Effects of levodopa and viscosity on the velocity and accuracy of visually guided tracking in Parkinson's disease

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Summary

Deficits in velocity generation and movement accuracy occur in Parkinson's disease and are postulated to contribute to the characteristic bradykinesia. In the present study, we attempted to clarify the relationship between the deficits in velocity generation and movement accuracy. Patients with Parkinson's disease and normal controls tracked visually displayed sinusoidal and step targets with the wrist. Performance was evaluated using measurements of velocity and error. Movement velocity was manipulated by two methods: (i) administration of levodopa; (ii) viscous loading. Dependencies of velocity and error on disease state, medication state and viscosity were examined. Visually guided pursuit tracking was characterized by intermittent and frequent velocity excursions in both the patients and controls. For sinusoidal tracking, levodopa significantly increased velocity in the severely affected parkinsonian patients. Prior to the administration of levodopa, step tracking velocity was significantly lower in all patients than in controls. The 'on' state produced an increase in velocity to control levels. Error was significantly greater in the parkinsonian subjects than in controls, but was unchanged by levodopa for both tracking tasks. Manipulations of viscosity produced greater changes in velocity than did levodopa, yet a similar independence with respect to accuracy remained. Velocity significantly changed by 40–60% in the two tracking tasks from the viscous to antiviscous loads. Error did not change significantly in 12 out of 14 comparisons of subgroups based on disease and medication state. This contradicts the hypothesis that patients with Parkinson's disease primarily reduce velocity during tracking to maintain acceptable accuracy in the presence of a defective error correction system. Although parkinsonian subjects tracked with reduced accuracy, both normal and parkinsonian subjects were able to compensate for significant changes in velocity due to external loading. Thus a propulsion deficit exists in parkinsonism that may be alleviated with either antiviscosity or levodopa. An error correction deficit is also present in parkinsonism, but is not modified by antiviscosity or levodopa.

Keywords: Parkinson's disease; pursuit tracking; viscous load; tracking error; velocity

Abbreviations: AV20 = antiviscous load; LED = light-emitting diode; rms = root mean square; V0 = no load; V20 = viscous load; UPDRS = United Parkinson Disability Rating Scale

Introduction

A cardinal symptom of Parkinson's disease is bradykinesia. One of the motor abnormalities associated with bradykinesia is a deficit in velocity generation, and considerable evidence supports this concept. In step movement tasks, velocity is reduced in parkinsonians compared with normals (Draper and Johns, 1964; Flowers, 1976; Hallett and Khoshbin, 1980; Baroni et al., 1984; Berardelli et al., 1986). Large amplitude movements in particular reveal this reduction, possibly reflecting an inability to scale velocity to match the required amplitude (Draper and Johns, 1964; Flowers, 1976). The decreased velocity is associated with reduced rates of rise of the agonist EMG burst (Godaux et al., 1992), multiple sequences of agonist and antagonist activation (Hallett and Khoshbin, 1980; Marsden, 1982), and slow, irregular
trjectories (Draper and Johns, 1964; Hallett and Khoshbin, 1980; Marsden, 1982). Levodopa increases both the velocity and the initial agonist EMG burst of step movements (Baroni et al., 1984; Berardelli et al., 1986; Weinrich et al., 1988; Pastor et al., 1992), as well as the velocity of self-paced movements (Johnson et al., 1994a).

Deficits in movement accuracy may also play a role in bradykinesia (Draper and Johns, 1964; Flowers, 1976, 1978; Sheridan and Flowers, 1990). Fundamental defects of error correction or accuracy in Parkinson's disease are difficult to differentiate from inaccuracies due to reduced velocity generation. Propulsion may not be adequate to satisfy the demands of endpoint accuracy (Draper and Johns, 1964). On the other hand, propulsion may be purposefully reduced to allow for acceptable accuracy under a faulty error correction process (i.e. 'a trade-off of speed against accuracy'; Sheridan and Flowers, 1990). However, levodopa does not decrease error in visually guided, predictable sinusoidal or step tracking (Johnson et al., 1994a), suggesting that accuracy and velocity generation may be uncoupled.

In summary, velocity generation is decreased in Parkinson's disease and augmented by levodopa. Although the results of several studies also suggest impairments of accuracy, the degree of dependence on the velocity generation deficit remains unclear. In the present study we attempt to clarify this relationship using a visually guided pursuit tracking task. Velocity was manipulated by two methods, levodopa administration and viscous loading, and the resultant changes in error were assayed. An abstract of some of this material has been presented previously (Johnson et al., 1994b).

**Methods**

**Patient population**

Twenty-five adults (mean age 64.4 years, range 48–80 years; 18 males, seven females) with idiopathic Parkinson's disease were studied. All parkinsonian subjects were taking carbidopa–levodopa preparations, with the dosage optimized over the course of therapy by clinical assessment. The subjects were studied prior to their morning dose of carbidopa–levodopa and at least 12 h after the last dose ('off' state) and 60–90 min after the usual dose ('on' state), according to the recommendations of the CAPIT study group (Langston et al., 1992). Disability was evaluated when the subjects were 'off' (prior to the morning dose of levodopa) using the United Parkinson Disability Rating Scale (UPDRS). The motor subset of the UPDRS was assessed when the subject was 'on' (after the morning dose of levodopa) as well. As shown in Table 1, the mean duration of Parkinson's disease was 9.2 years and the mean UPDRS total score 'off' was 39. An evaluation of the UPDRS score for the population revealed a bimodal distribution (Fig. 1A). Thus, the 'combined' group was divided into 'mild' (UPDRS 10–40) and 'severe' (UPDRS 41–80) subgroups. Figure 1B provides an internal validity check of the rating instrument by correlating the total UPDRS score with the motor subset of the UPDRS recorded for both the 'off' and 'on' states. For the 'off' state, the correlation was significant with \( r^2 = 0.81 \) \((P < 0.0001)\), as was the correlation for the 'on' state with \( r^2 = 0.43 \) \((P < 0.001)\). The correlation of the total UPDRS score with disease duration in years to the total UPDRS score with regression line shown \( r^2 = 0.23 \). (D) Correlation of levodopa dosage used in the a.m. (open circles) and daily (filled squares) with the UPDRS score.

**Table 1 Summary of the Parkinson's disease group**

<table>
<thead>
<tr>
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<th>Mean (1 SD)</th>
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<td>Duration (years)</td>
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<tr>
<td>UPDRS dyskinesia</td>
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Disease was evaluated when the subjects were 'off' and 'on' using the United Parkinson Disability Rating Scale (UPDRS). The motor subset of the UPDRS was assessed when the subject was 'on' (after the morning dose of levodopa) as well. As shown in Table 1, the mean duration of Parkinson's disease was 9.2 years and the mean UPDRS total score 'off' was 39. An evaluation of the UPDRS score for the population revealed a bimodal distribution (Fig. 1A). Thus, the 'combined' group was divided into 'mild' (UPDRS 10–40) and 'severe' (UPDRS 41–80) subgroups. Figure 1B provides an internal validity check of the rating instrument by correlating the total UPDRS score with the motor subset of the UPDRS recorded for both the 'off' and 'on' states. For the 'off' state, the correlation was significant with \( r^2 = 0.81 \) \((P < 0.0001)\), as was the correlation for the 'on' state with \( r^2 = 0.43 \) \((P < 0.001)\). The correlation of the total UPDRS score with disease duration in years to the total UPDRS score with regression line shown \( r^2 = 0.23 \). (D) Correlation of levodopa dosage used in the a.m. (open circles) and daily (filled squares) with the UPDRS score.
System hardware and recording techniques
The apparatus and recording techniques were described previously (Johnson et al., 1994a); only a brief summary is presented here. The subject was seated, the dominant hand was secured to a low mass manipulandum, and the ulnar axis of the arm was immobilized. A DC torque motor (Electrocraft model 644-06-011, torque constant 0.307 Nm A⁻¹) and optical angle encoder (BEI L25G, resolving 50 000 pulses per revolution) were aligned with the flexion–extension axis of the wrist joint. The subject was informed of wrist position and tracking target position via two horizontal arrays of 101 light-emitting diodes (LEDs). A closed-loop microprocessor-based control system was used to display the tracking target and wrist position, and to acquire position data. Angular wrist position was acquired at 2000 samples s⁻¹ and binned to 10 ms resolution.

Movement paradigms and data analysis
All 25 patients with Parkinson’s disease and the 18 normal subjects were evaluated using two tracking paradigms involving flexion and extension movements of the dominant wrist. The subjects with Parkinson’s disease were assessed by the testing battery prior to ('off') and after levodopa ('on'). These paradigms were similar to those used previously (Johnson et al., 1994a), with the exception of the addition of viscous loads to the manipulandum. For each paradigm, a practice session of at least half the test duration preceded the data collection and a rest period was provided between tests. The tracking tasks are described below.

Sinusoidal tracking
This paradigm required the subject to track, 'as accurately as possible', a repetitive and predictable ±36°, 0.25 Hz sinusoid by alternately flexing and extending the wrist. The subject was instructed to match the LED display of wrist position to a second LED display of the target. One minute of tracking was recorded.

Step tracking
This paradigm required the subject to track a ±36° step target presented using the LED display. As in the case of sinusoidal tracking, the subject was instructed to match the target display 'as accurately as possible' to a second LED display of wrist position. This task required quick flexion and extension wrist movements, as one period of step tracking consisted of (i) a 1 s hold at neutral position, (ii) a step to 36° extension and 1 s hold, (iii) a step to neutral position and 1 s hold, (iv) a step to 36° flexion and 1 s hold, and (v) a step back to neutral position. The 4 s period and ±36° excursion were identical to those of the 0.25 Hz sinusoid. One minute of tracking was recorded.

For both the sinusoidal and step tracking tasks, viscous loads were introduced to the manipulandum using a servo constructed with a DC torque motor and absolute position optical encoder in line with the axis of wrist flexion and extension (Lakie et al., 1984; Johnson et al., 1993). Viscous loads are defined as torques that are proportional to and directed against the angular joint velocity. Antiviscous loads are defined as torques that are proportional to and in the direction of the angular joint velocity. Antiviscous loads are not normally found in nature and provide assistance to movement that increases with the movement velocity. Specifically, the velocity is increased by decreasing the damping intrinsic to the wrist (Lakie et al., 1984). Three viscous load states were used and designated as torsional viscosity constant of 0.00020 Nms deg⁻¹ (V20), no viscosity (V0) and antiviscosity constant of −0.00020 Nms deg⁻¹ (AV20).

Various measures of velocity and error were obtained to evaluate the sinusoidal and step tracking performance. Velocity was derived from the recorded position by numerical differentiation. Both maximal and root mean square (rms) measures of velocity were obtained. The mean maximal velocity was obtained by identifying the absolute peak velocity in either flexion or extension for each tracking cycle and averaging over all tracking cycles. The rms velocity was also calculated for each tracking cycle and averaged over all tracking cycles. Error, the difference between the subject's actual wrist position and the desired target position, was determined. Both mean maximal and rms error were obtained. The first tracking cycle was not analysed.

Analysis of variance in the context of the split-plot experimental design was used to evaluate the changes in tracking resulting from manipulations of viscosity and levodopa (Montgomery, 1991). Scheffe's method of multiple comparisons was used to examine differences among means (P < 0.05). Subjects were classified according to disease state ('combined', 'mild', 'severe', 'normal'). The effects of the main factor of medication state ('off', 'on') and subplot factor of viscous load (V20, V0, AV20) on the velocity and error indices were evaluated for each disease state.

Results
All normals and subjects with Parkinson's disease performed the sinusoidal and step tracking tasks. Each subject performed the tasks with V20, V0 and AV20, in random order. First, the tracking kinematics as a function of disease state ('combined', 'mild', 'severe', 'normal') and medication state ('off', 'on') will be described. Secondly, the effect of viscous loads on the tracking velocity and error will be discussed.

Visually guided sinusoidal tracking
The slow, 0.25 Hz (4 s period) ±36° sinusoid was easily tracked by both normal and parkinsonian subjects, as the demands on velocity generation and frequency response were low. Position and velocity trajectories as a function of
medication state are shown in Fig. 2 for a mildly affected subject with Parkinson's disease (Fig. 2A–F). Also shown is the tracking performance of a normal control (Fig. 2G–I). The subject with parkinsonism had a 8-year duration of disease and a UPDRS total score of 31 (motor subset 'off' = 13, motor subset 'on' = 6). Dyskinesia, but not tremor, was clinically evident during testing. Another normal subject is shown for comparison (Fig. 3G–I) with kinematic profiles similar to the normal shown in Fig. 2. When 'off', the patient tracked with a sinusoidal profile (Fig. 3A) but undershot the target in both flexion and extension. The rms error was correspondingly large at 11.9°. The velocity trace (Fig. 2B) was qualitatively similar to that of the mildly affected subject and the normal shown in Fig. 2 except for a reduction in sinusoidal target in a purely sinusoidal fashion, the phase plots would be smoothly elliptical.

Fig. 2 Sinusoidal tracking for a mildly affected subject with Parkinson's disease and a normal control. (A) Position trace (solid line) and target (dashed line) for six sequential tracking cycles 'off'. (B) Velocity trace for same six tracking cycles 'off'. (C) Velocity versus position trajectories for each of the six tracking cycles in A and B. Tracking proceeds in a clockwise fashion. Discontinuities indicate that the tracked position did not match the full target cycle. (D–F) Same as A–C except for subject 'on'. (G–I) Same as A–C except for normal subject. Extension-directed position and velocity are positive, flexion-directed position and velocity are negative.

Levodopa dramatically changed the tracking and associated kinematics of severely affected subjects with Parkinson's disease. An example is shown in Fig. 3 for a subject with a 22-year duration of disease and a UPDRS total score of 61 (motor subset 'off' 26, 'on' 8). Dyskinesia, but not tremor, was clinically evident during testing. Another normal subject is shown for comparison (Fig. 3G–I) with kinematic profiles similar to the normal shown in Fig. 2. When 'off', the patient tracked with a sinusoidal profile (Fig. 3A) but undershot the target in both flexion and extension. The rms error was correspondingly large at 11.9°. The velocity trace (Fig. 2B) was qualitatively similar to that of the mildly affected subject and the normal shown in Fig. 2 except for a reduction in...
the amplitude of the velocity excursions. Frequent velocity excursions are evident in the phase plots (Fig. 3C), similar to those of the mildly affected patient and normal. There were roughly eight to 12 velocity excursions per half tracking cycle. When ‘on’, tracking produced larger transients in the wrist position (Fig. 3D) and correspondingly large peaks in the velocity profiles (Fig. 3E), some reaching 300° s$^{-1}$. These transients in the tracking position give a looping, oscillatory characteristic to the velocity excursions in the phase plots (Fig. 3F). However, this oscillation has a frequency content of 1–2 Hz, quite distinct from that expected from tremor entrainment. The duration of each velocity excursion also increased when ‘on’, allowing only four to six parabolic excursions per half cycle (Fig. 3C). Clinically, this kinematic profile was associated with dyskinetic movements involving the tracking arm. The mean maximal velocity increased from

82° s$^{-1}$ ‘off’ to 223° s$^{-1}$ ‘on’. The rms error increased to 17.9° ‘on’.

**Visually guided step tracking**

Following the step target requires an infinite frequency response and an infinitely large velocity to track with zero error. The subject must make an instantaneous sweep of 36°, hold, then reverse the 36° sweep, then hold. Thus, normals performed with greater error in this task compared with the sinusoidal task, averaging 16±2.5° rms error per cycle. The average rms error for sinusoidal tracking was only 6.5±2.2°.

An example of step tracking performance is shown in Fig. 4 for a patient with Parkinson’s disease (Fig. 4A–F) and a normal control (Fig. 4G–I). These data are from the same ‘severe’ patient whose results for sinusoidal tracking are shown in Fig. 3. When ‘off’, the wrist position (Fig. 4A)
consistently lagged the target. A reduction of both flexion and extension excursion relative to the target is evident. The average rms error was 30.8°. The patient, unable to generate the rapid changes in velocity needed to track the step function, used a tracking strategy that resulted in a sinusoid-like position trace. The velocity trace includes small amplitude excursions, similar to those in sinusoidal tracking (Fig. 3B). The phase-plane plots demonstrate multiple inflections over the tracking cycle, also similar to those in sinusoidal tracking (Fig. 3C). The step tracking performance of a normal subject is shown (Fig. 4G–I). Wrist position lagged the target slightly, but the excursions were well matched to the target. The velocity trace (Fig. 4H) consisted of pulses in the direction of the movement with a quiet baseline between. Only one or two parabolic velocity excursions occurred for each movement in flexion or extension (Fig. 4I). Constrictions of the velocity excursion occurred at 0° corresponding to the hold at neutral position and at ±36° corresponding to the extremes of flexion and extension.

When 'on', dramatic changes in tracking performance occurred in this subject with 'severe' Parkinson's disease. The patient tracked with prominent slow oscillations (Fig. 4D), which roughly followed the step target. The subject appeared to track the target by directing the slow oscillations into either flexion or extension. The stop at mid position was approximated when 'off', but not when 'on'. Large velocity peaks occurred periodically and alternated in flexion and extension directions (Fig. 4E). The amplitude of the velocity peaks was much larger 'on' than when 'off'. These large velocity excursions dominate the phase plots (Fig. 4F) and are similar to the excursions observed for sinusoidal tracking (Fig. 3F). In addition, the phase plots demonstrate cyclical trajectories consistent with oscillation. For example, oscillations in the 0 to +36° range corresponding to extension, were pronounced in the first, third and sixth tracking cycles. Similar cycles of oscillation in extension were present for this patient during sinusoidal tracking, and are most evident in the third, fourth and sixth tracking cycles (Fig. 3F). These oscillations appear relatively smooth.

The choice of kinematic indices suitable to describe tracking velocity and error is problematic due to the velocity excursions shown in Figs 2–4. Velocity and error could be characterized by either peak or rms values. The measures that best characterize tracking performance are not evident a priori. Therefore, both mean maximal and rms values were determined for velocity and error and then compared for the 'mild', 'severe' and 'normal' groups. The correlation of maximum and rms velocity for sinusoidal tracking was highly significant ($r^2 = 0.88$, $P < 0.0001$), as was the correlation of maximum and rms error ($r^2 = 0.95$, $P < 0.0001$). For step tracking, the correlations of velocity ($r^2 = 0.94$, $P < 0.0001$) and rms error ($r^2 = 0.81$, $P < 0.0001$) were also highly significant. Because of this similarity, maximal velocity and rms error were used for the remainder of the analysis (as in Johnson et al., 1994a).

**Effects of medication and disease states on tracking velocity and error**

The initial analysis concentrated on the differences between normals and parkinsonians and on the effects of levodopa. The differences in mean maximal velocity and rms error analysed across disease state ('combined', 'mild', 'severe', 'normal') and medication state ('off', 'on') are presented graphically in Fig. 5 for sinusoidal and step tracking. For sinusoidal tracking, there were significant changes in the mean maximal velocity due to medication state for several subgroups. The 'severe' subgroup demonstrated significant increases off to on for all three loads, and for the 'combined' group significant increases in velocity occurred for the V20 and V0 loads. These velocity increases in the on state for the 'combined' and 'severe' subgroups were actually large enough to distinguish them statistically from the 'normal' controls.

Patients with Parkinson's disease produced greater errors in tracking than normals. For the 'severe' subgroup both 'off' and 'on', rms error during sinusoidal tracking was significantly higher than that for normals for all three loads. For the 'mild' subgroup, rms error was significantly larger than in normals for the V20 and AV20 loads, but not for V0. In this subgroup, the loads appeared to exaggerate the deficits in movement accuracy. In spite of these deficits, levodopa had no significant effects on the rms error for any parkinsonian subgroup under any load. Therefore, while maximal velocity increased for some subgroups under some loads, rms error always remained constant.

As the total rms error represents both timing errors and path-matching errors, it was parcelled into measures of lag-lead and an rms error corrected for lag-lead. This was accomplished by stepping the tracking trajectory in 10 ms increments relative to the target trajectory. The minimum rms error and the tracking lag-lead at which this corrected rms error was obtained were recorded for each subject (similar procedures were used by Draper and Johns, 1964; Cassell et al., 1973; Flowers, 1978). For sinusoidal tracking in the 'combined' group, corrected rms error was reduced by 13% relative to the total rms error at a lag of 18 ms when 'off' and corrected rms error was reduced by 9% at a lag of 78 ms when 'on'. Changes of a similar magnitude were found for the population when subdivided into 'mild' and 'severe' subgroups. The timing-corrected rms error for all parkinsonian groups did not significantly differ as a function of medication state. The normal group demonstrated a 10% reduction in the total rms error when corrected for an average lag of 17 ms. Therefore, the error due to timing for this highly predictable tracking target was a small fraction of the overall rms error.

Step tracking was accomplished with relatively greater velocity than sinusoidal tracking, and the tracking velocity increased with the progression from viscous (V20) to antiviscous (AV20) loads (Fig. 5). The requirement for higher velocities for step tracking accentuated the differences
between normals and subjects with Parkinson’s disease. For all subgroups when ‘off’, mean maximal velocity was significantly lower in the parkinsonian subjects than in normal controls. However, when ‘on’, velocity increased to a point where there was no longer a significant difference between the normals and parkinsonian subjects. Although there was a trend for velocity to increase with levodopa, the increase from ‘off’ to ‘on’ was not statistically significant for any subgroup or load. One possibility for the failure to reach significance was the increased variability in velocity during step tracking. As observed for the sinusoidal tracking, rms error was greater in the ‘severe’ and ‘combined’ parkinsonian subjects compared with normals for all loads. This was true whether ‘off’ or ‘on’. Again, levodopa had no significant effect on the rms error. The timing-corrected rms error was reduced relative to the total rms error in the ‘combined’ group by 40% with a timing shift of 254 ms when ‘off’ and by 34% with a timing shift of 203 ms when ‘on’. Similar reductions were seen in the ‘severe’ and ‘mild’ subgroups.

The ‘normal’ group demonstrated a 32% reduction of the total rms error with a timing shift of 162 ms. The proportion of the total rms error due to timing error is greater for the step than for the sinusoid tracking, but again, no component of the tracking error significantly changed as a function of medication state for any subgroup.

The effects due to medication state were largely independent of those due to viscosity. This was evident by an extremely small interaction between the effects of levodopa and viscous load on velocity and error in the analyses (ANOVA F test for interaction, \( P > 0.2 \)). The effects due only to medication and disease states were analysed by pooling the data for all loads, and the results strictly parallel those obtained from the analysis based on the individual loads. Briefly summarized, significant increases in velocity ‘off’ to ‘on’ were found for the ‘severe’ group for sinusoidal tracking. Velocity was significantly higher than that of normals in the ‘combined’ and ‘severe’ groups when ‘on’. Error was significantly greater than in normals for all
parkinsonian subgroups both ‘off’ and ‘on’. Again, no change was found for error as a function of medication state. For step tracking, all parkinsonian subgroups had a significantly lower velocity when ‘off’ than normals. Velocity increased when ‘on’ and the difference between the parkinsonian patients and normals became insignificant. The error of the ‘combined’ and ‘severe’ groups was significantly higher than normals both ‘off’ and ‘on’. Thus, the medication effects shown in Fig. 5 remained remarkably consistent when analysed without regard to load.

**Effects of viscous loads on tracking velocity and error**

The tracking results suggest that the control of accuracy and velocity is independent. Maximal velocity increased in some conditions due to levodopa, yet rms error remained constant. These findings address directly the existing controversy as to whether the amount of error limits the velocity (Flowers, 1976; Sheridan and Flowers, 1990) or whether the velocity limits the accuracy (Draper and Johns, 1964) in Parkinson’s disease. To examine further the degree of coupling between these two aspects of motor control, viscous loading was used to manipulate velocity in both normal and parkinsonian subjects. In this manner, changes in tracking accuracy due to velocity could be determined. On average there was a 50% increase in the mean maximal velocity with the transition from viscosity to antiviscosity for both normals and subjects with Parkinson’s disease, indicating that the load was effective in modulating tracking velocity (Fig. 5).

Sinusoidal tracking position and velocity of a subject with ‘mild’ Parkinson’s disease and for a normal subject are shown as a function of viscous load in Fig. 6. The position and velocity traces exhibit a similar sinusoidal modulation for all loads. When ‘off’, the subject’s mean maximal velocity increased 79% as a result of viscous load manipulation from 79° s⁻¹ (V20) to 94° s⁻¹ (V0) to 138° s⁻¹ (AV20). The corresponding rms errors were 7.0° (V20), 6.2° (V0) and 9.3° (AV20). The phase plots of velocity versus position for a single (Fig. 6B) and six superimposed (Fig. 6C) tracking cycles demonstrate that the increased velocity was due to greater amplitudes of the velocity excursions. In the ‘normal’ control shown for comparison, the velocity increased from 88° s⁻¹ (V20) to 101° s⁻¹ (V0) to 199° s⁻¹ (AV20), a 126% change overall. However, rms error remained nearly constant at 5.4° (V20), 4.6° (V0) and 6.1° (AV20). The phase plots (Fig. 6B and C) reveal the same change in excursions with increasing velocity as seen for the parkinsonian subject. In the ‘on’ state, viscous loads modulated the patient’s mean maximal velocity by 100% from 73° s⁻¹ (V20) to 105° s⁻¹ (V0) to 147° s⁻¹ (AV20). The rms error ‘ON’ was slightly greater, ranging from 8.6° (V20) to 7.2° (V0) to 10.0° (AV20). Again, the increase in velocity due to load was produced by a greater amplitude of the velocity excursions.

Position and velocity profiles ‘on’ and ‘off’ during step tracking as a function of viscous loading are shown in Fig. 7 for another ‘mild’ parkinsonian patient and a control subject. As the load was changed from V20 to AV20, the position and velocity traces exhibited less damping at the endpoints of the rising and falling phases of the step. This finding was evident both ‘on’ and ‘off’, and also for the normal control. For the parkinsonian patient, viscous loading modulated velocity by 100% in the ‘off’ state [116° s⁻¹ (V20) to 197° s⁻¹ (V0) to 233° s⁻¹ (AV20)] and by 145% in the ‘on’ state [174° s⁻¹ (V20) to 248° s⁻¹ (V0) to 426° s⁻¹ (AV20)]. The rms error when ‘off’ fluctuated slightly: 17° (V20), 14° (V0) and 19° (AV20). When ‘on’ the rms error increased slightly as the load was varied from 19° (V20) to 21° (V0) to 22° (AV20).

The velocity versus phase plots demonstrate that the velocity increases due to viscous load manipulation occurred in an analogous manner to those of sinusoidal tracking. The parabolic velocity excursions progressively increased in
amplitude as the load was changed from V20 to V0 to AV20. In the parkinsonian patient the amplitude of these excursions increased by a factor of two, but in the normal subject they increased by a factor of three. However, the inflections in the phase plot trajectory were present for all loads and medication states. Note also the smaller amplitude oscillations at the midpoint of the tracking cycle (0°) and at the endpoints (±36°). The oscillations also increased with decreasing viscosity, indicating a decrease in damping.

Changes in tracking velocity and error due to viscous loads are summarized in Fig. 8 and Table 2 for sinusoidal and step tracking. For simplicity, in Fig. 8 only the ‘combined’ group is illustrated along with the ‘normal’ control group. This is justified by the low interaction of disease severity with viscosity [ANOVA F test for interaction, for the dependent variables of velocity (P > 0.6) and error (P > 0.8)]. However, the complete statistical analyses in Table 2 were based on all three parkinsonian subgroups (‘combined’, ‘mild’, ‘severe’). Here, the differences in velocity and error for the viscous (V20) and antiviscous (AV20) loads are compared. Several points are evident from the population data. First, mean maximal tracking velocity changed as a function of the viscous loads, increasing monotonically for the normal controls as well as for the parkinsonian subjects both ‘on’ and ‘off’ (Fig. 8). Velocity significantly increased when the load was changed from viscous (V20) to antiviscous (AV20) in both the sinusoidal and step tracking tasks. The velocity increase was significant for both tasks irrespective of disease state and medication state (Table 2). Secondly, the velocity of tracking was task dependent. The velocity requirements were much greater for the step than for the sinusoidal tracking task. Even the parkinsonian group was able to scale tracking velocity to meet the task requirements. Thirdly, tracking velocity changed as a function of medication state in a manner that was task specific (Fig. 8). For step tracking the highest maximal velocities were obtained by the ‘normal’ group, followed in descending order by the ‘combined’ group ‘on’ and the ‘combined’ group ‘off’. For sinusoidal tracking, levodopa increased mean maximal velocity and when ‘on’, the parkinsonian group actually exceeded that of the normals. This ‘paradoxical’ velocity increase was evident in Fig. 5 for the ‘severe’ and ‘combined’ groups.

The last two points relate to rms error. Fourthly, tracking error was greater in all groups for step compared with sinusoidal tracking (Fig. 8 and Table 2). Therefore, error was also task dependent. Fifthly, rms error remained nearly constant with loads. The only significant rms error changes due to load occurred in sinusoidal tracking in the ‘mild’ and ‘combined’ subgroups ‘off’. All other comparisons of rms
Table 2 Changes in mean maximal velocity and rms error due to viscous manipulation

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<td>Combined off</td>
<td>89 (10.8)</td>
<td>146 (51.5)</td>
<td>64*</td>
</tr>
<tr>
<td>Combined on</td>
<td>114 (41.9)</td>
<td>153 (39.9)</td>
<td>34*</td>
</tr>
<tr>
<td>Mild off</td>
<td>88 (12.4)</td>
<td>144 (44.2)</td>
<td>65*</td>
</tr>
<tr>
<td>Mild on</td>
<td>93 (18.9)</td>
<td>126 (19.5)</td>
<td>36*</td>
</tr>
<tr>
<td>Severe off</td>
<td>90 (9.3)</td>
<td>146 (36.9)</td>
<td>62*</td>
</tr>
<tr>
<td>Severe on</td>
<td>135 (48.4)</td>
<td>185 (34.5)</td>
<td>37*</td>
</tr>
<tr>
<td>Normal</td>
<td>92 (16.7)</td>
<td>128 (31.9)</td>
<td>39*</td>
</tr>
<tr>
<td>Sinusoidal tracking rms error (°)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined off</td>
<td>8.2 (2.7)</td>
<td>9.6 (3.7)</td>
<td>17*</td>
</tr>
<tr>
<td>Combined on</td>
<td>9.9 (5.4)</td>
<td>10.0 (4.5)</td>
<td>1</td>
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<tr>
<td>Mild off</td>
<td>7.0 (2.5)</td>
<td>8.6 (3.6)</td>
<td>22*</td>
</tr>
<tr>
<td>Mild on</td>
<td>7.0 (2.3)</td>
<td>7.9 (2.8)</td>
<td>13</td>
</tr>
<tr>
<td>Severe off</td>
<td>9.1 (2.7)</td>
<td>10.2 (3.7)</td>
<td>12</td>
</tr>
<tr>
<td>Severe on</td>
<td>12.8 (6.8)</td>
<td>12.3 (5.8)</td>
<td>-4</td>
</tr>
<tr>
<td>Normal</td>
<td>5.6 (1.1)</td>
<td>6.4 (1.8)</td>
<td>14</td>
</tr>
<tr>
<td>Step tracking velocity (deg s(^{-1}))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined off</td>
<td>151 (55.0)</td>
<td>239 (100.1)</td>
<td>58*</td>
</tr>
<tr>
<td>Combined on</td>
<td>178 (71.1)</td>
<td>272 (92.2)</td>
<td>53*</td>
</tr>
<tr>
<td>Mild off</td>
<td>143 (36.6)</td>
<td>253 (62.5)</td>
<td>77*</td>
</tr>
<tr>
<td>Mild on</td>
<td>181 (85.6)</td>
<td>268 (95.6)</td>
<td>48*</td>
</tr>
<tr>
<td>Severe off</td>
<td>160 (74.0)</td>
<td>222 (129.4)</td>
<td>39*</td>
</tr>
<tr>
<td>Severe on</td>
<td>175 (46.4)</td>
<td>277 (134.0)</td>
<td>58*</td>
</tr>
<tr>
<td>Normal</td>
<td>179 (81.2)</td>
<td>312 (71.5)</td>
<td>74*</td>
</tr>
<tr>
<td>Step tracking rms error (°)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined off</td>
<td>20.5 (9.2)</td>
<td>20.3 (8.3)</td>
<td>-1</td>
</tr>
<tr>
<td>Combined on</td>
<td>19.8 (6.6)</td>
<td>18.8 (5.7)</td>
<td>-5</td>
</tr>
<tr>
<td>Mild off</td>
<td>15.9 (3.6)</td>
<td>16.4 (3.8)</td>
<td>3</td>
</tr>
<tr>
<td>Mild on</td>
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<td>16.2 (4.0)</td>
<td>-1</td>
</tr>
<tr>
<td>Severe off</td>
<td>25.5 (12.2)</td>
<td>24.8 (11.0)</td>
<td>-3</td>
</tr>
<tr>
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<td>21.9 (6.5)</td>
<td>-7</td>
</tr>
<tr>
<td>Normal</td>
<td>16.0 (3.4)</td>
<td>16.0 (1.8)</td>
<td>0</td>
</tr>
</tbody>
</table>

*P < 0.05.

The constancy of error was even more striking for the step tracking task. No significant changes in error as a function of load were found for any subgroup (Table 2). This lack of change in error occurred in the presence of a significant and approximately two-fold velocity increase for all subgroups. Therefore, the large changes in velocity due to viscous loads did not affect tracking accuracy in either parkinsonian subjects or normal controls. This finding is similar to that observed for levodopa (Table 2) in which tracking error was also not affected. Despite large increases in velocity in both the normals and patients with Parkinson’s disease, the rms error remained relatively constant.

**Discussion**

Visually guided tasks can be divided into two general types. The first type includes unidirectional movements made 'as fast as possible' to an abruptly signalled target position, and we refer to these as step movements. In these tasks, the visual system detects the target onset and position and a feedforward, stereotyped bell-shaped velocity profile is produced (for review, see Georgopoulos, 1986). Only near the end of the movement visual feedback is heavily relied upon to obtain the final target position. Step movements can be used to discriminate patients with Parkinson’s disease from normals (Draper and Johns, 1964; Hallett and Khoshbin, 1980) and to quantify the effects of levodopa (Berardelli et al., 1986; Weinrich et al., 1988). The second type of paradigm, referred to as pursuit tracking, requires the subject to follow a moving target. Here the visual and proprioceptive systems are continuously active in correcting the position to match the target. This type of paradigm was sensitive enough to discriminate disease state in terms of tracking amplitude and lag (Cassell et al., 1973) and error (Flowers, 1978; Hocherman and Aharon-Peretz, 1994). The present study evaluated the sensitivity of pursuit tracking tasks to differentiate disease and medication state.
Visually guided pursuit tracking in normals and patients with Parkinson's disease

The early psychophysicists noted irregularities in position and velocity during tracking, leading them to speculate on the discontinuous nature of human pursuit tracking (Hick, 1948; Searle and Taylor, 1948; Taylor and Birmingham, 1948; Vince, 1948; Noble et al., 1955). Generally, the intermittency was believed to occur as part of the process of error correction. Stark (1968) described similar ‘steplike changes in position which occurred with irregular intervals and amplitudes’ during ramp and step tracking in normals. He referred to these irregularities as ‘saccades’, possibly representing a sampling intermittency in the tracking system. In contrast, Draper and Johns (1964) described rhythmic, intermittent steps in the velocity profiles in parkinsonian patients which they attributed to a motor control deficit. Others have noted irregular velocity trajectories in parkinsonian patients (Evarts et al., 1979; Weinrich et al., 1988; Flash et al., 1992; Hocherman and Aharon-Peretz, 1994). Irregular, repetitive EMG bursts were also noted during step movements in Parkinson’s disease (Hallett and Khoshbin, 1980).

The results of the present study demonstrate that position and velocity irregularities are prominent in both normals and patients with Parkinson’s disease. The tracking records (Figs 2–4, 6 and 7) are characterized by multiple reversals of velocity. The irregularities are best appreciated in the plots of position versus velocity, which reveal frequent parabola-like excursions of velocity. During the tracking cycle, velocity is intermittently injected or dissipated. This is consistent with the effect of a pulse of net torque into either flexion or extension, controlled in either a feedforward or feedback manner. Although distinguishing between these two possibilities is not yet possible, the feedback nature of the task suggests that these velocity excursions are related to the ongoing error correction process. These inflections persist in spite of prolonged practice, indicating that a resultant increase in predictive control does not smooth the velocity profile.

Lodopada markedly alters the temporal pattern of the velocity excursions in Parkinson's disease. In the most severely affected patients, the velocity excursions coarsen when 'on' (Figs 3 and 4), increasing in duration and amplitude. From the perspective of propulsion, the now less frequent output of torque pulses would decrease temporal responsiveness to changes in the desired trajectory. From the perspective of error correction, the decreased frequency of torque pulses would lead to a decrease in the number of corrections. The larger amplitudes of the velocity excursions may be compensatory in either case, rendering precise adjustments in position more difficult. Therefore, these changes in the velocity excursions could result in severe deficits in the control of movement, supporting the conclusion of Draper and Johns (1964) that these intermittencies constitute a major control abnormality in Parkinson’s disease.

Effects of disease and medication state on tracking velocity and error

It has often been reported that subjects with Parkinson's disease are not able to scale velocity to meet task requirements as well as normals (Draper and Johns, 1964; Flowers 1976; Hallett and Khoshbin, 1980; Berardelli et al., 1986). The present results comparing the velocity of the slow sinusoidal and faster step tracking tasks confirm these earlier observations. While normal subjects increased velocity by 120% from sinusoidal to step tracking, the parkinsonian subjects increased velocity by an average of only 65% irrespective of medication state. Thus, subjects with parkinsonism were able to increase tracking velocity, but only half as well as normals.

Parkinsonian subjects tracked the slow sinusoid with a velocity almost identical to that of the normals. No difference occurred until ingestion of levodopa, after which the severely affected parkinsonians significantly increased velocity. In fact, the velocity was increased to a level greater than that of normals. At the higher velocities demanded by step tracking, the parkinsonians when 'off' tracked significantly slower than normals. This difference was eliminated by levodopa. Therefore, levodopa improved the sensitivity of the tracking paradigm to differentiate the disease state. The velocity of sinusoidal tracking distinguished normals from parkinsonians when 'on' while the faster step tracking differentiated normals from parkinsonians when 'off'.

Error was a particularly sensitive measure of disease state. The error during sinusoidal tracking was significantly greater for all parkinsonian groups compared with normals, for both the 'off' and 'on' states. Error was greater than normals for the faster step tracking in the combined parkinsonian group and the severely affected subgroup for either medication state (Fig. 5). Levodopa had no significant effect on tracking error within any parkinsonian subgroup in either tracking task. Flowers (1978) found that parkinsonian patients had an increased tracking error relative to normals for both the total and timing-corrected rms error. This lack of medication effect was seen not only for total rms error, but also timing-corrected rms error. Furthermore, the resistance of error to change as a function of medication state cannot be attributed to insensitivity of the measure, since error distinguished parkinsonian subjects from normals irrespective of medication state in both tracking tasks. This lack of response to levodopa distinguished error from velocity. Therefore, a battery of tracking tasks that included simultaneous measures of velocity and error, and the effects of levodopa were all required to differentiate the parkinsonians from normal controls comprehensively.

Confounds of tremor and dyskinesia on the measurement of velocity and error

Tremor and dyskinesia complicate determinations of levodopa effects using either clinical rating scales or physiological
Velocity generation and error correction

Two motor deficits hypothesized to contribute to bradykinesia are decreased movement velocity (Draper and Johns, 1964; Flowers, 1976; Evarts et al., 1979; Hallett and Khoshbin, 1980; Baroni et al., 1984; Berardelli et al., 1986) and increased movement error (Draper and Johns, 1964; Flowers, 1976; Sheridan and Flowers, 1990). Two hypotheses have been formulated linking the reduction in velocity to the increase in error in Parkinson's disease. The first gives primacy to the reduction in velocity and relates the increase in error to this reduction (Draper and Johns, 1964). The second emphasizes the increase in error and explains the reduction in velocity as a strategy to compensate for the unacceptably increased error (Flowers, 1976; Sheridan and Flowers, 1990).

Viscosity, a load that is a function of velocity, provided an external method of altering the tracking velocity so that its effect on error could be directly measured. Thus, the two hypotheses could be directly tested. Viscous load manipulation significantly changed the velocity of sinusoidal tracking by 40–60% and that of step tracking by 50–70% for the normal and parkinsonian groups. For both sinusoidal and step tracking, antiviscosity increased the amplitude of the parabolic velocity excursions without altering the frequency of the excursions (Figs 6 and 7). If the error correction system in Parkinson's disease is the primary deficiency producing bradykinesia by a speed-accuracy tradeoff, then the addition of velocity by antiviscosity should have markedly increased tracking error. However, tracking rms error did not change in 12 of 14 subgroup comparisons (Table 2). The same result was obtained with levodopa. Tracking error did not change after a pharmacologically induced increase in velocity (Fig. 5). This constancy of error, despite changes in viscous loading or levodopa, indicates that parkinsonian subjects have a functioning error correction system capable of controlling a significant, externally introduced velocity change. This is not to say that their system is functioning at the same level as normals. The error was significantly higher for the subjects with Parkinson's disease relative to normals.

In summary, two lines of evidence point to a dissociation of velocity generation and accuracy during visually guided pursuit tracking in Parkinson's disease. First, the increased error in Parkinson's disease is resistant to levodopa, in contrast to velocity, which increases and approaches normal levels. Secondly, viscous loading significantly increases velocity with only rare changes in error. Therefore, the reduction of velocity is not the primary cause of increased error, as velocity can be increased with levodopa and antiviscosity without reducing the error. On the other hand, the increase in error is not the primary cause of the reduced velocity in bradykinesia. Error was neither reduced by levodopa nor viscosity in presence of large increases in velocity. With the propulsion and error correction systems responding independently to levodopa and external loads, a strict velocity and accuracy tradeoff cannot be established in bradykinesia. Understanding and treating Parkinson's disease will require a recognition of deficits in both propulsion and error correction.

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References


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