Trials

STUDY PROTOCOL

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Safety and effectiveness of transcutaneous auricular vagus nerve stimulation on patients with depersonalization-derealization disorder: study protocol for a randomized controlled trial

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Abstract

Background Depersonalization-derealization disorder (DPD) is a complex psychiatric condition marked by profound and often relentless feelings of detachment from one's self and surroundings. Transcranial electrical stimulation (taVNS) holds promise as a potential therapeutic approach for DPD. This study aims to investigate the safety and efficacy of taVNS in treating DPD.

Methods DPD patients were recruited as research subjects and randomly allocated to the experimental and control groups, with the former receiving active-taVNS treatment and the latter receiving sham stimulation treatment for 6 weeks. The efficacy of taVNS in treating DPD was evaluated by comparing scores for DPD symptoms, depression and anxiety symptoms, cognitive function, and social function before and after treatment between the two groups. The safety of taVNS in treating DPD was assessed by comparing general safety assessment results between the two groups of DPD patients.

Discussion This study will assess taVNS as a potential treatment for DPD, evaluating its safety, efficacy, and impact on patient outcomes and societal burden.

Trial registration Chinese Clinical Trial Registry, ChiCTR2300078183, Registered on 30 November, 2023, https://www.chictr.org.cn/showproj.html?proj=206119

Keywords Transcutaneous auricular vagus nerve stimulation, Depersonalization-derealization disorder, Effect

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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/).

Title {1}	Safety and effectiveness of transcutaneous auricular vagus nerve stimulation on patients with depersonalization-derealization disorder: Study protocol for a randomized controlled trial
Trial registration {2a and 2b}.	Chinese Clinical Trial Registry, ChiCTR2300078183, 。 Registered on 30 November, 2023, https://www.chictr.org.cn/showproj.html?proj=206119
Protocol version {3}	Protocol version 1, 2023-11
Funding {4}	This study is funded by Beijing Municipal Administration of Hospitals Incubating Program (PZ2023032)
Author details {5a}	1 The National Clinical Research Center for Mental Disorders & Beijing Key Laboratory of Mental Disorders, Beijing Anding Hospital, Capital Medical University, Beijing, 100088, China 2 Advanced Innovation Center for Human Brain Protection, Capital Medical University, Beijing, 100088, China
Name and contact information for the trial sponsor {5b}	This study was sponsored by Beijing Anding Hospital affiliated to Capital Medical University.
Role of sponsor {5c}	This is an investigator-initiated trial. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The investigators retain full control over all study-related decisions.

Introduction

Background and rationale {6a}

Imagine living in a world where you feel like a spectator in your own life. This is the reality for individuals battling depersonalization-derealization disorder (DPD), a complex psychiatric condition marked by profound and often relentless feelings of detachment from one's self and surroundings [1]. Strikingly emerging during the crucial developmental phase of adolescence, typically between the ages of 15 and 19, DPD plunges about one third of its sufferers into sporadic yet haunting episodes, with some enduring these experiences for months or even years [2–4]. As the disorder progresses, the frequency and intensity of these episodes often increase, severely disrupting social and cognitive functions and drastically diminishing the quality of life for those affected [5–7]. Alarmingly, despite affecting approximately 1% of the population, effective treatment options for DPD remain woefully limited [1].

Studies in the field suggest that serotonin reuptake inhibitors (SSRIs) may be helpful for DPD [8, 9], while more extensive placebo-controlled trials of fluoxetine have found no benefit [10]. Hollander et al. found that fluoxetine alleviates distress and concern caused by DPD without actually improving the depersonalization or derealization symptoms [11]. Therefore, SSRIs or clomipramine used alone are not suitable for treating DPD, and their use for patients with significant anxiety and depression symptoms may increase tolerance for DPD symptoms. Additionally, clinical evidence suggests that lamotrigine does not work alone [12]; two studies have found varying degrees of improvement in DPD patients when lamotrigine is used in combination with SSRIs [13, 14]. However, these results require further rigorous research to confirm. Naltrexone is an intravenous drug that can improve the symptoms of DPD [15], but it is not a practical long-term solution for treating DPD. Trials of clonazepam and SSRIs used in combination to treat DPD have been conducted, but the lack of controlled studies means that there is no clear conclusion [16]. Although psychological therapy can help patients understand or cope with symptoms of DPD, it does not explicitly alleviate DPD symptoms. Only a few studies have found cognitive-behavioral therapy and hypnosis to be effective for DPD [17–23]. A small sample study indicated that repetitive transcranial magnetic stimulation could improve self-identity deficits in some DPD patients [24], but the overall effectiveness for symptoms was low. Further clinical research is needed to confirm the efficacy of transcranial magnetic stimulation for DPD.

In the quest to unravel the mysteries of DPD, recent research has shed light on the potential role of corticolimbic disconnections, as proposed by Sierra and Berrios [25]. This theory, bolstered by compelling evidence from functional magnetic resonance imaging (fMRI) and PET studies, points to a fundamental disruption in brain connectivity as a cornerstone of DPD [26–29]. Enter the transcutaneous auricular vagus nerve stimulation (taVNS), an innovative approach that melds the ancient wisdom of acupuncture with modern neuroscientific understanding. By targeting specific ear acupoints, taVNS activates vagal afferents, stimulates the nucleus solitarius neurons, and engages the nucleus solitarius-insula-default mode network pathway, offering a promising avenue to alleviate symptoms of depression [30, 31].

The auricular nerve branch of the vagus is responsible for transmitting sensory information to the ear. Sensor fibers in the central region of the external ear are located

closer to the auricular cymba concha. The sensory neurons of the ear vagus nerve travel to the inferior ganglion and then deliver their signals to the solitary tract nucleus in the brainstem. The solitary tract is the primary recipient of sensory input from several vagus nerve branches and transmits signals to other body regions, including the locus coeruleus. The reticular activating system is a significant source of adrenaline-secreting projections that extend to the cortex, subcortex, and brainstem [32]. Evidence suggests that the locus coeruleus stimulation is responsible for most observed therapeutic effects of VNS and taVNS. Neuronal firing in the locus coeruleus results in a significant discharge of norepinephrine in the thalamus and hippocampus, a vital component of the noradrenergic pathway that controls alertness, arousal, and the fight-or-flight response [32]. The human vagus nerve stimulates metabolic processes in the forebrain, thalamus, and reticular formation. It also controls functions in the brainstem, the nucleus of the solitary tract, dorsal raphe nuclei, the amygdala, and the hippocampus [32].

Imaging studies conducted on DPD patients suggest that functional abnormalities exist in the neural circuits of the prefrontal cortex-edge and para-edge structures-post-cortical somatosensory related areas. Studies conducted on healthy individuals and depression patients have shown the modulation of activities in brain regions, such as the amygdala, insula, and frontal lobe, by VNS through the solitary tract nucleus-edge lobe network. This protocol systematically explores the relationship among DPD symptoms, vagus nerve function, and neuroimaging and investigates the neuroimaging mechanism of taVNS in producing therapeutic effects on DPD, which may provide a basis for further mechanism study and clinical practice.

Objectives {7}

This study posits a groundbreaking hypothesis: taVNS is safe and effective in treating DPD. Our research explores how this non-invasive technique modulates neural activity through vagus nerve stimulation, particularly in the prefrontal cortex and associated sub-cortical and cortical somatosensory-related areas. This has the potential to transform the therapeutic landscape for DPD, offering a novel, economical, and painless treatment modality. With no existing studies delving into the efficacy of taVNS for DPD, our research stands at the forefront of a possible paradigm shift in treatment, promising to alleviate the suffering of those plagued by this enigmatic disorder. The protocol is based on the SPIRIT reporting guidelines [33].

Trial design {8}

This is a randomized controlled, parallel-group, exploratory study with two groups: an active-taVNS group (test group) or a sham-taVNS group (control group). Before the initiation of the study, all participants will provide voluntary written informed consent to enroll in the screening phase.

During the screening phase, a self-designed general information questionnaire will be administered to collect the participants' general demographic and disease-specific data. Two or more attending psychiatrists then will evaluate whether the participants meet the DSM-5 diagnostic criteria. Laboratory tests will be administered to confirm that the participants meet the inclusion criteria.

Participants who pass the screening phase will move forward to the baseline phase, where the primary investigator will evaluate their overall condition and safety. Additionally, trained assessors will conduct symptom, cognitive, and social function assessments. Traditional Chinese medicine specialists will assess the participants' condition before MRI scans performed by imaging technicians. After completing all assessments, the participants will progress into the randomized treatment phase.

During the randomized treatment phase, participants will be randomly allocated into a 1:1 ratio to receive either active-taVNS or sham-taVNS twice daily for 6 weeks. The corresponding personnel will conduct symptom, cognitive, social function, and safety assessments at the conclusion of the second, fourth, and sixth weeks. The imaging technicians administered MRI scans of the participants' heads after week 6. The experiment process is shown in Fig. 1.

Methods: participants, interventions, and outcomes

Study setting {9}

This study enrolled participants who sought outpatient treatment at the Beijing Anding Hospital Capital Medical University between December 1, 2023, and November 30, 2025.

Eligibility criteria {10}

Following agreement from the participants' guardians, a psychiatrist reviewed them based on eligibility criteria. Those who met the criteria were invited to participate in the study.

The inclusion criteria are as follows: (1) patients diagnosed with depersonalization disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), a score greater than 70 on the Cambridge Depersonalization Scale (CDS); (2) age between 18 and 40 years old (inclusive); (3) comprehension of follow-up questionnaire survey; (4) no use of antipsychotic medication or the types and dosage of drugs were stable for 6 weeks and did not receive acupuncture treatment; (5) able and willing to complete data

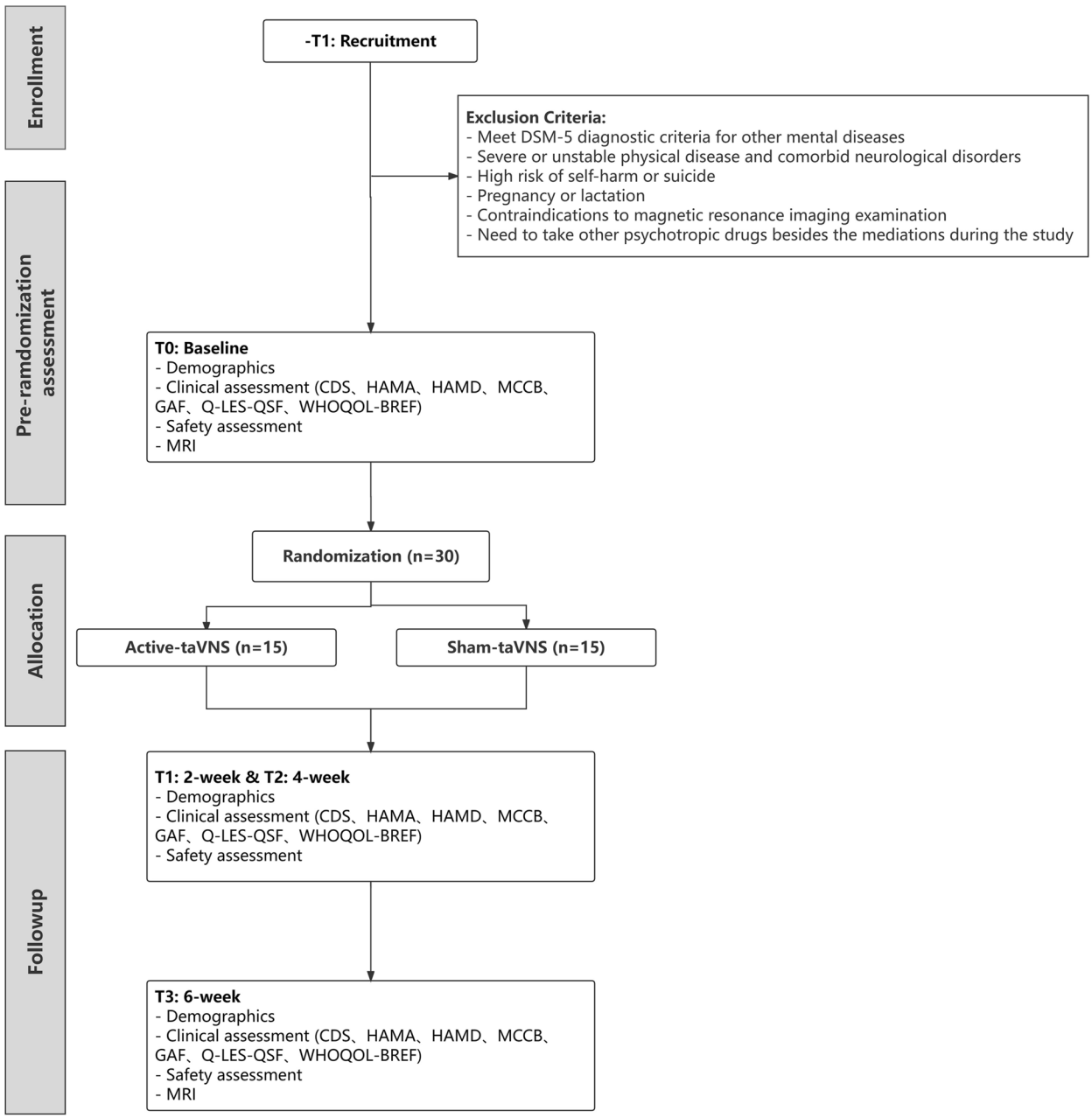

Fig. 1 Experiment process

collection through magnetic resonance imaging; and (6) signed informed consent form and follow the research plan.

The exclusion criteria are as follows: (1) meet DSM-5 diagnostic criteria for other mental diseases except for depersonalization disorder, such as schizophrenia, bipolar disorder, depression disorder, panic disorder, acute stress disorder, post-traumatic stress disorder, or other separation disorders; (2) severe or unstable physical disease and comorbid neurological disorders; (3) high risk of self-harm or suicide; (4) pregnancy or lactation; (5) contraindications to magnetic resonance imaging examination; (6) need to take other psychotropic drugs besides the regulations during the study.

Who will take informed consent? {26a}

The sub-investigators (SI) will be responsible for subject screening during the trial screening period.

Patients in the ward who may be eligible for enrolment will be selected and informed about the trial.

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

Patients will sign a separate informed consent form for storage of samples in a biobank for future research projects.

Interventions

Explanation for the choice of comparators {6b}

We chose sham-taVNS as the control group as it is essential for several reasons. Firstly, it helps control the placebo effect, ensuring that any observed therapeutic effects are due to actual taVNS rather than participants' psychological expectations. Secondly, it maintains the scientific rigor of the study by ensuring consistency between the control and experimental groups, with only the authenticity of the stimulation differing. Additionally, in a double-blind trial, sham-taVNS ensures that neither participants nor researchers know the group assignments, avoiding potential bias. Lastly, demonstrating that actual taVNS is significantly more effective than sham-taVNS enhances the persuasiveness of the clinical trial and provides strong scientific evidence for the treatment's efficacy.

Intervention description {11a}

The Huatuo brand of electronic acupuncture instrument (SDZ-IIB type, SuZhou Medical Supplies Factory Co., Ltd.) was used in this study to stimulate the vagus nerve through ear acupuncture. The electrodes stimulated the auricular and earlobe areas of both ears. The therapy was administered twice daily for 30-min sessions, 5 days weekly, over 6 weeks. In the active-taVNS group, the therapy involved using a density wave of 20 Hz and pulse width of 0.2 ms ± 30%, current of ≤ 50 mA (500Ω load impedance), using painless intensity. The sham-taVNS group did not receive any pulse stimulation. Both groups have a duration of 6 weeks.

Criteria for discontinuing or modifying allocated interventions {11b}

The dropout criteria are as follows: (1) withdrawal of informed consent by the participant; (2) suicidal behavior during the trial period; (3) serious adverse events during the trial period; (4) participant's withdrawal deemed necessary for safety or efficacy; (5) poor adherence to study protocol by participant; (6) participant seriously violates trial protocol; (7) pregnancy during the study period; (8) lost to follow-up.

Strategies to improve adherence to interventions {11c}

The project will be coordinated and managed under the organization and leadership of the project leader. There will be designated personnel responsible for subject enrollment, clinical evaluation, and testing to ensure the progress and quality of the project. One project coordinator will be appointed to handle inter-departmental coordination, the organization of training, and communication meetings as well as the procurement of equipment and consumables required for the project. The project leader will organize group meetings once every quarter to monitor the project's progress, promptly identify any issues in the implementation, and formulate solutions.

Two quality control personnel and two data verification personnel will be appointed. Before the project starts, a quality control plan for the project's implementation will be established, adhering strictly to the technical route and executing procedures and management systems for data collection, entry, and database management. After the project's initiation, there will be regular checks for quality and technical issues during the project's implementation, with timely feedback and corrections to ensure the quality of the project's execution.

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

Prohibited treatments

From the start of patient screening until the end of the treatment period, the use of the following medications or therapies is prohibited:

1) Any antipsychotic drugs, anti-anxiety medications, mood stabilizers (including anticonvulsants such as sodium valproate and carbamazepine)
2) Traditional Chinese medicines for treating central nervous system diseases
3) Electroconvulsive therapy, transcranial magnetic stimulation, transcranial direct current stimulation, and similar treatments
4) Systematic psychotherapy (e.g., psychoanalysis, cognitive insight therapy, desensitization therapy, hypnotherapy, etc.), although general supportive psychotherapy is allowed

Permitted concomitant treatments

1) For severe insomnia, sedative-hypnotic drugs may be used at night, with the total duration (including continuous and intermittent use) not exceeding 2 weeks. The permitted sedative-hypnotic drugs and their maximum dosages are as follows:

2) Non-benzodiazepine medications: zolpidem (not exceeding 10 mg/day, orally at bedtime), zaleplon (not exceeding 10 mg/day, orally at bedtime), zopiclone (not exceeding 7.5 m g/day, orally at bedtime), eszopiclone (not exceeding 3 mg/day, orally at bedtime)
3) Benzodiazepine medications: diazepam (not exceeding 10 mg/day, orally at bedtime), flurazepam (not exceeding 30 mg/day, orally at bedtime), alprazolam (not exceeding 0.8 mg/day, orally at bedtime), estazolam (not exceeding 2 mg/day, orally at bedtime), lorazepam (not exceeding 4 mg/day, orally at bedtime)
4) If agitation or excitability occurs, benzodiazepine medications (such as diazepam, flurazepam, alprazolam, estazolam, clonazepam, lorazepam) may be taken orally as needed. The dosage should not exceed the equivalent of 6 mg of lorazepam per day, and continuous use is not recommended (not more than three consecutive days, with a total treatment duration not exceeding 6 days)
5) Avoid using the aforementioned treatment medications within eight hours before scale assessment
6) For general somatic diseases, symptomatic treatment is allowed. For medications that need to be used long-term, it is recommended to maintain the same types and dosages during the study period

Provisions for post-trial care {30}

Upon the termination of the study, participants who are identified as needing further treatment will be assisted in finding suitable and appropriate follow-up care.

Outcomes {12}

Primary outcomes

The study's primary outcome is the change in the CDS score during the 6-week treatment period.

Secondary outcomes

Secondary evaluation measures are as follows: (1) changes in symptom evaluation at each visit during the 6-week treatment period, (2) changes in cognitive function scores at each visit during the 6-week treatment period, (3) changes in CDS and social function scores at each visit during the 6-week treatment period, (4) changes in rs-fMRI before and after the 6-week treatment period, and (5) changes in safety assessment at each visit during the 6-week treatment period will be analyzed to assess the efficacy and safety of the treatment. The detailed information of these assessments were described in the "Plans for assessment and collection of outcomes {18a}" section.

Participant timeline {13}

The participant timeline is shown in Table 1.

Table 1 Participant timeline

Timepoint	Pre-study screening/ consent	Baseline	Weeks 1 ~ 2	Weeks 3 ~ 4	Weeks 5 ~ 6
Enrollment					
Eligibility screen	×				
Informed consent	×				
Allocation	×				
Demographic information	×				
Medical history and treatment history	×				
Inclusion/exclusion form	×				
Clinical assessment					
CDS		×	×	×	×
HAMA		×	×	×	×
HAMD		×	×	×	×
MCCB		×	×	×	×
GAF		×	×	×	×
Q-LES-QSF		×	×	×	×
WHOQOL-BREF		×	×	×	×
Safety assessment		×	×	×	×
MRI		×			×
Intervention			×	×	×

Sample size {14}

It is hypothesized that active-taVNS will demonstrate a higher efficacy compared to sham-taVNS. While Cohen's conventional criteria suggest an effect size of 0.8 for a large effect, this threshold may be conservative for interventional studies. Gülkesen et al. [34] demonstrated that effect sizes larger than 0.8 can be reasonably anticipated in clinical interventions. Therefore, based on clinical expertise and the typically substantial immediate effects observed in taVNS interventions, we set a more ambitious effect size (d) of 1.2. Utilizing the "Two-sample T-tests using Effective Size" program within PASS 15 and setting the effect size (d) at 1.2 with a power of 0.8, it is calculated that a sample size of 12 individuals per group is required. Considering a dropout rate of 20%, each group will include 15 participants to ensure robustness in the study's findings.

Recruitment {15}

The study will recruit participants from Beijing Anding Hospital, Capital Medical University. All clinical personnel at the recruitment site will have access to an information sheet about the study, which they can present and discuss with patients. If this is still insufficient to recruit enough participants, advertisements with information about the study will be posted.

Assignment of interventions: allocation

Sequence generation {16a}

The participants were randomly assigned to either an active-taVNS group or a sham-taVNS group using a random number table generated by the SAS statistical software proc plan by the person in charge of statistics. The random number corresponds to the patient's enrollment sequence number.

Concealment mechanism {16b}

The sequence will be sealed in opaque envelopes and provided to the investigator.

Implementation {16c}

A research team member blinded to participant enrollment and assessment will generate the allocation sequence using a computer-generated random number program. The sequence will be sealed in opaque envelopes and provided to the investigator. Envelopes will be opened sequentially at the time of intervention allocation based on a unique identifier.

Assignment of interventions: blinding

Who will be blinded {17a}

An unaffiliated person will handle this task to maintain objectivity. Neither the evaluators nor the statisticians will have access to the allocation order. Additionally, healthcare personnel and therapists will not be notified of patients' random number assignment following the evaluation of baseline data.

Procedure for unblinding if needed {17b}

In the event of an emergency, if the investigator deems it necessary to unblind and gain insight into the treatment administered to the subject for the purpose of managing adverse events, unblinding may be initiated. This process should be executed by the investigator and meticulously recorded, encompassing the rationale for unblinding, the timestamp, the location, and the investigator's signature along with the date. Subsequent to unblinding, the case will be regarded as a dropout case, and all case data should be diligently preserved in its entirety.

Data collection and management

Plans for assessment and collection of outcomes {18a}

Participants will complete demographic information, symptom evaluation, cognitive function assessment, social function assessment, and fMRI at baseline and the end of sixth week.

Demographic information

A self-made general information questionnaire was used to collect demographic information such as gender, age, occupation, education years, and disease-related information.

Symptom evaluation

The CDS [35] was used to evaluate depersonalization symptoms in patients with DPD; the Hamilton Anxiety Scale (HAMA) [36] and Hamilton Depression Scale (HAMD) [37] were used to assess anxiety and depression symptoms in patients with DPD. The Chinese version of CDS demonstrates moderate test–retest reliability ($r=0.651$) and excellent internal consistency and split-half reliability (Cronbach's $\alpha=0.938$, Guttman split-half coefficient = 0.957). The criterion-related validity is satisfactory (Mann–Whitney $Z=-6.059$, $p<0.001$). The item-total correlation coefficients range from 0.321 to 0.777, all reaching statistical significance, indicating acceptable construct validity [38]. The reliability coefficient for total scores, as evaluated by a collaborative group from 14 psychiatric departments in China, ranges from 0.88 to 0.99 ($p<0.01$). In terms of validity, the empirical authenticity coefficient for clinical symptom severity is 0.92 [39]. The HAMA shows a total score reliability of 0.93, with reliability coefficients for individual symptom assessments ranging from 0.83 to 1.00. Furthermore, it effectively reflects the severity of anxiety states (coefficient = 0.36) [40].

Cognitive function assessment

The assessment employs the MATRICS Consensus Cognitive Battery [41]. The Trail Making Test A and Symbol Coding Test evaluate information processing speed, while the Hopkins Verbal Learning Test-Revised assesses word learning ability. The Brief Visuospatial Memory Test-Revised evaluates visual memory, and the Continuous Performance Test measures attention/alertness, with the Stroop Color-Word Test assessing attention inhibition. The test–retest reliability coefficients for the 10 MCCB tests range from 0.73 to 0.94, with a composite score reliability of 0.95 [42].

Social function assessment

The Global Assessment Function (GAF) [43] and the Short Form of Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-QSF) [44] are used to assess the social function, happiness, life quality, and satisfaction of patients with DPD. In contrast, the World Health Organization Quality of Life – BREF (WHOQOL-BREF) [45] is used to evaluate their quality of life and satisfaction comprehensively. The Chinese version of Q-LES-QSF and WHOQOL-BREF demonstrates satisfactory psychometric properties, with good internal consistency (overall $\alpha = 0.89$) and acceptable reliability across domains ($\alpha = 0.67–0.78$), while confirmatory factor analysis supported its four-factor structure (χ^2 (244) = 1836, RMSEA = 0.088, CFI = 0.909) and showed good discriminant validity between healthy individuals and those with chronic illness [46]. Internal consistency data revealed a high reliability evidenced by internal consistency Cronbach's α (0.87) for the Chinese Q-LES-Q-SF [47].

Safety assessment

Safety assessment involves collecting various indicators, including physical examination, vital signs, blood routine, urine routine, biochemistry, electrocardiogram, and other relevant measures. This assessment mainly focuses on measuring different health parameters to ensure an individual's safety and well-being. These indicators have been proven reliable in assessing an individual's health status and detecting potential health risks. Thus, it is crucial to conduct a comprehensive safety assessment using these various indicators to ensure the accuracy and reliability of the results. The trial will be terminated if the following conditions occur:

(1) If significant safety issues arise during the trial, the clinical study should be promptly halted
(2) If the trial reveals insufficient or negligible therapeutic effects of the investigational drug, rendering it clinically nonviable
(3) Challenges in assessing treatment efficacy may arise due to critical errors in the clinical trial protocol or substantial deviations in implementation, hindering the evaluation of treatment outcomes
(4) The applicant or regulatory authority may request the experiment's termination
(5) Upon early termination or upon study completion, the investigator will discontinue free transauricular vagus nerve stimulation treatment for participants. Patients will then be scheduled for an outpatient consultation to devise a future treatment plan

MRI MRI was conducted using a Siemens Magnetom Trio 3.0 TMR scanner. To minimize noise and head movement, participants lay flat on the scanning bed with a foam pad on their heads.

Resting-state functional magnetic resonance imaging (rs-fMRI) was utilized to extract the brain's spontaneous activity, static and dynamic functional connections, and functional network properties that reflect the brain's functional state. Data acquisition used a multilayer, simultaneously acquired gradient echo planar imaging sequence. The reference scanning parameters were axial, with TR/TE = 600/30 ms, flip angle = 90°, matrix = 80 × 80, FOV = 240 × 240 mm, slice thickness = 3 mm, no gap, number of layers = 50, number of frequency bands = 6, and parallel acceleration factor = 2. The resting state scan ended after a continuous scan of 8 min and 10 s. The high-resolution structural scan was acquired with the following parameters: voxel size = 1 mm^3, TR = 2530 ms, TE = 3.39 ms, flip angle = 90°, matrix = 256 × 256, field of view = 256 × 256 mm, slice thickness = 1 mm.

Plans to promote participant retention and complete follow-up {18b}

The assessors will contact participants who cancel or do not show up at appointments by phone and, if no contact is made, send the participant a letter according to established clinical routines.

Data management {19}

Prior to commencing participant enrollment

Research personnel will undergo comprehensive training on the completion of case report forms (CRFs) and scale scoring. This training aims to clarify the operational procedures outlined in the protocol, ultimately enhancing the consistency and reliability of the data.

Throughout the participant enrollment phase

Rigorous measures will be taken to verify the accuracy and completeness of all data records and reports. All forms will be meticulously filled out, ensuring alignment with the original data. Pertinent information for each subject, encompassing treatment modifications, concurrent medication, instances of loss to follow-up or withdrawals, and missed assessments, will be duly confirmed and documented.

Upon the culmination of participant enrollment

An exhaustive examination of the CRF records will be conducted to confirm the rectification of all errors or omissions. Corrections or annotations will be endorsed with the investigator's signature and date. Any inquiries arising from identified discrepancies will be promptly addressed, either through supplementation, correction, or explanation by the investigator. Furthermore, a dedicated data manager will undertake a secondary review of the scrutinized CRFs, with the objective of identifying any latent issues that may have previously evaded detection. This review process will facilitate subsequent supplementation or correction efforts.

During the data entry phase

Thorough data validation procedures will be applied, encompassing the detection and resolution of logical and other potential issues using established software programs. To ensure data accuracy, a dual data entry approach utilizing EpiData software will be implemented.

Confidentiality {27}

Each participant will be given a code upon enrollment. The statistics team will only see patient codes, and real information will not be disclosed. The statistics team will have access only to de-identified patient codes, and no real identifying information will be disclosed to them. Participant details will be securely stored on EpiData accessible only to authorized members of the trial team, including individuals from the Sponsor organization or relevant center sites where required for the trial. Access rights to the dataset will be limited to qualified personnel who are essential to the trial's conduct and oversight.

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

Blood samples collected in this study will be stored in the biobank of Beijing Anding Hospital for future safety and mechanistic analyses.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

Statistical analysis will be calculated using the SPSS 22.0 software. Based on the intention-to-treat principle, the primary efficacy evaluation will use the Full Analysis Set (FAS), which includes all subjects who have undergone baseline assessment and randomization. All statistical tests will be two-sided, and a p-value ≤ 0.05 will be considered statistically significant for the tested difference.

The measurement data for each visit of the subjects will be statistically described using mean ± standard deviation. For inter-group comparison of measurement data, T/Mann–Whitney-Wilcoxon tests will be selected based on the data distribution. The inter-group comparison of count data will be performed using the χ^2 test or Fisher's exact probability test. Changes in the scale scores relative to the baseline will be analyzed using a mixed-effects model repeated measures, where the change values at each time point before and after treatment will be used as the dependent variables, baseline scale scores will be used as covariates, grouping will be considered as a fixed effect, and intergroup differences will be presented and explained using adjusted means and their 95% CI.

The Rs-fMRI data analysis is as follows: the rs-fMRI data were preprocessed using the Data Processing Assistant and Resting-State fMRI (DPARSF) software package. Preprocessing steps included removal of the first ten time points, slice timing correction, motion correction, spatial normalization, and spatial smoothing (isotropic, with a Gaussian kernel full-width at half-maximum of 6 mm). Following the preprocessing steps, regression analysis was performed to reduce the impact of subject motion and other non-brain signals (including six motion parameters, global mean signal, white matter signal, and cerebrospinal fluid signal). The resulting fMRI data were then linearly detrended and band-pass filtered (0.01–0.08 Hz) to reduce the effects of physiological noise, such as respiration and heartbeat. Finally, various measures were calculated, including the amplitude of low-frequency fluctuations (ALFF), fractional ALFF (fALFF), functional connectivity, voxel-mirrored homotopic connectivity (VMHC), functional connectivity density, and network analysis.

Interim analyses {21b}

No interim analysis is planned within this trial.

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

To detect differences in treatment effects by gender, we will analyze the interaction between group and gender.

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

For participants who do not complete the full efficacy evaluation, non-responder imputation (NRI) will be employed to address missing data. In instances where participants withdraw prematurely or for other reasons, resulting in a missing primary outcome, the outcome will be considered inefficacious.

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

The authors plan to publish the study protocol, statistical analysis plan, and results. For detailed publication information, please contact the corresponding author.

Oversight and monitoring

Composition of the coordinating center and trial steering committee {5d}

A research team composed of the principal investigator, project leader, and recruitment staff will meet weekly to oversee trial recruitment and administrative tasks. The scientific research department of Beijing Anding Hospital will monitor trial conduct, including verifying signed informed consent, documenting inclusion/exclusion criteria, and confirming randomization for each participant. Data consistency checks between digital and source data will also be performed.

Composition of the data monitoring committee, its role and reporting structure {21a}

Given the low-risk nature of this study and its short duration, the data monitoring committee (DMC) will not be formed. Nevertheless, the scientific research department of Beijing Anding Hospital will conduct ongoing oversight of the research data.

Adverse event reporting and harms {22}

All adverse events (AEs) occurring during the study, whether or not considered device-related, will be recorded on the eCRF as outlined in the protocol. This includes all adverse device effects (ADEs). For each AE/ADE, the following information will be captured: description, onset and end dates, severity, assessment of device-relatedness, involvement of other potential causes, and actions taken. Ongoing follow-up is required until resolution or stabilization. The relationship between AEs and the device will be evaluated by a qualified investigator or the sponsor/manufacturer. All ADEs leading to participant withdrawal or persisting at study completion will be followed until a satisfactory outcome is achieved. Additionally, adverse events will be reported to relevant regulatory bodies, including the ethics committee of the Beijing Anding Hospital, Capital Medical University, Beijing, China, as required. These reports will indicate the expectedness, seriousness, severity, and causality of each event.

Frequency and plans for auditing trial conduct {23}

The roles of a coordinating center and trial steering committee are integrated within the principal investigator (PI) and research team. The PI assumes overall leadership, overseeing protocol development, participant enrollment, data collection, analysis, and reporting. Robust internal mechanisms are in place to ensure adherence to ethical, regulatory, and institutional standards. Regular team meetings and protocol reviews facilitate ongoing monitoring of study progress and timely responses to challenges.

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

The Ethics Committee of Beijing Anding Hospital, Capital Medical University, has granted ethical approval for this study. Any protocol amendments or procedural modifications will be submitted to this committee and to the relevant ethical review boards of collaborating institutions. All changes will be documented in the study registry. Prior to randomization, all participants will provide written informed consent.

Dissemination plans {31a}

All study findings will be published in peer-reviewed scientific journals. Authorship will follow the Vancouver guidelines to ensure proper recognition of all contributing authors. We will notify all participants of the trial results by preparing a lay summary in clear, accessible Chinese language. This summary will explain the main findings and their implications in non-technical terms and will be distributed to participants after study completion.

Discussion

DPD is characterized by persistent or recurrent experiences of feeling detached from or unrealistically changed in relation to one's own body or surroundings. Onset typically occurs in early adolescence or young adulthood, and the disorder often follows a chronic course with persistent or increasing episodes. DPD can significantly impair social functioning and cognitive abilities, leading to substantial reductions in quality of life for affected individuals and placing a significant burden on their families and society. Currently, there are no widely accepted effective treatments for DPD. Therefore, the development of novel therapeutic approaches is of paramount importance to improve patient outcomes and societal well-being.

This study aims to investigate the efficacy and safety of taVNS for the treatment of DPD. taVNS is a non-invasive neuromodulation technique that involves applying electrical stimulation to the auricular branch of the vagus nerve in the ear. It has demonstrated promising therapeutic effects in various psychiatric disorders, including depression, anxiety, and tinnitus.

The present study will employ a randomized, double-blind, sham-controlled design to evaluate the effectiveness of taVNS in reducing DPD symptoms and improving overall functioning. Participants will be randomly assigned to either an active taVNS treatment group or a sham control group. Both groups will receive daily taVNS or sham stimulation for a specified duration. Assessments of DPD symptoms, social functioning, cognitive function, and quality of life will be conducted at baseline, pre- and post-treatment, and at follow-up.

The findings of this study will provide valuable insights into the potential of taVNS as a safe and effective treatment for DPD. If proven efficacious, taVNS could offer a novel, non-invasive, and well-tolerated therapeutic option for individuals suffering from this debilitating disorder. This would not only significantly improve patient outcomes but also alleviate the burden on healthcare systems and society as a whole.

Trial status

Protocol version: version 1, 2023–11.
Started recruitment: January 1, 2024.
Recruitment completion: December 31, 2026.

Abbreviations

ADE	Adverse device effect
AE	Adverse event
CDS	Cambridge Depersonalization Scale
CRF	Case report form
DPD	Depersonalization-derealization disorder
fMRI	Functional magnetic resonance imaging
SSRI	Serotonin reuptake inhibitors
taVNS	Transcutaneous auricular vagus nerve stimulation

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We thank all participants enrolled in this study.

Authors' contributions {31b}
YZ and HJ conceived and designed the study. SZ, HZ, DY, and MF will perform the study. SZ will collect and analyze all data. YZ and SZ provided the first version of the manuscript. HJ revised and finalized the manuscript. All authors read and approved the final version of the manuscript.

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Data availability {29}
Authorized representatives from the sponsor, host institution, and regulatory authorities will have direct access to trial-related records for monitoring, auditing, and inspection purposes.

Declarations

Ethics approval and consent to participate {24}
The ethics committee of the Beijing Anding Hospital, Capital Medical University, Beijing, China, approved the study design (approval number: 2023292FS-2). Written informed consent will be obtained from all participants before randomization. The trial is registered at the Chinese Clinical Trial Registry (ChiCTR) website (https://www.chictr.org.cn/index.html). The trial results will be published in peer-reviewed journals and at conferences. Written, informed consent to participate will be obtained from all participants".

Consent for publication {32}
Not applicable. No identifying images or other personal or clinical details of participants are presented here or will be presented in reports of the trial results. The participant information materials and informed consent form are available from the corresponding author on request.

Competing interests {28}
The authors declare no competing interests.

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