Neural Networks ▮ (▮▮▮▮) ▮▮▮–▮▮▮

Contents lists available at ScienceDirect

Neural Networks

journal homepage: www.elsevier.com/locate/neunet

2011 Special Issue

Computational cognitive models of prefrontal-striatal-hippocampal interactions in Parkinson's disease and schizophrenia

Ahmed A. Moustafa *, Mark A. Gluck

Center for Molecular and Behavioral Neuroscience, Rutgers University-Newark, USA

ARTICLE INFO

Keywords:
Parkinson's disease
Deficit and nondeficit schizophrenia
Depression
Dopamine
Prefrontal cortex
Hippocampal region
Basal ganglia
Subtypes of brain disorders

ABSTRACT

Disruption to different components of the prefrontal cortex, basal ganglia, and hippocampal circuits leads to various psychiatric and neurological disorders including Parkinson's disease (PD) and schizophrenia. Medications used to treat these disorders (such as levodopa, dopamine agonists, antipsychotics, among others) affect the prefrontal-striatal-hippocampal circuits in a complex fashion. We have built models of prefrontal-striatal and striatal-hippocampal interactions which simulate cognitive dysfunction in PD and schizophrenia. In these models, we argue that the basal ganglia is key for stimulus-response learning, the hippocampus for stimulus-stimulus representational learning, and the prefrontal cortex for stimulus selection during learning about multidimensional stimuli. In our models, PD is associated with reduced dopamine levels in the basal ganglia and prefrontal cortex. In contrast, the cognitive deficits in schizophrenia are associated primarily with hippocampal dysfunction, while the occurrence of negative symptoms is associated with frontostriatal deficits in a subset of patients. In this paper, we review our past models and provide new simulation results for both PD and schizophrenia. We also describe an extended model that includes simulation of the different functional role of D1 and D2 dopamine receptors in the basal ganglia and prefrontal cortex, a dissociation we argue is essential for understanding the non-uniform effects of levodopa, dopamine agonists, and antipsychotics on cognition. Motivated by clinical and physiological data, we discuss model limitations and challenges to be addressed in future models of these brain disorders.

Published by Elsevier Ltd

1. Introduction

The prefrontal cortex, basal ganglia, and hippocampal region have been implicated in many psychiatric and neurological disorders, including Parkinson's disease (PD) and schizophrenia. In addition to the motor and psychiatric disorders, PD and schizophrenia are also associated with cognitive dysfunction (Abi-Dargham et al., 2002; Bodi et al., 2009b; Cohen, Barch, Carter, & Servan-Schreiber, 1999; Cools, Barker, Sahakian, & Robbins, 2001; Frank, Seeberger, & O'Reilly, 2004; Owen et al., 1993). We describe here our computational–neuropsychological approach to understand how disruption to different components of the prefrontal–striatal–hippocampal system gives rise to the pattern of cognitive deficits seen in PD and schizophrenia.

One goal of our theoretical work is to explain existing neuropsychological results. For example, the Moustafa and Gluck model simulates prefrontal–striatal interactions, along with dopaminergic manipulation, in learning and attention in medicated and unmedicated PD patients (Moustafa & Gluck, 2010). This model explains to key results. First, medicated PD patients are more impaired at feedback learning than unmedicated PD patients, as shown in empirical studies (Jahanshahi, Wilkinson, Gahir, Dharminda, & Lagnado, 2009). Second, medicated PD patients show enhanced attentional learning performance, as reported by Cools et al. (2001). We have also simulated the hippocampal–striatal interactions in cognition, and have shown how damage to the basal ganglia and/or hippocampus leads to cognitive deficits in PD and schizophrenia (Moustafa, Keri, Herzallah, Myers, & Gluck, 2010; Moustafa, Myers, & Gluck, 2009). Our Moustafa et al. (2010) model simulates performance in a learning- and-transfer generalization task (Keri, Nagy, Kelemen, Myers, & Gluck, 2005b; Myers, Shohamy, Gluck, Grossman, Kluger et al., 2003a; Weiler, Bellebaum, Brune, Juckel, & Daum, 2009), known as "acquired equivalence" in which prior training to treat two stimuli as equivalent increases generalization between them, even if those stimuli are superficially very dissimilar. In line with empirical results (Myers, Shohamy, Gluck, Grossman, Kluger et al., 2003a), this model explains why PD patients are worse at feedback learning, but better at transfer generalization, than schizophrenic patients.

PD and schizophrenia share many similarities at both the neural and cognitive levels. PD and schizophrenia are examples of

* Corresponding address: Center for Molecular and Behavioral Neuroscience, Rutgers University, 197 University Ave., Room 209, Newark, New Jersey 07102, USA. Tel.: +1 973 353 1080X3228; fax: +1 973 353 1272.
E-mail address: ahmedhalimo@gmail.com (A.A. Moustafa).

0893-6080/$ – see front matter. Published by Elsevier Ltd
doi:10.1016/j.neunet.2011.02.006

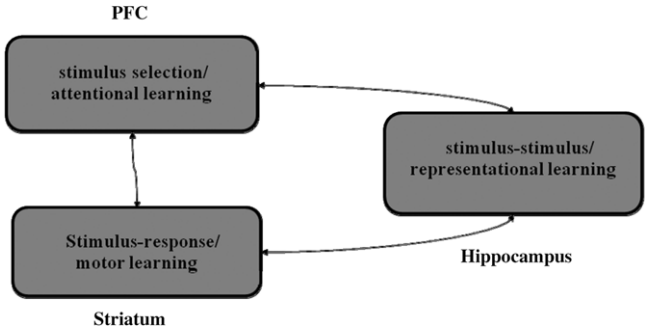


Fig. 1. A schematic of prefrontal–striatal–hippocampal system interactions, as proposed in our recent models (Gluck & Myers, 1993; Moustafa & Gluck, 2010; Moustafa et al., 2010). In our modeling framework, the prefrontal cortex (PFC) is key for attentional and stimulus selection for multi-dimensional stimuli; the striatum for stimulus–response and motor learning; the hippocampus for stimulus–stimulus representational learning. Our models simulate cognitive function in Parkinson's and schizophrenia.

disorders affecting the prefrontal–striatal–hippocampal circuits, and both disorders are also associated with dopaminergic dysfunction. Furthermore, while psychosis is diagnostic criterion for schizophrenia, clinical research has shown that a percentage of PD patients also have psychotic episodes that perhaps increase with the administration of dopaminergic medications (Marsh, 2004). These findings argue for a role for dopamine in the occurrence of psychotic episodes in PD and schizophrenia. Similarly, while bradykinesia is a diagnostic criterion for PD, research has reported the occurrence of Parkinsonian motor symptoms in schizophrenia due to the administration of antipsychotics, possibly because they decrease dopamine levels in the basal ganglia (Moratalla, Xu, Tonegawa, & Graybiel, 1996; Parr-Brownlie & Hyland, 2005; Sumaya, Byers, Irwin, Del Val, & Moss, 2004). In our modeling framework, we argue that the similarities of cognitive and psychiatric profiles of PD and schizophrenia are related to dysfunction to the same components of the prefrontal–striatal–hippocampal mechanism.

Before we review simulation results of our models (Moustafa & Gluck, 2010; Moustafa et al., 2010), we describe the functional connectivity of the prefrontal–striatal–hippocampal system. We then describe how disruption to different components of the prefrontal–striatal–hippocampal system leads to brain disorders, including PD and schizophrenia. We present new simulation results on the effects of subtypes of PD and schizophrenia on cognition. We then discuss limitations of existing (including our models) of PD and schizophrenia in light of clinical and physiological data. Finally, we discuss recent extension of our models that include the simulation of dopamines D1 and D2 receptors in the basal ganglia and prefrontal cortex; the extended model simulates the differential effects levodopa, dopamine agonists, and antipsychotics, on cognition.

2. The prefrontal–striatal–hippocampal system

The prefrontal cortex, basal ganglia, and hippocampus interact dynamically during motor and cognitive performance (Fig. 1). Several experimental studies have shown that the prefrontal cortex, hippocampal region, and basal ganglia are involved in similar motor and cognitive processes, including Pavlovian and instrumental conditioning, reversal learning, planning, and feedback learning (Albouy et al., 2008; Brasted, Bussey, Murray, & Wise, 2003; Corbit & Balleine, 2000; Dagher, Owen, Boecker, & Brooks, 2001; Ito, Everitt, & Robbins, 2005; Lansink, Goltstein, Lankelma, McNaughton, & Pennartz, 2009; O'Doherty et al., 2004; Parkinson et al., 2002; Peoples, Uzwiak, Gee, & West, 1997; van der Meer, Johnson, Schmitzer-Torbert, & Redish, 2010).

Anatomical studies have shown that the basal ganglia and frontal cortex are connected through corticostriatal loops (Alexander, DeLong, & Strick, 1986; Gerfen, 2000). Similarly, the hippocampus forms recurrent connectivity with various cortical areas, including the prefrontal cortex (Cavada, Llamas, & Reinoso-Suarez, 1983; Goldman-Rakic, Selemon, & Schwartz, 1984; Irle & Markowitsch, 1982; Rosene & Van Hoesen, 1977; Swanson, 1981). As we review below, many computational models focus on simulating the function of the corticostriatal (Frank, 2005; Guthrie, Myers, & Gluck, 2009; Moustafa & Maida, 2007) or corticohippocampal (Gluck & Myers, 1993; Gluck, Myers, & Meeter, 2005; McClelland, McNaughton, & O'Reilly, 1995; O'Reilly & Norman, 2002) connections. Anatomical studies have also identified hippocampal–striatal connections (see for example Shen & Tsai, 1995). There are at least two anatomical pathways through which the hippocampal region and basal ganglia might interact: the hippocampus sends information to the ventral striatum via the subiculum or to the prefrontal cortex which is then projected to the basal ganglia. The role of the hippocampal–striatal pathway in motor and cognitive processes has received less attention in the computational modeling field.

However, empirical research has shown that the striatal–hippocampal pathway is essential for the performance of cognitive tasks, including feedback learning. In rats, for example, it was recently reported that disconnecting hippocampus and ventral striatum impairs appetitive Pavlovian conditioning performance (Ito, Robbins, Pennartz, & Everitt, 2008). Also, fMRI imaging studies have found simultaneous hippocampus and basal ganglia activity during sequence learning task performance (Albouy et al., 2008).

In sum, various behavioral, anatomical, and physiological studies suggest that the prefrontal cortex, basal ganglia, and hippocampus are part of a single system that regulates complex motor and cognitive tasks.

The prefrontal–striatal–hippocampal system is modulated by various neurotransmitters, including dopamine and acetylcholine. Dopamine is produced in the midbrain and is projected to the basal ganglia, hippocampus, and prefrontal cortex. Research suggests that dopamine plays different functions in these brain structures. In the basal ganglia, several studies show that phasic dopamine is important for stimulus–response and feedback learning (Reynolds, Hyland, & Wickens, 2001; Schultz, Dayan, & Montague, 1997; Tsai et al., 2009; Wickens, Begg, & Arbuthnott, 1996). Our models assume that phasic dopamine is key for stimulus–response learning through synaptic modification in the basal ganglia (Guthrie et al., 2009; Moustafa & Gluck, 2010; Moustafa & Maida, 2007). Unlike the basal ganglia, dopamine in the prefrontal cortex is essential for attention and working memory (Iba & Sawaguchi, 2003; Servan-Schreiber, Carter, Bruno, & Cohen, 1998; Williams & Goldman-Rakic, 1995). Although most computational studies focus on simulating the function of dopamine in the basal ganglia and prefrontal cortex, research has identified a projection from the ventral tegmental area to the hippocampal region (Gasbarri, Packard, Campana, & Pacitti, 1994; Samson, Wu, Friedman, & Davis, 1990). Experimental data show that dopamine is also required for learning in the hippocampus, but this was shown to be related to long-term memory and novelty detection (Lisman & Grace, 2005; Rossato, Bevilaqua, Izquierdo, Medina, & Cammarota, 2009).

3. Brain disorders of the prefrontal–striatal–hippocampal system

Disruption to the prefrontal–striatal–hippocampal system leads to various neurological and psychiatric disorders, such as PD and schizophrenia. PD is associated with motor symptoms, including akinesia, tremor, and bradykinesia. Schizophrenia is a psychiatric disorder which is mainly associated with positive symptoms, such

Please cite this article in press as: Moustafa, A. A., & Gluck, M. A. Computational cognitive models of prefrontal-striatal-hippocampal interactions in Parkinson's disease and schizophrenia. Neural Networks (2011), doi:10.1016/j.neunet.2011.02.006

as delusions and hallucinations. Nondeficit schizophrenia is mainly associated with the occurrence of positive symptoms, while deficit schizophrenia is associated with positive symptoms and severe negative symptoms.

We use computational and empirical methods to study how PD and schizophrenia affect the prefrontal–striatal–hippocampal system. While PD typically impacts the frontostriatal circuitry, schizophrenia (particularly the "nondeficit" type) impairs hippocampal function (Buchanan et al., 1993; Farkas et al., 2008; Heckers et al., 1999; Polgar et al., 2010; Tamminga et al., 1992).

Parkinson's disease is a neurodegenerative disorder associated with reduced dopamine levels in the basal ganglia (Jellinger, 1999; Kish, Shannak, & Hornykiewicz, 1988). Many studies have also shown that PD is associated with decreased dopamine in the prefrontal cortex (Cutsuridis & Perantonis, 2006; Dagher & Robbins, 2009; Diaconescu, Menon, Jensen, Kapur, & McIntosh, 2010; Fera et al., 2007; Lanoue, Dumitriu, Myers, & Soghomonian, 2010; Prediger et al., 2006; Tadaiesky et al., 2008; Williams-Gray, Hampshire, Barker, & Owen, 2008). In addition to motor dysfunction, PD patients show impairment performing various cognitive tasks such as feedback learning (Bodi et al., 2009b; Frank et al., 2004) and reversal learning (Cools et al., 2001). PD is often associated with psychiatric symptoms, such as depression and psychosis, which has been shown to be associated with further dopamine reduction and impaired hippocampal function (Bruck, Kurki, Kaasinen, Vahlberg, & Rinne, 2004; Walter, Skoloudik, & Berg, 2010).

Dopamine medications, including levodopa and D2 agonists, are used to treat motor symptoms of PD (tremor, akinesia, and bradykinesia), but can either enhance or impair cognitive function (Cools et al., 2001; Feigin et al., 2003; Frank et al., 2004; Swainson et al., 2000). For example, various studies show that dopamine medications and agents impair stimulus–response learning in both PD patients (Gotham, Brown, & Marsden, 1988; Jahanshahi et al., 2009; Shohamy, Myers, Geghman, Sage, & Gluck, 2006) and healthy subjects (Breitenstein et al., 2006; Pizzagalli et al., 2007). In combination with dopamine medications, PD patients are often prescribed anticholinergic medications, such as Trihexyphenidyl, which are muscarinic receptor antagonists. The hippocampal region has a large density of these receptors (Levey, 1993); thus, it is possible that the administration of anticholinergic antagonists interferes with hippocampal function. In agreement with this and other studies (Ehrt, Broich, Larsen, Ballard, & Aarsland, 2010; Meco et al., 1984; Pondal, Del Ser, & Bermejo, 1996), we have recently shown that the administration of anticholinergics to PD patients impairs performance in hippocampal-based tasks (Herzallah, Moustafa, Misk, Myers, & Gluck, 2010).

Unlike PD, schizophrenia is typically associated with hippocampal dysfunction (Bogerts, Meertz, & Schonfeldt-Bausch, 1985; Goldman & Mitchell, 2004; Grace, 2010; Heckers, 2001; Keri, 2008; Weinberger, 1999). Schizophrenic patients also show declarative memory deficits, which suggest hippocampal-region dysfunction (Aleman, Hijman, de Haan, & Kahn, 1999; Cirillo & Seidman, 2003). Lesioning the hippocampus in animals is also used as a model of schizophrenia (Tseng, Chambers, & Lipska, 2009). In addition, Rametti et al. (2009) reported decreased hippocampal activity in schizophrenic patients performing declarative memory tasks. Research at our laboratory have shown that schizophrenic patients' performance on the learning-and-transfer acquired equivalence task is very similar to the performance of patients with mild Alzheimer's disease, hippocampal atrophy, and hypoxia (Bodi, Csibri, Myers, Gluck, & Keri, 2009a; Myers et al., 2008; Myers, Shohamy, Gluck, Grossman, Kluger et al., 2003a; Myers, Shohamy, Gluck, Grossman, Onlaor et al., 2003b), suggesting a common hippocampal dysfunction in all these patient groups. Though debatable, it is argued that the basal ganglia is generally intact in nondeficit schizophrenia (Okubo et al., 1997). For example, Bogerts et al. (1985) reported a decrease in hippocampal size but an intact basal ganglia structure in schizophrenic patients as seen in structural brain imaging.

Schizophrenia is often accompanied by negative symptoms, such as apathy and emotional withdrawal. Schizophrenic patients with severe negative symptoms, known as deficit schizophrenia, usually perform worse than nondeficit schizophrenic patients in multiple cognitive domains (Cascella et al., 2008). Using structural brain imaging, Buchanan et al. (1993)found that deficit, but not nondeficit, schizophrenia is associated with striatal damage. Supporting the role of prefrontal–striatal system in the occurrence of severe negative symptoms in schizophrenia (van Veelen, Vink, Ramsey, & Kahn, 2010), we have shown that that negative symptoms in schizophrenia are associated with feedback learning impairment (Farkas et al., 2008; Keri, 2008; Polgar et al., 2010), a behavioral task that typically recruits the frontostriatal system (Houk, 1995b).

Specifically, empirical studies that measured protein function associated with dopamine receptors implicate D1 receptors in the striatum for the occurrence of negative symptoms in schizophrenia (Monteleone, Di Lieto, Martiadis, Bartoli, & Maj, 2002). Similarly, using a PET scan, Okubo et al. (1997) have found that that the distribution of D1 receptors in the prefrontal cortex correlates with the severity of negative symptoms in schizophrenic patients (for similar finding, see Abi-Dargham, 2003). These findings are in agreement with why antipsychotics (D2 antagonists) usually do not treat D1-mediated negative symptoms of schizophrenia (Rueter et al., 2004). Notably, computational modeling and empirical work suggest that D1 agonists can be used to treat negative symptoms and cognitive deficits in schizophrenia (Loh, Rolls, & Deco, 2007; Roberts, Seymour, Schmidt, Williams, & Castner, 2010). D1 receptors are activated by phasic dopamine (Dalley et al., 2005; Goto & Grace, 2008; Richfield, Penney, & Young, 1989; Zweifel et al., 2009), which has been shown to be essential for learning in basal ganglia (Reynolds et al., 2001; Schultz et al., 1997; Tsai et al., 2009). Thus, impaired D1 receptor function in schizophrenic patients with severe negative symptoms explains feedback learning deficits in these patients, as we have found in our studies (Farkas et al., 2008).

Antipsychotics are used to treat psychiatric deficits, including positive symptoms, in schizophrenia, possibly by blocking D2 receptors in the striatum or hippocampus (Rueter et al., 2004). Unlike PD, very few studies have studied the effects of medications on cognition and symptoms severity in schizophrenia. This is perhaps due to the fact that withdrawal of medications in schizophrenia (unlike PD) is rarely done as it might have major effects on patients' health and life. Beside antipsychotics, schizophrenic patients are often prescribed anticholinergic medications; interestingly, like in PD, recent research has also shown that anticholinergics impair cognition, particularly working and long-term memory, in schizophrenic patients (Vinogradov et al., 2009). We provide here a summary of empirical findings on the effects of Parkinson's disease, schizophrenia, and associated medications on the prefrontal cortex, hippocampus, and basal ganglia in Table 1.

4. Cognitive dysfunction in PD and schizophrenic patients

Various behavioral tasks have been used to assess the nature of cognitive deficits in PD and schizophrenic patients, including feedback learning, reversal learning, and transfer generalization. We simulate cognitive performance in many of these tasks and briefly review here relevant empirical results on how PD and schizophrenia affect cognition. Finally, we present simulation results these behavioral tasks.

Please cite this article in press as: Moustafa, A. A., & Gluck, M. A. Computational cognitive models of prefrontal-striatal-hippocampal interactions in Parkinson's disease and schizophrenia. Neural Networks (2011), doi:10.1016/j.neunet.2011.02.006

Table 1
A summary of empirical results of the effects of Parkinson's disease and schizophrenia, as well as associated medications, on the prefrontal cortex, hippocampus, and basal ganglia., that our models simulate. Our modeling framework simulates many of the excising empirical data shown here, but also see model limitations and future directions. Abbreviations: DA, dopamine.

	Basal ganglia	Prefrontal cortex	Hippocampus
Unmedicated PD	Reduced DA	Reduced DA	
Medicated PD	Increased DA	Increased and perhaps overdosed with DA	
Nondeficit schizophrenia			Damaged and DA dysregulation
Deficit schizophrenia	Dysregulation of D1 receptors	Dysregulation of D1 receptors	Damaged and DA dysregulation
PD depression	Further reduced DA		Damaged
PD on anticholinergics	Reduced DA	Reduced DA	Damaged
Antipsychotics	Dysregulation of D1 receptors	Dysregulation of D1 receptors	

Feedback learning: In feedback learning tasks, subjects learn to associate the presentation of different stimuli with different responses, based on corrective feedback. Many experimental studies have shown that PD patients are impaired at feedback learning (Jahanshahi et al., 2009; Shohamy et al., 2006). In contrast, schizophrenic patients are generally intact on feedback learning tasks (Gomar et al., 2011; Keri et al., 2005a, 2005b; Leeson et al., 2009; Somlai, Moustafa, Keri, Myers, & Gluck, 2010). For example, Jahanshahi et al. (2009) have shown that medicated PD patients are more impaired than unmedicated PD patients at the "weather prediction" task, a multi-cue probabilistic categorization task, and both patient groups are more impaired than healthy controls. In the weather prediction task, subjects classify patterns composed of sets of two to four cards as being predictive of rain versus sunshine (Fera et al., 2005; Gluck, Shohamy, & Myers, 2002; Knowlton, Mangels, & Squire, 1996; Knowlton, Squire, & Gluck, 1994; Shohamy, Myers, Onlaor, & Gluck, 2004). In other studies using the weather prediction task, it was found that schizophrenic patients show intact feedback learning (Keri et al., 2005a, 2000; Weickert et al., 2002).

We have also found that schizophrenia patients show intact feedback learning performance in a different feedback learning task that tests learning from positive or negative feedback (Somlai et al., 2010). This is, however, in contrast to another study in which Waltz, Frank, Robinson, and Gold (2007) found that schizophrenic patients are impaired at learning from reward but not from punishment. The inconsistent results in the literature are perhaps because existing empirical studies test different subtypes of schizophrenic patients. Supporting this hypothesis, in our own prior studies (Farkas et al., 2008; Polgar et al., 2008), we have found that deficit, but not nondeficit, schizophrenic patients show feedback learning impairments (Farkas et al., 2008; Polgar et al., 2008). The correlation between feedback learning and the severity of negative symptoms in schizophrenia was also reported in the literature (Murray et al., 2008).

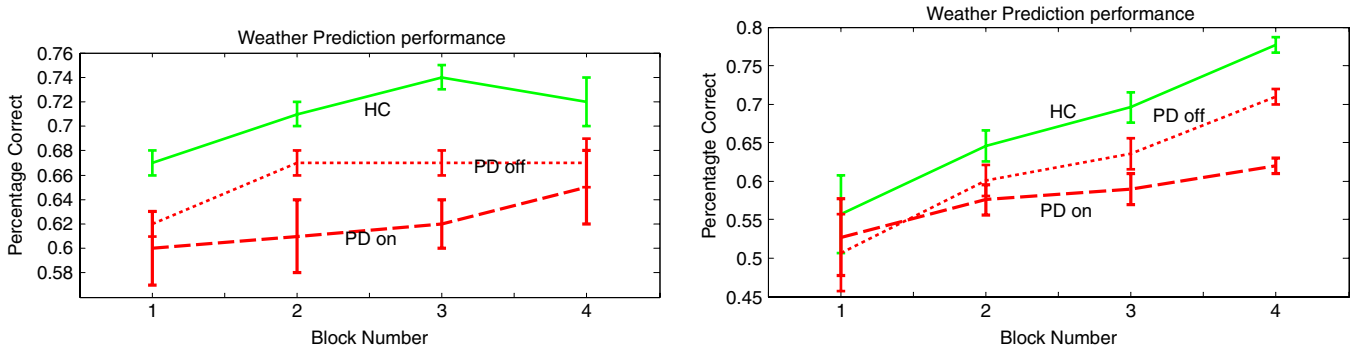
Reversal: In reversal learning tasks, subjects initially learn to associate different stimuli with different responses, and subsequently learn to associate the same stimuli with the opposite responses (i.e., reversal). Various studies show that the basal ganglia, hippocampus, and prefrontal cortex are important for reversal learning performance (Clatworthy et al., 2009; Cools et al., 2001; Cools & Frank, 2009; McDonald, Ko, & Hong, 2002; Mitchell, Rhodes, Pine, & Blair, 2008). For example, Pasupathy and Miller (2005) recorded from both the striatum and prefrontal cortex while a monkey performed a reversal task. They found that, within a trial, the striatum increased its activation before that of prefrontal cortex neurons, suggesting that both basal ganglia and prefrontal cortex are engaged during reversal learning processes. Cools et al. (2001) found that medicated PD patients are more impaired at reversal learning than unmedicated PD patients (also see Swainson et al., 2000). Furthermore, Jentsch, Olausson, De La Garza, and Taylor (2002) found that the administration of cocaine, which is a dopamine agonist, to monkeys lead to impairment performing reversal learning tasks. Similar results were found with the administration of quinpirole (a dopamine agonist) to rats (Boulougouris, Castane, & Robbins, 2009). It has been argued that dopamine medications overdose the prefrontal cortex and thus impair performance in reversal tasks (Cools et al., 2001). In line with this hypothesis, our model demonstrates that an increase in dopamine levels in the prefrontal cortex impairs reversal performance. Similarly, empirical studies show that schizophrenic patients are impaired at reversal learning (Leeson et al., 2009), possibly due to prefrontal dysfunction (McKirdy et al., 2009).

Learning-and-transfer: The Rutgers learning-and-transfer "acquired equivalence" task (Myers, Shohamy, Gluck, Grossman, Kluger et al., 2003a) is used to test the contributions of the basal ganglia and hippocampus to cognition. This task has two phases: acquisition and transfer. In the acquisition phase, subjects (and also the model) learn to associate two stimuli, while in the transfer generalization phase, subjects learn that cues become equivalent when they were previously associated with the same response. The transfer generalization phase includes two types of trials: retention and reversal. Retention trials are trials that were previously presented in the learning phase, while transfer trials include novel combinations of stimuli (see Myers, Shohamy, Gluck, Grossman, Kluger et al., 2003a). Several neuropsychological studies from our laboratory have argued that the associative learning and transfer generalization processes rely on different neural structures (Keri, 2008; Myers et al., 2008): initial associative learning relies on the integrity of the basal ganglia, whereas transfer generalization relies on the integrity of the hippocampal region. Specifically, we have shown that PD patients are more impaired at learning than schizophrenic patients, while the opposite is true for the transfer generalization phase: schizophrenic patients are more impaired than PD patients at transfer generalization (Keri et al., 2005b; Myers, Shohamy, Gluck, Grossman, Kluger et al., 2003a). Interestingly, Shohamy et al. (2010) found that the administration of antipsychotics to schizophrenic patients ameliorates their transfer generalization impairment on the same task.

In our models, different brain areas play different computational roles. In agreement with empirical (Dusek & Eichenbaum, 1997) and modeling (Cutsuridis & Wennekers, 2009) work, the hippocampus in our models is important for stimulus–stimulus representational learning (Gluck et al., 2005; Moustafa & Gluck, 2010; Moustafa et al., 2010). The hippocampus sends recoded information of input stimuli to the basal ganglia and prefrontal cortex for further processing. In our models, the basal ganglia is key for stimulus–response and reinforcement learning, in line with empirical results (Schultz et al., 1997; Tsai et al., 2009). Unlike the basal ganglia, the prefrontal cortex in our models is essential for stimulus selection during learning about multidimensional stimuli, in agreement with physiological studies (Iba & Sawaguchi, 2003). Importantly, our simulations explain how interactions among these brain areas give rise to complex cognitive and motor functions.

Our computational models also aim at understanding how damage to different components with the prefrontal–striatal–hippocampal system leads to cognitive dysfunction in PD and schizophrenia. Below, we provide simulation results of how our

Please cite this article in press as: Moustafa, A. A., & Gluck, M. A. Computational cognitive models of prefrontal-striatal-hippocampal interactions in Parkinson's disease and schizophrenia. Neural Networks (2011), doi:10.1016/j.neunet.2011.02.006



(a) Experiment.

(b) Model.

Fig. 2. Weather prediction task performance in medicated and unmedicated PD patients. Each block here is 50 trials. (a) Figure is adapted from Jahanshahi et al. (2009). (b): Simulation results are qualitatively similar to the results of Jahanshahi et al. (2009).

prefrontal–striatal and striatal–hippocampal models (Moustafa & Gluck, 2010; Moustafa et al., 2010) simulate feedback learning, reversal, and learning-and-transfer acquired equivalence in PD and schizophrenia. We start by describing simulation results of the effects of prefrontal–striatal dysfunction in PD patients, and then present simulation results of the effects of striatal–hippocampal dysfunction in PD and schizophrenia. We also present simulation results of the effects of PD depression, the administration of anticholinergics to PD, and nondeficit vs. deficit schizophrenia on cognition.

5. Simulation of prefrontal–striatal interactions in PD

We have recently designed a prefrontal–striatal model that simulates the effects of Parkinson's disease and dopamine medications on learning and attention (Moustafa & Gluck, 2010). Unlike prior models of Parkinson's disease, we have simulated the effects of prefrontal dopamine in attentional learning, and how this cognitive function is affected by Parkinson's disease and dopamine medications. In this model, we have simulated the differential effects of phasic and tonic dopamine on motor and cognitive processes, and how phasic and tonic dopamine might be affected by Parkinson's disease and dopamine medications. Phasic dopamine in our model is key for learning, while tonic dopamine is essential for the initiation of motor responses. The Moustafa and Gluck (2010) model argues that PD is associated with reduced phasic and tonic dopamine levels, while dopamine medications increase tonic dopamine and further decrease phasic dopamine signaling. Our simulation results show that unmedicated and medicated PD patients are impaired the weather prediction task (Fig. 2(a)), as found in empirical results (Figure 2a, Jahanshahi et al., 2009).

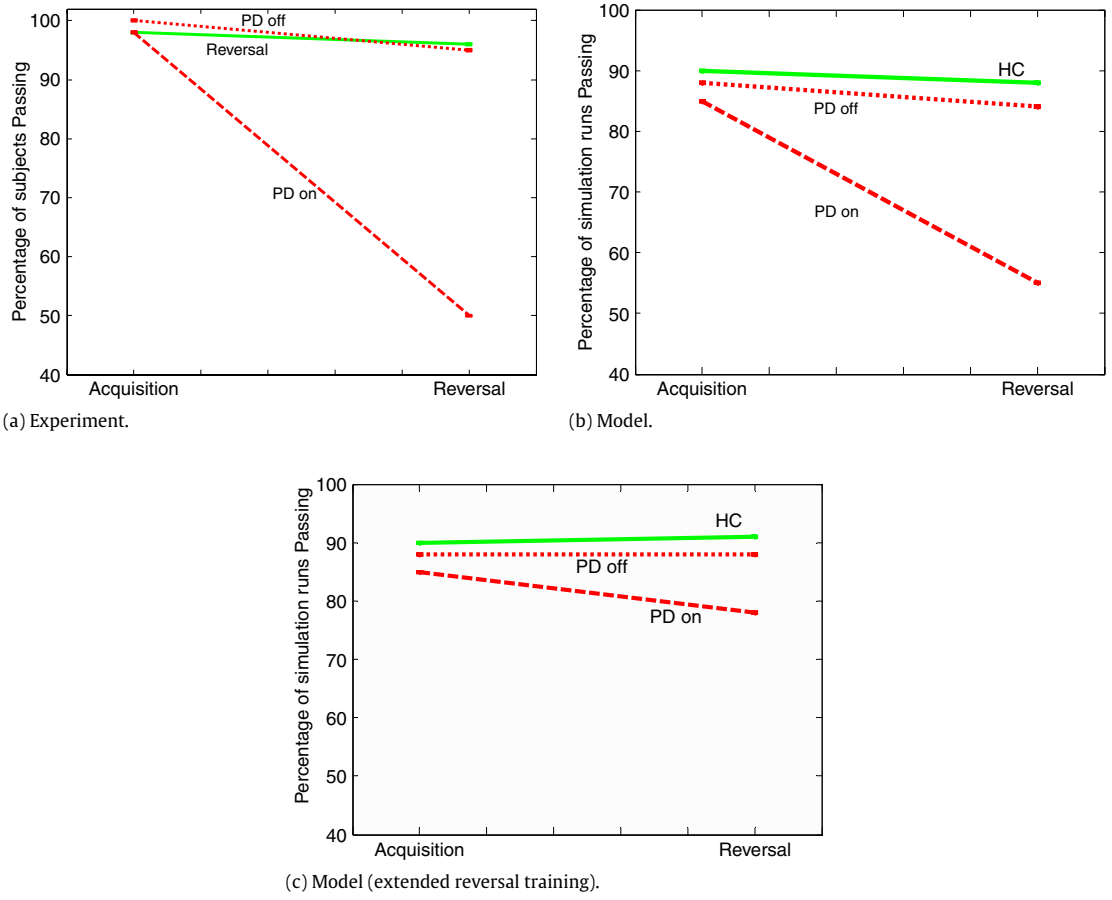
The Moustafa and Gluck model also simulates performance in probabilistic reversal learning tasks. This task consists of two phases: acquisition and reversal. The acquisition phase involves probabilistic classification of stimuli. On each trial of this phase, the model learns to select one of two stimuli (see Cools et al., 2001, for task details). 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. Following 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 probabilistic reversal task, we further ran the model on the exact same task but by increasing number of trials in the reversal phase to test extended learning on reversal performance. We assume that each run of the model corresponds to a different subject (each simulation run has different initial random values).

In simulating the original reversal task as published, we found that many of the simulation runs of the medicated PD network did not reach criterion performance in the reversal phase (Fig. 3(b)), which is qualitatively similar to the empirical results of Cools et al. (Fig. 3(a)). In other words, the model accounts for the finding that 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 of tonic dopamine in the prefrontal cortex, the model shifts attention to the other cue instead of learning to reverse responses. This in turn led to an increase number of errors in the reversal phase in many of the simulation runs of the medicated PD patients network. This delays correct reversal learning, and thus explains medicated PD patients' impaired performance in this phase. In the extended reversal task, we found that many of the runs of the medicated PD patients network were able to reach performance criterion in the reversal phase (Fig. 3(c)). The model here shows that impaired performance in medicated PD patients in the original reversal task as reported by Cools et al. (2001) is perhaps due to the use of a few number of trials in the reversal phase, which did not allow patients to learn the task. In sum, our prefrontal–striatal model accounts for the findings that medicated and medicated PD patients are more impaired than healthy controls at feedback learning, and that medicated PD patients are more impaired than unmedicated PD patients at reversal learning.

6. Simulation of striatal–hippocampal interactions in PD and schizophrenia

The Moustafa and Gluck (2010) model does not have a hippocampal module and is limited to the simulation of the frontostriatal connectivity in cognition. We have recently investigated the interactions among the basal ganglia and hippocampus in cognition Moustafa et al. (2010). The interaction of the hippocampus and the basal ganglia in cognition is not addressed by most existing models. The Moustafa et al. (2010) model integrates our earlier models of basal ganglia and hippocampal-region function, and their modulation by dopamine and acetylcholine. Like the Moustafa and Gluck (2010) model, the basal ganglia is key for reinforcement learning, motivated by dopamine signals coming from the ventral tegmental area and substantia nigra pars compacta (Reynolds et al., 2001; Wickens et al., 1996). In the Moustafa et al. (2010) model, the hippocampal region is required for stimulus–stimulus representation learning, as argued in our prior models (Gluck, Allen, Myers, & Thompson, 2001). In the Moustafa et al.

Please cite this article in press as: Moustafa, A. A., & Gluck, M. A. Computational cognitive models of prefrontal-striatal-hippocampal interactions in Parkinson's disease and schizophrenia. Neural Networks (2011), doi:10.1016/j.neunet.2011.02.006



(a) Experiment.

(b) Model.

(c) Model (extended reversal training).

Fig. 3. PD performance in the probabilistic reversal task using the prefrontal–striatal model. (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. Prefrontal dysfunction explains reversal deficits in PD patients.

(2010) model, the hippocampal region preprocesses input information and projects coded information to the basal ganglia for further computational processing. This model simulates performance in the learning-and-transfer "acquired equivalence" task described above (Myers, Shohamy, Gluck, Grossman, Kluger et al., 2003a).

The Moustafa et al. (2010) model has been applied to simulate the effects of Parkinson's disease and schizophrenia on learning and transfer generalization. We present here simulation results in terms of number of errors in the acquisition and transfer (including retention and transfer trials) phases. Consistent with the empirical results (Fig. 5(a)), the model shows that simulating a loss of dopamine function in the basal ganglia module, as in Parkinson's disease, leads to slow acquisition learning but intact transfer generalization (Fig. 4(c)). Damaging the hippocampal module in the model, as in schizophrenia, did not interfere with acquisition (Fig. 4(d)), which is line with empirical results (Fig. 4(b)). In contrast to feedback learning, our simulation results show that schizophrenic patients are impaired, but PD patients show intact performance, at the transfer generalization phase (Fig. 5(c) and (d)), which is in agreement with empirical results (Fig. 5(a) and (b)). In sum, our striatal–hippocampal model explains why PD patients are worse at learning, but better at transfer generalization, than schizophrenic patients.

7. Simulation of the effects of depression and anticholinergics on cognition in PD

Our earlier simulation results were limited to the simulation of standard PD and schizophrenia that are not associated with any additional symptoms, such as depression or negative symptoms. As shown above, subtypes of PD and schizophrenic patients have different cognitive profiles. In a recent neuropsychological study, we have tested the effects of depression and anticholinergic medications on learning and transfer generalization in PD patients (Herzallah et al., 2010). We have found that depressed PD patients are more impaired than nondepressed patients at feedback learning (Fig. 6(a)). In contrast, we have found that PD patients on anticholinergics are more impaired at transfer generalization than patients who are not on anticholinergics (Fig. 7(a)). Empirical studies have shown that PD depression (and major depression) is associated with further reduced dopamine levels than in nondepressed PD patients (Walter et al., 2010). Accordingly, we simulate depression in PD by further decreasing the learning rate parameter in the basal ganglia module. As in our empirical findings (Fig. 6(a)), our simulations show a qualitatively similar pattern of results (Fig. 6(b)). Furthermore, empirical research has shown that anticholinergics impair hippocampal function (Ehrt et al., 2010; Meco et al., 1984; Pondal et al., 1996). By removing the hippocampal module from the Moustafa et al. (2010) model, we show that the simulations of PD patients on anticholinergics are more impaired at transfer generalization than patients not on anticholinergics (Fig. 7(b)).

In sum, using parallel neuropsychological-computational methods, we show here that depression in PD patients is associated with impaired feedback learning, while the administration of anticholinergics to PD patients impairs transfer generalization.

Please cite this article in press as: Moustafa, A. A., & Gluck, M. A. Computational cognitive models of prefrontal-striatal-hippocampal interactions in Parkinson's disease and schizophrenia. Neural Networks (2011), doi:10.1016/j.neunet.2011.02.006

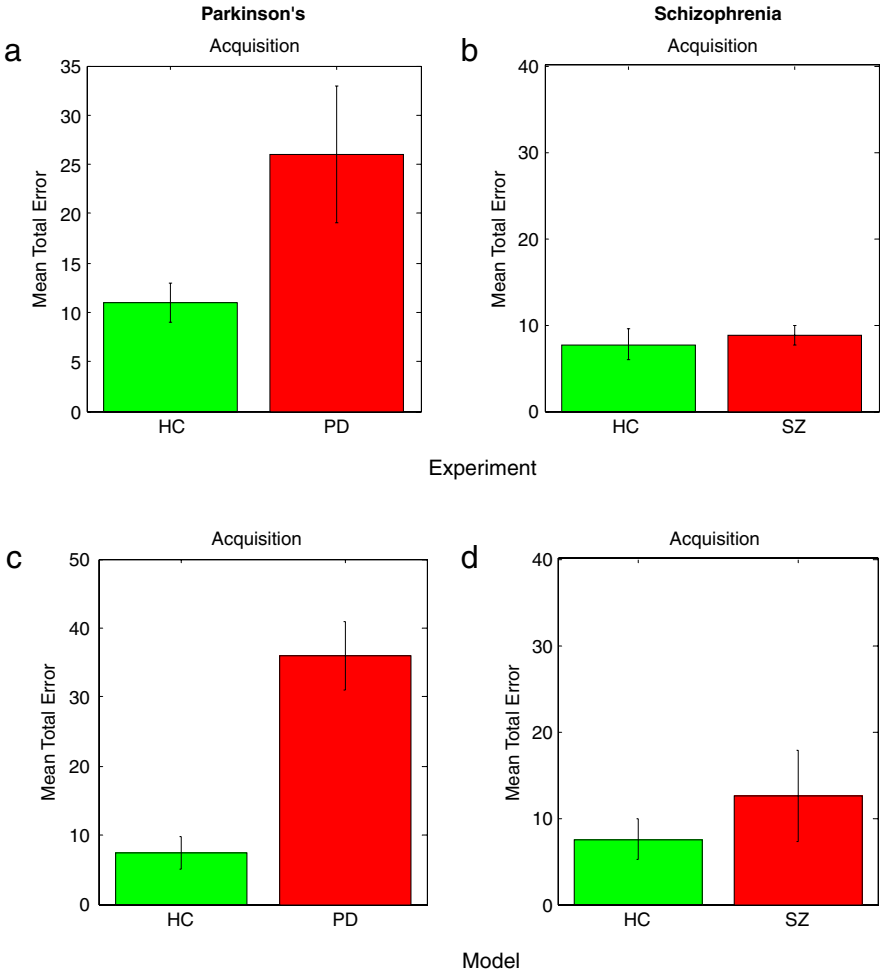


Fig. 4. PD patients but not schizophrenic patients are impaired at feedback learning. (a) PD patients (Myers, Shohamy, Gluck, Grossman, Kluger et al., 2003a). (b) Schizophrenic patients (Keri et al., 2005b) (c) simulation of PD patients' performance (d) simulation of schizophrenic patients' performance. Adapted from Moustafa et al. (2010). Adapted from Moustafa et al. (2010). Abbreviations: HC, healthy controls; PD, Parkinson's patients; SZ; schizophrenia.

8. Simulation of the effects of deficit and nondeficit schizophrenia on cognition

As mentioned above, various clinical studies have shown that deficit and nondeficit schizophrenic patients have different cognitive profiles.

At our laboratory, we have found that while deficit schizophrenic patients are impaired at both the learning and transfer phases of the acquired equivalence task, nondeficit schizophrenic patients only are impaired at the transfer phase of this task (Farkas et al., 2008). Research suggests that nondeficit schizophrenia is associated with hippocampal dysfunction, while deficit schizophrenia is associated with both hippocampal and striatal dysfunction (Buchanan et al., 1993; Heckers et al., 1999; Polgar et al., 2010; Tamminga et al., 1992). In agreement with experimental results showing that deficit schizophrenia is associated with hippocampal damage and dysfunction of D1 receptors in the basal ganglia (Monteleone et al., 2002), we simulate deficit schizophrenia by removing the hippocampus module and decreasing learning rate parameter in the striatal module in our striatal–hippocampal model (Moustafa et al., 2010). In agreement with empirical findings (Farkas et al., 2008), our simulations show that both deficit and nondeficit schizophrenic patients are impaired at transfer generalization, while deficit schizophrenic patients are more impaired at learning than nondeficit schizophrenic patients (Fig. 8(a) and (b)).

9. Discussion

We have built computational models of frontal–striatal (Moustafa & Gluck, 2010) and striatal–hippocampal interactions (Moustafa et al., 2010) to simulate cognitive performance in PD and schizophrenia. PD and schizophrenia affect the prefrontal–striatal–hippocampal system in different ways: PD is associated with fronto-striatal dysfunction, while nondeficit schizophrenia is associated with hippocampal dysfunction.

Our computational models simulate performance in a range of cognitive tasks, including feedback learning, reversal learning, and learning-and-transfer "acquired equivalence". Various empirical studies show that dopamine medications and agents impair stimulus–response learning performance in both PD patients (Gotham et al., 1988; Jahanshahi et al., 2009; Shohamy et al., 2006) and healthy controls (Breitenstein et al., 2006; Santesso et al., 2009). The Moustafa and Gluck (2010) model shows that a decreasing learning rate (due to increase of dopamine levels in the basal ganglia and prefrontal cortex) leads to impairment in performing the weather prediction task, in line with empirical results (Jahanshahi et al., 2009). The Moustafa and Gluck (2010) model also simulates the findings that medicated PD patients are impaired at performing reversal tasks, due to increase of dopamine levels in the prefrontal cortex. Simulation results show that during the reversal phase, increase of dopamine levels in the prefrontal cortex made the model shifts attention to different stimuli instead of learning to reverse responses, which

Please cite this article in press as: Moustafa, A. A., & Gluck, M. A. Computational cognitive models of prefrontal-striatal-hippocampal interactions in Parkinson's disease and schizophrenia. Neural Networks (2011), doi:10.1016/j.neunet.2011.02.006

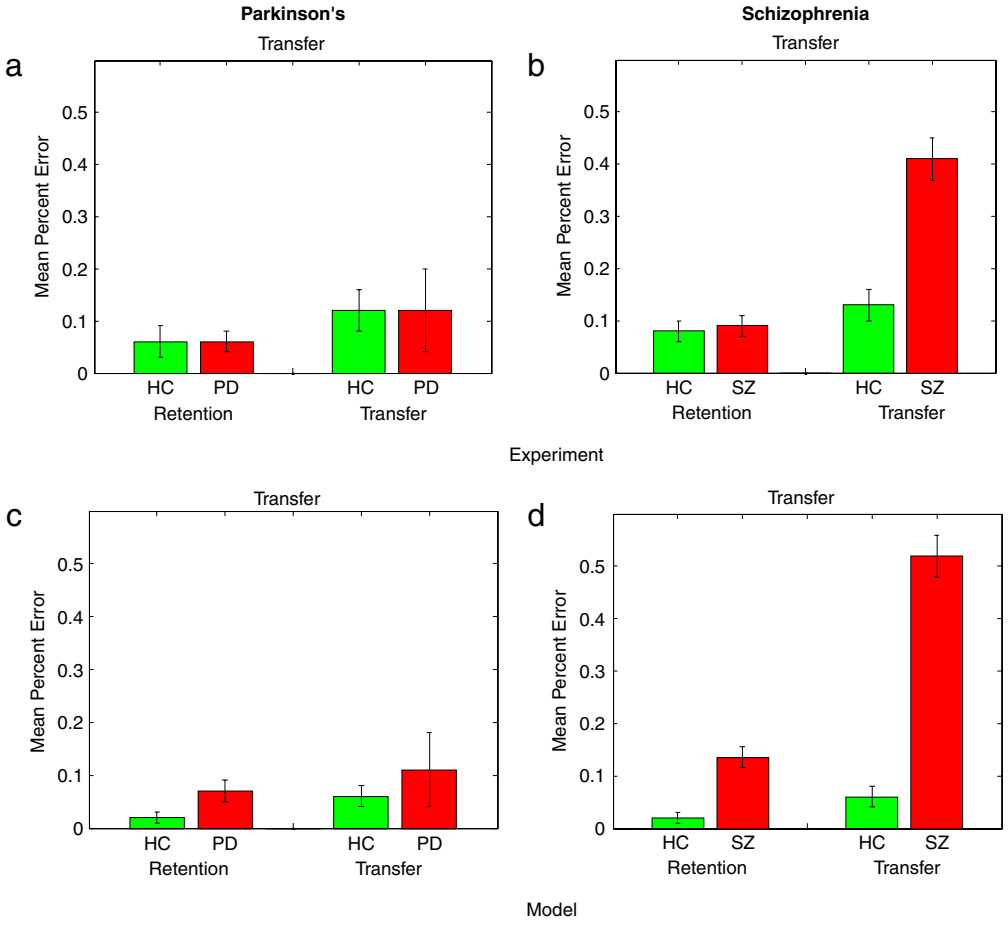
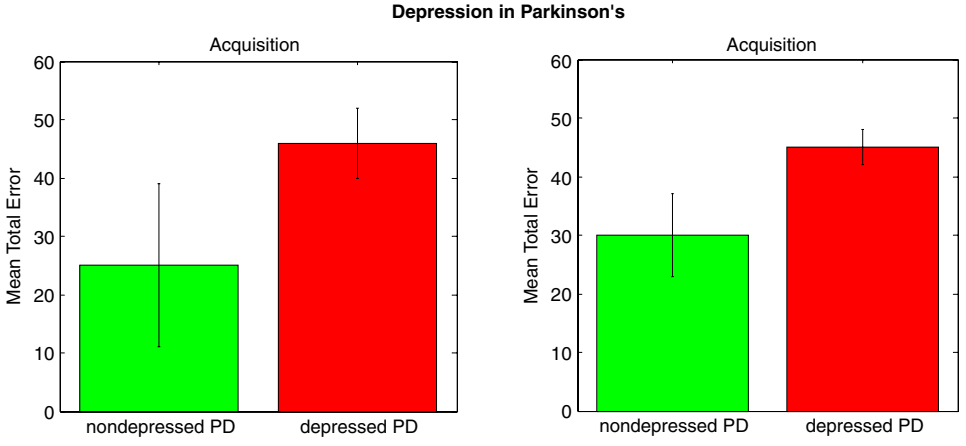


Fig. 5. Schizophrenic but not PD patients are impaired at transfer generalization of the learning-and-transfer task (a) PD patients (Myers, Shohamy, Gluck, Grossman, Kluger et al., 2003a). (b) Schizophrenic patients (Keri et al., 2005b) (c) simulation of PD patients' performance (d) simulation of schizophrenic patients' performance. Adapted from Moustafa et al. (2010).

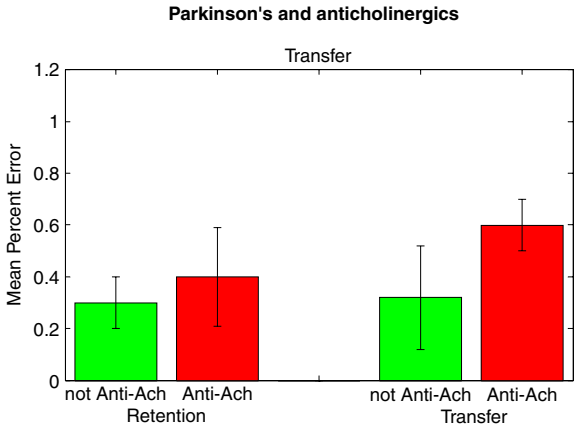


(a) Experiment (b) Model

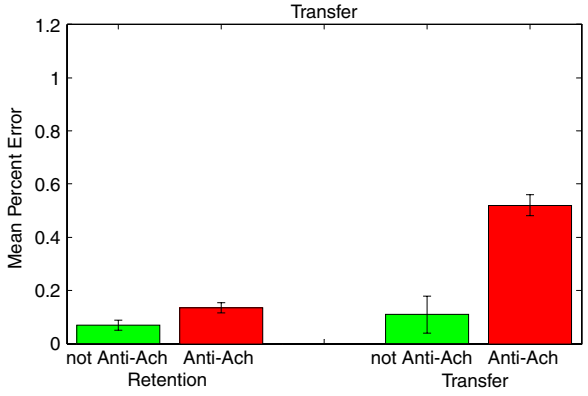
Fig. 6. Depressed PD patients are further impaired at feedback learning Herzallah et al. (2010). Simulation results of PD depression. (a) Empirical results of Herzallah et al. (2010). (b) Simulation results using the Moustafa et al. (2010) model.

delays learning. Specifically, we have found in our simulations that two factors influence reversal performance: (a) receiving negative feedback, (b) activation levels of prefrontal nodes (which, in our model, are manipulated by tonic dopamine levels). First, negative feedback decreases weights associated with the previously winning prefrontal node, and thus decreases its activation value in subsequent trials. In this case, the difference of activation values of prefrontal nodes becomes smaller than their differences during acquisition phase. Second, we simulate an increase in tonic dopamine by increasing gain value of a sigmoidal activation function, as previously proposed in models of schizophrenia (Amos, 2000; Cohen & Servan-Schreiber, 1992). In our model, increase in tonic dopamine levels increases activity of prefrontal nodes, which in turn enhances attentional shifting performance (see Schultz, 2007, for discussion). Specifically, increasing the gain value causes the sigmoidal function to

Please cite this article in press as: Moustafa, A. A., & Gluck, M. A. Computational cognitive models of prefrontal-striatal-hippocampal interactions in Parkinson's disease and schizophrenia. Neural Networks (2011), doi:10.1016/j.neunet.2011.02.006



(a) Experiment



(b) Model

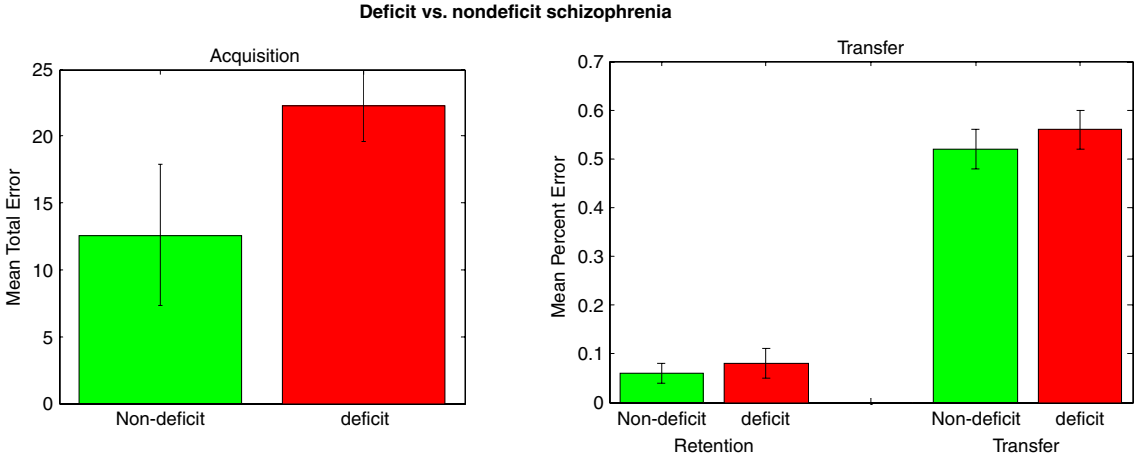
Fig. 7. PD patients on anticholinergics are impaired at generalization than PD patients not on anticholinergics. (a) Empirical results of Herzallah et al. (2010). (b) Simulation results using the Moustafa et al. (2010) model. Abbreviations: Anti-Ach refers to PD patients on anticholinergics, while "not Anti-Ach" refers to PD patients not on anticholinergics.

decrease the difference between the representations of inputs. In other words, increasing the gain value increases the competitive dynamics in the simulated prefrontal cortex and the likelihood to shift to a new dimension. From these two points, we have found that that an increase in tonic dopamine levels, as in medicated PD simulations) increase activity and competition among prefrontal nodes, which in turn enhance selecting different stimuli following negative feedback. This delays reversal learning since reversal learning is acquired more quickly if the model (and subjects) just learned to reverse motor responses (in the basal ganglia module), and not shift attention to other irrelevant cues (in the prefrontal module).

Interestingly, the same mechanism of reversal performance in our model also explains enhanced attentional performance in medicated PD patients as we showed in our earlier work (Moustafa & Gluck, 2010) and as reported experimentally (Cools et al., 2001; Swainson et al., 2000). Furthermore, the Moustafa and Gluck (2010) model shows that increasing the number of training trials in the reversal phase enhances performance of medicated PD patients. We conclude that impaired performance of medicated PD patients in the reversal task in the Cools et al. (2001)study is perhaps due to the use of a low number of trials in the reversal phase. Future experimental research should confirm (or disconfirm) model prediction.

Our models also simulate cognitive dysfunction in subtypes of PD and schizophrenia. In agreement with existing results (Herzallah et al., 2010), our simulation results show that depressed PD patients are more impaired than nondepressed patients on feedback learning. We also simulate the effects of anticholinergics on hippocampal function. Our simulation results show that the administration of anticholinergics to PD patients impair hippocampal function, and thus impair transfer generalization, in line with our empirical findings (Herzallah et al., 2010).

Furthermore, research has shown that deficit and nondeficit schizophrenia are associated with different neural and cognitive dysfunction. While nondeficit schizophrenia is associated with hippocampal dysfunction, deficit schizophrenia is additionally associated with frontostriatal dysfunction (Buchanan et al., 1993; Farkas et al., 2008; Heckers et al., 1999; Polgar et al., 2008, 2010; Tamminga et al., 1992). Our models also simulate cognitive dysfunction in deficit and nondeficit schizophrenic patients. As in our empirical findings (Farkas et al., 2008), our simulations show that while both deficit and nondeficit schizophrenic patients are impaired at transfer generalization, deficit schizophrenic patients only are impaired at feedback learning. Unlike other models of schizophrenia (reviewed below), our Moustafa et al. (2010) model simulates the effects of negative symptoms on cognition. In line with empirical results, we assumed that negative symptoms are



(a) acquisition (b) transfer

Fig. 8. Simulation of the effects of deficit and nondeficit schizophrenia on learning and transfer "acquired equivalence" task. Farkas et al. (2008) have found that nondeficit schizophrenic patients are impaired at the transfer generalization phase, but deficit schizophrenic patients are impaired at acquisition and transfer phases. (a) Simulation results of the effects of deficit and nondeficit schizophrenia on learning. (b) Simulation results of the effects of deficit and nondeficit schizophrenia on transfer generalization.

Please cite this article in press as: Moustafa, A. A., & Gluck, M. A. Computational cognitive models of prefrontal-striatal-hippocampal interactions in Parkinson's disease and schizophrenia. Neural Networks (2011), doi:10.1016/j.neunet.2011.02.006

associated with disregulation of striatal and frontal D1 receptors, and thus associated with impaired learning, as reported in many studies (Murray et al., 2008). One limitation of this model is it does not have a prefrontal module and thus does not simulate the effect of deficit and nondeficit schizophrenia on working memory. For example, Polgar et al. (2010) have recently shown that deficit schizophrenic patients are more impaired at working memory than nondeficit patients. This is perhaps due to more severe prefrontal dysfunction in deficit schizophrenic patients, which has been reported in the literature (Okubo et al., 1997).

9.1. Existing models of PD and schizophrenia

Below, we review how existing models of PD and schizophrenia relate prefrontal, hippocampal, or striatal dysfunction to cognitive and psychiatric deficits in these patients.

There are very few models that simulate cognitive performance in both PD and schizophrenia (Amos, 2000; Monchi, Taylor, & Dagher, 2000; Moustafa et al., 2010). Amos (2000) simulates performance in the Wisconsin Card Sorting Task in Parkinson's disease, Huntington's disease, and schizophrenic patients, using mathematical techniques similar to those used by Moustafa and Gluck (2010). The Amos model showed that decreasing activity of the prefrontal cortex explains working memory deficits in schizophrenia, and it also shows that decreasing activity in basal ganglia and prefrontal cortex modules simulates impaired performance in Parkinson's disease patients. In the Amos model, 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. As in our model, Amos argues that prefrontal cortex 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 prefrontal cortex from the basal ganglia informed prefrontal cortex whether to maintain or change the sorting rule (not modeled). The model simulated the occurrence of perseverative and random responses in prefrontal cortex-damaged and PD patients. Unlike our models (Moustafa & Gluck, 2010; Moustafa et al., 2009, 2010), the Amos model is not a learning model and does not simulate the role of the hippocampus in cognition.

Monchi and colleagues (Monchi et al., 2000) proposed a model that simulates the role of frontostriatal loops in working memory in PD and schizophrenic patients. This model argues that PD is associated with basal ganglia dysfunction, while schizophrenia is associated with both basal ganglia and frontal dysfunction. The model successfully accounts for various data on the effects of PD and schizophrenia on working memory. Specifically, Monchi et al. (2000) simulate PD by decreasing values of weights connecting prefrontal cortex and striatal units. Like Amos (2000) model, Monchi et al. did not simulate the role of dopamine in learning and does not incorporate a hippocampal module.

Most of the existing models focus on simulating the role of the frontostriatal and/or dopaminergic dysfunction in PD patients. Existing models of schizophrenia simulate the effects of frontal or hippocampal dysfunction on cognition and psychosis. Below, we review these models, starting by models of PD.

9.1.1. Models of frontostriatal dysfunction in Parkinson's disease

We here review computational models that address the effects of PD on cognition. Most, if not all, existing models of PD focus on simulating the functional contribution of the basal ganglia and/or prefrontal cortex to motor and cognitive processes (Amos, 2000; Frank, 2005; Guthrie et al., 2009; Moustafa & Gluck, 2010; Moustafa et al., 2009). The most common framework for simulating the role of the basal ganglia in feedback learning is the actor-critic model (Berns & Sejnowski, 1995; Houk, 1995a; Joel, Niv, & Ruppin, 2002; Redish, Jensen, Johnson, & Kurth-Nelson, 2007; Suri, Bargas, & Arbib, 2001; Suri & Schultz, 1998). 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, 1995). 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. Based on existing actor-critic models, Moustafa and Gluck (2010) simulate the effects of PD and dopamine medications on stimulus–response learning; our model assumes that dopamine medications increase tonic dopamine levels in the basal ganglia and prefrontal cortex. This in turn reduces phasic signaling of dopamine cells, and thus impairs learning (for similar assumptions, see Breitenstein et al., 2006).

The Moustafa and Gluck (2010) model also simulates performance in reversal learning tasks. Reversal learning is arguably more complex than stimulus–response learning, and there are fewer models of reversal learning than stimulus–response learning. Frank (2005) proposed a model that simulates performance in probabilistic reversal tasks. Unlike our model, Frank (2005) assumes that reversal deficits in medicated PD patients are due to impaired learning in the basal ganglia indirect pathway (which we did not incorporate in the model). A more recent model by Frank and Claus (2006) incorporates the orbitofrontal cortex and simulates performance in reversal tasks. Assuming that dopamine medications might perhaps overdose and thus impair the function of the orbitofrontal cortex (as argued by Cools et al., 2001), the Frank and Claus model can readily simulate reversal learning performance in medicated PD patients. Unlike the Frank (2005) model, we show that reversal deficits in medicated PD patients are perhaps due to prefrontal dysfunction, as originally argued by Cools et al. (2001). Although we provide an alternative interpretation of existing data on how dopamine medications might affect reversal learning performance, the Frank (2005) model and our model are plausible, and provide different predictions.

As similar to our model, 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 temporal difference (TD) algorithm. Like our models, Suri and Schulz assume that the striatum subserved motor responses, and that lateral connectivity of striatal neurons, simulated by a winner-take-all network, subserve action selection. In a neurophysiological study, Schultz et al. (1997) found dopamine phasic signals in healthy monkeys are associated with the presentation of rewarding stimuli during early trials of an instrumental conditioning task, but then time shift to the presentation of reward predicting stimuli in late training trials. Building on this finding, Suri and Schultz specifically argue that in PD, the dopamine reward signal is always associated with the time of the primary reward, whether predicted or not, and thus does not time shift to the presentation of reward predicting stimuli. This concept is known as the unconditional reinforcement signal. Training the model using an unconditional

Please cite this article in press as: Moustafa, A. A., & Gluck, M. A. Computational cognitive models of prefrontal-striatal-hippocampal interactions in Parkinson's disease and schizophrenia. Neural Networks (2011), doi:10.1016/j.neunet.2011.02.006

reinforcement signal, Suri and Schultz (1999) found that the model generated perseverative responses comparable to those found in PD patients. These results suggest that inappropriate time shifting of the dopamine phasic signal can explain the occurrence of perseverative responses in PD (for similar results, see Moustafa & Maida, 2007). Interestingly, a recent fMRI study supports the hypothesis of inappropriate time shifting of phasic dopamine signaling to the time of unconditioned stimuli in PD patients (Schott et al., 2007). The Suri and Schultz (1999) model did not simulate the effects of dopamine medications on cognition in PD patients.

At our laboratory, we have also built a computational model of prefrontal cortex and basal ganglia interactions during sequence learning performance in medicated and unmedicated PD patients (Guthrie et al., 2009). Like the Moustafa and Gluck (2010) model, Guthrie et al. assume that PD is associated with decreased phasic and tonic dopamine signaling, while dopamine medications increase tonic dopamine and further decrease the phasic signaling of dopamine cells. Unlike the Moustafa and Gluck (2010) model, the Guthrie model assumes that PD and dopamine medications mainly affect the basal ganglia, though experimental studies found evidence that dopamine medications do increase dopamine levels in the prefrontal cortex Carey, Pinheiro-Carrera, Dai, Tomaz, and Huston (1995); Dagher and Robbins (2009) and Diaconescu et al. (2010).

9.1.2. Models of prefrontal and hippocampal dysfunction in schizophrenia

Most existing models of schizophrenia simulate the contribution of either the prefrontal cortex (Cohen & Servan-Schreiber, 1992; Rolls, Loh, Deco, & Winterer, 2008; Wang, 2006), hippocampal region (Chen, 1995; Lisman, Pi, Zhang, & Otmakhova, 2010; Siekmeier, Hasselmo, Howard, & Coyle, 2007; Talamini & Meeter, 2009), or dopamine (Schmajuk, 2005) to cognitive dysfunction and/or the occurrence of psychotic episodes.

For example, Talamini and Meeter (2009) argue contextual processing deficits in schizophrenic patients are due to hippocampal and medial temporal lobe dysfunction. A recent empirical study by the same group confirmed model hypothesis (Talamini, de Haan, Nieman, Linszen, & Meeter, 2010). Similarly, Hasselmo and colleagues have simulated the role of the hippocampus, and particularly area CA1, in contextual processes (Siekmeier et al., 2007). Unlike the Talamini and Meeter (2009) model, Siekmeier et al. (2007) focus on simulating the function of NMDA receptors in contextual processing. Like these models, our striatal–hippocampal model also argues that hippocampal damage underlies some of the cognitive deficits observed in schizophrenic patients. For example, Moustafa et al. (2009) shows that hippocampal damage, as in schizophrenia, impairs contextual shifting. Furthermore, the Moustafa et al. (2010) model shows that transfer generalization deficits in schizophrenic patients are due to hippocampal dysfunction.

Other existing models relate cognitive dysfunction in schizophrenia to prefrontal damage. For example, Cohen and colleagues argue that cognitive and working memory deficits in schizophrenic patients are caused by a dysfunction to prefrontal dopamine (Cohen, Braver, & O'Reilly, 1996). Specifically, Cohen and colleagues argue that that schizophrenia is associated with decreased phasic dopamine and increased tonic dopamine in the prefrontal cortex (Braver & Cohen, 1999). In sum, these models suggest that different neural deficits underlie dissociable cognitive dysfunction in schizophrenic patients: while working memory dysfunction is caused by prefrontal damage, contextual learning and transfer generalization deficits are caused by hippocampal damage in schizophrenia.

Interestingly, like cognitive dysfunction, existing models also relate the occurrence of psychotic episodes in schizophrenia to either hippocampal, prefrontal, or dopaminergic dysfunction (Chen, 1995; Corlett et al., 2007; Lisman et al., 2010; Rolls et al., 2008). There are at least three theories regarding how neural dysfunction leads to psychotic symptoms in schizophrenia.

(1) Rolls et al. (2008) argue that prefrontal dysfunction is the mechanism underlying the occurrence of psychotic symptoms in schizophrenic patients. Rolls et al. argue that impaired working memory leads to aberrant maintenance of information in working memory. Rolls et al. argue that psychosis corresponds to the maintenance of a large amount of irrelevant information in working memory. Interestingly, a more recent model by Rolls and colleagues argue that cortical GABA dysfunction is responsible for psychotic episodes in schizophrenia (Rolls & Deco, 2010).

(2) In contract, Fletcher and colleagues (Corlett et al., 2007; Fletcher & Frith, 2008) argue that psychosis is related to disrupted prediction error signaling in the prefrontal cortex. In other words, Corlett et al. argue that disrupted error prediction learning leads to the reinforcement of random information that are not generally linked to reward. Frank (2008) has similarly argued that aberrant prediction error learning is responsible for positive symptoms in schizophrenia. In line with these ideas, McDannald and Schoenbaum (2009) have designed a new reward-based learning paradigm to test psychosis in rats. McDannald and Schoenbaum argue that psychosis is related to the aberrant association of neutral stimuli with rewarding stimuli, such that in schizophrenic animals, these neutral stimuli will function as rewarding stimuli. We are not aware of any simulation model that relates reward processes to psychotic episodes in schizophrenia.

(3) In contrast to the dopaminergic and prefrontal accounts for the occurrence of psychosis in schizophrenia, some argue that psychotic symptoms in schizophrenia are caused by hippocampal damage (Chen, 1995; Grace, 2010; Lisman et al., 2010). Chen (1995) proposed a one-layer attractor network which addresses how hippocampal dysfunction in schizophrenia leads to psychotic symptoms. This model assumes that psychosis is related to aberrant retrieval of information from memory. The Chen model shows that an increase of correlation of encoding inputs in the hippocampus interferes with retrieval processes, such that the model will retrieve wrong information at the wrong time. Chen argues that retrieval of wrong information from the hippocampus's long-term memory store corresponds to psychotic symptoms. Lisman et al. (2010) have provided an alternative theory to how hippocampal dysfunction leads to psychotic episodes. Like the Siekmeier et al. (2007) model, Lisman et al. focus on simulating the role of NMDA dysfunction in schizophrenia. Lisman et al. argue that NMDA dysfunction increases the activity of CA1, which in turn increase firing of dopamine, and thus causes psychosis. Similarly, Grace (2010), argue that hippocampal damage is responsible for increased dopamine levels in schizophrenia. Our computational models did not simulate the occurrence of psychotic episodes in schizophrenia (Moustafa et al., 2010).

Future models should simulate both cognitive and psychiatric dysfunction in schizophrenia within a single framework. Benefit of such models is to study correlations between psychiatric (e.g., psychosis, apathy, delusion) and cognitive (e.g., learning, working memory, cognitive control) variables in schizophrenia, as is the case in clinical studies (Murray et al., 2008).

Please cite this article in press as: Moustafa, A. A., & Gluck, M. A. Computational cognitive models of prefrontal-striatal-hippocampal interactions in Parkinson's disease and schizophrenia. Neural Networks (2011), doi:10.1016/j.neunet.2011.02.006

9.1.3. Models of prefrontal–striatal–hippocampal interactions

Few theoretical and simulation models have addressed the interactions among the prefrontal cortex, basal ganglia, and hippocampus, but did not simulate performance in neurological or psychiatric disorders (Grace, 2008; Hazy, Frank, & O'Reilly, 2006, 2007; Turnock & Becker, 2007). Hazy and colleagues (Hazy et al., 2006, 2007) proposed a model simulating roles of the prefrontal cortex, basal ganglia, and hippocampus in working memory and executive control. This model integrates features from existing models of the hippocampal models (O'Reilly & Norman, 2002) and basal ganglia models (O'Reilly & Frank, 2006), but also extends these models by providing a detailed model of phasic dopamine firing patterns (for similar ideas on development of phasic dopamine responses, see Brown, Bullock, & Grossberg, 1999). Like Frank, Loughry, and O'Reilly (2001) model, the Hazy et al. model assumes the basal ganglia is key for gating for perceptual information into working memory (for similar ideas, see Moustafa & Maida, 2007). Like our model (Moustafa & Gluck, 2010), the Hazy model incorporates data showing that the prefrontal cortex is key for maintenance of information in working memory. Unlike the O'Reilly and Frank (2006) model, the Hazy model also simulates the role of the hippocampus in working memory.

In another physiologically-inspired theoretical model, Grace (2008) argued that the ventral striatum is controlled by either the prefrontal and hippocampal system, such that increase of dopamine levels shifts the control from the prefrontal cortex to the hippocampus, and a decrease in dopamine levels shifts the control to the prefrontal system (Grace, 2008). The Grace model is not a simulation model, and it is not clear how it might relate to motor and cognitive processes. Recently, Turnock and Becker (2007) proposed a simulation model incorporating Grace's theoretical ideas, and further simulate performance in conditioning paradigms. Although the Turnock and Becker and Hazy models did not simulate performance in patient populations, they provide insights in the nature of interactions of the prefrontal cortex, basal ganglia, and hippocampus.

9.1.4. Future directions: simulation of the effects of levodopa, dopamine agonists, and antipsychotics

Although there are frontostriatal models of the effects of dopamine medications on cognition in PD (Frank, 2005; Guthrie et al., 2009; Moustafa & Gluck, 2010), none of these models addressed dissociable effects of the different dopamine medications, such as levodopa or non-ergot dopamine agonists, on cognition in PD patients. In addition, we are not aware of any computational model that simulates the effects of antipsychotics on cognition in schizophrenic patients. Below, we explain how an extension of our models can help understand the effects of levodopa, dopamine agonists, and antipsychotics on motoric, psychiatric, and cognitive processes.

Because levodopa, dopamine agonists, and antipsychotics target selective dopamine receptors, the simulation of different dopamine receptors in the basal ganglia and prefrontal cortex is essential for understanding the effects of these medications on motor and cognitive processes. Dopamines D1 and D2 receptors are often expressed in different neurons in the basal ganglia, hippocampus, and prefrontal cortex (Gerfen, 1992; Hopf, Cascini, Gordon, Diamond, & Bonci, 2003). One limitation of our models (Moustafa et al., 2010, 2009) is they do not simulate the functional roles of the different dopamine receptors in the basal ganglia and prefrontal cortex. Some existing models have addressed the function of dopamine receptors in striatum (Frank, 2005) and prefrontal cortex (Cohen, Braver, & Brown, 2002). Frank (2005) argued that D1 receptors in the basal ganglia are key learning from positive feedback, while D2 receptors are important for learning from negative feedback. The Frank model does not incorporate the different dopamine receptors in the prefrontal cortex, and does not simulate differential effects of levodopa vs. dopamine agonists on cognition. In contrast, Cohen et al. (2002) argued that D1 and D2 receptors in the prefrontal cortex play different roles, such that prefrontal D1 receptors are important for maintenance of information in working memory, while prefrontal D2 receptors are important for learning. Cohen et al. (2002) did not address how disruption to prefrontal dopamine receptors might relate to psychiatric or cognitive function in schizophrenia.

Physiological and behavioral studies have pointed out 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, while levodopa is a dopamine precursor, taken up by dopamine cells and converted into dopamine; thus, it acts on both D1 and D2 dopamine receptors. Behaviorally, neuropsychological studies have shown that unlike dopamine agonist, the administration of levodopa to healthy subjects and PD patients enhances learning (Beeler et al., 2010; Floel et al., 2008; Graef et al., 2010) and working memory (Costa et al., 2003; Fernandez-Ruiz, Doudet, & Aigner, 1999; Pascual-Sedano et al., 2008). In a new computational model, we have simulated the differential effects of levodopa and dopamine agonists on brain and cognition (Moustafa & Gluck, under review). This model argues that the dissociable effects of levodopa and dopamine agonists on cognition are related to their affinity to different dopamine receptors. Because D1 receptors are associated with learning, working memory, our model provides a mechanistic account for how levodopa (but not dopamine agonists) enhances learning and working memory.

Future models should address the effects of levodopa and dopamine agonists on impulse control disorders and levodopa-induced dyskinesia. For example, experimental studies have shown that dopamine agonists (and to a lesser extent levodopa) lead to impulse control disorders in PD patients (Weintraub, 2008). Our model suggests that impulse control disorders might be caused by an overstimulation of D2 receptors, which leads to a decrease in phasic dopamine firing. This, in turn, leads to impaired reward learning (Ray & Strafella, 2010), and, consequently, to repetitive reward-seeking behavior. Furthermore, the chronic administration of levodopa to PD patients leads to dyskinesia, a phenomenon known as levodopa-induced dyskinesia. In our model, this is because of levodopa's higher affinity for D1 receptors, which overstimulates motor learning, and thus eventually leads to dyskinesia (Sammut et al., 2006). Unlike levodopa, dopamine agonists have weaker affinity to D1 receptors, and are consequently less associated with dyskinesia. Future models should explicitly simulate the effects of levodopa and dopamine agonists on impulse control disorders and dyskinesia in PD patients.

Simulating the function of dopamine D1 and D2 receptors in the basal ganglia and prefrontal cortex will also help understand the effects of antipsychotics on cognition in schizophrenic patients. Empirical research have found that although antipsychotics decrease psychotic episodes, they might cause (a) Parkinsonism (phenomenon known as neuroleptic-induced Parkinsonism (Moratalla et al., 1996; Parr-Brownlie & Hyland, 2005; Sumaya et al., 2004) and (b) may not alleviate impairment in some cognitive functions in schizophrenic patients (Holmes et al., 2005).

In our modeling framework, antipsychotics cause Parkinsonism because they inhibit D2 receptors. While D1 receptors are overexpressed in the basal ganglia direct pathway, D2 receptors are more abundant in basal ganglia indirect pathway (Gerfen, 1992), which is essential for initiating motor responses (Gerfen, 2000; Kitagawa et al., 2009; Matsukawa et al., 2007; Tremblay et al., 2009). Thus, inhibiting D2 receptors increases the inhibitory function of the basal ganglia indirect pathway, which in turn attenuates the initiation of

Please cite this article in press as: Moustafa, A. A., & Gluck, M. A. Computational cognitive models of prefrontal-striatal-hippocampal interactions in Parkinson's disease and schizophrenia. Neural Networks (2011), doi:10.1016/j.neunet.2011.02.006

motor responses. Interestingly, first-generation (typical) antipsychotics, such as haloperidol, have higher affinity to D2 receptors and more associated with Parkinsonism than second-generation (atypical) antipsychotics, such as clozapine (Abi-Dargham & Laruelle, 2005; Joy, Adams, & Lawrie, 2006; Juckel et al., 2006). Building on the same theory, a further inhibition of D2 receptors by first-generation antipsychotics will further attenuates the initiation of motor responses, and thus explain why they are more associated with Parkinsonism than second-generation antipsychotics.

Furthermore, our model suggests that cognitive and working memory deficits in both medicated (Holmes et al., 2005) and unmedicated (van Veelen et al., 2010) schizophrenic patients may be due to dysfunction of D1 receptors in the prefrontal cortex (Abi-Dargham, 2003), which have shown to be important for working memory processes (Abi-Dargham et al., 2002; Castner & Goldman-Rakic, 2004; McNab et al., 2009; Sawaguchi, 2001; Williams & Goldman-Rakic, 1995). Antipsychotics mainly target D2 receptors and thus do not affect D1-mediated working memory. In addition, unlike second-generation antipsychotics, first-generation antipsychotics are more associated with impaired feedback learning (Bedard et al., 2000; Paquet et al., 2004; Purdon, Woodward, Lindborg, & Stip, 2003; Scherer et al., 2004). In our modeling framework, the administration of first-generation antipsychotics should further inhibit D2 receptors and thus decrease dopamine levels in the basal ganglia, which has been shown to be essential for feedback learning (Reynolds et al., 2001; Schultz et al., 1997; Tsai et al., 2009). A further decrease in basal ganglia dopamine by first-generation antipsychotics will further impair learning, and thus explain why they are more associated with impaired feedback learning than second-generation antipsychotics. In line with this theory, Zirnheld et al. (2004) have found that the administration of haloperidol to healthy subjects impairs learning. Future models should explicitly simulate the differential effects of first vs. second generation antipsychotics on psychiatric and cognitive function in schizophrenia.

9.2. Conclusion

Computational modeling has become an increasingly useful tool for understanding the complex linkages between brain and cognition. Our computational models incorporate the findings that the basal ganglia is key for stimulus–response learning (for similar ideas, also see Doya, 2000; Suri & Schultz, 1999), the hippocampus for stimulus–stimulus representational learning, and the prefrontal cortex for stimulus selection in learning (Gluck et al., 2005; Moustafa et al., 2010, 2009; Moustafa & Gluck, 2010). Our simulation results show how interactions among these brain systems explain cognitive performance in PD and schizophrenia, including feedback learning, reversal learning, and learning-and-transfer "acquired equivalence". Our models, for example, explain why PD patients show intact feedback learning, while schizophrenic patients show impaired feedback learning.

We also show that the simulation of function roles of the different dopamines D1 and D2 receptors in the prefrontal cortex and basal ganglia will explain the effects of levodopa, dopamine agonists, and antipsychotics on motoric, psychiatric, and cognitive processes. Future work is still needed to build on such prior models to simulate the dissociable effects of these medications on impulse control disorders, psychosis, dyskinesia, and Parkinsonism.

In contrast to other approaches that focus on simulating the role of a single brain area to the occurrence of motoric and cognitive dysfunction in brain disorders (Rolls & Deco, 2010), we adopt a systems-level approach to study how damage to different components of the prefrontal–striatal–hippocampal mechanism relates to cognitive dysfunction in subtypes of PD and schizophrenia and their associated medications.

References

Abi-Dargham, A. (2003). Probing cortical dopamine function in schizophrenia: what can D1 receptors tell us? *World Psychiatry*, *2*(3), 166–171.
Abi-Dargham, A., & Laruelle, M. (2005). Mechanisms of action of second generation antipsychotic drugs in schizophrenia: insights from brain imaging studies. *European Psychiatry*, *20*(1), 15–27.
Abi-Dargham, A., Mawlawi, O., Lombardo, I., Gil, R., Martinez, D., Huang, Y., et al. (2002). Prefrontal dopamine D1 receptors and working memory in schizophrenia. *Journal of Neuroscience*, *22*(9), 3708–3719.
Albouy, G., Sterpenich, V., Balteau, E., Vandewalle, G., Desseilles, M., Dang-Vu, T., et al. (2008). Both the hippocampus and striatum are involved in consolidation of motor sequence memory. *Neuron*, *58*(2), 261–272.
Aleman, A., Hijman, R., de Haan, E. H., & Kahn, R. S. (1999). Memory impairment in schizophrenia: a meta-analysis. *American Journal of Psychiatry*, *156*(9), 1358–1366.
Alexander, G. E., DeLong, M. R., & Strick, P. L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annual Review of Neuroscience*, *9*, 357–381.
Amos, A. (2000). A computational model of information processing in the frontal cortex and basal ganglia. *Journal of Cognitive Neuroscience*, *12*(3), 505–519.
Barto, A. G. (1995). Adaptive critics and the basal ganglia. In J. C. Houk, J. L. Davis, & D. G. Beiser (Eds.), *Models of information processing in the basal ganglia*. Cambridge, Mass: MIT Press, pp. xii, 382 p..
Bedard, M. A., Scherer, H., Stip, E., Cohen, H., Rodriguez, J. P., & Richer, F. (2000). Procedural learning in schizophrenia: further consideration on the deleterious effect of neuroleptics. *Brain and Cognition*, *43*(1–3), 31–39.
Beeler, J. A., Cao, Z. F., Kheirbek, M. A., Ding, Y., Koranda, J., Murakami, M., et al. (2010). Dopamine-dependent motor learning: insight into levodopa's long-duration response. *Annals of Neurology*, *67*(5), 639–647.
Berns, G. S., & Sejnowski, T. J. (1995). How the basal ganglia make decisions. In A. Damasio, H. Damasio, & Y. Christen (Eds.), *The neurobiology of decision making*. Springer-Verlag.
Bodi, N., Csibri, E., Myers, C. E., Gluck, M. A., & Keri, S. (2009a). Associative learning, acquired equivalence, and flexible generalization of knowledge in mild Alzheimer disease. *Cognitive & Behavioral Neurology*, *22*(2), 89–94.
Bodi, N., Keri, S., Nagy, H., Moustafa, A., Myers, C. E., Daw, N., et al. (2009b). Reward-learning and the novelty-seeking personality: a between- and within-subjects study of the effects of dopamine agonists on young Parkinson's patients. *Brain*, *132*(9), 2385–2395.
Bogerts, B., Meertz, E., & Schonfeldt-Bausch, R. (1985). Basal ganglia and limbic system pathology in schizophrenia. A morphometric study of brain volume and shrinkage. *Archives of General Psychiatry*, *42*(8), 784–791.
Boulougouris, V., Castane, A., & Robbins, T. W. (2009). Dopamine D2/D3 receptor agonist quinpirole impairs spatial reversal learning in rats: investigation of D3 receptor involvement in persistent behavior. *Psychopharmacology (Berlin)*, *202*(4), 611–620.
Brasted, P. J., Bussey, T. J., Murray, E. A., & Wise, S. P. (2003). Role of the hippocampal system in associative learning beyond the spatial domain. *Brain*, *126*(Pt. 5), 1202–1223.
Braver, T. S., & Cohen, J. D. (1999). Dopamine, cognitive control, and schizophrenia: the gating model. *Progress in Brain Research*, *121*, 327–349.
Breitenstein, C., Korsukewitz, C., Floel, A., Kretzschmar, T., Diederich, K., & Knecht, S. (2006). Tonic dopaminergic stimulation impairs associative learning in healthy subjects. *Neuropsychopharmacology*, *31*(11), 2552–2564.
Brown, J., Bullock, D., & Grossberg, S. (1999). How the basal ganglia use parallel excitatory and inhibitory learning pathways to selectively respond to unexpected rewarding cues. *Journal of Neuroscience*, *19*(23), 10502–10511.
Bruck, A., Kurki, T., Kaasinen, V., Vahlberg, T., & Rinne, J. O. (2004). Hippocampal and prefrontal atrophy in patients with early non-demented Parkinson's disease is related to cognitive impairment. *Journal of Neurology, Neurosurgery & Psychiatry*, *75*(10), 1467–1469.
Buchanan, R. W., Breier, A., Kirkpatrick, B., Elkashef, A., Munson, R. C., Gellad, F., et al. (1993). Structural abnormalities in deficit and nondeficit schizophrenia. *American Journal of Psychiatry*, *150*(1), 59–65.
Carey, R. J., Pinheiro-Carrera, M., Dai, H., Tomaz, C., & Huston, J. P. (1995). L-DOPA and psychosis: evidence for L-DOPA-induced increases in prefrontal cortex dopamine and in serum corticosterone. *Biological Psychiatry*, *38*(10), 669–676.
Cascella, N. G., Testa, S. M., Meyer, S. M., Rao, V. A., Diaz-Asper, C. M., Pearlson, G. D., et al. (2008). Neuropsychological impairment in deficit vs. non-deficit schizophrenia. *Journal of Psychiatric Research*, *42*(11), 930–937.
Castner, S. A., & Goldman-Rakic, P. S. (2004). Enhancement of working memory in aged monkeys by a sensitizing regimen of dopamine D1 receptor stimulation. *Journal of Neuroscience*, *24*(6), 1446–1450.
Cavada, C., Llamas, A., & Reinoso-Suarez, F. (1983). Allocortical afferent connections of the prefrontal cortex in the cat. *Brain Research*, *260*(1), 117–120.
Chen, E. Y. (1995). A neural network model of cortical information processing in schizophrenia. II—role of hippocampal–cortical interaction: a review and a model. *Canadian Journal of Psychiatry*, *40*(1), 21–26.
Cirillo, M. A., & Seidman, L. J. (2003). Verbal declarative memory dysfunction in schizophrenia: from clinical assessment to genetics and brain mechanisms. *Neuropsychology Review*, *13*(2), 43–77.
Clatworthy, P. L., Lewis, S. J., Brichard, L., Hong, Y. T., Izquierdo, D., Clark, L., et al. (2009). Dopamine release in dissociable striatal subregions predicts the different effects of oral methylphenidate on reversal learning and spatial working memory. *Journal of Neuroscience*, *29*(15), 4690–4696.

Please cite this article in press as: Moustafa, A. A., & Gluck, M. A. Computational cognitive models of prefrontal-striatal-hippocampal interactions in Parkinson's disease and schizophrenia. Neural Networks (2011), doi:10.1016/j.neunet.2011.02.006

Cohen, J. D., Barch, D. M., Carter, C., & Servan-Schreiber, D. (1999). Context-processing deficits in schizophrenia: converging evidence from three theoretically motivated cognitive tasks. *Journal of Abnormal Psychology*, *108*(1), 120–133.

Cohen, J. D., Braver, T. S., & Brown, J. W. (2002). Computational perspectives on dopamine function in prefrontal cortex. *Current Opinion in Neurobiology*, *12*(2), 223–229.

Cohen, J. D., Braver, T. S., & O'Reilly, R. C. (1996). A computational approach to prefrontal cortex, cognitive control and schizophrenia: recent developments and current challenges. *Philosophical Transactions of the Royal Society, Series B (Biological Sciences)*, *351*(1346), 1515–1527.

Cohen, J. D., & Servan-Schreiber, D. (1992). Context, cortex, and dopamine: a connectionist approach to behavior and biology in schizophrenia. *Psychological Review*, *99*(1), 45–77.

Cools, R., Barker, R. A., Sahakian, B. J., & Robbins, T. W. (2001). Enhanced or impaired cognitive function in Parkinson's disease as a function of dopaminergic medication and task demands. *Cerebral Cortex*, *11*(12), 1136–1143.

Cools, R., & Frank, M. J. (2009). Striatal dopamine predicts outcome-specific reversal learning and its sensitivity to dopaminergic drug administration. *Journal of Neuroscience*.

Corbit, L. H., & Balleine, B. W. (2000). The role of the hippocampus in instrumental conditioning. *Journal of Neuroscience*, *20*(11), 4233–4239.

Corlett, P. R., Murray, G. K., Honey, G. D., Aitken, M. R., Shanks, D. R., Robbins, T. W., et al. (2007). Disrupted prediction-error signal in psychosis: evidence for an associative account of delusions. *Brain*, *130*(Pt. 9), 2387–2400.

Costa, A., Peppe, A., Dell'Agnello, G., Carlesimo, G. A., Murri, L., Bonuccelli, U., et al. (2003). Dopaminergic modulation of visual–spatial working memory in Parkinson's disease. *Dementia and Geriatric Cognitive Disorders*, *15*(2), 55–66.

Cutsuridis, V., & Perantonis, S. (2006). A neural network model of Parkinson's disease bradykinesia. *Neural Networks*, *19*(4), 354–374.

Cutsuridis, V., & Wennekers, T. (2009). Hippocampus, microcircuits and associative memory. *Neural Networks*, *22*(8), 1120–1128.

Dagher, A., Owen, A. M., Boecker, H., & Brooks, D. J. (2001). The role of the striatum and hippocampus in planning: a PET activation study in Parkinson's disease. *Brain*, *124*(Pt. 5), 1020–1032.

Dagher, A., & Robbins, T. W. (2009). Personality, addiction, dopamine: insights from Parkinson's disease. *Neuron*, *61*(4), 502–510.

Dalley, J. W., Laane, K., Theobald, D. E., Armstrong, H. C., Corlett, P. R., Chudasama, Y., et al. (2005). Time-limited modulation of appetitive Pavlovian memory by D1 and NMDA receptors in the nucleus accumbens. *Proceedings of the National Academy of Sciences*, *102*(17), 6189–6194.

Diaconescu, A. O., Menon, M., Jensen, J., Kapur, S., & McIntosh, A. R. (2010). Dopamine-induced changes in neural network patterns supporting aversive conditioning. *Brain Research*, *1313*, 143–161.

Doya, K. (2000). Complementary roles of basal ganglia and cerebellum in learning and motor control. *Current Opinion in Neurobiology*, *10*(6), 732–739.

Dusek, J. A., & Eichenbaum, H. (1997). The hippocampus and memory for orderly stimulus relations. *Proceedings of the National Academy of Sciences*, *94*(13), 7109–7114.

Ehrt, U., Broich, K., Larsen, J. P., Ballard, C., & Aarsland, D. (2010). Use of drugs with anticholinergic effect and impact on cognition in Parkinson's disease: a cohort study. *Journal of Neurology, Neurosurgery & Psychiatry*, *81*(2), 160–165.

Farkas, M., Polgar, P., Kelemen, O., Rethelyi, J., Bitter, I., Myers, C. E., et al. (2008). Associative learning in deficit and nondeficit schizophrenia. *Neuroreport*, *19*(1), 55–58.

Feigin, A., Ghilardi, M. F., Carbon, M., Edwards, C., Fukuda, M., Dhawan, V., et al. (2003). Effects of levodopa on motor sequence learning in Parkinson's disease. *Neurology*, *60*(11), 1744–1749.

Fera, F., Nicoletti, G., Cerasa, A., Romeo, N., Gallo, O., Gioia, M. C., et al. (2007). Dopaminergic modulation of cognitive interference after pharmacological washout in Parkinson's disease. *Brain Research Bulletin*, *74*(1–3), 75–83.

Fera, F., Weickert, T. W., Goldberg, T. E., Tessitore, A., Hariri, A., Das, S., et al. (2005). Neural mechanisms underlying probabilistic category learning in normal aging. *Journal of Neuroscience*, *25*(49), 11340–11348.

Fernandez-Ruiz, J., Doudet, D., & Aigner, T. G. (1999). Spatial memory improvement by levodopa in parkinsonian MPTP-treated monkeys. *Psychopharmacology (Berlin)*, *147*(1), 104–107.

Fletcher, P. C., & Frith, C. D. (2008). Perceiving is believing: a Bayesian approach to explaining the positive symptoms of schizophrenia. *Nature Reviews Neuroscience*.

Floel, A., Vomhof, P., Lorenzen, A., Roesser, N., Breitenstein, C., & Knecht, S. (2008). Levodopa improves skilled hand functions in the elderly. *European Journal of Neuroscience*, *27*(5), 1301–1307.

Frank, M. J. (2005). Dynamic dopamine modulation in the basal ganglia: a neurocomputational account of cognitive deficits in medicated and nonmedicated Parkinsonism. *Journal of Cognitive Neuroscience*, *17*(1), 51–72.

Frank, M. J. (2008). Schizophrenia: a computational reinforcement learning perspective. *Schizophrenia Bulletin*, *34*(6), 1008–1011.

Frank, M. J., & Claus, E. D. (2006). Anatomy of a decision: striato-orbitofrontal interactions in reinforcement learning, decision making, and reversal. *Psychological Review*, *113*(2), 300–326.

Frank, M. J., Loughry, B., & O'Reilly, R. C. (2001). Interactions between frontal cortex and basal ganglia in working memory: a computational model. *Cognitive, Affective & Behavioral Neuroscience*, *1*(2), 137–160.

Frank, M. J., Seeberger, L. C., & O'Reilly, R. C. (2004). By carrot or by stick: cognitive reinforcement learning in parkinsonism. *Science*, *306*(5703), 1940–1943.

Gasbarri, A., Packard, M. G., Campana, E., & Pacitti, C. (1994). Anterograde and retrograde tracing of projections from the ventral tegmental area to the hippocampal formation in the rat. *Brain Research Bulletin*, *33*(4), 445–452.

Gerfen, C. R. (1992). The neostriatal mosaic: multiple levels of compartmental organization in the basal ganglia. *Annual Review of Neuroscience*, *15*, 285–320.

Gerfen, C. R. (2000). Molecular effects of dopamine on striatal-projection pathways. *Trends in Neurosciences*, *23*(10 Suppl.), S64–S70.

Gluck, M. A., Allen, M. T., Myers, C. E., & Thompson, R. F. (2001). Cerebellar substrates for error correction in motor conditioning. *Neurobiology of Learning and Memory*, *76*(3), 314–341.

Gluck, M. A., & Myers, C. E. (1993). Hippocampal mediation of stimulus representation: a computational theory. *Hippocampus*, *3*(4), 491–516.

Gluck, M. A., Myers, C., & Meeter, M. (2005). Cortico–hippocampal interaction and adaptive stimulus representation: a neurocomputational theory of associative learning and memory. *Neural Networks*, *18*(9), 1265–1279.

Gluck, M. A., Shohamy, D., & Myers, C. (2002). How do people solve the "weather prediction" task?: individual variability in strategies for probabilistic category learning. *Learning & Memory*, *9*(6), 408–418.

Goldman, M. B., & Mitchell, C. P. (2004). What is the functional significance of hippocampal pathology in schizophrenia? *Schizophrenia Bulletin*, *30*(2), 367–392.

Goldman-Rakic, P. S., Selemon, L. D., & Schwartz, M. L. (1984). Dual pathways connecting the dorsolateral prefrontal cortex with the hippocampal formation and parahippocampal cortex in the rhesus monkey. *Neuroscience*, *12*(3), 719–743.

Gomar, J. J., Pomarol-Clotet, E., Sarro, S., Salvador, R., Myers, C. E., & McKenna, P. J. (2011). Procedural learning in schizophrenia: reconciling the discrepant findings. *Biological Psychiatry*, *69*(1), 49–54.

Gotham, A. M., Brown, R. G., & Marsden, C. D. (1988). Frontal' cognitive function in patients with Parkinson's disease 'on' and 'off' levodopa. *Brain*, *111*(Pt. 2), 299–321.

Goto, Y., & Grace, (2008). Dopamine modulation of hippocampal–prefrontal cortical interaction drives memory-guided behavior. *Cereberal Cortex*, *18*(6), 1407–1414.

Grace, (2008). Physiology of the normal and dopamine–depleted basal ganglia: insights into levodopa pharmacotherapy. *Movement Disorders*, *23*(Suppl. 3), S560–S569.

Grace, (2010). Dopamine system dysregulation by the ventral subiculum as the common pathophysiological basis for schizophrenia psychosis, psychostimulant abuse, and stress. *Neurotoxicity Research*, *18*(3–4), 367–376.

Graef, S., Biele, Guido, Krugel, Lea K., Marzinzik, Frank, Wahl, Michael, Wotka, Johann, et al. (2010). Differential influence of levodopa on reward-based learning in Parkinson's disease. *Frontiers in Human Neuroscience*.

Guthrie, M., Myers, C. E., & Gluck, M. A. (2009). A neurocomputational model of tonic and phasic dopamine in action selection: a comparison with cognitive deficits in Parkinson's disease. *Behavioural Brain Research*.

Hazy, T. E., Frank, M. J., & O'Reilly, R. C. (2006). Banishing the homunculus: making working memory work. *Neuroscience*, *139*(1), 105–118.

Hazy, T. E., Frank, M. J., & O'Reilly, R. C. (2007). Towards an executive without a homunculus: computational models of the prefrontal cortex/basal ganglia system. *Philosophical Transactions of the Royal Society Series B (Biological Sciences)*.

Heckers, S. (2001). Neuroimaging studies of the hippocampus in schizophrenia. *Hippocampus*, *11*(5), 520–528.

Heckers, S., Goff, D., Schacter, D. L., Savage, C. R., Fischman, A. J., Alpert, N. M., et al. (1999). Functional imaging of memory retrieval in deficit vs. nondeficit schizophrenia. *Archives of General Psychiatry*, *56*(12), 1117–1123.

Herzallah, M., Moustafa, , Misk, A., Myers, C. E., & Gluck, M. A. (2010). Depression impairs acquisition, while anticholinergics impair transfer generalization in Parkinson's patients. *Cognitive and Behavioral Neurology*.

Holmes, A. J., MacDonald, A., 3rd, Carter, C. S., Barch, D. M., Andrew Stenger, V., & Cohen, J. D. (2005). Prefrontal functioning during context processing in schizophrenia and major depression: an event-related fMRI study. *Schizophrenia Research*, *76*(2–3), 199–206.

Hopf, F. W., Cascini, M. G., Gordon, A. S., Diamond, I., & Bonci, A. (2003). Cooperative activation of dopamine D1 and D2 receptors increases spike firing of nucleus accumbens neurons via G-protein betagamma subunits. *Journal of Neuroscience*, *23*(12), 5079–5087.

Houk, J. C. (1995a). Information processing in modular circuits linking basal ganglia and cerebral cortex. In J. C. Houk, J. L. Davis, & D. G. Beiser (Eds.), *Models of information processing in the basal ganglia*. Cambridge, Mass: MIT Press, pp. xii, 382 p.

Houk, J. C. (1995b). A model of how the basal ganglia generate and use neural signals that predict reinforcement. In J. C. Houk, J. L. Davis, & D. G. Beiser (Eds.), *Models of information processing in the basal ganglia*. Cambridge, Mass: MIT Press, pp. xii, 382 p.

Iba, M., & Sawaguchi, T. (2003). Involvement of the dorsolateral prefrontal cortex of monkeys in visuospatial target selection. *Journal of Neurophysiology*, *89*(1), 587–599.

Irle, E., & Markowitsch, H. J. (1982). Widespread cortical projections of the hippocampal formation in the cat. *Neuroscience*, *7*(11), 2637–2647.

Ito, R., Everitt, B. J., & Robbins, T. W. (2005). The hippocampus and appetitive Pavlovian conditioning: effects of excitotoxic hippocampal lesions on conditioned locomotor activity and autoshaping. *Hippocampus*, *15*(6), 713–721.

Please cite this article in press as: Moustafa, A. A., & Gluck, M. A. Computational cognitive models of prefrontal-striatal-hippocampal interactions in Parkinson's disease and schizophrenia. Neural Networks (2011), doi:10.1016/j.neunet.2011.02.006

Ito, R., Robbins, T. W., Pennartz, C. M., & Everitt, B. J. (2008). Functional interaction between the hippocampus and nucleus accumbens shell is necessary for the acquisition of appetitive spatial context conditioning. *Journal of Neuroscience*, *28*(27), 6950–6959.

Jahanshahi, M., Wilkinson, L., Gahir, H., Dharminda, A., & Lagnado, D. A. (2009). Medication impairs probabilistic classification learning in Parkinson's disease. *Neuropsychologia*.

Jellinger, K. A. (1999). Post mortem studies in Parkinson's disease—is it possible to detect brain areas for specific symptoms? *Journal of Neural Transmission*, *56*, 1–29.

Jentsch, J. D., Olausson, P., De La Garza, R., 2nd, & Taylor, J. R. (2002). Impairments of reversal learning and response perseveration after repeated, intermittent cocaine administrations to monkeys. *Neuropsychopharmacology*, *26*(2), 183–190.

Joel, D., Niv, Y., & Ruppin, E. (2002). Actor-critic models of the basal ganglia: new anatomical and computational perspectives. *Neural Networks*, *15*(4–6), 535–547.

Joy, C. B., Adams, C. E., & Lawrie, S. M. (2006). Haloperidol versus placebo for schizophrenia. *Cochrane Database of Systematic Reviews*, *4*, CD003082.

Juckel, G., Schlagenhauf, F., Koslowski, M., Filonov, D., Wustenberg, T., Villringer, A., et al. (2006). Dysfunction of ventral striatal reward prediction in schizophrenic patients treated with typical, not atypical, neuroleptics. *Psychopharmacology (Berlin)*, *187*(2), 222–228.

Keri, S. (2008). Interactive memory systems and category learning in schizophrenia. *Neuroscience & Biobehavioral Reviews*, *32*(2), 206–218.

Keri, S., Juhasz, A., Rimanoczy, A., Szekeres, G., Kelemen, O., Cimmer, C., et al. (2005a). Habit learning and the genetics of the dopamine D3 receptor: evidence from patients with schizophrenia and healthy controls. *Behavioral Neuroscience*, *119*(3), 687–693.

Keri, S., Kelemen, O., Szekeres, G., Bagoczky, N., Erdelyi, R., Antal, A., et al. (2000). Schizophrenics know more than they can tell: probabilistic classification learning in schizophrenia. *Psychological Medicine*, *30*(1), 149–155.

Keri, S., Nagy, O., Kelemen, O., Myers, C. E., & Gluck, M. A. (2005b). Dissociation between medial temporal lobe and basal ganglia memory systems in schizophrenia. *Schizophrenia Research*, *77*(2–3), 321–328.

Kish, S. J., Shannak, K., & Hornykiewicz, O. (1988). Uneven pattern of dopamine loss in the striatum of patients with idiopathic Parkinson's disease. Pathophysiologic and clinical implications. *New England Journal of Medicine*, *318*(14), 876–880.

Kitagawa, K., Kitamura, Y., Miyazaki, T., Miyaoka, J., Kawasaki, H., Asanuma, M., et al. (2009). Effects of pramipexole on the duration of immobility during the forced swim test in normal and ACTH-treated rats. *Naunyn-Schmiedeberg's Archives of Pharmacology*, *380*(1), 59–66.

Knowlton, B. J., Mangels, J. A., & Squire, L. R. (1996). A neostriatal habit learning system in humans. *Science*, *273*(5280), 1399–1402.

Knowlton, B. J., Squire, L. R., & Gluck, M. A. (1994). Probabilistic classification learning in amnesia. *Learning & Memory*, *1*(2), 106–120.

Lanoue, A. C., Dumitriu, A., Myers, R. H., & Soghomonian, J. J. (2010). Decreased glutamic acid decarboxylase mRNA expression in prefrontal cortex in Parkinson's disease. *Experimental Neurology*.

Lansink, C. S., Goltstein, P. M., Lankelma, J. V., McNaughton, B. L., & Pennartz, C. M. (2009). Hippocampus leads ventral striatum in replay of place-reward information. *PLoS Biology*, *7*(8), e1000173.

Leeson, V. C., Robbins, T. W., Matheson, E., Hutton, S. B., Ron, M. A., Barnes, T. R., et al. (2009). Discrimination learning, reversal, and set-shifting in first-episode schizophrenia: stability over six years and specific associations with medication type and disorganization syndrome. *Biological Psychiatry*, *66*(6), 586–593.

Levey, A. I. (1993). Immunological localization of m1–m5 muscarinic acetylcholine receptors in peripheral tissues and brain. *Life Sciences*, *52*(5–6), 441–448.

Lisman, J. E., & Grace, (2005). The hippocampal-VTA loop: controlling the entry of information into long-term memory. *Neuron*, *46*(5), 703–713.

Lisman, J. E., Pi, H. J., Zhang, Y., & Otmakhova, N. A. (2010). A thalamo–hippocampal–ventral tegmental area loop may produce the positive feedback that underlies the psychotic break in schizophrenia. *Biological Psychiatry*, *68*(1), 17–24.

Loh, M., Rolls, E. T., & Deco, G. (2007). A dynamical systems hypothesis of schizophrenia. *PLoS Computational Biology*, *3*(11), e228.

Marsh, L. (2004). Psychosis in Parkinson's disease. *Current Treatment Options in Neurology*, *6*(3), 181–189.

Matsukawa, N., Maki, M., Yasuhara, T., Hara, K., Yu, G., Xu, L., et al. (2007). Overexpression of D2/D3 receptors increases efficacy of ropinirole in chronically 6-OHDA-lesioned Parkinsonian rats. *Brain Research*, *1160*, 113–123.

McClelland, J. L., McNaughton, B. L., & O'Reilly, R. C. (1995). Why there are complementary learning systems in the hippocampus and neocortex: insights from the successes and failures of connectionist models of learning and memory. *Psychological Review*, *102*(3), 419–457.

McDannald, M., & Schoenbaum, G. (2009). Toward a model of impaired reality testing in rats. *Schizophrenia Bulletin*, *35*(4), 664–667.

McDonald, R. J., Ko, C. H., & Hong, N. S. (2002). Attenuation of context-specific inhibition on reversal learning of a stimulus-response task in rats with neurotoxic hippocampal damage. *Behavioral Brain Research*, *136*(1), 113–126.

McKirdy, J., Sussmann, J. E., Hall, J., Lawrie, S. M., Johnstone, E. C., & McIntosh, A. M. (2009). Set shifting and reversal learning in patients with bipolar disorder or schizophrenia. *Psychological Medicine*, *39*(8), 1289–1293.

McNab, F., Varrone, A., Farde, L., Jucaite, A., Bystritsky, P., Forssberg, H., et al. (2009). Changes in cortical dopamine D1 receptor binding associated with cognitive training. *Science*, *323*(5915), 800–802.

Meco, G., Casacchia, M., Lazzari, R., Franzese, A., Castellana, F., Carta, A., et al. (1984). Mental impairment in Parkinson's disease. The role of anticholinergic drugs. *Acta Psychiatrica Belgica*, *84*(4), 325–335.

Mitchell, D. G., Rhodes, R. A., Pine, D. S., & Blair, R. J. (2008). The contribution of ventrolateral and dorsolateral prefrontal cortex to response reversal. *Behavioural Brain Research*, *187*(1), 80–87.

Monchi, O., Taylor, J. G., & Dagher, A. (2000). A neural model of working memory processes in normal subjects, Parkinson's disease and schizophrenia for fMRI design and predictions. *Neural Networks*, *13*(8–9), 953–973.

Monteleone, P., Di Lieto, A., Martiadis, V., Bartoli, L., & Maj, M. (2002). Correlations between negative symptoms and peripheral *G* protein levels in mononuclear leukocytes of deficit and nondeficit schizophrenics. Preliminary results. *European archives of psychiatry and clinical neuroscience*, *252*(5), 214–218.

Moratalla, R., Xu, M., Tonegawa, S., & Graybiel, A. M. (1996). Cellular responses to psychomotor stimulant and neuroleptic drugs are abnormal in mice lacking the D1 dopamine receptor. *Proceedings of the National Academy of Sciences*, *93*(25), 14928–14933.

Moustafa, A. A., & Gluck, M. A. (Under review). Levodopa vs. dopamine agonists effects on cognition: a computational hypothesis.

Moustafa, A. A., & Gluck, M. A. (2010). Neurocomputational model of dopamine and prefrontal–striatal interactions during multicue category learning by Parkinson's patients. *Journal of Cognitive Neuroscience*.

Moustafa, A. A., Keri, S., Herzallah, M. M., Myers, C. E., & Gluck, M. A. (2010). A neural model of hippocampal–striatal interactions in associative learning and transfer generalization in various neurological and psychiatric patients. *Brain and Cognition*, *74*(2), 132–144.

Moustafa, , & Maida, A. S. (2007). Using TD learning to simulate working memory performance in a model of the prefrontal cortex and basal ganglia. *Cognitive Systems Research*, *8*, 262–281.

Moustafa, , Myers, C. E., & Gluck, M. A. (2009). A neurocomputational model of classical conditioning phenomena: a putative role for the hippocampal region in associative learning. *Brain Research*, *1276*, 180–195.

Murray, G. K., Cheng, F., Clark, L., Barnett, J. H., Blackwell, A. D., Fletcher, P. C., et al. (2008). Reinforcement and reversal learning in first-episode psychosis. *Schizophrenia Bulletin*, *34*(5), 848–855.

Myers, C. E., Hopkins, R. O., DeLuca, J., Moore, N. B., Wolansky, L. J., Sumner, J. M., et al. (2008). Learning and generalization deficits in patients with memory impairments due to anterior communicating artery aneurysm rupture or hypoxic brain injury. *Neuropsychology*, *22*(5), 681–686.

Myers, C. E., Shohamy, D., Gluck, M. A., Grossman, S., Kluger, A., Ferris, S., et al. (2003a). Dissociating hippocampal versus basal ganglia contributions to learning and transfer. *Journal of Cognitive Neuroscience*, *15*(2), 185–193.

Myers, C. E., Shohamy, D., Gluck, M. A., Grossman, S., Onlaor, S., & Kapur, N. (2003b). Dissociating medial temporal and basal ganglia memory systems with a latent learning task. *Neuropsychologia*, *41*(14), 1919–1928.

O'Doherty, J., Dayan, P., Schultz, J., Deichmann, R., Friston, K., & Dolan, R. J. (2004). Dissociable roles of ventral and dorsal striatum in instrumental conditioning. *Science*, *304*(5669), 452–454.

Okubo, Y., Suhara, T., Suzuki, K., Kobayashi, K., Inoue, O., Terasaki, O., et al. (1997). Decreased prefrontal dopamine D1 receptors in schizophrenia revealed by PET. *Nature*, *385*(6617), 634–636.

O'Reilly, R. C., & Frank, M. J. (2006). Making working memory work: a computational model of learning in the prefrontal cortex and basal ganglia. *Neural Computation*, *18*(2), 283–328.

O'Reilly, R. C., & Norman, K. A. (2002). Hippocampal and neocortical contributions to memory: advances in the complementary learning systems framework. *Trends in Cognitive Sciences*, *6*(12), 505–510.

Owen, A. M., Roberts, A. C., Hodges, J. R., Summers, B. A., Polkey, C. E., & Robbins, T. W. (1993). Contrasting mechanisms of impaired attentional set-shifting in patients with frontal lobe damage or Parkinson's disease. *Brain*, *116*(Pt. 5), 1159–1175.

Parkinson, J. A., Dalley, J. W., Cardinal, R. N., Bamford, A., Fehnert, B., Lachenal, G., et al. (2002). Nucleus accumbens dopamine depletion impairs both acquisition and performance of appetitive Pavlovian approach behaviour: implications for mesoaccumbens dopamine function. *Behavioural Brain Research*, *137*(1–2), 149–163.

Parr-Brownlie, L. C., & Hyland, B. I. (2005). Bradykinesia induced by dopamine D2 receptor blockade is associated with reduced motor cortex activity in the rat. *Journal of Neuroscience*, *25*(24), 5700–5709.

Pascual-Sedano, B., Kulisevsky, J., Barbanoj, M., Garcia-Sanchez, C., Campolongo, A., Gironell, A., et al. (2008). Levodopa and executive performance in Parkinson's disease: a randomized study. *Journal of International Neuropsychological Society*, *14*(5), 832–841.

Pasupathy, A., & Miller, E. K. (2005). Different time courses of learning-related activity in the prefrontal cortex and striatum. *Nature*, *433*(7028), 873–876.

Paquet, F., Soucy, J. P., Stip, E., Levesque, M., Elie, A., & Bedard, M. A. (2004). Comparison between olanzapine and haloperidol on procedural learning and the relationship with striatal D2 receptor occupancy in schizophrenia. *Journal of Neuropsychiatry Clinical Neuroscience*, *16*(1), 47–56.

Peoples, L. L., Uzwiak, A. J., Gee, F., & West, M. O. (1997). Operant behavior during sessions of intravenous cocaine infusion is necessary and sufficient for phasic firing of single nucleus accumbens neurons. *Brain Research*, *757*(2), 280–284.

Pizzagalli, D. A., Evins, A. E., Schetter, E. C., Frank, M. J., Pajtas, P. E., Santesso, D. L., et al. (2007). Single dose of a dopamine agonist impairs reinforcement learning in humans: behavioral evidence from a laboratory-based measure of reward responsiveness. *Psychopharmacology (Berlin)*.

Please cite this article in press as: Moustafa, A. A., & Gluck, M. A. Computational cognitive models of prefrontal-striatal-hippocampal interactions in Parkinson's disease and schizophrenia. Neural Networks (2011), doi:10.1016/j.neunet.2011.02.006

Polgar, P., Farkas, M., Nagy, O., Kelemen, O., Rethelyi, J., Bitter, I., et al. (2008). How to find the way out from four rooms? The learning of "chaining" associations may shed light on the neuropsychology of the deficit syndrome of schizophrenia. *Schizophrenia Research*, *99*(1–3), 200–207.

Polgar, P., Rethelyi, J. M., Balint, S., Komlosi, S., Czobor, P., & Bitter, I. (2010). Executive function in deficit schizophrenia: what do the dimensions of the Wisconsin card sorting test tell us? *Schizophrenia Research*, *122*(1–3), 85–93.

Pondal, M., Del Ser, T., & Bermejo, F. (1996). Anticholinergic therapy and dementia in patients with Parkinson's disease. *Journal of Neurology*, *243*(7), 543–546.

Prediger, R. D., Batista, L. C., Medeiros, R., Pandolfo, P., Florio, J. C., & Takahashi, R. N. (2006). The risk is in the air: intranasal administration of MPTP to rats reproducing clinical features of Parkinson's disease. *Experimental Neurology*, *202*(2), 391–403.

Purdon, S. E., Woodward, N., Lindborg, S. R., & Stip, E. (2003). Procedural learning in schizophrenia after 6 months of double-blind treatment with olanzapine, risperidone, and haloperidol. *Psychopharmacology (Berl)*, *169*(3–4), 390–397.

Rametti, G., Junque, C., Vendrell, P., Catalan, R., Penades, R., Bargallo, N., et al. (2009). Hippocampal underactivation in an fMRI study of word and face memory recognition in schizophrenia. *European Archive of Psychiatry and Clinical Neuroscience*, *259*(4), 203–211.

Ray, N., & Strafella, A. P. (2010). Dopamine, reward, and frontostriatal circuitry in impulse control disorders in Parkinson's disease: insights from functional imaging. *Clinical EEG and Neuroscience*, *41*(2), 87–93.

Redish, A. D., Jensen, S., Johnson, A., & Kurth-Nelson, Z. (2007). Reconciling reinforcement learning models with behavioral extinction and renewal: implications for addiction, relapse, and problem gambling. *Psychological Review*, *114*(3), 784–805.

Reynolds, J. N., Hyland, B. I., & Wickens, J. R. (2001). A cellular mechanism of reward-related learning. *Nature*, *413*(6851), 67–70.

Richfield, E. K., Penney, J. B., & Young, A. B. (1989). Anatomical and affinity state comparisons between dopamine D1 and D2 receptors in the rat central nervous system. *Neuroscience*, *30*(3), 767–777.

Roberts, B. M., Seymour, P. A., Schmidt, C. J., Williams, G. V., & Castner, S. A. (2010). Amelioration of ketamine-induced working memory deficits by dopamine D1 receptor agonists. *Psychopharmacology (Berlin)*, *210*(3), 407–418.

Rolls, E. T., & Deco, G. (2010). A computational neuroscience approach to schizophrenia and its onset. *Neuroscience & Biobehavioral Reviews*.

Rolls, E. T., Loh, M., Deco, G., & Winterer, G. (2008). Computational models of schizophrenia and dopamine modulation in the prefrontal cortex. *Nature Reviews Neuroscience*, *9*(9), 696–709.

Rosene, D. L., & Van Hoesen, G. W. (1977). Hippocampal efferents reach widespread areas of cerebral cortex and amygdala in the rhesus monkey. *Science*, *198*(4314), 315–317.

Rossato, J. I., Bevilaqua, L. R., Izquierdo, I., Medina, J. H., & Cammarota, M. (2009). Dopamine controls persistence of long-term memory storage. *Science*, *325*(5943), 1017–1020.

Rueter, L. E., Ballard, M. E., Gallagher, K. B., Basso, A. M., Curzon, P., & Kohlhaas, K. L. (2004). Chronic low dose risperidone and clozapine alleviate positive but not negative symptoms in the rat neonatal ventral hippocampal lesion model of schizophrenia. *Psychopharmacology (Berlin)*, *176*(3–4), 312–319.

Sammut, S., Dec, A., Mitchell, D., Linardakis, J., Ortiguela, M., & West, A. R. (2006). Phasic dopaminergic transmission increases NO efflux in the rat dorsal striatum via a neuronal NOS and a dopamine D(1/5) receptor-dependent mechanism. *Neuropsychopharmacology*, *31*(3), 493–505.

Samson, Y., Wu, J. J., Friedman, A. H., & Davis, J. N. (1990). Catecholaminergic innervation of the hippocampus in the cynomolgus monkey. *Journal of Comparative Neurology*, *298*(2), 250–263.

Santesso, D. L., Evins, A. E., Frank, M. J., Schetter, E. C., Bogdan, R., & Pizzagalli, D. A. (2009). Single dose of a dopamine agonist impairs reinforcement learning in humans: evidence from event-related potentials and computational modeling of striatal–cortical function. *Human Brain Mapping*, *30*(7), 1963–1976.

Sawaguchi, T. (2001). The effects of dopamine and its antagonists on directional delay-period activity of prefrontal neurons in monkeys during an oculomotor delayed-response task. *Neuroscience Research*, *41*(2), 115–128.

Scherer, H., Bedard, M. A., Stip, E., Paquet, F., Richer, F., Beriault, M., et al. (2004). Procedural learning in schizophrenia can reflect the pharmacologic properties of the antipsychotic treatments. *Cognitive & Behavioral Neurology*, *17*(1), 32–40.

Schmajuk, N. (2005). Brain-behaviour relationships in latent inhibition: a computational model. *Neuroscience & Biobehavioral Reviews*, *29*(6), 1001–1020.

Schott, B. H., Niehaus, L., Wittmann, B. C., Schutze, H., Seidenbecher, C. I., Heinze, H. J., et al. (2007). Ageing and early-stage Parkinson's disease affect separable neural mechanisms of mesolimbic reward processing. *Brain*, *130*(Pt. 9), 2412–2424.

Schultz, W. (2007). Multiple dopamine functions at different time courses. *Annual Review of Neuroscience*, *30*, 259–288.

Schultz, W., Dayan, P., & Montague, P. R. (1997). A neural substrate of prediction and reward. *Science*, *275*(5306), 1593–1599.

Servan-Schreiber, D., Carter, C. S., Bruno, R. M., & Cohen, J. D. (1998). Dopamine and the mechanisms of cognition: part II. D-amphetamine effects in human subjects performing a selective attention task. *Biological Psychiatry*, *43*(10), 723–729.

Shen, A. Y., & Tsai, C. T. (1995). Neural connection from hippocampus to nucleus accumbens and the subpallidal area and their contribution to locomotor activity. *Chinese Journal of Physiology*, *38*(2), 111–116.

Shohamy, D., Mihalakos, P., Chin, R., Thomas, B., Wagner, A. D., & Tamminga, C. (2010). Learning and generalization in schizophrenia: effects of disease and antipsychotic drug treatment. *Biological Psychiatry*, *67*(10), 926–932.

Shohamy, D., Myers, C. E., Geghman, K. D., Sage, J., & Gluck, M. A. (2006). *L*-dopa impairs learning, but spares generalization, in Parkinson's disease. *Neuropsychologia*, *44*(5), 774–784.

Shohamy, D., Myers, C. E., Onlaor, S., & Gluck, M. A. (2004). Role of the basal ganglia in category learning: how do patients with Parkinson's disease learn? *Behavioral Neuroscience*, *118*(4), 676–686.

Siekmeier, P. J., Hasselmo, M. E., Howard, M. W., & Coyle, J. (2007). Modeling of context-dependent retrieval in hippocampal region CA1: implications for cognitive function in schizophrenia. *Schizophrenia Research*, *89*(1–3), 177–190.

Somlai, Z., Moustafa, , Keri, S., Myers, C. E., & Gluck, M. A. (2010). General functioning predicts reward and punishment learning in schizophrenia. *Schizophrenia Research*.

Sumaya, I. C., Byers, D. M., Irwin, L. N., Del Val, S., & Moss, D. E. (2004). Circadian-dependent effect of melatonin on dopaminergic D2 antagonist-induced hypokinesia and agonist-induced stereotypies in rats. *Pharmacology, Biochemistry, & Behavior*, *78*(4), 727–733.

Suri, R. E., Bargas, J., & Arbib, M. A. (2001). Modeling functions of striatal dopamine modulation in learning and planning. *Neuroscience*, *103*(1), 65–85.

Suri, R. E., & Schultz, W. (1998). Learning of sequential movements by neural network model with dopamine-like reinforcement signal. *Experimental Brain Research*, *121*(3), 350–354.

Suri, R. E., & Schultz, W. (1999). A neural network model with dopamine-like reinforcement signal that learns a spatial delayed response task. *Neuroscience*, *91*(3), 871–890.

Swainson, R., Rogers, R. D., Sahakian, B. J., Summers, B. A., Polkey, C. E., & Robbins, T. W. (2000). Probabilistic learning and reversal deficits in patients with Parkinson's disease or frontal or temporal lobe lesions: possible adverse effects of dopaminergic medication. *Neuropsychologia*, *38*(5), 596–612.

Swanson, L. W. (1981). A direct projection from Ammon's horn to prefrontal cortex in the rat. *Brain Research*, *217*(1), 150–154.

Tadaiesky, M. T., Dombrowski, P. A., Figueiredo, C. P., Cargnin-Ferreira, E., Da Cunha, C., & Takahashi, R. N. (2008). Emotional, cognitive and neurochemical alterations in a premotor stage model of Parkinson's disease. *Neuroscience*, *156*(4), 830–840.

Talamini, L. M., de Haan, L., Nieman, D. H., Linszen, D. H., & Meeter, M. (2010). Reduced context effects on retrieval in first-episode schizophrenia. *PLoS One*, *5*(4), e10356.

Talamini, L. M., & Meeter, M. (2009). Dominance of objects over context in a mediotemporal lobe model of schizophrenia. *PLoS One*, *4*(8), e6505.

Tamminga, C. A., Thaker, G. K., Buchanan, R., Kirkpatrick, B., Alphs, L. D., Chase, T. N., et al. (1992). Limbic system abnormalities identified in schizophrenia using positron emission tomography with fluorodeoxyglucose and neocortical alterations with deficit syndrome. *Archives of General Psychiatry*, *49*(7), 522–530.

Tremblay, P. L., Bedard, M. A., Levesque, M., Chebli, M., Parent, M., Courtemanche, R., et al. (2009). Motor sequence learning in primate: role of the D2 receptor in movement chunking during consolidation. *Behavioral Brain Research*, *198*(1), 231–239.

Tsai, H. C., Zhang, F., Adamantidis, A., Stuber, G. D., Bonci, A., de Lecea, L., et al. (2009). Phasic firing in dopaminergic neurons is sufficient for behavioral conditioning. *Science*, *324*(5930), 1080–1084.

Tseng, K. Y., Chambers, R. A., & Lipska, B. K. (2009). The neonatal ventral hippocampal lesion as a heuristic neurodevelopmental model of schizophrenia. *Behavioral Brain Research*, *204*(2), 295–305.

Turnock, M., & Becker, S. (2007). A neural network model of hippocampal–striatal–prefrontal interactions in contextual conditioning. *Brain Research*.

van der Meer, M. A., Johnson, A., Schmitzer-Torbert, N. C., & Redish, A. D. (2010). Triple dissociation of information processing in dorsal striatum, ventral striatum, and hippocampus on a learned spatial decision task. *Neuron*, *67*(1), 25–32.

van Veelen, N. M., Vink, M., Ramsey, N. F., & Kahn, R. S. (2010). Left dorsolateral prefrontal cortex dysfunction in medication-naive schizophrenia. *Schizophrenia Research*, *123*(1), 22–29.

Vinogradov, S., Fisher, M., Warm, H., Holland, C., Kirshner, M. A., & Pollock, B. G. (2009). The cognitive cost of anticholinergic burden: decreased response to cognitive training in schizophrenia. *American Journal of Psychiatry*, *166*(9), 1055–1062.

Walter, U., Skoloudik, D., & Berg, D. (2010). Transcranial sonography findings related to non-motor features of Parkinson's disease. *Journal of the Neurological Sciences*, *289*(1–2), 123–127.

Waltz, J. A., Frank, M. J., Robinson, B. M., & Gold, J. M. (2007). Selective reinforcement learning deficits in schizophrenia support predictions from computational models of striatal–cortical dysfunction. *Biological Psychiatry*, *62*(7), 756–764.

Wang, X. J. (2006). Toward a prefrontal microcircuit model for cognitive deficits in schizophrenia. *Pharmacopsychiatry*, *39*(Suppl. 1), S80–S87.

Weickert, T. W., Terrazas, A., Bigelow, L. B., Malley, J. D., Hyde, T., Egan, M. F., et al. (2002). Habit and skill learning in schizophrenia: evidence of normal striatal processing with abnormal cortical input. *Learning & Memory*, *9*(6), 430–442.

Weiler, J. A., Bellebaum, C., Brune, M., Juckel, G., & Daum, I. (2009). Impairment of probabilistic reward-based learning in schizophrenia. *Neuropsychology*, *23*(5), 571–580.

Weinberger, D. R. (1999). Cell biology of the hippocampal formation in schizophrenia. *Biological Psychiatry*, *45*(4), 395–402.

Weintraub, D. (2008). Dopamine and impulse control disorders in Parkinson's disease. *Annals in Neurology*, *64*(Suppl. 2), S93–S100.

Please cite this article in press as: Moustafa, A. A., & Gluck, M. A. Computational cognitive models of prefrontal-striatal-hippocampal interactions in Parkinson's disease and schizophrenia. Neural Networks (2011), doi:10.1016/j.neunet.2011.02.006

Wickens, J. R., Begg, A. J., & Arbuthnott, G. W. (1996). Dopamine reverses the depression of rat corticostriatal synapses which normally follows high-frequency stimulation of cortex in vitro. *Neuroscience*, *70*(1), 1–5.
Williams, G. V., & Goldman-Rakic, P. S. (1995). Modulation of memory fields by dopamine D1 receptors in prefrontal cortex. *Nature*, *376*(6541), 572–575.
Williams-Gray, C. H., Hampshire, A., Barker, R. A., & Owen, A. M. (2008). Attentional control in Parkinson's disease is dependent on COMT val 158 met genotype. *Brain*, *131*(Pt. 2), 397–408.
Zirnheld, P. J., Carroll, C. A., Kieffaber, P. D., O'Donnell, B. F., Shekhar, A., & Hetrick, W. P. (2004). Haloperidol impairs learning and error-related negativity in humans. *Journal of Cognitive Neuroscience*, *16*(6), 1098–1112.
Zweifel, L. S., Parker, J. G., Lobb, C. J., Rainwater, A., Wall, V. Z., Fadok, J. P., et al. (2009). Disruption of NMDAR-dependent burst firing by dopamine neurons provides selective assessment of phasic dopamine-dependent behavior. *Proceedings of the National Academy of Sciences*, *106*(18), 7281–7288.

Please cite this article in press as: Moustafa, A. A., & Gluck, M. A. Computational cognitive models of prefrontal-striatal-hippocampal interactions in Parkinson's disease and schizophrenia. Neural Networks (2011), doi:10.1016/j.neunet.2011.02.006