Neuropsychiatric Disease and Treatment

CLINICAL TRIAL REPORT

Preliminary Study of Vagus Nerve Magnetic Modulation in Patients with Prolonged Disorders of Consciousness

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Background: The number of patients with prolonged disorders of consciousness (pDOC) is increasing. However, its clinical treatment remains challenging. To date, no studies have reported the effect of vagus nerve modulation (VNM) using repetitive transcranial magnetic stimulation (rTMS) in patients with pDOC. We aimed to evaluate the effect of vagus nerve magnetic modulation (VNMM) on pDOC patients.

Methods: We performed VNMM in 17 pDOC patients. The Revised Coma Recovery Scale (CRS-R), Glasgow scale (GCS), somatosensory evoked potentials (SEP) and brainstem auditory evoked potentials (BAEP) were assessed before and after treatment.

Results: Both CRS-R and GCS results showed significant improvement in p DOC patients after VNMM treatment. The CRS-R improved from 7.88 ± 2.93 to 11.53 ± 4.94. The GCS score also improved from 7.65 ± 1.9 to 9.18 ± 2.65. The number of BAEP grades I increased from 3 to 5 after treatment. The number of BAEP grades I increased from 3 to 5, grade II increased by 1, and grade III decreased from 4 to 1.

Conclusion: This study provides a preliminary indication of the potential of VNMM in the rehabilitation of pDOC patients. It provides the basis for a Phase 2 or Phase 3 study of VNMM in patients with pDOC.

Keywords: prolonged disorders of consciousness, vagus nerve modulation, evoked potentials, neuromodulation, transcranial magnetic stimulation

Introduction

With the development of medical technology, the mortality rate of patients with severe traumatic brain injury (TBI), stroke, and hypoxic-ischemic encephalopathy (HIE) has decreased significantly. At the same time, most survivors suffer from temporary or prolonged disorders of consciousness (DOC), and thus the number of patients with DOC is increasing year by year.[1] Studies have shown that patients with impaired consciousness lasting up to 1 month have only about a 50% or lower chance of spontaneous awakening, and most awakened patients remain severely disabled for life.[2] Prolonged disorders of consciousness (pDOC) not only impose a huge financial burden on families but also predispose them to ethical and legal issues.[3] However, there is a lack of effective wake-up promotion programs, and the clinical treatment of pDOC remains tricky.

Non-invasive neuromodulation techniques, such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), have been used to treat DOC, but with unsatisfactory results.[2] Consciousness is determined by both correct perceptions of the surroundings and oneself and normal arousal. Perception relies on the functional and structural integrity of the functional cortical network and cortical and subcortical neural network

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connections, whereas arousal is maintained by the brainstem's superior reticular activation system.[4,5] However, the currently used transcranial magnetic stimulation (TMS) modalities mainly excite the thalamus through cortical stimulation and do not achieve activation of the superior brainstem reticular system.[6]

It has been shown that the vagus nerve can join the superior reticular activation system through the solitary nucleus of the brainstem, thus participating in the modulation of the consciousness loop.[7] Vagus nerve modulation (VNM) includes vagus nerve stimulation (VNS) and Vagus nerve magnetic modulation (VNMM).[8,9] VNS is left vagus nerve modulation using implanted electrodes. VNMM is extracranial vagus nerve stimulation using repetitive transcranial magnetic stimulation. Studies have shown that VNS can improve motor function after stroke.[8,10–12] VNM also promotes the release of plasticity-enhancing neurotransmitters, such as acetylcholine, norepinephrine, etc.[8,13] However, VNS is less generalizable and acceptable due to its invasive nature in humans.[14] So then, the researchers chose to stimulate the vagus nerve ear branch using TMS to observe its effect on post-stroke dysphagia. The results showed that the extracranial vagus nerve can promote esophageal motor evoked potential (MEP) responses and effectively improve post-stroke swallowing disorders.[9] VNMM can provide similar effects as conventional VNS without surgery, avoiding the potential risks associated with surgical complications.

Based on these findings, this study used noninvasive VNMM to treat pDOC patients, observe its effect and safety in pDOC, and determine whether this innovative approach could be an effective complement to wake-promoting protocols.

Methods

All included patients were assessed for Coma Recovery Scale-Revised (CRS-R), somatosensory evoked potentials (SEP), and brainstem auditory evoked potentials (BAEP) prior to treatment. The same components were then assessed immediately after 20 VNMM treatments (Figure 1A). The data supporting the results of this study can be obtained from the corresponding author upon reasonable request.

Patients Selection

Inclusion criteria for this study:[1] met the definition of pDOC, diagnosed as coma, vegetative state/non-responsive awakening syndrome, minimally conscious state according to the Revised Coma Recovery Scale;[2,15] no history of epilepsy and no other central nervous system disorders unrelated to disorders of consciousness;[3] no use of central excitatory drugs during treatment;[4] consent of the patient and family was obtained and informed consent for treatment was signed before enrollment. Patients were excluded from the study in the following cases:[1] patients with contraindications to magnetic stimulation, such as those wearing pacemakers or containing metal in the skull;[2] patients with unstable vital signs (respiratory or hemodynamic instability), combined with severe cardiac, hepatic, renal, or pulmonary

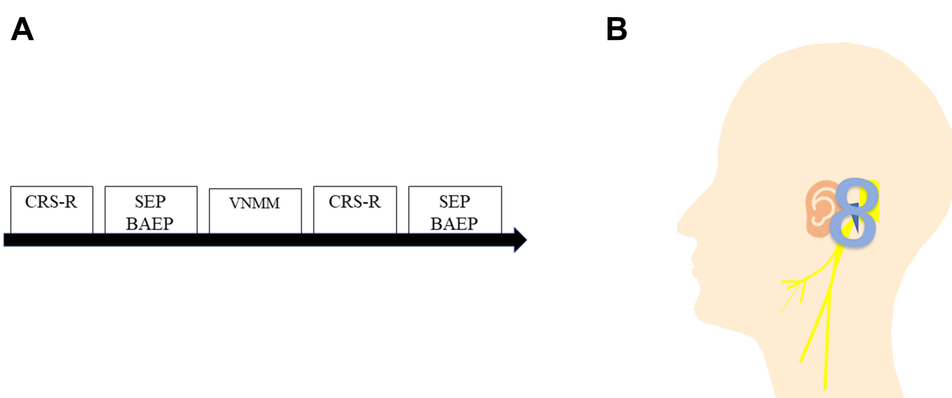

Figure 1 Study protocol (**A**) Timeline of the study protocol: pre-treatment assessment of CRS-R, SEP and BAEP, followed by the implementation of 20 VNM sessions and immediate post-treatment assessment of CRS-R, SEP and BAEP. (**B**) Stimulation target: the center of the figure-of-eight coil was placed on the left posterior auricular mastoid.

Abbreviations: CRS-R, The Coma Recovery Scale-Revised; SEP, Somatosensory evoked potentials; BAEP, Brainstem auditory evoked potentials; VNMM, vagus nerve magnetic modulation.

impairment or other serious medical conditions;[3] patients with a history of seizures; and[4] patients who were unable to cooperate with the assessment or therapist treatment methods.

The study was approved by the medical ethics committee of the affiliated hospital of north Sichuan medical college, and informed consent was obtained from all enrolled patients. This study complies with the Declaration of Helsinki. It was registered with the Chinese Clinical Trials Registry (ChiCTR2100053959). The authors expressly state that there is no conflict of interest with this article.

Vagus Nerve Modulation

The patient lies on the right side of the bed and stimulation was performed on the left mastoid using a figure-of-8 focusing coil as a guide, with the coil attachment stalk position noted to not interfere with the therapeutic manipulation (Figure 1B). Parameters: output intensity at 100% of resting motor threshold at a frequency of 10 Hz for 20 min/session,[16] once daily for 5 days per week for 4 weeks of treatment. This study used a TMS System (magneuro60 stimulator, Nanjing Vishee Medical Technology Co., Ltd., Nanjing, China).

Clinical Assessment

All assessments were performed by a physician who was not responsible for the treatment (Master Yang).

Clinical presentation remains the gold standard for the diagnosis of disorders of consciousness. CRS-R score is 23.[17] Patients are assessed in 5 areas: motor function, visual function, auditory function, communication function, oromotor function, and arousal. The CRS-R assessment is performed by a physician who is not in charge of VNMM treatment. Patients were diagnosed based on the highest score obtained in 3 CRS-R assessments performed within a week. Depending on the score, they are classified as coma, vegetative state/unresponsive wakefulness syndrome (VS/UWS), minimally conscious state 'minus' (MCS-), minimally conscious state 'plus' (MCS+), and exit minimally conscious state (EMCS).

The GCS score, which refers to the Glasgow Coma Index assessment, includes three aspects: eye-opening response, verbal response, and body movement.[18] It is a common indicator used in medicine to assess the degree of coma in patients. The total score of the GCS scale ranges from 3 to 15, with 15 points indicating conscious consciousness and 13–14 points indicating a mild disturbance of consciousness. The score of 9–12 was in moderate disturbance of consciousness. 3–8 was classified as a severe disturbance of consciousness. When the score is less than 8 as coma, less than 3 as deep coma or brain death.

Evoked Potentials

Evoked potentials can be used to detect the integrity of cortical and brainstem pathways in patients with impaired consciousness. Before and after treatment, patients' SEP and BAEP were examined by electromyography. The SEP and BAEP were clinically graded according to the results of the examinations, which were performed by a physician who was not in charge of VNMM treatment. SEP grading was performed according to Judson's grading criteria:[19] Grade I: normal CCT bilaterally; Grade II: prolonged or asymmetric CCT unilaterally or bilaterally; Grade III: the disappearance of cortical potential waves (N20 waves) unilaterally or bilaterally. BAEP grading was performed using Hall grading judgment criteria:[20] generally, the side with the worse BAEP examination result is used for grading, Grade I: normal; Grade II. Mild abnormality, good differentiation of I to V waves, but with one of the following conditions, such as I, III, or (and) V wave PL prolongation. I~III, III~V or (and) I~V wave IPL prolongation, III~V/I~III inter-peak delay ratio >1, V/I amplitude ratio <0. 5; Grade III: moderate abnormality: poor differentiation of III and/or V wave, poor repeatability or no V wave; Grade IV: severe abnormality: only I wave or no wave at all.

Safety Monitoring

Throughout the experiment, changes in the patients' vital signs were closely monitored. And record the adverse reactions we observed or reported by the patient's family.

Statistical Analysis

IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp, Armonk, NY, United States) was used for statistical analysis. 2-tailed P<0.05 was considered a statistically significant difference. Continuous variables were expressed as mean with standard deviation or median with interquartile range, whereas categorical data were expressed as counts and percentages. The Shapiro–Wilk test was used to assess if the scores confirmed a normal distribution. The rank sum test was used for categorical variables and the Wilcoxon for continuous variables. Percentage bar graphs were plotted using Excel 2020 software (Microsoft).

Results

The clinical characteristics of the patients are shown in Table 1. No patients withdrew from the study and did not experience any significant adverse events.

Clinical Assessment

The CRS-R showed a significant improvement after the VNMM intervention, compared to the pre-treatment period. (Figure 2 and Table 2). CRS-R improved from 7.88±2.93 to 11.53±4.94. GCS score also improved from 7.65±1.9 to 9.18 ±2.65. Compared with pre-treatment, both CRS-R and GCS scores were statistically significant (P<0.05). Significant improvements were seen in all six subscales of the CRS-R, except oromotor (Table 3).

Table 1 Baseline Characteristics of Patients with Prolonged Disorders of Consciousness

Patient Number	Age (Year)	Sex	Duration (Day)	Lesion	CRS-R	GCS	Disturbance of Consciousness
1	57	Male	150+	HS	5	7	VS/UWS
2	57	Male	180+	HS	8	8	MCS-
3	75	Male	60+	HS	9	10	MCS-
4	75	Male	90+	HS	11	10	MCS-
5	69	Female	40+	HS	11	9	MCS-
6	81	Female	30+	TBI	9	8	MCS-
7	56	Male	30+	HIE	5	6	VS/UWS
8	56	Male	50+	HIE	7	6	MCS-
9	51	Male	40+	HS	10	11	MCS-
10	47	Male	30+	TBI	10	8	MCS-
11	56	Male	30+	HS	12	9	MCS-
12	54	Female	80+	TBI	2	4	Coma
13	27	Male	90+	TBI	6	7	VS/UWS
14	47	Female	30+	TBI	9	8	MCS-
15	55	Male	60+	HS	4	4	Coma
16	74	Female	90+	HIE	5	7	VS/UWS
17	69	Male	50+	HS	11	9	MCS-

Note: The lower the GCS and CRS-R scores, the more severe the symptoms.
Abbreviations: HIE, hypoxic-ischemic encephalopathy; TBI, traumatic brain injury; IS, Ischemic Stroke; HS, hemorrhagic Stroke; GCS, Glasgow coma score; CRS-R, The Coma Recovery Scale-Revised; MCS-, minimally conscious state "minus"; VS/UWS, vegetative state/unresponsive wakefulness syndrome.

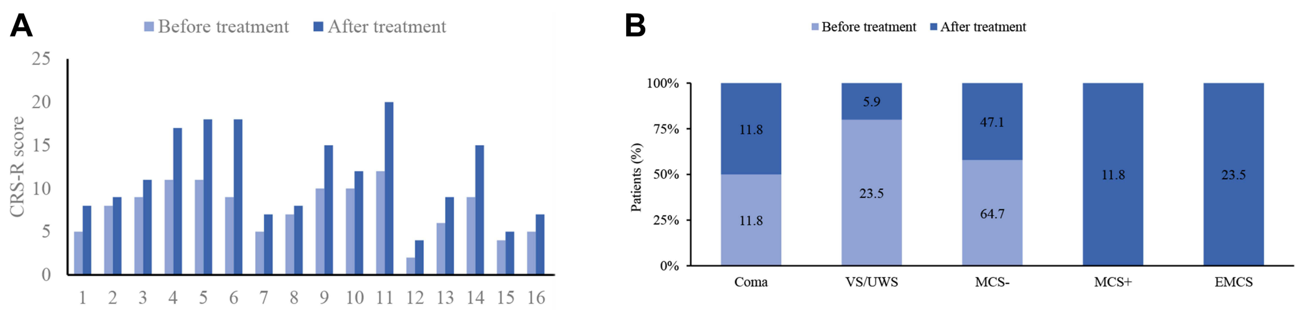

Figure 2 Behavioral responses to VNMM. (**A**) CRS-R scores of 17 patients before and after treatment. (**B**) The proportion of each state of consciousness before and after VNMM shows that higher states of consciousness (EMCS and (MCS+) were increased, while lower states of consciousness (VS/UWS and MCS-) were affected.
Abbreviations: VNMM, vagus nerve magnetic modulation; CRS-R, The Coma Recovery Scale-Revised; EMCS, exit minimally conscious state; MCS+, minimally conscious state "plus"; MCS-, minimally conscious state "minus"; VS/UWS, vegetative state/unresponsive wakefulness syndrome.

Evoked Potential Analysis

There was no significant change in SEP after treatment compared with that before treatment, and only one patient improved from grade II to grade I. In contrast, the BAEP improved more significantly after treatment than before treatment, and the number of BAEP class I increased from 3 to 5, class II increased by 1, and class III decreased from 4 to 1 after treatment, with statistically significant differences (P=0.025) (Figure 3 and Table 2).

Discussion

To our knowledge, this is the first protocol to study the effect and safety of VNMM in patients with pDOC. The results suggest that VNMM has the potential to promote awakening in pDOC patients and is expected to improve the conscious function of pDOC patients. After VNMM treatment, patients' behavioral responses were significantly better than before treatment. In addition, patients also showed more significant improvement in BAEP outcomes.

Table 2 Outcomes

	Before Treatment	After Treatment	P value
CRS-R	7.88±2.93	11.53±4.94	<0.001
GCS	7.65±1.9	9.18±2.65	0.001
SEP, n(%)			1
GradeI	6(35.29)	7(41.18)	
GradeII	9(52.94)	8(47.06)	
GradeIII	2(11.76)	2(11.76)	
BAEP, n(%)			0.025
GradeI	3(17.65)	5(29.41)	
GradeII	8(47.06)	9(52.94)	
GradeIII	4(23.53)	1(5.88)	
GradeIV	2(11.76)	2(11.76)	

Note: P value <0.05 as the threshold for statistical significance.
Abbreviations: GCS, Glasgow coma score; CRS-R, The Coma Recovery Scale-Revised; SEP, somatosensory evoked potentials; BAEP, brainstem auditory evoked potentials.

Table 3 Outcomes of the CRS-R Subscales

	Before Treatment	After Treatment	P value
Auditory	1 (1±2)	2 (2±3)	<0.001
Visual	1 (1±2)	2 (2±3)	0.001
Motor	3 (1±5)	5 (1±5)	0.008
Oromtor	1 (1±1)	1 (1±1)	0.157
Communication	0	0 (0±1)	0.02
Arousal Functions	2 (1±2)	2 (2±2)	0.025

Abbreviation: CRS-R, The Coma Recovery Scale-Revised.

Loss of consciousness is associated with a loss of connectivity in the default mode network, frontoparietal network, thalamocortical network, and cerebellar cortical circulation.[21,22] Further studies have revealed that the central thalamus is a specific node that supports arousal of the brain or central thalamic connections to various cortical areas.[23] Consciousness in a normal physiological state is determined by the correct perception of the surroundings and oneself and by normal arousal. Perception depends on the functional and structural integrity of the cortical functional network and the cortical and subcortical neural network connections, and arousal is maintained by the superior brainstem reticular agonist system.[4,5] TMS is a neuromodulation technique that generates an induced electric field by stimulating tissues using a pulsed magnetic field of a certain intensity, which activates cortical effects and excites neuromuscular to achieve neural remodeling and promote consciousness recovery. Currently, the targets of magnetic stimulation for pDOC are mostly focused on the prefrontal dorsolateral cortex and primary motor cortical areas.[24,25] The excitatory effect is mainly produced by indirect stimulation of the extensive cortical and subcortical tissues (especially the thalamus) connected to them. The currently used transcranial magnetic stimulation modalities mainly produce excitatory effects in the thalamus through cortical stimulation and do not achieve activation of the superior brainstem reticular system.

The superior vagal fibers are relayed to other nuclei in the brain through the solitary nucleus, which receives most of the afferent information from the vagus nerve. This sensory information is then integrated and projected to higher centers such as the medullary reticular formation and the nucleus accumbens, which is closely related to the brainstem superior reticular activation system. Studies have confirmed that vagal electrical stimulation has a pro-wake function, directly regulates brainstem activity, and reaches the dorsal nucleus of the middle suture and the thalamus via the nucleus accumbens, with positive effects on the reticular formation and thalamic metabolism.[7] In contrast, transcutaneous vagal

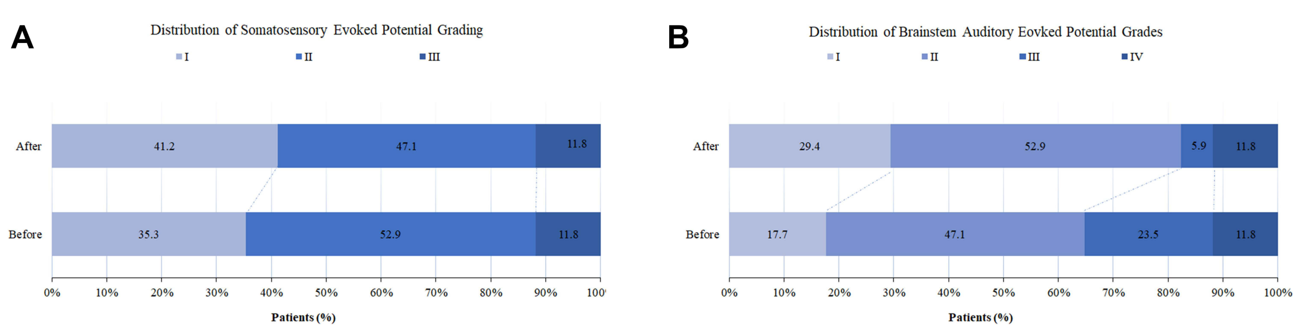

Figure 3 Distribution of evoked potential grading before and after treatment. (**A**) The proportion of each SEP grading before and after treatment is shown. This distribution shows that one patient changed from SEP grade II to grade I after treatment. (**B**) The proportion of each BAEP grading before and after treatment is shown. The results show a more significant improvement in BAEP in treated patients.

Abbreviations: SEP, somatosensory evoked potentials; BAEP, brainstem auditory evoked potentials.

electrical stimulation enters the isolated nucleus of the brainstem through the auricular branch of the vagus nerve and joins the superior reticular activating system, which is also involved in the modulation of the consciousness circuit.[26] This led us to ponder whether the vagus nerve could be a new target for magnetic stimulation in the treatment of patients with pDOC.

Previous studies have shown that left-sided VNM combined with hemiplegic limb training can improve motor function in rat stroke models or in patients with hemiplegia.[8,10–12] In addition, VNM also promotes the release of neurotransmitters such as acetylcholine and norepinephrine and cytokines such as brain-derived neurotrophic factors, thus mediating the process of neuroplasticity.[8,13] A clinical study showed that VNMM can promote esophageal MEP response and effectively improve post-stroke swallowing disorder.[9] However, no studies have reported the use of VNMM in patients with pDOC. Our findings suggest that VNMM can promote recovery in patients with PDOC (especially MCS patients). In the present study, we observed a mean increase of about 4 points in CRS-R scores after 20 VNMM treatments, while BAEP outcomes showed improvement. Our findings support that VNMM can improve patients with pDOC.

In previous studies, the mean increase in CRS-R in pDOC patients after intervention with high-frequency rTMS ranged from 1.25 to 1.57.[16,27] The increase in CRS-R scores in pDOC patients after intervention with tDCS, another commonly used neuromodulation technique, ranged from approximately 1.7 to 5.92.[28,29] In the present study after VNMM intervention, patients had a mean increase in CRS-R of approximately 4 points, which was significantly better than previous rTMS stimulation protocols and did not differ significantly from the effect of tDCS. In other words, compared with other noninvasive neuromodulation techniques, there was no significant difference in the effect of VNMM for pDOC. Moreover, VNMM compensates for some shortcomings of rTMS: first, pDOC patients with cranial defects can also be treated through the vagus nerve ear branch. Secondly, VNMM can modulate consciousness through the brainstem's superior reticular activating system as an effective complement to TMS for pDOC.[26] Finally, VNMM can be both antiepileptic and may also help patients to recover motor and swallowing functions.[9,12,30] It has the advantage of a single target with multiple benefits.

Safety Analysis

The safety of TMS has been widely reported, and no significant abnormal reactions have been observed during its use. Some studies have pointed out that TMS may have the risk of inducing adverse effects such as seizures, tinnitus, and headache. In a clinical study of magnetic modulation of the vagus nerve, there were no adverse events.[9] In the present study, all patients tolerated VNMM without any adverse reactions during treatment. However, there is still insufficient experience with the implementation of VNM, and clinicians should exercise caution when performing VNMM treatment.

Limitations

First, the small sample size of our study did not allow for a stratified comparison of patients' states of consciousness (coma, VS/UWS, MCS), and etiology (TBI, stroke, HIE, etc.). Second, no follow-up was performed to observe the long-term effects of VNMM on patients with prolonged disorders of consciousness. In addition, the study was self-controlled and not randomized. Therefore, future studies need to conduct randomized controlled trials to analyze the effect of VNMM in patients with prolonged disorders of consciousness and to focus on whether there are differences in the effect of VNMM in patients with prolonged disorders of consciousness of different etiologies and states of consciousness.

Conclusion

In the present study, we indicate that vagus nerve magnetic modulation holds promise as a novel therapeutic approach in patients with chronic disturbances of consciousness. In the available research data, MCS patients had the best effect, followed by UWS patients. And it has good security. This study provides a preliminary indication of the potential of VNMM in the rehabilitation of pDOC patients. It provides the basis for a phase 2 or phase 3 study of VNMM in patients with pDOC.

Acknowledgments

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Disclosure

The authors report there are no competing interests to declare.

References

1. Tohme S, Delhumeau C, Zuercher M, Haller G, Walder B. Prehospital risk factors of mortality and impaired consciousness after severe traumatic brain injury: an epidemiological study. *Scand J Trauma Resusc Emerg Med*. 2014;22:1. doi:10.1186/1757-7241-22-1
2. Schnakers C, Monti MM. Disorders of consciousness after severe brain injury: therapeutic options. *Curr Opin Neurol*. 2017;30(6):573–579. doi:10.1097/WCO.0000000000000495
3. Monti MM. *Brain Function and Responsiveness in Disorders of Consciousness*. Springer International Publishing Switzerland; 2016.
4. Jang SH, Chang CH, Jung YJ, Kim JH, Kwon YH. Relationship between impaired consciousness and injury of ascending reticular activating system in patients with intracerebral hemorrhage. *Stroke*. 2019;50(8):2234–2237. doi:10.1161/STROKEAHA.118.023710
5. Jang SH, Kim SH, Seo JP. Long-term recovery from a minimally responsive state with recovery of an injured ascending reticular activating system: a case report. *Medicine*. 2021;100(9):e23933. doi:10.1097/MD.0000000000023933
6. Thibaut A, Schiff N, Giacino J, Laureys S, Gosseries O. Therapeutic interventions in patients with prolonged disorders of consciousness. *Lancet Neurol*. 2019;18(6):600–614. doi:10.1016/S1474-4422(19)30031-6
7. Corazzol M, Lio G, Lefevre A, et al. Restoring consciousness with vagus nerve stimulation. *Curr Biol*. 2017;27(18):R994–r6. doi:10.1016/j.cub.2017.07.060
8. Cai PY, Bodhit A, Derequito R, et al. Vagus nerve stimulation in ischemic stroke: old wine in a new bottle. *Front Neurol*. 2014;5:107. doi:10.3389/fneur.2014.00107
9. Lin WS, Chou CL, Chang MH, Chung YM, Lin FG, Tsai PY. Vagus nerve magnetic modulation facilitates dysphagia recovery in patients with stroke involving the brainstem - A proof of concept study. *Brain Stimul*. 2018;11(2):264–270. doi:10.1016/j.brs.2017.10.021
10. Hays SA, Khodaparast N, Ruiz A, et al. The timing and amount of vagus nerve stimulation during rehabilitative training affect poststroke recovery of forelimb strength. *Neuroreport*. 2014;25(9):676–682. doi:10.1097/WNR.0000000000000154
11. Dawson J, Pierce D, Dixit A, et al. Safety, feasibility, and efficacy of vagus nerve stimulation paired with upper-limb rehabilitation after ischemic stroke. *Stroke*. 2016;47(1):143–150. doi:10.1161/STROKEAHA.115.010477
12. Xie YL, Wang S, Wu Q, Chen X. Vagus nerve stimulation for upper limb motor impairment after ischemic stroke: a meta-analysis. *Medicine*. 2021;100(46):e27871. doi:10.1097/MD.0000000000027871
13. Khodaparast N, Hays SA, Sloan AM, et al. Vagus nerve stimulation delivered during motor rehabilitation improves recovery in a rat model of stroke. *Neurorehabil Neural Repair*. 2014;28(7):698–706. doi:10.1177/1545968314521006
14. Bourdillon P, Hermann B, Sitt JD, Naccache L. Electromagnetic brain stimulation in patients with disorders of consciousness. *Front Neurosci*. 2019;13:223. doi:10.3389/fnins.2019.00223
15. Kondziella D, Bender A, Diserens K, et al. European academy of neurology guideline on the diagnosis of coma and other disorders of consciousness. *Eur J Neurol*. 2020;27(5):741–756. doi:10.1111/ene.14151
16. Xia X, Bai Y, Zhou Y, et al. Effects of 10 Hz repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex in disorders of consciousness. *Front Neurol*. 2017;8:182. doi:10.3389/fneur.2017.00182
17. Kalmar K, Giacino JT. The JFK Coma Recovery Scale--Revised. *Neuropsychol Rehabil*. 2005;15(3–4):454–460. doi:10.1080/09602010443000425
18. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. *Lancet*. 1974;2(7872):81–84.
19. Judson JA, Cant BR, Shaw NA. Early prediction of outcome from cerebral trauma by somatosensory evoked potentials. *Crit Care Med*. 1990;18(4):363–368. doi:10.1097/00003246-199004000-00003
20. Hall JW 3rd, Huang-fu M, Gennarelli TA. Auditory function in acute severe head injury. *Laryngoscope*. 1982;92(8 Pt 1):883–890. doi:10.1288/00005537-198208000-00009
21. Dimitri D, De Filippis D, Galetto V, Zettin M. Evaluation of the effectiveness of transcranial direct current stimulation (tDCS) and psychosensory stimulation through DOCS scale in a minimally conscious subject. *Neurocase*. 2017;23(2):96–104. doi:10.1080/13554794.2017.1305112
22. Lant ND, Gonzalez-Lara LE, Owen AM, Fernández-Espejo D. Relationship between the anterior forebrain mesocircuit and the default mode network in the structural bases of disorders of consciousness. *Neuroimage Clin*. 2016;10:27–35. doi:10.1016/j.nicl.2015.11.004
23. Weng L, Xie Q, Zhao L, et al. Abnormal structural connectivity between the basal ganglia, thalamus, and frontal cortex in patients with disorders of consciousness. *Cortex*. 2017;90:71–87. doi:10.1016/j.cortex.2017.02.011
24. Louise-Bender Pape T, Rosenow J, Lewis G, et al. Repetitive transcranial magnetic stimulation-associated neurobehavioral gains during coma recovery. *Brain Stimul*. 2009;2(1):22–35. doi:10.1016/j.brs.2008.09.004
25. Piccione F, Cavinato M, Manganotti P, et al. Behavioral and neurophysiological effects of repetitive transcranial magnetic stimulation on the minimally conscious state: a case study. *Neurorehabil Neural Repair*. 2011;25(1):98–102. doi:10.1177/1545968310369802
26. Yu YT, Yang Y, Wang LB, et al. Transcutaneous auricular vagus nerve stimulation in disorders of consciousness monitored by fMRI: the first case report. *Brain Stimul*. 2017;10(2):328–330. doi:10.1016/j.brs.2016.12.004
27. Liu X, Meng F, Gao J, et al. Behavioral and resting state functional connectivity effects of high frequency rTMS on disorders of consciousness: a sham-controlled study. *Front Neurol*. 2018;9:982. doi:10.3389/fneur.2018.00982
28. Martens G, Lejeune N, O'Brien AT, et al. Randomized controlled trial of home-based 4-week tDCS in chronic minimally conscious state. *Brain Stimul*. 2018;11(5):982–990. doi:10.1016/j.brs.2018.04.021

29. Zhang Y, Song W, Du J, Huo S, Shan G, Li R. Transcranial direct current stimulation in patients with prolonged disorders of consciousness: combined behavioral and event-related potential evidence. *Front Neurol*. 2017;8:620. doi:10.3389/fneur.2017.00620
30. He W, Jing XH, Zhu B, et al. The auriculo-vagal afferent pathway and its role in seizure suppression in rats. *BMC Neurosci*. 2013;14:85. doi:10.1186/1471-2202-14-85