Brain Stimulation 12 (2019) 361–363

Contents lists available at ScienceDirect

Brain Stimulation

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

Trigeminal nerve stimulation successfully awakened an unconscious patient

Dear Editor,

Disturbance of consciousness is due to the failure of the arousal system, which is very common among patients who suffer from severe brain injuries. Although therapeutic strategies for unconsciousness arousal have been studied worldwide for decades, no strong evidence could be seen from the clinical outcomes. Electrical stimulation, especially median nerve electrical stimulation (MNS), has drawn much attention for coma therapy in recent years, yet no report is found on trigeminal nerve electrical stimulation (TNS) in this area. Here, we present a case report of a patient with 3-month history of unconsciousness after pituitary tumor resection. The patient successfully gained consciousness from 6 weeks of continuous TNS. We report for the first time on coma arousal by TNS application, which provides unique insight for the future clinical works.

Case report

A 40-year-old man was presented to the rehabilitation department with a 3-month history of unconsciousness with history of pituitary tumor resection 3 months prior to admission, followed by lateral ventricle dilatation and disturbance of consciousness. Resuscitating therapies including hyperbaric oxygen therapy, comprehensive sensory stimulation, median nerve electrical stimulation (MNS) and conventional drugs were employed but no significant improvement was recorded.

Physical examination revealed normal vital signs, with normal cardiopulmonary findings. No obvious edema and hemorrhage were found on the computed tomography (CT) scan of the brain. Glasgow Coma Scale (GCS) revealed a cumulative score of 7 (Eye: 2; Verbal: 1; Motor: 4), demonstrating a severe state of unconsciousness. Additional clinical signs included diminished tendon reflexes of the limbs and a positive Babinski sign on the left side. Complete blood cell count, renal function test, liver function test and cerebrospinal fluid test were normal.

Diagnosis

Persistent vegetative state (PVS).

Novel therapeutic strategy to this patient

After receiving the informed consent of the patient's spouse, we started trigeminal nerve electrical stimulation (TNS) treatment on the patient. Low-frequency electrical neuromuscular stimulator was applied. 2 pairs of electrodes were attached to the bilateral superior orbital fissure and suborbital foramen to stimulate the ophthalmic nerve (V1) and the maxillary nerve (V2). The stimulation parameters were set at a current intensity of 18–20mA with a pulse width of 200 microseconds at 40 Hz for 30 sec/min. The TNS treatment was done continuously for 6 h per day for a total of 6 weeks.

Functional MRI (fMRI) examination was performed immediately before and after the TNS treatment to evaluate the patient's activity maps. First, several preprocessing steps were conducted as following: remove the first 10 vol, slice-timing correction, head motion correction, spatial normalization, nuisance covariates regression, band-pass filter (0.01–0.1 Hz), to remove the spurious noise. Then, we set each voxel as nodal, inter-nodal Pearson's correlation coefficient (r) as weight to construct the voxel wise network. Degree centrality (DC) for each voxel was computed by counting the number of the connections of the voxel with other voxels in the whole brain. Finally, we converted the DC value to z-scores, and compared the zDC value to detect the changes of brain activity.

Outcome

The patient gained spontaneous eye opening and exclamatory articulated speech four weeks after TNS treatment, with a GCS score 11 (Eye: 4; Verbal: 3; Motor: 4). We continued the therapy for 2 more weeks and successfully awakened the patient fully, with a GCS score of 15 (Eye: 4; Verbal: 5; Motor: 6).

During the therapeutic process, blood testing and cerebrospinal fluid test were found to be normal. The muscle strength of all four limbs was level 4. Diminished tendon reflexes and a positive Babinski sign on the left side remained unchanged. fMRI revealed significant differences of degree centrality (DC) between the pre-scan and post-scan of the patient in several brain regions (Fig. 1), which were located in cerebelum_Crus2 (CB_Crus2), inferior temporal gyrus (ITG), inferior frontal gyrus, triangular part (IFGtriang), postcentral gyrus (PoCG), precentral gyrus (PreCG), and supplementary motor area (SMA), indicated the brain activity changes after the TNS treatment.

Discussion

Disturbance of consciousness is very common among patients who suffered from severe brain injuries, such as traumatic brain injury (TBI) and major complications post-craniocerebral operation [1,2]. Several therapeutic attempts developed for unconsciousness arousal have been promising, including pharmacological agents,

https://doi.org/10.1016/j.brs.2018.11.001

A

Index	Peak location (AAL-90)	No. of voxels	Peak *d*-value	Peak coordinate in MNI space		
				x	y	z
1	CB_Crus2.L	100	4.43	-39	-72	-45
2	ITG.R	233	4.42	48	-48	-24
3	IFGtriang.L	94	-4.26	-45	21	0
4	PoCG.L	101	-4.31	-60	-18	24
5	PreCG.L	115	-4.97	-36	-21	60
6	SMA.R	107	-5.42	3	6	75

B

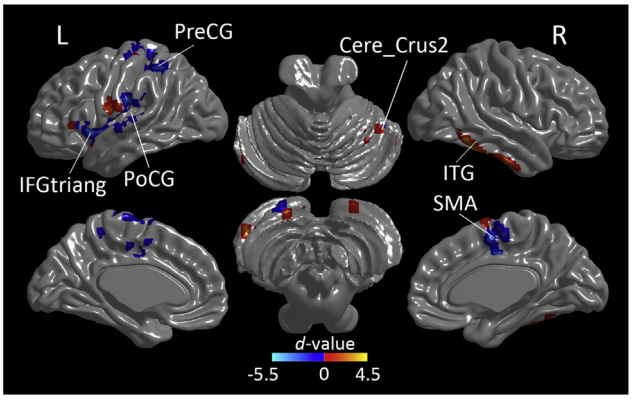

Fig. 1. Degree centrality analysis between the pre-scan and post-scan in the patient using fMRI scan. **(A)** Brain regions showing significant differences in the degree centrality (DC) between the pre-scan and post-scan in the patient ($d > 2.18$, cluster number>90, Uncorrected)). The brain regions were reported by the Anatomical Automatic Labeling (AAL-90) template with xjview8 (http://www.alivelearn.net/xjview/). **(B)** Brain regions with significant differences in the degree centrality (DC) between the pre-scan and post-scan in the patient ($d > 2.18$, cluster number>90, Uncorrected). The warm (cool) color means significantly increased (decreased) DC in the post-scan compared to the pre-scan in the patients. **Abbreviations:** CB_Crus2, cerebelum_Crus2; ITG, inferior temporal gyrus; IFGtriang, inferior frontal gyrus, triangular part; PoCG, postcentral gyrus; PreCG, precentral gyrus; SMA, supplementary motor area; L (R), left (right) hemisphere. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

hyperbaric oxygen therapy, comprehensive sensory stimulation, music therapy, transcranial magnetic stimulation and surgical treatment. Although vast studies have been conducted, no strong evidence was found for these approaches [3,4]. Thus, there is an urgent need to develop more effective strategies to enhance patient's full recovery.

Electrical stimulation for coma or PVS has been increasingly studied over the past decades, especially in the erea of MNS. However, the mechanisms of MNS on coma arousal were yet to be fully understood.

TNS appears to be an effective approach to manage some neurological disorders, such as epilepsy and depression [5,6]. Our patient gained full consciousness from 6 weeks of continuous TNS. To the best of our knowledge, TNS has never been reported to be used in coma or PVS before. Interestingly, *in vivo* study showed that TNS manifested neuroprotective effects in rat model of TBI [7]. The mechanism of TNS on neuroprotection after TBI may include cerebral blood flow (CBF) and metabolism improvement. In our case, we found increased DC in cerebellum and ITG.R after TNS, and decreased DC in several regions including IFGtriang, PoCG, PreCG and SMA. These brain regions have been suggested as being involved in a variety of functions, such as language, attention, working memory, visual consciousness, motor-related information processing and somatic sensory function, etc. [8–10]. Although the exact role of the DC alterations of these regions remains unknown, we speculate that the brain CBF and metabolism were regulated to some degree after TNS in this particular patient. In addition, there may be some other reasons for the effectiveness of TNS on unconsciousness awakening. One rationale is that the trigeminal nervous branches are peripheral portals to the central nervous system, and the sensory representation of the face in the cortex is disproportionately large compared to other parts of the body. Another hypothesis is that the sensory root of trigeminal nerve may have nerve fibers connecting with the reticular formation of the brain stem, while TNS may help maintain physiological arousal by activating the ascending reticular activating system.

Although the outcome of the patient in this case is encouraging, the precise mechanism of TNS is still unknown. Furthermore, we are not able to eliminate the possibility of spontaneous awakening in this patient. Thus, more in-depth researches should be done to provide sufficient evidence for a wider application of TNS on coma or PVS in clinical practice.

Conflict of interest disclosures

All the authors declare no conflict of interest.

Additional contribution

We thank the patient's wife for providing permission to share the information.

Funding information

This work was supported by grants from National Natural Science Foundation of China (81771201, 81671088, 81600959), Natural Science Foundation of Guangdong (2016A030311045), Guangzhou science and technology plan projects (201807010050) and Sun Yat-Sen Clinical Research Cultivating Program (SYS-C-201704).

References

[1] Dong L, Chen L, Shi T, Wei M, Zhang HZ, Li YP, et al. Combined monitoring of intracranial pressure and bispectral index in patients with severe craniocerebral trauma post-operatively. Clin Neurol Neurosurg 2016;148:42–4.
[2] Chua KS, Ng YS, Yap SG, Bok CW. A brief review of traumatic brain injury rehabilitation. Ann Acad Med Singapore 2007;36(1):31–42.
[3] Lei J, Wang L, Gao G, Cooper E, Jiang J. Right median nerve electrical stimulation for acute traumatic coma patients. J Neurotrauma 2015;32(20):1584–9.
[4] Lapitska N, Gosseries O, Delvaux V, Overgaard M, Nielsen F, Maertens de Noordhout A, et al. Transcranial magnetic stimulation in disorders of consciousness. Rev Neurosci 2009;20(3–4):235–50.
[5] DeGiorgio CM, Soss J, Cook IA, Markovic D, Gornbein J, Murray D, et al. Randomized controlled trial of trigeminal nerve stimulation for drug-resistant epilepsy. Neurology 2013;80(9):786–91.
[6] Shiozawa P, da Silva ME, Netto GT, Taiar I, Cordeiro Q. Effect of a 10-day trigeminal nerve stimulation (TNS) protocol for treating major depressive disorder: a phase II, sham-controlled, randomized clinical trial. Epilepsy Behav 2015;44:23–6.
[7] Chiluwal A, Narayan RK, Chaung W, Mehan N, Wang P, Bouton CE, et al. Neuroprotective effects of trigeminal nerve stimulation in severe traumatic brain injury. Sci Rep 2017;7(1):6792. Bisenius S, Trapp S, Neumann J, Schroeter ML. Identifying neural correlates of visual consciousness with ALE meta-analyses. Neuroimage. 2015;122:177-87.
[8] Buckner RL. The cerebellum and cognitive function: 25 years of insight from anatomy and neuroimaging. Neuron 2013;80(3):807–15.
[9] Zhao J, Liu J, Jiang X, Zhou G, Chen G, Ding XP, et al. Linking resting-state networks in the prefrontal cortex to executive function: a functional near infrared spectroscopy study. Front Neurosci 2016;10:452.
[10] Bisenius S, Trapp S, Neumann J, Schroeter ML. Identifying neural correlates of visual consciousness with ALE meta-analyses. Neuroimage 2015;122:177–87.

Shengnuo Fan[1]
Department of Rehabilitation Medicine, Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, 510120, China

Xiaoyan Wu[1], Mingwei Xie
Department of Radiology, Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, 510120, China

Xiao Li, Cuicui Liu
Department of Rehabilitation Medicine, Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, 510120, China

Yun Su
Department of Radiology, Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, 510120, China

Yuegui Chen, Shaoling Wu[*], Chao Ma[**]
Department of Rehabilitation Medicine, Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, 510120, China

[*] Corresponding author.

[**] Corresponding author.
E-mail addresses: wushaolinggz@126.com (S. Wu), ma_chao99@126.com (C. Ma).

10 October 2018
Available online 3 November 2018

[1] These authors contributed equally to this work.