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ABSTRACT

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Optimized peripheral tremor suppression could address many limitations of surgical or medicinal treatments of Essential Tremor, however it is not well understood how the tremorogenic activity is distributed among the muscles of the upper limb, and therefore how to optimize such suppression. We recorded electromyographic (EMG activity in the 15 major superficial muscles from the shoulder to the wrist while subjects performed postural and kinetic tasks similar to activities of daily living. We calculated the power spectral density and computed the total power in the tremor band (4–12 Hz for each muscle, from which we determined the distribution of tremorogenic activity among the 15 muscles for various conditions. Differences in distribution between conditions were quantified as Pearson correlation coefficients. All 15 muscles exhibited some tremorogenic activity. The anterior deltoid exhibited by far the most power, the wrist extensors had more power than other distal muscles, and the triceps longus showed the least power. Distributions among muscles was highly consistent across repetitions ($r = 0.91 \pm 0.07$ and somewhat stereotyped across subjects ($r = 0.58 \pm 0.31$. Differences in task (postural vs. kinetic, limb configuration, and subject characteristics (sex; tremor severity, onset, and duration had little effect on distribution ($r \geqslant 0.84$. Interestingly, the distribution of tremorogenic activity was highly correlated ($r = 0.94 \pm 0.08$ with the distribution of voluntary activity (power between 0.5 and 4 Hz. In particular, muscles opposing gravity had the highest amount of tremorogenic activity. This may explain in part why the distribution of tremorogenic activity was stereotyped across subjects.

Keywords: essential tremor, EMG, tremor distribution, upper limb, PSD

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I first would like to acknowledge the tireless help and patience of Dr. Charles in working with me to bring this thesis project to completion. He accepted to be my committee chair and welcomed me into the lab even though I was working part-time as an engineer off-campus. When that job turned into full-time employment before my thesis was finished, he worked with me and helped me press forward to get this research completed. He continued meeting with me on a weekly basis, even when those meetings had to be held over video calls. He encouraged and supported me in my efforts to stick with it, and I want to thank him for his dedication to me as a student. My family and I would also like to thank him for the unexpected financial support that we received to help with tuition costs.

I would also like to thank my wife, AmberLee, and our kids, Eliza and Benjamin, for their support and encouragement through the long nights of school work and thesis writing after getting home. I could not have finished without their help.

President Brigham Young said, “Every discovery in science and art, that is really true and useful to mankind has been given by direct revelation from God, though but few acknowledge it.” (Discourses of Brigham Young, sel. John A. Widtsoe (1954), 18–19). I would like to acknowledge the endless help I received from God and add my voice to Brigham Young’s: if you want to discover something true and useful, seek it through revelation.

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1 INTRODUCTION

Essential tremor (ET) is a movement disorder estimated to affect seven million people in the United States (2.2% of the population), making it one of the most common movement disorders [1]. ET is commonly observed as rhythmic shaking of the upper limbs in the range of 4–12 Hz [2, 3] and is typically observed as a postural and kinetic tremor [4]. As a result, ET patients frequently experience difficulty with many activities of daily living including eating, dressing, grooming, and writing. The two main treatment options are medication and deep brain stimulation (DBS). On average, medications reduce tremor by 50%, and are only effective for half of the patient population [4, 5]. DBS is more effective, reducing tremor by 60–90% [5] for 70–90% of ET patients [4]; however, due to the highly invasive nature of brain surgery, few patients choose DBS [6]. In light of the limitations of current treatment, many ET patients have expressed the need for an alternative treatment option [7].

Peripheral tremor suppression may provide an alternative to traditional treatments. One might envision, for example, a sleeve with embedded electronics that delivers low-level electrical stimulation [8-11] or vibratory stimulation [12, 13] to the tremoring muscle, or a passive [14-21] or active [22] orthosis/exoskeleton that suppresses tremor in certain joints. These and other potential peripheral tremor-suppressing strategies are under active investigation. However, a significant obstacle to developing effective tremor-suppressing devices is that we do

not currently know where best to intervene (which muscle or joint) because we do not know which muscles contribute most to a patient's tremor.

Although many prior studies have investigated muscle activity in ET, as far as we are aware no study has determined which muscles contribute most to a patient's tremor. Prior studies of muscle activity in tremor have generally focused on comparing tremor frequency and phase between muscles [23-29]. These studies found that muscles of the same limb have a common frequency, and reported that the frequency, as well as the phase between muscles, changes with muscle activity and limb position [24, 25]. In addition, prior studies of muscle activity in tremor have generally focused on a relatively small number of muscles (up to four) and degrees of freedom (DOF) (usually flexion-extension of the elbow and wrist), though some studies of Parkinsonian tremor have included up to 8 muscles [30, 31].

To move toward determining which muscles are most responsible for a patient's tremor, we measured both tremorogenic muscle activity and the resulting tremor in 25 patients with ET. More specifically, we measured tremorogenic activity in the 15 major superficial muscles of the upper limb and tremor in the 7 DOF spanned by those muscles while subjects performed postural and kinetic tasks representative of the most common activities of daily living. In a companion paper, Pigg et al. [32] presented the distribution of tremor among these 7 DOF. Here we present the distribution of tremorogenic activity among the 15 muscles.

2 METHODS

Data collection for this experiment was performed previously by Pigg et al. [32]. Here we present the details relevant to the current analysis.

2.1 Subject Information

Twenty-five subjects (14 male, 11 female) participated in the data collection, which took place at the National Institutes of Health (NIH) Clinical Center (Bethesda, MD). One subject's data were excluded from analysis because the subject's measured tremorogenic power was more than 3 standard deviations above the mean of the remaining subjects. Therefore, we present results from the remaining 24 subjects (Table 2.1). Each subject was diagnosed with Essential Tremor and had received a neurological exam within the past year by a neurologist specializing in movement disorders. Subjects were excluded from the study if their tremor included elements of other tremor disorders (e.g. Parkinson's Disease or Dystonia). Additional exclusion criteria included a medical history of stroke, head trauma, seizures, or psychotic disorders, or a current cardiac pacemaker or brain stimulator. The Essential Tremor Rating Assessment Scale (TETRAS) was used to evaluate the tremor severity of each subject. The evaluation was performed by a neurologist specializing in tremor or by a research assistant trained by the neurologist in administering the TETRAS. The TETRAS scores confirmed a broad distribution of tremor severity among the subjects (Table 2.1). Each subject provided informed consent in accordance with the Institutional Review Board of the NIH Clinical Center.

Table 2.1: Subject characteristics, sorted by mean power in the tremor band (4-12 Hz). The severity designation (mild, moderate, severe) is based on mean power. Dur., Hand., Ht, Wt, and Family Hist represent the duration of the disorder, handedness, height, weight, and family history of ET, respectively. The TETRAS score is divided into scores for activities of daily living (ADL), performance, and total score. NK stands for "not known."

Sex	Age	Age of Onset	Dur.	Hand.	Ht (cm)	Wt (kg)	Family Hist	TETRAS Scale			Measured	
								ADL	Perf.	Total	Power (%MVC2)	Severity
F	66	45	21	R	172	101	Yes	25	20	45	1.51	Mild
M	64	50	14	R	174	69	Yes	13	16	29	1.58	Mild
M	63	16	47	R	183	99	Yes	24	20.5	44.5	1.66	Mild
M	72	25	47	R	168	95	No	13	13.5	26.5	1.73	Mild
M	70	64	6	R	178	75	Yes	18	16.5	34.5	2.09	Mild
M	65	17	48	L	172	94	Yes	15	18	33	2.09	Mild
F	75	65	10	R	166	64	Yes	28	20	48	2.35	Mild
M	69	8	61	R	177	89	Yes	25	21.5	46.5	2.59	Mild
F	52	28	24	R	164	82	Yes	16	18.5	34.5	2.72	Mild
M	51	16	35	R	174	78	Yes	28	21	49	3.07	Mod
F	63	20	43	R	164	69	Yes	19	18	37	3.10	Mod
M	48	5	43	R	180	141	Yes	14	20	34	3.27	Mod
F	70	22	48	R	174	98	NK	15	22.5	37.5	3.46	Mod
M	69	49	20	R	176	111	Yes	22	25.5	47.5	3.70	Mod
F	45	14	31	R	173	113	Yes	16	18	34	3.81	Mod
M	64	13	51	R	178	105	Yes	28	18.5	46.5	3.90	Mod
M	56	17	39	R	176	85	Yes	23	17.5	40.5	3.93	Mod
F	61	35	26	R	164	61	Yes	24	20	44	4.03	Mod
F	81	57	24	R	166	53	Yes	30	26.5	56.5	5.77	Severe
M	69	65	4	R	175	105	Yes	7	14	21	5.89	Severe
M	69	17	52	R	187	118	Yes	29	37	66	6.91	Severe
M	58	25	33	L	187	111	Yes	29	35	64	7.14	Severe
F	20	5	15	R	168	57	Yes	30	32	62	8.54	Severe
F	76	55	21	R	168	67	Yes	26	28.5	54.5	10.37	Severe

2.2 Experimental Set-up

Subjects were instrumented with surface electromyographic (EMG) sensors. More specifically, fifteen EMG sensors with a 2 x 2 electrode grid and a 10 mm inter-electrode distance (Trigno IM sensors by Delsys, Inc.) were placed on the major superficial muscles contributing to motion in the 7 DOF of the right upper limb (from shoulder to wrist): pectoralis major, anterior deltoid, lateral deltoid, posterior deltoid, short and long heads of the biceps brachii, lateral and long heads of the triceps, brachialis, brachioradialis, pronator teres, flexor carpi radialis, flexor carpi ulnaris, extensor carpi radialis, and extensor carpi ulnaris. The sensors were placed near the middle of the body of the muscle and in line with the tendon. After each sensor was placed, the signal was visually inspected to ensure the muscle of interest was detected and cross-talk between sensors was small. Coban tape was used to further secure the sensors. Data were recorded at 1111 Hz. Subjects were also instrumented with 5 electromagnetic motion capture sensors (trakSTAR 3DGuidance by Ascension Technologies, Shelburne, VT) to track tremor in each DOF; the results of the motion-capture data were presented previously [32].

Subjects were seated at a table on which seven targets were mounted (Figure 2.1). Targets were made of a foam strip mounted on top of a wooden dowel to minimize resistance in case the subject made contact with the target during testing. The target locations were chosen to elicit postures and movements typical of activities of daily living and were scaled according to the subject's anatomy. Targets 1–5 were approximately level with the xyphoid process. Targets 1, 3, and 5 were aligned in the sagittal plane, distributed as follows. Target 5, which was closest to the subject, was placed approximately 4cm from the subject's body; target 1, which was farthest from the subject, was placed such that it could be reached with the tip of the index finger when the elbow was extended at 30°; and target 3 was placed halfway in between targets 5 and 1.

Targets 2 and 4 were placed in the same frontal plane as target 3 such that targets 1, 2, 4, and 5 formed a square (Figure 2.1B). Targets 6 and 7 were arranged vertically above target 5, level with the top of the subject's head and the subject's chin, respectively (Figure 2.1C).

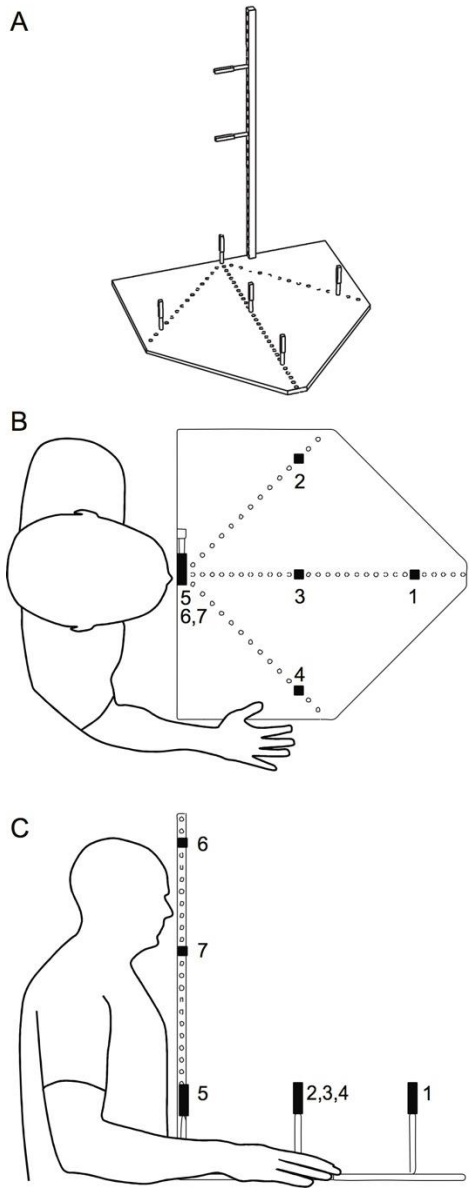

Figure 2.1: Arrangement of Targets. A: Seven targets were given at the ends of foam pieces mounted at scaled locations for each subject. B-C: Targets 1–5 lay in the horizontal plane (B), and targets 5–7 lay in the sagittal plane (C).

2.3 Experimental Protocol

The experiment consisted of postural and kinetic tasks to allow measurement of both postural and kinetic tremor. During postural trials, subjects pointed to a target for 30 seconds. Touching the target could potentially affect the tremor through sensory feedback, so subjects were asked to get close to the targets but not touch them. This was repeated for each of the 7 targets. In the kinetic trials, subjects moved between target 5 and another target for 30 seconds. Subjects were instructed to move back and forth at a comfortable speed and were allowed to touch the targets. This was repeated for each of the 6 targets (excluding target 5). Task type (postural vs kinetic) and target order were assigned pseudo-randomly before testing. Subjects rested their hand for 5–10 seconds between trials in a predefined area off to the right of the targets as shown in Figure 2.1B-C. The entire process was repeated three times for a total of 21 postural and 18 kinetic trials. The time to complete all of the trials was 30–45 minutes.

After testing, we measured subjects' maximum voluntary isometric contraction (MVC) in each muscle. Muscles were tested proximally to distally according to [33]. During the test, subjects were verbally encouraged to push or pull as hard as possible. After testing all 15 muscles, the process was repeated (proximally to distally) two more times, resulting in three recordings per muscle.

2.4 Data Processing

The EMG data were high-pass filtered using a fourth-order Butterworth filter with cutoff frequency of 20 Hz, followed by full-wave rectification. The data were then low-pass filtered using a fourth-order Butterworth filter with a cutoff frequency of 20 Hz. Each filter was applied both forward and in reverse to eliminate phase shift due to filtering. The MVC data were

processed in the same way, and the maximum of the three processed MVC trials for each muscle was used to normalize the EMG data of that muscle. The power spectral density (PSD) of the normalized EMG data was estimated using Welch's method (implemented via the pwelch function in MATLAB using 18 windows and 2^{16} points per window; all other inputs were set to default values). From the PSD we calculated the following measures for each muscle: power in the tremor band (4–12 Hz) and the amplitude and frequency of the tallest statistically significant peak in the tremor band. Power was calculated by numerically integrating the PSD from 4 to 12 Hz using the trapezoidal method. Peaks were detected using a sliding-window constant-false-alarm-rate detection algorithm [34], performed over the 4–12 Hz band with a 1.0 Hz window and 1.5 Hz sidebands. This algorithm detects a peak when the point at the middle of the sliding window is a local maximum (i.e. greater than its two neighbors) and more than two standard deviations above the mean of the sidebands, corresponding to an α-value of 0.05.

2.5 Statistical Analysis

2.5.1 Distribution of the amount of tremorogenic activity

The primary question we wanted to answer was how the tremorogenic activity was distributed among muscles, and how this distribution was affected by task (postural vs. kinetic), target (1–7), and subject characteristics (sex, severity, onset and duration of disorder).

2.5.1.1. Mean and variability

Mean: To determine the mean distribution, we averaged the power in each muscle across all trials for a given muscle and subject. We then averaged across all subjects to get overall

averages for each muscle. We used the number of subjects in each group as the sample size for standard error calculations.

Variability: We also determined the variability in the distribution over time and between subjects. Each subject repeated each condition (task and target) three times, each repetition being separated by about 10–15 min (i.e. 20–30 min between the first and third repetition), allowing us to determine the consistency of the distribution over time. To quantify consistency, we calculated the Pearson correlation coefficient for each of the three pairs of repetitions (rep1 vs rep2, rep1 vs rep3, and rep2 vs rep3) and averaged the resulting correlation coefficients across tasks and targets, resulting in one correlation coefficient per subject. We then calculated the mean, standard deviation, and range of these correlation coefficients across subjects. To determine the variability in distribution between subjects, we determined the mean distribution of each subject and then calculated the Pearson correlation coefficient for each of the 276 pairs of subjects (subject 1 vs subject 2, subject 1 vs subject 3, etc.). Finally, we computed the mean, standard deviation, and range of correlation coefficients across these 276 pairs.

2.5.1.2. Effect of task, target, and subject characteristics

To determine how the distribution of tremorogenic activity was affected by different conditions, we performed an ANOVA of power with the following factors: task (postural vs. kinetic), target (1–7, excluding 5), muscle (1–15), and subject (1–24), with subject as a random factor. We analyzed main effects and two-way interactions. Postural target 5 was excluded from this analysis because there was no corresponding kinetic target. Similar to above, differences between distributions of various factor combinations were quantified with Pearson correlation coefficients. Specifically, we calculated correlation coefficients between average distributions

for postural vs. kinetic tasks (1 pair), the seven postural targets (21 pairs), the six kinetic targets (15 pairs), male vs. female (1 pair), the three severity levels (3 pairs), the three age-of-onset levels (3 pairs), and the three duration levels (3 pairs). For factors with more than 1 pair, we reported the mean, standard deviation, minimum, and maximum of the correlation coefficients.

2.5.1.3. Comparison to the distribution of voluntary muscle activity

In investigating the distribution of tremorogenic activity among the muscles of the upper limb, we wondered if differences in tremorogenic activity between muscles might reflect differences in voluntary activity between muscles. For example, we wondered if the muscles that exhibited the most tremorogenic activity during postural tasks might be those muscles holding up the limb against gravity. To test this hypothesis, we correlated the total power in the tremor band to the total power in the "voluntary band" (0.5–4 Hz) for each trial. We excluded 0–0.5 Hz because the rectification step of the data processing shifted power from higher frequency ranges into this range and would artificially inflate the correlation between the voluntary and tremor bands. The power in the voluntary band was calculated the same way as the power in the tremor band.

2.5.2 Distribution of the frequency of tremorogenic activity

The second question we sought to answer was how the frequency of the tremorogenic activity varied between the muscles of the upper limb. Tremor frequency was taken as the frequency of the largest statistically significant peak in the tremor band. To determine how tremor frequency was affected by conditions, we repeated the ANOVA described above, but for peak frequency instead of power.

3 RESULTS

We processed the data as described above, resulting in power spectral density, from which we calculated the power in the tremor band and the frequency of the tallest statistically significant peak (Figure 3.1). Averaging the power across all muscles and all trials for each subject, we divided subjects into three severity groups (mild, moderate, and severe), as listed in Table 2.1. Although some trials did not exhibit visible tremorogenic muscle bursts in the time domain, 96.2% of trials exhibited significant peaks in power spectral density (range 92.8% to 99.1% for individual subjects). Spanning all subjects, flexor carpi radialis had the least number of significant peaks (93.8%), whereas anterior deltoid and extensor carpi radialis both had the highest number of peaks (97.2%).

3.1 Distribution of the amount of tremorogenic activity

3.1.1 Mean and variability

Mean: Some muscles exhibited much more tremorogenic activity than others (Figure 3.2). The ANOVA test confirmed that there were significant differences in power between muscles ($F(14) = 18$, $p < 0.001$). Anterior deltoid had the most power overall and much more power than neighboring proximal muscles (Table 3.1). The wrist extensors also had high amounts of power, especially compared to other distal muscles. The long head of the triceps muscle had the least amount of power.

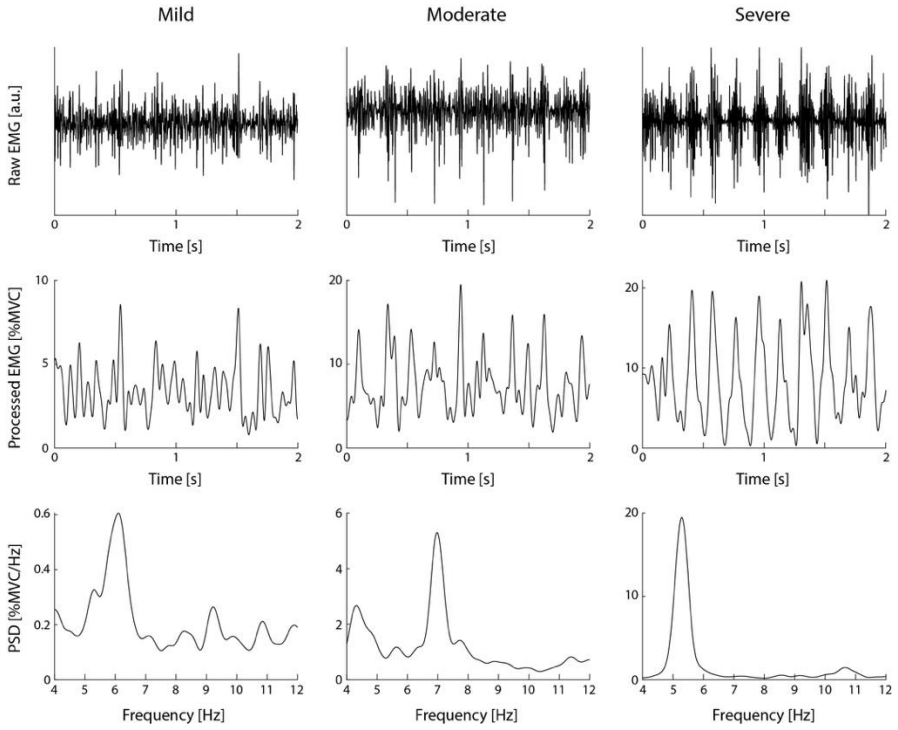

Figure 3.1: Raw EMG data (top row), processed EMG data (middle row), and power spectral density (PSD; bottom row) of the extensor carpi radialis from subjects with mild, moderate, and severe tremor (left, middle, and right column, respectively).

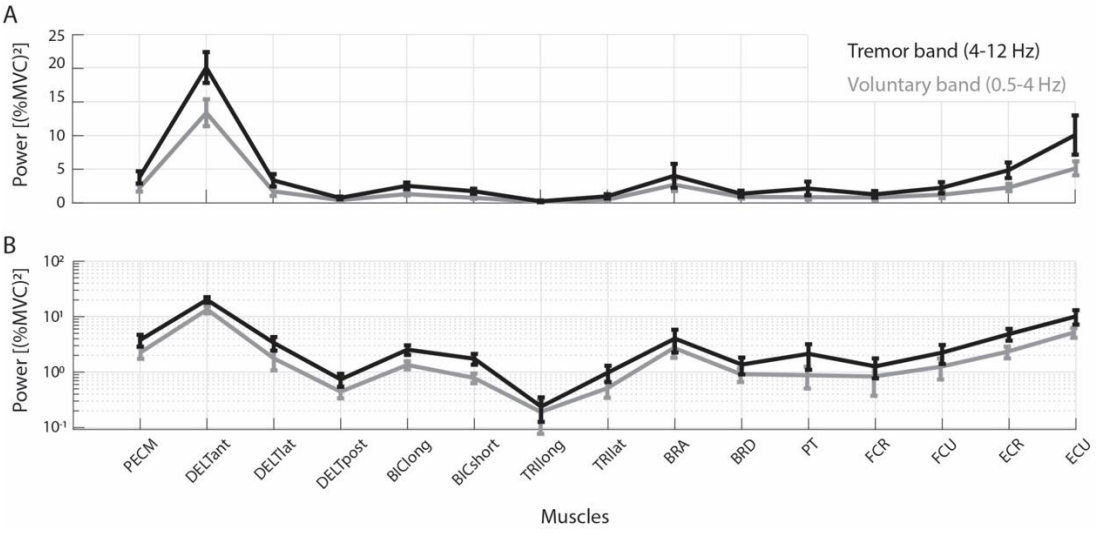

Figure 3.2: Distribution of power in the tremor band (4-12 Hz) and voluntary band (0.5-4 Hz) across muscles (averaged over all subjects), shown on a linear scale (A) and on a log scale (B). Muscle abbreviations are defined in Table 3.1.

Table 3.1: Mean tremor-band power in each muscle (averaged across all subjects), sorted from greatest to least power.

Muscle	Abbreviation	Tremor Power [(%MVC)2]
Anterior deltoid	DELTant	20.1
Extensor carpi ulnaris	ECU	10.1
Extensor carpi radialis	ECR	4.9
Brachialis	BRA	4.0
Pectoralis major	PECM	3.8
Lateral deltoid	DELTlat	3.4
Biceps (long head)	BIClong	2.5
Flexor carpi ulnaris	FCU	2.2
Pronator teres	PT	2.1
Biceps (short head)	BICshort	1.7
Brachioradialis	BRD	1.4
Flexor carpi radialis	FCR	1.3
Triceps (lateral head)	TRIlat	1.0
Posterior deltoid	DELTpost	0.7
Triceps (long head)	TRIlong	0.2

Variability: Individual subjects' distributions were very consistent: the correlation coefficients between repetitions under identical conditions, which were spaced about 10-15 minutes apart, were 0.91 ± 0.07 (0.70-0.99). The slight difference in correlation coefficients between postural and kinetic tasks (Table 3.2) was not significant ($p = 0.08$). Despite large differences in tremor power between subjects (Table 2.1), the distribution of power was also quite stereotyped across subjects: the correlation coefficients between subjects were 0.58 ± 0.31 (-0.15-0.99). The correlation coefficients were higher for postural tasks than kinetic tasks ($p < 0.0001$, Table 3.2). To illustrate the similarity in distribution across subjects, we ranked subjects' muscles from least average power to greatest average power (Figure 3.3).

Table 3.2: Pearson correlation coefficients (mean ± SD (range)) between the distributions (of tremorogenic activity among muscles) measured under identical conditions (subject, task, target) and between subjects' mean distributions, listed for all tasks (postural + kinetic) and separately for postural and kinetic tasks.

	All tasks	Postural tasks	Kinetic tasks
Repetitions	0.91 ± 0.07 (0.70-0.99)	0.89 ± 0.11 (0.57-0.99)	0.93± 0.06 (0.80-0.99)
Subjects	0.58 ± 0.31 (-0.15-0.99)	0.62 ± 0.34 (-0.11-1.00)	0.54 ± 0.32 (-0.10-0.99)

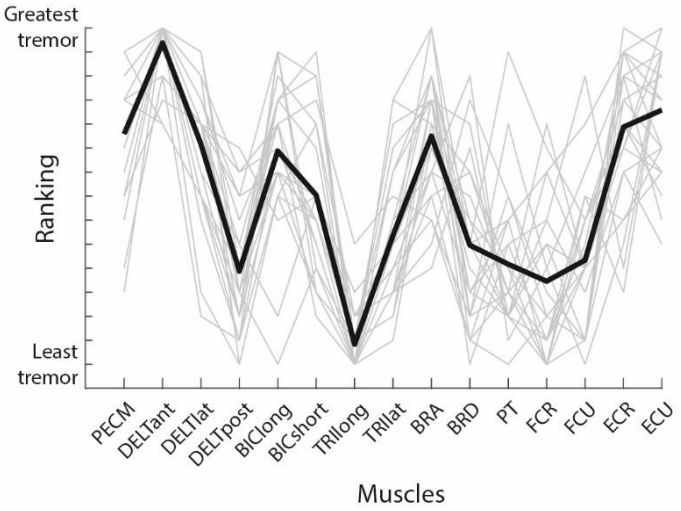

Figure 3.3: Muscles ranked from greatest to least tremor for individual subjects (gray lines) and averaged over all subjects (thick black line). Some muscles consistently ranked high (e.g. DELTant, Anterior deltoid) and some muscles consistently ranked low (e.g. TRIlong, triceps longus), whereas other muscles (e.g. DELTpost, posterior deltoid) ranked differently for different subjects. Muscle abbreviations are defined in Table 3.1.

3.1.2 Effect of task, target, and subject characteristics on distribution

The distribution of tremorogenic activity was quite independent of task, target, and subject characteristics (Table 3.3). Although the ANOVA test revealed a significant difference in power ($F(1) = 6.5$, $p = 0.015$) between postural and kinetic tremor, with kinetic tremor exhibiting

69% more power than postural tremor, the distribution among muscles was similar for postural and kinetic tremor (r = 0.95) (Figure 3.4A). Similarly, although different targets elicited different amounts of tremorogenic activity, the distribution among muscles was similar between targets (Figure 3.4B-C). The average correlation between distributions for different targets was r = 0.94 ± 0.04 (mean ± SD) for postural tasks and r = 0.91 ± 0.06 for kinetic tasks. Furthermore, there were no clear differences in distribution between subject characteristics (Figure 3.5), including sex (r = 0.95), tremor severity (r = 0.84 ± 0.12), disorder onset (r = 0.91 ± 0.03), and disorder duration (r = 0.87 ± 0.08).

Table 3.3: Effect of task, target, and subject characteristics (sex, severity, onset of disorder, and duration of disorder) on the distribution of tremorogenic activity among muscles, presented as Pearson correlation coefficients between distributions.

	Mean	SD	Min	Max
Task	0.95	--	--	--
Target (postural tasks)	0.95	0.04	0.85	0.99
Target (kinetic task)	0.91	0.06	0.75	1.00
Sex	0.95	--	--	--
Severity	0.84	0.12	0.74	0.98
Onset	0.91	0.03	0.88	0.93
Duration	0.87	0.08	0.80	0.96

3.1.3 Comparison to the distribution of voluntary muscle activity

In examining the distribution of tremorogenic muscle activity, we noticed that the muscles with the most tremorogenic activity might be those with the most voluntary muscle activity. For example, during postural tasks, it appeared that the muscles with the most tremorogenic activity

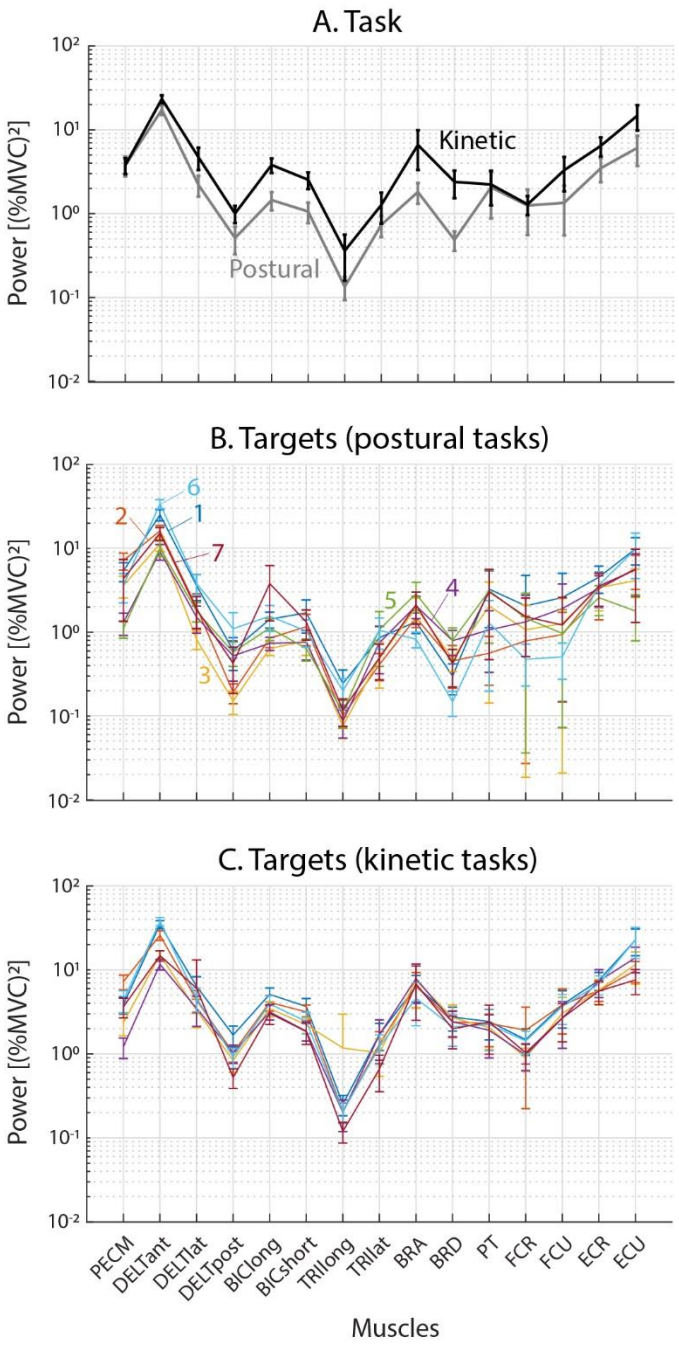

Figure 3.4: Effect of task (A) and target (B-C) on distribution of tremorogenic activity. The effect of target is given separately for postural tasks (B) and kinetic tasks (C). The line color associated with each target, defined in B, is the same for B and C (target definitions are given in Figure 2.1). Muscle abbreviations are defined in Table 3.1.

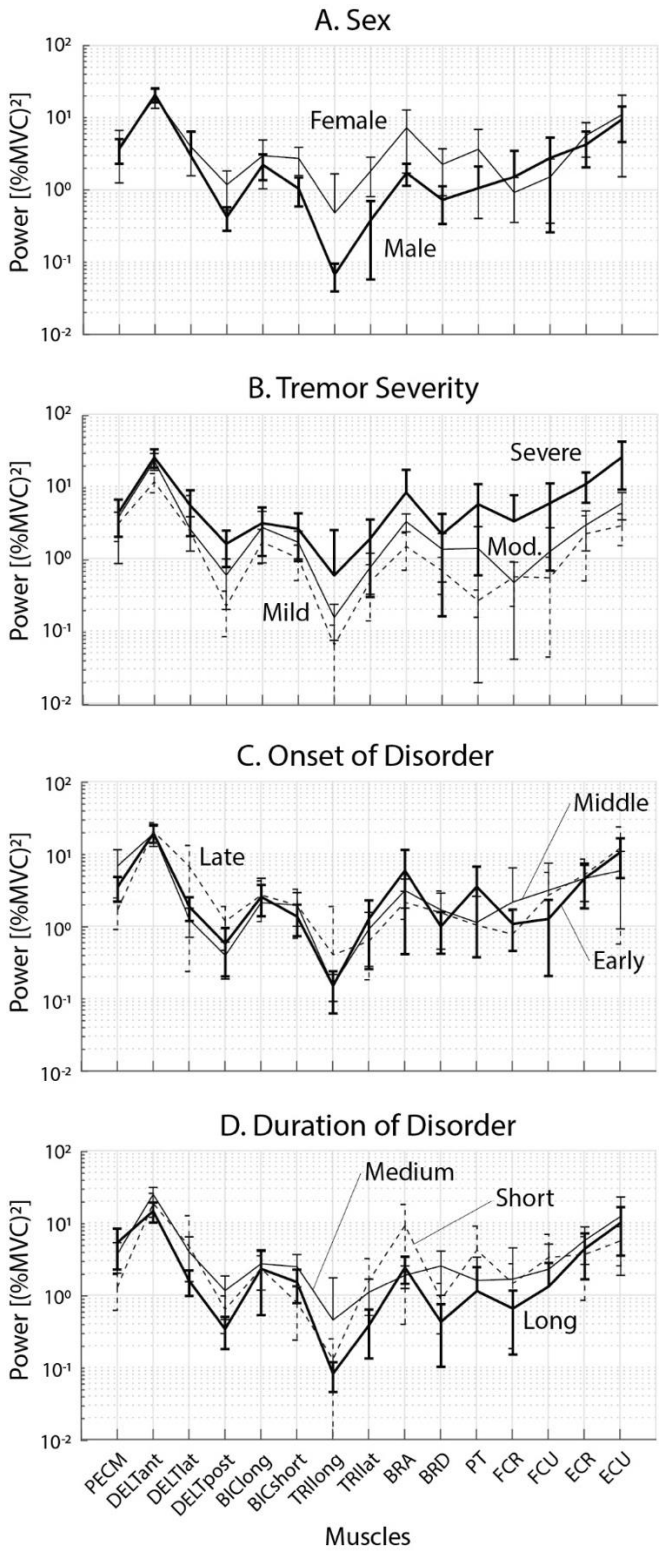

Figure 3.5: Effect of subject characteristics (sex, tremor severity, onset of disorder, and duration of disorder) on the distribution of tremorogenic activity. Muscle abbreviations are defined in Table 3.1.

might be those that opposed the gravitational torque of the limb. Consistent with our hypothesis, we found in individual trials that the distribution of tremorogenic activity was highly correlated with the distribution of voluntary activity: averaged across all trials, tasks, and subjects, the correlation coefficient was $r = 0.94 \pm 0.08$ (0.53-1.00). The mean distribution of tremorogenic activity was even more highly correlated with the mean distribution of voluntary activity (Figure 3.2): $r = 0.997$.

3.2 Distribution of the frequency of tremorogenic activity

A secondary purpose of the analysis was to determine if the frequency of tremorogenic activity was the same in all muscles. Determining peak frequency relies on a single point (the peak) and is therefore highly susceptible to measurement noise. Despite the sophistication of the peak detection algorithm we used (see Methods), it became clear that many of the peaks were spurious. For some subjects, especially those with severe tremor, most of the peaks had similar frequencies (e.g. within ±0.5 Hz), creating a baseline (Figure 3.6C). Occasionally there were peaks with frequencies that were significantly different from the baseline, but these outliers typically belonged to peaks that were smaller in amplitude. Furthermore, the frequency of these outlier peaks appeared random, and the frequency would usually return to the baseline on subsequent trials. Since peaks of smaller amplitude are more susceptible to noise, and since it is unlikely that the frequency of tremorogenic activity would change substantially from one trial to the next, only to return to the baseline on the next trial, we concluded that these outlier peaks were spurious. Since subjects with mild and moderate tremor had peaks of smaller amplitude, a larger proportion of their peaks were deemed spurious (Figure 3.6A-B). In some subjects with mild and even moderate tremor, most of the peaks were deemed spurious, and it was sometimes

difficult to make out a baseline at all. For this reason, in our analysis we relied more heavily on subjects with severe tremor.

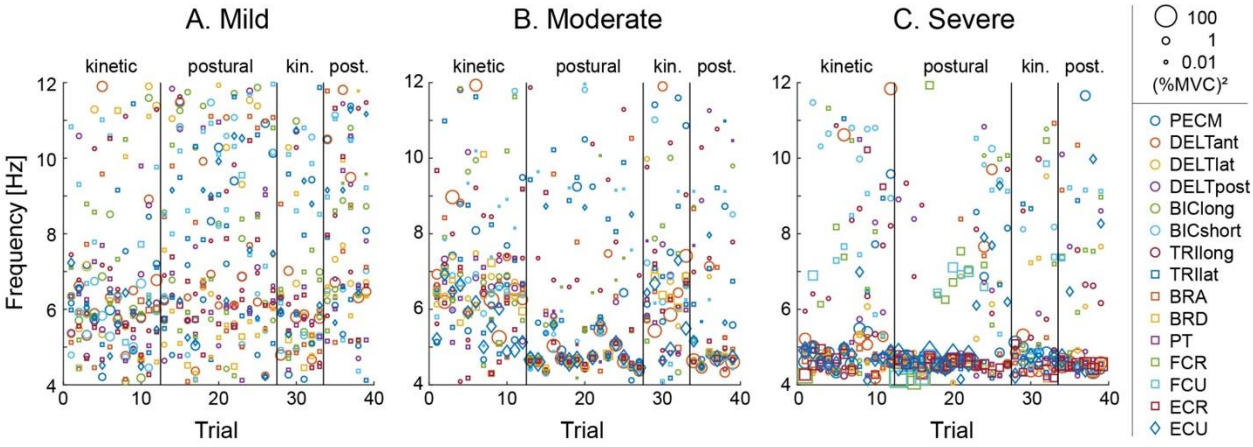

Figure 3.6: Frequency of the tallest statistically significant peak in the PSD of each muscle for each trial of a subject with mild (A), moderate (B), and severe (C) tremor. Trials are listed in chronological order, which involved kinetic trials, then postural trials, then kinetic trials, and finally postural trials, as indicated at the top of each subfigure. Marker size corresponds to peak amplitude (see legend in top right corner), and the color-shape of each muscle is shown in the bottom left legend (muscle abbreviations are defined in Table 3.1).

We did not find any convincing evidence in favor of a difference in peak frequency between muscles. Although an ANOVA of all subjects' data showed a statistically significant difference in peak frequency between muscles ($F(14) = 3.8$, $p < 0.001$), this difference vanished once we focused on subjects with severe tremor ($F(14) = 1.3$, $p = 0.25$). In addition, although a few subjects showed a visible difference in tremor frequency between postural and kinetic tasks (kinetic frequency > postural frequency; for example, see Figure 3.6B), the ANOVA for severe subjects did not reveal any significant differences ($F(1) < 0.001$, $p = 0.96$). Finally, we did not find any significant differences between targets, either ($F(5) = 2.0$, $p = 0.12$).

4 DISCUSSION

Peripheral tremor-suppression strategies are under active investigation as an alternative to pharmaceutical or surgical intervention strategies. However, we do not currently know which muscles are most responsible for the tremor and therefore which muscles should be targeted to most effectively suppress tremor. Past studies of tremorogenic muscle activity focused on frequency and phase analysis between muscles but have not investigated which muscles contribute most to a subject's tremor.

To move toward determining which muscles are most responsible for a patient's tremor, we characterized the distribution of tremorogenic activity and frequency among the 15 major superficial muscles of the upper limb. It is important to understand that characterizing the distribution of tremorogenic activity is not the same as identifying the muscles that contribute most to a subject's tremor because the muscles with the most tremorogenic activity are not necessarily the muscles that contribute most to a subject's tremor. To clarify, it is helpful to view tremor propagation as a multi-input multi-output system in which tremorogenic activity in the muscles of the upper limb are the inputs, tremulous displacements in the various degrees of freedom of the upper limb are the outputs, and the upper limb is the system that filters and mixes (i.e. convolves) the inputs on their way to becoming outputs [35]. In such a system, the outputs depend on the system as well as on the inputs. In other words, which muscles are most responsible for a subject's tremor depends on the dynamics of the upper limb as well as on which

muscles have the most tremorogenic activity. For example, in simulations of tremor propagation, we found that, given equal amounts of tremorogenic activity, distal muscles produce more tremor than proximal muscles [35]. Therefore, determining which muscles are most responsible for a subject's tremor requires more than simply characterizing the distribution of the inputs. Nevertheless, characterizing the distribution of the inputs is a necessary (though not sufficient) step.

4.1 Distribution of the amount of tremorogenic activity

4.1.1 Mean and variability

The distribution of tremorogenic activity was found to be very consistent over time ($r = 0.91$) and quite stereotyped across subjects ($r = 0.58$). We chose to quantify the amount of tremorogenic activity as the power in the tremor band because it is a robust measure. As the integral of the PSD over the tremor band, power is quite insensitive to noise, does not rely on a single point such as the peak, and is independent of peak-finding algorithms and parameters. Nevertheless, we also calculated the distribution of tremorogenic activity using another measure (peak amplitude) and a non-parametric averaging method (average of rankings), but we found similar distributions (not shown). In all cases, tremorogenic activity was greatest in the anterior deltoid, large in the wrist extensors, and smallest in the long head of the triceps muscle.

That the distribution of tremorogenic activity is similar between subjects ($r = 0.58$) is remarkable because there was, to the best of our knowledge, no a priori reason to assume that it should be similar. Our finding that distribution of tremorogenic activity is similar to the distribution of voluntary activity provides a potential explanation (see below).

4.1.2 Effect of task, target, and subject characteristics

Differences in task, target, and subject characteristics had surprisingly little effect on distribution (Figure 3.4 and Figure 3.5); mean correlation values between groups were all above 0.8 (Table 3.3). For example, kinetic tasks exhibited more tremorogenic activity than postural tasks but had a similar distribution ($r = 0.95$). Similarly, different targets elicited different amounts of power, with target 1 (farthest) and target 6 (highest) eliciting the most (Figure 3.4B-C). The similarity between the distribution of tremorogenic activity and the distribution of voluntary activity provides a potential explanation (see below). Nevertheless, the distribution of tremor was similar regardless of target (mean $r \geq 0.91$). Finally, subject characteristics (sex, severity, onset, duration) also had little effect on distribution ($r \geq 0.84$).

4.1.3 Comparison to the distribution of voluntary activity

The mean distribution of tremorogenic activity (Figure 3.2) exhibits a wave-like pattern in which activity is high in either the flexors or extensors of a joint, but not both. More specifically, it appears that the muscles with higher amounts of tremorogenic activity (anterior deltoid, biceps, brachialis, and wrist extensors) may be those used to hold up the limb against gravity in the postures required by our targets (Figure 2.1). To test this hypothesis, we correlated the distribution of power in the tremor band against the distribution of power in the voluntary band (Figure 3.2) and found a very high correlation ($r = 0.94 \pm 0.08$). In other words, the more a muscle was activated voluntarily, the more tremorogenic activity it produced. That the anterior deltoid, which holds up the entire limb, was found to have the largest amount of muscle activity,

is consistent with this observation. Similarly, the targets that were farthest and highest (targets 1 and 6) elicited the most tremorogenic activity in the anterior deltoid (Figure 3.4B-C).

A similar dependence between voluntary activity and tremorogenic activity was found by Puttaraksa et al, who estimated the power in the spike trains of motor units innervating forearm flexor and extensor muscles of subjects with Essential Tremor [36]. They found a positive correlation between the power at the voluntary-drive and tremor frequencies ($r = 0.6$) and suggested the following mechanism: because an increase in contraction increases the number of motor neurons recruited and the synchrony between motor neurons [37], motor neurons can sample more tremorogenic input. This mechanism, and the fact that voluntary activity is dictated by biomechanical factors (e.g. gravity, movement dynamics, desired limb impedance, etc.) and not tremor, strongly suggests a causal relationship in which increased voluntary activity causes increased tremor. Note that this is different from the rest tremor typical of Parkinson's Disease, where activities requiring voluntary activity (e.g. holding a posture) decrease tremor.

The correlation between tremorogenic activity and voluntary activity has several important implications. First, it may explain why the distribution of tremorogenic activity was relatively stereotyped between subjects ($r = 0.58$); since a given posture requires similar distribution of muscle activity between subjects, subjects would also exhibit a similar distribution of tremorogenic activity. Second, differences in the distribution of tremorogenic activity between postural and kinetic tasks (Figure 3.4A) may reflect differences in the voluntary activity of these tasks. Third, different limb configurations are known to elicit different amounts of tremor. For example, clinical examinations of tremor often include the "wing beating" posture (shoulders abducted and elbows flexed such that the two upper limbs are in the horizontal plane and the hands almost touch in front of the nose) because it tends to exacerbate tremor [38]. Such

differences in tremor elicited in different postures may be due to differences in the voluntary activity required to maintain these postures.

4.1.4 Comparison to the distribution of tremor

We recently characterized the distribution of tremor (i.e. tremulous joint displacement) among the seven main DOF of the upper limb (listed from proximal to distal): shoulder flexion-extension, abduction-adduction, and internal-external humeral rotation; elbow flexion extension; forearm pronation-supination; and wrist flexion-extension and radial-ulnar deviation [32]. In the context of the multi-input multi-output system mentioned above, tremorogenic muscle activity is the input, the upper limb is the system, and tremor is the output. Because the output depends on the system as well as the input, one must exercise caution in comparing inputs directly to outputs; understanding the relationships between the inputs and outputs requires a thorough system-dynamics analysis. Nevertheless, since we have now characterized the distribution of both the inputs (this thesis) and the outputs [32], we provide here a preliminary comparison between their distributions.

We found a number of consistencies between the distributions of tremorogenic activity and tremor. First, tremor was distributed on average as follows (from most tremor to least tremor): wrist flexion-extension, forearm pronation-supination, shoulder internal-external rotation, wrist radial-ulnar deviation, elbow flexion-extension, shoulder flexion-extension, and shoulder abduction-adduction. Our finding in this thesis that tremorogenic activity was greatest in the anterior deltoid and in the wrist extensors (Table 3.1) may explain in part the large amount of tremor in wrist flexion-extension and shoulder internal-external rotation. The prime pronators and supinators (both heads of the biceps; pronator teres; and brachioradialis) have intermediate

amounts of tremorogenic activity, but the mechanical impedance (resistance to movement) of the forearm is very small [39], so even this moderate amount of tremorogenic activity could explain the large tremor in pronation-supination. Second, both the distribution of tremorogenic activity and the distribution of tremor were found to be quite constant across repetitions and stereotyped across subjects (mean correlation coefficients of 0.91 and 0.58 for tremorogenic activity and 0.84 and 0.70 for tremor). Third, both distributions were relatively unaffected by subject characteristics (all mean correlation values were greater than 0.84 for tremorogenic activity and greater than 0.70 for tremor).

We also found some differences between the distributions of tremorogenic activity and tremor, in particular in the effect of task: whereas the distribution of tremorogenic activity was highly similar for postural and kinetic tasks ($r = 0.95$), the distributions of tremor in postural and kinetic tasks were only moderately correlated ($r = 0.48$). Furthermore, whereas the distribution of tremorogenic activity in postural tasks was as consistent as it was in kinetic tasks ($r = 0.89$ and 0.93 across repetitions, $r = 0.62$ and 0.54 across subjects, and $r = 0.95$ and 0.91 across targets), the distribution of tremor in postural tasks was far less consistent than in kinetic tasks (0.75 vs. 0.95 for repetitions, 0.39 vs. 0.72 for subjects, and 0.45 vs. 0.95 for targets). Differences between postural and kinetic tasks were not limited to distribution, but extended to overall power (summed across all DOF or muscles); whereas subjects showed far more tremor in kinetic tasks than in postural tasks (on average 80 times more), subjects exhibited similar amounts of tremorogenic activity in kinetic and postural tasks (kinetic was only twice as much on average). A more thorough analysis will be required to understand the origins and consequences of these similarities and differences between tremorogenic muscle activity and the resulting tremor.

4.2 Distribution of the frequency of tremorogenic activity

We did not find compelling evidence of differences in tremor frequency between muscles. Similarly, O'Suilleabhain et al reported a general consistency of frequency but found one subject (out of 8) with muscles in the same limb with tremorogenic activity differing by 1.3 Hz [27]. Also, Raethjen et al found the vast majority of intralimb muscles to have frequencies within 0.2 Hz, but occasionally the difference was more than 0.5 Hz [28]. Several other ET studies involving multiple muscles within the same limb were not specifically intended to identify similarities or differences in tremor frequency between muscles, but had findings in harmony with the hypothesis that tremorogenic activity in muscles of the same limb occurs at a common frequency [23-26, 29]. In addition, we did not find a significant difference in tremor frequency between postural and kinetic tasks in general. That said, as in [32], a few individual subjects did show an increased frequency in kinetic tasks. Schuhmayer et al. [40] found tremor frequency to be slightly higher for kinetic tasks than for a dot approximation test in which subjects held a pen over a target without touching it, which was similar to our postural test (in contrast, their "postural" test was not comparable to our postural test).

4.3 Limitations

In characterizing the distribution of tremorogenic activity in the upper limb, we focused our analysis on the 15 major superficial muscles associated with the 7 main DOF from the shoulder to the wrist. Although this group includes many prime movers, it excludes about half of the muscles from the shoulder to the wrist, as well as all of the muscles of the hand. Furthermore, we measured muscle activity using surface EMG, and we normalized EMG based on maximum voluntary contraction. Although this method of normalizing is standard, there were other options, including normalization based on maximum muscle force or joint torque.

As mentioned above, our analysis of tremor frequency relied on identifying the peak in power spectral density. Peak identification is susceptible to noise and relies on the algorithms and parameters of the peak detection method. We found a large number of spurious peaks, especially in subjects with mild and moderate tremor, and so relied for our analysis of tremor frequency more heavily on the subjects with severe tremor. Even so, our analysis of tremor frequency was clearly limited by the difficulty of identifying reliable peaks.

Finally, given our finding that the distribution of tremorogenic activity mirrors the distribution of voluntary activity, the distribution presented in this thesis is only valid for the postures and movements we tested. That said, the postures and movements included in our measurements represent many of the common postures and movements encountered during activities of daily living.

4.4 Conclusion

The anterior deltoid and wrist extensor muscles exhibited the most tremorogenic activity (especially compared to their neighboring muscles), and the long head of the triceps muscle showed the least tremorogenic activity. The distribution of tremorogenic activity across muscles was very consistent between repeated measurements and somewhat stereotyped across subjects. Furthermore, task, target, and subject characteristics had almost no effect on the distribution. The distribution of tremorogenic activity was highly correlated with the distribution of voluntary activity; muscles with more voluntary activity (e.g. those opposing gravity) exhibited more tremorogenic activity. We hypothesize that this correlation underlies the similarity in distribution between subjects.

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