Brain Stimulation 6 (2013) 798–804

Contents lists available at SciVerse ScienceDirect

Brain Stimulation

journal homepage: www.brainstimjrnl.com

CNS BOLD fMRI Effects of Sham-Controlled Transcutaneous Electrical Nerve Stimulation in the Left Outer Auditory Canal – A Pilot Study

Thomas Kraus [a,b,*,1], Olga Kiess [a,1], Katharina Hösl [a], Pavel Terekhin [c], Johannes Kornhuber [a], Clemens Forster [c]

[a] Department of Psychiatry and Psychotherapy, Friedrich-Alexander-University, Erlangen-Nuremberg, Germany
[b] Frankenalb-Klinik Engelthal, Clinic for Psychiatry, Psychotherapy, Psychosomatic Medicine, and Addiction Rehabilitation, Germany
[c] Institute of Physiology and Pathophysiology, Friedrich-Alexander-University, Erlangen-Nuremberg, Germany

ARTICLE INFO

Article history:
Received 29 January 2012
Received in revised form
3 January 2013
Accepted 15 January 2013
Available online 1 March 2013

Keywords:
Transcutaneous vagus nerve stimulation
tVNS
t-VNS
Vagus nerve stimulation
VNS
Brain stimulation
TENS
fMRI
BOLD
Anti-depressant
Psychiatric
Non-invasive

ABSTRACT

Background: It has recently been shown that electrical stimulation of sensory afferents within the outer auditory canal may facilitate a transcutaneous form of central nervous system stimulation. Functional magnetic resonance imaging (fMRI) blood oxygenation level dependent (BOLD) effects in limbic and temporal structures have been detected in two independent studies. In the present study, we investigated BOLD fMRI effects in response to transcutaneous electrical stimulation of two different zones in the left outer auditory canal. It is hypothesized that different central nervous system (CNS) activation patterns might help to localize and specifically stimulate auricular cutaneous vagal afferents.

Methodology: 16 healthy subjects aged between 20 and 37 years were divided into two groups. 8 subjects were stimulated in the anterior wall, the other 8 persons received transcutaneous vagus nervous stimulation (tVNS) at the posterior side of their left outer auditory canal. For sham control, both groups were also stimulated in an alternating manner on their corresponding ear lobe, which is generally known to be free of cutaneous vagal innervation. Functional MR data from the cortex and brain stem level were collected and a group analysis was performed.

Results: In most cortical areas, BOLD changes were in the opposite direction when comparing anterior vs. posterior stimulation of the left auditory canal. The only exception was in the insular cortex, where both stimulation types evoked positive BOLD changes. Prominent decreases of the BOLD signals were detected in the parahippocampal gyrus, posterior cingulate cortex and right thalamus (pulvinar) following anterior stimulation. In subcortical areas at brain stem level, a stronger BOLD decrease as compared with sham stimulation was found in the locus coeruleus and the solitary tract only during stimulation of the anterior part of the auditory canal.

Conclusions: The results of the study are in line with previous fMRI studies showing robust BOLD signal decreases in limbic structures and the brain stem during electrical stimulation of the left anterior auditory canal. BOLD signal decreases in the area of the nuclei of the vagus nerve may indicate an effective stimulation of vagal afferences. In contrast, stimulation at the posterior wall seems to lead to unspecific changes of the BOLD signal within the solitary tract, which is a key relay station of vagal neurotransmission. The results of the study show promise for a specific novel method of cranial nerve stimulation and provide a basis for further developments and applications of non-invasive transcutaneous vagus stimulation in psychiatric patients.

Introduction

Invasive vagus nerve stimulation (VNS) is becoming more and more established as a viable treatment option both in neurology and psychiatry [1–3]. Numerous studies have shown its central nervous effects and it has been repeatedly discussed as a novel device for neuropsychiatric treatment, especially in cases of otherwise treatment resistant epilepsies or major depressions. Apart from these effects, VNS seems to enhance cognition in patients with Alzheimer's disease [4], improves anxiety symptoms [5], and has proposed antinociceptive and immunomodulatory effects [6–8]. Moreover, weight loss was observed during chronic vagus nerve stimulation in depressed patients with obesity [9].

* Corresponding author. Frankenalb-Klinik Engelthal, Reschenbergstraße 20, 91238 Engelthal, Germany. Tel.: +49 9158 926 2201; fax: +49 9158 926 3201.
E-mail address: mail@thomaskraus.de (T. Kraus).

[1] Both authors contributed equally.

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http://dx.doi.org/10.1016/j.brs.2013.01.011

Finally, other studies have explored the potential use of VNS in the treatment of addictions and sleep disorders like narcolepsy [10].

The idea of stimulating the vagus nerve to modify central brain activity has been developed for over 100 years [11]. However, only in the mid-1980s did the method become available to effectively stimulate the 10th cranial nerve in man and animals [12]. In the method of invasive vagus nerve stimulation, neurosurgeons wrap a unidirectional wire around the vagus nerve in the neck. This wire is then connected to a battery-operated generator, which is implanted subcutaneously in the left chest wall, intermittently sending an electrical current through the wire and thus through the nerve, which then conveys a signal through neural impulses into the brain stem [13]. The information is thought to traverse the brain stem within the solitary tract and is synaptically transmitted in the dorsal medullary complex of the vagus [14]. The nucleus of the solitary tract is a crucial structure that projects to a variety of important brain areas, e.g., the locus coeruleus or the raphe nuclei [15–17]. Interactions with these pontine and medullary nuclei, which provide widespread noradrenergic and serotonergic innervation, are potentially relevant to explain VNS mechanisms [18]. Locus coeruleus (LC) neurons provide prominent noradrenergic innervations in the orbitofrontal cortex and the insula, including cortical regions that may represent emotional, i.e. limbic information [19].

Nevertheless, disadvantages of VNS are the risks of operation, including lesions of the vagus nerve, infection, hoarseness, shortness of breath and the requirement of surgical intervention when the battery runs out, which usually happens every 3–5 years [20]. Moreover, programming of the device can only be performed by an experienced physician [21]. Hence, in 2000, an alternative, non-invasive method of stimulating the vagus nerve was proposed [22]. First reported in 2003, reproducible Vagus Sensory Evoked Potentials from the scalp after transcutaneous nerve stimulation of the outer ear were detected, which suggested the feasibility of this non-invasive technique [23].

Recently, two studies have shown evidence of tVNS being effective in generating functional magnetic resonance imaging (fMRI) blood oxygenation level dependent (BOLD) signal activations in central nervous system structures [24,25]. Still, there is no evidence that the novel method of transcutaneous nerve stimulation in the area of the left outer ear is specific for the vagus nerve system. It is unclear which location within the auditory canal is most suitable for stimulating this nerve. While some authors [22,26] claim the anterior wall of the outer auditory canal to be the optimal stimulation point, anatomists found the postero-inferior wall of the external acoustic meatus, where the afferent fibers of the ramus auricularis of the vagus nerve reach the cutaneous surface, to be more suitable [27].

The aim of the present study was to investigate the immediate brain response to transcutaneous electrical stimulation of the sensory auricular branch of the vagus nerve (tVNS) by means of functional magnetic resonance imaging (fMRI) in healthy volunteers. fMRI has a high spatio-temporal resolution, does not require the use of radiopharmaceuticals and has proven to be safe and suitable for VNS-induced activation studies [28]. Due to the unclear location of the optimal stimulation site within the auditory canal, the subjects were divided into two groups and were either stimulated at the anterior wall or the posterior wall. These two different stimulation loci were to be compared concerning effectiveness in generating BOLD signal changes in the central nervous system. We hypothesized the feasibility of a transcutaneous stimulation of the vagal nerve system and aimed to confirm recently published fMRI studies that showed central nervous system effects of this novel stimulation method.

Methods

General procedure

In order to verify previous fMRI study results [24,25] and to address the question of whether this transcutaneous technique actually stimulates the vagus nerve, we designed a sham controlled fMRI study, stimulating the left outer auditory canal (anterior or posterior wall, respectively) and the center of the left ear lobe, the latter serving as the control. We oriented ourselves along the methodology of (invasive) vagus nerve stimulation, which is done at the left branch of the vagal nerve to minimize cardiac side effects. Furthermore, it remains to be determined whether there is a difference in stimulation effects according to the side stimulated. In future studies, bilateral stimulation should be addressed to compare the strength of stimulation depending on mono- vs. bilateral location.

Subjects

Sixteen healthy subjects, aged 20–37 years, participated in the fMRI study. Intake of illicit substances and excessive use of alcohol and smoking as well as clinically relevant physical and neurological disorders were ruled out by a self-made questionnaire. 8 subjects took part in the session of sham-controlled stimulation of an area of the anterior wall in the auditory canal, 8 were sham-controlled stimulated at the posterior side of the auditory canal. Since it was quite difficult to precisely attach two stimulation electrodes simultaneously in the auditory canal, it was not possible to do intra-individual comparisons regarding the stimulation site. Subjects gave their written informed consent and were instructed that they could withdraw from the experiment at any time. The study was approved by the local ethics committee. Before the experiment, the stimulation procedure and the protocol of the MRI measurements were explained to the subjects. They also gained a brief impression of the stimulation quality when the required individual stimulation intensity was determined (see below). All subjects were screened for their general physical condition and medication in advance to ensure primary health. Present or past psychiatric disorders as well as psychiatric medication served as exclusion criteria.

tVNS stimulation procedure

The stimulation electrode (anode) consisted of an MRI compatible silver plate (5 mm in diameter) connected to the stimulation device by a copper cable. It was placed in the left external acoustic meatus on the inner side of the tragus, an anatomical area that is known to receive its sensory innervation to a large extent from the vagus nerve [29,30]. The silver electrode was cleaned with alcohol and inserted with the fingers 1 cm into the outer canal of the ear at the anterior side or the posterior side of the wall and fixed with small plaster strips. For sham control, a second stimulation electrode (cathode) was cleaned with alcohol and attached with plaster strips to the left ear lobe using conventional ECG electrodes connected by copper wires. A more detailed description of the method including a drawing of the position of the stimulation electrode inside the auditory canal was published by our research group in 2007 [25]. There we also described how we determined the most effective stimulation parameters with regard to pulse width and frequency. Electrical stimuli (width 20 μs, frequency 8 Hz) were applied from a constant voltage source (Digitimer Type DS7A, serial D127A). Before each of the experiments, the individual threshold of stimulus intensity was determined, defined by the subjects as a maximum strong sensation that is just not painful and therefore could be well tolerated. To begin