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

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

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

HIGHLIGHTS

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

ABSTRACT

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

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder associated with reduced dopamine levels in the basal ganglia, particularly the dorsal striatum (Kish, Shannak, & Hornykiewicz, 1988; Rinne et al., 2000). In addition to motor dysfunction, PD patients show impairment performing various cognitive tasks such as planning (Dagher, Owen, Boecker, & Brooks, 1999; Owen, Doyon, Dagher, Sadikot, & Evans, 1998) and cognitive set shifting (Hayes, Davidson, Keele, & Rafal, 1998). PD patients also show impairment performing various working memory tasks, including delayed-response tasks (Partiot et al., 1996), the Wisconsin Card Sorting Task (Amos, 2000; Cooper, Sagar, Jordan, Harvey, & Sullivan, 1991; Lees & Smith, 1983; Owen et al., 1993; Pickett, Kuniholm, Protopapas, Friedman, & Lieberman, 1998), object and spatial span tasks...
that lesioning the basal ganglia in rats impairs stimulus–response learning. For example, Packard, Hirsh, and White (1989) found that lesioning the basal ganglia in rats impairs stimulus–response learning, but not long-term memory tasks. Jog, Kubota, Connolly, Hillegaart, and Graybiel (1999) recorded striatal neurons’ patterns of activity while rats performed a stimulus–response task, namely a T-maze task. Jog et al. found that the activation of striatal neurons increased while learning different motor plans in this task. These changes in firing patterns were associated with better performance, mainly a decrease in movement time and an increase in performance accuracy. The model we present here assumes that the basal ganglia are key for stimulus–response learning, consistent with several experimental and modeling studies.

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

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

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

Experimental studies suggest that the basal ganglia subserve stimulus–response learning. Graybiel (1998) noted that stimulus–response learning is (a) acquired very slowly and (b) usually occurs without awareness, processes that have been ascribed to the basal ganglia function (Frank). Lesion and physiological studies also confirm the key role of the basal ganglia in stimulus–response learning. For example, Packard, Hirsh, and White (1989) found that lesioning the basal ganglia in rats impairs stimulus–response learning.
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