collectively addresses how PD and dopamine medications affect performance in stimulus–response learning, reversal, and working memory tasks. This and similar adaptive network, or "connectionist" theories of human learning are reminiscent of statistical learning theories, the most influential of which is *Stimulus Sampling Theory*, developed by the late W. K. Estes and colleagues (Estes, 1961). Building on Estes' work, we are able to extend "connectionist" theories to account for broader conception of associations among representation of events, thereby addressing the shortcomings of earlier approaches in this domain.

1.1. Stimulus–response learning, reversal learning and working memory in PD

Experimental studies suggest that the basal ganglia subserve stimulus–response learning. Graybiel (1998) noted that stimulus–response learning is (a) acquired very slowly and (b) usually occurs without awareness, processes that have been ascribed to the basal ganglia function (Frank). Lesion and physiological studies also confirm the key role of the basal ganglia in stimulus–response learning. For example, Packard, Hirsh, and White (1989) found that lesioning the basal ganglia in rats impairs stimulus–response learning, but not long-term memory tasks. Jog, Kubota, Connolly, Hillegaart, and Graybiel (1999) recorded striatal neurons' patterns of activity while rats performed a stimulus–response task, namely a T-maze task. Jog et al. found that the activation of striatal neurons increased while learning different motor plans in this task. These changes in firing patterns were associated with better performance, mainly a decrease in movement time and an increase in performance accuracy. The model we present here assumes that the basal ganglia are key for stimulus–response learning, consistent with several experimental and modeling studies.

Various studies show that the basal ganglia and PFC are important for reversal learning (Clatworthy et al., 2009; Cools et al., 2001; Cools & Frank, 2009). For example, Pasupathy and Miller (2005) recorded from both the striatum and PFC while a monkey performed a reversal task. They found that, within a trial, the striatum increased its activation before that of PFC neurons, suggesting that both basal ganglia and PFC are engaged during reversal learning processes.

Working memory involves maintenance of information over a short-time period as well as initiation of motor responses based on active information. Like reversal learning, both the basal ganglia and PFC participate in working memory performance (Apicella, Scarnati, Ljungberg, & Schultz, 1992; Collins, Wilkinson, Everitt, Robbins, & Roberts, 2000; Gabrieli, 1995; Gabrieli et al., 1996; Kawagoe, Takikawa, & Hikosaka, 1998; Lawrence, 2000; Owen et al., 1998). For example, Gabrieli et al. (1996) tested working memory capacity in PD patients and healthy controls using verbal and arithmetic span tasks. In the verbal span task, subjects were instructed to remember the last word of a given sentence. Subjects were given up to seven sentences, and were instructed to report the words in the same order they were presented. However, the arithmetic span task was very similar to the verbal span task, with the only difference being that subjects had to remember digits instead of words. Gabrieli et al. found that PD patients showed a lower working memory span than that of normal subjects. PD patients reported a maximum of about three or four items in both tasks, while the control subjects reported all the items, suggesting a role for the basal ganglia for working memory performance. Furthermore, several studies reported that the PFC is important for maintenance of information in working memory (Goldman-Rakic, 1995; Sawaguchi & Iba, 2001). Sawaguchi and Iba found that inactivating PFC with muscimol interferes with performing working memory tasks, while it had a minor effect on performing a stimulus–response control task. Also, Sawaguchi and Iba (2001) reported that increasing the length of the delay interval, from 2 to 4 s, was associated with an increase in the number of errors in the working memory task. This finding provides converging evidence that the PFC is key in the active maintenance of information in working memory. Based on these studies, the model we present here assumes that the BG and PFC play different but integrative roles in working memory, such that the PFC is important for maintenance of information, whereas the basal ganglia are key for working memory-guided motor responses (i.e., the initiation of motor responses, based on working memory information maintained in the PFC (for similar ideas, see O'Reilly & Frank, 2006).

1.2. Model

We briefly describe our model in Fig. 1. The model architecture and learning equations are described in detail in the *Experimental Procedures* section below. The model attempts to explain how PD and dopamine medications either impair or enhance cognitive performance in stimulus–response and reversal learning as well as working memory tasks. Similar to our earlier models (Moustafa & Gluck, 2011; Moustafa & Maida, 2007), we use an extended actor–critic model to address these questions.

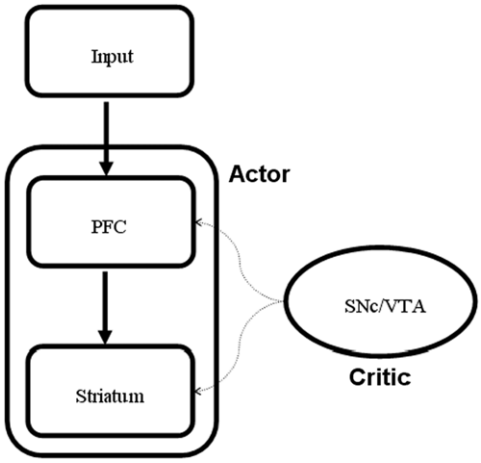


Fig. 1. The basal ganglia–PFC model showing relevant brain structures. The model has four modules: Input, PFC, motor response, and dopamine module. The critic corresponds to dopamine neurons whereas the actor corresponds to the prefrontal–striatal system. Learning (i.e., synaptic modification) takes place in both the PFC and Striatum modules. Learning is modulated by dopamine phasic responses projected from the critic. The Input layer sends topographic projections to the PFC layer. The PFC layer is fully connected to the Striatum (Motor) layer (i.e., every PFC unit is connected to every striatal unit). Activation of a unit in the Input layer represents input received from the environment; activation of a unit in the PFC layer represents attended-to stimuli; activation of a unit in the Striatum module represents a selected motor response. Dotted lines represent dopaminergic modulatory effects. Abbreviations: PFC, prefrontal cortex; SNc, substantia nigra pars compacta; VTA, ventral tegmental area.

Table 1
Simulation of the effects of Parkinson's disease and dopamine medications. Parkinson's disease is associated with decreased phasic and tonic dopamine levels in the basal ganglia and prefrontal cortex. Dopamine medications increase tonic dopamine levels but further decrease phasic signaling in the basal ganglia and prefrontal cortex. See Experimental Procedures section for description of all parameters. DA = Dopamine.

	Tonic DA	Phasic DA
Parkinson's Disease (PD)	↓	↓
Dopamine (DA) medication	↑	⇓

Actor–critic models are systems-level models concerned with modeling reinforcement-learning-based motor actions (i.e., learning to make motor actions that are followed by rewards). We assume that PFC is important for stimulus selection and maintenance of information in working memory, whereas the basal ganglia are key for stimulus–response learning. In the model, PD is associated with reduced dopamine levels in both the basal ganglia and PFC (see for example Rinne et al., 2000). Dopamine medications increase dopamine levels in both brain structures (see Table 1 for a summary).

In our model, we also simulate functional roles for phasic and tonic dopamine. Phasic mode is fast-acting and spans milliseconds, while tonic mode is long-acting and can span minutes. Experimental studies have shown that phasic and tonic dopamine activate different dopamine receptors (Ballion et al., 2009; also see Dreyer, Herrik, Berg, & Hounsgaard, 2010; Grace, 2008; Hauber, 2010; Sammut et al., 2006). Interestingly, Grace and colleagues Grace (2008) suggest that phasic dopamine is essential for synaptic modification (and thus learning), while tonic dopamine is key for the activation of postsynaptic neurons. Accordingly, we simulate changes in phasic dopamine signaling by changing the learning rate values according to disease and medication state (see *Learning algorithm* for more details. We simulate increase in tonic dopamine levels by increasing the gain parameter value, as previously proposed by Cohen and Servan-Schreiber (1992) and Servan-Schreiber, Printz, and Cohen (1990).

1.3. Experimental procedures

Here, we describe the model architecture and the learning algorithm used in the simulation results presented in this paper. The model architecture and learning rules are the same as in Moustafa and Gluck (2011), except that the model used here incorporates a working memory mechanism in the PFC module to simulate performance in various reversal and working memory tasks.

1.4. Model architecture

The model takes the form of an actor–critic architecture, in which the critic is important for reward and feedback-based learning and the actor is key for stimulus and action selection learning and working memory (Fig. 1). The critic and actor influence each other in that the critic sends a teaching signal to the actor to strengthen or weaken stimulus and action selection learning. The critic is not informed about what action the actor has selected, but it is informed about whether the action made had rewarding consequences. The model is trained using the temporal difference (TD) model, which we describe in the learning algorithm section below.

The model has four modules: Input, PFC, motor response, and dopamine module (see Fig. 1). The PFC layer is fully connected to the Motor response layer (Striatum module). Each node in the Input module represents a cue presented to the network. The Input and PFC modules have the same number of nodes ($n = 20$). The motor module has three nodes, each representing a different motor response. Input patterns presented to the network activate their corresponding nodes in the Input module. The Input module sends topographic projections to the PFC layer (in line with work done by Goldman-Rakic et al., suggesting that there is topographic representation of working memory in the PFC, which is maintained by learning (Goldman-Rakic, 1995). In our model, we simulate basic aspects of cortical anatomy, and assume perceptual input is projected to the prefrontal cortex via topographic connections. Here, we use a winner-take-all network to simulate inhibitory connectivity among PFC neurons. For simplicity, in the current simulations, we allow only one PFC node to be active at each time step. Here, we assume that competitive dynamics among PFC neurons is the brain mechanism underlying limited working memory processes. We also assume that negative feedback decreases the activity of most active PFC neurons, as simulated in the Amos model (Amos, 2000). As mentioned above, an increase in tonic dopamine levels is modeled as an increase in activity and competition among PFC neurons, which in turn enhance the selection of different stimuli following negative feedback.

The model has four parameters that are manipulated depending on the simulated subjects' disease status and dopaminergic medications. These parameters are two learning rate parameters (one each for the BG and PFC modules) and two gain parameters (BG and PFC modules).

Learning rate parameters simulate changes in phasic dopamine signaling (for experimental support, see Reynolds, Hyland, & Wickens, 2001; Tsai et al., 2009), whereas gain parameters simulate changes in tonic dopamine levels in the corresponding simulated brain structure (Cohen & Servan-Schreiber, 1992; Servan-Schreiber et al., 1990). We simulate PD by decreasing learning rate and gain values in the basal ganglia and PFC modules. In addition, we simulate the effects of dopaminergic medications by increasing gain values while concurrently decreasing learning rate values, beyond those used for healthy normals (Table 1).

The simulated striatum in the proposed model learns to map input stimuli to responses (for similar ideas, see Guthrie, Myers, & Gluck, 2009; Suri & Schultz, 1998). Like the PFC module, we use a winner-take-all network to simulate inhibitory connectivity among simulated BG neurons. At the cognitive level, the winning

node represents the selected motor response (for similar ideas, see Guthrie et al., 2009; Suri & Schultz, 1999). Unlike most existing basal ganglia models (Ashby, Ell, Valentin, & Casale, 2005; Frank, 2005; Houk, 1995a; Suri & Schultz, 1999), the basal ganglia in our model learns to map representations of selected stimuli and working memory information to motor responses.

Based on experimental findings (Carey, Pinheiro-Carrera, Dai, Tomaz, & Huston, 1995), dopaminergic medications increase dopamine levels in the PFC. Specifically, we simulate increase in PFC tonic dopamine levels by increasing the gain value of the sigmoidal activation function, as previously proposed by various computational models (Amos, 2000; Cohen, Aston-Jones, & Gilzenrat, 2004; Cohen & Servan-Schreiber, 1992; Servan-Schreiber, Cohen, & Steingard, 1996).

1.5. Learning algorithm

We assume that learning in the PFC and basal ganglia modules relies on phasic dopamine signals projected from the midbrain (for similar ideas, see Suri & Schultz, 1999). In this model, phasic dopamine signals are key for both stimulus selection and stimulus–response learning. The model is trained using the TD algorithm, described next, which simulates various characteristics of phasic dopamine firing (Schultz, Dayan, & Montague, 1997; Sutton & Barto, 1987, 1990). Let $TD(t)$ be the temporal difference error signal at time t (also known as the effective reinforcement); $R(t)$ be the reward presented at time t (reward is 1 when reward is presented after correct feedback and is 0 otherwise); $P(t)$ be the reward prediction at time t; γ be the discount factor (which determines how future reward affect reward predictions; is set to 0.99 in all simulation runs presented here). The TD error is computed as follows:

$$TD(t) = R(t) + \gamma P(t) - P(t-1) \tag{1}$$

At time step t, TD is positive if an unpredicted reward is received, zero if reward is predicted, and negative is predicted reward is omitted.

Let w_i be the weight connecting node i to the critic node; n be the number of Input nodes; and x_i be activation of input nodes (which take binary (0, 1) values). Reward prediction $P(t)$is computed by the critic node as follows:

$$P(t) = \sum_{i=1}^{n} w_i(t)x_i(t) \tag{2}$$

Now, we describe the equations of the actor module. Let w_{ji} be the weight connecting node i to node j; $\delta_{ji}(t)$ be the Gaussian noise associated with the weight w_{ji} (with zero mean and standard deviation of 0.025, also see Moustafa & Maida, 2007). Similar to weights in the Actor, we initialized critic weights using Gaussian noise with zero mean and standard deviation of 0.025. In our model, the Critic refines its prediction learning over time and the refined policy is implemented by changes in the incoming weights. The rule to describe these weight changes is given below. Thus, the change in Critic weight at time step t is proportional to the product of the TD error at that time step and the input value to the weight at that time step. It is also important to provide parameter values (especially those representing changes in dopamine levels), and make clear whether these changed across simulations.

All weights are perturbed using Gaussian noise, which is included to induce exploration in the system. Let u_{ji} be the perturbed weight connecting node i to node j. Perturbed weight values are computed as follows:

$$u_{ji}(t) = w_{ji}(t) + \delta_{ji}(t). \tag{3}$$

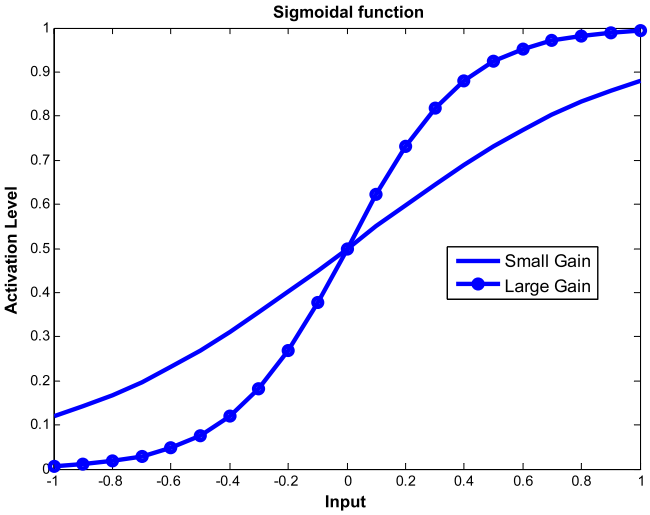


Fig. 2. An example showing the sigmoidal activation function with small and large gain values. Tonic dopamine effects in a simulated brain area (either the basal ganglia or PFC module) in the model are simulated by increasing gain value in the sigmoidal activation function representing that area, as initially proposed by Cohen and Servan-Schreiber (1992).

Activations of all nodes in the network are computed using a sigmoidal function (Fig. 2):

$$f(x) = \frac{1}{1 + e^{-G_m x}} \tag{4}$$

where G_m is the gain parameter (G_{pfc} for PFC and G_{bg} for basal ganglia module). Let n be the number of Input (or prefrontal) nodes. The input nodes take binary (0, 1) values. The activation of a node j is computed as:

$$A_j(t) = f\left(\sum_{i=1}^{n} u_{ji}(t)x_i(t)\right). \tag{5}$$

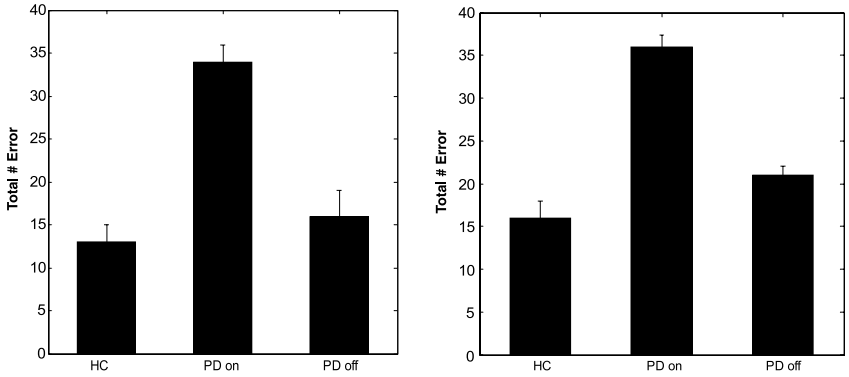
In the model, a winner-take all network computes the node with the highest activation in both the PFC and BG modules. We assume that winner-take-all competition among BG neurons is assumed to be the mechanism underlying the choice of motor responses. Similarly, we assume that winner-take-all competition among PFC neurons is the mechanism underlying stimulus selection processes.

$$A_j^p = \begin{cases} 1 & \text{if } A_j > \beta \,\&\, A_j > A_i \text{ for all } i \neq j \\ 0 & \text{otherwise} \end{cases} \tag{6}$$

where β is a threshold; A_j is the activation of node j; $A_j^p$is the activation of node j resulting from winner-take all computations (for similar ideas, see Barto, 1995; Berns & Sejnowski, 1995; Schultz et al., 1997; Suri & Schultz, 1999).

We simulate working memory as in our earlier models (Moustafa & Maida, 2007; see Frank, Loughry, & O'Reilly, 2001 for similar ideas). We assume that each PFC node can maintain a different stimulus in working memory. A PFC node maintains a cue in working memory if input passed the threshold (β). Maintained information in working memory in PFC influences motor learning in the BG module (see Fig. 1).

Learning in the model is based on the three-factor rule of learning—also known as the dopamine-based Hebbian learning rule (for similar ideas, see Guthrie et al., 2009). According to this rule, the phasic dopamine signal is essential for strengthening weights linking active nodes. It is also important for weakening weights linking an active node and another inactive node. Numerous computational models also incorporate this learning rule (Braver & Cohen, 2000; Guthrie et al., 2009; Suri & Schultz, 1999).



(a) Experiment. (b) Model.

Fig. 3. PD performance in the stimulus–response learning task. (a) Experimental results from Shohamy et al. (2006). (b) Modeling results.

Table 2
Parameter values used in the simulations, as found by exhaustive search for best-fit values for all subjects. Abbreviations: LR, learning rate; G, gain; BG, basal ganglia; PFC, prefrontal cortex. See Methods for description of all parameters.

Parameter	LR_{BG}	G_{BG}	LR_{PFC}	G_{PFC}
HC	0.15	1.2	0.09	1.4
PD off	0.08	0.07	0.04	0.07
PD on	0.06	1.8	0.02	1.99

Let LR_m be the learning rate. There are two learning rate parameters in the model, one for the PFC (stimulus selection) module and one for the basal ganglia (motor) response module. Let x_i represents the activation level of the presynaptic node. The weight update rule is,

$$w_{ji}(t+1) = w_{ji}(t) + LR_m TD(t) x_i(t) A_j^p. \quad (7)$$

In our model, we provide a good fit to experimental data in 3 different tasks and 3 different subject groups using a simplified model with 4 free parameters (learning rate and gain in basal ganglia and prefrontal cortex modules). We search the 4-dimensional space (for all 4 free parameters as mentioned above) to find best-fit parameter values (for similar methodology, see Frank, Moustafa, Haughey, Curran, & Hutchison, 2007). The 4 free parameters are learning rate in basal ganglia and prefrontal modules along with gain in these two modules. For each subject group, we searched the 4-dimensional space for best-fit parameter values that capture average performance in all 3 tasks (see Table 2). Best-fit parameter values are the ones closest to the average performance, using ordinary distance function.

2. Results

Below, we show how computational principles described above explain PD patients' behavioral performance in stimulus–response learning, working memory, and reversal tasks.

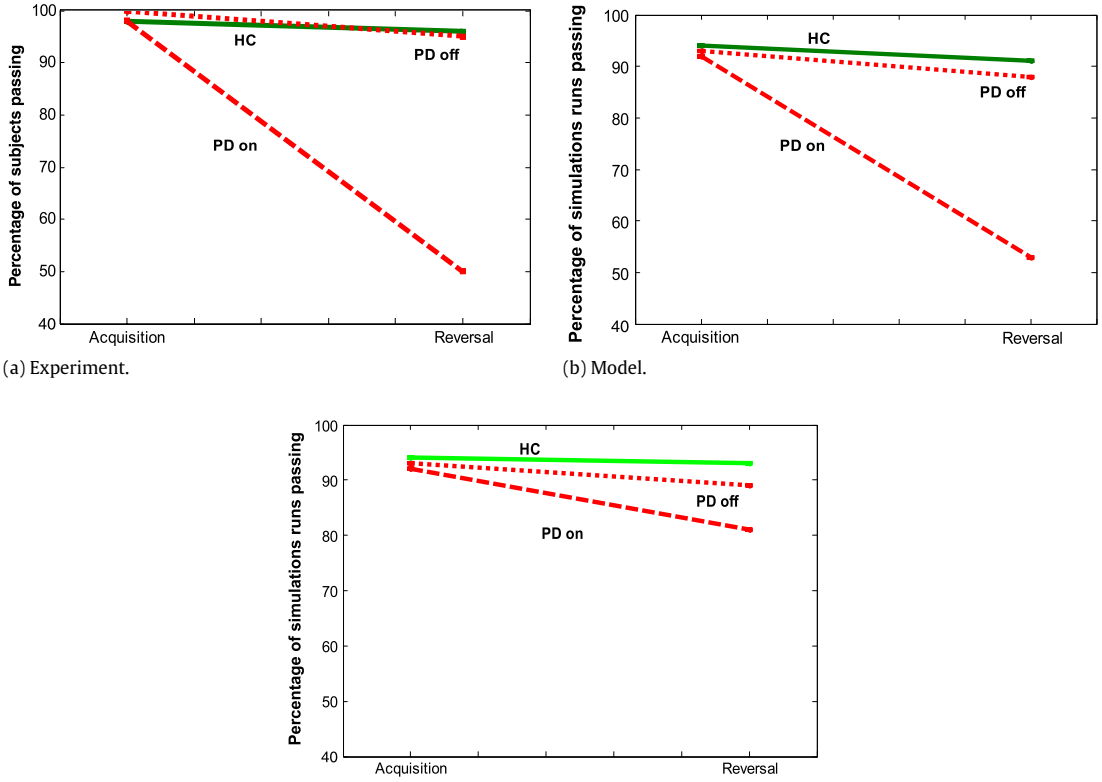
2.1. Simulation 1: dopamine medications impair stimulus–response and probabilistic reversal learning

In the stimulus–response learning task, the model is presented with two stimuli. On each trial, the model learns to predict which of two stimuli is associated with reward. The model is presented with eight different pairs of stimuli (trial types). The task design here is similar to the task used by Shohamy, Myers, Geghman, Sage, and Gluck (2006). On each trial, only one stimulus is associated with reward presentation. The number of trials in this task is 96 trials.

Simulation results shown in Fig. 3 imply that medicated PD patients should be more impaired at learning stimulus–response tasks than unmedicated patients, which is in agreement with the findings of Shohamy et al. and other results (Breitenstein et al., 2006; Jentsch et al., 2002; Shohamy et al., 2006). Decreasing the learning rate value (which simulates medicated PD patients, see Table 1) slows down stimulus–response learning, and thus explains medicated patients' impaired performance in this task (Fig. 3).

The probabilistic reversal task consists of two phases: acquisition and reversal. The acquisition phase involves probabilistic classification of stimuli. On each trial of this phase, the model learns to select one of two stimuli. One stimulus is designated as the correct stimulus, which is associated with 80% of positive feedback (and 20% negative feedback). The other stimulus is designated the opposite ratio of reinforcement. As in Cools et al. (2001), this phase has 40 trials. The second phase is the reversal phase in which reinforcement contingencies are reversed so that the previously incorrect stimulus is now correct and vice versa. As in the initial learning phase, the reversal phase has 40 trials. Similar to Cools et al. (2001), the learning criterion of any of the phases in our simulations is correct responses in eight trials. In addition to simulating the original probabilistic reversal task using the same number of trials, we ran the model with a larger number of trials in the reversal phase to test extended learning on reversal performance. Thus, the number of trials in original reversal phase is 40 trials, and it is 80 trials in the extended learning simulation. We assume that each run of the model corresponds to a different subject (each simulation run has different initial random values; see the *Experimental Procedures* section for details).

In our simulations of the original Cools et al. (2001) reversal task (Cools et al., 2001), we found that many of the simulation runs of the medicated PD network did not reach criterion performance in the reversal phase (Fig. 4(b)). In other words, medicated PD patients are more impaired at the reversal phase than unmedicated PD patients and controls. In the model, dopamine medications impair performance in the reversal phase. In the beginning of the reversal phase, the model receives negative feedback, and because of an increase in tonic dopamine function in the PFC, the model shifts attention to other cue instead of learning to reverse responses. This in turn leads to an increase in the number of errors in the reversal phase in many of the simulation runs of the medicated PD patients network (see parameter LR_{PFC} in Table 2). This delays correct reversal learning, and thus suggests an explanation for why medicated PD patients' performance is impaired in this phase. In the extended reversal task, where we double the original number of reversal trials, we found that many of the runs of the medicated PD network were able to reach performance criterion in the reversal phase (Fig. 4(c)). The model here suggest that impaired performance in medicated PD patients in the reversal task reported by Cools et al. (2001) may be due to the patients' use of too few trials in the reversal phase, which did not give them enough time to learn the task.



(a) Experiment.

(b) Model.

(c) Model (extended reversal training).

Fig. 4. PD performance in the probabilistic reversal task. (a) Experimental results from Cools et al. (2001). (b) Modeling results of the original reversal task. (c) Modeling results in the extended reversal learning tasks (see text). Increasing number of training trials of the reversal phase shows that PD patients can learn the reversal task.

2.2. Simulation 2: dopamine medications enhance working memory

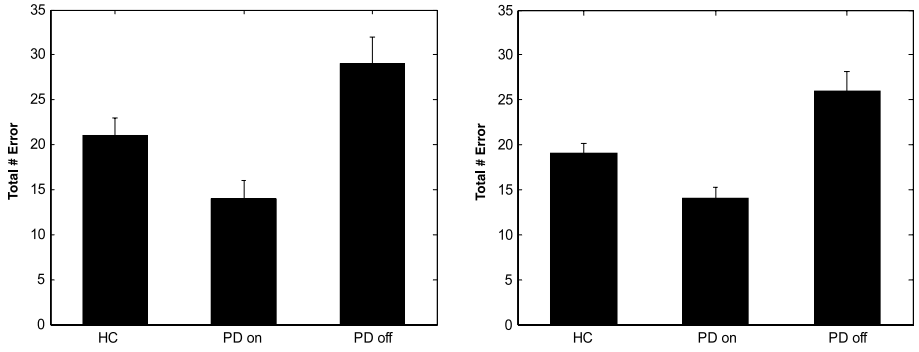
The model simulates performance in the AX-CPT working memory task, which consists of three performance phases, one of which requires working memory associations to be learned via reinforcement feedback. This task was originally used to test working memory function in schizophrenic patients by Barch et al. (1997), Barch et al. (2001), Braver and Cohen (2000), Cohen, Barch, Carter, and Servan-Schreiber (1999) and Servan-Schreiber et al. (1996). Recently, we used the AX-CPT task to test working memory function in PD patients on and off medications (Moustafa, Sherman, & Frank, 2008). Here, we show how our model simulates PD patients' performance in this task.

In the AX-CPT task, the model is presented with sequential letter stimuli (coded as A, B, X, Y in the human version). The model is trained to select a motor response when A is followed by X (AX "target" trials), and to select a different motor response otherwise (AY, BX, and BY trials). The task requires the model (and the subjects) to remember which cue (A or B) was presented before which probe (X or Y), so the model can respond correctly (hence it is a working memory task). Successful maintenance of contextual information in working memory allows the model (and presumably human subjects) to perform well at detecting the AX target sequence, but will likely make more false positive errors on the AY sequence (due to prepotent anticipation of an X). Context maintenance should improve performance on the BX case, because one can use the B to know not to respond to the X as a target. In the original Moustafa, Sherman et al. (2008) study, we measure working memory performance using the working-memory context index, which is the average performance in AY trials subtracted from average performance in BX trials. Here, we use accuracy instead of (BX–AY) to measure performance in the AX-CPT task, because accuracy takes into account performance in all trial types of the task (AX, AY, BX, and BY).

Simulation results show that simulated PD patients off medications are impaired at performing the AX-CPT task (Fig. 5). In our model, this is due to decreased tonic dopamine levels in the PFC, which we simulate by decreasing the gain parameter value in the PFC module to reflect PD-associated decrease in PFC tonic dopamine (see parameter G_{PFC} in Table 2). Consequently, input to the PFC module is less likely to pass the threshold and thus is less likely to be maintained in working memory. Conversely, increasing dopamine levels in the PFC in the model, as in medicated PD patients, enhances performance in working memory, as we reported in past experimental studies (Moustafa, Sherman et al., 2008).

3. Discussion

Our model provides an account for how the basal ganglia, PFC, and dopamine interact in stimulus–response, reversal learning, and working memory. In our model, the basal ganglia are key for motor learning while the PFC plays a critical role in stimulus selection and maintenance of information in working memory. The basal ganglia output to the motor cortex in our model is responsible for the initiation of motor responses. We argue that tonic dopamine levels control the initiation of motor responses and maintenance of information in working memory, whereas phasic dopamine responses facilitate learning to select correct motor responses via changes in synaptic plasticity in the basal ganglia, as reported experimentally (Reynolds et al., 2001; Wickens, Begg, & Arbuthnott, 1996). In agreement with many computational models (Daw, Niv, & Dayan, 2005; Frank, 2005; Guthrie et al., 2009; Houk, 1995b; Moustafa & Maida, 2007; Suri & Schultz, 1999), we argue that mesolimbic dopamine phasic signals projected to the striatum are important for reinforcing motor responses that lead to reward (however, see Dreher & Grafman, 2002, for a different theory of the function of phasic dopamine signaling).



(a) Experiment. (b) Model.

Fig. 5. PD performance in the AX-CPT working memory task. (a) Experimental results from Moustafa, Sherman et al. (2008). (b) Modeling results. Working memory context index (BX–AY) is the average performance in AY trials subtracted from average performance in BX trials (see text for description). Higher index values represent enhanced working memory performance.

In our model, PD is associated with decreased phasic and tonic dopamine levels in both the PFC and basal ganglia, as reported in several experimental studies (Cools, Miyakawa, Sheridan, & D'Esposito, 2010; Fera et al., 2007; Kish et al., 1988; Monchi, Petrides, Mejia-Constain, & Strafella, 2007; Prediger et al., 2006; Tadaiesky et al., 2008). Here, we argue that dopamine medications increase tonic dopamine levels (beyond those of healthy normals) in both the basal ganglia and PFC, but decrease the magnitude of phasic dopamine signaling in these brain structures which is in agreement with various experimental studies (Carey et al., 1995; Cools et al., 2010; Kaasinen et al., 2001; Muller, Ander, Kolf, Woitalla, & Muhlack, 2007; Ruocco et al., 2008; Silberstein et al., 2005). In our model, an increase in tonic dopamine levels increases the activity of postsynaptic cells, which regulates the intensity of the phasic dopamine response through its effect on extracellular dopamine levels (See Experimental Procedures for details). Empirical studies show that an increase in tonic dopamine levels increases the activity of postsynaptic cells, which regulates the intensity of the phasic dopamine response through its effect on extracellular dopamine levels (Schultz, 2007). This is in line with our model, in which increased tonic dopamine impacts phasic signaling of dopamine cells. On the other hand, we use learning rate parameters to simulate changes in phasic dopamine signaling (for experimental support, see Reynolds et al., 2001; Tsai et al., 2009).

Here, we further illustrate how our model simulates performance in stimulus–response, working memory, and reversal learning tasks in healthy controls and PD patients. For stimulus–response learning, as we mentioned above, various studies show that dopamine medications and agents impair stimulus–response learning performance in both PD patients (Gotham et al., 1988; Jahanshahi et al., 2010; Shohamy et al., 2006) and healthy controls (Breitenstein et al., 2006; Santesso et al., 2009). Our model shows that decreasing the learning rate (due to increase of dopamine levels in the basal ganglia and PFC with dopamine medications) leads to impairment in performing the aforementioned stimulus–response learning task (see simulation 1 results). As for working memory, the model shows that an increase in dopamine levels in the PFC, as seen in medicated PD patients, leads to enhanced working memory function (see simulation 2 results). In the model, this can be attributed to the increase in dopamine levels, which leads to an increase in PFC function and the resulting enhancement of gating and maintenance of information in working memory. This is in agreement with various experimental studies showing that dopamine medications enhance working memory performance in PD patients (Costa et al., 2003; Lange et al., 1992; Lewis et al., 2005; Marini, Ramat, Ginestroni, & Paganini, 2003; Moustafa, Sherman et al., 2008; Owen, Sahakian, Semple, Polkey, & Robbins, 1995). However, see Poewe, Berger, Benke, and Schelosky (1991) for an exception. Impaired performance in unmedicated PD patients compared to medicated PD patients can be attributed to decreased level of prefrontal dopamine, which in the model corresponds to a reduced gain value in the prefrontal module, which interferes with the maintenance of information in working memory. As for reversal learning, our model argues that medicated PD patients are impaired at performing reversal learning tasks due to increase of dopamine levels in the PFC. Simulation results show that during the reversal phase, increase of dopamine levels in the PFC made the model shift attention to different stimuli instead of learning to reverse responses, which delays learning. Interestingly, the same mechanism explains enhanced attentional performance in medicated PD patients, as we showed in our earlier work (Moustafa & Gluck, 2011) and as reported experimentally (Cools et al., 2001; Swainson et al., 2000).

Furthermore, the model shows that increasing the number of training trials in the reversal phase of the probabilistic reversal task enhances the performance accuracy (less number of errors) of medicated PD patients, making their performance on the reversal phase look like that of healthy subject simulations, which is a new a prediction of the model. We conclude that impaired performance of medicated PD patients in the reversal task in Cools et al. (2001) study is possibly due to the use of a small number of trials in the reversal phase. Future experimental research should examine this prediction.

The model presented here, along with our earlier model (Moustafa, Keri, Herzallah, Myers, & Gluck, 2010), demonstrates that a common set of computational assumptions allows us to simulate performance in both attentional and working memory processes. This is in agreement with experimental studies reporting a positive correlation between performance in attentional and working memory tasks (for review, see Kane & Engle, 2002; Silver & Feldman, 2005). Our models show that PFC, along with dopaminergic modulation, is essential for both attentional and working memory processes. Our model accounts for the various experimental data through two different mechanisms, whose effects are more pronounced depending on the task simulated. What we found is that Simulations 1 and 2 (especially acquisition phases of both) are very sensitive to basal ganglia learning rate parameter changes, while Simulation 3 is very sensitive to prefrontal gain parameter values, although changes in learning rate also have an effect on performance. Our interpretation for these findings is that the performance on AX-CPT task relies more heavily on the ability to maintain information in working memory (through a prefrontal maintenance mechanism), and that changes in learning rate affect performance but to a lesser extent. In summary, we have used the same computational principles to simulate performance in various tasks, including stimulus–response, reversal, and working memory, and provide a theory of the effects of PD and dopamine medications on these different cognitive domains.

3.1. Biological support for model features

There are various lines of biological support for model assumption that tonic dopamine relates to gain parameter and phasic dopamine affects learning, and how medications impact these biological processes. The assumption that tonic dopamine can be simulated using gain parameter is supported by computational models by Cohen, Braver, and O'Reilly (1996), Niv, Daw, Joel, and Dayan (2007), Servan-Schreiber, Bruno, Carter, and Cohen (1998). Various empirical studies also show relationship between tonic firing of dopamine and behavioral performance (Bilder, Volavka, Lachman, & Grace, 2004; Breitenstein et al., 2006). Similarly, the relationship between phasic dopamine and learning has been established in prior work by Schultz et al. (1997). Our model assumes that learning rate parameter corresponds to magnitude of phasic signaling and thus explains role of phasic signaling in learning. Our model additionally assumes that an increase in tonic dopamine leads to a decrease in phasic signaling. Supporting this assumption, Taverna, Ilijic, and Surmeier (2008) have shown that striatal D2-expressing neurons send inhibitory input to D1-expressing neurons in the striatum. This connectivity between D1 and D2-expressing cells might explain how an increase in tonic dopamine leads to a decrease in phasic signaling. Experimental studies have shown that phasic dopamine activates D1 receptors (Ballion et al., 2009; Dreyer et al., 2010; Sammut et al., 2006), whereas tonic dopamine activates D2 receptors (Ballion et al., 2009; Grace, 2008; Hauber, 2010). This dichotomy is also supported by anatomical (Richfield, Penney, & Young, 1989) and new empirical studies (Grieder et al., 2012). Thus, an increase in tonic dopamine can affect phasic signaling via this mechanism. An alternative mechanism is that tonic dopamine stimulates inhibitory D2 autoreceptors, thereby decreasing phasic dopamine responses (Grace, 1991). A similar neural mechanism exists in the prefrontal cortex (Trantham-Davidson, Neely, Lavin, & Seamans, 2004): activation of D2-expressing neurons in the prefrontal cortex (Wang & Goldman-Rakic, 2004) inhibits D1 cells (Williams & Goldman-Rakic, 1995), which is also in line with our model assumption.

3.2. Relation to other models

Our model bears similarity to many of the existing models of the basal ganglia and PFC, along with several unique features that differentiate it from previous work in this area. Below, we discuss similarities and differences between our work and past models.

There exist many basal ganglia models which simulate performance in stimulus–response learning (Berns & Sejnowski, 1995; Frank, 2005; Houk, 1995a; Suri & Schultz, 1998). The most common framework for simulating the role of the basal ganglia in stimulus–response learning is the actor–critic model. These models assume that there are two different systems responsible for reinforcement-based stimulus–response associations: (a) critic, which is responsible for reward-prediction learning, and (b) actor, which is responsible for stimulus–response learning (Barto). These systems are interrelated: the critic sends a reinforcement signal to the actor to either increase the likelihood of selecting the action it has just made if it has desirable consequences, or not to select the action just made if it does not have desirable consequences. The critic, on the other hand, is not informed about what action the actor has made. However, it is informed about whether the action made had rewarding consequences. As in our model, existing actor–critic models simulate the learning of stimulus–response tasks (Berns & Sejnowski, 1995; Khamassi, Girard, Berthoz, & Guillot, 2004; Suri, Bargas, & Arbib, 2001; Suri & Schultz, 1998). We are not aware of any model that simulates effects of dopamine medications on stimulus–response learning. Our model assumes that dopamine medications increase tonic dopamine levels. This in turn reduces phasic signaling of dopamine cells, and thus impairs learning.

Reversal learning is more complex than stimulus–response learning, as reversal learning involves the acquisition of stimulus–response relationships as well as learning to associate the same stimuli with different responses. Frank (2005) proposed a model that simulates performance in probabilistic reversal tasks. Unlike our model, Frank assumes that reversal deficits in medicated PD patients are due to dysfunctional learning in the basal ganglia indirect pathway (which we did not incorporate in our model). In a more recent model, Frank and Claus (2006) incorporate the orbitofrontal cortex and simulates performance in reversal tasks. Assuming that dopamine medications might overdose and impair the orbitofrontal cortex role in estimating the expected value of decisions and when reinforcement contingencies change (as shown by Cools et al., 2001), the Frank and Claus model can readily simulate reversal learning performance in medicated PD patients. Our model, however, is different from the Frank and Claus (2006) model in that it incorporates a PFC module, where feedback to PFC from the basal ganglia informs the PFC whether to maintain or change the reinforcement contingencies. In contrast to our model, the Frank and Claus model did not simulate the dissociable effects of DA meds on learning and working memory.

There are also a larger number of basal ganglia–PFC models of working memory. One of the earliest models of working memory is that of Changeux and Dehaene (1989). Their model simulated the role of PFC in active maintenance of information in working memory and the occurrence of perseverative responses as related to PFC damage. The model had two modules. The first consisted of an input layer directly connected to an output layer, which is key for associating stimuli with motor responses. The second module subserved maintenance of information in working memory. This module's performance was modified by learning that depended on reward presentation. The Changeux and Dehaene model showed that damage to, or not incorporating, the PFC, led to the occurrence of perseverative responses in working memory tasks. One limitation of this model is that it does not incorporate a basal ganglia module and thus is not applicable to explain behaviors in PD patients.

Frank et al. (2001) proposed a model that simulates performance in the 1-2-AX working memory task. This task requires the subject to maintain two cues in working memory in order to correctly select a response to a target sequence. Specifically, the subject is presented with a sequence of stimuli, one at a time, consisting of the stimuli 1, 2, A, B, X, or Y. If the subject last saw a 1, then the target sequence is an A followed by an X. If the subject last saw a 2, then the target sequence is a B followed by a Y. The Frank model assumed that the function of the basal ganglia is to gate information into working memory, while the function of PFC is active maintenance of information in working memory. O'Reilly and Frank (2006) proposed a similar model that incorporated the basal ganglia indirect pathway. The Frank models assume that PD and dopamine medications mainly affect dopamine levels in the basal ganglia, whereas our model assumes that the PFC is also affected by PD and dopamine medications. Furthermore, Braver and Cohen (2000) proposed a model that simulates performance in the AX-CPT task. This model incorporated interactions between sensory association cortex, PFC, the ventral tegmental area, and cortical motor areas. This model also assumes that dopamine neurons of the ventral tegmental area subserve gating of information into working memory. One limitation of the Braver and Cohen model is that it does not incorporate the role of basal ganglia in behavioral performance. The Braver model does not simulate performance in PD patients and did not simulate performance in stimulus–response or reversal learning tasks. However, unlike Frank's models of working memory (O'Reilly & Frank, 2006), our

model does not simulate performance in complex working memory tasks. The complex working memory task simulated by O'Reilly and Frank (2006), termed 12-AX task, involves the maintenance of two stimuli in working memory, while the AX-CPT task involves maintaining only one stimulus in working memory. Our model does not simulate the 12-AX task, since it uses a winner-take-all network to simulate the selection of one stimulus to maintain in the PFC. Further, it is not clear if the TD model can allow learning of complex working memory task, because in our model, learning progresses back in time to earliest predictors of reward, but in the 12-AX task, stimuli 1 and 2 are presented at different times (for discussion, see O'Reilly, Frank, Hazy, & Watz, 2007).

Suri and Schultz (1999) proposed a model that simulates performance in delayed-response tasks. In these tasks, a stimulus is presented to the subject (e.g., A or B), and after a delay period in which this stimulus is no longer present, the subject must select a motor response (e.g., R1 or R2) depending on which stimulus was presented before the delay. As in our model, this model incorporated an actor–critic architecture and was trained using the TD algorithm. Like our model, Suri and Schulz assume that the striatum subserves motor responses, and that lateral connectivity of striatal neurons, simulated by a winner-take-all network, subserves action selection. Monchi, Taylor, and Dagher (2000) proposed another model that simulates the role of the basal ganglia and PFC in different working memory tasks. These models assume that basal ganglia input to the PFC is key for maintenance of information in working memory. Monchi and colleagues simulate PD by decreasing values of weights connecting PFC and BG nodes. Unlike our model, Monchi and colleagues did not simulate the role of dopamine in learning.

Cohen and Servan-Schreiber (1992) proposed an earlier computational model of the role of PFC and dopamine in behavioral performance, with special reference to applications to studies of schizophrenia. As in our model, the PFC is key to active maintenance of information in working memory and dopamine projected to the PFC module increases the signal-to-noise ratio. As in the Cohen model, Amos (2000) proposed a computational model that simulated interactions between PFC and basal ganglia in the Wisconsin Card Sorting Task. As in our model, Amos assumes that PFC maintains the sorting rule (card, color, or shape) in working memory. The sensory association cortex encoded representations of input stimuli, and the striatum integrated cortical information and decided what action to perform. Feedback to PFC from the basal ganglia informed PFC whether to maintain or change the sorting rule (not modeled). The model simulated the occurrence of perseverative responses in PFC-damaged subjects and random responses in PD patients. Dopamine reduction (as in PD) was simulated by decreasing the gain parameters of the sigmoidal activation function, and lesioning was simulated by decreasing the output of neurons representing the lesioned area. One limitation of the Amos model is that it does not simulate learning processes and does not simulate dopamine medication effects on behavior.

In summary, previous models of frontal and BG function in learning did not account for the role of dopamine or did not simulate the role of the PFC (or other frontal areas) in learning and memory; others did not simulate the effects of dopamine-related disorders on performance on learning and memory functions. In our model, we try to account for the effects all these factors have on learning and reversal as well as working memory. We also simulate the performance of patients with PD on three different tasks at the same time, to investigate the effects of dopamine-related lesions on learning and memory functions.

3.3. Model limitations

Though our model simulates performance in various behavioral tasks, it has several important limitations. One limitation is that it does not simulate performance in more complex working memory tasks. Unlike the Frank et al. (2001) and O'Reilly and Frank (2006) models, our model does not simulate the effects of distractor presentation on working memory performance and does not simulate the maintenance of more than one item in working memory. In our model, learning progresses back in time to earliest predictors of reward, whereas in complex working memory tasks, multiple stimuli are presented at different times, which renders learning progression with time ineffective (for discussion, see O'Reilly et al., 2007). Future modeling work will address the simulation of these processes as well as the effects of changing delay length on working memory performance (see Sawaguchi & Iba, 2001). Another limitation of our current model is that it does not simulate differential effects of PD and dopamine medications on learning from positive or negative feedback, as reported in various experimental studies (Bodi et al., 2009; Frank et al., 2004; Moustafa, Cohen, Sherman, & Frank, 2008; Moustafa, Sherman et al., 2008; Palminteri et al., 2009). Furthermore, unlike Frank's and Cohen's models (Cohen, Braver, & Brown, 2002; Frank, 2005), our model did not simulate functional contributions of different dopamine receptors to performance. As in our model, Cohen et al. argue that tonic dopamine projected to the PFC is key for maintenance of information in working memory (also see Chadderdon & Sporns, 2006 for similar ideas). This can be attributed to the effects of tonic dopamine via D1 receptors in the PFC, which has been shown to mediate working memory function (Cohen et al., 2002).

Furthermore, previous research found that administration of levodopa to healthy subjects enhances associative learning (Knecht et al., 2004; Pessiglione, Seymour, Flandin, Dolan, & Frith, 2006). This is different from experimental studies and simulation results presented here showing that dopamine agents impair stimulus–response learning (Jahanshahi et al., 2010; Knecht et al., 2004; Pizzagalli et al., 2007). Given that levodopa and dopamine agonists have different effects on behavioral performance (see Breitenstein et al., 2006). Levodopa is converted to dopamine by dopaminergic neurons, and thus might balance phasic signaling of dopamine. This enhancement of phasic signaling of dopamine might enhance stimulus–response learning, as found in the Knecht et al. (2004) study. On the other hand, dopamine agonists act on postsynaptic cells and increase tonic firing of dopamine (Breitenstein et al., 2006). According to our model, increase in tonic dopamine reduce phasic signaling of dopamine cells, and thus might explain slow learning associated with dopamine agonists. Future experimental and computational studies should investigate differential effects of levodopa and dopamine agonists on behavioral performance.

Despite its limitations, our model provides a unified account for PD patients' performance in various behavioral tasks and provides new theories regarding how PD and dopamine medications might affect stimulus–response and reversal learning as well as working memory processes. Based on simulation results, we posit that reversal deficits in medicated PD patients are due to the low number of training trials used in the experimental studies (Cools et al., 2001). Our model shows that increasing the number of trials in the reversal phase leads to enhanced performance in medicated PD patients. The model also extends our previous model (Moustafa & Gluck, 2011) of attentional and category learning, and further simulates PD patients' performance in working memory and reversal tasks.

Important future directions based off of this work will include extending the current model to dissociate the effects of levodopa and dopamine agonists on learning. More research is needed to further investigate dose–response curves of medications, and how this correlates to cognitive function. In future models and experiments, it will be of key relevance to account for individual differences across patients in their response to medications as

potentially predicted by naturally occurring genetic variations in dopamine related genes (DAT1, DRD2, DARPP32). Finally, more work is needed to explore the potential application of these models as a framework for relating levels of activity in the model nodes to observable BOLD signals in fMRI studies of learning in PD patients, on and off medications.

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