The effect of Transcutaneous Vagal Nerve Stimulation on the processing of visceral pain signals: a High Resolution fMRI Study in Healthy Volunteers

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Transcutaneous auricular vagal nerve stimulation (taVNS) has been recently shown to have analgesic potential in patients with chronic functional abdominal (visceral) pain. Functional abdominal pain, as commonly seen in conditions such as irritable...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Gastrointestinal signs and symptoms
Study type	Interventional

Summary

ID

NL-OMON56195

Source
ToetsingOnline

Brief title
Effects of tVNS on visceral pain

Condition

- Gastrointestinal signs and symptoms

Synonym
abdominal pain, Visceral pain

Research involving
Human

Sponsors and support

Primary sponsor: Medisch Universitair Ziekenhuis Maastricht

Source(s) of monetary or material Support: Rome Foundation

Intervention

Keyword: fMRI, healthy volunteers, vagus nerve stimulation, visceral pain

Outcome measures

Primary outcome

To explore the possible functional brain differences between taVNS vs sham in the duodenal capsaicin experimental pain model.

Secondary outcome

1. To explore the degree of activation of the Cingulate Cortex, Insula, Thalamus, Prefrontal cortex, the Primary and Secondary Somatosensory Cortex, the Amygdala, Periaqueductal grey and possibly cerebellar structures as a result of taVNS, compared to sham stimulation, in the capsaicin-pain model;

2. To assess the correlation between fMRI findings and Visual Analogue Scores (VAS) for pain;

3. To assess the effect of taVNS vs sham on pulse rate variability, as a measure of vagal tone of the autonomous nervous system.

Study description

Background summary

One of the most common causes of abdominal pain are irritable bowel syndrome (IBS) and functional dyspepsia (FD). Abdominal pain in these conditions is of chronic nature with frequent fluctuations, including acute exacerbations even on a daily basis. The prevalence of IBS and FD in the general population is 6% and 10%. Over one third of patients seen in secondary care GI clinics has IBS or FD (Dutch Gastroenterologists* Association survey 2015), and pain is the most common and difficult to manage symptom. Despite the large volume of patients, conventional treatments often do not result in sufficient long-term

symptom relief. This leads to impaired quality of life and substantial socio-economic burden.

The fact that there is still limited scientific understanding of the underlying causes of these disorders hampers the development of more effective treatment strategies. Nonetheless, current consensus considers IBS and FD as *disorders of the gut-brain interaction,* reflecting the unique bidirectional communication between these two organ systems. Recent scientific efforts have focused on the vagus nerve because of its key role in homeostatic control. The vagus nerve carries afferent sensory from the gastrointestinal tract to the brainstem, in particular the nucleus tractus solitarius (NTS). Because the NTS is further connected with other key brain regions, it represents a unique relay station to higher cortical centers, including those responsible for conscious pain perception.

The vagus nerve has a single peripheral branch (the auricular branch), innervating the external ear. This location creates a *gateway* for influencing a large number of physiological processes and bodily states through electrical stimulation of the vagus nerve. Given its accessibility, transcutaneous stimulation of the auricular vagus nerve (taVNS) has been applied experimentally for diverse painful conditions including migraine and fibromyalgia. More recently, a first empiric trial in adolescents with functional abdominal pain has demonstrated analgesic properties of auricular VNS when applied daily for a period of 4 weeks and beneficial effects were also shown in a sub-analysis for patients who also met diagnostic criteria for IBS. In addition, a recent study using 7 Tesla functional magnetic resonance imaging (fMRI) has shown that taVNS is specifically able to activate the NTS. However, it remains unclear whether the activation of the NTS is indeed the putative mechanism leading to a clinical analgesic effect of taVNS by virtue of modulating nociceptive processing.

Recent advances in neuroimaging techniques now make it possible to study these mechanisms in detail and have opened new possibilities to gain insight into gut-brain communication mechanisms and the therapeutic effect of taVNS. Such mechanistic insight would enable further exploitation of taVNS as an innovative, low-risk treatment that has the potential to impact both acute and chronic components of abdominal pain.

Study objective

Transcutaneous auricular vagal nerve stimulation (taVNS) has been recently shown to have analgesic potential in patients with chronic functional abdominal (visceral) pain. Functional abdominal pain, as commonly seen in conditions such as irritable bowel syndrome (IBS), are believed to arise from a disturbance in the gut-brain interaction, in which the vagus nerve plays a paramount role. Brain imaging studies allow insight into the exact nature of the gut-brain interaction. We have recently established and validated an experimental model

for visceral pain for brain imaging based on the duodenal infusion of capsaicin, the pungent principle in red peppers. In this study in healthy volunteers, we will explore the potential mechanism of action of taVNS in this experimental pain model. We will specifically focus on the brainstem, in particular the nucleus of the solitary tract (NTS), as this is a key relay stations of vagal afferents originating from the intestine.

Aim:
1) To study the effect of taVNS vs sham stimulation on brain activation (in particular in the brain stem) with high-resolution 7-Tesla (7T) functional magnetic resonance imaging (fMRI) in the duodenal capsaicin experimental visceral pain model;
2) To investigate the effects of taVNS vs sham stimulation on subjective pain reporting;
3) To explore the effects of taVNS vs sham stimulation on the parasympathetic (vagal) tone.

Study design

An explorative 7T fMRI study

Intervention

Transcutaneous vagal nerve stimulation to the cymba concha of the right ear. As a control condition, sham stimulation to the right earlobe will be used, this area receives no vagal innervation. Infusion of capsaicin via a nasoduodenal tube will be used as co-intervention.

Study burden and risks

Volunteers will not benefit from participating in this study. There are no risks associated with the use of taVNS, including in magnetic resonance imaging (MRI). Moreover, taVNS in the MR environment has been approved by the Scannexus safety board and, thus far, 16 individuals healthy older individuals and 3 patients with preclinical Alzheimer*s disease) underwent simultaneous taVNS-fMRI at this prospective site, with this particular equipment before with nil procedural complications/adverse events (NL51297.068.14). Given the nature of taVNS (by definition, *neurostimulation*), it can induce a transient tingling feeling but does not cause pain. Ultra-high magnetic field MRI is very safe and no adverse events are anticipated when taking into account all contra-indications. Solely *Certified Users* will operate the MRI according to approved guidelines and protocol. Subjects will be screened for contraindications (metal implants etc.) prior to inclusion and again on the day of scanning. Some participants may experience mild vertigo, nausea or a metal taste when entering the MRI environment. In extremely rare cases, a small burn may arise due to heating caused by radiofrequency. All participants will be

informed about any unexpected medical findings (MRI findings). In the rare event the subject does not wish to be informed, they would not be permitted to participate in this study.
There are no significant risks associated with the introduction of a naso-duodenal tube by endoscopy, though the naso-duodenal tube may cause discomfort located in the nose or throat. Spraying 10% lidocaine on the nasal mucosa will minimize these symptoms.. Complications caused by replacement via endoscopy are rare (<0,2%). Possible complications are aspiration, bleeding and a sore throat. Capsaicin infusion may cause abdominal cramps, a burning sensation, abdominal pain, nausea or heartburn but symptoms will subside rapidly after discontinuation of the infusion. The nasoduodenal tube and infusion pump are safe to use in the magnetic field and has been tested for this purpose extensively. Completing questionnaires is non-invasive. Subjects will be informed about the risks and burdens of the measurements beforehand.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

• Of female sex;
• Healthy participants (defined as those without a pre-existing medical comorbidity)
• Age between 18 and 40 years;
• BMI between 18 and 30 kg/m2;
• All subjects should use some form of contraception (for IUDs only Mirena is accepted).
• All subjects should be right-handed.

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
• Presence of metallic prostheses, pacemakers, metal clips on blood vessels, metal parts in the eye, an intrauterine device (with the exception of the Mirena IUD), metal braces, tattoos and/or other metal objects;
• History of major head trauma or head/brain surgery;
• History of claustrophobia;
• History of severe or chronic cardiovascular, respiratory, urogenital, gastrointestinal/ hepatic, haematological/immunologic, HEENT (head, ears, eyes, nose, throat), dermatological/connective tissue, musculoskeletal, metabolic/nutritional, endocrine, neurological/psychiatric diseases, major surgery and/or laboratory assessments which might limit participation in or completion of the study protocol;
• Use of regular medication, including vitamin and iron supplementation, except oral contraceptives, within 14 days prior to start of the study;
• Pregnancy, lactation, wish to become pregnant;
• High alcohol consumption (>15 alcoholic units consumed per week);
• Using drugs of abuse;
• Administration of investigational drugs or participation in any scientific intervention study which may interfere with this study (to be decided by the principle investigator), in the 180 days prior to the study;
• Participants unable to provide informed consent
• Participants with any systemic disease or medications that may influence the autonomic nervous system (e.g. beta-agonists or Parkinson*s disease)
• Current smokers or current use of nicotine in any other way (including E-cigarettes and patches)
• History of clinical anxiety or depression, or a hospital anxiety or depression score >8
• Participants whom score 8 or more on the HADS-questionnaire at study commencement
• Patient whom have cardiovascular conduction problems

• Patient with cochlear implants
• Not meeting any of the inclusion criteria above
• Any evidence of structural brain abnormalities examined by anatomical MRI
will lead to exclusion

Study design

Design

Study type:	Interventional
Intervention model:	Other
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	17-04-2023
Enrollment:	24
Type:	Actual

Medical products/devices used

Generic name:	TENStem dental (transcutaneous vagal nerve stimulator)
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	20-09-2021
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	11-09-2023

Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL77978.068.21