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Variability of Hand Tremor in Rest and in Posture – A Pilot Study

Fariborz Rahimi PhD, *Member, IEEE*, Carina Bee BSc, Angela South MA, Derek Debicki MD, and Mandar Jog MD

***Abstract*—Previous, studies have demonstrated variability in the frequency and amplitude in tremor between subjects and between trials in both healthy individuals and those with disease states. However, to date, few studies have examined the composition of tremor. Efficacy of treatment for tremor using techniques such as Botulinum neurotoxin type A (BoNT A) injection may benefit from a better understanding of tremor variability, but more importantly, tremor composition. In the present study, we evaluated tremor variability and composition in 8 participants with either essential tremor or Parkinson disease tremor using kinematic recording methods. Our preliminary findings suggest that while individual patients may have more intra-trial and intra-task variability, overall, task effect was significant only for amplitude of tremor. Composition of tremor varied among patients and the data suggest that tremor composition is complex involving multiple muscle groups. These results may support the value of kinematic assessment methods and the improved understanding of tremor composition in the management of tremor.**

I. Introduction

TREMOR is an "involuntary approximately rhythmical and roughly sinusoidal movement" [1]. Although characteristics of tremor usually remain consistent, some tremors do not have a fixed rhythm and may be a symptom of a systemic movement disorder, such as Parkinson disease (PD). Tremor may also be the primary component in a movement disorder, such as Essential tremor (ET).

To date, treatment and management of tremor by oral medication has been generally ineffective. Propranolol and primidone, predominantly for ET, and are currently the medications of choice; however, these may have reduced efficacy for tremors of high amplitude, and raise concerning side effects of hypotension, mood, behavioral, and cognitive impairment.

While tremor is comparably a benign symptom of disease, it is often the one most targeted for treatment, as it presents social anxiety and inconvenience to daily living. Due to this, tremor presentation has become an important indicator in clinical standard of care for disease severity, progression, and medication inadequacy. Management of tremor focally by intramuscular injection of Botulinum neurotoxin type A (BoNT A), which aims to reduce muscle hyper-activity through neuronal activation, introduces an optimal alternative to increasing medication prescription and dosage in ET [2-4] and PD [5].

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Botulinum neurotoxin therapy for both ET and PD tremor have been reported in the literature in the past two decades. Predominant muscle groups injected are flexors and extensors [2-3], and to a lesser degree, pronation and supination [5].

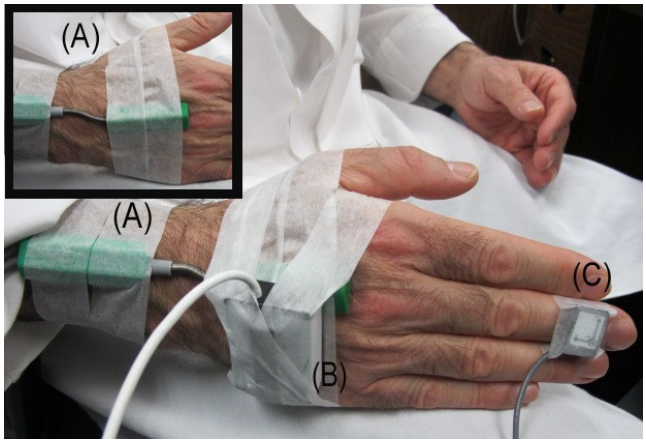

Fig. 1. Experimental setup including an electro-goniometer measuring wrist flexion-extension (A), an inclinometer measuring wrist pronation-supination and ulnar-radial deviation (B), and a tri-axial accelerometer (C).

Variability in the amplitude and frequency of postural tremor of the hand has been previously reported in normal subjects [6]. Additionally, intra-subject variability has been observed in individuals with ET [7].

Injection accuracy by site and dosage is key to the efficacy of BoNT A for hand tremor. Kinematic assessment tools may help to improve efficacy of injection practices.

In order to further understand the variability and composition of tremor, this study aims to address two main objectives: 1) to determine whether the amplitude and frequency of tremor differs in rest and in posture, and 2) to quantify any inter-trial variability between tremor in rest and in posture.

II. Methods

A. Patients

Inclusion criteria for study participants include ambulatory patients with ET and PD (Hoehn and Yahr score 2-4) with focal hand tremor as the primary symptom of their disease. These patients were enrolled in the study on the basis of their voluntary participation in BoNT A injection for focal hand tremor at the Movement Disorders Centre. Tremor kinematics were obtained in addition to pre-injection clinic

assessment routine of standard care. The patient demographic for the study was as follows: 8 patients, 4 males, 4 females, 6 PD, 2 ET, ages ranging from 47-74 years, mean age: 62.4 (SD=9.16), mean years since disease onset: 9.5 (SD=8.20), 5 participants with tremor in the dominant hand, and 3 with tremor in the non-dominant hand, average score of the tremor items of the Unified Parkinson disease Rating Scale (UPDRS) of affected/injected side: 4.4.

B. Experimental Setup and Procedure

Kinematics were recorded for 8 consenting participants during one 20-minute clinic visit. During this session, the participants were attached with three kinematic sensors (Noraxon, INC.). An electro-goniometer with two degrees of freedom (DOF) was placed at the wrist, collecting joint flexion-extension and ulnar-radial deviation. One inclinometer (2-DOF) on the back of the hand measured ulnar-radial deviation and wrist pronation-supination. One tri-axial accelerometer at the distal joint of the third metacarpal measured finger tremor acceleration. The placement of these devices was standardized for each participant (Fig. 1).

Data recorded from the sensors were wirelessly transmitted to a signal receiver and laptop computer placed nearby. The system was calibrated by a series of general tasks while wearing the kinematic sensors in the seated position quietly. In the first part of the experiment, participants performed 5s at neutral, and in 30° flexion, 30° extension, 30° pronation, 30° supination, and 20° ulnar and 20° radial deviation. This served to calibrate the sensors to determine baseline sensor location, as well as to confirm accuracy of sensor range for each DOF. Calibration was followed by a series of experimental tasks which examined resting tremor, classically assessed with hand relaxed in neutral on the patient's lap, and postural tremor, classically assessed with arms extended at shoulder height and hands pronated. Each task was performed in triplicate at 10s each. All participants were able to complete the designated tasks.

C. Data Analysis

At the beginning and end of each task, time was recorded manually, to facilitate data extraction of each task and trial. Reliability of raw data segments were verified to omit erroneous movements collected by the sensors. Three out of four signals provided by electro-goniometer and inclinometer were used in data analysis. The flexion-extension signal was gathered from the electro-goniometer, and the pronation-supination ulnar/radial deviation signals were gathered from the inclinometer. Signals from the accelerometer were not used for this study. Data averages from neutral conditions were subtracted from all signals.

All signals were sampled at 1500Hz and signal processing was conducted in MATLAB® (MathWorks, R2007b). All tremor signals were bandpass filtered (2-20Hz, least-squared finite impulse response filter, order 2000). To avoid filter transient effects, signals were symmetrically padded on both ends. Root-mean-squared (RMS) value of each tremor signal was calculated as amplitude of that component and overall tremor amplitude was constructed with the RMS of the 3 components. To evaluate contribution of each component to overall tremor, relative value of each component with respect to overall tremor were presented as percentages. To evaluate tremor frequency in each trial, power spectrum was estimated for the strongest of the 3 components with Welch`s method (*pwelch* in MATLAB). The maximum peak value of this spectrum was assigned to trials frequency.

Statistical analysis was conducted using STATISTICA™ (StatSoft®). Repeated univariate analysis of variance was used to analyze the effects of intra-trial variability and variability as a function of task. Data from the composition of the tremor was analyzed graphically and descriptively as sample size was not sufficient for reliable statistical analysis.

III. Results

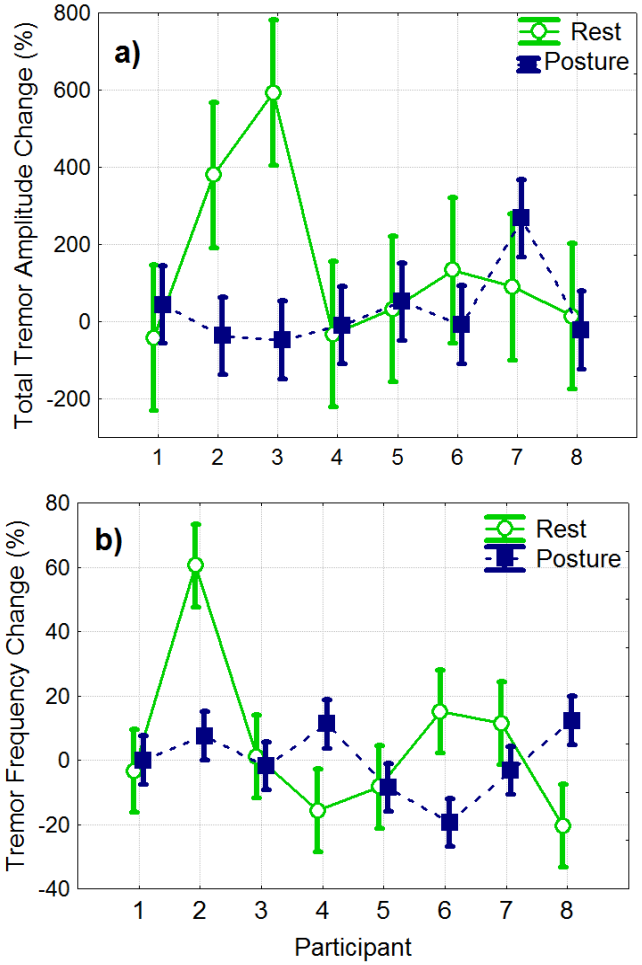

Fig. 2. Variability in total tremor amplitude change from Trial 1 to Trial 2, and from Trial 1 to Trial 3 between two tasks for all 8 participants, (a). Variability in tremor frequency change from Trial 1 to Trial 2, and from Trial 1 to Trial 3 and between two tasks for all 8 participants, (b). Data is presented as percentages change. Raw data for frequency at rest (mean=4.9, SD=0.9Hz); raw data for frequency in posture (mean=5.4, SD=1.1Hz); raw data for amplitude at rest

A. Trial Variability

Univariate repeated measures Analysis of Variance (ANOVA) performed for both rest and postural data using amplitude as the dependent variable suggest that there was no significant inter-trial variability for rest ($F(2,14)=1.06$, $p>0.05$)) or posture ($F(2,14)=2.47$, $p>0.05$).

For frequency of tremor, univariate repeated measures ANOVA performed for both rest and postural data suggest that there was no significant inter-trial variability for rest ($F(2,14)=0.9778$, $p>0.05$)) or posture ($F(2,14)=2.38$, $p>0.05$). This data suggest that while for some isolated cases, there appears to be variability between trials, the overall effect does not suggest significant inter-trial variability.

B. Task Differences

Using ANOVA, there was a significant effect of task (rest/posture) on amplitude of tremor ($F(1,7)=9.30$, $p<0.05$, $\eta^2_p=0.57$. This suggests that there was a moderate effect of task on amplitude with 57% of the variance in amplitude associated with task.

However, for frequency, there was no significant effect of task (rest/posture) ($F(1,7)=3.30$, $p>0.05$). This suggests that there was no effect of task on frequency associated with task.

Therefore, while there is an effect of task on amplitude of tremor, there is no effect on tremor frequency. While omnibus effects do not demonstrate difference, there does appear to be individual subjects with greater variability in frequency, amplitude, and the percentage of change (Fig. 3).

Since sample size was not sufficient at this point in this pilot study to conduct multivariate analysis on intra-trial and intra-tasks compositional data variability, we have reported this data descriptively (Fig. 4,5).

Graphical representations of the data suggest the composition of the tremor with regard to raw tremor amplitude is fairly consistent between rest and posture (composition: flexion-extensor, ulnar-radial, pronation-supination). Graphical data may suggest intra-trial and intra-task variability in tremor composition (Fig 5). Evaluation of individual subject data may suggest that the composition of tremor is not limited to flexor-extensor only, which currently is the primary injection site for treatment (Fig. 4,5) Additionally, the data may suggest that there may be a balance in the composition of the tremor among three muscle groups.

IV. Conclusion

Our findings may be in keeping with the intra-subject variability seen in other studies [7]. However, while individual patients may have inter-trial and inter-task variability, our preliminary results suggest that there is no significant overall inter-trial variability for either amplitude or frequency in our sample. There may be an effect of task for the amplitude of tremor; however, there appears to be no effect for frequency of tremor. Our results, along with others, may indicate that there are other sources contributing to variability, such as age, and methodological considerations.

While we are not able to draw significant inferences about the contribution of components composition of tremor on overall tremor effects, our preliminary data does suggest that the assessment of tremor is benefitted by looking at all components of the movement (flexion-extension, pronation-supination, ulnar radial deviation). Traditional injection sites have included mainly the flexor-extensor muscle groups, and to a lesser degree, pronation-supination [5].Our data suggest that this view be expanded, and that pronation-supination may play a greater role in tremor composition in some subjects, and that ulnar-radial muscle groups may also contribute substantially to the composition of tremor.

With this in mind, kinematic protocols may offer a unique method for evaluating tremor beyond the traditional metrics of amplitude and frequency by enabling the study of individual features of tremor composition. Treatments for tremor, such as BoNT A injection, may benefit from the information yielded by the study of tremor composition, enabling more precise injection techniques.

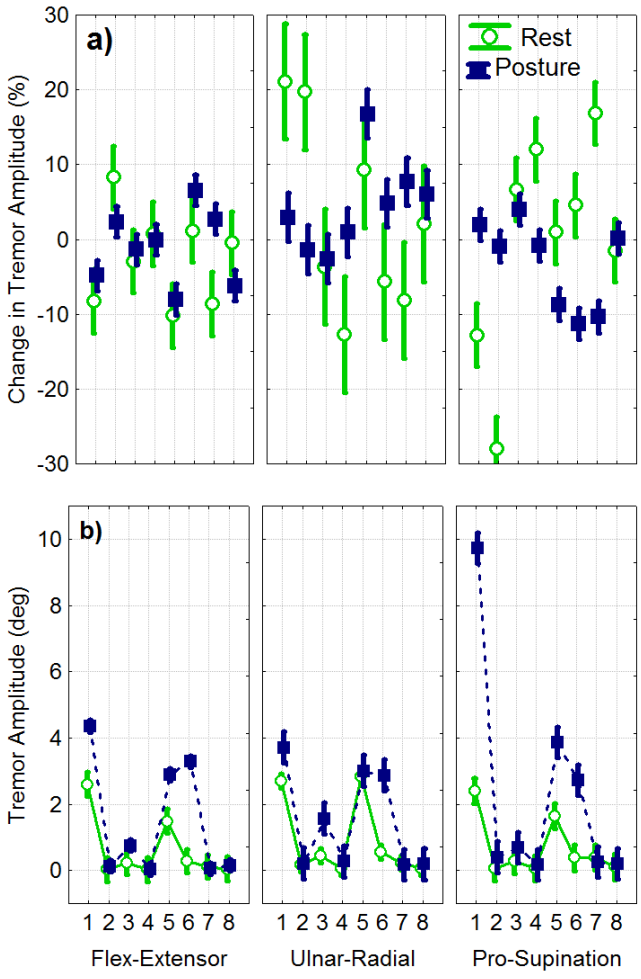

Fig. 3. Variability of change in tremor composition from Trial 1 to Trial 2, and from Trial 1 to Trial 3, and between tasks (a). Variability of tremor amplitude between three trials, between tasks, for all 3 DOF components, (b)

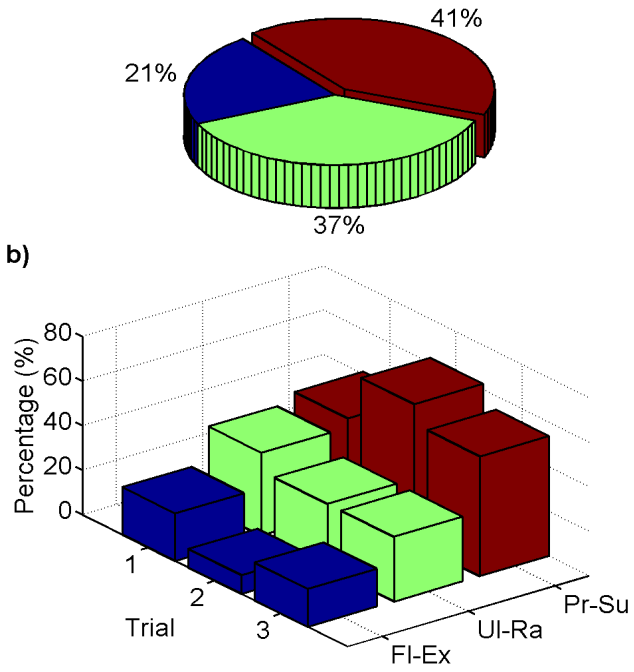

Fig. 4. Composition of wrist tremor for P#12 at rest. Contribution of each of the three components (flexion-extension, ulnar-radial deviation, and pronation-supination) in Trial 1, (a). Repeatability of tremor composition among three trials in rest, (b).

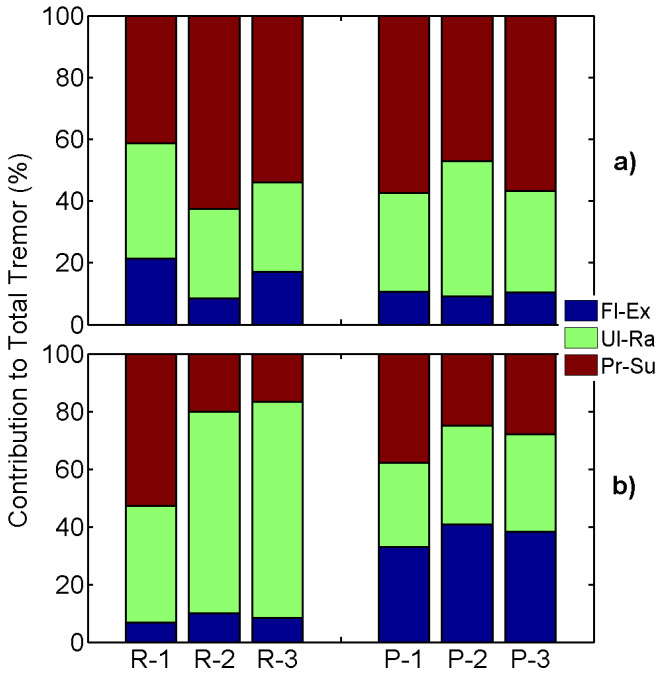

Fig. 5. Comparison of wrist tremor components in trials of rest (R1, R2, and R3) and posture (P1, P2, and P3). The same participant as in Fig. 1, (a). Participant #11 with clear change in tremor composition by change in task, (b).

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REFERENCES

[1] RJ Elble, WC Koller. Baltimore: Tremor Johns Hopkins University Press, 1990.

[2] KJ Jankovic, W Schwartz, A Clemence, A Aswad, and J Mordaunt. "A randomized, double-blind, placebo-controlled study to evaluate botulinum toxin type A in essential hand tremor," *Movement Disorders*. 11(3):250-6, 1996.

[3] MF Brin, KE Lyons, J Doucette, CH Adler, JN Caviness, CL Comella, RM Dubinsky, JH Friedman, BV Manyam, JY Matsumoto, SL Pullman, AH Rajput, KD Sethi, C Tanner, and WC Koller. "A randomized, double masked, controlled trial of botulinum toxin type a in essential hand tremor," *Neurology*. 56(11):1523-8, 2001.

[4] DM Simpson, A Blitzer, A Brashear, C Comella, R Dubinsky, M Hallett, J Jankovic, B Karp, CL Ludlow, J M Miyasaki, M Nau-mann, and Y So. "Assessment: Botulinum neurotoxin for the treatment of movement disorders (an evidence-based review)," *Neurology*. 70(19):1699-1706, 2008.

[5] JK Sheffield and J Jankovic. "Botulinum toxin in tic disorders and essential hand and head tremor, " in Manual of Botulinum Toxin Therapy, D. D. Daniel Truong and M. Hallett, Eds. Cambridge University Press, 2009.

[6] P Wade, MA Gresty, and LJ Findley. "A Normative Study of Postural Tremor of the Hand'. *Arch Neurol*. 39(6):358-362, 1982.

[7] S Calzetti, M Baratti, M Gresty, and L Findley. "Frequency/amplitude characteristics of postural tremor of the hands in a population of patients with bilateral essential tremor: implications for the classification and mechanism of essential tremor ". *Journal of Neurology, Neurosurgery, and Psychiatry*. 50:561-567, 1987.