

2017-09-01

Distribution of Essential Tremor in the Degrees of Freedom of the Upper Limb

Adam Charles Pigg
Brigham Young University

Follow this and additional works at: <https://scholarsarchive.byu.edu/etd>

BYU ScholarsArchive Citation

Pigg, Adam Charles, "Distribution of Essential Tremor in the Degrees of Freedom of the Upper Limb" (2017). *All Theses and Dissertations*. 7212.
<https://scholarsarchive.byu.edu/etd/7212>

This Thesis is brought to you for free and open access by BYU ScholarsArchive. It has been accepted for inclusion in All Theses and Dissertations by an authorized administrator of BYU ScholarsArchive. For more information, please contact scholarsarchive@byu.edu, ellen_amatangelo@byu.edu.

Distribution of Essential Tremor in the Degrees of Freedom of the Upper Limb

Adam Charles Pigg

A thesis submitted to the faculty of
Brigham Young University
in partial fulfillment of the requirements for the degree of
Master of Science

Steven K. Charles, Chair
Brian Jeffs
Jonathan D. Blotter

Department of Mechanical Engineering
Brigham Young University

Copyright © 2017 Adam Charles Pigg

All Rights Reserved

ABSTRACT

Distribution of Essential Tremor in the Degrees of Freedom of the Upper Limb

Adam Charles Pigg
Department of Mechanical Engineering, BYU
Master of Science

This study seeks to understand upper limb tremor in subjects with essential tremor (ET). A thorough understanding of tremor distribution will allow for the more effective development of tremor suppression devices, which offer an alternative to current treatments. Previous studies primarily focused on tremor in the hand only. This study seeks to characterize the distribution of tremor throughout the upper limb.

We measured tremor in 25 subjects diagnosed with ET using motion capture, which provided displacement information of the limb during multiple postural and kinetic tasks. Inverse kinematics allowed us to analyze the motion capture data in the 7 major degrees of freedom (DOF) of the upper limb. The power spectral density estimate was used to determine: relative tremor magnitude throughout the DOFs, tremor variation between tasks, variation between subjects, and frequency variations between DOFs.

Data analysis revealed that tremor increase is roughly proximal to distal. We also show that tremor magnitude in kinetic tasks is significantly higher than in postural tasks. Although we found some variation in tremor distribution between subjects, the roughly proximal to distal increase in tremor severity holds for several subsets of the study population. Finally, we found that tremor frequency doesn't vary significantly (< 1 Hz) between DOFs, in subjects with severe tremor.

Our study shows that tremor distribution is quite stereotyped between subjects with ET. Furthermore, we have shown that tremor is greatest in the distal DOFs. This provides a compelling starting point for the development of future tremor suppression devices.

Keywords: essential tremor, motion capture, inverse kinematics, power spectral density, tremor characterization, tremor distribution, upper limb, degrees of freedom

ACKNOWLEDGEMENTS

Funding for this research was provided by NIH Grant R15NS087447. This thesis is the product of many hands who have helped me along the way. I am truly grateful for the help and support of the staff of the Human Motor Control Section of the National Institute of Neurological Disorders and Stroke at the National Institutes of Health Clinical Center. I am especially grateful of the guidance and direction provided by Drs. Mark Hallett and Dietrich Haubenberger, and the assistance of Johanna Thompson-Westra, Dr. Carine Maurer, Dr. Karin Mente, Dr. Nancy Bowen, Barbara Kimber, Elaine Considine, Nguyet Dang, and Katy Finnell. The successfulness of the data collection for this project is directly related to their kindness and willingness to help a new clinical researcher.

If it wasn't for the guidance and direction of my graduate committee, the data collected at the NIH would be of little use to anyone. I appreciate the accessibility of my committee, as they were always willing to help me find a new method to look at the data, or provide guidance on my future endeavors. Thank you Dr. Blotter, Dr. Charles, and Dr. Jeffs, you have made this possible.

Finally, I'd like to recognize the important influence of my family. Their willingness to follow me into adventure and their never-ending support has been a constant in a sea of change. They are my guiding light. Thank you Esther, Ada, Eliana, and future Pigg-lets.

TABLE OF CONTENTS

LIST OF TABLES	v
LIST OF FIGURES	vi
1 INTRODUCTION	1
1.1 Background	1
1.2 Objective	2
2 METHODS	3
2.1 Subjects	3
2.2 Experimental Set-up	4
2.3 Experimental Protocol	6
2.4 Data Processing	7
3 RESULTS	11
3.1 Overall Distribution	11
3.2 Postural v. Kinetic Tremor	15
3.3 Subject Variability	15
3.4 Frequency	15
4 DISCUSSION	20
4.1 Background	20
4.2 Main Findings	20
4.3 Methods	22
4.4 Limitations	23
4.5 Conclusion	24
REFERENCES	25

LIST OF TABLES

Table 2-1: Subject Demographics.....	4
--------------------------------------	---

LIST OF FIGURES

Figure 2-1: Experimental Set-up.....	6
Figure 3-1: Representative Postural Test Data	11
Figure 3-2: Representative Test Data for a Single Subject.....	12
Figure 3-3: Comparison of Power in Postural and Kinetic Tests	13
Figure 3-4: Distribution of Tremor Magnitude Throughout the DOF	14
Figure 3-5: Differences in Kinetic and Postural Task Tremor Distribution	16
Figure 3-6: Subject Variability of Tremor	17
Figure 3-7: Tremor Distribution by Demographic Subgroup	18
Figure 3-8: Frequency Distribution Throughout the DOF of a Subject with Severe Tremor.....	19

1 INTRODUCTION

1.1 Background

Essential Tremor (ET) is one of the most common movement disorders, affecting approximately 7 million people in the U.S. [1]; and, although treatments are available, many patients are left without satisfactory treatment options. The most efficacious medications, propranolol and primidone, are only effective in 50% of patients and, on average, only provide a 50% reduction in tremor [2]. Botulinum toxin A injections also provide some tremor reduction but are accompanied by dose-dependent weakness in the hand [3], [4]. Surgical methods such as deep brain stimulation produce a greater reduction in tremor but are highly invasive; consequently, only few patients opt for surgical treatment (on the order of 1 in 30) [5]. In a recent survey designed to discover gaps in their current care, ET patients listed “a treatment approach other than just medications and surgery” as one of the top items [6].

Tremor-suppressing devices offer a potential alternative to medication and surgery, but optimizing these devices to provide the greatest benefit requires an understanding of how tremor is distributed throughout the upper limb. To clarify, the goal of tremor-suppressing devices is generally to reduce tremor at the hand, but tremor at the hand is the result of tremor at joints throughout the upper limb. To optimally suppress tremor at the hand, we must understand which joints contribute most to hand tremor. Surprisingly, the distribution of tremor among the joints of the upper limb is completely unknown for ET, though it has been investigated for physiological

tremor [7], [8], [9], [10]. Most past studies on ET have focused on tremor in a single joint (often wrist flexion-extension) or on endpoint tremor at the hand [11]. Although such focused approaches are clearly appropriate for many investigations, they do not reveal how different joints contribute to tremor at the hand.

1.2 Objective

To develop more effective tremor suppression devices, and to gain a more thorough understanding of ET, we characterized the distribution of tremor in the upper limb of 25 patients with ET. More specifically, we measured the displacement due to tremor in each of the seven main degrees of freedom (DOF) from the shoulder to the wrist. These data were used to determine the power and peak power in the 4-12 Hz band in each DOF. Comparing these measures between DOF allowed us to characterize the distribution of tremor throughout the upper limb. This information provides a more thorough understanding of ET and will enable future work to determine where a subject's tremor originates mechanically (which muscles) and how it propagates through the upper limb and results in tremor at the hand, which is necessary to developing more effective tremor suppression devices.

2 METHODS

2.1 Subjects

Twenty-five subjects with ET completed the study at the NIH Clinical Center in Bethesda, MD, but two subjects were later excluded because of technical difficulties during data collection, so here we present results from 23 subjects (Table 2-1). Prior to beginning the study each subject provided informed consent in accordance with NIH's Institutional Review Board. Within one year prior to the experiment, each subject underwent a neurological exam performed by a neurologist specializing in movement disorders. The neurologist assessed the subject's tremor and determined if it was consistent with ET or other tremor disorders. Subjects were excluded from our study if their history included stroke, head trauma, seizures, movement disorders other than Essential Tremor, psychotic disorders, or a current cardiac pacemaker or brain stimulator. In particular, if the subject's tremor was found to include elements from other tremor disorders (e.g. Parkinson's Disease or Dystonia), the subject was excluded from the experiment. Before the experiment, each subject was evaluated using The Essential Tremor Rating Assessment Scale (TETRAS) [12], [13],[14], which was performed by one of two people: a neurologist (DH) specializing in tremor or a research assistant (ACP) trained by DH in administering the TETRAS. The TETRAS was used to ensure that the study included a broad distribution of tremor severity (Table 2-1).

Table 2-1: Subject Demographics Not included in the table is handedness and family history of ET. All but two subjects were right handed, and all but two had a family history of tremor.

Subject	Sex	Age	Age of Onset	Duration	TETRAS Scales				Numerical
					ADL	Performance	Total	Severity	Severity
10	M	69	65	4	7	14	21	Mild	4.08E+04
20	M	72	25	47	13	13.5	26.5	Mild	2.66E+04
21	M	65	17	48	15	18	33	Mild	1.70E+04
8	M	48	5	43	14	20	34	Mild	1.74E+05
18	M	70	64	6	18	16.5	34.5	Mild	3.62E+04
24	F	52	28	24	16	18.5	34.5	Mild	1.34E+05
2	F	63	20	43	19	18	37	Moderate	3.48E+04
19	F	70	22	48	15	22.5	37.5	Moderate	8.45E+04
17	M	56	17	39	23	17.5	40.5	Moderate	1.62E+04
14	F	61	35	26	24	20	44	Moderate	4.48E+04
1	M	63	16	47	24	20.5	44.5	Moderate	1.56E+05
6	F	66	45	21	25	20	45	Moderate	5.84E+04
4	M	69	8	61	25	21.5	46.5	Moderate	1.90E+04
15	M	64	13	51	28	18.5	46.5	Moderate	4.22E+04
23	M	69	49	20	22	25.5	47.5	Moderate	3.94E+04
12	F	75	65	10	28	20	48	Moderate	6.72E+04
9	M	51	16	35	28	21	49	Moderate	6.83E+04
13	F	76	55	21	26	28.5	54.5	Moderate	4.22E+05
7	F	81	57	24	30	26.5	56.5	Severe	2.86E+04
25	F	20	5	15	30	32	62	Severe	4.44E+05
5	M	58	25	33	29	35	64	Severe	2.50E+05
3	M	69	17	52	29	37	66	Severe	5.20E+05
16	F	69	8	61	33	36	69	Severe	1.33E+06

2.2 Experimental Set-up

Five electromagnetic motion capture sensors (trakSTAR 3DGuidance by Ascension Technologies, Shelburne, VT) were placed on the trunk and right arm of subjects in the following locations: sternum, inferior to the suprasternal notch; acromion, straddling the acromial angle; dorsal aspect of the distal upper arm, proximal to the elbow; dorsal aspect of the distal forearm, a few centimeters proximal to the wrist joint center; dorsum of the hand, bridging the third and fourth metacarpals. A sixth motion capture sensor, placed on the end of a stylus,

was used for calibration. These sensors measure motion in 6 DOF with a static accuracy of 1.4 mm in translation and 0.5° in rotation. Data were collected at 360 samples/sec. Subjects were also instrumented with wireless surface EMG sensors (Trigno IM by Delsys, Natick, MA) over 15 muscles of the upper limb (data not included in this paper).

To calibrate the motion capture setup, we used the landmark calibration method recommended by the International Society of Biomechanics [15], with a slight modification to the landmarks on the hand to enable in-vivo use, as explained in detail in [16]. Briefly, the stylus was used to record the location of specific landmarks on the trunk and upper limb relative to the motion capture sensors. To locate the center of rotation of the glenohumeral joint, we found the instantaneous center of rotation from subjects' movements in shoulder flexion, extension, and abduction [16].

During the experiment, subjects were seated comfortably in front of a table. On top of the table were 7 targets distributed throughout the workspace of the subject (Figure 2-1). Each target was the end of a thin piece of foam mounted on a dowel. We measured tremor as subjects pointed at a target or moved between targets (see below), so foam targets were used because they would bend easily and interfere minimally with subject's tremor if the subject touched the target. The seven targets represented posture and movement locations common to activities of daily living. Five targets were arranged roughly in the horizontal plane (targets 1-5 in Figure 2-1). The closest target (target 5) was placed roughly 4 cm from the subject in the sagittal plane, approximately at the level of the xyphoid process. The target farthest from the subject (target 1) was also in the sagittal plane, placed so the subject could touch it with the tip of his/her index finger when the elbow was extended at 30 degrees. The three middle targets (targets 2-4) were placed halfway between the farthest and nearest target, with the left and right targets (targets 2

and 4) placed at 45 degree from the line connecting the closest and farthest targets. Two additional targets (targets 6 and 7) were placed directly above the closest target (target 5) at the level of the top of the subject's head and the bottom of the subject's chin, respectively (Figure 2-1).

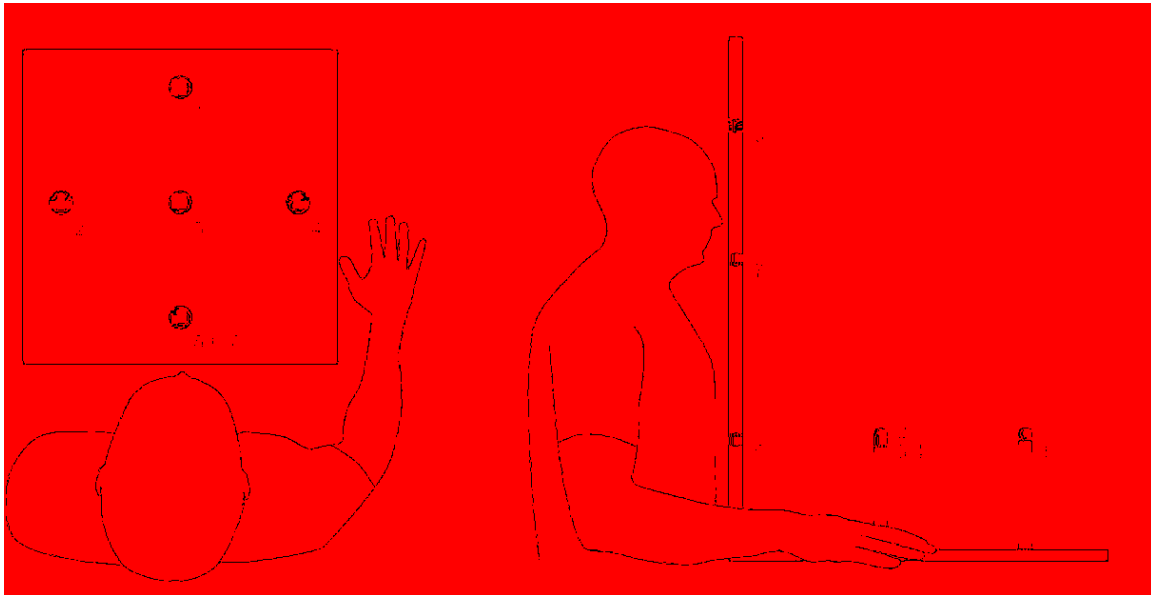


Figure 2-1: Experimental Set-up from top (left) and side (right) views. Both views show the subject's right hand in the rest position beside the set-up. The numbers refer to the targets which the subject pointed at, or touched, depending on the test (postural or kinetic).

2.3 Experimental Protocol

The experiment included postural and kinetic trials to allow us to measure both postural and kinetic tremor. During postural trials, subjects were instructed to point at a given target with their index finger, getting close to the target without touching it, and to hold that position for 30 seconds. We asked subjects to avoid touching the targets to minimize sensory feedback, which could potentially affect the tremor. Subjects repeated this task for each of the seven targets, in pseudo-random order. During kinetic trials, subjects moved back and forth between target 5 and a given target for 30 seconds. We instructed subjects to touch the targets and to move at a speed

that could be maintained comfortably for the duration of the test. Subjects repeated this task for each of the 6 targets (not counting target 5), also in pseudo-random order. Whether a given subject first performed the postural or kinetic trials was also randomized. At the end of each 30 second trial, subjects were asked to place their hand in a predefined area (Figure 2-1) for 5 to 10 seconds; this allowed some rest and provided a data marker for the beginning and end of each trial. After completing the postural and kinetic trials, subjects repeated the whole process two more times, resulting in 21 postural and 18 kinetic trials per subject. The total time to complete all of the trials was approximately one hour.

2.4 Data Processing

Following the inverse kinematics method described in [16], we converted the motion capture sensor data into joint angles in the following DOF (positive direction listed in parentheses): shoulder flexion-extension (flexion), shoulder abduction-adduction (adduction), shoulder internal-external humeral rotation (internal rotation), elbow flexion-extension (flexion), forearm pronation-supination (pronation), wrist flexion-extension (flexion), and wrist radial-ulnar deviation (ulnar deviation). The carrying angle of the elbow and axial rotation angle of the wrist (about the long axis of the third metacarpal) were assumed to be zero. As explained in [16], we followed the ISB recommendations [15] in defining all DOF except the three DOF in the shoulder. The ISB convention places anatomical shoulder position (zero flexion-extension, abduction-adduction, and humeral internal-external rotation) in gimbal lock, where joint angles are ill-defined. Since many of our postures and movements are close to anatomical shoulder position, we defined the shoulder DOF using a Z-X-Y rotation sequence, which moves gimbal lock far from anatomical shoulder position (in 90° of shoulder abduction). As mentioned above,

our definition parses shoulder movement into shoulder flexion-extension, abduction-adduction, and internal-external humeral rotation.

After converting the motion sensor data to joint angles, we calculated angular acceleration in each DOF using numerical differentiation. Prior to each differentiation, the data were filtered using a 10th order Butterworth filter with cut-off frequency at 20 Hz. The power spectral density of the acceleration data was estimated using Welch's method, implemented via Matlab's pwelch function. After testing several window sizes, 18 windows with 50% overlap were selected as it offered the best balance between frequency resolution, noise reduction, and peak detection.

The following tremor measures were calculated from the power spectral density of each DOF: the power in the tremor band (4-12 Hz) and the amplitude and frequency of the tallest peak in the tremor band. Power was determined by numerical integration of the power spectral density from 4 to 12 Hz. Peak detection was performed over the 4 – 12Hz band using a sliding-window constant-false-alarm-rate detection algorithm [17], with a 1.0 Hz window and 1.5 Hz sidebands. This method performs a statistical comparison between the maximum in the sliding window and the means of the sidebands. A maximum was considered to be a peak if its amplitude was statistically significantly greater than the sidebands ($\alpha = 0.05$), i.e. if its amplitude was at least 2 standard deviations above the mean of the sidebands. If more than three peaks were detected, the 3 peaks with the greatest amplitude were reported.

Data Analysis

The primary purpose of the analysis was to determine which DOF were most affected by tremor and how this distribution varied between tasks (postural vs. kinetic) and subjects. To ensure robustness in our results, we compared tremor between DOF using multiple measures and

multiple comparison methods. First, we compared the tremor-band power between DOF in the following ways: 1A) We summed the power in each DOF across all 39 trials and ranked the DOF in terms of total power, and 1B) we ranked the DOF in terms of power for each trial and summed up the rankings (1-7) across all 39 trials, resulting in a total ranking across all trials. Second, we repeated A-B using the amplitude of the tallest peak in the tremor band instead of power (2A and 2B). Since the methods performed similarly, all of the reported results use methods 1A and 1B.

To determine the effect of task (postural vs. kinetic) on tremor distribution, we repeated these four comparison methods (1A-B and 2A-B) separately for the 21 postural trials vs. the 18 kinetic trials. The effect of subject characteristics on tremor distribution was investigated for four characteristics: sex, age of onset, duration of disorder, and tremor severity. Dividing by sex separated the subjects into male (13 subjects) and female (10 subjects) groups. Dividing by age of onset resulted in three groups: early onset (≤ 20 years, 11 subjects), middle onset (> 20 and ≤ 60 years, 9 subjects), and late onset (> 60 years, 3 subjects). Disorder duration was determined by subtracting the subject's estimated age of onset from their current age and was divided into three groups: short duration (≤ 20 years, 5 subjects), medium duration (> 20 and ≤ 40 years, 8 subjects), and long duration (> 40 years, 10 subjects). Tremor severity was determined by summing a subject's power over all trials and DOF and dividing subjects according to total power into groups: mild tremor ($< 4 \times 10^4 \text{ deg}^2/\text{sec}^4$, 8 subjects), moderate tremor ($\geq 4 \times 10^4$ and $< 10^5 \text{ deg}^2/\text{sec}^4$, 7 subjects), and severe tremor ($\geq 10^5 \text{ deg}^2/\text{sec}^4$, 8 subjects). For all subject characteristics, the distribution of tremor among DOF was determined for each group by summing each subject's power in each DOF across all 39 trials and averaging across all subjects within a group. We then

compared the ranked DOF between groups. These comparisons were then repeated separately for the 21 postural trials vs. the 18 kinetic trials.

We were also interested in whether tremor in different DOF exhibited the same frequency. To characterize the dominant frequencies in each DOF, we created for each subject a histogram of the frequency of the tallest peak in each DOF across all 39 trials. These histograms were then compared across DOF.

3 RESULTS

3.1 Overall Distribution

As described above, raw sensor data were transformed into joint angles, filtered joint accelerations, and finally power spectral density estimates (Figure 3-1). Subjects exhibited a wide range of tremor amplitudes; between subjects, power spectral density peaks varied over several orders of magnitude (Figure 3-1).

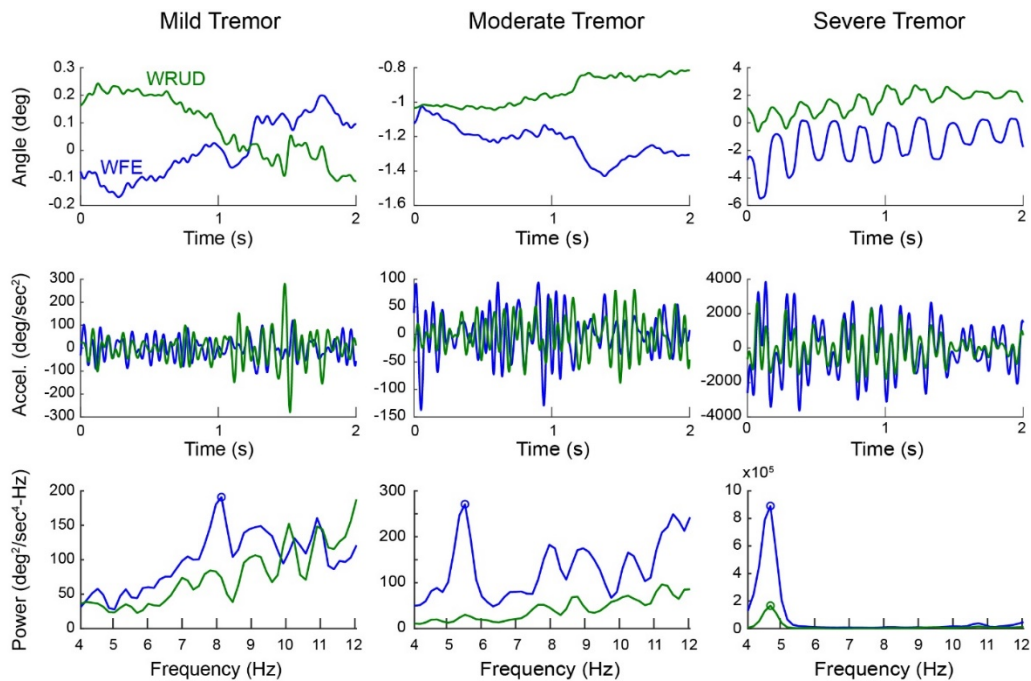


Figure 3-1: Representative Postural Test Data for wrist flexion-extension (WFE) and wrist radial-ulnar deviation (WRUD) in mild, moderate, and severe subjects. The top row shows joint angle data. The second row depicts angular acceleration, and the bottom row shows the power spectral density estimate for the 2 DOFs. Of particular consequence are the difference in tremor magnitudes between mild, moderate, and severe tremor, which is clearly seen in the scaling of the power spectral density estimates.

For most subjects, some DOFs clearly had more tremor than others (Figure 3-2). Whether compared in terms of tremor-band power or peak amplitude, the DOF usually separated into a clear hierarchy. On average, the DOF with the greatest tremor had about 26 times more power than the DOF with the least tremor (Figure 3-3). The exact order varied slightly between tasks (postural vs. kinetic) and subjects (see below), but averaged over all tasks and subjects, tremor increased roughly from proximal to distal except that SIE and WRUD were slightly out of order: SAA < SFE < EFE < WRUD, SIE < FPS, WFE (Figure 3-4).

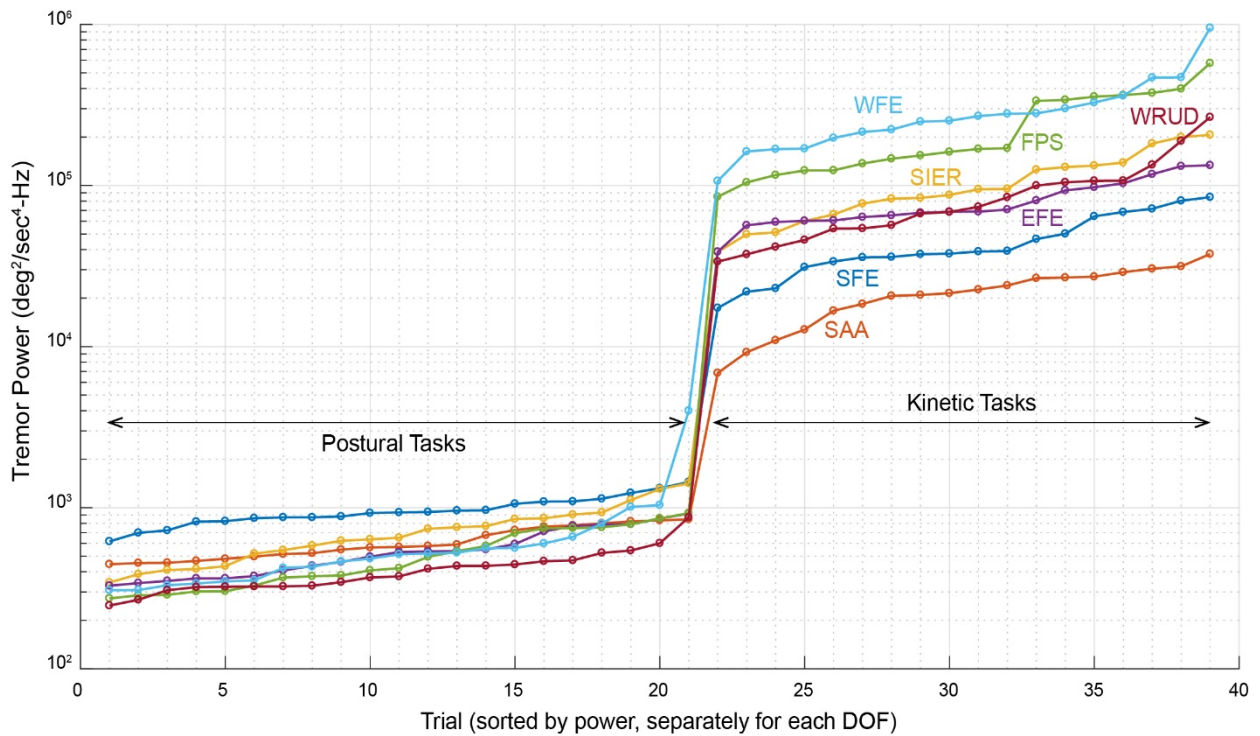


Figure 3-2: Representative Test Data for a Single Subject, sorted by increasing total power over all trials. Total power in postural trials (left) is up to 3 orders of magnitude lower than total power in kinetic trials (right).

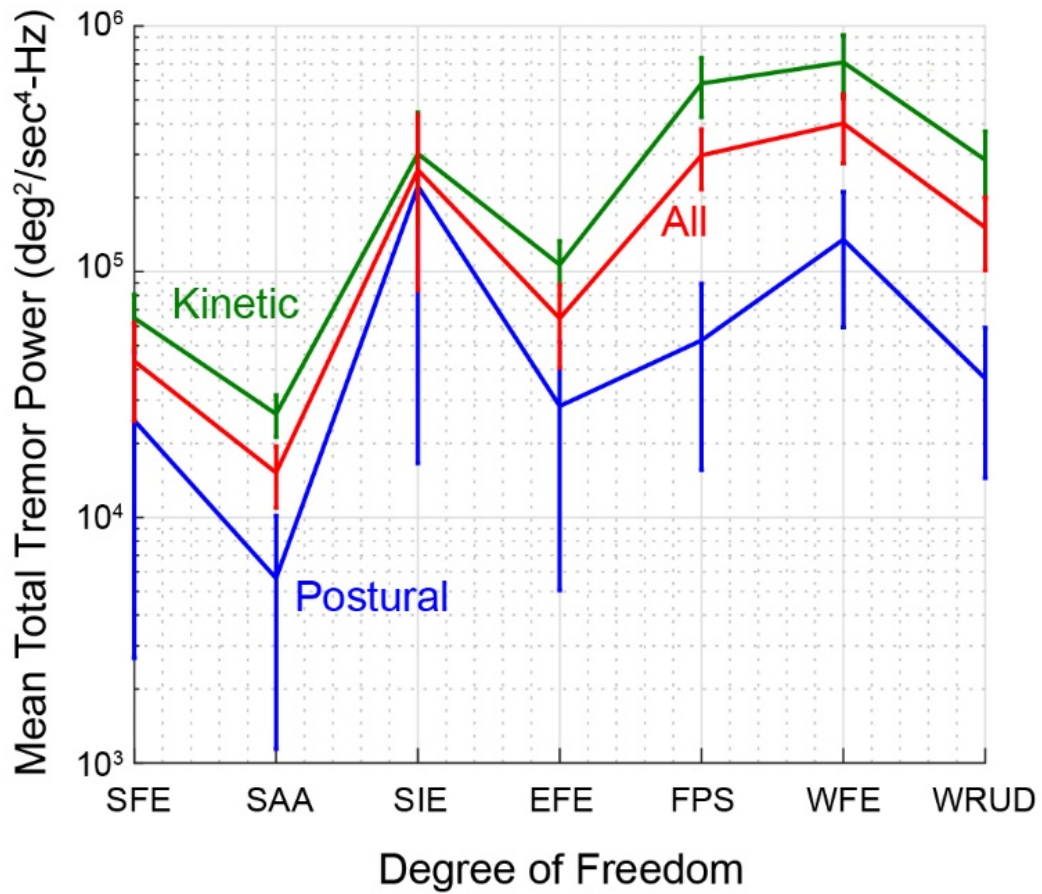


Figure 3-3: Comparison of Power in Postural and Kinetic Tests. The combined data is the average total power of all tests, postural and kinetic.

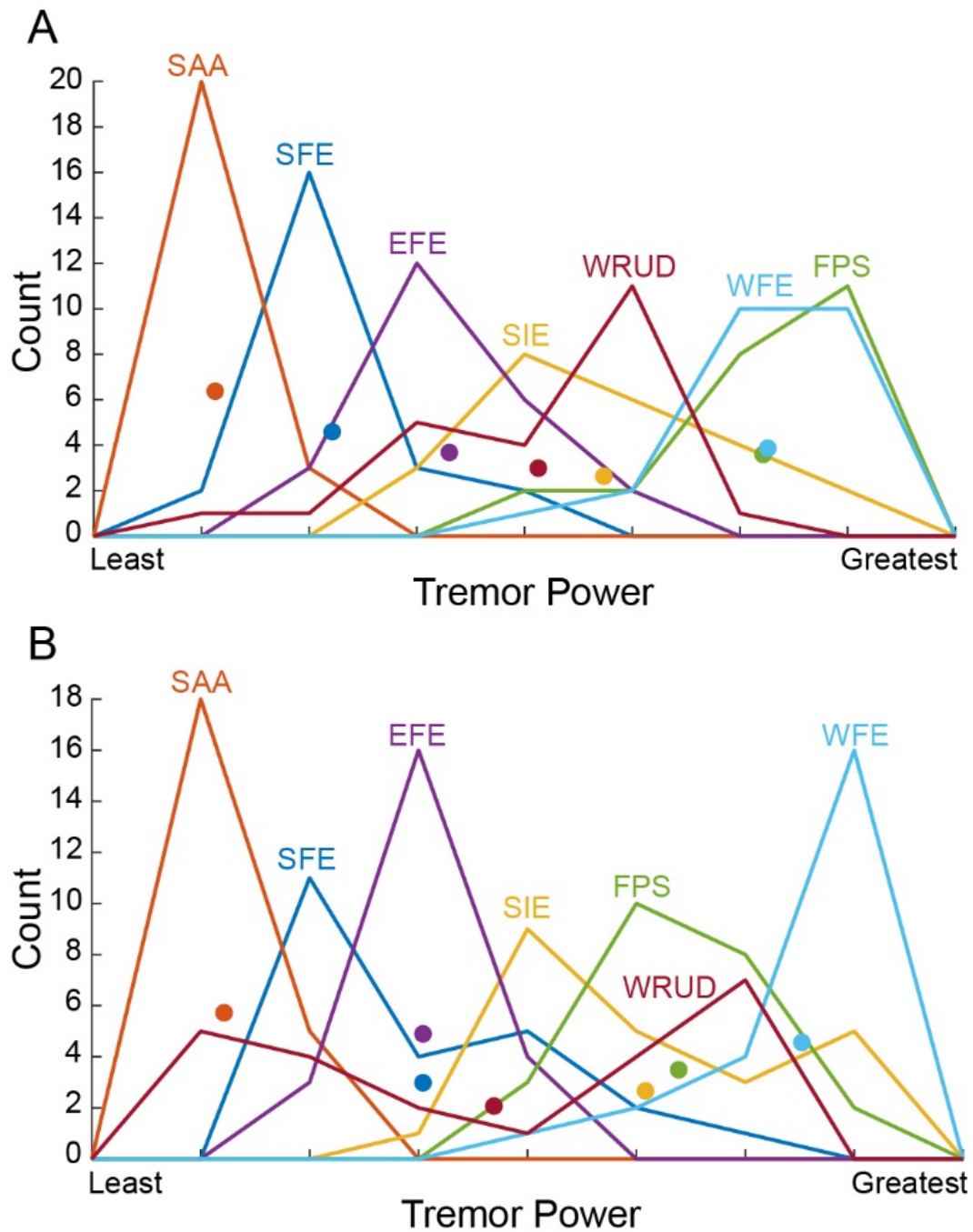


Figure 3-4: Distribution of Tremor Magnitude Throughout the DOF. A: Data analyzed using method 1A, summation of areas (e.g. total power). B: Data analyzed with method 1B, sorted areas. Count, on the y-axis, denotes the number of times that a DOF was given a particular ranking from least to greatest, for the 23 subjects. Centroids of the distributions noted with markers of the same color as the DOF.

3.2 Postural v. Kinetic Tremor

Subjects exhibited far more tremor during kinetic tasks than during postural tasks (Figure 3-3). Averaged across subjects, kinetic tremor had 67 times more power (range 1–286) than postural tremor. There were slight differences in tremor distribution between postural and kinetic tasks. However, in either task, SAA had the least tremor and WFE had some of the greatest tremor (Figure 3-5).

3.3 Subject Variability

The distribution of tremor varied somewhat between subjects, though most subjects showed a roughly proximal-to-distal increase in tremor (Figure 3-6). To determine if this variability was due to differences in subject characteristics, we plotted the distribution between DOF separately by sex, age of onset, duration of disorder, and tremor severity (Figure 3-7). The distribution was similar for all groups, indicating that these subject characteristics did not have a significant effect on tremor distribution.

3.4 Frequency

Peaks were detected in only some of the power spectral density plots. Overall, at least one peak was detected in a DOF's power spectral density in 81% of trials (range 70-90%). Subjects with more severe tremor generally exhibited clearer peaks (Figure 3-1). For severe subjects, the frequencies of the peaks in different DOF tended to fall within 1 Hz of each other, suggesting that the DOF within a limb tremored at the same frequency (Figure 3-8). We performed the same analysis for subjects with mild and moderate tremor but the results were unreliable because their power spectral densities exhibited fewer peaks.

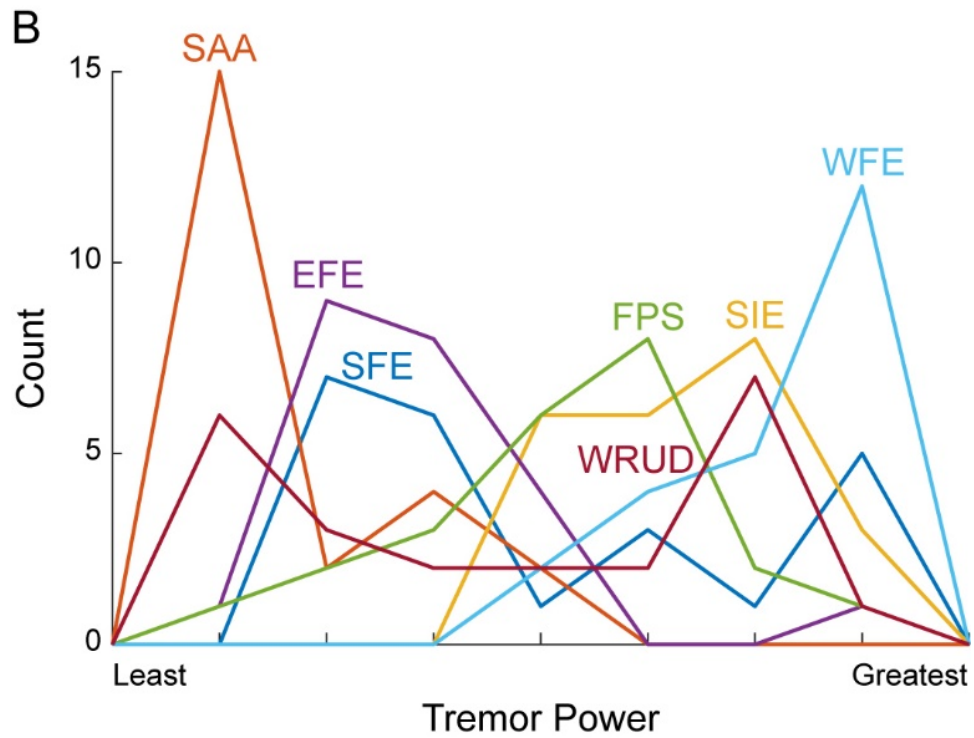
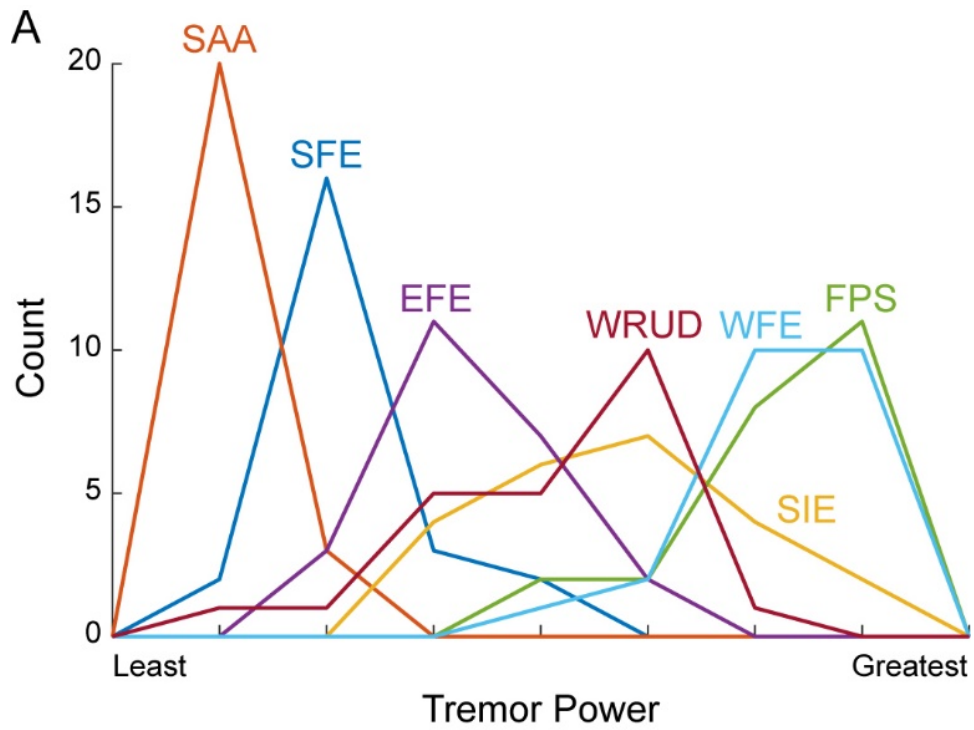


Figure 3-5: Differences in Kinetic and Postural Task Tremor Distribution. A: Kinetic tasks. B: Postural tasks. Although tremor increases roughly proximal to distal in both tasks, the distribution in kinetic tasks is much more apparent.

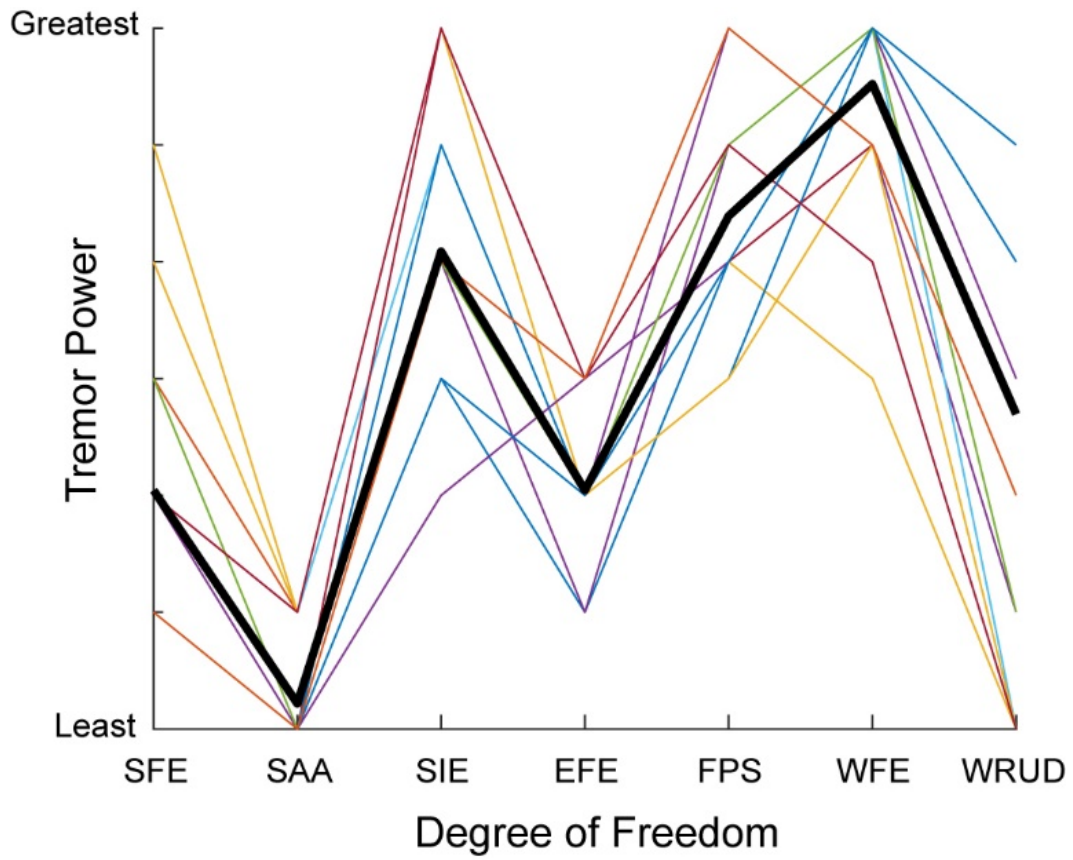


Figure 3-6: Subject Variability of Tremor. The bold line represents the average over 23 subjects.

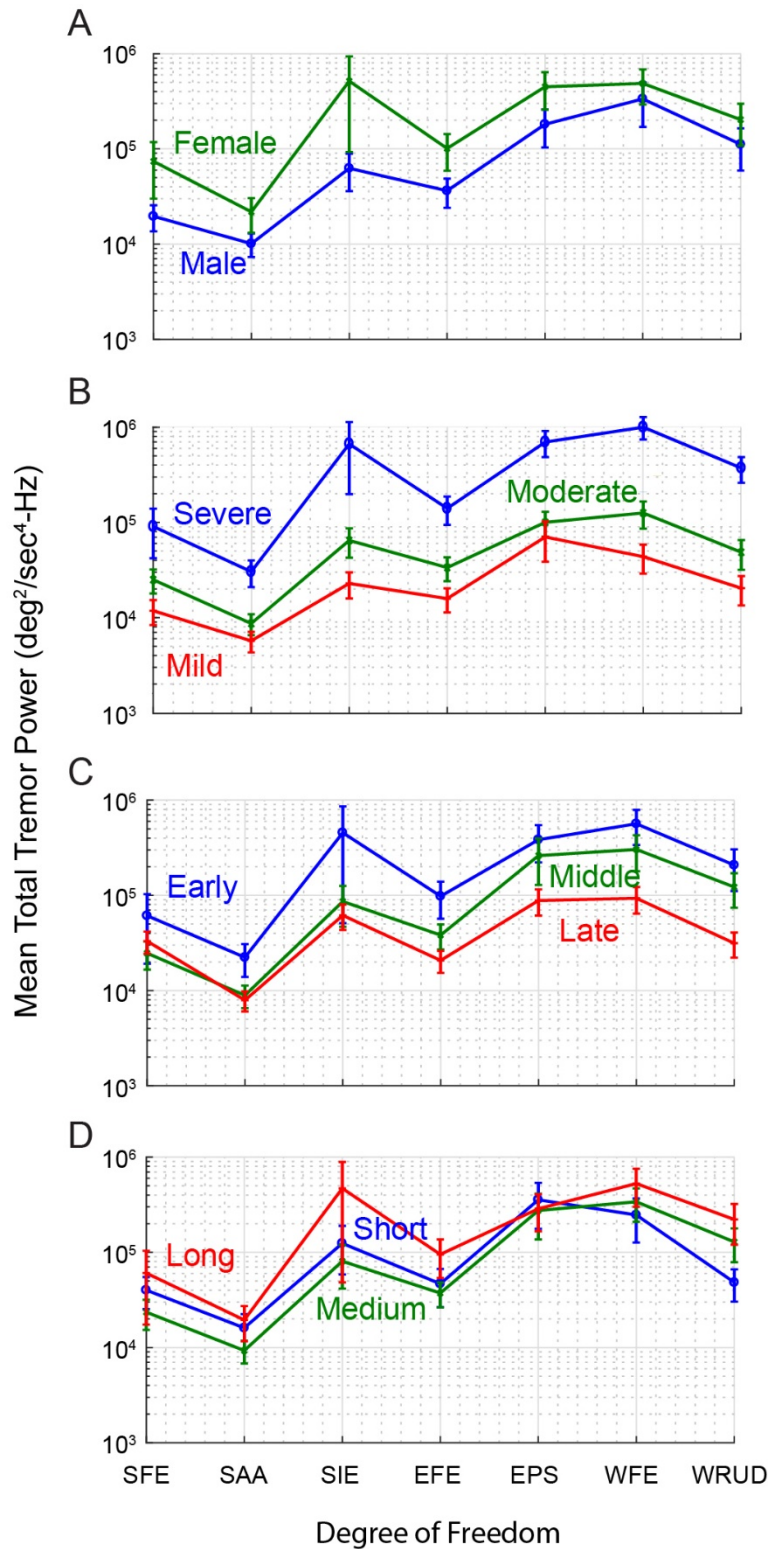


Figure 3-7: Tremor Distribution by Demographic Subgroup. Although there are slight variations within the subgroups, in general tremor increases from proximal to distal. A: Subjects analyzed by sex. B: Subjects analyzed by severity. C: Subjects analyzed by age of onset. D: Subjects analyzed by disorder duration.

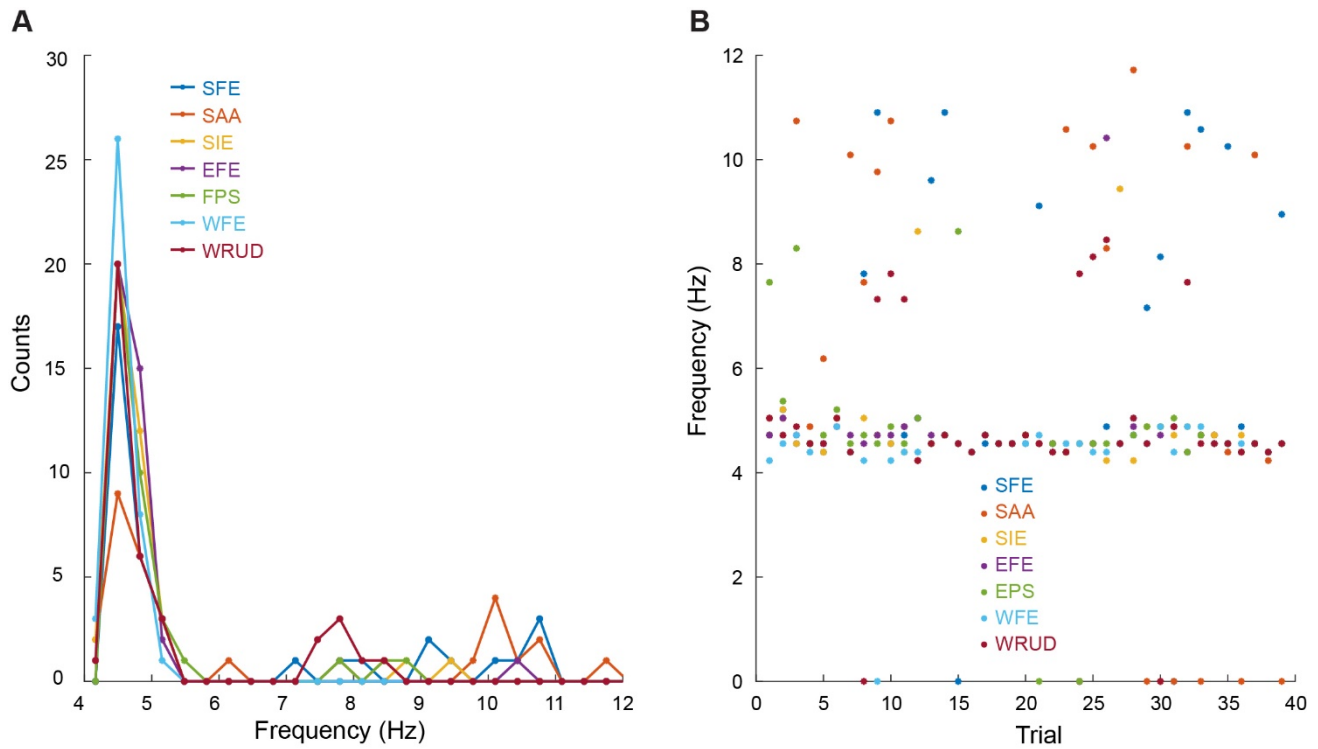


Figure 3-8: Frequency Distribution Throughout the DOF of a Subject with Severe Tremor. A: Graphical representation of histogram of peaks detected for each DOF. As shown, the vast majority of peaks fall within 4 to 5 Hz. This indicates that tremor frequency is roughly the same throughout all DOFs. B: Data for all DOFs over all tests (postural and kinetic) for the same subject. This is an alternative way of showing that the majority of peaks detected occurred around 5 Hz and reinforces the notion that tremor frequency is constant among DOFs regardless of test (postural or kinetic). Data points at 0 Hz indicate a trial where no peak was detected.

4 DISCUSSION

4.1 Background

Past research in ET has generally focused on tremor in a single DOF or at the hand. Such studies are certainly appropriate for isolating and understanding neuromuscular phenomena of tremor. However, tremor is also a musculoskeletal phenomenon; because the DOF of the musculoskeletal system are mechanically coupled, tremor spreads from a given muscle proximally and distally throughout the upper limb. Therefore, understanding tremor and how best to intervene also requires studies involving multiple DOF. Here we have taken a step in this direction by characterizing how ET is distributed among the DOF of the upper limb.

4.2 Main Findings

We found the distribution of tremor to be quite stereotyped: subjects' tremor tended to exhibit clear separation between DOF in terms of tremor amplitude (Figure 3-2) and increase in a roughly proximal-distal manner (Figure 3-4): $SAA < SFE < EFE < WRUD$, $SIE < WFE$, FPS . This distribution was relatively robust against differences in tasks (postural vs. kinetic) and differences between subjects (sex, age of onset, duration of disorder, and tremor severity). In their investigations of physiological tremor in healthy subjects with fully extended arms, Morrison and Newell similarly found that the linear acceleration of limb segments increased in a proximal-distal manner (in excess of what would be expected due to the kinematic chain) [7].

There is no a priori reason to assume that the distribution of ET would be stereotyped. Distal limb segments certainly “inherit” some of the movement of proximal limb segments, which can cause the absolute movement of limb segments to grow from proximal to distal. However, we quantified tremor in terms of the angular motion of one DOF relative to another, so the proximal-distal increase in tremor we observed is not a simple consequence of the kinematic hierarchy. Instead, the distribution of tremor should be viewed as the result of a multi-input multi-output filtering operation, with tremorogenic activity in various muscles as the inputs, the musculoskeletal system as the filter, and tremor in various DOF as the outputs [18]. In other words, tremor is the product of both the input and the filter. The filtering properties of the musculoskeletal system are similar between subjects and have been shown to favor a proximal-distal increase in tremor [18]. However, this is only half of the story since the distribution of tremor also depends on the distribution of tremorogenic activity among the muscles of the upper limb (the inputs). There is no a priori reason to assume that this distribution would be similar between subjects, especially since the amount of tremor varied over several orders of magnitude between subjects. The fact that the distribution of tremor was quite stereotyped suggests that the distribution of tremorogenic activity among the muscles of the upper limb may be stereotyped as well—as far as we know, this has not been measured.

We also found that subjects’ kinetic tremor was significantly greater than their postural tremor. This finding matches a previous study involving 369 ET patients in which patients’ postural and kinetic tremor were rated on a 4-point scale (0-3) during a standardized neurological exam [19]. Kinetic tremor was found to be statistically significantly larger than postural tremor, but only by about 0.5-1 point on average. Our quantitative data showed a greater difference; averaged across patients, kinetic tremor was 67 times greater than postural tremor.

In addition, we noted that tremor frequency generally varied little (<1 Hz) between DOF (verified only for severe tremor). Prior studies on tremorogenic muscle activity found high coherence in EMG between muscles of the same limb but low coherence between muscles of different limbs [20]. A system (such as the arm) driven by periodic input (such as tremorogenic muscle activity) will generally respond with periodic output at the same frequency, though the output may also contain additional frequencies. Therefore, our finding that different DOF of the same limb had similar tremor frequencies is consistent with the high intra-limb EMG coherence found in previous studies.

4.3 Methods

As far as we know, this is the first characterization of tremor in the 7 major DOF of the upper limb (shoulder to wrist) for any kind of tremor. Past studies of tremor involving multiple DOF sometimes characterized tremor in terms of linear acceleration of limb segments [7], [8], [9], [10]]. This approach describes the absolute motion of a body segment, which includes the motion of more proximal segments as well. In contrast, performing inverse kinematics allows one to isolate tremor to individual DOF. Also, past studies sometimes investigated tremor in postures close to the end of the range of motion of a DOF (e.g. with the elbow fully extended), effectively reducing the total number of DOF of the arm. We investigated upper-limb postures closer to the middle of the range of motion of the various DOF, which is more representative of postures in daily life.

Great care was taken to include only patients with ET. Before participating in our study, each subject was evaluated by a neurologist specializing in movement disorders. The neurologist assessed the subject's tremor and determined if it was consistent with ET. Subjects were

excluded if their tremor was found to include elements from other tremor disorders (e.g. Parkinson's Disease or Dystonia).

Detecting peaks in PSD is notoriously difficult, in part because the shape of the PSD depends somewhat on the method by which it is calculated. To achieve a robust estimate of the PSD, we used Welch's method and varied the number of windows between 8 and 38 to determine the optimal number of windows. We found that increasing the number of windows beyond 18 produced only slight changes in the PSD shape (and therefore in the peaks), so we used 18 windows instead of the default of 8 windows in Matlab's `pwelch` function.

4.4 Limitations

Since the goal of this study was to characterize the distribution of tremor in ET patients, we tried to enroll as many ET patients as possible. In the end we included 23 patients in our analysis. Although a larger population would have been preferred, our population was large enough to observe stereotyped behavior across a wide range of tremor severities, age of onset, and disorder duration.

Ideally, we would have measured tremor as subjects performed their normal activities of daily living (ADL). However, subjects were instrumented with a total of 20 sensors, some of which were tethered, making it difficult to perform ADL in a natural manner. That said, the postures and movements included in the experiment were chosen to approximate those required during ADL.

To characterize tremor, we used a motion capture system that measures position, performed inverse kinematics to obtain joint angles, differentiated twice to obtain joint accelerations, and calculated the PSD of joint acceleration. We chose to measure position (instead of directly measuring acceleration) to facilitate the inverse kinematics required to

separate motion into individual DOF. Unfortunately, numerical differentiation amplifies high-frequency noise, creating a noisy estimate of acceleration. We could have avoided differentiation by analyzing the PSD of joint angle instead of acceleration. We chose to characterize tremor in terms of the acceleration because this is more common practice (and would therefore allow for comparison with future studies) and because, compared to the PSD of joint angle, the PSD of joint acceleration emphasizes higher-frequency movements, including tremor, over lower-frequency movements such as those required during the kinetic tasks (differentiation preferentially amplifies higher-frequency content), making it easier to detect peaks in the tremor band. To minimize the effect of the noise amplified during differentiation, we low-pass filtered before each differentiation and computed the PSD using a large number of windows to further average out noise. Nevertheless, the remaining noise made it more difficult to detect peaks than it would have been using direct measurements of acceleration, especially in patients with mild tremor.

4.5 Conclusion

According to our observation that tremor increases in a roughly proximal-distal manner, efforts to suppress tremor should focus first on distal DOF. For example, a single orthosis targeting FPS, WFE, and WRUD could potentially suppress most of a patient's tremor. The fact that this distribution was relatively stereotyped between subjects indicates that a single design may benefit a large proportion of patients. Since tremor frequency was similar between DOF, low-pass filtering with a single (perhaps patient-specific) cut-off frequency may be effective for all DOF. That said, developing devices that suppress tremor in an optimal manner requires additional research to understand which muscles are most responsible for a patient's tremor—and therefore where to intervene most effectively.

REFERENCES

- [1] Louis, E.D. and Ottman, R. (2014). "How many people in the USA have essential tremor? Deriving a population estimate based on epidemiological data." Tremor Other Hyperkinet Mov (N Y) **4**: 259.
- [2] Elble, R.J. and Deuschl, G. (2009). "An update on essential tremor." Current Neurology and Neuroscience Reports **9**(4): 273-277.
- [3] Zesiewicz, T.A., et. al. (2013). "Update on Treatment of Essential Tremor." Current Treatment Options in Neurology **15**: 410-423.
- [4] Samotus, O., et. al. (2016). "Functional Ability Improved in Essential Tremor by IncobotulinumtoxinA Injections Using Kinematically Determined Biomechanical Patterns – A New Future." PLoS ONE **11**(4)
- [5] Kestenbaum, M., et al. (2015). "Estimating the Proportion of Essential Tremor and Parkinson's Disease Patients Undergoing Deep Brain Stimulation Surgery: Five-Year Data From Columbia University Medical Center (2009–2014)." Movement Disorders Clinical Practice **2**(4): 384-387.
- [6] Louis, E., et al. (2015). "Defining the Treatment Gap: What Essential Tremor Patients Want That They Are Not Getting." Tremor and Other Hyperkinetic Movements **5**(331).
- [7] Morrison, S. and Newell, K.M. (1996). "Inter- and intra-limb coordination in arm tremor." Experimental Brain Research **110**(3): 455-464.
- [8] Morrison, S. and Newell, K.M. (1999). "Bilateral organization of physiological tremor in the upper limb." European Journal of Applied Physiology and Occupational Physiology **80**(6): 564-574.
- [9] Morrison, S. and Newell, K.M. (2000). "Postural and resting tremor in the upper limb." Clinical Neurophysiology **111**(4): 651-663.
- [10] Morrison, S. and Newell, K.M. (2000). "Limb stiffness and postural tremor in the arm." Motor Control **4**(3): 293-315.

- [11] Elble, R.J. and McNames, J. (2016). "Using Portable Transducers to Measure Tremor Severity." Tremor and Other Hyperkinetic Movements **6**:375.
- [12] Elble, R., et al. (2008). "The essential tremor rating assessment scale (TETRAS)." Movement Disorders **23**(1): S357-S357.
- [13] Elble, R., et al. (2012). "Reliability of The Essential Tremor Rating Assessment Scale (TETRAS)." Movement Disorders **27**: S409-S409.
- [14] Elble, R., et al. (2012). "Inter-Rater Reliability of the Essential Tremor Rating Assessment Scale (TETRAS)." Neurology **78**.
- [15] Wu, G., et al. (2005). "ISB recommendation on definitions of joint coordinate systems of various joints for the reporting of human joint motion - Part II: shoulder, elbow, wrist and hand." Journal of Biomechanics **38**(5): 981-992.
- [16] Clark R., Dickinson T., Beardsley K., Loaiza J.F., Geiger D., and Charles S.K. "Tracking joint angles with electromagnetic sensors." In preparation.
- [17] McDonough, R.N. and Whalen, A.D. (1995). "Detection of signals in noise." Academic Press, San Diego, CA.
- [18] Davidson, A.D., and Charles, S.K., (2017). "Fundamental Principles of Tremor Propagation in the Upper Limb." Annals of Biomedical Engineering **45**: 1133-1147.
- [19] Louis, E.D., (2013). "The primary type of tremor in essential tremor is kinetic rather than postural: cross-sectional observation of tremor phenomenology in 369 cases." European Journal of Neurology **20**(4):725-727.
- [20] Raethjen, J., et al. (2000). "Multiple oscillators are causing parkinsonian and essential tremor." Movement Disorders **15**(1): 84-94.