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Force Development during Target-Directed Isometric Force Production in Parkinson's Disease

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Abstract

Performing various daily activities requires precise application and control of forces, which has been well addressed in neurologically healthy individuals. Recent experiments have demonstrated that in young, normal subjects generating rapid force pulses over various force amplitudes was accomplished by linearly increasing the rate of force development while keeping time to peak force approximately constant (i.e., a pulse-height control strategy). Using Parkinson's disease (PD) patients the present study examined whether PD patients use a pulse height control strategy during rapid and accurate isometric force production. Subjects were instructed to produce force pulses to three different target amplitudes (15%, 35%, & 55% of their maximal voluntary contractions) at their preferred speed and as fast as possible. When the task was performed as fast as possible, PD patients differed from controls by producing reduced rates of force development and prolonged times to peak force as a function of force amplitude. During performance of the task at preferred speed, which leaves the rate of force production unconstrained, PD patients did not show improved regulation of time to peak force in scaling different force amplitudes compared to controls. These results suggest that PD patients have a difficulty in utilizing a pulse-height control strategy and that such impairments are not dependent on speed.

Keywords

Parkinson's disease; Isometric force production; Force-rate control; Pulse-height control strategy; Speed constraint

Precise application and regulation of forces can be considered to be an essential factor to carry out our daily activities. The neuromuscular control processes underlying the performance of force production have been extensively studied due to its practical as well as theoretical implications for understanding how the central nervous system (CNS) achieves various characteristics of given tasks [5,10,15]. Many investigators have employed a constrained isometric force production paradigm to better identify force control characteristics of neural commands since it does not possess such complications in isotonic tasks as overcoming inertial limb resistance and coordinating visual perception and spatial orientation.

In the studies of motor impairments in Parkinson's disease (PD) the use of an isometric paradigm has provided measures of a relatively pure deficit in force production. It has been

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demonstrated that patients with PD have difficulties in regulation of force output as compared to healthy control subjects. Specifically, while PD patients exhibit a preserved ability to scale the force amplitude, their responses are characterized by prolonged development of the required force rate with segmented force increases resulting in several oscillations [25,26,29]. Thus, it appears that the basal ganglia as manifested in PD are involved in the modulation of isometric force output. Such abnormalities typically worsen with progression of the disease [23] and have been proposed as one of the potential causes of bradykinesia [21,24].

Previous studies on control characteristics of the rate of isometric force development have shown that in generating fast and accurate aiming forces over various force amplitudes neurologically healthy subjects modulate the rate at which force increases while keeping time to reach peak force relatively constant [10]. Thus, the duration of force development is largely independent of force amplitude resulting in highly stereotypic response trajectories of different force levels. This force control pattern is consistent with the notion of a *pulse-height* adjustment for rapid force impulses, a neural control strategy of fixing the time to peak force and modulating the speed or rate of force increase [15]. It has been recently shown that such invariant feature of force duration is prevalent at different speeds of force development [19]. According to Gordon and Ghez [15], the use of pulse-height control strategy during isometric force production allows simplifying the processes for the rapid and accurate control of force responses by reducing the number of control parameters to be specified.

In the present study, we investigated the extent to which PD influences force-rate control characteristics during isometric aiming force production. PD patients and age-matched control subjects were instructed to produce rapid and accurate target-directed isometric force pulses over various force amplitudes (15, 35, and 55% of their maximal voluntary contractions) at their preferred speed and as fast as possible. Earlier studies have reported that PD patients have an inherent limitation in the rate at which they can develop force during rapid and discrete isometric contractions [25,29]. Damage to basal ganglia structures has been shown to produce abnormalities in force recruitment [17,18] and such abnormalities are often compensated for by lengthening impulse duration to augment force output [1,16]. Recent studies using neuroimaging techniques in human have demonstrated that the internal segment of the globus pallidus and subthalamic nucleus in basal ganglia nuclei are directly related to the force development speed during isometric force production [28]. It is thus hypothesized that PD patients who exhibit a major dysfunction in basal ganglia circuits will have a difficulty in employing pulse-height control strategy that requires modulation of faster rates of force development with relatively constant duration to achieve larger force amplitudes.

Furthermore, we also examined to what extent the speed requirement of task differentially affects the force-rate control characteristics of PD patients. Previous studies have demonstrated that the influence of the disease on the motor control in PD is, to some extent, dependent on the speed constraint of the task [12]. When the speed was reduced such as at comfortable or moderate speed in which the speed no longer constrained subject's control, for example, the overall characteristics of movement kinematics, force modulation, and patterns of muscle activity of PD patients were qualitatively similar to those exhibited by normal controls [3, 12]. It is therefore expected that when allowance is made for the slow development of force production to the given force (e.g., their preferred speed), patients with PD will exhibit improved regulation of the rate of force development, suggesting that such impairments associated with PD are primarily due to the limited range of the task examined.

Eight patients with idiopathic non-demented PD (4 female, 4 male; mean age of 71 years, range 62–80 years) and 8 healthy elderly control subjects (4 female, 4 male; mean age of 68 years, range 61–82 years) participated in the experiment. All elderly and PD participants were right-hand dominant and naive to the experimental task and specific purposes of the study. PD

patients were tested after an overnight fast of at least 12 h from their last intake of PD medication (i.e., at the end of their drug cycle). The protocol was approved by the Institutional Review Boards of the Arizona State University. Informed consent was obtained from each subject before participation in the experiment.

The subject was seated in a rigid chair and the forearm was strapped in an immobilized manipulandum with the elbow flexed to 90° in a horizontal plane. The subject was instructed to grasp a vertical metal handle affixed near the end of the manipulandum with the wrist in a neutral position with regard to pronation and supination. A strain gauge (Gamma F/T transducer, manufactured by ATI Industrial Automation Inc.) positioned under the axis of elbow rotation measured the voluntary isometric force of elbow flexion. The targets and applied force were presented to the subject on a computer monitor positioned at eye level, 50cm away. The force data were recorded at a 500 Hz sampling rate and stored on a hard disk for later offline analysis.

After a few practice trials to familiarize the subjects with the tasks, maximum voluntary contractions (MVC) of elbow flexion were performed for three trials to compute the pre-determined submaximal target force amplitude: 15%, 35%, and 55% of the subject's MVC. During testing phase, subjects were instructed to produce an isometric force pulse of elbow flexion to each target force without any attempt to correct their force output once initiated. Subjects performed 15 trials at each target force amplitude. The task was performed at (1) their preferred speed and (2) as fast as possible and the order was counterbalanced across subjects.

Signals from the force transducer were digitally conditioned with a fourth-order Butterworth filter having a low-pass cutoff frequency of 50 Hz before trial-by-trial data analysis. The first-time derivative of force (dF/dt) was computed in each trial using the three-point-difference algorithm written in MATLAB M-files. The dF/dt trace was filtered with a second-order low-pass Butterworth filter with a cutoff frequency of 10 Hz to reduce noise. The maximum value of dF/dt trace was taken as peak dF/dt . The onset and offset of force production was determined with reference to the peak value of dF/dt in each trial. The landmark criterion was 5% of peak dF/dt . Time to peak force was defined as the time from the onset until peak force. To examine the effects of force amplitude and speed, a 2 (group) $\times$ 3 (15, 35, and 55% of MVC) $\times$ 2 (preferred and fastest speed) analysis of variance (ANOVA) with repeated measures on last two factors was performed. An alpha level of $P < 0.05$ was adopted to determine statistical significant differences for all computations.

The group averages for the relative peak force were not significantly different between the control and patient groups ($F=3.68$, $P=0.1$). The relative peak force showed significant main effects for force amplitude ($F=364.99$, $P<0.001$) and speed ($F=70.06$, $P<0.001$). However, none of group interactions were significant for the relative peak force. Thus, PD patients did not have a difficulty in scaling force amplitude according to the required force level.

Figure 1 shows typical examples of force trajectories and the first time derivatives (dF/dt) over 15, 35, and 55% MVC of a control subject and PD patient. The control subject demonstrated fast and ballistic force production with relatively constant time to peak force over varied force amplitudes (Fig. 1A). However, the PD patient exhibited slow development of force resulting in prolonged time to peak force with highly variable force responses. These force control characteristics for the PD patient were more pronounced as a function of force amplitude (Fig. 1B). In addition, the PD patient demonstrated decreased force rates with more oscillations during the course of force development relative to the control subject (Fig. 1D).

Figure 2 shows the group averages for the rate of force development and the time to peak force when the task was performed as fast as possible. In general, when the force amplitude varied from low to high, both groups showed similar increases in force rate (Fig. 2A). The ANOVA

indicated significant main effects for group ($F=7.77$, $P=0.03$) and force amplitude ($F=124.29$, $P<0.001$). Interaction for force amplitude $\times$ group was significant ($F=6.8$, $P=0.01$) with larger differences at the higher force amplitudes. This result indicates that although subjects with PD produced under-scaled force rates relative to controls, they maintained the ability to modulate the force rate according to the given force amplitude requirement of the task. However, the pattern of the time to peak forces was quite different between two groups when the force amplitude varied (Fig. 2B). On average, subjects with PD took longer to reach the peak force than control subjects ($F=6.74$, $P=0.04$). When the force amplitude increased, changes in the time to peak force of the control subjects tended to be relatively invariant. In contrast, the time to peak force of the patients increased with an increase in force amplitude showing that they needed more time to produce larger target forces. The ANOVA revealed that the main effect for force amplitude was not significant ($F=1.84$, $P=0.19$), but interaction for force amplitude $\times$ group was significant ($F=4.54$, $P=0.03$). Simple main effects analysis indicated that while the time to peak force over force amplitudes remained constant in control subjects ($F=0.43$, $P>0.25$), increases in force amplitude resulted in prolongation of the time to peak force in patients ($F=15.04$, $P<0.001$). These results indicate that whereas the control subjects modulated the force rate to achieve larger force amplitudes while keeping the time to peak force relatively constant, increases in force amplitude resulted in prolongation of the time to peak force in patients.

Figure 3 illustrates the group averages for the force rate (Fig. 3A) and the time to peak force (Fig. 3B) performed at preferred speed. In general, the force control characteristics when performed at their preferred speed were quite similar to those under the maximal speed condition; although control subjects produced higher force rates than subjects with PD ($F=6.45$, $P=0.04$), both groups were capable of increasing force rate according to the target force amplitude ($F=78.20$, $P<0.001$). While the time to peak force remained relatively constant over different force amplitudes in control subjects, this time was significantly prolonged with force amplitude in PD patients. The ANOVA indicated significant main effects for force amplitude ($F=4.58$, $P=0.03$) and interaction for force amplitude $\times$ group ($F=3.97$, $P=0.04$). Simple main effects analysis indicated that while the time to peak force stayed relatively constant in controls ($F=0.12$, $P>0.25$), it is still prolonged with force amplitude in PD even when the speed of force production was not emphasized ($F=36.49$, $P<0.001$). The 3-way group by force amplitude by speed ANOVA of the time to peak force was longer for the PD patients than control subjects ($F=8.75$, $P=0.02$). The main effect for speed was significant ($F=1.84$, $P=0.19$) with shorter time to peak force at fastest speed, but interaction for speed $\times$ group was not significant ($F=1.67$, $P=0.24$). Interaction for speed $\times$ force amplitude was significant ($F=5.82$, $P=0.02$) with larger differences at the higher force amplitudes. Overall, PD patients had difficulties in developing given forces at the same force rate as control subjects.

The primary objective of the present study was to assess the extent to which PD influences the force-rate control characteristics during rapid and accurate target-directed isometric force production. When the task was performed as fast as possible, neurologically normal subjects in the present experiment adjusted the amplitude of aimed force by controlling the rate of force development while keeping the time to peak force relatively constant. Thus, control subjects employed a pulse-height control strategy to modulate response trajectories over different force amplitudes [10,15]. In contrast, the force-rate control characteristics in the PD group were quite different from those exhibited by age-matched control subjects. Although PD patients were able to vary force rate according to force requirement of the task, their force-rate profiles were characterized by significantly lower and more variable rates of force development—even without overt tremor (Fig. 1D), and the time to peak force increased systematically as the target amplitude varied from low to high. Thus, it appears that PD patients could not achieve given forces by controlling the rate of force development as normal controls did [6,29], and tended to achieve higher forces by increasing the duration of force development.

The findings with respect to force-rate control patterns in PD are consistent with earlier studies that there may be underlying changes in the force-generating characteristics of the muscles due to basal ganglia dysfunction. Studies of motor unit (MU) behavior have shown that rapid and discrete muscle contraction requires the subject to recruit many single MUs simultaneously with a high firing rate within a relatively limited time [8,9]. However, disturbance in the basal ganglia circuits has been reported to produce deficits in MU recruitment and discharge mechanisms such as a prolonged recruitment of single MUs, reduced firing rates, and intermittent failure to sustain firing [7,18]. These abnormalities in the MU modulation properties are also in agreement with observations of impaired muscle activation control in PD. For example, during movement the typical electromyography (EMG) activity patterns of patients include reduced initial EMG burst [1,2], slow rate of EMG rise [11], and fractionated multiple EMG burst [20,27], indicating that PD patients may have a difficulty producing a given force by a single contraction. It has been suggested that such abnormalities are often compensated for by lengthening the duration of the EMG burst or reactivating additional cycles of EMG bursts to build up force to the target level [16,27]. Together, these fundamental changes in neuromuscular control mechanisms by the basal ganglia disorder may have contributed to the abnormal force-rate control characteristics in PD [1,29].

The present study examined also how the speed constraint of the task influences the force-rate control characteristics in PD. Studies of motor disorders in PD have demonstrated that the deficits in PD could be specific to the constraints imposed by the nature of the task to perform. For example, the influence of the disease on the motor control in PD was less marked when performing familiar tasks [3,13], tasks with a low spatial accuracy [22], and under visual guidance [4]. Speed requirement of the task also has been shown to selectively affect the impairments in PD [12]. When no emphasis of speed was placed such as a moderate or comfortable speed, control characteristics of force output during isometric tasks were not greatly different between control subjects and PD patients, indicating that the deficits of PD patients are speed dependent. In the present experiment, on the contrary, we did not observe such normalization of the deficits in PD under the reduced speed condition. When the task was performed at preferred speeds, which leaves the speed of force development unconstrained, control subjects maintained a pulse-height control strategy of force development, but PD patients exhibited an increasing time to peak force with force amplitude. Therefore, the impairments in the temporal regulation of force development in patients were not affected differentially by the speed requirement of task. This lack of improved regulation of the time to peak force with a minimized speed constraint suggests that PD patients probably do not take advantage of a reduced range of task parameters by the slow speed requirement in the control of force rate.

The discrepancies in results may be due to differences in the tasks in which the instruction regarding the speed of force production was given. As compared to other studies, the present subjects were not allowed to use corrective adjustments during force development even though they performed the task at reduced speed (i.e., at their preferred speed) because it is known that the use of error correction with slow rate of force rises in accomplishing the target force can result in changes in the control mechanisms involved in the force-rate modulation. For example, it has been reported that when allowance is made for the slow development of force healthy young subjects tend to adopt an unified 'default' control strategy in which they produce force gradually at relatively constant rates independent of force level (i.e., pulse-width control strategy) [5]. In addition, Gordon and Ghez [14] have demonstrated that alternating phasic activity of opposing muscles, a common EMG modulation pattern shown in fast isometric force aiming tasks, does not occur with relatively slow speed requirement. Subsequently, we believe that allowing the use of corrective adjustment or further reducing the speed requirement of force production would result in less distinct force-rate control patterns between the control

and patient groups. Overall, such subtle differences in instructions among studies may have introduced measurable variation in motor performance in PD.

In conclusion, the present study found that while normal controls employed faster rates of force development with relatively constant duration for larger force amplitudes, PD patients exhibited difficulties in utilizing such a pulse-height control strategy during rapid and accurate isometric aiming force production. These findings suggest that the basal ganglia disorder interferes with the control mechanism responsible for the explicit modulation of force rate to scale different force levels [29]. In addition, when the speed was reduced such as at preferred speed in which the speed no longer constrained subject's control, PD patients did not show improved regulation of the rate of force development, indicating that the abnormal force-rate control characteristics of the patients are not primarily due to the limited range of the task examined. Taken together, our data suggest that the deficits in modulating the rate of force development during isometric force production are more likely to be an intrinsic (i.e., non-selective) feature of the pathophysiology of PD.

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Fig 1. Examples of force (A, B) and rate of force development (C, D) trajectories aimed at their 15, 35, and 55% of MVC in a control subject and a PD patient (preferred speed). Data are aligned on the onset of force response.

Fig 2. Peak rate of force development (A) and the time to peak force (B) as a function of force amplitude. Mean values for all subjects in each group are plotted for the fastest speed condition.

Fig 3. Peak rate of force development (A) and the time to peak force (B) as a function of force amplitude. Mean values for all subjects in each group are plotted for the preferred speed condition.