Transcutaneous vagus nerve stimulation (tVNS) to acutely reduce emotional vulnerability and improve emotional regulation in borderline personality disorder (tVNS-BPD): study protocol for a randomized, single-blind, sham-controlled trial

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Abstract

**Background:** Borderline personality disorder (BPD) is considered a disorder of emotion regulation resulting from the expression of a biologically determined emotional vulnerability (that is, heightened sensitivity to emotion, increased emotional intensity/reactivity and a slow return to emotional baseline) combined with exposure to invalidating environments. Vagal tone has been associated with activity in cortical regions involved in emotion regulation and a lower resting state of vagal tone has been observed in BPD patients relative to healthy controls. Non-invasive transcutaneous vagus nerve stimulation (tVNS) has shown to reduce temper outbursts in adults with Prader-Willi Syndrome, to enhance recognition of emotions in healthy students and to improve depressive and anxiety symptoms. Furthermore, a single session of tVNS has been shown to acutely alter the recognition of facial expressions of negative valence in adolescents with MDD and increase emotion recognition in controls. However, the effect of tVNS on emotional vulnerability and regulation in individuals diagnosed with BPD has not been investigated. Our aims are to determine if tVNS is effective in acutely reducing emotional vulnerability and improve emotional regulation in BPD patients.

**Methods:** 42 patients will be randomized to a single session of tVNS or sham-tVNS while going through an affect induction procedure. It will consist of the presentation of one neutral and three negative affect-evoking 4-minutes-long videos in sequence, each of which is followed by a 4-minutes post-induction period during which participants will rate the quality and intensity of their current self-reported emotions (post-induction ratings) and the perceived effectiveness in managing their emotions during the video presentation. The rating of the current self-reported emotions will be repeated after every post-induction period (recovery ratings). Mixed models with individuals as random effect will be used to investigate the ratings at each stage of the study, taking into account the repeated measures of same individuals at baseline, pre-induction, post-induction and recovery).

**Discussion:** The study has potential to yield new insights into the role of vagal tone in emotion dysregulation in BPD and offer preliminary data on the effectiveness of tVNS as a possible non-invasive brain stimulation to treat a core symptom of BPD


**Administrative information**

Note: the numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers. The order of the items has been modified to group similar items (see http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/).
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Transcutaneous vagus nerve stimulation (tVNS) to acutely reduce emotional vulnerability and improve emotional regulation in borderline personality disorder (tVNS-BPD): study protocol for a randomized, single-blind, sham-controlled trial

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The Region Västragötaland – Sahlgrenska University Hospital provides resourcing and decision to submit the report for publication.

Introduction

Background and rationale

Borderline personality disorder (BPD) is a severe and persistent mental disorder clinically characterized by affective instability and interpersonal, identity, cognitive, and behavioural disturbances (1). Epidemiological studies have found that BPD occurs in 2%-6% of the general population (2), with even higher estimates in clinical samples, estimated at 11% of outpatient and 19% of inpatient samples (3).

According to Linehan’s Biosocial Theory of personality functioning (4), BPD is a disorder of emotion regulation resulting from a biologically based emotional vulnerability (that is, heightened sensitivity to emotion, increased emotional intensity/reactivity and a slow return to emotional baseline) combined with an invalidating childhood environment. The mechanisms underlying the emotional vulnerability in BPD are not well understood (5,6).

Vagal tone has been associated with activity in cortical regions involved in executive functions and emotion regulation. Lowered resting state vagal tone (lower vagal mediated heart rate variability - vmHRV) is associated with difficulties in emotion regulation and impulsivity (7). A lower vmHRV has been observed in a variety of psychiatric disorders, including BPD, compared to healthy controls (8). This finding is proposed to reflect a psychophysiological mechanism underlying difficulties in emotion regulation and impulsivity (9). Moreover, it has been suggested that BPD patients engage in self-harm to increase vagal tone in prefrontal areas resulting in improved regulation of emotions (10). A frontal-vagal network overlapping with functional nodes in the depression network, comprising dorsolateral prefrontal cortex (DLPFC), subgenual anterior cingulate cortex (sgACC), and the vagus nerve (VN), has been proposed as a target for neuromodulation treatments in depression, given the ability to impact heart rate and HRV (11). Therefore, the electrical stimulation of the vagus nerve (VNS) could potentially reduce emotional sensitivity and reactivity and improve affect regulation, with a potential downstream positive impact on general symptomatology and maladaptive behaviors in BPD patients.

Surgically implanted vagus nerve stimulation (iVNS) was approved in 2001 as an adjunct long-term treatment for treatment-resistant depression by the European Medicines Agency (EMA), and in 2005 by the Food and Drug Administration (FDA). Electrical stimulation of the vagus nerve provides stimulation to the nucleus tractus solitarii, which in turn modulates multiple regions of the brain via its neuronal connections to anatomically distributed subcortical and cortical regions of the brain. However, iVNS requires the surgical implantation of a pulse generator underneath the skin, connected to an electrode placed onto one of the branches of the cervical part of the vagus nerve (12). Surgical risks, technical challenges, and potential side effects have limited the use of iVNS in clinical practice.
Non-invasive transcutaneous vagus nerve stimulation (tVNS) methods have been developed to mitigate the risks of iVNS. There are currently two major ways to use tVNS. The first is to apply stimulation by using two skin electrodes by a hand-held device (e.g., gammaCore™, electroCore, Inc.) to the cervical portion of the vagus nerve (transcutaneous cervical vagus nerve stimulation or tcVNS) and the second is to apply stimulation by using two surface electrodes (e.g., NEMOS®, tVNS Technologies GmbH) to the ear (transcutaneous auricular vagus nerve stimulation or taVNS). In addition to these uses, a minimally invasive form of percutaneous auricular VNS (paVNS) can be performed with 2-3 miniature needle electrodes penetrating the skin in the targeted outer ear regions innervated mainly by the auricular branch of the vagus nerve (e.g., Auristim, DyAnsys) (13). The reason for ear stimulation (taVNS) is focused on anatomical studies that show afferent vagus nerve distribution in some parts of the ear (concha and lower half of the back ear over the mastoid process). It is thought that stimulation of the vagus nerve's auricular branch will stimulate the inferior ganglion, which projects to the nucleus tractus solitarii, and thus produce similar therapeutic effects to iVNS (14).

In addition to depression and epilepsy (major applications of iVNS), tVNS is also being studied for a variety of illnesses, including headache, tinnitus, atrial fibrillation, schizophrenia, and chronic pain (14). The mentioned tVNS approaches involve various devices and stimulation protocols (14). There is currently no strong data regarding the location and type of stimulation that is required to achieve a therapeutic effect. The most often used devices are gammaCore™ for stimulation at a neck site (FDA-authorized for acute and/or prophylactic treatment of primary headache) and NEMOS® for stimulation of the auricular branch of the vagus nerve on the ear (CE-marked for the treatment of epilepsy, depression, anxiety, pain and migraine). Most devices are battery-powered control units that allow patients to administer tVNS at home while doing other activities (for example, listening to music). The stimulation parameters used in studies of depressed patients range in stimulation frequency from 1.5 to 120 Hz, while the duration of stimulation ranges from 15-min at a frequency of 5 times per week, to 30-min at a frequency of twice per day (14). Not surprisingly, taVNS has been shown to modulate heart rate and HRV during the stimulation in a direction consistent with parasympathetic activation (15).

In animal studies, the stimulation of the vagus nerve through iVNS has been shown to produce an immediate dose-dependent anxiolytic effect (16) and to enhance fear extinction and reduce anxiety in a severe model of PTSD (17). In humans, tVNS has been shown to reduce anger outbursts in adults with Prader-Willi Syndrome (18), enhance recognition of emotions in healthy students (19), and improve depressive and anxiety symptoms in adults and adolescents with clinically-diagnosed depression albeit with uncertain evidence due to the scarcity of available controlled studies (20). Moreover, tVNS has shown to modulate amygdala functional connectivity in patients with depression (21). A single session of tVNS has been shown to acutely alter the recognition of briefly presented facial expressions of negative valence in adolescents with major depressive disorder (MDD) and increase emotion recognition in controls (22), as well as boost mood after prolonged effort exertion (23). In sum, tVNS has been shown to be safe and well-tolerated in humans at the doses tested, with local skin irritation being the most common side effect, followed by headache and nasopharyngitis (24).
To our knowledge, the effects of tVNS on emotional sensitivity and intensity/reactivity, return to emotional baseline, and emotion regulation in BPD has not yet been investigated.

**Objectives (7)**

The primary objective of the study is to assess the efficacy of one tVNS session compared to sham control to acutely reduce emotional reactivity in BPD patients. Secondary objectives are to assess the efficacy of one tVNS session compared to sham control to acutely a) reduce baseline emotional arousal, b) ease emotional recovery and c) improve emotional regulation in BPD patients.

**Trial design (8)**

This study will be conducted in accordance with SPIRIT guidelines for clinical trial protocols. The study will be a randomized, single-blind, sham-controlled trial with two parallel groups and repeated measures design.

Participants will be randomized to undergo a single 45-minutes session of either tVNS (intervention group) or sham-tVNS (control group) while undergoing an affect induction procedure. It will consist of the presentation of four (one neutral and three negative-affect-evoking) four-minute-long videos in sequence, each of which is followed by a four-minute post-induction period. The participants will rate the quality and intensity of their current self-reported emotions at baseline, after four-minutes tVNS (pre-induction ratings), after each video (post-induction ratings) and after four minutes after each video (recovery ratings) (Table 1).

**Methods: Participants, interventions and outcomes**

**Study setting (9)**

The study will be conducted on 42 outpatients with an established borderline personality disorder (BPD) diagnosis according to DSM-5. The participants will be recruited among those having an ongoing contact with the department of psychiatry for affective disorders at Sahlgrenska University Hospital in Gothenburg (Sweden).

**Eligibility criteria (10)**

Participants will be included in this study if they meet the following criteria: Swedish-speaking and able to provide informed consent to participate in the study; Female and between the ages 18 and 50 years old (the decision to include only women in the study is motivated by the higher frequency of BPD diagnosis in women and by the need to have a homogeneous study sample. The inclusion of men in future studies is not excluded); Current DSM-5 (Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition) diagnosis of BPD based on the Structured Clinical Interview for DSM-5 Personality Disorders (SCID-5-PD); Capable (in the Investigator's opinion) and willing to comply with all study requirements.
The participant will be excluded from the study if any of the following apply: Any unstable medical and/or neurological condition; Currently pregnant; Any significant neurological disorder or condition likely to be associated with increased intracranial pressure or cognitive impairment (e.g., a space occupying brain lesion, a history of stroke, a cerebral aneurysm, a seizure disorder, Parkinson's disease, Huntington's chorea, multiple sclerosis); Current diagnosis of delirium, dementia or another cognitive disorder secondary to a general medical condition; Established diagnosis of a developmental and neuropsychiatric disorder (e.g. Down syndrome, autism-spectrum disorder, ADHD); Non-correctable clinically significant sensory impairment (i.e., cannot hear or see well enough to complete the affect induction procedure, follow and answer the survey instructions and questions); Alcohol or substance use disorder (relating to opioids, cocaine, amphetamine or benzodiazepine) currently or within the past 1 month; Daily treatment with antiepileptics (e.g., carbamazepine, gabapentin, lamotrigine, levetiracetam, pregabalin, sodium valproate, topiramate) or benzodiazepines (last dose within 7 days before the screening to prevent eventual dampening of the central nervous system and/or vagus nerve excitability); Intracranial implant (e.g., aneurysm clips, shunts, stimulators, cochlear implants, or electrodes) or any other metal object within or near the head, excluding the mouth, that cannot be safely removed; History or diagnosis of bipolar or chronic psychotic disorder (e.g., schizophrenia, schizoaffective disorder).

The study will be performed by medical doctors.

Who will take informed consent? {26a}

Potential candidates will be referred to the study team by their caregivers or recruited on a voluntary basis by on site advertisements. The interested candidates will be contacted by the physician (investigator) over the phone to be informed about the study nature, to evaluate the potential interest in participating in the study and to preliminarily evaluate their eligibility. A copy of the informed consent will be sent via e-mail, by ordinary mail or given on site to the potential participants to give them time to read it before being invited to the laboratory and make a final decision about the eventual participation in the study. If interested, the participants will be invited to the lab to have further clarifications about the study procedure and their participation to the study and eventually sign the informed consent. The physician (investigator) will obtain informed consent from potential trial participants. The participant must personally sign and date the latest approved version of the informed consent form before any study specific procedures are performed.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

N/A. No other consents are needed from participants since the data collected will be used for the solely purpose of the study and no biological specimens will be collected.

Interventions

Explanation for the choice of comparators (6b)
Participant will be randomized to the active tVNS or sham tVNS. To reach an effective stimulation of the vagus nerve through tVNS, the electrode is placed at the left ear concha. The ear concha is principally innervated by the afferent branch of the vagus nerve (ABVN) (25). A common way to create a sham condition using tVNS is by attaching the stimulation electrodes to the center of the left ear lobe, which is known to be free of cutaneous vagal innervation (26) (Figure1). This method has the advantages that is well-known in literature, it is easy to use, and the participants can still feel a tickling sensation as for the active tVNS, making it more difficult to distinguish between the active and the sham conditions. The disadvantages are that the participants may have seen pictures of the active tVNS electrode placing leading to a possible unblinding and that the innervation of the ear lobe is still not completely clear leading to possible unwanted effects.

**Intervention description (11a)**

The participants will sit comfortably in front of computer monitor, with an adjustable height chair and will be reminded of potential provocative nature of the task (i.e., that the clips will contain profane language, sexual content, and violence). Three electrocardiographic (ECG) electrodes will be applied at the right collar and at the right and left lowest rib cage bones and two galvanic skin response (GSR) electrodes will be placed on the volar proximal phalanges of the fingers on the palms of the non-dominant hand. Participant will be instructed to maintain their visual attention to the computer monitor, avoid closing their eyes as much as possible, and will be told that the task is simply to immerse themselves into each video. Participants will be provided over-the-ear headphones, and the lights will be dimmed to further immerse participants into the videos. An investigator/research assistant will always remain seated quietly beside the participant but out the participant’s direct view.

A continuous ECG and GSR recording for the entire procedure will start and a baseline assessment of the current self-reported emotions using the Positive and Negative Affect Schedule (PANAS) (27), will be collected.

After the baseline assessment has been completed, the transcutaneous electrical vagus nerve stimulation, delivered through a tVNS device (tVNS® R - tVNS technologies, Germany), will start. First, the tVNS device will be described and the tVNS electrode positioned at either the ear concha (active tVNS) or ear lobe (sham tVNS). The device consists of a stimulation unit and an ear electrode that is worn like an earphone. The stimulation unit sends electrical impulses through the electrode, which stimulates a branch of the vagus nerve transcutaneously (through the skin) in the auricle. The device can stimulate at an intensity between minimum of 0.1 mA to a maximum of 5.0 mA with a biphasic waveform, an impulse duration of 28 sec on and 32 sec off and impulse frequency of 25 Hz. The stimulation intensity will be adjusted for every subject gradually by 0.1 mA at time until a tingling sensation or pulsation can be felt at the stimulation location. The stimulation should be clearly noticeable but not painful or uncomfortable. The device is CE-marked and approved for the treatment of following conditions: Anxiety, Asthma, Atrial Fibrillation, Autism, Cognitive Impairment, Crohn's Disease, Depression, Epilepsy, Fibromyalgia, Inflammation, Migraines, Parkinson's, Prader-Willi Syndrome, Sleep Disorders, Stroke, Tinnitus
Four minutes after the optimal stimulation dose has been reached, the affect induction procedure will start. The procedure, developed by Daros and colleagues has been shown to be able to evoke negative emotions in BPD patients (28). It consists in the presentation on a computer screen of four (one neutral and three affect evoking) four-minutes-long videos in sequence, each of which followed by a four-minutes post-induction period during which participants will rate the quality and intensity of the emotions perceived (PANAS) (post-induction ratings) and the perceived effectiveness in managing their emotions (PEME).

The neutral video depicts a mother attempting to show a father that their young son can play chess and elicited very low levels of emotions in an undergraduate sample (29). The three negative clips depicted a scene of domestic abuse between a man and pregnant female partner; a funeral scene where a young girl struggles with the death of her friend; and a scene involving sexual assault by a police officer toward a woman while her husband watches. The domestic abuse clip significantly increased negative mood in a community-sourced sample (30). The funeral clip elicited sadness in an undergraduate sample, whereas the sexual assault clip elicited anger, disgust, and contempt (29).

The titles and years of production of the films from which the videos are taken are *Searching for Bobby Fischer* (1993; neutral), *Nil by Mouth* (1997; domestic violence), *My Girl* (1991; funeral) and *Crash* (2004; sexual abuse).

After every post-induction period, for the three emotion inducing videos, the participants will have other 90 seconds to rate again the PANAS (recovery ratings) (see table 1). The neutral video will be always presented first to allow participants to orient themselves to the procedure. The three affect evoking videos will be instead presented in a random order using the “randomizer” function of a Qualtrics software (31) (see below). Each page will be locked with a visible timer to ensure that all participants will progress through the procedure at the same pace. If a participant will finish the questions in advance, he/she will be instructed to sit quietly until the next page appears.

At the end of the survey, participants will answer additional questions on the quality of their participation (PQE).

All the instructions, questions, videos and rating scales will be administered through an online Qualtrics survey (31), with time-fixed auto-advance according to the protocol defined exposition time for every step of the experiment (see table1).

The software IMotions (32) will be used to integrate the data collected from the Qualtrics Survey and from the ECG and GSR sensors.

**Criteria for discontinuing or modifying allocated interventions (11b)**

Each participant has the right to withdraw from the study at any time. In addition, the investigator may discontinue a participant from the study at any time if the investigator considers it necessary for any reason, including: ineligibility (either arising during the study or retrospective having been overlooked at
screening), significant protocol deviation, significant non-compliance with study requirements, an adverse event which requires discontinuation of the tVNS or results in inability to continue to comply with study procedures, emotional crisis which results in inability to continue to comply with study procedures or consent withdrawn.

The reason for withdrawal will be recorded in the electronic Case Report form (eCRF) (Qualtrics module) and in a research note in the patient research diary. If the participant is withdrawn due to an adverse event, the investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilized.

**Strategies to improve adherence to interventions {11c}**

The investigator will sit in the experiment room together with participant monitoring all the phases of the experiment and be available to help with any eventual problems or difficulties that may emerge in complying with the study procedure. All the instructions and the and the outcome scales will be administered on a computer screen using a Qualtrics survey with fixed time, enough to read the instructions and answer all the questions, and auto-advance (participants will not be able to advance to the next question by themselves). The participant will sit comfortably in front of a computer screen wearing a headset to reduce the influence of potential distracting environmental noise and facilitate the immersion in the task. A continuous ECG will be recorded throughout the experiment and an HRV analysis will be performed to be sure that tVNS was able to activate vagus nerve. The galvanic skin response (GSR) will be also measured throughout the entire procedure to control that the affect-inducing procedure was able to generate emotional arousal independently of the participants self-scores for emotional arousal. After the experiment completion, participants will be asked to evaluate the quality of their participation with questions on the perceived empathy with the video characters, eventual avoidance behaviors during the affect evoking procedure, the impact of the presence of the investigator in the room on their ability to attend the procedure, the level of attention during the task, the presence of eventual distractors or other barriers, suggestions to reduce the eventual burden of participation.

**Relevant concomitant care permitted or prohibited during the trial {11d}**

Participants consuming medications other than antiepileptics and benzodiazepines will be allowed to continue to consume them. No change in medications is required to participate in the study. Any medication taken during the study will be recorded in the eCRF (anamnestic module of the Qualtrics survey). Participants with an ongoing treatment with antiepileptics and benzodiazepines will be excluded from the study.

**Provisions for post-trial care {30}**

If the participant is withdrawn due to an adverse event, the investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilized. Eventual harm from trial participation will be covered by the Swedish ordinary patient injury insurance.
Outcomes (12)

The primary outcome will be the change in negative emotional arousal from baseline at immediately after the affect-induction (post-induction ratings) as assessed by PANAS. The emotional arousal will be measured through the self-reported ratings of negative emotions on the PANAS (PANAS-N) at five time-points (baseline, after the neutral video and after every of the three affect inducing videos or t1, t3, t4, t6 and t8) (See table 1). The means for the PANAS-N scores for each time point in which they are assessed will be used to test the null hypothesis of no difference between the tVNS and sham tVNS groups. The PANAS-N scores has already been used to measure the emotional arousal in previous studies using the same affect induction procedure with BPD patients and has been shown to be able to detect within and between groups differences (28). The GSR recording, a physiological measure of emotional arousal, will be performed throughout the entire procedure and used to validate the PANAS-N data.

Since an increased emotional reactivity/intensity, one of the three components of the emotional vulnerability together with emotional sensitivity and longer emotional recovery time, is central in the physiopathology of BPD and the underpinning for many of the related symptoms and dysfunctional behaviors (e.g., self-harm) (5), to test the effect of tVNS on this primary outcome may have direct clinical utility. The available psychological treatments are associated with an improvement in the emotional regulation of BPD patients but have uncertain effect on the underlying emotional vulnerability (33).

The secondary outcomes of the study include:

- Change in negative emotional arousal from baseline at prior to affect induction (pre-induction ratings) as assessed by PANAS.
- Change in negative emotional arousal from immediately after affect-induction at 4 minutes after affect induction (recovery ratings) as assessed by PANAS
- Perceived effectiveness in managing emotions (PEME) scores (0-9) during affect induction.

The change in negative emotional arousal from baseline at prior to affect induction measured through the PANAS-N scores have been included as a secondary outcome to test if tVNS can acutely reduce the baseline emotional arousal. It has been reported that BPD patients have higher resting-state emotional arousal levels, possibly explaining the elevated sensitivity to perceive emotion activation (i.e., emotion sensitivity) even with small emotional triggers (6). The means of the PANAS-N scores taken at baseline (t1) and 4 minutes after the tVNS/sham tVNS has begun, before the affect induction procedure (t2) (pre-induction scores), will be used to test the null hypothesis of no difference between the tVNS and sham tVNS groups.

In the same way, the change in negative emotional arousal from immediately after affect-induction at 4 minutes after affect induction has been chosen to test the effect of tVNS on the third component of emotional vulnerability (i.e., slow return to emotional baseline). The emotional arousal will be measured through the PANAS-N at six time-points, i.e., immediately after (t4, t6 and t8) and at 4 minutes after every of the three affect inducing videos (t5, t7 and t9). The means for the PANAS-N scores for each time point
in which they are assessed will be used to test the null hypothesis of no difference between the tVNS and sham tVNS groups.

The last secondary outcome will be the PEME during affect induction. Participants will be asked during postinduction period for each of the four videos (t3, t4, t6 and t8) about their perceived effectiveness in managing their emotions by asking them to rate “How difficult was it to manage your emotional response to this film clip?” from 1 = not at all to 9 = extremely. This scale will be interpreted as a subjective difficulty in regulating emotions in response to each video stimulus as done by Daros and coworkers (28).

**Participant timeline (13)**

Table 1. Schedule of enrolment, interventions, and assessments.

**Sample size (14)**

We are going to recruit 42 participants (21 participant per arm). The total sample size has been calculated using G*Power 3.1 Software to test an effect size of 0.25 with a power (1-\(\beta\))=0.8 for a sample with two independent groups (tVNS vs Sham-tVNS) and 4 dependent measures (PANAS-N score post-induction for neutral, funeral, sex-assault and domestic violence videos). The sample size needed is n=34. With an expected level of attrition of about 20%, the sample size has been increased by a factor of \(1/(1-0.2)=1.25\) or 25% to 42 subjects.

**Recruitment (15)**

The participants will be recruited among those having an ongoing contact with the psychiatry departments at Sahlgrenska University Hospital in Gothenburg, Sweden. The presence of a dedicated outpatient unit for personality disorder within the department of psychiatry for affective disorders with circa 1000 ongoing patients is expected to speed up the recruitment process to reach the target sample size. Potential candidates will be referred to the study team by their caregivers or recruited on a voluntary basis by on site advertisements. The interested candidates will be contacted by the investigator over the phone to be informed about the study nature, to evaluate the potential interest in participating in the study and to preliminarily evaluate their eligibility. A copy of the informed consent will be sent via e-mail, by ordinary mail or given on site to the participants to give time to read it before being invited to the laboratory and make a final decision about the eventual participation in the study.

**Assignment of interventions: allocation**

**Sequence generation (16a)**

The computerized random number generator is used to generate random sequences on a 1:1 basis. The random sequence will be put into a sealed, opaque, and sequentially numbered envelope by a team member not involved in the enrolment and investigation procedures. When the participant is admitted to the operating room the investigator will open the envelope to obtain a random sequence to determine the grouping. Participants with random sequences 1–21 are assigned to group tVNS, while 22–42 are
assigned to group sham tVNS. Each participant will be given a unique study sequential number on the envelope cover in the order of their participation in this study. The random sequences of all participants and its corresponding study sequential numbers will be recorded.

**Concealment mechanism (16b)**

Use of opaque sealed envelopes will ensure concealment until the interventions are assigned.

**Implementation (16c)**

A member of the research team not involved in the enrolment and investigation processes will generate the allocation sequence using a computer program and seal it in opaque envelopes. The envelopes will be handed over to the investigator that will open them according to the unique sequential number on the envelope at the intervention allocation.

**Assignment of interventions: Blinding**

**Who will be blinded (17a)**

Only the trial participants will be blinded (single-blind). The two treatments tVNS and sham tVNS will be potentially indistinguishable for participants but not for investigators, since both groups will perceive the electrical stimulation even if at two different locations at the ear (concha for tVNS and ear lobe for sham tVNS). The eventual collection of information by the participant on tVNS method and the correct positioning of the electrode to reach a stimulation of the vagus nerve, could lead to a potential unblinding for the participants too.

**Procedure for unblinding if needed (17b)**

In the event of an emergency, the investigator is to decide the necessity of unblinding the subject’s treatment assignment. If unblinding occurs, the investigator must record the reason for unblinding, as well as the date and time of the unblinding.

**Data collection and management**

**Plans for assessment and collection of outcomes (18a)**

**Data collection**

A Qualtrics Survey (31) module will be the electronic case report form (eCRF) and used as the source document for the anamnestic information collected at the screening and for all the baseline and subsequent assessments and evaluations with the exceptions of the two diagnostic interviews MINI and SCID-5-PD, that will be administered by the investigator in paper format.

**Screening**
The screening procedure will be completed at the lab after the informed consent is signed and before the study procedure will start, to check the eligibility to the study and collect background information that will be used to analyze and interpret the study results. The following information will be collected and recorded: Demographics (date of birth, gender), Medical History (details of any history of disease or surgical interventions), Concomitant Medication (all over the counter or prescription medication, vitamins, and/or herbal supplements); Physical Examination (height, weight and oral temperature; Resting pulse and blood pressure (BP) measurements will be measured after the participant has sat for at least five minutes). Substances assumed before the procedure (drugs, alcohol, nicotine, caffeine).

The BPD module of the SCID-5 PD and MINI will be administered to confirm the BPD diagnosis and exclude the diagnosis of bipolar disorder, alcohol or substance use disorder and history or diagnosis of bipolar or chronic psychotic disorder (e.g., schizophrenia, schizoaffective disorder).

**Borderline personality disorder general psychopathology**

The participants will complete the following additional self-report measures to assess BPD symptoms, self-harm and emotion dysregulation severity:

- **Difficulties in Emotion Regulation Scale (DERS)** to assess difficulties in emotion regulation. The DERS (34) is a 36-item self-report measure of six facets of emotion regulation. Items are rated on a scale of 1 (“almost never [0–10%]”) to 5 (“almost always [91–100%]”). Higher scores indicate more difficulty in emotion regulation (34).

- **Borderline Symptom List (BSL-23) and Borderline symptom list - behavior supplement (BSL-SUPP)** to quantify symptoms and behaviours associated with BPD. The Borderline Symptom List – Short Version (BSL-23) is a 23-item self-rating instrument for specific assessment of borderline personality disorder (BPD) symptomatology in adults (18+). The scale assesses DSM BPD diagnostic criteria (e.g., affective instability, recurrent suicidal behavior, gestures, or threats, or self-mutilating behavior, and transient dissociative symptoms) in addition to items that are based on borderline-typical empirical findings regarding self-criticism, problems with trust, emotional vulnerability, and proneness to shame, self-disgust, loneliness, and helplessness (35). The BSL-23 has a single factor structure and has excellent psychometric properties, with high internal consistency with a Cronbach's of 0.97 and test-retest reliability of 0.82 within 1 week (36).

**Self-reported Rating Measures**

The primary outcome will be measured through the PANAS (27). Before to undergo the tVNS and affect induction procedure, (“baseline” or t1), after 4-minutes tVNS and before the first video (“preinduction” or t2) and after each video (“postinduction” or t3, t4, t6 and t8), participants will be asked to provide affect ratings using the 20-item PANAS (27) (Table 1). The scale uses adjectives that describe mood states rather than discrete emotions and are rated from 1 = very slightly or not at all to 5 = extremely. The PANAS is used widely in mood induction procedures because of its good validity and test–retest...
reliability. At postinduction, participants provided self-report ratings on six basic emotions felt in response to each video (disgust, fear, anger, sadness, happiness, and surprise) on a scale from 1 = not at all to 7 = extremely. A total of 4-min after each negative video, participants provided another set of PANAS ratings to measure changes in mood over a longer period (“recovery” or t5, t7 and t9). The PANAS is a reliable and valid measure of the construct it is intended to assess (37)

Moreover, participants will be asked during postinduction about their perceived effectiveness in managing their emotions (PEME) by asking them to rate “How difficult was it to manage your emotional response to this film clip?” from 1 = not at all to 9 = extremely. This scale will be interpreted as a subjective difficulty in regulating emotions in response to each video stimulus.

Physiological Measurements

During the entire procedure continuous ECG recording in sitting position and a GSR will be performed using IMotions software (32) to integrate the sensors data with the affect-induction procedure and the self-reported measures.

For the ECG recording a 3-electrodes Shimmer 3 ECG device will be used. The electrodes will be placed at the right arm, right leg and left leg. The ECG recording will be used to measure the HRV variability as indicator of actual stimulation of vagus nerve in the tVNS group and as additional and indirect measure of emotion regulation in both groups.

For the recording of electrodermal activity (EDA, also known as galvanic skin response; GSR) recording will be used a 2 electrodes Shimmer GSR device. The GSR electrodes will be placed on the volar phalanges of the fingers (proximal, medial or distal) on the palms of the non-dominant hand. The GSR will be used to give an additional objective physiological measure of emotional arousal/intensity that in our hypothesis will parallel the PANAS ratings given by the participants.

Participation Quality Evaluation

After the completion of the stimulation procedure and assessment, the following additional questions will be administered to participant to evaluate the quality of their participation (Participation Quality Evaluation or PQE): *To what extent did you empathize with the characters in the film? (Repeated for all the four videos); Did you close your eyes during any of the videos in this part of the experiment? Did you feel extremely uncomfortable with regards to the content in the videos? Did you feel that you let yourself experience the emotions that you were experiencing? Was it difficult to do this because someone else was in the room with you? Had you seen any of the video clips used in this study before? How was your attention during the procedure? Was there anything distracting? Were there other barriers to your participation? Is there anything that could be improved or done to reduce your burden? Do you want to leave some other comments on something that you think is worthwhile or important?*

Plans to promote participant retention and complete follow-up (18b)
The study was designed to minimize as much as possible the burden for the participants. The entire procedure will be completed in a period of two hours during which the investigator will always be present in the room to assist the participant with all potential problems or difficulties experienced. In case of discontinuation of participation for any reason, the participant will be asked to complete the PQE (see above) to further assess the reasons for discontinuation if not directly expressed by the participant or evident to the investigator. A follow-up visit will be offered to the participant in case of discontinuation due to AE.

**Data management (19)**

eCRF entries will be considered source data since the CRF is the site of the original recording (e.g., there is no other written or electronic record of data). In this study the Qualtrics Survey module will be the eCRF and will be used as the source document for the anamnestic information collected at the screening and for all the assessments and evaluations.

All study data will be entered on the online Qualtrics Survey. Data will be protected in accordance with the "Qualtrics Security statement" (SOC 2 Type II Certification, ISO 27001, 27017, and 27018 Certifications, FedRAMP Authorization, HITRUST) and access available only to the research group. The data will be stored in the online Qualtrics Account owned by to the Principal Investigator (PI) and protected by a unique password.

The participants will be identified by a unique sequential study specific participants ID number and a unique randomization code. These two numbers will be recorded in the participant module in the IMotions software (32) and in the first page of the online Qualtrics Survey (31). The name and any other identifying detail will NOT be included in any study data electronic file. The data recorded in the IMotions software will be stored off-line in a dedicated computer, protected by a password that only the PI has access to.

All the other documents (e.g. MINI and SCID 5 PD) will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

**Confidentiality (27)**

The trial staff will ensure that the participants’ anonymity is maintained. The participants will be identified only by participant's ID number on the eCRF and any electronic database. All documents will be stored securely and only accessible by trial staff and authorized personnel. The study will comply with the Data Protection Act 1998 which requires data to be anonymized as soon as it is practical to do so.

**Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use (33)**

n/a. No biological specimens will be collected in this study.
Statistical methods

Statistical methods for primary and secondary outcomes (20a)

This is a randomized trial with repeated measures of a continuous outcome.

To address the repeated measures of same individuals (with ensuing issues with collinearity, and intra-individual variability) during the stages of the study (baseline, pre-induction, post-induction and recovery), mixed models with individuals as random effects will be used in the study (38). Potential covariates are factors collected at baseline. Treatment group, treatment state, and time will be entered as fixed effects to estimate effects from the sham/intervention effect at each time point. The mixed model can used for both continuous and dichotomous outcomes and will be applied as appropriate. As there are multiple possible variables and outcome measures in this study, adjustment for multiple tests could be necessary.

Interim analyses (21b)

No interim analysis is planned.

Methods for additional analyses (e.g. subgroup analyses) (20b)

The sample is small, so no subgroup analyses are planned a priori.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data (20c)

In case of missing response to the PANAS at any post-induction stage a mean value of other post-induction stage measurements will be used. Since the study is a single-session study under clinician oversight, we do not expect any missing variables.

Plans to give access to the full protocol, participant level-data and statistical code (31c)

Direct access will be granted to authorized representatives from the sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee (5d)

n/a. Not applicable to this research. This is a single-site academic study with a single meeting with every participant.

Composition of the data monitoring committee, its role and reporting structure (21a)

The study will be monitored by a local extern monitor independent from PI. The results of monitoring will be reported to the sponsor.
Adverse event reporting and harms {22}

All AE’s occurring during the study observed by the investigator or reported by the participant, whether or not attributed to the device under investigation will be recorded on the eCRF as specified in the protocol. All Adverse device effects (ADE) will be recorded in the eCRF.

The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to device, other suspect drug or device and action taken. Follow-up information should be provided as necessary.

The relationship of AEs to the device will be assessed by a medically qualified investigator or the sponsor/manufacturer and will be followed up until resolution or the event is considered stable.

All ADEs that result in a participant’s withdrawal from the study or are present at the end of the study, will be followed up until a satisfactory resolution occurs.

The Sahlgrenska University Hospital and the Department of Psychiatry for Affective Disorders will undertake an initial review of the information and ensure it is reported to the manufacturer. Events will be followed up until resolution, any appropriate further information will be sent by the research team in a timely manner.

Reporting to Läkemedelsverket will be done in liaison with the Chief Investigator and the Manufacturer.

In addition to the above reporting the Chief Investigator will submit once a year, throughout the trial, or on request a progress/safety report to Sahlgrenska University Hospital and Västra Götaland Region.

Frequency and plans for auditing trial conduct {23}

N/A. Not applicable to this research.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

The protocol, informed consent form, participant information sheet and any proposed advertising material have been submitted to the appropriate Research Ethics Committee (Etikprövningsmyndighet), regulatory authorities (Läkemedelsverket), and host institution (Sahlgrenska University Hospital) for written approval. The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

Dissemination plans {31a}

All results will be published in peer-reviewed scientific journals and all contributing authors will be included in accordance with the Vancouver recommendations.
Discussion

We have described our protocol for a randomized controlled trial to evaluate the efficacy of one tVNS session to acutely decrease emotional vulnerability and increase emotional regulation in patients with BPD.

To our knowledge this is the first study investigating the effect of tVNS in this patient group and the first trying to investigate in general the efficacy of tVNS in modulating emotional reactivity and emotional recovery in general.

We believe that our study will help to better understand the involvement of vagal tone in emotional vulnerability and regulation in BPD patients and possibly lead to the development of new treatment strategies. If tVNS will be shown to be efficacious in acutely reducing emotional reactivity and/or recovery in BPD patients, this method could be used as preventive or “as needed” intervention in these patients when confronting with emotionally loaded situations or to manage emotional crisis and in this way avoid dysfunctional self-regulating behaviors like, for example, self-harm or drug abuse. Moreover, in case of acute efficacy of tVNS on emotional vulnerability and/or emotional regulation there could be a potential for new treatment strategies for other psychiatric disorders characterized by emotional dysregulation and low vagal tone such as post-traumatic stress syndrome.

Trial status

tVNS-BPD-001, 10/OCT/2022 v.1.0. The recruitment began the 24/MAR/2023 and is expected to be completed the 31/SEP/2023

Abbreviations

ADE, Adverse Device Effect; AE, Adverse event; BPD, Borderline personality disorder; BSL-23, Borderline Symptom List 23; BSL-SUPP, Borderline symptom list - behavior supplement; DERS, Difficulties in Emotion Regulation Scale; ECG, Electrocardiogram; eCRF, Electronic case report form, GSR; Galvanic skin response; HRV, Heart Rate Variability; iVNS, Invasive Vagus Nerve Stimulation; MDD, Major Depressive Disorder; MINI, The Mini International Neuropsychiatric Interview; PANAS, Positive and Negative Affect Schedule; paVNS, Percutaneous auricular vagus nerve stimulation; PEME, Perceived Effectiveness in Managing Emotions; PI, Principal Investigator; PQE, Participation Quality Evaluation; SCID-5-PD, Structured Clinical Interview for DSM-5 Personality Disorders; taVNS, Transcutaneous auricular vagus nerve stimulation; tcVNS, Transcutaneous cervical vagus nerve stimulation, tVNS, Transcutaneous vagus nerve stimulation.

Declarations

Acknowledgements
We would like to thank Urban Norén for setting up randomization and Niklas Liljedahl for the important input on trial design.

Authors’ contributions

GG and SS designed the trial. GG will coordinate recruitment and data collection. GG and MLM will coordinate recruitment and data collection. GG, SS and HC prepared the statistical analysis plan. The statistical analysis will be led by HC. GG, SS, AD and AR developed the content of interventions. GG, SL, HC, MLM, AD, AR and SS contributed to the writing of the manuscript and approved the final version.

Funding

The study is funded by the Sahlgrenska Universitetssjukhus – Founder with the amount of 100 000 Swedish crowns for the year 2022.

Availability of data and materials

Direct access will be granted to authorized representatives from the sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

Ethics approval and consent to participate

The Investigator will ensure that this study is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996. The protocol, informed consent form, participant information sheet and any proposed advertising material have been approved by the Swedish Research Ethics Committee (Etikprövningsmyndighet), the 18 Nov 2022 with the diary number 2022-05841-01. Written, informed consent to participate will be obtained from all participants.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References


Table 1

Table 1 is available in the Supplementary Files section.

Figures

![Figure 1](image)

**Figure 1**

Positioning of the stimulation electrodes in the active (left) and in the sham (right) condition.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.doc