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## Analysis of Electromyographic Effects of Peripheral Sensory Stimulation on Essential Tremor in Tremor Suppression Study

Christian Jakob Metzner

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Honors Thesis

ANALYSIS OF ELECTROMYOGRAPHIC EFFECTS OF PERIPHERAL  
SENSORY STIMULATION ON ESSENTIAL TREMOR IN TREMOR  
SUPPRESSION STUDY

by  
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Submitted to Brigham Young University in partial fulfillment of graduation  
requirements for University Honors

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Brigham Young University  
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## Abstract

Electrical stimulation of peripheral muscles below motor neuron threshold (sensory stimulation) has shown potential as an effective, low-cost, and minimally invasive treatment for Essential Tremor (ET), one of the most common movement disorders. Past studies have shown that asynchronous sensory stimulation of antagonist muscles out of phase with tremor can suppress ET. Synchronous sensory stimulation, which stimulates antagonists simultaneously and is easier to implement, has yielded mixed results. To optimize available therapies and to understand tremor suppression mechanisms better, I investigated the effects of synchronous sensory stimulation with different stimulation frequencies on electromyographic tremor-band power and frequency in ET patients, expecting to see no significant stimulation effects on tremor signals at any stimulation frequency.

I studied the tremor effects of brief, synchronous sensory stimulation on the antagonistic flexor and extensor carpi radialis muscles by analyzing surface electromyograms (sEMG) that were recorded in an unpublished BYU study which tested 15 sensory stimulation frequencies from 10 to 150 Hertz on 21 ET patients. I extended this investigation by calculating sEMG-derived tremor-band power and frequency for pre- and poststimulation phases and comparing them across subjects using a mixed-model ANOVA.

Brief synchronous sensory stimulation did not result in tremor changes at any of the tested stimulation frequencies. There was no statistically significant interaction between phase and stimulation frequency for tremor-band power ( $p=0.45$ ) nor frequency ( $p=0.81$ ).

The lack of evidence for tremor suppression or tremor frequency changes is consistent with the hypothesis that brief sensory stimulation suppresses tremor via reciprocal inhibition reflexes, necessitating asynchronous stimulation instead of synchronous stimulation. I conclude that an asynchronous stimulation strategy or longer stimulation durations are necessary for future therapeutic applications of sensory stimulation for ET suppression.



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## **Electromyographic effects of peripheral sensory stimulation on Essential Tremor**

Essential Tremor (ET), which is characterized by a postural and kinetic tremor in the upper limbs, is one of the most common movement disorders, currently affecting an estimated 5% of the population worldwide (Elble & Deuschl, 2009; Shashank & Milton, 2022). Although the exact pathophysiology is still being actively explored, most studies indicate that ET is driven by an oscillatory tremor network in the central nervous system (Holtbernd & Shah, 2021; Schnitzler et al., 2009). Unstable oscillatory couplings between brain regions involved in voluntary movement (mainly the inferior olivary nucleus, the cerebellum, the thalamus, and the motor cortex) result in the rhythmic motor output characteristic of ET (Raethjen & Deuschl, 2011).

Unfortunately, the two most common and effective treatment methods, medication and deep brain stimulation (DBS), provide only partial relief for ET patients. Medication is the most common treatment, with propranolol and primidone having shown the highest efficacy (Elble & Deuschl, 2009). Both medications increase cortical inhibition, thus counteracting the increases in connectivity seen in the oscillatory tremor network (Vogelink et al., 2019). Still, only about 50% of patients see a reduction in tremor, with those patients showing only a 50% improvement (Elble & Deuschl, 2009). In addition, it is common for patients to experience moderate side effects such as headaches, dizziness, and nausea, as well as the need to increase dosage as they adapt to the medicine. Deep brain stimulation (DBS) of the thalamic ventral intermediate nucleus (VIM) is much more effective than medication, resulting in a 60% to 90% reduction in tremor (Kestenbaum, Ford, & Louis, 2015). Studies suggest that DBS of the VIM inhibits cerebello-thalamic pathways, one of the areas implicated in the central tremor network, potentially

explaining the tremor suppression effect (Milosevic et al., 2018). Still, only 1 in 30 ET patients choose DBS, likely because of the invasiveness (Kestenbaum, Ford, & Louis, 2015). Thus, due to concerns about side effects, inefficacy, or discomfort, many ET patients remain without satisfactory treatment options (Deuschl et al., 2011).

Electrical stimulation below motoneuron threshold (also called sensory stimulation) to suppress tremor has shown potential as a non-invasive alternative to medication and DBS (Pascual-Valdunciel, 2021b). Sensory stimulation involves electrically stimulating tremor-affected peripheral muscles, often using a transcutaneous electrical nerve stimulation (TENS) device. It stimulates below the motor neuron activation threshold but above the afferent neuron activation threshold, thus recruiting proprioceptive and cutaneous sensory afferent neurons without directly activating the muscles. Multiple studies have found that sensory stimulation on peripheral limbs can decrease tremor, although the effectiveness varies depending on specific stimulation parameters (Pascual-Valdunciel, 2021b).

Despite these encouraging first steps, the research in sensory stimulation for tremor suppression still faces two major limitations: first, the specific stimulation parameters have not been optimized for tremor suppression, and second, the tremor suppression mechanism itself is not well understood. These gaps in our understanding are evident when comparing different stimulation strategies and mechanism hypotheses.

In terms of optimizing stimulation parameters, we lack a clear understanding of which stimulation timing strategy and stimulation frequency are most effective. There are two basic stimulation timing strategies: the asynchronous and the synchronous strategy. In the asynchronous stimulation strategy (sometimes called the out-of-phase strategy), antagonist muscle groups are stimulated out of phase with each

other at the tremor frequency so that the stimulation opposes the tremor-induced muscle activity (Pascual-Valdunciel, 2021b). In synchronous stimulation, antagonist muscle groups are stimulated simultaneously, independent of the tremor frequency (Pascual-Valdunciel, 2021b). Synchronous stimulation is technologically easier to implement than asynchronous stimulation. Both stimulation strategies have yielded different results.

Dosen et al. (2015) observed that brief asynchronous, sensory stimulation over wrist and finger muscles suppressed tremor by 35-48%. Using the same stimulation paradigm, Dideriksen et al. (2017) reported an average 52% tremor reduction for nine tested patients. Isaacson et al. (2020) showed tremor reduction in 205 ET patients using asynchronous sensory stimulation over the median and radial nerves in a large clinical study, although their specific asynchronous strategy was independent of tremor unlike most other asynchronous stimulation studies.

Synchronous stimulation has been less successful but also less explored. Heo et al. (2015) found that brief, synchronous sensory stimulation over the surface of wrist and elbow muscles in 18 patients decreased postural tremor by up to 90% during stimulation. In contrast, Pascual-Valdunciel et al. (2021a) found that brief, synchronous sensory surface stimulation did not significantly affect the subjects' tremor. Interestingly, the same stimulation strategy applied intramuscularly even *increased* tremor by up to 48% in the short term. Note that all synchronous stimulation studies, as well as the asynchronous studies, used only one of two stimulation frequencies – either 100 or 150 Hz. The lack of experimentation with different stimulation frequencies and the contradicting results in studies using synchronous stimulation merit further exploration.

Beyond just missing a clear exploration of the parameter space, we still lack a clear understanding of the neural mechanisms by which sensory stimulation could suppress tremor. Previous researchers have suggested several variations on two hypothetical mechanisms connecting tremor suppression to the activation of afferent neurons by sensory stimulation (Pascual-Valdunciel et al., 2022). The first hypothesis proposes that signals from stimulated afferent neurons cause a disruption of tremorogenic oscillatory activity in the supraspinal tremor network. Some studies have shown that nerve stimulation can shift centrally generated tremor frequency under certain conditions, tentatively supporting this first hypothesis (Spiegel et al., 2002). More recent studies even managed to directly connect peripheral sensory stimulation to changes in central tremor network activity patterns (Hishinuma et al, 2019; Hernandez-Martin, 2021). The second hypothesis suggests that tremor is suppressed when stimulated afferent neurons activate spinal reflex circuitry, mainly the reciprocal inhibition reflex circuit. The success of asynchronous stimulation of antagonist muscles suggests that reciprocal inhibition plays a role in tremor suppression (Puttaraksa et al., 2019; Muceli et al., 2019). Nevertheless, there has been little conclusive evidence for either hypothesis. Understanding the effects of synchronous sensory stimulation on both tremor-band power and frequency could potentially help discriminate between the two proposed mechanisms (see Discussion).

Since the effects of synchronous stimulation remain unclear but could help elucidate the mechanisms for tremor suppression via sensory stimulation, I will focus my investigation on the ET tremor-band power and tremor-band frequency effects of brief, synchronous sensory stimulation at different stimulation frequencies. Beyond investigating the hypothetical tremor suppression mechanism of sensory stimulation, this will also address the gaps in our knowledge of optimized stimulation parameters.

My thesis will be based on data gathered in a study performed by the Neuromechanics Research Group at BYU that investigated the effects of synchronous sensory stimulation on postural tremor in ET patients as measured by hand acceleration data (Stringham et al., 2022; unpublished work). I will extend that past study, by analyzing the surface electromyography (sEMG) data recorded in these previous experiments. Given that sEMG measures muscle activity and thus descending neural drive, it might help us elucidate a more precise understanding of the neural mechanisms involved in sensory stimulation for tremor suppression. Given that the Neuromechanics Research Group found no significant effects of sensory stimulation on tremor suppression in the hand acceleration data, I expect to see no significant stimulation effects on the sEMG measures of tremor power and frequency at any of the tested stimulation frequencies, suggesting the relative importance of reciprocal inhibition over supraspinal mechanisms in mediating tremor suppression via sensory stimulation.

## **Methods**

### **Data Source**

The sEMG data that I analyzed was gathered by the Neuromechanics Research Group in a study investigating postural tremor power and frequency effects of brief, synchronous sensory stimulation over the antagonistic flexor and extensor carpi radialis muscles, testing a range of 15 stimulation frequencies from 10 to 150 Hz on 21 subjects (Stringham et al., 2022). Their study was conducted with approval from BYU's Institutional Review Board.

### ***Subjects***

All 21 subjects had been diagnosed with ET by a neurologist and were right-handed. One subject had an implanted DBS device which was turned off during the duration of the experiment and 13 subjects were on ET medication at the time of the

experiment. Following procedures approved by Brigham Young University's Institutional Review Board, written informed consent was obtained from all subjects.

### ***Experimental Preparation and Setup***

Researchers decided to stimulate the flexor carpi radialis (FCR) and its antagonists, the extensor carpi radialis longus and brevis (ECR; due to the proximity of these two extensor muscles, they were treated as a single unit). Using medical tape, one pair of 1" x 1" electrodes was secured over the belly of the FCR (approximately 3 inches apart) and another pair over the bellies of the ECR longus and brevis on whichever arm showed the most tremor. Both electrodes were connected to a TENS device. Along with the electrodes, sEMG sensors were placed over the FCR and ECR, and the adjacent flexor carpi ulnaris (FCU) and extensor carpi ulnaris (ECU) muscles.

Subjects were seated at a table with their elbow flexed approximately 45 degrees from full extension, their forearm resting comfortably on a support platform protruding from the table, and their palm facing down. Their shoulder was abducted approximately 45 degrees and flexed approximately 30 degrees. Using medical tape, a laser pointer was attached to the back of each subject's hand with a target attached to the wall in front of the patient. Researchers attached inertial measurement units to the back of the hand to also measure wrist acceleration.

To ensure that stimulation was strictly sensory, researchers measured the sensory and motor thresholds in all 21 subjects. These thresholds were measured for stimulation frequencies of 10, 50, 100, and 150 Hz and interpolated for the other 11 stimulation frequencies used in the experiment. For each of these 4 stimulation frequencies, thresholds were found by increasing current amplitude by 1 mA until a patient indicated a sensation (for the sensory threshold) or until involuntary muscle contraction was detected (for the motor thresholds). For 8 patients, researchers were

unable to successfully detect a motor threshold (due to severe tremor). For these subjects, the researchers used the maximum comfortably tolerable current amplitude, which was below the average motor threshold of all other subjects. To make sure these eight subjects did not significantly influence my results, I ran my statistical analysis with and without these subjects.

### ***Experimental Protocol***

Researchers performed 15 trials per subject, using 15 different stimulation frequencies in random order. The stimulation frequencies ranged from 10-150 Hz in 10 Hz increments (10 Hz, 20 Hz, ..., 140 Hz, 150 Hz). The TENS pulse width was set to 200  $\mu$ s. The current amplitude was set to be halfway between the subject-specific sensory and motor thresholds.

Each trial consisted of a pre-, per-, and post-stimulation phase (the BASE, STIM, and REST phase respectively). The BASE phase lasted 30 seconds and allowed researchers to measure the tremor power and frequency baselines before stimulation occurred. The STIM phase lasted 45 seconds and consisted of continuous stimulation of the FCR and ECR muscles at one of the 15 frequencies. The REST phase lasted 60 seconds without any further stimulation and was intended to measure any residual stimulation effects on tremor. In addition, it allowed sensory receptors and afferent neurons to return to resting state. EMG data was collected during all three phases, although STIM phase sEMG could not be used to represent muscle activity due to stimulation-induced artifacts.

Subjects were instructed to point the laser pointer on their hand at the target on the wall for the duration of a complete trial (to evoke a postural tremor). Between each group of 3 trials, researchers included a two-minute break for subjects to relax their wrists and forearms. The setup and experiment itself lasted about 2 hours per

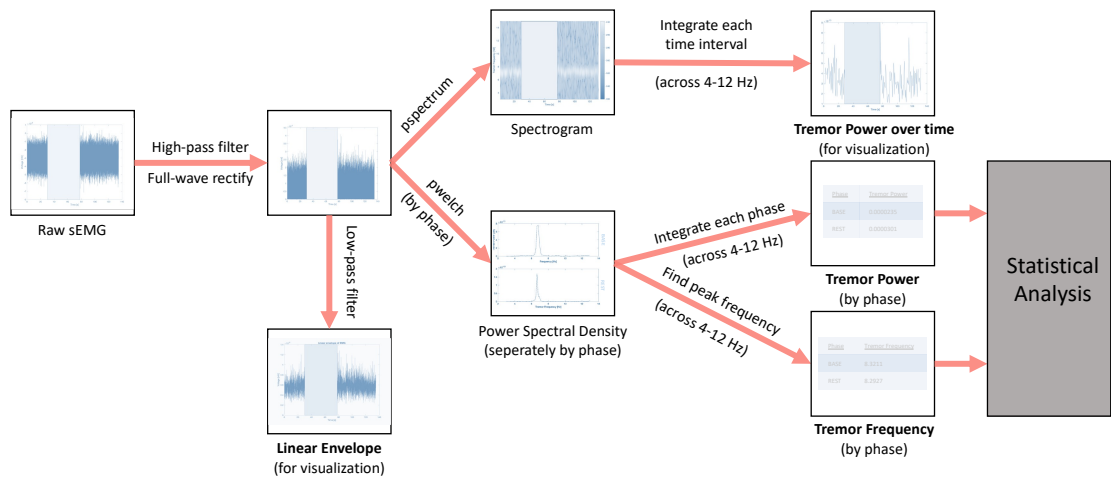
subject. Both acceleration and sEMG data (for the FCR, ECR, FCU, and ECU) were captured during each trial from the inertial measurement units and sEMG sensors respectively.

### **Data Processing**

Given the sEMG data, I processed it to determine the power and frequency of the tremor signal. Figure 1 outlines each step of the data processing pipeline. Figure 2 shows representative plots from each intermediate processing step.

Before determining tremor power and frequency, I preprocessed the sEMG recordings from each of the 4 muscles. The sEMG signals recorded during the STIM phase were dominated by stimulation-induced artifacts and were thus ignored. To remove movement artifacts and baseline drift, I filtered the sEMG signals from the BASE and REST phases using a fourth-order Butterworth high-pass filter with a cutoff frequency of 20 Hz. These filtered sEMG signals were then full wave rectified to enhance their motoneuron firing rate information content, thus allowing me to interpret them more confidently as proxies for motoneuron signals (Myers et al., 2003). Figure 2A shows the linear envelope of these pre-processed sEMG signals for 3 representative subjects. The filtered and rectified sEMG signals from each muscle were then used to find tremor power and tremor frequency.

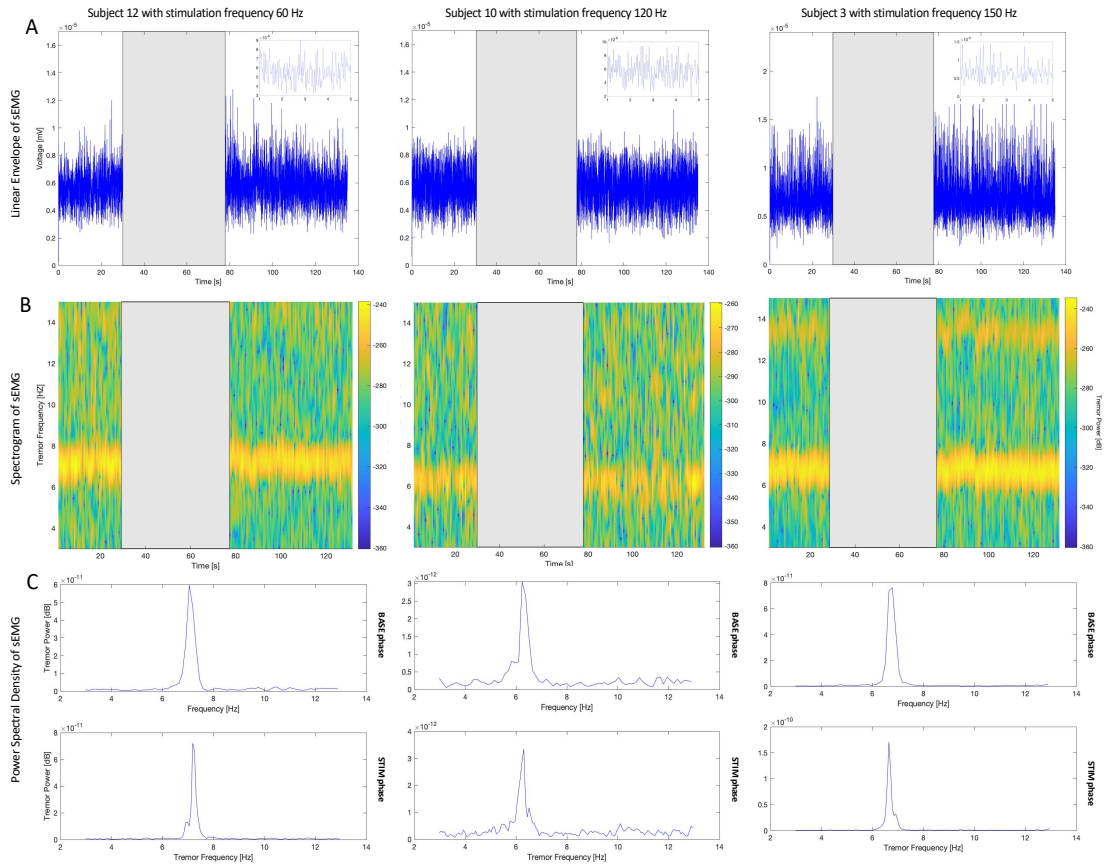




*Figure 1.* Outline of data processing pipeline for sEMG data from one trial. Via several steps, raw sEMG is processed into the linear envelope of sEMG over time, tremor power over time, tremor power by phase and tremor frequency by phase. Tremor power and frequency by phase are used for my statistical analysis.

### ***Computing Tremor-Band Power***

First, to visualize tremor power over time, I calculated the spectrogram of the sEMG signal from each muscle (using MATLAB’s `pspectrum` function, with type set to “spectrogram”, frequency limits ranging from 0-25 Hz, a time resolution of 6 seconds, and everything else set to default), resulting in a separate power spectrum for each 6-second interval (Figure 2B). Unlike voluntary movement, ET-induced muscle tremor occurs at frequencies between 4-12 Hz, the so-called tremor band (Vial et al., 2019). To specifically investigate tremorogenic signal power (independent of voluntary movements), I thus integrated the spectrograms for each 6-second interval across the tremor band using the trapezoidal method, resulting in sEMG tremor-band power over time for each recorded muscle (see Figure 3).



*Figure 2.* Intermediate processing results for 3 representative trials and subjects at different stimulation frequencies. A shows sEMG linear envelopes over the entire trial and over the first 5 seconds (inset plots). Notice the sEMG bursts characteristic of tremor in the inset plot. B shows the spectrograms of sEMG signal power over time between 3 and 15 Hz. Notice the bright yellow bands indicating higher power at tremor frequencies between 4 and 12 Hz. C shows the power spectral densities for the BASE phase (above) and REST phase (below). Notice the clear power peaks indicating a tremor frequency between 4 and 12 Hz.

Second, to simplify the statistical analysis of tremor power differences between phases, I returned to the high-pass filtered and rectified sEMG signals and calculated the power spectral densities in each of the two phases (BASE and REST) via MATLAB's `pwelch` function using the default values for the window, `noverlap`, and `nfft` inputs (Figure 2C). To isolate tremor-related signal power, I integrated power spectral density (using the trapezoidal method) across the tremor band (4-12 Hz) to yield a single measure of sEMG tremor-band power for each phase and recorded muscle

### ***Computing Tremor Frequency***

I used the power spectral densities calculated above to determine tremor signal frequency in the BASE and REST phases of the sEMG signal for each muscle. Power peaks in the tremor were identified using the sliding-window-constant-false-alarm-rate detection over 4-12 Hz, with a 1.0 Hz sliding window and 1.5 Hz sidebands (McDonough and Whalen, 1995). This method compares the maximum within a window to the means of the sidebands as the window slides across the frequency domain. If the sliding-window maximum was statistically significantly greater (at a 5% significance level) than the mean of the sidebands, I considered it a tremor power peak. Such tremor power peaks are evident in the representative power spectral densities for the BASE and REST phases in Figure 2C (although these peaks could be much harder to detect for other trials). The frequency of the highest tremor power peak (i.e., the frequency with the highest tremor power) was classified as the tremor frequency (Burne et al., 2002). This method yielded a single measure of sEMG tremor frequency for each phase and recorded muscle.

### **Statistical Analysis**

To test for an effect of stimulation frequency on tremor power and frequency, I performed mixed-model second-degree factorial ANOVAs of both integrated tremor-band power and tremor frequency. The following factors were included: phase (BASE and REST), stimulation frequency (15 levels from 10 to 150 Hz), muscle (FCR, ECR, FCU, and ECU), and subject (1-21), with subject as a random factor. I performed a post-hoc analysis using a Tukey Honest Significant Difference test.

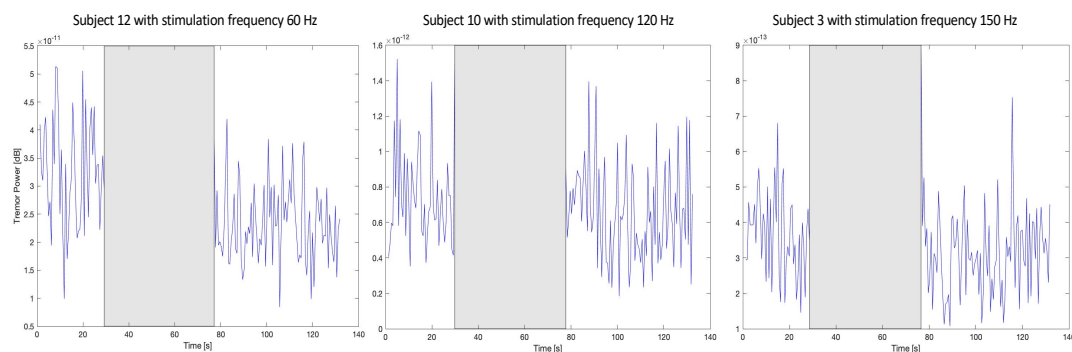
As mentioned above, researchers were unable to detect motor threshold for 8 subjects and used the maximum tolerable current rather than the stimulation current between motor and stimulation threshold. These missing observations may have

induced some bias into my effect estimates. Thus, I performed the same ANOVAs as described above on a subset of the data excluding those 8 subjects.

## Results

### Effect of stimulation frequency on tremor power

After processing sEMG data to spectrograms in the BASE and REST phase, I integrated the spectrograms across the tremor band (4-12 Hz) to yield tremor-band power vs time. Three representative tremor-band power over time plots can be seen in Figure 3.



*Figure 3.* Representative spectrogram integrals showing sEMG tremor-band power in the FCR over time for 3 representative trials and subjects. Note the apparent absence of significant alterations in tremor power patterns.

Combining results across all trials and subjects, the stimulation paradigm did not result in statistically significant tremor suppression—neither overall nor at any of the tested stimulation frequencies (Figure 4A). There was no statistically significant interaction between phase and stimulation frequency for sEMG-measured tremor power ( $p=0.45$ ) (Table 1). These results were robust to the exclusion of the 8 subjects where no motor threshold could be determined ( $p=0.57$ ). In addition, after extensive investigation, I did not find any consistent patterns in tremor power over time within either the BASE or REST phases or across the entire trial.

Table 1. ANOVA effects of stimulation frequency, stimulation phase, recorded muscle, and interactions on tremor power. Note that none of the p-values are significant.

<i>Effect on Tremor Power</i>	<i>Nparm</i>	<i>DF</i>	<i>DFden</i>	<i>F ratio</i>	<i>Prob &gt; F</i>
Stimulation Frequency	14	14	278.6	0.3657	0.9831
Phase	1	1	19.46	0.0103	0.9202
Muscle	3	3	59.61	1.1622	0.3317
Stimulation Frequency*Phase	14	14	1990	0.9915	0.4591
Stimulation Frequency*Muscle	42	42	1988	0.8048	0.8105
Phase*Muscle	3	3	1991	1.8092	0.1434

### Effect of stimulation frequency on tremor frequency

After processing sEMG data to power spectral densities in the BASE and REST phase, I found the tremor frequency by using the sliding-window-constant-false-alarm-rate detection algorithm to find tremor peaks. This algorithm successfully identified a tremor peak in the power spectrum for 97.1% of the six-second time windows in the sEMG data. More specifically, I only failed to detect a tremor frequency peak for 5.1% of the trials in the BASE phase and 0.8% of REST phase trials for the sEMG data.

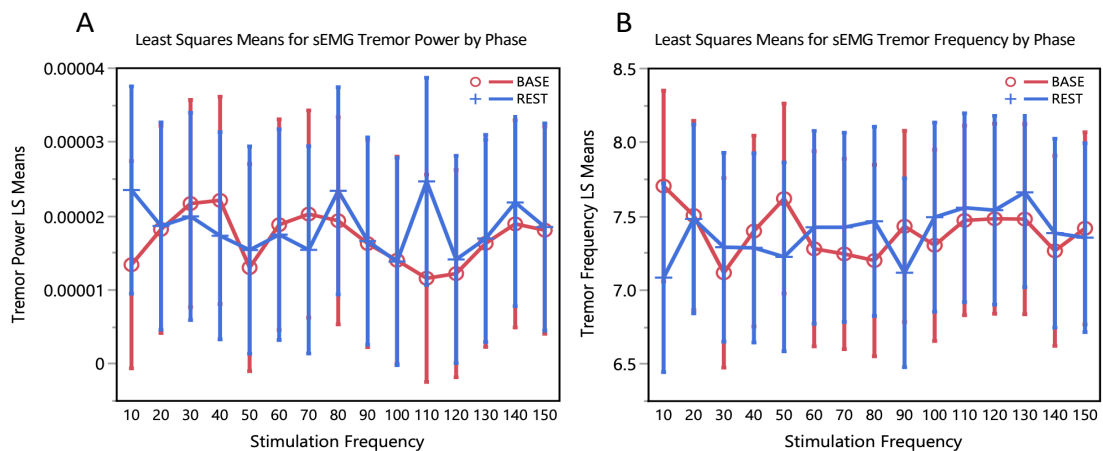


Figure 4. Least-Squares Means plots for tremor power and tremor frequency by phase. A shows the Least-Squares Means plot for tremor power. Note that BASE tremor power (red) does not significantly differ from REST tremor power (blue) at any of the 15 stimulation frequencies. B shows the Least-

Squares Means plot for tremor frequency. Note that BASE tremor frequency (red) does not significantly differ from REST tremor frequency (blue) at any stimulation frequency.

Combining results across all trials and subjects, the stimulation paradigm did not result in significant tremor frequency changes – neither overall nor at any of the tested stimulation frequencies (Figure 4B). The effect of phase interacting with stimulation frequency on tremor frequency was statistically insignificant ( $p=0.81$ ) (Table 2). These results were robust to the exclusion of the 8 subjects where no motor threshold was determined ( $p=0.23$ ). In addition, after extensive investigation, I did not find any patterns in tremor frequency over time within either the BASE or REST phases or across the entire trial.

*Table 2.* ANOVA effects of stimulation frequency, stimulation phase, recorded muscle, and interactions on tremor frequency. Note that none of the p-values related to stimulation frequency or phase are significant.

<i>Effect on Tremor Frequency</i>	<i>Nparm</i>	<i>DF</i>	<i>DFden</i>	<i>F ratio</i>	<i>Prob &gt; F</i>
Stimulation Frequency	14	14	278	0.5553	0.8979
Phase	1	1	20.26	1.6004	0.2202
Muscle	3	3	60.01	5.7229	<b>0.0016*</b>
Stimulation Frequency*Phase	14	14	2050	1.0014	0.4488
Stimulation Frequency*Muscle	42	42	2048	0.8283	0.7757
Phase*Muscle	3	3	2048	2.7534	<b>0.0142*</b>

## Discussion

This investigation tested the effect of synchronous sensory stimulation on tremor power and frequency using 15 stimulation frequencies between 10 and 150 Hz. Using 45-second synchronous stimulation over the FCR and ECR muscles with a 200  $\mu$ s pulse width and an amplitude between the motor and sensory threshold, I found no evidence of sEMG tremor suppression or tremor frequency changes from BASE to REST phase at any stimulation frequency. This demonstrates that brief, synchronous

sensory stimulation over antagonist muscles does not significantly affect tremor in ET patients.

### **Implications for future therapeutic applications**

My results further narrow the options of future therapeutic applications of sensory stimulation to suppress tremor. It confirms the results obtained by Pascual-Valdunciel (2021a) with regards to the inefficacy of brief synchronous sensory stimulation and indicates that for sensory stimulation to successfully reduce tremor, it should be applied either asynchronously or possibly, if synchronously, with a longer duration than the 45 second strategy employed in the experiment I analyzed. Examples of successful tremor suppression using brief, asynchronous sensory stimulation include Dosen et al. (2015), who found a 35-48% decrease in tremor severity for 5 ET patients, and Dideriksen et al. (2017), who found an average 52% decrease in tremor severity for 9 ET patients. Note that asynchronous sensory stimulation is highly dependent on timing the stimulus out of phase with the tremor signal. This requires precise measurement of incoming tremorogenic signals and online calculation of tremor frequency, which is much more difficult and costly than applying basic synchronous sensory stimulation. A simpler alternative could be to use long-duration synchronous sensory stimulation, although this has not yet been tested to the best of my knowledge. Studies using asynchronous (albeit independent of tremor frequency) sensory stimulation for a duration of 40 minutes have shown tremor reductions up to 72%, suggesting that long-duration, synchronous sensory stimulation could be more effective than our stimulation paradigm (Isaacson et al., 2020; Pahwa et al., 2019; Lin et al., 2018).

## **Implications for hypothetical mechanism of tremor suppression**

In addition to providing insights regarding future therapeutic applications, my results contribute meaningful insights regarding the hypothetical mechanism of tremor suppression through sensory stimulation. As mentioned in the Introduction, there are two major hypotheses regarding the mechanism of tremor suppression via sensory stimulation (Pascual-Valdunciel, 2022). First, the “supraspinal” hypothesis which posits that sensory stimulation disrupts the tremorogenic oscillations in the supraspinal tremor network via stimulation-induced afferent neuron signaling. Second, the “spinal circuit” hypothesis which states that tremor is suppressed when stimulated afferent neurons activate spinal reflex circuitry, mainly the reciprocal inhibition reflex, which then inhibits antagonistic muscle pairs out of phase with the tremor. I will discuss the implications of my results with regards to each hypothesis.

### ***Supraspinal Hypothesis***

Multiple authors have suggested that sensory peripheral stimulation sends signals that disrupt supraspinal tremorogenic oscillations (Pascual-Valdunciel, 2021b; Lin et al., 2018).

As mentioned in the Introduction, ET is driven by supraspinal pathological oscillatory activity originating in a network of coupled central nervous system structures (Schnitzler et al., 2009; Holtbernd & Shah, 2021). Sensory peripheral stimulation activates afferent neurons that send signals to the central nervous system which could possibly disrupt the long-term dynamics of this pathological oscillatory activity and thus decrease tremorogenic signaling to peripheral limbs. If this hypothetical mechanism were true, the stimulation timing strategy would likely be irrelevant (Dideriksen et al., 2017). Synchronous and asynchronous timing strategies would yield similar levels of tremor suppression as long as the afferent signals induced by



stimulation are substantial enough to disrupt the central tremor network. In addition, the tremor suppression effects would likely persist for a longer time after stimulation has ended since this mechanism disrupts tremor at the source itself (Britton et al., 1993). Finally, since the tremor frequency measured by sEMG signals originates in the central tremor network, we might see tremor frequency changes due to the disruption of central tremor network outputs (Spiegel et al., 2002).

Several previous studies lend credibility to the supraspinal hypothesis. Spiegel et al. (2002) directly observed shifts in the tremor frequency upon stimulation of proprioceptive neurons on subjects with Parkinsonian tremor, implying supraspinal effects of proprioceptive stimulation. Further studies have shown that stimulation of afferent neurons activate the VIM, one of the important components of the central tremor network and the target of tremor-suppressing DBS (Hanajima et al., 2004; Hernandez-Martin et al., 2021). Based on these previous studies, Pahwa et al. (2019) performed sensory stimulation, timed independently of tremor frequency, on the medial and radial nerves of ET patients for stimulation durations of 40 minutes, hoping to disrupt central tremor network oscillatory signals. This led to tremor reductions of up to 56%. In a larger clinical study, Isaacson et al. (2020) showed that the same stimulation protocol could reduce tremor for over 90 minutes after stimulation. The long-term reduction of tremor due to long-duration stimulation, timed independently of tremor frequency, matches both predictions made by the supraspinal hypothesis. These studies thus tentatively support the idea that sensory stimulation could suppress ET by disrupting supraspinal tremorogenic signaling to peripheral muscles.

My results do not lend additional support to the supraspinal tremor suppression hypothesis. My sEMG-measured tremor signals correlate to descending

input from supraspinal tremor networks (in addition to afferent feedback) (Farina, Merletti, & Enoka, 2014) and, unlike Britton et al. (1993) (who used stimulation above motoneuron threshold) and Spiegel et al. (2002) (who investigated Parkinsonian tremor), I did not observe any tremor frequency changes nor power reductions in the sEMG signal with the brief 45 second synchronous sensory stimulation paradigm. Thus, my results do not conform with the supraspinal hypothesis prediction. Nevertheless, Pahwa et al. (2019) and Isaacson et al. (2020) achieved long-term tremor reduction only when using a 40-minute stimulation duration. Given this evidence, my results indicate that any long-lasting disruption of the central tremor network's tremorogenic signals to the muscles requires significantly longer stimulation duration times. This might be necessary to induce short-term plasticity in the VIM or other central tremor network structures or simply to counteract tremorogenic oscillatory dynamics for long enough to disrupt them. The fact that the experiment I analyzed used a synchronous stimulation strategy is irrelevant to the discussion about the supraspinal hypothesis since central tremor network disruption by sensory stimulation should occur independently of stimulation timing.

### ***Spinal Circuit Hypothesis***

The spinal circuit hypothesis implies that an asynchronous sensory stimulation strategy out of phase with the tremor might counteract tremor-induced muscle contractions via reciprocal inhibition if stimulation is timed precisely. Reciprocal inhibition is when Ia-afferent neurons activate the muscle they originate from but also disynaptically inhibit the neural drive to antagonist muscles via spinal cord reflex circuitry (Latash, 2012). Sensory stimulation recruits Ia-afferent fibers and thus could activate the reciprocal inhibition mechanism. Thus, sensory stimulation can cause the

muscle over which stimulation is applied to contract reflexively (not directly) while inhibiting the neural drive to the antagonist muscle (Pascual-Valdunciel et al., 2019). Note that this reflexive contraction can occur even when we stimulate below motoneuron threshold (Hallet, 2012). By measuring the tremor frequency and timing the stimulation just right, sensory stimulation can activate Ia-afferents so that their inhibitory input to the antagonist muscle coincides with the arrival of tremor bursts at that muscle. Additionally, the reflex would contract the agonist muscle at the stimulation site thus mechanically opposing the tremor-induced antagonist muscle contraction. Thus, the contraction of the stimulated muscle and the inhibition of input to the tremor-activated muscle could instantaneously counteract alternating tremor activity in antagonistic muscle pairs. Note that unlike the supraspinal mechanism, the timing and strategy used are critical for the reciprocal inhibition mechanism to effectively suppress tremor (Dideriksen et al., 2017). Assuming this mechanism, synchronous sensory stimulation would not suppress tremor, but asynchronous sensory stimulation would. In addition, I would not expect any tremor frequency shifts nor any persistent tremor suppression since central tremor networks are not targeted.

Previous studies using asynchronous sensory stimulation have shown it to effectively reduce tremor instantaneously, lending support to the spinal circuit hypothesis. Using an asynchronous sensory stimulation paradigm, Dosen et al. (2015) observed that tremor suppression of up to 42% was achieved “while the stimulation was being delivered” but didn’t persist for long once stimulation had ended (unlike the prediction made by the supraspinal hypothesis). This short-term effect suggests that tremor suppression occurs via a spinal circuit reflexive mechanism, likely involving reciprocal inhibition. Dideriksen et al. (2017) achieved similar results to

Dosen et al. and concluded, with respect to the spinal circuit hypothesis, that “the appropriate timing of stimulation could be critical”. The Dideriksen study lends further support to the spinal circuit hypothesis by showing that intramuscular stimulation, which targets specifically proprioceptive Ia afferents, more effectively suppresses tremor than surface stimulation, which more broadly affects cutaneous sensory afferents. Unlike other cutaneous sensory afferents, proprioceptive Ia neurons directly mediate reciprocal inhibition, strengthening the argument that tremor suppression occurs mainly through reciprocal inhibition, as posited by the spinal circuit hypothesis.

My investigation bolsters the evidence for the spinal circuit hypothesis by showing that the stimulation strategy and timing matter for tremor suppression when the stimulation duration is brief. Since the spinal circuit hypothesis postulates that tremor suppression occurs via reciprocal inhibition, it predicts that brief and precise asynchronous sensory stimulation should be instantaneously effective. Brief, synchronous sensory stimulation on the other hand should not decrease tremor power nor change tremor frequency since simultaneous reciprocal inhibition from antagonist muscles would cancel each other out. These predictions are consistent with my results since I saw no tremor reduction nor tremor frequency change under the brief, synchronous sensory stimulation protocol. The unpublished analysis by the Neuromechanics Group made a similar conclusion regarding tremor as measured by wrist acceleration – including in the STIM phase (Stringham et al., 2022). My results thus harmonize with the idea that, under brief stimulation durations, tremor suppression occurs mainly via reciprocal inhibition.

My results confirm the conclusions drawn by Pascual-Valdunciel et al. (2021a), while contrasting with those obtained by Heo et al. (2015). It should be noted

that while Heo et al. found significant tremor decreases measured by acceleration of the finger, hand, and wrist, they did not find any significant tremor decreases in the forearm. In addition, they only used a 15 second pre-stimulation phase for each trial with a 5-minute breaks between trials where subjects were allowed to rest from the postural task. Given that the Heo et al. study asked subjects to stretch both arms forward for their postural task, 15 seconds may have not been enough time to establish a true postural tremor baseline that is comparable to post-stimulation tremor power. This is especially true when considering that Essential Tremor often worsens with large-amplitude and intentional movements, which would include a subject being asked to raise their arms up and forward (Sternberg et al., 2013). This could have biased some of the effects estimated by Heo et al. (2015). The BYU Neuromechanics Study Group researchers addressed these concerns by using a longer BASE phase and only using breaks between every 3 trials (Stringham et al., 2022). In addition, their postural task did not involve large displacements from the support platform on the table, likely minimizing the impact of intention-induced tremor, and further bolstering the validity of my results.

### **Limitations**

Several limitations should be noted with regards to my conclusions. First, the experiment did not include repetitions of trials with specific frequencies on any patients. Repeated trials could have lent additional power to my analysis and helped avoid estimation bias from measurement errors. Second, the experiment was conducted by stimulating the surface of the peripheral limb. In other studies, surface sensory stimulation has consistently yielded less conclusive results than intramuscular stimulation (Pascual-Valdunciel, 2021b) and might have disguised potential tremor

suppression effects. Nevertheless, I think this is unlikely given the high p-values associated with the ANOVA interaction terms.

Finally, the REST phase was only 60 seconds long which may not have been enough time to allow peripheral neural pathways to return to a resting state. There is little research on the recovery period of peripheral neural pathways after sensory electrical stimulation. Nevertheless, the Neuromechanics Research Group's decision was based on vibrational stimulation studies which indicate that 40-60 seconds is sufficient for muscle spindles to fully recover (Ribot-Ciscar, Rossi-Durand, & Roll, 1998). In addition, the BASE phase seems to be unaffected by the REST phase of previous trials.

### **Conclusion**

I conclude that brief, synchronous sensory stimulation over peripheral muscles is not effective in reducing postural tremor or changing tremor frequency as measured by sEMG, independent of stimulation frequency (in the range of 10-150 Hz). In conjunction with the studies that suppress tremor using brief, asynchronous sensory stimulation, my results are in harmony with the spinal circuit hypothesis of tremor suppression via reciprocal inhibition. Due to the brief 45-second stimulation duration used in the analyzed experiment, I cannot come to any definite conclusions regarding the supraspinal hypothesis of tremor suppression via central tremor network disruption.

Future research needs to be done on the tremor effects of synchronous sensory stimulation with longer stimulation durations – on the order of 40 minutes as seen in Pahwa et al. (2019) and Isaacson et al. (2020). Investigating the tremor suppression efficacy of this variation of synchronous sensory stimulation might open the door to simpler, more comfortable, and less costly therapeutic applications, especially when

considering that synchronous stimulation is much easier to implement than asynchronous stimulation. In addition, it would provide more conclusive evidence regarding the supraspinal hypothesis. If the supraspinal hypothesis held, I would expect long-duration synchronous sensory stimulation to lead to long-term tremor suppression and possible tremor frequency shifts. In such an experiment, researchers could compare the efficacy of intramuscular stimulation (which directly targets proprioceptive Ia afferents) to broad surface stimulation (targeting cutaneous sensory afferents) to tease out which exact pathways conduct disruptive afferent signals to the central tremor network, assuming the supraspinal hypothesis were accurate. To my knowledge no such study has been attempted, despite potentially solidifying the mechanistic explanations for long-term tremor suppression and increasing the number of therapeutic options available to ET patients.

Additionally, the spinal circuit tremor suppression hypothesis should be explored further using different stimulation parameters under an asynchronous stimulation timing strategy. To my knowledge, no study has evaluated the effect of different stimulation frequencies on tremor suppression using asynchronous sensory stimulation. In addition, combinations of long-duration synchronous and instantaneous asynchronous stimulation (for example consistently stimulating medial and radial nerves at low intensity while simultaneously alternating stimulation over tremor-affected muscles) might provide enhanced tremor suppression effects as well. Other parameters like pulse width, stimulation duration, and stimulation site also require further systematic investigation to optimize the brief, asynchronous sensory stimulation paradigm for future clinical applications.

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