Personalized Stimuli as Treatment for Resting Tremor in Parkinson's Disease

by

Marcus Ting Hin Cheung

B.A Sc., The University of British Columbia, 2015

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF
THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF APPLIED SCIENCE

in

THE FACULTY OF GRADUATE AND POSTDOCTORAL STUDIES

(Biomedical Engineering)

THE UNIVERSITY OF BRITISH COLUMBIA

(Vancouver)

August 2017

Abstract

Resting tremor in Parkinson's disease (PD) affects quality of life and individuals' ability to complete activities of daily living. Resting tremor has been shown to respond to transcranial alternating current stimulation (tACS) when delivered out of phase with the tremor. The present work aimed to further investigate potential tACS-based treatment mechanisms by designing and delivering personalized stimuli and extend our understanding of Parkinsonian resting tremor. Nine participants with tremor dominant PD received fourteen unique tACS stimuli to Primary Motor Cortex (M1) and Supplementary Motor Area (SMA). Effect on tremor was measured before and during stimulation via a 9 degree of freedom (DoF) motion sensor. The first principal component score was obtained from Principal Component Analysis (PCA) of these measures and the power of the data was compared before and during stimulation using a two-sample t-test. Four custom stimuli were designed by weighted linear combination of the data with the greatest effect on tremor; two of which were designed to be suppressive and two were designed to be augmentative towards tremor. Average power was calculated following delivery of the personalized and non-personalized stimuli. Regardless of whether tACS was delivered as a personalized or non-personalized stimuli, results indicate an increased average power during stimulation compared to no stimulation and an overall trend towards augmentation of tremor across participants. Supporting analyses, including Multivariate Empirical Mode Decomposition (MEMD) reinforce this finding, showing no clear trend towards any specific frequencies contributing to tremor suppression. The present results suggest that a broad spectrum frequency-based approach is not an effective means of suppressing tremor in people with PD and a phase-based or more targeted frequency approach may have more promise as a treatment mechanism for resting tremor in PD.

Lay Summary

Parkinson's disease is a degenerative neurological condition, prevalent in the aging population. A key symptom in many individuals is tremor in the extremities- particularly the hands and arms- while a person is at rest, thus making activities of daily living challenging. Resting tremor is often resistant to Parkinson's medication, thus increasing the need for alternate management options, particularly those that are non-invasive. In this thesis work, I aim to investigate an alternate method of managing resting tremor in Parkinson's disease using a non-invasive technique of applying electrical current - transcranial alternating current stimulation - to regions of the brain that are involved in controlling movement of the arms and hands. In doing this, I have two goals 1) to deliver a stimulus that is capable of reducing resting tremor in people with Parkinson's disease and 2) to customize this stimulus for each individual participant to create more tailored individual effects.

Preface

The author contributed to the design and selection of the research program by conducting a review of relevant literature to determine next steps to further recent work in the area of tremor in Parkinson's disease. The author designed and conducted a pilot study with research participants to explore the feasibility of the experimental protocol as well as the functionality of the research equipment. The main research study was designed and carried out by the author as the lead researcher, with assistance as needed from members of the research team. The author was responsible for data collection, analysis (including data processing and statistical analysis), interpretation of results and the writing of all parts of the thesis. Assistance from the research team was in the form of submission of the ethics application, recruitment of participants, collection of data and editing of the thesis document.

Approval for this research study (including the pilot and main study) was obtained by the University of British Columbia Clinical Research Ethics Board (Certificate # H16-01071), which received full board review. The author was involved in the submission of this application.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

BG	Basal ganglia
DAQ	Data acquisition
DBS	Deep brain stimulation
DoF	Degrees of freedom
EEG	Electroencephalogram
ET	Essential tremor
Hz	Hertz
IMF	Intrinsic mode functions
mA	Milliamp
MDS-UPDRS	Movement Disorders Society – Unified Parkinson's Disease Rating Scale
MEMD	Multivariate Empirical Mode Decomposition
PCA	Principal Component Analysis
PD	Parkinson's disease
rmANOVA	Repeated measures analysis of variance
SMA	Supplementary motor area
SNpc	Substantia nigra pars compacta
STFT	Short-time Fourier transform
STN	Subthalamic nucleus
tACS	Transcranial alternating current stimulation
tDCS	Transcranial direct current stimulation
TES	Transcranial electrical stimulation
tRNS	Transcranial random noise stimulation

Acknowledgements

I would like to thank the faculty, staff, and my lab mates at the University of British Columbia for their support in my work. I particularly want to thank my supervisor, Dr. Martin J. McKeown for his support, both on a scientific and personal level. He has always steered me in the right direction when I needed it and has truly inspired me with his passion and dedication in clinical research. I would also like to thank Dr. Jane Wang, my co-supervisor, for her help whenever I had questions about my research.

Furthermore, I like to extend a special thanks to my lab's research coordinator, Christina B. Jones, for her constant dedication in helping with different aspects of my research. Along the way, she has also taught me much knowledge and has supported me throughout times of hardship. I like to thank the rest of my lab mates for their unlimited support especially Saurabh Garg and Soojin Lee for any technical and research related questions.

Finally, I must express my gratitude to my beloved parents, sisters, brother-in-law, and niece for their limitless support and continuous encouragement throughout the whole process of my research. This accomplishment would not have been possible without them. Thank you.

Dedication

I would like to dedicate my thesis to my whole family, especially my parents.

Chapter 1: Introduction

1.1 Parkinson's disease

1.1.1 Parkinson's disease overview

Parkinson's disease (PD) is the second most common neurodegenerative disorder, second to Alzheimer's disease affecting up to 1% of Canadians over the age of 65. It is progressive and debilitating, resulting in stress on the health care system in terms of physician time and hospital resources. Thus, the management and treatment of PD continues to be increasing challenge for health care professionals.

1.1.2 Characteristic pathophysiology of Parkinson's disease

PD is characterized by the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc) [1]. Typically, individuals with PD have lost 50-70% of neurons in this brain region compared to a healthy individual in the same region [2]. On a cellular level, lewy bodies are the pathological hallmark of PD. They are a combination of neurofilament proteins as well as proteins responsible for proteolysis, which target other proteins for breakdown [2]. The loss of dopaminergic neurons leads to striatal dopamine deficiency that causes the symptoms of PD [3]. While it is difficult to confirm a diagnosis of PD on a molecular level, assessing the symptoms it produces is the norm for speculating whether a person is likely to have PD. Both motor and non-motor symptoms are prevalent in PD. The cardinal motor symptoms are bradykinesia (slowness of movement), rigidity, postural instability, and resting tremor [4]. Non-motor symptoms present in PD include depression, apathy, anxiety, and cognitive impairment.

Non-motor complications become progressively severe and troublesome as age advances in individuals with PD and thus increase the impact on their quality of life [5].

PD is also characterized by the pathological oscillatory synchronizations prevalent within and between brain regions [1]. More specifically, a study has shown that excessive synchronous activity is found throughout the cortico-basal ganglia (BG) network at the base of the brain [6]. The BG plays an important role in managing human movement and has three main pathways of processing information, the direct and indirect pathway via the striatum and the hyperdirect pathway via the subthalamic nucleus (STN) [7]. Studies suggest that dopamine depletion in the Parkinsonian state shows strong synchronization in the motor areas of the BG giving rise to the occurrence of motor symptoms [8].

1.1.3 Resting tremor in Parkinson's disease

While there are various motor symptoms seen in individuals with PD, resting tremor is the most common and one of the most easily recognized. Resting tremor is characterized by shaking in the limbs when the patient is awake and is not performing a motor action. It is an involuntary tremble that typically oscillates at low frequencies between 3 to 7 Hz in a supination-pronation fashion; resting tremor disappears with action or during sleep [4]. Resting tremor becomes more pronounced with physical and emotional stress such as anxiety. Tremor affects quality of life in people with PD who are inconvenienced when performing activities of daily living that would otherwise be completed with ease.

The exact mechanism of resting tremor in PD remains unclear. The relationship between relevant structures in the brain is currently still being explored. One study suggests that a possible mechanism of resting tremor in PD can be modeled after a dimmer-switch [9]. The

mechanism includes two circuits in the brain: the striato-pallidal circuit as part of the BG and the cerebello-thalamo-cortical circuit [9], [10]. The model illustrates that the death of dopaminergic cells in the retrorubral area A8 is the starting point where it causes the depletion of dopamine in the pallidum. As a result, pathological oscillatory activity emerges from the striato-pallidal circuit triggering activity in the cerebello-thalamo-cortical circuit through the primary motor cortex. Tremor episodes triggered by the striato-pallidal circuit are comparable to a light switch, while the cerebello-thalamo-cortical circuit produces the tremor and controls the amplitude, which is comparable to a light dimmer [9]. This model demonstrates a relationship between the BG and the cerebellothalamic circuit (Fig. 1). It is also important to mention that other studies have shown that the STN is an integral part of the mechanism of resting tremor in PD [11], [12]. The STN has a pathophysiological role in tremor activity due to the coherence between the tremor oscillations in the STN and the peripheral tremor activity [12]. It also receives anatomical projections directly from the motor cortex and has increased functional connectivity with the motor cortex in PD [13].

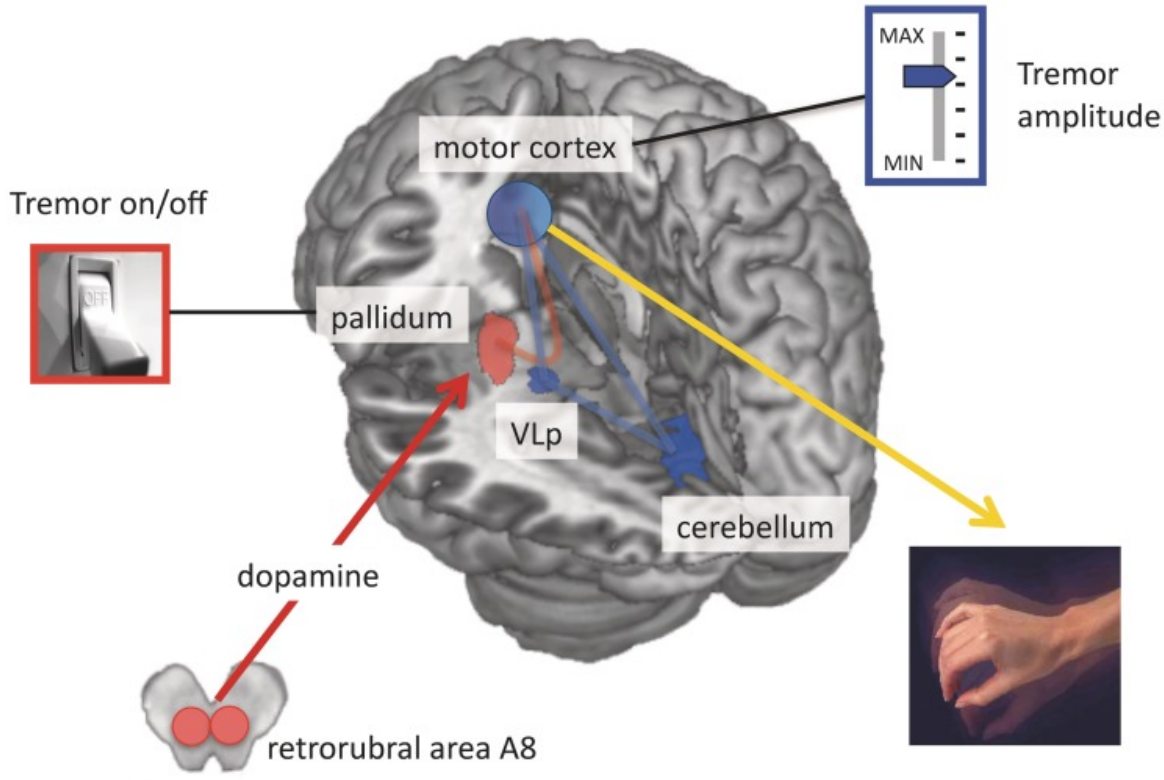

Figure 1. Striatal-pallidal circuit and cerebello-thalamo-cortical circuit. The relationship between the striato-pallidal circuit and the cerebello-thalamo-cortical circuit based on the dimmer-switch model. Model from Helmich, *et al*. [9].

1.1.4 Essential and other forms of tremor

PD tremor should not be confused with essential tremor (ET). Various types of tremor such as rest, postural, and kinetic tremor may be seen in both ET and PD [23]. Although similar in appearance, they have features, such as tremor frequency, characteristics, and other influencing factors that make them unique. ET frequency occurs between 5-10 Hz, while PD tremor frequency is 3-7 Hz [4]. ET occurs based on a flexion-extension fashion, decreases with rest, and increases with action. On the other hand, PD tremor is characterized by supination-

pronation, increases with rest, and decreases with action [4]. Postural tremor can be re-emergent in PD, but presents without latency in ET. Furthermore, kinetic tremor is not always present in PD, but is always present in ET [23]. Other differences include ET showing a symmetric limb tremor pattern whereas PD tremor is asymmetrical and ET can be suppressed with alcohol whereas PD tremor cannot [4].

1.1.5 Treatments for tremor in Parkinson's disease

Common pharmacological treatments for PD include dopaminergic drugs such as Levodopa and dopamine agonists. Levodopa remains the gold standard for treating motor symptoms in PD and is effective for treating bradykinesia and rigidity, but less so for tremor [14]. Long-term use of levodopa over the duration of five to ten years also contributes to the development of more motor complications in 80% of patients [15]. As such, using functional neurosurgery as a means to treat resting tremor in PD has gained interest. One such neurosurgery treatment currently used is Deep Brain Stimulation (DBS). This method places an electrode deep within the brain targeting structures in the BG. High frequency electrical pulses are generated from four or more contacts located at the distal end of the electrode [16]. These electrical pulses modulate pathological network activity beyond local neuronal cell bodies and change the firing rate and pattern of individual neurons in the BG [17]. Research indicates that stimulation of the STN can substantially reduce tremor in PD [18]. This manner of stimulation can help maintain stability for at least four years and stimulation at this site can significantly reduce the daily dose of dopaminergic medications such as Levodopa [17]. However, DBS is associated with risks of its own. Although it is an effective treatment method, risks such as surgical complications can cause various side-effects on PD individuals. Cases of hemorrhages and post-operative confusion

have been reported relating to the implantation of the electrodes. Some severe instances such as intracranial hemorrhages, lead to permanent neurological after-effects [19]. As such, surrogate treatments that are both non-pharmacological and non-invasive are actively being pursued, and many studies have suggested the possibility of using transcranial electrical stimulation (TES) [20]-[24]. Transcranial direct current stimulation (tDCS) is a form of TES that has been investigated since the 19th century [21]. TDCS provides a direct current through the skull, to the brain and is known for its capacity to modulate membrane resting potential [25]. Inducing tDCS causes voltage-gated neuronal channels to open and close such that it forces the release of neurotransmitters [25]. This process causes a depolarization of the postsynaptic neuron leading to an excitatory postsynaptic potential [25]. A cathodal stimulation is found to decrease excitability and an anodal stimulation produces the opposite effect [21], [25]. TDCS shows promise that externally applied stimulation can modulate neurons in the brain. However, in the past decade, transcranial alternating current stimulation (tACS) has grown in popularity due to its ability to modulate cortical rhythms [26]. This opens up new avenues of research in modulating brain oscillations, demonstrating the potential to treat pathological oscillatory diseases such as PD resting tremor. As such, tACS has gained much attention as a potential means for treatment.

1.2 Transcranial Alternating Current Stimulation

1.2.1 Transcranial Alternating Current Stimulation overview

TACS is an electrical stimulation technique by which an alternating current is externally applied through the skull to specific regions of the brain [20]. As the name implies, electrical current is delivered either at specific, individual frequencies or at a combination of frequencies,

predetermined by the experimenter [21]. TACS has grown in popularity in the past decade since it has been shown to be effective in modulating brain oscillations [21], [22], [25], [27]. Antal *et al*. have shown that tACS can improve cognition and motor performance via stimulation in the theta and alpha range of brain waves, respectively [20]. However, stimulation in the beta frequency deteriorates motor performance while stimulation in the gamma frequency interferes with attention [20]. A study has also shown that tACS stimulation at ripple frequency range (100-250 Hz) is associated with memory encoding [21]. Nonetheless, many studies that have performed tACS agree that modulating brain oscillations requires close attention to stimulation parameters [20], [21], [25].

1.2.2 Modulating the parameters of tACS

There are three main parameters (frequency, intensity, and the phase of the electrical stimulus) that can be modulated, with various combinations of each yielding differential effects on intrinsic cortical oscillations [22], [25]. At conventional electroencephalogram (EEG) frequencies ranging from 0.1 Hz to 80 Hz, tACS can interact with the ongoing rhythms in the cortex [28]. For instance, tACS at 15 Hz can elicit phosphenes when applied over the occipital cortex [28]. A 4 Hz tACS is able to disrupt low frequency oscillation generation related to interruption in declarative memory consolidation [25]. tACS applied in the low kHz range can increase excitability in neurons [20]. In order for tACS to elicit any cortical effects, a current of sufficient amplitude must be applied. The skin acts as a well-conducting medium, which short-circuits a large amount of current [29]. Current intensity must be balanced with participant safety and comfort and studies indicate that a tolerable level of tACS lies within a range of 0.2 mA to 2 mA [20], [22], [25], [30]. This range, however, varies greatly between individuals. Recent

studies have shown that by considering the phase of tACS in reference to the brain oscillations, different effects can be elicited [23], [24], [31]. In a study by Thut, when brain oscillations of the left and right visual hemispheres were forced into synchrony, an increase in coherence of the neuronal activity was seen [23]. Conversely, when they were forced out of synchrony, the opposite effect- a decrease in coherence - occurred.

Many studies use a tACS stimulus with a purely sinusoidal nature, (ie. a single frequency and phase) [18], [20], [25]. However, the stimulus may also contain combinations of frequencies [21]. Different effects are seen with a combination of frequencies. The more frequencies are involved, the closer the results of the stimulation are to approach transcranial random noise stimulation (tRNS) effects. TRNS is a method of stimulation that shows potential to desynchronize pathological rhythms in the brain [21].

A fourth parameter, the electrode montage must also be considered when applying tACS. The electrode montage dictates where the largest levels of electrical current will be focused and consequently, which area of the brain is being targeted. Conventionally, 5 x 7 cm sponge electrodes have been used since these electrodes allow for good conduction via saline, which is an electrolytic solution that acts as a medium between the sponge and the scalp [32]. They can be used over the hair and allow for uniform contact over the skin [32], which lowers cutaneous sensation [33]; this setup has been widely used in tDCS studies [34](Fig. 2a). However, recent studies suggest that this lacks focality [29]. Alternatively, multiple small stimulation electrodes, similar to those used for EEG recording, can help enhance the focal point of external brain stimulation [34] (Fig. 2b).

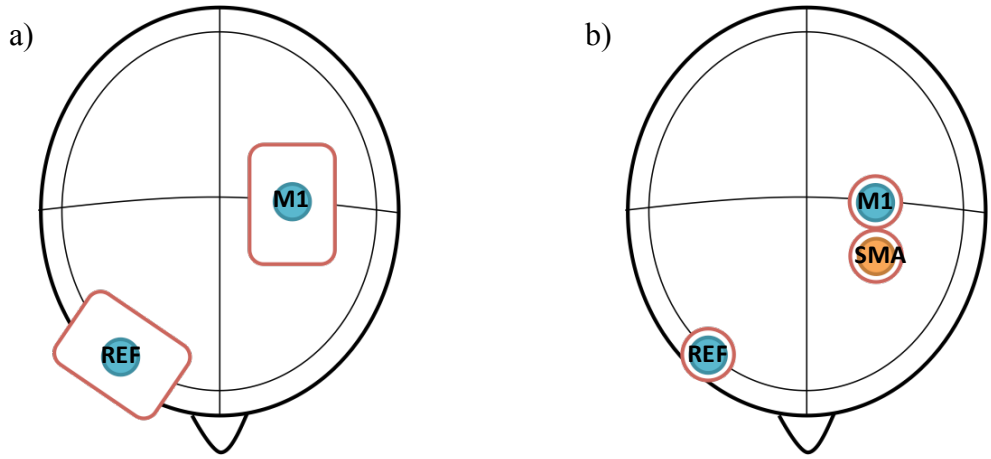

Figure 2. Electrode montage. a) Traditional tACS electrode montage targeting M1 and surrounding regions. b) Focal electrode tACS montage capable of targeting M1 and supplementary motor area, individually.

1.2.3 Application of tACS in rehabilitation

TACS has gained popularity over the last few years due to its potential as a rehabilitation technique for a variety of conditions [25]. Namely, it shows promise as an alternative to surgery and/or pharmaceuticals for the management of neurodegenerative diseases, such as PD [25]. In a recent study, Brittain *et al*., delivered a tACS stimulus over the motor cortex to reduce resting tremor in PD [35]. Motion sensors were placed on the tremulous limb to measure the rest tremor frequency, thus serving as a proxy for cortical oscillatory activity. The tACS stimulus was delivered at a frequency that was matched to the individual's tremor frequency (or at the first harmonic of the tremor frequency). Tremor frequency stimulation was first used to identify the timing of the cortical oscillations in an uncoupled state with the on-going tremor. After identifying the phase alignments that induce the greatest change in tremor amplitudes,

stimulation was repeated at specific phase alignments to elicit phase cancellation. The authors report an average of 50% reduction of resting tremor in PD, suggesting that tACS has a promising capacity as a tool for rehabilitation [35].

Although medication can help with some symptoms of PD, resting tremor generally does not respond well to dopaminergic medication [35]. DBS, on the other hand, is a very effective means of treating resting tremor in PD but as discussed, contains risks due to its invasive nature and specific criteria for individuals to be candidates for the surgery. TACS is able to circumvent these concerns due to its non-invasive and non-pharmacological nature, however much still needs to be learned about the efficacy of this method as a treatment for resting tremor in PD. Rodríguez-Ugarte *et al*.'s study published in 2016 suggests that standard protocols for tACS are currently lacking in the scientific community [25]. The impact of altering frequency, intensity, phase and/or electrode configuration or a combination of these parameters has not been investigated in detail. However, Brittain, *et al*. has made first steps in understanding brain wave modulation of resting tremor in PD [25], by a frequency-specific stimulation. The question is now raised on whether the brain can respond to a "smarter" and more personalized stimulus for resting tremor in PD. As such, the purpose of this thesis is to investigate the effects of tACS using specially designed, individually tailored stimuli on individuals with PD resting tremor.

1.3 Research hypotheses

The present study has 3 main research hypotheses which are as follows:

1. Resting tremor in PD will respond to personalized tACS stimuli with greater reductions in tremor measured by a motion sensor compared to standard non-personalized stimuli

2. Not all combinations of stimuli will produce reductions in tremor, some will result in amplification of tremor
3. Tremor response to a combined stimulus can be predicted by individual responses to individual stimuli

Chapter 2: Experimental Design and Analysis

2.1 Methods

Two sequential studies were conducted to investigate the effects of tACS on Parkinsonian resting tremor. Study 1 was a pilot study designed as an investigational method of trialing a variety of tACS stimuli to study whether they produced any effect on tremor. Information collected from this study was used to narrow down the set of stimuli delivered during Study 2. Study 2 was divided into two parts (Part 1: non-personalized stimuli and Part 2: personalized stimuli), to investigate whether stimuli could be linearly combined to produce differential effects on tremor, based on the hypotheses.

2.1.1 Participants

Five participants (5 males, mean age = 64.4 ± 6.3 years) with PD resting tremor were recruited for Study 1. In Study 2, fourteen participants with PD resting tremor agreed to participate. Due to low amplitude of tremor as well as an inconsistency of tremor, five participants were unable to complete Study 2. Data from nine participants (9 males, mean age = 65.9 ± 10.3 years) was included in the final analysis. Four of the five participants from Study 1 returned to participate in Study 2 and were included in both analyses. No healthy controls were recruited for the study as the main purpose was to evaluate the effect of personalized and non-personalized stimulation on an individual's tremor. Thus each individual acted as their own control, with stimulation data compared to resting state data for each trial and each stimulus variation. Each participant provided written informed consent prior to testing, and all experimental procedures were approved by the University of British Columbia Clinical Research

Ethics Board and the Vancouver Coastal Health Research Institute and were conducted in accordance with the Declaration of Helsinki.

Participation in both of the studies was limited to specific individuals. All subjects had been previously diagnosed with tremor-dominant PD in the upper limb(s). Participants who were diagnosed with other forms of tremor (including essential tremor) were excluded from the study. Subjects were excluded from participation if they had an implanted neurostimulator, such as DBS, or had any contraindications to tACS. Subjects with a history of seizures or migraines were also excluded.

Part III of the Movement Disorder Society-sponsored revision of the Unified Parkinson's disease rating scale (MDS-UPDRS) was used to determine the severity of resting tremor for each participant. Activities specific for evaluating resting tremor in the upper limbs were used and included: finger tapping, pronation-supination movements of hands and an evaluation of the amplitude and consistency of the tremor. To assess whether medication has an effect on the participant's resting tremor, participants were asked: "When was the last time you took medication?" and "Does medication have an impact in suppression of your tremor?"

2.1.2 Apparatus

During the stimulation procedure, participants were asked to sit in a comfortable position while the tACS stimuli were provided (Fig. 3). The stimuli were generated on a computer using MATLAB software (Mathworks, Natick, USA) and converted into analog voltage signals through a data acquisition (DAQ) module (NI USB-6343, National Instruments, USA). Because the stimuli need to be delivered as a current output, the voltage signals were delivered via the STMISOLA Current or Voltage Linear Isolated Stimulator from Biopac Systems, Inc. (Goleta,

CA, USA), which outputs an electrical current or an electrical gain voltage. The stimulator has two modes for current output: a high current (gain factor of 10 mA/volt) output and a low current (gain factor of 1 mA/volt) output. The low current output mode was used for both studies.

A custom designed EEG cap from Electro-Cap International Inc. (Eaton, OH, USA) with integrated stimulation electrodes was used to deliver tACS. Small EEG-like electrodes were selected as the medium between the stimuli and the participant as opposed to the more traditional sponge electrode montage. The above electrodes were chosen to allow for focal stimulation of multiple brain regions within a small region. The electrodes were placed in fixed positions according to the International 10-20 System. Participants were fit with the EEG cap based on their head circumference. Electrodes were placed bilaterally over two regions of primary motor cortex (C1/C2 and C3/C4), and along the midline over the supplementary motor area (SMA) (FCz) (Fig. 3c). Conductive gel was used as a medium between the electrodes of the cap and the scalp. Disposable pre-gelled electrodes (Biopac Systems Inc., Goleta, CA, USA) were placed on the shoulder, ipsilateral to the stimulation electrodes as a reference point for stimulation (Fig. 3b). The skin of the shoulder superior to the clavicle was lightly abraded and cleaned to create better electrode contact and to reduce resistance during stimulation.

Resting tremor was recorded using the Shimmer3 IMU portable motion sensor (Shimmer, Dublin, Ireland) secured to the dorsum of the tremulous hand (Fig. 3d). The sensor records nine degrees of freedom (DOF) – accelerometer, gyroscope, and magnetometer each in the X, Y, and Z direction and operates via a Bluetooth receiver. The sensor also has the capability to communicate with MATLAB through a serial terminal program – RealTerm, to save data as MATLAB variables for convenience of computations. The sensor is equipped with a time stamp function that tags the last sample of each serial buffer with the system time on the personal

computer in Unix format. A special program was written to convert the time in Unix format to the conventional date time of hours, minutes, and seconds. Another program was also written to identify the time stamp of each individual data in each data buffer to reveal time at which the stimulus was delivered.

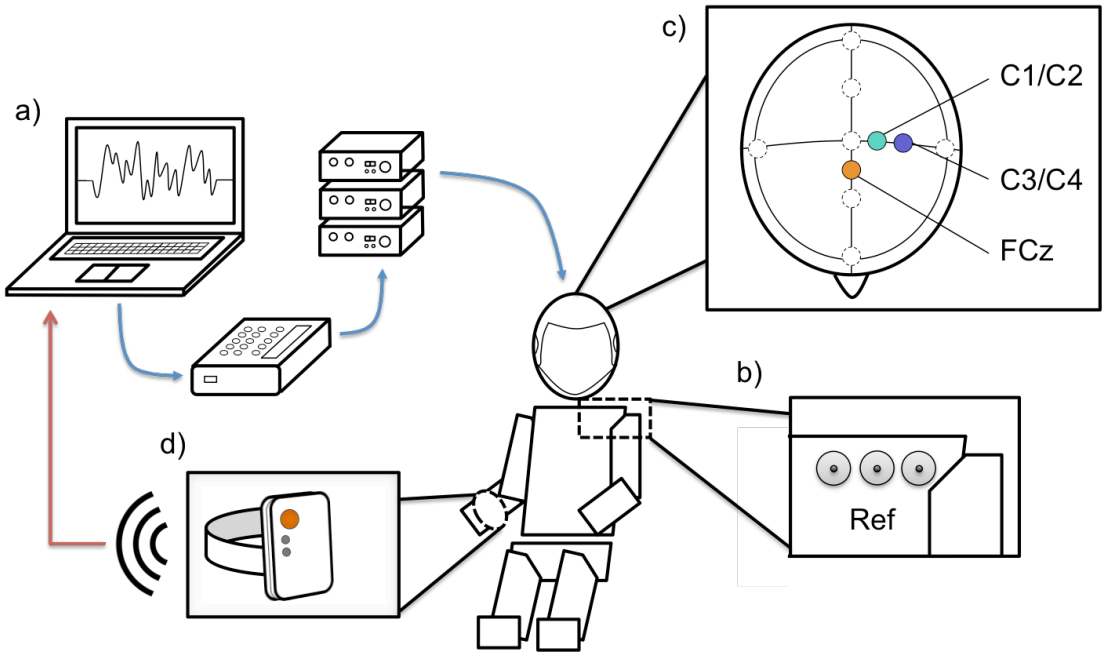

Figure 3. Experimental setup. a) The stimulating computer was connected to a DAQ board which output to three current stimulators. Each stimulator was connected to the participant via two electrode leads. The cathode was connected to the stimulating electrode and the anode was connected to b) a reference electrode placed on the shoulder. c) Electrodes were located bilaterally over two motor cortical areas; only the electrodes contralateral to the tremulous limb received stimulation. Supplementary motor area received stimulation via an electrode located along the midline. d) Tremor was recorded via a motion sensor placed on the hand and the resultant signal was broadcast back to the stimulating computer via Bluetooth.

2.1.3 TACS stimulus

Instead of providing a frequency-specific, purely sinusoidal tACS, stimuli containing a range of frequencies from 3 Hz to 7 Hz were selected. In this case, a Frequency sweep stimulus and a Multisine stimulus were chosen. A Frequency sweep signal increases linearly in frequency with respect to time (Fig. 4). A Multisine signal is a sum of sinusoid components such that each signal contains unique frequencies (Fig. 5). By minimizing the crest factor, the total signal power of Multisine is increased without changing the signal peak amplitude [36].

$$CF = \frac{max|I_{stim}(t)|}{RMS_I} \quad (1)$$

where CF is the crest factor, RMS_I means the root mean square of the applied current $I_{stim}(t)$. The hypothesis of the study was to see if weighted linearly combined stimuli would help suppress resting tremor in PD, as such, each of the Frequency sweep and Multisine stimuli were multiplied with a data taper that is orthogonal in nature. The Slepian or discrete prolate spheroidal sequences (Fig. 6) were chosen as multi-tapers since these vectors are mutually orthogonal. Each of the Frequency sweep and Multisine stimulus were multiplied in the time domain with seven different Slepian sequences generating seven orthogonal Frequency sweep stimuli and seven orthogonal Multisine stimuli. Figure 7 shows an example of a Frequency sweep stimulus multiplied to a level 1 Slepian taper, generating a stimulus orthogonal to the products of the other six. Each stimulus was generated with 1000 samples per second for twenty seconds. The maximum and minimum amplitudes of the stimuli were set at 1 mA and -1 mA, respectively, with no direct current offset.

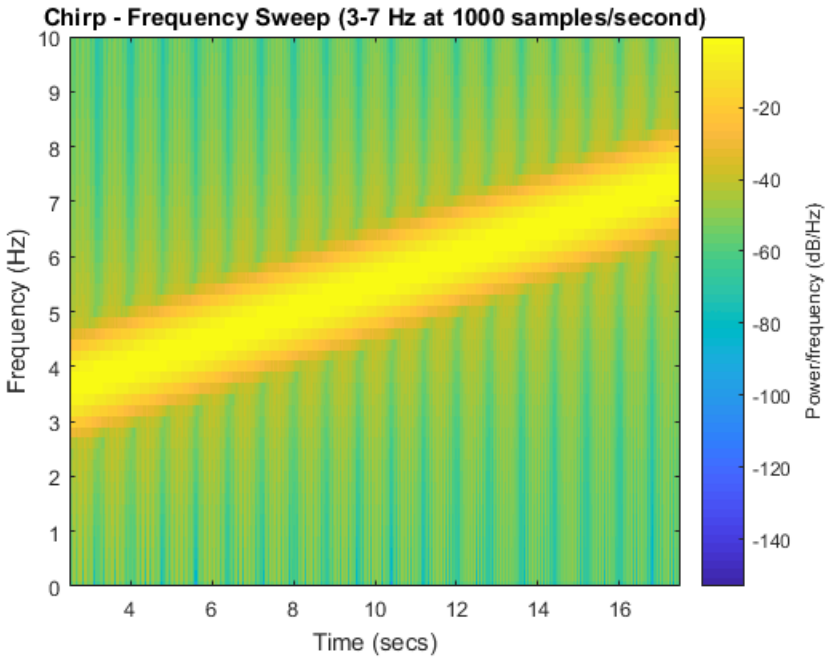

Figure 4. Frequency sweep stimulus spectrogram. Frequency sweep stimulus from 3-7 Hz at 1000 samples per second with frequency resolution of 0.25 Hz.

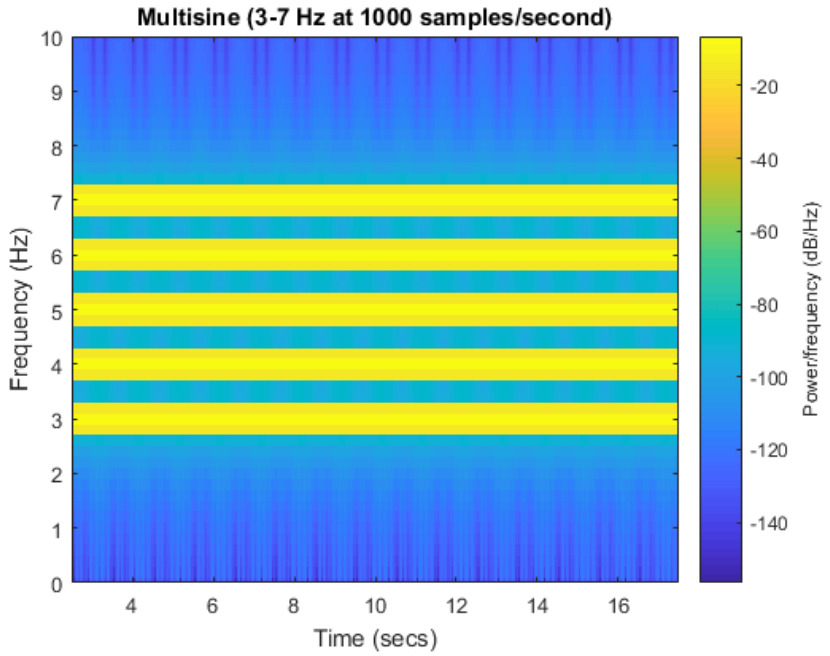

Figure 5. Multisine stimulus spectrogram. Multisine stimulus ranging from 3-7 Hz at 1000 samples per second with frequency resolution of 0.05 Hz.

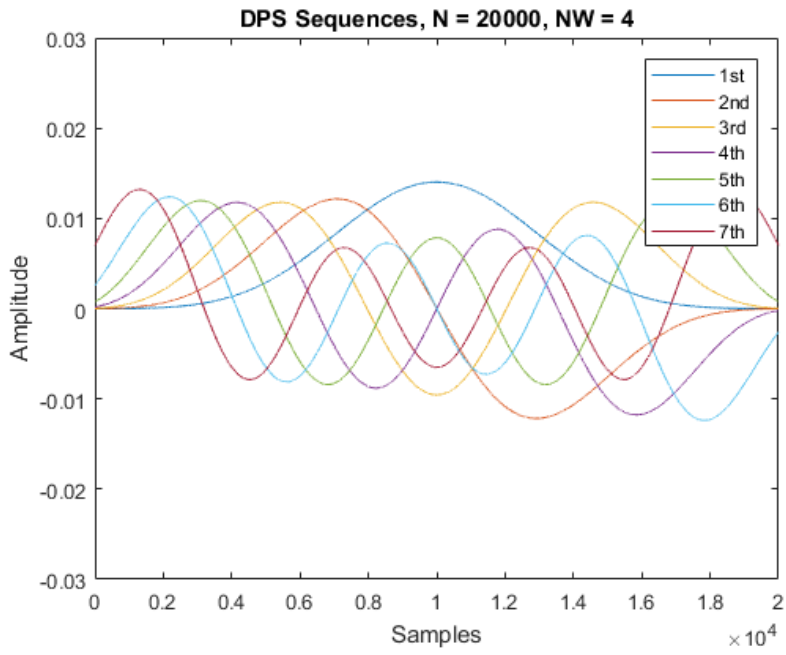

Figure 6. Slepians. Seven orthogonal tapers of discrete prolate spheroidal sequences or Slepians

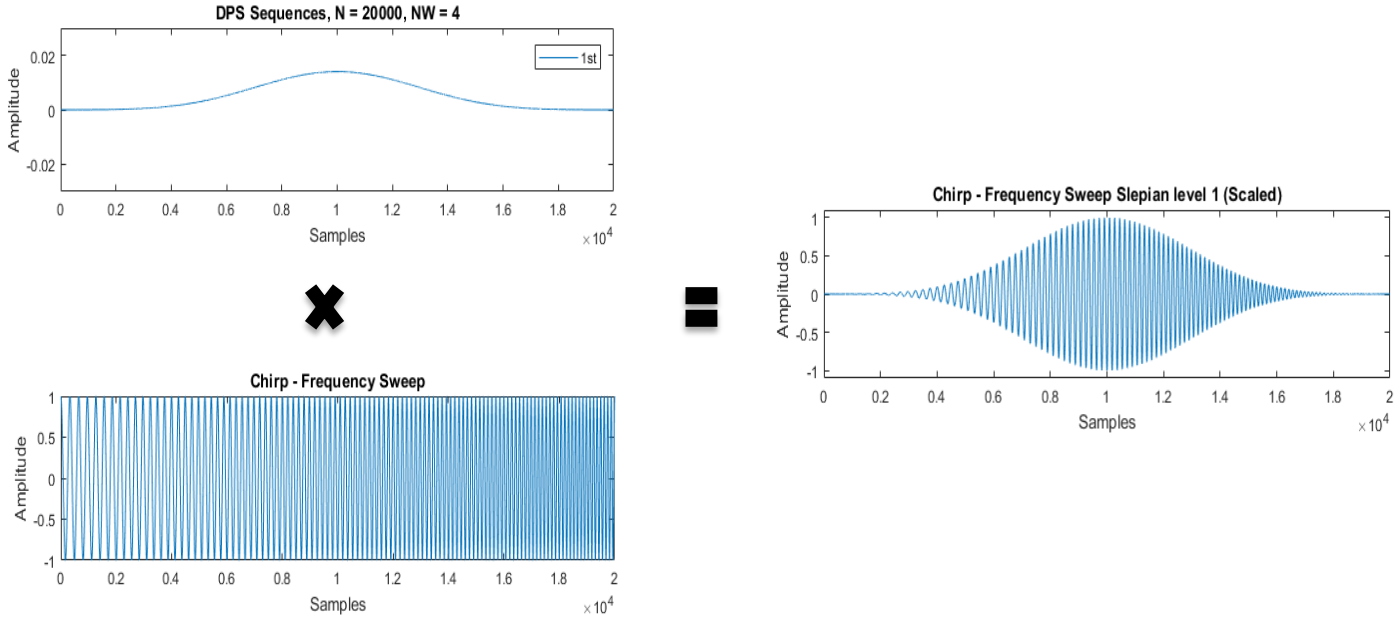

Figure 7. Generation of orthogonal stimuli. Frequency sweep stimulus multiplied to a level 1 Slepain taper in time domain, generating a stimulus orthogonal to the product of Frequency sweep and 6 levels of Slepian, respectively.

2.1.4 Experimental protocol: Study 1

Participants were asked to sit comfortably in the chair and place their arms in a resting position where their tremor is most prominent; this position was different for each participant, but most commonly were 1) forearms resting on the arms of the chair or 2) arms hanging by their side. Once the position is determined, participants maintained this position during stimulation for the remainder of the session. Tremor in each individual was attempted to be elicited by using a technique similar to that used in a clinical setting - participants were distracted by engaging in conversation or mental math, typically resulting in a worsening of tremor. The motion sensor was placed via elastic strap on the dorsal side of their tremor-dominant hand and a sixty second sample of their resting tremor without any stimulation was recorded.

Stimulation was provided above the primary motor cortex and the SMA contralateral to the most tremulous limb, as determined by the score on the MDS-UPDRS and by participant self-report. Stimulation was provided at a supra-sensory level. Mild skin irritations have been reported at a peak-to-peak stimulation of 2 mA [15]. Previous studies have also reported that current levels to a minimum of 0.2 mA are capable of eliciting cortical change [16]. As such, the stimulation intensity for this study was set between this range of 0.2 mA to 2 mA. A test to determine the highest level of stimulation at which the participant felt comfortable within the range was conducted by increasing the stimuli intensity by 0.05 mA increments. During each step, participants were asked to report their perceived level of discomfort associated with the stimuli, on a scale from 1-5 with steps as seen in Figure 8.

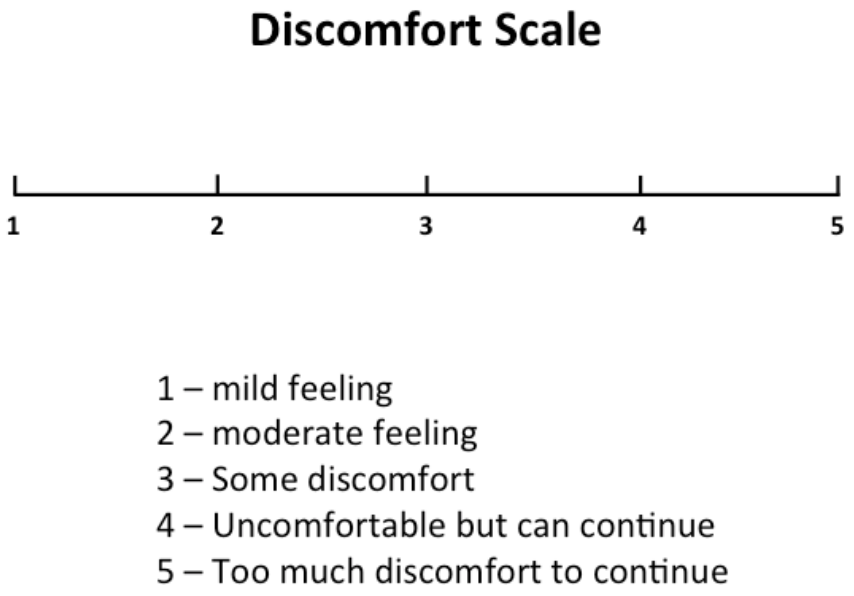

Figure 8. Discomfort scale. The intensity of the stimulus was increased until participants reported a 5 on the scale or until 2 mA, at which point the intensity was lowered to a point where the participant reported a discomfort level of 4 and agreed that they could tolerate this intensity for the duration of the session.

Twenty-one unique stimuli were then delivered for one trial each in a randomized order. Each trial consisted of a pre-stimulus period, a stimulation period and a post-stimulus recording period, each for twenty seconds within sixty seconds of recording (Fig. 9). The start and stop time of the stimulation are also recorded.

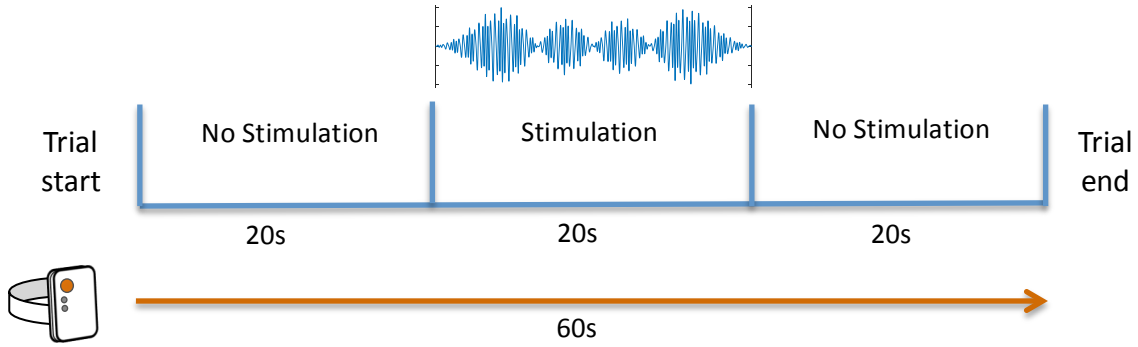

Figure 9. Sample trial. Example trial with a total duration of 60s. Each trial begins with 20s of no stimulation, followed by 20s of tACS stimulation, and upon completion, a second 20s block of no stimulation. Motion sensor data is recorded throughout the entire 60s duration of the trial.

2.1.5 Experimental protocol: Study 2

This study followed the same protocol as Study 1 up to and including the determination of stimulation intensity. Fourteen unique stimuli were then delivered in a pseudo-randomized order for twenty seconds within a sixty second recording. Each trial was repeated two times. Trials had the same layout as in Study 1 (Fig. 9). Following a similar approach as Study 1, we attempted to elicit a consistent tremor using a standardized approach. Participants were instructed to watch an interactive television show designed to engage cognitive processes consisting of a series of mind games such as memorization and recall, tracking, and awareness attention, all of which were timed tasks.

Following the completion of 28 trials, four new personalized stimuli were designed offline based on the motion sensor data recorded. The new stimuli were designed by a weighted

linear combination of stimuli selected from the prior fourteen. Each tremor recording contained data measured from the 9 DoF and were scaled between -1 and 1 in their respective units (accelerometer – m/s^2, gyroscope – deg/s, magnetometer - Gauss). The scaled data were projected on to the principal component space where the first principal component was used to reduce the data dimension from nine to one. The first principal component was chosen since it describes the internal structure of the data that best represents its variance and allows the transformed data to be a projection of the most informative viewpoint. Data before and during stimulation each composing of 20 seconds in length were extracted from the 60 second recording. The short-time Fourier transform was generated for each value and the magnitude squared was used to generate the spectrogram. A two-sample t-test was performed between the spectrogram values of before and during stimulation ranging from 3 to 7 Hz. A two-sample t-test was performed since the data before and during stimulation was assumed to be independent. Only tremor data where the t-test was significant ($p < 0.05$) was considered, where a positive t-value indicates tremor suppression and a negative t-value indicates tremor augmentation. Stimuli that produced each of these effects were separated and weighted based on the magnitude of their respective t-value. The weighted stimuli with positive t-values were linearly added together to produce a personalized stimulus designed to suppress tremor and the same was done with the weighted stimuli with negative t-values to produce a personalized stimulus designed to augment tremor (Fig. 10).

Four personalized stimuli were created for each individual. Of these, two were comprised of Frequency sweep stimuli and two were comprised of Multisine stimuli. One Frequency sweep and one Multisine stimuli were each designed as a theoretically ideal stimulus for a) augmenting and b) suppressing tremor. Each of the four stimuli were then delivered to assess their effect on

tremor with the same trial structure as above. Trials were delivered in a randomized order and were repeated three times.

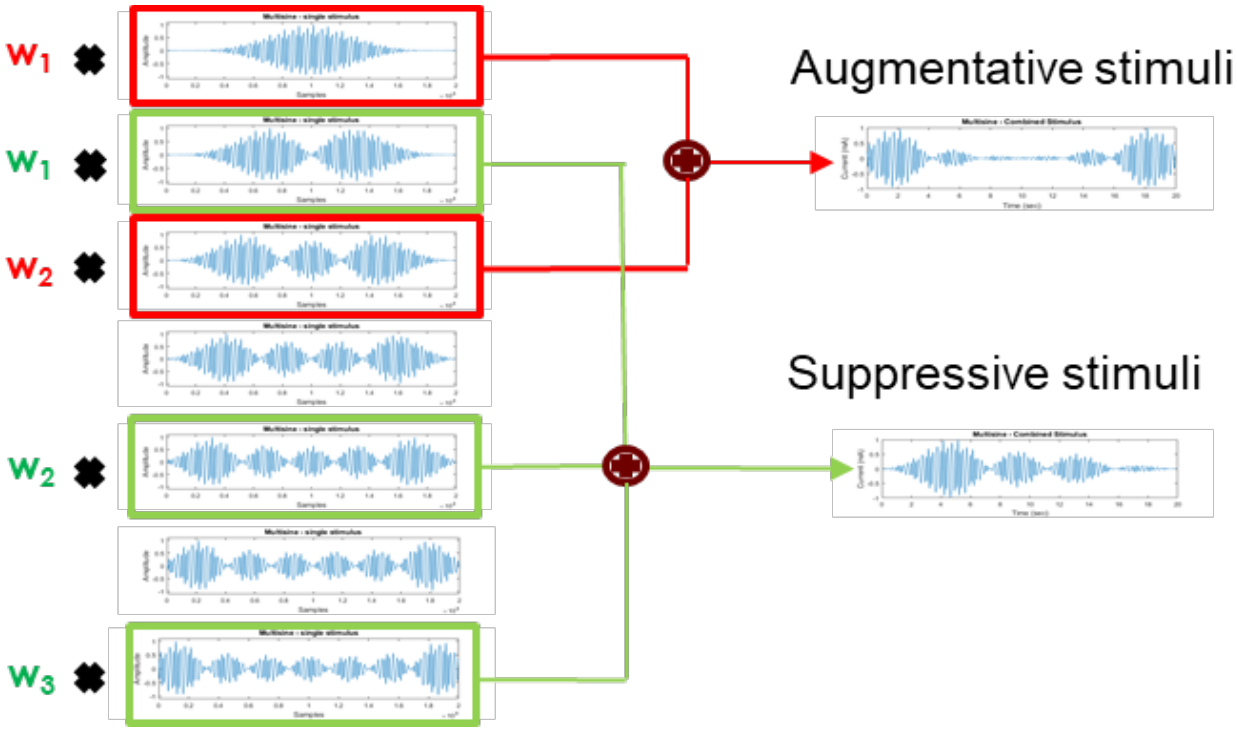

Figure 10. Weighted linear combination of stimuli. Selection of Multisine stimuli with suppressive effect (green) and augmentative effect (red), weighted, and linearly combined to produce a personalized stimulus each for tremor suppression and augmentation.

2.2 Data Analysis

2.2.1 Data pre-processing

Only tremor data collected in Study 2 (Parts 1 and 2) was analyzed. Data consisted of 3 motion parameters with 3 DoF each for a total of 9 DoF – Accelerometer (X, Y, Z), Gyroscope (X, Y, Z), and Magnetometer (X, Y, Z). The data for each recording were first pre-processed

through Principal Component Analysis (PCA). This pre-processing method was chosen to reduce the data dimension and also to standardize the data into the PCA space. PCA uses orthogonal transformation to convert a set of possibly correlated observations to principal components which are linearly uncorrelated variables. These principal components are orthogonal to each other and each describes the largest possible variance in the data set. The first principal component holds the greatest variance. The transformed data or the principal component score, S, is a matrix multiplication between the data, X, and the weights, W,

$$S_{ik} = X_{ij}W_{jk} \tag{2}$$

where i is the length of the data set, j is the number of features, and k is the vector of principal components of choice. For both studies, there were 9 features (the 9 DoF) and the first principal component score was used to represent the data from the most informative viewpoint. While PCA is a common method to produce a lower-dimensional picture, it is sensitive to the relative scaling of the data. As such, all the data was first scaled to between -1 and 1 in amplitude before PCA was applied. Furthermore, the position of the motion analysis device may vary between participants, which would also cause the reference point to vary. PCA allows for standardizing all participant data into the PCA space in order to eliminate bias as a result of slight differences between participant recordings.

The data after PCA was first processed through a short-time Fourier transform (STFT) to generate complex values containing both the time and frequency information. The squared magnitude of the output produces its spectrogram or power value where the information is normalized, allowing the energy of the STFT to equal the energy in the original time-domain signal. The two-sample t-test is then performed between the data before stimulation and the data

during stimulation while restricting the data to the tremor frequency of 3-7 Hz. Each input to the t-test is a $n \; x \; 1$ column vector (Fig. 11).

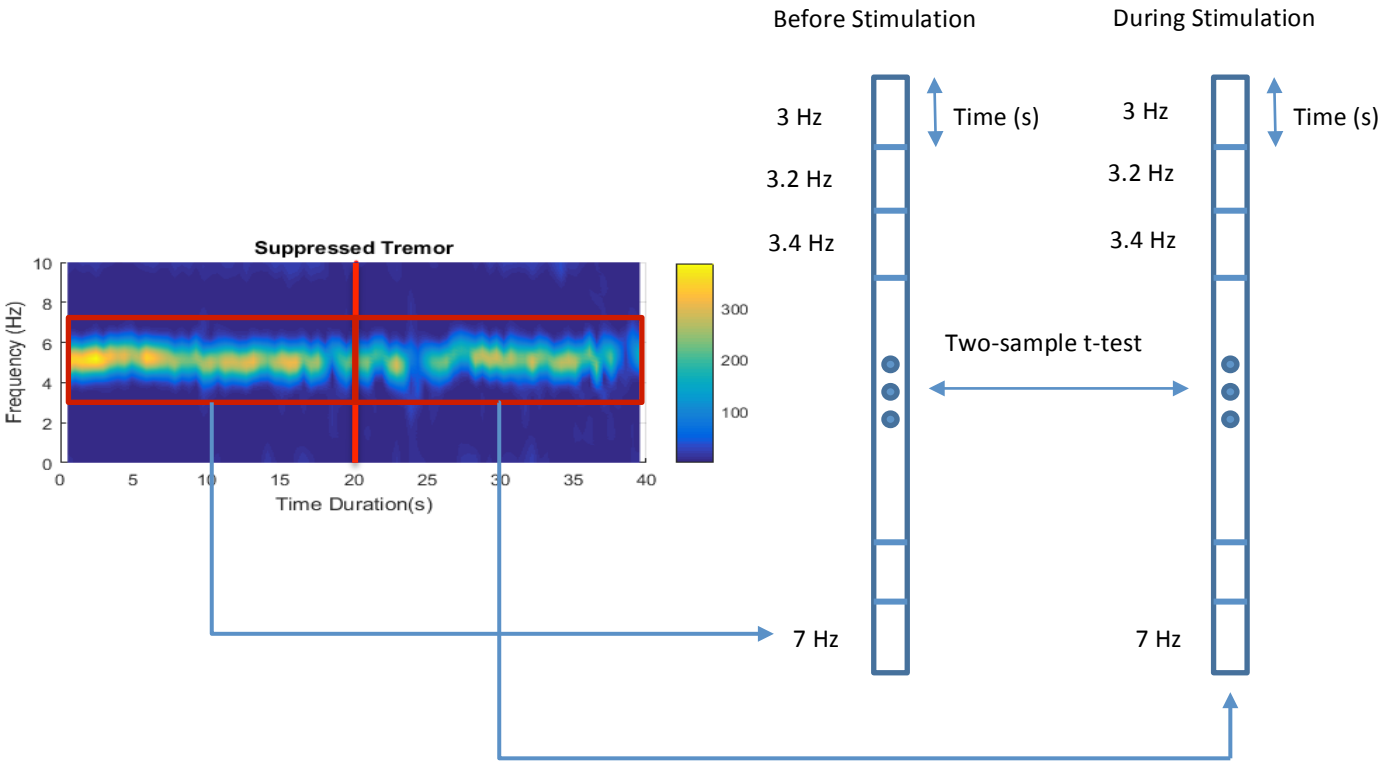

Figure 11. Two-sample t-test between before and during stimulation. A diagram of a two-sample t-test of power values occurring between before and during stimulation in 3-7 Hz.

2.2.2 Analysis of variance and outlier analysis

For each of the two studies, the data was testing for outliers using boxplots and normality was tested using Q-Q plots and by investigating kurtosis and skewness of the data set both prior to and during stimulation. No outlying data was found and thus all data was used for statistical analysis. All statistical tests were conducted using SPSS software (IBM, Armonk, USA) or MATLAB software (Mathworks, Natick, USA).

Average power data collected from Part 1 was examined using a two-way repeated measures Analysis of Variance (rmANOVA) and was conducted with within subject factors STIMULUS (on & off) and SLEPIAN (14 levels: Frequency sweep 1, 2…7 and Multisine 1, 2…7). The rmANOVA was used to investigate the effect of slepian and of stimulation across participants. To evaluate whether personalized stimuli were capable of altering tremor (Part 2), a 3-way rmANOVA was conducted on average power data. Three factors with two levels each were considered: TYPE (Frequency sweep & Multisine), STIMULUS (on & off), and STATE (suppress & augment).

2.2.3 Multivariate Empirical Mode Decomposition

Multivariate Empirical Mode Decomposition (MEMD) is an extension of empirical mode decomposition (EMD) for performing time-frequency analysis on non-linear and non-stationary multichannel data [37]. MEMD allows for simultaneous processing of multiple sets of data [38] and decomposes them into amplitude- and /or frequency-modulated components called intrinsic mode functions (IMF), which represent a series of oscillatory modes [37]. MEMD generally follows the algorithm of EMD in generating IMFs [38]. The 'detail' $d(t)$ is calculated by

$$d(t) = x(t) - m(t) \tag{3}$$

where $x(t)$ is the real-valued signal and $m(t)$ is the local mean of the envelope curves. If $d(t)$ satisfies the stoppage criteria, then $d(t)$ is considered an IMF [37]. However, the calculation of $m(t)$ is where MEMD differs from EMD. In MEMD, $m(t)$ is founded through averaging the envelopes of each projection signal in an *N*-dimensional space. The projection signal is the *N*-variate signal projected to selected direction vectors [38].

$$m(t) = \frac{1}{K}\sum_{k=1}^{K} e^{\theta_k}(t) \tag{4}$$

Here, e represents the multivariate envelope curves for a set of K direction vectors, and θ represents the angles denoting the direction of direction vectors [37]. In EMD, the local mean is calculated by a simple average:

$$m(k) = \frac{e_{min}(k) + e_{max}(k)}{2} \tag{5}$$

$e_{min}(k)$ represents the lower signal envelope and $e_{max}(k)$ represents the upper signal envelope [37]. The EMD method of calculating the local mean only allows EMD to process multivariate signal individually causing uncertainty in scaling between IMF groups [38]. With MEMD, the order of frequency components with one IMF group corresponds to the same order of other IMF groups [38]. Since we are looking at multivariate resting tremor data, we are interested in using MEMD to understand the behaviour of different frequencies before and during stimulation across participants.

In each data set, PCA was performed within each of the 3 measurement types and MEMD was used. A two-sampled t-test was then performed on each IMF between before and during stimulation to analyze the patterns of tremor suppression and augmentation. However, only peak frequencies between 3-7 Hz in the IMFs were of interest. An average of the t-values was conducted across the 3 measurement types and trials within their respective IMF components to analyze the frequency behaviour of tremor when the personalized stimuli was applied to the participant.

2.2.4 Fisher's Exact Test

In this study, stimuli were given without regard to the phase of the tremor. In order to see if this was important, we determined whether or not there was a relation between phase of the tremor at onset of the stimulus and the capacity of the stimulus to suppress tremor. We computed Fisher's exact test to analyze whether a non-random association exists between the phase and the t-values. The instantaneous phase of the tremor data at onset of the stimulus was acquired through Hilbert transform in MATLAB. Each personalized stimulus was delivered 3 times for all 9 participants. As such, for each of the four stimulus type, there are 27 x 1 phase values and 27 x 1 t-values when concatenated into a column vector. Each value in the two vectors are categorized into 10 uniform bins for the Fisher's exact test. The 27 x 1 phase value bin vector and 27 x 1 t-value bin vector serve as the inputs to the Fisher's exact test. The output of the test yields a result stating whether the association is significant ($p < 0.05$).

2.3 Results

2.3.1 Part 1 – Non-personalized stimulation

2-way rmANOVA resulted in a main effect of STIM ($p = 0.022$), where tACS significantly increased average power of tremor. This indicates that across the all levels of SLEPIAN, there was a difference between before and during stimulation. Figure 12 displays the average power for each participant, averaged across all slepians.

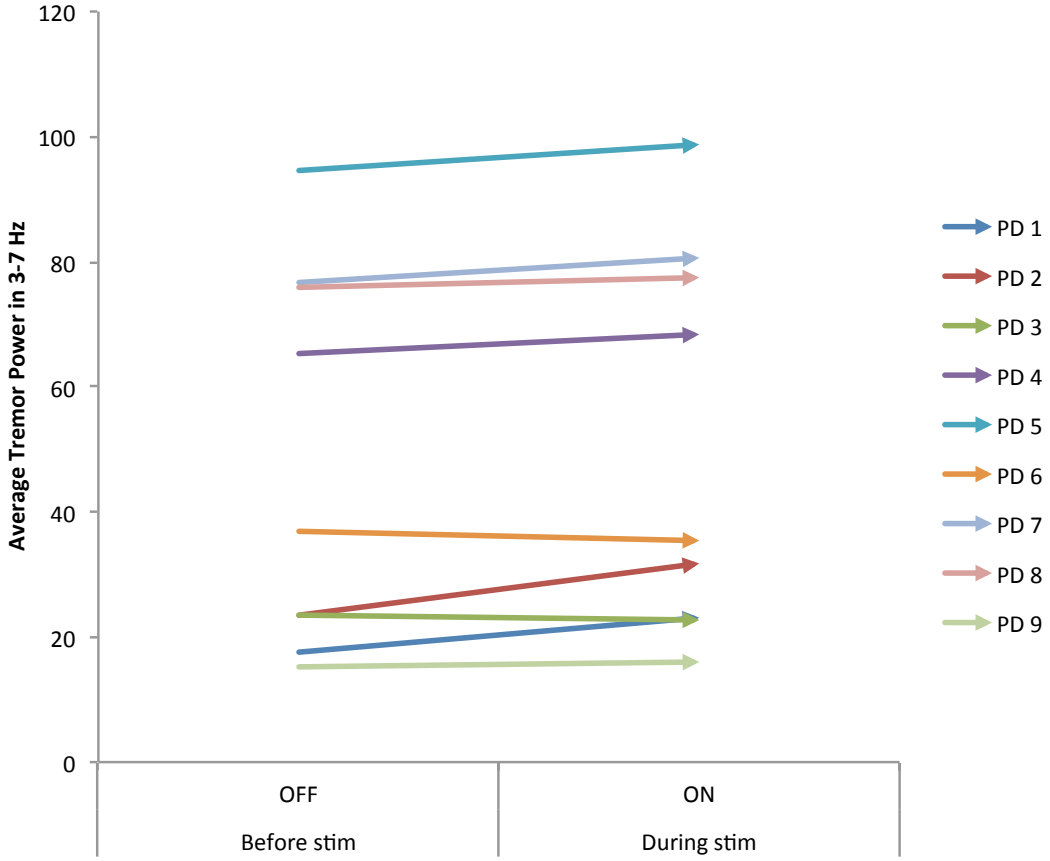

Figure 12. Part 1 average power. Average power in 3-7 Hz for each participant before and during stimulation, averaged across all 14 slepians.

2.3.2 Part 2 –Personalized stimulation

Following 3-way rmANOVA a main effect of STIM ($p = 0.048$) was also seen. TACS stimulation similarly resulted in an increase in average power of tremor; regardless of whether the personalized stimulus was delivered as Frequency sweep or Multisine stimulus, or as a suppressive or augmentative stimulus. Figure 13 indicates the significant increase average power for each participant, averaged across the Frequency sweep and Multisine stimuli and across the suppressive and augmentative stimuli.

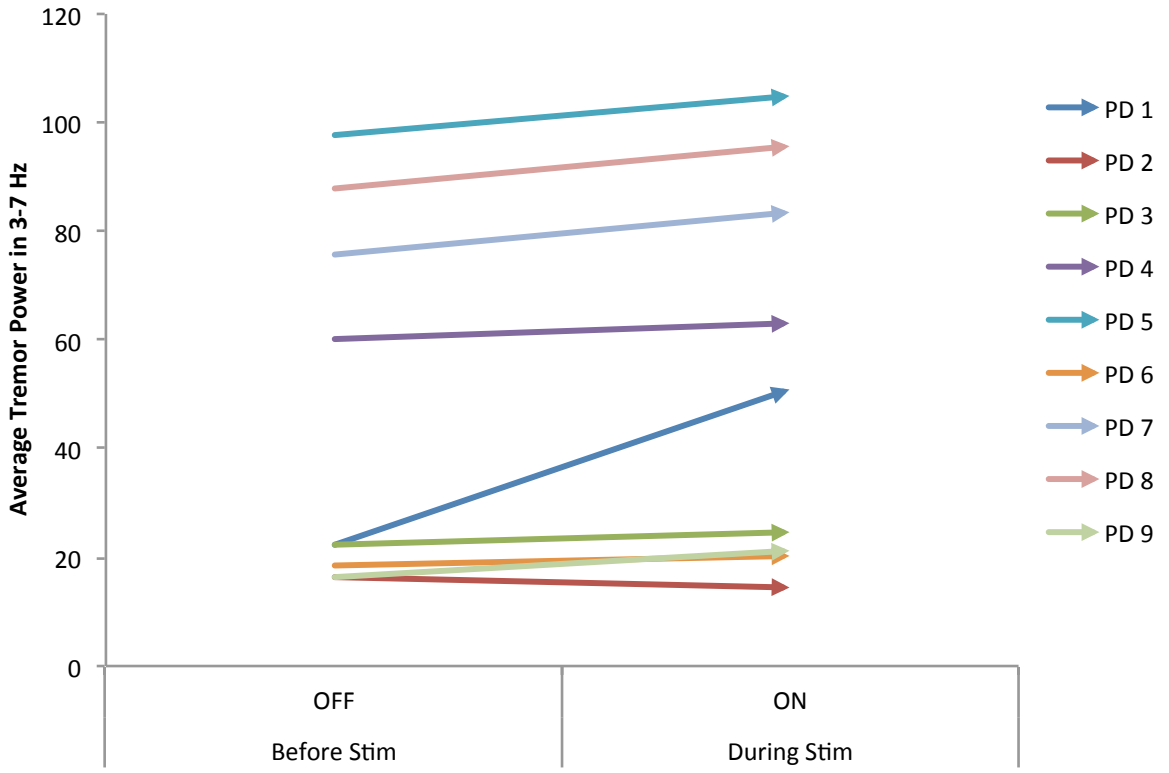

Figure 13. Part 2 average power. Average power in 3-7 Hz before and during tACS stimulation for each participant. Stimulus type and weight have been collapsed by averaging Frequency sweep and Multisine and suppressive and augmentative stimuli.

The results from the two sampled t-test between before and during stimulation for each tremor recording show that on average the personalized stimuli have a greater ability to augment tremor than they do to suppress tremor (Fig. 14). The bars in the positive direction indicate an increase in power during stimulation and the bars in the negative direction show the opposite effect. Table 1 shows a summary of the t-value results. Among the significant t-values (green shading where $p < 0.05$), more instances of tremor augmentation (red highlight) are present and only some instances of tremor suppression (blue highlight) can be seen.

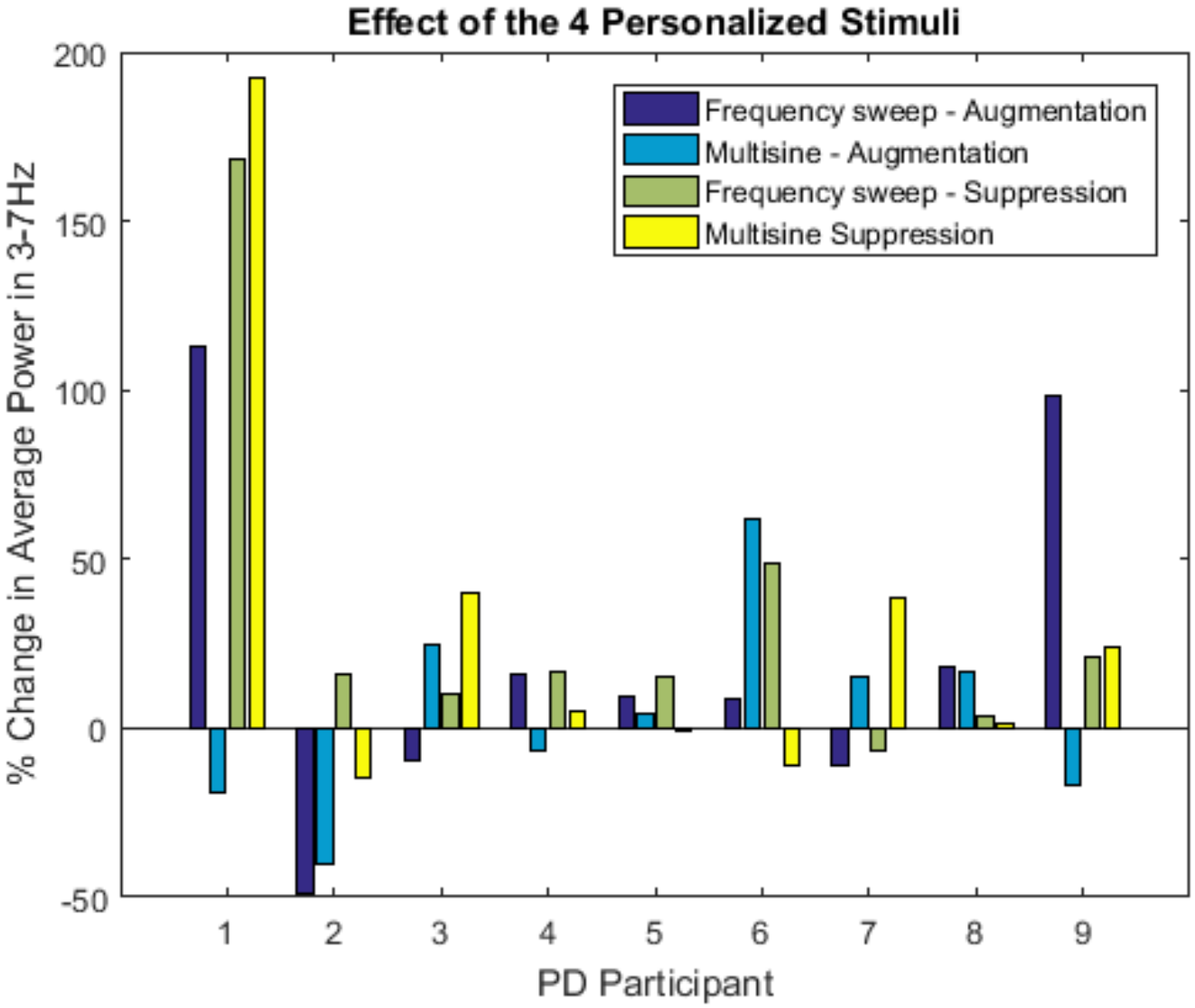

Figure 14. Effects of four personalized stimuli. Percent change in average power of tremor across 3 trials between before and during stimulation (during - before) in 3-7 Hz. Bars in the positive direction indicate tremor augmentation, and bars in the negative direction indicate tremor suppression.

	Averaged t-values			
	Augmentative Stimulus		Suppressive Stimulus	
	Frequency Sweep	Multisine	Frequency Sweep	Mulstisine
Participant	Averaged Trials	Averaged Trials	Averaged Trials	Averaged Trials
PD 1	-13.170	3.724	-15.978	-13.537
PD 2	12.431	9.474	-2.760	2.998
PD 3	1.687	-3.918	-1.495	-5.268
PD 4	-2.011	1.181	-2.687	-0.826
PD 5	-2.021	-0.893	-2.843	0.199
PD 6	-1.679	-9.268	-7.346	2.149
PD 7	2.381	-2.526	1.253	-5.824
PD 8	-3.255	-2.926	-0.730	-0.214
PD 9	-9.783	-3.510	2.527	-3.730

Table 1. Personalized stimulation t-statistics. T-values represent the change in average power across three trials between before and during stimulation in 3-7 Hz. Green shading represents a significant p-value ($p < 0.05$). Red numbers depict an increase in average power, contributing to augmented tremor. Blue numbers depict a decrease in average power, contributing to suppressed tremor.

MEMD analysis shows that different narrow bandwidth frequencies between 3-7 Hz (represented as IMFs) can respond differently to the personalized stimulus (Table 2). In a particular participant, the t-value of an IMF shows an increase in average power (augmentation in tremor). However, its neighboring IMF shows a decrease in average power (suppression in tremor).

		Averaged t-values			
		Augmentative Stimulus		Suppressive Stimulus	
		Frequency Sweep	Multisine	Frequency Sweep	Multisine
Participant	Frequency	Averaged Trials	Averaged Trials	Averaged Trials	Averaged Trials
PD1	IMF 2	-5.209	-3.099	-6.784	-5.557
	IMF 3	-14.207	-0.711	-12.550	-13.734
	IMF 4	2.163	-2.144	-2.502	7.082
PD2	IMF 2	8.702	-5.992	4.736	-6.657
	IMF 3	2.238	2.659	-6.034	-0.237
	IMF 4	4.888	-4.354	-0.186	-6.167
PD3	IMF 2	1.195	0.720	1.802	-0.992
	IMF 3	1.627	-1.211	-3.031	-2.690
	IMF 4	0.033	-3.386	-0.673	-6.699
PD4	IMF 2	0.836	3.717	-2.982	-2.862
	IMF 3	0.496	-0.354	1.365	-2.281
	IMF 4	2.267	-4.708	-0.731	1.424
PD5	IMF 2	0.199	-3.775	-2.839	-11.605
	IMF 3	-0.858	3.139	-0.775	11.887
	IMF 4	2.904	3.659	-1.881	-1.896
PD6	IMF 2	0.040	-2.865	-3.030	0.128
	IMF 3	-4.761	-8.418	-11.726	-0.266
	IMF 4	-1.742	0.682	2.370	2.420
PD7	IMF 2	2.460	-2.133	5.258	0.780
	IMF 3	0.629	-3.152	0.031	-9.197
	IMF 4	3.695	-1.245	6.261	-4.273
PD8	IMF 2	-1.212	-4.109	-3.228	3.228
	IMF 3	-1.795	-4.494	0.195	-0.345
	IMF 4	-0.406	-4.582	1.971	0.200
PD9	IMF 2	-3.958	0.115	0.805	1.056
	IMF 3	-7.496	2.644	0.143	-2.283
	IMF 4	2.306	-2.990	-0.368	4.260

Table 2. MEMD t-statistics. T-values represent the change in average power across three trials between before and during stimulation in 3-7 Hz. Orange cells depict an increase in average power, contributing to augmented tremor. Blue cells depict a decrease in average power, contributing to suppressed tremor. Each IMF represents a narrow bandwidth frequency between 3-7 Hz.

The Fisher's exact test showed that for each personalized stimulus type, a non-random association exists between the phase of tremor at onset of the stimulus and the capacity of the stimulus to suppress tremor (as indexed by previously-computed t-values). Quantitatively, the significance are as follows for the frequency sweep stimuli designed to suppress and augment tremor and the Multisine stimuli designed to suppress and augment tremor: $p = 4.212 \times 10^{-6}$, $p = 9.904 \times 10^{-7}$, $p = 1.039 \times 10^{-6}$, $p = 5.777 \times 10^{-6}$, respectively. Figure 15 a), b), c), and d) also respectively show the relation qualitatively.

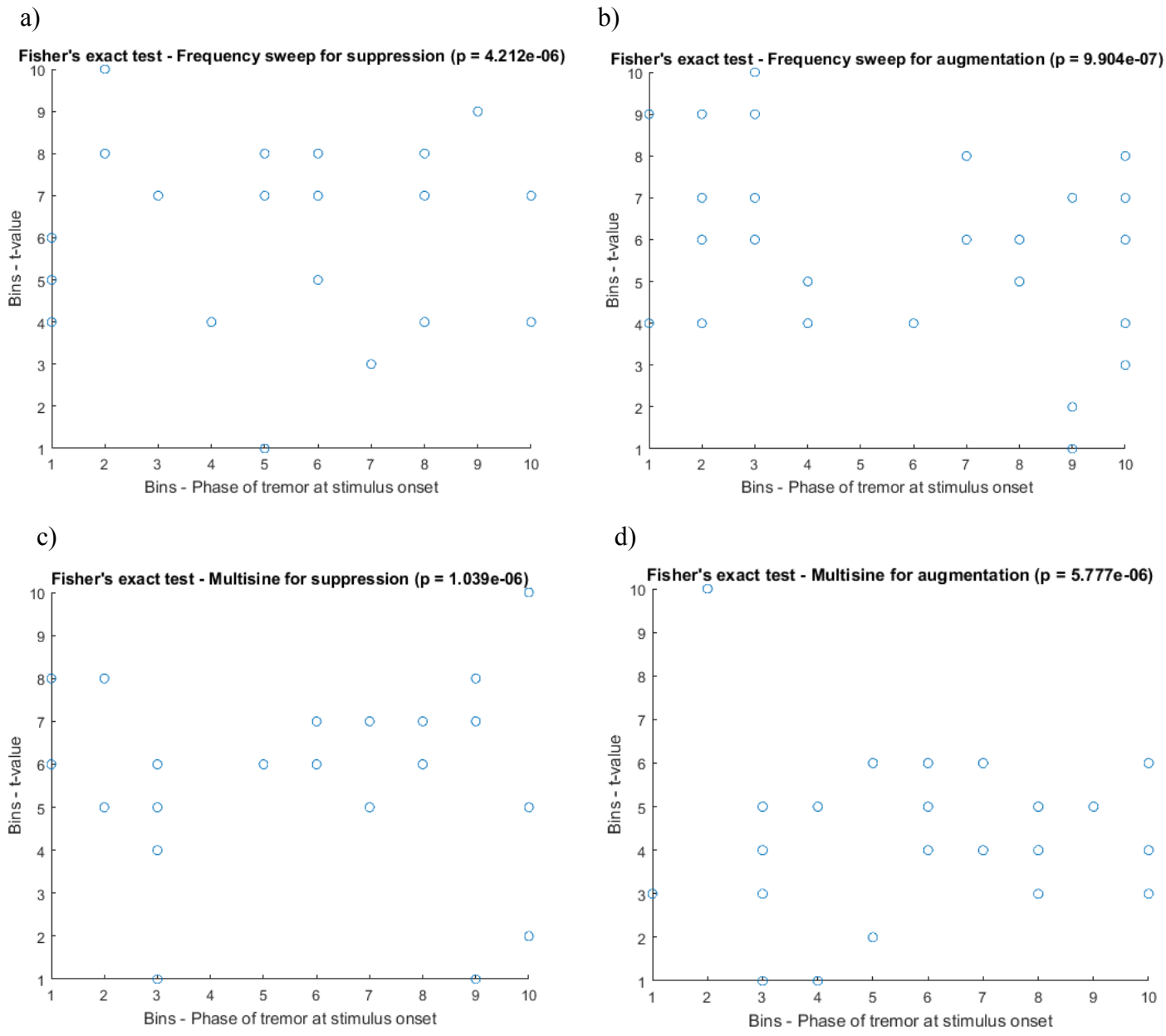

Figure 15. Fisher's Exact Test. Fisher's exact test for showing a non-random association between phase of tremor at onset of the stimulus and the capacity of the stimulus to suppress tremor for a) Frequency sweep for suppression b) Frequency sweep for augmentation c) Multisine for suppression d) Multisine for augmentation

2.4 Discussion

2.4.1 Effects of personalized stimuli on PD resting tremor

The aim of this thesis was to see whether a personalized tACS stimuli based on weighted linear combination of orthogonal stimuli could suppress resting tremor in PD. We chose to linearly combine the stimuli to see if the system would also act linearly. That is, if one stimulus resulted in a particular effect on tremor, then combining those with the same effect, we were interested to see if the same effect was amplified in tremor. Our results, however, indicate that individual stimuli that have a suppressive effect do not consistently demonstrate an accentuated suppressive effect when linearly combined and, in fact in many instances the opposite effect on tremor was seen. The same result was evident when combining stimuli designed to produce an augmentative effect – in that an additive or amplified effect was not present. However, an overall effect of the stimuli contributing to augmented tremor was present, suggestive of the fact that it may be easier to augment tremor than it is to suppress tremor. There are instances where on average across trials, tremor suppression occurs as seen in Table 1. This may indicate that the personalized stimulus is indeed optimal for that participant. This effect is not consistent across individuals and in many instances, the stimuli designed to suppress tremor actually result in tremor augmentation and vice versa. Since custom designed stimuli did not produce the effects expected, we were interested in further looking at the non-personalized stimuli, delivered in Part 1. All of the fourteen slepians delivered were statistically shown to be similar in effect and thus when we looked at their average effect across participants we note that seven of nine participants showed an increase in average power (of ~13%) – contributing to a worsening of tremor. Unlike Part 2 where the stimuli received by participants were inconsistent across participants (due to customization), here we could directly compare the effect across participants. We demonstrate an

overall effect towards the stimulation contributing to augmented tremor. Thus in both the cases of personalized and non-personalized stimuli, we find that there is a greater tendency towards tremor augmentation. However in two participants, power averaged across all slepians was decreased, suggestive of tremor suppression, though this was to a lesser degree (~ 3.3% average power decrease). Potentially for these two participants, a larger proportion of the slepian frequencies were closer to optimal for these individuals. From these results we can conclude two main findings 1) linear combination of tACS stimuli is not, on its own an effective means of designing personalized stimuli to suppress PD resting tremor and 2) response to stimuli appears to be highly variable, which supports the need for stimuli custom tailored to individuals, albeit with a different method than that which we used for the present study. As such, we looked at four main factors that are essential in tACS stimulation to investigate their role in the effects of personalized stimuli in PD resting tremor.

2.4.2 The role of frequency in personalized stimuli

In this study, the intention was to investigate an alternate method of suppressing tremor via phase-locking. Phase-locking requires a sophisticated real-time design to control the phase between the stimulus and tremor, which while possible in a lab setting, are complex to implement in a real-world environment which underscores the ultimate clinical goal of this work. For this reason, we were interested in providing a series of frequencies in the resting tremor range of 3-7 Hz, thus delivering a set of many possible options for tremor suppression, within a single stimulus. One downside to this technique is that within this range there may exist some frequencies that are tremor suppressive, juxtaposed with frequencies that are augmentative. An MEMD analysis was conducted to investigate in greater detail whether specific frequencies were

modulated similarly from the stimuli. As shown in Table 2, there are instances where the IMF 2, 3 and 4 (3-7 Hz) in some individuals do reflect a consensus in either tremor suppression or augmentation. On the other hand, there are also instances where t-value of a particular IMF shows positive signs of suppression while its neighboring IMF is negative. A clear trend of suppression or augmentation is not shown, suggesting that the two neighboring frequencies in tremor may be affected differently with the personalized stimuli. It is unclear from the current results whether greater control of a narrow bandwidth of tremor frequencies would have contributed to a greater instance of tremor suppression and the precise methods for how to design stimuli with properties capable of controlling these specific frequencies are outside the scope of this work. However, one clear finding is that the ability to have fine-tuned control over the frequency of tremor may be important in controlling tremor suppression, at least in part.

2.4.3 The role of phase in personalized stimuli

While we attempted to create phase independent personalized stimuli, it was also important to see what role phase plays in a weighted linear combination of stimuli. Especially since Brittain and colleagues were able to show substantial suppression of tremor using a phase-dependent strategy [24]. Our results indicate that there is a non-random association between the phase of tremor at the stimulus onset and the capacity of tremor suppression. This is a crucial finding for two reasons. Firstly, it is in support of Brittain's results suggesting that phase has an important role in altering tremor and secondly, it demonstrates that the personalized stimuli designed to not have a stationary phase component, are in actuality highly phase dependent. Potentially the design of personalized stimuli which are delivered at a particular phase (potentially out of phase with tremor as suggested by Brittain *et al*.) could allow for more

suppressive tremor effects and may explain why we witnessed variability between trials which were likely delivered at different phases of the tremor [30]. The qualitative representation of these relations for each personalized stimulus type is represented in Figure 15. Despite the highly significant quantitative result (p-values), the scatterplots do not seem to show obvious patterns of the association. This may be improved with optimization of bin width selection. Nonetheless, the quantitative results agree with Brittain *et al*.'s study that controlling the phase is an integral part of tACS stimulation in suppressing tremor [30].

2.4.4 The role of stimulus intensity and electrode montage

One significant point of difference between our work and that done previously is the difference in experimental setup using focal as opposed to conventional sponge electrodes as a medium for stimulation [30], [32], [34]. These electrodes allow for good conduction of saline, use over the hair, uniform contact over the skin [32], and low skin sensation [33]. However, this sacrifices focality [22]. In this study, we aimed to optimize the electrode montage by using a more focal approach in order to provide a more direct form of stimulation. This approach increases the likelihood that a higher current density will reach a particular area in the brain [22]. A multi-electrode approach was also used in our work so that more motor areas of the brain that control limb movement were being individually targeted - the primary and supplementary motor cortex – a setup that is impossible with sponge electrodes, given their size. As a concurrent goal of this work, we hoped to investigate the feasibility of a focal setup as the initial steps in creating a portable, wearable device. The electrode montage used closely follows that used by Brittain *et al*., but targets multiple areas with greater focality [30]. It is possible, however, the focality can still be improved upon. Datta *et al*. show that a concentric-ring configuration of electrodes

further improves focality which may have better optimized the delivery of the stimulus to the brain [39].

Stimulation intensity also plays a role as an important factor in replicating past results. Brittain *et al*. provided a stimulus intensity of 2 mA to all their participants [30]. However, in our study, not all participants were stimulated at the same intensity due to differing cutaneous thresholds. Our participants received a range of stimulation range between 1 mA to 2 mA, however this was fixed within a participant. Although stimulated at the highest tolerable level for our cohort of participants, the overall lower levels of intensity may have contributed to a smaller effect. Nonetheless, we were able to show that our stimuli had an effect on tremor. Further work may investigate whether there is a dose-dependent effect of stimulation intensity and can be done at higher intensities using techniques previously reported, such as numbing the stimulation site [40].

Chapter 3: Conclusion

In this thesis, we proposed an exploratory method of using a weighted linear combination of orthogonal stimuli to reduce resting tremor in PD. This work emphasizes the potential of personalizing a stimulus for a particular individual with PD in order to optimize tremor suppression. Frequency sweep and Multisine signals were chosen as the type of stimuli due to their capability in containing a range of frequencies. We used 7 different Slepian sequences as orthogonal tapers to transform each of the Frequency sweep and Multisine signals into orthogonal stimuli. Initial delivery of these stimuli allowed for a selection of the stimuli that produced an effect on tremor. Weights calculated from t-values comparing stimulation on versus off provided an emphasis on the more significant stimuli for either suppression or augmentation and were linearly combined with these weights taken into account. We demonstrate that a weighted linear combination of orthogonal stimuli is not alone an optimal method in designing a stimuli to affect tremor. We show that tremor is highly dependent on frequency, through MEMD analysis demonstrating that individual frequencies in tremor behave differently to the stimuli, and also through phase, from Fisher's exact test showing that tremor is indeed highly associated with phase. Although instances of data show tremor suppression, the frequency and phase relationship between the stimuli and tremor needs to be further investigated to optimize personalized stimuli.

One such method that may help to generate more tailored stimuli are optimization algorithms such as the genetic algorithm. These can be used such that candidate solutions are constantly evolved toward a better solution [41]. A set of properties such as frequency and phase can be constantly altered based on the behavior of tremor. For each generation, the candidates are evaluated based on their fitness to the objective function [42]– in our case, personalizing a

specific frequency and phase pattern for an individual with PD. The candidates that are more fit continue to mutate and alter until a specified number of generations have been evaluated [41], [42]. The genetic algorithm shows a more adaptive way to learn the system of each individual with tremor in order to generate a highly personalized stimulus. This could possibly eliminate the use of a pre-set range of frequencies and phase stimuli such as the ones used in this study – Frequency sweep and Multisine.

Other methods such as system identification could be used to construct a personalized model for each tremor pattern. The observed tremor data could be constructed into a mathematical model that describes tremor patterns based on a black-box structure [43]. An optimal experimental design should be considered in order to increase precision in estimation. In addition, the dynamic behavior of the system could be computed both in time and frequency domain to compare which set of parameters more closely describe the intended model.

Furthermore, tremor for each individual with PD in itself can be inconsistent. It has been recorded that stress and anxiety can elicit tremor [44]. However at present, there is no consistent method to ensure tremor is consistently present. Further studies should investigate methods to elicit tremor consistently, in order to enhance convenience of data collection as well as consistency within the data.

In conclusion, this thesis demonstrates that weighted linear combination of orthogonal stimuli may help suppress tremor in some instances, but more sophisticated forms of optimization algorithms such as genetic algorithms and system identification can help optimize a stimulus designed specifically for the PD individual with resting tremor.

Bibliography

[1] V. Krause, “Cortico-muscular coupling and motor performance are modulated by 20 Hz transcranial alternating current stimulation (tACS) in Parkinson's disease,” pp. 1–10, Jan. 2014.

[2] C. A. Davie, “A review of Parkinson's disease,” *British Medical Bulletin*, vol. 86, no. 1, pp. 109–127, Feb. 2008.

[3] “Parkinson’s Disease: Mechanisms and Models,” pp. 1–21, Sep. 2003.

[4] J. Jankovic, “Parkinson's disease: clinical features and diagnosis,” *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 79, no. 4, pp. 368–376, Apr. 2008.

[5] K. R. Chaudhuri, D. G. Healy, and A. H. Schapira, “Non-motor symptoms of Parkinson's disease: diagnosis and management,” *The Lancet Neurology*, vol. 5, no. 3, pp. 235–245, Mar. 2006.

[6] H. Bronte-Stewart, “High frequency deep brain stimulation attenuates subthalamic and cortical rhythms in Parkinson's disease,” pp. 1–18, May 2012.

[7] C. Bosch, P. Mailly, B. Degos, J. M. Deniau, and L. Venance, “Preservation of the hyperdirect pathway of basal ganglia in a rodent brain slice,” *Neuroscience*, vol. 215, no. C, pp. 31–41, Jul. 2012.

[8] A. Oswal, P. Brown, and V. Litvak, “Synchronized neural oscillations and the pathophysiology of Parkinson’s disease,” *Current Opinion in Neurology*, vol. 26, no. 6, pp. 662–670, Dec. 2013.

[9] R. C. Helmich, M. Hallett, G. Deuschl, I. Toni, and B. R. Bloem, “Cerebral causes and consequences of parkinsonian resting tremor: a tale of two circuits?,” *Brain*, vol. 135, no. 11, pp. 3206–3226, Nov. 2012.

[10] R. C. Helmich, M. J. R. Janssen, W. J. G. Oyen, B. R. Bloem, and I. Toni, “Pallidal dysfunction drives a cerebellothalamic circuit into Parkinson tremor.,” *Ann Neurol.*, vol. 69, no. 2, pp. 269–281, Feb. 2011.

[11] B. S. Jeon, S. H. Paek, J. Y. Lee, and H. J. Kim, “Bilateral subthalamic deep brain stimulation in Parkinson disease patients with severe tremor,” ..., 2010.

[12] R. Levy, W. D. Hutchison, A. M. Lozano, and J. O. Dostrovsky, “High-frequency synchronization of neuronal activity in the subthalamic nucleus of parkinsonian patients with limb tremor.,” *J. Neurosci.*, vol. 20, no. 20, pp. 7766–7775, Oct. 2000.

[13] S. Baudrexel, T. Witte, C. Seifried, F. von Wegner, F. Beissner, J. C. Klein, H. Steinmetz, R. Deichmann, J. Roeper, and R. Hilker, “Resting state fMRI reveals

increased subthalamic nucleus-motor cortex connectivity in Parkinson's disease.," *NeuroImage*, vol. 55, no. 4, pp. 1728–1738, Apr. 2011.

[14] F. Sprenger and W. Poewe, "Management of motor and non-motor symptoms in Parkinson's disease.," *CNS Drugs*, vol. 27, no. 4, pp. 259–272, Apr. 2013.

[15] C. Hammond, H. Bergman, and P. Brown, "Pathological synchronization in Parkinson's disease: networks, models and treatments," *Trends in Neurosciences*, vol. 30, no. 7, pp. 357–364, Jul. 2007.

[16] S. Breit, J. R. B. Schulz, and A. L. Benabid, "Deep brain stimulation," *Cell Tissue Res*, vol. 318, no. 1, pp. 275–288, Aug. 2004.

[17] X. L. Chen, Y. Y. Xiong, G. L. Xu, and X. F. Liu, "Deep Brain Stimulation," *Intervent Neurol*, vol. 1, no. 3, pp. 200–212, 2012.

[18] J. S. Perlmutter and J. W. Mink, "Deep Brain Stimulation," *Annu. Rev. Neurosci.*, vol. 29, no. 1, pp. 229–257, Jul. 2006.

[19] A. L. Benabid, S. Chabardes, J. Mitrofanis, and P. Pollak, "Deep brain stimulation of the subthalamic nucleus for the treatment of Parkinson's disease," *The Lancet Neurology*, vol. 8, no. 1, pp. 67–81, Jan. 2009.

[20] A. Antal, "Transcranial alternating current stimulation (tACS)," pp. 1–4, Jun. 2013.

[21] W. Paulus, "Transcranial electrical stimulation (tES - tDCS; tRNS, tACS) methods.," *Neuropsychological Rehabilitation*, vol. 21, no. 5, pp. 602–617, Oct. 2011.

[22] C. S. Herrmann, S. Rach, T. Neuling, and D. Strüber, "Transcranial alternating current stimulation: a review of the underlying mechanisms and modulation of cognitive processes," *Front. Hum. Neurosci.*, vol. 7, p. 279, 2013.

[23] G. Thut, "Modulating Brain Oscillations to Drive Brain Function," *PLoS Biol*, vol. 12, no. 12, p. e1002032, 2014.

[24] J.-S. Brittain, P. Probert-Smith, T. Z. Aziz, and P. Brown, "Tremor Suppression by Rhythmic Transcranial Current Stimulation," *Current Biology*, vol. 23, no. 5, pp. 436–440, Mar. 2013.

[25] M. Rodrıguez-Ugarte, N. Sciacca, E. Iánez, and J. M. Azorın, "Transcranial Direct Current Stimulation (tDCS) And Transcranial Current Alternating Stimulation (tACS) Review," *researchgate.net*.

[26] A. Antal, K. Boros, C. Poreisz, L. Chaieb, D. Terney, and W. Paulus, "Comparatively weak after-effects of transcranial alternating current stimulation (tACS) on cortical excitability in humans.," *Brain Stimulation*, vol. 1, no. 2, pp. 97–

105, Apr. 2008.

[27] Y. Cabral-Calderin, K. A. Williams, A. Opitz, P. Dechent, and M. Wilke, "Transcranial alternating current stimulation modulates spontaneous low frequency fluctuations as measured with fMRI," *NeuroImage*, vol. 141, no. C, pp. 88–107, Nov. 2016.

[28] A. Antal, "Transcranial alternating current stimulation (tACS)," pp. 1–4, Jun. 2013.

[29] C. S. Herrmann, "Transcranial alternating current stimulation: a review of the underlying mechanisms and modulation of cognitive processes," pp. 1–13, Jun. 2013.

[30] J.-S. Brittain, P. Probert-Smith, T. Z. Aziz, and P. Brown, "Tremor Suppression by Rhythmic Transcranial Current Stimulation," *Current Biology*, vol. 23, no. 5, pp. 436–440, Mar. 2013.

[31] R. F. Helfrich, T. R. Schneider, S. Rach, S. A. Trautmann-Lengsfeld, A. K. Engel, and C. S. Herrmann, "Entrainment of brain oscillations by transcranial alternating current stimulation.," *Curr. Biol.*, vol. 24, no. 3, pp. 333–339, Feb. 2014.

[32] A. F. DaSilva, M. S. Volz, M. Bikson, and F. Fregni, "Electrode positioning and montage in transcranial direct current stimulation.," *JoVE*, no. 51, pp. 1–12, May 2011.

[33] P. Minhas, A. Datta, and M. Bikson, "Cutaneous perception during tDCS: role of electrode shape and sponge salinity.," *Clin Neurophysiol*, vol. 122, no. 4, pp. 637–638, Apr. 2011.

[34] P. Faria, A. Leal, and P. C. Miranda, "Comparing different electrode configurations using the 10-10 international system in tDCS: A finite element model analysis," presented at the 2009 Annual International Conference of the IEEE Engineering in Medicine and Biology Society, 2009, pp. 1596–1599.

[35] J.-S. Brittain, P. Probert-Smith, T. Z. Aziz, and P. Brown, "Tremor Suppression by Rhythmic Transcranial Current Stimulation," *Current Biology*, vol. 23, no. 5, pp. 436–440, Mar. 2013.

[36] P. A. Forbes, C. J. Dakin, A. M. Geers, M. P. Vlaar, R. Happee, G. P. Siegmund, A. C. Schouten, and J.-S. Blouin, "Electrical Vestibular Stimuli to Enhance Vestibulo-Motor Output and Improve Subject Comfort," *PLoS ONE*, vol. 9, no. 1, pp. e84385–8, Jan. 2014.

[37] N. Rehman and D. P. Mandic, "Multivariate empirical mode decomposition," *Proceedings of the Royal Society of London A: Mathematical, Physical and Engineering Sciences*, vol. 466, no. 2117, pp. rspa20090502–1302, Dec. 2009.

[38] Y. Lv, R. Yuan, and G. Song, “Multivariate empirical mode decomposition and its application to fault diagnosis of rolling bearing,” *Mechanical Systems and Signal Processing*, vol. 81, pp. 219–234, Dec. 2016.

[39] A. Datta, M. Elwassif, F. Battaglia, and M. Bikson, “Transcranial current stimulation focality using disc and ring electrode configurations: FEM analysis.,” *J Neural Eng*, vol. 5, no. 2, pp. 163–174, Jun. 2008.

[40] L. Pelosi, M. Stevenson, G. J. Hobbs, A. Jardine, and J. K. Webb, “Intraoperative motor evoked potentials to transcranial electrical stimulation during two anaesthetic regimens.,” *Clinical Neurophysiology*, vol. 112, no. 6, pp. 1076–1087, Jun. 2001.

[41] J. Horn, N. Nafpliotis, and D. E. Goldberg, “A niched Pareto genetic algorithm for multiobjective optimization,” presented at the First IEEE Conference on Evolutionary Computation. IEEE World Congress on Computational Intelligence, 1994, pp. 82–87.

[42] D. Whitley, “A genetic algorithm tutorial,” *Statistics and Computing*, vol. 4, no. 2, pp. 65–85, Jun. 1994.

[43] L. Ljung, *System Identification*, 4 ed., vol. 19, no. 8. Hoboken, NJ, USA: John Wiley & Sons, Inc., 1999, pp. 1–19.

[44] H. J. Lee, W. W. Lee, S. K. Kim, H. Park, H. S. Jeon, H. B. Kim, B. S. Jeon, and K. S. Park, “Tremor frequency characteristics in Parkinson's disease under resting-state and stress-state conditions.,” *J. Neurol. Sci.*, vol. 362, pp. 272–277, Mar. 2016.