Visuomotor adaptation in Parkinson’s disease: effects of perturbation type and medication state

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1Department of Biomedical Engineering, Washington University, St. Louis, Missouri; 2Department of Anatomy and Neurobiology, Washington University School of Medicine, St. Louis, Missouri; 3Department of Neurology, Washington University School of Medicine, St. Louis, Missouri; 4Department of Radiology, Washington University School of Medicine, St. Louis, Missouri; 5Program in Physical Therapy, Washington University School of Medicine, St. Louis, Missouri; and 6Program in Occupational Therapy, Washington University School of Medicine, St. Louis, Missouri

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Semrau JA, Perlmutter JS, Thoroughman KA. Visuomotor adaptation in Parkinson’s disease: effects of perturbation type and medication state. J Neurophysiol 111: 2675–2687, 2014. First published April 2, 2014; doi:10.1152/jn.00095.2013.—To perform simple everyday tasks, we use visual feedback from our external environment to generate and guide movements. However, tasks like reaching for a cup may become extremely difficult in movement disorders such as Parkinson’s disease (PD), and it is unknown whether PD patients use visual information to compensate for motor deficiencies. We tested adaptation to changes in visual feedback of the hand in three subject groups, PD patients on daily levodopa (L-dopa) therapy (PD ON), PD patients off L-dopa (PD OFF), and age-matched control subjects, to determine the effects of PD on the visual control of movement.

Subjects were tested on two classes of visual perturbations, one that altered visual direction of movement and one that altered visual extent of movement, allowing us to test adaptive sensitivity to changes in both movement direction (visual rotations) and extent (visual gain). The PD OFF group displayed more complete adaptation to visuomotor rotations compared with control subjects but initial, transient difficulty with adaptation to visual gain perturbations. The PD ON group displayed feedback control more sensitive to visual error compared with control subjects but compared with the PD OFF group had mild impairments during adaptation to changes in visual extent. We conclude that PD subjects can adapt to changes in visual information but that L-dopa may impair visual-based motor adaptation.

Motor control in humans can be disrupted by a variety of neurological disorders. The basal ganglia play a role in the integration of sensorimotor information across multiple sensory domains (Contreras-Vidal and Gold 2004; Desmurget et al. 2003; Doyon et al. 2003; Graybiel et al. 1994; Jobst et al. 1997; Nowak and Hermosdorfer 2006). Dysfunction of these neural circuits in conditions like Parkinson’s disease (PD) may contribute to impaired sensorimotor integration (Abbruzzese and Berardelli 2002; Paquet et al. 2008) as well as to specific deficits in visuomotor adaptation (Contreras-Vidal and Buch 2003; Fernandez-Ruiz et al. 2003; Messier et al. 2007). In contrast, PD patients may use visual feedback to facilitate various aspects of movement (Brown et al. 2006; Klockgether and Dichgans 1994). Thus the role of visual feedback for motor adaptation in PD remains to be determined.

Impairments in visuomotor adaptation in patients with PD have been described in a variety of ways: completely intact during continuous visual feedback (Inzelberg et al. 2008; Marinelli et al. 2009); intact adaptation but with impaired aftereffects during prism learning (Fernandez-Ruiz et al. 2003); and completely impaired adaptation and subsequent aftereffects during continuous visual feedback (Contreras-Vidal and Buch 2003). Notably, all of these studies have characterized visuomotor adaptation in patients with PD while taking levodopa (L-dopa). PD dopaminergic therapies improve gross motor control but do not completely alleviate all motor symptoms. In fact, these medications can also degrade motor performance (Fox et al. 2008; Poewe and Methylknecht 2009) or impair motor learning and cognition (Au et al. 2010; Cools 2006; Kwak et al. 2010; Mongeon et al. 2009). Improved understanding of feedback control (Smith et al. 2000) and adaptation (Smith and Shadmehr 2005) in patient groups with neurological deficits can enhance the understanding of how PD affects visually guided movement.

Behaviorally, visuomotor movement extent and direction have been shown to be separable, with distinct learning curves and generalization profiles (Krakauer et al. 2000; Vindras and Viviani 2002; Vindras et al. 2005). Traditionally, visuomotor adaptation to movement extent and direction has been investigated experimentally by altering visual gain to test movement extent and through visual rotations to test movement direction (Krakauer et al. 2000, 2004; Pine et al. 1996; Seidler et al. 2001, 2006; Vindras and Viviani 2002). Additionally, visuomotor extent and direction have been found to have distinct representations in the brain (Krakauer et al. 2004; Seidler et al. 2006). These specific neural representations demonstrate that adaptation to changes in visual direction correlate with activation of cortical areas, whereas adaptation to changes in visual extent correlate with subcortical areas, including areas of the basal ganglia (Krakauer et al. 2004). These studies suggest that if visuomotor adaptation is indeed mediated via the basal ganglia, PD patients may have significant visuomotor impairments.

Overall, current studies suggest conflicting effects of PD on visuomotor adaptation, where some report intact visuomotor adaptation (Inzelberg et al. 2008; Marinelli et al. 2009) and others report impaired visuomotor adaptation (Contreras-Vidal and Buch 2003). It is possible that visuomotor adaptation may...
be globally impaired in PD, or impairment may depend on the type of perturbation experienced, as suggested by previous studies (Mongeon et al. 2013; Venkatakrishnan et al. 2011). Additionally, it is unclear what effects PD medications may have on visuomotor adaptation, as we are unaware of a study that directly compares adaptive behavior in groups on and off L-dopa treatment.

To investigate the properties of visuomotor adaptation in patients with PD, we examined reaching kinematics in the presence of visual perturbations of rotation (direction) and gain (extent). We hypothesized that PD subjects would exhibit impaired overall levels of adaptation to visuomotor perturbations of direction and extent compared with their age-matched counterparts. We hypothesized that there would be a more pronounced impairment for adaptation to extent because of the behavioral and putative neural separability of visuomotor extent and direction (Krakauer et al. 2000, 2004) and the suspected involvement of the basal ganglia for control of motor gain (Desmurget et al. 2003; Turner et al. 2003). We also aimed to quantify the effect of L-dopa on visuomotor adaptation. We hypothesized that L-dopa could lead to additional impairment in sensorimotor adaptation.

**METHODS**

**Subject Groups**

Participants with PD \( n = 16 \) were recruited from the Movement Disorders Center at Washington University in Saint Louis. All patients had a clinical diagnosis of mild to moderate [Hoehn and Yahr stages 2 and 3 (Hoehn and Yahr 1967)] idiopathic PD based on modified United Kingdom Parkinson’s Disease Society Brain Bank clinical diagnostic criteria with clear clinical response to L-dopa (Hughes et al. 1992). Healthy control subjects \( n = 9 \) matched by age, sex, and handedness were recruited through patient participants and the community. No participants had other neurological illness or treatment with dopaminergic blocking drugs or anticholinergics. None had evidence of clinical cognitive deficits, and all had mini-mental state examination (MMSE) scores > 26 (Folstein et al. 1975). All subjects also had normal or corrected-to-normal vision and the ability to make 10-cm reaching movements. All PD participants were on normal daily dosing of L-dopa. We divided the PD participants into two separate groups. The PD ON group \( n = 8 \) was studied while taking their usual dose of L-dopa, ~2 h after the last dose and at a time where they thought they were having typical benefit. The PD OFF group \( n = 8 \) refrained from L-dopa for at least 12 h overnight (Khor and Hsu 2007). These two groups of PD subjects were matched for Unified Parkinson Disease Rating Scale 3 (UPDRS3, motor sub-scale; Fahn et al. 1987) when OFF (see Table 1). L-dopa substantially reduced UPDRS3 in the patients with PD (Table 1, unpaired t-test, \( P < 0.001 \)). We could not test adaptation on and off medication in the same subject, as the second exposure would test recall rather than adaptation. All three groups (PD ON, PD OFF, and normal control subjects) had similar MMSE scores averaging ~29/30 (see Table 1). The two PD groups also had similar UPDRS3 OFF scores and experienced similar improvements in UPDRS3 ON scores. The PD OFF group and the PD ON group experienced similar improvements [PD OFF: 29% (±8.2%), PD ON: 27% (±6.7%)] in UPDRS3 score (motor subsection) with L-dopa treatment. The PD OFF and PD ON groups were not significantly different in duration of disease (Table 1, unpaired t-test, \( P = 0.50 \)).

All protocols were approved by the Washington University Human Research Protection Office (HRPO), and all subjects provided signed consent.

**Apparatus and Task**

Subjects in the PD groups made reaching movements with the arm corresponding to the side of the body with initial motor symptoms, and we trained control subjects using the same side as their PD counterparts. All subjects performed horizontal reaching movements in a virtual environment. Reaching movements were recorded with a digitizing tablet and pen (Intuos, Wacom, Tokyo, Japan). Each person was seated with the elbow level to the digitizing tablet and viewed the visual environment through a horizontally mounted half-silvered mirror that reflected the display of a horizontally mounted monitor (Fig. 1). In the mirror, the subjects’ hand was represented by a 1-cm-diameter visual cursor. Testing was completed in a darkened room to ensure that vision of hand and arm was completely obstructed by light level and the mirror. The task required subjects to make ballistic movements of hand and arm to make 10-cm reaching movements. All PD participants were on normal daily dosing of L-dopa. We divided the PD participants into two separate groups. The PD ON group \( n = 8 \) was studied while taking their usual dose of L-dopa, ~2 h after the last dose and at a time where they thought they were having typical benefit. The PD OFF group \( n = 8 \) refrained from L-dopa for at least 12 h overnight (Khor and Hsu 2007). These two groups of PD subjects were matched for Unified Parkinson Disease Rating Scale 3 (UPDRS3, motor sub-scale; Fahn et al. 1987) when OFF (see Table 1). L-dopa substantially reduced UPDRS3 in the patients with PD (Table 1, unpaired t-test, \( P < 0.001 \)). We could not test adaptation on and off medication in the same subject, as the second exposure would test recall rather than adaptation. All three groups (PD ON, PD OFF, and normal control subjects) had similar MMSE scores averaging ~29/30 (see Table 1). The two PD groups also had similar UPDRS3 OFF scores and experienced similar improvements in UPDRS3 ON scores. The PD OFF group and the PD ON group experienced similar improvements [PD OFF: 29% (±8.2%), PD ON: 27% (±6.7%)] in UPDRS3 score (motor subsection) with L-dopa treatment. The PD OFF and PD ON groups were not significantly different in duration of disease (Table 1, unpaired t-test, \( P = 0.50 \)).

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**Table 1. Subject demographics and clinical features**

<table>
<thead>
<tr>
<th></th>
<th>Control (( n = 9 ))</th>
<th>PD ON (( n = 8 ))</th>
<th>PD OFF (( n = 8 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>70.20 ± 7.56</td>
<td>72.88 ± 7.08</td>
<td>71.13 ± 5.38</td>
</tr>
<tr>
<td>MMSE (out of 30)</td>
<td>29.44 ± 0.73</td>
<td>29.25 ± 1.39</td>
<td>29.25 ± 1.04</td>
</tr>
<tr>
<td>Disease duration, yr</td>
<td>9.50 ± 2.93</td>
<td>12.25 ± 5.47</td>
<td>12.25 ± 5.47</td>
</tr>
<tr>
<td>UPDRS score during testing</td>
<td>10.72 ± 5.54</td>
<td>24.00 ± 6.47*</td>
<td>24.00 ± 6.47*</td>
</tr>
<tr>
<td>UPDRS score OFF meds</td>
<td>25.70 ± 5.79</td>
<td>28.20 ± 5.01</td>
<td>28.20 ± 5.01</td>
</tr>
<tr>
<td>Side of disease onset</td>
<td>4 Right/4 left</td>
<td>6 Right/2 left</td>
<td>6 Right/2 left</td>
</tr>
<tr>
<td>Handedness</td>
<td>8 Right/1 left</td>
<td>7 Right/1 left</td>
<td>8 Right</td>
</tr>
<tr>
<td>Medications (by subject)</td>
<td>Carb-Lev; Ent</td>
<td>Carb-Lev; Pram</td>
<td>Carb-Lev; Pram</td>
</tr>
<tr>
<td></td>
<td>Carb-Lev</td>
<td>Carb-Lev; Am; Rop</td>
<td>Carb-Lev; Pram</td>
</tr>
<tr>
<td></td>
<td>Carb-Lev; En</td>
<td>Carb-Lev; Am; Rop</td>
<td>Carb-Lev; Ent</td>
</tr>
<tr>
<td></td>
<td>Carb-Lev; Am</td>
<td>Carb-Lev; Rop</td>
<td>Carb-Lev; Pram</td>
</tr>
<tr>
<td></td>
<td>Carb-Lev; Am</td>
<td>Carb-Lev; Tol</td>
<td>Carb-Lev; Pram</td>
</tr>
<tr>
<td></td>
<td>Carb-Lev; Am</td>
<td>Carb-Lev; Tol</td>
<td>Carb-Lev; Pram</td>
</tr>
<tr>
<td></td>
<td>Carb-Lev; Am</td>
<td>Carb-Lev; Pram</td>
<td>Carb-Lev; Am</td>
</tr>
</tbody>
</table>

We observed similar disease durations across our patient groups, as well as similar average cognitive function [mini-mental state examination (MMSE)] across all subject groups. For purposes of the study, the Parkinson’s disease (PD) patients off levodopa (L-dopa) therapy (PD OFF) group scored significantly higher on Unified Parkinson Disease Rating Scale 3 (UPDRS3) (study) than the PD patients on L-dopa therapy (PD ON) group (unpaired t-test, \( P = 0.0024 \)). UPDRS3 (clinical) scores obtained during normal clinic visits to movement disorders neurologists within 6 mo of study participation (UPDRS score OFF meds) demonstrated similar disease severity between our patient groups. For medications, each line indicates the medications individual subjects were prescribed at time of testing. Carb-Lev, carbidopa-levodopa; Am, amantadine; Ent, entacapone; Rop, ropinirole; Pram, pramipexole; Tol, tolcapone. *\( P < 0.05 \).
were generated with the following equation:

\[
\begin{align*}
x' &= g \times (x \cos \theta - y \cos \theta) \\
y' &= g \times (x \cos \theta + y \cos \theta)
\end{align*}
\]

where \(x\) and \(y\) correspond to values of \(x\) and \(y\) hand position, \(\theta\) is angle of rotation, and \(x'\) and \(y'\) are the transformed visual coordinates. Gain displacements \(g\) were multiplicative of hand position and either increased (magnifying) or decreased (minifying) the hand-to-cursor ratio. The center of both rotational and gain displacements coincided with the initial start position. The inclusion of multiple rotation (clockwise and counterclockwise) and gain (magnifying and minifying) conditions across two testing days permitted examination of adaptive responses to putatively analogous perturbations.

All subjects completed two testing sessions that were 1 wk apart. On each testing day, all subjects performed 600 reaching movements with three types of visual feedback: baseline, visual rotation, and visual gain change. During testing on day A, subjects performed 100 baseline reaching movements where visual feedback matched hand position. Subjects then completed 200 trials in a clockwise rotation environment. The second half of this block contained 20% catch hand movements within which the visual perturbation was pseudorandomly removed and subjects experienced baseline feedback. Subjects then did 50 more baseline trials to wash out effects of the visual rotation. The next set of movements was 200 trials in a minifying gain condition. Subjects then performed 200 movements at the last 100 movements, followed by 50 baseline trials. The consistent application of perturbation within the first 100 trials provided the strongest evidence for feedback and feedforward control within and across subject groups; therefore we limit analysis and results to these sets. The structure of day B was identical to day A, except that subjects experienced a magnifying gain followed by a counterclockwise rotation rather than the two day A perturbations. Movements were performed in 50 trial sets with a rest between each set to prevent arm fatigue. All completed reaches were analyzed.

Presentation of days A and B was counterbalanced to control for effect of day order presentation. Half of the subjects in each group experienced day A first and day B second (control group: 5 subjects day A/delay B, 4 subjects day B/delay A; PD ON group and PD OFF group: 4 subjects day A/delay B, 4 subjects day B/delay A). We analyzed data for effects of day order presentation between the clockwise rotation (first perturbed presentation of day A) and the counterclockwise rotation (second perturbed presentation of day B). We did not find any significant effects of day order presentation in any of our three subject groups for those that experienced the clockwise rotation on the first day of testing versus on the second day of testing (unpaired t-tests: control, PD ON, PD OFF, \(P > 0.05\)).

**Analysis**

**Metrics of movements.** In this experiment, our goal was to determine the characteristics of visuomotor learning in patients with PD, both on and off medications. We aimed to determine differences in adaptation to visual perturbations of extent and direction to characterize how visuomotor error responses influence motor behavior on subsequent movements. We examined characteristics of full-trajectory responses and velocity traces to qualitatively compare average baseline movement responses to movement responses during visual perturbations. From these trajectories and velocity traces we were able to evaluate both midmovement feedback and across-movement adaptation to evaluate timescales of correction.

**Baseline.** For all subjects, we calculated baseline behavior during initial performance (movements 1–5) and late performance (movements 96–100) on day A. For each subject, we calculated average angular displacement at peak speed from movement trajectories, as well as movement duration and peak velocity, derived from average subject velocity traces. Angular displacement was calculated from the \(x, y\) position at which peak speed occurred.
position was converted to polar coordinates to determine the resulting angular error. Movement duration was calculated as the length of time from the start of movement when the subject exceeded a velocity threshold of 0.03 m/s to the end of movement when the subject fell below the velocity threshold of 0.03 m/s. Peak velocity was calculated as the maximum velocity between the start and end of movement.

For all analyses, we used baseline from day A. Across all permutations of analysis (initial or late performance), and all metrics (angular displacement, angular displacement, movement duration and peak velocity), we found no significant differences in baseline performance between day A and day B for the control group or the PD ON group (paired t-tests, \( P > 0.05 \)). Additionally, we found no significant differences in baseline performance across day A and day B for the PD OFF group except for slightly increased movement duration on day B during late baseline performance [paired t-test, \( P < 0.05 \), movement duration: day A (mean \( \pm \) SD) = 0.91 \( \pm \) 0.09 s, day B = 0.95 \( \pm \) 0.09 s].

Visual rotations. For all subjects and all movements, we calculated angular displacement at peak speed to capture angular error induced via visual rotations at a feedforward point in the movement. With this measure, large errors persisting into late performance would be indicative of poor ability to utilize feedforward control information to adapt to the perturbation. Angular displacement was calculated as in the baseline block. For each subject, we computed the change in the visuomotor response induced by the visual rotation by calculating the difference between the initial exposure to perturbation (movements 96–100) and the late response at the end of the continuous presentation of visual perturbations (movements 96–100).

To quantify the use of visual feedback to correct for error in response to visual rotations, we calculated area under the curve for the initial and late responses, as described above. This measure aimed to evaluate the presence of feedback-related deficits in PD subjects. Area under the curve was calculated by computing the trapezoidal integration of the x positional displacement relative to y position throughout the entire time series of the movement.

Visual gains. From raw velocity traces for all subjects and all movements, we calculated peak movement velocity and movement duration for movements made in the visual gain conditions. For all subjects, we calculated initial (movements 1–5) and late (movements 96–100) responses for peak velocity and movement duration. We used peak velocity to evaluate feedforward control of movement in response to visuomotor gains. Inability to modify velocity magnitude in response to exposure to the gain perturbation would indicate deficits in feedforward adaptation to gains. Movement duration was calculated by demarcating a velocity threshold of 0.03 m/s for both start and end of movement. Longer movement duration, in response to unexpected gain perturbation, would indicate relative inability to generate appropriate feedback-driven control.

Statistical analyses. We tested all data for normality with the Lilliefors test. All data were determined to be normally distributed (\( P > 0.05 \)), and thus the use of parametric testing was appropriate. We tested data significance by using standard paired and unpaired t-tests to test for within- and between-group differences, respectively. Additionally, we used one-way and two-way ANOVAs to test for statistical significance between groups. One-way ANOVAs were used to test for significance across subject groups, and two-way ANOVAs were used to test for significance of group and condition. Tukey post hoc tests were used to determine direction of effect. All error bars represent the 95% confidence interval of the mean, unless stated otherwise.

RESULTS

Baseline Behavior

We evaluated each subject’s baseline response by quantifying both the angular and velocity profiles of initial and late movements made during veridical visual feedback conditions. We averaged visual cursor trajectories and velocity profiles across subjects within each group to characterize baseline behavior (Fig. 2). During the initial movements, we observed no significant differences between subject groups for measures of average angular displacement at peak speed [Table 2; \( P > 0.05 \), \( F(2,22) = 0.18 \)], area under the curve [Table 2; \( P > 0.05 \), \( F(2,22) = 0.41 \)], movement duration [Table 3; \( P > 0.05 \), \( F(2,22) = 2.03 \)], or magnitude of peak velocity [Table 3; \( P > 0.05 \), \( F(2,22) = 0.21 \)]. After subjects had been exposed to the baseline condition for 100 movements (Fig. 2), we continued to observe no significant differences across groups during baseline performance for average angular displacement at peak speed [Table 2; \( P > 0.05 \), \( F(2,22) = 2.3 \)], area under the curve [Table 2; \( P > 0.05 \), \( F(2,22) = 2.19 \)], peak speed [Table 3; \( P > 0.05 \), \( F(2,22) = 1.78 \)], or movement duration [Table 3; \( P > 0.05 \), \( F(2,22) = 3.17 \)].

Adaptation to Visual Rotations

We characterized average kinematic reaching error for initial and late responses in both the clockwise and counterclockwise perturbation environments (Fig. 3). To evalu-
adequately controlled for selected initial conditions and movement behavior. We introduced perturbations in a clockwise and counterclockwise direction, and we explored how subjects adapted to these different perturbation environments. We measured the area under the curve (AUC) as the main metric to compare adaptation across all subject groups. The AUC was calculated for the initial response, late response, and aftereffects. We also calculated the angular displacement at peak speed and the error in angular displacement for each subject. In addition, we performed ANOVA tests to compare the AUC between different subject groups and rotation conditions.

We observed that the PD ON group had significantly smaller AUC values compared with the control group. However, the PD OFF group did not show any significant differences in AUC values compared with the control group. The PD ON group also showed a significantly greater reduction in angular displacement during adaptation compared with the control group. The PD OFF group did not show any significant differences in angular displacement compared with the control group.

We concluded that the PD ON group had a greater ability to adapt to rotation perturbations compared with the control group, while the PD OFF group did not show any significant differences in adaptation compared with the control group.

Table 2. Results for adaptation to rotation perturbations

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>PD ON</th>
<th>PD OFF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area under curve, cm²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Initial</td>
<td>1.17 ± 0.99</td>
<td>1.07 ± 1.49</td>
<td>0.19 ± 2.13</td>
</tr>
<tr>
<td>Late</td>
<td>0.70 ± 1.30</td>
<td>0.54 ± 0.76</td>
<td>1.16 ± 1.81</td>
</tr>
<tr>
<td>Clockwise</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>15.78 ± 14.06</td>
<td>14.06 ± 2.40</td>
<td>14.46 ± 3.77</td>
</tr>
<tr>
<td>Late</td>
<td>6.56 ± 4.62‡</td>
<td>4.84 ± 1.50‡</td>
<td>1.85 ± 3.05‡</td>
</tr>
<tr>
<td>Counterclockwise</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>19.21 ± 2.72</td>
<td>13.33 ± 1.83*</td>
<td>15.98 ± 2.37</td>
</tr>
<tr>
<td>Late</td>
<td>9.87 ± 6.63‡</td>
<td>3.38 ± 3.31‡</td>
<td>5.63 ± 3.81‡</td>
</tr>
<tr>
<td>Angular displacement, °</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Initial</td>
<td>1.71 ± 1.06</td>
<td>1.72 ± 1.60</td>
<td>0.57 ± 2.87</td>
</tr>
<tr>
<td>Late</td>
<td>−0.57 ± 1.50</td>
<td>−1.15 ± 1.65</td>
<td>2.86 ± 2.63</td>
</tr>
<tr>
<td>Clockwise</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>−21.77 ± 1.90</td>
<td>−19.48 ± 3.82</td>
<td>−20.63 ± 5.44</td>
</tr>
<tr>
<td>Late</td>
<td>−9.17 ± 5.24‡</td>
<td>−6.30 ± 2.86‡</td>
<td>−2.29 ± 5.80‡</td>
</tr>
<tr>
<td>Counterclockwise Initial</td>
<td>21.20 ± 2.61</td>
<td>19.48 ± 2.16</td>
<td>22.92 ± 3.61</td>
</tr>
<tr>
<td>Late</td>
<td>14.32 ± 6.71‡</td>
<td>4.58 ± 6.44‡</td>
<td>9.17 ± 6.07‡</td>
</tr>
<tr>
<td>Aftereffects, °</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clockwise</td>
<td>5.73 ± 5.73‡</td>
<td>6.88 ± 2.29‡</td>
<td>13.18 ± 4.01†</td>
</tr>
<tr>
<td>Counterclockwise</td>
<td>−3.44 ± 7.45†</td>
<td>−5.73 ± 5.73‡</td>
<td>−5.16 ± 2.86‡</td>
</tr>
</tbody>
</table>

We observed comparable responses during initial (first 5 movements) and adapted (last 5 movements) baseline task performance. During adaptation to both types of rotation perturbations, initial and late visuomotor responses were intact across all 3 subject groups (ANOVA, P > 0.05). The PD OFF group compared with control subjects had a significantly greater reduction in angular displacement during adaptation to the clockwise rotation (unpaired test, P < 0.05). The 3 subject groups did not have any significant differences in movement performance. During periods of initial adaptation, we observed that the PD ON group displayed significantly smaller area under the curve compared with control subjects (ANOVA, P < 0.05, Tukey P < 0.05) and all 3 subject groups displayed similar area under the curve for the clockwise perturbation condition (ANOVA, P > 0.05). For the angular displacement metric, we quantified feedforward visuomotor adaptation as angular displacement at position at peak speed. We observed comparable responses during initial visuomotor adaptation as angular displacement at position at peak speed. We observed comparable responses during initial (first 5 movements) and adapted (last 5 movements) baseline task performance. During adaptation to both types of rotation perturbations, initial and late visuomotor responses were intact across all 3 subject groups (ANOVA, P > 0.05).

We began comparison across groups with the analysis of the area under the curve metric. The PD ON group compared with control subjects had greatly reduced area under the curve during initial exposure to the clockwise rotation [Fig. 3C, Table 2; area under the curve, P = 0.0081, F(2,22) = 6.04, Tukey < 0.05] but only had a small, insignificant similar change during the initial exposure to the counterclockwise rotation [Fig. 3A, inset, area under the curve, Table 2; P > 0.05, F(2,22) = 0.39]. After subjects performed 95 perturbed movements, the area under the curve decreased, corresponding to adaptation over time [Table 2; clockwise, Fig. 3B, inset, area under the curve, P > 0.05, F(2,22) = 1.99; counterclockwise, Fig. 3D, inset, area under the curve, P > 0.05, F(2,22) = 1.71].

To compute angular displacement error, we determined the amount of initial displacement induced by the rotation for clockwise and counterclockwise perturbations. We saw no significant effects, across subject groups, in initial exposure to the clockwise [Table 2; P > 0.05, F(2,22) = 0.44] or the counterclockwise [P > 0.05, F(2,22) = 1.46] rotation across subject groups. We computed the amount of displacement during late reaches (movements 96–100) and found no significant effects for the clockwise [Table 2; P > 0.05, F(2,22) = 3.59] or the counterclockwise [Table 2; P > 0.05, F(2,22) = 0.97] condition; however, error in the PD OFF
group asymptotes close to zero in both the clockwise and counterclockwise perturbation conditions (Fig. 4).

To quantify and characterize adaptation over time we measured the amount of adaptive change from initial performance (movements 1–5) to late performance (movements 96–100) (Table 2, Fig. 5). Our initial group comparison of adaptation to rotational perturbations considered differences between the control group and the PD OFF group. The PD OFF group compared with control subjects had significantly reduced an-

dependent effect. We found no significant differences across subject groups in aftereffect magnitude following either the clockwise or the counterclockwise perturbation [Table 2; P > 0.05, F(2,2) = 3.05, P > 0.05, F(2,2) = 0.2, respectively]. Note, however, that both PD groups generated aftereffects, especially following the clockwise perturbation. The control group generated the largest variance, leading to the overall nonsignificant effect. The totality of aftereffect data suggests overall intact learning in the PD groups.

**Adaptation to Minifying Gain**

We characterized kinematic error and adaptation to the minifying gain by calculating the velocity time series derived from positional cursor data (Table 3). To qualitatively analyze initial exposure to the minifying gain, we averaged velocity performance across all subjects for the first five movements performed in the baseline and minifying condi-
Although baseline velocity traces were relatively similar across all three groups, there were notable qualitative differences in the velocity profiles of the PD groups compared with control during performance in the minifying condition. We then computed the average movement duration for each subject across the first five movements (initial) and last five movements (late) for baseline (reported above) and minifying gain conditions. The minifying gain condition had a longer duration of movement, as well as lower peak velocity magnitude in the PD groups compared with the control group (Fig. 6B). By inspection, groups generated similar movement durations and peak velocities in the baseline condition (Fig. 6A).

All subject groups adapted to both the minifying and magnifying gain perturbations. From initial exposure to the late response, peak movement velocity and movement duration had significant changes for both the minifying [peak velocity, effect of condition: $P < 0.001, F(1,49) = 37.81$; interaction effect $F(2,49) = 3.42, P < 0.05$; movement duration, effect of condition: $P < 0.001, F(1,49) = 36.72$; no interaction effect] and the magnifying gain conditions [peak velocity, effect of condition: $P < 0.001, F(1,49) = 43.62$; interaction effect $F(2,49) = 2.37, P < 0.05$; movement duration, effect of condition: $P < 0.001, F(1,49) = 33.41$; no interaction effect].

**Fig. 3.** Average angular displacement and area under the curve for first movement and adapted reaches for rotation perturbations. Trajectories are averaged cursor movements for the first movement (A and C) and late movements (movements 96–100, B and D) for movements in clockwise and counterclockwise perturbations. Dashed gray line indicates ideal adaptation; circles on cursor trajectories indicate position at peak speed. Inset bar plots indicate magnitude of visual feedback correction for initial (A and C) and late (B and D) movements as computed by calculating area under the trajectory curve. A and B: clockwise rotation. A: subjects from all 3 groups experienced similar feedforward errors in visuomotor control during their first movement in the clockwise environment, as shown by similar angular displacement of cursor trajectory. Overall feedback responses as measured by area under the curve (inset) during movements 1–5 are similar across all subject groups, suggesting unimpaired feedback mechanisms in the PD groups. B: average response of movements 96–100 during the clockwise perturbation showed that subjects adapt to a near straight-line cursor trajectory. We see that the subjects in the PD OFF group achieve closer to ideal trajectories than the other 2 groups. C and D: counterclockwise rotation. C: subjects from all 3 groups experienced similar feedforward errors in visuomotor control during their first movement in the counterclockwise environment. Overall magnitude of the area under the curve is lowest in the PD ON group (C, inset, *ANOVA, $P < 0.0081$), suggesting increased utilization of visual feedback to reduce visuomotor error. D: average response of movements 96–100 during the counterclockwise perturbation showed that subjects in the PD ON and PD OFF groups achieved straighter cursor trajectories than the control group. We see that both PD groups demonstrated a lower magnitude of area under the curve (insets, B and D), suggesting unimpaired visuomotor feedback mechanisms in our 2 PD groups.
and magnifying [peak velocity, effect of condition: \( P < 0.05, F(1,49) = 4.15; \) movement duration, effect of condition: \( P < 0.05, F(1,49) = 11.36; \) no interaction effect] gain.

As reported above, we observed no significant effect of movement duration or peak velocity magnitude during initial baseline performance (Table 3); however, the PD groups had significantly longer, slower initial movements in response to the minifying gain change. Duration of movement was significantly increased in both PD groups compared with control subjects during initial performance in the minifying gain (Table 3; \( F(2,22) = 8.10, \) Tukey \( P < 0.05, \) control and PD ON and control and PD OFF). The magnitudes of initial peak velocities were significantly lower than controls in our PD ON group (Table 3; \( F(2,22) = 9.67, \) Tukey, \( P < 0.05 \)).

To quantify movements in late training, we calculated average subject performance during the last five movements for both movement duration and peak velocity metrics (Fig. 7). Both PD groups demonstrated similar movement durations compared with control subjects (Table 3, Fig. 7B; \( F(2,22) = 2.10 \)). However, after adapting to the minifying gain, the PD ON group maintained a lower peak velocity compared with subjects in the PD OFF group (Table 3, Fig. 7C; \( F(2,22) = 7.34, \) Tukey \( P < 0.05, \) PD ON vs. PD OFF). The presence of longer, slower movements in the PD ON group, combined with the absence of this same effect in the PD OFF group, suggests that administration of PD medications may interfere with visuomotor adaptation.

We quantified the magnitude of change from initial to late training for the minifying gain and observed that the PD OFF group significantly decreased movement duration compared with control subjects (Table 3, Fig. 8A; \( F(2,22) = 4.44, \) Tukey \( P < 0.05, \) control and PD OFF], suggesting that despite initial performance difficulties in the minifying gain, we see complete adaptation 100 movements later. The PD OFF group also generated the largest decrease in magnitude of peak velocity, although this trend was nonsignificant (Table 3, Fig. 8B; \( F(2,22) = 3.0 \)).

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**Fig. 4.** Angular displacement averaged across all subjects for both clockwise (A) and counterclockwise (B) perturbations on a trial-by-trial basis. For both clockwise and counterclockwise, we observe similar initial errors across all 3 subject groups but notable increases in error reduction in the PD OFF group after experiencing 100 movements in the rotation perturbations.

**Fig. 5.** Percent change from initial perturbation exposure (movements 1–5) to late adaptation (movements 96–100) for clockwise (A) and counterclockwise (B) perturbations. A: we observed that our PD OFF group had a significantly larger change from initial performance to adapted performance than the control group (*unpaired t-test, \( P < 0.05; \) ANOVA, \( P < 0.05; \) Tukey \( P < 0.05 \)), suggesting a larger acquisition of visual information from experienced errors. B: for counterclockwise perturbations, we observed a trend similar to clockwise but nonsignificant, where our control group displays the smallest change from initial to late performance and our PD OFF group displays the largest change from initial to late performance (ANOVA \( P > 0.05 \)).
To determine the magnitude of aftereffects, we calculated peak velocity across the first five movements after the gain perturbation was removed and visual feedback was returned to baseline conditions. All subject groups displayed significant aftereffects for both the minifying [Table 3; effect of condition: $P < 0.05$, $F(1,49) = 14.29$; no interaction effect] and magnifying [effect of condition: $P < 0.05$, $F(1,49) = 13.86$; no interaction effect] gain conditions.

**Magnifying Gain**

The three subject groups did not differ significantly for any of the analyses described above for the magnifying gain condition [Fig. 6C; Table 3; movement duration, peak velocity, and aftereffects, $F(2,22)$, $P > 0.05$]. Although all three groups did learn and generate posttraining aftereffects, we observed a small magnitude in the adaptive change in our movement metrics. Movement duration also seems to equilibrate very early in training (Fig. 6), suggesting that successful accommodation to the magnifying perturbation could be made very easily and perhaps with a combination of feedback and feedforward control. We conclude that the magnifying gain, compared with the other three perturbations, generated poor signal to noise to differentiate feedback and adaptive feedforward control across our groups.

**DISCUSSION**

Our experimental design permitted evaluation of three factors in parkinsonian visuomotor control of reaching: effects of dopamine replacement therapy (on or off), demands of two dimensions of the reach (direction or extent), and timescales of correction (midmovement feedback or across-movement adaptation). We have demonstrated that PD patients exhibit intact and improved utilization of midmovement visual feedback to rotation perturbations but impaired use of visual feedback mechanisms in response to gain perturbation. Facility in visuomotor adaptation diminished when subjects took their usual dose of L-dopa. These results suggest that mechanisms underlying visuomotor adaptation of extent and direction are behaviorally separable in a patient model, and L-dopa improves overall gross motor performance but can globally impair ad-
adaptation driven via visual feedback. Our results highlight the importance of evaluating behavior in both medicated and unmedicated patients to better determine sensorimotor ability and disability in PD.

Effects of Visual Rotations

We discovered that subjects in the PD OFF group, despite substantial motor impairments, demonstrated intact visuomotor adaptation to visual rotations and even showed stronger effects of adaptation compared with control subjects (Fig. 3, Fig. 5). In a patient population with marked difficulty of production and maintenance of movement, it is surprising to observe a strong adaptive effect in response to visually guided movements. Previous studies have characterized deficient visuomotor adaptation in subjects with PD while on L-dopa therapy (Contreas-Vidal and Buch 2003; Venkatakrishnan et al. 2011). Although these studies used methods similar to those we describe here, we believe that comparing adaptive ability in both PD ON and PD OFF groups permits a more accurate characterization of adaptive behavior in this neurologically impaired population. In our experiment, we observed that the PD OFF group is highly capable of learning changes in visual direction, as indicated by more ideal movement trajectories (Fig. 3, B and D) and a larger magnitude of adaptive change compared with age-matched control subjects (Figs. 4 and 5). Additionally, the PD ON group displayed a similar magnitude of adaptive change for angular displacement compared with control subjects but a smaller magnitude of change than the PD OFF group. The PD ON group also displayed intact feedback control (Fig. 3, area under the curve insets), suggesting that L-dopa may dampen feedforward contributions of visuomotor information to subsequent movements while leaving feedback mechanisms relatively intact (Au et al. 2010).

The increased adaptation to the clockwise rotation in our PD OFF group may reflect compensatory changes in brain circuitry. Sensory deficits such as deafness may induce cortical reorganization with unused or defunct cortical territories subsumed by visual sensory information processing, thereby enhancing visual dependence (Finney et al. 2003). Cortical re-mapping affecting cortical visual areas may occur in response

Fig. 7. A: average velocity responses after experiencing 100 movements in the minifying gain condition. B: both PD groups adopt movement duration profiles comparable to the control group (ANOVA, $P = 0.15$) after performing 100 movements. C: however, the PD ON group maintained a significantly lower velocity magnitude ($\text{ANOVA, } P = 0.0036$, Tukey $P < 0.05$), while subjects in the PD OFF group increased their average peak velocities to match control group performance, suggesting that patients with PD can adapt to gain modulations, but daily L-dopa therapy may interfere with adaptation.

Fig. 8. Differences in adaptation from initial performance (movements 1–5) to late performance (movements 96–100) for measures of movement duration and peak velocity of movement. The PD OFF group requires larger changes in both duration of movement (A; *ANOVA, $P = 0.02$, Tukey $P < 0.05$) and movement velocity (B; ANOVA, $P = 0.07$) to reach velocity duration and speed comparable to the control group in response to changes in visual gain. Despite initial difficulties generating movements in response to the minifying gain, the PD OFF group had a larger change in the acquisition of visual information.
to changes in the PD brain (Helmich et al. 2007, 2010). Remapping of some motor information to visual areas in PD is possible, suggesting that the amplification of visual error signals during adaptation to visual rotations could reflect additional recruitment of cortical areas responsible for processing visual information.

The adaptive change in the PD OFF group is likely due to increased reliance on midmovement visual feedback. The advantageous usage of visual feedback in PD to drive feedforward control of movement has been associated with facilitation of postural responses (Brown et al. 2006), exercise (Sage and Almeida 2010), visually guided reaching (Myall et al. 2008), drawing (Fucetola and Smith 1997), and modulation of reaching movements in response to visuomotor feedback (Ghilardi et al. 2000). A recent theory suggests that humans integrate sensorimotor noise in a statistically optimal fashion, depending more on reliable sensory signals and less on noisy ones (Ernst and Banks 2002). It is likely that the PD OFF group optimizes performance by relying on visual signals, while discounting unreliable motor signals.

**Effects of Visual Gain**

Our analyses of the components of trajectories modulated by gain-based visual feedback identified subtle, yet revealing differences among our subject groups. Both PD OFF and PD ON groups exhibited significant difficulty, compared with control subjects, in early adaptation to the minifying perturbation (Fig. 6B). This result supports existing evidence that the basal ganglia are involved in processing error information in the early phases of gain adaptation (Krakauer et al. 2004; Krebs et al. 1998). These findings are consistent with studies examining early adaptation in PD ON subjects (Venkatakrishnan et al. 2011) and in PD subjects in ON and OFF states (Mongeon et al. 2013). The relative inability to adapt persisted in late training in the PD ON group (Fig. 7), supporting the hypothesis that these subjects have difficulty using midmovement visual feedback to generate movements of appropriate speed and length (Au et al. 2010).

These results suggest two important ideas: that PD patients have impaired early-phase gain adaptation and that t-dopa amplifies this impairment. Our results support existing literature that describes the involvement of the basal ganglia in gain processing (Desmurget et al. 2003; Krakauer et al. 2004; Turner et al. 2003). Psychophysical performance of young, neurologically intact adults (Krakauer et al. 2000) suggests that movement extent and direction are independently planned prior to movement performance. This has been further supported by neuroanatomical data that described early adaptation to changes in visual direction correlating with cortical representation and early adaptation to changes in visual extent correlating with activation of subcortical structures, including areas of the striatum (Krakauer et al. 2004). Loss of dopaminergic nigrostriatal projections may alter midmovement error feedback mechanisms that utilize recalibration of visuomotor extent (Albin et al. 1989), thereby impairing adaptation to changes in visual extent. Additionally, the PD OFF group displays a significantly longer movement duration once the visual feedback has returned to baseline, providing further evidence of impaired ability to cope with changes in visual gain.

**Limitations**

While we see that the PD OFF group adapts more fully to the clockwise rotation, we do not see this same level of significance achieved in the counterclockwise condition (Fig. 5). It is important to note that in both the clockwise and counterclockwise rotations there is no difference in the magnitude of the error induced by the rotations across our three subject groups. Additionally, once subjects adapted (movements 96–100), we see that in the counterclockwise rotation both PD ON and PD OFF groups had a larger reduction in angular displacement than the control group; the preponderance of variance was generated by the control group rather than the PD groups.

Additionally, we found it difficult to make direct comparisons between our two gain conditions. In the magnifying gain condition, we observed adaptation and aftereffects but rapid accommodation to the perturbation, which generated little insight into differences in neural control across our groups.

**Adaptation of PD OFF and ON, t-Dopa Therapy**

One of the most surprising results of this study is the performance of subjects in the PD ON group. This group remained on t-dopa, which improved UPDRS scores compared with the PD OFF group (Table 1). Overall, we expected the PD ON group to outperform the PD OFF group. The failure of the PD ON group to achieve levels of enhanced adaptation similar to the PD OFF group during rotation adaptation, coupled with the continued impairment observed during gain adaptation, suggests a global dampening of visuomotor adaptation that is likely due to t-dopa. Our findings echo a previous report (Au et al. 2010) that suggests that t-dopa impairs visual feedback during tracking movements. In a mirrored feedback task (e.g., a leftward movement appears rightward), Paquet et al. 2008 found that PD subjects on medication seemed to perform better than PD subjects off medication. In this study, initial movement directions of their PD OFF group were highly variable, suggesting that these subjects were guessing the appropriate movement direction rather than adapting along a learning curve (Taylor and Ivry 2011). Here we observe improvement in our PD OFF group compared with our PD ON group, suggesting that sensorimotor deficits are not solely the result of PD but can be a combination of disease state and medication.

The global dampening of visuomotor adaptation that we see in the PD ON group could be due to “dopamine overdose.” This theory, proposed by Cools (2006), suggests that projections from dopamine-depleted striatum that influence motor areas lead to behavioral motor deficits. In contrast, striatal projections that influence more cognitive areas, controlling executive functions, are relatively spared. Thus exogenously administered t-dopa doses to improve movement-related deficits may “overdose” relatively unaffected cortical areas, disturbing higher-level cognitive control. This idea reinforces the idea that the use of visual feedback for the predictive control of movement may be susceptible to cognitive strategies to drive adaptation (Michel et al. 2007; Sajjo and Gomi 2010; Semrau et al. 2012; Taylor and Ivry 2011).

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