



The impact of Parkinson's disease on sequence learning: Perceptual pattern learning and executive function

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ABSTRACT

The current study examined the contribution of brain areas affected by Parkinson's disease (PD) to sequence learning, with a specific focus on response-related processes, spatial attentional control, and executive functioning. Patients with mild PD, patients with moderate PD, and healthy age-matched participants performed three tasks—a sequence learning task with a spatial pattern that was incidental to response selection, a spatial cuing task, and neuropsychological tests of executive function. Whereas moderate PD patients failed to show significant sequence learning, mild PD patients performed comparably with controls. Neither group of PD patients was impaired in the control of spatial attention. Sequence learning was correlated with neuropsychological measures of executive function but not with the ability to control spatial attention. These results suggest that the contribution of the brain areas affected by PD to sequence learning extends beyond motor learning to include the learning of perceptual patterns and involves executive function, including cognitive flexibility and set shifting.

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1. Introduction

Everyday behaviors commonly involve the serial production of responses, many of which are over-learned and performed with little attention or effort. For example, the everyday use of computers involves repetitive performance of specific manual responses and rapid shifts of visual attention. Navigation through multiple computer screens to locate a regularly accessed file occurs with little effort because the sequence of necessary motor responses and spatial locations to be attended to becomes well practiced. The acquisition and performance of sequential behavior patterns has been shown to rely upon brain activity in the cerebellum and cortico-striatal circuits, including the basal ganglia and premotor, prefrontal and parietal cortices (e.g., Grafton, Hazeltine, & Ivry, 1995; Rauch et al., 1997). The current study focuses on the brain areas affected by Parkinson's disease (PD), among which cortico-striatal circuits are central. Our goal is to identify the computational role these areas play in the learning of sequenced information.

Sequence learning has been studied extensively using the serial reaction time (SRT) paradigm developed by Nissen and Bullemer (1987). In this task, participants respond based upon visual or auditory stimulus features, such as spatial position, color, or tone frequency. In a *sequenced block*, a stimulus feature and the corresponding response follow a fixed sequence that repeats throughout

the block of trials. Learning of the stimulus–response sequence is indicated when faster reaction times are found in *sequenced* blocks relative to *random* blocks, in which stimuli are presented in a pseudo-random order.

Neurophysiological and neuropsychological studies using the SRT task suggest that sequence learning involves the basal ganglia. Neuroimaging studies of healthy populations show greater basal ganglia activation in sequenced than in random blocks of the SRT task (Aizenstein et al., 2004; Grafton et al., 1995; Hazeltine, Grafton, & Ivry, 1997; Rauch et al., 1997; Van der Graaf, Maguire, & Leenders, 2006). Impairments in sequence learning on the SRT task have repeatedly been found in patients with cortico-striatal dysfunction, such as patients with PD (Ferraro, Balota, & Conner, 1993; Helmuth, Mayr, & Daum, 2000; Jackson, Jackson, Harrison, Henderson, & Kennard, 1995; Pascual-Leone et al., 1993) and patients with Huntington's disease (Willingham & Koroshetz, 1993). Interestingly, sequence learning is normal in patients with focal unilateral basal ganglia lesions (Exner, Koschack, & Irle, 2002; Shin, Aparicio, & Ivry, 2005), pointing to the possibility that cortical regions and basal ganglia may jointly contribute to sequence learning.

Although many studies converge on the idea that sequence learning depends upon the cortico-striatal circuits affected by PD, the computational contributions of these circuits remain unclear. We considered three possibilities. First, the cortico-striatal circuitry affected by PD may support the acquisition of motor sequences. Problems that Parkinson's patients have in program-

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ming complex series of motor responses (Benecke, Rothwell, Dick, & Marsden, 1986; Harrington & Haaland, 1991) and evidence from the animal literature linking basal ganglia functioning to the learning of response-related contingencies (Aldridge & Berridge, 1998; Graybiel, 1998; Matsumoto, Hanakawa, Maki, Graybiel, & Kimura, 1999; Packard & Knowlton, 2002) support this idea. Thus, one expectation is that PD patients may be impaired in learning sequences of motor responses but not sequences of perceptual events. Previous studies show mixed results with respect to the impact of PD on non-motor sequence learning. Some studies demonstrated normal learning of response-incident sequences of perceptual information (Helmuth et al., 2000; Smith, Siegert, McDowall, & Abernethy, 2001; Smith & McDowall, 2006 Westwater, McDowall, Siegert, Mossman, & Abernethy, 1998) and others demonstrated impaired learning of similar types of sequences (Shin & Ivry, 2003; Smith & McDowall, 2004).

A second possible contribution of the cortico-striatal function compromised by PD relates to the control of spatial attention. Parkinson's patients are impaired on tasks that require self-directed control of spatial attention (Briand, Hening, Poizner, & Soreno, 1999; Pollux & Robertson, 2001; Uc et al., 2005; Wright, Geffen, & Geffen, 1995; Yamaguchi, Tsuchiya, & Kobayashi, 1998) with a few exceptions (Bennett, Waterman, Scarpa, & Castiello, 1995; Rafal, Posner, Walker, & Friedrich, 1984; Sharpe, 1990). Furthermore, control of spatial attention tends to worsen with increased PD severity (Yamada, Izyuinn, Schulzer, & Hirayama, 1990), and such a range in spatial attention performance may contribute to the observed variability in SRT learning among PD patients. Neuroimaging evidence has indicated that SRT performance activates aspects of cortico-striatal circuitry critical to the control of visuospatial attention (Bischoff-Grethe, Goedert, & Willingham, 2004; Daselaar, Rombouts, Veltman, Raaijmakers, & Jonker, 2003; Olson, Rao, & Moore, 2006; Poldrack, Sabb, & Foerde, 2005; van der Graaf et al., 2006), namely, the caudate and the prefrontal and parietal cortices (Corbetta, 1998; Posner & Dehaene, 1994). Presumably this pattern of activation reflects the fact that the vast majority of these sequence learning studies used spatial information to cue responses. Thus, cortico-striatal circuitry may influence sequence learning performance by virtue of its role in controlling spatial attention.

Finally, the cortico-striatal circuits affected by PD are central to executive functions that appear to be crucial for the formation of sequence representations, such as attention switching and working memory (e.g., Gotham, Brown, & Marsden, 1988; Salmon & Filoteo, 2007). Sequence learning in the SRT task requires attentional resources (Curran & Keele, 1993; Jimenez & Mendez, 1999; Nissen & Bullemer, 1987; Stadler, 1995) and is associated with verbal working memory capacity (Frensch & Miner, 1994; Howard & Howard, 1997; Schwartz, Howard, Howard, Hovaguimian, & Deutsch, 2003). A role for executive function in SRT learning is further supported by findings of increased prefrontal activation on sequenced, relative to random, blocks of the SRT task (Aizenstein et al., 2004; Grafton et al., 1995; Hazeltine et al., 1997; van der Graaf et al., 2006). Among PD patients, decline in executive function, namely working memory and cognitive flexibility, may weaken sequence learning.

The goal of our research was to test these hypothesized functions of the cortico-striatal circuits affected by PD in sequence learning. Unfortunately, cortico-striatal contributions to sequence learning through response-related learning processes, spatial attentional control, or executive functioning are difficult to evaluate because SRT tasks typically emphasize all three components simultaneously. In our study, we utilized experimental tasks that differentially emphasized these processes. Specifically, we employed three tasks—a sequence learning task that eliminated the demand for response sequence learning by presenting a

response-incident spatial sequence, a spatial cuing task that emphasizes the control of visuospatial attention, and neuropsychological tests of executive function that stressed working memory and cognitive flexibility.

In addition to utilizing multiple tasks, we capitalized on the fact that sequence learning varies with the degree of disease severity in Parkinson's patients (Doyon et al., 1997). To the extent that cortico-striatal functioning contributes differentially to the three types of processes examined here, performance on the three experimental tasks should differ as a function of disease severity in Parkinson's patients. Therefore, we tested three groups of participants—Parkinson's patients with moderate symptoms, those with mild symptoms, and a healthy age-matched control group.

Our predictions were that if the cortico-striatal circuits affected by PD influence sequence learning through the learning or programming of motor patterns, PD patients should perform normally on the non-motor sequence learning task. In contrast, if cortico-striatal involvement in sequence learning lies in the control of spatial attention, Parkinson's-related deficits should be found in both the sequence learning and spatial cuing tasks, especially for the Parkinson's patients with more severe symptoms. Furthermore, performance on the two tasks should be correlated with each other. Finally, if the cortico-striatal circuits damaged in PD support executive functions that are important for sequence learning, we would predict PD-related deficits on both the sequence learning task and the neuropsychological tests. These should each vary with PD severity and correlate with each other.

To anticipate the main results, (a) sequence learning was worse for the moderate PD patients than for the mild PD patients and the healthy controls; (b) neither group of PD patients were impaired in the control of spatial attention on the spatial cuing task, nor was spatial attention correlated with sequence learning; (c) neuropsychological measures of executive function indicated poorer functioning in the moderate than in the mild Parkinson's patients, and these neuropsychological measures were correlated with sequence learning. These results suggest that the contribution to sequence learning by the cortico-striatal circuits affected by PD extends beyond the learning of manual motor response sequences. Further, the data support the hypothesis that these circuits also influence sequence learning via certain executive functions.

2. Methods

Participants completed three tasks—a sequence learning task, a spatial cuing task, and a set of neuropsychological tests commonly used to assess prefrontal function. The order of these three tasks was counterbalanced across participants within each group.

2.1. Participants

Twelve Parkinson's patients with mild symptoms (Hoehn & Yahr Stage 1), 10 Parkinson's patients with moderate symptoms (Hoehn & Yahr Stage 2 or 3), and 10 healthy age-matched controls participated in the study. Patients' disease severity was rated according to the Mentation, Behavior, Mood, and Activities of Daily Living subscales of the Unified Parkinson's Disease Rating Scale (UPDRS; Fahn & Elton, 1987). The UPDRS ratings and the demographic and neuropsychological characteristics of the participants are summarized in Table 1. The three participant groups were similar in age and education level. The two patient groups differed in the duration since diagnosis, $t(20) = 3.75, p < .001$. The two groups differed slightly in the incidence of drug-induced dyskinesias; 3 of the 12 patients in the mild PD group and 5 of the 10 patients in the moderate PD group exhibited visible dyskinesias at some point during the testing session. All patients were tested while on their

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