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Research report

The pattern of striatal dopaminergic denervation explains sensorimotor synchronization accuracy in Parkinson's disease

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HIGHLIGHTS

- We assessed paced finger tapping in Parkinson's disease (PD) patients.
- We measured striatal dopaminergic denervation using ^{11}C-dihydrotetrabenazine PET.
- Cluster analysis subgrouped PD patients based on dopaminergic denervation.
- PD patient subgroups qualitatively differed in paced finger tapping accuracy.
- Subgrouping patients may explain the mixed literature of temporal processing in PD.

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ABSTRACT

The basal ganglia are thought to play a critical role in duration perception and production. However, experimental evidence for impaired temporal processing in Parkinson's disease (PD) patients is mixed. This study examined the association between striatal dopaminergic denervation in PD patients and sensorimotor synchronization. Twenty-eight mild-to-moderate stage PD patients synchronized finger taps to tone sequences of either 500 ms, 1000 ms or 1500 ms time intervals while ON levodopa (L-DOPA) or placebo pill (on separate test days) with the index finger of their more and less affected hands. We measured the accuracy and variability of synchronization. In a separate session, patients underwent ^{11}C-dihydrotetrabenazine (^{11}C-DTBZ) PET scanning to measure in vivo striatal dopaminergic denervation. Patients were less accurate synchronizing to the 500 ms target time interval, compared to the 1000 ms and 1500 ms time intervals, but neither medication state nor hand affected accuracy; medication state, hand nor the target time interval affected synchronization variability. Regression analyses revealed no strong relationships between synchronization accuracy or variability and striatal dopaminergic denervation. We performed a cluster analysis on the degree of dopaminergic denervation to determine whether patient subgroup differences underlie our results. Three patient subgroups showed behavioral differences in synchronization accuracy, but not variability, paralleling their pattern of denervation. These findings provide further evidence for the role of the basal ganglia and dopamine in duration production and suggest that the degree of striatal dopaminergic denervation may explain the heterogeneity of performance between PD patients on the sensorimotor synchronization task.

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1. Introduction

A central goal in the temporal processing literature is to identify the neural bases of duration perception and production. Duration perception and production rely upon a distributed neural network that includes the basal ganglia, cerebellum, supplementary motor area, premotor cortex and prefrontal regions [1–4]. However, the role of these specific regions within the timing network is not yet well understood, due in part to rather mixed findings from both the neuropsychological and neuroimaging literature.

One approach to untangle the mixed literature on the neural bases of duration perception and production has been to group studies by task characteristics such as the type of task (e.g., perceptual vs. motor) and timescale (e.g., subsecond vs. suprasecond) to determine whether these factors differentially recruit regions of the timing network [cf. 5–9]. Accordingly, differential activation within the timing network has been shown for the *automatic* timing of subsecond durations that 'do not require attention' and *cognitively controlled* timing of suprasecond discrete events [7,10]. Automatic timing tends to activate motor and premotor cortices, while cognitively controlled timing recruits prefrontal and parietal cortices. However, regions such as the basal ganglia and cerebellum tend to be activated for both automatic and cognitively controlled timing, suggesting that these regions support general temporal processing function [7,10,11]; but see [12].

There is debate regarding the specific roles of the basal ganglia and cerebellum in temporal processing, but the basal ganglia are hypothesized to serve as the putative 'internal clock' [13,14]. Animal and psychopharmacological studies support this hypothesis, showing that altered dopamine levels within the basal ganglia systematically distort duration perception and production [15–19]. Moreover, lesions or dopaminergic denervation of the basal ganglia in Parkinson's disease (PD) impair duration perception and production across a range of tasks and timescales, while anti-Parkinson's medications (e.g., L-DOPA) may reverse timing impairments in PD patients [18,20–27]. Taken together, these findings suggest that the basal ganglia may serve as the internal clock and that the clock might be modulated by dopamine.

Although a range of evidence supports a critical role for the basal ganglia and dopamine in duration perception and production, support for impaired temporal processing in PD patients is rather mixed. PD patient subgroup differences may explain, in part, this mixed literature. For example, subgrouping PD patients by primary symptoms, disease duration or temporal processing variability has shown subgroup differences in temporal processing [19,28,29]. Recently, Merchant et al. [28] showed that PD patients can be subgrouped by variability on a battery of duration perception and production tasks using cluster analysis. Notably, the authors found no differences between low-variability patients and controls, but high-variability patients performed worse on duration perception and production tasks compared to both controls and low-variability patients. Merchant et al. [28] emphasize the critical need to consider patient subgroups when investigating duration perception and production in patients, but the neural mechanisms underlying patient subgroup differences are unknown.

The current study aimed to determine whether striatal dopaminergic denervation in PD patients, as measured by reduced dopamine binding potential, is associated with the coordination of motor timing to a predictable, external rhythm—sensorimotor synchronization [30]. Specifically, we tested whether dopaminergic denervation is associated with sensorimotor synchronization in the more and less affected hand of PD patients when they were ON and OFF Ll-DOPA. Moreover, we examined whether subgrouping PD patients by their degree of striatal dopaminergic denervation revealed performance differences on the sensorimotor synchronization task.

We used positron emission tomography (PET) to measure in vivo striatal denervation in PD patients. ^{11}C-DTBZ is a ligand that binds to the type-2 vesicular monoamine transporter (VMAT2), which is a target for quantitative imaging of striatal synaptic terminals, where the signal is >95% dopamine [31]. Low binding signals in a ^{11}C-DTBZ PET scan imply more severe denervation of nerve terminals in the striatum, or depletion of the neurotransmitter dopamine.

PD patients synchronized finger taps with an equally timed (isochronous) tone sequence while ON L-DOPA and placebo. Patients tapped with the index finger of the more and less affected hand, separately, to three target time intervals (500 ms, 1000 ms and 1500 ms).

We predicted that greater striatal denervation in PD patients would result in worse accuracy and greater variability in sensorimotor synchronization. Additionally, we predicted that subgrouping PD patients by the degree of dopaminergic denervation would reveal patient subgroup differences in sensorimotor synchronization.

2. Methods and Materials

2.1. Participants

Twenty-eight volunteers with PD participated and received monetary compensation. We obtained complete data from 23 patients and partial data from five patients, due to equipment error or difficulty performing the task (see Table 1). A PD specialist diagnosed patients with mild-to-moderate (Hoehn and Yahr Stages I–III) idiopathic PD and evaluated patients' motor symptoms using the motor section of the Unified Parkinson's Disease Rating Scale [UPDRS; [32]]. Patients were on a stable dosage of anti-Parkinson's medication for the previous six months and completed all measures while ON L-DOPA and placebo. We excluded individuals with neurological or psychiatric diseases other than PD from the study and used the Mini-Mental State Exam [MMSE; [33]] and Montreal Cognitive Assessment [MOCA; [34]] to assess cognitive ability. Patients also performed the Grooved Pegboard test (Lafayette Instruments, Lafayette, IN) to assess bradykinesia. Table 1 provides additional patient characteristics.

We collected sensorimotor synchronization data from 45 healthy control participants (65.3 years of age ± 8.2; 8 females) for behavioral comparisons with patients. Controls participated in a single testing session that followed the same procedure, except for PET scanning. We present the average control group data graphically rather than statistically as a reference for patient performance since our focus is on patient subgrouping. All participants signed a consent form approved by the Institutional Review Board of the University of Michigan.

2.2. Apparatus

E-Prime software (Psychology Software Tools, Inc., Pittsburgh, PA) controlled stimulus presentation and response collection. Stimuli were acoustic sequences (comprised of 500 Hz sine-wave tones with a 50 ms duration) delivered at a clearly audible volume through a speaker located in front of patients. Patients responded via key presses ('Z') on a computer keyboard.

2.3. Procedure

Patients participated in two behavioral testing sessions corresponding to ON and OFF medication states; medication order was counterbalanced (13 patients tested ON L-DOPA first).

We used a double-blind placebo controlled design with a single dose of L-DOPA (200 mg) for all patients to reduce the variability