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Visuomotor control in patients with Parkinson's disease

Jing Chen [a], Shu-Leong Ho [b], Tatia Mei-Chun Lee [c,d], Richard Shek-Kwan Chang [b], Shirley Yin-Yu Pang [b], Li Li [a,e,*]

[a] Department of Psychology, The University of Hong Kong, Hong Kong, China
[b] Division of Neurology, University Department of Medicine, The University of Hong Kong, Hong Kong, China
[c] Laboratory of Neuropsychology, The University of Hong Kong, Hong Kong, China
[d] The State Key Laboratory of Brain and Cognitive Science, The University of Hong Kong, Hong Kong, China
[e] Neural Science Program, New York University Shanghai, 1555 Century Avenue, Pudong New Area, Shanghai 200122, China

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ABSTRACT

Previous studies have suggested that the deteriorated visuomotor control in patients with PD (Parkinson's disease) is due to deficits in various aspects of the sensory-motor processing rather than motor control itself. In the current study, by taking a control-theoretic approach, we systematically examined how PD and antiparkinsonian medication affect visuomotor control and the underlying sensory-motor system.

We tested 20 PD patients in both ON and OFF medication states and 20 demographically matched healthy controls with a commonly used manual control task. Specifically, in each 95-s trial, participants were instructed to use a joystick to control a randomly moving target to keep it centered on a computer display. We found that although antiparkinsonian medication improved visuomotor control in PD patients, they still showed significantly decreased control precision (measured by RMS error) and response amplitude (gain) as well as increased response delay (phase lag) compared with healthy controls.

Our model-driven analysis revealed that PD impairs the responsiveness and the predicting ability of the sensory–motor system as well as the stability of the neuromuscular system. Taking antiparkinsonian medication improves the responsiveness of the sensory–motor system. More importantly, it improves the ability of the sensory–motor system to make sensory predictions of the current control actions (see Wolpert et al., 1995) to anticipate the input error signals and generate control responses ahead of time up to the level of healthy controls. However, taking antiparkinsonian medication does not improve the stability of the neuromuscular system. These results support the claim that the effect of antiparkinsonian medication on visuomotor control is mainly through improving visual-stimulus-dependent sensory–motor processing.

The present study provides the first quantitative examination of the effects of PD and antiparkinsonian medication on the visual-stimulus-dependent sensory–motor and visual-stimulus-independent neuromuscular systems underlying visuomotor control. The findings have practical implications for developing sensitive assessment tools to evaluate the efficacy of different therapies for PD and preliminary screening and training tools for fitness-to-drive in PD patients.

1. Introduction

Parkinson's disease (PD), a neurodegenerative disorder affecting the basal ganglia, occurs due to the progressive loss of dopaminergic neurons in the substantia nigra (SN, a nucleus of the basal ganglia). Using a variety of manual tracking paradigms, earlier studies have shown that visuomotor control is impaired in PD patients (Bowen et al., 1972; Cassell et al., 1973; Eidelberg and Dunmier, 1973; Flowers, 1975; Stark, 1968), which is associated with basal ganglia dysfunction and the reduced functions of other motor brain regions that connect to basal ganglia such as motor cortices and cerebellum (e.g., Playford et al., 1992; Wu and Hallett, 2013). Recent anatomical studies reveal that the basal ganglia are also connected to a large and diverse set of cortical areas for cognitive functions (see Middleton and Strick, 2000, for a review), supporting the claim that that the basal ganglia is not only a motor area but also involved in functions extending beyond motor activities (Doya, 2000; Maschke et al., 2006). Accordingly, it has been proposed that the impairments in visuomotor control in PD

* Corresponding author at: Neural Science Program, New York University Shanghai, 1555 Century Avenue, Pudong New Area, Shanghai 200122, China.
E-mail address: ll114@nyu.edu (L. Li).

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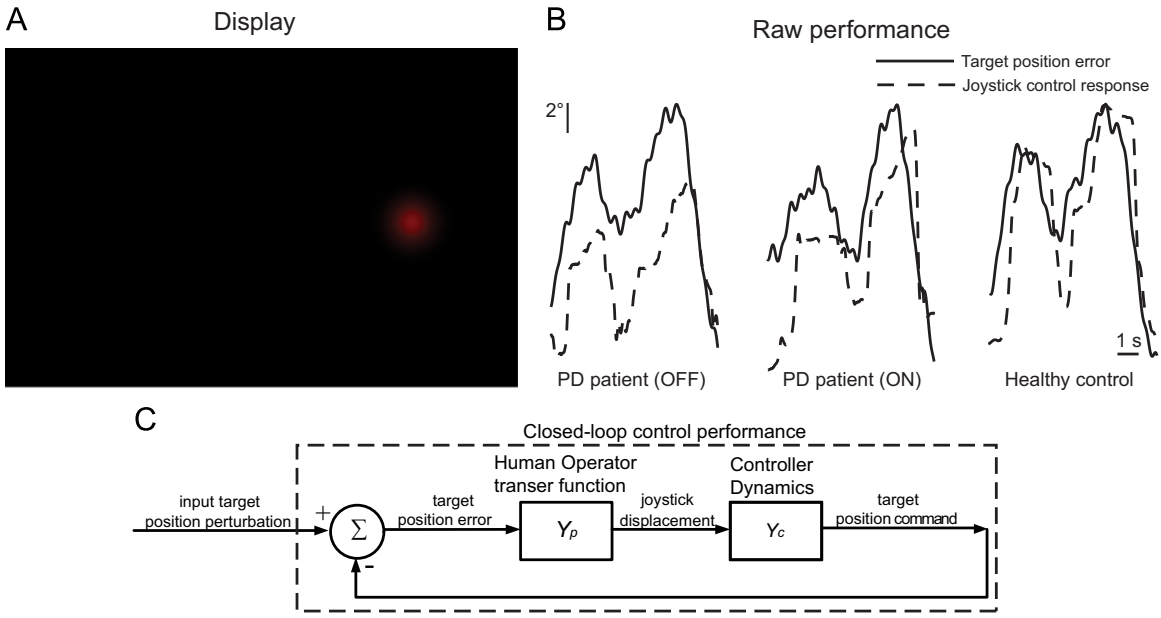

Fig. 1. (A) An illustration of the display used in the visuomotor control task. The target moves along the horizontal axis of the screen and displays a rightward error from the center of the screen (37°H × 21°V). (B) Typical raw performance data from part of a trial for a PD patient with a moderate state of disease (H&Y scale = 3) in both the OFF and ON medication states (left and middle panels) as well as for an age-matched healthy control (right panel). The solid lines depict the input target position error and the dotted lines depict the output joystick control response. (C) Simplified block diagram of the closed-loop manual control task. Human operator transfer function (Y_p) captures the participant's control performance, and the controller dynamics (Y_c) specifies the joystick control dynamics.

patients are due to deficits in various aspects of the sensory–motor processing rather than motor control itself (e.g., Flowers, 1978a, 1978b; Inzelberg et al., 2008; Richards et al., 1993).

The behavioral evidence supporting the above proposal comes from several research studies. For example, Bowen et al. (1972) studied visuomotor control in patients with lateralized PD (i.e., PD affects one hemisphere more than the other due to asymmetrical dopamine denervation in the brain such that patients show predominantly left- or right-side motor symptoms). They found that patients primarily with left-side symptoms (i.e., right hemisphere dysfunction) showed impaired performance only in the left hand when performing a simple repetitive motor task (such as tapping a button). However, these patients showed bimanual impaired performance in a manual tracking task that required the processing of visuospatial information in the right hemisphere (e.g., Corballis, 2003). These PD patients thus appeared to have deficits not only in motor ability but also in processing visuospatial information for online motor control. Hocherman and Giladi (1998) further showed that patients with the early stage of lateralized PD had bimanual impairment in the tracking speed and accuracy in two manual tracking tasks. The impaired tracking performance observed before the occurrence of any motor symptom in their asymptomatic hand suggests that the deficits in visuomotor control in PD patients are beyond motor impairment.

Inzelberg et al. (2008) correlated PD patients' performance on a manual tracking task with the clinical assessment measures of their motor symptoms. They found that the impaired control performance in PD patients was correlated with the clinical measures of gait and posture impairments more strongly than with upper limb dysfunction. Several recent studies showed that PD patients who suffer from freezing of gait (PD-FOG) had more deficits in visuospatial processing than those who did not (Almeida and Lebold, 2010; Nantel et al., 2012; Martens et al., 2014). Furthermore, a resting-state functional magnetic resonance imaging (fMRI) study also revealed that PD-FOG patients exhibited significantly reduced functional connectivity within visual networks compared to PD-nonFOG patients (Tessitore et al., 2012). These findings suggest that the poor visuomotor control performance in PD patients is also due to impairments in visual information processing.

In addition to impairments in visual information processing, Flowers (1978a) showed that while PD patients were able to track a target moving in a regular and predictable pattern, their tracking performance deteriorated when the target was momentarily removed from the screen. Flowers proposed that the degraded control performance was not due to the impairment in PD patients' motor system but arose from a failure to generate an internal plan for tracking. To test this hypothesis, Stern et al. (1983) used a similar experimental paradigm and found that the poor visuomotor control performance in PD patients was related to their impaired ability to coordinate sensory processing with motor functions for the execution of motor commands (see also Richards et al., 1993). Several other studies also showed that while PD patients depend on visual information to accurately point to a target, their poor pointing performance compared with healthy controls is due to their deficits in processing proprioception and/or the integration of proprioception and vision information (e.g., Adamovich et al., 2001; Keijsers et al., 2005).

The findings of the above mentioned studies support the claim that the impaired visuomotor control in PD patients is due to deficits in various aspects of the sensory–motor processing rather than motor control itself. Although several previous studies have examined the effects of PD and dopamine on sensory–motor processing (e.g., Hanna-Pladdy and Heilman, 2010; Isaias et al., 2011; Sawamoto et al., 2008), none was able to provide quantitative evaluations of the effects of PD and antiparkinsonian medication on the visual-stimulus-dependent sensory-motor and visual-stimulus-independent neuromuscular control systems underlying visuomotor control. To address this issue, in the current study, we took a control-theoretic approach and asked patients to perform on a typical visuomotor control task to specifically measure the effects of PD and antiparkinsonian medication on their performance and to compare it with that of demographically-matched healthy controls. The task we used was a common closed-loop manual control task that required participants to use visual information (such as the position and/or the velocity

information of a target) to integrate with the predictions of the sensory feedback of their current actions and continuously adjust their control responses to achieve the desired outcome. Specifically, the display showed a target moving randomly along the horizontal axis of the screen, and participants were instructed to use a joystick to control the target movement to keep it as close to the center of the screen as possible (Fig. 1A). This widely-used manual control task allows us to evaluate many aspects of visuomotor control, such as precision, amplitude, and delay of the control response, and can thus reveal specific deficits that PD patients have in visuomotor control compared with healthy controls. We then fit the human performance data to an extensively validated Crossover model (Anderson, 1970; Hess, 1977; Li et al., 2005, 2006, 2011; McRuer, 1980; McRuer et al., 1965; McRuer and Klein, 1975; McRuer and Krendel, 1959) to understand how PD and antiparkinsonian medication affect the sensory–motor system underlying visuomotor control.

2. Methods

2.1. Participants

Twenty-three clinically confirmed idiopathic PD patients were recruited from the Movement Disorder Clinic of Tung Wah Hospital (Hong Kong, SAR). Two patients did not complete this study. Further review of the medical records screened out another patient due to the diagnosis of a cataract during the period of testing. This yielded a final sample of 20 PD patients. We then recruited 20 demographically matched healthy controls from the Social Center for the Elderly (the Central and Western Distinct, Hong Kong) and among patients' spouses and relatives to participate in the study.

All PD patients were diagnosed by movement disorder specialists using the criteria of the UK Parkinson's Disease Society Brain Bank (Hughes et al., 1992). There were no other neurological diseases in the PD patient group. None of the PD patients or healthy controls had a history of intracranial surgery, traumatic brain injury, psychiatric illness, prescription/street drugs, alcohol abuse, or eye disease. Neither the patient nor the control group demonstrated any sign of dementia, with scores on the Cantonese version of the Mini-Mental State Examination (CMMSE: Chiu et al., 1994) larger than 24 (19 is the cut-off value for the indication of cognitive impairment). All participants had a corrected binocular Freiburg visual acuity of 0.5 (corresponding to the Snellen fraction of 20/40) or better. Independent-samples t-tests revealed that patients and controls did not differ significantly in terms of age, years of formal education, and CMMSE score ($t(38) < 1.56$, $p > 0.13$). Both groups had an equal male-to-female ratio of 2.33 (see Table 1).

PD patients were tested both ON (approximately 60–90 min after taking their usual dose of antiparkinsonian medication) and OFF (at least 12 h overnight withdrawal) medication. Prior to the commencement of the experiment, the severity of PD and the disease progression were assessed with the Hoehn and Yahr (H&Y) scale (Hoehn and Yahr, 1967) when patients were ON medication. 50% PD patients were at a mild stage of disease (H&Y scale = 1–2), 40% a moderate stage (H&Y scale = 2.5-3), and 10% a severe stage (H&Y scale = 4).

All participants were right-handed. PD patients were asked to use the hand on the side that was *more* impaired by the disease to perform the manual control task. Right before each experiment session in which patients were ON or OFF medication, PD patients' disease-related disabilities were evaluated with the Unified Parkinson's Disease Rating Scale (UPDRS, Fahn and Elton, 1987) by a clinical doctor specialized in movement disorders. The more impaired side was determined by the motor asymmetry evaluation using the motor UPRDRS (Part III). Specially, left- and right-sided motor composite scores for upper and lower limbs were computed by summing the individual items of tremor (items 20 and 21), rigidity (item 22) and bradykinesia (items 23–26) of the motor UPRDRS (Part III). A motor asymmetry score was calculated as the value of the left- minus right-sided motor composite score. Positive values indicate left sided motor onset (LMO) and negative values indicate right sided motor onset (RMO).We had 9 patients with LMO and 10 patients RMO. One patient's more affected side changed from left to right from the ON to OFF state and was asked to use the left hand to perform the task in both states to be conservative of the antiparkinsonian medication effect. As a result, 10 PD patients used their dominant right hand and 10 used their non-dominant left hand to perform the manual control task. Healthy controls were age- and gender-matched with the patient group and for the hand used to perform the task. This resulted in half of the health-controls using their dominant hand and the other half using their non-dominant hand to perform the task as well.

Each patient's current antiparkinsonian medication regimen was recorded. 20% patients were treated with levodopa in the form of varying doses of carbidopa+levodopa or benserazide+levodopa. 70% patients were taking combinations of levodopa and other antiparkinsonian medications (e.g., dopamine agonists, MAO-B inhibitors, COMT inhibitors, trihexyphenidyl, and amantadine). 10% patients either took MAO-B inhibitors in conjunction with trihexyphenidyl without levodopa, or received a dopamine agonist only. To compare patients on different medication regimens, we calculated the levodopa equivalent dose (LED) using the standard conversion formulae (Tomlinson et al., 2010). The total LED was obtained by adding together the LED for each antiparkinsonian medication. The clinical characteristics of PD patients are presented in Table 1.

This study was approved by the Institutional Review Boards of the University of Hong Kong/Hospital Authority Hong Kong West Cluster. All participants provided written informed consent in accordance with the Declaration of Helsinki.

Table 1
Participant demographics and clinical characteristics of PD patients. Upward arrow indicates that higher scores are better, and downward arrow indicates the opposite. CMMSE = Cantonese version of the Mini-Mental State Examination. Motor UPDRS score = total scores of UPDRS-III. LED = Levodopa equivalent dose.

Group		Age (years)	Gender (M/F)	Education (years)	CMMSE (↑)	Hand used to perform task (left/right)	Duration of disease (years)	Hoehn and Yahr stage (↓)	Motor UPDRS score (OFF) (↓)	Motor UPDRS score (ON) (↓)	Total LED (mg/day)
Patients (n=20)	Mean (SD)	59.70 (7.68)	14/6	8.70 (3.56)	27.00 (1.89)	10/10	7.57 (4.80)	2.30 (0.95)	28.55 (14.63)	15.45 (13.44)	500.05 (309.22)
Controls (n=20)	Mean (SD)	61.00 (6.22)	14/6	10.15 (2.18)	27.75 (2.53)	10/10					

Table 2
Magnitudes (a_i) and frequencies (ω_i) of the seven harmonically unrelated sinusoids for the input position perturbation function u.

i	a_i	ω_i(Hz)
1	2	0.1
2	2	0.14
3	2	0.24
4	0.2	0.41
5	0.2	0.74
6	0.2	1.28
7	0.2	2.19

2.2. Visual stimuli and experimental setup

The visuomotor control task used in the study was a typical compensatory manual control task with random inputs. A red round target with a Gaussian luminance profile (σ: 0.4°; peak luminance: 8.8 cd/m2) was displayed on a uniform black background (2.2 cd/m2) (Fig. 1A). During a trial, the horizontal position of the target on the screen was perturbed by a function (u) consisted of the sum of seven harmonically unrelated sinusoids, which was given as a function of time (t) by

$$u(t)=D\sum_{i=1}^{7} a_i \sin(\omega_i t+\rho_i), \quad (1)$$

where a_i and ω_i represent the amplitude and frequency of the i^{th} sine component, respectively (Table 2), and ρ_i is a random phase offset drawn from the range of $-\pi$ to π for each trial. This sum-of-sinusoids perturbation series made the movement of the target appear random (see McRuer and Krendel, 1974) and allowed for a frequency-based analysis of the human operators' control response (Y_p in Fig. 1C). Disturbance gain D was set to a value of 1.98°, which led to an average speed of the uncorrected target motion of 5.65°/s (peak: 21.67°/s).

The joystick displacement was proportional to the target movement velocity. Accordingly, the control dynamics of the joystick was velocity control, and the controller dynamics (Y_c in Fig. 1C) were implemented as:

$$Y_C=\frac{1}{S}, \quad (2)$$

where s was the Laplace transform variable. The joystick position was sampled at 60 Hz, resulting in 16.67 ms (i.e., 1 frame) of system feedback delay. The maximum of the joystick displacement was set to correspond to a peak target movement rate of 20°/s.

The visual stimuli were displayed on a Dell ST2420L 24-inch LCD monitor (37°H × 21°V) at a 60 Hz refresh rate. At the beginning of each 95-s trial, the target appeared at the center of the screen and began moving when participants pulled the trigger of a high-precision joystick (Flybox, B&G Systems, Palo Alto, CA). Participants were asked to move the joystick left-to-right to control the horizontal movement of the target to keep it as close to the center of the screen as possible. The target initially moved leftward or rightward pseudo-randomly according to the sum-of-sinusoids perturbation function, but its movement was soon controlled as the participant moved the joystick to keep the target centered on the screen. The viewing distance was about 0.8 m from the screen. Participants' cyclopean eye (i.e., their visual straight ahead) was calibrated to align with the center of the screen in the beginning of the experiment.

2.3. Procedure

An experiment session included six trials of the manual control task. Healthy controls only took part in one experiment session. PD patients were tested both ON and OFF medication and thus participated in two experiment sessions. All PD patients completed the experiment in the ON–OFF medication order (see Fig. 2). Although the order of testing on the manual control task was always from the ON to OFF medication state in PD patients, the practice effect could only reduce the effect of antiparkinsonian medication on visuomotor control. The same logic applies to the reason why the control group did not repeat the manual control task, as repeating the task could only improve the performance of the control group thus enlarging the performance difference between PD patients and healthy controls. It is thus conservative to test the control group once and test PD patients ON medication first and then OFF medication. It is also more efficient to train patients to learn a visuomotor control tasks ON than OFF medication (Soliveri et al., 1997). As such, it is common for studies on PD not to counterbalance the testing order of OFF and ON medication or to test healthy controls twice (e.g., McIntosh et al., 2014; Peterson et al., 2012).

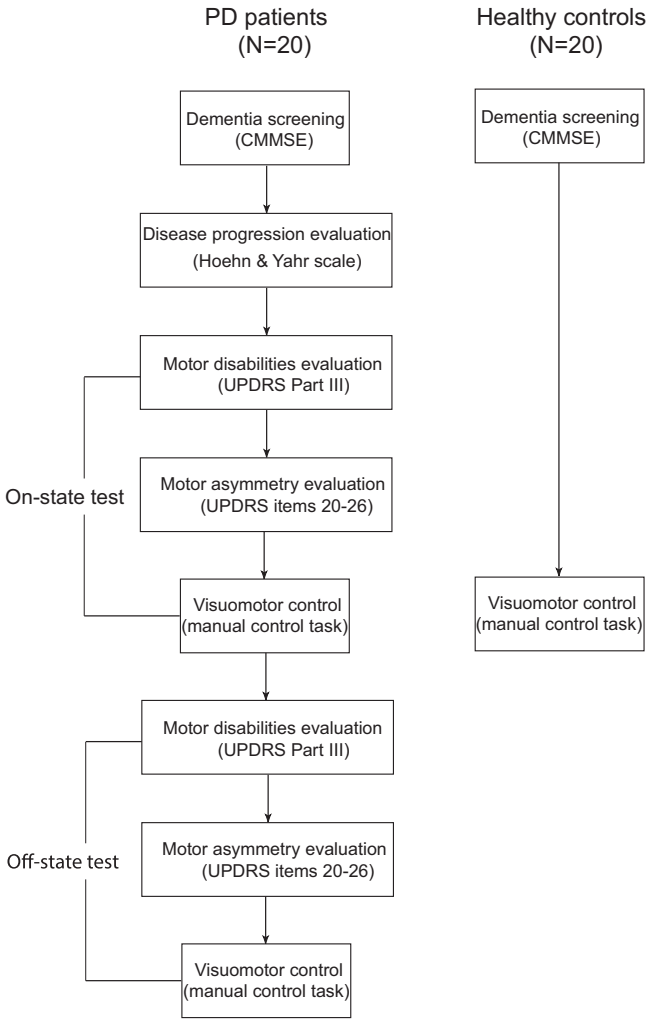

Fig. 2. An illustration of the experimental procedure.

Before each experiment session commenced, participants received practice trials to get familiar with the task and the joystick control dynamics. The practice continued until participants' control performance appeared stable, which required 4–8 trials for healthy controls, 6–10 trials for PD patients ON medication, and 2–5 trials for PD patient OFF medication (note that patients were tested in the ON–OFF medication order). To avoid fatigue and ensure sufficient break time, participants were instructed to take as much break as needed in-between trials.

2.4. Data analysis

For the clinical measures of PD-related motor symptoms, we calculated the total scores of the motor subset of the UPDRS (Part III). For the performance on the manual control task, we recorded the time series of the target position error (i.e., the target position relative to the center of the screen) and the joystick control output. For each 95 s trial, we analyzed the data from the last 90 s. The data from the first 5 s were discarded to ensure that only the steady control response was analyzed.

We computed several control performance metrics to evaluate different aspects of visuomotor control. The overall control performance error was measured as the root mean square (RMS) of the time series of the recorded target position error, which indicates the precision of the control performance. To examine the amplitude and delay of participants' control response specific to the input perturbation frequencies, we performed frequency (Bode) analyses on the recorded time series data. Specifically, we Fourier transformed the time series of both the target position error (in deg of visual angle) and the joystick control output (in % of maximum joystick displacement), and computed the control response amplitude (i.e., gain in % of max/deg) and delay (i.e., phase lag in deg) by taking the ratio of the Fourier coefficients of the target position error and joystick displacement at each input perturbation frequency.

Before we examined the extent to which visuomotor control was impaired in PD patients compared with healthy controls, we compared the control performance of the patient group who used their left non-dominant hand to perform the control task with that of the patient group who used their right dominant hand. We did not find any significant difference between these two groups of patients both ON and OFF medication for all the above performance metrics ($t(18) < 1.56$, $p > 0.13$ and $t(18) < 1.58$, $p > 0.13$ for the OFF and ON states, respectively). We then compared the control performance between the LMO and RMO patients and did not find any significant difference between these two groups of patients both ON and OFF medication for all the performance metrics, either ($t(17) < 1.61$, $p > 0.12$ and ($t(17) < 1.52$, $p > 0.14$ for the OFF and ON states, respectively). We thus treated the PD patients as one patient group when comparing their control performance with that of healthy controls. Depending on the performance metrics, we conducted either independent samples t-tests or 2 (patients vs. controls) × 7 (perturbation frequency) mixed-design ANOVAs[1]. To examine how the degraded visuomotor control performance in PD patients was related to their clinically diagnosed motor disabilities, we correlated each performance metric with the motor UPDRS score.

To examine the effect of antiparkinsonian medication on visuomotor control, we conducted paired samples t-tests and 2 (OFF vs. ON) × 7 (perturbation frequency) repeated-measures ANOVAs on each performance metric. Furthermore, we correlated the total daily levodopa-equivalent doses (LED) with the control performance improvement from the OFF to ON medication state.

For t-tests, we used the Welch–Satterthwaite method to adjust the degrees of freedom for any violation of variance homogeneity indicated by Levene's test. For ANOVAs, we used the Greenhouse–Geisser corrections to adjust the degrees of freedom for any violation of the sphericity assumption. We used Newman–Keuls tests for the post-hoc analyses. We computed Pearson's r for correlation analyses except for situations that involved the motor UPDRS ranking scores, in which case we computed Spearman's ρ instead.

[1] To compare the control performance of PD patients ON and OFF medication with healthy controls, we conducted two separate independent samples t-tests or 2 (patients vs. controls) × 7 (frequency) mixed–design ANOVAs depending on the performance metrics.

2.5. Modeling

The control performance metrics we took evaluate participants' overall control performance as well as their control response specific to the input perturbation frequencies. These measurements, however, cannot reveal how PD and the antiparkinsonian medication affect the sensory–motor system underlying visuomotor control. To address this issue, we modeled participants' control performance on the manual control task (captured by the human operator transfer function Y_p in Fig. 1C), using a Crossover Model (McRuer and Krendel, 1959; McRuer et al., 1965).

The Crossover Model is a quasi-linear dynamic model that can successfully describe human control behavior when performing a variety of closed-loop manual control tasks such as driving and piloting aircraft (e.g., Anderson, 1970; Hess, 1977; McRuer, 1980; McRuer and Klein, 1975). We have previously applied a modified version of the Crossover Model to understand the visual cues that people use for the active control of object motion (Li et al., 2005, 2006) and self-motion (Li et al., 2011). In this model, the human operator transfer function (Y_p) is given by:

$$Y_p = \frac{K_p e^{-s\tau}(sT_L + 1)}{s^2/\omega_n^2 + 2s\xi_n/\omega_n + 1}, \tag{3}$$

where K_p represents the overall gain in the control compensation indicating the responsiveness of the sensory–motor system to the input error signal, τ represents the reaction time indicating the time it takes for the sensory–motor system to process the input error signal and generate a control command, and T_L represents a lead time constant indicating the extent to which the sensory–motor system can make sensory predictions of the current control actions (see Wolpert et al., 1995) to anticipate the input error signals and generate control responses ahead of time.

In this model, the neuromuscular system of the human operator and the physical properties of the controller (e.g., the joystick in the current study) are lumped together to form a second-order low-pass filter ($\frac{1}{s^2/\omega_n^2 + 2s\xi_n/\omega_n + 1}$), which is characterized by a damping ratio ξ_n and an undamped natural frequency ω_n. ω_n and ξ_n are the parameters of the neuromuscular-plus-joystick system which is not affected by the input error signal, and s was the Laplace transform variable. T_S combines ω_n and ξ_n to form a system time constant indicating how fast the neuromuscular system is able to reestablish its initial steady state after any disturbance. Depending on the value of ξ_n, T_S is given by:

$$T_S = \frac{1}{\xi_n \omega_n} (0 < \xi_n \leq 1) \tag{4}$$

or

$$T_S = \frac{1}{(\xi_n - \sqrt{\xi_n^2 - 1})\omega_n} (\xi_n > 1). \tag{5}$$

The smaller the T_S, the faster the neuromuscular system is able to return to its initial steady state and the more stable it is.

Model parameters were determined by using a weighted (by variance) iterative least-squares procedure (i.e., χ^2 fit, see Sweet et al., 2003 for details) to get a best fit to the performance data with the human operator transfer function (Y_p). For each healthy control, there were 5 parameter values to fit 14 data points. For each PD patient, there were 10 parameter values to fit 28 data points (PD patients were tested both ON and OFF medication). Table 3 shows the range of the Pearson's correlation coefficient (r) between the model estimates and the performance data, the model explained variance (r^2), and the reduced χ^2 for the model estimates for both heath controls and PD patients. In sum, the Crossover Model explained 60.5% to 99.96% of the variance in the control performance data, which indicates a reasonably good fit.

3. Results

3.1. Overall visuomotor control performance

Fig. 1B depicts the typical control response of an age-matched healthy control (right panel) and a PD patient at a moderate stage of disease (H&Y scale=3) in both ON and OFF medication states (left and middle panels). As shown by the figure, the control response was a scaled and delayed version of the input target position error, with the response at the highest frequencies smoothed out. The PD patient appeared to generate a larger delay and lower amplitude of control response than did the healthy control, which also appeared to be worse when OFF than ON medication.

Table 3
The range of the Pearson's r between the model estimates and control performance data, r^2, and the range of the reduced χ^2 for the model estimates for PD patients and healthy controls.

	PD: OFF state	PD: ON state	Healthy controls
Pearson's r	0.874–0.9994	0.778–0.9996	0.975–0.9998
r^2 (%)	76.4–99.88	60.5–99.92	94.98–99.96
Reduced χ^2	0.2–2.27	0.07–1.19	0.11–2.95

The mean RMS target position error averaged across six trials and 20 participants is plotted against participant group in Fig. 3A. Independent-samples t-tests revealed that PD patients generated significantly larger RMS target position error than did healthy controls for both OFF and ON medication states ($t(38)=3.90$, $p=0.00038$, Cohen's $d=1.24$ and $t(38)=2.82$, $p=0.0077$, Cohen's $d=0.90$, respectively). The mean RMS target position error for PD patients OFF (mean $\pm$ SD: $5.64 \pm 0.95°$) and ON ($5.40 \pm 1.05°$)

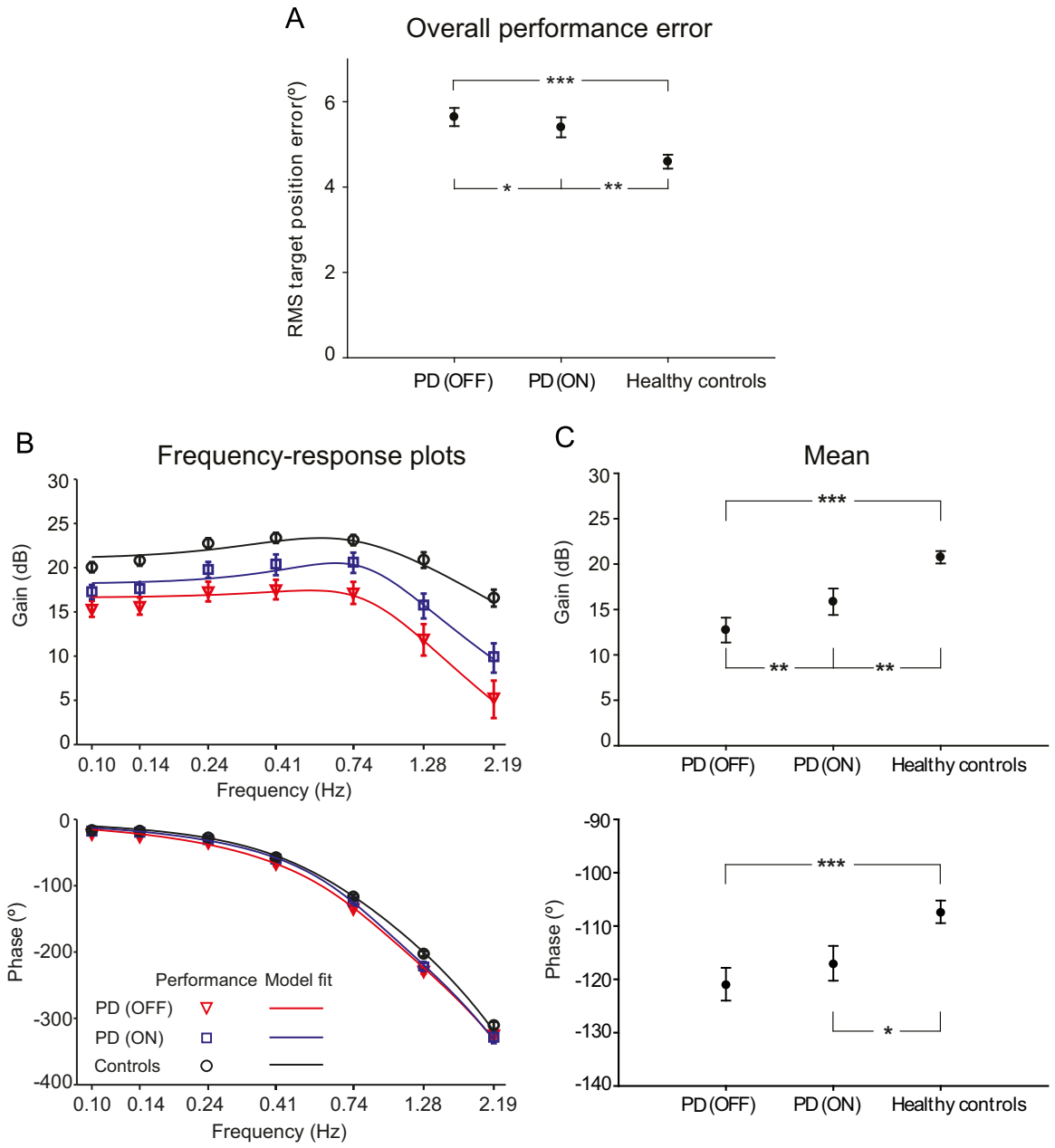

Fig. 3. Participants' performance on the manual control task. (A) Mean RMS target position error against participant group. (B) Frequency–response (Bode) plots of the control performance for PD patients (in both OFF and ON states) and healthy controls. The upper panel presents the mean gain and the lower panel the mean phase, averaged across 20 participants for each participant group. Solid curves represent the best-fitting simulations of the Crossover Model. (C) Mean Gain (upper panel) and mean phase (lower panel) averaged across seven input perturbation frequencies. Error bars are SEs across 20 participants (some of them are smaller than the data symbols). *: $p<0.05$, **: $p<0.01$, and ***: $p<0.001$.

Table 4
Summary of the results of visuomotor control performance.

	PD OFF vs. Controls			PD ON vs. Controls			PD OFF vs. PD ON		
	Independent-samples *t*-tests			Independent-samples *t*-tests			Paired-samples *t*-test		
RMS error	$p=0.00038$			$p=0.0077$			$p=0.046$		
Mean gain	$p<<0.0001$			$p=0.0042$			$p=0.0014$		
Mean phase	$p=0.00081$			$p=0.018$			$p=0.14$		
	2 × 7 mixed-design ANOVA			2 × 7 mixed-design ANOVA			2 × 7 repeated-measures ANOVA		
	Main effects		Interaction	Main effects		Interaction	Main effects		Interaction
	Group	Frequency		Group	Frequency		Medication	Frequency	
Gain	$p<<0.0001$	$p<<0.0001$	$p<<0.0001$	$p=0.0042$	$p<<0.0001$	$p=0.00012$	$p=0.0014$	$p<<0.0001$	$p=0.017$
Phase	$p=0.00081$	$p<<0.0001$	$p=0.042$	$p=0.018$	$p<<0.0001$	$p=0.75$	$p=0.14$	$p<<0.0001$	$p=0.20$

medication was 23% and 18% larger than that of healthy controls ($4.59 \pm 0.73°$), respectively, indicating that the precision of the control response of PD patients regardless of their medication state was worse than that of healthy controls. A paired-samples *t*-test revealed that after taking antiparkinsonian medication, PD patients showed a small (4%) but significant reduction in the RMS error, indicating an improvement in the control precision ($t(19)=2.13$, $p=0.046$, Cohen's $d=0.48$; see the results summary in Table 4).

3.2. Frequency response analysis results

The RMS target position error measures the overall performance error, which can be driven by input visual signals or motor execution noise. In addition, the RMS target position error cannot differentiate whether the performance error arose from inappropriate response amplitude or time delay. We thus performed a frequency-response analysis to obtain the response amplitude (i.e., gain) and time delay (i.e., phase lag) at each input perturbation frequency (Fig. 3B). The decrease in control gain and the steady phase roll-off at high frequencies are typical characteristics of low-pass control in closed-loop manual control tasks (Jagacinski and Flach, 2003; Li et al., 2005, 2006).

3.2.1. Control gain

To compare the control gain of PD patients ON and OFF medication with healthy controls (Fig. 3B, upper panel), we conducted two separate 2 (patients vs. controls) × 7 (frequency) mixed–design ANOVA on the control gains. For the OFF medication ANOVA, both the main effects of participant group and frequency were significant ($F(1,38)=27.63$, $p<<0.0001$, $\eta^2=0.42$, and $F(1.78, 67.55)=91.75$, $p<<0.0001$, $\eta^2=0.71$, respectively) and so was their interaction effect ($F(6,228)=16.19$, $p<<0.0001$, $\eta^2=0.30$). For the ON medication ANOVA, both the main effects of participant group and frequency were also significant ($F(1,38)=9.25$, $p=0.0042$, $\eta^2=0.20$, and $F(2.74, 104.06)=61.77$, $p<<0.0001$, $\eta^2=0.62$, respectively) and so was their interaction effect ($F(6, 228)=4.82$, $p=0.00012$, $\eta^2=0.11$). While PD patients regardless of their medication state generated smaller control gains than did healthy controls across all input perturbation frequencies, Newman–Keuls tests revealed that their control gains showed a significant drop at the two highest frequencies of 1.28 Hz ($p<0.0023$) and 2.19 Hz ($p<0.000022$) and the control gains of healthy controls showed a significant drop only at the highest frequency of 2.19 Hz ($p<0.0001$).

To compare PD patients' control gains across the two medication states, we conducted a 2 (OFF vs. ON) × 7 (frequency) repeated-measures ANOVA. Both the main effects of medication state and frequency were significant ($F(1,19)=13.95$, $p=0.0014$, $\eta^2=0.42$ and $F(2.17,41.31)=61.12$, $p<<0.0001$, $\eta^2=0.76$, respectively) and so was their interaction effect ($F(2.88,54.67)=3.74$, $p=0.017$, $\eta^2=0.16$). Newman–Keuls tests revealed that taking antiparkinsonian medication increased the control gains specifically at the middle and high perturbation frequencies (0.24–2.19 Hz, $p<0.008$).

Fig. 3C (upper panel) plots the mean control gain averaged across the seven input perturbation frequencies against participant group. The mean control gain for PD patients OFF (12.73 ± 6.05 dB) and ON (15.85 ± 6.52 dB) medication was 39% ($t(27.94)=5.26$, $p<<0.0001$, Cohen's $d=1.67$) and 24% ($t(38)=3.04$, $p=0.0042$, Cohen's $d=0.96$) less than that of the healthy controls (20.75 ± 3.05 db), respectively. After taking the antiparkinsonian medication, the mean control gain for PD patients increased by 25% ($t(19)=3.73$, $p=0.0014$, Cohen's $d=0.83$; see the results summary in Table 4).

3.2.2. Phase lag

To compare the phase lag of PD patients ON and OFF medication with healthy controls (Fig. 3B, lower panel), we again conducted two separate 2 (patients vs. controls) × 7 (frequency) mixed–design ANOVA on the phase lags. For the OFF medication ANOVA, both the main effects of participant group and frequency were significant ($F(1, 38)=13.25$, $p=0.00081$, $\eta^2=0.26$ and $F(1.77,67.36)=1521.46$, $p<<0.0001$, $\eta^2=0.98$, respectively) and so was their interaction effect ($F(6,228)=2.22$, $p=0.042$, $\eta^2=0.06$). For the ON medication ANOVA, both the main effects of participant group and frequency were also significant ($F(1, 38)=6.16$, $p=0.018$, $\eta^2=0.14$ and $F(1.97, 74.79)=1054.89$, $p<<0.0001$, $\eta^2=0.97$, respectively), but their interaction effect was not ($F(6,228)=0.57$, $p=0.75$). While PD patients regardless of the medication state generated larger phase lags than did healthy controls across all input perturbation frequencies, Newman–Keuls tests revealed that PD patients OFF medication generated larger phase lags than did the healthy controls specifically at the two high frequencies (0.74 and1.28 Hz, $p<0.041$).

To compare PD patients' phase lags across the two medication states, we conducted a 2 (OFF vs. ON) × 7 (frequency) repeated-measures ANOVA on the phase lags. Only the main effect of frequency was significant ($F(1.56, 29.65)=464.81$, $p<<0.0001$, $\eta^2=0.96$). The main effect of medication state and the interaction effect of medication state and frequency were not significant ($F(1,19)=2.37$, $p=0.14$ and $F(2.25,42.78)=1.65$, $p=0.20$, respectively), indicating the phase lags were similar across the two medication states in PD patients.

Fig. 3B (lower panel) plots the mean phase lag averaged across the seven input perturbation frequencies against participant group. The mean phase lag for PD patients OFF ($-120.93° \pm 13.73°$) and ON ($-117.00° \pm 14.59°$) medication was 13% ($t(38)=3.64$, $p=0.00081$, Cohen's $d=1.15$) and 9% ($t(38)=2.48$, $p=0.018$, Cohen's $d=0.78$) larger than that of the healthy controls ($-107.35 \pm 9.46°$), respectively. After taking antiparkinsonian medication, the mean phase lag for PD patients decreased for a small amount by 3% but did not reach the significance level ($t(19)=1.54$, $p=0.14$).

In summary, the amplitude and time delay of the control response in PD patients were impaired compared with demographically-

matched healthy controls, expressed as lower control gains and larger phase lags. Taking antiparkinsonian medication only improved patients' response amplitude in visuomotor control, but not to the level of healthy controls (see the results summary in Table 4).

3.3. Correlation analysis results

A paired-sample *t*-test on the motor UPRDRS (Part III) scores of PD patients ON and OFF medication revealed that after taking antiparkinsonian medication, their motor symptoms were relieved ($t(19)=6.51$, $p<<0.0001$, Cohen's $d=1.46$), with the mean motor UPDRS score decreased by 46% from the OFF (mean ± SD: 28.55 ± 14.63) to ON medication state (15.45 ± 13.44). To examine how the impaired visuomotor control performance in PD patients was related to their clinical motor symptoms, we computed the Spearman correlations between their motor UPRDRS scores and their visuomotor control performance metrics that we took (Table 5). PD patients' motor UPRDRS scores were marginally negatively correlated with their control gains in both the OFF ($\rho=-0.44$, $p=0.054$) and ON ($\rho=-0.43$, $p=0.058$) medication states. The motor UPRDRS scores were not correlated with the RMS errors or phase lags.

We then examined the impact of disease progression on visuomotor control in PD patients. We computed the Spearman correlations between patients' H&Y scale scores and their control performance metrics (see Table 5). PD patients' H&Y scale score were marginally negatively correlated with their control gains in the OFF ($\rho=-0.44$, $p=0.051$) medication state and negatively correlated with their control gains in the ON medication state ($\rho=-0.48$, $p=0.032$). Again, the H&Y scale scores were not correlated with the RMS errors or phase lags.

To evaluate the effects of antiparkinsonian medication on visuomotor control in PD patients, we linearly regressed the improvement in each of our performance metrics against the total levodopa equivalent dose (LED) per day. Fig. 4 plots the improvement in the RMS error, control gain, and phase lag against the total LED per day. The reduction in the RMS error with the increase in the total LED was significant ($r=0.48$, $p=0.034$). The increase in the control gain with the increase in the total LED was approaching significance ($r=0.39$, $p=0.092$). There was no significant correlation between the reduction in the phase lag and the total LED ($r=0.30$, $p=0.20$).

3.4. Modeling results

The Crossover Model allows us to perform a quantitative evaluation of the effects of PD and antiparkinsonian medication on the sensory–motor system underlying visuomotor control. The overall gain K_p, the reaction time τ, and the lead time constant T_L capture the visual-stimulus-dependent characteristics of visuomotor control. In contrast, the system time constant T_S captures the visual-stimulus-independent characteristics of the neuromuscular system.

Fig. 5 shows frequency response plots illustrating how varying K_p, τ, T_L, and T_S in the Crossover Model affects the gain and phase of the human operator transfer function Y_p. Specifically, increasing gain K_p while keeping the other parameters constant causes an overall increase in gain (Fig. 5A); increasing reaction time τ causes an increase in phase lag in the high-frequency range (Fig. 5B); increasing lead time constant T_L causes an increase in gain but a slight decrease in phase lag in the high-frequency range (Fig. 5C); and increasing system time constant T_S (indicating a decrease in the stability of the neuromuscular system) causes an increase in both gain and phase lag mostly at the undamped natural frequency of the neuromuscular system (Fig. 5D). The impaired visuomotor control performance in PD patients could be due to the change in any of these model parameters that describe the characteristics of the sensory–motor system underlying visuomotor control.

By fitting the model to each participant's performance data, we estimated K_p, τ, T_L, and T_S in the Crossover Model of the human operator transfer function Y_p (Fig. 1C and Eq. (3)) for each participant. The fitted curves in Fig. 3B show that the model accurately described the averaged participants' control performance. Below we present the model fitting data.

Fig. 6 plots the mean of fitted model parameters against participant group. K_p for PD patients OFF (mean ± SD: 6.58 ± 2.83% max/deg) and ON medication (7.80 ± 3.16% max/deg) was 42% ($t(38)=4.64$, $p<<0.0001$, Cohen's $d=1.47$) and 31% ($t(38)=3.28$, $p=0.0022$, Cohen's $d=1.04$) smaller than that for healthy controls (11.26 ± 3.51% max/deg), respectively. K_p improved by 19% from the OFF to ON medication state for PD patients ($t(19)=2.36$, $p=0.029$, Cohen's $d=0.53$; see Table 6 for the results summary). This indicates that while the responsiveness of the sensory–motor system to input error signals in PD patients regardless of their medication state was smaller than that of the healthy controls, it improved after taking antiparkinsonian medication.

T_L for PD patients OFF medication (0.17 ± 0.14 s) was 55% smaller ($t(28.52)=3.04$, $p=0.005$, Cohen's $d=0.95$) than that of the healthy controls (0.38 ± 0.28 s). T_L for PD patients ON medication (0.40 ± 0.42 s) was 5% larger ($t(19)=2.87$, $p=0.01$, Cohen's $d=0.64$) than that for PD patients OFF medication and was not significantly different from that for healthy controls ($t(38)=0.17$, $p=0.86$; see Table 6 for the results summary). This indicates that taking antiparkinsonian medication increased PD patients' ability to predict input error signals and generate lead control to the level of healthy controls.

T_S for PD patients OFF (0.57 ± 0.60 s) and ON (0.54 ± 0.33 s) medication was 78% ($t(19.93)=1.88$, $p=0.074$, Cohen's $d=0.58$) and 69% ($t(21.98)=2.83$, $p=0.01$, Cohen's $d=0.91$) larger than that for healthy controls (0.32 ± 0.09 s), respectively. T_S was similar across the two medication states in PD patients ($t(19)=0.44$, $p=0.67$; see Table 6 for the results summary). This indicates that the stability of the neuromuscular system in PD patients is in general worse than that in the healthy controls, and taking antiparkinsonian medication did not help.

τ for PD patients OFF (0.29 ± 0.07 s) and ON (0.31 ± 0.06 s) medication was similar ($t(19)=1.55$, $p=0.14$) and comparable to that for healthy controls (0.31 ± 0.03 s, $t(27.06)=1.14$, $p=0.27$ and $t(38)=0.20$, $p=0.85$, respectively; see Table 6 for the results summary). This indicates that the reaction time of the sensory–motor system underlying visuomotor control was not affected by Parkinson's disease or antiparkinsonian medication.

Table 5
Spearman's ρ (and p value) between the motor UPDRS scores, H&Y scale scores, and performance metrics of visuomotor control.

n's	PD: OFF state			PD: ON state		
	RMS error	Mean gain	Mean phase	RMS error	Mean gain	Mean phase
Motor UPDRS scores	0.14 (0.553)	**−0.44 (0.054)**	0.35 (0.135)	0.18 (0.457)	**−0.43 (0.058)**	0.29 (0.216)
H&Y scale	0.10 (0.689)	**−0.44 (0.051)**	0.39 (0.089)	0.25 (0.283)	**−0.48 (0.032)**	0.26 (0.263)

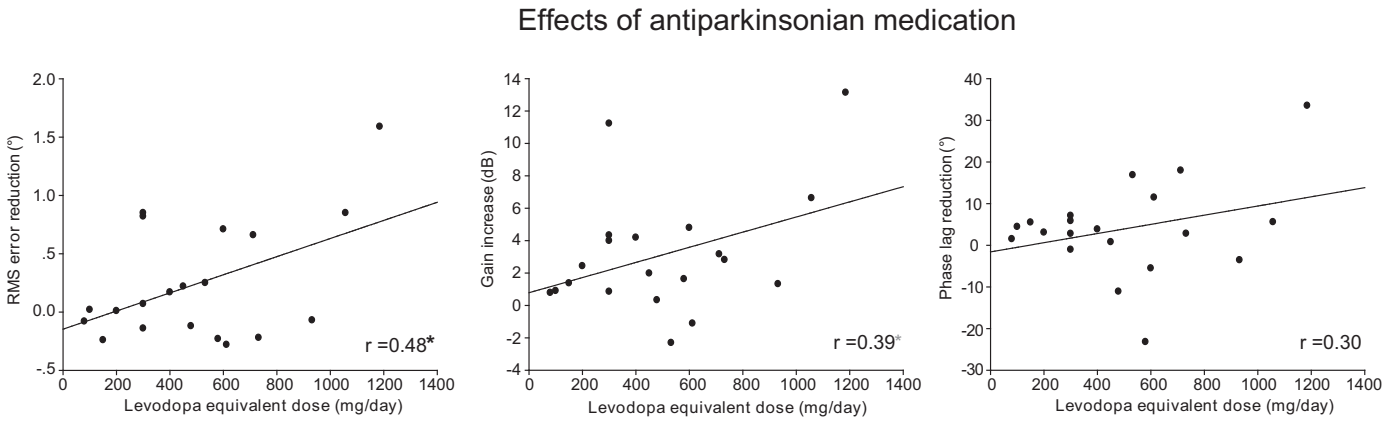

Fig. 4. The improvement in RMS error, gain, and phase lag of the visuomotor control performance from the OFF to ON state for PD patients against total levodopa equivalent dose per day. Solid lines indicate the fitted linear regression lines. *: $p < 0.1$, *: $p < 0.05$.

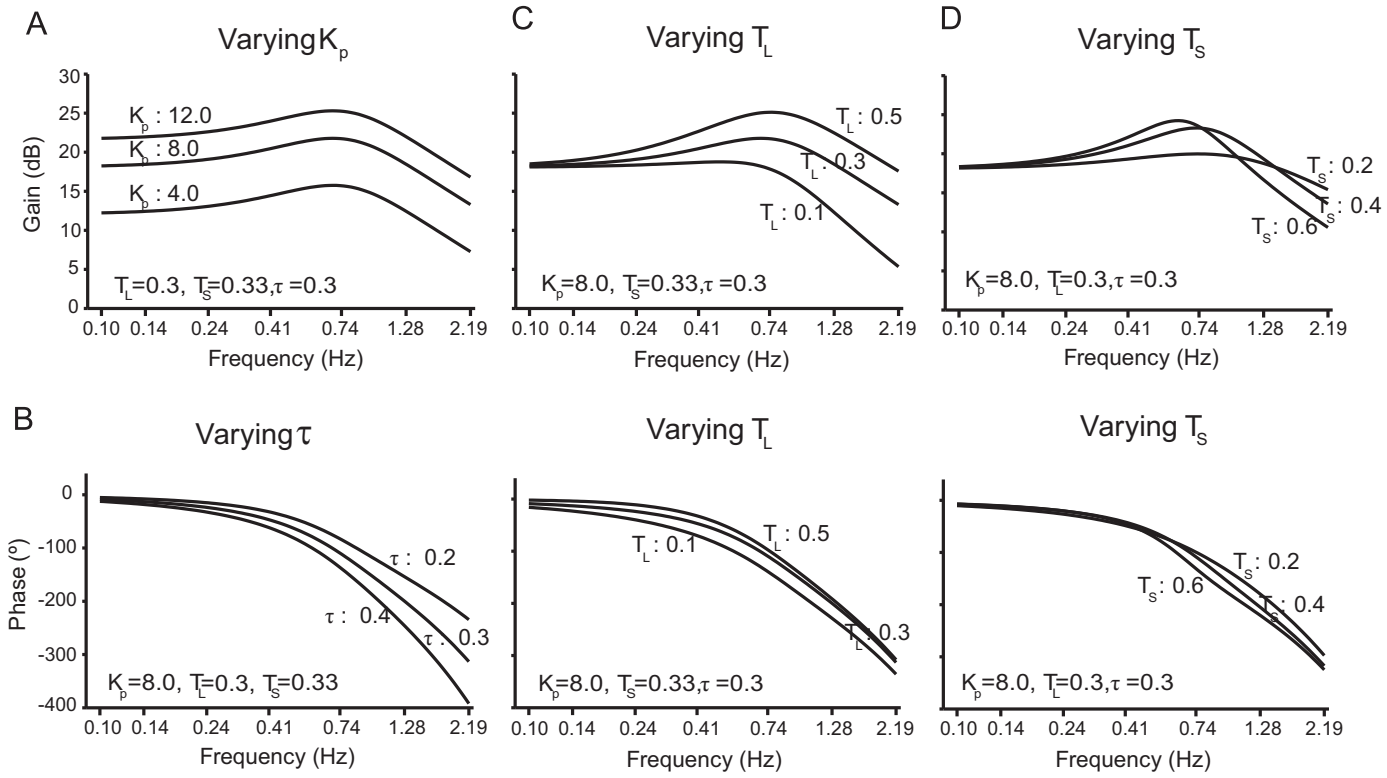

Fig. 5. Frequency response (Bode) plots depicting effects of varying (A) K_p, (B)τ, (C) T_L, and (D) T_S in the Crossover Model of the human operator transfer function (Y_p).

4. Discussion

4.1. Visuomotor control in PD patients

In this study, we used a control-theoretic approach to examine visuomotor control in PD patients. We found that manual tracking of a randomly moving target in PD patients was impaired compared with healthy controls, as indicated by lower control precision, smaller response amplitude, and larger response delay. After taking antiparkinsonian medication, PD patients' control performance improved on the control precision and response amplitude but did not reach the level of healthy controls. The effectiveness of antiparkinsonian medication was also shown by the positive correlation between the dose taken per day and the improvement in the precision and response amplitude of visuomotor control. Although the order of testing on the manual control task was always from the ON to OFF medication state in PD patients, the practice effect could only reduce the effect of antiparkinsonian medication on visuomotor control and would not undermine our findings here.

Our results are consistent with the findings from previous studies that examined manual tracking of a predictable or a randomly moving target (Cassell et al., 1973; Flowers, 1978b; Gibson et al., 1987; Stark, 1968; Stevenson et al., 2014). However, several other previous studies that used similar manual tracking tasks also showed no difference in the tracking performance between PD patients and healthy controls, and/or that the administration of antiparkinsonian medication did not help (Au et al., 2010; Baradaran et al., 2013; Bloxham et al., 1984; Johnson, et al., 1994, 1996; Oishi et al., 2011). We surmise that the discrepancy between the results of these studies could be due to methodological differences as well as differences in clinical characteristics of PD patients tested. To illustrate, our current study tested a wider range of tracking frequencies (0.1–2.19 Hz) than previous studies (0.2–1.5 Hz), and we found a difference in the control performance

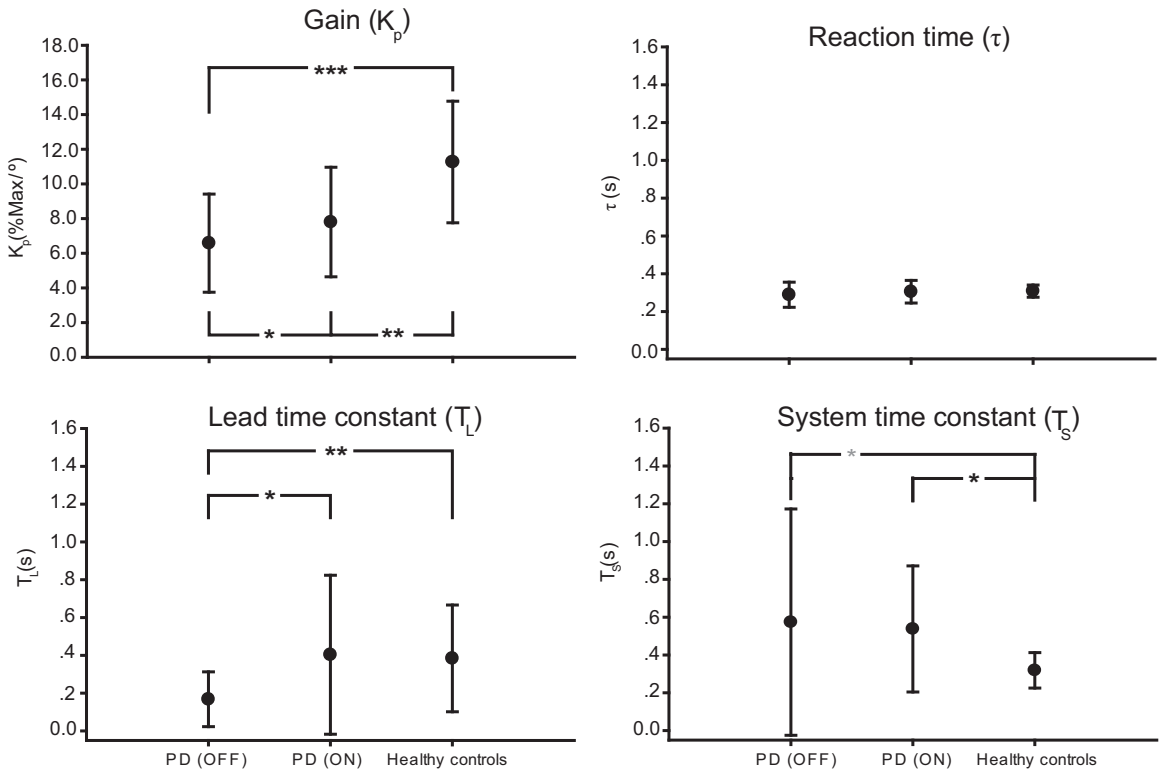

Fig. 6. Modeling results for the visuomotor control performance data. Best-fitting model gain K_p, reaction time τ, lead time constant T_L, and system time constant T_S against participant group. Error bars are SEs across 20 participants. *: $p < 0.1$, *: $p < 0.05$, **: $p < 0.01$, and ***: $p < 0.001$.

Table 6
Summary of the modeling results.

	PD OFF vs. Controls Independent-samples *t*-tests	PD ON vs. Controls Independent-samples *t*-tests	PD OFF vs. PD ON Paired-samples *t*-test
K_p	$p < < 0.0001$	$p = 0.0022$	$p = 0.029$
T_L	$p = 0.0050$	$p = 0.86$	$p = 0.010$
T_S	$p = 0.074$	$p = 0.010$	$p = 0.67$
τ	$p = 0.27$	$p = 0.85$	$p = 0.14$

between PD patients and healthy controls and the effect of antiparkinsonian medication. Furthermore, Hufschmidt and Lucking (1995) proposed that a two-dimensional manual tracking task, such as the one used by Bloxham et al. (1984), is less sensitive than a one-dimensional tracking task, such as the one used by Flowers (1978b) and in the current study, in revealing visuomotor control impairments in PD patients. This is due to the fact that a one-dimensional task requires a complete reversal of movement direction, which is impaired in PD patients. Last, studies that tested PD patients with a less severe stage of disease (H&Y scale ≤ 3) reported no difference in tracking performance between patients and controls and no effect of antiparkinsonian medication (Au et al., 2010; Baradaran et al., 2013; Oishi et al., 2011).

For the visuomotor performance metrics that we took in the current study, only the response amplitude is significantly correlated with the UPDRS motor score of PD patients, suggesting that basic repetitive motor functions evaluated in clinical assessments contribute to the response amplitude but not the precision or response delay of the control performance on a typical closed-loop manual control task. This could be due to the fact that the manual control task that we used to examine visuomotor control requires more than basic motor functions evaluated in clinical assessments. Specifically, it requires the sensory–motor system to use the visual information of the target (such as its position and velocity information) and integrate it with the predictions of sensory consequence of the joystick movement to guide subsequent motor control. Any failure in these steps leads to deteriorated control performance (Kording and Wolpert, 2004; Shadmehr et al., 2010; Vaziri et al., 2006). Not surprisingly, patients' response amplitudes are also significantly correlated with their H&Y scale scores, indicating that the more disease progression, the lower the visuomotor control response amplitude. This is likely due to the fact that both the H&Y scale and UPDRS involve clinical evaluations of patients' basic motor functions.

4.2. Effects on sensory–motor system underlying visuomotor control

Traditional clinical assessments, such as the UPDRS, only provides a qualitative description of basic motor dysfunctions in PD patients and is not sensitive to minor motor abnormality in the early stage of disease (e.g., Visser et al., 2006). Thus, researchers tried to use a variety of manual tracking tasks for a more sensitive measurement of fine visuomotor control deficits in PD patients and to evaluate the effectiveness of antiparkinsonian medication (Au et al., 2010; Badarny et al., 2006; Giladi et al., 1999; Hocherman et al., 1998; Johnson et al., 1994, 1996; Oishi et al., 2011). However, none of these studies systematically evaluated the effects of PD and antiparkinsonian medication on various aspects of visuomotor control.

The control-theoretic approach we took and the model-driven analysis we conducted in the current study for the first time allows us to perform quantitative evaluations of the effect of PD and antiparkinsonian medication on the visual-stimulus-dependent sensory-motor processing and visual-stimulus-independent neuromuscular systems underlying visuomotor control. Our modeling results show that PD impairs the responsiveness and the predicting ability of the sensory–motor system (see Wolpert et al., 1995) as well as the stability of the neuromuscular system. Taking antiparkinsonian medication improves the responsiveness of the

sensory–motor system. More importantly, it improves the ability of the sensory–motor system to predict target position error given the current control movement and generate lead control ahead of time up to the level of healthy controls. Interestingly, taking antiparkinsonian medication does not improve the stability of the neuromuscular system. These results support the claim that the effect of antiparkinsonian medication on visuomotor control is mainly through improving visual-stimulus-dependent sensory–motor processing. As it has been proposed that cerebellum plays a major role of mediating the predicting ability of the sensory–motor system (Blakemore et al., 2001; Cerminara et al., 2009; Doya, 2000; Miall et al., 1993), the improvement on such ability after taking antiparkinsonian medication observed in the current study is consistent with the findings of previous studies showing that levodopa therapy helps restore cerebellar function (e.g., Festini et al., 2015; Martinu and Monchi, 2013; Stevenson et al., 2011).

Our finding that the stability of the neuromuscular system in PD patients does not improve after taking antiparkinsonian medication appears to be in conflict with previous findings showing a decrease in the undamped natural frequency after taking antiparkinsonian medication (Au et al., 2010; Oishi et al., 2011). However, these studies did not separate visual-stimulus-dependent control response from visual-stimulus-independent control response, and thus failed to examine the extent to which the improvement in visuomotor control is due to more efficient sensory–motor processing rather than motor response itself.

Our modeling results do not show any effect of PD or antiparkinsonian medication on the reaction time of the sensory–motor system underlying visuomotor control. In fact, it still remains in controversy whether PD or antiparkinsonian medication affects reaction times (see Gauntlett-Gilbert and Brown, 1998, for a review). While some studies found such effects (e.g., Jahanshahi et al., 1992; Brown et al., 1993; Montgomery and Nuessen, 1990; Zappia et al., 1994), others did not (e.g., Harrison et al., 1995; Girotti et al., 1986; Jordan et al., 1992; Velasco and Velasco, 1973). For simple motor response tasks to indicate choices, the reported increased reaction times in PD patients compared with healthy controls are associated with these patients in a complete withdrawal from antiparkinsonian medication (e.g., Zappia et al., 1994).

4.3. Visuomotor control and driving

The closed-loop manual control task used in the current study shares common attributes with a range of visuomotor control tasks experienced in our daily life. For example, lane keeping, a basic control task during driving, mimics our manual control task in that it requires the driver to constantly adjust the controller (i.e., the steering wheel) to minimize the vehicle's lateral deviation errors to keep the vehicle centered in the lane. Indeed, a recent study from our lab showed that for normal healthy participants who were trained with our manual control task for as short as 40 min, their performance on a lane-keeping task improved as much as participants who were trained on the lane-keeping task itself. In contrast, participants who did not undergo any training did not show any improvement on lane keeping (Chen et al., 2015). Furthermore, in another study in which we used our manual control task to evaluate visuomotor control abilities of patients with homonymous hemianopic who could not see one side of the visual field, we found that these patients showed impaired manual control performance mirroring their real-world driving disabilities as indicated by increased lane position variability and less efficient steering to correct lane position (Niehorster et al., 2013).

It has been reported that drivers with PD make significantly more errors than healthy controls in lane keeping during an on-road driving test (Wood et al., 2005). Currently, there is no standard method to evaluate driving behavior in PD patients, and guidelines for assessing their fitness to drive are subjective in many countries (Klimkeit et al., 2009). Given the findings of the current study and the similarity between our manual control task and lane keeping, we propose that our manual control task can serve as a preliminary screening and training tool for fitness-to-drive in PD patients. The advantages of our manual control task over on-road driving tests are that (1) our task can quantitatively evaluate various aspects of visuomotor control and can thus provide detailed information to determine at which point a PD patient should be classified as unsafe to drive, (2) the device required for our task is easily accessible and cost effective, and (3) the task is simple enough such that PD patients have no difficulty to perform it. In fact, 10% of PD patients in our study were in a severe stage of disease (H&Y scale=4). Nevertheless, they could all perform the task after a few practice trials.

5. Conclusions

In this study, we tested PD patients both ON and OFF mediation and demographically-matched healthy controls with a commonly used manual control task to examine the effects of PD and antiparkinsonian medication on visuomotor control. We found that although antiparkinsonian medication improved visuomotor control in PD patients, they still showed a significant decrease in the control precision (RMS error) and response amplitude (gain) as well as a significant increase in the response delay (phase lag) compared with healthy controls. Our model-driven analyses show that PD impairs the responsiveness of the sensory–motor system to input visual error signals and its ability to anticipate error signals to generate control response ahead of time. Furthermore, PD also impairs visual-stimulus-independent aspects of visuomotor control by decreasing the stability of the neuromuscular system. The administration of antiparkinsonian medication improves the responsiveness and predicting ability of the sensory–motor system but does not increase the stability of the neuromuscular system. The findings of this study have practical implications for developing sensitive assessment tools to evaluate the efficacy of different therapies for PD and preliminary screening and training tools for fitness-to-drive in PD patients.

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