PROTOCOL TITLE:

Assessing the Physiologic Effect of taVNS During a Cold Pressor Test (NCT ID: 00113453)

PRINCIPAL INVESTIGATOR:

- Christopher W. Austelle, M.D.

1.0 Objectives / Specific Aims

Aim 1. Assess whether the parasympathetic effects of transcutaneous auricular vagus nerve stimulation (taVNS) are able to attenuate the sympathetic response curve elicited by a validated cold pressor test.
We will recruit 24 neurotypical subjects (ages 18-65) in order to have at least 14 completers. The subjects must be at baseline healthy, and not have a history of major mental or medical illness (see more below for full inclusion/exclusion criteria). Each subject will undergo phone screen and be consented prior to participating in the study. Each subject will participate in 1 study visit, where they will participate twice in the validated cold pressor test while concurrently receiving active or sham taVNS. Subjects will participate in both treatment conditions (active and sham taVNS), however the order in which they participate will be randomized (half will receive active taVNS first, half will receive sham first). The cold pressor test is a validated stress induction technique and has been shown to produce a reliable sympathetic response, as shown by acute elevations in sympathetic physiologic markers (heart rate, blood pressure/mean arterial pressure, cardiac output, etc). In prior studies, taVNS has been shown to produce a marked and significant parasympathetic response in neurotypical subjects, shown by acute reductions in the same markers as above. Both taVNS and the validated cold pressor test have been shown to be safe and feasible in neurotypical subjects. We hypothesize that subjects receiving active taVNS will have an attenuated sympathetic response to the cold pressor test compared to those receiving sham stimulation.

Aim 2. Assess whether taVNS affects the subjective pain/stress response to a validated cold pressor test.
Subjects will be asked to rate subjective pain and stress before, during, and after the cold pressor test. We hypothesize that these subjective ratings will be reduced in the group receiving active taVNS compared to the sham group.

Aim 3. Assess the acute effects of transcutaneous auricular vagus nerve stimulation (taVNS) on anxiety.
In other pilot trials using taVNS, as well as past trials with implanted VNS, results have shown taVNS and implanted VNS to have an anxiolytic effect. We hypothesize that taVNS will have a similar anxiolytic effect on subjects in this trial. This work will provide pilot data for subsequent studies to investigate the anxiolytic effects of taVNS.

2.0 Background

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.

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 (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.

Preclinical and clinical trials show that implanted vagus nerve stimulation (VNS) may be an effective anxiolytic treatment and may improve outcomes in anxiety disorders. In order to develop therapeutic taVNS for psychiatric problems, investigating the effects of taVNS during a stress induction technique would be a logical first step. The cold pressor test (CPT) is a valid and reliable test that allows us to elicit a sympathetic stress response in neurotypical subjects in a safe and monitored environment. The CPT was first introduced in the 1930s by Hines and Brown (Hines, 1932). CPT exposure leads to profound changes in cardiovascular parameters most notably a rise in blood pressure through peripheral vasoconstriction and to a lesser extend cardiac output resulting from an increase in both vascular alpha-adrenergic and cardiac beta-adrenergic drive (Greene et al., 1965; Lovallo, 1975; Yamamoto et al., 1992). The CPT will also allow us to investigate if the parasympathetic actions of taVNS are able to attenuate the typical sympathetic response of the CPT. To date, there have not been any similar studies looking at the effects of taVNS on a provoked sympathetic stress response.

3.0 Intervention to be studied

The intervention we are studying is called transcutaneous auricular vagus nerve stimulation (taVNS). taVNS is simply electrical nerve stimulation administered at the ear which targets the auricular branch of the vagus nerve. taVNS will be administered using the Digitimer DS7a nerve stimulation system that has an FDA 510k approval. taVNS is a non-significant risk method that has been approved by the MUSC IRB for many ongoing taVNS trials.

The Digitimer DS7a manual has been uploaded the MUSC IRB portal and can be found here: https://www.digitimer.com/product/human-neurophysiology/peripheral-stimulators/ds7a-ds7ah-hv-current-stimulator/

- Cervical VNS is FDA approved for medication resistant epilepsy as well as medication resistant depression (Livanova). FDA pivotal trials are underway for paired cervical VNS with rehab for stroke (microtransponder). Noninvasive cervical VNS is FDA approved for treating cluster headache (electrocore). To date there are no FDA approved indications for taVNS.
- We will use the device during each study visit for up to 5 minutes while subjects concurrently participate in the cold pressor test. Subjects will receive both stimulation conditions over the course of the study visit (active taVNS x1, sham taVNS x1). Subjects will be blinded to stimulation condition, but the research team will know whether patients are receiving active or sham stimulation. The order in which subjects receive either active or sham stimulation will be randomized (half will receive active taVNS first, half will receive sham taVNS first).

4.0 Study Endpoints

Outcomes will include vital signs, and ratings of anxiety, pain, and stress. Over the course of the study visit, physiological measures will be collected before, during, and after a cold pressor test (more about data collection below). Visual analog measures of anxiety, stress, and pain will be collected throughout each study visit.

Primary Outcome:
Given that safety and feasibility of taVNS and this intervention have already been established by prior studies, the primary outcomes in this study will be the physiological measures collected at each study visit (Badran, 2019). Both taVNS and the validated cold pressor test have been shown to be safe and feasible in neurotypical subjects (Badran 2018a, b, c; Lovallo, 1975). Biopac equipment will be used to continuously measure heart rate/variability (HRV) and blood pressure to assess autonomic responses.

Secondary Outcome:
Subjective measures of pain, stress, and anxiety will also be collected before, during, and after the cold pressor test (with concurrent taVNS). These will be measured using visual analog scales. Baseline measures of anxiety and mood will also be collected at the initial visit.

5.0 Inclusion and Exclusion Criteria/ Study Population

This study seeks to recruit from a broad range of individuals in order to 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. 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, women of childbearing age 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
- Non-treatment-seeking community members

Exclusion Criteria

- Diagnosis of COVID-19 in the past 14 days
- Facial or ear pain or recent ear trauma.
- Metal implant devices in the head, heart or neck.
- History of brain stimulation or other brain surgery.
- History of myocardial infarction or arrhythmia, bradycardia.
- Use of B-blockers, antiarrhythmic medication (sodium/potassium/calcium-channel blockers), or blood pressure medications.

- Active respiratory disorder.
- 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.
- Individuals suffering from frequent/severe headaches.
- Individuals with a reported history of any mental health disorder or taking any psychotropic medications.
- Moderate to severe alcohol or substance use disorder.
- Pregnancy

6.0 Number of Subjects

We will recruit 24 adults in order to have at least 14 completers.

7.0 Setting

All participants will complete the study tasks in a dedicated research suite, the Psychophysiology Center, in the Brain Sciences Department. 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. 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. 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. 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 the inclusion/exclusion criteria and they agree participate, subjects will be provided with available participation dates. They will also be provided with instructions on how to locate 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.

9.0 Consent Process

The consent form will be provided to participants at the in-person visit. 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 signing the consent form, they will also be offered a hard copy which will be provided during the in-lab scheduled participation date.

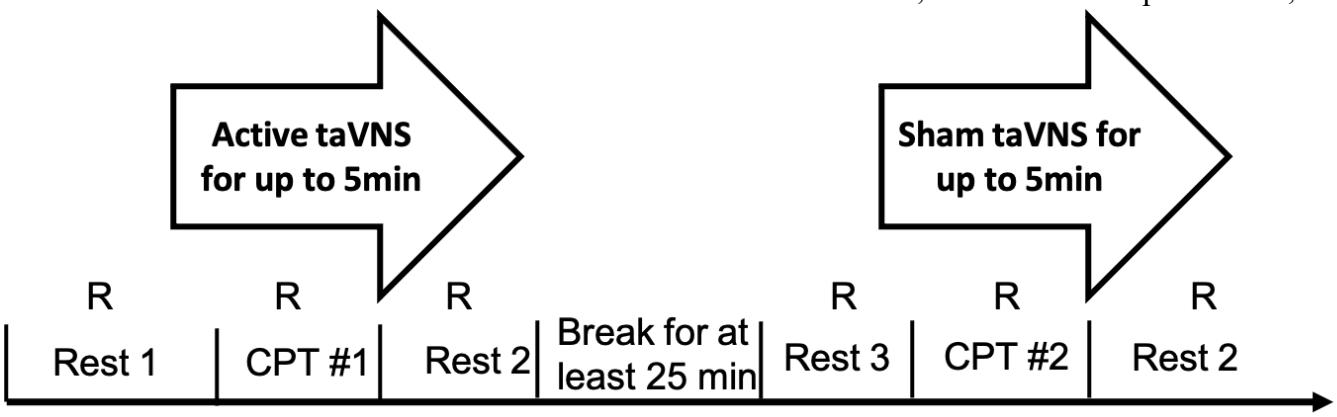
10.0 Study Design / Method

After completing the phone screener, participants will be invited to in-lab participation for 1 visit: they will be provided available times and instructed on how to locate 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.

Prior to arrival to the research space, after phone screening, participants will be consented at the in-person visit (see Section 9.0). Subjects will present to the laboratory for 1 visit. Once participants have arrived in the laboratory for the visit, if they are a woman of childbearing age, 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.

During the laboratory visit, subjects will twice participate in a validated stress induction technique known as the Cold Pressor Test (CPT) while concurrently receiving either active or sham transcutaneous auricular vagus nerve stimulation (taVNS). Over the course of 2 cold pressor tests, subjects will receive both stimulation conditions (half will be randomized to receive active stimulation first and half will receive sham stimulation first). Physiologic measures will be collected before, during, and after each CPT, and there will be a resting period of at least 25 minutes between each CPT. Subjective measures of anxiety, stress, and pain will also be collected throughout the procedure. See Figure 2 for a timeline of the study visit's course.

Figure 2. Study visit timeline (for participant randomized to receive active taVNS first)



Timeline consists of 2 cold pressor tests (CPT) and 2 stimulation conditions (active and sham). The cold pressor test (CPT) will last for up to 3 minutes. Subjects will receive either active or sham taVNS for up to 5 minutes (stimulation will start prior to CPT and continue throughout the duration of the CPT). The order in which participants receive active or sham taVNS will be randomized, but all participants will receive both treatment conditions. Physiologic data will be continuously measured throughout the course of each visit.

Cold Pressor Test: The CPT was first introduced in the 1930s by Hines and Brown (Hines, 1932). CPT exposure leads to profound changes in cardiovascular parameters most notably a rise in blood pressure throughout peripheral vasoconstriction and to a lesser extend cardiac output resulting from an increase in both vascular alpha-adrenergic and cardiac beta-adrenergic drive (Greene et al., 1965; Lovallo, 1975; Yamamoto et al., 1992). On the subjective level participants experience the CPT as painful and report heightened levels of perceived stress and arousal during and immediately after the water-bath (Zoladz et al., 2014). A plethora of research has contributed to the validation and standardization of the CPT.

Prior studies have shown an enhanced response, in terms of sympathetic parameters, to a bilateral feet CPT (Larra, 2015). This is what will be used in this trial. As in previous studies (Larra, 2015; Bachman, 2018), the CPT will consist of participants immersing both feet into ice-water (water temperature around 2-3 degrees Celsius) for up to 3 minutes. The water-bath will be a rectangular tub with ample volume to submerge the subject's feet completely with ice-water.

Upon arrival, subjects will be asked to sit comfortably in a chair as electrodes are applied to collect physiological data (see physiology section below). The protocol will start with a resting period during which heart rate and blood pressure will be assessed. Subjects will receive a 2-minute warning prior to the start of the CPT. Subjects will be asked to rate subjective anxiety, stress, and pain during this resting period. After the resting period, subjects will be exposed to the CPT for up to 3 minutes. During the exposure to the ice water, subjects will again rate subjective anxiety, stress, and pain. The stress procedure will be followed by another resting period, during which heart rate and blood pressure will continue to be monitored. Again, participants will rate subjective anxiety, stress, and pain.

taVNS: The taVNS stimulation administered during the study *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 electrodes 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 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.

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.

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

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), and according to published guidelines (Blumenthal et al., 2005; Boucsein et al., 2012; Gatchel et al., 1973; Keil et al., 2014).

Telephone screening information will be stored in a locked filing cabinet in the Brain Stimulation Lab, along with each participant's signed informed consent. Data regarding subject's ratings of subjective anxiety/stress/pain will be stored in the Redcap database. Information about the participant (including their identifiable private information and/or any identifiable biospecimens) may have all of their identifiers removed and used for future research studies or distributed to other researchers for future research without additional informed consent from them or their legally authorized representative.

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. 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 transferred to an MUSC Box account that is only linked to the participant's code.

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. 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.

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 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.

Ear Stimulation: Ear stimulation is safe, however there are some risks associated with stimulating the ear: There may be local discomfort. This will likely be temporary. In extreme cases burns might occur. We will video monitor any potential burns and will stop stimulation and advise subjects to apply vitamin E cream. Tissue surrounding the ear may be sensitive, sore or feel slight numbness. Hopefully this will be temporary and will go away after stimulation is turned off.

Potential Headache, Dizziness, and Facial Pain: Ear stimulation might cause headaches or face pain, which should resolve shortly after treatment.

Safety in case of pregnancy: This protocol will exclude pregnant women. The risks of using taVNS with pregnant women are currently unknown. If in the screening and consent a patient is a woman of childbearing age, a urine pregnancy test will be completed.

Cold Pressor Test: Prior studies have shown the safety and feasibility of the cold pressor test in neurotypical populations. Subject's discomfort will be monitored closely and throughout the test. Previous studies have shown that neurotypical participants are able to tolerate and complete the cold pressor test without residual discomfort following the test. Subjects will have the option to withdraw at any time throughout the test if discomfort is too great or per their preference. Of note, active taVNS is hypothesized to attenuate the sympathetic response to the cold pressor test. Thus, one out of the two cold pressor tests may have a higher risk of discomfort (subjects will receive active and sham taVNS in randomized order).

Risk of Increased/Decreased Heart Rate: The Cold Pressor Test is associated with an acutely elevated heart rate. Other studies have shown the safety and feasibility of this technique, and elevations in heart rate have been shown to stay within the normal range of physiologic functioning. taVNS is also associated with decreases in heart rate. The safety and feasibility of taVNS has also been shown by prior studies. Study staff will closely monitor changes in heart rate, as well as patient's comfort levels, and will respond to changes accordingly.

Questionnaire Risk: There are no anticipated risks to the participant. However, the participant may feel that some of the questions we ask are stressful or upsetting. If they do not wish to answer a question, they may skip it and go to the next question, or they may stop immediately. Also, being assessed for study entry, including the possibility that they may not meet criteria for entering the study may be distressing. If they become upset or distressed as a result of their participation in the research project, the research team will be able to arrange for a one-on-one meeting with our team psychiatrist.

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.

Unknown Risks: There is always the possibility of other risks for a relatively new technology. The Study team will let the participant know if they learn anything that might make the participant change their mind about participating in the study.

Our commitment to patients is to take all reasonable steps to help them find treatments for worsening psychiatric symptoms. If the subject's psychiatric conditions worsen (specifically suicidality or suicide ideation), we will provide the National Suicide Prevention Hotline call or text number (1-800-273-8255) to the subject or advise the subject to go to the nearest Emergency Department or call 911.

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 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

There is no plan to inform subjects of the results of the study, but they can always contact the research staff and ask. If there are significant new findings during the course of the study, they will be notified.

18.0 Drugs or Devices

We are asking for a non-significant risk determination of this device. IRB 1 has consistently given NSR status for all prior taVNS studies at MUSC, including studies in stroke patients (Badran), brain damaged newborns learning to feed (Jenkins), Parkinson's Disease (Hinson, Badran) and healthy volunteers (Badran).

References

Bachmann, P., Zhang, X., Larra, M. F., Rebeck, D., Schönbein, K., Koch, K. P., & Schächinger, H. (2018). Automated bilateral feet cold pressor test. *International Journal of Psychophysiology,* 124:62-70.

Badran BW, Jenkins DD, DeVries WH, et al. (2018a) Transcutaneous auricular vagus nerve stimulation (taVNS) for improving oromotor function in newborns. *Brain Stimulation*, 11:1198-200.

Badran BW, Dowdle LT, Mithoefer OJ, et al. (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*, 11:492-500.

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.

Badran BW, Yu AB, Adair D, et al. (2019) Laboratory Administration of Transcutaneous Auricular Vagus Nerve Stimulation (taVNS): Technique, Targeting, and Considerations. *Journal of visualized experiments : JoVE.*

Badran BW, Jenkins DD, Cook D, et al. (2020) Transcutaneous Auricular Vagus Nerve Stimulation-Paired Rehabilitation for Oromotor Feeding Problems in Newborns: An Open-Label Pilot Study. *Front Hum Neurosci*, 14:77.

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.

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.

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

Greene, M. A., Boltax, A. J., Lustig, G. A., and Rogow, E. (1965). Circulatory Dynamics during the Cold Pressor Test. The American journal of cardiology, 16, 54-60.

Hines, E. A., and Brown, G. E. (1932). A standard stimulus for measuring vasomotor reactions: its application in the study of hypertension. Proceedings of the Staff Meeting of the Mayo Clinic (7), 332-335.

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.

Larra, M. F., Schilling, T. M., Röhrig, P., & Schächinger, H. (2015). Enhanced stress response by a bilateral feet compared to a unilateral hand Cold Pressor Test. *Stress*, *18*(5), 589–596.

Lovallo, W. (1975). The cold pressor test and autonomic function: a review and integration. Psychophysiology, 12(3), 268-282.

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.

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.

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.

Yamamoto, K., Iwase, S., and Mano, T. (1992). Responses of muscle sympathetic nerve activity and cardiac output to the cold pressor test. The Japanese journal of physiology, 42(2), 239-252.

Zoladz, P. R., Kalchik, A. E., Hoffman, M. M., Aufdenkampe, R. L., Lyle, S. M., Peters, D. M., Brown, C. M., Cadle, C. E., Scharf, A. R., Dailey, A. M., Wolters, N. E., Talbot, J. N., and Rorabaugh, B. R. (2014). ADRA2B deletion variant selectively predicts stress induced enhancement of long-term memory in females. Psychoneuroendocrinology, 48, 111-122.