Non-pharmacological Interventions to Improve Stress and Sleep Among College Students

NCT05218109

3/3/22

1. **Project title**

   Non-pharmacological interventions to improve stress and sleep among college students

2. **Investigators**

   Sarah Bottari (co- PI)

   Liva LaMontagne (co-PI)

   John Williamson (co-I; mentor of student PI)

   David Diehl (co-I; mentor of student PI)

   Jennifer Doty (co-I; mentor of student PI)

3. **Abstract**

Chronic poor sleep is prevalent among college students and has wide-ranging negative consequences, including poorer academic performance, increased health risk behaviors, and greater risk for mental health problems. Despite this fact, estimates suggest that 80-90% of students with chronically poor sleep are not receiving help from their college or university. Likewise, college student mental health, which shares a bidirectional relationship with sleep quality, has become a significant and growing public health concern. Estimates suggest that roughly one third of college students meet criteria for a clinically significant mental health problem, and rates of depression, anxiety, and suicidality are rising. Digital mental health programs, delivered via mobile app, present one promising approach to address this need and expand treatment accessibility. In particular, mindfulness mobile apps have achieved both mental health and sleep benefits across several randomized controlled trials in student populations; however, adherence and sustained use after interventions have been low. Thus, it is important to address barriers to sustained mindfulness practice in order to optimize user outcomes.

The current study explores using tVNS as a potential method to alleviate barriers to establishing a habit of mindfulness practice. In mindfulness interventions it is not uncommon for participants to report an initial escalation of anxiety and distress as they directly engage with negative thoughts. While accepting, decentering, and deriving meaning from these negative reactions is an important feature of the psychotherapeutic process in mindfulness interventions, they can also lead to disengagement or drop out from the intervention. Similarly, difficulty learning the skill of meditation is also common and can contribute to participant dropout. tVNS may exert an anxiolytic effect through effects on limbic structures and activation of the parasympathetic nervous system. Moreover, tVNS increases positive affect (i.e. calm) and has been linked to improved interoceptive awareness, which are two other potential psychological mediators of mindfulness interventions. Thus, these two separate treatment approaches appear complementary, yet there are no published trials using them in combination. **The proposed study will enable us to evaluate the utility of this combined treatment approach in enhancing college student sleep and mental health, with potentially broader impacts for clinical populations.**

4. **Background**

Insufficient sleep in the United States has recently been recognized as a public health epidemic.[1] College students are at increased risk of experiencing poor sleep due to a “perfect storm” of challenging biological, social, and environmental factors, including delayed circadian rhythm, early class times, residential sleep environments, high stress levels, increased social demands, and greater substance and electronic use.[2–4] Chronic poor sleep is prevalent among college students;

more than one third have identified sleep difficulties as “traumatic or very difficult to handle.”[5] Despite the prevalence and increasingly well-known negative consequences of poor sleep,[2,6] sleep health has not historically been prioritized as an area for intervention on college campuses. For instance, according to the 2018 Center for Collegiate Mental Health annual report, approximately 11,000 students reported sleep disturbances on intake, yet less than one percent had that concern prioritized by clinicians.[7] Moreover, when sleep questions were included as part of a universal behavioral health screening survey, more than 10% of students requested support for their sleep concerns.[8] Thus, there is a clear unmet need for sleep intervention among college students.

Importantly, sleep and mental health share a bidirectional relationship, and the prevalence of sleep problems on college campuses parallels the high rates of anxiety and depressive symptoms.[9] In large national studies, approximately 41% of United States college students report moderate to severe depressive symptoms and 34% report moderate to severe anxiety symptoms.[10] These mental health problems are associated with a variety of negative outcomes, including greater substance use, poorer academic performance, increased self-harm behaviors, and suicidal ideation and attempts.[11] While counseling centers can be found on most college campuses, the increased demand for mental health services has unfortunately not been met with a proportional increase in counseling center staff and funding. As a result, many counseling centers are under-resourced and operate at full capacity with waitlists for much of the year.[12] On a nation-wide survey of college counseling center directors, 90% raised concerns that students may not be receiving treatment when it is most needed.[13] As a result, there is growing interest in digital mental health interventions, such as mindfulness apps, to expand treatment accessibility and improve student well-being and sleep quality.[14–16]

Though digital mindfulness interventions offer many potential sleep and mental health benefits for college students, rates of adherence and sustained use of mindfulness apps have been low.[17,18] Thus, more research needs to examine facilitators to the uptake and sustainability of mindfulness practice, as well as complementary treatment methods that can boost the perceived effectiveness of mindfulness practice. The current study explores tVNS as one such complementary treatment. tVNS is a safe, non-invasive form of vagus nerve stimulation (FDA-approved for the treatment resistant depression and epilepsy). tVNS targets the auricular branch of the vagus nerve through stimulation at sites of the external ear, such as the inner tragus.[19] It has been shown to affect vagally mediated components of the limbic system that are critical to sleep and mood via activation of the nucleus of the solitary tract (NTS).[20,21] Moreover, tVNS has been shown to increase parasympathetic tone,[22] which can have a beneficial effect on both sleep and mood.[23,24] Stimulation of the vagus nerve has been associated with reductions in daytime sleepiness,[25] decreased sleep latency,[26] greater slow wave sleep,[26,27], and longitudinal improvements in self-reported sleep quality[28–30] in clinical and preclinical studies. tVNS has also been associated with improvements in anxiety and depressive symptoms.[30–32] Thus, tVNS may be a convenient means to improve sleep and mental health outcomes among college students engaging in mindfulness practice, although this potential has not yet been empirically tested. The current study will evaluate the feasibility, acceptability, and efficacy of this novel combined treatment approach relative to mindfulness-only and control conditions.

5. Specific Aims

The goal of the proposed research project is to explore the acceptability and efficacy of a combined transcutaneous vagus nerve simulation (tVNS) and mindfulness intervention in enhancing sleep and well-being among college students and compare it to mindfulness-only and control conditions with the hypothesis that the combined intervention will have greater efficacy due to synergistic brain effects of tVNS and mindfulness. In addition to experimental results, the proposed project will

generate effect size data to inform future trials of the combined approach and assess the feasibility and acceptability of our study design.

Specific Aim 1: To evaluate the feasibility and acceptability of sustained engagement with the Brightmind mindfulness app among college students.

Research question 1.1: Do students find this app acceptable and engage with it consistently across a 4-week period?

Research question 1.2: What are the barriers and facilitators to sustained engagement with the app?

Hypothesis 1.3: Participants who spend more time engaging with the app will see greater improvements in mental health (e.g., stress, anxiety, depressive symptoms, positive affect) and HRV compared to participants who spend less time engaging with the app.

Specific Aim 2: To obtain preliminary effect size data on the efficacy of the Brightmind mindfulness app in improving proximal and distal mental health outcomes among college students

Hypothesis 2.1: Participants in the mindfulness-only group will demonstrate greater improvements in mental health (e.g., stress, anxiety, depressive symptoms, positive affect) than participants in the control group

Hypothesis 2.2: Overnight heart rate variability (HRV), positive affect, and interoceptive awareness will be greater in the mindfulness-only group compared to the control group.

Hypothesis 2.3: HRV will increase from before to after each mindfulness session.

Specific Aim 3: Determine feasibility and acceptability of the combined tVNS + mindfulness intervention.

Research question 3.1: Do students find this combined intervention acceptable and demonstrate adequate adherence (i.e. use tVNS or sham + mindfulness for at least 10 minutes/day at least 4 days/week for 2 weeks)?

Research question 3.2: What are the barriers and facilitators to adherence with the combined intervention?

Hypothesis 3.3: The combined intervention will be well-tolerated and receive positive acceptability ratings.

Specific Aim 4: Develop effect size data on the efficacy of the combined tVNS + mindfulness intervention in improving sleep and mental health among college students.

Hypothesis 4.1: Participants in the tVNS + mindfulness group will demonstrate greater improvements in sleep quality and quantity than participants in the sham + mindfulness group or control groups.

Hypothesis 4.2: Participants in the tVNS + mindfulness group will demonstrate greater improvements in mood and mood related factors (e.g., stress, anxiety, depressive symptoms, positive affect) than participants in the sham + mindfulness group or control groups.

6. Research Plan

6.1 Study timetable and logistics. The study will consist of an intake-training session and a 4-week intervention phase. Participants will complete brief weekly online surveys during the intervention phase and a follow-up online survey 4-weeks after the end of the intervention period. Face-to-face interaction with subjects will take place at the University of Florida McKnight Brain Institute (MBI) during the intake-training visit, the return of study equipment, and the distribution of participant payment

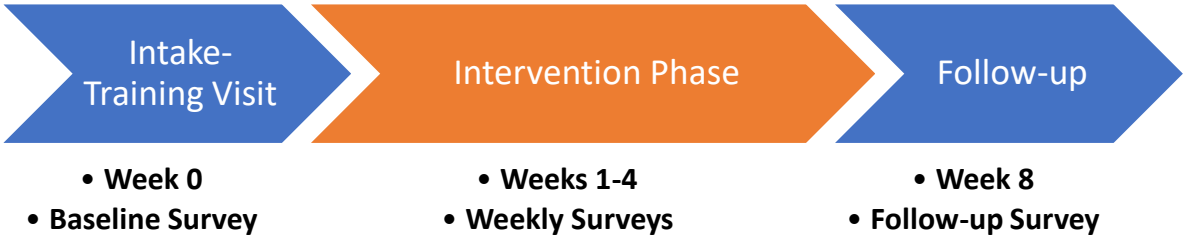

Figure 1 Visualization of the study protocol and timeline.

6.2 Experimental design. As participants are scheduled for intake visits, they will be assigned to either a tVNS group (tVNS + mindfulness or sham + mindfulness) or a non-tVNS group (mindfulness only or control) by the research coordinator based on practical considerations (i.e. tVNS device availability) to expedite study completion. Within each of these groups, participants will be randomized via alternating order to either the active or control condition (in other words, once a participant is assigned to a tVNS group, they will then be randomized to either the tVNS + mindfulness or sham + mindfulness group). This process will repeat until each group has the target number of participants.

In the initial visit, a research assistant will review the appropriate informed consent form. During this process, participants assigned to a stimulation group (tVNS + mindfulness or sham + mindfulness) will be told that they have been randomized to receive one of two different types of noninvasive vagal nerve stimulation, that we think one of the conditions may be more effective, and that they have a 50/50 chance of being in that group. For participants randomized to the non-stimulation groups (mindfulness only or control), they will be told that they have been randomly assigned to use one of two mobile app interventions, that we think one of the interventions may be more effective, and that they have a 50/50 chance of being in that group. After providing written informed consent, participants will 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, and any data collected will be kept in a locked filing cabinet.

After passing the screening, participants will complete an online survey that will include measures of mood, well-being, pain, daytime sleepiness, and sleep quality (see section 6.6 for specific measures).

These measures are self-report and will establish a baseline for each participant. They will be provided with and trained on the following equipment depending on their group assignment:

- **Brightmind Meditation mobile mindfulness app** (Brightmind Meditation, LLC; https://www.brightmind.com): Participants in each of the three active treatment groups (tVNS + mindfulness, sham + mindfulness, and mindfulness-only) will be provided with free access to the Brightmind mobile mindfulness app. During the intake session, they will download the app and complete an orientation to learn its features. They will be asked to practice mindfulness meditation through the app for 10 minutes each evening during the 4-week

intervention phase, with compliance defined as using the app 10 minutes/day for at least 4 days/week.

- **Control task**: Participants in the control group will be provided with the link and instructions for a control task (an online number puzzle: https://play2048.co/) that has been used in previous studies of mindfulness apps.[33] They will be asked to engage with this control task for 10 minutes each evening during the 4-week intervention phase, with compliance defined as engaging with the task 10 minutes/day for at least 4 days/week. Participants in the control group will receive free access to the Brightmind mindfulness app after study completion.
- **Soterix Medical RELIfit-Tragus Device** (Soterix Medical Inc.; https://soterixmedical.com/research/tavns): Participants in the tVNS + mindfulness and sham + mindfulness groups will be provided with the Soterix Medical RELIfit-Tragus device, as well as its accompanying equipment (e.g., device charger, gel, cleaning materials). During the intake session, they will be trained on procedures for using the device, including gel application, electrode placement, and device configuration. Once the research assistant confirms that the participant 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. Participants will be instructed to take a picture that hides the identifying features of the face. Participants will be asked to administer tVNS concurrently with mindfulness practice for at least 4 days per week for the first 2 weeks of the intervention phase. They will be asked to send a picture of the application of the electrodes for each stimulation session. If a picture of the application indicates improper placement, a research assistant will contact the participant via phone or email to review proper form.
- **Fitbit Wristband** (Fitbit LLC): All participants will be provided with a Fitbit wristband for overnight sleep and HRV measurement. They will be instructed on the best method for wearing the band during the initial visit. Participants will be asked to wear the wristband overnight each night for the 4-week intervention phase, with compliance defined as wearing the device overnight at least 4 nights/week.
- **Polar H10 Chest Strap** (Polar Electro; https://www.polar.com/us-en/products/accessories/h10_heart_rate_sensor): All participants will be provided with a Polar H10 chest strap for HRV measurement during mindfulness practice. They will be instructed on the best method for wearing the chest strap during the initial visit. In addition, the research assistant will assist them in downloading a mobile app for data collection/storage and pairing it with the Polar H10 band for HRV recording. They will be asked to wear the chest strap during at least one mindfulness practice session per week during the 4-week intervention period.

After receiving study equipment and completing training procedures, participants will begin the intervention phase at home. They will be provided with written and/or video instructions as a reminder of procedures for the intervention phase depending on their group (summarized in **Table 1**). Study staff will also be available to answer questions or provide reminders via email and/or phone. During the intervention phase, participants will complete brief weekly online surveys consisting of some of the measures administered at baseline (see section 6.6). The survey will be sent via an electronic link to participants' email address or phone number. At the completion of the 4-week intervention phase, the research assistant will coordinate with the participant to schedule a time to return study equipment and distribute participant payment. Participants will be compensated for their time and effort (see section 10).

Group	Intervention Phase Procedures

tVNS + mindfulness (*n* = 20)	- Practice mindfulness meditation through the Brightmind Meditation app for 10 minutes each evening for 4 weeks - Administer tVNS concurrently with mindfulness practice at least 4 days per week during the first 2 weeks of the intervention phase - Wear the Polar H10 chest strap during mindfulness practice at least 1x/week - Wear the Fitbit overnight for 4 weeks
Sham + mindfulness (*n* = 20)	- Practice mindfulness meditation through the Brightmind Meditation app for 10 minutes each evening for 4 weeks - Administer sham stimulation concurrently with mindfulness practice at least 4 days per week during the first 2 weeks of the intervention phase - Wear the Polar H10 chest strap during mindfulness practice at least 1x/week - Wear the Fitbit overnight for 4 weeks
Mindfulness only (*n* = 20)	- Practice mindfulness meditation through the Brightmind Meditation app for 10 minutes each evening for 4 weeks - Wear the Polar H10 chest strap during mindfulness practice at least 1x/week - Wear the Fitbit overnight for 4 weeks
Control (*n* = 20)	- Engage with the control task for 10 minutes each evening for 4 weeks - Wear the Polar H10 chest strap during the control task at least 1x/week - Wear the Fitbit overnight for 4 weeks

Table 1. Intervention phase procedures for each experimental group.

6.3 Subjects. This study utilizes a between-participant design and will recruit 80 healthy college students aged 18 – 30. Pregnant women may not participate in this study—pregnancy tests provided by the study will be used for women of child-bearing age randomized to a tVNS group prior to starting the study and after the consenting process. Pregnancy tests will only be given in the intake session.

6.4 Recruitment and Retention. We will recruit a volunteer sample of undergraduate students from the Gainesville, Florida community who are interested in managing stress. We will post IRB-approved flyers around the community and on the UF campus. The flyers include a survey link where interested students can provide their contact information if they believe they qualify for the study to allow study staff to contact them to schedule an intake appointment. The investigators will be involved in recruitment of participants from multiple sources, including campus tabling events, posting flyers on UF campus and through GatorWell, emails to relevant listservs, making announcements during undergraduate classes, and through word of mouth. The investigators will also post announcements to Facebook and Twitter (see Social Media Strategy). Subjects will be expected to provide their own means of transportation.

6.5 Inclusion/Exclusion Criteria. Participants will include adults between the ages of 18-30, consistent with the typical college population. Participants must own a smartphone, be able to read and write English, and not be in ongoing psychotherapy.

Major medical illnesses including diagnosed severe neurological illnesses (e.g., stroke, seizure history), medical conditions associated with neurological effects (e.g. heart, kidney disease), 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. These elements will be assessed via self-report.

Sleep medications and/or psychotropic medications are exclusionary. Current illicit or prescription drug abuse (within the last two months) will result in exclusion or delay. Marijuana or alcohol abuse >2 weeks out will be acceptable for inclusion. 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. This may include questions about their medical history, psychiatric history, substance use history, and current medications. Since our study requires a return visit, this questionnaire may also include participant contact information.

Behavioral. The following tests may be included in the online surveys:

Pittsburg Sleep Quality Index (PSQI):[34] This 19-item scale yields component scores for seven different domains of sleep quality: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. We will use this measure to assess for changes in self-reported sleep quality across the study period. This measure may be administered at intake, week 2, week 4, and follow-up.

Epworth Sleepiness Scale (ESS):[35] This 8-item questionnaire assesses daytime sleepiness by having participants rate their usual chances of dozing off while engaged in common activities. We will use this measure to assess for changes in self-reported daytime sleepiness across the study period. This measure may be administered at intake, week 2, week 4, and follow-up.

Patient Health Questionnaire-8 (PHQ-8):[36] This 8-item questionnaire assesses depressive symptoms, and we will use it as a mental health outcome measure. We will adjust the time scale to asking about symptoms over the past week. This measure may be administered at intake, week 2, week 4, and follow-up.

Generalized Anxiety Disorder-7 (GAD-7):[37] This 7-item questionnaire screens for symptoms of generalized anxiety disorder and characterizes their severity, and we will use it as a mental health outcome measure. We will adjust the time scale to asking about symptoms over the past week. This measure may be administered at intake, week 2, week 4, and follow-up.

Perceived Stress Scale (PSS):[38] This 10-item questionnaire measures the degree to which situations in one's life are appraised as stressful. In particular, it gauges how unpredictable, uncontrollable, and overloaded respondents find their lives. We will adjust the time scale to asking about symptoms over the past week and use this measure to track potential changes in stress levels. This measure may be administered at intake, weekly, and at follow-up.

Positive and Negative Affect Schedule (PANAS):[39] *Positive emotions* (overall, serenity, joviality, self-assurance) and *negative emotions* (overall, sadness, fear, hostility) will be

measured with 17 adjectives each. This measure will be used to assess changes in self-reported emotions. This measure may be administered at intake, weekly, and at follow-up.

Multidimensional Assessment of Interoceptive Awareness-2 (MAIA-2):[40] Interoceptive awareness will be assessed as a potential proximal outcome of mindfulness practice. We will use the body listening (3 items), trusting (3 items), and self-regulation (4 items) subscales (10 items total). These subscales may be administered at intake, weekly, and at follow-up.

Applied Mindfulness Process Scale (AMPS):[41] The AMPS scale measures mindful emotion regulation – decentering, positive emotion regulation, and negative emotion regulation. This measure will be used to assess for changes in mindful emotion regulation associated with longitudinal use of the mindfulness app. The 15-item scale may be administered at intake, week 2, week 4, and follow-up.

The Nondual Awareness Dimensional Assessment - State (NADA-S).[42]This 3-item scale measures mindfulness-related processes of self-transcendence. We use it to assess changes in self-transcendence associated with the use of the mindfulness app. The scale is administered at intake, weekly, and at follow-up.

PERMA Profiler:[43] This questionnaire measures flourishing across 5 domains: positive emotion, engagement, relationships, meaning, and accomplishment following Dr. Seligman's well-being theory. We will use this 19-item measure to assess for changes in self-reported well-being. This measure may be administered at intake, week 4, and at follow-up.

Pain Numeric Rating Scale: Participants will be asked to rate their current pain level on a scale from 0-10 (0 = no pain at all, 10 = highest level of pain imaginable), as tVNS and mindfulness may provide pain relief. This measure may be administered at intake, weekly, and at follow-up.

System Usability Survey (SUS):[44] This is a standard version of a usability scale. Participants 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 after the completion of the intervention phase (week 4).

Acceptability of Intervention Measure (AIM), Intervention Appropriateness Measure (IAM), and Feasibility of Intervention Measure (FIM):[45] These brief 4-item scales measures the degree to which participants believe an intervention is acceptable, appropriate, and feasible. These measures will only be given after the completion of the intervention phase (week 4).

Physiological. Subjects will be given a Fitbit brand wristband that offers real-time physiological data acquisition to use to monitor their sleep quantity, quality, and overnight heart rate variability (HRV) during the intervention phase. Participants will also be given a Polar H10 chest strap to use during mindfulness sessions, measuring their momentary HRV. Participants may be provided a preassigned account and password for these wearable devices, which may be accessed by the research team to manage raw data.

Analysis Plan.

- To analyze feasibility data, we will qualitatively examine rates of recruitment and drop out/attrition and compare them to prior research. Quantitatively, to examine whether dropout is selective, participants who completed the study will be compared to participants who dropped out on group via chi-square independence test. To analyze acceptability data, outcomes regarding tolerance and acceptability will be compared between the groups via

ANOVA. In addition, we will perform thematic analysis of participant responses to open-ended questions about feasibility and acceptability.

- To examine trajectory of sleep and mental health/well-being over time, multilevel modeling (MLM) analyses will be conducted using unrestricted full information maximum likelihood in R via the "lme4" package. Separate models will be conducted using each sleep and mental health/well-being outcome measure as a dependent variable. Linear and quadratic time trends will be estimated, and intervention group will be included as a moderator. To examine adherence, the number of minutes participants spend engaged with the app or tVNS device per week will be averaged. Then, an MLM will be conducted using average weekly engagement as the dependent variable and time (linear and quadratic) and group as predictors. Retention rates between intervention groups will be compared using an independent samples t-test.

Nerve Stimulation. The auricular branch of the vagus nerve projects to the brainstem and is accessible via electrical stimulation through surface electrodes. Stimulation produces vagus sensory evoked potentials not induced with off-target stimulation.[20,21]

Earpiece Placement: All subjects will be instructed to place the Soterix device earpiece on their left ear such that the stimulation electrode is positioned over the inner tragus and the return electrode is positioned just anterior to the tragus to minimize off-target stimulation per local pilot protocol (see Figure 2). Subjects will demonstrate their ability to set up the stimulator—including earpiece placement—and text the picture of the electrode placement with their faces occluded, similar to Figure 2. Research 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 for each stimulation session via SMS.

Stimulation Device: We will use the Soterix Medical RELIfit-Tragus transcutaneous electrical nerve stimulation devices. For details, see "Device type" in my.irb. Stimulus pulses will be alternating in polarity to reduce tissue irritation and will be delivered at 20Hz, 200 μs pulse width, within the range of published stimulus parameters.[46–48]

Calibration: Participants will undergo calibration during the intake-training visit. Prior to calibration, participants will be informed that the stimulation intensity will be slowly increased until they report any discomfort and then reduced to a comfortable level for the remainder of the study. Individual sensitivity to tVNS stimulation will then be evaluated with a structured stepped-ramp protocol, with a brief pause at each step during which the participant will be asked what the stimulus felt like to them and if they experienced any discomfort. The stimulation intensity will then set to 80% of the discomfort threshold for the active tVNS group and near to 0% (just enough to keep device on) of the discomfort threshold for the sham stimulation group. If the participant reports irritation with stimulation during this ramp up procedure (which can last ~15 minutes), electrode adhesion will be checked (if there is poor contact, it can affect the sensation) and stimulation intensity will be reduced if necessary (any change will be documented). If the participant further indicates discomfort, stimulation will be discontinued. If the patient evidence dizziness/lightheadedness or if a comfortable level of stimulation is not achievable at calibration, the participant will be removed from the study (this will be documented).

Blinding: Participants will be blinded to condition and told that, after calibration, the stimulus intensity will be set to below the calibration (discomfort threshold) level and that they may not feel the stimulation once reduced. We have used this form of psychological sham approach in

the past.[22] Participants will be provided with a maximum of 14 blinding codes that correspond with the appropriate stimulation parameters and intensity depending on their group assignment. These blinding codes must be entered into the tVNS device in order for stimulation to be administered. They are one-time use only, meaning that participants will not be able to administer tVNS more frequently than instructed in the study protocol. Moreover, participants will be told that these blinding codes correspond to stimulation parameters/intensity that is calibrated to them only, and that they are not safe to be used on other people (e.g., friends, roommates). The picture of earpiece placement that participants send with each stimulation session should act as a further control against participants allowing others to use the stimulation device. The blinding codes will also specify stimulation length, with a maximum of one hour (after which, stimulation will be turned off). Of note, stimulation also turns off if there is not good connectivity between the earpiece and the tragus (e.g., if the earpiece falls off or if it is placed on another part of the body without adequate connectivity).

At-Home Device Use: Per the Soterix website: "The Soterix Medical taVNS device is intended for use by, or under the direct or remote supervision of, a trained healthcare practitioner." We have discussed this statement via email with Abhishek Datta, CEO and CTO of Soterix Medical, who clarified that "By trained health care practitioner- we simply mean someone who is aware of taVNS, technology, risks, etc. and knows how to administer the technique", and "By remote supervision- the system can be self-administered. The subject or caregiver (proxy in some cases) would need to be trained on placing the electrodes before they become eligible. The system is designed such that the administrator (PI, clinical center personnel,etc) sets the desired dose (duration, frequency, pulse width, etc) before handing it off to the subject. The subject can only deliver stimulation as prescribed by the clinic [or lab] (i.e. cannot misuse). So basically a researcher can remotely supervise administration." This email correspondence is attached as supplementary material. Given this clarification, our study protocol (e.g., with staff training participants on electrode placement/device use and subsequent at-home self-administration with "remote supervision") is consistent with Soterix Medical's intended use of the device. We will be receiving pictures of electrode placement for each stimulation session.

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) investigation.

Figure 2 Non-invasive vagal nerve stimulation earpiece placement.

Mindfulness Mobile App: The Brightmind mindfulness training app provides lessons by leading American mindfulness teacher and neuroscience research consultant Shinzen Young.[49] His exercises have been shown to be effective in reducing physiological stress reactivity and improving positive affect in previous randomized experimental studies among community adults in the Pittsburgh area.[50,51] A full description of the lessons is attached as supplemental material. Participants in our study will be instructed to start with the "Stress Less" introductory course of 8 sessions. Every session includes a brief explanation of how the practice helps reduce stress.

- Session 1, Get Grounded – focus on hearing sound or silence, physical body sensations, focus on what you see, acknowledge emotional state, let stressful thoughts and feelings come and go in the background with relaxed body and slight smile
- Session 2, Relaxation – enjoy rest and relaxation, notice what relaxation feels like by tensing and loosening muscles in every part of body, then whole body
- Session 3, Training Positivity – come up with word or phrase that helps overcome stress, mentally repeat; find a positive, relaxing mental image, hold it; create positive emotional sensation in body that relates to positive phrase and image
- Session 4, Untangle and Be Free – notice mental images or blank screen, notice mental talk or silence, notice emotional sensations in body or rest – develop flexibility, observer mindset
- Session 5, Soothing Sound – noting technique – acknowledging and focusing on sensory experience - sounds or silence, every few seconds
- Session 6, Focused Relaxation – noting relaxation in body every few seconds, tightening & loosening of muscles
- Session 7, Anchoring Awareness in the Body – noting physical sensations, labeling technique – name sensory experience, "feel"
- Session 8, You're Not (Just) Your Thoughts – noting mental talk or silence every few seconds, observer mindset, labeling technique – name mental talk "hear", absence of mental talk "rest"

After finishing the introductory course, participants will gain access to suggested next courses, "Mindful Awareness" (7 sessions) and "Deepen Your Practice" (8 sessions).

Participants will be provided a pre-assigned account and password to use with this app, which will be accessed by the research team to manage raw data collected through the app (e.g., session type, number of sessions, and time spent in the app). The use of pre-assigned accounts and passwords will make it such that any data collected by the app will be de-identified.

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, redness, discomfort, and tingling/mild 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. Other less common potential side effects (observed in <1% of study populations) include nausea, headache, heart palpitations, dizziness, vocal hoarseness, and nasopharyingitis.[46,47] It is important to note that these less common side effects were primarily found in studies of clinical populations with a variety of stimulation methods (e.g., cervical stimulation, bilateral stimulation, longer lengths of stimulation) that are not being used in this study. Thus, while these side effects have been observed in some prior studies, we do not anticipate that are likely to occur in this study of healthy college students.

We will be using a Soterix Medical taVNS device. Their website describes the device safety thusly:

> "*taVNS on the other hand, delivers electrical stimulation to the auricular branch of the vagus nerve (ABVN), an easily accessible target that innervates the human ear (Peukar*

and Filler 2002). Over the last decade, several groups have demonstrated the safety and tolerability of this method, including central and peripheral nervous system effects, and behavioral effects in neuropsychiatric populations (Kreuzer et al 2012, Clancy et al 2014, Rong et al 2016, Bauer et al 2016). taVNS is also being explored in individuals to enhance cognitive and social functioning (Jacobs et al 2015,Jongkees et al 2018,Colzato et al 2018). Furthermore, side-effects of taVNS are minimal, with skin irritation or redness being the most common side-effect. In a review of 51 studies with 1322 human participants receiving tVNS, the most common side effect was local skin irritation (%18). Authors conclude tVNS is well tolerated and safe (Redgrave et al., 2018).""

- Peuker, E.T., & Filler, T.J. The nerve supply of the human auricle. Clinical Anatomy. 15 (1), 35-37 (2002).
- Kreuzer, P.M. et al. Transcutaneous vagus nerve stimulation: retrospective assessment of cardiac safety in a pilot study. Frontiers in Psychiatry. 3, 70 (2012)
- Clancy, J.A. et al. Non-invasive vagus nerve stimulation in healthy humans reduces sympathetic nerve activity. Brain Stimulation. 7 (6), 871-877 (2014).
- Rong, P. et al. Effect of transcutaneous auricular vagus nerve stimulation on major depressive disorder: A nonrandomized controlled pilot study. Journal of Affective Disorders. 195, 172-179 (2016).
- Bauer, S. et al. Transcutaneous vagus nerve stimulation (tVNS) for treatment of drug-resistant epilepsy: a randomized, double-blind clinical trial (cMPsE02). Brain Stimulation. 9 (3), 356-363 (2016).
- Jacobs, H.I., Riphagen, J.M., Razat, C.M., Wiese, S., & Sack, A.T. Transcutaneous vagus nerve stimulation boosts associative memory in older individuals. Neurobiology of Aging. 36 (5), 1860-1867 (2015)
- Jongkees, B.J., Immink, M.A., Finisguerra, A., & Colzato, L.S. Transcutaneous Vagus Nerve Stimulation (tVNS) Enhances Response Selection During Sequential Action. Frontiers in Psychology. 9, 1159 (2018).
- Colzato, L.S., Ritter, S.M., & Steenbergen, L. Transcutaneous vagus nerve stimulation (tVNS) enhances divergent thinking. Neuropsychologia. 111, 72-76 (2018).
- Redgrave J, Day D, Lueng H, Laud PJ, Lindert R, Ali A, and Majid A. Safety and tolerability of tVNS in humans; a systematic review. Brain Stimulation 11, 1225-1238.

Note, the devices used in these studies are diverse (all TENS unit variants). Soterix's device is based on their commonly used TENS unit platform used in neuromodulation studies around the world (e.g., TDCS).

7.2 *Mindfulness Practice*: Mindfulness practice can reveal or bring into greater focus uncomfortable thoughts, emotions, or bodily sensations. These experiences are similar to those that a person might experience in everyday life or while using other commercially available mindfulness apps. The Brightmind Meditation app is structured to begin with positive and relaxing experiences to minimize user discomfort or frustration as they develop mindfulness skills.

7.3 Mood Assessments: Questions about mood and personality can sometimes be uncomfortable (e.g., talking about things that make you sad or anxious). If participants experience distress while completing these questionnaires, they will be instructed to contact a research assistant who will be able to provide community mental health resources.

7.4 Wearable Sensors: The wrist monitor is comparable to wearing a standard wristwatch. If the band is too tight, there is a risk of skin irritation. Similar risks apply to the chest band. Both bands are adjustable to ensure participant comfort.

7.5 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 participant 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 Participant Payments guidelines, the subject's contact information and student identification/social-security-number will be redacted form the questionnaires and payment receipts.

7.6 Data and Safety Monitoring Plan. 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

A potential benefit of participating in this study is experiencing a short-term improvement in mood and sleep quality. No direct long-term benefits can be reasonably expected from this study, except if the mindfulness training app intervention shows preliminary efficacy and participants continue using it on their own after the study is over. The information garnered from this study may provide valuable data on the optimization of the tVNS technology, which has the potential to be a cheap, effective, and safe tool for augmenting effects of mindfulness practice.

9. Conflict of Interest

There are no known conflicts of interest.

10. Participant Payment

Participants will be compensated for their time and effort participating in the study. The amount is specified on my.irb.ufl.edu and the consent form.

References

1. Liu Y, Wheaton AG, Chapman DP, Cunningham TJ, Lu H, Croft JB. Prevalence of Healthy Sleep Duration among Adults--United States, 2014. MMWR Morb Mortal Wkly Rep. 2016 Feb 19;65(6):137–141. PMID: 26890214

2. Hershner SD, Chervin RD. Causes and consequences of sleepiness among college students. Nat Sci Sleep. 2014 Jun 23;6:73–84. PMCID: PMC4075951

3. Prichard JR, Cunningham B, Broek L. Enhancing College Student Sleep: Programming strategies that could work on your campus. meeting of the American College Health Association, Boston, MA. 2013.

4. Prichard JR. Sleep Predicts Collegiate Academic Performance: Implications for Equity in Student Retention and Success. Sleep Medicine Clinics. Elsevier; 2020 Mar 1;15(1):59–69. PMID: 32005350

5. Association ACH. American college health association-national college health assessment II: Undergraduate reference group executive summary spring 2019. Hanover, MD: American College Health Association. 2019;132.

6. Hartmann ME, Prichard JR. Calculating the contribution of sleep problems to undergraduates' academic success. Sleep Health. 2018 Oct 1;4(5):463–471.

7. Health C for CM. Center for collegiate mental health 2018 annual report. Center for Collegiate Mental Health University Park; 2018.

8. Shepardson RL, Funderburk JS. Implementation of Universal Behavioral Health Screening in a University Health Setting. J Clin Psychol Med Settings. 2014 Sep 1;21(3):253–266.

9. Taylor DJ, Gardner CE, Bramoweth AD, Williams JM, Roane BM, Grieser EA, Tatum JI. Insomnia and Mental Health in College Students. Behavioral Sleep Medicine. Taylor & Francis; 2011 Mar 25;9(2):107–116.

10. Duffy ME, Twenge JM, Joiner TE. Trends in Mood and Anxiety Symptoms and Suicide-Related Outcomes Among U.S. Undergraduates, 2007–2018: Evidence From Two National Surveys. Journal of Adolescent Health. 2019 Nov 1;65(5):590–598.

11. Oswalt SB, Lederer AM, Chestnut-Steich K, Day C, Halbritter A, Ortiz D. Trends in college students' mental health diagnoses and utilization of services, 2009-2015. J Am Coll Health. 2020 Jan;68(1):41–51. PMID: 30355071

12. Xiao H, Carney DM, Youn SJ, Janis RA, Castonguay LG, Hayes JA, Locke BD. Are we in crisis? National mental health and treatment trends in college counseling centers. Psychological Services. US: Educational Publishing Foundation; 2017;14(4):407–415.

13. Gallagher RP. National Survey of College Counseling Directors 2014. University of Pittsburg, PA: International Association of Counseling Services, Inc. 2014.

14. Lattie EG, Adkins EC, Winquist N, Stiles-Shields C, Wafford QE, Graham AK. Digital Mental Health Interventions for Depression, Anxiety, and Enhancement of Psychological Well-Being Among College Students: Systematic Review. Journal of Medical Internet Research. 2019 Jul 22;21(7):e12869.

15. Davies EB, Morriss R, Glazebrook C. Computer-delivered and web-based interventions to improve depression, anxiety, and psychological well-being of university students: a systematic review and meta-analysis. Journal of medical Internet research. JMIR Publications Inc., Toronto, Canada; 2014;16(5):e130.

16. Huberty J, Green J, Glissmann C, Larkey L, Puzia M, Lee C. Efficacy of the Mindfulness Meditation Mobile App “Calm” to Reduce Stress Among College Students: Randomized Controlled Trial. JMIR Mhealth Uhealth [Internet]. 2019 Jun 25 [cited 2021 Mar 28];7(6). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6614998/ PMCID: PMC6614998

17. Flett JAM, Hayne H, Riordan BC, Thompson LM, Conner TS. Mobile Mindfulness Meditation: a Randomised Controlled Trial of the Effect of Two Popular Apps on Mental Health. Mindfulness. 2019 May 1;10(5):863–876.

18. Laurie J, Blandford A. Making time for mindfulness. Int J Med Inform. 2016 Dec;96:38–50. PMID: 26965526

19. Peuker ET, Filler TJ. The nerve supply of the human auricle. Clin Anat. 2002 Jan;15(1):35–37. PMID: 11835542

20. Frangos E, Ellrich J, Komisaruk BR. Non-invasive access to the vagus nerve central projections via electrical stimulation of the external ear: fMRI evidence in humans. Brain Stimul. 2015;8(3):624–636. PMCID: PMC4458242

21. Kraus T, Kiess O, Hösl K, Terekhin P, Kornhuber J, Forster C. CNS BOLD fMRI effects of sham-controlled transcutaneous electrical nerve stimulation in the left outer auditory canal - a pilot study. Brain Stimul. 2013 Sep;6(5):798–804. PMID: 23453934

22. Lamb DG, Porges EC, Lewis GF, Williamson JB. Non-invasive Vagal Nerve Stimulation Effects on Hyperarousal and Autonomic State in Patients with Posttraumatic Stress Disorder and History of Mild Traumatic Brain Injury: Preliminary Evidence. Front Med [Internet]. 2017 [cited 2019 Dec 29];4. Available from: https://www.frontiersin.org/articles/10.3389/fmed.2017.00124/full

23. Porges SW, Doussard-Roosevelt JA, Stifter CA, McClenny BD, Riniolo TC. Sleep state and vagal regulation of heart period patterns in the human newborn: an extension of the polyvagal theory. Psychophysiology. 1999 Jan;36(1):14–21.

24. Jung DW, Lee YJ, Jeong D-U, Park KS. New predictors of sleep efficiency. Chronobiology international. Taylor & Francis; 2017;34(1):93–104.

25. Malow BA, Edwards J, Marzec M, Sagher O, Ross D, Fromes G. Vagus nerve stimulation reduces daytime sleepiness in epilepsy patients. Neurology. 2001 Sep 11;57(5):879–884. PMID: 11552020

26. Hallböök T, Lundgren J, Köhler S, Blennow G, Strömblad L-G, Rosén I. Beneficial effects on sleep of vagus nerve stimulation in children with therapy resistant epilepsy. European Journal of Paediatric Neurology. 2005 Nov 1;9(6):399–407.

27. Valdés-Cruz A, Magdaleno-Madrigal VM, Martínez-Vargas D, Fernández-Mas R, Almazán-Alvarado S. Long-term changes in sleep and electroencephalographic activity by chronic vagus nerve stimulation in cats. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2008 Apr 1;32(3):828–834.

28. Luo M, Qu X, Li S, Zhao J, Zhao Y, Jiao Y, Rong P. [Transcutaneous vagus nerve stimulation for primary insomnia and affective disorder:a report of 35 cases]. Zhongguo Zhen Jiu. 2017 Mar 12;37(3):269–273. PMID: 29231433

29. Jiao Y, Guo X, Luo M, Li S, Liu A, Zhao Y, Zhao B, Wang D, Li Z, Zheng X, Wu M, Rong P. Effect of Transcutaneous Vagus Nerve Stimulation at Auricular Concha for Insomnia: A Randomized Clinical Trial [Internet]. Evidence-Based Complementary and Alternative Medicine. Hindawi; 2020 [cited 2021 Jan 9]. p. e6049891. Available from: https://www.hindawi.com/journals/ecam/2020/6049891/

30. Kong J, Fang J, Park J, Li S, Rong P. Treating Depression with Transcutaneous Auricular Vagus Nerve Stimulation: State of the Art and Future Perspectives. Front Psychiatry [Internet]. 2018 [cited 2020 Apr 16];9. Available from: https://www.frontiersin.org/articles/10.3389/fpsyt.2018.00020/full

31. Fang J, Rong P, Hong Y, Fan Y, Liu J, Wang H, Zhang G, Chen X, Shi S, Wang L, Liu R, Hwang J, Li Z, Tao J, Wang Y, Zhu B, Kong J. Transcutaneous Vagus Nerve Stimulation Modulates Default Mode Network in Major Depressive Disorder. Biological Psychiatry. 2016 Feb 15;79(4):266–273.

32. Grolaux PJD. Transcutaneous Vagus Nerve Stimulation in Private Healthcare Center: A Small-Scale Investigation Targeting Anxiety, Irritable Bowel Syndrome and Chronic Pain. Journal of Neurology & Neuromedicine [Internet]. 2019 Oct 17 [cited 2021 Jan 23];4(5). Available from: https://www.jneurology.com/articles/transcutaneous-vagus-nerve-stimulation-in-private-healthcare-center-a-small-scale-investigation-targeting-anxiety-irritable-bowel-syndrome-and-chronic-pain.html

33. Walsh KM, Saab BJ, Farb NA. Effects of a Mindfulness Meditation App on Subjective Well-Being: Active Randomized Controlled Trial and Experience Sampling Study. JMIR Ment Health. 2019 Jan 8;6(1):e10844. PMCID: PMC6329416

34. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989 May;28(2):193–213.

35. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. sleep. Oxford University Press; 1991;14(6):540–545.

36. Kroenke K, Strine TW, Spitzer RL, Williams JBW, Berry JT, Mokdad AH. The PHQ-8 as a measure of current depression in the general population. J Affect Disord. 2009 Apr;114(1–3):163–173. PMID: 18752852

37. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med. 2006 May 22;166(10):1092–1097. PMID: 16717171

38. Cohen S, Kamarck T, Mermelstein R. Perceived stress scale. Measuring stress: A guide for health and social scientists. 1994;10:1–2.

39. Watson D, Clark LA. The PANAS-X: Manual for the positive and negative affect schedule-expanded form. 1999;

40. Mehling WE, Acree M, Stewart A, Silas J, Jones A. The Multidimensional Assessment of Interoceptive Awareness, Version 2 (MAIA-2). PLOS ONE. Public Library of Science; 2018 Dec 4;13(12):e0208034.

41. Li MJ, Black DS, Garland EL. The Applied Mindfulness Process Scale (AMPS): A process measure for evaluating mindfulness-based interventions. Pers Individ Dif. 2016 Apr 1;93:6–15. PMCID: PMC4742344

42. Hanley AW, Nakamura Y, Garland EL. The Nondual Awareness Dimensional Assessment (NADA): New tools to assess nondual traits and states of consciousness occurring within and beyond the context of meditation. Psychol Assess. 2018 Dec;30(12):1625–1639. PMCID: PMC6265073

43. Butler J, Kern ML. The PERMA-Profiler: A brief multidimensional measure of flourishing. Intnl J Wellbeing [Internet]. 2016 Oct 13 [cited 2021 Mar 28];6(3). Available from: https://www.internationaljournalofwellbeing.org/index.php/ijow/article/view/526

44. Brooke J. Sus: a “quick and dirty’usability. Usability evaluation in industry. 1996;189.

45. Weiner BJ, Lewis CC, Stanick C, Powell BJ, Dorsey CN, Clary AS, Boynton MH, Halko H. Psychometric assessment of three newly developed implementation outcome measures. Implementation Science. 2017 Aug 29;12(1):108.

46. Yap JYY, Keatch C, Lambert E, Woods W, Stoddart PR, Kameneva T. Critical Review of Transcutaneous Vagus Nerve Stimulation: Challenges for Translation to Clinical Practice. Front Neurosci [Internet]. 2020 Apr 28 [cited 2021 Feb 14];14. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7199464/ PMCID: PMC7199464

47. Redgrave J, Day D, Leung H, Laud PJ, Ali A, Lindert R, Majid A. Safety and tolerability of Transcutaneous Vagus Nerve stimulation in humans; a systematic review. Brain Stimulation. 2018 Nov 1;11(6):1225–1238.

48. Van Leusden JWR, Sellaro R, Colzato LS. Transcutaneous Vagal Nerve Stimulation (tVNS): a new neuromodulation tool in healthy humans? Front Psychol [Internet]. 2015 Feb 10 [cited 2020 Apr 21];6. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4322601/

49. Young S. What Is Mindfulness? A Contemplative Perspective. In: Schonert-Reichl KA, Roeser RW, editors. Handbook of Mindfulness in Education: Integrating Theory and Research into Practice [Internet]. New York, NY: Springer; 2016 [cited 2021 Oct 27]. p. 29–45. Available from: https://doi.org/10.1007/978-1-4939-3506-2_3

50. Lindsay EK, Young S, Smyth JM, Brown KW, Creswell JD. Acceptance lowers stress reactivity: Dismantling mindfulness training in a randomized controlled trial. Psychoneuroendocrinology. 2018 Jan;87:63–73. PMID: 29040891

51. Lindsay EK, Chin B, Greco CM, Young S, Brown KW, Wright AGC, Smyth JM, Burkett D, Creswell JD. How mindfulness training promotes positive emotions: Dismantling acceptance skills training in two randomized controlled trials. J Pers Soc Psychol. 2018 Dec;115(6):944–973. PMCID: PMC6296247