International Journal of Neuroscience

ISSN: 0020-7454 (Print) 1543-5245 (Online) Journal homepage: https://www.tandfonline.com/loi/ines20

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To cite this article: Zeyu Shou, Zhilong Li, Xueying Wang, Miaoyang Chen, Yang Bai & Haibo Di (2020): Non-invasive brain intervention techniques used in patients with disorders of consciousness, International Journal of Neuroscience, DOI: 10.1080/00207454.2020.1744598

To link to this article: https://doi.org/10.1080/00207454.2020.1744598

Published online: 02 Apr 2020.

INTERNATIONAL JOURNAL OF NEUROSCIENCE
https://doi.org/10.1080/00207454.2020.1744598

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REVIEW

Non-invasive brain intervention techniques used in patients with disorders of consciousness

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ABSTRACT

Aim of the study: With the development of emergency medicine and intensive care technology, the number of people who survive with disorders of consciousness (DOC) has dramatically increased. The diagnosis and treatment of such patients have attracted much attention from the medical community. From the latest evidence-based guidelines, non-invasive brain intervention (NIBI) techniques may be valuable and promising in the diagnosis and conscious rehabilitation of DOC patients.

Methods: This work reviews the studies on NIBI techniques for the assessment and intervention of DOC patients.

Results: A large number of studies have explored the application of NIBI techniques in DOC patients. The NIBI techniques include transcranial magnetic stimulation, transcranial electric stimulation, music stimulation, near-infrared laser stimulation, focused shock wave therapy, low-intensity focused ultrasound pulsation and transcutaneous auricular vagus nerve stimulation.

Conclusions: NIBI techniques present numerous advantages such as being painless, safe and inexpensive; having adjustable parameters and targets; and having broad development prospects in treating DOC patients.

ARTICLE HISTORY
Received 13 December 2019
Revised 18 February 2020
Accepted 9 March 2020

KEYWORDS
Disorders of consciousness; non-invasive brain intervention; transcranial magnetic stimulation; transcranial electric stimulation

1. Introduction

With the development of medical first aid technology and critical care technology, increasingly more patients with brain injury can survive from severe brain injury [1]. After coming out of a coma, some patients wake up, but most of them enter a state of loss of consciousness called disorders of consciousness (DOC). In clinical practice, DOC patients are divided into being in a vegetative state/unresponsive wakefulness syndrome (VS/UWS) or in a minimally conscious state (MCS) according to the clinical manifestation of the content of awareness [2–4]. Patients with MCS usually exhibit signs of consciousness behaviours, whereas those with VS/UWS show no consciousness behaviour response to external stimulus [5,6]. The classification, diagnosis, treatment and prognosis of DOC patients are long-standing difficult issues in clinical practice.

At present, multiple therapeutic schemes for DOC have been proposed, including pharmacological and non-pharmacological methods [7,8]. Pharmacological drugs such as amantadine and zolpidem are considered effective in improving patients' consciousness [9], which remains to be clarified in the future to provide adequate evidence for clinical guidance. Along with the development of biomedical engineering technology, much attention has been given gradually to the application of neuro-modulatory therapies in DOC clinics. Neuro-modulatory therapies can be classified into invasive and non-invasive according to the need for surgical assistance. Invasive brain stimulation, such as deep brain stimulation (DBS) [10,11], spinal cord stimulation [12,13] and vagus nerve stimulation (VNS) [14,15]. Generally, the invasive brain stimulation is difficult to be widely accepted because of its high risk of injection, complicated nurse as well as high expenses. By contrast, non-invasive brain intervention (NIBI) is convenient, safe and cost effective, and it has been well received so far. Among the various NIBI techniques, extensive studies have been conducted on direct neuro-modulation-based transcranial direct current stimulation (tDCS) [16,17], transcranial magnetic stimulation (TMS) [18] and indirect neuro-

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modulation-based music therapy [19,20], among others.

Neuro-modulation directly targets the cerebral cortex using electricity, magnetism, or ultrasound, and it directly interferes with the nerve activity of the cerebral cortex, thus regulating the nerve function, excitability and connectivity. Generally, the neuro-excitability of DOC patients decreases, and the activity pathway is disconnected after brain nerve damage, which affects the information integration ability of the brain and impairs the expression of consciousness. In this regard, the conscious rehabilitation of patients can be promoted by directly affecting the activity characteristics of neuronal circuits. Numerous articles have examined the intervention effects of tDCS, TMS and their variants, the different targets and the intervention paradigms in DOC [21–23]. Furthermore, indirect neuro-modulation mainly affects the brain-related nerve pathways from the outside to the inside by stimulating the peripheral nerve pathways. For example, music stimulation uses rhythmic music to affect the brain's auditory system through the auditory pathway input, thereby interfering with the expression of the content of consciousness [24]. Note that there is still no effective clinical intervention model available so far despite the continuous improvement in relevant research.

Accordingly, our research reviews the related studies on NIBI for DOC in combination with the elaboration and analysis of the current parameters, experimental settings and effects of NIBI. This review is expected to contribute to a clear summary of the current research progress of NIBI for DOC.

2. Transcranial magnetic stimulation

2.1. TMS in DOC assessment

TMS is a safe, non-invasive and painless technique [25] delivered in the form of mono-pulse, paired-pulse and repetitive pulse [26]. When TMS pulse is delivered to the brain, a transient time-varying magnetic field is generated. It then creates an electric field in a nearby conductor through electromagnetic conduction. The electric field generated in the cerebral cortex depolarises the neurons, causing a brief synchronous firing in the area underlying the TMS coil.

2.1.1. Transcranial magnetic stimulation–electromyography (TMS-EMG)

When TMS is applied to the motor cortex, suprathreshold TMS pulses can depolarise the cortical spinal cord neurons directly or across synapses, resulting in the activation of the surrounding muscles dominated by the stimulated cortical area. This type of high-voltage electric shock produces a brief and relatively synchronous muscle response to the primary motor cortex (M1), that is, the motor evoked potential (MEP). The MEPs can be recorded by EMG, and the amplitude of the MEPs can be used as an index of the cortical and spinal cord excitability [27]. Moreover, the duration of the myoelectric silent period can reflect the integrity of the cortical and corticospinal pathways. TMS-EMG can objectively assess the excitability of the motor cortex and the integrity of the motor pathways by directly detecting the duration of the myoelectric silent period [28]. In recent years, TMS-EMG has been widely used to measure the excitability of the human motor cortex under different conditions. Studies have shown that the damage of the cortical inhibition circuit in motor region of DOC patients could be evaluated by the TMS-EMG. For example, Lapitskaya *et al.* performed TMS-EMG in DOC patients (24 VS/UWS and 23 MCS) with 14 healthy controls [28]. They stimulated the motor regions, and the responses of the contralateral first dorsal interosseous muscle were recorded. Compared with the healthy control group, the patients showed several lower indexes of average amplitudes of maximal peak-to-peak M-wave, MEP, sensory evoked potential (SEP) and short-latency afferent inhibition (SAI), but higher resting motor threshold (RMTs). The significantly altered of transmissions of inhibitory and excitatory neurons in VS/UWS patients could also been measured by paired-pulse TMS [29]. Compared with the healthy control group, the phenomena of intracortical inhibition (ICI) and intracortical facilitation (ICF) in VS/UWS patients were significantly reduced.

2.1.2. Transcranial magnetic stimulation–electroencephalography (TMS-EEG)

Although TMS-EMG can effectively measure the excitability, inhibition, plasticity and connectivity of the cerebral cortex, it is limited to the study of the cerebral motor cortex, and MEPs are affected not only by the cortical mechanism but also by the excitability of the spinal cord and muscle characteristics. The combination of TMS and EEG enables a more direct detection of the state of the brain and the dynamics in the motor and non-motor cortex [27]. It provides the possibility of the non-invasive detection of brain excitability, time-resolved connectivity and transient state of the brain. TMS stimulates the cerebral cortex and induces an intracerebral current, which can depolarise the corresponding cell membrane. As a result, it opens the voltage-sensitive ion channel, initiates the action potential and generates the synaptic activation. This synaptic activation can be directly reflected in the EEG, which records the linear projection of the postsynaptic current [30], namely, the TMS-evoked potentials (TEPs).

TMS-EEG has been proved to be an up-and-coming technology in detecting brain conditions and interpreting the functions of specifying neural circuits [27]. It facilitates our understanding of the underlying mechanism of human consciousness. There is growing evidence that consciousness depends not only on certain circuits but also on the integrations of distant brain regions through the cortex–cortex and cortico-thalamic–cortex connections [31,32]. TMS-EEG, which measures effective connectivity, indicates the ability to distinguish the brain states of reduced or loss of consciousness (sleep and anaesthesia) from normal consciousness (awake and dreaming). Marcello *et al.* assessed the brain responsibility of six subjects from waking to non-rapid eye movement (NREM) sleep by combining TMS and high-density EEG [33]. In an awake state, the EEG showed a series of waves following the stimulus and moving a few centimetres away to the connecting cortical area. Whereas in NREM sleep, the following responding waves were stronger but quickly disappeared without spreading away from the stimulus site. For the first time, the changes in cortical ability in information integration during consciousness loss were presented to be captured by an effective connection [33]. These findings were further verified by TMS-EEG during general anaesthesia [34]. Therefore, evidences pointed out that TMS-EEG is a reliable approach to measure the effective connectivity through the subcortical afferent nerve and efferent pathway, which related with consciousness states.

In 2012, Rosanova *et al.* evaluated the effective connectivity in DOC patients by TMS-EEG [35]. For VS/UWS patients, TMS triggers a simple local response in EEG. It indicates the broken effective connection, which is similar to that during unconscious sleep or anaesthesia. By contrast, in MCS patients, TMS always triggered a compound EEG activation but less complexity compared with the activation in awake subjects. TMS-EEG was found to be an effective method for distinguishing different consciousness states and tracking the conscious recovery of DOC patients. Ragazzoni *et al.* measured TMS-EEG in 13 DOC patients (including 8 VS/UWS and 5 MCS) [36]. The results showed that the amplitudes of the ipsilateral and contralateral TEPs decreased in 4 of the 5 MCS patients. Five of the 8 VS/UWS patients had bilateral TEPs defects, but only 3 patients showed decreased ipsilateral TEP amplitudes. The results indicated that cortical responsiveness and connectivity were seriously impaired in VS/UWS patients and that TEPs were retained in most MCS patients but with abnormal characteristics. However, note that TEPs can only be evoked at the preserved brain regions with both functional and structural features [37]. To quantify the TEPs, Casali *et al.* proposed the perturbation complexity index (PCI) [38], which describes the complexity of TMS-induced brain activity and indexes the levels of consciousness. Then, a large number of DOC patients (43 VS/UWS and 38 MCS) were enrolled to test the PCI in indexing the different conscious states [39]. The results showed that the PCI value of 0.31 is a significant demarcation for distinguishing MCS and VS/UWS. It was also verified by a multi-modal research. Twenty-four patients with non-acute DOC or locked-in syndrome (LIS) [12 cases of traumatic patients, 9 cases of UWS, 11 cases of MCS, 2 cases of emergence from MCS and 2 cases of LIS] received a combination measurement of the JFK Coma Recovery Scale-Revised (CRS-R), FDG-PET and PCI [40]. High consistent results were found between the FDG-PET and PCI (22 of the 24 DOC patients). The patients with PCI above 0.31 showed the presence of consciousness, and those with PCI below 0.31 showed a lack of awareness.

In addition to the detection of consciousness, TMS-EEG showed the ability of the tracking effects of treatment in DOC patients [41]. The TEPs and the global mean field power (GMFP) of an MCS patient significantly changed during a 20-day treatment. Along with consciousness rehabilitation, the fluctuation of TEPs and GMFP tended to be gradually similar to that of the healthy subjects [41].

2.2. TMS in DOC intervention

TMS acts continuously on a certain area of the brain with a fixed frequency and intensity, and this process is called repetitive transcranial magnetic stimulation (rTMS). rTMS can depolarise neurons, change the state of the cortex and excite or inhibit the function of the local cerebral cortex between the stimulation coil and the distant region. In this way, rTMS can be used to enhance certain cognitive processes or regulate the activity of specific brain regions [26], and the characteristics of its modulation effect mainly depend on frequency, intensity and duration. High-frequency and high-intensity rTMS can produce the sum of excitatory postsynaptic potentials, thus leading to an abnormal nerve stimulation at the stimulation site. The effect of a low-frequency stimulation is the opposite. In addition, when the stimulation is over, rTMS maintains its regulatory effect by altering cortical excitability, which would not happen under TMS-EEG. The theta burst stimulation pattern (TBS) is a specific form of rTMS. Two different TBS patterns are described: intermittent theta burst stimulation pattern (iTBS) and continuous theta burst stimulation paradigm (cTBS). cTBS decreases cortical excitability, whereas iTBS increases cortical excitability. Compared with the traditional rTMS, TBS has a more powerful and lasting effect on cortical excitability [42].

As shown in Table 1, studies have demonstrated that rTMS can be used as a non-invasive intervention for DOC patients [43]. However, currently, the research on rTMS cannot come to a consistent conclusion because of the different stimulation frequencies, intensity, targets as well as paradigms of rTMS. rTMS can cause more significant disturbance than a single TMS and has a profound effect on the subcortical region. rTMS with a range of high frequency (5, 10 and 20 Hz) has been demonstrated to have effects when modulating brain activities in DOC patients. A study showed that 6 of the 10 DOC patients who received 5 Hz rTMS intervention began to develop visual tracking, emotional response and even indicative action. Moreover, the Glasgow coma score (GCS) and CRS-R scores were significantly increased between the second and fourth week [44]. rTMS was also shown to modulate the slow wave activity power of MCS patients [45]. Studies with 10 Hz rTMS showed broad intervention effects in DOC patients [46], especially in MCS patients [47]. rTMS with 20 Hz performed at the M1 area significantly changed the long-term behavioural (6 h) and neurophysiological activities of an MCS patient [43]. However, 20 Hz rTMS at M1 remains controversial. Studies showed no treatment effects of 20 Hz rTMS at M1 for DOC patients, both for MCS [45] and VS/UWS patients [48]. In conclusion, the therapeutic effect of rTMS on DOC patients is still not obvious, but more MCS patients benefit from current rTMS studies than VS/UWS patients. As a therapeutic intervention to change and regulate neurological activity in the coma recovery period, rTMS is still worthy of further study [49].

3. Transcranial electric current stimulation

Transcranial electric current stimulation (tECS) regulates nerve excitability by applying a weak current to the scalp, thus causing local changes in brain excitability by regulating the resting membrane potential. In general, cathodal stimulation hyperpolarises neurons, thereby weakening the excitability of the brain, whereas anodic stimulation depolarises neurons, thus increasing the excitability of the brain. The most commonly used tECS techniques mainly include tDCS, oscillatory transcranial direct current stimulation (o-tDCS), transcranial alternating current stimulation, transcranial random noise stimulation and transcranial pulsed current stimulation (tPCS). Among them, tDCS is the most widely used in clinical treatment.tDCS changes the threshold of resting potential and causes excitatory changes in the cerebral cortex with a constant and weak direct current stimulation in the target area of the brain. This direct current is generally 1-2 mA. tDCS is delivered through a BrainStim battery-driven electric stimulator wire to a pair of surface rubber electrodes (usually 35 cm^2) inside a saline-soaked sponge and arranged according to the type of conditioning (a cathode, black electrode; an anode, red electrode). A weak and constant direct current can either depolarise (anodal tDCS) or hyperpolarise (cathodal tDCS) neurons, thereby increasing or decreasing the cortical excitability [50]. These characteristics make tDCS applicable to various aspects. Initially, tDCS was used only for the detection of a normal human brain until Hummel *et al.* first applied tDCS to clinical treatment [51]. Since then, tDCS has been widely used in clinical treatment, such as drug addiction [52], stroke [53], epilepsy [54], Parkinson's disease [55], chronic pain [56], Alzheimer's disease [55], depression [57] and other diseases.

A large amount of research data proves that tDCS can promote the awakening of DOC patients (Table 2). Some DOC patients exhibit various degrees of improvement of consciousness after receiving tDCS stimulation. These intervention effects are verified by GCS, CRS-R, the full outline of unresponsiveness (FOUR) and other assessment methods such as EEG. The application of tDCS on DOC was first reported by Angelakis *et al.* (2013). In this experiment, the anode was placed on the left dorsolateral prefrontal cortex (DLPFC) or the left sensorimotor cortex with 2 mA and repeated stimulation (5 times), and the CRS-R scores increased in 3 out of 10 patients [58]. However, this experiment did not set up a control group but conducted a sham stimulation before the repeated active stimulation, which could not prevent the confusion with the spontaneous recovery of patients [15]. Therefore, the later researchers adopted a double-blind, randomised controlled trial to solve this hidden danger. In the following studies, the experiments were

Table 1. Studies used repetitive transcranial magnetic stimulation in patients with disorders of consciousness.

Studies	Patients	Targets	Frequency	Protocol	Measurement	Main results
Ying Xie, et.al.	VS:11 MCS:7 Coma:2	Right DLPFC	5Hz	28 sessions in 4 weeks	CRS-R EEG GCS	Six patients demonstrated improvement in their levels of consciousness.
Laura Rosa Pisani, et. al.	UWS:6 MCS:4	Left M1	5Hz	1500 biphasic-pulses delivered in 5 trains of 300 stimuli	CRS-R EEG	Slow wave activity power of patients with MCS increased, but there was no significant change in patients with VS.
Xiaoyu Xia, et. al.	VS/UWS:11 MCS:7	Left DLPFC	10 Hz	1000 pulses, 10 arrays, each array 10 s, a pause of 60 s in between	EEG CRS-R	Delta and theta band power decreased; alpha and beta bands increased
Antonino Naro, et. al.	VS/UWS:10	Right DLPFC	10 Hz	1000 pulses, 20 arrays, each array 5 s, a pause of 20 s in between	CRS-R MRI EEG EMG	3 patients showed a short-lasting increase of the CRS-R scoring, from 2 to 3 points.
Paolo Manganotti, et. al.	VS:3 MCS:3	Left/right M1	20 Hz	1000 pulses, 10 arrays, each array 5 s, a pause of 20 s in between	CRS-R EEG DRS MRI	One MCS patient increased CRS-R from 10 to 18. Delta power increased at C4 and F3 at 35 min after stimulation; Beta power at F3 increased immediately after stimulation.
Fangping He, et. al.	VS:3 MCS: 3	Left M1	20 Hz	1000 pulses, 20 arrays, each array 2.5 s, a pause of 28 s in between	CRS-R, EEG	One patient showed a good clinical response. The CRS-R total score changed from 6 to 8 and the CRS-R motor scoring changed from 1 to 3.
Xiaoyan Liu, et. al.	VS/UWS: 2 MCS:5	Left M1	20 Hz	1000 pulses, 20 arrays, each array 2.5 s, a pause of 28 s in between	CRS-R, fMRI MRI	The CRS-R total score was improved in one MCS patient. the CRS-R total score increased from 15 to 23.
Massimo Cincotta, et. al.	VS:11	Left M1	20 Hz	one second trains repeated five times with train interval of 5 s; 30 s pause before the following series; total of 1000 pulses	CRS-R EEG CGI-I	There was no significant change in all of them.
Min Wu, et. al.	UWS:4 MCS:4	Left DLPFC	TBS	2s trains of bursts were repeated every10 seconds for a total of 192 s with 600 pulses.	CRS-R EEG	The CRS-R scores were increased in all 4 patients with MCS and 3 of 4 patients in a UWS after 5 days.
Theresa Louise-Bender Pape, et. al.	VS:1	Right DLPFC	5Hz	300 paired-pulse trains per session; 100 ms inter-pulse and 5s inter-train intervals; 30 sessions in 6 weeks	CT EEG MRI	Trend toward significant neurobehavioral gains temporally related to provision of rTMS
Francesco Piccione, et. al.	MCS:1	Left M1	20 Hz	10 trains of 100 stimuli; single session	EEG GOS CRS-R	Meaningful behaviors increased, along with changes of frequency power in the EEG
Ping Liu, et. al	VS:5 MCS:5	Left M1	20Hz	Single session of 1,000 stimuli delivered in 20 trains; each train lasted 2.5 s with a 28 s inter-train pause	CRS-R Transcranial Doppler ultrasound	No significant changes in CRS-R total scores; MCS group exhibited significant increases in peak systolic velocity and mean flow velocity of left middle cerebral artery.
Xiaoyu Xia, et. al.	VS/UWS:11 MCS:5	Left DLPFC	10 Hz	One session of 1,000 pulses (10 s of 10 Hz trains; repeated 10 times with an inter-train interval of 60 s); 20 sessions	CGI-I CRS-R EMG	CRS-R scores increased in 5 MCS and 4 of 11 VS/UWS patients.
Yang Bai, et. al.	MCS:1	Left DLPFC	10 Hz	20 consecutive days; daily sessions consisted of 1000 pulses；one session included 10 trains, each train lasted 10 s with a 60 s inter-train pause	CRS-R TMS-EEG EEG	A increase of consciousness level according by CRS-R score and PCI value.

MCS: minimally conscious state; VS: vegetative state; UWS: unresponsive wakefulness syndrome; DLPFC: dorsolateral prefrontal cortex; CRS-R: JFK Coma Recovery Scale-Revised; GOS: Glasgow outcome scale; GCS: Glasgow coma scale; CGI-I: Clinical Global Impression-Improvement scale; DRS: Disability Rating scale; PCI: perturbation complexity index; EEG: electroencephalogram; EMG: electromyography; MRI: Magnetic resonance imaging; fMRI: functional magnetic resonance imaging; CT: computerized tomography;.

Table 2. Studies used transcranial direct current stimulation in patients with disorders of consciousness.

Current intensity	Studies	Patients	Targets	Protocol	Main results
2 mA	Efthymios Angelakis et al.	7 UWS 3 MCS	Anodic：DLPFC Cathodal: right eye brow	Active:20 minutes per day, 5 days per week, for 2 weeks. Sham: 20 minutes per day, 5 days per week, for 1weeks.	4 UWS: CRS-R total scores improve
	Aurore Thibaut et al.	25 UWS 30 MCS	Anodic：Left DLPFC Cathodal: right supraorbital region	Single session: 2mA,20min,	13 (43%) patients in MCS and 2 (8%) patients in VS/UWS further showed post anodal tDCS-related signs of consciousness
	Antonino Naro et al.	12 VS 10 MCS 2 EMCS 1 LIS	Anodic：Left DLPFC Cathodal: Cz	Single session: 1 mA ,10 min	10 MCS (T0 and T60 a MEP amplitude increase); 4 VS (MEP amplitude increase)
	Aurore Thibaut et al.	21 MCS	Anodic：Left DLPFC Cathodal: right supraorbital region	Active:20 minutes two days, 4 days per week, for 1 week. Sham: 20 minutes per day, 4 days per week, for 1week	The transient improvement of signs of consciousness following tDCS in patients in sub-acute; chronic MCS seems to require grey matter integrity and/or residual metabolic activity in three brain regions
	Cavaliere Carlo et al	16 MCS	Anodic：Left DLPFC Cathodal: right eye brow	Single session: 2 mA ,20 min	tDCS responders showed an increased left intra-network connectivity for regions co-activated with left DLPFC, and significantly with left inferior frontal gyrus
	Aurore Thibaut et al.	16 MCS	Anodic：Left DLPFC Cathodal：right eye brow	20min per day, one time per day. five days per week, for one weeks	9 patients respond (56%)
	Bai Yang et al.	9 UWS 7 MCS	Anodic：Left DLPFC Cathodal: right supraorbital	Single session: 2 mA ,20 min	No behavior effects; Changes in cortical excitability after tDCS
	Zhang et al.	Real:5VS,8MCS Sham:6VS,7MCS	Anodic：Left DLPFC Cathodal: right supraorbital	20min per day, two times per day. five days per week, for two weeks	Significant improvement in CRS-R in MCS patients
	Huang Wangshan. et al.	33 MCS	Anodic：Posterior parietal cortex Cathodal: right supraorbital	20min per day, five days per week	4 patients recovered reproducible and 1 systematic command following, 1 patient regained an intentional communication, 2 recovered visual pursuits, 1 regained the ability to recognize objects and 1 recovered intelligible verbalization.
	Anna Estraneo et al.	7 VS 6 MCS	Anodic：Left DLPFC Cathodal: right supraorbital	20min per day, two times per day. five days per week, for two weeks	3 MCS and 2 VS have improvement of CRS-R
	Cai et al.	18 MCS 10 UWS	Anodic: Pz Cathodal: Cz, P3, P4, Poz	20min per day, one times per day. seven days per week, for two weeks	Total CRS-R scores of 85.7% (24/28) of the patients increased. CRS-R scores of 94.4% (17/18) MCS patients increased.
	Min Wu et al.	9 UWS 7 MCS	Anodic：Left DLPFC Canodic: right supraorbital	20min per day, ten times per day. seven days per week, for one week	Left tDCS facilitated the excitability of the prefrontal cortex, whereas only one patient had a positive outcome. Targeting the right DLPFC was less effective, merely leading to activation of the stimulation site, with no effect on the state of arousal.
1 mA	Antonino Naro et al.	19 MCS 21 UWS	premotor cortex	Single session: 1 mA ,10 min	MCS patients presented with TDCS - induced SICI enhancement, while UWS patients did not.
	Antonino Naro et al.	14 VS 12 MCS	Placed between Fp1 and Fp2	Single session: 1 mA ,10 min	The MEP amplitude increased significantly. The MEP amplitudes of ICF and SICI conditions increased significantly

MCS: minimally conscious state; VS: vegetative state; UWS: unresponsive wakefulness syndrome; EMCS: emerging minimally conscious state; LIS: lock-in syndrome; DLPFC: dorsolateral prefrontal cortex; CRS-R: JFK Coma Recovery Scale-Revised; MEP: muscle evoked potential; ICF: intracortical facilitation;. SICI: Short interval intracortical inhibition.

divided into two categories based on current amplitude: 2 mA and 1 mA.

In the study using a 2 mA current, different tDCS protocol setups lead to different results. As far as stimulus targets are concerned, the anode is usually placed on the left-DLPFC, and the constant stimulation of this area has been demonstrated to improve a variety of cognitive abilities in healthy individuals [59]. Cavaliere *et al.* found that DLPFC is an area of multimodal extrinsic control networks (ECN). Physiologically, ECN is negatively correlated with resting state networks (RSN) and participates in the regulation of self-awareness. In the DOC patients, the functions of ECN and RSN regions gradually recovered with the recovery of consciousness [60]. Thibaut *et al.* performed a single stimulation of a patient's left-DLPFC with a current of 2 mA, and the results showed that tDCS found a significant consciousness-related behaviour in MCS patients. Thirteen patients had an increase in CRS-R scores in 30 MCS patients, and 2 patients had an increase in CRS-R scores in 25 VS/UWS patients [61].

Huang *et al.* placed anodes on the posterior parietal cortex of 33 MCS patients (derived from Thibaut *et al.*) and applied a direct current with 2 mA for a duration of 20 min. The results showed that compared with the 2 patients with the sham stimulation, 9 patients significantly improved their CRS-R scores during the period of active stimulation [62]. The stimulation of the prefrontal cortex (left-DLPFC) also transiently improved signs of consciousness in MCS patients [63]. Similarly, a latest study stimulated the left-DLPFC and the right-DLPFC cortex of 9 patients with UWS and 7 patients with MCS by tDCS. The results showed that the left anodal tDCS could be more effective for modulating the cortical excitability than tDCS on the right-DLPFC [64].

In addition to target selection, Thibaut *et al.* studied the repeated tDCS in DOC patients. Repeated tDCS stimulation on the left prefrontal lobe (5 days) could promote the recovery of consciousness in some MCS patients, and this effect could last up to one week after the end of the stimulus. Alonzo *et al.* used tDCS to stimulate healthy subjects every day. They found that repeated tDCS stimulation could induce a larger MEPs amplitude, which could reflect the cumulative effect of stimulation, whereas a single tDCS could not induce a similar response [65]. These results are consistent with the observation in the experiment. Subsequent studies found that the number of responders increased with the increase in the number of stimuli and that the duration of the effect also increased [66].

Aside from behavioural assessment, neuroimage and electrophysiology assessment also revealed the effects of tDCS on the brain activities of DOC patients. Yang Bai *et al.* measured TMS-EEG in the tDCS stimulation of DOC patients and found that tDCS effectively regulated the excitability of the cortex in DOC patients [67]. However, tDCS induced different cortical excitability changes between MCS and VS/UWS patients in the temporal and spatial distributions. Thibaut *et al.* showed that the response of MCS patients to tDCS depends on their residual brain metabolism and gray matter integrity. Compared with those of the healthy controls, the FGD-PET results of the tDCS responders showed local hypometabolism in the middle prefrontal cortex or anterior cingulate cortex, medial thalamus and caudate nucleus. The non-responders of tDCS showed an impaired metabolism in similar areas, but it more extensive in the middle prefrontal cortex, caudate nucleus and left thalamus and more pronounced in the precuneus and left prefrontal cortex [61]. The resting state functional magnetic resonance imaging (fMRI) of 16 MCS patients showed that the left-lateral network connection of the left-DLPFC co-activated region of the tDCS responders increased, with the left inferior frontal gyrus showing a significantly increased connection. In the non-responders, the connection between the left-DLPFC and the midline cortical structure (including the anterior cingulate cortex and the anterior cuneiform lobe) was enhanced in MCS patients [60].

Using a 1 mA current, Naro *et al.* tested MEPs amplitude, intracortical short-suppression (SICI) and ICF with tDCS on DOC patients. The results showed that MEPs amplitude, SICI and ICF intensity were only significantly modulated by tDCS in MCS patients and that SICI modulation was significantly correlated with the CRS-R scores of the patients [50]. They considered that the functional activity of the cortex after brain injury depends on the plasticity of its remaining synapses.

In addition to tDCS, tACS, o-tDCS and tPCS can also be used in the intervention of DOC patients. The mechanism of action of tACS and tDCS is similar to a certain extent. tACS mainly acts on the cerebral cortex of DOC patients through AC stimulation to improve the excitability of the cerebral cortex [68]. The subjects receiving tACS on the right-DLPFC showed that tACS could specifically modulate the large-scale cortical operative connectivity and excitability in MCS patients and some UWS patients. This outcome can be interpreted as a potential means of assessment for DOC [69].o-tDCS is a more complex waveform composed of an oscillating direct current, which can be sinusoidal, rectangular or polymorphic [70,71]. According to Naro *et al.*, the cerebellum stimulated with o-tDCS with a rectangular amplitude of 5 Hz could increase the coherence and spectral power of the theta and gamma bands in the frontal lobe and significantly improve the CRS-R scores of patients [72].

Recently, High-definition transcranial direct current stimulation was shown as a new type of technology and improvement of the traditional tDCS for DOC intervention [73]. Compared with the conventional tDCS, High-definition transcranial direct current stimulation has better spatial targeting of the stimulation and enhanced neural regulation function. Particularly, MCS patients showed a significant improvement in their CRS-R scores and EEG activities after two weeks' treatment.tPCS can use weak pulse currents in different frequency ranges to induce currents to reach the cortical and subcortical structures to regulate neuronal activity in the cerebral cortex. Jaberzadeh *et al.* showed that converting a direct current to a unidirectional pulse current could improve the enhancement effect of corticospinal excitability and introduced this new mode as tPCS [17]. Although no study has been conducted yet on the application of tPCS in DOC, an appropriate tPCS paradigm may also be used in the intervention of DOC through the advancements in research.

4. Music stimulation

Music can be defined as a combination of tones and beats, among others, over a period of time. It is very important in people's daily life, as hearing familiar music can produce special memories and emotions [74]. This kind of memory is mainly autobiographical memory, and evocative emotions are positive and intense. Music can also evoke nostalgic emotions [75]. Neuroimaging studies have shown that the medial prefrontal cortex plays a central role when we experience episodic memory triggered by songs we remember from the past [76]. Mechanically, the entire limbic system, including the amygdala, hippocampus, parahippocampal gyrus, nucleus accumbens, ventral tegmental area, anterior cingulate gyrus and orbitofrontal cortex, is activated while listening to music [77]. Music perception requires complex processing, including many cognitive functions [76]. Therefore, music stimulation can be used as a clinical intervention. It is defined as the planned and purposeful use of music to meet the social, psychological, physical and spiritual needs of individuals in the evolutionary process to produce therapeutic effects. In 2006, Schellenberg *et al.* found that musical stimuli could have a positive effect on cognitive processes [78]. Many studies demonstrated that listening to a short piece of music could improve the ability of follow-up language grammar processing in patients with basal ganglia injury [79], Parkinson's disease [80] and developmental language disorders [81].

Music can be part of the best candidate methods to stimulate the brain operation process of DOC patients, and it can help patients to achieve higher cognitive levels (Table 3). Thus far, music has been extensively used in DOC treatment. As early as 2005, research showed that a patient diagnosed with VS/UWS had increased participation in activities after exposure to live music and familiar songs and that the diagnosis changed from VS/UWS to MCS [82,83]. In recent years, many experiments have examined the beneficial effects of music on DOC patients. By stimulating music samples with four different complexities, the autonomic nervous response with emotional value was observed in DOC patients [84]. A neuroimaging study showed that in 2 MCS patients, 5 VS/UWS patients and 21 healthy subjects, some well-known songs such as "Les Toreador" (Bizet's "Carmen") that are familiar to the patients could activate the superior temporal gyrus [85]. One case of VS/UWS improved to MCS in four months after the end of the study. In addition, an experiment examined patients (three cases of MCS and two cases of VS/UWS) and healthy subjects using music and repeating noise under the scanning function of fMRI connection twice, respectively. The results showed that, although DOC patients usually lose long-term functional connectivity, music stimuli could increase functional connectivity in areas of the auditory network compared with noise [86]. Another study compared the effects of music stimulation, call-name stimulation and habitual stimulation on the EEG parameters (wavelet energy and nonlinear dynamics analysis) of 9 MCS and 10 VS/UWS patients. The results showed that the highest degree of EEG response was from the call-name stimulation, followed by habit and music stimulations. Significant differences in the EEG wavelet energy and response coefficient were found between habit and music stimulation and between habit and call-name stimulation [87]. All of the abovementioned studies reflect the changes in the cognitive and brain status of DOC patients in music stimulation.

5. Near-infrared laser stimulation (N-LT)/ focused shock wave therapy (F-SWT)

For the mechanism of N-LT, cytochrome c oxidase (CCO) in the mitochondria of brain cells absorbs near-

Table 3. Studies used music intervention in patients with disorders of consciousness.

Studies	Patients	Music	Protocol	Evaluation	Main results
Wendy L. Magee et. al.	1 VS	Live music performance & personally meaningful music		movements or affective behaviors that occur in contingent relation to relevant environmental stimuli	She showed emotional responses to particular pieces of music and instruments within and across different sessions.
Francesco Riganello et. al.	9VS/UWS	Boccherini (Minuet); Grieg (The morning); Tchaikovsky (Pathetic-1st movement); and Mussorgsky（Night on bald mountain）Four music samples	Listen to each sample randomly, within 10 min of each 60s	normalized units of Low Frequency (nuLF) and Sample Entropy (SampEn) of Heart Rate Variability (HRV) parameters. (The first 3 min of tachogram recorded during the listening of four musical samples.)	1. The VS/UWS group showed a reduction of nuLF as well as SampEn comparing music of increasing Formal Complexity and General Dynamics. 2.These results put in evidence that the internal structure of the music can change the autonomic response in patients with DOC.
Yuka Okumura et. al.	2 MCS 5 VS	The sound source was set at a 120 beats per minute tempo and 2/4 rhythm. "**Baseline sound stimulation (BSS):** add to the sound source the sound of a quarter note (a beep sound); **Instrument sound stimulation (ISS):** add a quarter note sound from a crash cymbal at the second rhythm to the BSS; **A music stimulation (MS):** add instrumental music of the first 16 measures of 'Les Toreador' from 'Carmen' Suite No.1 by Bizet to the BSS	Three types of auditory tasks were constructed as follows: Task I (BSS for 30 seconds), Task II (BSS for 15 seconds followed by BSS with ISS for 15 seconds) and Task III (BSS for 15 seconds followed by BSS with MS for 15 seconds). Every task auditory volume was set at 90 dB.	fMRI: (15-25 seconds after the beginning of each type of Task)	2. Healthy adults, MCS patients and one VS: activate the bilateral superior temporal gyri. 2.One VS improved to MCS 4 months after the study.
Lizette Heine et. al.	3MCS 2UWS	Five musical excerpts preferred by the patient (2minuites each) were combined to create a musical stimulus of a duration of 10 min, which overlaps with the duration of the functional scan.	Music sample is preferred for 10 minutes, and noise samples (repeated noise in MRI scanners) for 10 minutes. And the two stimulations were separated by a delay of 10 min.	The functional scan was acquired twice during one MRI scanning session.	1. Have effects on patients' auditory network (implied in rhythm and music perception) and on cerebral regions linked to autobiographical memory. 2. Increased functional connectivity during the music condition (vs. the control condition) in cortical structures linked to music perception, autobiographical memory and consciousness for DOC patients.
Jingqi Li et. al.	9MCS 10VS	**Music stimulation:** the Chinese classical music "Jasmine" **Call-name stimulation:** the patient's name was called by relatives. **Habit stimulation:** patients were stimulated either by wiping alcohol on the lips for alcoholic patients, or by introducing the smell of cigarette smoke for smoking patients.	music stimulations for 90s; Call-name stimulation for 90s; habit stimulation for 36s. And each stimulation was separated by a delay of 60s. The entire process was repeated three times.	Resting-state EEG	Results showed that the highest degree of EEG response was from the call-name stimulation, followed by habit and music stimulations.

MCS: minimally conscious state; VS: vegetative state; UWS: unresponsive wakefulness syndrome; EEG: electroencephalogram; MRI: Magnetic resonance imaging.

infrared light, thus increasing the mitochondrial products adenosine triphosphate, nicotinamide adenine dinucleotide, tabolism of oxygen and increases the production of reactive oxygen species, which can activate some redox-sensitive transcription factors. Under the combined action of the above mechanisms, N-LT can up-regulate cellular respiration and enhance the activity of brain cells [88].

F-SWT stimulates the endothelial nitrogen oxide production to promote nerve regeneration while stimulating the fibroblast growth factor to promote nerve regeneration. In the treatment of hip joint necrosis with extracorporeal shock wave, the concentrations of nitric oxide, vascular endothelial growth factor (VEGF) and fibroblast growth factors in serum were systematically increased within four weeks. In animal models, VEGF promotes functional regeneration after spinal cord contusion and slows down secondary degeneration. In this context, some scholars have hypothesised that extracorporeal shock waves can restore the dysfunctional synaptic connections in the brain [89].

Studies showed that N-LT and F-SWT could be applied to the rehabilitation of stroke and diabetic foot ulcers, respectively, with significant effects [88,89]. Moreover, N-LT/F-SWT can also be used as a new treatment for patients with DOC. In 2016, a study enrolled 14 UWS and 2 MCS patients and randomly divided them into two groups of N-LT (8 UWS/VS) and F-SWT (6 UWS/VS and 2 MCS). The N-LT group established and marked 5 points along a horizontal line on the upper edges of two sphenoid fossae, and then stimulated the points for 10 min each time five times a week for four weeks. The F-SWT group was stimulated on both sides of the skull for 10 min each time three times a week for four weeks. A female UWS in the F-SWT group stopped the intervention because of seizures. According to the CRS-R, FOUR scale, and SMART scale assessments, the consciousness status of the two groups was improved and continuously maintained after the intervention [90].

6. Low-intensity focused ultrasound pulsation (LIFUP)

As a controllable nerve stimulation, LIFUP directly regulates the deep brain nucleus such as the thalamus, and it not only reversibly stimulates the neuron activity but also inhibits it [91]. Studies have demonstrated that LIFUP can treat neurological disorders such as chronic pain, obesity and Parkinson's disease through neural inhibition [91].

LIFUP can perform non-invasive focusing through the skull. Combined with fMRI, it can be used as a novel method for treating DOC. The stimulation of the thalamus (frequency: 100 Hz; pulse width: 0.5 ms; Ispta: 720 mW/cm2; stimulations: 10 times, with each time lasting 30 s with an interval 30 s) of a male brain trauma patient improved the CRS-R scores of the patient. More importantly, three days after LIFUP, the patient showed complete language comprehension, reliable responses to instructions and communication skills (through 'yes'/'no' gestures). Five days after the stimulation, the patient tried to walk. However, assessing whether the observed effect is causally related to LIFUP stimulation is currently impossible, and further investigation is needed to explain the significance of this interesting finding [92].

7. Transcutaneous auricular vagus nerve stimulation (taVNS)

VNS is a nerve stimulation technology that modulates functional brain activity through the electrostimulation of the vagus nerve. The afferent vagus nerve branches project into the nucleus of the solitary tract, which is attached to the thalamus, amygdala, forebrain and the medullary network. Anatomical studies have demonstrated that the vagus nerve has an afferent branch on the auricle [93]. The direct electrical stimulation of this branch may produce effects similar to those of classical VNS without the potential risks associated with surgery, and this stimulation is called taVNS.

The first case of taVNS being used for treating DOC patients was reported in 2017 [94]. The study showed that a direct electrical stimulation applied to a female VS/UWS patient's bilateral ear concha, with an intensity of 4–6 mA at a frequency of 20 Hz (less than a 1 ms wave width) twice daily for 30 min each in four consecutive weeks, increased the CRS-R score (from 6 to 13) of the patient after a four-week treatment. In addition, brain fMRI was performed and showed that the functional connectivity among the posterior cingulate/precuneus and hypothalamus, thalamus, ventral medial prefrontal cortex and superior temporal gyrus increased respectively, but the functional connectivity between the posterior cingulate/precuneus and cerebellum decreased. Thus, the improvement of the patient was closely related to the taVNS treatment, although the possibility of a spontaneous coincidental recovery could not be excluded [94].

8. Discussion and conclusion

Human consciousness is one of the most mysterious and challenging issues in human science. Along with consciousness injury and rehabilitation, DOC provides a natural clinical model for consciousness research. An increasing number of neuroscientists have paid attention to consciousness research to find solutions for the clinical difficulties in DOC. Although many efforts

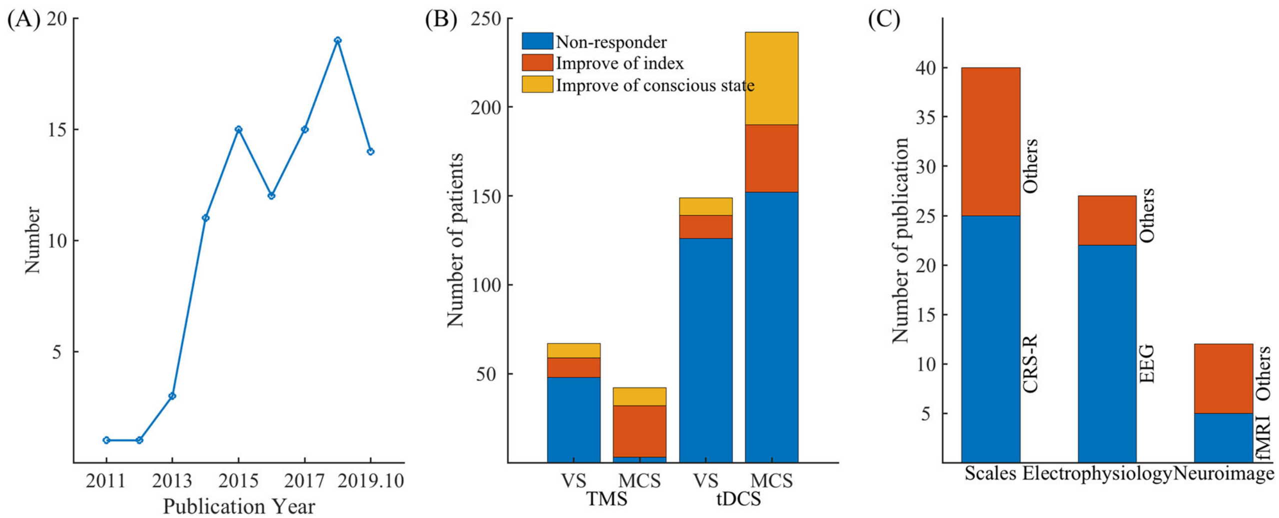

Figure 1. (A) Number of publications that used NIBI techniques in DOC. (B) Number of patients that reported improvement in TMS and tDCS therapies. Improvement of the conscious state means the patients showed a higher conscious state after the therapy. Improvement of index means the patients did not show an increase of conscious state but showed improvement in consciousness-related neuro-electric or neuroimaging features. (C) Evaluation tools used to assess the NIBI effects on DOC.

have been made, the diagnosis and treatment of DOC patients remain a dilemma. Recently, the development of neuro-modulation interventions shed lights on DOC patients. Specifically, as avoiding the disadvantages of traditional invasive brain stimulation, NIBI techniques are becoming more accepted (Figure 1 (A)). Among them, TMS (based on the magnetic effect) and tDCS (based on the electric effect) are considered the most promising techniques. They have significantly enriched the clinical tools for DOC assessment and intervention.

Generally, the basic intention of neuro-modulatory therapies for DOC is to directly or indirectly alter the activities of the cortical neurons. They enhance the excitability of the neuronal groups by inducing impulses or changing the membrane potential and then activating the consciousness-related pathways and networks. Although these neuro-modulatory technologies have both excitatory and inhibitory effects, they are mostly used as an excitatory paradigm in DOC research. Among these neuro-modulatory technologies, TMS and tECS are considered the most promising treatment methods for DOC. Many protocols based on TMS or tECS have been proposed for DOC intervention, and they include repetitive TMS under 10 Hz and 20 Hz, TBS and tECS with direct or alternating current at 1 mA and 2 mA. For the target sites, whether in TMS or tECS protocols, the frontal or parietal cortex is always given more attention because, according to the current consensus, human consciousness is more related to neural activities in the frontal and parietal regions (the exact consciousness-related neurons are still controversial) .

Although the results show the potential treatment effects for DOC patients, only a few patients benefited from TMS or tDCS therapies (Figure 1 (B)). Based on the cases reported in publications, only 8.3% of VS/UWS patients obtained consciousness improvement after TMS or tDCS. In comparison, a higher percentage of MCS patients responded to TMS or tDCS therapy: 25.6% of MCS patients showed improvement of consciousness after TMS and 21.5% improved after tDCS. Moreover, although they did not obtain an increase in the consciousness state, about 74.4% of MCS patients in TMS research and 15.7% of MCS patients in tDCS showed signs of a positive improvement of brain activities as reflected by EEG and fMRI, among others. Therefore, this study offers two suggestions:

1. tDCS and TMS can facilitate the consciousness rehabilitation of DOC patients.
2. MCS can benefit more than VS/UWS from TMS or tDCS therapy.

The CRS-R scale is commonly used to assess patients' responses to the NIBI techniques. It is usually used as a golden criterion to determinate whether patients respond to the interventions. However, as they are based on the patients' responses to external stimulation, the CRS-R results are easily affected by non-conscious factors, such as the fatigue of patients, behavioural disability and the subjective interpretation of the implementers. In addition, the CRS-R scale cannot reflect the slight improvement in the underlying neural activities. It can be unsuitable in detecting the modulation effects in a short-term protocol, in which the efficacy of NIBI may be too weak to induce behavioural changes. Therefore, more sensitive methods, including neuro-electric or neuroimaging tools are used to evaluate the effect of NIBI. Among these tools, EEG and fMRI are the frequently used ones (Figure 1 (C)). The combination of TMS and EEG also helps in the assessment of DOC patients. By capturing the real-time responses of the underlying neuron groups to the TMS pulse, TMS-EEG can measure the neural excitability, plasticity and connectivity features of the brain. From the perspective of information integration theory, local neural excitability and inter-neural connectivity, which separately represent the complexity and integration of the brain, are fundamental features of human consciousness. Therefore, PCI, which quantifies the complexity and integration of the TMS-EEG signal, is considered to be an effective way to distinguish patients with different consciousness states.

However, results from the current research are still insufficient to conclude the absolute efficacy of NIBI in the DOC clinic. On one hand, only a few clinical trials used extremely double-blind controlled design and large samples to reduce the effects from individual differences, such as time after injury, aetiology, location and size of brain injury. On the other hand, long-term therapy (monthly scale) with a follow-up outcome tracking should be conducted to determine the exact treatment effects.

Furthermore, the improvement of technologies or protocols is required to strengthen their efficiency in DOC. Firstly, the closed-loop concept may bring a new perspective to NIBI in DOC. Compared with the blind randomised intervention, the conditioned intervention under a real-time EEG assessment can be more precise in measuring neuro-excitability [95] and induce a stronger effect on the excitability modulation [96]. Therefore, the closed-looped TMS or tDCS therapies are valuable when tested in DOC research. Secondly, most NIBI therapies modulate the brain activities with a single target. In the future, multi-targets or network modulations should be conducted as an improved method to simultaneously activate the hubs of consciousness pathway. Finally, aside from cortical stimulation, subcortical stimulation should also be taken into account by NIBI therapies. The non-invasive stimulation of the deep brain nuclei (e.g. thalamus) has been proven helpful in the consciousness rehabilitation of DOC patients [92], but it still needs to be validated with controlled clinical experiments. Exploring the effects of some novel techniques, such as temporally interfering with the electric stimulation [97] in the DBS of DOC patients, is also valuable.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work was supported by the National Natural Science Foundation of China (61901155, 81920108023); Medicine and Health Science and Technology Project of Zhejiang Province (2019RC254); Innovation and Entrepreneurship Training Program for College students in China (201910346034); Science and Technology Innovation Program for College students in Zhejiang Province (2019R426040).

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