

**DEVELOPING A NEUROFEEDBACK BASED INTERVENTION TO REDUCE
TREMOR IN ESSENTIAL TREMOR**

by

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ABSTRACT

Essential Tremor (ET), the most common adult movement disorder, can interfere with activities of daily living (ADLs). ET is difficult to treat and many individuals with ET try many combinations of treatments, including but not limited to: pharmacotherapies, physio/occupational therapies, or surgical intervention. While neurofeedback (NF) has been implemented successfully to treat other movement disorders, its impact on ET is unclear. The purpose of this study was to determine whether adults (n=9) diagnosed with ET were able to use auditory NF to manipulate the theta/beta ratio (TBR) over motor cortex. Results showed individual variability across all participants, with no significant change in TBR for either trained condition. When compared to healthy participants, baseline values for TBR were higher and more variable between participants. Overall, the results of this study provide future research with framework and criteria for the design and implementation of NF training for ET.

LIST OF ABBREVIATIONS USED

ADL	Activities of Daily Living
DBS	Deep Brain Stimulation
EEG	Electroencephalography
EMG	Electromyography
ET	Essential Tremor
Hz	Hertz
MRI	Magnetic Resonance Imaging
NF	Neurofeedback
NFT	Neurofeedback Training
PD	Parkinson's Disease
SCP	Slow Cortical Potential
TBR	Theta/Beta Ratio

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I. Introduction

Most people may not contemplate the steadiness of their limb throughout the day, but it is crucial for performing many daily tasks. Whether pouring a beverage, writing, or reaching out to grab a fork out of a drawer, the ability to steady a limb is a determinant of accuracy for many movements. Tremor – the rapid back and forth motion of the limbs and/or upper body (Rogasch & Todd, 2013)– can interfere with the control of precise movements. Many different types of tremor exist, including ataxic, rubral and postural tremors. Tremor can be mild or severe, and can affect single or multiple areas of the body at once. Among the numerous reasons why an individual could develop tremor (including Parkinson’s Disease (PD) and Multiple Sclerosis), the most common cause is Essential Tremor (ET) (Elble et al., 2013). Characterized by a 4-8 Hz symmetric postural tremor (Tamás, Pálvölgyi, Takáts, Szirmai, & Kamondi, 2006), ET has been thought to be caused by oscillations from different sources within the brain working together to form a neural network (Filip, Lungu, Manto, & Bareš, 2016; Hellriegel, Schulz, Siebner, Deuschl, & Raethjen, 2012; Raethjen & Deuschl, 2012; Rogasch & Todd, 2013).

Common treatment suggestions for individuals with a mild tremor are often dependent upon the severity of tremor, but may include pharmacotherapy or physiotherapy/occupational therapy (Kocabicak, Terzi, Alptekin, & Temel, 2013). Unfortunately, as the origin of ET remains elusive, treatment options generally tackle symptoms rather than work to eliminate the underlying cause. Physio or occupational therapists often work with patients to help perform the ADLs which are most important to them, and can typically fit the patient with adaptive tools, or show them techniques to accomplish tasks despite the tremor. Physiotherapy generally does not alleviate the

physical tremor of ET, but is helpful to patients who had lost the ability to perform daily tasks. In cases of severe tremor, more invasive treatment options have had promising results such as Deep Brain Stimulation (DBS) (Lyons, 2011), thalamotomy (Elias et al., 2016), and gamma knife surgery among others (Grimaldi & Manto, 2013). In addition to the invasive and risky nature of these more severe treatment options, they are also very costly, and possess a lengthy list of side effects which are not often warranted in individuals with less severe tremor, or at an early stage of ET.

While treatments to deal with physical symptoms of ET are effective for some patients with less severe tremor, there are few non-invasive options that address the neural underpinnings of tremor. There is emerging evidence that ET is centrally driven and emerging from a network of oscillators which comprise the physiological central motor system (Hellriegel et al., 2012; Raethjen & Deuschl, 2012; Rogasch & Todd, 2013). This research has focused on four main areas: the sensorimotor cortex, brainstem, cerebellum, and the thalamus. Numerous studies have found that thalamic activity is present upon the generation of tremor, as well as patterns of electrical activity showing strong correlations to tremor frequency using electromyography (EMG) (Hellwig et al., 2001; Hellwig, Schelter, Guschlbauer, Timmer, & Lücking, 2003; Raethjen & Deuschl, 2012; Schnitzler, Müns, Butz, Timmermann, & Gross, 2009). Disruption to any part of the aforementioned oscillatory network by stroke has been shown to reduce/alleviate tremor in some cases (Dupuis et al., 2010).

Neurofeedback training (NFT), is an operant conditioning technique which allows the user to learn to self-regulate brain activity through the use of real-time feedback. One of the most cost-efficient options for recording this activity is electroencephalography

(EEG). EEG uses small electrodes placed on top of the head to record electrical activity being produced in certain frequency bands, and presents that information back to the user. The term frequency band describes an interval or range of electrical activity, which represents the synchronous firing of neurons. Typically during EEG NFT, a researcher will focus on specific frequencies over one area of the brain (Gevensleben et al., 2009; Gruzelier, 2014; Vernon, 2005). Research efforts using NFT have been shown to alleviate symptoms in PD patients, individuals with ADHD, as well as epilepsy, to name a few (Azarpaikan, Torbati, & Sohrabi, 2014; Bink et al., 2015; Gevensleben et al., 2009; Mayer & Arns, 2016; Walker, 2008). To implement NFT for patients with ET, this study focused on using EEG to provide feedback on the theta band (4-8 Hz) activity due to its established effects on balance, attention, and tremor amplitude (Azarpaikan et al., 2014; Hellriegel et al., 2012; Reiner, Rozengurt, & Barnea, 2014) as well as low beta band (13-20 Hz) activity because of links to attentional focus, alertness and concentration (Egner & Gruzelier, 2003). The power from both frequency bands can be shown to an individual as a theta/beta ratio (TBR) with the goal of altering the ratio through NFT. When increasing TBR, the aim is to increase power in the theta band and/or decrease power in the beta band, whereas decreasing TBR depicts a lower power in the theta band and/or higher power in the beta band. Through altering TBR over motor cortex in people with ET, perhaps the aforementioned oscillatory network could be disrupted, lessening tremor severity.

This study broadly aimed to provide proof of concept for the use of NFT in patients who have been diagnosed with ET. The purpose of the study was to assess whether individuals with ET were able to enhance or suppress TBR over the motor cortex

using auditory NFT. This purpose tested the hypothesis that individuals with ET would be able to manipulate TBR over motor cortex. More specifically, if participants were able to manipulate TBR, it was expected that there would be an increase in TBR production over motor cortex (C3, Cz, C4) from baseline to retention trials in the enhance condition, and a decrease in TBR produced from baseline to retention in the suppress condition. The following null hypotheses were also tested: 1) There was no difference in baseline TBR or power within the theta and beta frequency bands when comparing between a population diagnosed with ET and an asymptomatic control population; 2) Tremor severity did not correlate to either TBR, or power within the theta or beta frequency bands.

An accelerometer was used to measure the extent of patients' tremor during the course of the study. A mobile-EEG system (Debener, Minow, Emkes, Gandras, & de Vos, 2012) was used to record power in the theta (4-8 Hz) as well as low beta (13-20 Hz) frequency bands over the motor cortex of 9 ET patients. Through a custom data collection and online analysis script (Matlab, v. 2016a) power in the theta frequency band was averaged in real time and divided by power in the low beta frequency band, giving the TBR. While undergoing each training, the participant was able to hear (via over the ear headphones) different auditory pitches that corresponded to how much TBR they were producing.

Participants completed NFT under two conditions: enhancing or suppressing the TBR. Participants were informed of common techniques which could be used in each condition. Enhancing theta power as well as decreasing low beta power have been best achieved in individuals who are relaxed, or meditative. The opposite has been shown in

individuals who are alert, or cognitively focused on a task (Gevensleben et al., 2009). Each training condition was completed in separate sessions, with each session beginning with a baseline recording. Following training in each condition the participant was asked to use the technique that they had found most successful to complete a retention trial, with no NF present. To test the study hypothesis, TBR during training as well as the change from baseline to retention will be compared between conditions. Offline baseline data from the clinical population as well as an asymptomatic control population was analyzed so that TBR, as well as theta and beta frequency band power could be compared between groups. Correlations were run from accelerometer data measuring displacement of the most affected limb (cm) to simultaneous EEG recordings reflecting TBR, power in theta, as well as power in beta.

II. Literature Review

2.1 Prevalence of ET

As the most common cause of adult tremor (Elble et al., 2013), ET has often been referred to as one of the most prevalent adult movement disorders, through exact estimates of the prevalence are difficult to determine. Estimates of the prevalence of ET cover a wide margin: 0.08 to 220 cases per 1000 (as outlined in a systematic review by Louis, Ottman and Hauser (1998)). As discussed within this review, some of the variation may be because few studies performed worldwide had considered entire communities rather than only those individuals who visited doctors or hospitals when determining the prevalence of ET. In their review, Louis, Ottman and Hauser (1998) suggested that prevalence of ET was often underreported, as an individual within the community might not seek medical attention before their tremor reached a debilitating stage. Studies that took into account entire communities reported prevalence as 4.1 to 39.2 cases per 1000 providing a more stable estimate of the prevalence.

More recently, in a review of current research by Lorenz & Deuschl (2007), ET seems to continue to range in prevalence (0.4-3.9%) depending on which diagnostic criteria are being used. Three larger population-based surveys were discussed that all used more specific diagnostic criteria in Italy, Spain and Turkey which estimated prevalence of the disorder at 4% (ages 50-89), 4.8% (65+ years), and 3.06% (40+ years), respectively (Benito-León, Bermejo-Pareja, Morales, Vega, & Molina, 2003; Dogu et al., 2003; Wenning et al., 2005). These more recent findings seem to agree that as a population ages, so does the prevalence of ET. When considering those above the age of 60, the prevalence of ET increased to 13.0-50.5 cases per 1000. With the current

population aging rapidly and life expectancy progressively increasing, the prevalence of ET will only continue to grow.

2.2 Current Clinical Presentation and Treatment of ET

Essential Tremor is classified as a 4-8 Hz postural tremor, which can limit the daily activity of those it affects by altering their ability to perform motor movements (such as drinking, writing, or using tools) steadily (Elble et al., 2013). Each individual who is affected by ET is unique in that they may have a more or less severe tremor amplitude and it may affect different/multiple parts of the body unlike any other (Louis, Ottman, & Hauser, 1998). A typical diagnosis of ET is made by a neurologist specializing in movement disorders, after referral by a physician, who may choose to use an assortment of criteria to confirm a diagnosis (Louis, 2018). In one study in particular, researchers used more strict diagnostic criteria in which three neurologists were required to agree on ET diagnosis before a participant was considered to have ET: Out of 472 patients who screened positively for ET using a questionnaire, only 183 were confirmed as having ET by all three neurologists (Benito-León et al., 2003)

As there is no current understanding of what makes ET tremor occur, there is no sole treatment option that effectively ceases tremor activity in all those affected. Individuals with less severe tremor, (i.e., they can perform activities of daily living, still maintain their independence, are able to continue with activities which make them happy, etc.) are often given a first line of treatment options such as the drugs, propranolol or primidone, to see if they will have any individual success (Louis, 2018). In the past, patients found that consuming alcohol decreased tremor. This tremor suppression method

(while not widely promoted) is still used by many ET patients to get through tasks or times when they feel the need to mask their tremor (Voller et al., 2014). Physicians most frequently recommend lifestyle changes such as cutting out caffeine or other stimulants from their diets, as well as pharmacological options like the beta blockers mentioned above. It is important to note that while these methods work very well for some patients, they may be less effective for others, and some patients do not see results at all (Grimaldi & Manto, 2013).

In a 2015 questionnaire which was given to over 1400 individuals diagnosed with ET, 16.1% of respondents indicated that the current treatment was not effective enough (Louis, Rohl, & Rice, 2015). In response to the same survey, many respondents indicated that they felt assessments were subjective and not personalized, that treatments were only combatting tremor itself and not dealing with the underlying day-to-day issues that they faced, and 1/3 of participants felt as though their doctor was not well educated with respect to tremor. Researchers from this study indicated that most patients diagnosed with ET would benefit from a multidisciplinary care team, consisting of psychologists, medical doctors, neurologists, occupational therapists, physiotherapists, etc. The involvement of occupational and physiotherapists not only allows diagnosed individuals to receive continued monitoring of progression or decline in abilities, but to be able to work on individualized issues that they are having in order to better promote success in ADLs. As ET is such an individualized disorder, with severity as well as location of tremor being unique for all who are diagnosed, the ability to use strength training, tremor suppressing orthoses, or weighted utensils among many other adaptive and non-invasive

methods (O'Connor & Kini, 2011) is an option that not all who are diagnosed with ET are given.

Other non-invasive methods which have shown promising results are injections of botulinum toxin, as well as ultrasound therapy. Botulinum toxin (botox) injections to the forearm of the affected limb were shown to have mild/moderate improvement on tremor severity at four weeks post-treatment (Grimaldi & Manto, 2013). Adverse effects from this treatment method included finger weakness in the treated limb. In a randomized control trial in 2016, Magnetic Resonance Imaging (MRI) guided ultrasound thalamotomy was used as a treatment option for ET (Elias et al., 2016). MRI guided ultrasound thalamotomy is a procedure which uses MRI to establish images of exact locations within the brain. Once the correct locations are chosen, high temperature acoustic energy is used to lesion specific locations within the brain. Results were very promising, improving tremor scores on the contralateral side from treatment by 47%, and quality of life scores by 46%. Sham condition reported an almost negligible effect on both tests. At 12 months post-treatment, reduction of tremor persisted on the contralateral side from treatment, although no reduction in tremor scores were apparent on the ipsilateral side.

For more severe tremor, treatment options are available such as Deep Brain Stimulation (DBS), radiofrequency thalamotomy, focused ultrasound guided by Magnetic Resonance Imaging (MRI), or radiosurgery such as gamma knife surgery. While these treatment options have been shown to be successful in individuals with a severe tremor, they are also costly and invasive options which are not always warranted for individuals with a less severe form of tremor. Individuals who are at the early stages of ET may not

be presented with these options by their physicians due to the invasive nature, or may choose not to use them as potential risks include hemorrhage; transient confusion; infection; and fracture, misplacement, or migration of the implanted device (Lyons, 2011).

2.3 Neural explanations of ET

Although Essential Tremor is common, the neural explanations or underpinnings of the condition are not well-understood. While reviews of post-mortem, neuropathological research in ET have reported cases of degeneration within the cerebellum, as well as fewer Lewy bodies in the brainstem (Louis & Vonsattel, 2008), other studies have found a cortico-muscular coherence in the contralateral side of tremor (Raethjen, J., Govindan, R. B., Kopper, F., Muthuraman, M., & Deuschl, G. (2007), and others still have found that thalamic lesions strongly reduce tremor scores (Koller et al., 1997). One current and widely accepted hypothesis is that the tremor in ET stems not from one sole location, but instead from a network of oscillators that work in series to generate the tremor (Dupuis, Evrard, Jacquerye, Picard, & Lermen, 2010; Hellriegel et al., 2012; Hellwig et al., 2001, 2003; Raethjen & Deuschl, 2012). Four main areas are thought to comprise this network are the primary motor cortex, brainstem (inferior olive), cerebellum, and thalamus (Schnitzler et al., 2009).

From a neurophysiological standpoint, it is known that one of the main indications of ET is a postural tremor (Heldman et al., 2011; Hellriegel et al., 2012; Hellwig et al., 2001), supporting the notion that it is centrally driven rather than dependant on reflex mechanisms in the periphery (Raethjen et al., 2007). Within the central nervous system,

the cerebellum is a hub of activity which has known projections to both the thalamus and brainstem (Deuschl, Raethjen, Lindemann & Krack, 2001). As reflected by the work of Hellwig et al. (2001), and also by Raethjen and colleagues (2007), corticomuscular (4-8Hz) coherence vanishes before the tremor subsides which supports the notion that the motor cortex may be only one component or output of a larger network which promotes tremor.

Supporting the theory of this four-part network, a case study by Dupuis and colleagues in 2010, examined four patients post-stroke who had been previously diagnosed with ET. These four patients presented with no tremor on the same side as was affected by lesions to the following locations: subcortical cerebellar hemisphere; posterior limb of internal capsule; pontine nuclei; sensorimotor cortex. In one patient with lesions around the rolandic and pre-rolandic fissures, a lesser tremor returned three months post-stroke, however in the other three patients the tremor did not return. Findings from these four cases were then discussed relative to findings from twelve previously reported cases who all had damage to the pathway between the sensorimotor cortex and the cerebellum. These previous case studies, as summarized by Dupuis and colleagues, showed that damage to the thalamus during stroke due to lesion (inclusive of hemorrhage), lacune, or ischemia all resulted in persistent loss of tremor. Authors dubbed these strokes “curative strokes”, suggesting that damage to any part of the oscillatory neural network which was generating the condition could potentially reduce/alleviate the tremor.

In line with this, repetitive transcranial magnetic stimulation to the motor cortex has been shown to alter tremor amplitude (Rogasch & Todd, 2013). In a study of healthy

participants, baseline measures of physiological tremor (7.8-12.2 Hz) using EMG as well as an accelerometer were recorded during a finger pointing task. Participants then received 10 minutes of either real or sham inhibitory repetitive magnetic brain stimulation and were measured for tremor again. Results showed that repetitive magnetic brain stimulation of the motor cortex significantly increased action tremor. Although increasing tremor amplitude is not desired, this study was one of the first to show that targeting the motor cortex had an effect on tremor amplitude.

More encouraging in the context of ET, Hellreigel, Schultz, Siebner and colleagues (2012) attempted to suppress corticospinal excitability using cortical theta-burst stimulation over the primary motor cortex. Ten patients with ET, and ten healthy controls were first measured for baseline tremor using accelerometry of the first dorsal interosseous. Each participant then received two sessions of 80% active and 30% passive targeted theta-burst stimulation over the left primary motor hand area. Results showed that real, but not control theta-burst, stimulation reduced the tremor amplitude measured through the accelerometer. Although the effects could not be seen by clinical testing standards, researchers believed that a longer treatment period as well as longer follow-up periods would have a clinically observable impact on tremor.

Taken together, these studies suggest that disrupting any part of the previously mentioned neural network and specifically targeting the motor cortex could reduce if not alleviate tremor. This provides a rationale to begin to explore a non-invasive method such as NF as a potential tool to disrupt this network through altering activity in the motor cortex.

2.4 Neurofeedback

Recording biological signals of the body in a manner that can be displayed back to an individual is the premise of biofeedback. Whether capturing the range of specific movements using accelerometry, or electrical impulses of neurons within muscles or the brain, showing these signals to the one producing them in real time has been regarded as an established method to enable a user to self-control or regulate abnormalities (Egner & Gruzelier, 2004). EMG biofeedback has been eluded in research concentrating on behavioural relaxation therapy as a method of reducing tremor, with authors noting that participants who had not benefitted from behavioral relaxation therapy alone, might progress faster while using EMG biofeedback (Lundervold, Belwood, Craney, & Poppen, 1999). This notion was supported by a study which examined 13 individuals diagnosed with ET who had completed a combination of relaxation therapy and produced significantly lower tremor scores after treatment (Lundervold & Poppen, 2004). Although the physical symptoms of ET are captured when viewing EMG biofeedback, if the current theory of a neural network of activity sparking tremor onset is correct, developing a way to self-regulate neural activity could also be of use.

Research into NFT (also known as EEG biofeedback) started in the 1960s, when the discovery was made that electrical activity within the brain could be controlled and manipulated through the use of instantaneous feedback (Louis et al., 1998). Most NF at that time (and even still) was shown as a measure of spectral power, event related potentials, or slow cortical potentials. Much of the research into EEG biofeedback was sidelined in the 1980s due to flawed studies and clinical overstatement, leading people to believe that the self-regulation of alpha waves was a simplistic process that was

controlled through relaxation. As stated by Gruzelier in 2013, as the concept of “brain training” became more fashionable, it became even more crucial to find validated and useful results for NFT. Only a few specialists remained focused on EEG biofeedback, until these validated and useful results began to resurface in the early 2000s. It was then that research at the university level began to commence once more.

2.5 Theta Neurofeedback

Neurofeedback techniques to alter the output of theta (4-8 Hz) have been studied for many different applications, including but not limited to: cognitive performance, sports and more recently targeting attentional deficits due to ADHD and balance in individuals with Parkinson’s disease (Azarpaikan et al., 2014; Vernon, 2005). An increase in theta production has long been thought to occur when individuals are in a meditative or relaxed state (Aftanas & Golocheikine, 2001; Becerra et al., 2012; Egner & Gruzelier, 2003; Ros et al., 2009), and has also now been found to occur during long-term memory potentiation and encoding (Gruzelier, 2014).

In 2005, a systematic review was written which examined many EEG studies and evaluated both the results and effectiveness of each included study. Theta augmentation had been shown to correlate with decreased arousal and attentional performance (Beatty et al., 1973), with a marginal improvement in dance performance as well as musical abilities (Egner & Gruzelier, 2003; Raymond et al., 2005). Vernon noted however that because these studies failed to find any changes from baseline to post-training within EEG measurements, that any changes in performance could have been the result of any number of outside factors and could not be contributed to EEG alone. He suggested that

future research incorporate the following measures: taking pre- and post-NFT measurements of EEG to determine effectiveness of training; when possible, take baseline measurements every time a participant return to the lab to account for changes in arousal; and to include a control group when dealing with an intervention (Vernon, 2005).

Keeping in line with these measures, Gruzelier (2014) created a review of past studies which examined the effectiveness of alpha/theta NF on enhancing performance. Alpha/theta training is the concept of increasing theta-band (4-8 Hz) output to a level that exceeds alpha-band (8-12 Hz) output (Gruzelier, 2014). While mentioning studies which examined alpha/theta training over the occipital (O2) (Moore, 2000), parietal (Pz) (Egner et al, 2002), and frontal (F3) (Egner & Gruzelier, 2004) lobes of the brain, all authors noted improvements in musicality and performance scores after participating in alpha/theta training monitored over the respective sites.

Other researchers have instead found improvements with both inhibiting and suppressing the theta frequency band power. In 2009, Ros and colleagues aimed to optimize microsurgical skills using two protocols: SMR-theta training, which aims to increase beta (12-15 Hz), while inhibiting theta (4-8 Hz); and alpha-theta training, both monitored over the motor-cortex (Cz). Participants underwent eight, 30-minute sessions of their respective forms of NF while simultaneously enrolled in a two-three month nationally standardized surgical training curriculum. The control group had no NFT however was still enrolled in the surgical training course. There was a significant increase in ratings from judges of both overall technique and suture skills for the SMR-theta group (n=10), and improvements on both tasks (although not statistically significant) for the

alpha/theta group (n=10) when comparing to the controls (n=8) (Ros et al., 2009). These findings would suggest that while only inhibition of theta revealed statistically significant results, theta NFT in any capacity over the motor cortex has a positive impact on fine motor movements when compared to no NFT.

2.6 Beta Neurofeedback

When Beta activity was first described in 1929 by Hans Berger, all activity in frequency bands above 13 Hz was labelled as Beta (Kropotov, 2016). Since then, research has developed different names for frequency bands at intervals above 30 Hz (e.g., gamma), and has shown a need to distinguish between frequency bands within the original 13-30 Hz range as well. In general, the broad beta (13-30 Hz) frequency band is often associated with movement. These different stages of motor movements have been linked with varying amplitudes within the 13-30 Hz range: with an increase in activity being linked to tonic holds or contractions (Jenkinson & Brown, 2011), and a decrease in power linked with voluntary movements or a readiness to move (Tzagarakis, Ince, Leuthold, and Pellizer, 2010).

Tzagarakis et al., (2010) explored the event-related desynchronization of the higher end of the beta frequency band (16-28 Hz) and found beta desynchronized ~120ms after a movement cue onset in humans. Similar findings were observed using macaque monkeys with a ~110ms delay after cue onset before beta desynchronization began (Zhang et al., 2008). These findings lead both sets of authors to conclude that power in the higher level beta frequency band seems to accompany motor preparation, or neural activity just before movement. This is consistent with the opinion that higher

frequency bands are often associated with higher arousal levels, similar to the level of alertness and arousal that might be evident while planning to make a movement, contrasted with a sedentary focused attention which would be more in line with a lower frequency band.

The low beta (13-20 Hz) frequency range is most often associated with attentional focus. More specifically, increasing amplitudes within the low beta range seems to reduce inattentive/impulsive qualities in some attentional disorders (Egner and Gruzelier, 2004). A significant reduction in seizure quantity for patients with epilepsy has also been shown for the 12-15 Hz frequency range, with high re-test reliability as subjects from one study discussed were able to regulate brain activity accordingly and maintained clinical effects 10 years after treatment (Mayer & Arns, 2016).

Beta frequency band research has been limited by the tools available to measure it. The two most common techniques are scalp EEG, which typically has quite a low signal amplitude for capturing higher frequencies such as high-beta, as well as capturing local field potentials from electrodes implanted during DBS, which are typically only placed in one locale (Crowell et al., 2012). While undergoing a DBS procedure, Crowell and colleagues (2012) were able to use subdural awake-state electrocorticography to examine local field potentials of the primary motor cortex in 30 patients (10 Parkinson's Disease (PD), 10 dystonia, 10 ET). Crowell et al., (2012) noted that the spectral power of dystonia and ET patients was under 15 Hz in all conditions of movement, where PD patients were showing peak power in the 21-30 Hz range. In summary, this study emphasized (using very precise measurements) that while the higher 21-30 Hz beta frequency band may be of interest in some conditions of movements in PD, the ET population alpha-beta spectral

peaks were measured to be within the low-beta (13-20 Hz) range. In line with the aforementioned research, the focus of this study will be within the lower (12-20 Hz) range of the beta frequency band to more accurately capture neural activity when a participant is seated with eyes closed, and not actively preparing to move.

2.7 The Theta/Beta Ratio

In order to use feedback from two frequency bands simultaneously, a ratio of the amplitudes measured from each frequency band individually can be fed back to the participant. With both theta and beta in mind, it is possible to obtain a ratio of beta/theta, or theta/beta amplitudes: the latter of the two being most widely used in research. The aim of most theta/beta training has been to instill a capacity within participants to reduce theta amplitudes while simultaneously increasing beta amplitudes. A typical technique or instructional cue for this type of training would be to maintain attentiveness, or to keep the mind alert while staying focused on the task at hand (Studer et al., 2014)

The most common application of Theta/Beta Ratio (TBR) NFT is in children with attention deficit disorder (ADD)/attention deficit hyperactivity disorder (ADHD). It has been noted that individuals with ADD/ADHD typically have higher resting theta amplitudes, and lower beta amplitudes than a healthy population and that the medications given to individuals with ADD/ADHD have been shown to decrease TBR (Angelidis, Hagnaars, van Son, van der Does, & Putman, 2018; Gevensleben et al., 2009). In a clinical trial working with children diagnosed with ADHD, Gevensleben and colleagues (2009) implemented an eight-week testing protocol in which participants were randomly assigned to either an intervention or mock intervention group. Within the intervention group, visual-based NFT (TBR: 4-8 Hz/13-20 Hz) and slow cortical potential (SCP)

training to alter cortical excitation (electrical) levels over the sensorimotor cortex. The control group was given a similarly styled attention skills training paradigm, in which they performed computer-game style attention tasks with no NF. When scored by parents and teachers on several different behavioral rating scales, both NF and slow cortical potential training showed a significant decrease in ADHD symptoms. This study provided a large sample size in contrast to others and was also able to keep strict control conditions which closely mimicked the design of the intervention.

In healthy individuals, NFT training with the TBR has been shown to decrease response time as well as increase excitability (Studer et al., 2014) and cognitive control (Angelidis, Hagenars, van Son, van der Does, & Putman, 2018). Using a population comprised solely of ‘healthy’ individuals, without clinical diagnosis of ailment, disease or disorder, Studer and colleagues (2014) were able to test two protocols previously tested on individuals with ADHD: one aiming to target the TBR, while the second used SCP training. Owing to a sample size they were unable to produce significant effects, but did note that participants who had been labelled as “good performers” (i.e., those who were able to manipulate TBR amplitudes after sufficient training), were exhibiting increased response speed as well as attentional focus. Motor system excitability measures within this same cohort were said to be comparative to the effects of methylphenidate (trade name: Ritalin) known to be a stimulant or focus aid for individuals with ADHD.

In anxious individuals, who typically suffer from lower working memory capacity, memory training has been shown to increase frontal theta/beta ratio (TBR) (Angelidis et al., 2018). During the previously mentioned study, 74 otherwise healthy individuals were assessed using a self-reported trait anxiety questionnaire, and then asked to complete both

spontaneous frontal EEG sampling of TBR and a dot probe task with differing threat-levels (time limits). High TBR seemed to indicate an ability to avoid highly threatening pictures, and direct attention to more mildly threatening stimuli. Authors also noted that participants which they dubbed “resilient” with low TBR, and low trait anxiety, seemed to be drawn to highly threatening stimuli, and less likely to exhibit the capacity to exert cognitive control.

Another clinical application for NFT, more specifically a variation of TBR training looking at theta as well as sensorimotor rhythm (SMR, 12-15 Hz) amplitudes, is in people with epilepsy. SMR amplitude training in this specific population has been shown to have anticonvulsant effects. The mechanism of action behind this has been linked to the SMR frequency band regulating brain excitability thresholds, which prevents over-excitation, leading to fewer/no seizure activity (Mayer & Arns, 2016). In a meta-analysis of NFT for the purposes of treating epilepsy, they concluded that SMR or SCP training consistently decreased seizure activity for patients who had severe cases of epilepsy and had no other treatment alternative (Tan et al., 2009).

Azarpaikan, Torbati and Sohrabi (2014) also used a variation of theta/SMR NFT to try to enhance balance in individuals with PD. Researchers speculated that because an improvement in attention had been shown to improve standing balance, that an NFT protocol targeting an increase in SMR/ decrease in theta would also enhance balance. 16 participants underwent eight, 30-minute sessions in which they played video games with the intent of increasing low beta/SMR (12-15 Hz) and decreasing theta (4-7 Hz) over the occipital lobe, basal ganglia and cerebellum (O1-O2). Whenever amplitude would increase in the theta band, the game would stop. A control group was fitted with a sham

EEG generator, which stopped the game at random times to simulate the real NF condition. Results showed that although the dynamic and static balance between control and experimental groups were similar before NFT, after NFT balance scores were significantly increased in the experimental group. Researchers concluded that the experimental groups NFT increasing power within SMR and decreasing power within theta had effectively increased their balance scores.

2.8 Neurofeedback and Tremor

Due to large differences in what causes each type of tremor (e.g., PD vs. ET), it should be noted that it is unlikely for all types of tremor to respond to the same intervention in the same way. Most NFT research into the motor-movement-related field of tremor has been associated with the beta frequency band range, likely due in part to its previously mentioned connection with motor planning and execution (Engel & Fries, 2010; Gilbertson, 2005).

Parkinsonian patients are known to present with abnormally low amplitudes of early beta synchrony, sometimes called Bereitschaftspotential, or BP1 (Fumuro et al., 2013). When treated with dopamine replacement therapy or DBS, those same levels of BP1 are elevated. In 2013, Fumuro and colleagues were the first to treat PD patients using beta (13-30 Hz) frequency band NFT in the hopes of elevating BP1 and potentially creating a non-invasive treatment method for PD. Targeting the central motor cortex (C3, C1, Cz, C2, C4), the authors were able to split participants by performance into “good” and “poor” performers. After NFT, the “good” performers were capable of increasing levels of BP1. In a critique of this article, authors caution that more research is needed

surrounding BP1's clinical role in PD, as well as more explanation into what constitutes a "good" or "poor" performer (Suppa, 2013). Within the same diagnostic pool of individuals, electrical activity levels within the beta frequency band seem to remain consistent across basal ganglia and motor cortex, with a reduction over any of these areas seeming to assist the capability of the individual to perform motor movements (Meyniel & Pessiglione, 2013). Though not as widely researched, NFT has also been suggested for the treatment of Gilles-de-la-Tourette syndrome for its connection to executive control (Farkas, Bluschke, Roessner, & Beste, 2015).

2.9 Conclusions

Individuals with Essential Tremor need a reliable, non-invasive treatment for tremor. Current published research in neuroscience- in particular that which has looked at theta NFT in other tremor conditions as well as transcranial magnetic stimulation over the motor cortex- has provided a strong rationale for the use of NFT for ET. While the beta frequency band is a signal of interest over the motor cortex due to its links to movement preparation, the theta frequency band with links to arousal and attention, cognitive control, and fine motor movements is an area of interest when considering ET as well. TBR which encompasses both of these frequency bands, has been used in the past to treat conditions such as epilepsy, Parkinsonian tremor as well as ADHD. While its use in ET is not known thus far, targeting the motor cortex and eventually altering how neurons are firing at this location could be a way to disrupt the network causing tremor. This study could provide a much-needed proof of concept: that ET patients can manipulate TBR production through NFT. This concept would then be used in future research to provide

ET patients with a treatment option which would be cost effective, non-invasive and self-regulated to reduce if not alleviate the amount of postural tremor experienced.

III. Objectives and Hypotheses

3.1 Objectives

The objectives of the current work are to:

1. Ascertain whether or not individuals who have been diagnosed with ET are able to use auditory NF techniques to alter TBR
2. Compare baseline collection of TBR as well as theta and beta frequency band power in those with ET to participants without ET from a previously collected study
3. Compare upper limb tremor amplitude to TBR, theta, and low beta amplitudes to determine if a correlation between tremor and brain activity is evident.

3.2 Hypotheses

1. We hypothesize that individuals diagnosed with Essential Tremor will be able to use auditory NF of the TBR (4-8 Hz/13-20 Hz) amplitudes to alter production of TBR over the motor cortex, as measured at electrodes over C3, CZ, and C4 locations. Specifically, we expect to see an upward trend in TBR amplitude from baseline to retention in the enhance condition, or downward trend in TBR amplitude during the suppress condition.

The present study also chose to test whether the following null hypotheses could be rejected:

1. TBR, as well as amplitudes in the theta and beta frequency bands separately will be similar between healthy and patient populations.

2. Tremor amplitude will have no effect on TBR or on amplitudes in either theta or beta frequency bands.

IV. Methods

4.1 Participant population

Nine participants with ET (five male) were recruited through neurologists within the neurology department at the QEII hospital in Halifax, Nova Scotia. Participants had been diagnosed with ET by their respective physicians and had individually contacted the research team, as well as read informed consent documents prior to visiting the lab. Exclusion criteria were formed surrounding a need for consent as well as determining that the patients' tremor was solely the result of ET, and therefore participants under the age of 18, or those with neurocognitive impairments, significant traumatic brain injury, or PD were excluded. Referring physicians were informed of all exclusion criteria. Participants were reimbursed for some study related expenses such as bus fare, and/or parking. Participants also received an honorarium of \$10 CAD/hour.

4.2 Materials and measures

TBR activity was measured using a mobile EEG system (Debener et al., 2012) comprised of an EASYCAP electrode cap and EMOTIVE amplifier. The system consists of a research grade wet electrode cap attached to a modified wireless EMOTIVE amplifier. Cortical electrical activity was measured over 14 electrode sites as depicted in *Figure 1*, within the international 10-20 system of electrode placement (Falk Minnow Services, 2001). The incoming sampling frequency from the amplifier was 128 Hz.

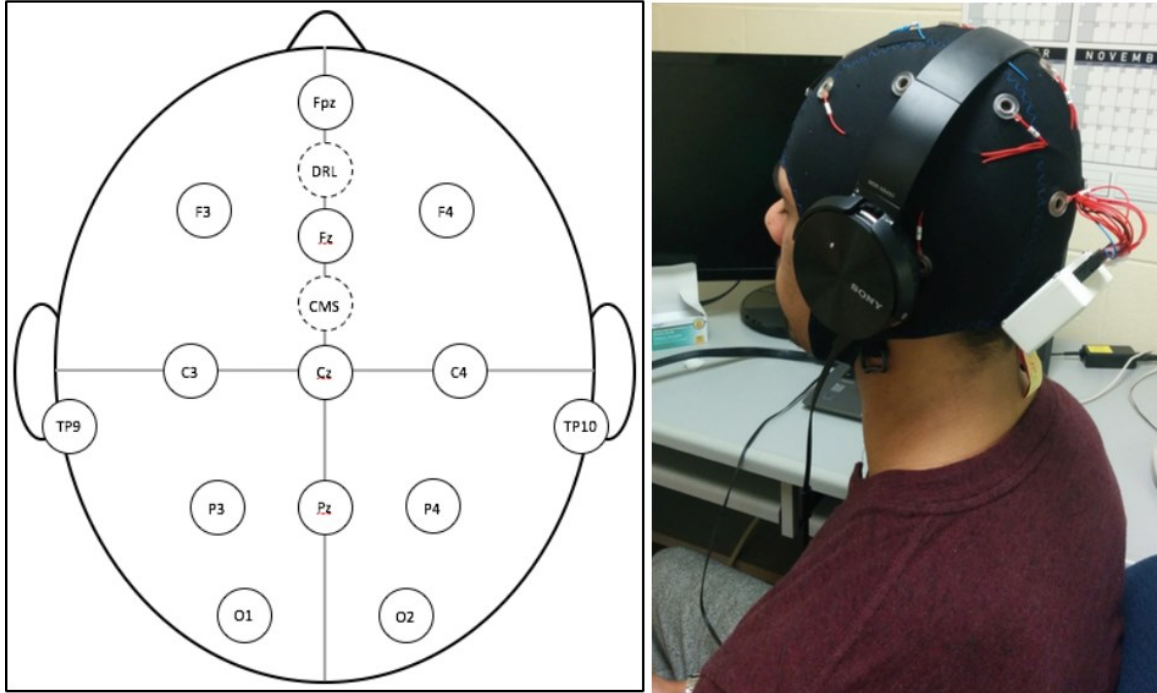


Figure 1. Mobile EEG System. Left: Electrode placement of the mobile EEG system. Right: Neurofeedback set up with EasyCap, modified Emotive Amplifier and over the ear headphones for audio neurofeedback.

Once fitted with the cap, baseline data over motor cortex (C3, Cz, C4) was collected and analyzed (see *Online Data Analysis* section below) using a custom Matlab script. This script measured power in both theta (4-8 Hz) as well as beta (13-20 Hz) frequency bands, calculated the ratio of theta/beta, and then determined appropriate cut-off ranges (described below) using standard deviations of mean TBR across the baseline collection.

For trials with NF, participants heard a tone through over the ear headphones which were set to a volume personalized for each participant based on personal preference. The tone corresponded to real-time TBR production, and participants were instructed that a change in pitch of this tone indicated a change in electrical activity levels within their brain. The pitch played to the participant was determined based on ranges

pre-determined by previous performance described in more detail in the *Online Data Analysis* section below.

A secondary outcome measure of tremor amplitude was measured using a tri-axial accelerometer. Tremor amplitude of the most affected limb was measured in three conditions (as described within the procedures section). The accelerometer was affixed to the dorsum of the patients' self-declared most affected limb. Using Velcro straps, the accelerometer was positioned snug yet comfortably, approximately 9cm distal to the ulnar epicondyle (replicating Timmer et al., 1996). Tremor for each of these conditions was measured for 30s while EEG data was simultaneously recorded from the 14 EEG channels using a custom MATLAB script.

4.3 Study design

The design of this study was within-subject, where participants performed two sessions of NFT; one to enhance the TBR, and one to suppress. Each session (as shown in Figure 2, Left) took approximately two hours to complete, including time for set-up, instructions, and clean up. For most participants, the sessions were completed on separate days with the order of the conditions counterbalanced across participants. Because the study worked with a clinical population, an exception was made (as shown in Figure 2, Right) for participants who lived outside of the Halifax Regional Municipality who preferred to do both sessions on one day (n=1). In this case, one half hour break was allotted between sessions so that the participant could rest, and the entire session was three hours in length. Participants completed a three-minute long baseline EEG collection block. They then completed three, 30-second blocks to measure tremor amplitude along

with EEG recordings. Next, they completed eight, three-minute-long blocks of NF training, separated by 30 seconds to two minutes of rest. Training was followed by a three-minute post-training block with no NF. The same three 30 second blocks to measure tremor amplitude and simultaneous EEG were performed post-retention trial in order to ensure a consistent reading of tremor severity was attained for each participant.

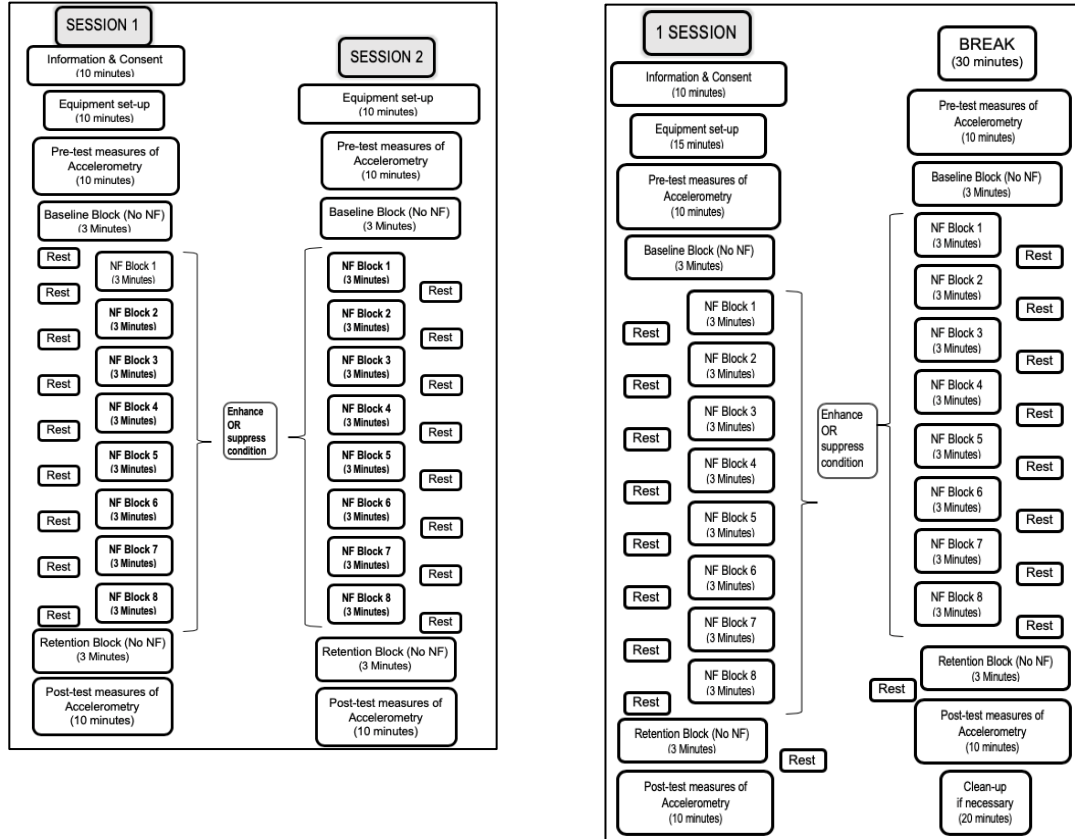


Figure 2. Study schedule. Left: Breakdown of two-day study Right: Breakdown of single-day study

4.4 Procedures

Upon entering the lab for the first time, a member of the research team reviewed the informed consent form with the participant. The procedure for the study was verbally explained to the participant. After informed signed consent, the participant was fitted

with the EEG cap, as well as the accelerometer on the dorsal surface of the hand on the limb most affected by tremor based on participant self-report. Electro-conductive gel was used under each of the 14 electrodes to ensure good conductivity between the scalp and electrode. Minimal impedance of all 14 electrode sites was confirmed using OpenVibe Acquisition software. The lowest and highest pitched audible tones (from inaudible to highest pitch: 10 Hz, 262 Hz, 330 Hz, 392 Hz) were played through over the ear headphones to ensure an appropriate volume for each participant for the duration of testing. When participants returned for their second testing session, the same volume setting as the first session was used.

Pre-test measures of tremor severity were recorded before trials began. Three conditions were measured in 30-second increments both pre and post-testing using the accelerometer. The first was resting measure of tremor activity with the participant holding their most affected limb up against gravity, parallel to a desk. The second was a dynamic measure (i.e., recording during an action) of a self-reported tremor inducing task. Participants were asked to recreate an action that they felt induced a high level of tremor (e.g. holding a coffee cup, fork, pencil, etc.). Props were found around the surrounding area to assist this condition (e.g., if the participant noted a particular problem drinking coffee in the mornings, a coffee cup was found so that the participant could reproduce the action similar to what they were used to at home). The final condition was a static measure of the grip used during Condition 2, without the prop. Eyes open EEG data from 14 electrode sites was simultaneously collected at this time.

During the NFT trials, participants were asked to remain seated with eyes closed and as still as possible for each 3-minute collection. When each training block started, the

participant was instructed to listen to the tones and to make the sound ‘get quieter or go away’. The inaudible tone was played while the participant was producing the desired amount of TBR production over the motor cortex, and tones increased in pitch as they began to deviate from the desired production value. For the purposes of this study, the tones decreased independent of the condition type (enhance/suppress). This use of pitch meant that as participants moved toward their goal state, the tone sounded like it was quieting and going away. During each condition, the participant was given a verbal description of appropriate techniques shown to either enhance or suppress TBR.

After each training block, the research team member running the study asked the participant for their own opinion on their success, and indicated whether the newly-determined cut-off value (described in detail within the next section) had shown that the technique they had been trying was successful or not. A sample of techniques gathered from these informal discussions with the participants is shown in Appendix A, Table 1. Techniques which were deemed the most successful by the participants are indicated by an asterisk. During rest blocks, participants were encouraged to get up and move around the room, get a drink of water, use the restroom, or ask questions as needed. Participants were instructed to take a 30-second break even if they did not require one between blocks to think of what they would like to accomplish in the next block. Once eight blocks of training were complete, the participant was instructed to take a longer (one minute) rest and to think back to which technique they thought produced their best results. For the final three-minute retention block, participants were instructed that there would be no tones played through the over-the-ear headphones. They were asked to follow the same

seated, eyes closed, procedure but to use whichever technique they thought had worked best for them in that sessions, as opposed to trying a new technique.

4.5 Online Processing

Power amplitudes from both theta (4-8 Hz) and low beta (13-30 Hz) frequency bands were recorded from the Cz, C3 and C4 regions over the motor cortex during a baseline collection of resting neural activity. The baseline collection was used to determine thresholds for each sound that would be played to the participant for NFT training. As training progressed, the thresholds were modified to reflect each previous trial, meaning that if the participant performed very well and increased TBR in the first training trial of the enhance condition, the second training trial would have higher thresholds and would seek an increase in power beyond what was expected in training trial 1.

Using a histogram of TBR from the previous trial, the peak frequency of TBR was used as the highest cut-off range. If participants were producing amplitudes of TBR equal to or above this range during the next trial, they would hear silence, indicating the highest level of success. This acceptable amplitude was divided by five to create five equally spaced bins: the lowest was between 0-1/5 of the acceptable amplitude; the second between 1/5-2/5; third between 2/5-3/5; fourth between 3/5-4/5; and fifth was an amplitude higher than 4/5 of the “acceptable amplitude”. Depending on the condition (either enhancing or suppressing the TBR), the cut-off range deemed the most successful would play a tone below the level of human detection (10 Hz), and each subsequent cut-off range would play a higher pitched solid tone.

In each testing block, after three seconds of data collection, a zero-phase butterworth band-pass filter was used to extract the same 4-8 Hz and 13-20 Hz signals in three second increments. In order to eliminate filtering artifacts while maintaining a fast filter-speed, the first and last second of each data fragment were discarded. The middle second of data (128 samples) was averaged for each frequency band as described for baseline collection and then the ratio between the two values was calculated. The middle section of data was used to reduce the effect of aliasing artifacts from the filter on the NF signal. The average from this middle second was data was compared to previously described thresholds to determine which tone would be audibly presented to the participant for the next second. In short, tones were updated on a second-by-second basis based on a real-time moving average which compared the average TBR amplitude from the previous second of data to pre-determined threshold values from the previous trial.

4.6 Offline Processing

Raw data was extracted from C3, C4 and CZ for each collection, and was filtered (23040 samples each block) into theta frequency band, beta frequency band, and TBR amplitudes using a custom matlab script designed by the lead researcher. Each block of data had the first second of collection trimmed to remove any filtering artifacts, and the average amplitude of each frequency band and the TBR was calculated for each block (e.g., baseline, training blocks and post-test). Using eeglab, each block of data collection went through ICA based artifact rejection and was visually examined for abnormalities and noise in 1-second intervals by plotting the three channels of interest alongside each other as well.

Accelerometer data was first visually examined (graphing x, y and z components) to determine which axis to use. It was determined that the y axis was the axis of greatest movement for all participants. Next, each participants' data (along the y axis) for each trial was analyzed using FFT, and peak power and amplitude were pulled for each of the twelve trials performed by each participant (two days of testing, 3 trials before data collection and three trials after data collected on each day). While each individual participant performed the same three motions before and after data collection, the second and third motions were individualized dependant on what they had self-reported in their initial assessment. ET is a very individualized condition in that some individuals are affected by certain grips or movements while others are not, and to varying degrees. For this reason, subsequent analysis focused only on the condition which produced the highest peak power of tremor for each participant. Using a Fast Fourier Transform, the peak power of each movement condition from both pre and post training was derived. For each participant, only one movement condition which produced the highest power in both pre and post-training consistently in both training conditions (enhance/suppress) was analyzed.

4.7 Statistical Analyses

For the EEG data, average theta power, average beta power and the average TBR was analyzed using a two condition (enhance, suppress), by eight training block repeated measures ANOVA. To assess changes from baseline to post test, these same variables were entered into a two Condition (enhance, suppress) x two Block (baseline, post-test) repeated measures ANOVA.

To explore whether the participants with ET have similar levels of theta and beta band activity, previously collected data from a control population without ET (n=11) was also analyzed. Both studies collected 3 minutes of baseline collection using the same EasyCap set-up, in the same laboratory environment. The control data was analyzed using the same script as outlined above producing an average baseline value for theta and beta band power for each non-ET participant. To obtain a single average value for theta and beta band power for the ET participants, only baseline values from their primary exposure to EEG (first day in the lab) were used. The ET and Non- ET data were compared using three independent samples t-tests looking at power in theta, power in beta, and TBR respectively.

Correlations were assessed between EEG and accelerometer data collected at the same time. While the EEG data from accelerometry collection was filtered and trimmed using an exact replica of offline methodology used to analyze NFT data, accelerometry data (peak amplitude) were also analyzed. After performing Fast Fourier Transforms of every trial within all three movement patterns for both baseline and retention in both conditions, peak values for each ET participant were individually visually examined to determine which movement pattern produced the most severe tremor amplitude consistently. Once a movement pattern was chosen for each participant, the peak scores while performing that movement pre and post testing were averaged from the participants first day in the lab. Correlations were then made by contrasting EEG data in the TBR as well as theta and beta frequency bands with accelerometer data of peak amplitude across participants.

V. Results

5.1 Participants

Nine participants were recruited through neurologists and agreed to participate. Participant characteristics are shown in Table 1. One participant was only able to complete one of the two conditions (suppress). As noted previously, data was visually examined first to remove sections with excess noise, and was then analyzed using EEGLab (Matlab) software to reject artifacts based on ICA. Excessive noise due to bouts of coughing in the enhance condition (one day) of testing from one participant could not be recovered using the artifact rejection. This session had to be excluded for this participant. For repeated measures analysis these participants had to be excluded, but for between group and individual data presentation, their data was included.

A control population that did not present with symptoms of ET who had also been naïve to NF protocols and training was used to compare baseline measurements of neural activity over the motor cortex. Descriptive statistics for this asymptomatic control population (n=12) are also reported in Table 1.

Table 1 **Participant Descriptive Statistics.**

Population	n	Age	sex	Length of diagnosis
ET	9	65.11±5.64	3F, 6M	16.06±14.48
Control	12	26.92±11.33	9F, 3M	N/A

Age and length of diagnosis expressed as years ± standard deviation

5.2 Neurofeedback results

Figure 3 shows both average performance of all participants (parts (a) and (b)) as well as a breakdown of individual performance by all participants in both the Enhance (parts c and d) and Suppress (parts e and f) conditions. There were no significant effects of Condition $F(1,6)=0.593, p=0.470$, Block $F(7,42)=.942, p=.485$ or interaction $F(7,42)=1.910, p=.092$ for TBR during the training trials. The same can be said for the transfer from baseline to retention when considering Condition $F(1,6)=.267, p=.642$, Block $F(1,6)=1.728, p=.237$ or interaction $F(1,6)=.000469, p=.983$.

In order to delve deeper into the individual components of these results, TBR was broken down into the original theta (4-8 Hz) and beta (13-20 Hz) frequency bands and offline data was reassessed to examine both frequency bands individually. Within Figure 4, the theta ratio is shown both as an average of all participants across training, and from baseline to retention. It can also be seen broken down into individual data for both enhance and suppress conditions across training and from baseline to retention. No significant effect of Condition, $F(1,6)=.132, p=.729$, Block, $F(1,6)=.819, p=.400$, or interaction $F(1,6)=.559, p=.483$ were shown for theta power from baseline to retention. However, there was a statistically significant effect of block on theta power amongst the training trials, $F(7,42)=2.674, p=.022$, where theta power showed an increase across blocks of the training trials. No effects were shown for condition, $F(1,6)=.131, p=.730$ or interaction $F(7,42)=1.225, p=.311$).

Power within the beta frequency band while training TBR is examined in Figure 5. It can be seen that on average, participants performed similarly with respect to power in the beta frequency range when both trying to enhance or suppress TBR. Looking at

Figure 5, panels c-f, individual results showed a lot of variation, with no effect of condition $F(1,6)=.113, p=.748$, block $F(7,42)=.929, p=.495$, nor interaction $F(7,42)=.735, p=.644$ showing statistical significance in training, nor from baseline to retention trials: condition $F(1,6)=.047, p=.835$, block $F(1,6)=.025, p=.879$, interaction $F(1,6)=.807, p=.404$.

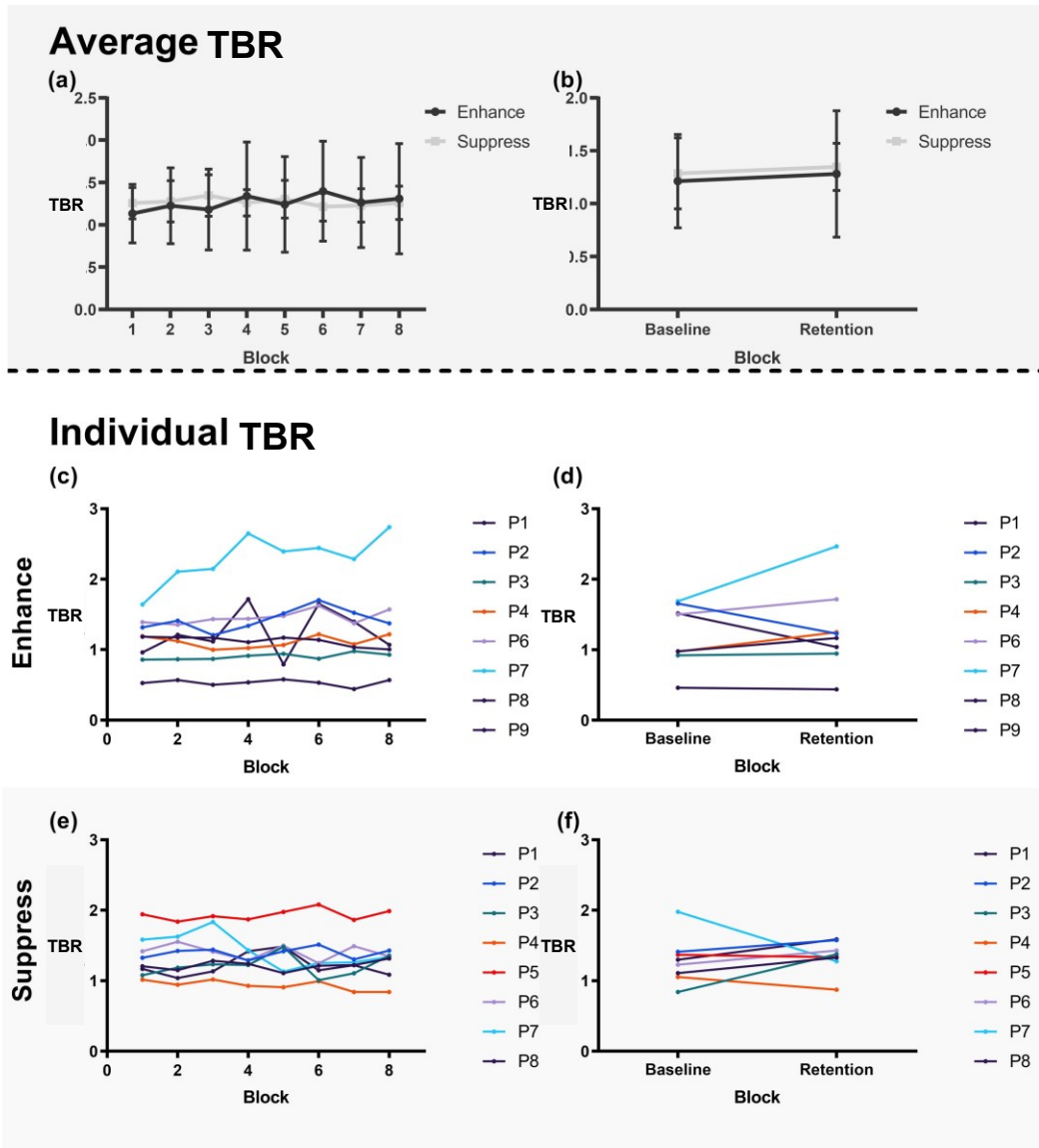


Figure 3. **TBR activity.** Average power from all participants in TBR shown across (a) training blocks, as well as (b) from baseline to retention. Graphs (c) and (d) are showing individual TBR amplitudes of participants during both training blocks as well as retention trials while aiming to enhance TBR. Graphs (e) and (f) look at individual participants while aiming to suppress TBR, across eight training blocks and then from baseline to retention.

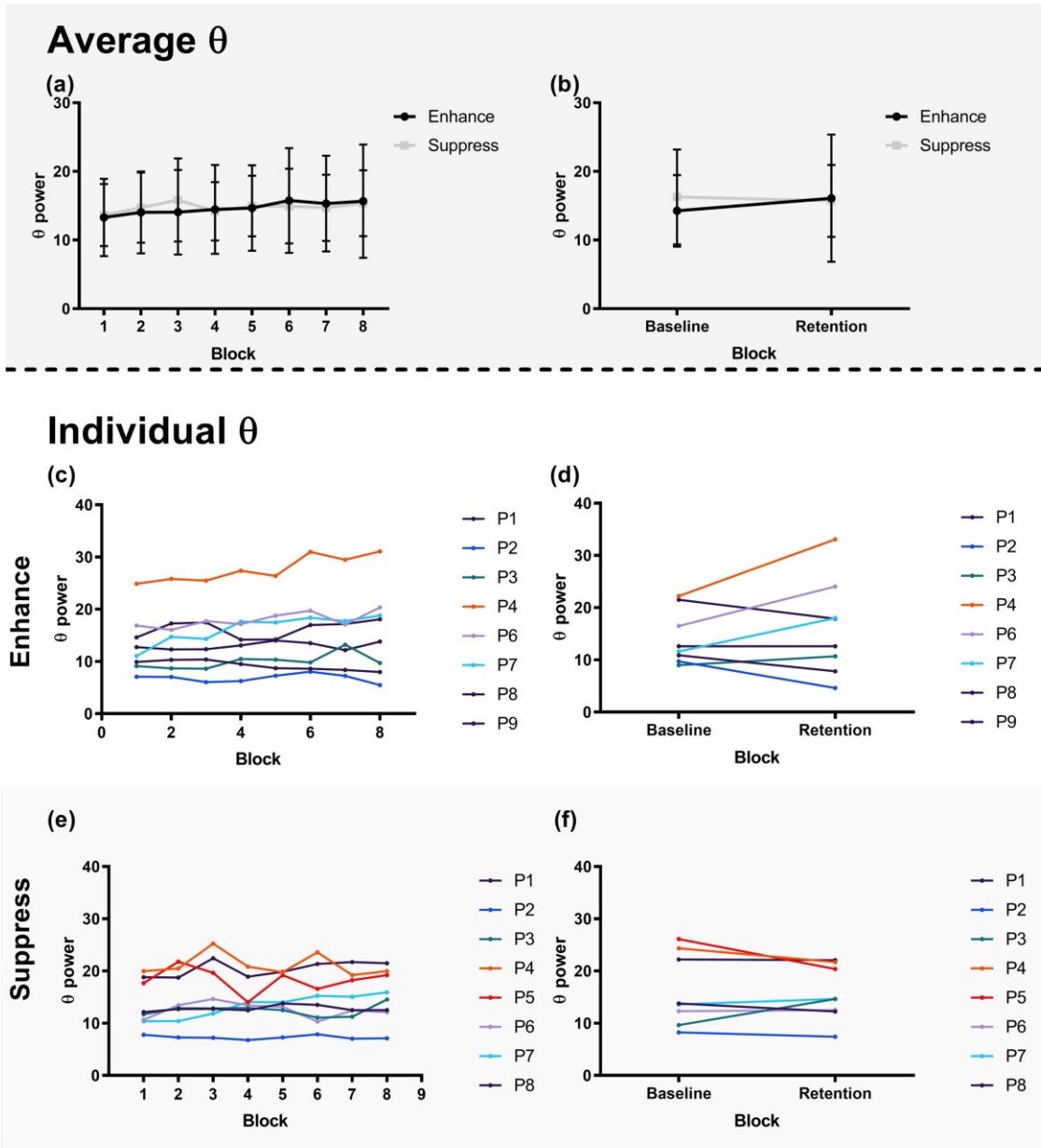


Figure 4. **Theta activity.** Power in the theta frequency band for all participants in both enhance and suppress conditions is shown across training blocks in part (a) as well as from baseline to retention in part (b). Broken down to look at individual data, theta frequency band power is shown in the enhance condition (c) across training blocks, and (d) from baseline to retention trials, as well as suppress condition (e) training blocks, and (f) from baseline to retention.

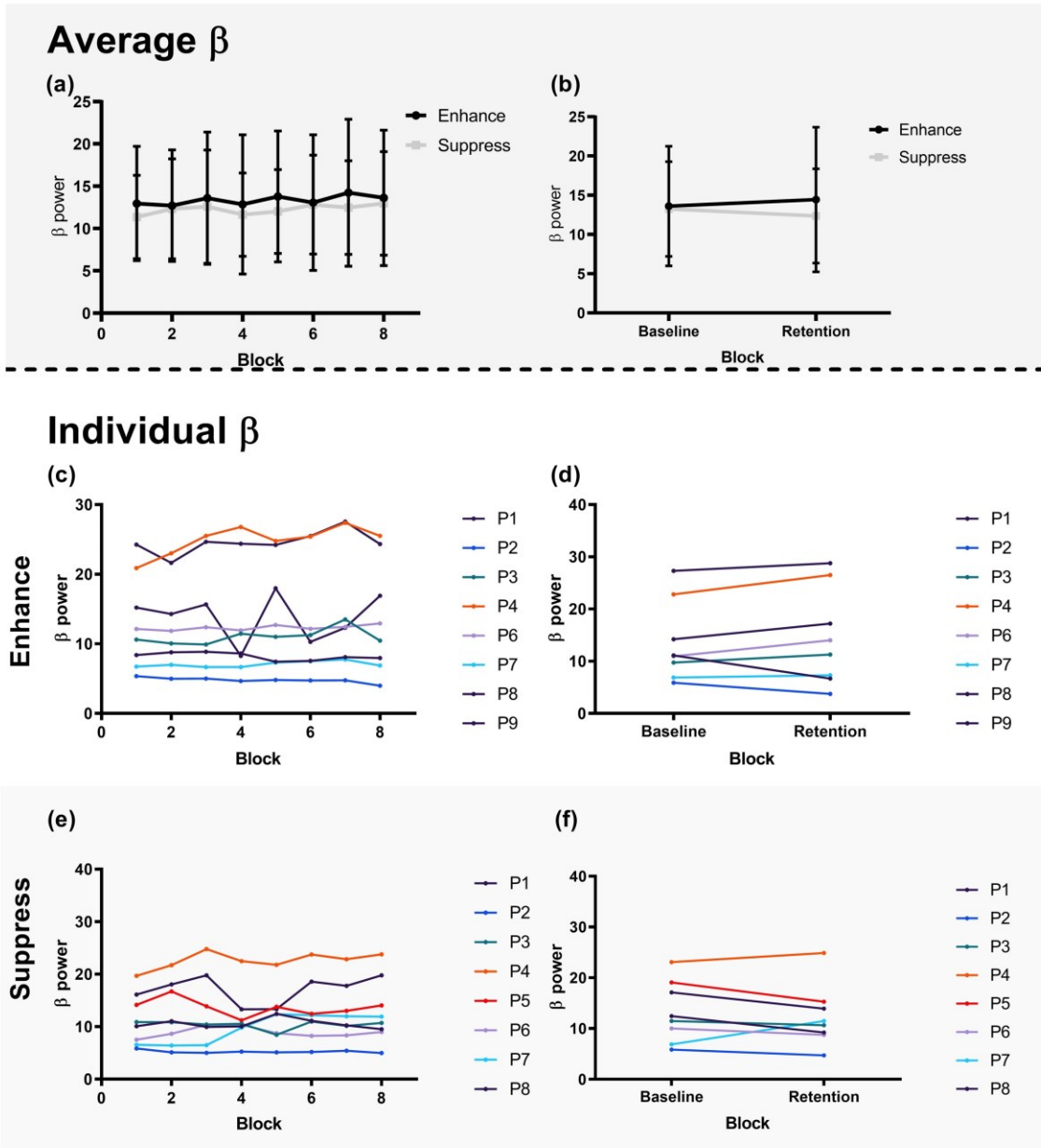


Figure 5. Beta activity. Both (a) and (b) showing average beta power of all participants across training blocks as well as pre and post training. (c) Individual beta band power across training trials while aiming to enhance TBR. (d) Individual beta band power from baseline to retention after training to enhance TBR. While aiming to suppress TBR, (e) showing training blocks while (f) showing both pre and post NFT.

5.3 Accelerometry results

To determine whether tremor severity was linked to electrical neural activity over the motor cortex, a Kendall's tau-b correlation was run to examine the relationship between tremor amplitude (displacement in cm) and TBR, as well as power within the theta and beta frequency bands. Non parametric statistics were used to account for the small sample size and the presence of one outlier (Figure 6). Tremor amplitude showed a significant, positive relationship with both the TBR ($\tau_b=.556, p=.037$), and theta band power ($\tau_b=.611, p=.022$). No significant effect on beta power and amplitude ($\tau_b=.333, p=.211$) was found. These same graphs as shown in Figure 6 can be viewed with the outlier removed in Appendix B.

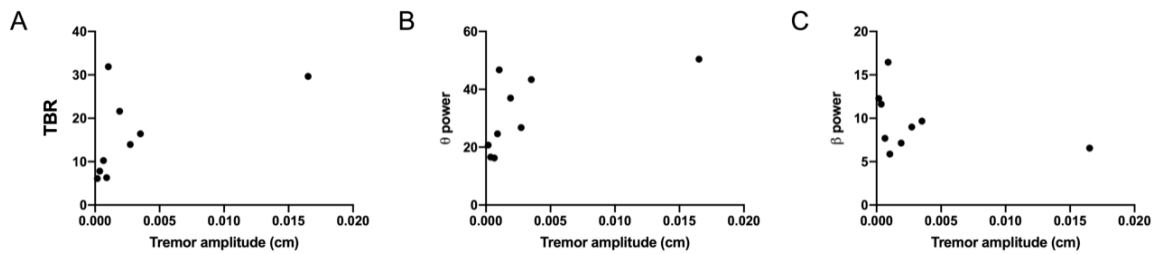


Figure 6. Correlations. (A) Tremor amplitude (cm) correlated with average TBR at the time of the accelerometer recording. (B) Tremor amplitude (cm) correlated to power in the theta frequency band (C) Tremor amplitude (cm) correlated to power in the beta frequency band.

5.4 Baseline EEG In Reference to a Control Population

TBR was significantly higher in the control group compared to the ET group, $t(18)=3.343, p=.004$, with the ET population presenting with lower TBR over motor cortex. While theta power showed no significant effect $t(18)=.301, p=.769$, beta power $t(18)=1.926, p=.069$ approached statistical significance indicating that the larger difference in TBR amplitude between populations was likely driven by differences within the beta frequency band.

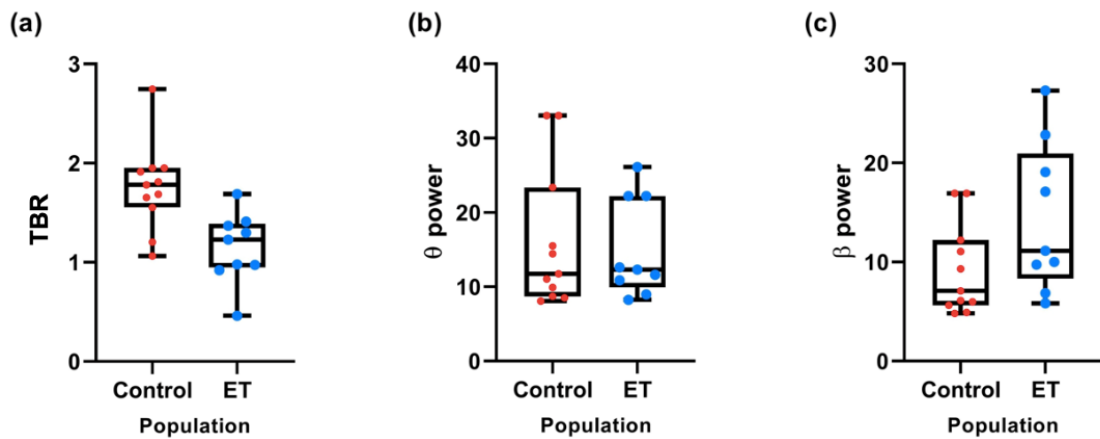


Figure 7. Baseline results compared to a control population. (a) TBR as measured from baseline recordings of the first exposure to NFB in both healthy and ET populations. (b) Theta power measured from offline analysis of baseline. (c) Beta power from both populations.

VI. Discussion

This research project aimed to determine whether auditory NFT could be used in participants with Essential Tremor to manipulate either theta or beta frequency bands over the motor cortex. More specifically, we sought to determine whether participants who had been diagnosed with ET could use a single session of NFT to manipulate cortical activity in two separate sessions: either enhancing, or suppressing the TBR. In addition to this main goal, two secondary goals aimed to characterize our sample of participants with ET. First, accelerometry measures of the tremor were related to simultaneous EEG measurements of TBR, as well as power from the theta and beta frequency bands. Second, baseline activity from participants with ET were also compared with those measured in a control (healthy) population to investigate whether there were differences in EEG activity between the two samples.

Overall, TBR was not affected by a single session of NFT in either enhance or suppress conditions through comparison of the baseline and retention block. TBR also did not change significantly throughout the training trials. Breaking down the TBR into both frequency bands, the beta frequency band also showed no significant change during training in either enhance or suppress or after training when comparing baseline to retention trials. An increase theta frequency band power across training trials in both conditions was observed. Given that this increase occurred in both conditions during training, it is likely a reflection of the participants becoming more tired, irresponsive to the tones, or less aroused in general. No significant effect was found during the transfer from baseline to retention trials, suggesting that a single session of auditory NFT is not sufficient to manipulate theta band power production in a specific direction.

When comparing baseline EEG TBR production between cohorts, participants diagnosed with ET had significantly lower TBR over motor cortex compared to a control population. Looking at theta and beta frequency bands individually, theta power was not significantly different between groups, however beta frequency band power approached a significant difference. Because TBR is a ratio of both theta and beta frequency band production, the large difference in TBR is likely driven by the smaller scale difference in beta frequency band production. This suggests that individuals with ET could potentially have a higher amplitude of resting beta frequency band production than those without.

When examining correlations made between accelerometer recordings of tremor amplitude with EEG recordings of TBR and theta and beta frequency band power individually over motor cortex, tremor amplitude seems to be positively linked with production of theta frequency band power and consequently TBR. Due to the small sample size, these findings require further research using a larger cohort before any inferences can be made.

6.1 Summary of current results in line with past literature

While results did show slight differences in activity within the theta frequency band from trial to trial while training, most aspects of neural activity within the TBR or theta/beta bands respectively were not affected by one session of training in either direction. This is consistent with current literature which estimates that eight sessions of NFT are sufficient to develop an ability to selectively control power production in a given frequency band (Azarpaikan et al., 2014; Vernon et al., 2003). Many NF research studies have chosen to use more than eight training sessions. For example, one study examining

theta absolute power in reference to cognitive decline in an elderly population chose to use 30, 30-minute sessions of training over a period of twelve weeks (Becerra et al., 2012). Another chose to use 9 double sessions of 50 minute training with children diagnosed with ADHD to target TBR and SCP (Gevensleben et al., 2009).

It was important for the purposes of this study that both enhance and suppress conditions were tested as a means to determine whether auditory NF in either direction could be utilised by individuals with ET. One session of each condition was determined to be appropriate as this study sought to determine whether auditory NF was an appropriate tool for the given population, rather than trying to instill a lasting capability to manipulate the signal in a particular direction, as more research is needed to determine which direction of training should be chosen.

A current limitation of NF research that could have impacted the results of the current study is the phenomenon of NF inefficacy, or non-performers to NF. As outlined in a review of the topic by Alkoby, Abu-Rmileh, Shriki, & Todder, (2017), it is difficult to quantify the inefficacy problem as most NF studies vary in terms of methodology (e.g. length and number of training sessions, or frequency band(s) targeted). A large proportion of NF research also typically fails to report a number of non-performers, and tends to only report on group differences, leaving out the individual variation within the NF group of interest. This makes it difficult even to speculate whether or not non-performers exist within the reported sample. One study in particular by Studer et al., (2014), assigned participants to one of three groups, TBR, SCP, or control (no NFT) and had NF subjects complete 20 50min sessions of NFT. Researchers were able to break participant groups down further into two categories: poor performers (whose scores

drifted in an alternate or nullified direction from that which was intended) and good performers (who were able to self-regulate power in the trained frequency band in the desired direction by the last four sessions of training). The groups were statistically different from each other, however this study failed to mention the exact proportion of good to poor performers within their sample.

In the context of this research, NF inefficacy would be hard to determine after just one session of NFT in either direction. Looking at the data represented in parts d and f of Figure 3 which represents changes in TBR in both Enhance and Suppress conditions, a lot of individual variation is evident. One participant in particular (Participant 7) can be noted to increase TBR from baseline to retention in the Enhance condition, and then decrease TBR from baseline to retention during the Suppress condition, akin to a “good” performer in the aforementioned studies which would classify participants. In contrast, Participant 2 can be noted going in the opposite direction from what was desired in both conditions. A wide range of performance scores is evident in this small sample, and it would be difficult to determine a cut-off for “good” or “poor” performance based on this study alone. Future research using a larger cohort and more testing sessions might be able to clearly view the effects of NF inefficacy.

A significant positive correlation was found between TBR and tremor amplitude, as well as theta frequency band power and tremor amplitude. This is to say that individuals with higher theta and consequently higher TBR seemed to present with a higher tremor amplitude, or a more severe tremor. It is important to note that EEG activity was captured over the entire C3, Cz, C4 range over the motor cortex. An argument could be made that only cortical electrical activity contralateral to the most

affected (measured) limb should have been examined. However, with one of the main components of an ET diagnosis being a symmetrical postural or kinetic tremor, activity over the entire motor cortex was included. It is also important to note that given the neurophysiological assumptions made regarding the network of areas promoting the tremor, that the timing of when the EEG/accelerometer recordings are being taken should be considered. According to Raethjen and colleagues (2007) the motor cortex might not be as effective as targeting other areas within this tremor generating network at suppressing tremor after the tremor is ongoing. This also puts into question whether or not a biofeedback component or EMG related measure of feedback would be a suitable addition to testing protocols in the future as the timing of corticomuscular synchronizations could be further examined.

There are many factors such as disease duration, age, or medication state that could account for the link between tremor severity and peak in TBR. A larger sample size will be required to explore what factors underlie the relationship between tremor and theta power and also better model the relationship. There does appear to be some variability in the relationship as within the small sample size of the current study, there was one outlying individual who had a high tremor amplitude. Non-parametric correlations were used to account for this outlier. With the outlier removed, a significant linear relationship between tremor amplitude and theta power can be better viewed when the outlier is removed as shown in Appendix A. Overall, future work with a larger sample and a broader range of tremor severity can better characterize this relationship.

Compared to a control sample without ET, the sample of individuals with ET seem to have a wider range of power produced in the beta frequency band, as well as a

higher average beta frequency band power as shown in Figure 7. This difference between populations was reflected even more when viewed as TBR. As evidenced in past research carried out on other clinical populations, EEG has the most success when a neurological signature is known and can be addressed. For example, in individuals with ADHD, EEG research has reported higher TBR than that of a control population many times (Angelidis et al., 2018). In line with these findings, when TBR is decreased in individuals with ADHD, due to prescribed psychostimulants or EEG, individuals indicate an increased capacity for attentiveness and cognitive control (Angelidis et al., 2018; Doppelmayr & Weber, 2011; Farkas et al., 2015). Thus, while acknowledging the small sample size of both cohorts, further investigation into baseline levels within the TBR and beta frequency band specifically in ET contrasted to a healthy, asymptomatic population may be warranted.

As TBR is a ratio, it provides information from two separate frequency bands in a singular format which can then be fed back to participants. While the main benefit of using TBR over choosing to focus on a singular frequency band is its ability to capture more data, the sensitivity of TBR could be an important concept for NFT within patient populations. When looking at Figure 7 in particular, it becomes evident that because theta and beta frequency bands typically operate in opposition of each other, TBR is able to highlight smaller scale differences in populations, when looking at either frequency band on its own was uneventful.

This study was able to break down TBR into its respective frequency bands and subsequently looked at changes in the theta and beta frequency bands independently as well. Theta frequency band power in the ET population showed a positive correlation

with tremor severity (amplitude), suggesting that lower theta frequency band power may coincide with a less severe tremor. Beta frequency band power, however, was elevated in individuals with ET when compared to an asymptomatic population. An interesting speculation would be that in terms of this study, we were asking participants to either lower theta and increase beta, or vice versa, where this very preliminary data may suggest that in order to mimic a healthy population, ET participants would need to lower power in both frequency bands.

6.2 Neurofeedback as an intervention for Essential Tremor

Although many speculations for the cause of tremor in Essential Tremor exist, a network of locations within the brain have been linked with tremor onset: primary motor cortex, brainstem, cerebellum, and thalamus. It can be speculated based on past research, that in order to disrupt the oscillating network thought to instigate tremor, a section or component would need to be affected. The present study looked solely at neural activity in TBR over the motor cortex, specifically C3,Cz, C4, as targeting the motor cortex with NF had been done with a healthy control population (n=12) using the same equipment and lab setting. Documented cases of damage to parts of this network, including motor cortex have facilitated tremor suppression/reduction, some with lasting effects (Dupuis et al., 2010). As outlined by Lorenz & Deuschl (2007), DBS and thalamotomy have been proven effective for use in ET in many large studies, however the risk that comes with these procedures is high. The current study has shown preliminary evidence of an increase in beta frequency band power over the motor cortex in participants with ET compared to an asymptomatic population. Targeting an area of the brain with NF,

although not as severe a means as brain surgery, has the potential to alter neuronal activity which could potentially cease to produce the right conditions for the network causing tremor to continue.

As shown in Figure 6, theta frequency band power over the motor cortex correlated positively with tremor amplitude in the present study. In 2013, research was conducted to eliminate the small action tremor in healthy individuals using repetitive transcranial magnetic stimulation. Instead what researchers showed was an increase in tremor amplitude of about 120% in 26 healthy controls. Although it wasn't what they had intended to report, the authors realized that stimulating the motor cortex as such could produce an action tremor, which was still an interesting finding (Rogasch & Todd, 2013). Taken together, this information could show support for the notion that reducing theta frequency band power and stimulation of the motor cortex could result in reduced tremor amplitude.

6.3 Limitations

As mentioned previously, the largest limitations of this work was the small sample size. The small sample size was related to the challenges of recruiting a clinical population. To ensure that the study only included those with ET, and not people with other disorders, participants had to have been previously diagnosed by a neurologist, receive study information during an appointment with said neurologist, and choose to contact researchers before receiving an appointment time for testing. As the population was limited to individuals who had been diagnosed with Essential Tremor and referred

from a registered neurologist this limited the number of people contacted likely resulting in a small sample size.

The single session of NFT in either condition was also a limitation of this study as it made discerning whether or not a lasting improvement or ability to self-control TBR very unlikely. As stated previously, past research has indicated a need for upwards of eight NFT sessions in order to observe noticeable effects. For the present study, it was important to be able to test the clinical population with both enhancing and suppressing TBR, and to do so in a time-efficient manner. It was also important for this study, as some members of the clinical population live out of town, that participants be able to complete all testing in a single day, which would not have been possible with multiple sessions of NFT.

Even with only one session of testing, theta frequency band power seemed to increase across training trials regardless of whether participants were aiming to enhance or suppress TBR. One possible explanation for this is that participants were instructed to use different techniques during the training trials, and it is possible that by chance they used a similar battery of techniques on both days of testing. The more likely scenario is that within the eight blocks of training, while hearing the melodic tones of the auditory NF, participants become less aroused, more calm and/or more tired, and subsequently increase theta frequency band production. It is possible that the longer break between the training trials and subsequent retention trial would be enough to disrupt this calming effect of training, which would explain why the increase in theta was not seen when comparing baseline to retention trials.

Lastly, the age difference between the clinical and control populations was quite large, meaning that the differences in neural activity between groups could be a factor of age, and have nothing to do with a diagnosis of ET. In one study examining age-related differences in beta activity over the motor cortex, it was noted that older adults presented with event-related synchronization of beta while ankle proprioception was assessed whereas younger adults did not (Toledo, Barela, Manzano, & Kohn, 2016). It was speculated by authors that older adults might possess less effective pathways within the brain, which would call for higher levels of processing to achieve the same results or outcomes as younger adults. If this were the case, this could explain why the ET population of the current study presented with higher levels of beta, however might not explain the similar levels of theta frequency band power.

6.4 Methodological Strengths

The participants recruited for this study were all previously deemed to have ET by neurologists which made it more likely that the participants had ET and not another tremor disorder. Accessibility to the research facility was also made as unrestricted as possible, and the lab facilities included a washroom with a hand-held shower where participants could wash their hair before leaving, making the transition to the rest of their day as fluid as possible.

In line with past research indicating a strong need for consistent and well-defined methodology, the current study was able to keep measures such as volume of feedback, length of trials, time of day of testing, etc. consistent both between participants and on subsequent visits to the lab for each participant. Using an open-access model of data

collection equipment also allowed for the unveiling of more detailed information with respect to signal collection and analysis (available to view in Appendix F), which goes unreported in similar studies which use proprietary equipment and software. The research space was kept as quiet as possible at all times, and when NF collection was ongoing, the room was dark and participants' eyes were closed, negating the large muscle movements associated with blinking which are often misconstrued as theta frequency band activity.

During each training session, a moving window of real-time feedback was used to update the participants' progress in terms of TBR produced over the motor cortex. This was a novel phenomenon to the research team and required a custom data collection script, but was a vast improvement over previous versions of collection software where feedback tones were playing simultaneously which could cause discomfort for participants. When the aim of enhancing TBR is to remain calm and meditative, the quality of sound played as feedback could be a large determinant of success.

The custom data collection script also allowed researchers to use thresholds for each trial that were based on the participants own same-day baseline values. In line with the review of current NFT practices made by D. J. Vernon (2005), collecting a new baseline value for each day of testing is important regardless of a similar time of day of testing, as individual factors such as stress, anxiety, and sleep could all factor in to neural activity being produced during testing. The thresholds for each participant were also able to be updated after every completed trial to reflect the most up-to-date neural activity and also to encourage improvement from one trial to the next. Furthermore, individualized thresholds controlled for difference between participants as evidenced in the individual variation in TBR, theta and beta band power in Figures 3-5. If the same threshold had

been used across all participants the NFT would have been very difficult or very easy for different participants.

6.5 Conclusion

In summary, this research study was able to use auditory tones to provide individuals with ET with real-time NF of TBR over the motor cortex. There was no evidence found to support the idea that individuals with ET could use auditory NFT to enhance or suppress the TBR after one session. However, when compared to a control population asymptomatic of ET, baseline recordings of TBR from participants with ET were larger than the control group and showed larger variability between participants. Looking at the components of TBR, a higher resting beta frequency band power was likely the driving force behind this difference between groups.

Future research is needed to examine a larger population using more training sessions in order to create an ability to manipulate power of a particular frequency band as is typical for the asymptomatic population. Evidence gained from the current study including the positive correlations between theta frequency band power and tremor amplitude and the potential differences in beta band power can provide information for the NFT design of this future work.

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APPENDIX A

Table 1. Sample of recorded techniques.

	Enhance Condition	Suppress Condition
Description of techniques:	<ul style="list-style-type: none"> - Picturing going for a walk - Relaxing - Praying* - Thinking about songs/singing* - Meditating* - Being quiet - Picturing the beach - Counting - Making lists - Feeling loved* 	<ul style="list-style-type: none"> - Getting mad* - Trying to remember past conversations or timelines* - Counting in intervals* - Remembering birthdays - Picturing running* - Seeing different bright colours - Creating math problems and trying to solve them* - Solving day-to-day problems - Remembering arguments*

** Techniques deemed most successful by participants*

APPENDIX B

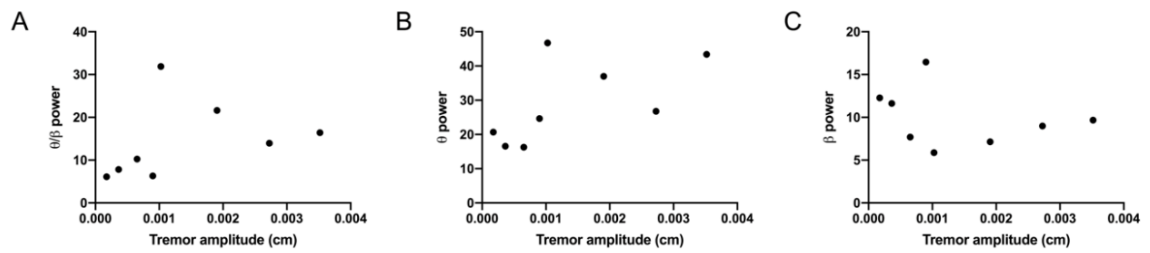


Figure 1. Correlations shown without outlier present. (A) Tremor amplitude correlated with average TBR at the time of the accelerometer recording. (B) Tremor amplitude correlated to power in the theta frequency band (C) Tremor amplitude correlated to power in the beta frequency band.

APPENDIX C



Information Sheet

Developing a neurofeedback based intervention to reduce tremor in Essential Tremor

Introduction

Essential Tremor is the most common movement disorder. It involves shaking of the arms, legs and/or head. You are being asked to consider participating in this study because you have been diagnosed with Essential Tremor by your physician.

What is this study looking at?

- Essential Tremor seems to be linked with activity in multiple areas of the brain
- Neurofeedback is a technique that involves measuring your brain activity. We then display your brain activity back to you so you can use this feedback to change your brain activity.
- We would like to see whether or not patients with essential tremor can use this training to manipulate a particular brain wave known as theta band activity.

If I agree to the study, what do I do?

- 1) Someone from our research team will contact you to set up a time when you are available to come meet with us
- 2) You will come into the lab and we will put an EEG cap on your head which measures the activity inside your brain. EEG is used to measure electrical signals in the brain. We use a gel in order to apply the cap, which is similar to gel used in an ultrasound.
- 3) We will also place an accelerometer (a fancy word for equipment that measures movement) and an electromyography (EMG) electrode (a sticker that measures the activity of your muscles) on your arm that you find most affected by the tremor.
- 4) You will spend some time sitting with your eyes closed and listening to a sound using headphones, which will let you know what your brain waves are doing. To change your brain activity, you will try to make the sound go away. We will give you some tips on how to make this happen.
- 5) When the study is over, we will give you a private space where you can wash your hair if you wish to get rid of the gel that is left over from the recording.

How much time does the study take?

You can choose one of two options:

- 1) Two (2) two (2) hour sessions
- 2) One (1) four (4) hour session, where we give you lots of rest breaks

Will this impact my current care?

This study is strictly voluntary, so should you decide not to participate at any time, your care will not change.

How do I learn more?

To volunteer for this study, please contact us by calling 902-494-3572.

Romeo File No. 1021921 Version 2.0 March 4, 2017

APPENDIX D



STUDY TITLE:	Developing a Neurofeedback-Based Intervention to Reduce Tremor in Essential Tremor
PRINCIPAL INVESTIGATOR:	Dr. Heather F. Neyedli Dalhousie University, Stairs House School of Health and Human Performance 6230 South Street Halifax, N.S. B3H 4R2 Office location: Dalplex, Kinesiology Suite, Rm 215F) (902) 494-6786
STUDY SPONSOR:	Dr. Heather Neyedli
FUNDER:	This study is being funded by the Nova Scotia Health Research Foundation

1. Introduction

You have been invited to take part in a research study. A research study is a way of gathering information on a treatment, procedure or medical device or to answer a question about something that is not well understood. Taking part in this study is voluntary. It is up to you to decide whether to be in the study or not. Before you decide, you need to understand what the study is for, what risks you might take and what benefits you might receive. The research team will tell you if there are any study timelines for making your decision. This consent form explains the study.

Please ask the research team to clarify anything you do not understand or would like to know more about. Make sure all your questions are answered to your satisfaction before deciding whether to participate in this research study.

The researchers will:

- Discuss the study with you
- Answer your questions
- Be available during the study to deal with problems and answer questions

Essential Tremor is the most common movement disorder, typically occurring in older adults. Individuals with Essential Tremor often suffer shaking in their upper limbs which can make it difficult to eat, drink, and perform many daily tasks. You are being asked to consider participating in this study because you have been diagnosed with Essential Tremor by your physician.

If you decide not to take part or if you leave the study early, your usual health care will not be affected.

2. Why Is This Study Being Conducted?

Essential Tremor seems to be caused by a number of brain areas that are activated in a kind of rhythm with each other. It appears these brain areas 'feed off' each other, with activity in one area making things worse in other areas. Current drug treatments for Essential Tremor have unwelcome side effects. Neurofeedback may be another way to treat essential tremor. Neurofeedback involves us measuring your brain activity then displaying your brain activity back to you. We then ask you to use this feedback to change the activity. In this study we would like to see whether patients with Essential Tremor can produce more or less of a specific brain wave that has been linked with Essential Tremor (called theta band activity), through neurofeedback training. If participants are capable of altering the amount of theta band activity produced, we could begin to study whether theta band activity has an effect on the severity of the tremor.

3. How Long Will I Be In The Study?

The length of this study for participants is either a one (1) time four (4) hour session, or two (2) two hour sessions. Data collection for all participants for the entire study is expected to take about 2 years to complete and the results should be known in 2 years.

4. How Many People Will Take Part In This Study?

It is anticipated that about 40 people will participate in this study at Dalhousie University.

5. How Is The Study Being Done?

This study will take place in the Cognitive and Motor Performance Laboratory in the Kinesiology Suite of Dalplex (Dalhousie University). Should you decide to participate, you will be coached through neurofeedback training in two condition. These neurofeedback training sessions are included in the estimated time to complete the study. If you are coming to us locally (from the Halifax Regional Municipality), you will complete the study over two (2) days, spending two (2) hours at Dalplex for each visit. If you are coming from outside the HRM, or if you are otherwise unable to complete the study in two visits, you may choose to complete the study in one (1) four (4) hour visit. You will be asked to indicate your preference to a member of our research team when you contact us initially regarding your interest in this study.

6. What Will Happen If I Take Part In This Study?

You have just been given the information sheet provided by our research team. If you agree to take part in this study, you will be asked to determine a suitable time to come in to the laboratory at Dalplex. You will not need to wear anything specific, comfortable clothes are fine though we ask, if possible, for you not to wear any hair product such as hair spray or gel.

Upon entering Dalplex, our research team will explain these steps to you again, answer any remaining questions you may have, and begin to fit the wireless electroencephalogram (EEG) cap on your head. This process is quick and painless, just like putting on a ball cap, and requires the use of electro-conductive gel. This gel is the same as that which is used to perform ultrasounds. We will provide an area with supplies (shampoo, towels, etc.) for you to wash the gel out

of your hair after the visit is completed. Once the cap has been fitted on your head, you will be fitted with an accelerometer (a small band around the arm that is most affected by tremor, that will allow us to measure the amount your arm tremors during the exercise), and we will fit an electromyography (EMG) electrode on the muscle of that limb (a sticky patch, much like a sticker, that will tell us how much your muscle is activating during the study). You will then take a seat in a dark room with a member of our research team, who will explain the training exercises to you and give you a set of over the ear headphones. You will complete neurofeedback training exercises on both visits. Should you choose to do all testing in one day, you will be given a 30 minute rest period, before starting the second neurofeedback training session. You will be asked to try to alter your thought patterns, and will listen to noises in the headphones that will tell you when you are successful.

After the neurofeedback training trials are completed, we will record several trials using the wireless EEG cap but there will be no sounds from the headphones.

If you choose not to complete the study at any time during the course of your visit, the session will be discontinued, and you may leave the facility.

7. Are There Risks to The Study?

The biggest risk of this study will be fatigue (tiredness). If you choose to complete the study in one day, you will likely be sitting upright, wearing the EEG cap for 4 hours. We will be able to provide breaks to alleviate some of this fatigue, and will provide lots of space for caregivers to assist should you need them. Our research team will also be able to assist you when needed. As the gel used to make the EEG equipment work will be on your scalp, facilities and products will be readily available for you to wash your hair. If your tremor is one that makes it uneasy for you to wash your hair yourself, a member of the research team will assist you using a hand-held shower head.

There may be side effects that the researchers do not expect or do not know about and that may be serious. Tell your study doctor immediately about any new or unusual symptoms.

8. Are There Benefits of Participating in This Study?

We cannot guarantee or promise that you will receive any benefits from this research. However, your participation may or may not help other people with Essential Tremor in the future.

9. What Happens at the End of the Study?

It is anticipated that the results of this study will be published and or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your express permission.

10. What Are My Responsibilities?

As a study participant you will be expected to:

- Follow the directions of the research team;
- Report all medications being taken or that you plan on taking;
- Report any changes in your health to the research team;
- Report any problems that you experience that you think might be related to participating in the study;

11. Can My Participation in this Study End Early?

Yes. If you chose to participate and later change your mind, you can say no and stop the research at any time. If you wish to withdraw your consent, please inform the research team. If you choose to withdraw from this study, your decision will have no effect on your current or future medical treatment and healthcare. Should you decide to leave the study early, any data previously collected will either be kept for analysis (if there are enough completed trials), or destroyed. Your name will only be linked to your data through a randomly chosen number, and this master list will be kept in the Principal Investigator's (Heather Neyedli's) locked office. Published data will not be linkable to you personally.

Also, the Nova Scotia Health Research Foundation, the Nova Scotia Health Authority Research Ethics Board and the principal investigator have the right to stop patient recruitment or cancel the study at any time.

Lastly, the principal investigator may decide to remove you from this study without your consent for any of the following reasons:

- You do not follow the directions of the research team;
- There is new information that shows that being in this study is not in your best interests;

If you are withdrawn from this study, a member of the research team will discuss the reasons with you and plans will be made for your continued care outside of the study.

If you withdraw your consent, the information about you that was/were collected before you left the study will still be used. No new information about you will be collected without your permission.

12. What About New Information?

You will be told about any other new information that might affect your health, welfare, or willingness to stay in the study and will be asked whether you wish to continue taking part in the study or not.

13. Will It Cost Me Anything?

Compensation

Participation in this study may or may not involve any additional costs to you. You will be reimbursed for some study related expenses such as bus fare, and parking. Please bring your receipts with you. You will receive a small honorarium of \$10/hour to thank you for your time commitment to this study.

Research Related Injury

If you become ill or injured as a direct result of participating in this study, necessary medical treatment will be available at no additional cost to you. Your signature on this form only indicates that you have understood to your satisfaction the information regarding your participation in the study and agree to participate as a subject. In no way does this waive your legal rights nor release the principal investigator, the research staff, the study sponsor or involved institutions from their legal and professional responsibilities.

14. What About My Privacy and Confidentiality?

Protecting your privacy is an important part of this study. Every effort to protect your privacy will be made. If the results of this study are presented to the public, nobody will be able to tell that you were in the study.

However, complete privacy cannot be guaranteed. For example, the principal investigator may be required by law to allow access to research records.

If you decide to participate in this study, the research team will ask you for the following information:

- Age
- Handedness
- Affected Limb
- Length of diagnosis (year of diagnosis, or # of months)

Access to Records

Other people may need to look at your personal information to check that the information collected for the study is correct and to make sure the study followed the required laws and guidelines. These people might include:

- The Nova Scotia Health Authority Research Ethics Board (NSHA REB) and people working for or with the NSHA REB because they oversee the ethical conduct of research studies within the Nova Scotia Health Authority.

Use of Your Study Information

Any study data about you that is sent outside of the Nova Scotia Health Authority will have a code and will not contain your name or address, or any information that directly identifies you.

De-identified study data may be transferred to:

- Nova Scotia Health Research Foundation

Study data that is sent outside of the Nova Scotia Health Authority will be used for the research purposes explained in this consent form.

The research team and the other people listed above will keep the information they see or receive about you confidential, to the extent permitted by applicable laws. Even though the risk of identifying you from the study data is very small, it can never be completely eliminated.

The research team will keep any personal information about you in a secure and confidential location for 7 years and then destroy it according to NSHA policy. Your personal information will not be shared with others without your permission.

After your part in the study ends, we may continue to review your health records for safety and data accuracy until the study is finished or you withdraw your consent.

You have the right to be informed of the results of this study once the entire study is complete.

The REB and people working for or with the REB may also contact you personally for quality assurance purposes.

Your access to records

You have the right to access, review, and request changes to your study data.

15. Declaration of Financial Interest

The Nova Scotia Health Research Foundation is reimbursing the principal investigator and/or the principal investigator's institution to conduct this study. The amount of payment is sufficient to cover the costs of conducting the study.

16. What About Questions or Problems?

For further information about the study you may call the principal investigator, who is the person in charge of this study

The principal investigator is Heather Neyedli
Telephone: (902) 494-6786

17. What Are My Rights?

This section is standard as per TCPS 2 Article 3.2 (h).

You have the right to all information that could help you make a decision about participating in this study. You also have the right to ask questions about this study and your rights as a research participant, and to have them answered to your satisfaction before you make any decision. You also have the right to ask questions and to receive answers throughout this study.

If you have any questions about your rights as a research participant, contact Patient Relations at (902) 473-2133 toll free (1-855-799-0990) or healthcareexperience@nshealth.ca

In the next part you will be asked if you agree (consent) to join this study. If the answer is “yes”, please sign the form.

18. Consent Form Signature Page

This section is standard as per TCPS 2 Article 3.2, 3.5, 3.9, 3.12 and 4.1. All appropriate elements must be included.

I have reviewed all of the information in this consent form related to the study called:
Developing a Neurofeedback-Based Intervention to Reduce Tremor in Essential Tremor

I have been given the opportunity to discuss this study. All of my questions have been answered to my satisfaction.

This signature on this consent form means that I agree to take part in this study. I understand that I am free to withdraw at any time without affecting my future care.

Signature of Participant _____ ____ / ____ / ____
Name (Printed) Year Month Day*

Signature of Person Conducting
Consent Discussion _____ ____ / ____ / ____
Name (Printed) Year Month Day*

Signature of Investigator _____ ____ / ____ / ____
Name (Printed) Year Month Day*

**Note: Please fill in the dates personally*

I will be given a signed copy of this consent form.

APPENDIX E



Subject ID Number: _____

Subject Information Form

Developing a neurofeedback based intervention to reduce tremor in Essential Tremor

Sex: _____

Age: _____

Handedness (Circle): Right Left

How long ago was the original Essential Tremor diagnosis made? _____

Circle the areas of the body that are most affected by tremor:

Right Arm

Left Arm

Head/Face

Trunk

Right Leg

Left Leg

APPENDIX F

Table 1. Detailed breakdown of collection scripts.

Script #	Title	Purpose/key features:
1	Baseline EEG	<ul style="list-style-type: none"> - Collect 180 seconds of continuous EEG data from 14 channels of the custom EEG-cap using Matlab and saves data from the entire cap as well as an alternate three-channel version (C3, Cz, C4) to two locations: the workspace of Matlab (for faster use later) and onto the computer for future analysis
2	Collect Accelerometer	<ul style="list-style-type: none"> - Collect 30s of accelerometer data using Matlab, through a custom accelerometer fitting onto the back of the fifth digit. - Simultaneously collect EEG data from 14 electrode sites and save data to computer for future analysis. - Label both collections according to whether they occur pre/post training as well as what movement type is performed
3	Thresholds	<ul style="list-style-type: none"> - Consider data saved from Script #1 - Filter 180 seconds of data into both theta and beta frequency bands, and analyze TBR. - Histogram of TBR, removal of any outliers - Prompt researcher to accept the cut-off for outliers based on the histogram - Sort remaining data, and create 5 thresholds for use in the training trials

Script #	Title	Purpose/key features:
4	Block training	<ul style="list-style-type: none"> - Separate training into 8 blocks. - Record 180 seconds of data using EEG cap - Start filtering 3-second snippets of data (after the first 3 seconds) into TBR - Cut off 1-second ends of snippet to eliminate filtering artifacts - Using previously determined thresholds, determine which tone to play based on condition of training by averaging the 1-second of data remaining - Play tone to participant - Continue recording, filtering, adjusting tone every second, for 180 seconds - Save data using label according to which training block and condition is occurring - Determine new thresholds for next block - Pause script between each block to allow for breaks.
5	Retention	<ul style="list-style-type: none"> - Similar to baseline script, different labels
6	Analysis EEG	<ul style="list-style-type: none"> - Visually inspect data for abnormalities - ICA component rejection using EEGLab - Complete all filtering on raw EEG data again (theta, beta, TBR) to ensure reliability - Compile data (all trials, both training conditions, all participants) into one table

Script #	Title	Purpose/key features:
7	Analysis Accelerometer	<ul style="list-style-type: none"> - Visually inspect data for abnormalities - Fast Fourier Transform to determine peak power in each of the 6 accelerometer collections for each participant. - Also filter and analyze raw EEG data from the same collection time.