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Regularity of force tremor in Parkinson's disease

David E. Vaillancourt[a,b,*], Andrew B. Slifkin[a,c], Karl M. Newell[a,c]

[a]Department of Kinesiology, The Pennsylvania State University, 146 Rec Hall, University Park, PA, 16802, USA
[b]The Gerontology Center, The Pennsylvania State University, 105 Henderson, University Park, PA, 16802, USA
[c]Department of Biobehavioral Health, The Pennsylvania State University, Health and Human Development East, University Park, PA, 16802, USA

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Abstract

Objectives: The study examines the time-dependent structure of force tremor to investigate two hypotheses: (1), the regularity of tremor can help in discriminating normal aging from that of Parkinson's disease (PD); and (2), there is increased tremor regularity with increases in the severity of PD.

Methods: Eight young (21–29 years), eight elderly (68–80 years), and eight PD (68–80 years) subjects produced constant grip force at 5, 25 and 50% of their maximal voluntary contraction by squeezing two load cells with their index finger and thumb under a vision and no vision condition. Spectral analysis and approximate entropy (ApEn) were used, respectively, to analyze the frequency and time-dependent structure of tremor.

Results: The analyses showed that there were no differences in the amplitude and modal frequency of force tremor between groups. The ApEn was significantly lower in the PD group compared with the controls. For the PD group, the linear relations between the total scores taken from the Unified Parkinson's Disease Rating Scale-motor section and the dependent variables were $r^2 = 0.71$ ($P < 0.01$) for ApEn, $r^2 = 0.20$ ($P > 0.05$) for the modal frequency, and $r^2 = 0.23$ ($P > 0.05$) for the standard deviation. Surrogate analyses revealed that the time-dependent structure of tremor provided additional information beyond that of amplitude and modal frequency analyses.

Conclusions: These findings indicate that tremor analyses should not be limited to just the frequency and amplitude of the oscillation, and that the time-dependent structure of tremor is useful in differentiating tremor in healthy people from those with PD. The hypothesis that more regular tremor in PD is due to a loss of multiple neuronal oscillators contributing to the tremor output is discussed.

Keywords: Force tremor; Parkinson's disease; Regularity; Time series; Unified Parkinson's disease rating scale

1. Introduction

Tremor is defined as an involuntary, approximately rhythmic, and roughly sinusoidal movement that is associated with multiple neural feedback loops at the spinal and supraspinal levels of the nervous system (Elble and Koller, 1990; Hallett, 1999; McAuley and Marsden, 2000). The presence of tremor in Parkinson's disease (PD) is a fundamental feature used in the determination of disease onset and progression (Fahn and Elton, 1987; Weiner and Lang, 1989). The characterization for tremor in PD includes an increase in resting limb motion and a reduction in resting tremor frequency at 4–6 Hz (Deuschl et al., 1998; Findley et al., 1981; Gelb et al., 1999). Reports also suggest that patients with PD may have a postural tremor with increased amplitude between 5 and 12 Hz (Brown et al., 1997; Lance et al., 1963) and recent studies have shown an action (force) tremor between 5 and 12 Hz (Forssberg et al., 2000). However, there are limited studies that have directly examined force tremor in PD.

The traditional methods for examining tremor are based on the assessment of its modal frequency and the amplitude (Homberg et al., 1987). However, in many cases, there are no differences in the frequency and amplitude characteristics of the tremor in individuals with PD and healthy aging people. Several reports have estimated that 20–35% of PD patients show no clinical signs of tremor (Elble and Koller, 1990; Marsden, 1990). Thus, analysis of the frequency and amplitude characteristics of tremor may not be sufficient to fully characterize individuals with PD.

There may be a change in the time-dependent structure of tremor even when there is no change in the modal frequency and amplitude of tremor (Edwards and Beuter, 2000;

* Corresponding author. School of Kinesiology (M/C 194), University of Illinois at Chicago, 901 West Roosevelt Road, Chicago, IL 60608, USA. Tel.: +1-312-355-1712; fax: +1-312-355-2305.
E-mail address: court1@uic.edu (D.E. Vaillancourt).

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Timmer et al., 1993). For example, simulations of the time and frequency structure of a time series indicate that the time-dependent structure of a signal can change independently of its amplitude and modal frequency (Theiler et al., 1992). Even though the modal frequency can remain unaffected, there is an alteration in the time-dependent structure of the signal and this is referred to as a change in the regularity of physiological output (Lipsitz and Goldberger, 1992; Pincus and Goldberger, 1994). Regularity can be quantified by approximate entropy (ApEn) in the time domain (Pincus, 1991). Vaillancourt and Newell (2000b) examined the time-dependent structure of resting and postural tremors in PD and showed that despite no difference in the frequency and amplitude of tremor, subjects with PD had an increase in the regularity of tremor compared with matched controls. These results suggest that analysis of the time-dependent structure of tremor may enhance the characterization of PD.

The current report examines grip force in young, elderly, and subjects with PD in order to examine the hypothesis that analyses of the regularity of tremor can help in discriminating normal aging from PD. Regularity was quantified by ApEn analysis of the individual digit and total force oscillations. In order to examine the generality of the changes in regularity with PD, force tremor was examined under a vision and no vision condition in each of 3 force requirements: 5, 25 and 50% maximum voluntary contraction (MVC) force levels. To assess the relation between changes in the regularity of tremor with changes in the severity of PD, we also examine the relation between ApEn with scores from the Unified Parkinson's Disease Rating Scale (UPDRS). Since previous work indicates a reduction in ApEn with disease, it was expected that there would be positive correlations between the regularity of tremor and the severity of PD.

2. Materials and methods

2.1. Subjects

Eight individuals diagnosed with PD (mean age, 72 years; range, 68–80 years; $SD = 4$ years), 8 healthy elderly controls (mean age, 72 years; range, 68–80 years; $SD = 5$ years), and 8 young individuals (mean age, 25 years; range, 21–29 years; $SD = 2$ years) participated in the study. In addition to age, the elderly control subjects were additionally matched for gender, handedness (4 left and 4 right-handed), height (control: mean = 1.74 m, range = 1.52–1.82 m; Parkinson's: mean = 1.74 m, range = 1.51–1.87 m) and weight (control: mean = 80.1 kg, range = 66–95 kg; Parkinson's: mean = 71.9 kg, range = 61–86 kg) to a respective PD subject. The young control subjects were also matched for handedness to the elderly and subjects with PD. All subjects gave informed consent to all experimental procedures, which was approved by the local Institutional Review Board.

Table 1 shows a summary of the characteristics of the young, elderly and those with PD. The healthy control subjects had no clinical evidence of tremor. All patients with PD remained on medication during testing. Two raters using the UPDRS-motor section evaluated the level of disease in each patient. The relation between the evaluations of the two raters was significant for both the Spearman (0.95; $P < 0.01$) and Kendall Tau statistics (0.85; $P < 0.01$). Table 1 includes the UPDRS-motor section scores, the Hoehn and Yahr scores, and each subject's rating from questions 20 and 21 from the UPDRS (Fahn and Elton, 1987). Questions 20 and 21 are the ratings of the resting and postural tremor, respectively, from the most affected side of each patient with PD.

2.2. Apparatus

The subjects with PD used their most affected limb to produce the index finger–thumb grip. Since control subjects were matched for handedness to each subject with PD, the controls used the same hand as the patient they were matched with. Subjects were seated in a chair with their forearm resting on a table and hand pronated in a neutral position with the third, fourth and fifth phalanges flexed comfortably. Two load cells (Entran ELFS-B3, NJ) with a diameter equal to 1.27 cm were used to measure compressive force (N) and

Table 1
Subject details

Subject	Young		Elderly		Parkinson's					
	Sex	Age	Sex	Age	Sex	Age	Hoehn and Yahr scale	UPDRS total	RT[a]	AT/PT[b]
1	F	22	F	72	F	71	II	8	0	1
2	M	25	M	66	M	68	III	33	0	2
3	M	21	M	68	M	68	III	23	0	1
4	M	29	M	70	M	68	II	24	1	1
5	M	27	M	74	M	73	II	25	0	2
6	M	26	M	76	M	75	III	31	0	3
7	F	25	F	75	F	74	II	13	0	1
8	M	25	M	80	M	80	III	35	1	2

[a] The RT score is the total for each patient from the most affected side on question 20 of the UPDRS.
[b] The AT/PT score is the total for each patient from the most affected side on question 21 of the UPDRS.

were attached to the grip apparatus located 36 cm in front of their body midline (Vaillancourt et al., 2001).

The force from each load cell was amplified through separate Coulborn Type A (Strain Gage Bridge) S72-25 amplifiers, with an excitation voltage of 10 V and an amplifier gain of 100. A 16 bit A/D converter sampled each force channel at 100 Hz. The smallest increment of change the A/D board could detect was 0.0016 N. Custom written computer software was used to control data acquisition and storage during the experiment. At each sampling interval, the two samples from each load cell were summed and displayed on the video monitor (located 48.6 cm in front of the subject's eyes and 100 cm from the ground). The 17 inch video monitor (CTX International, CA) had 1200 pixels horizontally and 1000 pixels vertically. On the video monitor, the subjects viewed a red, horizontal target line that spanned the monitor's width and also saw a yellow trajectory line that represented the raw, total force output from the load cells.

2.3. Procedures

In the initial portion of the experiment, the subject's MVC was estimated (Slifkin et al., 2000). Subsequently, subjects performed trials where they were instructed to match the yellow trajectory line to the red horizontal target line. They were instructed to maximize their performance during each trial. During the experiment, subjects produced force under a no vision, and vision condition, and at each of 3 force levels: 5, 25 and 50% of the subject's MVC. With vision, subjects received continuous visual feedback for the 20 s trial. The no vision condition consisted of visual feedback presentation over the initial 8 s; after this time, the yellow trajectory line disappeared from the video monitor. Subjects were instructed to maintain their force level at the red target line despite receiving no visual feedback about their performance. We had subjects perform under alternating vision conditions (V, NV) for 10 consecutive trials at each force level. The order of the force levels was randomized across all subjects.

2.4. Data analysis

The data were processed according to the following two procedures: (1), the last 8 s of each trial were analyzed to ensure that subjects had reached a constant level of force; and (2), an 18th order bandpass, Butterworth filter focused the analysis at frequencies between 3 and 30 Hz. Previous work indicates that those oscillations associated with sensorimotor processes are below 4 Hz and processes related to physiological and pathological tremor are expressed at higher frequencies above 4 Hz (Freund and Hefter, 1993; McAuley et al., 1997; Slifkin et al., 2000; Vaillancourt and Newell, 2000a; Vaillancourt et al., 2001).

To assess differences in the amount of force tremors, the within-trial standard deviation of the force time series was calculated, and for frequency analysis, Fourier analysis was applied (Jenkins and Watts, 1968). Auto-spectral analysis was performed using Welch's averaged periodogram method. The window size (256) was also selected to approximate a 0.3906 Hz frequency bin for each power spectral estimate. Within the power spectrum, the modal frequency at the peak power was determined. The modal frequency was taken above 4 Hz, which is consistent with previous research on force tremor oscillations (Elble and Randall, 1976; Forssberg et al., 2000).

In order to examine the time-dependent structure, the ApEn was calculated on the force signal (Pincus, 1991; Pincus and Goldberger, 1994; see appendix of Slifkin and Newell, 1999). ApEn returns a value between 0 and 2 and it reflects the predictability of future values in a time series based on previous values. For example, a sine wave has accurate short- and long-term predictability and this corresponds to an ApEn value near 0. If varying amplitudes of white Gaussian noise are added to a sine wave, then the ApEn value would increase. This increases the uncertainty of making future time series predictions when random elements are added. For a completely random signal (viz. white Gaussian noise), each future value in the time series is independent and not predictable from previous values, and the ApEn value tends to be toward 2. The same algorithm and parameter settings ($m = 2$; $r = 0.2$ *standard deviation of the signal) were used here and in our previous work (Slifkin and Newell, 1999; Slifkin et al., 2000; Vaillancourt and Newell, 2000b).

Surrogate data analysis was also used to determine if the time-dependent structure changes independently of the frequency and amplitude of the time series. The surrogate data produced by the algorithm maintains the same amplitude and frequency distribution as the original signal, but loses its temporal order. Thus, if there were no differences in the time-dependent structure of PD force tremors from surrogate data, then one would expect no differences in the comparison. In contrast, if there is a difference between the ApEn values from the original time series and the surrogate data, then this would highlight the importance of examining the time-dependent structure of tremor in PD. The phase-randomized surrogate data technique (Theiler et al., 1992; Schreiber and Schmitz, 2000) was calculated on the force output time series according to the following method: (1), the Fourier transform of the original data was determined; (2), the phases of the Fourier transform were randomly shuffled; and (3), the surrogate data were generated by taking the inverse Fourier transform of that data.

2.5. Statistical analysis

The dependent variables described in the preceding sections were placed in a 3-way analysis of variance (ANOVA) with a between-subjects factor for subject group (Parkinson's/elderly/young) and repeated measures on vision (vision/no vision) and force level (5, 25 and 50% MVC). Each data point in the ANOVA was the average of 5 trials in each unique condition. When relevant, Tukey's

honestly significant difference (HSD) test was used to determine the specific effects contributing to the general ANOVA. Pearson correlation coefficients were computed for the scores on the UPDRS-motor section and the dependent variables: ApEn, standard deviation, and modal frequency. All statistics were evaluated as significant when there was less than a 1% chance of making a type I error ($P < 0.01$). All statistical analyses were completed using Statistica statistical package (StatSoft, Inc., OK).

3. Results

3.1. Amplitude of force tremor

Fig. 1 illustrates a force tremor time series from the index finger, thumb, and total force output recordings from a young, elderly, mild PD (stage II Hoehn and Yahr), and moderate PD subject (stage III Hoehn and Yahr). The time series of the first 3 panels from the young, elderly and mild PD subjects appear to be relatively similar in amplitude. In fact, the standard deviation of each force time series was very similar across all force recordings (range: index, 0.03–0.04 N; thumb, 0.03–.004 N; total, 0.03–0.06 N). However, the ApEn differed considerably. The mild PD subject had a 10% reduction in ApEn and the moderate PD subject had a 35% reduction in ApEn when compared with the elderly control subject.

The standard deviation of the force time series was used as an index of the amplitude of force tremor. Table 2 shows that the PD group had a slightly higher standard deviation at each force level, but differences in the group averages

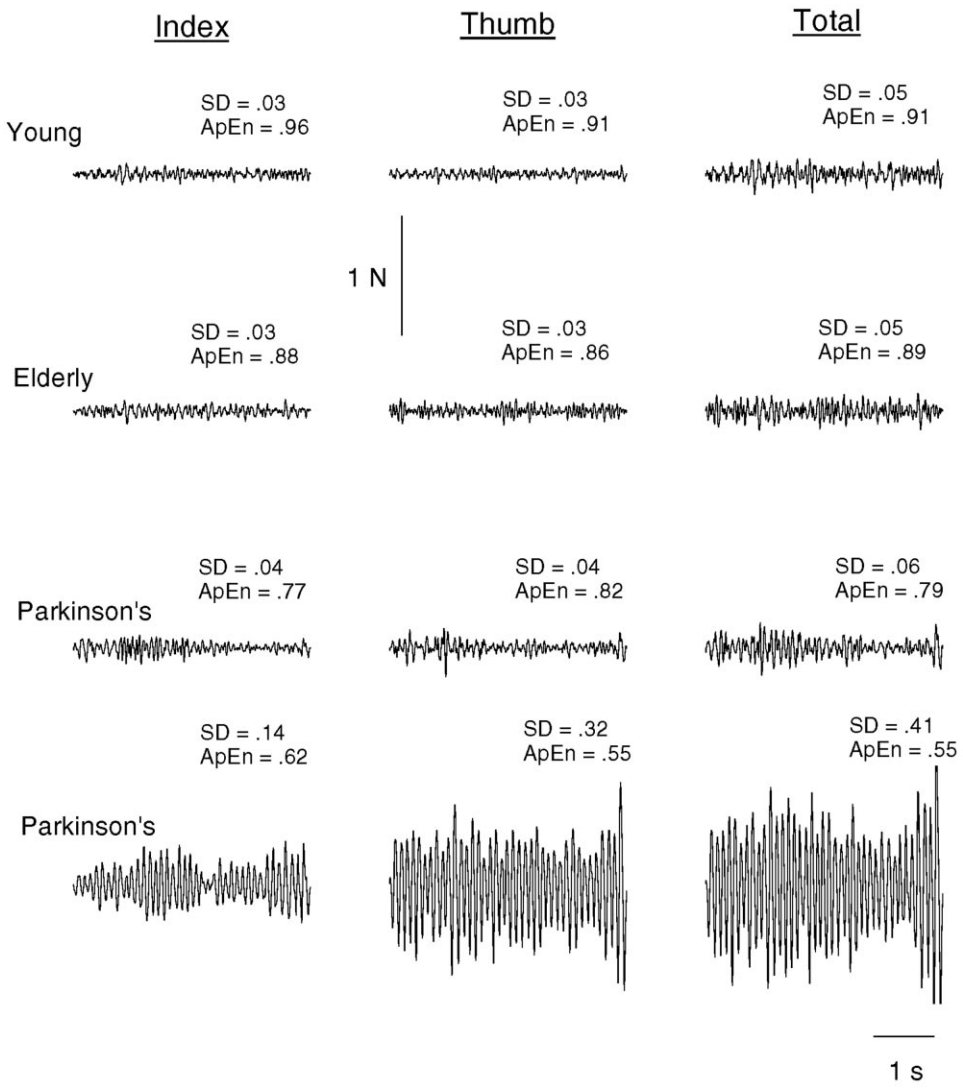

Fig. 1. Force tremor with vision at 25% MVC from a young, matched elderly, mild PD (stage II Hoehn and Yahr), and a moderate PD subject (stage III Hoehn and Yahr). The first column is the index finger, the second column is the thumb, and the third column is the total force output from index finger and thumb. The standard deviation and ApEn values are shown for each signal for the subjects. There was no difference in the force tremor amplitude between the first 3 subjects, but the moderate PD subject had a high amplitude force tremor. ApEn was lower for both PD subjects compared with the controls.

Table 2
Amplitude and modal frequency analysis of total force as a function of group

	Young			Elderly			Parkinson's		
	5%	25%	50%	5%	25%	50%	5%	25%	50%
Standard deviation (*N*)	0.03	0.09	0.25	0.03	0.10	0.22	0.08	0.15	0.36
Modal frequency (Hz)	7.48	7.43	7.76	7.49	7.74	7.65	7.34	7.16	7.27

(Parkinson's, 0.20 N; elderly, 0.11 N; young, 0.12) did not approach significance ($P = 0.58$). Similarly, the index finger ($P = 0.56$) and thumb standard deviations ($P = 0.48$) failed to show significant differences between the groups. As expected, with increases in force level, there was a 500% increase in the standard deviation from the 5 to the 50% MVC condition for the index, thumb and total force signals (*P* values were <0.01; Sutton and Sykes, 1967). There were no group interactions with force and vision (P values were >0.05). Thus, the amplitude of force tremor between the two subject groups was similar and changed in the same way across force levels.

3.2. Modal frequency of tremor

The power spectrum from the same subjects in Fig. 1 is depicted in Fig. 2. In the young, elderly and mild PD subjects (stage II Hoehn and Yahr) there was a low amplitude, broad-banded spectrum from 6 to 12 Hz. There was no predominant peak in the spectrum that would differentiate between the elderly control and the mild PD subject. In contrast, the moderate PD subject (stage III Hoehn and Yahr) has a strong 5 Hz force tremor that dominated the spectrum. Two of the subjects with PD showed force tremor similar to that shown in Fig. 2 and the other 6 subjects had a more broad-banded force tremor from 6 to 12 Hz. On visual inspection, it was difficult to differentiate the force tremor spectrum in these 6 subjects with PD from either the healthy young or elderly control subjects.

A 3-way ANOVA was calculated to determine if quantitative differences existed among the subject groups, across the force levels and between vision conditions for the modal frequency. This analysis was applied separately for each of the index finger, thumb and total force signals. The results are shown in Table 2. Over all the vision and force conditions, and across the index finger ($P = 0.39$), thumb ($P = 0.28$) and total force ($P = 0.47$) signals, there were no differences in the modal frequency between the PD, elderly and young subject groups. Similarly, there was no effect for vision, nor was there an effect for the force level on the modal frequency of the index finger (*P* values were >0.05), thumb (*P* values were >0.05), and total (*P* values were >0.05) force output. Specifically, the PD, elderly and young groups had a modal frequency that varied between 6 and 12 Hz with the exception of the two Parkinson's subjects who had a strong 5 Hz force tremor (Fig. 2). In summary, these results suggest a high degree of stability for the modal frequency of the force tremor oscillation over group, force, and vision conditions. Additionally, the modal frequency was consistently within the 6–12 Hz range for the index finger, thumb and total force output. There was a tendency for the presence of broad-banded power between 6 and 12 Hz in the power spectra of most subjects.

3.3. Time-dependent structure of tremor

The regularity of force tremor was analyzed using ApEn (Pincus, 1991). Fig. 3 shows the averages of ApEn for the PD, elderly, and young subject groups for the index finger, thumb, and total force output. Significant group differences in ApEn were found for the total force output with the average values for the PD group ($m = 0.70$) being lower than those of the young ($m = 0.91$) and elderly ($m = 0.90$) subjects ($P < 0.01$). Similarly, the index finger and thumb force output showed a significant main effect with a reduction in ApEn for the PD group ($P < 0.01$). Tukey's HSD test revealed that the group differences were due to the reduction in the ApEn scores for the PD group compared with the young and elderly groups. There was no significant difference between the young and elderly groups. As a function of increasing force level, the ApEn decreased in the total force from 0.89 at 5% MVC to 0.79 for the 25 and 50% MVC force levels ($P < 0.01$). A similar reduction in ApEn as a function of force level was obtained for the separate index finger and thumb force output signals ($P < 0.01$). Most of the differences in ApEn as a function of force occurred between the 5 and 25% force levels (Fig. 3). There were no group interactions with force or vision (*P* values were >0.05).

Fig. 4 shows the spread of ApEn values for each subject at the 5, 25 and 50% MVC force levels under the full vision condition. While there is some overlap between two of the subjects with PD and the control groups, there does appear to be a clear separation between the controls and subjects with PD. These results show that ApEn differentiates the subjects with PD from the young and elderly subjects across a wide range of force levels, with and without vision, and the time-dependent structure of force output was more regular in the PD group.

3.4. Regularity and UPDRS rating scale

To investigate the relation between force tremor regularity and the severity of PD, correlations were calculated

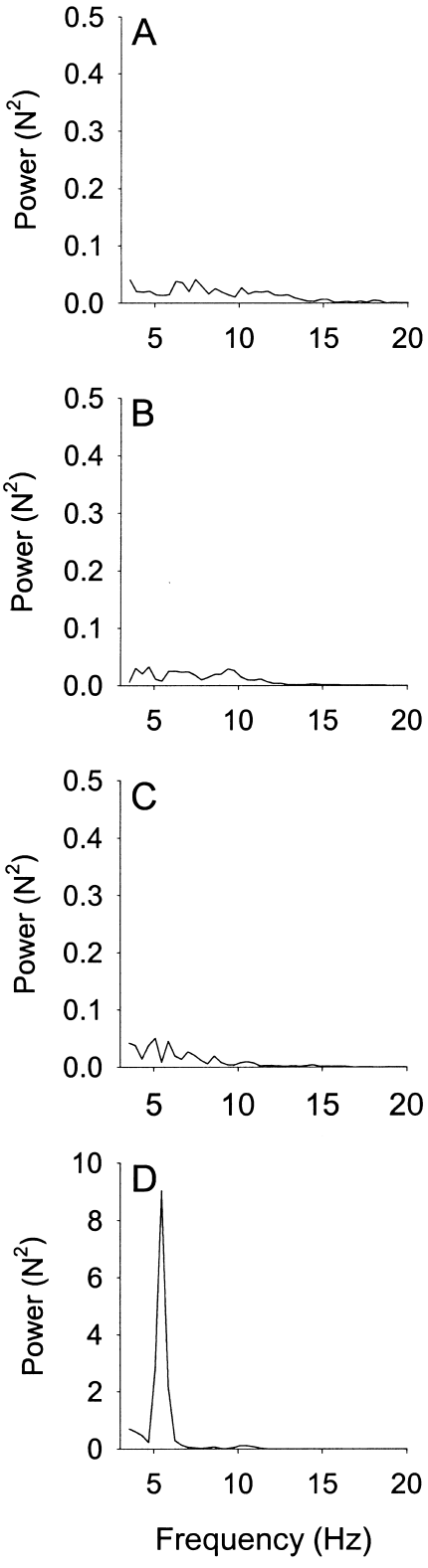

Fig. 2. Power spectrum from the total force from the same subject shown in Fig. 1 with vision at 25% MVC. The spectral profile from young (A), elderly (B), mild PD (C), and moderate PD (D) subjects. There was a broad-band tremor between 6 and 12 Hz for the young, elderly, and mild Parkinson's subjects. The moderate Parkinson's subjects had a predominant peak at 5 Hz.

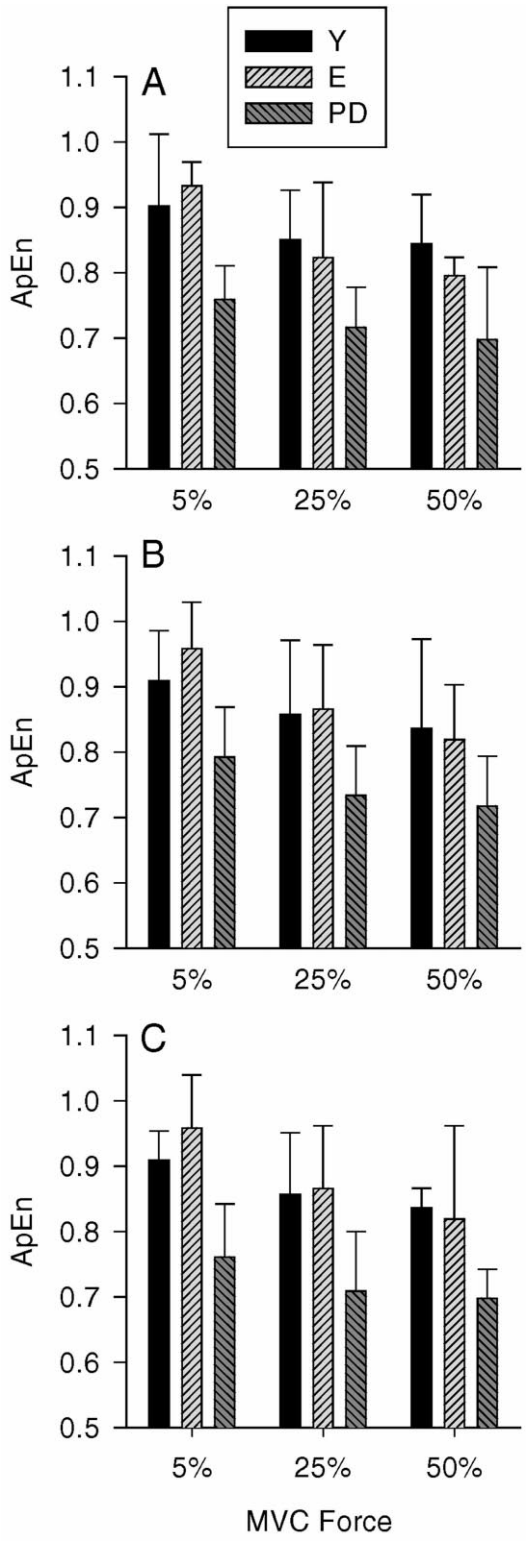

Fig. 3. ApEn for the index finger, thumb, and total force output for each group as a function of MVC force level. (I) shows the ApEn values from the index finger force tremor; (TH) are the ApEn values for the thumb force; and (T) shows the ApEn values for the total force output data. The mean ApEn values were averaged across the subjects in each group across the vision and no vision conditions, and across the 5 trials. Standard deviation bars show the variability of the ApEn values in each group. Overall, there were lower ApEn values with force and for the PD group.

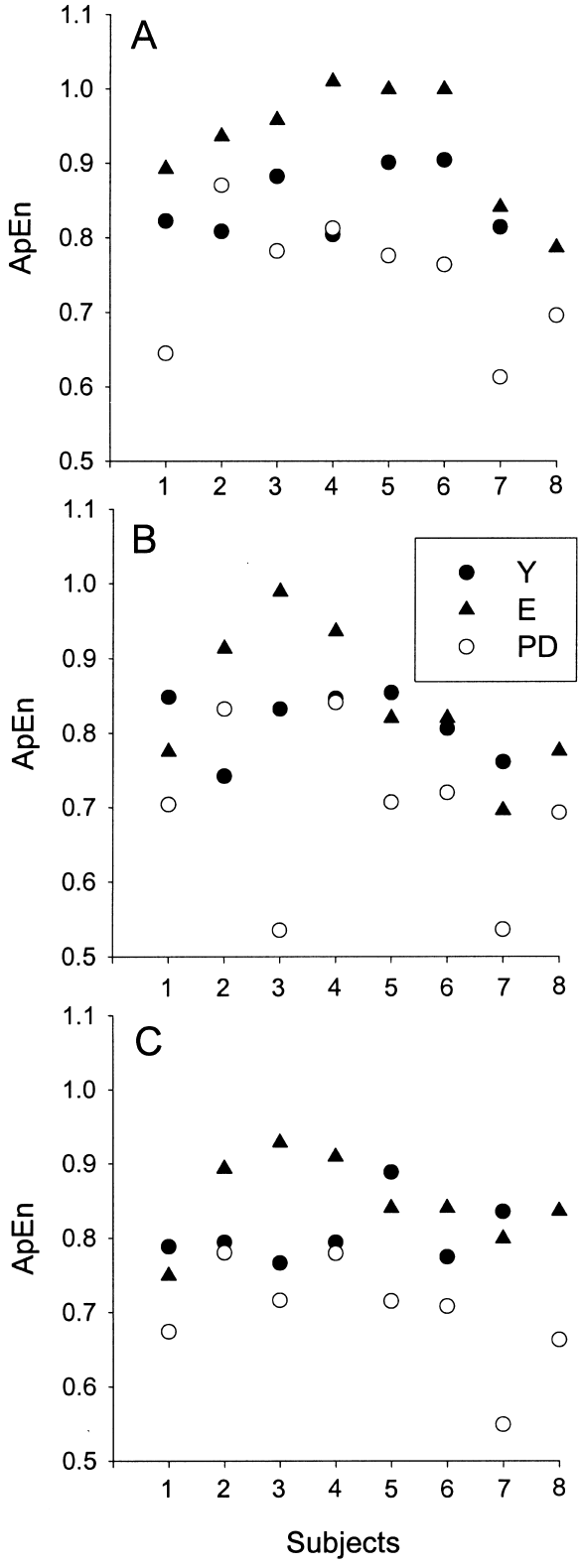

Fig. 4. ApEn values for the young, elderly, and PD groups at the 5, 25 and 50% MVC force levels under the full vision condition. Each data point represents the average across 4 trials. (A), (B) and (C) represent the 5, 25 and 50% MVC conditions, respectively.

between the total scores from the UPDRS-motor section and each of the following dependent variables from the total force output: ApEn, modal frequency, and standard deviation. The UPDRS score represents the total value obtained from the motor examination (section III: questions 18–31) portion of the scale. The correlations of the modal frequency ($r = 0.45$; $P = 0.22$) and standard deviation ($r = 0.48$; $P = 0.25$) with the UPDRS did not reach significance. However, Fig. 5 demonstrates that ApEn had a high negative correlation with the severity of PD ($r = -0.84$; $r^2 = 0.071$; $P < 0.01$). In other words, there was reduced ApEn with increases in the UPDRS score. Thus, the time-dependent structure of force tremor appears to be a good quantitative indicator of the severity of PD.

3.5. Surrogate data

Surrogate data analyses were performed to directly determine if the time-dependent structure of the tremor oscillation is independent of the frequency and amplitude of tremor (Theiler et al., 1992; Schreiber and Schmitz, 2000). This was accomplished by using the phase-randomized surrogate data technique (see Section 2). This method maintains the amplitude and frequency structure in a time series. The null hypothesis tested by the surrogate data was that the time-dependent structure of tremor provides no information beyond measures of the frequency and amplitude of the signal. To test the null hypothesis, 20 surrogates of each trial and for all subjects in the experiment were constructed to determine if there was a significant difference

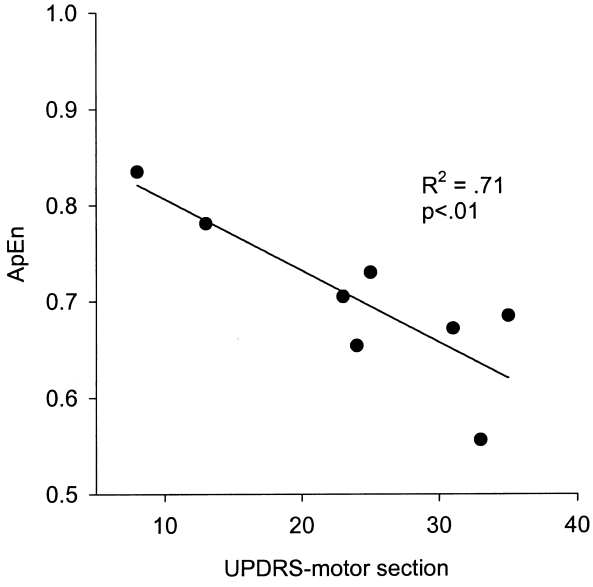

Fig. 5. Linear regression for the total force tremor between the ApEn values and the scores from the UPDRS-motor section. The UPDRS scores represent the total score from questions 18 to 31 of the scale. The slope was −0.007 and the *y*-intercept was 0.8807 for the regression model, which provided a good prediction between ApEn and the severity of PD. The results indicate a reduction in ApEn (increased regularity) with increases in the UPDRS-motor section scores.

in ApEn between the surrogate and the original time series. If the null hypothesis was true, then two out of 20 surrogate data sets (alpha = 0.05) would not be different from the original time series. To reject the null hypothesis, at least 19 of the simulated surrogate time series had to have increased ApEn values.

Fig. 6 shows an example of the total force output from an elderly control subject at 25% MVC. This illustrates that the amplitude of force output ($SD = 0.2215$ N) was equivalent in the original and surrogate time series. Furthermore, the frequency distribution was similar between the original and surrogate time series. However, the ApEn was higher in the surrogate data than in the original time series. While the ApEn difference of 0.03 seems small, this was a highly reliable result across the index finger, thumb, and total force output for the young (P values were <0.01), elderly (P values were <0.01), and subjects with PD (P values were <0.01). Of the 20 surrogate data sets generated for each unique condition, the one-tailed t tests revealed that all 20 surrogates had higher ApEn values than the original time series. Therefore, the null hypothesis can be rejected and this indicates that the time-dependent structure of tremor provides an independent parameter in the examination of tremor.

4. Discussion

4.1. Time-dependent structure of force tremor

The present report examined the two following hypotheses: (1), analysis of the time-dependent structure of tremor aids in differentiating tremor in PD from normal aging; and (2), there is increased regularity with increased severity of PD. The main findings demonstrate an increase in the regularity of force tremor of subjects with PD compared with the young and elderly controls. Regularity was quantified by ApEn in the time domain with lower ApEn values corresponding to increased regularity in force tremor (Pincus and Goldberger, 1994; Pincus, 1991). There was a 15–22% reduction in ApEn for the PD group compared with young and elderly control subjects across the index finger, thumb, and total force output. Moreover, force tremor was more regular in PD across 5, 25 and 50% MVC and in the vision and no vision conditions. Thus, the greater regularity in the force output of individuals with PD represents a general finding across the index finger, thumb and total force output signals that is not limited to the force level chosen.

The difference in ApEn between the PD and control subjects is not simply a result of a reduction in the modal

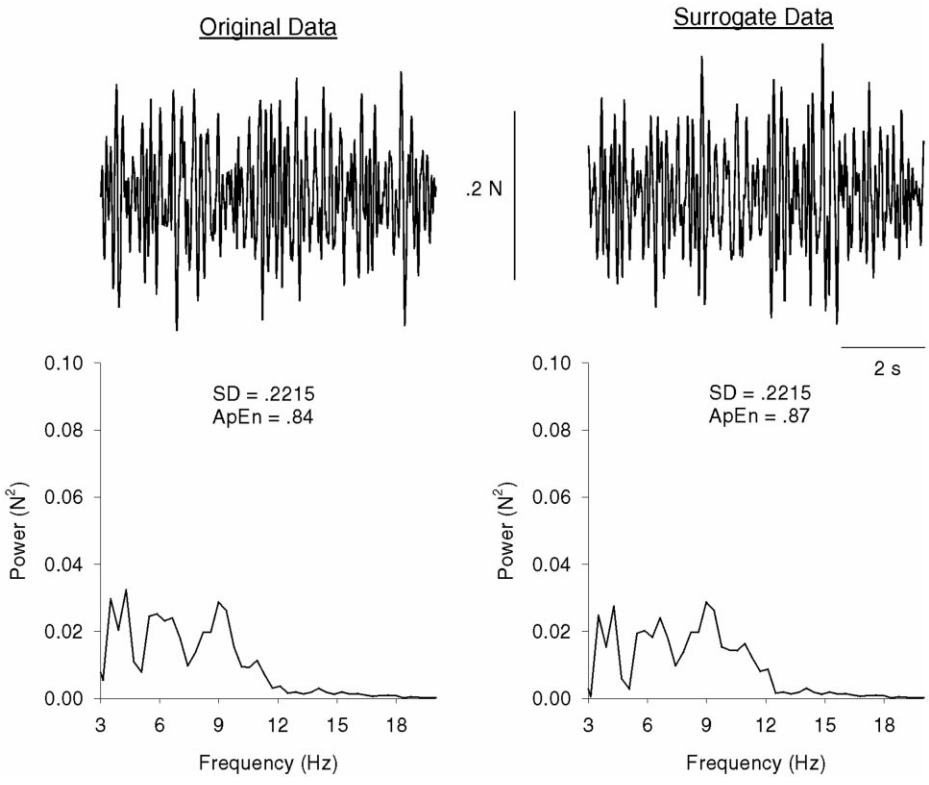

Fig. 6. Time series and power spectrum of force tremor at 25% MVC in an elderly control subject and the corresponding phase-randomized surrogate. The column showing the original data indicates that the standard deviation is 0.22 N and the ApEn is 0.84. The surrogate data also had a standard deviation of 0.22 N, but the ApEn was 0.87. This small difference in ApEn was statistically different (one-tailed t test; $P < 0.01$) between the original data and the surrogate data simulations for the PD, elderly and young subjects. The bottom panels indicate that along with the amplitude, the frequency distribution of the signal was preserved in the surrogate data compared with the original force data.

frequency of force tremor. In fact, the group average modal frequency of PD, elderly, and young subjects was between 6 and 12 Hz (mean, ~7.5 Hz) across all vision and force level conditions. Moreover, the surrogate data analysis showed that the ApEn values from the original data were significantly different from the ApEn values of the phase-randomized surrogate data (Theiler et al., 1992). This finding is significant because it suggests that the time-dependent structure of tremor provides additional information beyond the standard frequency analyses of tremor.

The results failed to show a difference in the amplitude of tremor between the control and PD groups. Two of the subjects with PD exhibited large amplitude force tremor with a predominant peak at 5 Hz, but the 6 other subjects with PD did not exhibit high amplitude tremors. These two subjects with PD had the highest UPDRS ratings compared with the other 6 subjects with PD. In a similar task, it was found that subjects with PD have higher amplitude force tremors than matched controls (Forssberg et al., 2000). It is likely that if more subjects with PD and high amplitude tremors participated in this study, then we would have seen a significant difference between the control and PD groups. However, the fact that no difference was found for amplitude between groups, while there were between group differences in ApEn, highlights the importance of using time-dependent measures in assessing tremor in PD.

Another significant finding in this study was that there was a strong, negative correlation between scores from the UPDRS-motor section and the ApEn values ($r^2 = 0.71$; Fig. 5). On the other hand, neither the modal frequency nor the amplitude of tremor had a significant correlation with the UPDRS. These findings clearly show a relation between the regularity of force tremor and the severity of PD. The findings from this study do not downplay the importance of frequency and amplitude analyses, but show that analysis of the time-dependent structure of tremor enhances characterizations of tremor in PD.

In this study, the subjects with PD were on anti-Parkinsonian medication during testing and the medication could have mediated tremor regularity. While we cannot clearly attribute the findings from this study to the pathophysiology of PD versus the effects of the treatment of PD, previous studies do suggest that medication would cause more irregular, and not regular, tremor oscillations. For instance, it has been shown that a more regular force output (lower ApEn values) corresponds to a higher force output variability (increased standard deviation; Slifkin et al., 2000). Additionally, when correlating the ApEn values with the standard deviation values of the total force tremor signal from all of the subjects in this study, the r value equaled -0.40 ($P < 0.01$). Since anti-Parkinsonian medication reduces tremor amplitude (Elble and Koller, 1990; Weiner and Lang, 1989) and there is a negative correlation between ApEn and the standard deviation of force tremor, then it is likely that anti-Parkinsonian medication would increase, and not decrease, the ApEn. Future studies should examine tremor regularity in patients with PD on and off anti-Parkinsonian medication to resolve this issue.

4.2. Possible implications for pathophysiology of tremor

The physiology and pathophysiology of tremor has traditionally been associated with multiple neural feedback loops at the spinal and supraspinal levels of the nervous system (Elble and Koller, 1990; Hallett, 1999; McAuley and Marsden, 2000). Spectral analysis has been the primary analysis tool used to determine the frequency of the neural and mechanical oscillations. The findings from the current study showed that the time-dependent structure of tremor also provides important information for tremor quantification. In addition, the time-dependent structure of tremor also has important implications for understanding the physiology and pathophysiology of tremor (Lipsitz and Goldberger, 1992; Vaillancourt and Newell, 2001).

While spectral analysis has been used to reveal the specific frequency of neural and mechanical oscillations, the time-dependent structure is more related to the variability in the timing of the tremor oscillations (Vaillancourt and Newell, 2000b). The variability in the timing of tremor oscillations measured by ApEn is also strongly related to the relative contribution from multiple frequency rhythms to the tremor output. For instance, tremor that is dominated by one frequency originating from a strong neural oscillator (e.g. 4–6 resting tremors in PD) would have a low amount of variability in the timing of the tremor output, and this would correspond to a high degree of regularity (low ApEn). In contrast, tremor that originates from a network of multiple neural oscillators would have more variability in the timing of the tremor output reflected by a high degree of irregularity (high ApEn). Thus, it is proposed that the finding that there is increased tremor regularity with increases in the severity of PD is due to a shift in the contribution from multiple neural oscillators to a reduced number of neural oscillators that contribute to the tremor output (Brown et al., 1997; McAuley et al., 2001; Vaillancourt and Newell, 2000b).

4.3. Conclusions

In summary, this study has shown that despite no between group differences in the modal frequency and amplitude of tremor, there is an increase in the regularity of force tremor in PD as compared with age-matched elderly and young control subjects. While the first symptom that most PD patients report to a physician is unilateral tremor with increased amplitude (Weiner and Lang, 1989), there may be changes in the regularity of tremor that occur independently of increases in tremor amplitude. For instance, the findings from this study and from previous work on resting and postural tremors (Edwards and Beuter, 2000; Vaillancourt and Newell, 2000b) indicate that the time-dependent structure of tremor may change without changes in the frequency and amplitude of the oscillation. The findings

from this study extend these observations by showing a positive relation between tremor regularity (ApEn) and the severity of PD (UPDRS).

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