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Parkinson's Disease Differentially Affects Adaptation to Gradual as Compared to Sudden Visuomotor Distortions

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Abstract

Patients with Parkinson's disease (PD) have difficulties in movement adaptation to optimize performance in novel environmental contexts such as altered screen cursor-hand relationships. Prior studies have shown that the time course of the distortion differentially affects visuomotor adaptation to screen cursor rotations, suggesting separate mechanisms for gradual and sudden adaptation. Moreover, studies in human and non-human primates suggest that adaptation to sudden kinematic distortions may engage the basal ganglia, whereas adaptation to gradual kinematic distortions involves cerebellar structures. In the present studies, participants were patients with PD, who performed center-out pointing movements, using either a digitizer tablet and pen or a computer trackball, under normal or rotated screen cursor feedback conditions. The initial study tested patients with PD using a cross-over experimental design for adaptation to gradual as compared with sudden rotated hand-screen cursor relationships and revealed significant after-effects for the gradual adaptation task only. Consistent with these results, findings from a follow-up experiment using a trackball that required only small finger movements showed that patients with PD adapt better to gradual as against sudden perturbations, when compared to age-matched healthy controls. We conclude that Parkinson's disease affects adaptation to sudden visuomotor distortions but spares adaptation to gradual distortions.

Keywords

Parkinson's disease; Internal model; Trial and error learning; Sensory perception; Motor processes

1. Introduction

Aiming and drawing movements require the transformation of visual information about the spatial location of the target with respect to end-effector position into motor commands.

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This visuomotor transformation needs to be modified in response to altered environments, such as screen-cursor rotations (Ghilardi et al., 2000; Kagerer, Contreras-Vidal, & Stelmach, 1997; Robertson & Miall, 1999; Roby-Brami & Burnod, 1995). Under such distortions, one must practice to acquire a sensorimotor representation or internal model of the novel environment. Research suggests that the process of adaptation to a kinematic distortion depends on the time course of the perturbation (Buch, Young, & Contreras-Vidal, 2003; Kagerer et al., 1997; Robertson & Miall, 1999). Indeed, adaptation to gradual distortions results in smaller errors and larger after-effects than adaptation to sudden ones (Buch et al., 2003; Kagerer et al., 1997). The small trial-to-trial errors in gradual adaptation imply that subjects had access to a relatively accurate representation of the visuomotor transformation for hand movement. Thus, they were able to use information about the current state of the visuomotor transformation together with memorization of error correction signals to plan the next movement (Roby-Brami & Burnod, 1995). Robertson and Miall (1999) used an inactivation paradigm in nonhuman primates to test the hypothesis that different time courses for distortions engaged different neural mechanisms. It was found that dentate nucleus inactivation in monkeys impaired adaptation to gradual distortions, while sparing adaptation to sudden distortions, suggesting a critical role of cerebellar structures in adaptation to gradual kinematic distortions. It has also been shown that patients with Parkinson's disease (PD) are impaired in adaptation to sudden kinematic distortions (Contreras-Vidal & Buch, 2003). Here, we provide evidence from two adaptation studies suggesting that PD differentially affects adaptation to gradual as compared to sudden visuomotor distortions. These findings provide additional support for separate neural substrates for sudden and gradual adaptation, and have implications for developing intervention programs in PD.

2. Methods

Two studies are reported here. The studies differed in: their experimental paradigm (sequential visuomotor adaptation using a cross-over design in the first study versus visuomotor adaptation with catch trials in the follow-up study), tool (hand-held digitizing tablet in the first study versus finger-controlled track ball in the second study), and type and extent of movement (moderate hand movements in the first study versus modest movements of the index and middle fingers in the second study). To facilitate presentation, the *Methods*, and *Results* are presented sequentially for each study next, followed by an integrated overall *Discussion* section.

2.1 Experiment 1: Adaptation of center-out reaching movements on a digitizing tablet

2.1.1 Methods

Participants: Six right-handed patients with idiopathic PD (73.5 ± 4.5 yrs ($M \pm SD$), 3 males & 3 females, with Hoehn&Yahr scores 2.9 ± 0.7 , Mini-Mental State Examination (MMSE) scores (23.6 ± 0.9 out of 25, as the orientation questions of the MMSE were not given as participants were tested at various locations) participated in this study after giving informed consent as approved by the Institutional Review Board at INSERM (CPRB, Paris, France). All subjects were right-handed, had normal or corrected-to-normal vision and were treated with dopaminergic medications at the time of testing.

Procedure: Participants were instructed to perform center-out pointing movements (10 cm) using a pen on a digitizer tablet (12 inch WACOM InTuos). The position of the pen-tip was sampled in real time at 200 Hz using OASIS™ (KIKOsoft, Nijmegen) software. Feedback of the pen-tip was presented in the form of a white screen cursor. Subjects were instructed to make point-to-point movements as fast and as straight as possible, when ready, by moving the screen cursor from a common central starting location to one of four target circles (45° ,

135°, 225°, 315°) displayed on the computer screen. Direct vision of the hand/pen movement was occluded. Subjects performed 320 trials, 40 trials each in pre and post-exposure (no rotation) and 240 trials in exposure phase. During the exposure trials, the screen cursor-hand movement relationship was rotated 60° clockwise in one step (*Sudden*) or progressively (*Gradual*) in 6 steps of 10° rotation each (40 trials/step). A cross-over experimental design was used in which participants received both types of distortions in 2 different sessions with order of presentation counterbalanced.

Data analysis: Data were low-pass filtered with cut-off of 5 Hz with an 8th order dual-pass Butterworth filter. For each trial, initial directional error (IDE, in degrees) score was calculated as the angle between a vector from initial position of the pen-tip to that at 80 ms after movement onset and a vector extending from start position to target. IDE is thought to represent the state of the internal model of the novel visuomotor transformation (Contreras-Vidal & Buch, 2003). Additionally, root mean square error (RMSE, in cm) was calculated as a measure of average deviation of movement trajectory from a straight line. The dependent measures were statistically analyzed with non-parametric Kruskal-Wallis analysis of variance for within and across distortion block differences, owing to non-Gaussian nature of data. Post-hoc comparisons were performed with Wilcoxon Signed-Rank test for within subject differences between pre and post-exposure differences.

2.1.2 Results—All pre-exposure error scores were similar in both distortion conditions ($p > .05$). However, during the exposure phase, IDE scores across the first 4 blocks of 40 trials were significantly different in the gradual as compared with the sudden condition (block 1: $\chi^2 = 7.41$, $df = 1$, $p < .01$; blocks 2–4: $\chi^2 = 8.308$, $df = 1$, $p < .005$). The last 2 blocks of exposure were not different between sudden and gradual conditions (block 5–6: $\chi^2 < 2.7$, $df = 1$, $p > .1$). The RMSE scores followed a similar trend as IDE during exposure. Importantly, post-exposure IDE and RMSE scores were significantly different from pre-exposure in the gradual condition only ($p < .05$), and not different in the sudden condition ($p > .138$; see Figs. 1A and 1B).

2.2. Experiment 2: Adaptation of center-out cursor movements controlled by a trackball

2.2.1 Methods

Participants: 17 patients with idiopathic PD (72.8 ± 7.4 yrs ($M \pm SD$), 11 males & 6 females, Hoehn & Yahr scores 2.7 ± 0.6) and 17 healthy controls (68.5 ± 7.3 yrs, 11 males & 6 females) participated in this study after giving informed consent as approved by the Institutional Review Board of the University of Maryland, College Park. The mean Unified Parkinson's disease Rating scale (UPDRS) scores for the motor section was 27.8 ± 10.1 . Subjects were randomly assigned to one of 4 groups: PD-Gradual ($N = 9$), PD-Sudden ($N = 8$), Control-Gradual ($N = 9$), Control-Sudden ($N = 8$). All patients and healthy controls were right-handed, except for one healthy control that was left-handed; and had normal or corrected-to-normal vision. Patients were being treated with dopaminergic medications. The mean Mini-Mental State Examination (MMSE) score for patients was 28.4 ± 1.06 and for healthy controls was 28.9 ± 1.19 . There was no difference between ages of patients and controls ($p > .05$).

Procedure: Participants were instructed to performed center-out drawing movements (5 cm) of a screen cursor to one of three randomly appearing peripheral targets (at 30°, 90°, 150°) by controlling a trackball with relatively small movements using the index & middle fingers. Trackball movements were sampled at 100 Hz and displayed in real time on a monitor as the cursor while direct vision of finger movement was occluded. Subjects performed 249 trials, 34 trials each in pre-exposure (no rotation) and 180 trials in exposure phase including 35 randomly interspersed catch trials (no rotation) to study after-effects. During exposure to

visuomotor distortion phase, screen cursor-trackball movement relationship was rotated clockwise up to 40° either in one step (*Sudden*) or progressively (*Gradual*) in 20 steps of 2° rotation each (9 trials/step). Thus, we reduced the amount of rotation (as blocks greater than 40° in Experiment 1 did not show differences in sudden and gradual conditions; see Results Section 2.1.2) and the step size in the gradual condition.

Data analysis: Data were low-pass filtered with cut-off of 10 Hz with a 4th order dual-pass Butterworth filter. For each trial, initial directional error (IDE, in degrees) score was calculated as the angle between a vector from initial position of the trackball to that at peak velocity after movement onset and a vector extending from start position to target. Peak velocity was used to compute IDE since the movement was very small (Anguera, Russell, Noll, & Seidler, 2007). IDE represented the state of the internal model of the novel environment and was compared as the primary dependent variable across all 4 groups in the *last block of exposure* (mean, 40° rotation), *last catch trial*, *difference between last catch trial and last block* (mean). Two-way analysis of variance (ANOVA) was performed (disease by distortion) and pre-planned contrasts set up to compare (1) adaptation conditions (Sudden vs. Gradual) and (2) PD groups with respective controls.

The relationship between the immediate trials preceding and succeeding the catch trial with the errors in the catch trial was also explored in greater detail in Experiment 2. This was important since the error in opposite direction in a catch trial has been shown to impact adaptation in successive trials on a trial-by-trial basis (Diedrichsen, Hashambhoy, Rane, & Shadmehr, 2005; Thoroughman & Shadmehr, 2000). Thus, a multiple linear regression model was developed, based on the linear state-space model originally specified for adaptation to sudden distortions by Thoroughman and Shadmehr (2000) as follows:

$$Y_n = \beta_0 + \beta_1 Y_{n-1} + \beta_2 U_{n-1} + \beta_3 U_n$$

Here Y represents IDE in a given trial within the exposure phase, U represents whether the visual feedback distortion was present ($U = 1$, if present) or not ($U = -1$) and n represents the trial number. Thus, the linear model predicts that the error in each trial depends not only on the presence of visual distortion within the trial, but also on the error and the presence of visual feedback distortion in the previous trial. Our objective was to quantify and describe the trial-by-trial changes in adaptation to gradual and sudden visuomotor distortions, particularly in patients with PD, which is still unknown. Moreover, the model could be used to characterize the progressive dampening in learning, if any, caused by the visual feedback of the errors in the opposite direction of adaptation in the catch trial. It is likely that this may help better understand the potential mechanisms underlying performance differences in visuomotor adaptation to gradual versus sudden distortions.

In order to improve the generality of predictions while avoiding over-fitting, a “leave-one-out” (LOO) cross-validation procedure was employed. Using the LOO approach, for each group and condition, the model was optimized for a training set consisting of all but one subject, and the performance tested on this subject to predict his/her error scores. This procedure was repeated for all subjects in successive iterations to obtain the mean predicted scores and mean fit statistic (R^2) for each of the four groups of participants. The LOO procedure has been shown to give an almost unbiased estimate for the generalization error (Chapelle, Vapnik, Bousquet, & Mukherjee, 2002).

2.2.2 Results—All pre-exposure error scores were similar across all 4 groups ($p > .05$). For *last catch trial IDE*, disease by distortion interaction was not significant ($F(1, 30) = 1.04, p = .3154$) while disease main effect was significant, $F(1, 30) = 7.9, p = .0086$. The

disease by distortion interaction was not significant when comparing *the difference between last catch trial & last block of exposure mean IDE* ($F(1, 27) = 1.77, p = .1947$); however, there was a significant main effect for disease ($F(1, 27) = 4.76, p = .038$). Pre-planned contrasts revealed a significant difference between patients and controls only in the sudden condition for the *last catch trial mean IDE* ($p = .0132$; Fig. 2A). The *difference between last catch trial & last block of exposure mean IDE* was also significantly different between patients and controls in the sudden condition ($p = .0210$; Fig. 2B). This dependent measure of difference depicted a measure of the state of acquisition of a novel sensorimotor representation as the subjects switched from exposure trial with 40° rotation to a *catch* trial with no rotation.

Additionally, the multiple linear regression was significant for all groups at all iterations during the LOO validation procedure ($p < .001$), suggesting that the model was able to explain a significant portion of the variance in the IDE changes during adaptation in all four groups. Interestingly, we found that the model's predictions were better for the pattern of adaptation in the sudden distortion conditions than the gradual (see Fig. 3, Table 1). This difference was particularly evident in the controls wherein the trial-by-trial pattern of changes in errors, including that in the catch trials was nicely captured in the group that received sudden versus that which received gradual distortions. While in the sudden groups, the model had better predictions for the controls (mean R^2 (across all predictions) = .7465) than for the patients (mean $R^2 = .5430$) considering greater variability in patients' performance, surprisingly, in the gradual groups, the models had almost identical prediction levels for both patients and controls (mean $R^2 = .3833$ and .3758 respectively, see Table 1). Additionally, the models' parameters for both patients and controls in the gradual condition appeared to weight the visual distortion in the current trial half as much as that for the corresponding patients and controls in the sudden condition (Fig. 4), indicating that participants in the gradual condition programmed their movements based strongly on their experience/knowledge of the state of the visuomotor environment in their prior trial rather than the current one. Further, the predicted model weighted the visual distortion in the previous trial negatively only for the patient groups, and even more so for the sudden as compared to gradual group. This is probably understandable since patients with PD are known to rely highly on visual feedback of movements (Vaillancourt, Slifkin, & Newell, 2001), which in this case was variable on a trial-by-trial basis due to changing errors. However, the constant terms predicted in the model were lower for the patient groups compared to their own corresponding controls in both sudden and gradual distortion conditions, probably relating to the slightly impaired performance in patients as compared to their controls. Interestingly, this coefficient was predicted to be lower in the patients in the sudden as compared to the gradual distortion group (Fig. 4).

3. Discussion

Overall, the main finding across our two studies is that Parkinson's disease differentially affects adaptation to gradual as compared with sudden kinematic perturbations. The first study used a cross-over, counterbalanced protocol in which patients with PD performed both types of visuomotor distortions. Consistent with prior studies (Contreras-Vidal & Buch, 2003), patients with PD showed significant after-effects during post-exposure only in the gradual adaptation paradigm, plausibly mediated by cerebellar structures (Robertson & Miall, 1999), in conjunction with a widespread neural network comprising primary motor cortex along with posterior parietal cortex and premotor cortical areas involved in mediating sensorimotor adaptation (Anguera, Reuter-Lorenz, Willingham, & Seidler, 2010; Mandelblat-Cerf, Paz, & Vaadia, 2009; Tanaka, Sejnowski, & Krakauer, 2009). Adaptation performance during gradual as against sudden exposure was superior up to 40° screen cursor rotation; this suggests that during progressive acquisition of the internal model of the

kinematic distortion, accumulation of visuomotor errors led to a switch to a sudden adaptation regime, such that in the last two blocks of trials, neither of the two types of distortion could be differentiated. Nevertheless, significant after-effects in gradual condition at post-exposure trials suggest that the accumulated visuomotor errors (or the hypothesized switch to purely extra-cerebellar mechanisms) did not interfere with prior learning. Experiment 1 used a cross-over design and thus it did not include age-matched controls (it has been shown that elderly subjects can adapt to both types of distortions; Buch et al., 2003). The advantage of this type of experimental design is that all subjects serve as their own controls and the error variance is reduced thus reducing the sample size needed; whereas its main disadvantage is that the washout period for prior adaptation may be lengthy or unknown. Nevertheless, the randomization and counterbalancing would have cancelled out any potential effects due to incomplete washout from prior adaptation. As discussed elsewhere, the impaired adaptation to sudden distortions in patients with PD could be due to several factors, including hypometria/bradykinesia, noisy visual feedback of movement, reduced kinaesthesia, reduced plasticity, and/or impaired selection of the internal model for setting the initial direction of movement (Contreras-Vidal & Buch, 2003).

To minimize the motor demands in the production of large movement amplitudes, Experiment 2 used a trackball that was controlled by small finger movements. Moreover, instead of using a sequential adaptation paradigm in which after-effect trials followed exposure trials, we used *catch* trials throughout the exposure condition and compared adaptation to sudden and gradual distortion in a group of patients with PD and their matched controls. As expected, the results from Experiment 2 also showed lesser after-effects (last *catch* trial IDE) in the patients with PD as compared to their controls in the sudden condition suggesting that sudden distortions engaged visuomotor adaptation mechanisms to a lesser extent in the patients. This outcome, coupled with the fact that patients and controls in the gradual condition demonstrated comparable after-effects, indicates that when the time course of these visuomotor distortions varies gradually, patients can better correct for errors on a trial-to-trial basis and acquire a sensorimotor mapping of the novel environment.

It is likely that a gradually introduced change in the visuomotor mapping may obviate the need for context recognition and engage the cerebellar error-corrective mechanisms more strongly. That is, gradual adaptation would be performed based on the (small) error in the prior trials and the current state of the internal model, rather than searching for appropriate mappings. This suggests that gradual distortions may be useful to bypass basal ganglia mechanisms that are required for contextual recalibration, and this may explain the beneficial effects of this regime in patients with PD. In fact, computational models explaining underlying neural substrates of visuomotor adaptation support this dissociation between cerebellar and basal ganglial contribution (Grosse-Wentrup & Contreras-Vidal, 2007). In addition, the recent discovery of neural connections between the cerebellum and basal ganglia in non-human primates (Hoshi, Tremblay, Féger, Carras, & Strick, 2005) also suggests that there may be other underlying neural mechanisms mediated by the cerebellum that may plausibly be recruited by a gradual regime. Further support is provided by prism adaptation studies in which “true” adaptation is postulated to occur in the later stage of the process of adaptation which is slower and comprises of realignment i.e., reduction of smaller terminal errors; which is mediated by the cerebellar hemisphere ipsilateral to the deviation introduced by the prisms (Pisella, Rode, Farnè, Tilikete, & Rossetti, 2006).

It was found that modeling of the trial-by-trial changes in errors during the time course of the adaptation during exposure to sudden and gradual visuomotor distortions had better predictions for the sudden conditions, and even more so for the controls than the patients. This suggests that the impact of each preceding trial on the planning and performance of the successive trial differs within the gradual regime as compared to the sudden one.

Interestingly, the predictions were comparable for controls and patients in the gradual conditions. Since the original model was developed in the context of visuomotor adaptation to sudden/abrupt distortions (Thoroughman & Shadmehr, 2000), it is understandable that the model's performance on data in the sudden conditions is better. However, the fact that this model's performance is lower, given data from adaptation to gradual conditions, suggests that the model is improperly specified in terms of trial-by-trial changes occurring during a gradual regime of adaptation. In other words, it is likely that the underlying neural computations combining preceding trial performance and current trial requirements is different in the context of adaptation to gradually varying distortions as against sudden/abrupt ones, which further strengthens the notion that different mechanisms are involved in these two types of kinematic adaptations. One possible speculation is that the task demands in terms of visuomotor distortions differ: the sudden regime requires a shorter time window of error sampling and computation in the neural domain in order to plan the subsequent trial. However, while adapting motor performance in the gradual regime, there is a greater variability in task demands over time (as the amount of distortion increases in steps), which may require longer sampling windows, i.e., inclusion of more prior trials in computing and planning the trajectory in the subsequent trial at any given time point. This would require inclusion of additional parameters in the current model in order to study performance changes in the gradual regime. We would like to propose that the site of these computations are likely to differ at the neural level, and probably corroborates the evidence for different neural substrates for these two types of adaptation, namely, cerebellar regions for adaptation to gradually varying distortions and basal ganglia regions for adaptation to sudden distortions.

In summary, patients with PD demonstrated a comparable ability to correct for errors on a trial-to-trial basis, across two hand movement categories such as pointing involving larger amplitude arm movements and tracking involving small amplitude finger movements in the gradual regime used in the present studies. This implies the possibility that shaping of sensorimotor behavior by gradually varying distortions/changes may be generalized from fine motor skills involving finger movements to other movements involving larger muscle groups as in arm and leg movements. Therefore, these findings may be useful for developing more effective intervention strategies for patients with PD to overcome their motor and learning deficits in both fine motor skills, such as handwriting as well as gross motor skills such as reaching and locomotion.

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Figure 1.
(A) Mean and standard deviation (SD) of IDE (deg) and (B) RMSE (cm) in Pre- and Post-exposure blocks for Sudden and Gradual distortion conditions (Experiment 1).
* $p < 0.05$

Figure 2. Mean and standard error of IDE (deg) between patients and controls for (A) last catch trial mean and (B) difference between last catch trial & last block of exposure (Experiment 2).
* $p < 0.05$

Figure 3.

Changes in IDE (deg) during adaptation to gradual and sudden visuomotor distortions in patients with PD (A & B) and controls (C & D), as seen in experimental data and predicted scores from the linear regression model (Experiment 2). The black '+'s represent IDE in exposure trials during which distortion was present and black filled circles represent IDE in catch trials in the experimental data; blue '+'s represent IDE in exposure trials as predicted by the model and blue filled circles represent predicted IDE in catch trials.

Figure 4.

Mean coefficients and standard errors for the predicted model for gradual and sudden visuomotor distortions in patients with PD (A & B) and controls (C & D) respectively (Experiment 2). β_1 and β_2 represent the coefficients weighting the error (IDE) and the presence/absence of distortion in the trial preceding the current respectively, β_3 represents the coefficient weighting the visual distortion in the current trial, and β_0 represents the constant term in the model.

Table 1Linear Regression model fit statistic R^2 across all groups for all LOO cross-validations

	PD Gradual	PD Sudden	Control Gradual	Control Sudden
Iteration 1	0.3835	0.5858	0.3799	0.7644
Iteration 2	0.3589	0.5158	0.4644	0.7705
Iteration 3	0.3989	0.5973	0.3611	0.7389
Iteration 4	0.4008	0.6008	0.4083	0.7387
Iteration 5	0.3705	0.5292	0.3648	0.7639
Iteration 6	0.4051	0.4543	0.3660	0.7507
Iteration 7	0.3358	0.5475	0.3847	0.7217
Iteration 8	0.3908	0.5130	0.3539	0.7229
Iteration 9	0.3379	-	0.3662	-
<i>Mean</i>	0.3758	0.5430	0.3833	0.7465
<i>S.D.</i>	0.0266	0.0505	0.0345	0.0189

* Multiple linear regression was significant in all 4 groups at all iterations, $p < 0.001$.