Brain Stimulation 12 (2019) 824–826

Contents lists available at ScienceDirect

Brain Stimulation

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

Transcutaneous auricular vagus nerve stimulation in treating post-stroke insomnia monitored by resting-state fMRI: The first case report

Keywords:
Post stroke insomnia
taVNS
Neuromechanism
New technique
Case report

To the Editor

Post-stroke insomnia (PSI) is one of the most frequent complications in the patients with cerebrovascular diseases. About 37–59% of the stroke patients report insomnia complaints [1]. Moreover, researches have indicated that insomnia is related to the increased cardiocerebrovascular morbidity and decreased stroke outcome [2]. Cognitive behavioral therapy (CBT) and drug intervention are the common treatments for PSI, however, because of dissatisfacted efficiency and side effects of drugs [1], it is very urgent to find an effective, safe and convenient complementary and alternative therapy. Transcutaneous auricular vagus nerve stimulation (taVNS) has a beneficial effect on depression with insomnia and primary insomnia [3,4]. Could it be effective for people with PSI? This case report would explore the efficacy and neuromechanism for the PSI patient treated with taVNS (clinical trial number: ChiCTR-TRC-13003519). BOLD-fMRI was performed before and after four weeks' taVNS.

The patient, male, 64 years old, suffered from left temporal lobe hemorrhage due to hypertension seven months ago. He had been diagnosed as PSI and treated by the licensed neurologists and Chinese medicine practitioners in the hospital. After two months of intermittent treatment with Western medicines (Estazolam, 1 mg per night before sleeping) and Chinese herbal medicine plus body acupuncture, the symptoms of insomnia had not been effectively controlled, and still complained as difficulties in initiating sleep (sleep onset needs to 60–100 min), frequent awakenings, early morning awakening and non-restorative sleep (the effective sleep duration was only 3 h). Before receiving the treatment, the patient had been enrolled and notified of the insomnia trial procedure, and signed the informed consent form.

The patient was trained to apply of taVNS by himself as our previous study [4], and then he finished taVNS treatment at home without receiving other treatment for insomnia. The treatment was performed twice a day (in the early morning and late evening), and his bilateral auricular concha areas were stimulated with taVNS with the intensity of 4–6 mA and the frequency of 20 Hz (wave width less than 1 ms). Each stimulation was conducted for 30 min in four consecutive weeks. The main efficacy index was evaluated by the Pittsburgh Sleep Quality Scale (PSQI).

fMRI images were obtained by 3.0T MRI(Skyra, Siemens, Germany), and the echo planar imaging (BOLD) sequence was conducted for 7 min each time (TR/TE = 2500 ms/30 ms, slice thickness = 3 mm, number of slices = 43). A Brain fMRI for healthy person was also performed as the normal control.

After four weeks of taVNS treatment, the patient's symptoms of insomnia were significantly improved. The falling asleep time was reduced to less than 30 min, and sleep duration was up to 7 h. The therapeutic effect was still lasted in the follow-up period (three months after post-treatment). The PSQI score dropped from 13 points to 8 points (the cutoff score for non-insomnia symptoms).

The posterior cingulate cortex (PCC), which is a central node within the default mode network (DMN), was selected to examine the FC of DMN by seed-based approach (software: SPM8, http://www.fil.ion.ucl.ac.uk/spm and DPARSF, http://www.restfmri.net/forum/DPARSF). Brain regions beyond a corrected threshold level (0.4) were considered having significant FC changes. The FC between PCC and other nodes of the DMN showed hyperconnectivity before treatment (Fig. 1A), but it decreased following four weeks' taVNS treatment (Fig. 1B and D). However, FC between PCC and lingual gyrus (LING), and the cortex surrounding calcarine fissure (CAL), striatum (pallidum, putamen), thalamus increased after taVNS treatment (Fig. 1C).

Discussion

Our result showed the significant improvement after taVNS compared with medication for this patient. Regarding the brain mechanism, the most widely accepted pathophysiology model of insomnia is the hyperarousal theory. Recent insomnia functional imaging studies have suggested that the changed DMN functional connectivity is associated with the hyperarousal symptoms, and the brain regions of DMN may exist higher levels of activity during the sleep stages [5,6]. DMN in insomnia also showed hyper-responses to sleep-related stimuli, and the effective CBT could reduce the hyper-responses [6]. In our previous study, we had found that taVNS can significantly modulate the DMN connectivity and reduce symptoms in depression patients accompanied with insomnia [4]. In the present study, PCC and other brain regions belonging to the DMN showed higher functional connectivity

https://doi.org/10.1016/j.brs.2019.02.016

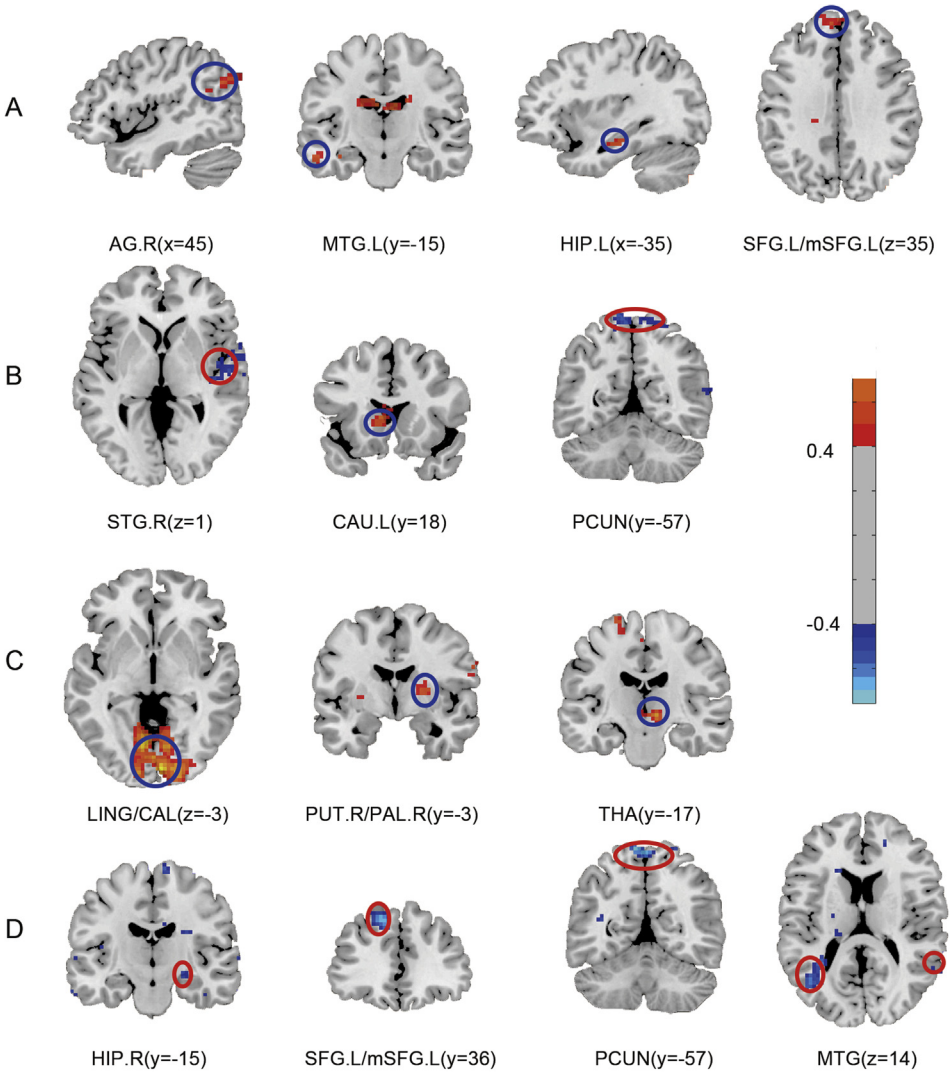

Fig. 1. PCC FC of patient compared with healthy people'(A) before and (B) after taVNS treatment. (C) Increased and (D) Decreased PCC FC changes following taVNS treatment. L: left, R: right. AG, angular gyrus; MTG, middle temporal gyrus; HIP, hippocampus; SFG, superior frontal gyrus; mSFG, medial superior frontal gyrus; STG, superior temporal gyrus; CAU, caudate nucleus; PCUN, precuneus; LING, lingual gyrus; CAL, calcarine fissure and surrounding cortex; PUT, putamen; PAL, pallidum; THA, thalamus. Color bar shows the intensity of FC.

before treatment and the DMN connectivity decreased after four weeks of taVNS treatment. So the modulation effects on DMN functional connectivity may be major contribute to the effectiveness of taVNS on PSI.

Expect for an important node of DMN, the angular gyrus (AG) has been known as the involvement in the modulation of visuospatial attention. PCC also play a role of spatial information processing. FC between PCC and AG increased in the patient, suggesting that compensatory mechanisms may have been employed, which could be mediated by taVNS. Previous researches have revealed visual processing capacity reduced in sleep deprived persons and taVNS treatment can relieve blurring symptoms in depressed patient by modulating LING functional change [7,8]. Given that the LING and CAL are within the visual-related occipital gyrus, it is likely that the role of taVNS in PSI might be related to visual cortex functional change.

The basal ganglia (BG) participate in part of emotional function through association with frontal lobe and thalamus [9], and reduced FC in the striatum and thalamus may suggest an emotional circuit disorder [10]. We found PCC and brain regions of BG related to emotion showed higher functional connectivity after taVNS treatment. It is speculated that taVNS on the emotional circuit may benefit of PSI.

To our knowledge, this is the first case of taVNS in a patient with PSI. The current case study shed light on that taVNS may potentially provide a new portable, self-managed and safe technique for treating PSI patients. A larger sample size of randomized controlled trial is still needed to confirm our preliminary findings.

Acknowledgment

This paper is supported by National Natural Science Foundation of China (81473780,81774433), Joint Sino-German Research Project (GZ1236), Beijing Municipal Science and Technology Commission (Z161100002616003). There are no conflicts of interest. We thank Yan-Zhi Bi PhD., Miss Xiao-Jiao Li, Dr.Yu Wang, Dr. Shao-Yuan Li, Dr. Li-Wei Hou, Miss Jin-Ling Zhang, and Mr. Ming Han for their experiment assistance or excellent revising opinions to this manuscript.

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25 January 2019
Available online 21 February 2019

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