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# A distinct biomarker of continuous transcutaneous vagus nerve stimulation treatment in major depressive disorder

Yiheng Tu [a, 1], Jiliang Fang [b, 1], Jin Cao [a, d], Zengjian Wang [a], Joel Park [a], Kristen Jorgenson [a], Courtney Lang [a], Jun Liu [b], Guolei Zhang [b], Yanping Zhao [b], Bing Zhu [c], Peijing Rong [c, **], Jian Kong [a, *]

[a] Department of Psychiatry, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA, USA
[b] Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing, China
[c] Institution of Acupuncture and Moxibustion, China Academy of Chinese Medical Sciences, Beijing, China
[d] School of Acupuncture Moxibustion and Tuina, Beijing University of Chinese Medicine, Beijing, China

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ABSTRACT

*Background:* Major depression is the fourth leading cause of disability worldwide and poses a socio-economic burden worldwide. Transcutaneous vagus nerve stimulation (tVNS) is a promising noninvasive clinical device that may reduce the severity of major depression. However, the neural mechanism underlying continuous tVNS has not yet been elucidated.

*Objective:* We aimed to explore the effect of hypothalamic subregion functional connectivity (FC) changes during continuous tVNS treatment on major depressive disorder (MDD) patients and to identify the potential biomarkers for treatment outcomes.

*Methods:* Forty-one mild to moderate MDD patients were recruited and received either real or sham tVNS treatment for 4 weeks. We used a seed-to-whole brain approach to estimate the FC changes of hypothalamic subregions and their surrounding control areas during continuous tVNS treatment and explored their association with clinical outcome changes after 4 weeks of treatment.

*Results:* Of the thirty-six patients that completed the study, those in the tVNS group had significantly lower scores on the 24-item Hamilton Depression (HAM-D) Rating Scale compared to the sham tVNS group after 4 weeks of treatment. The FC between the bilateral medial hypothalamus (MH) and rostral anterior cingulate cortex (rACC) was significantly decreased during tVNS but not during sham tVNS. The strength of this FC was significantly correlated with HAM-D improvements after 4 weeks of tVNS.

*Conclusion:* The FC between the bilateral MH and rACC may serve as a potential biomarker for the tVNS state and predict treatment responses. Our results provide insights into the neural modulation mechanisms of continuous tVNS and reveal a potential therapeutic target for MDD patients.



## Introduction

Major depressive disorder (MDD), characterized by persistent sadness, pessimism, social withdrawal, low self-confidence, and compromised cognitive disabilities [1], has been recognized as the fourth leading cause of disability worldwide [2]. Despite the availability of a variety of treatments, around 30% of patients fail to respond to antidepressant medication [3] or psychological treatment [4]. Vagus nerve stimulation (VNS) is an effective Food and Drug Administration (FDA) approved method for treatment-resistant MDD [5–7]. However, the involvement of surgery, as well as potential side effects have largely limited its application [8].

* Corresponding author. Psychiatry Department, Massachusetts General Hospital, Harvard Medical School, Building 120, 2nd Ave, Suite 101C, Charlestown, MA 02129, USA.
** Corresponding author. Institute of Acupuncture and Moxibustion, China Academy of Chinese Medical Sciences, No 16. Dongzhimen Nan Xiao Street, Dongcheng District, Beijing 100700, China.
*E-mail addresses:* drrongpj@163.com (P. Rong), kongj@nmr.mgh.harvard.edu (J. Kong).
[1] Tu and Fang are co-first authors.

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Recently, transcutaneous VNS (tVNS), a noninvasive and safe variant of traditional VNS, has drawn the interest of researchers for treating MDD [8–12]. tVNS stimulates the afferent auricular branch of the vagus nerve located on the surface of the ear and produces a similar effect to classical VNS in reducing depressive symptoms without any surgical intervention [11,13]. Although tVNS has shown promising results in treating MDD patients in several studies [8,10,11], its underlying mechanism remains poorly understood.

Using functional magnetic resonance imaging (fMRI), investigators have studied resting-state functional connectivity (rsFC) changes before and after four weeks of treatment [10,14] and fMRI signal changes evoked by intermittent real and sham tVNS using a block design [8,9,15]. Yet, the neural mechanism of tVNS during continuous stimulation, which is the way tVNS is applied in our clinical report [11] and others [13], has rarely been studied. In this manuscript, we propose that continuous electrical stimulation may bring the brain into a new state, known as the "the continuous tVNS state" (for abbreviation, we call it the 'tVNS state' in the rest of the paper), offering researchers a new angle to explore the neural modulation and therapeutic effects of tVNS.

The hypothalamus is known to mediate many neuroendocrine and neurovegetative functions [16–18]. Through the hypothalamic-pituitary-adrenal (HPA axis), the hypothalamus drives both the acute cortisol response to stress and cortisol secretion in a circadian rhythm [19–21]. Although the maladaptive activation of the HPA axis is characterized across many studies of depressed patients, other hypothalamic functions and nuclei have remained largely unexplored. A recent study demonstrated decreased hypothalamic functional connectivity (FC) with the subgenual cortex in psychotic major depression, which suggests that hypothalamic communication with the rest of the brain is critically important for many physiological and psychological functions [22]. Therefore, studying how tVNS can modulate the FC of different hypothalamic subregions and its association with clinical improvement can provide us with a better understanding of the mechanism of tVNS and the pathophysiology of depression.

Recently, FC analyses have been widely used to explore the biomarkers for neurologic and psychiatric diseases in order to extend the focus from isolated regions to a network of regions [23–25]. Thus, in the present work, we explored baseline FC differences between the hypothalamus and other brain regions during continuous real and sham tVNS, as well as during the no-stimulation resting state before tVNS stimulation. In addition, we explored the association between FC strength during baseline treatment and clinical improvement after four weeks. We hypothesized that real but not sham tVNS would significantly modulate the FC of the hypothalamus in MDD patients, and this FC may serve as a distinct biomarker for the tVNS state, as well as predict treatment outcomes.

## Material and methods

The present study is based on a brain imaging study nested in a clinical trial (ChiCTR-TRC-11001201). The inclusion criteria (e.g., comorbidities, medications) and intervention details (e.g., equipment, MRI environmental setup, electrical stimuli) can be found in the clinical report [26]. In our prior imaging studies, a subset of 35 patients was used to investigate changes in the resting-state default mode network (DMN) after four weeks of tVNS treatment [10], and a subset of 38 patients was used to study the changes in fMRI signals induced by intermittent tVNS [9]. In this study, we focus on how 6 min of continuous tVNS modulates the FC of the hypothalamus, a key region in the limbic system, using a seed-to-whole-brain approach. This continuous tVNS dataset at baseline has never been analyzed or published before.

### *Participants*

The study was approved by the Institutional Ethics Committee of the China Academy of Chinese Medical Sciences. All experiments were performed in accordance with approved guidelines. Due to safety and ethical concerns and to increase the homogeneity of the study, we only included participants with mild or moderate depressive symptoms. All patients were recruited using advertisements and by sending flyers to the hospitals involved in the study. Forty-one patients with mild or moderate MDD were recruited for the trial. ICD-10 classification of mental and behavioral disorders was used for the diagnosis of MDD. Patients who voluntarily provided informed consent and met inclusion criteria were enrolled in this study.

Inclusion criteria: 1) Meets ICD-10 diagnosis standards for a depressive episode: mild (2 typical + 2 other core symptoms), moderate (2 typical + 3 other core symptoms); 2) 18–70 years of age; 3) Willing to stop taking anti-depressive or other psychiatric medications 2 weeks before beginning the intervention; 4) Junior high or higher level education; 5) Exhibit symptoms for 2 weeks to 2 years.

Exclusion criteria: 1) Ongoing addiction to drugs and/or alcohol; 2) Bipolar disorder; 3) Organic mental disorder; 4) Drug-induced depression; 5) Seasonal affective disorder; 6) Severe medical disorders; 7) Pregnant women; 8) Postpartum depression; 9) Dementia or other cognitive disorders; 10) Patients who do not agree to sign the consent form.

### *Procedures*

A single-blinded clinical trial was used to investigate the antidepressant effects of real tVNS treatment. The first cohort of patients all received real tVNS treatment for 12 weeks. After demonstrating the effect of tVNS, we recruited a second cohort of patients who received four weeks of sham tVNS before shifting to real tVNS for eight weeks. At the beginning of the treatment (baseline), the fMRI scans were applied during both resting state and 6-minutes of continuous real or sham tVNS. In this manuscript, we compared FC differences during continuous real tVNS and sham tVNS on the right ear at baseline, as well as predicted treatment outcomes after four weeks (Fig. 1, **A**).

### *Intervention*

The stimulation points for real tVNS are located in the auricular concha area where there is rich vagus nerve branch distribution (Fig. 1, **B**). Real tVNS was applied on the concha area of both ears simultaneously during the treatments except during the MRI scan in which tVNS was applied on the right ear. After being disinfected, electrodes were attached to the ear area (i.e. auricular concha) at the stimulation site. Stimulation parameters included: 1) density wave adjusted to 20 Hz with a wave width less than 1 millisecond and 2) intensity adjusted based on the tolerance of the patient (typically between 4 and 6 mA). Each treatment lasted 30 min and was carried out twice a day (i.e. once in the morning and once again in the evening), at least 5 days per week, for the duration of the treatment period (4 weeks). Patients were also instructed to record any side effects of treatment in a diary each day.

The treatment procedure of sham tVNS was the same as real tVNS except that the stimulation points for sham tVNS were located at the superior scapha (outer ear margin midpoint) where there is no vagus nerve distribution [26,27] (Fig. 1, **B**).

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