Accepted Manuscript

Title: Variability, Regularity and Coupling Measures Distinguish PD Tremor from Voluntary 5 Hz Tremor

Authors: S. Morrison, N. Cortes, K.M. Newell, P.A. Silburn, G. Kerr

PII: S0304-3940(12)01509-1
Reference: NSL 29416

To appear in: Neuroscience Letters

Received date: 30-7-2012
Revised date: 22-10-2012
Accepted date: 17-11-2012

Please cite this article as: S. Morrison, K.M. Newell, P.A. Silburn, G. Kerr, Variability, Regularity and Coupling Measures Distinguish PD Tremor from Voluntary 5<ce:hsp sp=¨0.25¨/>Hz Tremor, Neuroscience Letters (2010), doi:10.1016/j.neulet.2012.11.040

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.
• Young adults were able to produce a tremor similar in frequency to PD tremor
• PD tremor was more variable and irregular than voluntarily generated 5 Hz tremor
• Stronger coupling between the arms was seen for voluntary tremor responses
• Variability measures can be used to discern between different tremor forms
Title: Variability, Regularity and Coupling Measures Distinguish PD Tremor from Voluntary 5 Hz Tremor

Authors: S. Morrison\textsuperscript{1}, N. Cortes\textsuperscript{2}, K.M. Newell\textsuperscript{3}, P.A. Silburn\textsuperscript{3,4,6}, G. Kerr\textsuperscript{3,4}

Affiliations
\begin{itemize}
  \item \textsuperscript{1}School of Physical Therapy, Old Dominion University, VA, USA
  \item \textsuperscript{2}Sports Medicine Assessment, Research & Testing Laboratory, George Mason University, Manassas, VA, USA
  \item \textsuperscript{3}School of Exercise and Nutrition Sciences, Queensland University of Technology, QLD, Australia
  \item \textsuperscript{4}Movement Neuroscience Program, Queensland University of Technology, QLD, Australia
  \item \textsuperscript{5}Department of Kinesiology, Pennsylvania State University, PA, USA.
  \item \textsuperscript{6}Center for Clinical Research, University of Queensland, QLD, Australia
\end{itemize}

Resubmitted: 22\textsuperscript{nd} October 2012

Corresponding Author: Steven Morrison

Address: School of Physical Therapy
Old Dominion University
VA 23529

Phone: 757-683-6757
FAX: 757-683-4410
Email: smorriso @odu.edu
Abstract

A characteristic of Parkinson’s disease (PD) is the development of tremor within the 4-6 Hz range. One method used to better understand pathological tremor is to compare the responses to tremor-type actions generated intentionally in healthy adults. This study was designed to investigate the similarities and differences between voluntarily generated 4-6 Hz tremor and PD tremor in regards to their amplitude, frequency and coupling characteristics. Tremor responses for 8 PD individuals (on-and off-medication) and 12 healthy adults were assessed under postural and resting conditions. Results showed that the voluntary and PD tremor were essentially identical with regards to the amplitude and peak frequency. However, differences between the groups were found for the variability (SD of peak frequency, proportional power) and regularity (Approximate Entropy, ApEn) of the tremor signal. Additionally, coherence analysis revealed strong inter-limb coupling during voluntary conditions while no bilateral coupling was seen for the PD persons. Overall, healthy participants were able to produce a 5 Hz tremulous motion indistinguishable to that of PD patients in terms of peak frequency and amplitude. However, differences in the structure of variability and level of inter-limb coupling were found for the tremor responses of the PD and healthy adults. These differences were preserved irrespective of the medication state of the PD persons. The results illustrate the importance of assessing the pattern of signal structure/variability to discriminate between different tremor forms, especially where no differences emerge in standard measures of mean amplitude as traditionally defined.

Key Words: Tremor, Parkinson’s disease, Variability, Complexity, Bilateral Coupling
Introduction

A general feature of pathological tremor forms is that they are characterized by increased amplitude and a lower frequency in comparison to physiological tremor [1-3]. Typically, the limb oscillations associated with neurological disorders like Parkinson’s disease (PD) and essential tremor are restricted to a single dominant peak located between 4-6 Hz [2, 4]. In contrast, tremulous motion in healthy adults is more broadband, with peaks commonly being observed between 2-4 Hz, 8-12 Hz and, for finger tremor only, as high as 18-24 Hz [3, 5]. These pronounced differences in frequency and amplitude facilitate the discrimination between pathological and normal physiological tremor signals. However, how to accurately discriminate between 4-6 Hz tremors arising from different neurological sources (e.g. PD, essential tremor) from tremor generated voluntarily and/or related to psychogenic factors is a question of continuing interest [6-8].

One method used to assess the properties of tremor has been to compare the responses of tremor-type actions generated voluntarily to those of pathologies [8-11]. While voluntarily producing oscillatory motion within the 8-12 Hz range of physiological tremor is not achievable for healthy individuals [12], producing rhythmical limb motion at or around the frequency of many forms of pathological tremor (e.g. 4-6 Hz) is within the functional boundaries of the voluntary movement [9-11]. Previous studies have reported that tremor generated voluntarily by healthy adults under these conditions exhibits similar frequency characteristics, and is often indistinguishable in regards to amplitude, from that observed in individuals with neurologic disorders [8-11].

Given the similarities in appearance between these tremor forms, there is an obvious interest in how to discriminate between the different oscillatory outputs. One means by which to assess
these differences is to identify the pattern of regularity and variability in the respective tremor signals. Previous research has highlighted that, in addition to amplitude and frequency differences, the tremor under pathological conditions is often less complex and variable than physiological tremor assessed from healthy adults [13-15]. Another means by which to assess tremor differences is to evaluate the level of coupling of tremor between limbs. Previous studies have reported no coupling of tremor between the arms in healthy adults of differing ages[16-18] or for persons with PD, irrespective of their medication state [19, 20]. However, increased coupling between the limbs can be seen for other movement forms in healthy adults, persons with PD[21, 22] and for patients with essential tremor [23]. One suggestion is that inter-limb independence is an intrinsic feature of tremor production of healthy individuals and so assessments of the degree of coupling can be used to distinguish between different tremor forms.

The aim of this study was to investigate the similarities and differences between voluntarily generated 4-6 Hz tremulous movement and PD tremor in regards to their amplitude, frequency and coupling characteristics. It was predicted that the voluntary tremor will exhibit similar frequency and amplitude characteristics to that of the PD patients. Further, for the PD individuals, these similarities will be preserved irrespective of their medication state [3, 24]. It was also predicted that there will be notable differences in tremor regularity, variability and coupling which will distinguish between the different individuals.

Methods

Subjects

Twelve young control subjects (six males, six females, age 24±5.1 yrs), and eight Parkinsonian patients (two males, six females, 65.1±3.2 yrs) gave informed consent to participate
in this study. All control participants were right-hand dominant, physically active, had normal or corrected-to-normal vision, and reported no known neurological/cognitive disorders, or history of neuromuscular injury that could influence performance. All Parkinson patients were assessed using the UPDRS-motor section by a trained neurologist and all exhibited resting and postural tremors bilaterally. Additional subject inclusion details and results have been reported previously.[3] All participants provided written informed consent and completed a medical history questionnaire prior to testing to determine health status. All experimental procedures complied with University IRB guidelines and were in accordance with the Declaration of Helsinki.

Experimental Design

For all participants, bilateral tremor responses were recorded under both resting and postural conditions. For the PD patients, resting tremor was measured independently from both arms which were allowed to hang relaxed and unsupported by their side [3, 25]. For the postural tremor condition, participants performed a pointing task with both arms held parallel to the ground [3]. For the upper limb, the shoulders were flexed 90° in the sagittal plane, elbows fully extended, and forearms pronated. The index finger of each arm was extended at the metacarpophalangeal joint with the thumb adducted and remaining fingers flexed to form a loose fist.

For the simulated postural and resting tremor movements, healthy individuals were asked to adopt the same postural or resting positions as described above. They were then instructed to perform rapid alternating wrist flexion-extension movements with both arms. Prior to data collection, subjects were given 4 trials of practice to generate the required frequency of tremor
motion in each position. An auditory metronome set at 5 Hz was provided during this period to allow each person to ensure they were aware of the required movement frequency.

Equipment

All testing procedures were performed while individuals adopted a standing position. Hand and finger tremor were measured using four uniaxial Coulbourn accelerometers (V94-41) and amplified through a Coulbourn transducer coupler (V75-25A, sample rate 100 Hz). The accelerometers were attached to the hand (middle of third metacarpal) and index finger (dorsal distal aspect) of each arm so the measurement axis was perpendicular to the ground during pointing. Six 30 s trials were performed within each condition (total number of trials: 12). Rests were provided between trials/conditions to reduce the effects of fatigue.

Data Analysis

The accelerometer data were filtered by a second-order Butterworth low-pass digital filter (cutoff frequency 50 Hz). All data analysis was performed using custom software developed in Matlab version 7.0 (Mathworks R14).

Time Series Analysis: Average tremor amplitude involved calculating the root mean square (RMS) of the tremor signal (window size 100 ms).

Frequency Analysis: This was performed on the filtered tremor data between 0-40 Hz using Welch’s averaged, modified periodogram method (512 data point Hanning window). The dependent measures calculated were; maximum amplitude of each signal (peak power), the frequency at which the peak power was observed (peak power frequency, PPF), the variability of PPF (SD PPF) and the distribution of power across the tremor signal (proportional power). The
proportional power variable provides an estimate of the relative proportion of power (expressed as a percentage of total power) that occurs within successive 1 Hz frequency bins. All dependent measures were calculated for all trials per condition and across all subjects.

**Signal Regularity:** The degree of regularity of the accelerometer signals was assessed using Approximate Entropy (ApEn) analysis. ApEn measures the conditional probability of the signal by providing a measure of the (logarithmic) likelihood that runs of patterns that are close for \( m \) observations remain close on the next incremental comparisons \((m+1)\). This analysis returns a single value for the tremor signal within the range of 0-2. Typically, a signal with higher ApEn values is described as being less regular (or more complex). Conversely, a signal with a lower ApEn would be described as more regular (less complex) [26].

**Coupling Analysis:** Estimation of the degree of coupling of tremor between arms was determined by applying cross correlation (Pearson product moment) and coherence analyses. The correlation analysis was conducted over multiple time lags (range ±5 s). The peak correlation coefficient and the lag at which this peak was observed were recorded. Coherence analysis was performed to assess the degree of coupling in the frequency domain and the maximum (peak) coherence value determined. This analysis was performed within the range 0-20 Hz (window size 512 data points, binwidth 0.1953 Hz). To assess whether the coherence values were significantly different from zero, a 95% confidence interval was calculated [27].

**Statistical Analysis**

A repeated measures mixed generalized linear model (GLM) was used to assess for differences in the dependent measures. A two-way model was used to identify differences in the tremor measures between groups (young, PD \( \text{ON/OFF} \) medication) and across tremor conditions.
Where significant effects were reported, post hoc evaluations were performed using Tukey’s Honestly Significant Difference (HSD) test. All statistical analyses were performed using SAS statistical software (SAS Institute Inc., NC), with the risk of Type I error set at $p < 0.05$.

### Results

#### Tremor Similarities

**Tremor RMS Amplitude:** No significant differences in mean RMS amplitude were observed for the tremor responses between the PD patients and the healthy adults simulating a 5 Hz tremor. No significant differences were found, for the PD group, between the on/off medication state.

**Tremor Frequency:** The resting and postural tremor forms for all groups were characterised by a single dominant frequency peak, present between 4-6 Hz. For the simulated group, the resting tremor peak was 5.16 Hz and, under postural conditions, 4.98 Hz. For the PD patients, the resting tremor peaks were at 5.26 Hz (on-medication) and 5.34 Hz (off-medication). The postural tremor peaks for these same individuals were at 5.03 Hz (on-medication) and 5.18 Hz (off-medication). No significant difference was observed between groups or conditions (resting, postural) in regards to the frequency of peak power (PPF). Furthermore, no differences in peak power or PPF were observed between the two simulated conditions for the healthy adults. Figure 1 illustrates the typical tremor responses, power spectral and proportional power profiles for a single PD$_{OFF}$ individual and a healthy adult producing a 5 Hz tremor. The tremor responses across the postural and resting conditions are shown in this figure. Figure 2 depicts the major
similarities in mean tremor RMS amplitude and PPF between the different groups and conditions.

Insert Figures 1 & 2

Differences in Tremor

Tremor Frequency: A significant group by condition interaction effect was observed for the SD of PPF ($F_{2,26}=14.33; p<0.001$) and proportional power measures ($F_{2,26}=22.67; p<0.001$). For the SD PPF results, post hoc analysis revealed that the tremor for the PD ON/OFF patients was more variable (higher SD) than for the simulated conditions (all $p$’s$<0.001$, see figure 3). This effect was found across the resting and postural conditions. For the proportional power analysis, a greater percentage of the total power (>60%) was observed within the 5-6 Hz range under simulated conditions (all $p$’s$<0.001$, see figure 3). This effect was found across both conditions.

Tremor Regularity: A significant group by condition effect was observed for the ApEn values for finger tremor ($F_{2,26}=26.25; p<0.001$). Post hoc analysis revealed that the tremor for the PD ON/OFF patients, under both resting and postural conditions, was more complex (higher ApEn) than the tremor produced under simulated conditions (all $p$’s$<0.001$, see figure 3). No differences in ApEn scores were observed within each group between the resting and postural tremor conditions.

Figure 3

Coupling Relations
For the correlation analysis, there was a significant group-by-condition effect for the strength of the coupling relation between arms ($F_{2,26}=7.88; p<0.001$). Post hoc analysis revealed that the strength of the bilateral coupling was significantly greater under simulated conditions than for the PD_{ON/OFF} individuals (all $r$ values $< 0.12; p <0.05$; see figure 4). There was no evidence of coupling of tremor between the arms for the PD individuals irrespective of the tremor form assessed or their medication state (on/off). All peak correlation values were found at 0 s lag.

The coherence analysis provided a similar pattern of results with a significant group-by-condition effect being found ($F_{2,26}=23.15; p<0.001$). Subsequent analysis highlighted significant differences between the simulated and PD_{ON/OFF} tremor (all $p$’s<0.05). For the PD_{ON/OFF} tremor, there was no evidence of any coupling of tremor between limbs or any differences as a function of medication state. However, a significantly higher level of coupling was observed under simulated conditions (figure 4). All significant coherence peaks were between 4-6 Hz.

**Discussion**

This study was designed to examine the similarities and differences between Parkinsonian tremor and that generated voluntary at 5 Hz by healthy adults. There were no differences in modal frequency or overall amplitude of the tremor between the healthy participants and the PD_{ON/OFF} persons. However, there were significant differences in the structure of variability of the tremor responses between groups. The simulated tremor was more regular (lower ApEn), less variable in frequency (lower SD of PPF, more power within a narrower frequency range)
and was more strongly coupled between limbs than the tremor recorded from PD individuals. These differences were preserved irrespective of the medication state of the PD persons.

**Similarities between Voluntary and PD Tremor**

One of the major distinguishing neurological features of Parkinson disease is the presence of enhanced tremor under resting and/or postural conditions [28]. These tremulous oscillations are typically observed between 4-6 Hz and reflect changes in the underlying neural mechanisms driving tremorgenesis. Since PD tremor differs dramatically in both frequency and amplitude from the physiological tremor observed in healthy adults, various studies have compared the responses of tremor-type actions generated voluntarily to that of pathologies [8-11]. Such comparisons are employed to provide additional information about the dynamics of pathological tremor. For example, as the voluntary tremulous action can be generated within a similar frequency range, comparisons can be made between two comparable oscillatory outputs. A central finding of the current study is that, in terms of terms of peak frequency and amplitude, there was no difference in the tremor for healthy adults and individuals with Parkinson’s disease. The tremor response of all individuals was characterized by a single dominant frequency peak between 4-6 Hz, irrespective of whether the tremor was recorded under postural or resting conditions.

An additional finding of note was the lack of tremor differences for the PD patients between their on and off medication state. Generally, the use of anti-parkinsonian medication produces a decrease in the amplitude of resting/postural tremor with little concurrent change in tremor frequency or inter-limb coupling [20, 24, 29]. However, the extent of any amplitude decline can
be highly variable between PD individuals [3, 19, 28], an observation which may contribute to the lack of any tremor differences between the on-off medication state in the current study.

Differences between Voluntary and PD Tremor

While there were no significant differences between the PD_{ON/OFF} and voluntary 5 Hz tremulous movements with regards to peak frequency and mean RMS amplitude, fundamental differences between the tremor in the two groups were observed for the pattern of regularity of the variability. Of particular note, the voluntary generated tremor was more regular (lower ApEn) and more tightly restricted around 5 Hz (lower SD of PPF, greater proportion of power within 5-6 Hz) than the tremor for the PD_{ON/OFF} group, irrespective of their medication state. This finding provides an interesting addition to reports which have focused on comparing PD tremor to physiological tremor [13-15]. In these studies, PD tremor is typically less variable and more regular than the tremor for healthy adults of a similar age. Taken together, these results illustrate that even though the neuromotor driving signal for individuals with PD is constrained to a very narrow frequency range, their tremor response still exhibits a moderate degree of variability. Indeed, the PD tremor exhibited a higher degree of variability and was more irregular (more complex) than the voluntary tremor responses.

One additional difference in tremor between the groups relates to the degree of coupling between limbs. For the PD individuals, the results of the specific analyses (i.e., cross correlation, coherence) showed no evidence of any inter-limb coupling. In contrast, under simulated (voluntary) tremor conditions, there was a significantly high level of coupling between the arms. For the coherence results, this strong bilateral relation was within 4-6 Hz, which coincided with the frequency range at which the simulated tremor was performed. The bilateral differences in
coupling strength probably reflect underlying variation in the neural mechanisms driving each oscillatory output. In Parkinson’s disease (and assessments of tremor in healthy adults), the prevailing view is the tremor within each limb is generated independently from uncoupled or parallel oscillators within the CNS [3, 20, 30]. In contrast, during rhythmical actions generated voluntarily, the level of coupling between contralateral limb segments tends to be strong [21, 31]. One hypothesis is that this coupling reflects the act of voluntarily increasing the neural drive to selected muscle groups [31].

Overall, our findings reveal that tremor in PD patients was more irregular, variable and characterized by a lack of bilateral coupling compared to voluntary 5 Hz tremulous motion performed by healthy adults. The results reveal the sensitivity of measures of signal structure/variability to discriminate between groups and conditions in tremor analysis, beyond that provided by standard measures of (mean) tremor amplitude. Further, comparisons between healthy adults and patients with neurological disorders could incorporate assessments of voluntary oscillatory 4-6 Hz movement in order to distinguish between various tremor forms.
References


Figure Captions

Figure 1  Representative examples of the tremor signal for a single PD\textsubscript{OFF} participant and a healthy subject voluntarily generating a 5 Hz tremor. The respective power spectral and proportional power profiles for each tremor signal are also shown. Tremor responses were recorded under postural and resting conditions.

Figure 2  Similarities in tremor amplitude (mean RMS) and modal frequency (peak power frequency, PPF) between the PD\textsubscript{ON/OFF} and healthy subjects. Overall group mean results for the resting and postural conditions are shown. Error bars shown in each figure represent one SE of the mean.

Figure 3  Differences in tremor regularity (mean ApEn) and variation (SD of PPF) between the PD\textsubscript{ON/OFF} and healthy subjects. Results are shown for both the resting and postural conditions. Error bars represent one SE of the mean. Significant group differences between the PD and the voluntary tremor responses are denoted with an asterisk (*).

Figure 4  Significant differences in level of inter-limb coupling between groups based upon changes in mean peak correlation and coherence values. Error bars represent one SE of the mean. Significant differences in the level of coupling between the PD\textsubscript{ON/OFF} and healthy groups are denoted with an asterisk (*).
Figure 2

Graph showing Mean RMS Tremor Amplitude (m.s\(^{-2}\)) for Simulated, PD on (PDon), and PD off (PDoff) conditions in Resting and Postural Conditions. The graphs indicate a comparison of right and left fingers.

- Resting Conditions:
  - Simulated: Lower amplitude compared to PD on and off conditions.
  - PD on (PDon): Higher amplitude than rest.
  - PD off (PDoff): Average amplitude between PD on and rest.

- Postural Conditions:
  - Simulated: Slightly higher amplitude compared to PD on and off conditions.
  - PD on (PDon): Noticeably higher amplitude than PD off and rest.
  - PD off (PDoff): Similar to rest but slightly higher.

Frequency of Peak Power (Hz) is also shown, with similar trends observed across conditions.
Figure 3

Postural Conditions

Resting Conditions

SD of PPF (Hz)

Mean ApEn

Voluntary
PDon
PDoff

Right Finger

Left Finger

* indicates significant difference.
Figure 4