The Safety, Tolerability, and Efficacy of Electrical Nerve Stimulation on Physiological Activity and Golf Performance

by

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A Dissertation Presented in Partial Fulfillment
of the Requirements for the Degree
Doctor of Philosophy

Approved April 2020 by the
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May 2020

ABSTRACT

Electrical nerve stimulation is a promising drug-free technology that could treat a variety of ailments and disorders. Methods like Vagus Nerve Stimulation have been used for decades to treat disorders like epilepsy, and research with non-invasive vagus nerve stimulation has shown similar effects as its invasive counterpart. Non-invasive nerve stimulation methods like vagus nerve stimulation could help millions of people treat and manage various disorders.

This study observed the effects of three different non-invasive nerve stimulation paradigms in human participants. The first study analyzed the safety and efficacy of transcutaneous auricular vagal nerve stimulation in healthy humans using a bilateral stimulation protocol with uniquely designed dry-hydrogel electrodes. Results demonstrate bilateral auricular vagal nerve stimulation has significant effects on specific parameters of autonomic activity and is safe and well tolerated. The second study analyzed the effects of non-invasive electrical stimulation of a region on the side of the neck that contains the Great Auricular Nerve and the Auricular Branch of the Vagus Nerve called the tympanomastoid fissure on golf hitting performance in healthy golfers. Results did not show significant effects on hitting performance or physiological activity, but the nerve stimulation had significant effects on reducing state-anxiety and improving the quality of feel of each shot. The third study analyzed the effects of non-invasive nerve stimulation of cervical nerves on the back of the neck on putting performance of yips-affected golfers. Results demonstrated that cervical nerve stimulation had significant effects on improving putting performance but did not have significant effects on physiological activity. Data from these studies show there are potential applications for

non-invasive electrical nerve stimulation for healthy and athletic populations. Future research should also examine the effects of these stimulation methods in clinical populations.

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LIST OF ABBREVIATIONS

ABVN – Auricular Branch of the Vagus Nerve

ADAA – Anxiety and Depression Association of America

ANOVA – Analysis of Variance

BP – Blood Pressure

BVP – Blood Volume Pulse

CBT – Cognitive Behavioral Therapy

CES – Cranial Electrotherapy Stimulation

DBS – Deep Brain Stimulation

DSM-IV – Diagnostic and Statistical Manual for Diagnosing Mental Disorders

EAM – External Acoustic Meatus

EEG – Electroencephalogram

EMG - Electromyogram

FDA – Food and Drug Administration

fMRI – functional Magnetic Resonance Imaging

GABA – Gamma-Aminobutyric Acid

GAD – Generalized Anxiety Disorder

GAN – Great Auricular Nerve

HF – High Frequency of Heart Rate Variability

HR – Heart Rate

HRV – Heart Rate Variability

LC – Locus Coeruleus

LF – Low Frequency of Heart Rate Variability

NTS – Nucleus of the Solitary Tract

OCD – Obsessive Compulsive Disorder

PD – Panic Disorder

PFC – Pre-Frontal Cortex

PTSD – Post-Traumatic Stress Disorder

RMSSD – Root Mean Square of Successive Differences between Normal Heartbeats

RR – Interval between Successive Heartbeats

SDNN – Standard Deviation of Normal Sinus Beats

SN – Solitary Nucleus

SNRI – Selective Norepinephrine Reuptake Inhibitor

SSRI – Selective Serotonin Reuptake Inhibitor

STAI – State-Trait Anxiety Inventory

taVNS – Transcutaneous Auricular Vagus Nerve Stimulation

tcVNS – Transcutaneous Cervical Vagus Nerve Stimulation

tDCS – Transcranial Direct Current Stimulation

TES – Transcutaneous Electrical Stimulation

TMS – Transcranial Magnetic Stimulation

tVNS – Transcutaneous Vagus Nerve Stimulation

VLF – Very Low Frequency of Heart Rate Variability

VNS – Vagus Nerve Stimulation

CHAPTER 1

INTRODUCTION

Anxiety in America

Over 18% of individuals in the United States (US) have an anxiety disorder, making anxiety the most prevalent mental health condition in the US (ADAA, 2018). Anxiety symptoms may not be as visually obvious as symptoms of other disorders such as depression, bipolar disorder, or schizophrenia, but they can be just as disabling. While there are many types of anxiety disorders, the following are most common in the United States.

Generalized Anxiety Disorder (GAD)

GAD is a common mental disorder that typically has an early age of onset, can last for a short amount of time or for a lifetime, and has a high degree of comorbidity with other anxiety and mood disorders. Symptoms of GAD include pervasive anxiety that lasts for at least six months, motor tension, and hyperarousal. Symptoms have significant effects on daily life including sleep problems, headaches, jitters, nausea, tense muscles, and trembling or hot flashes. Patients diagnosed with GAD also may show signs of fatigue or difficulty concentrating at work. In order to be diagnosed with GAD, the DSM-IV (Diagnostic and Statistical Manual for diagnosing Mental Disorders) requires presence of three symptoms out of a list of six to be present for a duration of at least six months and must cause clinically significant distress or functional impairment (Martin, 2003). The symptoms include motor tension, autonomic hyperactivity, vigilance and scanning, apprehensive expectation, and others.

It is estimated between 9-15 million people in the US over the age of 18 years suffer from symptoms of GAD. However, roughly only 3.2 million people would meet the criteria as having diagnosable GAD, with women being twice as likely to be diagnosed than men (Mayo Clinic, 2017). GAD is typically treated with medication and/or Cognitive Behavioral Therapy (CBT). Most common medications for GAD include selective serotonin reuptake inhibitors (SSRI's) and benzodiazepines.

Panic Disorder (PD)

Panic Disorder is an anxiety disorder characterized by frequent and unexpected panic attacks. Panic attacks are abrupt episodes of intense fear or discomfort that peak within 10 minutes and include feelings of unreality, detachment from self, and intense fear of losing control, choking, going crazy, feelings of having a heart attack or even dying (Martin, 2003). It is generally unknown what causes PD, but it often develops after an intense or traumatic experience. Those with panic disorder often worry about the consequences of a prior attack or having another attack in the near future. In order to be diagnosed with PD, the DSM-IV requires patients to have recurrent unexpected panic attacks and persistent concern about having further attacks, worry about the implications of the attacks, or a significant change in behavior due to the attacks (Martin, 2003).

Approximately 2.4 million people in the US have panic disorder, with women being twice as likely to be diagnosed as men (ADAA, 2018). The most common treatments for PD are psychotherapy like CBT, and medications like SSRI's, selective norepinephrine reuptake inhibitors (SNRI's), and benzodiazepines.

Post-Traumatic Stress Disorder (PTSD)

PTSD is an anxiety disorder that develops in response to a terrifying or traumatic event. Symptoms include flashbacks, nightmares and severe anxiety, as well as uncontrollable thoughts about the event. Patients often change the way they live in order to avoid stimuli associated with the traumatic event, which severely affects their ability to function normally in society. In order to be diagnosed with PTSD, symptoms must persist for at least 1 month and patients must demonstrate clinically significant distress and functional impairment (Martin, 2003).

Approximately 7.7 million adults in the US have PTSD, and women are more likely to be diagnosed than men. Roughly 10-20% of all military veterans will develop PTSD, but the disorder is not only associated with combat exposure. Rape and sexual abuse are the most common reasons for developing PTSD. Psychotherapy is the most common treatment for PTSD, and includes CBT, exposure therapy, and mindfulness techniques. Medications are typically limited to SSRI's and SNRI's but may include benzodiazepines for patients unresponsive to SSRI's (Mayo Clinic, 2017).

Obsessive Compulsive Disorder (OCD)

OCD is an anxiety disorder characterized by intrusive and recurrent thoughts, impulses and images that cause distress and impairment, and performance of ritualized behaviors to relieve anxiety obsessions that usually take up at least 1 hour of a patient's day. The DSM-IV defines obsessions as recurrent thoughts, images, or impulses that are intrusive and inappropriate, and compulsions as repetitive behaviors like constant handwashing or mental acts like repeating words or counting. To be diagnosed with

OCD, patients must demonstrate that symptoms significantly impair quality of life, and that the patient sees the symptoms as unreasonable (Martin, 2003).

OCD affects roughly 2.2 million adults in the US and is equally common among men and women. The most common treatments include CBT and exposure therapy, and medications are typically limited to antidepressants like SSRI's (Mayo Clinic, 2017).

Anxiety in the Brain

The development of functional magnetic resonance imaging (fMRI) and other imaging techniques has radically contributed to the expansion of our understanding of what brain structures and chemicals are involved in anxiety disorders. The amygdala is known to play a role in processing explicit sensory stimuli and emotional responses to stimuli associated with fear (Charney, 2003), and has been shown to have increased blood flow when a patient experiences a panic attack (Benkelfat et al., 1995). The pre-frontal cortex (PFC) is also known to play a role in modulating anxiety and other emotional behaviors. PFC structures are thought to participate in interpreting higher-order significance of experiential stimuli and modifying behavioral responses related to the stimuli (Charney, 2003). The PFC shares extensive reciprocal projections with the amygdala, through which it can modulate amygdala-mediated responses to emotional stimuli (Garcia et al., 1999).

While various regions in the brain have been implicated in various anxiety disorders, neurotransmitters also play a highly influential role in modulating anxiety. Knowledge of which neurotransmitters and chemicals are involved with anxiety disorders has led researchers to develop a variety of medications to treat symptoms.

Serotonin

Serotonin is a neurotransmitter whose production originates in the raphe nuclei and whose pathways project widely throughout the forebrain (Kocsis et al., 2006). Serotonin plays a fundamental role in regulating brain states like anxiety, and an increased serotonergic tone has been correlated with a reduction in anxiety (Heninger & Charney, 1988). While the mechanism underlying the anxiolytic effects of serotonin are unknown, it is recognized that medications that inhibit the reuptake of serotonin results in a reduction in anxiety symptoms.

Dopamine

Dopamine is the brain's natural "feel good" chemical and is produced in the midbrain in the ventral tegmental area and the substantia nigra. It's pathways project to the cortex, striatum, and limbic nuclei. There are many ways in which dopamine affects anxiety symptoms. Increases in dopaminergic signaling appear to mediate feelings of self-efficacy and confidence and lead to reduced anxiety. However, dopamine is upregulated with norepinephrine in anxiety states, and while medications that increase dopamine help some patients reduce anxiety, they also make the symptoms worse for others (Zarrindast & Khakpai, 2015).

Norepinephrine

Norepinephrine is a chemical associated with sympathetic activity, and neurons that produce the chemical originate primarily in the locus coeruleus in the pons and project widely throughout the central nervous system (Charney, 2003; Goddard et al., 2009). Symptoms of anxiety such as elevated heart rate, blood pressure, and muscle tension are mediated by norepinephrine, and antagonists of norepinephrine receptors

are used to combat specific symptoms of anxiety. Propranolol is a popular drug called a beta-blocker that blocks the beta2-norepinephrine receptor, and is used to reduce heart rate, hand tremors, and quivering voice associated with fear of public speaking. However, this type of drug is only effective at reducing the physical symptoms of anxiety and does not affect the cognitive or emotional aspects of anxiety.

GABA

Gamma-aminobutyric Acid is the brain's main inhibitory neurotransmitter. Increases in GABA and GABA-receptor activity almost always result in anxiolytic effects. Alcohol and drugs like benzodiazepines mediate GABA-receptor activity and promote the open configuration of chloride channels, which decreases the likelihood of action potentials occurring. While the modulating of GABA-ergic pathways can immediately reduce symptoms of anxiety, compensatory mechanisms associated with these circuits, especially from the use of benzodiazepines, can result in tolerance, withdrawal symptoms, and addiction (Mohler, 2011; Ravindran & Stein, 2010). Drugs that increase GABA-ergic activity are typically used as a last resort.

Current Methods to Treat Anxiety Disorders

A patient's primary care provider is usually the main assessor and treatment provider for all patients with anxiety disorders (Stein et al., 2004). The patient's primary care provider is not responsible for treating the anxiety disorder, but rather is responsible for assessing a diagnosis and writing a prescription for treatment of the disorder. Drugs are almost always the first line of defense for treating anxiety disorders. If a patient has a history of unresponsiveness to a given drug, or due to contraindications a patient cannot take a drug, psychotherapy is typically prescribed next. However, forms

of psychotherapy such as Cognitive Behavioral Therapy are almost always prescribed alongside a medication regimen as well.

Pharmacology

Selective Serotonin Reuptake Inhibitors (SSRIs) are most commonly prescribed as antidepressants, but are considered the first line of therapy for anxiety disorders (Mayo Clinic, 2019), and they are the only class of drug with strong evidence of efficacy for Post-Traumatic Stress Disorder (Stein et al., 2004). SSRIs work by inhibiting the reuptake of serotonin by neurons in the brain, and therefore cause more serotonin to be available to improve communication between neurons throughout the brain. SSRIs have the smallest rate of side effects for patients who consume the medication. Those side effects include nausea, headache, drowsiness, dry mouth, insomnia, nervousness, dizziness, sexual problems, and possible weight gain or weight loss. The mechanism as to how SSRIs lead to reduction of anxiety symptoms is not fully understood, but all SSRIs are thought to work in a similar way. The most common SSRIs are fluoxetine (Prozac), sertraline (Zoloft), citalopram (Celexa), and escitalopram (Lexapro). SSRIs are not known to be addictive, but withdrawal-like symptoms can occur with a sudden stop of treatment.

Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) are also commonly prescribed antidepressants but can also be prescribed for anxiety disorders. However, SRNIs are only prescribed after the failure of an SSRI (Mayo Clinic, 2019). SNRIs work by blocking the reuptake of serotonin and norepinephrine, which results in more of these neurotransmitters in the brain and improved communication between neurons, leading to reduced anxiety and improved mood. SNRIs do not always work to reduce anxiety, as

some patients experience an exacerbation of symptoms due to increased levels of norepinephrine (Ravindran & Stein, 2010). SNRIs have similar side effects as SSRIs. The most common SNRIs include venlafaxine, desvenlafaxine (Pristiq), and duloxetine. SNRIs are not known to be addictive, but withdrawal-symptoms are most likely to occur with venlafaxine.

Benzodiazepines have been used to treat anxiety disorders for many years and are considered the most effective at treating acute symptoms of anxiety (Ravindran & Stein, 2010). Benzodiazepines work by binding to specific GABA receptors and increasing the frequency of opening of each GABA receptor's associated chloride channel. As a result, Benzodiazepines can reduce anxiety symptoms almost immediately. There are also many risks involved with long term use of benzodiazepines. Side effects include physiological and psychological dependence, potential fatalities upon withdrawal, impaired cognition and coordination, potential lethal overdose when mixed with alcohol, and inhibition of memory encoding (Mohler, 2011). Due to high likelihood of side effects, benzodiazepines are prescribed as a last resort or for very short periods of time. Alprazolam is the most common short-acting benzodiazepine and is FDA cleared for the treatment of panic disorder and General Anxiety Disorder. Clonazepam is another popular benzodiazepine that has shown efficacy in treating social anxiety disorder (Ravindran & Stein, 2010). There is limited evidence that benzodiazepines are effective at treating PTSD or OCD.

Psychotherapy

Because medications have a list of side effects, non-drug solutions have become increasingly popular to treat anxiety disorders. Psychotherapy is a form of anxiety treatment that deals with the mental side of anxiety. Patients can learn to talk their way

out of anxiety, overcome the fear of it, and shift from a negative state of mind to a positive one without having to take drugs. The most popular forms of psychotherapy include Cognitive Behavior Therapy, exposure therapy, and mindfulness.

Cognitive Behavior Therapy (CBT) is a type of talk therapy where a patient works with a mental health counselor multiple times per week for many weeks. The mental health counselor's job is to help reduce the patient's negative thinking and to help improve their outlook on life in general. CBT has received the greatest amount of empirical support for the treatment of anxiety disorders and is almost always prescribed to patients with anxiety disorders, even when physicians prescribe medication as well (Foa et al., 2002; Stein et al., 2004). CBT is viewed very highly as an anxiety disorder treatment because it does not require any medication, but it is extremely expensive long term and requires a large amount of time from the patient. Primary care physicians acknowledge that CBT is the most desirable form of anxiety treatment, but due to the lack of CBT therapists and affordable sessions, it is difficult to simply prescribe CBT to all patients (Blane et al., 2013).

Exposure therapy is the method of gradually and systematically presenting anxiety-inducing thoughts, images, or situations to a patient. The patient experiences anxiety during the thought, image, or situation, and is exposed to it for long enough where eventually their anxiety will naturally subside, and they begin to realize there is no reason to be anxious. Ideally, the patient would be exposed to less anxious situations over time until they eventually overcome their anxiety associated with the event (Sars & van Minnen, 2015)

Mindfulness is a type of behavioral therapy the patient does on their own. It involves training the mind to focus on being in the present, being grateful to be in the present, and to shift one's mind towards acceptance of the situation. The benefits include being able to perform the technique anytime and anywhere, and it is free to perform. However, it does take large amounts of time to learn to perform and can be quite challenging for patients to keep their mind focused on one particular thing for such a long time. Mindfulness comes from Buddhist psychology and is very closely associated with meditation. Typical mindfulness sessions involve the patient sitting in a comfortable position and breathing deeply through their nose and putting their attention on simply being in the present moment and to be grateful for being in the present moment. Mindfulness has been successfully integrated into many CBT programs for the treatment of panic disorder and post-traumatic stress disorder. However, more research is needed to fully characterize the efficacy of mindfulness in other anxiety disorders.

Devices

Transcranial Magnetic Stimulation (TMS) is a method of using focused magnetic waves to stimulate above the scalp with the goal of invoking excitation or inhibition of cortical neurons. TMS is typically used to treat depression by increasing neuronal activity but has recently been used to treat symptoms of anxiety (Pallanti & Bernardi, 2009). It works by placing an electromagnetic coil against the scalp, which painlessly delivers magnetic pulses that stimulate neurons in the target region under the scalp. Its top advantages are that it is drug-free and is considered safe with few side effects. However, its main disadvantage is that it cannot target deeper brain structures like the caudate nucleus, thalamus, amygdala, hippocampus, and other structures implicated in

disorders like OCD and panic disorder (Cirillo et al., 2019). While TMS is not an FDA-cleared treatment for anxiety, it has shown some positive clinical results in treating PTSD and panic disorder (Pallanti & Bernardi, 2009).

Deep Brain Stimulation (DBS) is a method that involves inserting small electrodes into deeper structures in the brain for the purpose of increasing or decreasing activity in that brain region to treat symptoms of Parkinson's Disease and drug-resistant depression. It is an expensive method that involves surgically implanting a neurostimulator in the body that runs lead wires up into and deep into the brain. There are many risks involved with implanting electrodes into the brain. Risks from surgery include bleeding in the brain, misplacement of leads, stroke, infection, and seizure. Risks from post-implantation include seizure, infection, headache, stroke, hardware complications, and temporary pain and swelling at the implantation site. In regard to treating anxiety symptoms, it is mostly limited to treating OCD and is typically one of the last methods suggested by a doctor, but some studies testing DBS in an OCD population have reported response rates of over 50% (Greenberg et al., 2010).

Vagus Nerve Stimulation

Vagus Nerve Stimulation (VNS) is a very popular treatment that refers to any method that stimulates the vagus nerve. Researchers in the last few decades have demonstrated that VNS produces physiological responses associated with treating epilepsy, drug-resistant depression, and anxiety disorders. VNS was originally a method that involved implanting a stimulator that ran lead wires to the cervical branch of the vagus nerve. It is expensive and involves all the risks associated with surgical implantation of any medical device. In the 1990's, VNS was approved by the FDA to treat

refractory epilepsy and later for refractory depression (Ben-Menachem et al., 2015). Researchers began to explore the effects of VNS on anxiety after noticing mood improvements in psychiatric patients treated with VNS for epilepsy (Chavel et al., 2003). While the mechanism is not fully understood, VNS has shown to be a promising method of treating anxiety disorders (George et al., 2008).

Anatomy of the Vagus Nerve

The Vagus Nerve is the 10th cranial nerve. It iss a major component in the autonomic nervous system and regulates the function of various organs, glands, and involuntary muscles throughout the body. The nerve contains both motor (20%) and sensory (80%) pathways that travel throughout the upper body. Motor pathways descend from the nucleus ambiguous and the nucleus dorsalis nerve vagi in the brainstem and connect visceral organs like the lungs, heart, pancreas, and gastrointestinal tract with the central nervous system (Tracy, 2009). Sensory afferent fibers of the vagus nerve travel upwards towards the brainstem and terminate in the nucleus tractus solitarious (NTS) and spinal trigeminal nucleus, which then sends fibers either directly or indirectly to different brain regions responsible for regulation of neurotransmitters like serotonin, dopamine, and norepinephrine. Regions include dorsal raphe nuclei, locus coeruleus, amygdala, hypothalamus, thalamus and orbitofrontal cortex. These regions play important roles in emotion regulation and have been implicated in stress-related mental disorders, including PTSD (Campanella & Bremner, 2016; Fang et al., 2016; Howland, 2014).

The vagus nerve is a bilateral nerve that has both left and right branches. These branches both either descend (efferent fibers) from the brainstem into the upper body or

ascend (afferent fibers) from the body to the brainstem and into various regions in the brain. Efferent and afferent fibers of the left and right branches of the vagus nerve have similar projections throughout the body, but the right efferent branch of the vagus nerve primarily mediates cardiac function, whereas the left branch does not (Howland, 2014).

The cervical branch of the vagus nerve has both left and right branches that course through the neck and is made up of both efferent and afferent fibers. Stimulation of right cervical efferent fibers is often used for the treatment of heart failure, as well as epilepsy (De Ferrari & Schwartz, 2011). However, the left cervical branch is often targeted for the treatment of epilepsy and other disorders for the purpose of avoiding effects on the heart.

The Auricular Branch of the Vagus Nerve (ABVN) emerges from the superior ganglion of the vagus nerve within the jugular foramen and runs between the internal jugular vein and the bony wall of the jugular foramen towards the mastoid canaliculus (Tekdemir et al., 1998). It is an afferent branch that has distribution in the tragus, concha, cymba conchae, and acoustic meatus of the ear (Mercante et al., 2018). These branches terminate mainly in the solitary nucleus, spinal trigeminal nucleus, cuneate nucleus and dorsal horn of the C1, C2, and upper C3 cord segments, and it is has been shown that there may be monosynaptic connections between afferent fibers of the ABVN and solitary nucleus neurons (Nomura & Mizuno, 1984). Cadaveric studies have shown the ABVN to divide into two branches extracranially, one branch running posteriorly to the facial nerve and joining with the posterior auricular nerve, and the other running anteriorly to the facial nerve and entering into the wall of the external acoustic meatus (Tekdemir et al., 1998).

Transcutaneous Vagus Nerve Stimulation

Non-invasive VNS can be performed by electrically stimulating auricular branches or cervical branches of the vagus nerve and has shown similar effects to invasive VNS with much fewer side effects (Yuan & Silberstein, 2015). Therefore, tVNS is currently being researched for its effects on anxiety, depression, epilepsy, and a variety of other disorders. There are two main forms of tVNS: transcutaneous cervical vagus nerve stimulation (tcVNS), and transcutaneous auricular vagus nerve stimulation (taVNS).

tcVNS

Transcutaneous cervical vagus nerve stimulation (tcVNS) is a method of applying mild electric impulses on the neck, over an area where the pulse is located, in the vicinity of the cervical branch of the vagus nerve. It can be performed on either the left or right side of the neck. fMRI studies have shown that tcVNS activates primary vagal projections including the nucleus of the solitary tract, parabrachial area, primary sensory cortex, and the insula, and deactivates areas like the hippocampus, visual cortex, and spinal trigeminal nucleus (Frangos & Komisaruk, 2016). Recently, a handheld tcVNS device called GammaCore was cleared for the treatment of pain associated with episodic cluster headache and migraine. The device is placed on the neck over the vicinity of the vagus nerve and uses small pulses of electricity that last for two minutes (Howland, 2014). Patients can use the device several times per day as needed. While the FDA has cleared tcVNS for headache, it has not yet cleared the method to treat other disorders. Much research is currently being performed to test the efficacy of tcVNS for the treatment of disorders like epilepsy, depression, and anxiety. tcVNS has also been shown to decrease sympathetic function and to modulate parasympathetic/sympathetic automatic tone in

patients exposed to traumatic stress (Gurel et al., 2020), which indicates the method may be a promising solution to treating PTSD.

taVNS

Transcutaneous auricular vagus nerve stimulation (taVNS) is a method of applying mild electric impulses to areas in and around the ear that contain branches of the vagus nerve. Studies have shown that taVNS can produce similar effects induced by VNS and trigeminal nerve stimulation, likely due to their common connections in the spinal trigeminal nucleus (Kraus et al., 2007, 2013; Kreuzer et al., 2014). fMRI studies have shown activation in the nucleus of solitary tract (NTS) and the locus coeruleus (LC) when stimulating in the external acoustic meatus, with greater activation when stimulating the anterior wall of the auditory canal vs. the posterior wall of the auditory canal (Frangos & Komisaruk, 2016; Kraus et al., 2013). However, a study aimed at determining the optimal location in the ear for effective taVNS found that the cymba conchae produced the strongest activation in the NTS and LC compared to tragus and acoustic meatus, with the acoustic meatus producing the weakest activation of the NTS and LC (Yakunina et al., 2017). Therefore, the cymba conchae has been proposed as the optimal location for taVNS therapy. NTS and LC are areas responsible for the production of norepinephrine, a neurotransmitter implicated in anxiety disorders like PTSD and Panic Disorder (Goddard et al., 2009). taVNS has shown promising results in the treatment of anxiety disorders like PTSD (Lamb et al., 2017), and could ultimately help millions of people reduce symptoms of anxiety and stress in general (Badran et al., 2018; Clancy et al., 2014; Warren et al., 2019).

Dissertation Goal

The goal of this dissertation is to further characterize and quantify the effect of non-invasive vagus nerve stimulation on physiological activity, as well as characterize its safety and tolerability in human subjects. Chapter 2 describes an experiment that analyzed the effects of tVNS in healthy humans. The experiment consisted of using a unique dry hydrogel earbud electrode that provided a simpler user experience and improved patient comfort during stimulation, as well as a mix of various stimulation waveform parameters to stimulate the auricular branch of the vagus nerve. Changes in resting physiological levels like heart rate, heart rate variability, brain activity, skin conductance, skin temperature, and respiration rate were quantified. Safety and tolerability outcomes were also quantified by asking patients to subjectively assess their level of comfort or discomfort during the stimulation, and to document any adverse effects such as skin irritation or headache after receiving the stimulation.

While non-invasive VNS is a technology with exciting potential, current electrode designs for non-invasive VNS are not ideal for a variety of potential populations, such as elite athletes with anxiety disorders. However, nerves of the cervical plexus are more easily accessible than vagal nerve afferents and allow for more user-friendly electrode designs. Since nerves in the cervical plexus converge in similar brain structures as the vagus nerve (spinal trigeminal nucleus and NTS), stimulating these nerves may produce similar effects as non-invasive VNS (Diamond et al., 2011; Piovesan et al., 2003). The proposed research aims to quantify the effects of stimulating nerves of the cervical plexus on physiological activity, anxiety symptoms, and sports performance. Chapter 3 discusses the effects of non-invasively stimulating a region containing the Auricular

Branch of the Vagus Nerve and the Great Auricular Nerve on physiological activity and golf hitting performance, and Chapter 4 discusses the effects of non-invasive cervical nerve stimulation on physiological activity and putting performance of yips-affected golfers. Chapter 5 discusses a summary of the results found in this research and proposes future research that can be performed with each of the stimulation methods discussed in this paper.

CHAPTER 2

SAFETY AND EFFICACY OF BILATERAL AURICULAR VAGAL NERVE STIMULATION IN HEALTHY INDIVIDUALS

Abstract

Transcutaneous vagus nerve stimulation (tVNS) is a non-invasive drug-free method that consists of using small electrical impulses to activate branches of the vagus nerve in the ear. The effects of tVNS have been well studied over the last couple decades to determine efficacy to treat various disorders, and the method is mostly used to treat epilepsy. The vast majority of tVNS protocols are for stimulating in the left ear in the concha or the tragus, but no studies have reported both the safety and efficacy of bilateral stimulation in the external acoustic meatus. Bilateral stimulation in the acoustic meatus provides new electrode design opportunities for new patient populations, so this study aimed to quantify the effects of bilateral stimulation on physiological activity and its safety and tolerability in healthy individuals. Sixty-seven healthy participants received one of three different bilateral stimulation waveforms (30Hz, 300Hz, or 3000Hz) or a sham stimulation waveform (0Hz, 0mA). Resting physiological activity was quantified before and after receiving 10 minutes of one of the four conditions. Safety and tolerability data were collected through questionnaires after receiving the treatment. The data showed that only the SDNN and RMSSD component of heart rate variability were significantly increased compared to a sham, indicating bilateral stimulation in the acoustic meatus is an effective method of increasing heart rate variability. Other metrics like heart rate and skin temperature also significantly changed in the stimulation groups, but they also significantly changed in the sham group. The data also demonstrates that all three

bilateral stimulation paradigms were not significantly different from a sham regarding safety and tolerability. Safe and effective bilateral stimulation paradigms open the door to new product designs that could improve the user experience for a variety of patient populations, such as patients with anxiety disorders.

Introduction

Transcutaneous Vagus Nerve Stimulation (tVNS)

Transcutaneous stimulation of the cervical and auricular branches of the vagus nerve (ABVN) has been shown to induce short-term and long-term brain plasticity (Ben-Menachem et al., 2015), as well as modulating brain circuits and triggering the physiological responses associated with those brain circuits (Fang et al., 2016; Frangos & Komisaruk 2015; Kraus et al., 2007). Transcutaneous auricular vagal nerve stimulation has also been shown to produce similar results as an implantable VNS device in epilepsy populations (Bauer et al., 2015), has been tested with stroke rehabilitation when paired with traditional rehabilitation exercises (Childs et al., 2017) and has been demonstrated to reduce sympathetic activity (Clancy et al., 2014; Ylikoski et al., 2017). Studies have shown that electrically stimulating branches of the vagus nerve, including the ABVN, can safely produce biochemical, behavioral, and physiological effects that are necessary for learning a new skill or enhancing performance (Jacobs et al., 2015; Sellaro et al., 2015; Steenbergen et al., 2015), and can improve working memory and other cognitive functions (Jongkees et al., 2018).

Waveform and Electrode Design

Auricular vagal nerve stimulation has demonstrated effects on parasympathetic and other physiologic activity, but stimulation parameters of the electrical waveform

(pulse width, frequency, unilateral vs. bilateral, etc.) may be critical to producing a desired response and it is unknown if there is an optimal waveform design for effective taVNS. Bilateral stimulation at the cymba concha using a waveform with 3Hz frequency and 1.5ms pulse width has shown to produce a significantly decreased heart rate, systolic blood pressure, and LF/HF ratios in humans (Popov et al., 2013; Zamotrinsky et al., 2001). Unilateral stimulation at the right tragus using a waveform of 30Hz has shown to reduce the LF/HF ratio and increase Heart Rate Variability (HRV) in healthy individuals (Clancy et al., 2014), while 20Hz and 25Hz waveforms did not show the same effects on cardiovascular parameters (Borges et al., 2019; Stavrakis et al., 2015). 8Hz stimulation in the left external acoustic meatus did not show any significant effects on heart rate or blood pressure before or after tVNS (Kraus et al., 2007). While few studies have explored the effects of various waveform parameters in rat models (Borland et al., 2016; Hulsey et al., 2016), there is not enough data to conclude that any particular stimulation paradigm is optimal for producing a desired physiological response in humans.

Electrode design is another essential component to effective stimulation and must be considered when treating different populations. Auricular vagal nerve stimulation electrodes are effective for clinical populations (Mercante et al., 2018), but they are not ideal for patients and consumers looking to use them for skill learning or performance enhancement. Designs that use electrode clips targeting the tragus and earlobe produce discomfort due to mechanical pinching and movement from the user (Badran et al., 2019). They also utilize a high impedance conductive silicone or rubber that is not ideal for transcutaneous electrical nerve stimulation. Another design utilizes a pair of small stainless-steel ball electrodes positioned in the concha and external ear,

which results in stimulation discomfort due to high current densities in the electrode (Warren et al., 2019). Other designs use conductive rubbers or silicones that must be soaked in a gel or a saline solution before inserting into the external acoustic meatus (Neuvana, 2019). While this reduces impedance at the electrolyte/skin interface, high current densities (>2mA/cm^2) from uneven current distribution still cause discomfort during stimulation. There is a clinical need for an electrode design that offers improved comfort and improves the overall user experience during stimulation.

Safety of Electrical Stimulation

Medications are known to come with a list of side effects that can adversely affect a patient's health. One of the major benefits of electrical nerve stimulation is the fact that it is drug-free and therefore avoids the risks that come with medication. However, electrical nerve stimulation comes with its own list of side effects that may adversely affect patient health. Side effects of general transcutaneous electrical stimulation (TES) have been reported in a large number of studies in the past couple decades (Antal et al., 2017) and include skin irritation, mild tingling sensation, moderate fatigue, itch under the stimulus electrode, headache, nausea, insomnia, burning sensations, dizziness, and discomfort during treatment.

Side effects of tVNS have been demonstrated to be low risk and similar to side effects of standard TES devices. One study looking at the effects of tVNS on pain in 48 healthy subjects assessed the tolerability of tVNS and found the most common effects were feelings of slight pain, pressure, prickling, itching, or tickling at the site of the electrodes. There were no serious adverse events during the study and every participant completed the entire 1-hour stimulation session (Busch et al., 2012). In another study

looking at the effects of tVNS over 20 weeks on patients with epilepsy, patients reported treatment related adverse events of headache, ear pain, application site erythema, vertigo, fatigue, and nausea, with 7% in the treatment group rating the adverse effects as "severe" (Bauer et al., 2016). Another study assessing pain and tolerability of tVNS in healthy individuals found that 75% of patients who received active stimulation reported low pain levels (1 or 2 on a Likert-scale), and the stimulation was well tolerated by all participants (De Couck et al., 2017).

Safety and tolerability of unilateral tVNS (stimulation in one ear) has been well documented, but a consistent question raised by researchers about safety is the safety of bilateral stimulation where the electrodes are placed in both ears and current may pass across the face. There have been a handful of tVNS studies that used a bilateral stimulation paradigm protocol (Popov et al., 2013; Wang et al., 2014; Zamotrinsky et al., 1997, 2001), but these studies failed to assess the safety and tolerability of the stimulation parameters. It is also known that efferent vagal fibers that lead to the heart are located on the right side of the body, and therefore tVNS is typically performed on the left side in order to avoid heart-related adverse effects (Nemeroff et al., 2006). However, anatomical studies suggest the auricular branches on both sides of the head are made up of mostly afferent fibers that lead to the brainstem and stimulating auricular branches in the right ear have been shown to be safe and well tolerated (De Couck et al., 2017).

Experiment Aims

In this experiment, we used uniquely designed earbud electrodes to stimulate the auricular branch of the vagus nerve in the external acoustic meatus (EAM). Cadaveric

studies have demonstrated the EAM is supplied by the ABVN (Gupta et al., 1986; Tekdemir et al., 1998). The earbud electrodes were designed to maximize wear comfort and comfort during stimulation by utilizing a dry and soft hydrogel that provides maximum skin contact within the contours of the ear canal. The earbuds did not require any soaking in a saline or gel solution. Comfortable stimulation is ideal because the stimulation should not distract the patients or induce any pain that may cause confounds in the data during recording. We also aimed to identify optimal stimulation parameters to produce the desired physiological responses by assessing three different waveforms and a sham. We compared effects on physiological activity of three bilateral taVNS (electrode coupling in both ears) waveforms. Following the stimulation protocol, safety and tolerability data were collected for each of the stimulation paradigms.

Hypotheses

We hypothesized electrical stimulation of auricular branches of the vagus nerve would cause a statistically significant change in heart rate, heart rate variability, skin conductance, skin temperature, and respiration rate (physiological activity).

We hypothesized there would be a statistically significant difference in physiological activity between the different waveform parameters.

We hypothesized there would be no difference in the safety and tolerability between the sham and active stimulation groups.

Methods

The experiment consisted of participants performing a baseline computerized task while having biometrics (heart rate, heart rate variability, skin conductance, skin temperature, and respiration rate) recorded. Participants then received either active or

sham transcutaneous auricular vagal nerve stimulation (taVNS). After the treatment, participants performed the same computerized task while having biometrics recorded.

The computerized task was a 13-minute passive auditory mismatch negativity stimuli task. The task consisted of a series of randomized frequent and infrequent tones with an inter-stimulus period of 500ms. Stimuli was presented over a pair of headphones and participants were instructed to passively listen to the tones while they watched a silent nature video. Biometrics were monitored during the task, both before and after the stimulation.

Participants were then randomized to receive 10 minutes of either active or sham stimulation. Active stimulation was one of three different stimulation settings:

- 30Hz bilateral taVNS
- 300Hz bilateral taVNS
- 3000Hz bilateral taVNS.

Participants watched a silent nature video while receiving 10 minutes of either active or sham stimulation (Figure 1, Table 1). Participants were instructed to increase the stimulation intensity by intervals of 0.25mA until a comfortable setting, or the maximum output of 20mA was reached. Biometrics were recorded during the stimulation task. After the stimulation task, participants performed the same 13-minute passive auditory mismatch negativity stimuli task while having biometrics recorded.

Safety and tolerability data were collected immediately after completing the last stimulation task. An online survey assessing stimulation protocol safety and tolerability was taken on REDCap. The questions consisted of yes/no, 10-point Likert scale, and open-ended questions asking patients to subjectively assess their level of comfort or

discomfort during the stimulation. Participants also took a 12-question online survey assessing stimulation protocol safety and tolerability 24 hours after participating in the study. The questions consisted of yes/no, 10-point Likert scale, and open-ended questions.

Safety and Tolerability Questions

For each question, participants gave a yes or no answer, followed by a subjective rating between 1-10, with 1 being minimal experience and 10 being maximum experience.

1. Rate your overall comfort.
2. Did you find the experience relaxing?
3. Did you experience any discomfort or pain?
4. Did you experience any dizziness?
5. Did you experience any blurred vision?
6. Did you experience any headache?
7. Did you experience skin itching or irritation?
8. Did you experience any discomfort or pain within 24 hours?
9. Did you experience any dizziness within 24 hours?
10. Did you experience any blurred vision within 24 hours?
11. Did you experience any headache within 24 hours?
12. Did you experience any skin itching or irritation within 24 hours?

Data Analysis Approach

Heart Rate and Heart Rate Variability were recorded using a Blood Volume Pulse (BVP, 128Hz sampling rate) sensor clipped to the index finger of the pointer finger of the

left hand. The BVP signal was filtered (high-pass 0.5Hz, low-pass 3Hz) and exported for RR interval detection and analysis in the Kubios HRV Premium software. Time-domain (HR, SDNN, RMSSD, HRV amplitude) and frequency-domain (normalized low frequency and high frequency power, LF/HF ratio) HRV values were computed.

Skin conductance (32Hz sampling rate, μSiemens) was measured using electrodes attached to the underside of the pointer finger and the middle finger of the left hand. Skin temperature (32Hz sampling rate, Fahrenheit) was measured using a small tipped ceramic thermistor taped to the ring finger of the left hand. Respiration rate was measured using a Velcro-elastic respirations sensor strapped to the abdomen (32Hz sampling rate). Respiration activity was filtered (high-pass 0.5Hz, low-pass 1Hz), and the level trigger market transform was applied to mark the inhalation peak of each breath cycle. Respiration intervals were used to calculate breaths per minute.

Baseline data for all physiological metrics were recorded during the last 10 minutes of the baseline task, and post-stimulation data was recorded during the first 10 minutes of the post-stimulation task. A one-way ANOVA in SPSS was used to examine the main and simple effects of tVNS stimulation conditions, time (baseline, stimulation, post-stimulation), and time*condition on physiological activity. Post hoc t-tests were used to analyze significance between specific groups. Bonferroni correction was applied to the alpha-level to control for multiple comparisons.

A Pearson's chi-squared test was used to quantify the relationship between post-stimulation and 24-hour reports (yes or no) of discomfort, dizziness, blurred vision, headache and skin irritation from taVNS protocols (sham, 30Hz, 300Hz, 3000Hz). A one-way ANOVA was used to compare average comfort, relaxation, discomfort,

dizziness, blurred vision, headache, and skin irritation ratings (1-10) between each protocol group.

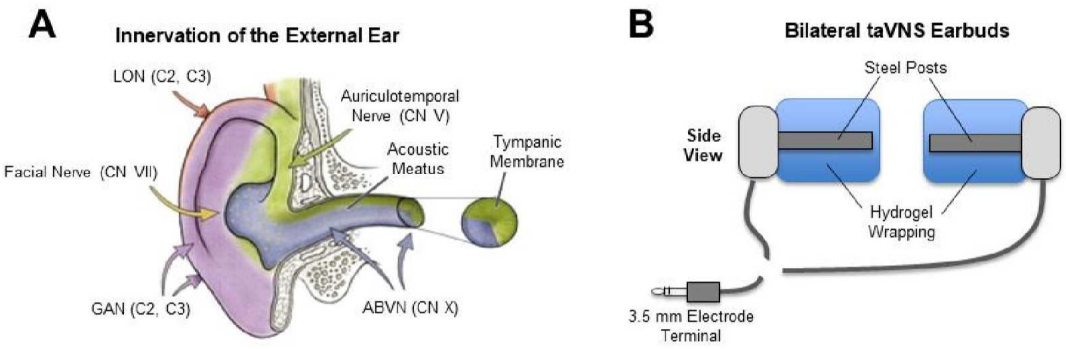

Figure 1. Overview of transdermal auricular vagal nerve stimulation approaches. A) Anatomical illustration showing cranial (Cranial Nerve X auricular branch of the vagus nerve= ABVN) and cervical (C2, C3 great auricular nerve = GAN) nerves that innervate the external ear. We targeted the ABVN using custom (B) ear bud taVNS electrodes inserted into the acoustic meatus in both ears.

Table 1

Stimulation Parameters

Condition	*Frequency (Hz)*	*Pulse Width (µS)*	*Pulse Gap (mS)*	*Current (mA)*
Active - Bilateral	30	50	50	0-20
Active - Bilateral	300	350	50	0-20
Active - Bilateral	3000	50	50	0-20
Sham	0	0	0	0

Results

The following table describes the demographic information of the participants in this study.

Table 2

Demographic Information

Stim Parameters		Intensity	Gender			Age		
Frequency	*Pulse Width*	*Mean ± SD*	*N*	*Male*	*Female*	*Minimum*	*Maximum*	*Mean ± SD*
All Active	variable	10.35 ± 7.34	47	35	12	18	48	23.91 ± 5.96
0 Hz Sham		0.00 ± 0.00	20	14	6	18	29	21.20 ± 2.91
30 Hz	50	14.42 ± 6.24	16	13	3	18	39	24.81 ± 5.55
300 Hz	350	2.73 ± 1.70	15	11	4	18	31	22.20 ± 4.44
3000 Hz	50	14.14 ± 5.64	16	11	5	18	48	24.63 ± 7.429

In total, there were 47 participants in the combined active group and 20 participants in the sham group. The mean age in the combined active group was 23.91 ± 5.96 years and the mean age in the sham group was 21.20 ± 2.91 years. The average intensity was 10.35 ± 7.34 mA for all active groups combined, 14.42 ± 6.24 mA in the 30Hz group, 2.73 ± 1.70 mA in the 300Hz group, and 14.14 ± 5.64 mA in the 3000Hz group. Statistical differences between age and gender were not computed.

Physiological Activity

Table 3

Mean Values for All Active and Sham Conditions

	Active (n=47)			SHAM (n=20)		
Variables	*Pre*	*Stim*	*Post*	*Pre*	*Stim*	*Post*
Heart Rate (bpm)	73.61 ± 1.50	71.65 ± 1.46	71.33 ± 1.36	78.71 ± 1.91	76.94 ± 1.94	76.71 ± 1.77
SDNN (ms)	44.45 ± 2.63	48.83 ± 2.58	51.67 ± 2.73	35.89 ± 2.16	40.83 ± 2.32	40.50 ± 2.99
RMSSD (ms)	41.36 ± 2.87	46.47 ± 3.05	48.38 ± 3.02	30.66 ± 2.12	35.32 ± 2.66	34.41 ± 2.78
HRV (Hrmax - Hrmin)	25.79 ± 1.22	30.75 ± 2.35	29.77 ± 1.50	24.64 ± 1.42	29.59 ± 1.39	27.43 ± 1.81
HF Power	41.69 ± 2.24	41.82 ± 1.96	38.60 ± 1.91	39.56 ± 3.24	43.07 ± 3.50	38.71 ± 2.69
LF Power	58.25 ± 2.24	58.10 ± 1.97	61.35 ± 1.91	60.41 ± 3.24	56.87 ± 3.51	61.25 ± 2.69
LF/HF	1.81 ± .19	1.72 ± .17	1.93 ± .17	1.92 ± .28	1.73 ± .29	1.86 ± .22
Resp Rate (bpm)	16.44 ± .48	16.51 ± .51	16.58 ± .46	16.32 ± .67	16.22 ± .67	16.30 ± .67
Hand Temp (°F)	94.03 ± .39	92.97 ± .53	92.36 ± .58	93.58 ± 1.05	91.94 ± 1.22	90.75 ± 1.49
Skin Conductance (µS)	11.67 ± 2.50	13.93 ± 3.11	15.14 ± 3.63	3.47 ± .63	6.29 ± 1.82	5.91 ± 2.28

Table 4

Mean Values for Active and Sham Conditions

	30Hz (n=16)			300Hz (n=15)			3000Hz (n=16)			SHAM (n=20)		
Variables	*Pre*	*Stim*	*Post*	*Pre*	*Stim*	*Post*	*Pre*	*Stim*	*Post*	*Pre*	*Stim*	*Post*
Heart Rate (bpm)	72.75 ± 2.53	70.39 ± 2.49	70.39 ± 2.25	75.97 ± 2.52	73.97 ± 2.45	73.17 ± 2.28	72.25 ± 2.79	70.74 ± 2.71	70.54 ± 2.62	78.71 ± 1.91	76.94 ± 1.94	76.71 ± 1.77
SDNN (ms)	42.20 ± 4.84	46.33 ± 4.30	48.63 ± 4.53	42.66 ± 4.23	46.51 ± 4.01	50.14 ± 3.64	48.37 ± 4.65	53.50 ± 5.00	56.15 ± 5.76	35.89 ± 2.16	40.83 ± 2.32	40.50 ± 2.99
RMSSD (ms)	37.70 ± 4.21	42.69 ± 4.14	44.98 ± 4.44	39.49 ± 5.22	43.77 ± 5.36	47.13 ± 4.86	46.77 ± 5.45	52.77 ± 6.11	52.96 ± 6.30	30.66 ± 2.12	35.32 ± 2.66	34.41 ± 2.78
HRV (Hrmax - Hrmin)	25.02 ± 2.41	25.99 ± 1.30	28.83 ± 3.13	27.20 ± 1.96	28.58 ± 1.88	28.77 ± 1.77	25.24 ± 2.01	37.55 ± 6.35	31.65 ± 2.71	24.64 ± 1.42	29.59 ± 1.39	27.43 ± 1.81
HF Power	40.86 ± 4.19	40.36 ± 3.40	39.20 ± 3.28	41.57 ± 3.58	41.10 ± 2.85	37.86 ± 3.71	42.62 ± 4.05	43.96 ± 3.94	38.68 ± 3.13	39.56 ± 3.24	43.07 ± 3.50	38.71 ± 2.69
LF Power	59.09 ± 4.19	59.60 ± 3.40	60.76 ± 3.28	58.35 ± 3.58	58.83 ± 2.86	62.09 ± 3.72	57.33 ± 4.05	55.92 ± 3.96	61.25 ± 3.14	60.41 ± 3.24	56.87 ± 3.51	61.25 ± 2.69
LF/HF	1.84 ± .28	1.83 ± .31	1.85 ± .26	1.72 ± .28	1.63 ± .22	1.99 ± .27	1.85 ± .42	1.71 ± .36	1.96 ± .35	1.92 ± .28	1.73 ± .29	1.86 ± .22
Resp Rate (bpm)	15.87 ± .88	16.16 ± .86	16.29 ± .68	16.97 ± .80	17.05 ± .83	17.36 ± .80	16.51 ± .86	16.36 ± .98	16.14 ± .90	16.32 ± .67	16.22 ± .67	16.30 ± .67
Hand Temp (°F)	93.85 ± .56	92.68 ± .90	91.77 ± 1.12	95.28 ± .30	94.51 ± .35	94.26 ± .37	93.03 ± .91	91.82 ± 1.15	91.18 ± 1.13	93.58 ± 1.05	91.94 ± 1.22	90.75 ± 1.49
Skin Conductance (μS)	8.13 ± 3.26	10.33 ± 3.68	7.96 ± 3.55	13.91 ± 5.23	17.41 ± 6.60	22.96 ± 8.09	13.32 ± 4.54	14.32 ± 5.91	14.97 ± 6.42	3.47 ± .63	6.29 ± 1.82	5.91 ± 2.28

Table 3 shows physiological data for each of the 10-minute recording periods for all the active conditions combined (n = 47) and the sham condition (n = 20). Table 4 shows physiological data for each of the 10-minute recording periods for each active condition and the sham condition.

Statistical Analyses by Condition

Table 5

*Statistical results from treatment Time * taVNS Condition ANOVAs*

Variable	Main Effects (P-values)			Simple Effects of Condition (P-values)			Simple Effects of Time (P-values)	
	Time	*Time * Cond*	*Condition*	*Baseline*	*Stim*	*Post*	*Sham*	*Active*
Heart Rate (bpm)*	**.019**	.940	**.031**	.056	**.044**	**.028**	**.015** [3]	**.000** [3]
SDNN (ms)*	**.001**	.523	**.025**	.050	.064	**.019**	.075	**.000** [3]
RMSSD (ms)*	**.002**	.517	**.010**	**.024**	**.029**	**.007**	.134	**.000** [2,3]
HRV (HRmax - HRmin)*	**.017**	.880	.475	.582	.756	.369	.148	**.002** [2,3]
HF Power	.066	.567	.938	.600	.741	.973	.276	.148
LF Power	.064	.563	.933	.596	.746	.976	.274	.145
LF/HF Ratio	.368	.759	.954	.739	.980	.803	.654	.327
Resp Rate (bpm)	.949	.927	.781	.892	.750	.737	.972	.860
Hand Temp (°F)*	**.000**	.160	.340	.624	.364	.223	**.000** [2,3]	**.000** [2,3]
Skin Conductance (µS)*	.176	.832	.063	**.034**	.119	.108	.322	.140

Note: *Mauchly's test of sphericity (p<.05), Greenhouse-Geisser alpha reported; Simple Effects - Time: Pairwise Comparisons (Bonferroni) Time * Cond [2]Pre vs. Stim (p<.05) [3]Pre vs. Post (p<.05)

Table 6

*Pairwise Comparisons Condition * Time (Bonferroni)*

	Sham		Active	
Variables	Pre-Stim	Pre-Post	Pre-Stim	Pre-Post
Heart Rate (bpm)*	.681	**.012**	.127	**.000**
SDNN (ms)*	.259	.096	.063	**.000**
RMSSD (ms)*	.348	.234	**.028**	**.000**
HRV (HRmax - HRmin)*	.294	.499	**.036**	**.010**
HF Power	.537	1.000	1.000	.277
LF Power	.531	1.000	1.000	.218
LF/HF Ratio	1.000	1.000	1.000	1.000
Resp Rate (bpm)	1.000	1.000	1.000	1.000
Hand Temp (°F)*	**.001**	**.000**	**.002**	**.000**
Skin Conductance (µS)*	.393	1.000	.212	1.000

Statistical analyses by ANOVA revealed significant main effects of time for heart rate, SDNN, RMSSD, HRV, and hand temperature, and main effects of Condition for heart rate, SDNN, and RMSSD only.

In the sham group, ANOVA revealed a significant effect over time for heart rate and hand temperature. Post hoc testing using Bonferroni corrected two-tailed independent t-tests revealed there was a significant decrease in heart rate between baseline and post-stimulation periods in the sham group ($p = 0.012$, $d = 0.99$). There was also a significant decrease in hand temperature between baseline and stimulation time points ($p = 0.001$, $d = 2.48$), and between baseline and post-stimulation time points ($p < 0.001$, $d = 2.23$).

In the combined active group, ANOVA revealed a significant effect over time for heart rate, SDNN, RMSSD, HRV, and hand temperature. Post hoc testing using Bonferroni corrected two-tailed independent t-tests revealed there was a significant decrease in heart rate between baseline and post-stimulation time points ($p < 0.001$, $d = 1.59$). There was a significant increase in SDNN between baseline and post-stimulation time points ($p < 0.001$, $d = 2.69$). For RMSSD, there was a significant increase between

baseline and stimulation time points ($p = 0.028$, $d = 1.73$) and between baseline and post-stimulation time points ($p < 0.001$, $d = 0.2.38$). For HRV (HRmax – HRmin), there was a significant increase between baseline and stimulation ($p = 0.036$, $d = 2.78$) and between baseline and post-stimulation ($p = 0.010$ $d = 2.95$). For hand temperature, there was a significant increase between baseline and stimulation ($p = 0.002$, $d = 2.30$) and between baseline and post-stimulation ($p < 0.001$, $d = 3.45$).

Statistical Analyses by Separate Frequencies

Table 7

*Statistical results from treatment Time * taVNS Frequency ANOVAs*

Variable	Main Effects (P-values)			Simple Effects of Frequency (P-values)			Simple Effects of Time (P-values)			
	Time	Time * Freq	Frequency	Baseline	Stim	Post	Sham	30 Hz	300 Hz	3000 Hz
Heart Rate (bpm)*	**.009**	.989	.118 [1,3]	.180	.154	.128	**.016** [3]	**.009** [3]	**.003** [3]	.083
SDNN (ms)*	**.000**	.953	.072 [3]	.156	.141	.069	.081	**.034** [3]	**.014** [3]	**.008** [3]
RMSSD (ms)*	**.000**	.921	**.029** [3]	.059	.059	**.032**	.142	**.012** [3]	**.012** [3]	**.029** [3]
HRV (HRmax - HRmin)*	**.007**	.157	.321	.800	.101	.638	.123	.245	.756	**.000** [2,3]
HF Power	.058	.906	.980	.945	.879	.994	.284	.855	.460	.249
LF Power	.056	.906	.979	.944	.875	.994	.281	.854	.454	.246
LF/HF Ratio	.267	.941	.998	.976	.976	.976	.662	.996	.332	.566
Resp Rate (bpm)	.893	.905	.800	.823	.876	.682	.973	.648	.638	.694
Hand Temp (°F)*	**.000**	.459	.210	.292	.257	.181	**.000** [2,3]	**.012** [3]	.280	**.023** [3]
Skin Conductance (µS)*	.115	.446	.118 [2]	.113	.311	.090	.329	.501	**.005**	.878

Note: *Mauchly's test of sphericity (p<.05), Greenhouse-Geisser alpha reported; Main Effects - Frequency: Planned Contrasts [1]30 Hz vs. Sham (p < .05) [3]3000 Hz vs. Sham (p <.05); Simple Effects - Time: Pairwise Comparisons (Bonferroni) Time * Freq [2]Pre vs. Stim (p<.05) [3]Pre vs. Post (p<.05)

Table 8

*Pairwise Comparisons Freq * Time (Bonferroni)*

	Sham		30 Hz		300 Hz		3000 Hz	
Variables	*Pre-Stim*	*Pre-Post*	*Pre-Stim*	*Pre-Post*	*Pre-Stim*	*Pre-Post*	*Pre-Stim*	*Pre-Post*
Heart Rate (bpm)*	.702	**.013**	.470	**.008**	.730	**.002**	1.000	.080
SDNN (ms)*	.274	.104	.611	**.027**	.754	**.010**	.348	**.005**
RMSSD (ms)*	.364	.247	.414	**.010**	.646	**.008**	.226	**.034**
HRV (HRmax - HRmin)*	.251	.497	1.000	.277	1.000	1.000	**.001**	**.016**
HF Power	.555	1.000	1.000	1.000	1.000	.681	1.000	.557
LF Power	.549	1.000	1.000	1.000	1.000	.670	1.000	.323
LF/HF Ratio	1.000	1.000	1.000	1.000	1.000	.859	1.000	1.000
Resp Rate (bpm)	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
Hand Temp (°F)*	**.002**	**.000**	.070	**.009**	.425	.439	.059	**.023**
Skin Conductance (µS)*	.406	1.000	.884	1.000	.329	.059	1.000	1.000

Analyses using ANOVA revealed significant changes heart rate, SDNN, RMSSD, and hand temperature in the 30Hz group. Post hoc testing using Bonferroni corrected two-tailed independent t-tests revealed there was a significant decrease in heart rate between baseline and post-stimulation time points ($p = 0.008$, $d = 0.99$), an increase in SDNN between baseline and post-stimulation ($p = 0.027$, $d = 1.38$), an increase in RMSSD between baseline and post-stimulation ($p = 0.010$, $d = 1.67$), and an decrease in hand temperature between baseline and post-stimulation ($p = 0.009$, $d = 2.56$).

In the 300Hz group, ANOVA revealed significant changes in heart rate, SDNN, RMSSD, and skin conductance. Post hoc testing using Bonferroni corrected two-tailed independent t-tests between baseline/stimulation and baseline/post-stimulation revealed there was a significant decrease in heart rate between baseline and post-stimulation ($p = 0.002$, $d = 1.17$), a significant increase in SDNN between baseline and post-stimulation ($p = 0.010$, $d = 1.90$), and a significant increase in RMSSD between baseline and post-stimulation ($p = 0.008$, $d = 1.51$).

In the 3000Hz group, ANOVA revealed significant changes in SDNN, RMSSD, HRV, and hand temperature. Post hoc testing revealed there was a significant increase in SDNN between baseline and post-stimulation ($p = 0.005$, $d = 1.49$), a significant increase in RMSSD between baseline and post-stimulation ($p = 0.034$, $d = 1.05$), significant increases in HRV between baseline and stimulation ($p = 0.001$, $d = 2.94$) and between baseline and post-stimulation ($p = 0.016$, $d = 2.72$), and a significant decrease in hand temperature between baseline and post-stimulation ($p = 0.023$, $d = 1.81$).

Safety and Tolerability

Table 9
Safety and Tolerability Questions

Question	Condition				Frequency			
	Chi-Squared Test		Anova		Chi-Squared Test		Anova	
	X^2	*p*	*F*	*p*	X^2	*p*	*F*	*p*
Rate your overall comfort.			1.137	.290			2.252	.091
Did you find the experience relaxing?	1.530	.216	0.607	.439	2.355	.502	0.312	.817
Did you experience any discomfort or pain?	0.877	.349	0.709	.403	2.399	.494	0.858	.468
Did you experience any dizziness?	0.432	.511	0.422	.518	3.236	.357	1.066	.370
Did you experience any blurred vision?	2.386	.122	2.400	.126	2.386	.496	0.775	.512
Did you experience any headache?	0.432	.511	0.422	.518	3.519	.318	1.164	.331
Did you experience skin itching or irritation?	1.336	.248	1.226	.272	4.555	.207	1.414	.247
Did you experience any discomfort or pain within 24-hours?	0.426	.514	0.415	.522	3.413	.332	1.126	.346
Did you experience any dizziness within 24-hours?								
Did you experience any blurred vision within 24-hours?	0.417	.518	2.223	.141	1.937	.586	0.726	.541
Did you experience any headache within 24-hours?	0.426	.514	0.415	.522	3.413	.332	1.126	.346
Did you experience skin itching or irritation within 24-hours?								

Note. Condition: Sham vs. Active; Frequency: Sham vs. 30 Hz vs. 300 Hz vs. 3000 Hz

Results of the yes or no safety questions were analyzed by a chi-squared test, and results of the subjective ratings were analyzed by ANOVA. The chi-squared test revealed there was no significant number of adverse effects between sham and all active groups combined. The test also revealed there was no significant number of adverse effects in either of the active groups. Analyses by ANOVA revealed there were no significant adverse effects between any of the treatment groups (sham vs. 30Hz vs. 300Hz vs. 3000Hz; see Appendix A for safety charts).

Discussion

It is well documented that the auricular branch of the vagus nerve contains afferent branches in both left and right ears located in the cymba concha, the tragus, and the acoustic meatus (Butt et al., 2019). Anatomical studies demonstrate the right vagus nerve has direct connections to the heart, and therefore the majority of tVNS paradigms consist of left ABVN stimulation to avoid heart-related adverse effects. Only a handful of studies have used bilateral stimulation paradigms in humans (Popov et al., 2013; Zamotrinsky et al., 2001), but these studies failed to assess the safety and tolerability of the method. Results from this present study support the hypothesis that three different

bilateral stimulation waveforms in the acoustic meatus were not significantly different in safety and tolerability compared to a sham. Each of the waveforms, including the sham, were safe and well tolerated and had significant effects on physiological activity.

Effects on heart rate

When analyzing each of the separate conditions rather than all the active conditions combined, there were significant changes in heart rate in the sham group (baseline/post-stimulation, $p = 0.013$, $d = 1.08$), the 30Hz group (baseline/post-stimulation, $p = 0.008$, $d = 0.99$), and the 300Hz group (baseline/post-stimulation, $p = 0.002$, $d = 1.17$). There were no significant changes in heart rate in the 3000Hz group. Even though heart rate was significantly reduced, it was reduced by less than 3bpm in all the groups. In this present study, it is difficult to conclude that the reduced heart rate in the 30Hz and 300Hz groups were a result of the tVNS, since heart rate was reduced in the sham group as well. Based on past literature, the effect of tVNS on heart rate remains unclear. Many tVNS studies have reported no significant changes in heart rate, but only a handful have demonstrated significant reductions in heart rate. Zamotrinsky et al. (2001) reported a significant reduction in heart rate after 3Hz bilateral stimulation in the cymba concha in 38 individuals with coronary artery disease. Clancy et al. (2014) reported a significant reduction in heart rate between active and sham after 15 minutes of 30Hz tVNS in the right tragus in 48 healthy individuals. Another study found a significant reduction in heart rate after 1 hour of 25Hz tVNS in the left concha in 48 healthy individuals (Busch et al., 2013). Based on data from this present study and past research, it appears that stimulation frequency has the most impact on heart rate, rather

than stimulation location or participant health. However, further research is needed to understand tVNS effects on heart rate.

Effects on HRV – SDNN and RMSSD

Vagal nerve activity has commonly been assessed by measuring heart rate variability, and therefore effective stimulation of the ABVN should have effects on HRV. Results from this study demonstrate that the three bilateral stimulation paradigms had significant effects on the SDNN and RMSSD components of HRV, whereas the sham stimulation did not, suggesting bilateral tVNS in the acoustic meatus is an effective method to increase HRV. In the 30Hz group, there was a significant change between baseline and post-stimulation SDNN ($p = 0.027$, $d = 1.38$) and RMSSD ($p = 0.010$, $d = 1.67$). In the 300Hz group, there was a significant change between baseline and post-stimulation SDNN ($p = 0.010$, $d = 1.90$) and RMSSD ($p = 0.008$, $d = 1.51$). In the 3000Hz group, there was a significant change between baseline and post-stimulation SDNN ($p = 0.005$, $d = 1.49$) and RMSSD ($p = 0.034$, $d = 1.05$). A recent study found that 1 hour of 25Hz tVNS in the right concha caused a significant change only in the SDNN component of HRV (De Couck et al., 2017). The SDNN value increased from 45.03 ± 16.19ms to 51.7 ± 19.2ms ($p = 0.001$, $d = 0.73$) after 1 hour. In this present study, the resting values of SDNN in the active groups and their changes were similar to the values in the De Couck et al. study (Table 4), but effect sizes were larger in this study. Bretherton et al. found that 15 minutes of 30Hz tVNS in an elderly population (> 55 years) significantly increased RMSSD values from 28ms to 31ms ($p < 0.001$). These values were much lower than the values in this present study, but that is expected because parasympathetic activity is known to decrease with age.

The HF component of HRV is considered an indicator of parasympathetic activity, and the LF component is considered an indicator of sympathetic activity (Shaffer & Ginsberg, 2017). Most HRV research looks for changes in the HF and LF components of HRV. Clancy et al. (2014) reported a significant decrease in the LF/HF ratio after 15 minutes of stimulation in the right tragus, indicating a reduction in sympathetic activity. Since there were no significant changes in the frequency components of HRV in this study, it is questionable whether stimulating in the acoustic meatus is effectively hitting the ABVN. However, past fMRI research does indicate that stimulating in the acoustic meatus is an effective form of vagus nerve stimulation based on activation in brain regions containing vagus nerve connections like the anterior cingulate cortex (Kraus et al., 2007). Since the effects on HRV were limited to the time components of HRV, it is likely that tVNS affects HRV through an indirect method of activating brain regions involved in autonomic regulation, rather than directly affecting cardiac activity. Age may also play a major role in how tVNS affects HRV. Clancy et al. suggested that tVNS would be most effective on patients with lower HRV and higher sympathetic activity (Clancy et al., 2014), and older individuals typically have lower HRV and higher sympathetic activity compared to young people. The average age of participants in this study was less than 24-years-old, but there was still a significant increase in the time components of HRV in all tVNS groups.

Effects on Hand Temperature

Changes in skin temperature are often indicative of changes in parasympathetic or sympathetic activity. Increases in finger skin temperature indicate increased parasympathetic activity and decreases in finger skin temperature indicate increased

sympathetic activity. Skin temperature decreased in every group in this study, but was only significant in the sham, 30Hz, and 3000Hz groups. This would suggest that sympathetic activity increased in each group, but the temperature decrease was likely caused by the mechanical components of the sensors on the hand restricting blood flow to the fingertips rather than by the stimulation, especially considering skin temperature decreased in the sham group as well.

Effects on safety

No serious adverse effects were observed in any of the groups after 10 minutes of continuous tVNS or 24 hours after the treatment. There were no patients who experienced any dizziness within 24 hours or skin itching or irritation within 24 hours after the stimulation in any of the groups. Considering how there is no current output in the sham group, any adverse effect in the sham group would not be related to the stimulation. There were no significant differences in safety and tolerability of any of the stimulation waveforms compared to the sham, so therefore the data supports the hypothesis that the three different waveforms would not have different safety and tolerability data compared to the sham.

Past research also concludes that various tVNS paradigms are safe and mostly tolerable. Busch et al. found no serious adverse effects after 1 hour of stimulating in the left concha with an average stimulation intensity of 1.6mA (Busch et al., 2013). Bauer et al. performed a double blind randomized clinical trial testing the NEMOS device by Cerbomed in an epilepsy population and found a handful of adverse effects (Bauer et al., 2016). Patients in the study used the tVNS device in the left concha for 4 hours a day for 20 weeks at an average stimulation intensity of 0.5 ± 0.47mA. In the active group, 22 out

of 37 patients experienced 74 treatment-related adverse effects over the treatment period. Of the treatment related adverse effects, 18.9% were headache, 16.2% were ear pain, 8.3% were application site erythema, 8.1% were vertigo, 2.7% were fatigue, and 5.4% were nausea. Out of all the adverse effects, 40.5% were labeled as mild and only 16.2% were labeled as severe. The study showed that tVNS is not free of adverse effects, but the method is safe and tolerable in most cases, as there were 5 participants in the active group that dropped out due to intolerance of treatment related headache, exhaustion, and nausea (Bauer et al., 2016).

Unilateral stimulation in the left ear is most often used in tVNS studies, but other studies have compared right ear stimulation with left ear stimulation (De Couck et al., 2017) and assessed the physiological effects of bilateral stimulation (Zamotrinsky et al., 1997, 2001). This present study was the first to assess the safety and tolerability of a range of bilateral stimulation paradigms (30Hz, 300Hz, 3000Hz), and results demonstrate that bilateral stimulation, while not completely free from common stimulation-related adverse effects, is safe and well tolerated in healthy individuals.

Limitations, Observations, and Future Research

This study only assessed the safety and efficacy of tVNS in a fairly young and healthy patient population. While there were some significant effects on physiological activity, it is difficult to conclude that bilateral tVNS would have the same effects on other clinical populations or patient populations of specific genders, age, or physical fitness levels. Significant clinical effects may be observed in sedentary or older populations with characteristically lower parasympathetic activity levels.

Two of the active stimulation groups had fairly high average stimulation intensity values compared to past studies (Bauer et al., 2016; Yakunina et al., 2016). The 30Hz group had an average intensity of 14.42 ± 6.24mA and the 3000Hz group had an average intensity of 14.14 ± 5.64mA. The higher average intensity compared to past studies is likely due to the electrode design. We used a dry hydrogel material as the electrolyte that makes contact with the skin, and while impedance of the hydrogel was not measured, it likely had a much higher impedance than steel ball electrodes seen in the Cerbomed device, and therefore required a higher intensity for the participants to feel the stimulation. It is also likely that pulse width plays an important role in the patient's ability to sense the stimulation. The 30Hz and the 3000Hz waveforms both had 50μS pulse widths, and the 300Hz waveform had a 350μS pulse width with an average stimulation intensity of 2.73 ± 1.70mA. It is often assumed that higher output currents would cause more adverse effects, however the data suggests that tVNS in the acoustic meatus at intensities up to 15mA are safe and tolerable in a healthy patient population.

The efficacy of the tVNS paradigms were assessed during a passive audio task where the participants were instructed to sit passively and stay calm during the whole test period. Future research should assess the efficacy of tVNS in other environments that invoke physiological or psychological responses such as a startle response or a mild anxiety attack, rather than neutral responses. This would help determine the true clinical impact tVNS could have in a variety of patient populations rather than just young and healthy individuals.

Another limitation of this study was the timeframe of which the data was collected and averaged. Data from this study showed significant effects on cardiac related

parameters, but the data was averaged from a 10-minute period in the baseline, stimulation, and post-stimulation task, which limited our ability to see any immediate effects of the treatments. Future research should analyze the immediate effects of various stimulation waveforms. Most tVNS treatment protocols consist of using a device for many hours a day over a long period of time (Bauer et al., 2016), but if tVNS can be demonstrated to have significant immediate effects, it can be applied to new patient populations such as those looking for drug-free relief during a panic or anxiety attack.

Conclusion

The results of this study demonstrate that bilateral auricular vagal nerve stimulation in the external acoustic meatus has effects on some resting physiological activity of healthy individuals and is safe and well tolerated. The most important finding of this study is that bilateral stimulation with our unique dry-hydrogel electrode design is safe and well tolerated, which opens the door to future product designs that incorporate bilateral stimulation paradigms. However, further research is needed to understand the clinical effects of bilateral auricular vagal nerve stimulation, as this study only observed effects in young and healthy individuals.

CHAPTER 3

EFFECTS OF AURICULAR NERVE STIMULATION ON PHYSIOLOGICAL ACTIVITY AND GOLF HITTING PERFORMANCE OF HEALTHY INDIVIDUALS

Abstract

Transcutaneous electrical nerve stimulation is a promising drug-free technology that could treat a variety of conditions, including performance anxiety in golfers. The vagus nerve is a key component in the parasympathetic nervous system, and the anxiolytic effects of vagus nerve stimulation in humans has been well documented. The great auricular nerve (GAN) is part of the cervical plexus and has similar connections in the brainstem as the vagus nerve. In the last few decades, the great auricular nerve has been a nerve target for treating pain, but little is known about the physiological effects of GAN stimulation. This study aimed to quantify the effects of GAN stimulation on physiological activity and golf hitting performance of healthy golfers. Ten minutes of bilateral GAN stimulation at the tympanomastoid fissure on the side of the neck was compared with sham stimulation (0mA) on 18 golfers during a hitting task. Results revealed a significant increase in quality of feel of each shot ($p = 0.05$, $d = 0.83$) and a significant decrease in state anxiety ($p = 0.005$, $d = 0.42$). There were no significant changes in other performance or physiological metrics. While GAN stimulation enhanced feel of the golf swing but did not affect hitting performance of healthy golfers, it may be an effective drug-free treatment for performance anxiety and may help golfers and other athletes keep calm during high-anxious situations.

Introduction

Anxiety in Golf

Anxiety in golf and other sports can be described as an unpleasant motivational state that consists of a cognitive side (worrying thoughts) and a somatic side (physical symptoms). Many golfers perform their best when they are anxious because they have a heightened focus and can keep their physical symptoms under control. However, uncontrolled negative thoughts and anxiety symptoms often lead to uncharacteristically poor performance. Typical scenarios that lead to performance anxiety in golfers include the first tee shot ("first tee jitters"), playing in front of a crowd, playing with a lead, competing against a particular individual, and having to make short breaking putts (Smith et al., 2003). Symptoms of anxiety include tense muscles, elevated heart rate, sweaty palms, jerky and mechanical movements in the swing, and yips in the putting stroke, chipping or full swing. Anxiety is often considered part of the mental game of golf, and the best golfers excel at keeping their anxiety under control. However, many golfers struggle with anxiety and end up losing their interest in the game because they are unable to overcome the problem. Neuromodulation technology is a promising drug-free method that may help golfers, athletes, and common people keep their anxiety symptoms under control and improve their quality of life.

Neuromodulation in Golf

Studies looking at effects of non-invasive electric neuromodulation on human performance mostly consist of transcutaneous direct current stimulation (tDCS) applied to the left dorsolateral prefrontal cortex. One study found that tDCS may enhance flow state activity in video gaming and other sports (Gold & Ciorciari, 2019). Another study

found that active tDCS resulted in greater putting accuracy compared to sham tDCS in novice golfers (Zhu et al., 2015). Studies have shown that expert athletes show lower amounts of activity in brain regions like the posterior cingulate, the amygdala-forebrain complex, and the basal ganglia compared to novice athletes (Milton et al., 2007). In order to truly enhance human performance, stimulation methods should aim to modulate brain activity associated with reduced anxiety and increased flow state (mental state of peak performance). Peripheral nerve stimulation may be a more suitable alternative to tDCS due to easier access to peripheral nerves and their communications with brain regions involving fear, anxiety, and flow state activity.

The GAN has been used as a target in Auricular Acupuncture for hundreds of years to treat a variety of ailments such as epilepsy and pain (Shu et al., 2004; Usichenko et al., 2017). Shu et. al. found decreases in glutamine and increases in GABA in the hippocampus of a rat having an experimentally induced seizure after stimulating the GAN in the ear. Nerve tracing studies have shown that the GAN has connections in the nucleus of the solitary tract (NTS), the solitary nucleus (SN) of the medulla oblongata, the spinal trigeminal nucleus and communicates (thin nerve fibers connect to the two nerves) with the auricular branch of the vagus nerve (ABVN) (Ginsberg & Eicher, 2000; Liu & Hu, 1988). fMRI studies have shown that stimulation of the GAN at the earlobe caused deactivation in the hippocampus, posterior cingulate gyrus, parahippocampal gyrus, and the amygdala, regions associated with the fear and anxiety response (Yakunina et al., 2017). Because the GAN targets and synapses in similar brain structures as the ABVN, it may be an effective stimulation target for the treatment of anxiety. There are a handful of devices known as Cranial Electrotherapy Stimulation (CES) devices that

have been approved by the FDA to treat insomnia, anxiety, depression, and pain. One of these devices is called Alpha Stim, a device that uses ear-clip electrodes to bilaterally stimulate branches of the GAN on the ear lobe. Studies have demonstrated that this device may be an effective treatment for anxiety disorders like Post-Traumatic Stress Disorder and General Anxiety Disorder (Barclay & Barclay, 2014). One recent study found that 10 minutes of bilateral GAN/ABVN stimulation in 9 Olympic archers caused a significant decrease in resting heart rate of 10.6 bpm after stimulation (Pre: 77.03 ± 14.52 bpm, Post: 66.43 ± 8.53 bpm) (Rodriguez, 2020). However, no studies have analyzed how GAN stimulation might affect performance anxiety in golfers. This present study aims to quantify the effects of GAN stimulation on physiological activity, performance anxiety and hitting performance of healthy golfers.

Anatomical locations within the ear for transcutaneous vagus nerve stimulation (tVNS) and GAN stimulation require electrode designs that are not ideal for a variety of potential patient populations, such as athletes with performance anxiety. Dry electrode designs would cause too much skin irritation for an athlete to consider using when trying to relax, and wet electrode designs are too complicated of a user experience, as the athlete would need to carry a bottle of gel or saline with them at all times in order to use the electrode. Therefore, we proposed to stimulate over a location called the tympanomastoid fissure on the side of the neck and below the ear, a region behind the earlobe and anterior to the mastoid process that contains the ABVN and the GAN (Kiyokawa et al., 2014). This location is easier to access than locations within the ear and does not require custom electrodes for each patient to achieve maximum comfort during

stimulation. We used the same dry-hydrogel electrode design that was used in the experiment discussed in Chapter 2.

Hypothesis

We hypothesized that non-invasive electrical nerve stimulation of the GAN would cause a statistically significant change in performance outcomes in a golf hitting task.

We hypothesized that non-invasive electrical nerve stimulation of the GAN would cause a statistically significant change in physiological activity (heart rate, heart rate variability, brain activity, muscle tension, skin conductance, skin temperature, respiration rate) and psychological activity (STAI score).

We hypothesized that non-invasive electrical nerve stimulation of the GAN would cause a statistically significant change in the motion of the golf swing.

Methods

Volunteer golfers reported to TopGolf in Scottsdale, Arizona to complete a hitting task over a period of one hour or less. Throughout the study, we measured brain activity, heart rate, heart rate variability, skin conductance, skin temperature, muscle tension, and blood pressure of each participant. We also measured golf performance metrics that consisted of swing speed, tempo, feel, and accuracy of each shot.

Participants were healthy golfers aged 18-75 years of age with a handicap of 20 or lower. We excluded minors, adults who are unable to consent, and prisoners from participating in this study.

Golfers wore the Muse brain sensing headband (with Opti Brain software) and had their clubs fitted with the Blast motion sensor to capture swing metrics. Once fitted with sensors, golfers were allowed to hit five warm-up shots at the 150-yard target to get

comfortable with the setup. After the warmup, the first hitting baseline trial began. Golfers hit 10 shots at the 150-yard target, with the goal of hitting each shot as close to the center as possible. Each shot was recorded for accuracy, swing speed, swing tempo, swing time, and feel of the shot on a scale of 1-10, with 10 being the best shot they have ever hit. Brain activity in the one second before swing initiation was recorded for each shot as well. For each shot the golfer made in the target, they were awarded $5. After the 10 shots were hit, the golfer hit an 11th shot. The 11th shot had to land in the target if the golfer wanted to keep any of the money they just made. If they missed the 11th shot, they lost all their earned money. Golfers then rated on a scale of 1-10 how anxious they felt over the 11th shot, with 10 being the most anxious they have ever felt playing golf.

After the first baseline hitting task, golfers sat down and were fitted with the remaining sensors while they completed the State Trait Anxiety Inventory (STAI) survey. Then five minutes of resting biometrics was recorded. After the five-minute rest period, we gave the golfer 10 minutes of auricular nerve stimulation (Figure 2, Figure 3, Table 10). Participants were instructed to increase the stimulation intensity until a comfortable setting, or the maximum output had been reached.

After the stimulation, golfers hit 10 more golf shots at the 150-yard target, with the same conditions as the first hitting baseline period. For each shot made in the target, they earned $5. They then hit an 11th shot again and must have made the shot in the target in order to keep the money they had made throughout the entire study session. Golfers rated on a scale of 1-10 how anxious they felt over the 11th shot.

After the 11th shot, golfers were fitted with the biosensors as they completed the STAI once more. We then recorded five minutes of resting biometrics. After the five minutes, participants completed a questionnaire asking about their experience.

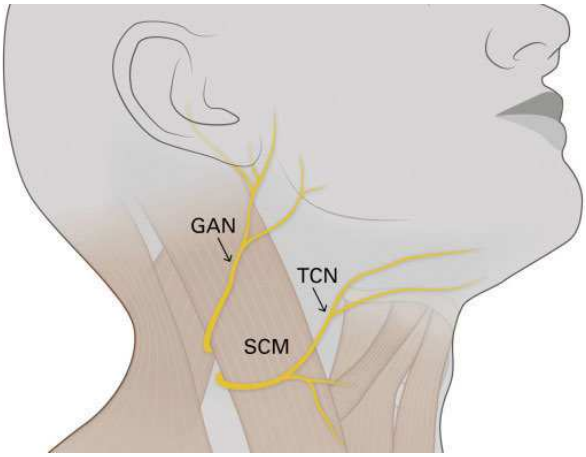

Figure 2: GAN target for stimulation

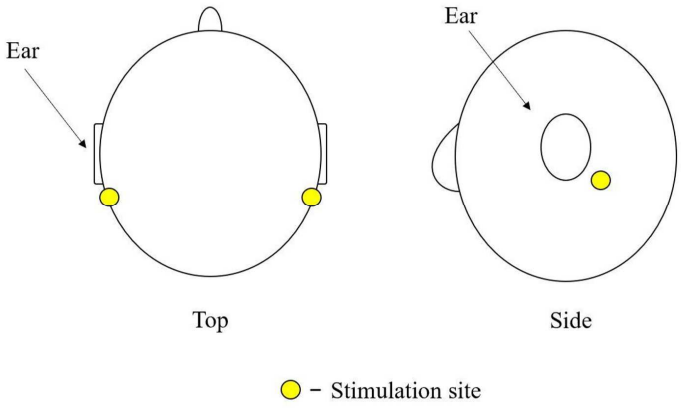

Figure 3: Location of biphasic electrical stimulation of the GAN over the tympanomastoid fissure

Table 10
Stimulation Parameters

Condition	*Frequency (Hz)*	*Pulse Width (uS)*	*Pulse Gap (mS)*	*Current (mA)*
Active - Biphasic	100 Hz	540	4.5	0 - 10
Sham	0	0	0	0

Data Analysis Approach

The Muse headset along with Opti Brain software was used to collect EEG at the FP1 and FP2 locations. EEG activity was only collected during the hitting task. During each shot, EEG was captured in the one second before the start of the swing. EEG activity was separated into frequency components (theta 4-7Hz, alpha 8-12Hz, beta1 13-20Hz, beta2 21-30Hz) using a Fast Fourier transformation, and the pre-stimulation values were compared with the post-stimulation values using a two-tailed independent t-test for all participants in the active and sham groups.

The Nexus system was used to record heart rate and HRV (2048Hz sampling rate) using electrodes placed on the chest, galvanic skin response (32Hz sampling rate) and skin temperature (32Hz sampling rate) using electrodes placed on left hand fingers, and EMG (2048Hz sampling rate) activity using electrodes placed on the upper left and right trapezius muscles. Blood pressure was monitored using a Life Source blood pressure cuff. Physiological activity was averaged in each of the 5-minute resting periods, and pre-stimulation and post-stimulation values was compared using a two-tailed independent t-test for all participants in the active and sham groups.

The Blast Motion sensor was used to collect swing tempo, swing speed, and swing time. Shot accuracy was measured by taking the score reported by the TopGolf scoring software. Each shot was given a score between 5 and 10, with 5 being in the outside circle

of the target and 10 being in the center circle of the target. A score of 0 was used if the target was missed completely. Participants rated the feel of each shot on a scale of 1-10, with 10 being the best feeling shot ever and 1 being the worst shot ever. Both score and feel were averaged for all 10 shots in each hitting task and pre-stim and post-stim values were compared using a two-tailed independent t-test for all participants in the active and sham groups. A chi-squared test was used to compare the shot made outcome in the pressure shot scenario in both groups.

The State-Trait Anxiety Inventory survey was used to measure anxiety throughout the study. The S-Anxiety scale (STAI Form Y-1, Spielberger, 2010) "consists of twenty statements that evaluate how respondents feel 'right now, at this moment.' Scores on the S-Anxiety scale increase in response to physical danger and psychological stress and decrease as a result of relaxation training. The S-Anxiety scale has been found to be a sensitive indicator of changes in transitory anxiety experienced by clients and patients in counseling, psychotherapy, and behavior-modification programs. The scale has also been used extensively to assess the level of S-Anxiety induced by stressful experimental procedures and by unavoidable real-life stressors such as imminent surgery, dental treatment, job interviews, or important school tests". Pre-stim and post-stim STAI values were averaged in both active and sham groups and were compared using a two-tailed independent t-test.

Results

Performance Metrics

The only significant change in motion or performance measures was in the feel of the golf swing. The golfers rated the feel closer to 10 in the active condition compared to

the sham condition (Table 11). There were no significant changes in any of the other performance metrics during both active and sham groups.

The average baseline score, swing speed, and shots made were higher in the active group, but there was no significant change in score, swing speed, and shots made post stimulation in either group. A two-tailed independent t-test (pre-stim, post-stim) revealed that feel of each shot was significantly improved in the active group only ($p = 0.05$, $d = 0.83$).

Table 11
Mean Performance Values for Active and Sham Treatment

	Active (n=10)			Sham (n=8)		
Metric	*Pre*	*Post*	*p-value*	*Pre*	*Post*	*p-value*
Feel	6.83 ± .92	7.43 ± .73	**0.05**	6.41 ± 1.34	6.61 ± 1.24	0.65
Score	3.83 ± 2.52	3.75 ± 2.53	0.84	1.78 ± 2.09	1.80 ± 2.05	0.97
Swing Tempo	2.94 ± .57	2.90 ± .54	0.21	2.97 ± .74	3.02 ± .75	*0.08*
Swing Time (s)	1.06 ± .12	1.05 ± .11	0.53	1.09 ± .12	1.10 ± .13	0.76
Swing Speed (mph)	78.24 ± 7.69	76.23 ± 6.56	0.14	63.43 ± 12.32	63.33 ± 11.26	0.91
Shots Made	5.70 ± 3.62	5.60 ± 3.60	0.85	2.75 ± 3.15	3.00 ± 3.34	0.83

Pressure Shot Performance

Of the 10 golfers in the active group, 2 golfers did not make any shots and therefore did not have a pressure shot to hit. Of the 8 golfers in the sham group, three did not make any shots and therefore did not have a pressure shot to hit. Two-tailed independent t-tests revealed there were no significant changes in feel, score, swing tempo, swing time, swing speed, and anxiety over the shot between baseline and post stimulation in both active and sham groups. A chi-squared test revealed no significant change in shots made in the pressure shot scenario in both groups.

Table 12

Mean Pressure Shot Performance Values for Active and Sham Treatment

	Active (n=8)			Sham (n=5)		
Metric	*Pre*	*Post*	*p-value*	*Pre*	*Post*	*p-value*
Feel	6.88 ± 2.95	7.13 ± 1.73	0.79	7.80 ± 1.30	8.00 ± 1.41	0.85
Score	4.00 ± 3.42	4.63 ± 4.03	0.73	2.40 ± 3.29	3.40 ± 3.13	0.47
Swing Tempo	3.04 ± .48	3.00 ± .44	0.48	2.80 ± .17	2.80 ± .26	1.00
Swing Time (s)	1.08 ± .07	1.10 ± .09	0.40	1.02 ± .16	1.03 ± .17	0.90
Swing Speed (mph)	78.20 ± 4.82	77.20 ± 3.27	0.51	64.33 ± 16.29	66.33 ± 15.95	0.32
Shot Made	5.00	5.00	0.56	2.00	3.00	0.13
Anxiety	5.75 ± 1.58	5.00 ± 1.51	0.27	3.00 ± 2.55	3.20 ± 2.17	0.78

Physiological Metrics

In the active group, a two-tailed independent t-test revealed a significant reduction in STAI scores between baseline and post stimulation timepoints ($p < 0.05$, $d = 2.84$). STAI scores were also negatively correlated with feel in the active group ($r = -0.6$, $p = 0.07$), but the correlation was not significant. There were no other significant changes in physiological activity between baseline and post stimulation timepoints in the active group.

In the sham group, two-tailed independent t-tests revealed a significant reduction in Systolic and Diastolic blood pressure values ($p < 0.05$). There were no other significant changes in physiological activity between baseline and post stimulation timepoints in the sham group.

Table 13

Mean 5-min Physiological Response Values for Active and Sham Treatment

	Active (n=10)			Sham (n=8)		
Metric	*Pre*	*Post*	*p-value*	*Pre*	*Post*	*p-value*
EMG Left (mV)	18.45 ± 15.15	10.99 ± 4.58	0.15	16.24 ± 3.91	16.19 ± 6.60	0.99
EMG Right (mV)	10.53 ± 5.77	8.93 ± 3.56	0.32	12.59 ± 6.25	18.54 ± 11.31	0.10
HR (bpm)	86.26 ± 17.59	85.17 ± 16.33	0.38	83.88 ± 16.19	84.66 ± 15.04	0.70
RR (ms)	21.21 ± 3.96	21.35 ± 3.96	0.86	18.07 ± 2.01	18.57 ± 2.51	0.63
Skin Conductance (uS)	11.87 ± 5.75	8.62 ± 2.99	0.13	8.45 ± 3.49	9.73 ± 2.04	0.19
Skin Temperature (F)	98.73 ± .72	98.85 ± .65	0.54	97.29 ± 2.00	97.78 ± 1.59	0.54
RMSSD (ms)	44.67 ± 18.28	47.62 ± 8.35	0.72	37.55 ± 25.28	43.43 ± 35.82	0.68
VLF (ms^2)	13.99 ± 3.95	13.61 ± 8.35	0.89	16.65 ± 11.98	12.29 ± 4.89	0.28
LF (ms^2)	55.27 ± 14.06	60.33 ± 12.23	0.31	50.18 ± 13.69	48.98 ± 16.98	0.90
HF (ms^2)	27.71 ± 14.39	26.06 ± 11.41	0.75	33.18 ± 16.50	34.21 ± 17.37	0.90
LF/HF	3.12 ± 2.57	2.44 ± 1.14	0.45	2.09 ± 1.45	2.09 ± .96	1.00
BP Systole (mmHg)	116.30 ± 9.68	115.60 ± 8.57	0.81	113.75 ± 9.74	107.63 ± 9.62	**0.03**
BP Diastole (mmHg)	81.00 ± 10.76	75.30 ± 6.77	*0.07*	79.50 ± 4.75	73.00 ± 4.81	**0.03**
Pulse (bpm)	84.50 ± 19.48	80.60 ± 16.97	*0.06*	80.75 ± 11.47	80.88 ± 12.12	0.96
STAI	41.10 ± 14.65	26.10 ± 4.09	**0.01**	34.75 ± 13.58	28.50 ± 7.25	*0.08*

EEG Activity – FP1 and FP2

EEG activity was measured for each shot at locations FP1 and FP2 and only the data during the 1-second before the start of the swing was used for data analysis. A Fast Fourier transform using the Opti Brain application was used to separate the EEG signal into its frequency components. Two-tailed independent t-tests did not reveal any significant changes in activity over FP1 and FP2 locations between baseline and post stimulation timepoints in either active or sham groups. One participant in the sham group had poor signal quality during each hitting task and therefore did not contribute to the data analysis. Correlation tests were performed between EEG activity and score, EEG activity and STAI scores, and EEG Activity and feel. The only significant correlations that were found were between FP2 Theta and post-stimulation STAI scores ($r = 0.68$, $p = 0.03$) and between FP2 Alpha and post-stimulation STAI scores ($r = 0.69$, $p = 0.03$).

Table 14

FP1 Values for Total Shots for Active and Sham Treatment

	Active (n=10)			Sham (n=7)		
Metric	*Pre*	*Post*	*p-value*	*Pre*	*Post*	*p-value*
Total	4.02 ± 2.57	4.10 ± 1.97	0.90	6.23 ± 4.04	7.70 ± 7.84	0.58
Theta	4.33 ± 2.31	4.10 ± 2.04	0.66	7.14 ± 5.16	8.57 ± 9.58	0.65
Alpha	2.17 ± .90	2.20 ± .84	0.90	2.51 ± 1.21	4.10 ± 3.93	0.34
Beta 1	1.61 ± 1.39	1.49 ± 1.74	0.53	1.94 ± 1.09	3.03 ± 2.82	0.18
Beta 2	1.03 ± .51	.98 ± .36	0.64	1.37 ± .70	1.87 ± 1.43	0.21

Table 15

FP2 Values for Total Shots for Active and Sham Treatment

	Active (n=10)			Sham (n=7)		
Metric	*Pre*	*Post*	*p-value*	*Pre*	*Post*	*p-value*
Total	4.13 ± 3.11	4.18 ± 2.06	0.95	4.33 ± 2.14	5.27 ± 3.16	0.31
Theta	4.61 ± 2.85	4.09 ± 2.13	0.49	8.24 ± 11.48	5.97 ± 3.93	0.64
Alpha	2.42 ± 1.59	2.00 ± .87	0.36	4.25 ± 4.63	2.88 ± 1.85	0.48
Beta 1	1.66 ± 1.03	1.43 ± .54	0.48	2.93 ± 3.37	2.02 ± 1.31	0.52
Beta 2	1.10 ± .65	.99 ± .43	0.51	1.75 ± 1.56	1.43 ± .72	0.64

EEG Synchrony – FP1 and FP2

EEG synchrony activity was measured over locations FP1 and FP2 and only the data during the 1-second before the start of the swing was used for data analysis. Synchrony activity was quantified using synergy, or coherence across theta, alpha, and beta frequencies over each electrode. Two-tailed independent t-tests did not reveal any significant changes in synchrony activity over FP1 and FP2 locations between baseline and post stimulation timepoints in either active or sham groups. One participant in the sham group had poor signal quality during each hitting task and therefore did not contribute to the data analysis.

Table 16

FP1 Synchrony for Total Shots for Active and Sham Treatment

	Active (n=10)			Sham (n=7)		
Metric	*Pre*	*Post*	*p-value*	*Pre*	*Post*	*p-value*
Synergy (%)	65.42 ± 3.62	64.72 ± 2.38	0.53	67.13 ± 3.68	66.95 ± 3.02	0.92

Table 17
FP2 Synchrony for Total Shots for Active and Sham Treatment

	Active (n=10)			Sham (n=7)		
Metric	*Pre*	*Post*	*p-value*	*Pre*	*Post*	*p-value*
Synergy (%)	64.74 ± 4.84	65.20 ± 4.01	0.70	66.52 ± 6.75	65.91 ± 3.41	0.78

Discussion

Neuromodulation is a promising technology that could provide effective drug-free anxiety relief and performance enhancement for many types of athletes and non-athletes in general. This study aimed to quantify a novel method of peripheral nerve stimulation on physiological activity and hitting performance of healthy golfers. The data did not support the hypotheses that GAN stimulation would cause a significant change in hitting performance or physiological activity, but the stimulation did cause a significant increase in feel and a significant decrease in anxiety levels.

Effect on Performance

The data does not support the hypothesis that GAN stimulation would cause a significant change in performance metrics, except for feel, compared to a sham. In the sham group, there were no significant changes in any of the performance metrics, and there were no apparent trends in the data. In the active group, there was no noticeable change in score, swing tempo, swing time, and the number of shots made. Swing speed in the active group was reduced by 2mph, suggesting there may have been a relaxation effect after stimulation, but the change was not significant.

While not a direct indicator of performance, feel was significantly increased after GAN stimulation in the active group only (Pre: 6.83, Post: 7.43, $p = 0.05$, $d = 0.83$). Feel of the shot is not dependent on the outcome of the shot, but rather how the shot literally

felt. Higher feel shots typically result in better outcomes, as golfers can learn to associate good shots with the right feel, but it is not always the case. Past studies looking at how neurofeedback training affects putting performance have demonstrated significant improvements in performance, but non-significant improvements in feel (Crews et al., 2016; Gook et al., 2018). Considering how the golfers in this current study in the active group had higher baseline performance scores than in the sham group, it was unlikely there would be a significant increase in performance. However, the increase in feel in the active group only is indicative that GAN stimulation may be an effective treatment for golfers who have decreased feel due to performance anxiety, and therefore may improve performance during moments of high anxiety. One would expect that as feel increases, state anxiety would decrease. Data from this study revealed a negative correlation ($r = -0.6$, $p = 0.07$) between post stimulation feel and STAI scores in the active group, which suggests that if GAN stimulation increases feel, it would decrease state anxiety.

There were no significant changes in pressure shot performance metrics in either active or sham groups. In the active group, there was an increase in feel (pre: 6.88 ± 2.95, post: 7.13 ± 1.73, $d = 0.11$) and a decrease in subjective anxiety levels (pre: 5.75 ± 1.58, post: 5 ± 1.51, $d = 0.49$), but these changes were not significant. However, there were a number of participants that did not complete the pressure shot. In the active group, there were only 8 golfers that performed well enough to hit a pressure shot, and in the sham group, there were only 5 golfers. It is likely that the length of time between receiving the treatment and hitting the pressure shot was the reason there was no significant change in pressure shot outcomes. The acute anxiolytic effects of the stimulation may have faded by the time the golfers had to hit the second pressure shot.

There was a decrease in pressure shot anxiety in the active group and an increase in pressure shot anxiety in the sham group (Pre: 3.00 ± 2.55, Post: 3.20 ± 2.17, $d = 0.08$), but the changes were not significant. GAN stimulation may have the greatest effect on performance immediately after treatment is finished. However, it is difficult to make any reasonable conclusions about the effect of GAN stimulation on performance under pressure as there were very few participants that completed the pressure shot.

Effect on Psychological Activity

The data suggests that GAN stimulation has a significant effect on psychological activity by reducing state-anxiety levels. In the active group, there was a significant reduction in STAI score (Pre: 41.10 ± 14.65, Post: 26.10 ± 4.09, $p < 0.05$, $d = 2.84$). According to the State-Trait Anxiety Inventory for Adults – Manual, scores between 20-37 are considered "Mild", scores between 38-44 are considered "Moderate", and scores between 45-80 are considered "Severe". Patients with "Severe" levels of anxiety would be considered clinically anxious, and patients with "Mild" levels of anxiety would be considered healthy. Therefore, clinically meaningful reductions in anxiety should reduce STAI scores from "Severe" or high "Moderate" to low "Moderate" or "Mild" levels. STAI scores were reduced in the sham group, but the change was not significant. The STAI score reduction may have been greater in the active group because the baseline STAI scores were 6.35 points higher than the baseline scores in the sham group (41.10 ± 14.65 in the active group compared to 34.75 ± 13.58 in the sham group); however, the difference in baseline scores between the two groups was not significant.

Past research using the STAI to assess acute changes in anxiety levels indicate treatments are more likely to be effective the higher the baseline state anxiety. One study

observing the effects of a 20-minute mindfulness technique in 20 individuals reported a change in STAI from 49.6 points to 29.5 points in the active group, compared to 47.9 points to 47.3 points in the sham group (Pawlow et al., 2003). Another study testing a 30-minute mindfulness technique in 24 individuals reported significant changes in STAI scores from 39.3 points to 29.2 points in the active group and 37.8 points to 30.4 points in the sham group (Knowlton & Larkin, 2006). No studies have looked at the effects of GAN stimulation on changes in STAI scores, but one study looking at the effects of earlobe stimulation for 60 minutes in 17 individuals reported a change in STAI scores from 34.9 points to 38.9 points in the active group and 31.5 points to 34.6 points in the sham group (Hill, 2015). Past research has shown that high-anxious individuals show bigger reductions in anxiety levels compared to low-anxious individuals. This suggests that GAN stimulation may be more effective at reducing state-anxiety the higher a person's state-anxiety score. If a person is only feeling mildly anxious, there likely will not be any clinically meaningful anxiolytic effect from GAN stimulation.

Effect on Physiological Activity

There were no significant changes in heart rate between baseline and post stimulation in either group. This may not necessarily mean that GAN stimulation has no effects on heart rate because heart rate was likely higher to account for the physical motion of hitting the golf shots. It was also a relatively hot day and the study was conducted outside, so it is likely that heart rate would tend to stay higher to account for the heat of the day and the physical nature of the hitting task. As none of the participants reported severe levels of anxiety, it would be interesting to observe the effects of GAN stimulation on severely anxious golfers with higher resting heart rates. The data does,

however, provide evidence that bilateral GAN stimulation does not have adverse effects on the heart such as causing bradycardia.

Heart Rate Variability is a common method of analyzing cardiac activity that involves measuring the time differences between successive heartbeats (RR intervals). Changes in HRV activity are often associated with changes in human performance, and therefore, HRV is a common metric to be measured in sport studies. This study analyzed the HRV time component root of the mean squared differences of successive RR intervals (RMSSD) and the frequency components very low frequency (VLF, <0.04Hz), low frequency (LF, 0.04Hz – 0.15Hz), high frequency (HF, 0.15Hz – 0.4Hz) and the low frequency-high frequency ratio (LF/HF). RMSSD is associated with short-term rapid changes in heart rate and would be expected to increase after successful vagus nerve stimulation (DeGiorgio et al., 2010). The HF component of HRV is associated with parasympathetic activity, and the LF is a measure of both sympathetic and parasympathetic activity. The ratio LF/HF has been proposed as an index of sympathetic to parasympathetic balance of heart rate fluctuation (De Couck et al., 2017; DeGiorgio et al., 2010). Successful stimulation of the vagus nerve should both increase the HF and decrease the LF components on HRV (Anon, 1996).

There were no significant changes in any of the HRV metrics after GAN stimulation. It was expected that GAN stimulation would have similar effects as tVNS on HRV due to similar projections in the brain stem as the vagus nerve. It is known that the vagus nerve is the main nerve that controls HRV, but even stimulating the vagus nerve does not consistently produce a change in HRV as one would expect. De Couck et. al. (2017) found that stimulating the ABVN in the concha for 10 minutes did not produce

any significant change in HRV metrics, and other studies looking at invasive VNS found that the method does not increase HRV (Jansen et al., 2011; Setty et al., 1998). Inconsistent effects on HRV may be due to indirect effects on the heart, as the GAN and ABVN are afferent branches that travel towards the brainstem, rather than directly to the heart.

Effect on Brain Activity

While there were no significant changes in EEG activity after treatment in either active or sham groups, there were some interesting observations. In the active group, power values in each frequency band hardly changed after stimulation at both FP1 and FP2 locations, whereas in the sham group, there appeared to be a trend of decreased activity over FP2 and increased activity over FP1. While not statistically significant, it is clear that EEG power over FP1 was higher in the sham group compared to the active group, and the sham group had a lower average hitting accuracy during both hitting tasks. Past sports studies have demonstrated that higher activity in the left hemisphere 1 second before the putt is associated with poor performance (Crews & Landers, 1993; Salazar et al., 1990), and while the GAN stimulation did not cause an improvement in hitting accuracy, it also did not cause left hemispheric EEG activity to increase, which means it may have actually had an effect on hitting performance. However, the data does not support any claims that GAN stimulation had any effect on EEG activity. Further research is needed to understand the effects of GAN stimulation on EEG activity over FP1 and FP2 locations.

Synergy is another measurement of brain activity that describes synchrony of brain activity across theta, alpha, and beta frequency bands and it can be calculated from

a single electrode or from multiple electrodes at once to quantify whole brain synchrony. Past research has demonstrated that high-performing business people have higher synergy levels in frontal brain structures (Harung & Travis, 2012), and EEG neurofeedback protocols that train to increase synergy in golfers have led to significantly increased synergy levels and improved putting performance (Crews et al., 2016, 2018; Gook et al., 2018). This suggests that methods and devices that affect synergy levels may affect performance. However, data from this study did not show a significant effect on synergy levels. Gook et. al. (2018) showed a significant increase in synergy levels after neurofeedback training from 67.94 ± 3.94 percent to 72.67 ± 4.18 percent, which was correlated with improved performance, whereas baseline synergy values in this study were 65.41 ± 3.62 percent over FP1 and 64.74 ± 4.84 percent over FP2, with no significant change over either location and no correlations with performance. More research is needed to understand optimal synergy levels for peak performance.

Limitations of the Study

The main limitation of this study was the small sample size of golfers with a wide range of skill level. The study did not analyze the effect of GAN stimulation on golfers of separate skill levels. There were no significant changes in brain activity or performance metrics other than feel in either active or sham groups, but there may have been significant changes in these metrics if observed strictly in an expert population or a novice population. Gold et. al. (2019) found that 20 minutes of tDCS did not improve video game performance of trained players but did improve performance of untrained players. Novice and untrained athletes have more room to improve than elite athletes, and therefore, it is more likely that a treatment would improve the physical performance

in a novice population and have minimal effect on an elite population. However, feel is a major component of performance, and if GAN stimulation improves feel, then it will likely have effects on performance of elite athletes, especially during high-pressure, real-world situations where anxiety is likely to negatively affect feel and performance.

Novice golfers have been shown to have higher levels of brain activity than expert golfers just before hitting a shot, especially in the posterior cingulate area, as they must process more sensory information than an expert to successfully execute a shot (Milton et al., 2007). Other studies have shown that lower motor skills in athletes correlate to higher activity in the posterior cingulate gyrus (Janke et al., 2000; Puttemans et al., 2005). A common cause of poor performance in expert golfers is overthinking and over-processing information before hitting a shot. Since GAN stimulation has been shown to decrease activity in the posterior cingulate gyrus (Yakunina et al., 2017), it may produce a more noticeable effect on performance and brain activity in an expert population alone, as it may help them stop overthinking and return to an automatic state of performance.

It has been hypothesized that novices have greater activity in limbic areas in the brain compared to experts because they must exert more energy to process the golf swing (Milton et al., 2007). High activity in these areas may be essential if a novice wants to efficiently learn the golf swing, so GAN stimulation may reduce the novice's ability to learn the golf swing. However, it could also be argued that because GAN stimulation has shown to decrease activity in the amygdala (Yakunina et al., 2017) and significantly reduces state anxiety, it could be an effective treatment for golfers of any level who experience anxiety before or during a round.

Regarding the nerve target, stimulation was applied on the side of the neck behind the earlobe and anterior to the mastoid process, and over a location called the tympanomastoid fissure. This location is known to contain branches of the GAN and the ABVN (Kiyokawa et al., 2014), but ABVN branches at this location are not as superficial as GAN branches, and may not truly be activated, hence the non-significant effects on cardiac-related metrics. fMRI studies similar to past protocols like Kraus et. al. (2007) should be performed to observe brain activity in regions known to have vagal projections to verify if stimulating at this location truly does activate the ABVN or just the GAN alone.

Conclusion

The results of this study demonstrate that GAN stimulation at the tympanomastoid fissure did not have significant effects on hitting performance or physiological activity of healthy golfers, but it did significantly improve quality of feel for each shot and reduce state anxiety after a golf hitting task. Future research should assess the effects of GAN stimulation in a novice or elite athlete populations alone and should include only severely anxious athletes. More research is needed to verify the anxiolytic effects of GAN stimulation in athletes, but GAN stimulation is a promising technology that could help all types of people reduce anxiety during stressful situations.

CHAPTER 4

EFFECTS OF CERVICAL NERVE STIMULATION ON PHYSIOLOGICAL ACTIVITY AND GOLF PUTTING PERFORMANCE OF YIPS-AFFECTED GOLFERS

Abstract

The “yips” is a major neurophysiological problem that has plagued the golf world for decades. Golfers who contract the yips demonstrate uncharacteristically poor motor performance, and mostly resort to alcohol and drugs like beta-blockers or benzodiazepines to treat it, often unsuccessfully. Cervical nerves on the back of the neck target similar brain structures as the vagus nerve, which are known to modulate brain activity associated with anxiety, depression, and fear. Cervical nerve stimulation may be an effective treatment for yips-affected golfers. In this study, 10-minutes of active cervical nerve stimulation was compared with sham stimulation for its effects on physiological activity and putting performance of 28 yips-affected golfers. Results revealed a significant improvement in putting performance in the active group compared to the sham group. The active group made more putts ($p < 0.05$, $d = 0.27$), had lower centimeter error from the hole ($p < 0.05$, $d = 0.41$), and increased feel of each putt ($p < 0.05$, $d = 0.07$) compared to the sham group, but there was no significant change in physiological activity in either group. Cervical nerve stimulation did not have effects on physiological activity associated with the yips, but it did improve putting performance of yips-affected golfers.

Introduction

The “yips” is a term used by golfers and other athletes to describe an involuntary sudden movement when performing an action that requires fine motor control, such as

putting and chipping. Physically, yips are manifested in golfers by symptoms of jerks, tremors, or freezing in the hands or forearms during the putting or chipping motion that results in a poorly executed shot and an average increase of 4.9 strokes per 18 holes (Smith et al., 2003). Because choking implies performance beneath optimal levels, yips are most often acquired by elite golfers rather than novice golfers. There is much debate over whether the yips is a psychological disorder associated with performance anxiety, or if it is a task specific dystonia that develops after years of practicing poor movements (Adler et al., 1993; Smith et al., 2000). There is evidence to support both theories, but evidence suggests that performance anxiety exacerbates yips symptoms regardless of the cause.

Fear is a primary component of yips-affected golfers. The fear response is controlled by the amygdala, the hypothalamus, and the brain stem (Davis, 2000). When a person is in a state of fear, the hippocampus is activated to assess the conflict and determine if the conflict is to be approached or avoided (McNaughton & Gray, 2000). While there is much research that shows which brain structures are involved in fear and anxiety, there is limited research that assesses the neurophysiology of yips-affected golfers, specifically on which emotions (fear, anxiety, frustration, self-focus, etc.) trigger the performance anxiety experienced. Treatments that suppress the symptoms of fear while simultaneously shifting the player's focus from self to desired outcome could have significant effects on improving performance.

There is not much known about how golfers treat their performance anxiety, but the most common treatments for performance anxiety in general include beta blockers and alcohol. Studies have shown that between 20-30% of musicians with performance

anxiety take beta blockers to relieve their symptoms, and up to 34% drink alcohol for relief (Fishbein et al., 1988; Steptoe, 1989). One review study found that beta blockers improved the control of symptoms associated with sympathetic hyperactivity, such as hyperventilation, tremors, sweating, and elevated heart rate (Kenny, 2005). However, they come with a list of side effects like nausea and drowsiness, and they are banned in many competitive sports leagues, so they are not an ideal long-term solution for reducing performance anxiety.

Interest in non-invasive neuromodulation techniques to enhance human performance and reduce anxiety symptoms has been growing in recent years because of their drug-free nature. Transcranial direct current stimulation (tDCS) is a popular method that has been studied in human performance research in the last decade, but few studies have assessed peripheral nerve stimulation on human performance, and none on yips-affected golfers. Cranial and cervical nerves should be primary targets in neuromodulation therapy due to their connections with the central nervous system and indirect effects on physiological activity. Transcutaneous auricular vagus nerve stimulation may be an effective treatment method for reducing yips in golfers, but current electrode designs are not ideal for a competitive golf population.

Cervical nerve stimulation on the back of the neck may also be an effective target for anxiety in yips-affected golfers. Anatomical and electrophysiology studies have shown that stimulation of the upper cervical nerves produces changes in the caudal part of the spinal trigeminal nucleus (Pfaller & Arvidsson, 1988; Piovesan et al., 2003), the same region in the brain stem that receives afferents from the vagus nerve (Chandler et al., 1996) and projects to other regions like the locus coeruleus and amygdala. Upper cervical

nerves converge on the trigeminocervical complex, a region that contains the spinal trigeminal nucleus and the lateral cervical nucleus. This region has been shown to receive afferents from cervical, trigeminal, and vagal nerves and modulates neurotransmitters like serotonin and GABA (Chandler et al., 1996; Piovesan et al., 2003). From a clinical perspective, cervical nerve stimulation research and application has mostly been used for treating pain (Falco et al., 2004), headache (Matharu et al., 2003) and has demonstrated similar effects as VNS on treating headache (Bossut et al., 1992). Due to similar connections in brain structures as the vagus nerve, cervical nerve stimulation may produce similar effects as VNS and taVNS in regard to reducing performance anxiety and symptoms of fear that exacerbate the yips. This study aimed to quantify the effects of cervical nerve stimulation on physiological activity and putting performance of yips-affected golfers.

Hypotheses

We hypothesized that the cervical nerve stimulation on the back of the neck would cause a statistically significant change in heart rate, brain activity, and heart rate variability.

We hypothesized that cervical nerve stimulation on the back of the neck would significantly improve golf putting performance of yips-affected golfers.

Methods

Volunteer golfers who self-reported to having the yips were recruited to participate in this study. They reported to the Opti Brain office in Tempe to complete the study. The study consisted of participants hitting 65 10-foot putts within one hour. We

captured brain activity, heart rate, and heart rate variability of each participant during the study.

Participants included golfers aged 18-75 years of age with self-reported yips. Minors, adults who were unable to consent, and prisoners were not included in the study.

Participants started by hitting five practice putts to get a feel for the task. They then hit the first round of 10 putts from the 10-foot range as a baseline condition (Baseline). In order to add stress to elicit a yip, participants were told they would receive $1 for every putt they made. After the 10 putts, they were told they must make an 11th putt if they wished to keep any of the money they had just earned. All putts were video recorded from the waist and below to document the yip. Subjective ratings of quality of feel for each putt (1-10 rating, 10 being the best feeling putt), distance the ball ends up from the hole in cm, and number of putts made were recorded. Brain activity in the one second before putting stoke initiation was recorded for each putt, as well as subjective feel and distance from the hole.

After the 10-putt round, we then recorded 60 seconds of resting brain activity and heart rate. Participants then received 10 minutes of either active or sham stimulation (Figure 4, Figure 5, Table 18). Participants were instructed to increase the stimulation intensity until a comfortable setting, or the maximum output was reached. After the 10 minutes, 60 seconds of brain activity and heart rate were recorded one more time.

After the 10-minute treatment, they performed a final round of hitting 10 putts from the 10-foot range (Post). Participants were awarded with $1 for every putt they

made. They then had to make an 11th putt if they wished to keep the money they had just earned, but this time if they missed the 11th putt, they would lose all the money they had earned from the entire study. Brain activity, feel, and distance from the hole were recorded during each putt.

After completion of the study, a final survey was given to assess participants' perception of the nerve stimulation.

Figure 4: Cervical Nerves

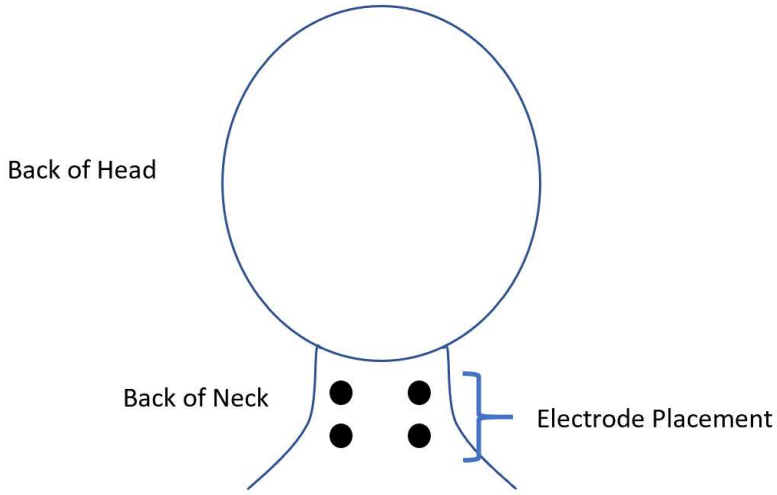

Figure 5: Placement of electrodes for biphasic cervical nerve stimulation

Table 18
Stimulation Parameters

Condition	*Frequency (Hz)*	*Pulse Width (uS)*	*Pulse Gap (mS)*	*Current (mA)*
Active - Biphasic	100 Hz	540	4.5	0 - 10
Sham	0	0	0	0

Data Analysis Approach

The Muse headset (256Hz sampling rate) along with Opti Brain software was used to monitor average EEG levels from FP1, FP2, T9, and T10 locations during resting conditions and performance conditions. During each putt, EEG was captured in the one second before the start of the backstroke. Synergy (coherence) was the metric used to quantify brain activity. A Polar Heart Rate Monitor (256Hz sampling rate) assessed heart rate and heart rate variability. Two-tailed independent t-tests were used to compare data from Baseline and Post putting tasks in both active and sham groups.

Performance was measured by quantifying the number of putts made, the distance in cm the ball ends up from the hole for putts missed, and how each putt felt on a scale of 1-10, with 10 being the best feel. Performance data from Baseline and Post putting tasks were compared using two-tailed independent t-tests for all participants in the active and sham groups. A chi-squared test was used to analyze the difference in putts made in the pressure putt scenario for both groups.

Results

Performance Metrics

In the active group, two-tailed independent t-tests revealed a significant improvement in number of putts made ($p = 0.02$, $d = 0.27$), cm error ($p = 0.01$, $d = 0.41$) and quality of feel for each putt after stimulation ($p < 0.01$, $d = 0.07$). In the sham group, there were improvements in number of putts made and quality of feel for each putt, but the changes were not significant. There was also a decrease in mean centimeter error for each putt after the sham treatment, but the difference was not significant.

Table 19

Mean Performance Values for Active and Sham Treatment

	Active (n=17)			Sham (n=11)		
Metric	*Pre*	*Post*	*p-value*	*Pre*	*Post*	*p-value*
Putts Made	5.24 ± 2.49	7.12 ± 2.34	**0.02**	4.82 ± 2.44	6.45 ± 2.54	0.12
Error (cm)	15.72 ± 15.25	6.1 ± 7.09	**0.01**	15.07 ± 10.57	9.22 ± 8.29	0.19
Feel	7.35 ± 1.45	8.23 ± 1.45	**0.00**	7.38 ± 1.64	8.12 ± 1.51	*0.09*

Pressure Putt

All golfers in the study made at least one putt in each condition and therefore had the chance to make a pressure putt. Two-tailed independent t-tests revealed there were no significant changes in any of the performance metrics for the pressure putt condition in either active or sham groups. In the active group, there was a decrease in mean centimeter error for each putt after the treatment ($d = 0.2$), but reduction was not significant. In the sham group, there was an increase in mean centimeter error for each putt after the treatment ($d = 0.3$), but the increase was not significant.

Table 20

Mean Pressure Putt Values for Active and Sham Treatment

	Active (n=17)			Sham (n=11)		
Metric	Pre	Post	p-value	Pre	Post	p-value
Putt Made	10.00	10.00	0.68	7.00	8.00	0.53
Error (cm)	9.69 ± 17.50	6.31 ± 11.69	0.58	6 ± 11.14	10.54 ± 15.98	0.44
Feel	8.13 ± 1.73	8 ± 1.60	0.80	8.18 ± 1.94	8 ± 2.32	0.82

Physiological Metrics

Two-tailed independent t-tests revealed no significant changes in heart rate or the low-frequency/high-frequency ratio component of heart rate variability after treatment in either active or sham groups. There was a slight decrease in heart rate in both groups, but the decrease was not significant.

Table 21

Mean Physiological Values for Active and Sham Treatment

	Active (n=17)			Sham (n=11)		
Metric	*Pre*	*Post*	*p-value*	*Pre*	*Post*	*p-value*
Heart Rate	73.14 ± 17.18	71.13 ± 15.03	0.10	75.85 ± 11.37	73.44 ± 13.21	0.16
LF/HF	1.45 ± 1.15	1.33 ± 1.52	0.83	1.52 ± 1.07	1.49 ± 1.33	0.96

EEG 1-min Rest

EEG activity was monitored for 60 seconds immediately before treatment and immediately after treatment in both active and sham groups. Synergy was used to quantify average EEG synchrony activity from the FP1, FP2, T9, and T10 locations. Two-tailed independent t-tests revealed there were no significant changes in synergy after treatment in either active or sham groups.

Table 22

Mean EEG Values for Active and Sham Treatment for 1 min Rest

	Active (n=17)			Sham (n=11)		
Metric	*Pre*	*Post*	*p-value*	*Pre*	*Post*	*p-value*
Total	1.91 ± 1.31	1.52 ± 0.76	0.26	2.13 ± 1.53	1.53 ± 0.65	0.18
Synergy (%)	72.037 ± 5.22	71.62 ± 5.98	0.79	70.50 ± 6.95	69.94 ± 6.79	0.84

EEG Average for 10 Putts

EEG activity was monitored for each stroke during each condition, and only the data during the 1-second before the start of the putting motion was used for data analysis. Synergy was used to quantify average EEG synchrony activity at the FP1, FP2, T9, and T10 locations. Two-tailed independent t-tests revealed there were no significant changes in synergy during the post stimulation putting task in either active or sham groups. There were no correlations between synergy and any of the performance metrics.

Table 23

Mean EEG Values for Active and Sham Treatment for 10 Putts

	Active (n=17)			Sham (n=11)		
Metric	*Pre*	*Post*	*p-value*	*Pre*	*Post*	*p-value*
Total	2.73 ± 1.66	2.41 ± 1.67	0.32	4.80 ± 4.47	3.56 ± 2.82	0.39
Synergy (%)	71.19 ± 5.18	71.06 ± 3.21	0.89	66.56 ± 6.76	66.02 ± 6.46	0.68

Discussion

Effect on Performance

The data supports the hypothesis that cervical nerve stimulation significantly improved putting performance compared to a sham in yips-affected golfers. All performance metrics in the active group had a significant change from baseline. In the active group, the number of putts made increased from 5.24 ± 2.49 to 7.12 ± 2.34 ($p < 0.05$, $d = 0.27$), centimeter error decreased from 15.72 ± 15.25 to 6.1 ± 7.09 ($p < 0.05$, $d = 0.41$), and feel for each putt increased from 7.35 ± 1.45 to 8.23 ± 1.45 ($p < 0.05$, $d = 0.07$). It is possible that performance improved because of increased familiarity with the putting task, as each golfer hit 40 putts between the baseline and the post stimulation putting tasks. However, the sham group did not demonstrate significant changes in performance using the same protocol, so it is unlikely the improvement in the active group was due to familiarity alone.

In the sham group, there was an increase in the number of putts made, reduced centimeter error, and an increase in feel of each putt after treatment, but these changes were not significant. The non-significant performance improvements in the sham group are likely due to the familiarity effect as the golfers became more familiar with the putting task between baseline and post stimulation putting periods. One study found tDCS increased the number of putts made over time in a putting task compared to sham,

but also concluded that the increase in the number of putts made in the sham group was due to the familiarity effect (Zhu et al., 2015). One might conclude that a possible yips solution could be to increase the number of putts hit during practice, but past studies suggest that yips-affected golfers do not get better with more practice (Smith et al., 2000).

While there were performance improvements during the normal putting tasks, there were no significant improvements in performance during the pressure putt scenario after stimulation in either of the groups. In the active group, centimeter error was reduced, but the change was not significant likely because the baseline values were low as well, whereas in the normal putting task, centimeter error was much higher in the baseline condition. In both groups, quality of feel was reduced, but it may not have been a significant change because the average baseline feel for the pressure putt was higher than the average baseline feel for the normal putts. The data suggests that cervical nerve stimulation has minimal to no effect on putting performance when putting performance is already high. However, this statement would likely be true for any type of intervention. One potential reason there was no significant effect on pressure putt performance is the length of time between receiving the stimulation and hitting the pressure putt. It is possible the acute anxiolytic effects of the cervical nerve stimulation faded over time and had little effect on the golfer during the actual pressure putt. A second reason could be a difference in experience between the golfers in each group, as some golfers felt more comfortable under pressure and some did not. A third reason could also be due to the golfers only hitting one putt rather than many pressure putts, which reduces the chance of seeing any significant change from one data point. Cervical nerve stimulation may

have the greatest effect on performance immediately after the treatment, but more research is needed to understand its effects. A positive takeaway for golfers is that the stimulation did not make performance any worse, so there is no harm in using cervical nerve stimulation to see if it may have an effect on putting performance for any performance level.

Effect on Heart Rate and HRV

Heart rate variability is a common method of analyzing cardiac activity that involves measuring the time differences between successive heartbeats (RR intervals). Changes in HRV activity are often associated with changes in human performance; and therefore, HRV is a common metric to be measured in sports studies. In the frequency domain, the high frequency (HF) component of HRV is associated with parasympathetic activity, and the low frequency (LF) is a measure of both sympathetic and parasympathetic activity. The ratio LF/HF has been proposed as an index of sympathetic to parasympathetic balance of heart rate fluctuation (De Couck et al., 2017; DeGiorgio et al., 2010).

Past research has shown that vagus nerve modulates parasympathetic activity, and vagus nerve stimulation increases the HF component of HRV (Anon, 1996). Due to similar connections in the spinal trigeminal nucleus and brainstem as the vagus nerve, cervical nerve stimulation was hypothesized to cause changes in heart rate variability. The data does not support the hypothesis that cervical nerve stimulation has a significant effect on heart rate or heart rate variability.

Heart rate dropped from 73.14 ± 17.18 to 71.13 ± 15.03 bpm in the active group and from 75.85 ± 11.37 to 73.44 ± 13.21 bpm in the sham group, but neither of these

changes were significant. There may have been insignificant effects due to the participants being in a parasympathetic dominant state as indicated by their low baseline heart rate values (Active: 73.14 ± 17.18, Sham: 71.13 ± 15.03) and LF/HF values (Active: 1.45 ± 1.15, Sham: 1.52 ± 1.07). Clancy et. al. concluded that tVNS would be more effective on people with higher baseline LF/HF ratios where with a baseline value of 3 or greater, a drop of 1 would occur, whereas with a baseline value of 1 or less, there would be hardly any change (Clancy et al., 2014). However, De Couck et. al. (2017) reported that 15 participants who received active tVNS for 1 hour had an increase in LF/HF ratio (Pre: 2.5 ± 2, Post: 3.7 ± 3.7). Results from that study led the researchers to question whether HRV metrics are reliable indicators of vagal nerve activity in people. While effective vagal or cervical nerve stimulation may be dependent on the patient's resting autonomic state, more research is needed to make any conclusions on if cervical nerve stimulation has any effect on HRV.

Another reason there may have been no significant change in resting heart rate is because heart rate was measured a couple minutes after the stimulation rather than during the stimulation. This may have been just enough time for heart rate to recover back to baseline if it had been affected during the stimulation. Clancy et. al. (2014) showed that tVNS significantly reduced resting heart rate during stimulation (Pre: 65 ± 1.16 bpm, Post: 63 ± 1.79 bpm) but was not measured after stimulation. Future studies assessing cervical nerve stimulation should measure physiological metrics during stimulation, as it may have acute effects on physiological activity.

Effect on EEG Activity

This study looked at how cervical nerve stimulation affects synergy levels in yips-affected golfers. Synergy is a term that describes synchrony of brain activity, or power levels, in the theta, alpha, and beta frequency bands. Synergy can be calculated over a single electrode or can be combined over many electrodes to quantify whole brain synchrony. Past research has hypothesized that higher performing athletes and businesspeople have high synergy levels in frontal executive areas of the brain (Harung & Travis, 2012). Synergy is a relatively unexplored EEG metric in human performance research, as most research has looked at EEG coherence, which is a measure of power levels in one frequency band between two or more electrode locations. Babiloni et. al. (2011) found that in expert golfers there was greater intra-hemispheric alpha coherence in bilateral parietal-frontal and parietal-central regions in successful putts compared to unsuccessful putts. Synergy goes further than just comparing power levels in one frequency, but compares power levels across theta, alpha, and beta frequencies.

It has been hypothesized and demonstrated that higher synergy levels in the 1 second before the onset of the putting motion leads to improved putting performance, and therefore neurofeedback training that focuses on increasing synergy levels has become a popular research method (Crews et al., 2016, 2018; Gook et al., 2018). While neurofeedback is often used to influence synchrony in the brain, cervical nerve stimulation was hypothesized to influence synchrony 1 second before the putting motion as well. However, results from this study showed that cervical nerve stimulation did not have a significant effect on synergy levels.

There may have been no significant effect on synergy levels because the baseline synergy levels were relatively high and there was not much room to improve (ceiling

effect). Gook et. al. (2018) showed a significant increase in synergy levels after neurofeedback training from 67.94 ± 3.94 percent to 72.67 ± 4.18 percent, which was correlated with improved performance, whereas baseline synergy values in this study were 72.04 ± 5.22 percent during the 1-minute rest period and 71.19 ± 5.18 percent during the putting task. Post-stimulation synergy levels in the control group were much lower than synergy in the active group, and the active group showed an improvement in performance while the control group did not. This might suggest that synergy levels around or above 70% may lead to better performance. However, there was no correlation between synergy and putts made ($r = 0$), synergy and feel ($r = 0.3$), or between feel and putts made ($r = 0.2$) in the active group. Even though the cervical nerve stimulation did not increase synergy levels in this study, it would be interesting to observe the effects of the stimulation on a population with baseline synergy levels much lower than 70%.

Other Observations

This study included a small sample size and a group of golfers with a wide range of skill. It cannot be concluded from this data that cervical nerve stimulation can improve performance of specifically high or low skilled golfers, and therefore future studies should examine the effects of cervical nerve stimulation on high and low skilled populations separately. Past research has demonstrated that brain stimulation techniques like tDCS can improve putting performance of low skilled putters (Zhu et al., 2015). Data from this study and past research indicates that low-skilled golfers may benefit from cervical nerve stimulation under normal conditions, while high-skilled golfers may benefit from cervical nerve stimulation the most during high-anxious situations.

Future studies assessing the effects of cervical nerve stimulation should also incorporate new ways to create stressful situations in the lab as they would be on the actual golf course. However, it is difficult to recreate fearful situations, such as putting in front of a large crowd, that could cause anxiety and fear for the golfer. One possible method could be a form of exposure therapy where golfers are livestreamed to a social media platform such as Facebook during the putting task. This would simulate putting in front of an audience. Depending on their performance, they will Venmo some dollar amount to a random viewer. For example, if they perform poorly, they must send money to random viewers. If they perform well, they don't have to send money. This would be great practice for golfers looking to emulate real competitive situations where they practice putting when they are more self-conscious due to the livestream.

Conclusion

The results of this study demonstrate that cervical nerve stimulation did not have any significant effects on resting physiological activity, but it did have significant effects on improving putting performance of yips-affected golfers. More research is needed to determine if cervical nerve stimulation is effective at reducing the physiological and psychological symptoms of high anxious and yips-affected golfers. If cervical nerve stimulation improves putting performance and can be shown to reduce physical and psychological symptoms of yips during high stress situations, it may be an effective drug-free solution that both athletes and everyday people could benefit from.

CHAPTER 5

CONCLUSIONS AND FUTURE RESEARCH

Future Research

Data presented from these studies demonstrate there are real world clinical applications to various types of non-invasive electrical nerve stimulation techniques. Research from studies such as these should lead to new medical device developments for improving patient health and user experience, but further research is necessary to further understand the efficacy and usability of the various stimulation techniques. Table 24 summarizes the results found in each study presented in this dissertation.

Table 24

Summary of Research Findings

Reference	Indication studied	n	Stimulation protocol	Efficacy	Non-efficacy
Chapter 2	Healthy volunteers	67	10 minutes. 30Hz, 300Hz, or 3,000Hz. Bilateral taVNS in acoustic meatus	30Hz: Significant increase in SDNN and RMSSD 300Hz: Significant increase in SDNN and RMSSD 3,000Hz: Signficant increase in SDNN and RMSSD	No effects on Heart Rate, HF Power, LF Power, LF/HF ratio, Respiration rate, hand temperature, and skin conductance
Chapter 3	Healthy golfers	18	10 minutes. 100Hz. Bilateral GAN at tympanomastoid fissure	Significant increase in feel. Significant decrease in STAI scores	Golf Performance: No effects on score, swing tempo, swing time, swing speed, and shots made. Physio: No effect on EMG, HR, skin conductance, skin temperature, RMSSD, VLF, LF, HF, LF/HF, blood pressure, or pulse. EEG: No effect on theta, alpha, beta1, or beta 2 activity. No effect on Synergy
Chapter 4	Yips-affected golfers	28	10 minutes. 100Hz. Cervical nerves on back of the neck	Significant increase in putts made and feel. Significant decrease in cm error from the hole.	No effects on LF/HF or Synergy

Bilateral tVNS Improvements

The objectives of Chapter 2 were to determine the safety and efficacy of bilateral transcutaneous auricular vagus nerve stimulation in healthy individuals. Across all three stimulation waveforms, there were significant increases in SDNN and RMSSD of heart rate variability, and there were no significant differences in safety and tolerability

compared to a sham. This indicates bilateral tVNS in the acoustic meatus can safely and effectively modulate parasympathetic activity in resting healthy individuals. However, these results were collected while participants performed a passive resting task. A future study should observe the effects of bilateral tVNS on healthy individuals as they perform a simple active task, such as a timed arithmetic test or an object identification task, as well as assessing subjective anxiety levels. Healthy participants will perform a simple computerized task, receive 10 minutes of bilateral tVNS or sham, and then perform the task again. Having the participants perform an active task will have different psychological effects compared to a passive task, and therefore may have different physiological effects. If bilateral tVNS can be shown to improve psychological, physiological, or performance outcomes during a simple active task, new stimulating protocols and training methods can be developed to help healthy individuals optimize or enhance performance, such as workplace performance.

Effects of short-term stimulation (<15 minutes) and long-term stimulation (1 or more hours) have been studied in various populations (Butt et al., 2019), but future studies should assess the immediate effects of stimulation. There may be immediate effects on physiological activity within the first 15-60 seconds of stimulation, but those effects cannot be seen when the data is averaged over tens of minutes. The protocol described in Chapter 2 is sufficient to perform this type of study, but data analysis should divide the recorded data into 10-20 second segments for analysis. This way, we can see how the body reacts to the stimulation in real time rather than generally to a single treatment session. If significant physiological changes can be detected within seconds of active stimulation, it would lead to new stimulation protocols (ex. 15 seconds on, 2

minutes off) for acute treatments of various disorders. Understanding the immediate effects of tVNS will help researchers and developers optimize tVNS protocols for patients.

In Chapter 2, three different frequencies were assessed for their ability to produce physiological responses. It was observed that in the 300Hz group, the maximum current tolerated by each patient was roughly 80% lower than in the 30Hz and the 3000Hz groups. This is likely because there was a larger pulse width in the 300Hz group. An open question remains about the role of pulse width in producing a physiological response. Future studies should choose a frequency most often used in past research (25Hz or 30Hz) and test the effect of different pulse widths on physiological activity. Past tVNS research has demonstrated significant physiological effects using waveforms between 20μS and 500mS of various frequencies (Butt et al., 2019), but it would be interesting to test the effects of one frequency across a range of different pulse widths.

Past research indicates electrodes that stimulate the auricular branch of the vagus nerve in various parts of the external ear such as the concha, the tragus, and the acoustic meatus most consistently affect heart rate variability parameters like SDNN, RMSSD, and the LF/HF ratio. Studies like those performed by Bretherton et al. (2019) and Clancy et al. (2014) suggest that the higher a patient's resting sympathetic activity, the bigger the impact of the tVNS treatment on HRV will be. Therefore, older and more sedentary patient populations may benefit most from tVNS treatment considering they tend to have higher sympathetic and lower parasympathetic activity than younger individuals. However, tVNS may also be effective in athletic populations that require reduced sympathetic output for peak performance such as golfers.

Golfers are always looking for new methods and techniques to improve their game. One study should assess the acute effects of bilateral tVNS on putting performance in a competitive golf population. In such a study, golfers would perform a putting task, receive 2 minutes of stimulation (which would be a realistic amount of time a golfer would self-treat on the actual golf course), and then perform the putting task again. Pre-stim and post-stim psychological, physiological, and performance metrics would be recorded and analyzed. If bilateral tVNS could demonstrate improvements in any of these outcomes, new devices and treatment protocols could be developed to help competitive golfers improve putting during a round. Studies should also analyze how the method affects symptoms of first tee jitters, another common golf problem exacerbated by anxiety.

Bilateral GAN Stimulation Improvements

The objectives of Chapter 3 were to analyze the effects of great auricular nerve stimulation on hitting performance, physiological, and psychological activity of healthy golfers. The data demonstrated that 10 minutes of GAN stimulation improved the quality of feel of each shot and reduced state anxiety during a hitting task but did not have any effect on resting physiological activity. This study included a small sample size of golfers of various skill levels, and therefore it is difficult to understand the applicability of GAN stimulation to golfers. Future studies should assess the effects of GAN stimulation in a strictly novice or elite golf population. Novice and elite golfers will likely have different physiological responses under performance conditions due to their difference in experience, so if GAN stimulation does indeed have significant effects on physiological activity, it is most likely observable in a strictly novice or elite population. One study

reported that novice golfers have increased activity in brain regions like the amygdala and posterior cingulate areas compared to elite golfers (Milton et al., 2007) due to increased mental effort to learn the golf swing. Additionally, an fMRI study found that GAN stimulation at the earlobe caused deactivation in those same areas (Yakunina et al., 2017). Therefore, GAN stimulation may most likely have significant effects on performance in a strictly elite population.

Another future study should look at other golf performance tasks such as putting or chipping. Putting and chipping require finer control of movement compared to hitting and performance can be significantly affected by poor feel and high anxiety. Therefore, if GAN can improve feel and anxiety in a hitting task, it could also improve performance on and around the green. Various protocols should be tested to understand the effect of GAN stimulation on putting or chipping performance of high-anxious golfers. One protocol should be to analyze performance after 10 minutes of stimulation, such as the protocol described in Chapter 3 where the task is performed after the stimulation. However, the effects of the stimulation may wear off before the golfer can complete the post-stimulation task. The other protocol should be to analyze performance during the stimulation, where the golfer must hit putts or chips while receiving stimulation at a comfortable and non-distracting level or receiving a short burst of stimulation before each individual shot. The simple motion of hitting each putt or chip would results in higher physiological activity compared to a resting state, and high-anxious golfers may have even higher physiological activity. It is possible that GAN stimulation would have significant effects on physiological activity in the middle of a performance task and therefore should be explored. If GAN stimulation is found to be more effective during

performance compared to just before performance, this would lead to new ways athletes would implement this technique, and even new device designs.

Another important study that should be performed is an fMRI study to observe the effects of GAN stimulation on brain activity and to see which brain structures are affected by GAN stimulation. Yakunina et al. (2017) found that stimulating the GAN at the earlobe caused deactivation in the hippocampus, posterior cingulate gyrus, parahippocampal gyrus, and the amygdala. However, no fMRI studies have observed the effects of GAN stimulation at the tympanomastoid fissure. Anatomical studies (Ginsberg & Eicher, 2000; Liu & Hu, 1998) have shown the great auricular nerve has connections in similar regions in the brainstem as the auricular branch of the vagus nerve, such as the nucleus of the solitary tract (NTS) and the spinal trigeminal nucleus. These studies are foundational to the hypotheses that GAN stimulation may have similar effects as auricular tVNS. However, fMRI studies should be performed to verify that GAN stimulation activates similar brain structures as tVNS.

GAN stimulation was also demonstrated to significantly reduce state-anxiety as indicated by reduced STAI scores. It would be interesting to observe the effects of GAN stimulation in a clinical population that consistently experiences high state-anxiety like those diagnosed with PTSD or addiction disorders. Future studies should observe the immediate effects of GAN stimulation during moments of high anxiety such as a panic attack and should also observe the long-term effects of daily use on treating anxiety disorders. High drug-consumption rates and expensive treatments are major problems for populations like those with PTSD. If GAN stimulation can demonstrate efficacy in a

clinical population like PTSD, it could revolutionize the way patients manage their mental health by saving money and reducing drug consumption.

Cervical Nerve Stimulation Improvements

The objectives of Chapter 4 were to assess the effects of cervical nerve stimulation on physiological activity and putting performance of yips-affected golfers. The results demonstrated that 10 minutes of cervical nerve stimulation did not have an effect on resting heart rate or LF/HF ratio values or on brain synergy values, but it did have a significant effect on performance outcomes. The study also only included participants with "self-reported" yips. There was no validated screening protocol that made sure each participant was indeed affected with the yips. Future studies should have stricter screening protocols and should only include participants who score in the moderate to severe range on clinically validated anxiety questionnaires like the STAI.

Future research testing cervical nerve stimulation with yips-affected golfers should also study the effects on a real putting green on a real golf course. Yips-affected golfers often do not have trouble hitting good putts during practice, but once they get over the ball and the putt actually means something, they experience the yips. Testing on a real golf course would be a more realistic test environment and would likely cause different physiological responses in each golfer compared to putting on an artificial putting green in a laboratory. Cervical nerve stimulation was shown to have significant effects on performance in a laboratory but should also be explored in a real-world setting. Since the cervical nerve stimulation also significantly improved feel in each golfer, another future study should assess the effects of the treatment in a novice population only. A novice population has more room to improve compare to an elite

population, so it would be interesting to see if short-term cervical nerve stimulation can improve both feel and performance in a novice golf population.

Like suggestions made for GAN stimulation research, fMRI studies should also be completed for non-invasive cervical nerve stimulation to understand which brain structures are involved with cervical nerve stimulation. Anatomical studies have shown that cervical nerves share common connections in the brainstem as the vagus nerve (Chandler et al., 1996; Pfaller & Arvidsson, 1998; Piovesan et al., 2003), which suggests cervical nerve stimulation may have similar effects as tVNS. If we verify which brain structures are involved through fMRI, we can generate new hypotheses and identify more specific clinical applications for non-invasive cervical nerve stimulation.

Comparing the Three Methods

Even though each study tested a different nerve stimulation method on a different patient population, the data suggests that bilateral tVNS is more effective at modulating physiological activity (HRV) compared to GAN stimulation or cervical nerve stimulation, and GAN and cervical nerve stimulation methods are more effective at influencing psychological activity than the bilateral tVNS method is. However, each method has a very different usability factor, and future researchers may want to compare the efficacy of each stimulation method with the same patient population. If it could be shown that one stimulation method is more effective than the others in one population, then engineers could focus on developing devices according to that stimulation method to meet patient needs. If no significant differences in efficacy are found between each stimulation method for one particular patient population, then engineers should choose

the stimulation technique that leads to a medical device designed for optimized user experience for the intended patient population.

Optimized Electrode Design

Once a patient population has been identified, engineers should focus on designing electrodes that are ergonomic and comfortable during treatment. For example, bilateral tVNS electrodes designed for a PTSD population may not be optimized for an athletic population. If the patient intends to use bilateral tVNS in a clinical setting or at home for long periods of time, a custom hydrogel electrode that is perfectly fitted to the patient's ear should be developed. Custom electrodes would maximize wear comfort and comfort during stimulation, and while they would be much more expensive than a one-size-fits-all electrode, the comfort during treatment would be worth the price. If a patient only intends to use a bilateral tVNS for a short period of time, such as for acute treatment of anxiety, cheaper one-size-fits-all electrodes such as dry ear-clip electrodes would likely be more practical since they are affordable and have a quicker application time. Major variables involved in the design of an electrode include anatomical location, length of treatment session, patient demographics, wet vs. dry electrodes, design appeal, affordability, and usability.

Duration of Treatment

Efficacy of short-term and long-term tVNS has been studied in various patient populations, but no studies have observed the effects of long-term non-invasive GAN stimulation or non-invasive cervical nerve stimulation in any patient population. Since GAN and cervical nerve stimulation demonstrated improvements in feel and anxiety, another future study should look at how daily use of GAN or cervical nerve stimulation

affects mood over time, such as in patients with depression. Long-term daily use devices like Alpha Stim or Fisher Wallace are CES devices cleared by the FDA to treat anxiety and depression, however, these devices are expensive and have poor user experiences (Barclay & Barclay, 2014). It is worth investigating the long-term effects of daily GAN or cervical nerve stimulation on anxiety and depression, because if significant improvements are found, engineers could develop new medical devices that are superior to current CES devices and provide patients a more affordable and satisfying user experience.

Bringing the Technology to Market

Non-invasive electrical nerve stimulation is a rapidly emerging technology in the biotechnology field. Many studies have demonstrated significant improvements in a variety of clinical conditions, and the fact that it is drug-free has led to major investments in companies and startups looking to develop these technologies for patients who are desperate for drug-free solutions. Future nerve stimulation devices will have inconspicuous designs that look like everyday consumer products while being used. Past studies have reported that consumer wearable sensing devices are capable of detecting effective cervical tVNS (Gurel et al., 2020), so future devices may also operate on a closed-loop system based on sensors like Fitbit and Apple Watch that constantly monitor physiological metrics, and activate the stimulation when certain physiological thresholds are met.

Bringing a new medical device to market is an extremely time consuming and capital-intensive process. There are rigorous engineering and safety standards the device must comply with to be considered a medical device, which typically requires many

months and often years of costly design labor, prototyping, and testing. Clinical data using the final designed medical device must also be collected from the intended patient population, which means medical device companies must perform extensive research into their potential market opportunity and understand patient needs before they spend money developing a device. Once the device has been developed, the device must often be used in a clinical trial to demonstrate safety, efficacy, and usability with the intended patient population. All of these processes are required to bring a medical device to market, and it often takes years and millions of dollars. However, good research with quality data and design documentation can significantly reduce the time it takes to bring a medical device to market. Therefore, studies with less than 50 participants such as those discussed in this paper should be a highest priority when designing new medical devices, and the future research suggestions made in this paper will lead to new insights and new medical devices that improve quality of life.

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APPENDIX A

SAFETY AND TOLERABILITY OF BILATERAL TVNS FIGURES

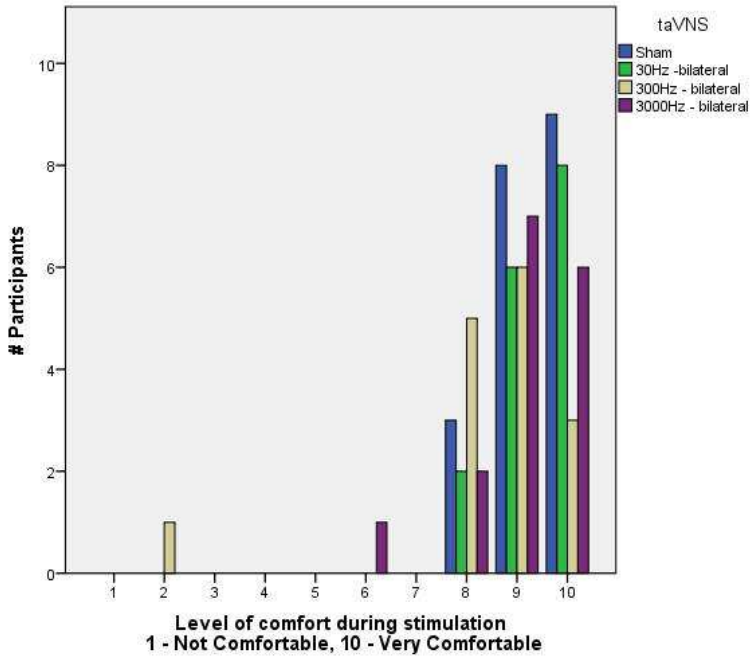

Figure 22: Level of comfort during stimulation

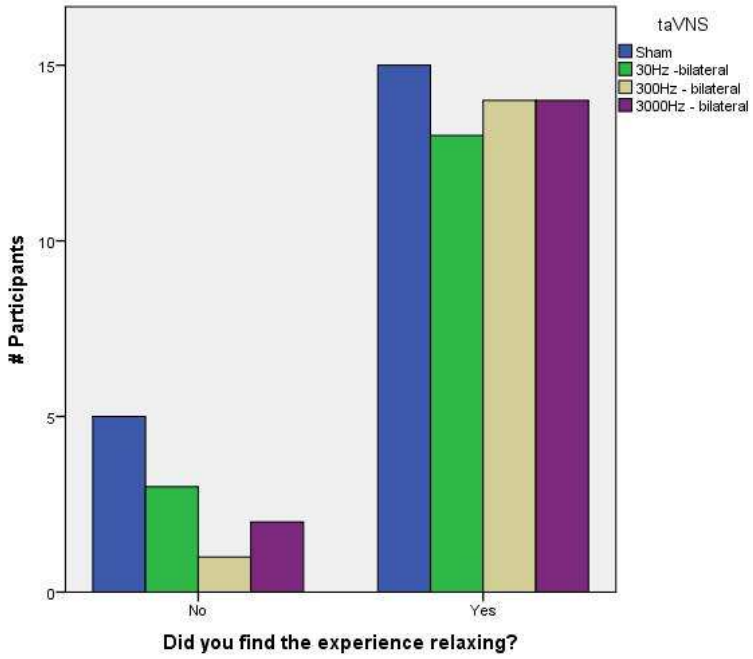

Figure 33: Yes/No relaxation

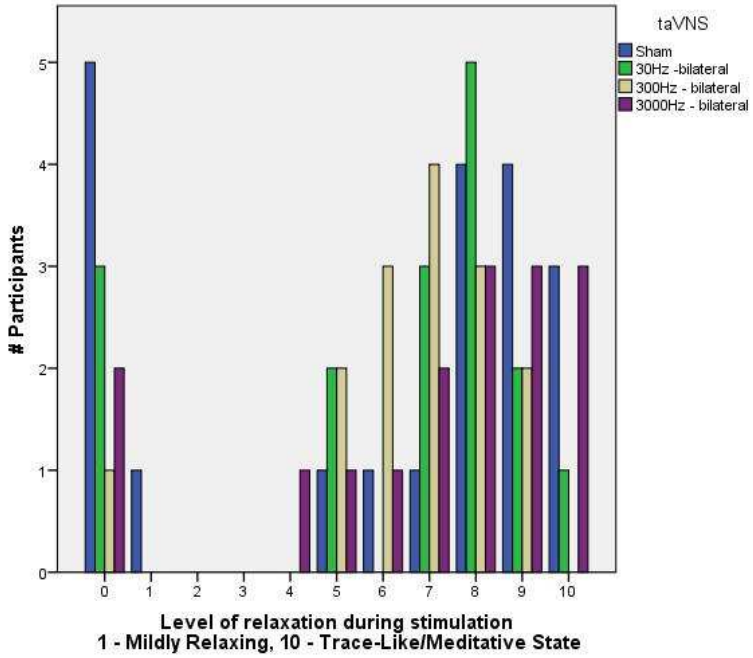

Figure 44: Level of relaxation during stimulation

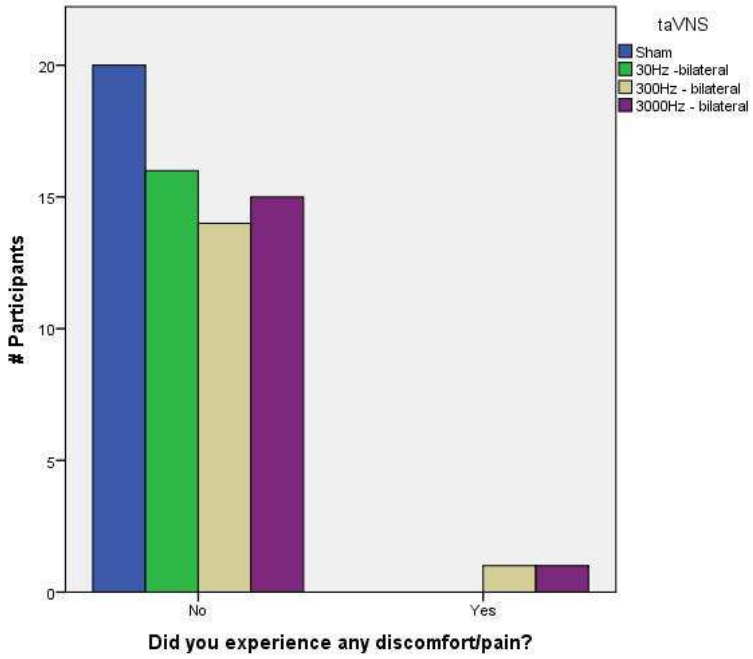

Figure 55: Level of comfort during stimulation

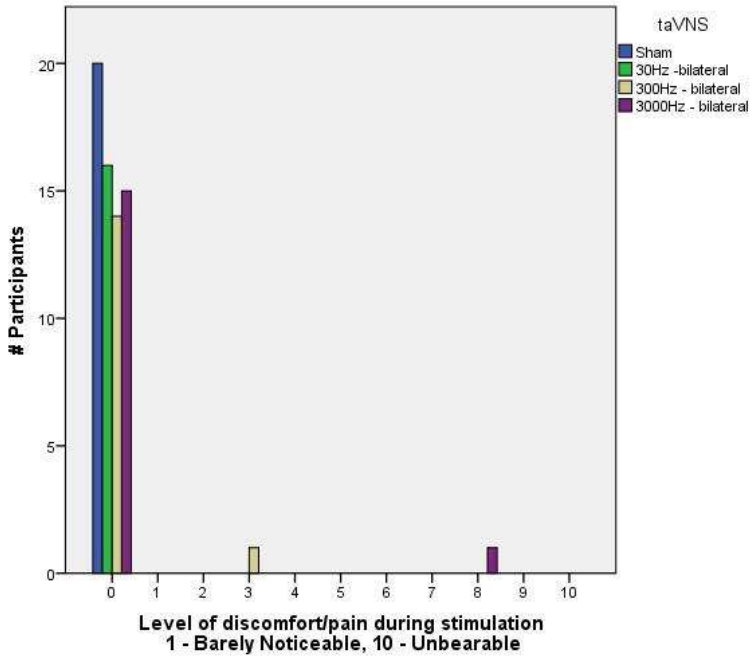

Figure 66: Level of discomfort/pain during stimulation

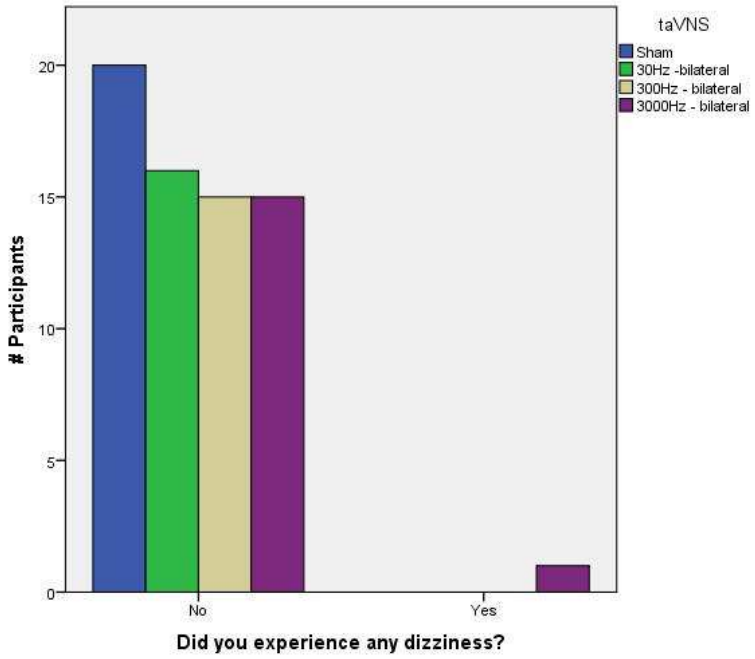

Figure 77: Yes/No dizziness

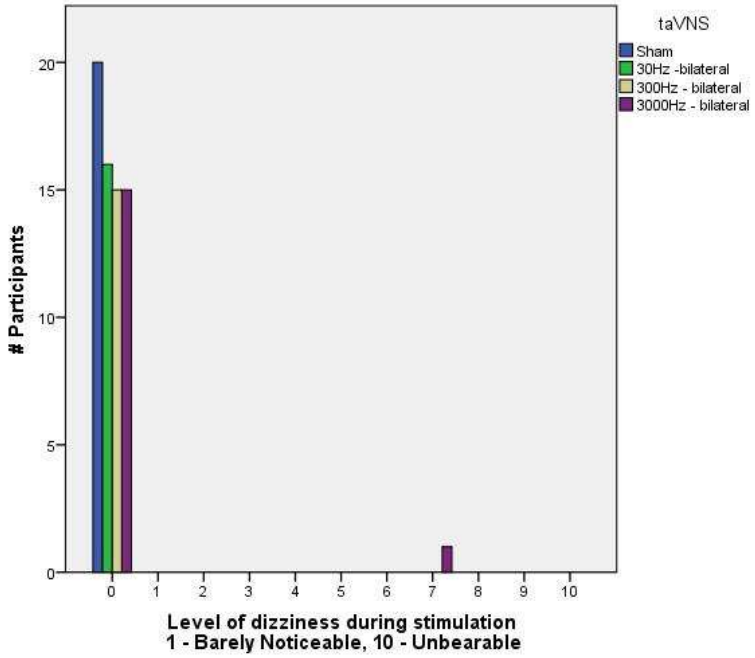

Figure 88: Level of dizziness during stimulation

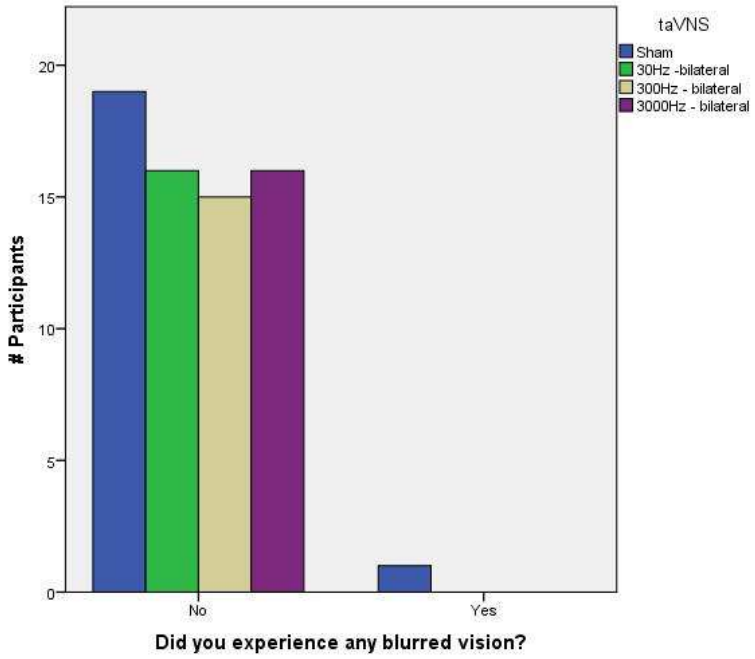

Figure 99: Yes/No blurred vision

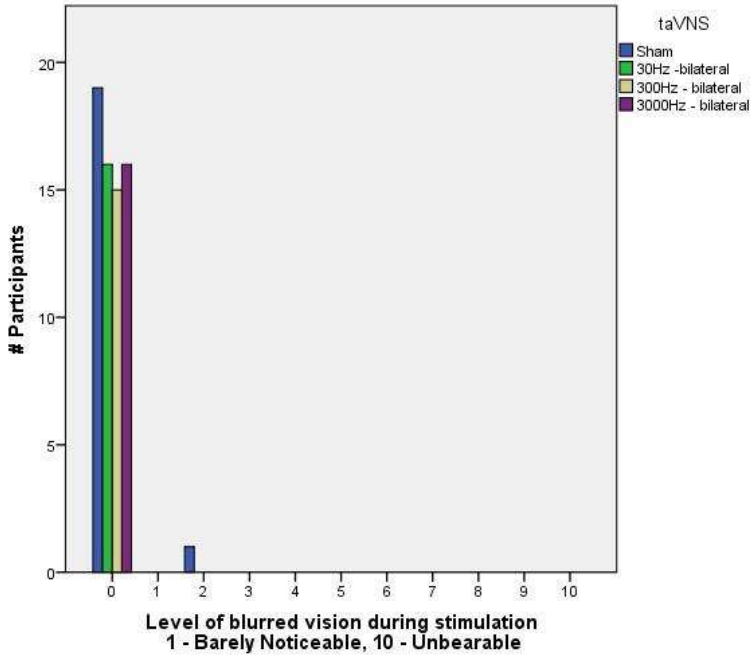

Figure 30: Level of blurred vision during stimulation

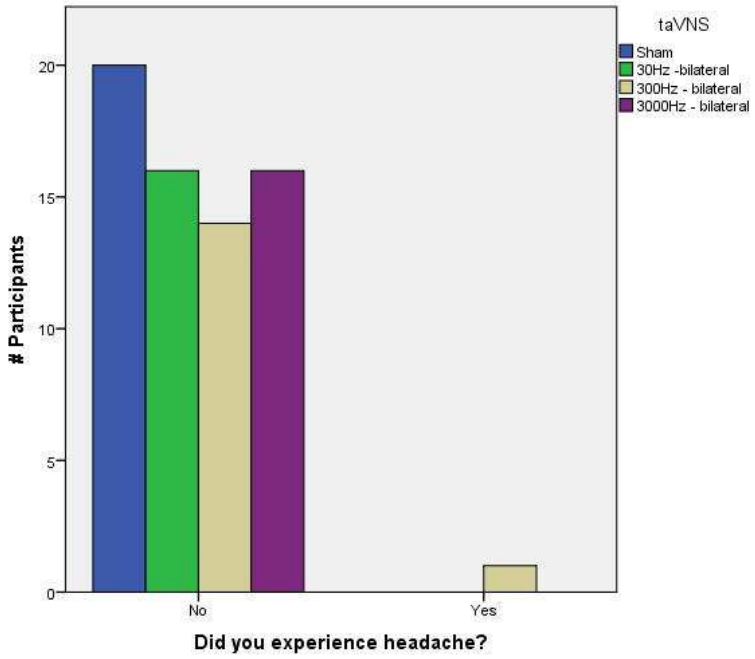

Figure 31: Yes/No headache

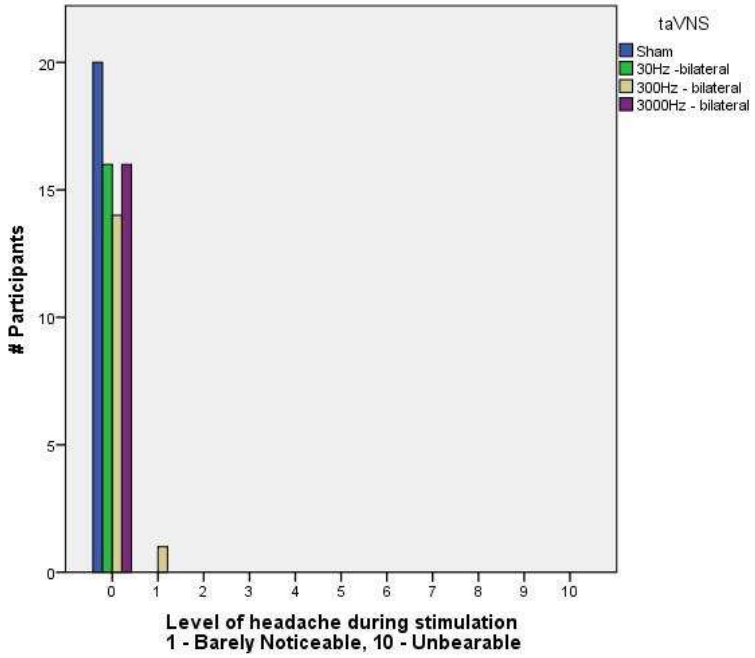

Figure 32: Level of headache during stimulation

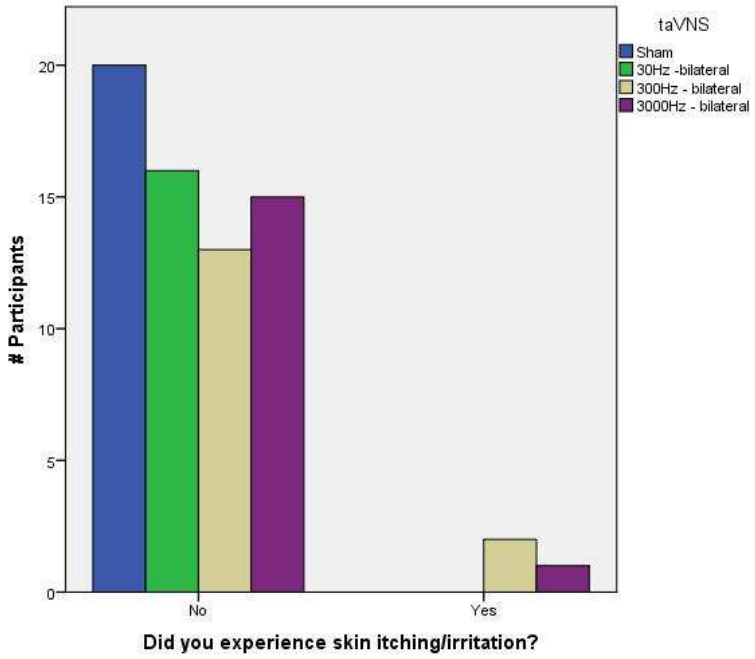

Figure 33: Yes/No skin itching/irritation

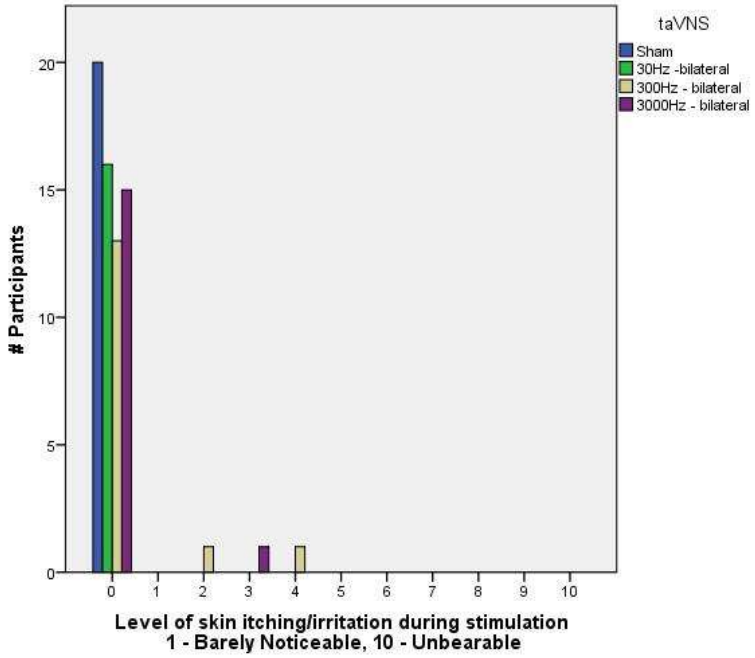

Figure 34: Level of comfort during stimulation

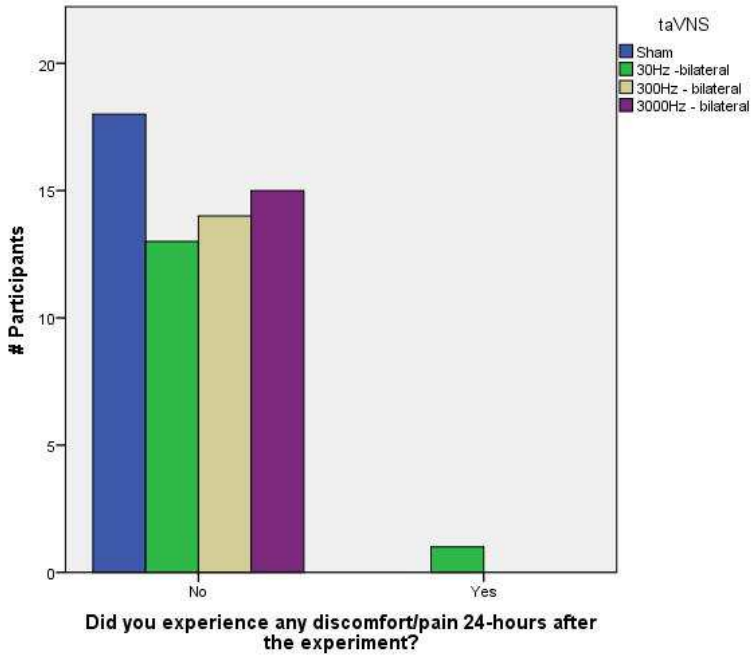

Figure 35: Yes/No discomfort/pain after 24 hours

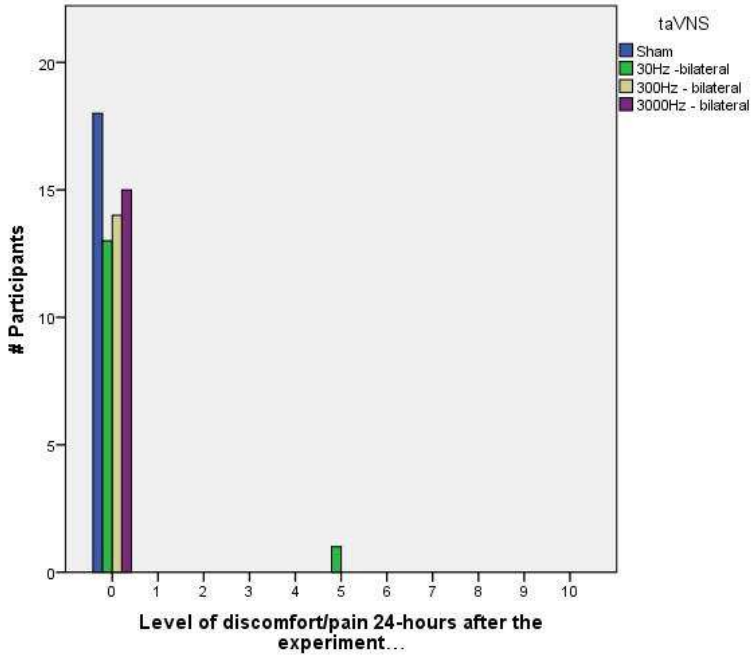

Figure 36: Level of discomfort/pain after 24 hours

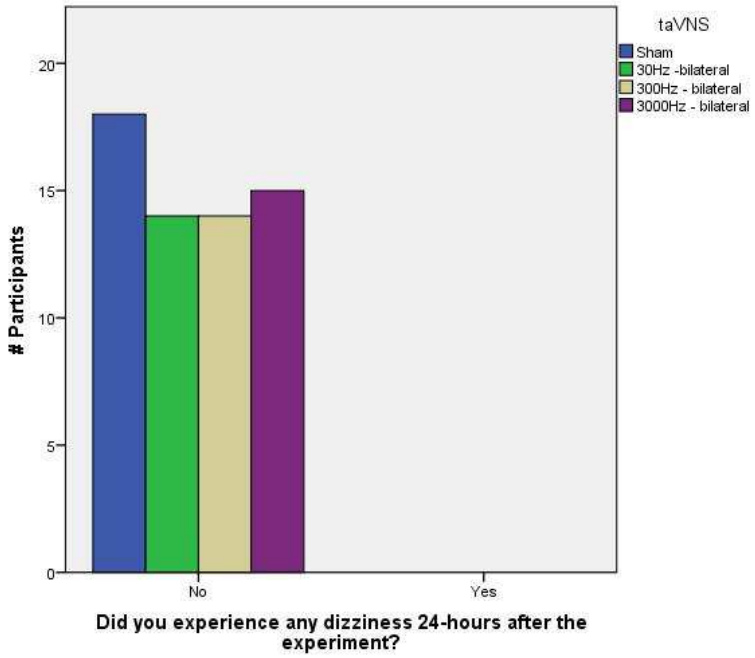

Figure 37: Yes/No dizziness after 24 hours

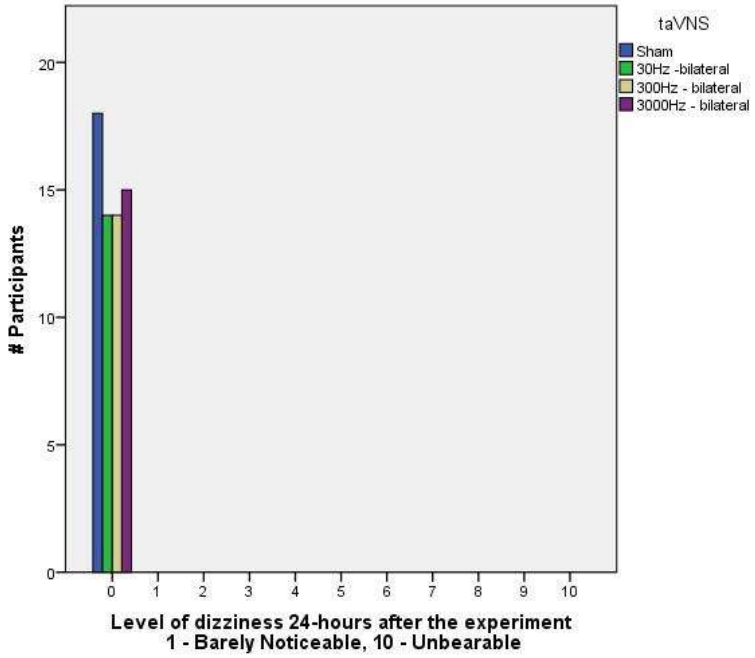

Figure 38: Level of dizziness after 24 hours

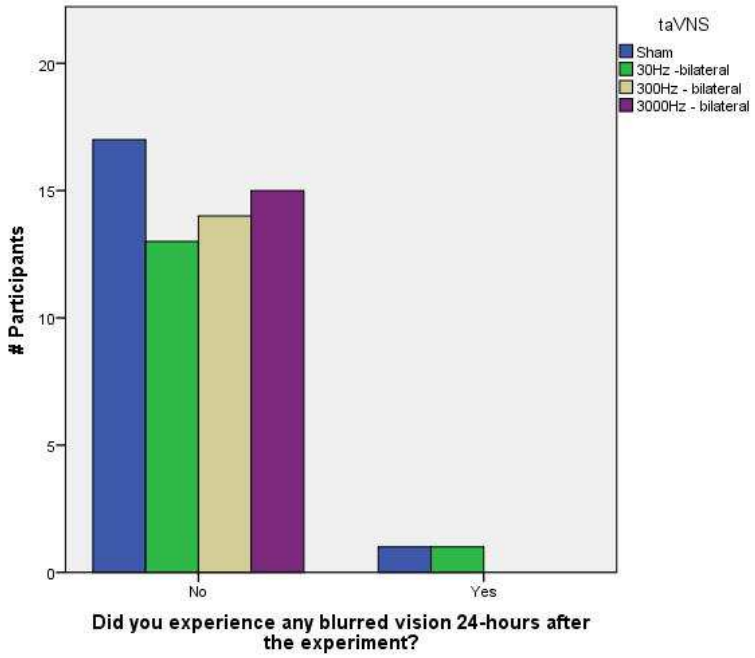

Figure 39: Yes/No blurred vision after 24 hours

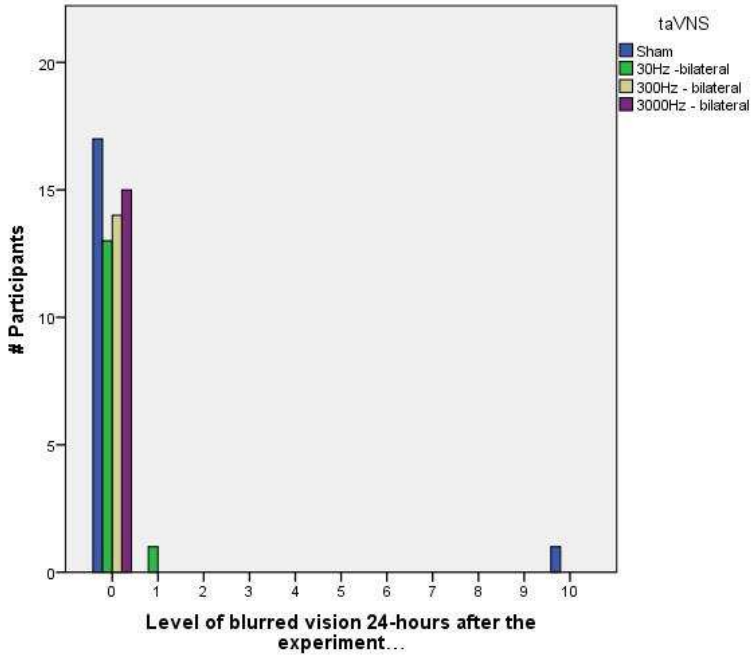

Figure 40: Level of blurred vision after 24 hours

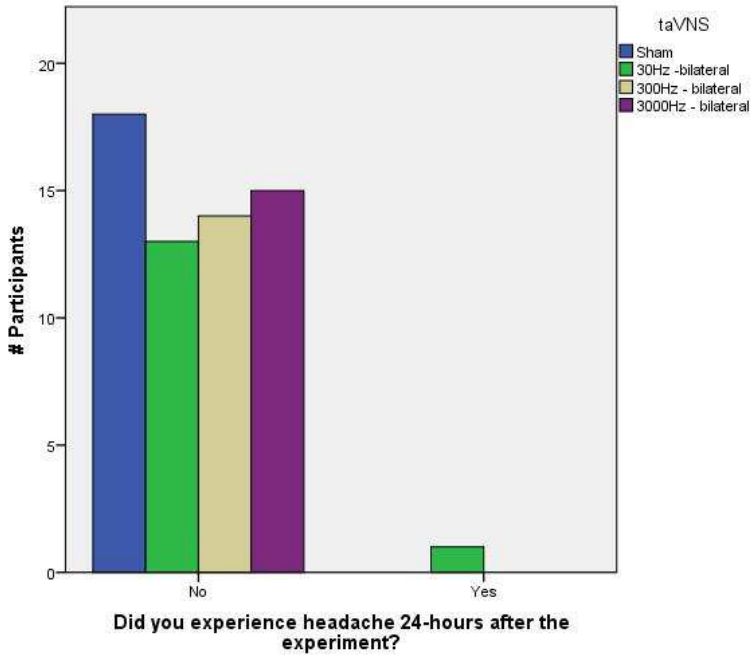

Figure 41: Yes/No headache after 24 hours

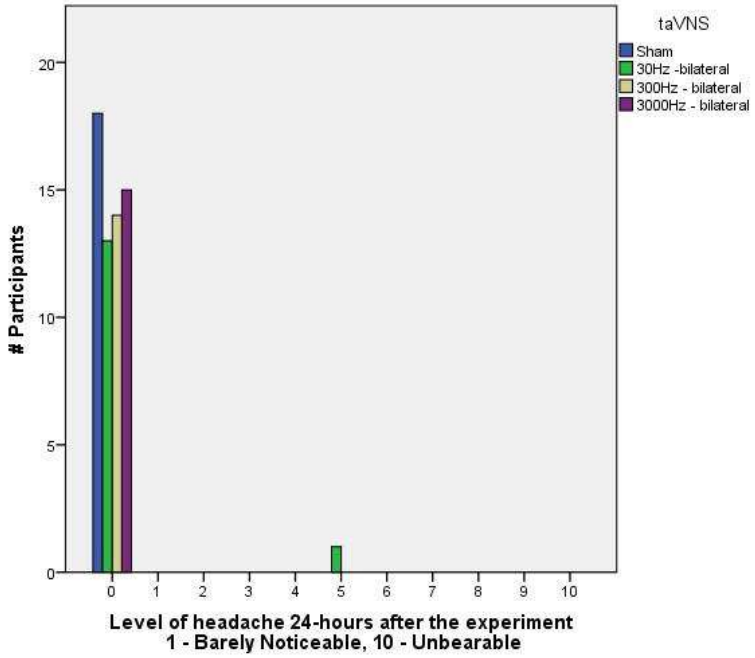

Figure 42: Level of headache after 24 hours

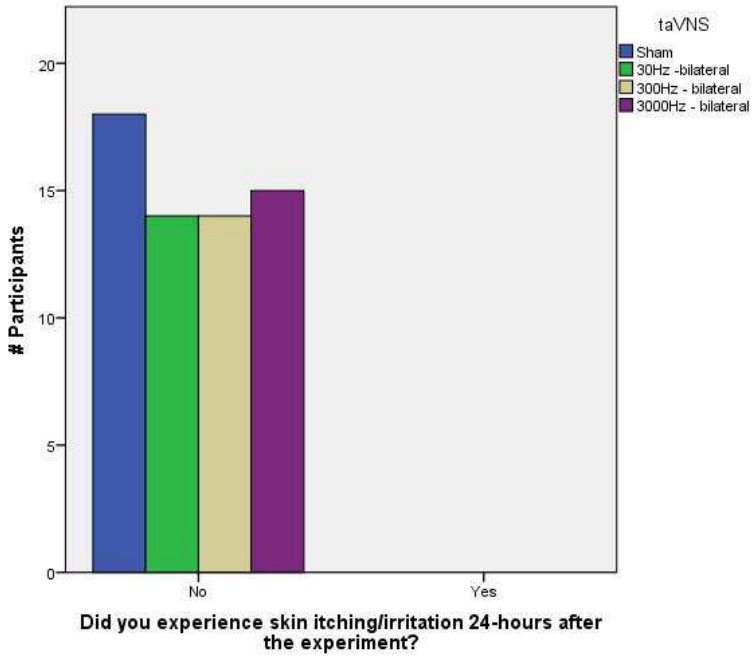

Figure 43: Yes/No skin itching/irritation after 24 hours

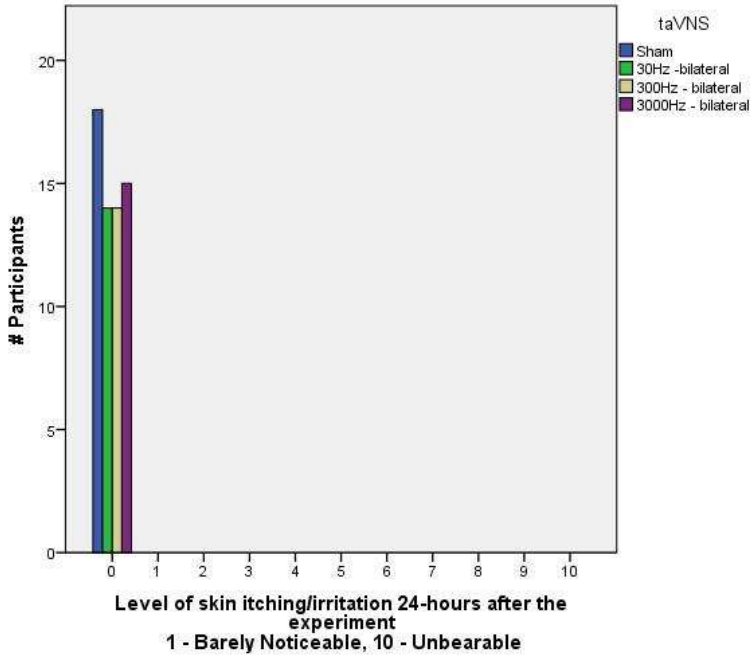

Figure 44: Level of skin itching/irritation after 24 hours

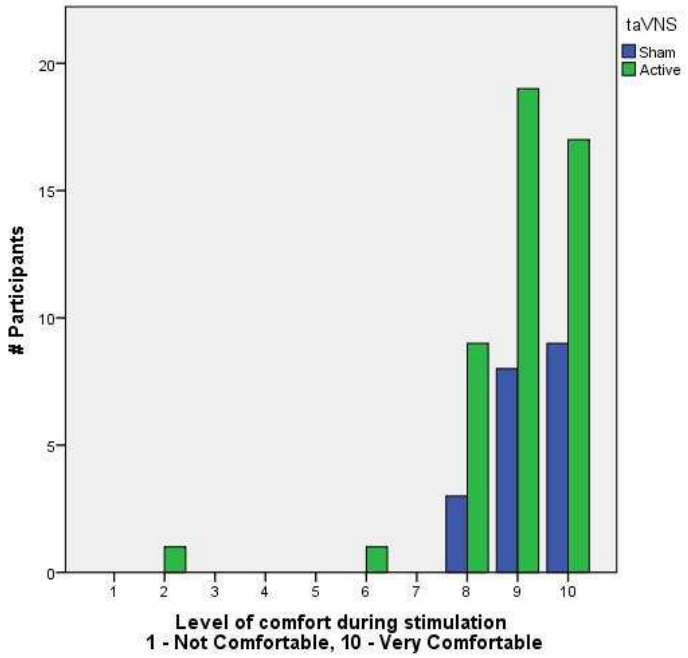

Figure 45: Level of comfort during stimulation

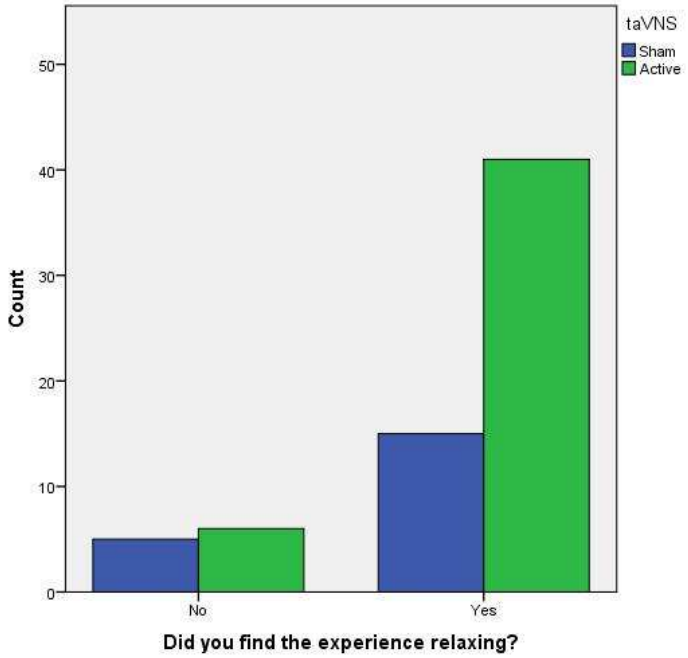

Figure 46: Yes/No relaxation

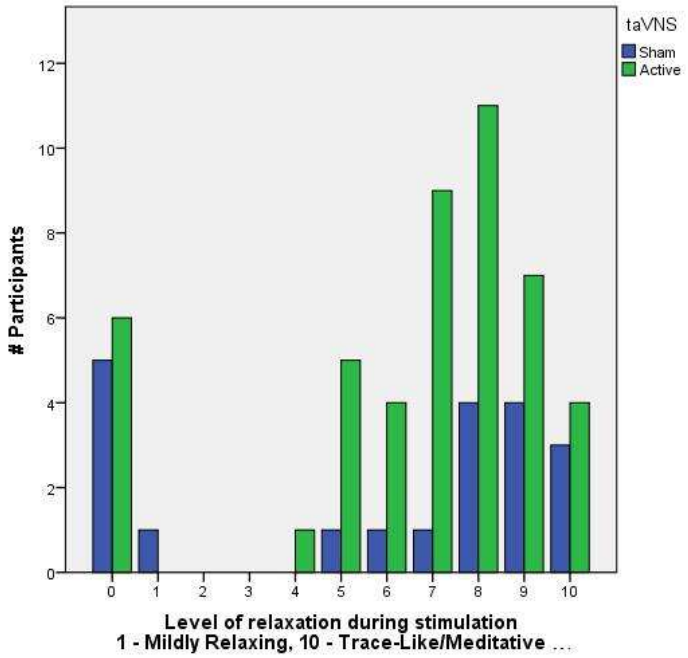

Figure 47: Level of relaxation during stimulation

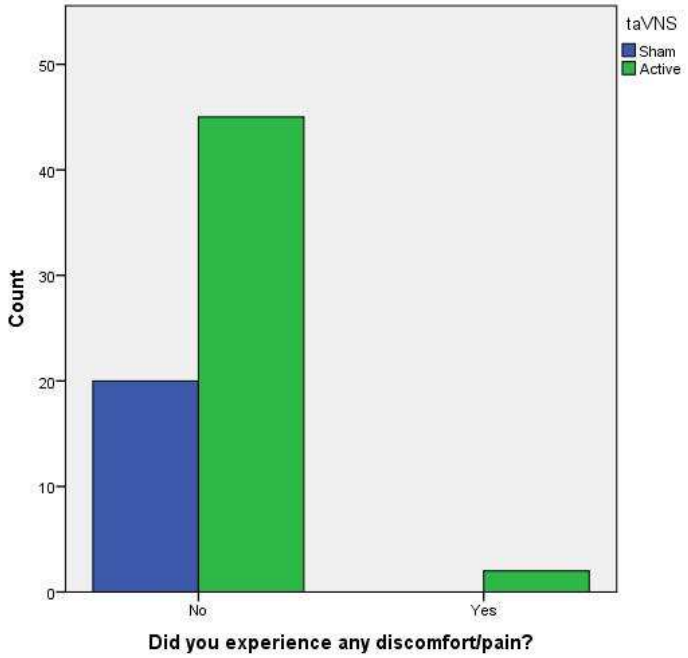

Figure 48: Yes/No discomfort/pain

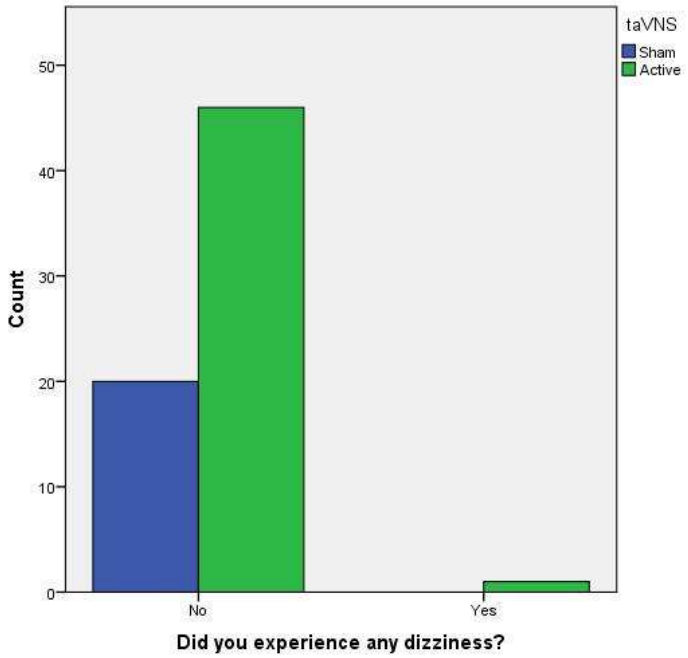

Figure 49: Yes/No dizziness

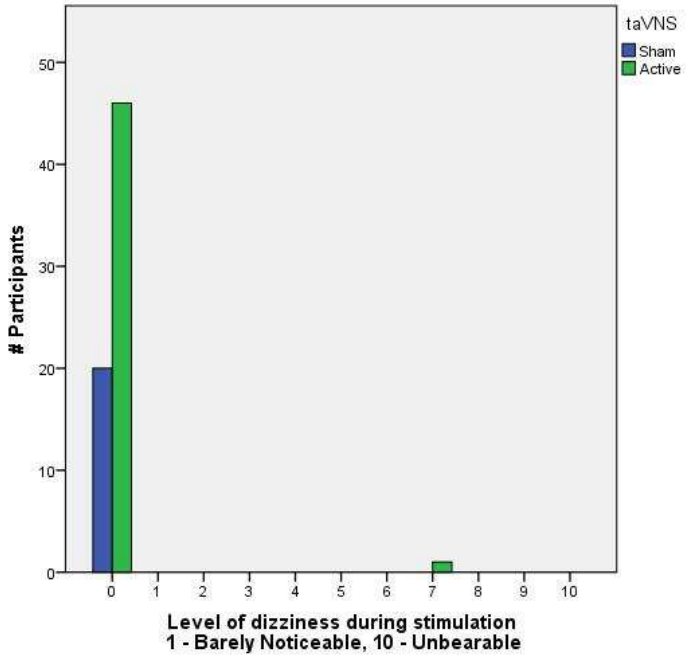

Figure 50: Level of dizziness during stimulation

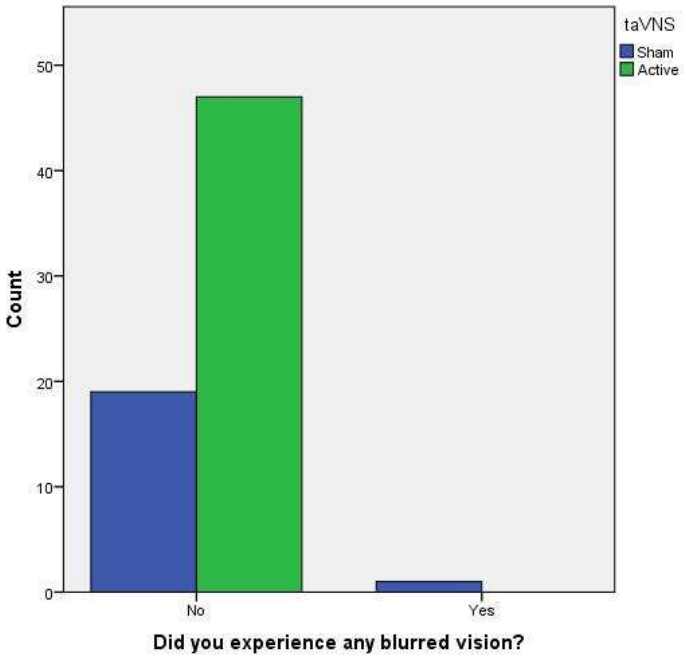

Figure 51: Yes/No blurred vision

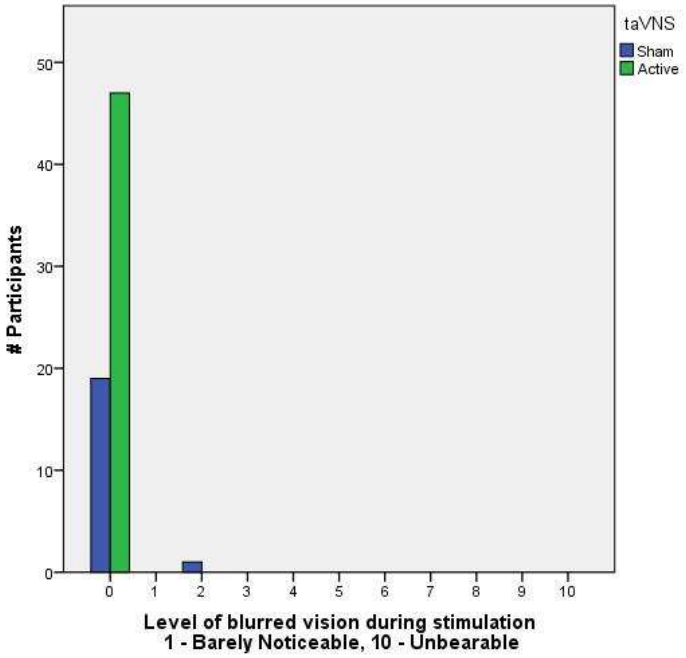

Figure 52: Level of blurred vision during stimulation

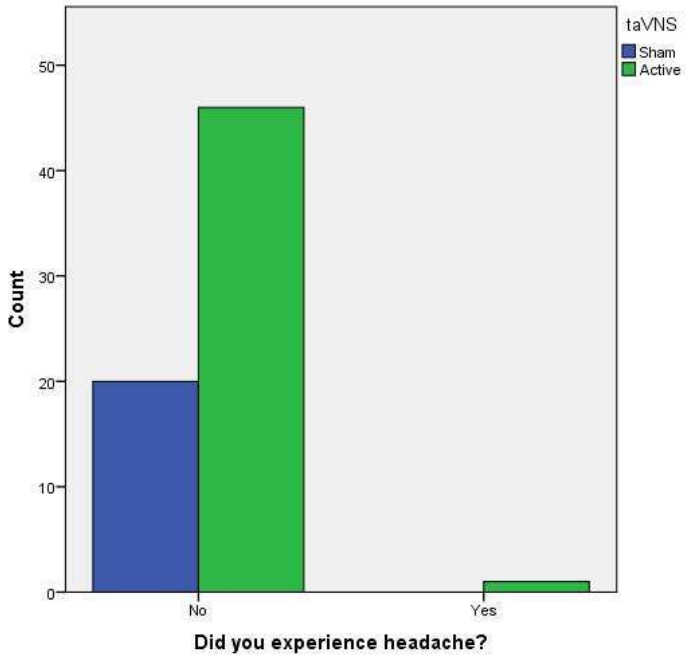

Figure 53: Yes/No headache

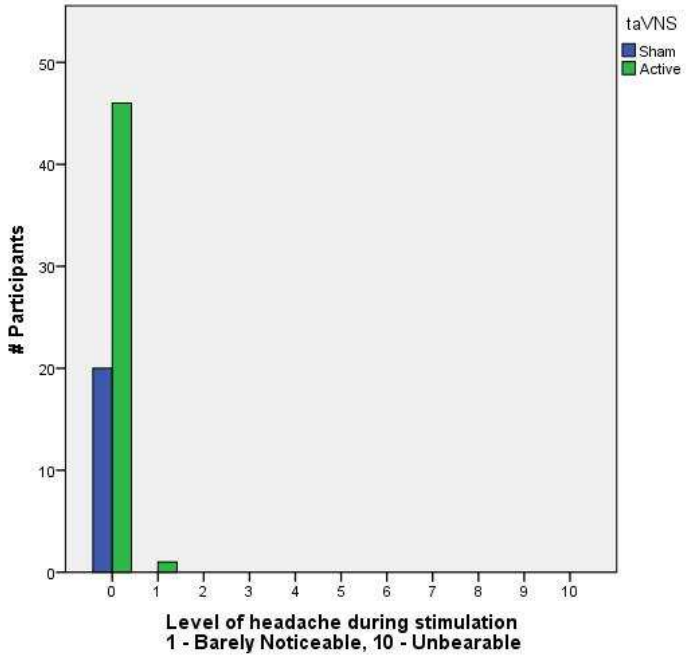

Figure 54: Level of headache during stimulation

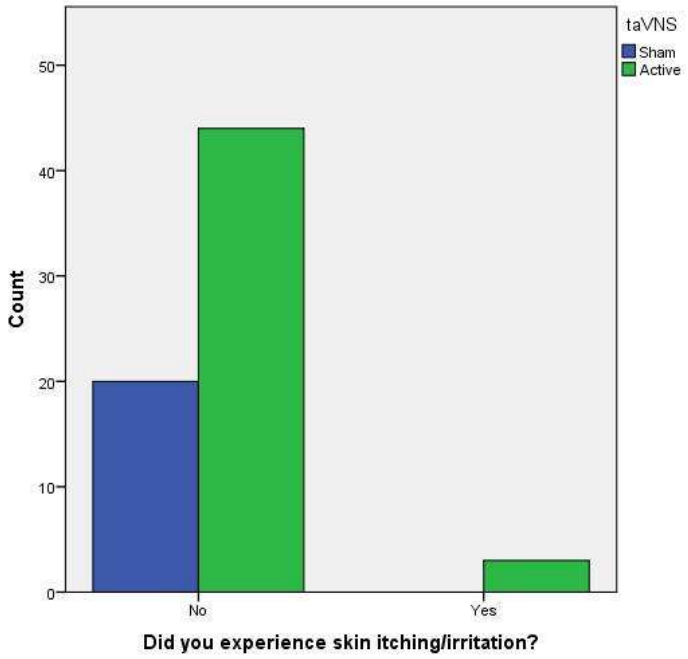

Figure 55: Yes/No skin itching/irritation

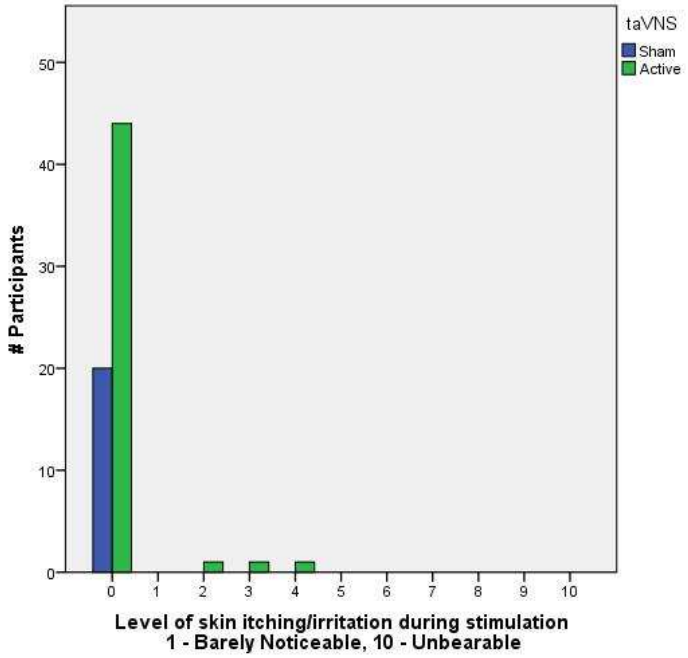

Figure 56: Level of skin itching/irritation during stimulation

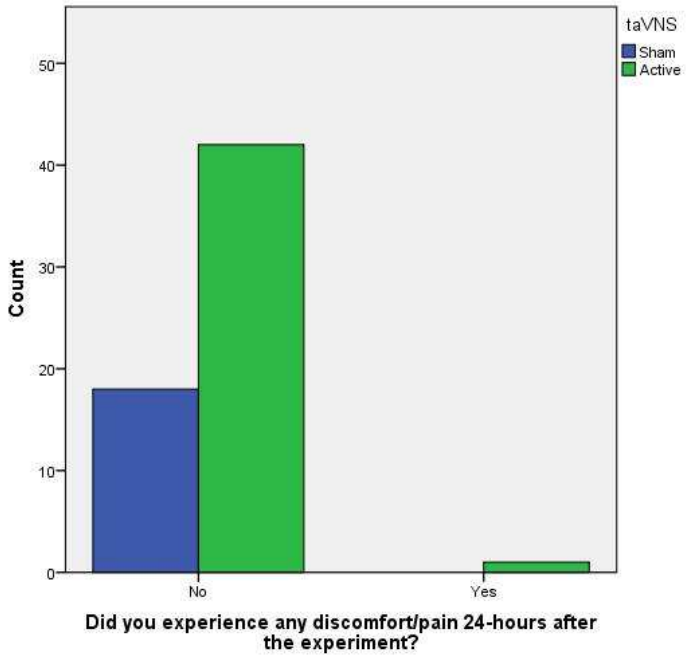

Figure 57: Yes/No discomfort/pain after 24 hours

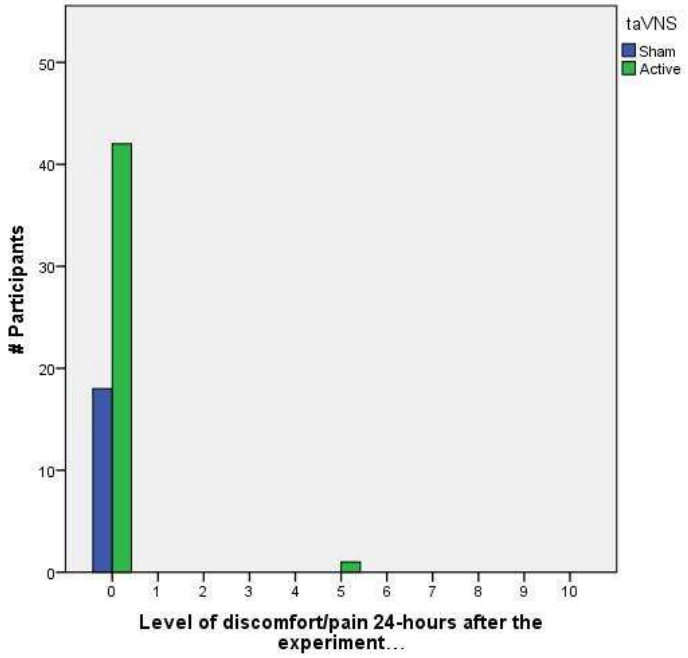

Figure 58: Level of discomfort/pain after 24 hours

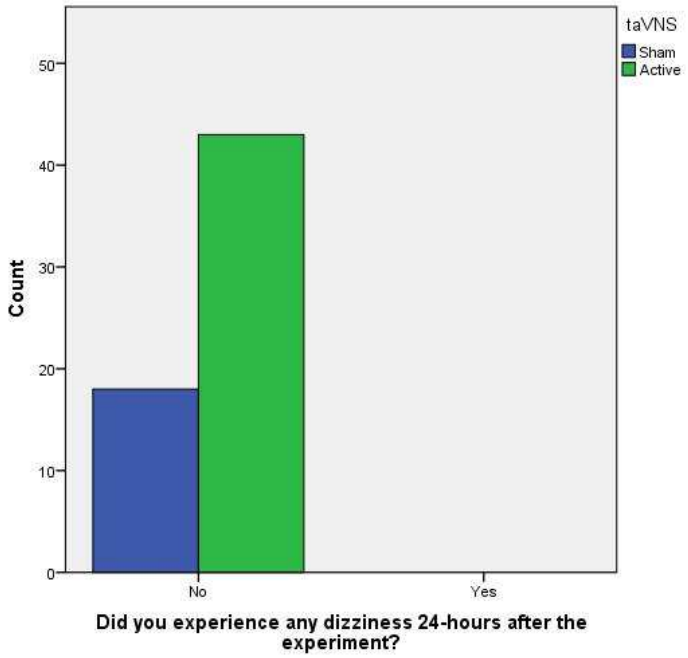

Figure 59: Yes/No dizziness after 24 hours

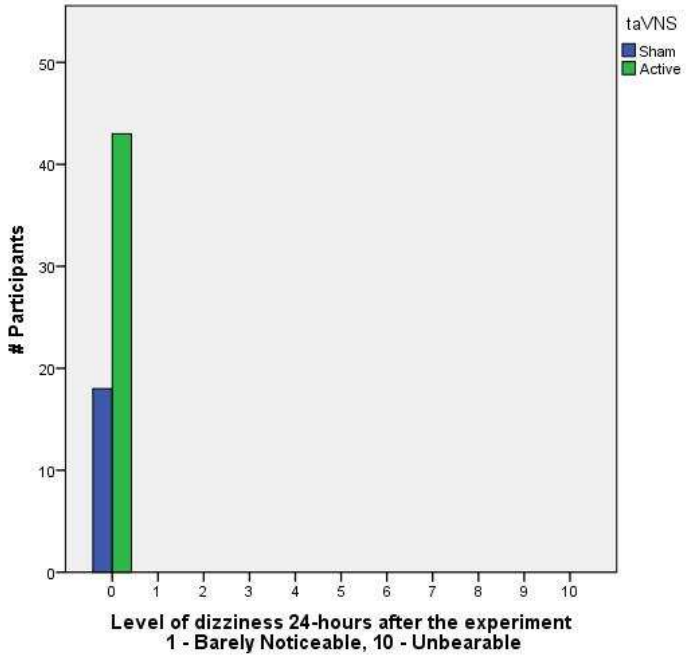

Figure 60: Level of dizziness after 24 hours

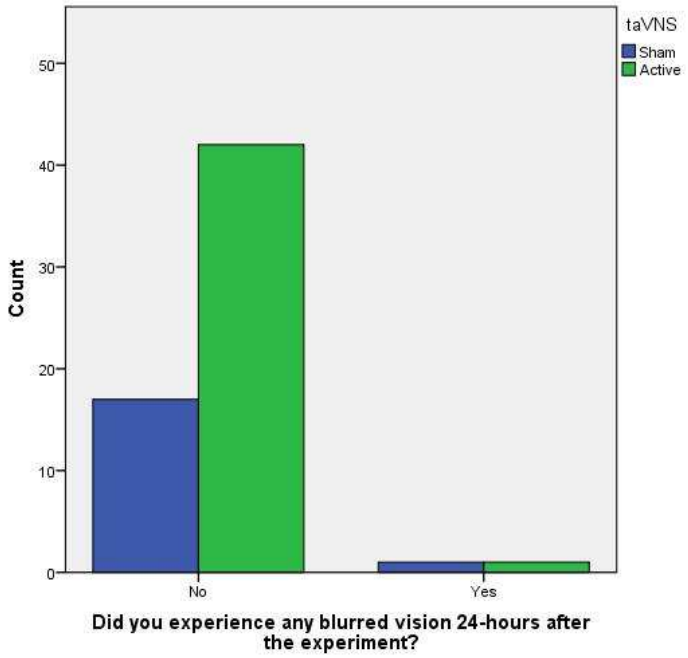

Figure 61: Yes/No blurred vision after 24 hours

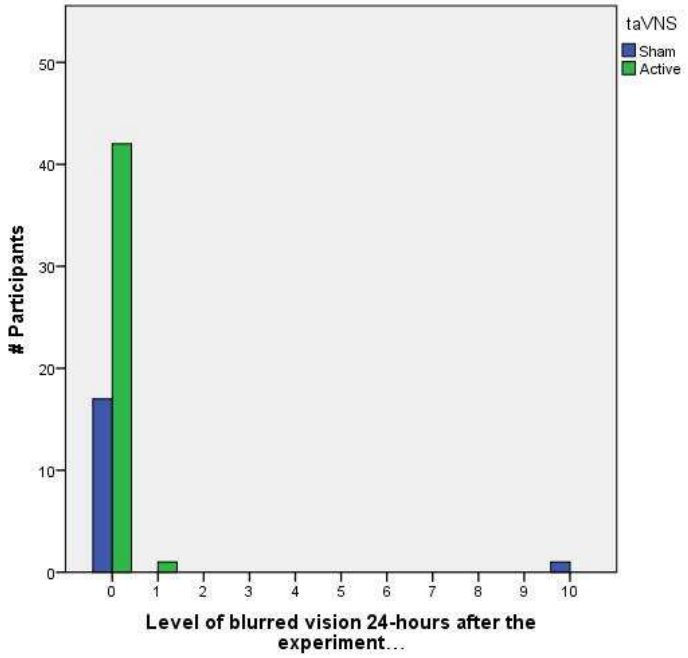

Figure 62: Level of blurred vision after 24 hours

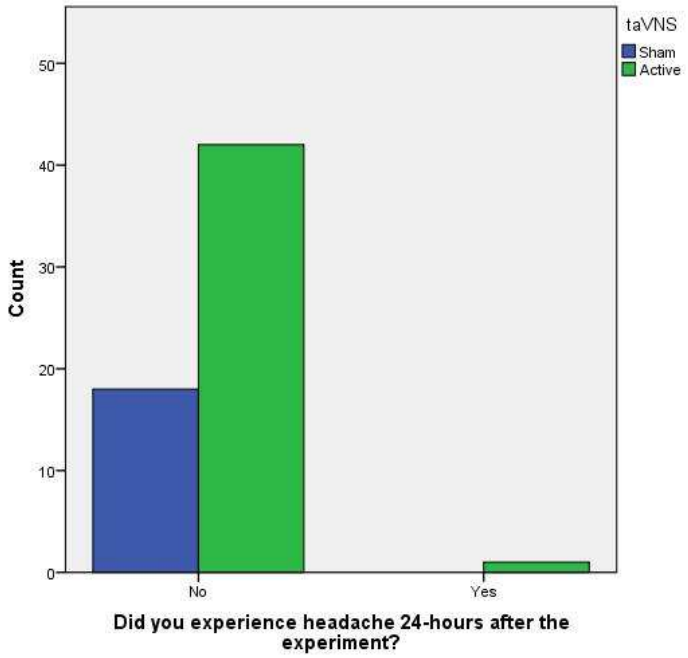

Figure 63: Yes/No headache after 24 hours

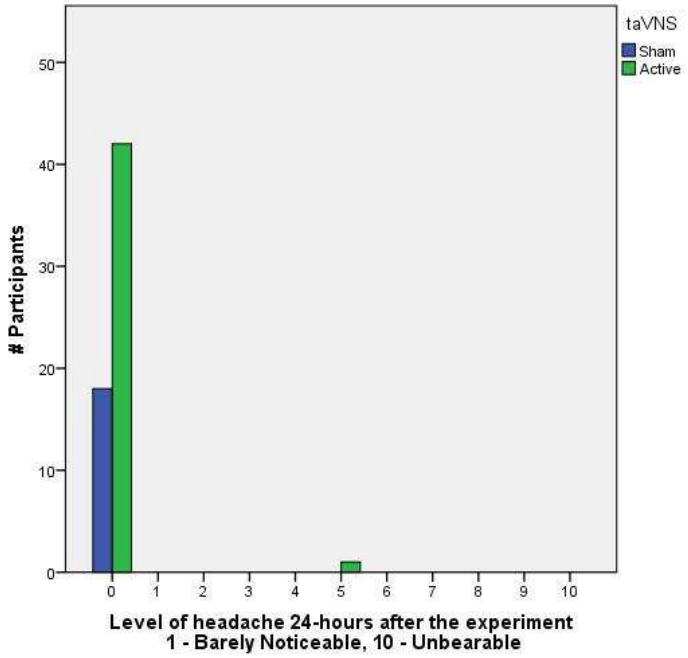

Figure 64: Level of headache after 24 hours

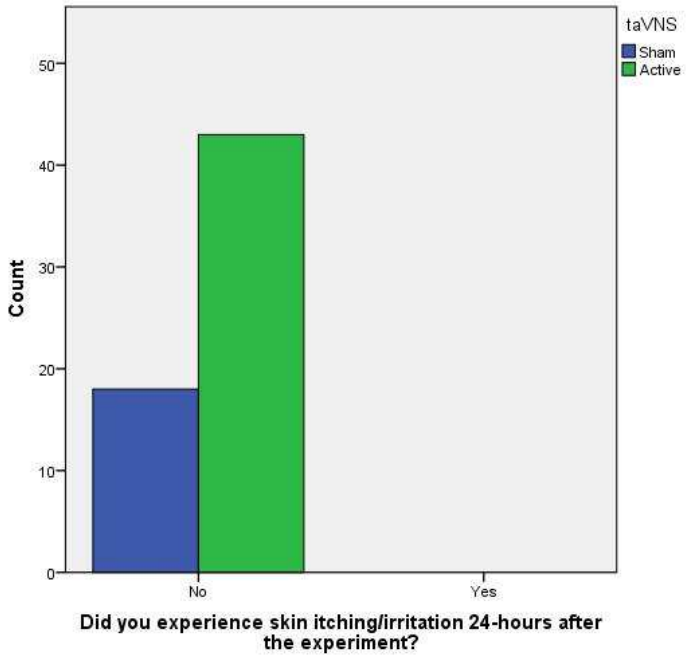

Figure 65: Yes/No skin itching/irritation after 24 hours

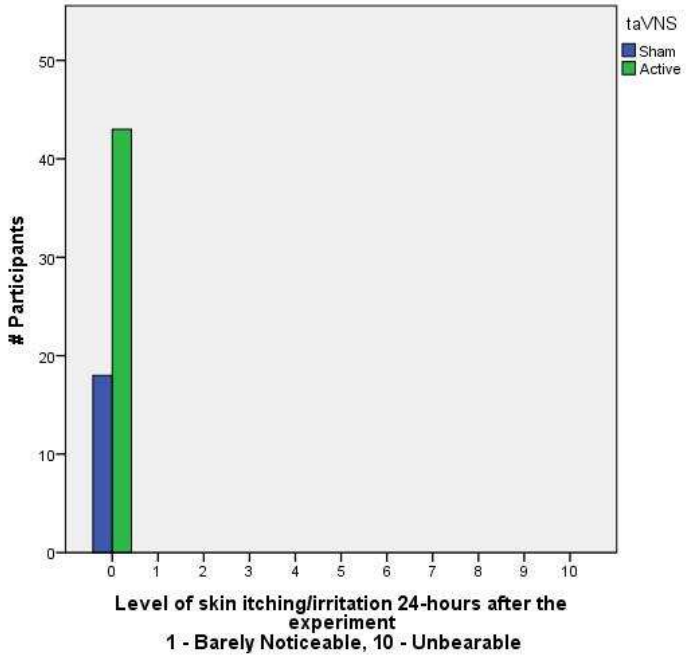

Figure 66: Level of skin itching/irritation after 24 hours

APPENDIX B

IRB APPROVED CONSENT FORMS

SUBJECT CONSENT FORM

Modulation of sensory processes by transcutaneous electrical nerve stimulation (TENS)

SCHOOL OF BIOLOGICAL AND HEALTH SYSTEMS ENGINEERING:
ARIZONA STATE UNIVERSITY

INTRODUCTION

The purposes of this form is to provide you (as a prospective research participant) information that may affect your decision as to whether or not to participate in this research and to record the consent of those who agree to be involved in the study.

PRINCIPAL INVESTIGATOR & RESEARCH ASSOCIATES

William Tyler, Ph.D., (PI, Associate Professor, School of Biological and Health Systems Engineering); Maria Fini (graduate student, SBHSE), Nicholas Hool (graduate student, SBHSE), Taylor Hearn (graduate student), and Sarah Wyckoff, Ph.D. (research assistant professor).

STUDY PURPOSE

This research is funded by the Department of Defense and is part of a multi-institutional effort designed to investigate and develop methods for enhancing skill training and learning. The particular research effort being conducted here is designed to evaluate how peripheral nerves that normally transmit sensory information to the brain can be used to trigger acute plasticity in other sensory brain circuits. We are interested in determining how different shapes and timing variables of weak electrical nerve stimulation can influence auditory, visual, and somatosensory processing. Information gained from this research will be used to develop training protocols for enhancing or accelerating skilled learning.

DESCRIPTION OF RESEARCH STUDY

You will be one of approximately 160 able-bodied healthy individuals to be asked to participate in this project. You will be asked to perform the following procedures in the Tyler Laboratory in room 158C Physical Education Building East.

(As you read please check the boxes).

Preparation stage (up to 30 minutes):

- ❑ You will have your head fitted with an electroencephalogram (EEG) cap (similar to a swim cap) that will measure non-invasively the activity of your brain. The EEG cap may be filled with gel to ensure good contact. In some cases up to 20 single EEG electrodes may be placed on your head instead of a cap.

- ❑ You will be connected to a heart rate monitor that is a strap worn across your chest.

- ❑ You will have gel electrodes placed on your forehead, side of your face, and/or behind your neck. These electrodes will be used to deliver brief electrical pulses to your skin at different times throughout the experiment as explained below.

- ❑ A small buzzer device may be placed upon your index finger or you will be asked to place your finger on a small vibrating element at some points during the experiment.

- ❑ You will be seated in front of a computer monitor that is connected to a computer. You may be asked to wear headphones in some parts of the experiment. Otherwise you will be asked to sit passively and follow the directions on the screen. Up to three optical sensors will monitor your facial temperature, your eye position and eye blinks, your pupil dilation, and your facial expressions. During the experiments your passive responses to various visual, auditory, and somatosensory stimuli will be monitored.

Testing (up to 35 minutes):

- ❑ Once you have been fully connected to the hardware and situated in front of the monitor testing will begin.

- ❑ You will first become acquainted with different types of transcutaneous electrical nerve stimuli (TENS) that you may experience during the testing period. These should be comfortable and at no point should cause you pain or distress. We will record a series of baseline responses to ensure that you are comfortable and that your heart rate has reached a baseline before beginning testing.

- ❑ You will be asked to follow the directions on the monitor once the testing begins. You will be presented with a series of auditory stimuli consisting of tones, visual stimuli consisting of objects and patterns presented on the monitor, and vibrotactile stimuli by vibrating a small piezo element affixed to your finger. We will record your brain's passive responses using EEG. You will be asked to remain relaxed throughout these recordings. We will also record changes in your heart rate, pupil dilation, eye motion, facial expression, facial temperature, and eye blinks in response to these auditory, visual, and somatosensory stimuli.

- ❑ At different time points throughout the presentation of auditory, visual, and somatosensory stimuli, we will deliver weak electrical pulses to the trigeminal and cervical nerves where gel electrodes have been placed upon your head, neck, and face. The delivery of these pulsed currents is safe, should be comfortable, and

should not cause you any pain or distress. If at any point during the study you should become uncomfortable or experience pain please notify the researcher.

- ❑ At the end of the study you will be asked to complete a short questionnaire asking you to rate and comment about your experience.

RISKS

This study has been designated to have a Minimal Risk Level. There have been no known severe adverse events associated with the use of TENS. There is a low-risk for some minor side-effects or adverse reactions however. Subjects with sensitive skin may experience skin irritation in the area where electrodes are applied. Some subjects may experience a headache and other painful sensations during or following the application of electrical stimulation. Some subjects may experience a sensation of hearing ringing tones after electrical stimulation.

Skin Irritation Risk
Minor skin irritation can occur if electrodes are placed over broken skin or wounds. We will avoid placing electrodes over these areas. Moreover, we will inspect the skin prior to electrode placement to further reduce the potential for minor irritation. Mild redness has been reported at the site of electrode placement, but this is an acute effect of vasodilation as opposed to inflammation and thus does not indicate damage.

Skin Discomfort Risk
Skin sensations during TENS are transient, most prominent at the onset and offset of stimulation and do not persist beyond the timeframe of stimulation. With proper use the most common sensation from TENS is tingling at the electrode site, which is not uncomfortable or painful. However depending on the amplitude of the current, uncomfortable sensations may occur, including a sensation of pain or heat. To minimize these sensations, we are using electrodes that have been specially designed to distribute current across the electrode-skin interface. In addition subjects will be able to decrease the current amplitude or abort the stimulation paradigm if they become uncomfortable at any time.

Headache
A rare side effect of TENS and transdermal cranial nerve modulation is the occurrence of a mild headache. This occurs in less than about 10% of subjects at incidence rates similar to sham procedures during both acute and repeated use procedures. Mild headaches typically resolve within a couple hours with no further complications. If a subject experiences a headache or discomfort, they may continue use at any time.

Inclusion criteria

- Healthy male or females ages 18-65 years of age

Exclusion criteria

Please check each box acknowledging that you do NOT have this condition or exclusion criteria.

- ❑ I am NOT currently undergoing treatment or medication for neurological or psychological disorder, including addiction
- ❑ I do NOT have a medical implant (such as a pacemaker, cochlear implant, brain stimulation device)
- ❑ I do NOT have migraines or frequent headaches
- ❑ I do NOT have a history of panic attack or acute anxiety disorder
- ❑ I have NOT experienced frequent fainting or experienced vaso-vagal syncope or neurocardiogenic syncope even once.
- ❑ I do NOT have Raynaud's disease
- ❑ I do NOT have Tempromandibular joint (TMJ) disorder or other facial neuropathy
- ❑ I do NOT have history of concussions or brain injury
- ❑ I do NOT have history of significant face/head injury or if you have cranial or facial metal plate or screw implants
- ❑ I do NOT have a history of hospitalization for neurological or psychological disorder
- ❑ I have NOT had a recent hospitalization for surgery/illness
- ❑ I do NOT have vision or hearing that is uncorrectable (corrected vision or hearing is okay)
- ❑ I am NOT to my knowledge pregnant
- ❑ I have NOT had recent drug or alcohol treatment (within past 3 months)
- ❑ I do NOT have high blood pressure, heart disease, or diabetes

BENEFITS

While you will not directly benefit from participation, your participation may help investigators better understand how the brain learns, as well as how to enhance learning or training procedures.

NEW INFORMATION

If the researchers find new information during the study that would reasonably change your decision about participating, then they will provide this information to you.

CONFIDENTIALITY

Every effort will be made to maintain the confidentiality of your participation in this project. Each subject's name will be paired with a code number by the principal investigator. This code number will appear on all written materials. The list pairing the subject's name to the assigned code number will be kept separate from all research materials and will be available only to the principal investigator. Confidentiality will be maintained within legal limits.

WITHDRAWAL

You may choose to withdraw from the study at any time. If you do withdraw, then any data collected from you prior to your withdrawal will only be used under your verbal consent.

COMPENSATION

For this study, you (the participant) will be compensated $10 in the form of cash or a gift card for participation.

COMPENSATION FOR ILLNESS AND INJURY

If you consent to participate in the study, then your consent does not waive any of your legal rights. However, no funds have been set aside to compensate you in the event of an injury.

VOLUNTARY CONSENT

1. I understand that informed consent is required of all persons participating in this project.

2. All procedures have been explained to me and all my questions have been answered to my satisfaction.

3. Any risks and/or discomforts have been explained to me.

4. Any benefits have been explained to me.

5. I understand that any questions that I have concerning the research study or my participation in the research study, before or after my consent, will be answered by William Tyler, Ph.D. or research associates, Tyler Laboratory, School of Biological and Health Systems Engineering, PEBE 158C, at 480-965-9270.

I also understand that if I have questions about my rights as a subject/participant in this research, or if I feel I have been placed at risk, I can contact the Chair of the Human subjects Institutional Review Board, through the ASU Research Compliance Office, at 480-965-6788

6. I have been told that I may refuse to participate or to stop my participation in this project at any time before or during the project. I may also refuse to answer any question.

7. All information that is obtained in connection with this project and that can be identified with me will remain confidential as far as possible within legal limits. Information gained from this study that can be identified with me may be released to no one other than the principal investigator. The results may be published in scientific journals, professional publications, or educational presentations without identifying me by name.

8. I understand that cases of injury and reports of non-compliance, as well as information regarding subject health will be reported to the Department of Navy Human Research Protection Program (DoN HRPP) and to the U.S. Navy Space and Naval Warfare (SPAWAR) Systems Center (SSC) Pacific.

9. This form explains the nature, demands, benefits and any risk of the project. By signing this form I agree knowingly to assume any risks involved. My participation is voluntary. I may choose not to participate or to withdraw my consent and discontinue participation at any time without penalty or loss of benefit. In signing this form, I am not waiving any legal claims, rights or remedies. A copy of this consent form will be offered to me.

Agreement for the Use of Video Recordings

If you consent to participate in this study, please indicate whether you agree to be recorded on video during the study by checking the appropriate box below. If you agree, please also indicate whether the video clips can be used for publication/presentations. If you do not agree to be recorded in video, or for the video to be used in publications/presentations, you will still be eligible for participation in this study. Recording videos is useful to our study since we collect data about psychophysiological responses using multiple optical sensors.

- ❑ I agree to be recorded in video during the experiment.
- ❑ I agree that the video recordings can be used in publication/presentations.

My signature means that I agree to participate in the study.

_____	_____	_____
Subject's Signature	Printed Name	Date

INVESTIGATOR'S STATEMENT

"I certify that I have explained to the above individual the nature and purpose, the potential benefits and possible risks associated with participation in this research study, have answered any questions that have been raised, and have witnessed the above signature. These elements of Informed Consent conform to the Assurance given by Arizona State University to the Office for Research Integrity and Assurance to protect the rights of human subjects. I have provided (offered) the subject/participant a copy of this signed consent document"

Signature of Investigator_____ Date_____

SUBJECT CONSENT FORM

Effect of Vagus Nerve Stimulation on EEG, Motion and Performance of Elite Golfers

SCHOOL OF BIOLOGICAL AND HEALTH SYSTEMS ENGINEERING
ARIZONA STATE UNIVERSITY

INTRODUCTION

The purposes of this form is to provide you (as a prospective research participant) information that may affect your decision as to whether or not to participate in this research and to record the consent of those who agree to be involved in the study.

PRINCIPAL INVESTIGATOR & RESEARCH ASSOCIATES

William Tyler, Ph.D., (PI, Associate Professor, School of Biological and Health Systems Engineering); Nicholas Hool (graduate student, SBHSE); Sarah Wyckoff, Ph.D. (Co-PI, Research Assistant Professor).

Co-Investigator Nicholas Hool is the developer of the intellectual property of the Hoolest VNS hardware utilized in the experiment, and holds equity in Hoolest Performance Technologies Inc.

STUDY PURPOSE

The purpose of this investigation is to determine whether vagus nerve stimulation can influence EEG, motion parameters, and performance among healthy and elite golfers. Vagus nerve stimulation is hypothesized to activate the parasympathetic (relaxation) response, which will result in more accurate golf shots.

DESCRIPTION OF RESEARCH STUDY

You will be one of approximately 30 golfers to be asked to participate in this project. You have already completed the online screening questionnaire and meet the inclusion criteria. You will be asked to perform the following procedures at TopGolf located at 9500 Talking Stick Way, Scottsdale AZ, 85256.

Preparation stage (up to 10 minutes):

1) You will have your head fitted with one small electroencephalogram (EEG) headset that will measure non-invasively the activity of your brain.
2) You will be connected to a heart rate monitor with electrodes that stick on your chest, EMG electrodes that stick to your shoulders, and GSR electrodes that stick to your fingers.
3) Your golf club will be connected to the Blast motion sensor.
4) You will take a standard anxiety survey.

Testing (up to 45 minutes):

1) Once you have been fully connected to the hardware, demographic data will be collected.
2) Your blood pressure will then be taken, and they you will sit for 5 minutes as we measure your resting biometrics.

3) Sensors will then be removed, except for the brain sensor. You will then hit 5 warm up shots
4) You will then hit 10 shots as close to the center of the 150-yard target as possible, with the opportunity to earn money.
5) You will then receive 10 minutes of VNS treatment. You will become acquainted with different types of transcutaneous electrical nerve stimuli (TENS) that you may experience during the testing period. These should be comfortable and at no point should cause you pain or distress. We will record a series of baseline responses to ensure that you are comfortable and that your heart rate has reached a baseline before beginning testing.
6) We will then record 5 minutes of resting biometrics. We will also record blood pressure.
7) You will complete 10 more shots with the opportunity to earn money.
8) At the end of the study you will be asked to complete a short questionnaire asking you to rate and comment about your experience.

RISKS

There have been no known severe adverse events associated with the use of TENS. There is a low-risk for some minor side-effects or adverse reactions however. Subjects with sensitive skin may experience skin irritation where electrodes are applied. Some subjects may experience a headache and other painful sensations during or following the application of electrical stimulation. Some subjects may experience a sensation of hearing ringing tones after electrical stimulation.

Skin Irritation Risk

Minor skin irritation can occur if electrodes are placed over broken skin or wounds. We will avoid placing electrodes over these areas. Mild redness has been reported at the site of electrode placement, but this is an acute effect of vasodilation or increased blood flow.

Skin Discomfort Risk

Skin sensations during TENS are transient, most prominent at the onset and offset of stimulation and do not persist beyond the timeframe of stimulation. With proper use the most common sensation from TENS is tingling at the electrode site, which is not uncomfortable or painful. However depending on the amplitude of the current, uncomfortable sensations may occur, including a sensation of pain or heat. If such sensations become present you will be able to decrease the current amplitude or abort the stimulation paradigm at any time.

Headache

A rare side effect of TENS and transdermal cranial nerve modulation is the occurrence of a mild headache. This occurs in less than about 10% of subjects at incidence rates similar to sham procedures during both acute and repeated use procedures. Mild headaches typically resolve within a couple hours with no further complications. If a subject experiences a headache or discomfort, they may continue use at any time.

BENEFITS

Benefits to participants include learning possible techniques to enhance hitting performance and the possibility of earning funds for successful performance.

SUBJECT CONSENT FORM

NEW INFORMATION

If the researchers find new information during the study that would reasonably change your decision about participating, then they will provide this information to you.

CONFIDENTIALITY

Every effort will be made to maintain the confidentiality of your participation in this project. Each subject's name will be paired with a code number by the principal investigator. This code number will appear on all written materials. The list pairing the subject's name to the assigned code number will be kept separate from all research materials and will be available only to the principal investigator. Confidentiality will be maintained within legal limits.

WITHDRAWAL

You may choose to withdraw from the study at any time. If you do withdraw, then any data collected from you prior to your withdrawal will only be used under your verbal consent.

COMPENSATION

For this study, you (the participant) will be asked to make a series of putts, two rounds of 10 putts each. For every shot made in the target circle, you will earn $5.00 in TopGolf credit up to a maximum of $100.00.

COMPENSATION FOR ILLNESS AND INJURY

If you consent to participate in the study, then your consent does not waive any of your legal rights. However, no funds have been set aside to compensate you in the event of an injury.

VOLUNTARY CONSENT

1) I understand that informed consent is required of all persons participating in this project.
2) All procedures have been explained and my questions have been answered to my satisfaction.
3) Any risks and/or discomforts and any benefits have been explained to me.
4) I understand that any questions that I have concerning the research study or my participation in the research study, before or after my consent, will be answered by William Tyler, Ph.D. or research associates, Tyler Laboratory, Biological and Health Systems Engineering, PEBE 158C, at 480-965-9270. I understand if I have questions about my rights as a subject/participant in this research, or if I feel I have been placed at risk, I can contact the Chair of the Human subjects Institutional Review Board, through the ASU Research Compliance Office, at 480-965-6788
5) I have been told that I may refuse to participate or to stop my participation in this project at any time before or during the project. I may also refuse to answer any question.
6) All information that is obtained in connection with this project and that can be identified with me will remain confidential as far as possible within legal limits. Information gained from this study that can be identified with me may be released to no one other than the principal investigator and members of the approved study team. The results may be published in scientific journals, professional publications, or educational presentations without identifying me by name.
7) This form explains the nature, demands, benefits and any risk of the project. By signing this form I agree knowingly to assume any risks involved. My participation is voluntary. I may

choose not to participate or to withdraw my consent and discontinue participation at any time without penalty or loss of benefit. In signing this form, I am not waiving any legal claims, rights or remedies. A copy of this consent form will be offered to me.

AGREEMENT FOR THE USE OF VIDEO RECORDINGS

If you consent to participate in this study, please indicate whether you agree to be recorded on video during the study by checking the appropriate box below. If you agree, please also indicate whether the video clips can be used for publication/presentations. If you do not agree to be recorded in video, or for the video to be used in publications/presentations, you will still be eligible for participation in this study. Recording videos is useful to our study since we collect data about psychophysiological responses using multiple optical sensors.

- ❑ I agree to be recorded in video during the experiment.
- ❑ I agree that the video recordings can be used in publication/presentations.

My signature means that I agree to participate in the study.

_____	_____	_____
Subject's Signature	**Printed Name**	**Date**

INVESTIGATOR'S STATEMENT

"I certify that I have explained to the above individual the nature and purpose, the potential benefits and possible risks associated with participation in this research study, have answered any questions that have been raised, and have witnessed the above signature. These elements of Informed Consent conform to the Assurance given by Arizona State University to the Office for Research Integrity and Assurance to protect the rights of human subjects. I have provided (offered) the subject/participant a copy of this signed consent document"

_____	_____
Signature of Investigator	**Date**