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Effects of auricular vagus nerve stimulation on increased pain sensitivity

Submission date 04/03/2026	**Recruitment status** No longer recruiting	[_] Prospectively registered [_] Protocol
Registration date 05/03/2026	**Overall study status** Completed	[X] Statistical analysis plan [_] Results
Last Edited 05/03/2026	**Condition category** Signs and Symptoms	[_] Individual participant data [X] Record updated in last year

Plain English summary of protocol
Plain English summary of protocol not provided at time of registration

Contact information

Type(s)
Principal investigator, Scientific, Public

Contact name
Dr Mikołaj Szulczewski

ORCID ID
https://orcid.org/0000-0003-1251-3498

Contact details
Institute of Psychology of the Polish Academy of Sciences
Warsaw
Poland
00-378
+48 22 583 13 80
mszulczewski@psych.pan.pl

Additional identifiers

OSF preregistration ID
https://osf.io/twqux

Study information

Scientific Title

Randomized crossover study of transcutaneous auricular vagus nerve stimulation compared with sham stimulation on high-frequency stimulation–induced secondary mechanical hypersensitivity in healthy women

Study objectives
The study aims to examine whether transcutaneous auricular vagus nerve stimulation (taVNS), compared with sham stimulation, reduces experimentally induced secondary mechanical hypersensitivity following high-frequency stimulation (HFS) in healthy women. A secondary objective is to examine whether taVNS affects affective state (pleasant and unpleasant arousal).

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 08/06/2022, Ethics Committee Research UZ Leuven (Herestraat 49, Leuven, B-3000, Belgium; +32 16 34 86 00; ec@uzleuven.be), ref: S66478

Primary study design
Interventional

Allocation
Randomized controlled trial

Masking
Blinded (masking used)

Control
Placebo

Assignment
Crossover

Purpose
Basic science

Study type(s)

Health condition(s) or problem(s) studied
Experimental secondary mechanical hypersensitivity induced by high-frequency stimulation in healthy women.

Interventions
The study uses a randomized within-subject crossover laboratory design with two conditions: transcutaneous auricular vagus nerve stimulation (taVNS) and sham stimulation.

Participants attend two laboratory visits conducted on separate days. In one session, participants receive taVNS and in the other session, sham stimulation. The order of the two conditions is counterbalanced across participants.
Randomisation of condition order was performed using block randomisation. Before the experiment, a list was generated in LibreOffice Calc in which each row contained the order of

conditions and a random number generated by LibreOffice Calc's random number generator. The random numbers were then ordered from low to high and this new sequence of ordered conditions was followed, with the first signed-up participant assigned to the first row, the second to the second row, and so on.

At the beginning of each session, three electrocardiogram (ECG) electrodes are attached to monitor cardiac activity throughout the experiment. After a 5-minute baseline recording period, participants report their affective state and rate the intensity and unpleasantness of mechanical pinprick stimulation applied to the volar forearm of both arms.
High-frequency electrical stimulation (HFS; 2.5 mA) is then applied to one forearm to induce secondary mechanical hypersensitivity. Affective state ratings are collected again following HFS.
Electrical stimulation of the left ear is delivered using a DS5 constant-current stimulator (Digitimer Ltd., UK) controlled by MATLAB.
In the taVNS condition, a modified NEMOS® electrode is used, with its contacts combined into one pole, while an EEG electrode serves as the second pole. The electrodes are positioned at the cymba conchae and cavum concha to stimulate auricular regions innervated by the vagus nerve.

In the sham condition, two EEG electrodes are attached to the earlobe.
Stimulation intensity is individually calibrated using a 0–100 sensation scale to reach an intense but non-painful level. Stimulation begins after the HFS procedure and continues until 20 minutes after HFS, during which the post-stimulation assessments are conducted.
Affective state ratings are collected again during the post-stimulation assessment period.
Mechanical pinprick stimulation is then repeated and participants rate the intensity and unpleasantness of the stimuli. The area of secondary hyperalgesia is assessed by applying pinprick stimulation at 1 cm intervals along the forearm while participants report any change in perceived intensity.
After a 20-minute break, a final pinprick stimulation procedure identical to the previous assessment is performed and rated by the participant. At the end of the session, participants report any experienced side effects.

Intervention Type
Device

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
DS5 constant-current stimulator, NEMOS® electrode

Primary outcome(s)
1. Secondary mechanical hypersensitivity measured using numerical ratings of pain intensity and unpleasantness evoked by mechanical pinprick stimulation (64 mN) using a 0–100 numerical rating scale at baseline, after high-frequency stimulation and stimulation (taVNS or sham), and 20 minutes after stimulation

Key secondary outcome(s))
1. Affective state measured using pleasant and unpleasant arousal assessed via bipolar scales from the Swedish Core Affect Scale (Västfjäll et al., 2002) at baseline, directly after high-frequency stimulation, and 20 minutes after high-frequency stimulation

2. Heart rate variability measured using root mean square of successive differences between normal heartbeats (RMSSD) derived from electrocardiography (ECG) at baseline, during stimulation (taVNS or sham), and after stimulation

Completion date
14/11/2022

Eligibility

Key inclusion criteria
1. Healthy women aged 18–35 years
2. Able to understand spoken and written English
3. Able and willing to comply with study procedures and provide informed consent

Healthy volunteers allowed
Yes

Age group
Adult

Lower age limit
18 years

Upper age limit
35 years

Sex
Female

Total final enrolment
37

Key exclusion criteria
1. Bradycardia, cardiac arrhythmia, or any cardiac disease
2. History of or current neurological disorder
3. Current psychiatric disorder
4. Other serious medical condition
5. Use of chronic and ongoing medication (women using contraceptive pills are allowed)
6. Pregnancy
7. Use of recreational drugs within the past week
8. Recovery from serious trauma or an operation
9. Previous participation in studies using the same stimulation device

Date of first enrolment
07/07/2022

Date of final enrolment
14/11/2022

Locations

Countries of recruitment
Belgium

Sponsor information

Organisation
KU Leuven

ROR
https://ror.org/05f950310

Funder(s)

Funder type

Funder Name
Narodowe Centrum Nauki

Alternative Name(s)
National Science Centre, NCN

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
Poland

Funder Name
Fonds Wetenschappelijk Onderzoek

Alternative Name(s)
Research Foundation Flanders, Flemish Research Foundation, Research Foundation – Flanders, Fonds voor Wetenschappelijk Onderzoek - Vlaanderen, The FWO, Het FWO, FWO

Funding Body Type
Government organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
Belgium

Funder Name
Onderzoeksraad, KU Leuven

Alternative Name(s)
Research Council, KU Leuven

Funding Body Type
Private sector organisation

Funding Body Subtype
Universities (academic only)

Location
Belgium

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Statistical Analysis Plan			05/03/2026	No	No