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Integration Deficiencies Associated with Continuous Limb Movement Sequences in Parkinson's Disease

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Abstract

The present study examined the extent to which Parkinson's disease (PD) influences integration of continuous limb movement sequences. Eight patients with idiopathic PD and 8 age-matched normal subjects were instructed to perform repetitive sequential aiming movements to specified targets under three accuracy constraints: 1) low accuracy ($W=7$ cm) - minimal accuracy constraint, 2) high accuracy ($W=0.64$ cm) - maximum accuracy constraint, and 3) mixed accuracy constraint - one target of high accuracy and another target of low accuracy. The characteristic of sequential movements in the low accuracy condition was mostly cyclical, whereas in the high accuracy condition it was discrete in both groups. When the accuracy constraint was mixed, the sequential movements were executed by assembling discrete and cyclical movements in both groups, suggesting that for PD patients the capability to combine discrete and cyclical movements to meet a task requirement appears to be intact. However, such functional linkage was not as pronounced as was in normal subjects. Close examination of movement from the mixed accuracy condition revealed marked movement hesitations in the vicinity of the large target in PD patients, resulting in a bias towards discrete movement. These results suggest that PD patients may have deficits in ongoing planning and organizing processes during movement execution when the tasks require to assemble various accuracy requirements into more complex movement sequences.

Keywords

Parkinson's disease; Movement control; Dynamics of end-effector's motion; Harmonicity; Energy dissipation

1. Introduction

Performing many activities of daily living commonly involves the execution of several movements in a sequence. Basal ganglia impairments as manifested in Parkinson's disease (PD) are known to affect performance of sequential tasks [1,2], yet the underlying mechanisms of these motor abnormalities are poorly understood. Kinematic analysis of movements executed in a sequence has revealed that while in normal subjects sequential movements were often organized and executed in a combined manner, PD patients typically exhibited delays

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between movement segments [3]. These results suggest that the dysfunctions of the basal ganglia may reduce the capacity to perform several segments in an integrative manner during the completion of a sequence in PD.

Deficient sequencing of several movements in PD is known to become particularly accentuated when task complexity increases [4]. Weiss et al. demonstrated that when a smaller size of target was added in multi-stroke aiming movements, for example, it caused PD patients to produce a more pronounced movement slowing in the execution of that segment [5]. Similar deficits also have been reported with key pressing [1,2] and discrete segment movements [3,6] when the tasks required combining different motor acts in a movement sequence in PD. These findings suggest that it is a dysfunctional mechanism for switching between subprograms that are attributable to the integration deficits observed during complex sequential movements in PD. Rand et al. proposed that additional processing demands caused by imposing movement difficulty on one segment in a sequence might result in the impaired switching between responses in PD [7]. A deficit in storing and maintaining the plan of an action [8] and a lack of anticipation for the upcoming targets [9] while performing sequential movements have also been reported to account for a difficulty in making transitions between successive responses in PD.

Although earlier studies have provided converging evidence regarding the characteristics of the motor impairments during sequential movements in PD, their performances were mostly concerned with serial movements (e.g., 2–3 targets, up to 7 target, except for Onla-or and Weinstein[10]). Thus, the initial starting point was from discrete motion, and disturbed sequencing in PD was in many cases addressed with planning and organizing processes of movement sequences occurred prior to the movement initiation. Given that the basal ganglia are involved in the control of ongoing movement and motor program implementation during its execution [11,12], it is thus not clear how sequencing problems associated with PD is manifested during repetitive sequential tasks that require continuous update and execution of planning and organization processes while performing movement sequences.

To this aim, the present study examined the extent to which Parkinson's disease influences planning and execution in an ongoing sequence using more continuous limb movement sequences. Subjects were asked to perform a repetitive aiming movement in a reciprocal fashion toward a specified target region imposed by various accuracy requirements. Since the movement data from this experiment were cyclical in nature, the abnormalities of PD patients during sequential motor tasks were analyzed with not only kinematic measures that were mainly focused on movement timing but also the index of harmonic motion (H), a quantitative measure that serves to identify the degree to which an end-effector's trajectory approximates harmonic (cyclical) movement. The latter measure has been proposed to allow a detailed analysis of movement structure particularly involving a transition from one movement component in the sequence to the next [13].

2. Materials and methods

2.1. Subjects

Eight patients with idiopathic non-demented PD (four females, four males; mean age of 69 years, range 58–78 years) and eight healthy elderly control subjects (four females, four males; mean age of 70 years, range 62–81 years) participated in the experiment (Table 1). All elderly and PD participants were right-hand dominant and naive to the experimental tasks and specific purposes of the study. Since the symmetry of motor deficits in PD patients could confound the results, we included PD patients with bilateral symptoms or patients with unilateral symptoms on their dominant side for the experiment. PD patients were tested in the morning while at the end of their drug cycle (i.e., *off* medication). The average Hoehn and Yahr score was 2.4 (range

1–3). The protocol was approved by the Institutional Review Board of the Arizona State University. Informed consent was obtained from each subject before participation in the experiment.

2.2. Apparatus and procedure

The apparatus consisted of a horizontal lever (42 cm long) that was affixed at the proximal end to a near frictionless vertical axle, which allowed the lever to move in the horizontal plane over the table surface. The movement of the lever was monitored at a 200-Hz sampling frequency by a potentiometer attached to the lower end of the axle, and then stored on a computer for later offline analysis. The targets consisted of 5 cm-long rectangles with specific widths (W). Three terminal accuracy conditions were formed: (1) low accuracy $W=7$ cm; (2) high accuracy $W=0.64$ cm; and (3) mixed accuracy with a large target, $W=7$ cm (elbow flexion), and a small target, $W=0.64$ cm (elbow extension). The target amplitude (A) was fixed in all three conditions at 18.5 cm (25.2° of rotation between target centers). The index of difficulty (ID), defined by $\log_2(2A/W)$, was 2.40 for the low accuracy condition, and 5.85 for the high accuracy condition. The subjects performed three blocks of ten trials in each accuracy condition, and the order was counterbalanced across subjects. Each trial lasted 15 s, with 30 s rest between trials, and 5 min of rest between accuracy conditions. The subjects were instructed to move the lever to the defined target as accurately and as rapidly as possible, but with more emphasis placed on the accuracy of the task. On average, PD patients and normal controls produced 22.9 and 25.2 movement reversals in the low accuracy condition, 9.9 and 10.6 movement reversals in the high accuracy condition, and 13.6 and 15.3 movement reversals in the mixed accuracy condition. When the participant made apparent errors during their attempts, the trial was repeated. These error trials usually occurred earlier in testing session for some participants, but the rate was less than 5% of their overall responses in both groups. These events rarely occurred later in testing phase.

2.3. Data analysis

Signals from the potentiometer were digitally conditioned with a fourth-order Butterworth filter, with a low-pass cutoff frequency of 50 Hz. All dependent measures were computed based on every half-cycle of movement between two target strikes within each trial. The individual trial time-series were used to compute movement time (MT) and dwell time (DT). The first-time derivative of the position data (i.e., velocity) was computed in each trial and filtered with a cutoff frequency of 10 Hz to reduce noise. The onset of movement was determined with reference to the value of the peak velocity. From the point of peak velocity, a backwards search was performed to find the first point in the velocity trace that was 5% of the peak velocity. From this point, if the next values of the velocity trace remained below 5% of the peak velocity for at least 25 ms (five sampled points), then the landmark was taken to indicate the onset of movement. Movement offset was determined by searching forward from the peak velocity value to find the last point that was 5% of the peak velocity value before movement reversal (Fig. 1A). Based on the onset and offset points from the velocity trace, movement time was defined as the interval separating these threshold crossings. Dwell time was a measure of the time spent on a target when the end-effector's motion was stationary over the target.

To examine the degree to which the end-effector motion was harmonic (cyclical) and inharmonic (discrete) in nature, an index of movement harmonicity (H) was computed on the basis of every half-cycle of the angular acceleration time-series around movement reversals [13]. A customized computer algorithm was used to normalize the acceleration signals by their absolute maximum values, and identified all inflection points within each half-cycle window. The H-value was computed as the ratio of minimal to maximal local extrema from the individual half cycle (Fig. 1B); for time-windows of half-cycle motion with one inflection point positive and one negative (or vice versa), the H-value was set to zero. A value of $H=1$ was

obtained when the acceleration trace was sinusoidal with only a single peak, indicating a simple harmonic or cyclical motion, while a value of $H=0$ was yielded when an acceleration reached zero level, suggesting an inharmonic or discrete motion at movement reversals over the target. Typically, under low accuracy conditions the H -value is one, indicating the simple harmonic or cyclical nature of a repetitive aiming motion, while with increasing accuracy constraints the value of H comes to zero or near zero, reflecting the nature and/or tendency of the end-effector's motion toward a string of discrete segments [14]. The full-cycle H -value was computed from the two half-cycle estimates in a target pair.

2.4. Statistical analysis

To examine the effects of the accuracy condition and target size on the dependent measures of MT, DT, and half-cycle H , a 2 (group) $\times 3$ (accuracy condition) $\times 2$ (target size) analysis of variance (ANOVA) with repeated measures on the last two factors was performed. The full-cycle H data, averaged across both targets in a trial, were analyzed in a three-accuracy condition (low, high, mixed) repeated measures ANOVA. An alpha level of $P < 0.05$ was adopted to determine the statistically significant differences for all computations.

3. Results

3.1. Harmonicity: full-cycle H

Accuracy condition had a significant influence on the movement dynamics in both groups (Fig. 2). Movement trajectory in the low accuracy condition was cyclical with maximum acceleration occurring over the targets (Hooke portrait, first row in Fig. 2), and maximum velocity occurring at the midpoint between target strikes (phase plane) in both groups. Overall, 72.6% of the trials for normal subjects and 70.3% of the trials for the patients in the low accuracy condition had full-cycle H -values > 0.5 . The sequential movement in the high accuracy condition was discrete in both groups, with many equilibrium points (acceleration=0, velocity=0) associated with movement reversal (Hooke portrait, third row in Fig. 2) over the targets, and maximum velocity before the midpoint between target strikes (phase plane). Almost all of the trials in the high accuracy condition had full-cycle H -values < 0.5 in both groups (98.1% and 99.2% of the trials for normal subjects and PD patients, respectively). The mixed accuracy condition did not result in two separate discrete movements in either group. This was evident in that maximum acceleration occurred as the pointer moved across the large target (Hooke portrait, second row in Fig. 2). Although equilibrium points occurred with movement reversal over the small target in the mixed accuracy condition, the shape of the acceleration profile was different from that observed for the small target in the high accuracy condition. In the mixed accuracy condition, the mean full-cycle H -value of the control group (0.37) was significantly higher than that of the PD group (0.31) [$F(1,9)=17.32$, $P<0.01$].

3.2. Harmonicity: half-cycle H

The group averages (SE) of the half-cycle H data are shown in Fig. 3. On average, PD patients produced lower half-cycle H -values than normal subjects, but the difference between the two groups did not reach significance. Accuracy condition had a significant impact on the half-cycle values in both groups. The half-cycle H -values of both groups in the low accuracy condition were significantly higher than those in the high accuracy condition and mixed accuracy condition, with half-cycle H -values in the mixed accuracy condition significantly higher than those in the high accuracy condition [$F(2,18)=144.2$, $P<0.01$]. A significant interaction between accuracy condition and target size was found in the half-cycle H data [$F(2,18)=108.2$, $P<0.01$]. Tests of this interaction indicated that both groups showed decreased half-cycle H -values to the large target in the mixed accuracy condition as compared with half-cycle H -values to the large target in the low accuracy condition, while showing increased half-cycle H -values to the small target in the mixed accuracy condition as compared with those to

the small target in the high accuracy condition. However, a detailed comparison between groups indicated that PD patients showed a greater decrease in the half-cycle H-values to the large target in the mixed accuracy condition (10.4%) than control subjects (1.3%), and the result was marginally significant [$F(1,9)=4.55$, $P=0.05$]. In contrast, the percentage changes in the half-cycle H-values to the small target in the mixed target condition were insignificant in both groups.

3.3. Movement time

The group averages (SE) for the MT data are plotted in the Fig. 4. In general, the MT of PD patients (846.9 ms) was longer than that of normal subjects (778.2 ms), but the difference between the two groups did not reach significance. The ANOVA indicated a significant main effect for accuracy condition [$F(2,18)=128.1$, $P<0.01$]. MTs in the low accuracy condition were shorter than MTs in the high accuracy and mixed accuracy conditions, with MTs in the mixed accuracy condition significantly longer than MTs in the low accuracy condition in both groups. A significant interaction between accuracy condition and target size was found in the MT data [$F(2,18)=32.5$, $P<0.01$]. Tests of this interaction indicated that both groups showed increased MTs moving to the large target in the mixed accuracy condition, as compared with MTs to the large target in the low accuracy condition, while MTs to the small target in the mixed accuracy condition were shortened as compared with those to the small target in the high accuracy condition. However, a more detailed comparison between groups indicated that changes in MTs to the large target in the mixed accuracy condition differed between groups. Relative to the large target in the low accuracy condition, PD patients exhibited more increases in MT to the large target in the mixed target condition (29.2%) than normal subjects (21.8%), but the result just failed to reach significance [$F(1,9)=4.37$, $P=0.06$]. In contrast, changes in MT to the small target in the mixed target condition, as compared with the small target in the high accuracy condition, were not significantly different between groups (20.3 and 21.2% for PD patients and normal subjects, respectively).

3.4. Dwell time

The group averages (SE) of the DT data are shown in Fig. 5. On average, PD patients produced a longer DT (193.3 ms) than normal subjects (159.9 ms), but the difference failed to reach significance. The ANOVA indicated a significant main effect for accuracy condition [$F(2,18)=103.81$, $P<0.01$]. For both groups, much longer DTs occurred in the high accuracy condition than in the low accuracy condition, with DTs in the mixed accuracy condition being significantly different from those in the low and high accuracy conditions. A significant interaction between accuracy condition and target size was found in the DT data [$F(2,18)=75.03$, $P<0.01$]. Tests of this interaction indicated that both groups showed longer DTs on the small target than on the large target in the mixed accuracy condition, with no significant difference between the same size targets in the low and high accuracy conditions. A detailed comparison between groups, however, indicated that the changes in DTs on the large target in the mixed target condition differed between groups. While the DT on the large target in the mixed target condition remained relatively constant (0.8%) in normal subjects, it increased in PD patients (20.8%), and the interaction between group and accuracy condition on the large targets was significant [$F(1,9)=7.64$, $P=0.02$]. In contrast, the changes in DTs to the small target in the mixed target condition were not significantly different between groups (7.6 and 10.3% of normal subjects and patients, respectively).

4. Discussion

The purpose of this study was to examine the effect of different accuracy demands of target pairs on the extent to which repetitive aiming movements are organized and executed in a discrete or cyclical manner in people with PD. Movement kinematics along with an index of

harmonicity on the end-effector's motion provided converging evidence that the performance of repetitive sequential aiming movements by PD patients was differentially altered depending on the accuracy constraints imposed on components in a sequence. The kinematic results demonstrated that PD patients exhibited similar characteristics of sequential movements to age-matched controls when the accuracy constraint was equal in a target pairing. However, when different accuracy requirements were imposed on each movement component (i.e., a large and small target in a sequence), the patients exhibited increased DTs over the large target relative to DTs over the same size target in the low accuracy condition. Thus, PD patients appear to have a difficulty in initiating the next movement (i.e., small target) when the accuracy constraint was mixed in a target pairing compared to age-matched controls.

Such a lengthened transition period between segments of the sequence was also reflected in the way the movements were controlled. Close examination of the Hooke portraits from the mixed accuracy condition showed more oscillations of the end-effector's trajectory and accordingly lower values of movement harmonicity when making reversal movements over the large target in PD patients. This indicates that PD patients tended to break up the sequential performance into separate actions, thus executing both movement components in a discrete manner. In normal controls, on the other hand, a movement characteristic to the large target was cyclical, while it was discrete to the small target. Thus, both discrete and cyclical movements were combined, performing as a series of chained cycles with each cycle being anchored on a small target under the mixed accuracy condition. These observations suggest that PD patients appear to be impaired in functionally combining discrete and cyclical movements to meet a task requirement, which probably lead to a bias towards discrete movement characteristics when the execution of the subsequent movement contained a high accuracy constraint in a sequence [15].

These results are in agreement with earlier studies showing that the complexity of accuracy constraints imposed on each movement component may be a limiting factor in the control of multiple aiming movements in PD [5,16]. Rand et al., for example, observed a pronounced movement delay between the termination of a movement and the initiation of the subsequent one when sequential movements contained different levels of accuracy constraint during non-repetitive sequential tasks [7]. One possible explanation for the exaggerated hesitations is that due to the disease the ability of PD patients to switch from one motor plan to another are impaired particularly when the sequential movements require changing or modifying response patterns during execution. Harrington and Haaland have reported that PD patients produced a longer inter-response time between movement components than normal controls when switching from one component in the sequence to the next required changing (heterogeneous) hand postures compared to repeating same (repetitive) response [4]. Similar deficits also have been observed with speech [17], drinking actions [18], drawing [12], and force control [19] when the tasks required combining different motor acts in a movement sequence in PD.

It is reasonable to assume that accentuated execution demands by imposing different levels of tasks on movement component in a sequence may escalate processing demands for shifting between movement sequences more for PD patients than for normal subjects [5,7]. Since movement execution toward the large target (ID=2.4) does not require a greater use of visual evaluation for a precise termination of movement, the data of slow transition over the large target in the mixed accuracy condition probably reflect a difficulty in anticipating the imperative changes in the requirements of the upcoming movement while moving to the large target when a high accuracy constraint is imposed on the subsequent movement in PD. Apparently normal controls could perform this task in a smooth and continuous manner, thus they must be simultaneously preparing the next movement while performing the current target strike. Accordingly, it seems that the delay around the large target allowed PD patients to have more time to take into account for the accuracy requirement of the incoming movement.

Together, it is conceivable that PD patients were not able to plan ahead when a change in the requirement of the upcoming movement is needed while performing the current target strike, that is, less use of feed-forward processing during movement execution may be attributable to the pronounced integration deficiencies associated with repetitive sequential aiming tasks in PD. This finding is consistent with the research by Smiley-Oyen et al. which suggests that more segmented planning and control in PD is associated with the lack of anticipation for the upcoming targets when executing movement sequences [9].

The basal ganglia, together with their cortical projection regions, are known to be responsible for the organization and execution of multiple movements in a sequence [20]. Unitary discharge recording and inactivation studies on animals have reported that basal ganglia nuclei such as the striatum, caudate nucleus, and pallidal neurons are related to the performance of sequential motor tasks [21,22]. For example, after a blockade of the striatum by infusing MPTP, monkeys exhibited a tendency to break up movements during sequential push-button motor tasks [23], implicating a deficit in integrating multi-segment motions into a unit. In addition, studies using neuroimaging and stimulation techniques in humans have demonstrated that multiple cortical areas such as the supplementary motor area (SMA), premotor area, posterior parietal area, and cerebellum are involved in the organization processes of complex sequential movements [24, 25]. When compared to normal subjects, PD patients have shown relatively reduced activation in the SMA, to which the circuit of BG largely projects, while performing sequential movements [26]. Some studies have reported overactivity in the parietal and lateral premotor areas and the cerebellum during more complex sequential movements in PD, reflecting that the lack of BG input to the SMA might be compensated by higher activity in these brain regions [27,28]. Consistent with these observations, therapeutic stimulation and lesioning of the globus pallidus and subthalamic nucleus induced increases in the activation of the SMA and anterior cingulate cortex, and improved the performance of fast sequential arm movements [29,30]. Hence, it appears that the observed bias towards discrete motion in the mixed accuracy case by present PD patients may have been the consequence of BG circuit disturbances as a result of the disease for the integration and execution of different motor acts into a unified single action.

In summary, the results of the present study showed that the impaired integrating capability of PD patients was selectively accentuated depending on the task difficulty. PD patients performed repetitive sequential movements similarly to age-matched controls when the accuracy requirements in a target pairing were the same. When faced with different accuracy demands on each movement component, however, the patients exhibited a less smooth transition with more movement irregularities resulting in a lengthened transition period before initiating the next movement with a high accuracy constraint. These findings suggest that PD patients may have deficits in switching between movement segments when planning and organizing processes require to assemble various accuracy requirements into a movement sequence during its execution. Our study extends the findings of previous studies regarding deficient integrations of subsequent movements and a lack of anticipatory control for movement sequences to a situation of continuous sequential aiming movements.

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Fig. 1.

Computation of dwell time (DT) and movement time (MT) values and the harmonicity measure (H). (A) DT and MT computation using several cycles of motion for the high accuracy condition trial (position: dashed line, velocity: solid line). (B) Computation of H for a trial from the mixed accuracy condition. The H-value was determined from the minima and maxima in the acceleration trace for every half-cycle of motion as defined by the vertical lines (position: dashed line, acceleration: solid line).

Fig. 2.

End-effector trajectories (normalized) representative of the low, mixed, and high accuracy conditions plotted in the form of Hooke portraits (*left column*) and phase planes (*right column*) for a normal subject (A) and a PD patient (B).

Fig. 3. Half-cycle H-values for movement to the large target (A) and the small target (B) as a function of low vs. mixed and high vs. mixed accuracy conditions, respectively. Means and standard errors (SE) for all subjects in each group are plotted.

Fig. 4. Movement time (MT) for the large target (A) and the small target (B) as a function of low vs. mixed and high vs. mixed accuracy conditions, respectively. Means and standard errors (SE) for all subjects in each group are plotted.

Fig. 5.

Dwell time (DT) for the large target (A) and the small target (B) as a function of low vs. mixed and high vs. mixed accuracy conditions, respectively. Means and standard errors (SE) for all subjects in each group are plotted.

Table 1

Characteristics of subjects in PD patient group

Patient number	Age (years)	UPDRS scores* Pt. III (Off meds)	Medication**
1	58	31	SCR, SR, P
2	59	23	SR, M
3	78	39	CB, A
4	69	41	SR, P, A
5	69	26	M, SR
6	81	32	LD, CD, M
7	61	37	LD, M, A
8	72	29	SR, A, E

* Rating according to the motor section (part III) of the Unified Parkinson's Disease Rating Scale (UPDRS) with higher numbers indicating greater disability.

** A=Amantidine, CD=Carbidopa, E=Eldepryl, LD=Levodopa M=Mirapex, P=Permax, SCR=Sinemet CR, SR=Regular Sinemet.