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Force production characteristics in Parkinson's disease

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Summary

This experiment examined the preparation and the production of isometric force in Parkinson's disease (PD). PD patients, elderly, and young subjects generated force levels that were a percentage of their maximum (15, 30, 45, and 60%). Subjects were cued on the upcoming target force level and they were asked to produce the required response as fast as possible. PD patients showed a similar progression of force variability and dispersion of peak forces to that of control subjects, implying they have an accurate "internal model" of the required forces. Force production impairments were seen, however, at the within-trial level. PD patients had more irregular force-time curves that were characterized by changes in the rate of force production. The results suggest a more "noisy" output from the motor system and an inability to produce smooth forces. PD patients were also substantially slower in initiating a force production and the delay was localized in the pre-motor reaction time.

Introduction

Patients with Parkinson's disease (PD) have been shown to adequately prepare a motor response albeit more slowly (Bloxham et al. 1984; Evarts et al. 1981; Heilman et al. 1976; Stelmach and Worringham 1988; Stelmach et al. 1986; Yokochi et al. 1985). Such results have suggested to many (Marsden 1982, 1984, 1985; Sheridan et al. 1987) that the overall form of the motor program is intact in PD. The execution of movements, however, has been shown to be slower and more variable (Draper and Johns 1964; Flowers 1976; Hallett and Khoshbin 1980; Sheridan et al. 1987).

Sheridan et al. (1987) recently suggested that the increased variability of movement (both in time and space) exhibited by PD patients is related to an inherent variability in force production. Indeed, force variability has been shown to be a major limiting factor of motor performance (Newell et al. 1984; Schmidt et al. 1979). Sheridan et al. (1987) identified three potential sources for the increased force variability in PD: 1) an incorrect computation of the required force, 2) a defective memory for computed forces and 3) a noisy output from the motor system.

It was therefore necessary to study the characteristics of force production in PD under varied conditions. Stelmach and Worringham (1988) asked PD patients to perform an isometric force production task, aiming at different target force levels. Quite surprisingly, PD patients were as accurate as control subjects in producing 25, 50, or 75% to of their maximum force. Further, as visual feedback was unavailable throughout the force production, the results not only suggested that PD patients can correctly compute a required force, but that they also have an accurate "internal model" of the required force.

The PD patients executed the force task differently, though. They needed more time to achieve the peak force and also required more time to initiate their responses. The experimental design, however, did not allow a detailed quantification and a systematic analysis of force variability. If PD patients can be trained to produce different levels of force, this will allow a more complete examination of their force production and control capabilities. In the present experiment, we evaluated force control by 1) examining the relationship between the peak force produced and its variability, 2) determining, for a given force level, how the force variability is different in PD patients and whether the progression and the overall force variability for PD patients differs from that of control subjects, and 3) quantifying the "smoothness" in the PD patients' force production. EMG signals were also used to decompose reaction time (RT) into pre-motor and motor components to determine the locus of PD deficits in initiating force. This experiment, therefore, considered how effectively PD patients can repeatedly generate appropriate rapid force impulses.

Methods

Subjects

Seven patients with idiopathic PD (6 males and 1 female), seven elderly subjects (6 males and 1 female) and seven young subjects (5 males and 2 females) were examined. A description of the PD patients is presented in Table 1. The mean age of the PD patients was 65.7 years (range of 60-73), the mean age of the elderly was 67.1 years (range of 61-73), and the mean age of the young was 24.6 years (range of 18-31). PD patients followed their normal schedule of medication during the day of the experiment, but we attempted to manage the drug cycle by testing the patients within the same relative temporal period of their drug cycle. Control subjects were free from any signs or symptoms of neurological disease. All subjects gave informed consent for the procedures used.

Apparatus and subject position

The apparatus consisted of a force transducer (Interface SSM-500) attached to a rigid, wall-mounted shelf. A vertically aligned plastic plate was attached to the force transducer. The transducer output was directed to an amplifying circuit prior to being fed to a PDP 11/73 micro-computer. Muscle discharge patterns from the biceps brachii and triceps lateralis were recorded using physiological amplifiers having a common mode rejection of 87 dB at 60 Hz. Pre-spaced (2.5 cm) Ag-AgCl surface electrodes were placed over the muscle bellies. The electromyographical (EMG) signals were pre-amplified at the source (35x), full wave rectified, band-pass limited from 40 Hz-4 kHz, and filtered with a time constant of 2.5 ms. All signals (force, biceps EMG, triceps EMG) were digitized at 500 Hz.

A light emitting diode (LED) display panel faced the subject. There was a vertical array of 4 LEDs labelled 15%, 30%, 45%, and 60%. The upper arm and forearm of the subject rested on a padded surface of the shelf with the elbow being tlexed in the horizontal plane at an angle of approximately ninety degrees. The palmar surface of the subject's wrist (at the level of the carpal bones) made contact with the plastic plate attached to the transducer. An attempt to bring the palm toward the trunk led to the development of force in a direction along the recording axis of the force transducer. PD patients were tested on their more affected side; elderly and young subjects, on their non-dominant side.

Procedure

After electrode placement, subjects received instructions and the task was demonstrated. The experiment began with an assessment of maximal flexor force, in which the subject was required to develop maximal force against the transducer in a contraction lasting between 2 to 4 s. Average peak force was calculated from those trials and served as an estimate of maximal force for the remainder of the experiment. Subjects were then instructed to produce 15, 30, 45, or 60% of their own maximum as fast as possible, and without any attempt to correct their responses once they were initiated. A variable height chair was used to ensure the upper arm and the forearm were both in plane parallel to the floor. Peak force feedback was provided after every trial. Specifically, subjects were told to adjust their force production on the following trials if the amount of force they had produced deviated more than 7~c of the target force level. EMG activity in the biceps and triceps muscles was monitored on-line via an oscillscope (Tektronix 5110) and subjects were instructed to relax their arm as much as possible before the initiation of a trial.

Each trial started with a ready signal (the four LEDs were simultaneously activated for 1 s). A second later, the LED cueing the required force level was activated for one second. The same LED served as an imperative signal and was reactivated a second later signalling the subject to initiate a response. There were twelve practice trials (three at each of the four target force levels) The experimental trials followed and consisted of eight randomly presented blocks of ten trials, two for each target force level. Al1 experimental trials were used for data analysis.

Data analysis

The force-time curves were smoothed with a Butterworth second-order filter with dual pass to remove high frequency artifacts and any phase lag (10 Hz cut-off frequency). The onset and the peak amplitude of each trace were then determined through interactive graphics (Walter 1984). The EMG data were smoothed using a moving window average (10 ms window) and the onsets were also determined through interactive graphics methods. The time interval between the onset of the stimulus and the onset of agonist EMG was defined as the pre-motor reaction time, whereas the time interval between the onset of agonist EMG and onset of force production was the motor reaction time.

To determine how the force variability progressed during the movement and whether the progression

for the PD patients differed from that of the control subjects, we used a procedure recently employed by Darling and Cooke (1987). The force-time series obtained for each force level were first synchronized with respect to the onset of force production. Point-to-point force variability throughout an entire condition was then evaluated.

A variability ratio was computed to determine how consistently and reliably the subjects generated force impulses. The ratio gives an index of the variability over the force production. The onset and peak force of the average force-time traces were first determined through interactive graphics and the area under the curve computed. The same temporal landmarks were then used to determine the area under the variability-time curve divided by the area under the mean force-time curve. For a given force level, a greater variability in reproducing a given target force would be indicated by a greater ratio.

Such force variability analyses, however, reduce any within-trial force production irregularities (Bendat and Piersol 1971; Schomaker and Thomassen 1986). To quantify those within-trial irregularities we adapted a measure of smoothness and economy of movement first suggested by Nelson (1983; Flash and Hogan 1985). The number of sign changes in the second derivative of force gives an indication of the number of changes in the rate of force production. A more optimal and smoother force production should be characterized by a smaller number of sign changes.

Finally, in order to determine whether PD patients were more variable at attaining a given target force than elderly or young subjects, relative peak force variability (i.e., ratio of the standard deviation of peak force to the maximum peak force, expressed in percentage) was used as a measure of dispersion. It is important to mention that peak force variability reflects the accuracy with which subjects can repeatedly produce a given peak force and, contrary to the other measures of variability (i.e., point-to-point variability, variability ratio, and changes in the rate of force production), it does not provide clear indications as to the processes by which subjects achieve peak force. The reverse is also true; that is, measures derived from the force-time series provide information about force control per se, but not about variability at the target.

Unless otherwise mentioned the results for the dependent variables were submitted to a group (PD, elderly, and young) by target force level (15, 30, 45, and 60% of maximum) analysis of variance (ANOVA) with repeated measures on the second factor.

Results

Peak force

On average, the absolute maximum peak force was smaller for PD patients (86 N) than for the elderly and young subjects (115 N and 130 N, respectively) and these PD patients produced smaller forces than the elderly and young subjects at each of the four target force levels (on average 19, 35, 50, and 63%). However, PD patients were able to produce peak forces that approximated the different target force levels. There were no group differences in the percent of peak force ($P > 0.05$), indicating that PD patients had an accurate "internal model" of the required force.

Force variability

Representative force-time curves (45 % of subject's maximum) for a PD patient, an elderly, and a young subject are presented in Fig. 1. The traces are from a block of ten trials and were all synchronized upon the temporal location of peak force. Figure 2 presents the relative peak force variability as a function of the four target force levels. Overall, the young subjects tended to be less variable (8.4 %) than PD patients (9.5%) and the elderly (9.4 %) , but the main effect of group as well as the group by target force interaction were not significant ($p > 0.05$). For the three groups, an increased force production was associated with a negatively accelerating increased peak force variability ($F(1,54) = 48.07$ and 7.51, $ps < 0.01$, for the linear and quadratic components of the main effect of target force, respectively). Hence, PD patients were able to accurately produce a required force and did not show more relative dispersion at the target than the elderly and young subjects at any of the four target force levels.

Representative point-to-point force variability curves (refer to Methods section for computational details) are presented in Fig. 3 for two PD patients, an elderly, and a young subject. The overall pattern of force variability was similar for all subjects. There was a gradual rise in variability with the average temporal location of peak force (arrows in Fig. 3) corresponding to some degree to the temporal location

of the largest force variability. PD patients, though, showed a much slower rate of force development (on average, 62 vs. 213, and 208 N/s for the elderly and young subjects), that yielded a slower rise of variability than control subjects. Interestingly, two of the PD patients showed a more rapid initial rise of variability with the largest force variability occurring early during force production; a substantial decrease in variability then followed before the temporal location of peak force (e.g., Fig. 3). The variability ratio did not yield group differences (0.141 for the PD patients vs. 0.143 and 0.139 for the elderly and the young; $P > 0.05$), showing that PD patients did not have a greater between-trial force variability, and as such, had a correct memory or "internal model" for the required force. Overall, PD patients were capable of repeatedly producing a target force with no more target dispersion and overall between-trial variability than control subjects.

To get an indication of the smoothness of force production, the number of sign changes occurring in the second derivative of force was evaluated. These results are presented in Table 2. More sign changes were observed in PD patients than in the elderly and young subjects (6.8 vs. 3.4 and 3.2; $F(2,18) = 6.57$ $P \sim 0.01$). These results were unaffected by the target force levels ($P > 0.05$). Hence, PD patients were less optimal in producing a required target force as their force-time curves were characterized by more irregularities in the rate of force production.

Time-to-peak force and average rate of force development

In addition to the force production irregularities, PD patients needed nearly twice as much time to achieve peak force as the elderly and the young subjects (657, 388, and 376 ms, respectively; $F(2,18) = 2.79$, $P < 0.08$, for the main effect of group). The groups were also affected differently by the various force levels ($F(6,54) = 2.66$, $P < 0.05$ for the interaction of group by target force level). A decomposition of the interaction into its orthogonal components showed that the time-to-peak force/target force slopes differed in their linear part ($F(2,18) = 3.82$, $P < 0.05$) This implies that, whereas the time-to-peak force systematically increased with an increase in the required target force level for the PD patients (from 521 ms to 781 ms) and the elderly (from 295 ms to 497 ms), it stayed relatively constant for the young subjects (from 337 ms to 376 ms).

At each of the four target force levels, PD patients had lower rates of force development than both the elderly and the young subjects (on average, 62, 213, and 208 N/s, respectively; $P < 0.05$). The three groups produced proportionately larger rates of force development at the larger target force levels ($F(1,18) = 161.80$ and 26.87, $ps < 0.001$, for the linear and quadratic components of the main effect of target force).

Response initiation

Reaction time (RT) was also evaluated to further investigate the nature of the delays in initiating a force pulse that were previously observed by Stelmach and Worringham (1988). On average, PD patients were slower than both the elderly and young subjects (470, 329, and 281 ms, respectively; $P < 0.05$). For the three groups, RT decreased with an increased target force level (380, 349, 359, and 352 ms for the 15%, 30%, 45%, and 60% target force levels respectively; $F(2,18) = 2.19$, $P < 0.05$), for the main effect of target force. A comparison of means showed that the RT at the 15% target force level was longer than at the three other force levels ($P < 0.05$) supporting the suggestion that slower rates of force development influence reaction time (Carlton et al. 1987). Further, the RT of PD patients was on average more than twice as variable (within-subject standard deviation) as the elderly and the young subjects (157, 72, and 50 ms, respectively; $P < 0.01$). Thus, at all levels of target force, PD patients were slower and more variable in the initiation of responses than elderly and young subjects.

To further explore the lengthening of RT observed in PD patients, RTs obtained on the 15% and 30% target force levels were decomposed into pre-motor and motor components. Due to significant tremor at rest and unstable baseline muscular activity, it was not possible to obtain precise EMG onsets in two PD patients. The data obtained for the remaining 5 PD patients, as well as the mean for the elderly and the young subjects are presented in Table 3. The motor component of the RT was similar for the three groups and was unaffected by the target force level ($P > 0.05$). On average, for the 15% and the 30% target force, the motor RT was 68 ms for the PD patients, 74 ms for the elderly, and 61 ms for the young. In contrast, PD patients had substantially longer pre-motor RT (448 ms) than both the elderly (259 ms) and the young subjects (230 ms; $F(2,16) = 6.28$, $P < 0.01$). The observed 218 ms increase in the pre-motor component of RT supports Marsden's (1985) suggestion that the commonly observed longer RT seen in PD patients are almost totally accounted for by delays in pre-motor processes.

Discussion

Force variability is an important determinant of movement performance. In the present experiment, various characteristics of force control were quantified to determine how PD patients' force control is impaired. PD patients exhibited a similar dispersion of their peak forces and overall force variability to that of control subjects. This capability of repeatedly producing a given target force with comparable accuracy to that of control subjects argues against the suggestion that PD patients' inherent movement variability is due to an incorrect computation of the required force or a defective memory for computed forces (Sheridan et al. 1987). Tremor itself can not account for these results. Indeed, if the results were a simple reflection of tremor, more changes in the rate of force production should have been observed with an increased target force as PD patients needed more time to attain peak force in those trials. Such was not the case, suggesting a more complex and fundamental motor impairment. Hence, PD patients exhibited a less optimal force control (Flash and Hogan 1985). Force production impairments were, however, observed. Whereas the force-time curves of the elderly and the young subjects were characterized by smooth initiation and force control throughout the production, the PD patients' curves were characterized by a greater number of changes in the rate of force production.

The irregularities observed at the within-trial level may be the result of a saturation problem; that is, of a limitation in the amount of activity that can be put into an EMG burst (Hallett and Khoshbin 1980). Berardelli et al. (1986b), however, have reported that the first agonist does not saturate in PD patients. They suggested that, in PD, there is a breakdown of the link between "perceptual appreciation" of the goal and "delivery of the appropriate instructions" to the motor cortex. Such a suggestion implies that PD patients rely on a closed-loop mode of movement control (Flowers 1978; Cooke et al. 1978; Stern et al.1982). Because, of the relatively long time-to-peak force observed in PD patients (on average 659 ms), such a possibility can certainly not be precluded. The Berardelli et al. suggestion also raises the possibility that more irregularities may be observed for larger forces since larger forces could induce multiple breakdowns. Such a suggestion, however, is not supported by our results since the number of "sign changes" was constant across all target force levels. Nevertheless, it is possible that the force irregularities observed are the consequence of a failure to send signals to the high-threshold motor units. Further, the ability of PD patients to perform the task without visual feedback with similar betweentrial variability to that of control subjects argues against the generality of previous hypotheses that PD patients are critically dependent on such feedback (Frith et al. 1986; Cooke et al. 1978; Flowers 1976, 1978; Stern et al. 1982).

Milner-Brown et al. (1979) reported that, even when voluntarily attempting to maintain a force, some motor units in PD patients stop firing for prolonged period or fire at abnormally low frequencies (2-3 Hz). Some prolonged postexcitatory inhibition between the spike bursts for tremorous patients has also been reported (Dietz et al. 1974). Moreover Abbs et al. (1987) have shown that, when asked to sustain a given force level with oro-facial muscles' PD patients exhibit greater variability. Hence, force production irregularities in PD may be the result of difficulties in maintaining or sustaining a given contraction because of irregular motor unit frequencies as well as pauses and delays in the units recruitment Alternatively, abnormalities in reciprocal inhibition could also explain some of the irregularities. In support of this argument, Hayashi et al. (1988) recently reported that, upon initiation of a voluntary ankle dorsiflexion, PD patients exhibited a facilitation of the soleus motoneurones whereas normal subjects exhibited an inhibition.

In addition to the irregularities observed, PD patients took nearly twice as much time to achieve peak force as the elderly and young subjects did. There is certainly an inherent limitation in the rate at which PD patients can develop force. Nevertheless, although they are somewhat restricted in their range of speeds, PD patients can generally vary their movement speed (Berardelli et al. 1986; Hallett and Khoshbin 1980; Teasdale and Stelmach 1988). Since an increasing time-to-peak force produces a decrease in force variability (Gordon and Ghez 1987; Hancock and Newell 1985; Newell et al. 1984), PD patients may have traded accuracy of force production for slower speed of force production. Such an interpretation is reminiscent of classical speed-accuracy tradeoffs observed in the motor control literature (e.g., Fitts 1954; Schmidt et al. 1979). Such changes in response strategy have been observed extensively in elderly populations (e.g., Welford 1958; Salthouse 1979). Hence, it is possible that a portion of the slowness observed in PD patients is the result of an emphasis on greater accuracy. Sanes (1985), using a Fitts' task, obtained results suggesting such an interpretation. In Sanes' experiment, movement impairments in PD patients were induced by increasing movement difficulty through requiring increased movement accuracy and increasing movement amplitude.

It is possible that PD patients, over the course of many years, develop strategies that emphasize spatial accuracy without any awareness of doing so (Evarts et al. 1981). In everyday life activities, the incentives to be spatially accurate far outweigh the incentives to move fast. Hence, a portion of the increased latencies observed in PD patients may not only be the result of structural deficits related to PD but also of an altered movement strategy used to cope with the disease itself.
In the present experiment, PD patients' longer RTs were almost totally accounted for by delays in the pre-motor RT (on average, 98%). There has been recent suggestion (Sheridan et al. 1987) that PD patients are unable to make use of advance information as presented in this experiment. Using precuing techniques, Stelmach et al. (1986), however, have shown otherwise. In their experiment the PD group had a higher reaction time intercept but not a steeper slope with an increase in the number of response alternatives from 1 to 8. Hence, the increased reaction time in PD is not an inability to preprogram a response before entering the reaction time period.

For neurologically normal subjects, Carlton et al. (1987) recently reported that there is a natural relationship between rate of force production and RT such that RT exponentially decreases as the rate of force production increases, until an asymptote is reached at moderate to high force development rates. Because of their slower rate of force development, PD patients are "working" on a different portion of the suggested RT/rate of force development function. This implies that, when compared to control subjects' a portion of the RT slowness in PD patients, may be attributed to an overall slowness inflicted by the disease, and not simply to some specific central impairments.

Such an explanation, however, does not preclude the possibility that, in PD, some slowness in initiation is associated with delays in pre-motor processes (Pullman et al. 1986; Yokochi et al. 1985). Response slowing has also been linked to sensory and attentional mechanisms where speculations have focused on the lack of a preparatory set and/or increased reliance upon sensory cues (Stern and Mayeux 1986; Stern 1986). Pullman et al. (1988) also raised the possibility that additional brain structures, such as preparatory set-related cells located in the supplementary motor area (Tanji et al. 1980), are also responsible for longer reaction times observed in PD patients. Hence, problems with preparatory set might also explain some of the slowness in the initiation of force production in the present experiment.

Overall, PD patients did not show more dispersion at attaining a given target force than control subjects and they were able to repeatedly generate a given force level. Force impairments were seen at the within-trial level as more changes in the rate of force production. PD patients are deficient in producing a smooth and optimal (Flash and Hogan 1986) force-time curve rather than a desired peak force, implying a more noisy output but an accurate "internal model" of the required force.

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Table 1. Profile of Parkinson's disease subjects.

Subject No.	Age (yrs)	Duration of disease	Hoehn & Yahr scale	Predominant symptoms	Medication
1	65	8	III	Severe bradykinesia, mild rigidity, moderate tremor	Sinemet
2	73	22	IV	Severe bradykinesia, severe tremor	Sinemet Amantadine
3	62	3	II	Minor bradykinesia, mild rigidity, moderate tremor	Sinemet
4	60	18	IV	Severe bradykinesia, severe tremor	Sinemet Pergolide Imiprine
5	60	7	III	Moderate bradykinesia, Moderate rigidity, Severe tremor	Sinemet Artane
6	69	2	I	Minor bradykinesia, mild tremor	Artane
7	71	16	II	Moderate bradykinesia, mild tremor, moderate rigidity	Sinemet

Table 2. Mean number of sign changes for PD patients, elderly and young subjects

	Target force			
	15%	30%	45%	60%
PD	6.1 (3.3)[a]	6.6 (4.0)	6.6 (2.5)	7.7 (4.2)
Elderly	3.8 (1.1)	3.3 (0.7)	3.1 (0.5)	3.4 (0.7)
Young	3.2 (1.0)	3.2 (0.9)	3.3 (1.1)	3.3 (1.1)

[a] Between-subject standard deviations

Table 3. Mean and between-subject standard deviation (ms) of pre-motor and motor reaction time for the 15% and 30% target force levels

Target force						
	15%			30%		
	PMT	MT	RT	PMT	MT	RT
PD	493 (194)[a]	71 (19)	564 (197)	405 (192)	66 (13)	471 (194)
Elderly	268 (61)	82 (31)	350 (67)	251 (38)	65 (17)	316 (49)
Young	244 (56)	61 (37)	305 (57)	216 (29)	60 (20)	276 (28)

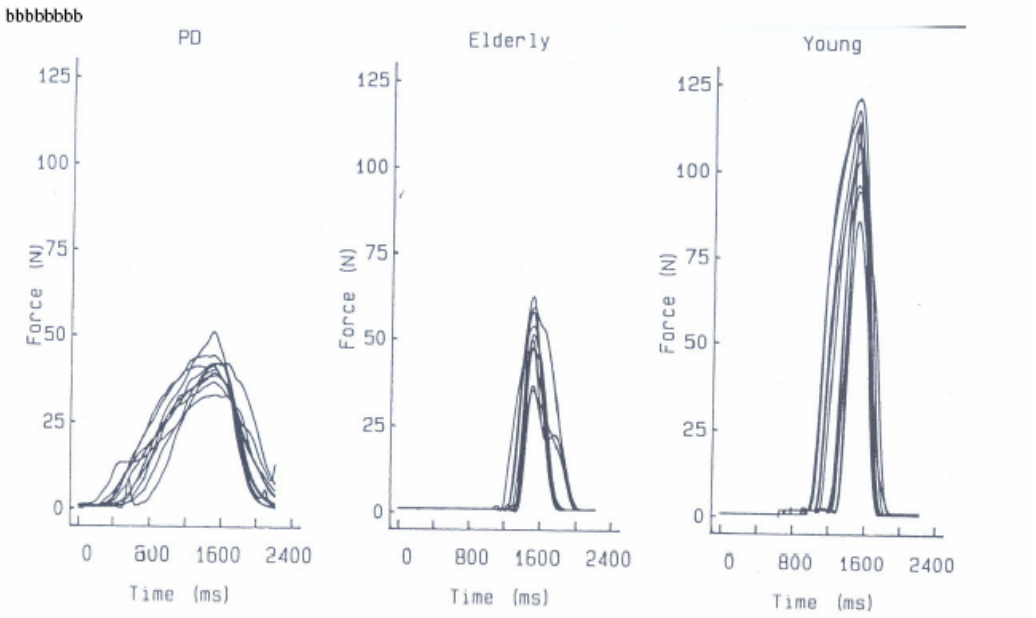

Fig. 1. Representative trials (45% of subject's maximum) for PD Patient 1, an elderly and a young subject

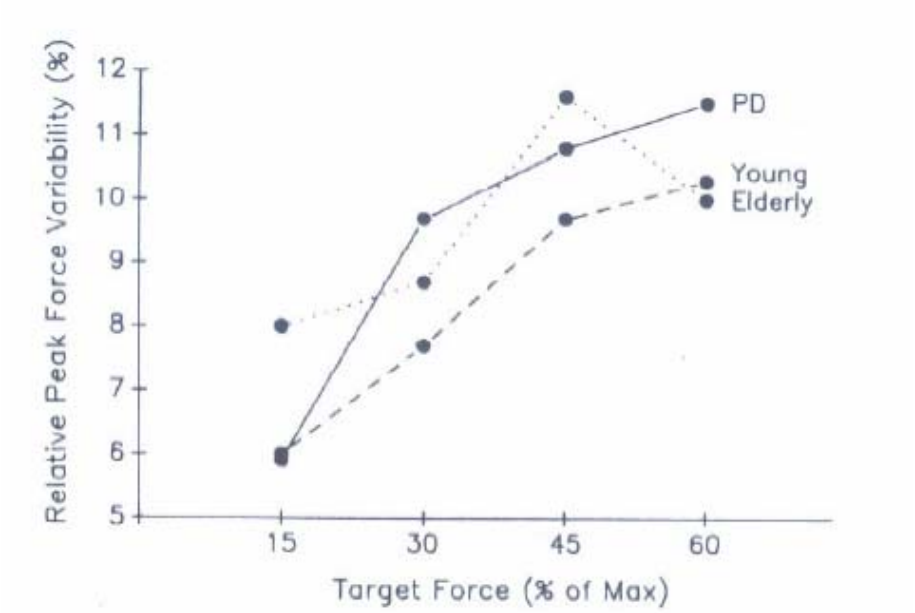

Fig. 2. Relative peak force variability for each group and target

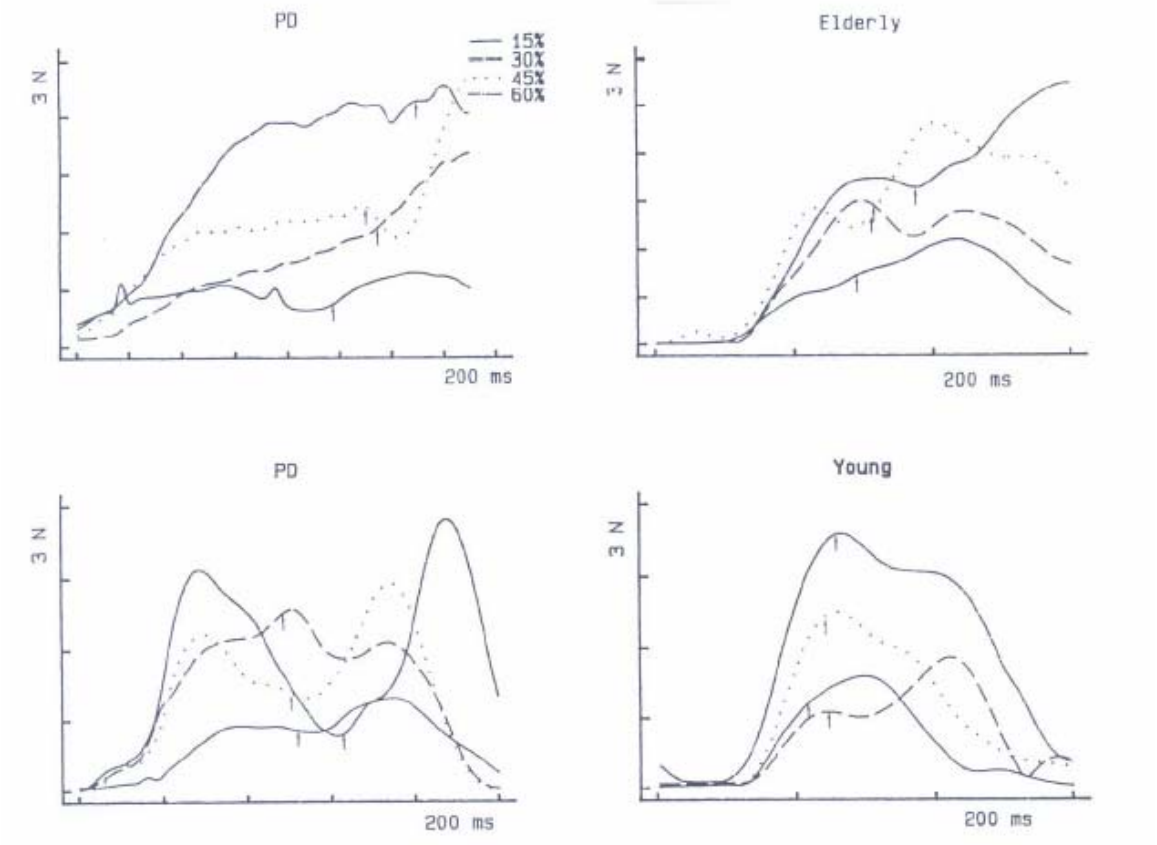

Fig. 3. Representative point-to-point force variability curves for PD Patient 1 (top), PD Patient 6 (bottom), an elderly, and a young subject. The force-time traces were first synchronized at onset and point-to-point variability was then computed for each force level. The arrows in the figure indicate the temporal location of the mean peak force.