PROTOCOL TITLE:

Optimizing Transdiagnostic Non-invasive Vagus Nerve Stimulation to Enhance Learning

PRINCIPAL INVESTIGATOR:

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1.0 Objectives / Specific Aims

Improving treatment for anxiety and related conditions is essential, as anxiety disorders, for example, have a lifetime prevalence of 16.6% (Remes et al., 2016) and remission rates at only 51% after frontline exposure therapy (Springer et al., 2018). Enhancing acceptability and improving treatment refractory rates are *key*. Transcutaneous auricular vagus nerve stimulation (taVNS) is a brain stimulation candidate for disorders characterized by sympathetic hyper-activity (i.e., fight-or-flight; Badran et al., 2018c), including but not limited to generalized anxiety disorder, social anxiety disorder, panic disorder, and posttraumatic stress disorder. In fact, taVNS is thought to target transdiagnostic mechanisms, those mechanisms which are not diagnosis specific and cut across psychiatric illnesses. These include inflexible stress responses, heightened anxious arousal, and impaired cognitive processing (Deuchars et al., 2018). There are many advantages to taVNS over other stimulation technology, as it is non-invasive, affordable, and safe enough to implement at home or in the cognitive-behavioral therapy (CBT) clinical setting, without immediate MD oversight. A major limitation to the development of therapeutic taVNS is a lack of evidence for the optimal stimulation intensity. Failing to fully assess dose responses and mechanisms of taVNS is a major barrier to implementation in transdiagnostic interventions.

To establish the clinical viability of taVNS, it will be essential to determine optimal dosing to impact cognitive control and fear learning and associated biomarkers. Recent research suggests that there is a bidirectional relationship between sympathetic responses and cognitive control implicated in adaptive learning processes (Taylor et al., 2019; 2020). Also, anxiety is linked to heightened perception of heart rate changes (subjectively and neurally; Judah…Taylor & Grant, 2018), both factors which in turn influence cognitive functioning and learning processes, fear or otherwise, and this cascade may be modulated via vagal tone. Therefore, this study will determine the optimal taVNS dose and its influence on the course of fear learning and basic cognitive processes during goal-directed activity, while evaluating the psychophysiological profile in each context.

In order to develop therapeutic taVNS for psychiatric problems, a necessary first step is to establish the appropriate parameters that will modulate cognitive and affective responses among healthy participants. We will first recruit 45 healthy participants (randomized to 9 different dose durations) to determine the dose-response curve for taVNS on a range of vagally-mediated physiological measures and subjective mood. At a single session, heart rate variability (HRV), skin conductance (SC), and electroencephalography (EEG) will be measured at baseline, concurrently with stimulation, during learning and cognitive tasks and finally during a recovery period. Utilizing rest, learning and recovery conditions concurrent with multiple physiological measures we will demonstrate whether there is process- or physiological modality-specific modulation or co-activation across domains and measures. Our team of experts in brain stimulation, neuroscience, and psychophysiology are uniquely suited to accomplish these tasks. After establishing the dose-response curve, the findings of our dosing may be evaluated an additional sample of 45 participants seeking treatment for anxiety or trauma related disorder.

An additional goal of this study is to evaluate invasive vagus nerve stimulation (VNS) to determine how taVNS relates to other established forms of brain stimulation via the vagus nerve. VNS is currently FDA approved for depression and epilepsy, and research has indicated that patients also report decreased anxiety symptoms. Therefore, patients with previously implanted VNS, will be invited to complete this study. They will be administered similar tasks as participants who receive taVNS, and a full psychophysiological profile will be assessed. This study will only recruit individuals who currently have implanted VNS, given the invasive procedure. Although VNS is FDA approved, nearly 150,000 patients have received VNS worldwide over the past 25 years. Therefore, limited patients in the study area have received VNS, so this study expects to recruit <5 patients for this study goal.

Aim 1. Establish the dose-response curve secondary to transauricular vagus nerve stimulation (taVNS) for vagally-mediated physiological indicators at rest. We hypothesize that a dose-response curve will be observed with higher doses than typically administered in taVNS protocols being more efficacious in affecting physiological responding. Exploratory Aim 1a. Examine whether dose-response curves vary as a function of physiological measure (e.g., EEG/HRV, etc.). Exploratory Aim 1b. Examine whether a dose-response curve emerges for state measures of mood and interoceptive sensitivity.

Aim 2. Establish the dose-response curve secondary to transauricular vagus nerve stimulation (taVNS) for vagally-mediated physiological indicators during fear and cognitive challenge. We hypothesize that higher doses than typically administered in taVNS protocols will be more efficacious in affecting physiological responding and performance. Exploratory Aim 2a. Examine whether dose-response curves vary as a function of different physiological measures. Exploratory Aim 2b. Examine whether a dose-response curve emerges for cognitive and/or fear learning performance.

Aim 3. Assess tolerability and feasibility among a sample of participants with anxiety and trauma related symptoms. We hypothesize that utilizing taVNS among participants with anxiety and trauma symptoms will be well tolerated and will modulate autonomic arousal and fear processes, as indicated in physiological indicators.

Exploratory Aim 3. Examine whether invasive VNS and taVNS result in similar modulation of physiological measure (e.g., EEG/HRV, etc.), state measures of mood and interoceptive sensitivity, and across similar cognitive and affective tasks.

2.0 Background

The vagus nerve is the longest cranial nerve and maintains parasympathetic control over the heart, lungs, and digestive track, while also providing the prefrontal cortex with somatic and visceral feedback (Chalmers et al., 2014; Porges, 2001). It contains a variety of fibers which provide sympathetic and parasympathetic innervation and carry somatic and visceral afferent and efferent information. Given the vagus nerve's contributions to cardiac functioning, it is often indexed using heart rate variability (HRV; beat-to-beat changes in the heart rate), also referred to as vagal tone. Pharmacological blockade of the vagus results in increased heart rate suggesting that cardiac activity is regulated by inhibitory vagal control. Chronic stress, on the other hand, leads to protracted sympathetic disinhibition, inflexible parasympathetic activity, and maladaptive cognitive responses. In fact, low vagal tone and poor inhibition of sympathetic activity (i.e., fight-or-flight) is implicated in a range of psychiatric conditions and mental health problems, including emotion regulation difficulties, anxiety, depression, and PTSD.

Aberrations in cardiac activity are central to both the state expression of anxiety, as well as its pathological form. During the acquisition of fear, the vagus nerve provides visceral feedback to the brain and during extinction, the vagus inhibits sympathetic responses such as heart rate (Pappens et al., 2014). This critical brain-body communication which facilitates inhibitory fear extinction is hijacked in anxiety, as prolonged disinhibition of cardiac activity leads to persistent elevations in sympathetic responding regardless of the absence of threat. Thus, low vagal tone is considered a biomarker of anxiety and related psychopathology (Chalmers et al., 2014). Given that engagement in new learning (both reinforcement from positive feedback and inhibition of fear responses) are essential components to attain improvements via CBT and exposure

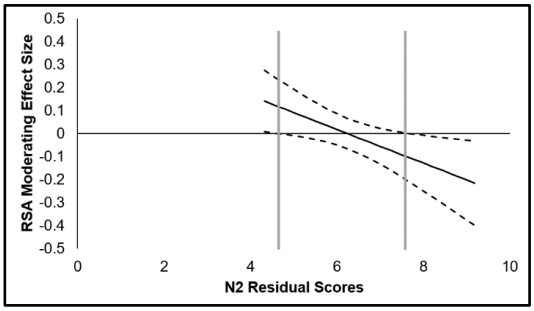

Figure 1. Moderating effect of RSA on the relation between negative cognitions and ERP indicator of cognitive control (Taylor et al., 2020).

therapy (Craske et al., 2008; 2014), it is predictable that disorders characterized by low vagal tone show poor treatment responsivity. In fact, our research suggests that parasympathetic responses are protective against the otherwise harmful effects of repetitive negative thinking (RNT) on cognitive control (Taylor et al., 2020; see Figure 1). Thus, given the linkage between vagal tone and psychiatric problems, interventions that non-invasively target the vagus nerve to regulate inhibition of sympathetic activity may be therapeutic for psychiatric conditions characterized by inflexible parasympathetic responses such as anxiety disorders.

Brain stimulation techniques have been used to identify mechanisms of action and treat mental health conditions, and evidence of afferent and efferent vagal contributions has been shown using a variety of stimulation techniques. In fact, vagal innervation of cardiac responses, observed via HRV, may be modulated using vagus nerve stimulation resulting in increases in parasympathetic activity (Zamotrinsky et al., 2001), providing additional support for this connection. Stimulating the vagus also is a therapeutic intervention approved for the treatment of depression and can be accomplished by implantation of electrodes. Studies investigating VNS show that it affects brain regions linked to mood regulation, and clinical trials using VNS for depression show efficacy in reducing depressive symptoms, as well as reduced anxiety symptoms. A potential mechanism for its anxiolytic effects is that VNS stimulates the locus ceruleus, a primary norepinephrine (NE) site, which is essential to regulating arousal and stress responses. Those with anxiety and other related problems tend to show greater NE reactivity, thus VNS may aid its down regulation (George et al., 2000).

A draw back to administration of VNS is that it requires implantation, which reduces the feasibility of VNS as a tool for clinicians. Researchers have developed a safe, non-invasive, as well as easy to use stimulation technique, taVNS, which modulates afferent projections via stimulation of the vagus nerve through the human ear (Badran et al., 2018a; see Figure 2). Using conductive gel, an electrode is applied to the tragus cartilage of the left ear and pulsed electrical stimulation is delivered at a tolerable intensity for half hour to an hour, thus, stimulating the auricular branch of the vagus nerve (ABVN). This method has been shown to activate afferent vagal networks and early work shows promise for treatment of psychiatric conditions linked to overactive sympathetic responses (Badran et al., 2018c). Studies have recently demonstrated some efficacy for taVNS for reduction in symptoms of depression, including RNT, sleep disturbances and anxiety. However, mechanisms, parameters, and the neurobiological effects are not well established (Badran et al. 2018b). Trials studying the efficacy of taVNS have shown inconsistent results, which are largely attributable to incomplete consideration of stimulation parameters and corresponding modulation in the psychophysiological profile taVNS purportedly targets. This study aims to parameterize, then employ this emerging form of stimulation and explore its effects on learning and cognitive control, while fully evaluating the physiological mechanisms which are affected during and after stimulation.

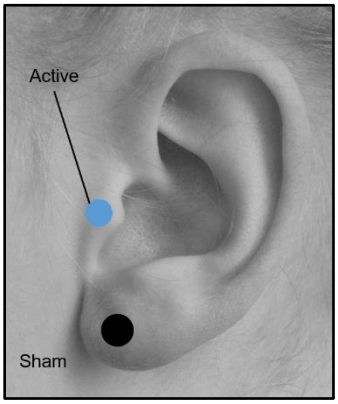

Figure 2. TaVNS active and sham stimulation electrode placement

3.0 Intervention to be studied

The stimulation system, custom developed at the MUSC Brain Stimulation Laboratory, consists of a commercially available, FDA-cleared (K172381) Digitimer DS7A constant current stimulator (Digitimer Ltd., USA) used with custom-built electrodes built by Dr. Bashar Badran in MUSC's Brain Stimulation Lab. This is a safe, non-invasive, and easily implemented stimulation technique which does not require MD oversight. TaVNS modulates afferent projections via stimulation of the vagus nerve through the human ear (Badran et al., 2018a) and early work shows promise for treatment of psychiatric conditions linked to overactive sympathetic responses (Badran et al., 2018c). Studies have recently demonstrated some efficacy for taVNS for reduction in symptoms of depression, including RNT, sleep disturbances and anxiety.

However, mechanisms, parameters, and the neurobiological effects are not well established (Badran et al. 2018b). Researchers on this study are experts in the development, application, and clinical use of brain stimulation techniques, and in particular are pioneers in the development and investigation of taVNS technology and its application for psychiatric treatments.

Using conductive gel, an electrode is applied and pulsed electrical stimulation is delivered at a tolerable intensity for at least half an hour, thus, stimulating the auricular branch of the vagus nerve (ABVN). The active condition will be direct electrical stimulation delivered to the inner side of the left tragus (anode in the ear canal, cathode on the surface of the tragus) based on Dr. Bashar Badran and Dr. Lisa McTeague's prior work. The left earlobe, used as control, has minimal ABVN innervation. The control stimulation condition will utilize identical stimulation parameters as the active condition.

Stimulation parameters will consist of 500 μs pulse width and 10 Hz frequency. Stimulation current will be delivered at 200% of each participant's individual perceptual threshold (PT) and repeated for each stimulation condition (tragus and earlobe). PT procedure entails single pulses of stimulation to the target area and obtaining verbal confirmation of stimulation perception while modulating the current intensity via parametric estimation by sequential testing (PEST) method. This allows for determination of the minimum current intensity perceived by the participant at a specific target location.

Participants will be randomized to one of 9 dose durations with 5 participants per dose, increasing in 10 minute increments of active stimulation, ranging between 10 and 90 minutes of stimulation. All active sessions per dose will be delivered contiguously and at the end of the stimulation period, and sham stimulation at the beginning. This is to ensure that all participants have the same lapse of time between pre- and post-stimulation recording. That is, if a participant is randomized to 60 minutes of active stimulation, the first 30 minutes would be sham stimulation. After establishing the optimal dose-duration a sample of treatment seeking individuals will be recruited. This dose will be administered to individuals with anxiety and trauma symptoms to ensure that effects are sustained and to determine feasibility and tolerability.

An additional group of individuals with implanted VNS also will be evaluated after 30 minutes of stimulation. Patients at MUSC who participated in the Microtransponder Vivistim trial or other research/treatments involving VNS will be recruited to complete similar cognitive and affective tasks while psychophysiological responses are measured across 3 sessions: control (no stimulation), implanted VNS, and noninvasive taVNS. This will serve as a comparator for whether taVNS is activating similar brain and physiological regions as invasive forms of vagus nerve stimulation. This will also indicate whether mechanisms of taVNS and VNS are comparable. In order to truly determine comparability of these two forms of VNS, it is imperative to assess within subject brain, body, cognitive, and emotional responding across both implanted and non-invasive VNS.

4.0 Study Endpoints

The following indices will be measured to assess modulation of resting and cognitive/emotional challenge via taVNS dose. Each will be processed and scored according to published guidelines (Blumenthal et al., 2005; Boucsein et al., 2012; Gatchel et al., 1973; Keil et al., 2014). Biopac equipment will be used to continuously measure **heart rate/ variability (HRV)** and **skin conductance (SC)** to assess autonomic responses. SC increases are indicative of a sympathetically mediated orienting response (Dawson et al., 2011; Bradley, 2009). Previous studies evaluating taVNS have employed the SC within the context of fear extinction, but have not demonstrated an effect (Burger et al., 2016; 2017), though faster rates of extinction were shown. HR deceleration also is indicative of the orienting response, while higher HR variability is indicative of regulated emotional responding (Appelhans & Luecken, 2006; Bradley, 2009). Decelerations in HR after taVNS have been demonstrated under certain parameters (Badran et al., 2018b). **Pupillometry**

will be assessed to determine anxious arousal and defensive responding as a function of taVNS. Pupil dilation will be measured with a Tobii eyetracker. Previous data has shown that taVNS modulates pupil dilation. Thus, this will be used to aid in determining the optimal dose duration of taVNS.

EEG will be measured using a 32-channel BrainVision actiCHamp system. Data will be processed with BrainVision Analyzer software. Resting EEG will be measured pre-, post-, and concurrently with stimulation, and will be explored for taVNS dose dependent modulation in frequency bands and coherence of the **EEG power spectrum**. For data collected during the learning/attention task, multiple **event-related potentials** (ERPs) and **steady-state visually evoked potentials** (ssVEPs) will be assessed. A variety of ERPs indicative of attention (i.e., orienting, discrimination) will be evaluated across a variety of contexts after stimulation, including fear learning and extinction, and learning more broadly. Some studies have shown taVNS linked enhancements in the P300, an orienting response (Warren et al., 2020), whereas other studies have not (Warran et al., 2019; Keute et al., 2019). A recent evaluation found taVNS related ERP modulations indicative of enhanced cognitive control (i.e., N2; Pihlaja et al., 2020), which is typically increased during engagement of attention and is enhanced during cognitive conflict. Enhancements in the N2 are typically seen across internalizing disorders, and our previous work demonstrates that the N2 is modulated under internal and external threat (Taylor et al., 2020; Moran, Taylor, & Moser, 2012; White, Grant, Taylor et al., 2018). In addition, ssVEPs which are collected by flickering visual stimuli, may be assessed during stimulation. These potentials are modulated by attentional and motivational factors and will provide real-time dose-dependent data regarding taVNS related modulations in attention. Given the extant and emerging literature on the effects of taVNS on brain activity, these ERPs and other relevant ERPs will be explored.

Participants will complete subjective measures of anxiety and depression and related difficulties as well as Self-Reported Units of Distress (SUDs) during stimulation and the tasks and acceptability/tolerability measures (see Section 10.0 Study Design/Methods for surveys and other measures).

The above measures will also be assessed for participants with implanted invasive VNS and then subsequently with noninvasive taVNS.

5.0 Inclusion and Exclusion Criteria/ Study Population

This study seeks to recruit from a broad range of individuals ensure generalizability, though some exclusion criteria are necessary to ensure participant safety. Participants will call the lab and complete a phone screener which assesses for the following criteria. The recruited sample will be 50% female evenly counterbalanced across active stimulation duration and sham conditions. No racial or ethnic groups will be excluded during recruitment, nor will any other individuals with diverse backgrounds. However, participants must be English speaking, as the study consent and other tasks are presented in the English language. Risks of taVNS to a fetus are currently unknown. Thus, individuals identifying as having childbearing potential will be screened for pregnancy during the phone screener and will be provided a pregnancy test prior to stimulation to confirm they are not pregnant.

Inclusion Criteria

- Ages 18-65 years
- English speaking

- Healthy, Non-treatment-seeking community members who do not have a mental health diagnosis and individuals seeking treatment for an anxiety, mood, trauma-related, or obsessive-compulsive disorder.

- Treatment and non-treatment-seeking community members with anxiety, mood, trauma-related, or obsessive-compulsive disorder or symptoms.

- Patients at MUSC who have received implanted VNS for depression or stroke recovery.

Exclusion Criteria

- Diagnosis of COVID-19 in the past 14 days

- Facial or ear pain or recent ear trauma for the taVNS group only.

- Metal implant devices in the head, heart or neck for the taVNS group only.

- History of brain stimulation or other brain surgery for the taVNS group only.

- History of myocardial infarction or arrhythmia, bradycardia for the taVNS group only.

- Use of B-blockers, antiarrhythmic medication (sodium/potassium/calcium-channel blockers), or blood pressure medications for the taVNS group only.

- Active respiratory disorder for the taVNS group only.

- Personal or family history of seizure or epilepsy or personal use of medications that substantially reduce seizure threshold (e.g., olanzapine, chlorpromazine, lithium).

- Personal history of head injury, concussion, or self-report of moderate to severe traumatic brain injury for the taVNS group only.

- Individuals suffering from frequent/severe headaches for the taVNS group only.

- Individuals with lifetime evidence of severe psychiatric disorder (e.g., schizophrenia) or neurological disorder for the taVNS group only.

- Moderate to severe alcohol or substance use disorder.

- Pregnancy

6.0 Number of Subjects

This study will recruit 90 community individuals who meet the above inclusion and exclusion criteria, 50% of which will be female. Participants (n = 45) who are healthy controls will be recruited to establish the dose response curve. Then this dose will be administered to 40 individuals with anxiety and trauma related symptoms. Participants with implanted VNS (n = 5) will be recruited for similar procedures.

7.0 Setting

All participants will complete the study tasks in a dedicated research suite, the Psychophysiology Center, in the Brain Sciences Department within the IOP. The space to be used here is currently assigned to researchers on this study team and is well equipped for stimulus-controlled physiological recording. In addition, this space is used only for research protocols and thus is accessed at limited times. Studies assigned to this space may only enter during their assigned hours to ensure participant confidentiality and privacy. This also ensures COVID-19 related precautions may be taken: limiting use of space to no more than the participant and the study researcher and allowing time between participants for cleaning/sanitation, requiring the use of masks for researchers and participants.

8.0 Recruitment Methods

Participants will be recruited from the Charleston community and from the population of individuals who present to IOP for mental health treatment. Potential participants will be recruited via flyers (see advertisements) placed at approved sites at MUSC's library and hospital, as well as within the IOP; in addition, online advertisements will be placed on scra.org, on facebook.com, on researchmatch.org, and on nextdoor.com. Separate recruitment materials will either be targeted to adults seeking treatment for anxiety, mood, trauma-related or obsessive-compulsive disorder, or to the Charleston community at large. Appropriate approvals will be received prior to posting flyers.

When a potential participant contacts about the study, trained research assistants will overview all procedures and specify the expected duration and compensation (see Phone Recruitment script). The PI and Co-I will train staff in answering questions related to study procedures. After providing information about the study, a phone screener will be completed. Participants will be asked to complete this portion in a private setting. Should participants meet for the inclusion/exclusion criteria, and they agree participate, subjects will be provided with available participation dates, an online consent form, and will be sent the study's Redcap survey. They will also be provided with instructions on how to locate IOP and the lab space. Participants will be asked to refrain from alcohol use and intense physical activity 24 hours before the study, as well as refrain from caffeine 6 hours and tobacco 2 hours prior to the study. Participants will be encouraged to sleep as they usually do the night before the study.

In order to recruit participants with implanted VNS, the principal investigator will contact clinicians at MUSC to disseminate information about this study to patients with VNS, including the MUSC Center for Rehabilitation Research and the MUSC Comprehensive Stroke Center. Clinicians and researchers will be provided a script (see VNS Recruitment Script). Clinicians will be asked to only invite patients: 1) who have completed VNS treatment/research or 2) whose VNS treatment/research protocol will not be affected by 30 minutes of stimulation.

9.0 Consent Process

The consent form will be sent to participants via RedCap after the phone screen is complete and prior to being sent the RedCap surveys. Participants will be given ample time to read the consent form and a researcher will describe the content of the consent form to ensure understanding, including describing the laboratory measures, study duration, and equipment and materials. The researcher will describe confidentiality/privacy measures, participant right to withdraw, risks/benefits, and compensation. In addition, participants will be prompted to ask questions throughout consenting to further ensure understanding. After electronically signing the consent form, an electronic copy will be made accessible to the participant for their records. They will also be offered a hard copy which will be provided during the in-lab scheduled participation date.

10.0 Study Design / Methods

After completing the phone screener, participants will be invited to in-lab participation: they will be provided available times and instructed on how to locate IOP and the laboratory space. They will be asked to refrain from the following prior to the study: Tobacco use within 2 hours, Caffeine within 6 hours, Alcohol within 24 hours, and intense physical activity within 24 hours. Participants will be asked to sleep as they usually do the night before the study. The study will take up to two hours and thirty minutes.

Prior to arrival to the research space, after phone screening, participants will be provided online informed consent (see Section 9.0). After participants have been informed of the nature of the study and consent to the study procedures, they will be sent a series of questionnaires to be completed online using the RedCap survey platform. They will be asked to complete these questionnaires in a private setting to ensure their confidentiality. None of the items on these questionnaires address suicidality. However, surveys will be monitored for extreme scores indicating severe mental health issues or indication of suicidal or homicidal ideation/risk, and those participants will be contacted *immediately* via phone to assess for safety. Several attempts will be made to reach at risk participants. They will be assessed for safety again, upon arrival to the lab. Questionnaires will include a measure of demographics, Penn State Worry Questionnaire (PSWQ; Meyer et al., 1990), the Attentional Control Scale (ACS; Derryberry & Reed, 2002), the Childhood Trauma Questionnaire (CTQ; Bernstein & Fink, 1998), Connor Davidson Resiliency Questionnaire (Connor & Davidson, 2003), Contrast Avoidance Questionnaire (CAQ; Llera & Newman 2017), PTSD Symptom Scale – Self-Report (PSS-SR; Falsetti et al., 1993), the Perseverative Thinking Questionnaire (Ehring et al., 2011), the Social Interaction Anxiety Inventory/Social Phobia Scales Short forms (SIAS-SPS; Fergus et al., 2012), the Intolerance of Uncertainty Scale (Carleton et al., 2007), Difficulties with Emotion Regulation Scale (Gratz & Roemer, 2004), and the Generalized Anxiety Disorder 7-item scale (GAD-7; Spitzer, 2006).

Once participants have arrived to the laboratory, if they identify as an individual of childbearing potential, they will be provided with a pregnancy test strip to take in privacy. They will be provided instructions on how to use the test, as well. After completing the pregnancy test, participants with negative results will be asked to continue to the remaining study procedures, whereas those with a positive result will be debriefed, compensated for their time, and released.

Next, electrodes will be attached which will measure a variety of responses, including electroencephalography, electrocardiography, electrooculography, electromyography (startle reflex), and electrodermal activity. Tobii eye tracker software will be set-up to monitor and record pupil dilation and eye tracking. TaVNS electrodes (active and sham) will be attached to participants who do not have implanted VNS. A computer monitor will be adjusted for appropriate eye level. Peripheral physiology (e.g., heart rate) data will be collected using a Biopac MP150 hardware and amplifier along with AcqKnowledge software, and brain activity will be collected using an Actichamp active sensor cluster and amplifier. Stimuli (e.g., learning tests) will be presented using Presentation software. The following questionnaires will be administered during electrode set up: Positive and Negative Affect Schedule – Short Version (PANAS; Thompson, 2007), the Beck Depression Inventory- II, (BDI-II; Beck et al., 1996), State Trait Anxiety Inventory (STAI; Spielberger et al., 1983), the Anxiety sensitivity index (ASI-3; Taylor et al., 2007). Participants will be asked when they last used Tobacco, Caffeine, Alcohol, engaged in intense physical activity, and when they last took medication, along with what those medications include. They also will be asked to report on their typical sleep habits and sleep from the night before – these will be asked in the Health Behaviors Survey. A measure of tolerability for

stimulation will be administered periodically throughout the study. Responses (particularly those on the BDI-II (Item #9 – suicide ideation) will be monitored for endorsements of suicidal ideation. See section 13 for study team response to suicidal ideation.

After all electrodes are attached, a 1) baseline (5-10 min) physiology measurement will be taken. Then stimulation will begin. See additional information in Section 3.0 (Intervention to be Studied). Participants in the taVNS group (not having implanted VNS) will be randomized to one of 9 doses with 5 participants per dose, increasing in 10 minute increments of active stimulation. All active sessions per dose will be delivered contiguously and at the end of the stimulation period, and sham stimulation at the beginning. This is to ensure that all participants have the same lapse of time between pre- and post-stimulation recording. That is, if a participant is randomized to 60 minutes of active stimulation, the first 30 minutes would be sham stimulation.

For participants with previously implanted vagus nerve stimulation devices, stimulation will be delivered for 30 minutes. They will subsequently be invited to revisit the lab to receive non-invasive taVNS delivered in a comparable manner to the healthy subjects for 30 minutes.

Additional physiology measurements will be taken 2) concurrent with stimulation and during a final recovery measurement (5-10 mins) after stimulation has concluded.

During the base, recovery, and during 3 time points during the 90-minute stimulation period (i.e., 30 minutes, 60 minutes, and 90 minutes), a Passive Auditory Oddball Task will be administered. During this task a relaxing movie (i.e., silent sand art film) is presented concurrent with standard and deviant tones; MMN task from the ERP Compendium of Open Resources and Experiments - ERP CORE; Kappenman et al., 2020; Eriksen & Eriksen 1974).

For participants with previously implanted VNS devices, the same Passive Auditory Oddball task will be administered. Additional tasks will be administered, including a visual search task, during which an array of shapes are presented on a computer screen. Participants must identify and click on a target shape (N2pc task from the ERP Compendium of Open Resources and Experiments - ERP CORE; Kappenman et al., 2020). A cued picture viewing task will be administered consistent with other research at MUSC department of psychiatry studies. Cues (shapes) are presented followed by either an unpleasant, pleasant, or neutral picture. Pictures are from the International Affective Picture System (Lang et al., 2005). Similar research is being conducted at MUSC by co-investigator Christopher Sege using these pictures and task design. Finally, a fear learning and extinction task will be administered. Participants will see different shapes/colors appear on the computer screen. Some of the shapes/colors will be paired with the sound of a person screaming (Glen et al., 2012). White noise bursts will be played during these tasks at random times.

During the physiology/task assessment participants will be provided with a brief break from computer tasks. During this time, the Montreal Cognitive Assessment (MOCA; Nasreddine, 2004) will be administered to ensure there is no major cognitive decline.

Then a 3) finally during a recovery period (5-10 min) resting physiology measurement will be taken. After all the tasks are completed, participants will be debriefed about the purpose of the study, compensated for their time, and released. Participants will be reimbursed using a Clincard with the amount of $100. They will be provided with the ClinCard along with relevant information (e.g., ATM withdrawal fees, how to use) prior to leaving the in-lab procedures.

Participants with implanted VNS will be asked to return for a second visit, during which they will receive no stimulation, but will be asked to complete the same tasks. The order of stimulation versus no

stimulation lab visits will be randomized. They will be reimbursed using a Clincard with the amount of $180 for the first 2 lab visits and surveys. Should participants with implanted devices agree to a third in-lab visit for 2.5 hours, they will be reimbursed with an additional $80.00 to their ClinCard.

Several procedures will be taken to minimize risks over the course of the study:

Physiology: For sensors that are attached to skin there is some risk for mild local irritation or redness, thus adhesives are removed with caution/gently. Participants are informed that EEG involves the use of a water based gel during the consent process as some participants report they dislike having the gel in their hair. There are rare instances of static shock during EEG. Thus participants are seated in non-metal chairs and experimenters use caution so as to not increase risk of electrical shock, such as using a grounded EEG system.

TaVNS: The taVNS stimulation administered during the stu*dy is non-invasive but includes some risk.* Participants will be screened for potential contraindications to taVNS prior to invitation to the lab (see Section 5.0 for exclusion criteria; e.g., ear trauma/pain, metal implants). The device has safety mechanisms to prevent electrical surges. Skin will be prepared using 70% alcohol swabs prior to electrode attachment to ensure sanitation and stimulation power is safe. Metal jewelry also will be removed from the head. Stimulation is applied using similar electrodes to those used in EEG and a water based conductive gel, and participants will be assessed after application/prior to stimulation for discomfort related to the electrode. Participants will be assessed during stimulation for discomfort or adverse events over the course of stimulation, though studies have demonstrated few concerns of safety. Participants are encouraged to share report of discomfort and are reminded prior to the study they may discontinue at any point. The ear also will be cleaned and inspected for irritation/redness after stimulation. The ear stimulation delivered during the study is includes some risk. Participants in previous research using this stimulation describe the feeling as a “tickle” or “pricking” sensation. Some report mild irritation. Our researchers will inspect the ear after stimulation given previous research has documented some redness from the stimulation.

VNS: Participants being recruited to complete this study with VNS, will include subjects with previously implanted devices and who have been given permission by their physician to activate their own stimulator without health risks. These participants who may administer their own stimulation have been given a “magnetic wand” or button to activate their stimulator in order to encourage post-stroke motor function. No severe adverse effects have been reported with implanted devices after implantation. However, mild discomforts/risks have been reported including nausea and dysphagia (swallowing difficulties) which resolve by the end of the day after stimulation. Participants will be encouraged to report discomfort and will be assessed periodically for these discomforts. To ensure that ongoing VNS treatment is not affected, only those who have completed VNS treatment/research or whose VNS treatment/research will not be affected by 30 minutes of stimulation will be recruited for the study.

Surveys: Some report mild discomfort when reporting on these topics, so study staff, including the PI and Co-I, will be available to debrief participants in distress, if needed. The PI will be available to provide counseling resources if participants are interested, and in the case of suicidal ideation and intent (see Section 13.0) immediate and appropriate response will be provided, including encouraging the participant to remain with experimenters (even if study is terminated) to ensure the participant is in a safe location. The study personnel are clinically trained to identify participants in distress. However, these surveys involve minimal and low-base rate for risk.

Tasks: The tasks involve no more than minimal risk. The scenes and tones played during the study are not distressing in nature. To ensure comfort, participants will be allowed to adjust to the tones starting the task. Participants will be monitored for distress. For participants with implanted VNS who complete the fear learning task, the screaming sounds can generate mild temporary distress. Studies show that this mild temporary distress typically dissipates by the end of the task, as it includes a phase of "fear extinction" where symbols are presented unpaired with a feared stimulus. The picture viewing task, used in several studies here and at other research labs, consists of some unpleasant pictures, which can evoke sadness or fear. However, these feelings do not persist beyond the picture viewing task and participants who report sadness or fear indicate the emotions are of a manageable intensity. Participants will be assessed for these discomforts throughout, and will be monitored for extreme discomfort. Should participants indicate the discomfort is of extreme intensity, the tasks will be discontinued. Participants may discontinue at any point without consequence.

Confidentiality: To protect confidentiality of study-specific measures, only the participant code, and no potentially identifying information (e.g., name, date of birth) will ever be associated with these measures. In addition, self-report data will not include identifiable information. Self-report data are in Likert format and will be linked only to a participant code. Thus, no data will be identifiable. However, there is still a small risk of loss of confidentiality of participant information in this study. Steps taken to protect confidentiality are described further in the **Data Management** section.

12.0 Data Management

Power: Dose-response studies are not powered in the traditional manner. To resolve the shape of the continuous dose response function, it is statistically more efficient to select more doses as opposed to more participants (O'Quigley & Conaway, 2010; Kuljus et al., 2006). The number of observations within each dose primarily accounts for sampling variability, which could be achieved with 2-3 observations. Capturing variability is essential to the planned analyses, which underweight the points of greatest variability in estimating the response curve. Thus, the sample size of N = 45 was determined sufficient to accomplish Aim 1 to establish a dose-response curve. Of note, Dr. McTeague is running three funded projects with these dose-response techniques in optimizing repetitive transcranial magnetic stimulation (rTMS). An additional, sample of 45 participants are included in the case of data loss and to replicate dose-response findings/assess feasibility/tolerability on participants with anxiety or trauma related disorder or symptoms.

Analyses: The psychophysiological data will be processed using standard protocols which have previously been used in this lab and in various other studies (Sege et al., 2017, 2018, Taylor et al., 2020; Grant et al., 2015), and according to published guidelines (Blumenthal et al., 2005; Boucsein et al., 2012; Gatchel et al., 1973; Keil et al., 2014).

Dose-response relationships will be assessed using the multiple comparisons procedure with modeling (MCP-Mod) approach pre- to post-stimulation changes in physiology and behavior. To determine the reliability of a dose response, MCP-Mod fits a set of pre-specified candidate dose-response curves to the data using a multiple-comparisons technique. The pre-specified dose-response curves to be tested would be Emax, logistic, and linear. Significant curves would then be used to develop inferences on optimal doses for a follow-up adaptive-dosing design, with doses more finely resolved around the probable point of maximal efficacy as determined in this project.

Confidentiality and Quality Control: All study personnel will complete Social-Behavioral-Educational research CITI training, and also complete in-lab training regarding data security practices. Study personnel will be trained in the IRB protocol. The investigator, and co-investigators will be available to monitor data collection to ensure quality, confidentiality, and adherence to the IRB protocol.

The majority of this study's procedures will take place in the study's research suite, which is a private room with limited access. Regarding documentation, participant names will appear only on the IRB-approved Consent, HIPAA, and payment forms. After the participant electronically signs the consent form on HIPAA-compliant RedCap, a random identification code will be assigned to the individual, and all data collection will be referenced to the code rather than name or other identifying information. Questionnaires will be completed in a HIPAA-compliant RedCAP interface. There is some risk to loss of confidentiality due to the remote nature of consent and questionnaires. It cannot be guaranteed that participants will complete these study portions in private spaces, though they will be encouraged to do so for their protection. Payment forms will be collected and stored separately from data in a locked cabinet for up to 6 years.

After participation, RedCAP data will be downloaded in excel format to the secure MUSC server. Finally, physiology data files will also be linked only to participant code; these data will be recorded on password-protected local drives at the IOP.

In terms of publication, data will be published in aggregate form, so invidual participants will not be identifiable in the final manuscript. No identifying information will be published.

13.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

The PI and co-Is will be responsible for monitoring the data collection and safety of participants. This study involves some risk, though previous research at MUSC using the same stimulation parameters has demonstrated no major or minor adverse events during or after stimulation when assessing skin discomfort, irritation, headache, facial pain and dizziness, heart rate, respiration, and self-reported pain (Badran et al., 2018). Researchers identified redness at stimulation location and pain ratings in this study were means of 2.1 and 1.2 (out of 10) for the tragus and the ear lobe, respectively. Of the MUSC patients with implanted VNS, only those who have been provided clearance from their doctors to deliver 30 minutes of stimulation at home and unmonitored by physicians as part of their treatment protocol will be recruited. The stimulation parameters used in this study are the same stimulation parameters that participants self-administer at home. However, Brain Stimulation Lab physicians will be readily available should adverse events occur.

The questionnaire, experimental, and physiological data will be monitored to ensure the safety of subjects. During the study participants will be inquired about their comfort with regard to the stimulation and will be informed (prior to stimulation) that they may terminate at any point. Participants will be assessed for adverse events in the current study, including skin discomfort, irritation, headache, facial pain and dizziness.

Quality Control: Regular data verification meetings will take place weekly with the PI, co-Is, and the study personnel to ensure proper procedures are followed (consenting, data collection and de-identification), ensure study/experimental protocol adherence, and to assess for adverse events. In addition, study personnel will be trained to contact the PI immediately, in the case of an adverse event. Events determined by the PI to be unanticipated problems involving risks to subjects or others, or to be an adverse event, in accordance with HRPP guideline 4.7, will be reported by the

PI to the IRB as soon as possible and after no later than 10 working days, per IRB policy described in guideline 4.7.

Access & Safety Training: Research staff assisting with physiological data collection will receive first aid and CPR certification to assess and respond to participant emergencies during the study. The PI and Co-I each have expertise in physiological and clinical data collection, and will be responsible for training any additional research staff in proper procedures for sensor use/ placement and handling of data.

Suicidal Intent: Suicidal ideation, intent or planning will be screened as part of this study. The PI and Co-I are trained in clinical psychological interview techniques and suicide risk and safety interventions. The PI or Co-I will be completing study procedures or will be immediately available (in the study building) in the case suicidal or other safety concerns are identified. Any participants disclosing suicidal intent or planning will be assessed immediately for safety and will be referred to clinical staff within the IOP for further evaluation. For participants at imminent risk, this will include arrangement of an emergency outpatient appointment or an in-house consult with a psychiatrist to determine need for hospitalization, as well as notification of campus police in the event that a participant deemed to be imminently at risk refuses to cooperate with a hospitalization plan.

14.0 Withdrawal of Subjects

Participants will be informed during consenting that they are free to withdraw from the study at any time. They will be informed that they are not obligated to participate once the study is initiated and in particular will be reminded prior to taVNS/VNS stimulation they may discontinue stimulation and/or the experiment at any point.

Study advertisements will not state the amount of compensation to be provided, so as to prevent potential subjects from participating out of need. Study personnel will not pressure any participant to engage in the study or in parts of the study. Research personnel may choose to end participation early if the subject appears or expresses distress by the study procedures.

15.0 Risks to Subjects

Physiology: The study procedures may involve non-invasive recording of EEG, EMG, and ECG, so the risk with this is minimal. For external sensors used for ECG and EMG, adhesive disks are used. Removal of these adhesives may result in mild local irritation or redness. For EEG measurement, little to no risks are involved. A water soluble gel which contains sodium is used, but this gel does not cause irritation. This gel rinses easily with water, though some participants report they dislike having the gel in their hair. Participants are informed of the gel prior to arrival at the lab. EEG does not transmit any electrical signals and only measures electrical activity naturally produced in the human body. The electrode cap fits comfortably and participants are assessed throughout setup procedures to ensure their comfort.

TaVNS: The taVNS stimulation administered during the study *is non-invasive but includes some* risk – similar to that of EEG or other physiological recording. Our system is a commercially available, FDA-cleared Digitimer DS7A constant current stimulator (Digitimer Ltd., USA; for additional information see https://www.digitimer.com/product/human-neurophysiology/peripheral-stimulators/ds7a-ds7ah-hv-current-stimulator/). Several research groups at MUSC and elsewhere have demonstrated the safety and tolerability of taVNS (Kreuzer et al., 2012; Badran et al., 2019; Clancy et al., 2014). Participants will be screened for potential contraindications to taVNS prior to invitation to the lab (see Section 5.0 for exclusion criteria; e.g., ear trauma/pain, metal implants). The device has safety mechanisms to prevent

electrical surges. Skin will be prepared using 70% alcohol swabs) prior to electrode attachment to ensure sanitation and stimulation power is safe. Metal jewelry also will be removed from the head. Stimulation is applied using similar electrodes to those used in EEG and a water based conductive gel, and participants will be assessed after application/prior to stimulation for discomfort related to the electrode. Perceptual Threshold (PT) will be determined (see 3.0 Intervention to be studied for details; Badran et al., 2019) using a step-up/step-down parametric search. Stimulation will be applied at the level of 200% of PT. Participants will be assessed during stimulation for discomfort or adverse events over the course of stimulation, though studies have demonstrated few concerns of safety. The ear also will be cleaned and inspected for irritation/redness after stimulation. The ear stimulation delivered during the study is includes some risk. Participants in previous research using this stimulation describe the feeling as a "tickle" or "pricking" sensation. Some report mild irritation. Our researchers will inspect the ear after stimulation given previous research has documented some redness from the stimulation. Because dose duration of taVNS is being investigated and this treatment is still experimental there is chance unknown risks may occur, though the likelihood of these risks occurring is low.

VNS: Although implantation of VNS involves an invasive procedure, this study will only recruit individuals with previously implanted VNS. Thereafter, stimulation may be delivered noninvasively via remote access/computer/external button or via magnetic wand. In safety studies of the Microtransponder VNS system that was researched at MUSC, some patients report nausea or difficulties swallowing the day of stimulation. Some report neck tingling and/or hoarseness. The full publication on safety can be found here: https://www.ahajournals.org/doi/pdf/10.1161/STROKEAHA.115.010477

Surveys: During the questionnaire portion of the study, participants will be asked to report on personal experiences and symptoms. Some report mild discomfort when reporting on these topics, but that risk is low. Again, it will be ensured that study staff, including the PI and Co-I, will be available to debrief participants in distress, if needed. If adverse effects occur during the study, researchers will terminate the study, provide debriefing, and contact the PI or Co-I for further assistance. Study personnel will be trained to identify participants in distress. However, these procedures involve minimal and low-base rate for risk.

Tasks: The tasks involve no more than minimal risk. The loud noises which may be played and some of the pictures which may be shown during the study may result in momentary mild distress. However, several studies have used similar procedures, and the risk of this is low, with participants reporting mild, temporary distress. To ensure comfort, participants will be allowed to adjust to the noises starting the task and will be reminded of their right to withdraw at any point.

Confidentiality: Because physiological recordings are generally non-sensitive, risk of disclosure of these data is very minimal. This study does involve risk of disclosure of sensitive information (e.g., self-report of mental health symptoms) collected during study-specific assessment. To protect confidentiality of study-specific measures, only the participant code, and no potentially identifying information (e.g., name, date of birth) will ever be associated with these measures. In addition, self-report data will not include identifiable information. Self-report data are in Likert format and will be linked only to a participant code. Thus, no data will be identifiable. However, there is still a small risk of loss of confidentiality of participant information in this study. Steps taken to protect confidentiality are described further in the **Data Management** section.

16.0 Potential Benefits to Subjects or Others

There are no direct benefits to subjects for participating. Participants may learn about the procedures involved in psychological research. Benefits to society include knowledge about how physiology is linked to attention and learning. Such basic knowledge may ultimately lead to establishing more effective ways

of helping people who suffer from problems related to their mood or anxiety. The main aim of this project is to establish the dose-response curve for taVNS, a necessary first-step to implement taVNS in the clinical setting and assess potential mechanisms of action. The data collected in this pilot project will be used to inform larger scale research aimed at assessing taVNS paired exposure therapies for anxiety and trauma-related disorders.

17.0 Sharing of Results with Subjects

Physiological results collected in this study are currently useful at the group, not individual, level; as such, results will not be shared with subjects. Participants will be given the opportunity to be debriefed regarding the purpose and hypotheses of the study after it is completed.

18.0 Drugs or Devices

The Digitimer DS7A Constant Current Stimulator is FDA cleared (K051357), is non-invasive, and has an excellent safety profile. However, limited use of the device will nonetheless be maintained. The research space is locked with limited access to only trained researchers.

References

Appelhans, B. M., & Luecken, L. J. (2006). Heart rate variability as an index of regulated emotional responding. *Review of General Psychology*, *10*(3), 229-240.

Badran, B. W., Alfred, B. Y., Adair, D., Mappin, G., DeVries, W. H., Jenkins, D. D., ... & Bikson, M. (2019). Laboratory administration of transcutaneous auricular vagus nerve stimulation (taVNS): technique, targeting, and considerations. *Journal of visualized experiments: JoVE*, (143).

Badran, B. W., Brown, J. C., Dowdle, L. T., Mithoefer, O. J., LaBate, N. T., Coatsworth, J., ... & Bikson, M. (2018a). Tragus or cymba conchae? Investigating the anatomical foundation of transcutaneous auricular vagus nerve stimulation (taVNS). *Brain Stimulation*, *11*(4), 947.

Badran, B. W., Dowdle, L. T., Mithoefer, O. J., LaBate, N. T., Coatsworth, J., Brown, J. C., ... & George, M. S. (2018b). Neurophysiologic effects of transcutaneous auricular vagus nerve stimulation (taVNS) via electrical stimulation of the tragus: a concurrent taVNS/fMRI study and review. *Brain Stimulation*, *11*(3), 492-500.

Badran, B. W., Mithoefer, O. J., Summer, C. E., LaBate, N. T., Glusman, C. E., Badran, A. W., ... & Borckardt, J. J. (2018c). Short trains of transcutaneous auricular vagus nerve stimulation (taVNS) have parameter-specific effects on heart rate. *Brain Stimulation*, *11*(4), 699-708.

Beck, A. T., Steer, R. A., & Brown, G. (1996). Beck depression inventory–II. *Psychological Assessment*.

Bernstein, D. P., & Fink, L. (1998). *Childhood trauma questionnaire: A retrospective self-report: Manual*. Harcourt Brace & Company.

Blumenthal, T. D., Cuthbert, B. N., Filion, D. L., Hackley, S., Lipp, O. V., & Van Boxtel, A. (2005). Committee report: Guidelines for human startle eyeblink electromyographic studies. *Psychophysiology*, *42*(1), 1-15.

Boucsein, W. (2012). *Electrodermal activity*. Springer Science & Business Media.

Bradley, M. M. (2009). Natural selective attention: Orienting and emotion. *Psychophysiology*, *46*(1), 1-11.

Bradley, M. M., & Lang, P. J. (1994). Measuring emotion: the self-assessment manikin and the semantic differential. *Journal of behavior therapy and experimental psychiatry*, *25*(1), 49-59.Bradley, M. M., & Lang, P. J. (2006). Motivation and emotion. *Handbook of Psychophysiology*, *2*, 581-602.

Burger, A. M., Verkuil, B., Fenlon, H., Thijs, L., Cools, L., Miller, H. C., ... & Van Diest, I. (2017). Mixed evidence for the potential of non-invasive transcutaneous vagal nerve stimulation to improve the extinction and retention of fear. *Behaviour Research and Therapy*, *97*, 64-74.

Burger, A. M., Verkuil, B., Van Diest, I., Van der Does, W., Thayer, J. F., & Brosschot, J. F. (2016). The effects of transcutaneous vagus nerve stimulation on conditioned fear extinction in humans. *Neurobiology of Learning and Memory*, *132*, 49-56.

Clancy, J. A., Mary, D. A., Witte, K. K., Greenwood, J. P., Deuchars, S. A., & Deuchars, J. (2014). Non-invasive vagus nerve stimulation in healthy humans reduces sympathetic nerve activity. *Brain stimulation*, *7*(6), 871-877.

Connor, K. M., & Davidson, J. R. (2003). Development of a new resilience scale: The Connor-Davidson resilience scale (CD-RISC). *Depression and anxiety*, *18*(2), 76-82.

Craske, M. G., Kircanski, K., Zelikowsky, M., Mystkowski, J., Chowdhury, N., & Baker, A. (2008). Optimizing inhibitory learning during exposure therapy. *Behaviour Research and Therapy*, *46*(1), 5-27.

Craske, M. G., Treanor, M., Conway, C. C., Zbozinek, T., & Vervliet, B. (2014). Maximizing exposure therapy: An inhibitory learning approach. *Behaviour Research and Therapy*, *58*, 10-23.

Dawson, M. E., Schell, A. M., & Courtney, C. G. (2011). The skin conductance response, anticipation, and decision-making. *Journal of Neuroscience, Psychology, and Economics*, *4*(2), 111.

Derryberry, D., & Reed, M. A. (2002). Anxiety-related attentional biases and their regulation by attentional control. *Journal of Abnormal Psychology*, *111*(2), 225.

Deuchars, S. A., Lall, V. K., Clancy, J., Mahadi, M., Murray, A., Peers, L., & Deuchars, J. (2018). Mechanisms underpinning sympathetic nervous activity and its modulation using transcutaneous vagus nerve stimulation. *Experimental Physiology*, *103*(3), 326-331.

Ehring, T., Zetsche, U., Weidacker, K., Wahl, K., Schönfeld, S., & Ehlers, A. (2011). The Perseverative Thinking Questionnaire (PTQ): Validation of a content-independent measure of repetitive negative thinking. *Journal of behavior therapy and experimental psychiatry*, *42*(2), 225-232.

Eriksen, B. A., & Eriksen, C. W. (1974). Effects of noise letters upon the identification of a target letter in a nonsearch task. *Perception & Psychophysics*, *16*(1), 143-149.

Falsetti, S. A., Resnick, H. S., Resick, P. A., & Kilpatrick, D. G. (1993). The Modified PTSD Symptom Scale: A brief self-report measure of posttraumatic stress disorder. *The Behavior Therapist*, *16,* 161–162.

Fergus, T. A., Valentiner, D. P., McGrath, P. B., Gier-Lonsway, S. L., & Kim, H. S. (2012). Short forms of the social interaction anxiety scale and the social phobia scale. *Journal of personality assessment*, *94*(3), 310-320.

Gatchel, R. J., & Lang, P. J. (1973). Accuracy of psychophysical judgments and physiological response amplitude. *Journal of Experimental Psychology*, *98*(1), 175.

George, M. S., Sackeim, H. A., Rush, A. J., Marangell, L. B., Nahas, Z., Husain, M. M., ... & Ballenger, J. C. (2000). Vagus nerve stimulation: a new tool for brain research and therapy. *Biological Psychiatry*, *47*(4), 287-295.

Judah, M. R., Shurkova, E. Y., Hager, N. M., White, E. J., Taylor, D. L., & Grant, D. M. (2018). The relationship between social anxiety and heartbeat evoked potential amplitude. *Biological Psychology*, *139*, 1-7.

Kappenman, E. S., Farrens, J. L., Zhang, W., Stewart, A. X., & Luck, S. J. (2020). ERP CORE: An open resource for human event-related potential research. *NeuroImage*, 117465.

Keil, A., Debener, S., Gratton, G., Junghöfer, M., Kappenman, E. S., Luck, S. J., ... & Yee, C. M. (2014). Committee report: publication guidelines and recommendations for studies using electroencephalography and magnetoencephalography. *Psychophysiology*, *51*(1), 1-21.

Keute, M., Demirezen, M., Graf, A., Mueller, N. G., & Zaehle, T. (2019). No modulation of pupil size and event-related pupil response by transcutaneous auricular vagus nerve stimulation (taVNS). *Scientific Reports*, *9*(1), 1-10.

Kreuzer, P. M., Landgrebe, M., Husser, O., Resch, M., Schecklmann, M., Geisreiter, F., ... & Langguth, B. (2012). Transcutaneous vagus nerve stimulation: retrospective assessment of cardiac safety in a pilot study. *Frontiers in psychiatry*, *3*, 70.

Kuljus, K., Von Rosen, D., Sand, S., & Victorin, K. (2006). Comparing experimental designs for benchmark dose calculations for continuous endpoints. *Risk analysis*, *26*(4), 1031-1043.

Llera, S. J., & Newman, M. G. (2017). Development and validation of two measures of emotional contrast avoidance: The contrast avoidance questionnaires. *Journal of anxiety disorders*, *49*, 114-127.

Meyer, T. J., Miller, M. L., Metzger, R. L., & Borkovec, T. D. (1990). Development and validation of the penn state worry questionnaire. *Behaviour Research and Therapy*, *28*(6), 487-495.

Moran, T. P., Taylor, D., & Moser, J. S. (2012). Sex moderates the relationship between worry and performance monitoring brain activity in undergraduates. *International Journal of Psychophysiology*, *85*(2), 188-194.

O'Quigley, J., & Conaway, M. (2010). Continual reassessment and related dose-finding designs. *Statistical science: a review journal of the Institute of Mathematical Statistics*, *25*(2), 202.

Pappens, M., Schroijen, M., Sütterlin, S., Smets, E., Van den Bergh, O., Thayer, J. F., & Van Diest, I. (2014). Resting heart rate variability predicts safety learning and fear extinction in an interoceptive fear conditioning paradigm. *PloS one*, *9*(9), e105054.

Pihlaja, M., Failla, L., Peräkylä, J., & Hartikainen, K. M. (2020). Reduced Frontal Nogo-N2 with uncompromised response inhibition during transcutaneous Vagus Nerve Stimulation—More efficient cognitive control?. *Frontiers in Human Neuroscience*, *14*, 391.

Porges, S. W. (2001). The polyvagal theory: phylogenetic substrates of a social nervous system. *International Journal of Psychophysiology*, *42*(2), 123-146.

Remes, O., Brayne, C., Van Der Linde, R., & Lafortune, L. (2016). A systematic review of reviews on the prevalence of anxiety disorders in adult populations. *Brain and Behavior*, *6*(7), e00497.

Sege, C. T., Bradley, M. M., & Lang, P. J. (2017). Escaping aversive exposure. *Psychophysiology*, *54*(6), 857-863.

Sege, C. T., Bradley, M. M., & Lang, P. J. (2018). Avoidance and escape: Defensive reactivity and trait anxiety. *Behaviour Research and Therapy*, *104*, 62-68.

Spielberger, C. D., & Reheiser, E. C. (2003). Measuring anxiety, anger, depression, and curiosity as emotional states and personality traits with the STAI, STAXI, and STPI. *Comprehensive Handbook of Psychological Assessment*, *2*, 70-86.

Spitzer, R. L., Kroenke, K., Williams, J. B., & Löwe, B. (2006). A brief measure for assessing generalized anxiety disorder: the GAD-7. *Archives of internal medicine*, *166*(10), 1092-1097.

Springer, K. S., Levy, H. C., & Tolin, D. F. (2018). Remission in CBT for adult anxiety disorders: A meta-analysis. *Clinical Psychology Review*, *61*, 1-8.

Szeska, C., Richter, J., Wendt, J., Weymar, M., & Hamm, A. O. (2020). Promoting long-term inhibition of human fear responses by non-invasive transcutaneous vagus nerve stimulation during extinction training. *Scientific Reports*, *10*(1), 1-16.

Taylor, D. L., Grant, D. M., Frosio, K. E., Kraft, J. D., Nagel, K. M., Deros, D. E., & White, E. J. (2020). Neural indices of orienting, discrimination, and conflict monitoring after contextual fear and safety learning. *Cognitive, Affective, & Behavioral Neuroscience*, *20*(5), 917-927.

Taylor, D. L., Grant, D. M., Kraft, J. D., Frosio, K. E., White, E. J., Judah, M. R., & Mills, A. C. (2019). The role of parasympathetic activity in the relationship between worry and neural indicators of attentional control. *Psychology & Neuroscience*.

Thompson, E. R. (2007). Development and validation of an internationally reliable short-form of the positive and negative affect schedule (PANAS). *Journal of cross-cultural psychology*, *38*(2), 227-242.

Warren, C. M., Tona, K. D., Ouwerkerk, L., Van Paridon, J., Poletiek, F., van Steenbergen, H., ... & Nieuwenhuis, S. (2019). The neuromodulatory and hormonal effects of transcutaneous vagus nerve stimulation as evidenced by salivary alpha amylase, salivary cortisol, pupil diameter, and the P3 event-related potential. *Brain Stimulation*, *12*(3), 635-642.

Warren, C. V., Maraver, M. J., de Luca, A., & Kopp, B. (2020). The effect of transcutaneous auricular vagal nerve stimulation (taVNS) on P3 event-related potentials during a bayesian oddball task. *Brain Sciences*, *10*(6), 404.

White, E. J., Grant, D. M., Taylor, D. L., Frosio, K. E., Mills, A. C., & Judah, M. R. (2018). Examination of evaluative threat in worry: Insights from the error-related negativity (ERN). *Psychiatry Research: Neuroimaging*, *282*, 40-46.

Zamotrinsky, A. V., Kondratiev, B., & de Jong, J. W. (2001). Vagal neurostimulation in patients with coronary artery disease. *Autonomic Neuroscience*, *88*(1-2), 109-116.