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Official Study Title
Impact of taVNS on Stress Levels in University Students

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Confidentiality Statement

Methods

Study design

This study will be a blinded, randomized, sham-controlled trial using a convenience sample of university students from the Egas Moniz School of Health and Science. Assessments will be conducted at three time points: pre-intervention (baseline), immediately post-intervention, and 1-month follow-up. The study will be designed to evaluate feasibility and tolerability as primary objectives, with preliminary efficacy estimates as secondary objectives.

Participants

Eligibility criteria will include: (a) being enrolled as a university student, (b) age ≥ 18 years, and (c) high to very high psychological distress (K-10 ≥ 22).

Exclusion criteria will be: initiation or dose change of psychotropic medication within the prior 3 months, substance dependence, ongoing psychological or psychotherapeutic treatment, self-reported formal mental disorder diagnosis (collected via participant self-report without formal diagnostic verification), or contraindications for taVNS (e.g., pregnancy, history of dizziness or seizures, cochlear implants, ear plastic surgery, or auricular malformations).

The final sample will comprise 40 participants, equally distributed across groups (taVNS: n = 20; sham: n = 20).

Sample size justification

This randomized trial will be primarily designed as a feasibility and tolerability study. No a priori power calculation will be conducted; the target sample size of 40 participants (20 per group) will be determined pragmatically based on logistical constraints and the aim of obtaining preliminary estimates of outcome variability and change over time.

Given the small sample and very small anticipated time×group effect, the study will not be powered to detect small between-condition differences and should be interpreted primarily in terms of feasibility, tolerability, and overall within-subject improvements.

Measures

Perceived stress. Perceived stress will be assessed using the 10-item Perceived Stress Scale (PSS-10 (Cohen et al., 1983)), scored from 0 ("never") to 4 ("very often"), summed to a total score ranging from 0 to 40, with higher scores reflecting higher perceived stress. Internal consistency (Cronbach's alpha) in this study will be 0.76 (pre-intervention), 0.83 (post-intervention), and 0.89 (follow-up).

Psychological distress. Psychological distress will be assessed using the 10-item Kessler Psychological Distress Scale (K-10 (KESSLER et al., 2002; Pereira et al., 2019)), scored from 1 ("never") to 5 ("always") in reference to the preceding 30 days, summed to a total score ranging from 10 to 50, with higher scores reflecting greater distress. A score of ≥ 22 will indicate high to very high distress. Internal consistency (Cronbach's alpha) in this study will be 0.81 (pre-intervention), 0.87 (post-intervention), and 0.91 (follow-up).

Sociodemographic and clinical screening. A sociodemographic questionnaire will be used to characterize the sample (age and sex) and to gather clinical information relevant to exclusion criteria (including medical comorbidities, psychotropic medication use, participation in psychotherapeutic groups, and self-reported mental disorder diagnosis).

Procedures

Recruitment will take place via brief in-person classroom information sessions, after which interested students will access an online link to enroll. Following the provision of informed consent, candidates will complete a baseline assessment (sociodemographic questionnaire, PSS-10, and K-10). Eligible participants will be contacted by email to schedule sessions.

Participants will be randomly allocated (1:1) to taVNS or sham stimulation using an online research randomizer (https://www.randomizer.org/) following eligibility confirmation. Allocation will be concealed from participants until debriefing. Participants will be informed that they will be assigned to one of two stimulation protocols differing in electrode placement; they will not be informed of the existence of a sham condition, and this information will only be provided after completion of the 1-month follow-up assessment (debriefing).

All stimulation sessions will be conducted in a university laboratory, delivered by trained study personnel. Personnel will be aware of electrode placement (tragus vs. earlobe) but will be blinded to the interpretation of placement as "active" versus "sham."

Immediately before the first session, exclusion criteria will be re-checked; no participant will be expected to meet exclusion criteria at that time.

The intervention will comprise five consecutive daily sessions of 30 minutes each, delivered using the Parasym® Device (Parasym Health Inc., London, UK) with a preset pulse width of 250 μs and frequency of 20 Hz. Stimulation intensity will be individually titrated at the start of each session to a "comfortable but noticeable" sensory level and adjusted as needed across sessions to maintain this level. The sole procedural difference between groups will be electrode placement: in the taVNS group the electrode will be positioned on the left tragus, whereas in the sham group it will be positioned on the left earlobe.

Following the fifth session, participants will complete post-intervention questionnaires (PSS-10 and K-10) and will be contacted by email 1 month later to complete the follow-up assessment.

Upon study completion and debriefing, sham participants will be offered stimulation with electrode placement on the tragus; none will have accepted at the time of writing.

Adverse events will be monitored before and after each session through open-ended questioning and observation. No clinically significant adverse reactions will be recorded beyond transient mild redness at the stimulation site in some participants, and no participant will report stimulation-related side effects during or after taVNS sessions.

Statistical analysis

Analyses will be performed using IBM SPSS Statistics version 30. Descriptive statistics (means, standard deviations, frequencies) will characterize the sample and outcomes. Internal consistency will be assessed using Cronbach's alpha.

Primary analyses will test changes over time and group differences using a repeated-measures MANOVA with time (pre-intervention, post-intervention, follow-up) as the within-subject factor and group (taVNS vs. sham) as the between-subject factor, using two correlated dependent variables (PSS-10 and K-10). This will be followed by univariate repeated-measures ANOVAs (one per outcome) and Bonferroni-corrected pairwise comparisons across time points.

Assumptions will be tested prior to analysis. Sphericity will be evaluated using Mauchly's test, and multivariate normality will be assessed using Box's M test. When Box's M is significant, Pillai's trace will be used as a robust multivariate test statistic.

All randomized participants will be included in the analysis, and there will be no missing data. Alpha will be set at .05 (two-tailed) for all tests.

Informed Consent

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_____,_____.

(Place) (DD Month YYYY

Dear Sir/Madam,

Within the scope of the project *"Effects of transcranial direct current electrical stimulation of the right and left dorsolateral prefrontal cortex or non-invasive vagus nerve stimulation in adult individuals with chronic stress"*, developed at the **Laboratory of Functional Physical Assessment in Physiotherapy (LAFFFi)** at **Egas Moniz**, under the supervision of **Professor Dr. Luciano Maia Alves Ferreira**, your participation is kindly requested.

The aim of the study is to investigate the effects of transcranial direct current electrical stimulation and non-invasive vagus nerve stimulation in adults with chronic stress. Participation involves completing **five questionnaires** assessing symptoms, psychological distress and stress scales, sleep quality, and demographic data, taking approximately **25 minutes** (to be filled in *before, after, and one month after the interventions*). You will also take part in the **non-invasive neuromodulation protocol**, consisting of **cranial or auricular electrical stimulation**, which is indicated for the treatment of chronic stress. The intervention will comprise **five sessions of 20 minutes each**, carried out over the course of one week and supervised by an experienced professional.

During the study, minimal risks may occur, such as embarrassment, mild discomfort, or lack of time to complete the questionnaires during the first and last sessions. During or after treatment, you may experience mild side effects (such as drowsiness, pain, itching, or tingling sensations in the stimulated area). It is important to emphasize that these reactions are rare, mild, and limited to the stimulation period.

Participation in this study is **voluntary**. Choosing not to participate will not result in any disadvantage or penalty.

This study may offer **potential benefits**, including the possibility of non-pharmacological treatment, reduction of stress symptoms, and improvement in sleep quality.
The data collected will be used **exclusively for statistical analysis and/or publication purposes**, and will be processed by the supervisor(s) and/or their authorized representatives. All data will be handled **anonymously and confidentially**.
(Strike out what does not apply)
I AGREE / DO NOT AGREE to participate in this study, confirming that I have been fully informed about the study's conditions and have no further questions.

(Signature of the participant or, in the case of minors, of the parent/guardian)