Brain Stimulation 12 (2019) 377–379

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

The effect of transcutaneous auricular vagus nerve stimulation on treatment-resistant depression monitored by resting-state fMRI and MRS: The first case report

Dear editor

Major depressive disorder (MDD) has a high prevalence rate and constitutes a leading cause of disability worldwide. Although there are various antidepressants available, approximately 35% of patients still can not achieve remission and progress to treatment-resistant depression (TRD) [1]. TRD is defined as an absence of response to at least two types of antidepressant drugs with adequate dose/duration [2]. Invasive vagus nerve stimulation (VNS) is a neural-modulation therapy, which has been approved for TRD by Food and Drug Administration in 2005 (FDA). However, the surgery-related side effects have limited its application. The transcutaneous auricular VNS (taVNS) was therefore developed and has shown similar efficacy to invasive VNS in MDD patients [3–5]. However, whether taVNS is also effective for TRD remains unknown. Therefore, we are conducting a clinical trial to confirm effectiveness of taVNS and to explore the potential mechanism (trial number: ChiCTR-1800014277).

A 55-year-old male with 20-year history of MDD was recruited in April 2018. This patient had failed to respond to 5 antidepressants including selective serotonin reuptake inhibitor (SSRI) paroxetine, citalopram, escitalopam, sertraline, and selective serotonin and noradrenline reuptacke inhibitor (SNRI) duloxetine. TRD diagnosis was confirmed by a senior psychiatrist (HX Wang) according to the criteria mentioned above [2]. At enrollment, the 17-item Hamilton Depression Scale (HAMD-17), 14-item Hamilton Anxiety Scale (HAMA-14), self-Rating Depression Scale (SDS), and self-Rating Anxiety Scale (SAS) scores of the patient were 18/20/46/55 respectively. The patient had been non-responsive to stable-dose escitalopam (SSRI) treatment more than 8 weeks before the baseline visit.

Given that previous researches have used a combination of VNS and antidepressants to treat TRD [3] and sudden withdrawal can cause symptoms to worsen, we assigned the patient taVNS and sertraline (SSRI)-(H:10980141) (50 mg/day). The taVNS started on April 10th and lasted for 8 weeks. The stimulator's ear electrode clips were attached to bilateral ear concha twice a day (in the morning and evening), each for 30 minutes with following parameters: intensity in 4–6 mA, frequency in 20 Hz, wave width less than 1 ms. The research protocol was approved by the ethic committee of Guang' anmen Hospital and the written informed consent was obtained from the patient.

BOLD fMRI and Mega-press ^{1}H-MRS scan were performed on a 3.0 T MRI scanner (MagnetomSkyra, Siemens, Germany) before and after 8-week taVNS. The BOLD fMRI scans lasted 6 minutes and 9 seconds (TR = 2500 ms, TE = 30 ms, 3 mm thickness, 43 slices). T1-weighted structural images were acquired with three dimensional fast spoiled gradient-echo sequence (TR = 5000 ms, TE = 2.98 ms, 1 mm thickness). MRS was conducted to examine the concentrations of amino acid neurotransmitters including gamma-aminobutyric acid (GABA) and glutamate (Glu). The region of interest (ROI) for MRS scan was located at the rostral anterior cingulate cortex (rACC) with the box size $35 \times 30 \times 25$ mm^3.

The preprocessing of resting-state fMRI data included slice timing, motion correction, regression out of motion parameters, linear trend, signals of cerebrospinal fluid and white matter, and whole-brain, normalization to Montreal Neurological Institute (MNI) space and re-sampling with $3 \times 3 \times 3$ mm^3 resolution, filtering with 0.01–0.1 Hz, and smoothing with 4 mm Gaussian kernel. We selected the bilateral rACC as the seed regions given its central role in emotional and cognitive processing [6]. The left and right rACC were defined with the central coordinates (−4, 37, 0; 4, 37, 0) and a radius of 3 mm. We extracted the mean time courses of signals of the seed regions and computed their correlations with the rest of the whole brain. Differences in functional connectivity (FC) before and after treatment beyond a given threshold level (0.5) cluster size (100 voxels) were considered to have a prominent change.

After treatment, the symptoms were improved and the scores of HAMD/HAMA/SDS/SAS decreased to 1/2/20/22. The patient did not show any relapsed symptoms at 3-month follow-up at Spt. 20th. We found increased right rACC FC with the lingual gyrus, and increased left rACC FC with the insula, dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), middle cingulate cortex (MCC), and precuneus (Fig. 1). The GABA/Glu concentrations before and after treatment were 0.0204/0.0781 and 0.0125/0.0701, indicating a prominent decrease.

Discussion

To our knowledge, this is the first case report that investigated the efficacy and neural mechanism of taVNS in TRD patient. The depressive symptoms were reduced by more than 50% after 8 weeks, suggesting a responsiveness to treatment. The symptomatic improvement was accomplished by increased FC between the left rACC and a set of regions including the bilateral precuneus, bilateral insula, right DLPFC, left ACC, left MCC, and between the right rACC

https://doi.org/10.1016/j.brs.2018.11.013
1935-861X/© 2018 Elsevier Inc. All rights reserved.

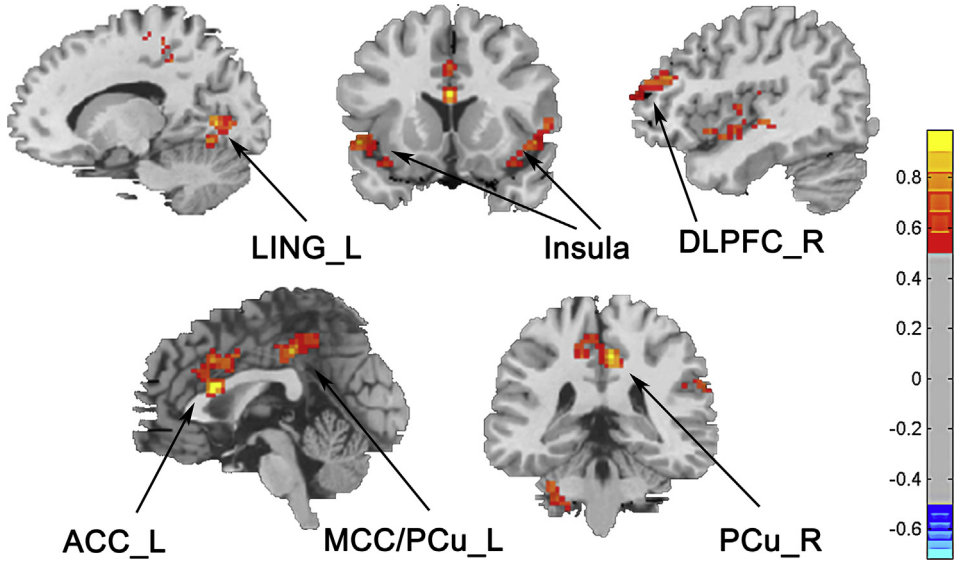

Fig. 1. Changes in rACC FC following taVNS treatment. Red colors indicate the brain reg-ions showing increased rACC FC in post-treatment compared with pre-treatment. L, left; R,right. DLPFC, dorsolateral prefrontal cortex; ACC, anterior cingulate cortex; MCC, middle cingulate cortex; PCu, precuneus; LING, lingual gyrus. Color bar indicates the intensity of FC.

and left lingual gyrus, but decreased neurotransimitter concentrations of GABA and Glu.

The precuneus is a central component within the DMN, which is highly active at rest and is involved in self-related cognitive activity. The DLPFC and ACC are key brain regions in emotion and reward information regulation [7]. Being a hub for emotional and saliency processing, the insula is considered important in MDD neuropathology, and is a potential predictor for taVNS efficacy in MDD patients [8]. More relevantly, the FC in these regions have been modulated by VNS [3,5,8].

TRD patients are associated with decrease FC mainly in the anterior and posterior DMN. Disturbed activity in the DMN has been associated with self-reflection, affective cognition, and emotion regulation that characterize MDD [9]. The treatment outcome of this case suggests that taVNS could enhance the FC of the DMN. Therefore, the enhanced FC might be the main cause of improved depressive symptoms as similar as our previous taVNS on MDD [5,8]. Given that the lingual gyrus is within the visual-related occipital cortex, it is likely that the relieving of blurring symptoms might be mediated by the functional change in this region.

In addition, we found decreased concentrations of GABA and Glu in the patient following treatment. A previous study has shown abnormal GABA/Glu cycling in the occipital cortex and ACC of TRD patients [10]. We therefore speculate that lowering the GABA and Glu concentrations in the rACC might be involved in taVNS for TRD.

It would be ideal to include patients free of medication. However, the recruitment of drug-naive patients with TRD has ethical concern. For safety considerations, and to ensure the consistency of medication in the clinical trial, we designed to give all patients sertraline (SSRI). Given that the patient had been non-responsive to sertraline, we could believe that the clinical improvement and brain function changes of the patient were largely induced by taVNS rather than antidepressant. Further studies with more cases are needed to confirm our findings.

Acknowledgment

This paper is supported by the Fundamental Research Funds for National Natural Science Foundation of China (81774433), National Natural Science Foundation Youth Project of China (81701779), Beijing Municipal Science and Technology Commission (Z161100002616003), Joint Sino-German Research Project (GZ1236), Guangdong Province Higher Vocational Colleges & Schools Pearl River Scholar Funded Scheme (2018) A1-AFD018181Z3905. There are no conflicts of interest. We thank Associate Professor Jian-Kong, Professor Chun-Hong Liu, Dr. De-Qiang Gao, Miss Li-Lan Wang for their excellent revising opinions to this manuscript.

References

[1] Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. Acute and longer–term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry 2006;163(11):1905–17. https://doi.org/10.1176/ajp.2006.163.11.1905.

[2] Sackeim HA. The definition and meaning of treatment–resistant depression. J Clin Psychiatr 2001;62(16):10–7 [PubMed: 11480879].

[3] Conway CR, Chibnall JT, Gebara MA, Price JL, Snyder AZ, Mintun MA, et al. Association of cerebral metabolic activity changes with vagus nerve stimulation antidepressant response in treatment–resistant depression. Brain Stimul 2013;6(5):788–97. https://doi.org/10.1016/j.brs.2012.11.006.

[4] Hein E, Nowak M, Kiess O, Biermann T, Bayerlein K, Kornhuber J, et al. Auricular transcutaneous electrical nerve stimulation in depressed patients: a randomized controlled pilot study. J Neural Transm 2013;120(5):821–7. https://doi.org/10.1007/s00702-012-0908-6.

[5] Fang J, Rong P, Hong Y, Fan Y, Liu J, Wang H, et al. Transcutaneous vagus nerve stimulation modulates default mode network in major depressive disorder. Biol Psychiatry 2016;79(4):266–73. https://doi.org/10.1016/j.biopsych.2015.03.025.

[6] Pizzagalli DA. Frontocingulate dysfunction in depression: toward biomarkers of treatment response. Neuropsychopharmacology 2011;36(1):183–206. https://doi.org/10.1038/npp.2010.166.

[7] Umemoto A, HajiHosseini A, Yates ME, Holroyd CB. Reward–based contextual learning supported by anterior cingulate cortex. Cognit Affect Behav Neurosci 2017;17(3):642–51. https://doi.org/10.3758/s13415-017-0502-3.

[8] Fang J, Egorova N, Rong P, Liu J, Hong Y, Fan Y, et al. Early cortical biomarkers of longitudinal transcutaneous vagus nerve stimulation treatment success in depression. Neuroimage Clin 2016;14(C):105–11. https://doi.org/10.1016/j.nicl.2016.12.016.
[9] de Kwaasteniet BP, Rive MM, Ruhé HG, Schene AH, Veltman DJ, Fellinger L, et al. Decreased resting–state connectivity between neurocognitive networks in treatment resistant depression. Front Psychiatr 2015;6:28. https://doi.org/10.3389/fpsyt.2015.00028.
[10] Price RB, Shungu DC, Mao X, Nestadt P, Kelly C, Collins KA, et al. Amino acid neurotransmitters assessed by ^{1}H MRS: relationship to treatment–resistance in major depressive disorder. Biol Psychiatry 2009;65(9):792–800. https://doi.org/10.1016/j.biopsych.2008.10.025.

Xiao-Jiao Li[1]
Department of Radiology, Guang' anmen Hospital, China Academy of Chinese Medical Sciences, Beijing, China

Li Wang[1], Hong-Xing Wang
Department of Neurology, Xuanwu Hospital, Capital Medical University, Beijing, China

Lei Zhang, Guo-Lei Zhang
Department of Radiology, Guang' anmen Hospital, China Academy of Chinese Medical Sciences, Beijing, China

Pei-Jing Rong[**]
Institute of Acupuncture and Moxibustion, China Academy of Chinese Medical Sciences, Beijing, China

Ji-Liang Fang[*]
Department of Radiology, Guang' anmen Hospital, China Academy of Chinese Medical Sciences, Beijing, China

[**] Corresponding author. Institute of Acupuncture and Moxibustion, China Academy of Chinese Medical Sciences, No. 16 Dongzhimen Nan Xiao Street, Dongcheng District, Beijing, 100700, China.

[*] Corresponding author. Guang' anmen Hospital, China Academy of Chinese Medical Sciences, No. 5 Bei xian'ge Street, Xicheng District, Beijing, 100053, China.
E-mail address: drrongpj@163.com (P.-J. Rong).
E-mail address: fangmgh@163.com (J.-L. Fang).

1 November 2018
Available online 27 November 2018

[1] Co-first author: Xiao-Jiao Li and Li Wang contributed to the manuscript equally.