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

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\textbf{Abstract}

\textit{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.

\textit{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.

\textit{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.

\textit{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 unspecified 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.

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\textbf{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].
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].

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
with, electrical contact was tested by slowly increasing voltage. A bright, prickling sensation, twinge or stabbing pain indicated that there was insufficient contact of the silver plate to the skin. In that case, only very small voltages of about 5–10 V were achieved, compared to commonly well-tolerated stimulation values of about 30 V in the event of correct electrode position. In case of contact difficulties, the electrode was immediately removed and the procedure for installing and fixing the electrode was repeated until the subjects experienced a comfortable electro-massaging sensation. The mean stimulation intensity in the active group was 32.6 V (min 14 V, max 57 V, SD 13.4), in the sham group mean intensity was 30.0 V (min 9 V, max 55 V, SD 13.5). The two groups did not differ significantly (Wilcoxon’s V = 70.5, P > 0.1). Four stimulation periods of 30 s were applied, each followed by a resting period of 1 min.

Functional magnetic resonance imaging of the brain (fMRI)

In the MRI scanner, subjects lay in the supine position and were asked not to move throughout the entire scan time. Their heads were fixed by rubber pads to minimize head movements. They were visually monitored by a physician during the whole session. Imaging was performed using a 1.5 T Siemens Sonata MRI Scanner (Siemens, Erlangen, Germany). Functional data were collected using a multi slice echo planar imaging technique (EPI). Each functional dataset consisted of 130 blocks visualizing 20 slices (see Fig. 1) (TR = 3000 ms, TE = 60 ms, flip angle = 90°, scan time = 3 s per block of 20 slices, slice thickness = 4 mm, field of view = 220 × 220 mm², data matrix = 128 × 128) [31]. Possible head movements of the subjects were corrected online using the prospective acquisition correction of the scanner [32]. Stimulation was administered during blocks 11–20, 41–50, 71–80 and 101–110. For each subject a T1 weighted magnetization prepared rapid gradient echo (MP RAGE) dataset [33] was recorded with high 3D resolution, covering the whole brain (160 sagittal slices, thickness 1 mm, in-plane resolution 0.98 × 0.98 mm², field of view: 220 × 220 mm², data-matrix: 256 × 256) after the 3 functional trials.

Functional MRI data were statistically analyzed for changes in the blood oxygenation level dependent (BOLD) signal, using BrainVoyager QX® version 1.6.3 (Brain Innovations, Netherlands, www.brainvoyager.com). The three-dimensional pre-processing of the functional data included movement correction, slice scan time correction, high frequency filtering, and removal of linear trends. The signal was low pass filtered (cut-off frequency 0.8 Hz) and accounted for the hemodynamic response delay [34]. For group analysis of the cortical activations, all individual brain data were transformed into Talairach space [35], data points were labeled using Talairach Daemon [36]. Since Talairach transformation does not cover the brain stem regions, manual special transformations of the brain stem data to one reference brain stem were performed as described in one of our previous studies [37]. Changes in the blood oxygenation level (BOLD) signal were evaluated statistically, using a general linear model (GLM) with the stimulus function as a predictor. In this analysis higher t-values show higher correlations, which usually are due to higher increases of the signal during stimulation as compared with baseline. Significant positive t-values were interpreted as increases of the BOLD signal and inversely for negative t-values. Contrasts were calculated between anterior and posterior stimulation condition as well as between each condition and sham stimulation. Positive t-values denote higher changes of the BOLD signal during condition 1 as compared with the BOLD changes during condition 2 and inversely for negative t-values. To minimize activation noise, only clusters with a minimum size of 100 mm² were considered. Activated areas were anatomically identified by comparing the activation maps with a printed brain atlas [38]. The brain regions of interest (ROI) considered for further analysis were those found to be involved in the processing of the stimuli used in our previous study [24]. In addition the following areas of the brain stem were included in the list of ROI: Locus coerules, which is involved in stress reactions, and nuclei of the vagal nerve (nucleus ambiguus, dorsal nucleus, solitary nucleus). Findings were further verified by processing the centroid coordinates with the Talairach Daemon client software (http://ric.uthsa.edu). For the analysis of the fMRI data, P < 0.001 was considered to be significant.
Results

The results are summarized in Table 1. In general, stimulation of the anterior or posterior wall led to activations and deactivations of certain brain regions, especially of frontal and limbic areas. In contrast, sham stimulation resulted in only a few activations of the certain brain regions, especially of frontal and limbic areas. In the anterior or posterior wall led to activations and deactivations of certain brain regions, especially of frontal and limbic areas. In the anterior stimulation vs. sham stimulation in the left and right hemisphere, stimulation of the anterior wall leads to higher BOLD changes than stimulation of the posterior wall. In the left parahippocampal gyrus, the right thalamus pulvinar, the effect was the other way round, i.e. posterior stimulation evoked higher BOLD changes than anterior stimulation.

**Anterior stimulation vs. sham**

Activations by anterior tVNS were found in the left insula and in the left medial frontal gyrus. There was significantly less activation during anterior stimulation as compared with sham stimulation in the left parahippocampal gyrus, which is part of the limbic system. Further, there was a tendency toward the same effect in the left posterior cingulate and the right thalamus pulvinar, which both failed to be significant.

**Posterior stimulation vs. sham**

There was significantly less activation during posterior stimulation as compared with sham stimulation in the left and right superior frontal gyrus, the right medial frontal gyrus, and the left subgenual cingulate, which is part of the limbic system. Further, there was a tendency toward the same effect in the left anterior cingulate and the left uncus, which both failed to be significant.

**Anterior versus posterior stimulation**

fMRI of tVNS shows prominent contrasts between anterior and posterior stimulation (see Fig. 1). In most brain regions, stimulation of the anterior wall leads to higher BOLD changes than stimulation of the posterior wall. In the left parahippocampal gyrus, the left posterior cingulate and the right thalamus pulvinar, the effect was the other way round, i.e. posterior stimulation evoked higher BOLD changes than anterior stimulation.

### Table 1

Changes in BOLD signal by anterior vs. posterior stimulation.

<table>
<thead>
<tr>
<th>Brain region (Total N = 16)</th>
<th>Anterior stimulation</th>
<th>Posterior stimulation</th>
<th>Sham stimulation</th>
<th>Contrast anterior vs. sham</th>
<th>Contrast posterior vs. sham</th>
<th>Contrast anterior vs. posterior</th>
<th>Talairach coordinates</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>T</td>
<td>p</td>
<td>T</td>
<td>p</td>
<td>T</td>
<td>p</td>
<td>T</td>
</tr>
<tr>
<td>Left hemisphere</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncus</td>
<td>2.74</td>
<td>0.006</td>
<td>-3.46</td>
<td>&lt;0.001</td>
<td>0.96</td>
<td>&gt;0.1</td>
<td>0.55</td>
</tr>
<tr>
<td>Medial frontal gyrus BA10</td>
<td>5.07</td>
<td>&lt;0.001</td>
<td>-3.17</td>
<td>0.002</td>
<td>0.33</td>
<td>&gt;0.1</td>
<td>4.18</td>
</tr>
<tr>
<td>Superior frontal gyrus</td>
<td>3.72</td>
<td>&lt;0.001</td>
<td>-2.89</td>
<td>0.004</td>
<td>-0.30</td>
<td>&gt;0.1</td>
<td>3.20</td>
</tr>
<tr>
<td>Insula</td>
<td>4.31</td>
<td>&lt;0.001</td>
<td>-2.69</td>
<td>0.007</td>
<td>-1.09</td>
<td>&gt;0.1</td>
<td>5.79</td>
</tr>
<tr>
<td>Parahippocampal gyrus BA37</td>
<td>-4.04</td>
<td>&lt;0.001</td>
<td>-3.84</td>
<td>&lt;0.001</td>
<td>2.05</td>
<td>0.003</td>
<td>-3.90</td>
</tr>
<tr>
<td>Posterior cingulate BA31</td>
<td>-4.18</td>
<td>&lt;0.001</td>
<td>-0.70</td>
<td>&gt;0.1</td>
<td>-1.08</td>
<td>&gt;0.1</td>
<td>2.39</td>
</tr>
<tr>
<td>Anterior cingulate BA32</td>
<td>0.51</td>
<td>&gt;0.1</td>
<td>-4.97</td>
<td>&lt;0.001</td>
<td>-1.86</td>
<td>&gt;0.1</td>
<td>0.97</td>
</tr>
<tr>
<td>Subgenual cingulate BA 25</td>
<td>1.01</td>
<td>&gt;0.1</td>
<td>-4.59</td>
<td>&lt;0.001</td>
<td>-1.84</td>
<td>&gt;0.1</td>
<td>2.96</td>
</tr>
<tr>
<td>Right hemisphere</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Anterior cingulate BA32</td>
<td>4.36</td>
<td>&lt;0.001</td>
<td>-2.61</td>
<td>0.009</td>
<td>2.34</td>
<td>0.019</td>
<td>1.44</td>
</tr>
<tr>
<td>Superior frontal gyrus BA10</td>
<td>3.64</td>
<td>&lt;0.001</td>
<td>-4.61</td>
<td>&lt;0.001</td>
<td>3.74</td>
<td>&lt;0.001</td>
<td>0.46</td>
</tr>
<tr>
<td>Medial frontal gyrus</td>
<td>4.01</td>
<td>&lt;0.001</td>
<td>-3.94</td>
<td>&lt;0.001</td>
<td>3.25</td>
<td>0.001</td>
<td>0.31</td>
</tr>
<tr>
<td>Parietal lobe</td>
<td>5.81</td>
<td>&lt;0.001</td>
<td>-1.20</td>
<td>&gt;0.1</td>
<td>3.63</td>
<td>&lt;0.001</td>
<td>0.54</td>
</tr>
<tr>
<td>Thalamus pulvinar</td>
<td>-3.33</td>
<td>&lt;0.001</td>
<td>2.18</td>
<td>0.030</td>
<td>0.47</td>
<td>&gt;0.1</td>
<td>3.25</td>
</tr>
<tr>
<td>Brain stem area</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Locus coeruleus</td>
<td>-2.11</td>
<td>0.035</td>
<td>-1.13</td>
<td>&gt;0.1</td>
<td>1.81</td>
<td>&gt;0.1</td>
<td>-3.85</td>
</tr>
<tr>
<td>Area of solitary tract</td>
<td>-1.76</td>
<td>&gt;0.1</td>
<td>-1.52</td>
<td>&gt;0.1</td>
<td>2.09</td>
<td>&lt;0.05</td>
<td>-3.93</td>
</tr>
</tbody>
</table>

Results of tVNS in the left auditory canal. t-values and corresponding p-values were obtained from the general linear model (GLM) of the group analysis (*p < 0.001 significant). Positive t-values represent an increase of the BOLD signal during stimulation, while a negative t-value results from a significant drop of the BOLD signal during stimulation in the respective brain region. In the contrast analysis, positive t-values represent a greater change of BOLD signal during anterior stimulation compared with sham or posterior stimulation. The Talairach coordinates denote the center of gravity of the cluster as found by the group analysis. Note that the minimum cluster size was 100 mm³.

**Brain stem areas**

In the brain stem areas (locus coeruleus, solitary tract), we found effects only comparing stimulations of the anterior wall with sham stimulation, with a stronger BOLD signal decrease during anterior stimulation (see Fig. 2).

Discussion

The results of this study support the hypothesis of the feasibility and efficacy of a transcervaneous vagus nerve stimulation to generate confined BOLD signal changes in healthy subjects. Results of our previous study [25] were confirmed. Again, limbic deactivations were prominent, especially in the area of the parahippocampal gyrus and the posterior cingulate cortex. The confirmation of tVNS results is strong, because now not only sham controls have been performed but also anterior and posterior stimulation has been compared in the left outer canal of the ear. These comparisons are of a high statistical significance.

Left anterior auricular electrical nerve stimulation induced robust deactivations of the parahippocampal gyrus, posterior cingulate cortex and right thalamus pulvinar. Moreover, tVNS led to strong activations of frontal brain regions like the superior frontal gyrus or the medial frontal gyrus.

Furthermore, brain stem signals could be detected. In particular, the brain stem effects seem to depend on the anterior stimulation, especially if compared with sham stimulation. Most anatomists presume that the posterior and lower wall of the meatus acusticus externus is innervated by the vagal nerve [27]. This suggests an involvement of vagal afferents (as in VNS) in both stimulation conditions, either via direct activation of vagal afferents in the anterior wall or an indirect involvement of this system activated by posterior stimulation. Projections from anterior cingulate cortex (ACC) to the vagal control system have been described [39]. Deactivation of the ACC during posterior stimulation may have induced a slight (not significant) BOLD signal decrease in the solitary nucleus such that no contrast could be detected between the anterior and posterior stimulation condition.
The study provides data to support the hypothesis of specifically stimulating vagal nerve fibers by the novel method of transcutaneous electrical nerve stimulation at the outer canal of the ear, especially if done at the anterior side of the meatus acusticus externus. The results confirm the claims of Fallgatter et al. [23], who identified Vagus Sensory Evoked Potential (VSEP) measured as far field potential probably originating in vagus nuclei in the brain stem only after stimulation at the inner side of the tragus of the right ear, and not at the lobulus auriculae, the scapha, the crus antihelicis superior or the top of the helix. In our study, we found changes in fMRI brain activation that strongly resemble observations in the classical invasive vagus nerve stimulation (VNS) [40]. There, different neuroimaging techniques, like single photon emission computed tomography (SPECT), positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), have been used to assess changes in brain activation patterns during VNS [40]. One of the most consistent findings of acute VNS effects is a diminished activity in limbic structures like the hippocampus, amygdala, and cingulate areas [41,42], for example accompanied by a decrease of limbic cerebral blood flow [43].

In the present study, tVNS led to BOLD fMRI deactivations of the parahippocampal gyrus, posterior cingulate cortex and right thalamus. These regions are known to be of importance in the pathophysiology of depressive states [44] where limbic hyperactivity might underlie abnormal emotional processing [45] and has been reported in the medial and inferior frontal cortex and basal ganglia, namely the caudate nucleus and the putamen, during induction of negative affect [46]. Depressed patients showed decreases in blood flow in right anterior cingulate and increased blood flow in left and right posterior cingulate, and left parahippocampal gyrus, compared with healthy volunteers [47]. Prior to treatment of unmedicated major depressed patients, a significant hypometabolism in various frontal regions and a significant hypermetabolism in the right hippocampus and parahippocampal gyrus were observed compared with controls. Metabolic activity in treatment responders showed a normalizing pattern in almost all the areas that had been characterized by metabolic abnormality at baseline, except for the medial prefrontal cortex. These results indicate that depressed patients remitted with antidepressant treatment were accompanied by alteration of regional glucose metabolism in the prefrontal cortical, limbic and paralimbic regions [48].

In general, most results were generated by anterior tVNS. Nevertheless, posterior tVNS has the tendency to decrease the BOLD signal in the limbic areas like the uncus, the anterior and subgenual cingulate cortex. The anterior cingulate cortex is a key structure of cognitive control of emotion [49]. Anterior cingulate activation is related to a positivity bias and emotional stability in successful aging [50], i.e., a successful process of emotional adaptation to the challenge of aging. Anterior cingulate cortex inhibition seems to play a major role in cognitive control in late-life depression [51].

The technique of tVNS is similar to the well-known transcutaneous electrical nerve stimulation, called TENS, which has proven to be of great therapeutic benefit in pain relief throughout the world [52,53]. The auricular TENS technique has again been proven to electrically stimulate specific brain regions. Infrared laser acupuncture found similar BOLD fMRI changes in healthy individuals [54]. Regions with significantly increased activation included the limbic cortex (cingulate) and the frontal lobe (middle and superior frontal gyrus). Laser acupuncture tended to be associated with ipsilateral brain activation and contralateral deactivation, which therefore cannot be simply attributed to somatosensory stimulation. Whether the change in prefrontal cortex is a primary event or secondary to changes in subcortical nuclei is unclear, but the relationship of treatment response to this suggests that it is biologically plausible that laser acupuncture might be an effective antidepressant treatment through its effects on the above brain regions. New technologies are necessary and need to be established in the field of antidepressant treatment, tVNS representing one of the promising new principles [55]. tVNS may provide a new method of cranial non-invasive electrical nerve stimulation to supplement the invasive method of vagus nerve stimulation that has become increasingly popular in neurology and psychiatry.

Limitations

There are several limitations to this pilot study that should be noted. The samples used in the current study were not large and our observations solely reflect the acute changes in brain activation induced by tVNS. Comparable studies of invasive VNS tend to refer to long-term effects, which will have to be addressed in future tVNS studies. The physiological impact and possible adverse effects of tVNS in long-term use remain open. Furthermore, potential differences in the effects of tVNS in healthy controls and in patients with specific disorders (e.g., depression) should be kept in mind and clarified in future clinical studies. Anterior-sham and posterior-sham stimulation were performed in two different subject groups, so inter-individual anatomical variability has to be taken into account when considering contrasts. Electrodes and the stimulation may produce artefacts on the BOLD signal; however, the changes in the BOLD signal were very slow and followed the on and off of the electrical stimulation with a latency which is in accordance with the time course to be expected from the neurovascular coupling of the BOLD source [56]. It may be that the stimulations produced effects on the brain activations which outlast the stimulation periods and compromised the baselines. Moreover, it remains unclear whether vagal afferences are the decisive cause of the displayed fMRI hypo- and hyperactivations by tVNS. Alternatively, cranial nerves other than the vagus nerve, like the glossopharyngeal nerve or the trigeminal nerve, might also be responsible for the observed effects, because the outer ear has several innervations [57]. Therefore, further studies are necessary to confirm tVNS induced activations of brain stem nuclei like the tractus
nucleus solitarius. The question of how such effects might be excluded also remains.

Conclusion

The proposed novel method of electrical transcutaneous vagus nerve stimulation (tVNS) leads to prominent changes in cerebral activation patterns, showing marked deactivation of limbic and temporal brain areas in functional magnetic resonance imaging. Further studies now have to clarify whether the prominent effects of this new method might be attributed to vagus nerve or to other specific or unspecified cranial nerve activations.

In this confirmative study to examine the effects of a potential non-invasive vagus nerve stimulation in healthy subjects, the best area of stimulation with regard to efficacy, practicability and subjects’ convenience was found to be the anterior wall of the left outer auditory canal. Prospective studies are required to show long-term effects of tVNS and its impact on patients with neuropsychiatric diseases.

References


