Combined measures of movement and force variability distinguish Parkinson's disease from essential tremor

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Abstract

Objective: To examine whether behavioral and electrophysiological measures of motor performance accurately differentiate Parkinson's disease (PD) and essential tremor (ET).

Methods: Twenty-four patients (12 PD; 12 ET) performed isometric force, ballistic movements, and tremor tasks. Receiver operating characteristic (ROC) analyses were conducted on all dependent measures that were significantly different between the two patient groups.

Results: Patients with PD were more impaired on measures of movement deceleration than ET. Patients with ET were more impaired on measures of force variability than PD. ROC analyses revealed that sensitivity and specificity were excellent when combining measures during the isometric force task (torque rise time and force variability; 92% sensitivity and 92% specificity; AUC = 0.97). When combining measures across the force and movement tasks, the ROC analysis revealed improved sensitivity and specificity (force variability and peak deceleration; 92% sensitivity and 100% specificity; AUC = 0.99).

Conclusions: Combining measures of force variability and movement deceleration accurately differentiate patients with PD from those with ET with high sensitivity and specificity.

Significance: If validated in a larger sample, these measures can serve as markers to confirm the diagnosis of PD or ET and thus, enhance decision making for appropriate treatments for patients with these respective diseases.

Introduction

Parkinson's disease (PD) and Essential tremor (ET) are among the most common movement disorders, yet misdiagnoses still occur because both groups can present with action tremor and slowness (Shahed and Jankovic, 2007). There are very few objective diagnostic tests for PD or ET. Dopamine tracer imaging shows substantial promise in differentiating PD from ET (Breit et al., 2006; Doepp et al., 2008; Isaias et al., 2010; Lee et al., 1999; Marshall and Grosset, 2003). However, the costly and sometimes invasive procedures can make it difficult and impractical to test all individuals. A potential solution to this would be differentiating PD from ET patients through objective behavioral and electrophysiological methods. This approach has been used to identify differences in movement speed and variability between ET and healthy individuals (Deuschl et al., 2000; Köster et al., 2002; Schwartz et al., 1999; Trillenberg et al., 2006) and between PD and healthy individuals (Pfann et al., 2001; Vaillancourt et al., 2004). Several studies have attempted to identify kinematic differences between PD and ET patients, but no differences have been observed (Duval et al., 2006; Montgomery et al., 2000). Identifying measures that differentiate PD from ET is highly desirable because the prognosis and early treatment options are different for each movement disorder.

One of the most characteristic features of PD is slowness of movement—bradykinesia. Bradykinesia can occur during the acceleration and/or deceleration phases of a movement. Bradykinesia is commonly linked with deficits in the basal ganglia (Berardelli et al., 2001; Prodoehl et al., 2010). Physiological studies of bradykinesia demonstrate that patients often exhibit abnormal muscle activation patterns that directly affect movement speed (Hallett and Khoshbin, 1980). Abnormal changes in the amplitude and/or duration of the agonist and antagonist bursts occur in both PD and ET (Berardelli et al., 1996; Pfann et al., 2001). Contrary

to the basal ganglia deficits typically associated with PD, ET is commonly linked with cerebellar abnormalities (Deuschl and Elble, 2009; Louis and Vonsattel, 2008). Enhanced variability in movements is commonly seen in cerebellar diseases (Hallett et al., 1991) and ET (Farkas et al., 2006). It is also the case that PD can be associated with increased movement variability (Sheridan and Flowers, 1990), although it is unclear if the variability is similar to that observed in ET.

The main objective of this study was to identify the parameters from isometric, movement, and tremor tasks that dissociate patients with PD from ET with high sensitivity and specificity. The hypothesis was that patients with PD would be more impaired on measures of speed or rate of force production (bradykinesia) than patients with ET, whereas patients with ET would be more impaired on measures of force variability than patients with PD. The study also determined if combining measures from movement and force variability would reliably and objectively distinguish PD from ET with high sensitivity and specificity.

Methods

Subjects

A total of 24 participants (12 PD and 12 ET patients) were recruited for this study (Table 1). Eligibility for inclusion in this study was restricted to patients who had a confirmed diagnosis of strictly ET or PD according to movement disorders neurologists. PD diagnosis was consistent with the guidelines set forth in the United Kingdom PD Society Brain Bank criteria (Hughes et al., 2001). ET diagnosis was consistent with the guidelines set forth in the Consensus Statement of the Movement Disorder Society on Tremor (Deuschl et al., 1998). From subsections of the Unified Parkinson's Disease Rating Scale (UPDRS) for PD patients and the Fahn, Talosa, Marin Tremor Rating Scale for ET patients, rest tremor in the PD patients was significantly higher than ET patients (PD mean = 2.8; ET mean = 0.1; t= -3.99; $p < 0.001$) (Table 2). Postural and action tremor were not different between groups (postural: PD mean = 2.5; ET mean = 3.4; t= 1.36; p= 0.19; action: PD mean = 2.5; ET mean = 3.1; t= 0.87; p= 0.40). The most clinically affected hand was tested for all patients. All patients in the PD group were tested off medications following overnight withdrawal. Of the 12 ET patients, nine were taking medications and were tested on their medications. As shown in the results section, the receiver operator characteristics analysis works well for those patients taking medication and for those patients taking no medication. All participants provided full written informed consent prior to participating in the study.

Behavioral Tasks and Data Acquisition

Ballistic movements

The manipulandum bar rotated in the horizontal plane (Vaillancourt et al., 2004). The seated subject abducted the shoulder 90° and rested the forearm on the bar. The subjects viewed

a computer monitor that displayed a cursor, positioned along the horizontal axis. A marker on the screen represented the initial position, and another marker, 6° wide, was centered at the 72° distance. All subjects were asked to perform ballistic, single degree of freedom elbow flexion movements. Figure 1 represents one trial of the movement task. An auditory beep signaled the subject to begin each movement. Subjects were given 10 practice movements prior to recording 30 experimental trials. Subjects were instructed to move as fast as possible to the target. Surface electromyography (EMG) in the biceps and triceps (lateral head) muscles and kinematic parameters were measured. EMG signals were amplified (gain = 1000) and band-pass filtered between 20 and 450 Hz (Delsys Inc., Boston, MA). All signals in all tasks were sampled at 1000 Hz using a 12-bit A/D converter.

Isometric force

Subjects produced isometric elbow flexion force set to 50% of their maximal voluntary contraction (MVC) (Robichaud et al., 2005). Subjects were seated with their arm placed on the same manipulandum that was used in the ballistic movement task, but the metal bar was locked in place with the elbow flexed 90°. Prior to force control experiments, maximum torque was determined as the peak torque achieved from three 6s trials. During the force control experiment, torque was displayed on a computer screen. A second marker on the screen represented the 50% MVC target. An auditory beep alerted the subject to begin the trial by moving the torque marker as fast as possible to the target. Figure 2 represents one trial of the isometric force task. Subjects were instructed to maintain torque as accurately and steadily as possible at the target and to relax their muscles after they hear a final beep. Ten trials were collected for each subject.

Tremor

Subjects were positioned into a comfortable chair. The subject's limb was positioned on the supportive surface so that the elbow joint was flexed to about 90°, the shoulder joint was slightly abducted, and the forearm was pronated (Sturman et al., 2004). A calibrated Coulbourn type V 94-41 accelerometer was taped 2cm to the middle of the third metacarpal point. Acceleration was amplified with an excitation voltage of ±5V. Surface EMG was also placed on the wrist extensor digitorum muscles.

We examined resting and postural tremor (Sturman et al., 2004). During resting tremor, subjects relaxed the forearm and let their wrist dangle unsupported over the edge of the supportive surface for 30s. During postural tremor, subjects maintained their wrist and hand in a neutral, extended position. Subjects were asked to count backwards from 100 by 4,6,7, or 8 during both resting and postural conditions. Cognitive secondary tasks have been shown to enhance resting tremor in PD (Deuschl et al., 1998; Marsden and Owen, 1967). Three trials were performed for each condition.

Data Processing and Analysis

Ballistic movements

The mechanical channels were digitally low-pass filtered with a dual pass second-order Butterworth filter with 20 Hz cutoff frequency. The EMG signals were digitally full-wave rectified and then low-pass filtered with a dual pass second-order Butterworth filter with 50 Hz cutoff frequency. A custom written algorithm (MatLab) was run to mark movement onset and offset, EMG onset and offset, and time to peak kinematic variables(Vaillancourt et al., 2004). Based on the marked kinematic and EMG signals, the following dependent measures were calculated (Figure 1): peak velocity, peak acceleration, peak deceleration, agonist duration, Qag, Qant1, Qant2, antagonist centroid time, and co-contraction from the marked movement onset to

peak velocity (Cocontraction1) and from peak velocity to end of movement (Cocontraction2). Refer to Vaillancourt et al. (2004) for a detailed description of each dependent measure.

Isometric force

A custom written algorithm (Matlab) was run on the data to identify torque onset and offset during rising and falling phases of the torque signal (Robichaud et al., 2005). The following measures were calculated: 1) torque rise time, the duration of time between the onset and offset of the rising phase of the torque signal (dashed lines 1 and 2 in Figure 2), 2) torque decline time, the duration of the time between the onset and offset of the falling phase of the torque signal (dashed lines 5 and 6 in Figure 2), 3-4) variability of the torque signal, the standard deviation (SD) and coefficient of variation (CV) during the steady state contraction (dashed lines 3 and 4 in Figure 2), and 5) power spectral analysis of the torque signal. To calculate torque rise and decline times, torque onset and offset times during the rise and declining phases of the torque signal was determined (Robichaud et al., 2005).

The torque spectral analysis during 4 seconds of steady state isometric contraction (dashed lines 3 and 4 in Figure 2) was calculated using Fourier analysis in Matlab. Power of the torque signal was divided into four frequency bins: 0-2, 2-4, 4-8, and 8-12 Hz. These bins were selected to focus on the visuomotor control processes encompassing the 0-2 Hz and 2-4 Hz bins, and tremor processes encompassing the 4-8 Hz and 8-12 Hz bins (Elble and Koller, 1990; Vaillancourt and Newell, 2003).

Tremor

Before data analysis, the EMG signals were digitally rectified, and both the EMG and acceleration data were downsampled by a factor of 5 to 200Hz (Sturman et al., 2004). The acceleration and EMG data were digitally filtered using a 4^{th} order Butterworth filter with a high-

pass cutoff frequency of 2 Hz and low-pass cutoff frequency of 60 Hz for the EMG signals and 30 Hz for the acceleration signals. All data analyses were performed on the entire 30s data segment. There were 4 dependent measures determined for the tremor conditions. The dependent variables were modal frequency, amplitude, magnitude of tremor-EMG coherence, and approximate entropy (ApEn).

The frequency, amplitude, coherence, and regularity of tremor were quantified (Sturman et al., 2004). The modal frequency of tremor was determined using autospectral analysis of the acceleration signal. The amplitude of tremor was calculated by the root-mean-square (RMS) tremor displacement from the modal frequency of tremor (Stiles, 1976). The regularity of tremor was calculated using approximate entropy (ApEn), a measure of the time-dependent structure of the signal (Pincus, 1991). An ApEn value of 0 represents a completely predictable signal, whereas an ApEn value of approximately 2 represents a completely random, independent and unpredictable signal. The coherence between the acceleration and EMG signal estimates the degree of motor unit entrainment affecting the acceleration signal (Halliday et al., 1999). Peak coherence in the 1 to 8 Hz bins between the acceleration and EMG signals was calculated and a 95% CI was determined (Vaillancourt et al., 2003). This frequency range was chosen based on previous literature demonstrating that most of the power related to abnormal tremor occurred at low frequencies (Elble and Koller, 1990).

Statistical analysis

The dependent measures in the isometric, movement, and tremor tasks were analyzed using Student's t-test for independent samples, comparing the two patient groups (PD and ET). Since the main objective of this study was to identify parameters to distinguish PD from ET, each t-test was interpreted as statistically significant with $p < 0.002$ after Bonferroni correction

(0.05/23 = 0.002). This correction is very conservative and designed to protect against including parameters in differentiating the groups that may be statistically significant by chance since we performed 23 analyses. The torque power signals were compared using a mixed-model repeated measures analysis of variance (ANOVA) design; a between-subjects factor for group and a within-subject factor for frequency (0-2 Hz, 2-4 Hz, 4-8 Hz, and 8-12 Hz bins). Post-hoc t-tests were run within each frequency to examine the interaction between group and frequency. These analyses were interpreted as significant with $p < 0.05$.

Since one of the main goals of this study was to discriminate PD from ET, receiver operating characteristic (ROC) analysis was subsequently run on all dependent measures determined to be significantly different between the two groups. The area under the curve (AUC), threshold values, sensitivity and specificity values were determined. Threshold values provided a cut-off value that could differentiate between the two groups at the highest sensitivity and specificity. Dependent measures were also used to form combinations of two measures and a second ROC analysis was run on the combined scores to identify combinations with the best discriminating power.

Results

Group differences in movement, variability, and tremor

All group statistics are provided in Table 3. ET patients showed significantly higher peak deceleration profiles than PD (Figure 3A). Ten other measures also reached statistical significance when the Bonferroni correction was not applied, and these measures are identified with a single asterisk in Table 3A. We interpret these results as behaviorally significant if they are in agreement with previous studies in the literature, but we did not include them in the ROC analysis. For example, patients with ET moved faster than patients with PD (Figure 3B). Longer agonist durations were observed in the ET patients (Figure 3C). The ET patients produced more antagonist activity (Qant1 and Qant2) throughout the entire movement when compared to the PD group. Even though the ET group showed consistently less agonist activity (Qag), the difference was not significant. There were no differences found in the antagonist centroid time (time to the bulk of antagonist activity). Thus, while several dependent measures related to movement speed and agonist and antagonist activity would be considered different at a less conservative alpha level, peak deceleration was the only statistically significant movement variable at the conservative Bonferroni-adjusted alpha level.

MVC was not significantly different between groups (PD mean = 42.7 Nm; ET mean = 51.3 Nm; t=1.13; p=0.27). Individuals with PD took longer to achieve the target force level than patient with ET (Figure 3D). PD patients, on average, also look longer to shut off their force output than patients with ET but significance was not reached at the Bonferroni-adjusted alpha level. ET patients were more variable in their force production than patients with PD, as shown by the SD and CV during steady state contractions (Figure 4A-4B).

Similar to several group differences in the movement and isometric tasks, significance was not reached for all of the tremor measures after a conservative Bonferroni correction. Several measures did reach statistical significance when the Bonferroni correction was not applied, and these measures are identified with a single asterisk in Table 3B. Again, we did not include these measures in the ROC analysis. For example, the PD group, on average, presented higher EMG-tremor coherence than the ET group in the resting condition (Table 3). The PD group also showed higher mean tremor amplitude than the ET group in the resting condition. There were no differences found between groups in the modal frequency and ApEn values. During postural tremor, there were no differences found between groups in the RMS amplitude, EMG-tremor coherence, or ApEn values.

Spectral Analysis of Force Output Variability

Figure 4C shows total power in each frequency band (0-2 Hz, 2-4 Hz, 4-8 Hz, and 8-12 Hz) for each patient group. The 2-way repeated measure ANOVA resulted in a significant main effect for group [$F(1, 22) = 5.61$; $p < 0.05$], frequency [$F(3, 66) = 7.99$; $p < 0.001$], and group by frequency interaction [$F(3, 66) = 2.77$; $p < 0.05$]. The group by frequency interaction was examined with separate t-tests at each frequency bin. ET patients had greater power at the 0-2 Hz frequency bin [t=2.78, $p < 0.05$]. ET patients had greater power in the 2-4 Hz frequency bin with the p-value approaching significance [t=2.06, $p=0.051$]. The 4-8 Hz [t=1.75, $p =0.094$], and 8-12Hz [t=1.13, $p =0.271$] frequency bins were not significantly different from the PD group.

ROC Analyses

The ROC analysis was performed on the dependent measures that were significantly different at the Bonferroni-adjusted alpha level between groups in Table 3. This analysis demonstrated that all 4 variables had areas under the ROC curve (AUC) greater than 0.90 (Table 4). These 4 variables were within 2 categories, measures of speed and force variability. The single variable with the highest AUC was the SD of the torque signal during steady state contraction (AUC=0.95) (Table 4).

A combined score was computed for all possible two combinations of measures (6 total combinations) based upon a ratio relative to the threshold value determined for each dependent measure by the ROC analysis. Since some parameters are measured in different units, the combined scores were computed by the following approach showing a combined score with two variables:

$$\text{Combined Score} = \frac{\text{Variable 1}}{\text{Threshold value for Variable 1}} + \frac{\text{Variable 2}}{\text{Threshold value for Variable 2}}$$

ROC analysis for combined measures showed that all 6 combinations were sufficient to obtain an AUC of at least 0.95 between the PD and ET groups (Table 5). Figure 5A indicates that within the isometric task alone, combining the CV_steadystate and torque rise time provided an AUC = 0.97 with high sensitivity (0.92) and specificity (0.92). Figure 5B shows the ROC analysis indicating 92% sensitivity and 100% specificity when combining peak deceleration and coefficient of variation of force.

Discussion

This study investigated behavioral and electrophysiological methods to objectively distinguish PD from ET. There were two main findings. First, measures related to bradykinesia such as peak deceleration during a ballistic movement task or torque rise time during the isometric task were slower in patients with PD than ET. Measures of force variability such as the standard deviation or coefficient of variation during steady state force were higher in patients with ET than PD. Second, combining measures of torque rise time and variability (coefficient of variation of steady state force) within an isometric task provided high sensitivity and specificity (92% sensitivity, 92% specificity; AUC = 0.97) for distinguishing PD from ET. Moreover, combining measures from the isometric and movement tasks (coefficient of variation of steady state force and peak deceleration) further improved sensitivity and specificity for distinguishing PD from ET (92% sensitivity, 100% specificity; AUC = 0.99).

Results from this study showed that patients with PD were slower than patients with ET whether studied using an isometric task or a movement task. A possible explanation to why PD patients are slower than ET patients could be due to the fact that the basal ganglia-thalamo-cortical circuit is mostly affected in PD, whereas the cerebellar-thalamo-cortical circuit is mostly affected in ET (Fasano et al., 2010; Louis and Vonsattel, 2008; Wichmann and DeLong, 1996). A proposed deficit in PD is the insufficient recruitment of force during the initiation of movement, which generates a slower pace throughout the rest of the movement in patients with PD (Berardelli et al., 2001). Individuals with ET, as seen in our findings with the shorter torque rise time, did not exhibit as much of a problem with the recruitment of force as PD. Previous studies have shown that ET patients are slower when compared to healthy individuals (Duval et al., 2006; Montgomery et al., 2000), especially towards the end of movements (Deuschl et al.,

2000; Trillenberg et al., 2006). This abnormality towards the end of movements is related to the delayed second agonist burst and asymmetrical acceleration profiles in ET (Britton et al., 1994; Köster et al., 2002). In agreement with previous studies, the ET patients in the current study also exhibited longer first agonist burst durations and greater antagonist burst activity than the PD patients (Köster et al., 2002; Zackowski et al., 2002) at non-corrected alpha levels. Further, reduced peak deceleration in patients with PD was significant at the corrected alpha level, suggesting that PD patients have a greater problem slowing the movement than patients with ET and that this variable is an important measure for distinguishing these two patient groups.

Another finding from this study was that the patients with ET were more variable at producing force than the patients with PD. Enhanced movement variability has been observed in ET during grasping movements (Deuschl et al., 2000), ballistic movements (Britton et al., 1994), and repetitive movements (Farkas et al., 2006). The spectral analysis showed that differences in force variability between the two groups were primarily due to the greater power in the 0-2 Hz bandwidth in the ET patients (Figure 4C). Even though the power in the 4-8 Hz bandwidth was not different between groups, the power in the 4-8 Hz bandwidth did contribute to the overall force variability in both groups. It is possible that since some of the patients with ET were tested on medication, this may have reduced postural tremor in the 4-8 Hz bandwidth. Nonetheless, the greater power in the 0-2 Hz bandwidth has previously been associated with sensorimotor error correction processes (Vaillancourt and Newell, 2003), suggesting this mechanism may be impaired in ET.

Many have argued that the variability observed in patients with ET is primarily due to tremor. However, several studies have not found a significant correlation between tremor severity and movement (Deuschl et al., 2000; Farkas et al., 2006). Consistent with this

observation is the fact that VIM DBS has been shown to reduce tremor in ET during a wrist flexion movement, but had no effect on the delayed antagonist burst (Zackowski et al., 2002). These studies support the idea that movement deficits and tremor may be due to separate mechanisms in ET (Fasano et al., 2010), and the current findings provide further support for this hypothesis.

The current findings that the isometric task was the task that yielded the most discriminating combination of measures suggest the possibility that a single task could be conducted to distinguish PD from ET. This single task approach would be the most time- and cost-effective. However, combined measures of movement and isometric tasks (i.e. measures of peak deceleration and force variability) provided the best discrimination between PD and ET. Developing multivariate approaches that target specific mechanisms in PD and ET may therefore have promising implications for an objective diagnosis in the future. If validated in a larger sample, these measures can provide additional support for the correct diagnosis by general neurologists, since the opportunity to see a movement disorders specialist may not be feasible to many patients. These measures also have the potential to serve as markers that enhance decision making for movement disorder specialists who are determining treatments based on an ET or PD diagnosis.

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Tables

Table 1. Patient characteristics

Patient	Gender	Age	Hand tested	Handedness	Disease duration (yr)	Medication
ET	F	74	L	R	2	none
ET	M	68	R	R	15	propanolol and primidone
ET	M	75	R	R	30	primidone
ET	M	71	R	R	56	clonazepam
ET	F	60	L	L	20	primidone
ET	F	60	R	R	4	propanolol
ET	M	37	L	R	1	none
ET	M	76	R	R	5	propanolol
ET	F	63	L	R	2	primidone
ET	M	67	R	R	2	propanolol
ET	M	57	R	R	1	none
ET	F	72	R	R	5	primidone
PD	F	68	R	R	14	L-dopa, amantidine, selegiline
PD	M	66	L	R	8	L-dopa, selegiline
PD	M	64	L	R	5	L-dopa, rasagiline
PD	M	66	L	R	9	L-dopa, entacapone
PD	F	61	R	R	3	amantadine, ropinirole
PD	F	60	L	R	22	L-dopa, pramipexole
PD	M	50	R	R	8	L-dopa, pramipexole, amantadine
PD	M	66	R	R	10	L-dopa, pramipexole
PD	F	63	L	R	7	pramipexole
PD	M	65	L	R	2	pramipexole
PD	M	57	L	R	3	pramipexole, amantadine
PD	F	66	L	R	2	L-dopa, pramipexole, entacapone

ET = Essential tremor, PD = Parkinson's disease; F = female, M = male; R = right, L= left.

Table 2. Patient tremor rating scale

	Rest Tremor				Action Tremor		Postural Tremor	
Patient	**RUE**	**LUE**	**RLE**	**LLE**	**RUE**	**LUE**	**RUE**	**LUE**
ET	0	0	0	0	1	1	2	2
ET	0	0	0	0	1	1	1	0
ET	0	0	0	0	2	2	2	2
ET	0	0	0	0	3	3	3	3
ET	0	0	0	0	2	2	2	2
ET	0	0	0	0	3	3	3	3
ET	0	0	0	0	1	2	1	2
ET	0	0	0	0	1	1	0	0
ET	0	0	0	0	0	0	2	2
ET	0	0	0	0	1	1	0	0
ET	0	0	0	0	3	3	3	3
ET	0	1	0	0	0	0	2	1

	Rest Tremor				Action/Postural Tremor	
Patient	**RUE**	**LUE**	**RLE**	**LLE**	**RUE**	**LUE**
PD	0	0	0	0	1	1
PD	3	2	1	1	1	0
PD	0	0	0	0	1	1
PD	3	2	0	0	2	1
PD	1	0	0	0	1	1
PD	3	0	0	0	3	1
PD	3	1	1	0	2	1
PD	0	1	0	0	1	1
PD	1	1	2	2	1	1
PD	0	2	0	0	1	3
PD	2	0	0	0	1	2
PD	1	1	0	0	1	1

ET = essential tremor, PD = Parkinson's disease; RUE = right upper extremity; LUE = left upper extremity; RLE = right lower extremity; LLE= left lower extremity. ET patients were examined using the Fahn, Talosa, Martin Tremor Rating Scale. PD patients were examined using the Unified Parkinson's Disease Rating Scale (UPDRS).

Table 3A. Movement and isometric task analyses

	ET mean (SD)	PD mean (SD)	t-value, p-value
Movement Condition			
Peak velocity (deg/s) *	435 (114)	318 (65)	3.06, p < 0.01
Peak acceleraton (deg/s^2) *	4207 (2040)	2499 (843)	2.68, p < 0.05
Peak deceleration (deg/s^2) **	4549 (1975)	2190 (777)	3.85, p < 0.001
Time to peak velocity (s)	0.19 (0.05)	0.22 (0.06)	-1.63, p = 0.12
Agonist duration (s) *	0.23 (0.09)	0.13 (0.04)	3.29, p < 0.01
Antagonist centroid time (s)	0.26 (0.05)	0.28 (0.07)	-1.09, p = 0.29
Qag	0.68 (0.3)	0.6 (0.5)	0.47, p = 0.64
Qant1 *	0.44 (0.2)	0.19 (0.1)	3.59, p < 0.01
Qant2 *	0.42 (0.3)	0.16 (0.1)	3.23, p < 0.01
Cocontraction1 (%) *	46.85 (13)	33.97 (14)	2.28, p < 0.05
Cocontraction2 (%)	57.45 (11)	50.37 (9)	1.70, p = 0.10
Isometric Condition			
Torque rise time (s) **	0.40 (0.22)	0.77 (0.14)	-4.95, p < 0.0001
Torque decline time (s) *	0.61 (0.17)	0.83 (0.29)	-2.22, p < 0.05
SD_steadstate **	1.07 (0.45)	0.43 (0.20)	4.47, p < 0.001
CV_steadstate **	0.04 (0.01)	0.02 (0.01)	4.41, p < 0.001

* indicates a significant result p < 0.05.
** indicates a Bonferroni-corrected significant result p < 0.002.
SD = standard deviation; CV = coefficient of variation

Table 3B. Tremor analysis

	ET mean (SD)	PD mean (SD)	t-value, p-value
Rest condition			
RMS amplitude *	0.09 (0.1)	1.42 (1.9)	-2.42, p < 0.05
Frequency	5.79 (0.7)	5.69 (0.9)	0.33, p = 0.74
EMG-tremor coherence *	0.23 (0.1)	0.54 (0.3)	-3.23, p < 0.01
ApEn	0.52 (0.05)	0.47 (0.09)	1.70, p = 0.10
Postural condition			
RMS amplitude	0.51 (0.4)	0.87 (0.8)	-0.83, p = 0.42
Frequency *	6.36 (0.7)	5.71 (0.8)	2.19, p < 0.05
EMG-tremor coherence	0.49 (0.3)	0.40 (0.2)	0.75, p = 0.46
ApEn	0.56 (0.04)	0.54 (0.04)	1.11, p = 0.28

* indicates a significant result p <0.05.

RMS = root-mean-square ; EMG = electromyogram ; ApEn = approximate entropy

Table 4. ROC analysis on individual variables

Variables	AUC	Threshold Value	Sensitivity	Specificity
SD_steadstate	0.95	0.52	1.00	0.83
CV_steadstate	0.91	0.03	0.92	0.92
Peak deceleration	0.91	2757.90	0.92	0.83
Torque rise time	0.91	0.64	0.92	0.83

Receiver operator characteristics (ROC) analysis was run on all dependent measures that were significantly different after Bonferroni correction between patient groups (Table 3).

Table 5. ROC analysis on combinations of variables

Variables	AUC	Sensitivity	Specificity
CV_steadystate + Peak deceleration	0.99	0.92	1.00
CV_steadystate + Torque rise time	0.97	0.92	0.92
SD_steadystate + Torque rise time	0.97	0.83	1.00
Peak deceleration + SD_steadystate	0.96	0.92	0.92
Peak deceleration + Torque rise time	0.96	0.92	0.92
CV_steadystate + SD_steadystate	0.95	1.00	0.83

AUC = area under the curve.

Figures

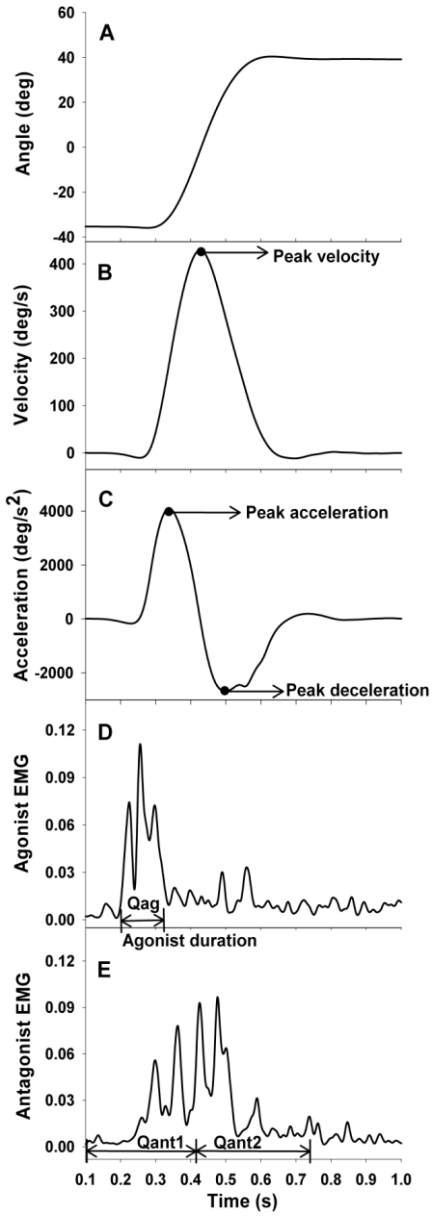

Figure 1. Example of ballistic movement task: Representative example of an individual trial from a ballistic flexion movement. (**A**) elbow position, (**B**) velocity, (**C**) acceleration, and (**D**) rectified agonist and (**E**) antagonist EMG activity are shown. Dependent measures- peak velocity, peak acceleration, peak deceleration, agonist duration, Qag, Qant1, and Qant2 are indicated in the figure.

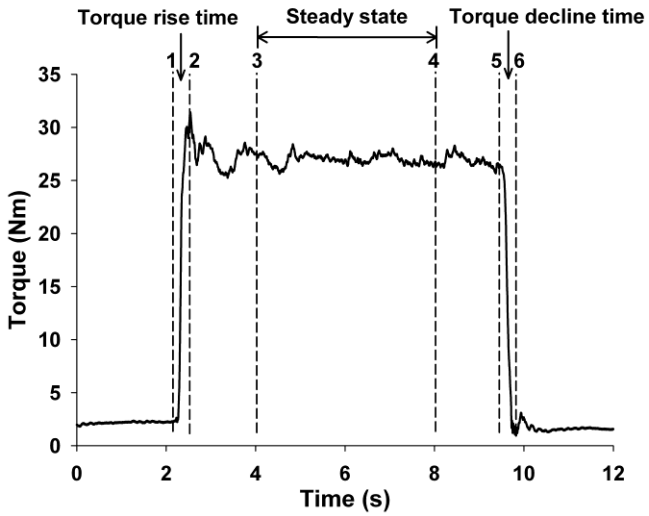

Figure 2. Example of isometric contraction task: Representative example of an isometric contraction task. Torque signal with dependent measures, torque rise time, torque decline time, and steady state period are indicated on the figure with dashed lines.

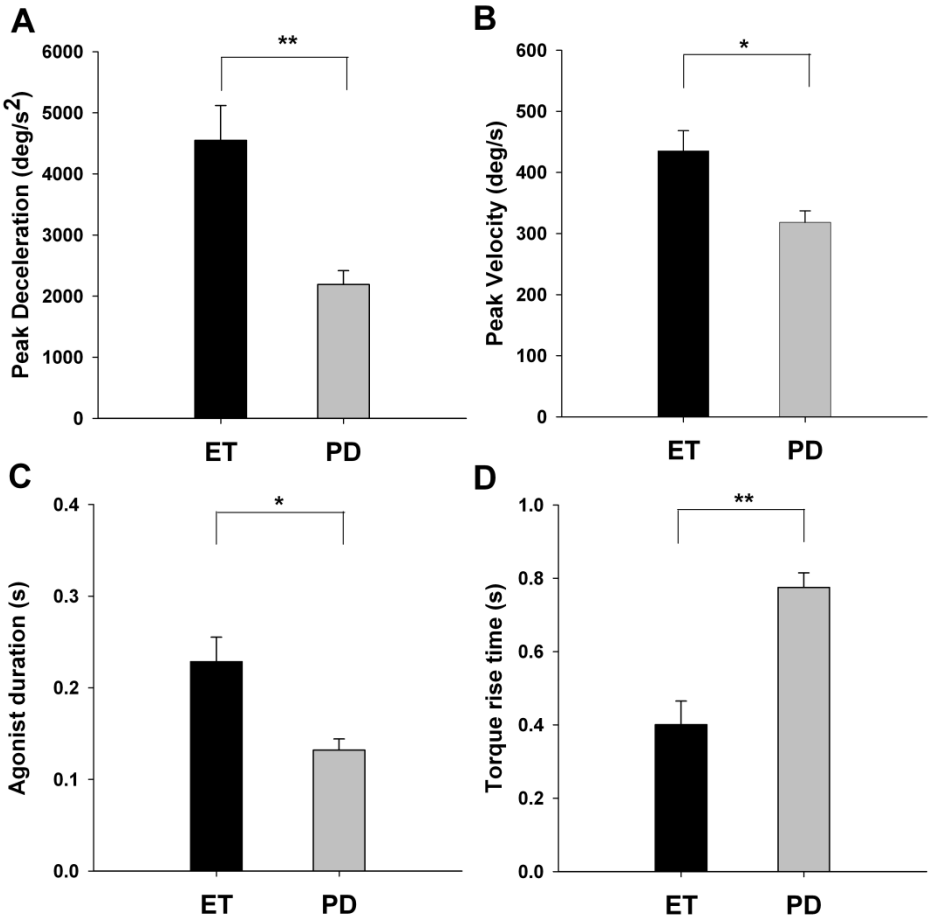

Figure 3. Measures of bradykinesia and muscle activity between groups: (**A**) Peak deceleration, (**B**) peak velocity, and (**C**) agonist duration during ballistic movement task in the ET group (black bars) and PD group (gray bars). (**D**) Torque rise time during isometric contraction task in the ET group (black bars) and PD group (gray bars). Data are the mean and standard error. * indicates a significant result $p < 0.05$. ** indicates a significant Bonferroni-adjusted result $p < 0.002$.

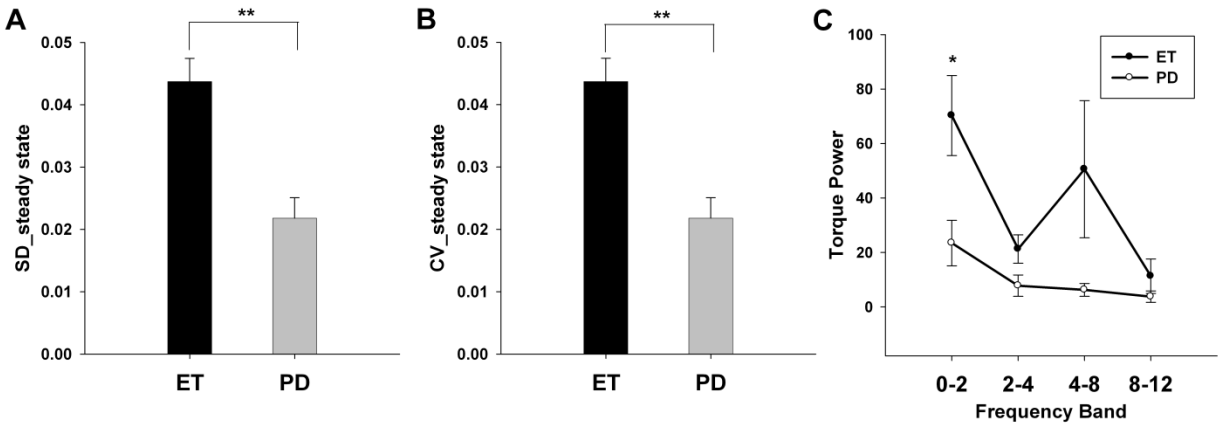

Figure 4. Force variability and torque power between groups: (**A**) Standard deviation and (**B**) coefficient of variation of the torque signal during the steady state period of the isometric contraction task in the ET group (black bars) and PD group (gray bars). (**C**) Total power in each of the frequency bands, 0-2Hz, 2-4Hz, 4-8Hz, and 8-12Hz, during the steady state period of the isometric contraction task in the ET group (filled circles) and PD group (open circles). Data are the mean and standard error. * indicates a significant result $p < 0.05$. ** indicates a significant Bonferroni-adjusted result $p < 0.002$.

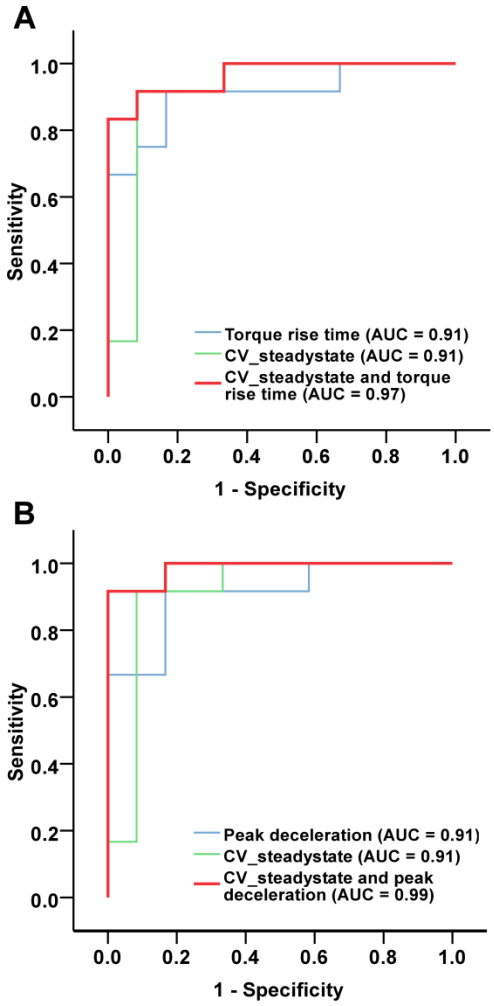

Figure 5. Receiver operator characteristics (ROC) analysis: Results from ROC analysis on the combinations of dependent measures. (**A**) ROC curve for torque rise time, CV_steadystate force, and the combination of these measures. (**B**) ROC curve for peak deceleration, CV_steadystate, and the combination of these measures.