Functional Neural Correlates of Transcutaneous Vagal Nerve Stimulation: Effects of Anatomical Site and Waveform Parameters * An exploratory High Resolution fMRI Study in Healthy Volunteers

Published: 08-08-2018
Last updated: 11-04-2024

The aim of this exploratory (pilot) study is 1) To study the effect of tVNS with high-resolution 7-Tesla (7T) functional magnetic resonance imaging (fMRI) and concomitant autonomic monitoring by cardiac and respiratory waveform analytics; 2) To...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Observational non invasive

Summary

ID

NL-OMON50574

Source
ToetsingOnline

Brief title
Neural collerates of tVNS

Condition

- Other condition

Synonym
Hyperalgesia / chronic pain

Health condition

Chronische pijnsyndromen

Research involving
Human

Sponsors and support

Primary sponsor: Medisch Universitair Ziekenhuis Maastricht
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: fMRI, High-resolution 7 Tesla, Transcutaneous vagal nerve stimulation

Outcome measures

Primary outcome

Blood oxygenation level dependent (BOLD) signal activity in the central autonomic network (CAN) during tVNS.

Secondary outcome

* Voxel-wise dependent BOLD signal activity in the NTS of the brainstem; insula cortex; ACC hypothalamus; thalamus and amygdala during auricular tVNS (parameter set 1).

* Voxel-wise dependent BOLD signal activity in the NTS of the brainstem; insula cortex; ACC; hypothalamus; thalamus and amygdala during cervical tVNS (parameter set 1).

* Voxel-wise dependent BOLD signal activity in the NTS of the brainstem; insula cortex; ACC; hypothalamus; thalamus and amygdala during auricular tVNS (parameter set 2).

* Voxel-wise dependent BOLD signal activity in the NTS of the brainstem; insula cortex; ACC; hypothalamus; thalamus and amygdala during cervical tVNS (parameter set 2).

Voxel-wise dependent BOLD signal activity in the NTS of the brainstem; insula cortex; ACC; hypothalamus; thalamus and amygdala during subliminal auricular tVNS.

* Functional connectivity / Network Connectivity of CAN regions during "active tVNS" block [to all 5 points as identified above]

* Graph theory measures of brain connectivity during "active tVNS" block [to all 5 points as identified above], including modularity, efficiency and small-world properties.

Study description

Background summary

The autonomic nervous system (ANS) is a bidirectional brain-body interface that serves to integrate changes in the external environment with the internal milieu and maintain homeostasis. Comprising of two broadly opposing arms, the sympathetic (SNS) and parasympathetic nervous systems (PNS), the functions of the ANS are considerable, spanning from metabolic control to cardiorespiratory regulation and pain processing. Whilst it is well documented that the brain is the central hub for the regulation of autonomic function, the use of neuroimaging to investigate the association between brain morphology and autonomic function, not least with advanced neuro-analytical techniques, is far from comprehensive.

The main branch of the PNS is the vagus nerve. Although the vagus is predominantly composed of afferent nerves, the efferent arm is postulated to play a pivotal role in modulating visceral nociception, gastrointestinal motility cardioregulation , and inflammation. Similarly, the SNS, due to its multiple interactions with the peripheral and central nervous system, may also influence peripheral inflammation and nociception.

Neuroanatomy of the vagal nerve: Efferent vagal nerve (the tenth cranial nerve, *CN X*) fibres arise in the dorsal motor nucleus (DMNx) and the nucleus ambiguus (NA), innervating the foregut, midgut, and aspects of the hindgut. Afferent vagal fibres, meanwhile, originate in the mucosal or muscle layers of the GI tract and have cell bodies in the nodose ganglia, which relay sensory information to the nucleus tractus solitarii (NTS) located in the area

postrema. This is in close proximity to the DMNx forming the *dorsal vagal complex*, an area of key importance in autonomic and limbic responses to interoceptive physiology. From the dorsal vagal complex, visceral information ascends to subcortical areas, including the hypothalamus, thalamus and amygdala via the parabrachial nucleus. In turn this relays on to higher cortical areas such as the insula cortex, cingulate and prefrontal cortices * which is frequently referred to as the *central autonomic network* (CAN). The CAN modulates visceral function and perception through descending inhibition. Taken together, this bi-directional neurophysiological pathway has proposed to be a major constituent component of the *brain-gut axis*, and has been a focus of more than three decades of animal and human research

Quantifying activity of the ANS: Advances within autonomic neuroscience have facilitated the development of many techniques to quantitatively assess autonomic function, such as the evaluation of heart rate variability (HRV). Moreover, with advances in signal waveform analytics it is possible to derive autonomic indices from both electrocardiogram (ECG) and respiratory waveform data. Amongst such measurements to objectively quantify SNS and PNS activity are the cardiometrically derived parameters, referred to as cardiac sympathetic index (CSI) and cardiac vagal tone (CVT), respectively. In contrast to the traditional derivation of autonomic activity, such as by HRV, both CSI and CVT yield superior temporal resolutions and have been associated with multiple neurophysiological functions, including pain processing and the neuro-endocrine-immune axis.

Perturbation of autonomic tone in clinical disorders: Whilst the ANS* primary function is to maintain bodily homeostasis, it plays an important role at both a central and peripheral level in modulating the pain experience. Specifically, the SNS and PNS are considered to be pro and anti-nociceptive respectively, with the parasympathetic nervous system posited to have anti-nociceptive activity due to vagal nerve-mediated activation of key brain areas implicated in descending analgesia. Furthermore, an imbalance of the ANS occurs frequently in chronic pain disorders, such that the parasympathetic tone is relatively diminished. Moreover, abnormal resting SNS and PNS activity has been reported in a number of clinical disorders such as functional chest pain, irritable bowel syndrome (IBS), inflammatory bowel disease, fibromyalgia, Ehlers-Danlos syndrome and diabetes mellitus.

Neuromodulation of the ANS: The above observations, illustrating that autonomic tone is perturbed in a variety of clinical conditions provides a rationale for suggesting that increasing vagal tone may influence disease processes, or possibly even attenuate them.
Over the last decade or so, techniques that modulate autonomic tone have been investigated as potential methods to modify ANS tone in clinical disorders, so called *autonomic neuromodulation*. One such method that has received much attention is vagal nerve stimulation, a form of *neurostimulation* to the tenth cranial nerve, the vagus nerve. Electrical vagal nerve stimulation (VNS) was

first used in humans in 1988 and is an efficacious treatment for drug-resistant epilepsy. Traditional VNS is undertaken in a procedure where a bipolar helical electrode is placed around the cervical vagal nerve, which is connected to a pulse generator placed in a subcutaneous pocket in the chest, not dissimilar to a cardiac pacemaker. However, this method of VNS necessitates surgical implantation with its attendant risks and complications. Recently, an external transcutaneous VNS (tVNS) method, consisting of small electrodes to interface with the concha of the outer ear has become available. The auricular branch of the vagus nerve innervates the concha of the ear and is located directly under the skin, making it a suitable target for transcutaneous stimulation. tVNS has been demonstrated to be safe, well tolerated and have a high degree of user-friendliness.

Gaps in our knowledge;
1) site of stimulation: In addition to auricular-targeted tVNS, the cervical branch of the vagus nerve over the neck has been suggested an additional/alternative stimulation site. However, there is presently minimal, if any, evidence to suggest the utility of one stimulation site over another from an efficacy perspective. Simply put, it is not known if one site offers *superior* vagal nerve stimulation to the other. The vast majority of tVNS studies do not concurrently measure autonomic indices in real-time, further casting doubt on what tVNS is actually stimulating. In addition, there remains minimal evidence whether both even achieve a neural signature of parasympathetic activation with the use of fMRI.

2) waveform parameters of stimulation:
To date there is a paucity of set waveform parameters used in tVNS. Rather, waveform frequency and intensities seem to vary drastically between studies. Moreover, some groups have even gone so far as to patent individual waveform characteristics (40). That being said, similar to the choice of auricular or cervical sited tVNS, there is a lack of evidence to support the use of particular electrical waveform parameters. Moreover, we question whether in-fact there is a specificity of waveform parameters to achieve tVNS, or rather variable/random frequencies achieve comparable results.

The advent of 7 Tesla MRI: The advantage of scanning at 7 Tesla (7T) over 1.5 Tesla and 3 Tesla is increase in the Signal to Noise Ratio (SNR), Contrast to Noise Ratio (CNR), resolution and/or a decrease in scanning time. The benefit of scanning at 7T is believed to outweigh the small risk of dizziness while entering the bore (not during the actual scan itself). Note that the 7 Tesla scanner is becoming more and more standard and is certified for research. Worldwide, there are more than 50 scanners used for human basic and clinical research and no negative effect have been reported. According to the guidelines from the U.S. Food and Drug Administration (FDA), clinical MR systems using static magnetic fields up to 8.0 Tesla are considered *non-significant risk* for adult patients (level was set in 2003) (http://www.mrisafety.com/safety_article.asp?subject=229). The human body is

non- magnetic and therefore the static magnetic field (up to 14 Tesla or more) does not harm biological tissue. People, including elderly and patients, tolerate the experience of a 7T scanner without many difficulties or long-term side effects. In The Netherlands, there currently are three 7 Tesla instruments (Leids Universitair Medisch Centrum, University Medical Center Utrecht, and Donders Institute for Brain, Cognition and Behaviour, located in Nijmegen). These groups have been carrying out patient research for several years, with local ethical approval and no reported adverse effects or safety issues. Moreover, the use of tVNS in a 7T MR environment is concurrently studied at the Maastricht Scannexus MR site with nil procedural complications reported to date [Protocol ID NL51297.068.14].

Summary of Study rationale:
There exist multiple knowledge gaps in the use of tVNS, which concurrently hinder the advancement of this research niche, not least the development of neuromodulatory devices for patient populations. In particular, to summarise, these knowledge gaps are the following:
i) Do auricular or cervical tVNS differ in effect and/or efficacy in neuromodulation, including at the brain level? and
ii) Do fixed or variable waveform parameters differ in effect and/or efficacy in neuromodulation, including at the brain level?

Study objective

The aim of this exploratory (pilot) study is 1) To study the effect of tVNS with high-resolution 7-Tesla (7T) functional magnetic resonance imaging (fMRI) and concomitant autonomic monitoring by cardiac and respiratory waveform analytics; 2) To explore the functional brain differences (using functional magnetic resonance imaging, fMRI) between cervical [neck] vagal nerve stimulation and auricular [ear] vagal nerve stimulation; 3) To explore the functional brain differences between various vagal nerve stimulation parameters.

Primary objective:
To explore the possible functional brain differences between auricular and cervical tVNS.

Secondary objectives:
1. To explore the functional brain differences between various stimulation parameters in cervical-tVNS.
2. To explore the functional brain differences between various stimulation parameters in auricular-tVNS.
3. To compare brain effects between 1) and 2).
4. To explore the differences in auricular and cervical tVNS in augmenting PNS tone.
5. To explore the differences in varying tVNS parameters in augmenting PNS tone.
6. To explore if stimulus epoch duration relates to demonstrable change in functional brain activity and/or PNS tone.

7. To explore brain effects of subliminal (sub-threshold) auricular tVNS.

Study design

Exploratory cross-sectional study (pilot study)

Intervention

Transcutaneous vagal nerve stimulation.

There are 4 main sub-interventions of this:
i) Auricular fixed-frequency tVNS;
ii) Cervical fixed-frequency tVNS;
iii) Auricular variable-frequency tVNS and
iv) Cervical variable-frequency tVNS.

Subjects will be randomised to receive either fixed or variable-frequency first, however subjects will always receive both frequencies (in other words, randomisation only determines the order of stimulation type. 2 visits will be planned with a wash-out period of two weeks in between.
Visit 1 subjects will receive both forms of cervical stimulation, visit 2 subjects will receive both forms of auricular stimulation. In addition, subjects will receive subliminal auricular stimulation at the end of visit 2.

Study burden and risks

Volunteers will not benefit from participating in this study. There are no risks associated with the use of tVNS, including in magnetic resonance imaging (MRI). Moreover, tVNS in the MR environment has been approved by the Scannexus safety board and, thus far, 16 individuals (13 healthy older individuals and 3 patients with preclinical Alzheimer*s disease) underwent simultaneous tVNS-fMRI at this prospective site, with this particular equipment before with nil procedural complications/adverse events (NL51297.068.14). Given the nature of tVNS (by definition, *neurostimulation*), it can induce a transient tingling feeling but does not cause pain. Moreover, the equipment to be used in this study, which are also used in the aforementioned study, has been closely developed in line with the Respiratory-gated Auricular Vagal Afferent Nerve Stimulation (RAVANS) system (Napadow lab * Boston). 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.

Contacts

Public
Medisch Universitair Ziekenhuis Maastricht

Universiteitssingel 50
Maastricht 6229 ER
NL
Scientific
Medisch Universitair Ziekenhuis Maastricht

Universiteitssingel 50
Maastricht 6229 ER
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

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 be on oral contraceptives
* All subjects should be right-handed.
* Inclusion will be determined on the basis of availability. They should be

able to attend for 2 scanning sessions.

Exclusion criteria

* Presence of metallic prostheses, pacemakers, metal clips on blood vessels, metal parts in the eye, an intrauterine device, 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, hematological/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;
* Any evidence of structural brain abnormalities examined by anatomical MRI will lead to exclusion
* 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
* Patient whom have cardiovascular conduction problems
* Patient with cochlear implants
* Not meeting any of the inclusion criteria above
* Participants whom score 8 or more on the HADS-questionnaire at study commencement

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-11-2020
Enrollment:	16
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	08-08-2018
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	03-03-2020
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	10-09-2020
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	NL65751.068.18
Other	Nummer clinicaltrials.gov volgt