Home Operations Utilizing Stimulation

NCT04484285
Protocol & Analysis Plan

July 19, 2020

1. Project Title

Home Operations Utilizing Stimulation

2. Investigators

Eric Porges	(PI)
Damon Lamb	(Co-Investigator)
John Williamson	(Co-Investigator)
Adam Woods	(Co-Investigator)
Joe Gullet	(Co-Investigator)
Ron Cohen	(Co-Investigator)
Jesse Dallery	(Co-Investigator)

3. Abstract

The vagal nerve is a major component of the autonomic nervous system and mediates the physiological responses of major organs during moments of stress and learning, including brain areas that modulate cognitive performance. Vagal nerve stimulation (VNS) has been indicated to improve stress response and to enhance neuroplasticity by directly impacting brain structures critical for cognition. Historically, VNS methods required neurosurgery and were reserved for medically intractable epilepsy or other severe conditions. Today, vagal nerve stimulation can be performed with a minimal-risk non-invasive approach without surgery through a technique called transcutaneous Vagal Nerve Stimulation (tVNS). This project will utilize a home-operated stimulator in healthy young adult and healthy older populations to provide a proof of concept of practical home-use stimulation.

4. Background

4.1 Significance of Vagal Nerve. The vagal nerve can influence brain areas important in cognition, . including the hippocampus, an area strongly associated with memory function, the amygdala, an area important in stress response, and the locus coeruleus (LC), the brain's sole source of norepinephrine (NE). The LC also projects directly to the hippocampus. Vagal nerve stimulation (VNS) has been shown to upregulate NE, which plays a critical role in cognitive functions.

As VNS may influence multiple aspects of cognition, The proposed work is significant as tVNS has the potential to be a cheap, effective, and safe tool for cognitive augmentation, work transfer, and improved economic contribution of disadvantaged populations to the workforce. This study will provide a proof of concept of at-home applications.

4.2 Ethical Considerations. All technological developments have the potential to disrupt or distort society. As such, considerations of the ramifications and consequences of implementing a human-technology augmentation tool should occur before and during the development.

5. Specific Aims

5.1 Long-term Goal. The long-term goal of our transdisciplinary scholarship is to contribute theoretical, methodological, and empirical knowledge to understanding the consequences and applications of non-invasive nerve stimulation. Building on our research of neurostimulation, we will explore consequences of non-invasive nerve stimulation within diverse samples of consenting adults. Our translational, integrative research will contribute insights regarding the design of home-applications of tVNS to improve cognition.

5.2 Objectives.

Aim 1. Confirm that home application of tVNS is practical and does not cause undue burden on human subjects. Nerve stimulation will be administered immediately prior to subjects sleeping.

Aim 2. Develop methods to improve feasibility of tVNS application. Subjects will consistently demonstrate the ability to self-apply stimulation electrodes properly.

6. Research Plan

6.1 Study time table and logistics. The study will consist of an intake-training session and a 4 – 7 day application, followed by a second visit for the subject to return the study equipment and receive payment. Face-to-face interaction with subjects will take place at the University of Florida McKnight Brain Institute. For a subset of subjects, they will complete a 20-minute motivational interviewing session on their first day of participation while receiving stimulation according to the universal parameters.

6.2 Experimental Design. In the initial visit, a research assistant will review the informed consent form and have the subject complete a brief health questionnaire as part of our inclusion/exclusion screening (see section **6.5**). If participants screen out after signing the informed consent, the session will end.

After passing the screening, a research assistant will connect an ECG to measure subjects' heart rate while they complete a battery of assessments that will include anxiety measures, sleep quality, and general cognition (see section **6.6** for specific measures). These assessments are self-report and will establish a baseline for each subject. There will be a five-minute period where subjects will be seated without completing any task to establish a heart-rate baseline.

The research assistant will train subjects on how to apply the electrodes and to calibrate the stimulator. Once the research assistant confirms that the subject understands how to apply the electrodes and set the stimulator, the research assistant will demonstrate how to take a picture of the electrode application to check the quality of the application. Subjects will be instructed how to take a picture that hides the identifying features of the face. The subject will be instructed to send a picture of the application of the electrodes for 4 – 7 nights just before going to bed. The stimulator will run for no more than 1 hour and then turn off. Participants might be asked to wear a noninvasive bio-monitoring wristband at home and will be instructed on the best method for wearing the band during the initial visit. The research assistant will provide written and/or video material with instructions for the subject to take home.

Subjects will leave the session and take pictures of their application of the electrodes for 4 – 7 nights. After collecting at least 4 pictures that indicate proper electrode placement, the research assistant will contact the subject to schedule the return of the study equipment and to distribute the subject's payment. If a picture of the application indicates improper placement, a research assistant will contact the subject via phone or email to review proper form. If a subject is unable to provide 4 quality pictures after 7 days, a research assistant will contact the subject to schedule the return of the study equipment and distribute the subject's payment.

When subjects return, they will complete most of the same battery of assessments as before. A research assistant will then give the subject a brief survey to report on his or her experience. Following the interview, subjects will be paid according to their level of compliance (see section **10**).

6.3 Subjects. This study utilizes a between-subject design and will recruit two cohort groups differing by age.

Younger Cohort. We will recruit up to 20 healthy individuals aged 18 – 50. Pregnant women may not participate in this study—pregnancy tests provided by the study will be used for women of child-bearing

age prior to starting the study and after the consenting process. Pregnancy tests will only be given in the intake session

Older Cohort. We will recruit up to 20 healthy individuals aged 51 – 85.

Subset of Participants. There will be a randomly selected, at a ratio greater than or equal to 1, subset of participants drawn from the two cohorts to complete the extra item of the motivational interview. These participants will otherwise meet all the other inclusion and exclusion criteria stated above.

6.4 Recruitment and Retention. We will meet our recruitment objectives for participants based on the availability of adults near UF in Gainesville, Florida. We will post flyers around the community and on UF campus. The flyers include contact information that allows potential subjects to contact the study team if they believe they qualify for the study. The investigators will be involved in recruitment of participants from multiple sources, including recruiting at campus tabling events, posting flyers on UF campus, and through word of mouth. Subjects will be expected to provide their own means of transportation.

6.5 Inclusion/Exclusion Criteria. Participants for one cohort will be adults between the ages of 18-55, consistent with the typical college population. Participants for the other cohort will be adults between the ages of 56 – 85. Participants must read and write English.

Major medical illnesses including diagnosed severe neurological illnesses (e.g., stroke, seizure history), autoimmune disorders, and severe psychiatric diseases (e.g., schizophrenia) will be excluded. Participants with any history of brain surgery, tumor, intracranial metal implantation, pacemakers or other implanted devices will be excluded.

Sleep medications and/or psychostimulants are exclusionary. Subjects in the older cohort will NOT be excluded for taking blood pressure and cholesterol medication. Participants who are pregnant will be excluded. If participants have a history of adverse reaction to electrical nerve stimulation, they will be excluded.

6.6 Measures

General Questionnaire. This questionnaire will include basic demographic and health questions that will be self-reported by the subjects. Since our study requires a return visit, this questionnaire may also include subject contact information.

Behavioral. The following tests will be administered:

> *System Usability Survey (SUS):* This is a standard version of a usability scale. Subjects will be given 10 statements regarding the usability of the equipment they used, and they will report how much they agree with each statement on a 1 – 5 scale. This measure will only be given in the returning session.

Physiological. During the study visits at the MBI, subject heart rates will be monitored with an ECG connected to our BIOPAC setup. Subjects will be given an Empatica brand medical-grade wearable device (wristband) that offers real-time physiological data acquisition to use to monitor their heart rate during the home stimulation sessions.

Psychological. For a subset of randomly selected participations, they will receive a 20-minute motivational interview related to alcohol use on the first night of their participation. This is not a therapeutic intervention. The interview will be conducted on the university approved Zoom platform.

Nerve Stimulation. The auricular branch of the vagus nerve projects to the brain stem and is accessible via electrical stimulation through surface electrodes. Stimulation produces vagus sensory evoked potentials not induced with off-target stimulation

Electrode Placement: This study will utilize a between-subject design, meaning each subject will be in either the tVNS stim group or the alternate stim group. Subjects will be instructed to place a self-adhesive hydrogel stimulation electrode over the auricular branch of the ear lobe. The return electrode for tVNS will be placed just anterior to the tragus to minimize off-target stimulation per local pilot protocol. The alternate stim return electrode will be on the opposite side of the earlobe. Subjects will demonstrate their ability to set up the stimulator—including electrode attachment—and text the picture of the electrode placement with their faces occludedResearch assistants will also provide a link with an instructional video that participants can refer to in order to ensure they have properly placed their electrodes. Participants will be asked to send a photo of their electrode placement everyday via SMS.

Investigational Device Exemption (IDE): An Investigational Device Exemption is not necessary per communication with the FDA and rules governing assessment of risk if the study is a non-significant risk (NSR) device investigation.

7. Possible Discomforts and Risk

7.1 Transcutaneous Vagal Nerve Stimulator. Previous studies using some form of stimulation found that some side effects may occur including itching, discomfort, and local pain at the stimulation site. These side effects usually end shortly after stopping stimulation. If the electrodes are not well placed then participants might experience mild pain, although the researchers will adjust the electrode placement if this happens. Researchers will also explain how to adjust electrodes for when the subjects are at home.

7.2 Breach of Confidentiality. Breach of confidentiality is highly unlikely because all information will be identified with a participant code and stored in a locked file cabinet. Only study staff will have access to this database. All staff are or will be fully trained in relevant ethical principles and procedures, including confidentiality.

Once a subject completes the entirety of the study (i.e. returns the equipment and/or receives payment) and the payment is updated according to UF's Human Subject Payments guidelines, the subject's contact information and student identification/social-security-number will be redacted form the questionnaires and payment receipts.

7.3 Data and Safety Monitoring Plan. Because the proposed study does not comprise a clinical trial, a formal Data and Safety Monitoring Board has not been planned. The investigative team will meet regularly to discuss data and safety monitoring issues. Any issues identified during the course of these meetings will be handled in a manner consistent with the University of Florida's policies.

8. Possible Benefits

In addition to effects on cognitive brain circuitry, simultaneous and related impacts on stress regulation may uniquely place this technology as a viable tool to improve the performance of disadvantaged populations. This information may provide valuable data on the optimization of this technology both in identifying who may most benefit as well as targets for titration of stimulation approach. tVNS has the potential to be a cheap, effective, and safe tool for cognitive augmentation.

9. Conflict of Interest

There are no known conflicts of interest.

10. Subject Payment

10.1 Total Possible. Subjects may earn between $5 – $150, depending on their compliance.

10.2 Level-A Compliance. Subjects who are able to provide at least 4 pictures of proper electrode placement within 4 – 7 days will be given $150 once the study equipment is returned.

10.3 Level-B Compliance. Subjects who are unable to provide at least 4 pictures of proper electrode placement within 4 – 7 days will be given $100 once the study equipment is returned.

10.4 Level-C Compliance. Subjects who screen fail or are unable to demonstrate an understanding of the study protocol in the intake session will be compensated $5 or $10, respectively.

11. Analysis Plan

The primary objective of this investigation is to evaluate the practicality and efficacy of the home intervention, with a particular emphasis on its usability and acceptance amongst participants. To this end, the System Usability Scale (SUS), a validated and widely employed metric, will be employed as the primary outcome measure. The SUS permits participants to provide insightful and quantifiable assessments of their experience, thereby enabling a comprehensive understanding of the intervention's usability profile.

This study will adopt an age-stratified analytical approach, partitioning participants into distinct cohorts based on their age. Subsequently, the mean SUS scores and corresponding standard deviations will be calculated for each age category, allowing for an examination of the intervention's usability patterns across different age groups. Additionally, the study will compute the mean SUS scores and standard deviations for the entire participant pool