Archival Report

Biological Psychiatry

Transcutaneous Vagus Nerve Stimulation Modulates Default Mode Network in Major Depressive Disorder

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ABSTRACT

BACKGROUND: Depression is the most common form of mental disorder in community and health care settings and current treatments are far from satisfactory. Vagus nerve stimulation (VNS) is a Food and Drug Administration approved somatic treatment for treatment-resistant depression. However, the involvement of surgery has limited VNS only to patients who have failed to respond to multiple treatment options. Transcutaneous VNS (tVNS) is a relatively new, noninvasive VNS method based on the rationale that there is afferent/efferent vagus nerve distribution on the surface of the ear. The safe and low-cost characteristics of tVNS have the potential to significantly expand the clinical application of VNS.

METHODS: In this study, we investigated how tVNS can modulate the default mode network (DMN) functional connectivity (FC) in mild or moderate major depressive disorder (MDD) patients. Forty-nine MDD patients were recruited and received tVNS or sham tVNS (stVNS) treatments.

RESULTS: Thirty-four patients completed the study and were included in data analysis. After 1 month of tVNS treatment, the 24-item Hamilton Depression Rating Scale score reduced significantly in the tVNS group as compared with the stVNS group. The FC between the DMN and anterior insula and parahippocampus decreased; the FC between the DMN and precuneus and orbital prefrontal cortex increased compared with stVNS. All these FC increases are also associated with 24-item Hamilton Depression Rating Scale reduction.

CONCLUSIONS: tVNS can significantly modulate the DMN FC of MDD patients; our results provide insights to elucidate the brain mechanism of tVNS treatment for MDD patients.

Keywords: Default mode network, fMRI, Functional connectivity, Major depressive disorder, Transcutaneous vagus nerve stimulation, Vagus nerve stimulation

http://dx.doi.org/10.1016/j.biopsych.2015.03.025

Major depressive disorder (MDD) is the fourth leading cause of disability worldwide (1) and is projected to become the second leading cause of disability worldwide by the year 2020 (2,3). Despite the critical need, current treatments for this disorder are far from satisfactory due to high nonresponse rates to treatments, high relapse rates, and frequent intolerable side effects (1,3).

Vagus nerve stimulation (VNS) is a relatively new Food and Drug Administration approved somatic treatment for treatment-resistant depression that can produce significant and clinically meaningful antidepressant effects (1,4–6). However, the involvement of surgery, perioperative risks, and potentially significant side effects has limited this treatment to patients who have been treated for depression in the past but have failed to respond to at least four prescribed medications and/or established somatic treatment options such as electroconvulsive therapy for MDD (7).

To overcome the potential barriers of applying VNS, a noninvasive VNS method, transcutaneous vagus nerve stimulation (tVNS), has been developed. The rationale for using tVNS on the ear is based on anatomical studies that suggest that the ear is the only place on the surface of the human body where there is afferent vagus nerve distribution (8,9). Thus, direct stimulation of the afferent nerve fibers on the ear should produce an effect similar to classic VNS in reducing depressive symptoms but without the burden of surgical intervention (10,11). In past years, tVNS has been applied to treat MDD (10) and other disorders such as epilepsy (12,13), and prediabetes (14). Yet, the underlying mechanism of tVNS remains unclear.

In past decades, with the aid of brain imaging tools, accumulating evidence has demonstrated that MDD is associated with structural and functional abnormalities in brain circuits involved in emotional processing, self-representation, reward, and external stimulus (stress, distress) interactions (15–22); these brain regions include the hippocampus, amygdala, anterior cingulate cortex, and medial prefrontal cortex.

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 ISSN: 0006-3223

Interestingly, these brain regions also fall within the default mode network (DMN), a brain network believed to be involved in self-referential processing, affective cognition, and emotion regulation (23,24).

Thus, the DMN functional connectivity (FC) has drawn investigators' attention in MDD research (25–29). Studies have found DMN functional connectivity changes in MDD patients (30–36), and these changes are associated with psychiatric measurements, such as rumination score, in MDD patients. For instance, studies have found increased functional connectivity of DMN with the subgenual anterior cingulate cortex in MDD patients (26,30). After transcranial magnetic stimulation treatment, the abnormal increase in functional connectivity of DMN and subgenual anterior cingulate cortex was reduced (34). These studies demonstrated that the FC of DMN can be a useful tool in understanding the underlying mechanism of MDD treatment.

In this study, we investigated the resting state functional connectivity (rsFC) changes after the longitudinal tVNS as compared with sham tVNS (stVNS) in patients with mild or moderate depressive symptoms. We hypothesize that the longitudinal tVNS may significantly modulate the rsFC of DMN and reduce symptoms in MDD patients.

METHODS AND MATERIALS

Study Population

Forty-nine patients with mild or moderate MDD were recruited for the trial. ICD-10 classification of mental and behavioral disorders was used for diagnosis of MDD. Patients who voluntarily provided informed consent and met inclusion/exclusion criteria were enrolled in this study.

Inclusion criteria included the following: 1) patient meets ICD-10 diagnosis standard: mild (two typical + two other core symptoms) or moderate (two typical + three other core symptoms); 2) patient is 16 to 70 years of age; 3) patient stopped taking antidepressive medication or other psychiatric medications 2 weeks before the intervention started; 4) patient has a junior high school education and can understand the scales; and 5) patient has exhibited symptoms for at least 2 months but no longer than 2 years.

Exclusion criteria included the following: 1) patients with current addiction to drugs; 2) patients with severe depression or suicidal thoughts; 3) patients with other severe organic diseases, such as severe heart disease, kidney failure, etc; and 4) patients who did not agree to sign the consent form.

Recruitment Procedures

All patients were recruited using advertisements and by sending flyers to the four hospitals involved in the study. In this study, tVNS was the only treatment the patients received. Due to safety concerns and to increase the homogeneity of the study, we decided to include only patients with mild or moderate depressive symptoms. After passing a prescreening, potentially eligible patients provided informed consent in the presence of a study physician.

We used a single-blinded clinical trial to investigate the antidepressant effects of solo tVNS treatment. The first cohort received tVNS. After demonstrating the effect of tVNS, we recruited the second cohort of patients who received 4 weeks of sham tVNS as a control in this study.

Intervention

After screening, all patients were trained to apply the tVNS or stVNS. All subsequent treatments were self-administered by the patients at home. Patients were also instructed to complete a patient diary booklet each day to describe any side effects corresponding with or temporally related to treatment. The investigators checked all booklets at the end of 4-week treatment. All procedures performed in the stVNS treatment group were identical to the procedures for the tVNS group.

tVNS Treatment

Location. The points for tVNS are located in the auricular concha area where there are rich vagus nerve branch distributions (Figure 1).

Intervention Procedure. Patients took a seated position or laid on their side. After the stimulation points were disinfected according to standard practice, ear clips were attached to the ear area (auricular concha) at the stimulation site. Stimulation parameters included the following: 1) density wave adjusted to 20 Hz, with a wave width less than 1 ms; and 2) intensity adjusted based on the tolerance of the patient (4–6 mA). Each treatment lasted 30 minutes and was carried out twice a day, at least 5 days per week, for the duration of the treatment period (4 weeks).

stVNS Treatment

Location. The stimulation points for stVNS are located at the superior scapha (outer ear margin midpoint) where there is no vagus nerve distribution (Figure 1).

Since all treatments were self-administered by the MDD patients, all patients were required to complete daily entries in a diary that was checked during assessments (at the end of week 4) to enhance compliance.

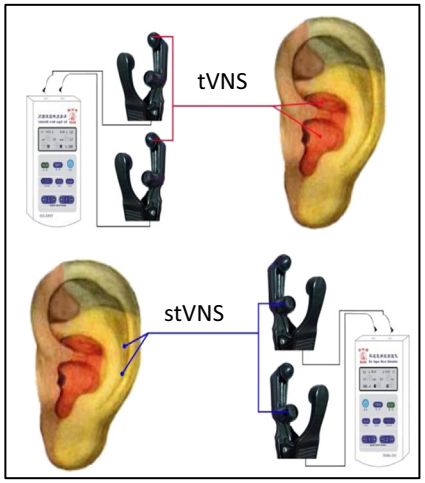

Figure 1. Locations of the stimulation electrodes on the auricular surface for transcutaneous vagus nerve stimulation (tVNS) and sham transcutaneous vagus nerve stimulation (stVNS).