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L-dopa impairs learning, but spares generalization, in Parkinson's disease

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Abstract

In this study we examined the effect of dopaminergic modulation on learning and memory. Parkinson's patients were tested 'on' versus 'off' dopaminergic medication, using a two-phase learning and transfer task. We found that dopaminergic medication was associated with impaired learning of an incrementally acquired concurrent discrimination task, while patients withdrawn from dopaminergic medication performed as well as controls. In addition, we found a dissociation of the effect of medication within a single two-phase task: patients tested 'on' medication were not impaired at the ability to generalize based on learned information. The deficit among medicated patients appeared to be related specifically to the concurrent, incremental, feedback-based nature of the task: such a deficit was not found in a version of the task in which demands for concurrent error-processing learning were reduced. Taken together with a growing body of evidence emphasizing a role for midbrain dopamine in error-correcting, feedback-based learning processes, the present results suggest a framework for understanding previously conflicting results regarding the effect of medication on learning and memory in Parkinson's disease.

Keywords: Dopamine; Learning; Memory; Basal ganglia; Cognition

1. Introduction

Converging evidence suggests that the midbrain dopamine system plays an important role in learning and memory. Electrophysiological studies have shown that midbrain dopamine neurons may contribute to reward-related or novelty-related learning (Horvitz, 2000; Schultz, 2002; Schultz & Dickinson, 2000; Schultz, Dayan, & Montague, 1997). Functional imaging studies in humans have also indicated a role for midbrain dopamine regions in several aspects of incremental learning, such as in the processing of reward, of expectancy of reward, and of error-correcting feedback (Aron et al., 2004; Delgado, Nystrom, Fissell, Noll, & Fiez, 2000; Delgado, Stenger, & Fiez, 2004; Knutson, Fong, Adams, Varner, & Hommer, 2001; Poldrack et al., 2001).

Neuropsychological studies of patients with dopamine dysfunction have also shown that midbrain dopamine may play an important role in particular types of learning and memory. In Parkinson's disease, there is a profound loss of dopamine-containing neurons in the substantia nigra compacta (SNc), leading to dopamine depletion in the striatum. Studies have shown that the loss of dopamine that occurs in Parkinson's disease leads to a variety of learning and memory deficits, particularly on tasks that involve incremental, feedback-based learning of cue-outcome associations (Canavan et al., 1989; Cools, Barker, Sahakian, & Robbins, 2001a; Cools, Barker, Sahakian, & Robbins, 2001b; Gotham, Brown, & Marsden, 1998; Knowlton, Mangels, & Squire, 1996; Myers et al., 2003; Shohamy et al., 2004a; Shohamy, Myers, Onlaor, & Gluck, 2004b; Swainson et al.,

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2000; Vriezen & Moscovitch, 1990). By contrast, Parkinson's patients are generally not impaired on tasks which involve declarative, non-feedback-based learning, or tasks that require flexible use of knowledge (Knowlton et al., 1996; Myers et al., 2003; Shohamy et al., 2004a)—functions which are thought to rely on the medial temporal lobe (Eichenbaum, 2002; Gabrieli, 1998; Gluck & Myers, 1993; Robbins, 1996; Squire & Zola, 1996). Taken together, these findings imply that modulation of dopamine levels in Parkinson's disease should have selective effects on learning and memory function depending on the specific task demands.

Studies examining the effect of dopaminergic medication on cognitive function in Parkinson's disease are generally consistent with this idea. Parkinson's disease is most commonly treated with L-dopa, a dopamine precursor synthesized into dopamine in the brain leading to increased dopamine levels. Studies which specifically examined the effect of L-dopa treatment on cognition suggest that the effect of L-dopa depends on the specific task demands—with L-dopa sometimes remediating, sometimes having no effect, and sometimes impairing cognition (Cools et al., 2001a; Fournet, Moreaud, Roulin, Naegele, & Pellat, 2000; Frank, Seeberger, & O'Reilly, 2004; Gotham et al., 1988; Mattay et al., 2002; Swainson et al., 2000). However, most of these prior studies focused on 'frontal'-like executive function tasks (such as working memory, planning, and set-shifting) and did not directly examine learning and memory per se. For example, Parkinson's patients are impaired on the Tower of London task and associated spatial working memory tests, and L-dopa ameliorates this deficit (Lange et al., 1992; Owen et al., 1992, 1993). Overall, there is considerable evidence suggesting that L-dopa often improves cognitive performance on tasks that depend on 'frontal' executive or working memory processes, especially in mild to moderate Parkinson's patients. By contrast, less is known of the impact of L-dopa on learning and memory, and most studies reporting learning and memory impairments in Parkinson's disease have tested only medicated patients (e.g. Canavan et al., 1989; Knowlton et al., 1996; Myers et al., 2003; Shohamy et al., 2004a, 2004b).

Recent studies have begun to examine the effect of L-dopa on learning and memory. These have shown that L-dopa sometimes improves and sometimes worsens performance, depending on the specific task demands (Frank et al., 2004; Cools et al., 2001a, 2001b; Swainson et al., 2000; Czernecki et al., 2001). For example, Cools et al. (2001a, 2001b) demonstrated that L-dopa impaired performance on a probabilistic reversal task, but facilitated task-switching performance in the same patients. Frank et al. (2004) examined the effect of L-dopa on a reinforcement based learning task, and found that L-dopa impaired learning that was based on negative outcomes, but facilitated learning that was based on positive outcomes. These findings emphasize the fact that the effects of L-dopa can differ even within a single task, depending on highly specific modifications to task demands.

Understanding the circumstances under which L-dopa facilitates or impairs learning and memory is important not only from a clinical perspective, but could also potentially provide important insights into the neural mechanisms underlying the role of dopamine in learning and memory. In particular, electrophysiological studies demonstrate that midbrain dopamine neurons respond to behaviorally important stimuli in a temporally specific, stimulus-specific manner: the signal occurs only in response to certain stimuli, and it is rapid and brief (Horvitz, 2000; Schultz, 2002; Schultz et al., 1997). These studies suggest that phasic dopamine signals (as opposed to tonic, ongoing dopamine release) may be critical for learning that involves incremental acquisition of stimulus-outcome associations via error-correcting feedback.

L-dopa, however, is thought to cause global increases in tonic dopamine levels in target areas, such as the neostriatum, consistent with recent pharmacological studies in rodents suggesting that L-dopa acts via non-dopaminergic neurons (Miller & Abercrombie, 1999; Tanaka et al., 1999; Yamato, Kannari, Shen, Suda, & Matsunaga, 2001). If midbrain dopamine signals are indeed critical for providing stimulus-specific, feedback-based information, enhanced levels of dopamine in the striatum coming from the 'wrong' neurons at the 'wrong' time may disrupt or mask critical stimulus-specific and temporally specific signals essential for feedback-based error-correction learning.

The purpose of the present study was to examine the effect of L-dopa on learning and memory in patients with mild to moderate Parkinson's disease, using an incremental learning task. In this task, participants are presented with a series of pairs of objects, and are required to learn to respond to the rewarded object in each pair. This task is similar to other incremental learning tasks previously shown to be impaired in Parkinson's patients (e.g. Canavan et al., 1989; Myers et al., 2003). In addition, we sought to assess whether the effects of medication are specific to incremental learning. To that end, following acquisition, participants were tested on a transfer/generalization phase, in which they were required to use what they have learned in the first phase to predict rewarded objects among a new set of stimuli. This kind of transfer has been shown to rely on the medial temporal lobe (Eichenbaum, Mathews, & Cohen, 1989; Myers et al., 2003; Preston, Shrager, Dudukovic, & Gabrieli, 2004), and is expected to be intact in patients with Parkinson's disease. In addition, given that transfer is not based on trial-by-trial feedback, rather presumably on representational changes that occur over time, performance on the transfer phase would not be expected to be affected by L-dopa.

Finally, we sought to assess which specific aspects of incremental learning might be most critical in contributing to learning deficits in Parkinson's disease. Drawing on electrophysiological, modeling and neuroimaging evidence for the role of midbrain dopamine regions in error-correcting feedback-based learning, we hypothesized that L-dopa would impair learning processes that rely on such error-correcting feedback, but might spare learning that does not involve such processes. To that end, in Experiment 2 we manipulated the degree to which learning involved error-processing and com-