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# The effect of transcutaneous vagus nerve stimulation on pain perception – An experimental study

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ABSTRACT

*Background:* Recent preclinical work strongly suggests that vagus nerve stimulation efficiently modulates nociception and pain processing in humans. Most recently, a medical device has offered a transcutaneous electrical stimulation of the auricular branch of the vagus nerve (t-VNS) without any surgery.
*Objective:* Our study investigates whether t-VNS may have the potential to alter pain processing using a controlled design.
*Methods:* Different submodalities of the somatosensory system were assessed with quantitative sensory testing (QST) including a tonic heat pain paradigm in 48 healthy volunteers. Each subject participated in two experimental sessions with active t-VNS (stimulation) or sham t-VNS (no stimulation) on different days in a randomized order (crossed-over). One session consisted of two QST measurements on the ipsi- and contralateral hand, each before and during 1 h of a continuous t-VNS on the left ear using rectangular pulses (250 μS, 25 Hz).
*Results:* We found an increase of mechanical and pressure pain threshold and a reduction of mechanical pain sensitivity. Moreover, active t-VNS significantly reduced pain ratings during sustained application of painful heat for 5 min compared to sham condition. No relevant alterations of cardiac or breathing activity or clinical relevant side effects were observed during t-VNS.
*Conclusions:* Our findings of a reduced sensitivity of mechanically evoked pain and an inhibition of temporal summation of noxious tonic heat in healthy volunteers may pave the way for future studies on patients with chronic pain addressing the potential analgesic effects of t-VNS under clinical conditions.


## Introduction

Recent work suggests that the vagus nerve, traditionally considered a purely parasympathetic efferent nerve, provides an exceeding important route for information into the central nervous system [1]. In the past few years, vagus nerve stimulation (VNS) has been developed as a method to physically alter relevant brain functions, thus offering a clinically useful non drug-based anti-convulsive and antidepressant therapy option [1,2].

The known anatomic projections of the vagus nerve and its association with many different brain functions involved in the perception of pain suggest that VNS might also have applications in the therapy of different pain syndromes. Several experimental animal studies in mammals have demonstrated an inhibitory effect of VNS on the electric response of spinal nociceptive neurons as well as on nociceptive behavior [3–7]. The neurophysiological data

*Abbreviations:* ALL, Dynamic mechanical allodynia; ANS, Autonomic nerve system; BDI, Beck depression inventory; bpm, Beats per minute; cm, Centimeters; cpm, Cycles per minute; CDT, Cold detection threshold; CPT, Cold pain threshold; HPT, Heat pain threshold; HR, Heart rate; MDT, Mechanical detection threshold; MPS, Mechanical pain sensitivity; MPT, Mechanical pain threshold; NRS, Numeric rating scale; PHS, Paradoxical heat sensation; PPT, Pressure pain threshold; QST, Quantitative sensory testing; RD, Respiration depth; RF, Respiration frequency; SCID, Structured clinical interview for psychiatric diseases; SCL, Skin conductance level; SOMS-2a, Screening for somatoform symptoms of the last 2 years; STAI, State and trait anxiety inventory; THP, Tonic heat pain; TSL, Thermal sensory limen; t-VNS, Transcutaneous vagus nerve stimulation; VDT, Vibration detection threshold; WDT, Warm detection threshold; WUR, Wind up ratio; μS, Micro-Siemens.

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from these animal experiments are supported by some observational studies in humans, suggesting a pain-modulating effect of vagus nerve stimulation under conventional VNS. With regard to headache syndromes, several case reports [8–10] and one observational report on 4 therapy-refractory migraine and 2 cluster headache patients exist [11] underlining a reduction of headache frequency or intensity following VNS in patients with seizures, who concurrently suffered from migraine.

Invasive VNS is an approved treatment for drug-resistant epilepsy [2]. Besides recognized clinical efficacy there are some disadvantages including the irreversible nature of the electrode implant in the majority of cases, electrode fractures, deep wound infections, transient vocal cord palsy, cardiac arrhythmia under test stimulation, electrode malfunction, and posttraumatic dysfunction of the stimulator [12]. Frequent side effects of chronic, invasive VNS such as hoarseness, cough, dyspnea, and pain are mainly due to bidirectional stimulation of efferent and afferent fibers within the mixed cervical branch of the vagus nerve. Invasiveness and adverse events of VNS have hampered the conduction of clinical trials in other indications than epilepsies. The recently introduced technique of transcutaneous vagus nerve stimulation (t-VNS®) [13] combines selective, non-invasive and reversible access to vagus nerve afferents with a low risk profile. t-VNS targets the cutaneous receptive field of the auricular branch of the vagus nerve at the outer ear (inner side of the tragus) [14] and has been shown to activate cerebral vagal patterns in f-MRI studies [15,16]. Several lines of evidence from anatomical and clinical studies reveal the topographic anatomy and the functional impact of the auricular branch of the vagus nerve on the autonomic nervous system [17]. Both invasive and transcutaneous VNS excite thick-myelinated fibers of vagus nerve branches that project to the main therapeutic target the nucleus of the solitary tract in the brainstem. Preclinical data emphasize equivalent anticonvulsive effects of both methods [18]. Based upon the common mode of action of invasive and transcutaneous VNS and first clinical data, the t-VNS® device received CE approval for the intended use in drug-resistant epilepsy and depression.

Our study aimed at investigating pain perception during a t-VNS approach in a sample of 48 healthy subjects using a randomized, controlled, double-blinded cross-over design. For assessing different submodalities of peripheral and central nociception, we used the quantitative sensory testing procedure developed by the German Research Network on Neuropathic Pain including a tonic heat pain paradigm to obtain a full sensory profile of each single subject [19]. We also investigated whether t-VNS had an effect on the parameters of the autonomic nervous system (skin conductance levels, heart rates and respiration activity).

## Methods

### *Study*

The study was approved by the local ethics committee (University of Regensburg, Germany, Proposal Nr. 09/119). Informed consent was obtained from all subjects.

### *Subjects*

Forty-eight healthy subjects were finally enrolled in the study. All subjects were undergraduate students from the local university. They underwent a neurological examination and were interviewed by a psychiatrist, who additionally administered the SCID-1 Screening instrument [20,21]. Exclusion criteria were the history of a migraine, low back pain or other (chronic) pain syndromes, any cardiac or respiratory diseases, psychiatric disorders, neurological syndromes or the use of psychotropic drugs. In addition, subjects were excluded with BDI Scores $\geq$ 18 indicating a depressive disorder [22], SOMS-2A scores $\geq$ 7 indicating a high physical disability [23] and STAI scores indicating increased state anxiety as compared to a normative sample of students of the same age ($\geq$41) [24]. All subjects had to be without any acute pain medication for at least one week before starting the investigation.

### *Design and randomization*

We used a randomized, controlled and double-blinded study design. All subjects received an active t-VNS and an inactive t-VNS (sham) using a cross-over design. After enrollment, all subjects were randomized to one of these two t-VNS branches (active–sham or sham–active). Since all pain measurements were conducted on the ipsi- and contralateral side, as described below, the sequence of measurements on both sides was randomized in the same way (ipsilateral–contralateral or contralateral–ipsilateral). The experimenter, who analyzed the data, was blinded for this randomization procedure.

### *Vagus nerve stimulation*

The transcutaneous vagus nerve stimulator (STV02, Cerbomed, Erlangen, Germany) consisted of a small stimulation unit and a bipolar stimulation electrode placed into the left concha at the inner side of the tragus by direct contact on the skin. The electrode was placed on an acrylic body for a comfortable fit in the pinna [25]. The skin was cleaned with a small disposable alcohol pad [26]. The stimulator could be plugged into a docking station for uploading stimulation programs and settings from a PC or storing events during a stimulation on a hard disc drive. The stimulus was a modified monophasic rectangle impulse with a pulse width of 250 μS. Stimulation frequency was kept at 25 Hz, which is known to activate vagal nerve fibers [27]. The stimulation amplitude (current intensities) could be varied between 0.25 and 10 mA. During the sham stimulation, a current intensity of 0.0 mA served as the control condition.

The non-nociceptive t-VNS predominantly addressed A-beta fibers within the vagal auricular branch. Due to habituation effects a re-adjustment of stimulation intensity was necessary, which was performed on every subject within the first 5 min before starting the intervention. The current was elevated step-by-step up to a level where a constant tingling sensation was reached. The stimulation intensity was always kept below a pain threshold, thus avoiding any pricking or burning sensations. After the adjustment phase the stimulation parameters kept stable in the active group and returned to 0.0 mA in the sham group within 30 s. During the study, one of the experimenters reprogrammed the VNS device settings with a laptop computer connected via the docking station.

The experimenter who interacted with the subjects and conducted all pain measurements was blinded to all device settings. The subjects were not informed about the respective order or the protocol of the stimulation sequences. Moreover, they were not instructed about the effects to be expected during the different stimulation conditions. It was explained to all subjects that both stimulation interventions would be equivalent types of “nerve stimulation”, though they might perceive them differently.

### *Pain measurements*

The standardized quantitative sensory testing (QST) battery [19] assembles a comprehensive list of robust and validated short form tests representing all relevant submodalities of the somatosensory