Current Status of Neuromodulatory Therapies for Disorders of Consciousness

Xiaoyu Xia¹ · Yi Yang¹ · Yongkun Guo² · Yang Bai³ · Yuanyuan Dang¹ ·
Ruxiang Xu¹ · Jianghong He¹

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Abstract Treatment for disorders of consciousness (DOCs) is still a Gordian knot. Evidence-based guidelines on the treatment of DOC patients are not currently available, while neuromodulation techniques are seen as a potential treatment. Multiple neuromodulation therapies have been applied. This article reviews the most relevant studies in the literature in order to describe a clear picture of the current state of neuromodulation therapies that could be used to treat DOC patients. Both invasive and non-invasive brain stimulation is discussed. Significant behavioral improvements in prolonged DOCs under neuromodulation therapies are rare. The efficacy of various such therapies remains a matter of debate. Further clinical investigations of existing techniques in larger samples properly controlling for spontaneous recovery are needed, and new approaches are awaited.

Keywords Disorder of consciousness · Neuromodulation · Deep brain stimulation · Spinal cord stimulation · Repetitive transcranial magnetic stimulation · Transcranial direct current stimulation

Introduction

Consciousness can be defined by two components: arousal (wakefulness, also called vigilance or alertness) and awareness (perception of self and environment) [1, 2]. Disorders of consciousness (DOCs) develop from acute coma, which typically resolves within 2 weeks. They affect both the arousal level and the contents of consciousness [3]. Depending on these features, DOCs encompass a wide spectrum of diseases with indistinct boundaries [4, 5]. The vegetative state (VS, also known as the unresponsive wakefulness syndrome, UWS) and the minimally conscious state (MCS) are major subgroups [6]. By definition, the VS is a condition of wakeful unconsciousness [7], whereas the MCS is characterized by minimal, but definite, behavioral evidence of self-awareness or environmental awareness [3, 8]. An MCS can exist as a transitional state reflecting improvement in consciousness following a VS [3].

With advances in neurocritical care, the number of DOC patients is continuously growing as more patients with severe brain injury survive [9]. This presents tremendous pressure and challenges to clinical treatment. The treatment of DOCs is still challenging for clinicians due to the current lack of evidence-based guidelines for their treatment [3]. Many potential pharmacological and non-pharmacological interventions have been tried and evaluated in the last decade. So far, few have shown encouraging enhancement of consciousness. Only Amantadine and transcranial direct-current stimulation (tDCS) have been verified as having a limited ability to improve functional recovery in strictly-designed randomized double-blind controlled studies [10, 11]. Among the range of treatments to facilitate recovery, neuromodulation techniques aim to modulate neural circuits that more directly mediate arousal and

✉ Jianghong He
he_jianghong@sina.cn

¹ Department of Neurosurgery, PLA Army General Hospital, Beijing 100700, China

² Department of Neurosurgery, Zhengzhou Central Hospital Affiliated to Zhengzhou University, Zhengzhou 450007, China

³ International Vegetative State and Consciousness Science Institute, Hangzhou Normal University, Hangzhou 311121, China

attention [12]. Neuromodulatory therapies with electrophysiological techniques have become a new promising approach in therapeutic trials for DOC patients [13].

In this paper, we review the most relevant studies in the literature in order to provide a clear picture of the current status of neuromodulatory therapies that can be used to treat DOCs. A search was performed in PubMed using two key concepts: coma in the broad sense and neuromodulatory techniques. Search words included: (“DBS” OR “Deep brain stimulation” OR “SCS” OR “Spinal cord stimulation” OR “rTMS” OR “repetitive transcranial magnetic stimulation” OR “tDCS” OR “transcranial direct current stimulation”) AND (“coma” OR “disorders of consciousness” OR “minimally conscious state” OR “MCS” OR “vegetative state” OR “persistent vegetative state” OR “VS” OR “unresponsive wakefulness syndrome” OR “UWS”). Both invasive brain stimulation (deep brain stimulation [DBS] and epidural spinal cord stimulation [SCS]) and non-invasive brain stimulation (NIBS; repetitive transcranial magnetic stimulation [rTMS], and tDCS) are discussed.

Invasive Brain Stimulation

Invasive brain stimulation for the treatment of DOCs, including DBS and SCS, is based on the surgical implantation of a medical device. The device acts as a brain pacemaker by sending electrical impulses to specific parts of the central nervous system. The implanted hardware consists of three components: the implanted pulse generator (IPG), the lead, and the extension. The IPG is a battery-powered neurostimulator that is placed subcutaneously and provides electrical pulses. The lead contains electrodes that deliver the electrical pulses to the spinal cord or brain tissue. The extension is an insulated wire that subcutaneously connects the IPG with the lead. The type and placement of the lead differ between the DBS and SCS procedures (Table 1).

Deep Brain Stimulation

DBS is a method of electrically stimulating the deep structures of the brain. Extracellular direct currents of variable frequencies, voltages, and pulse widths are generated and delivered *via* implanted devices. DBS has been used as a therapy to treat a wide variety of clinical situations, such as Parkinson’s disease [15–17], essential tremor [18], and dystonia [19]. It has been applied not only to different brain regions in the same pathology but also to the same brain region in various pathologies [13]. The mechanisms underlying the action of DBS are multiple, complex, and not fully clear even in Parkinson’s disease

where it has been widely applied [17]. It is thought to have both local and systemic effects. The local effects are mainly consequences of changes in the activity of both afferent and efferent axonal fibers, rather than cell bodies in the stimulated area [20]. The systemic effects mean that DBS can induce overall changes in activity throughout the connected network [21].

As early as 1968, researchers attempted to treat DOCs with DBS [22]. However, only sporadic case reports or small case series were available until 2007, after which research in this area grew rapidly. Vanhoecke *et al.* recently published a systematic review of cases and the ethics of DBS for DOCs [23]. As no new evidence has been reported since 2017, we again reviewed the 19 articles included in that review. The DBS implantation targets are diverse in these reports: the mesencephalic reticular formation (cuneiform nucleus) [24, 25], pallidum [26], and various thalamic areas. According to the mesocircuit model, which has been proposed to account for the pathophysiological mechanisms underlying DOCs [3], a crucial role for neurons within the central thalamus has been proposed. The central thalamus has attracted increasing attention as a recommended target because of its critical role in the regulation of arousal [27, 28].

A landmark study in this field, the methodologically rigorous single-subject trial carried out by Schiff and colleagues in 2007 is worth noting [14]. A 38-year-old male MCS patient was bilaterally implanted with stimulating electrodes within the anterior regions of the intralaminar thalamic nuclei. A double-blind crossover study with alternating DBS-ON and DBS-OFF over a 2-month period showed a statistically significant DBS-dependence of the measurements [Coma Recovery Scale-Revised (CRS-R) arousal subscale, limb control measure, and oral-feeding scale] in this study and demonstrated the efficacy of DBS in this particular patient. In another case study [29], although the stimulation target and parameters were the same as in Schiff *et al.* [14], a patient with MCS did not show an improvement in the CRS-R score, while changes in sleep dynamics recorded in the EEG were reported after DBS [30]. Magrassi *et al.* reported the results of the Cortical Activation by Thalamic Stimulation (CATS) study on the effects of bilateral chronic stimulation of the anterior intralaminar thalamic nuclei and adjacent paralaminar regions in DOC patients [31]. Among 40 DOC patients evaluated, only 3 (2 VS and 1 MCS) were selected for implantation of bilateral thalamic electrodes and underwent chronic stimulation for a minimum of 18 months and a maximum of 48 months. Each showed improvement in the CRS-R score and EEG evaluation, and beneficial effects on spasticity and myoclonus, but none returned to a fully conscious state. In 2017, Chudy *et al.* reported another case series of 14 patients (10 VS and 4

Table 1 A brief comparison of SCS and DBS for DOC treatment.

	DBS	SCS
Lead	A coiled wire insulated in polyurethane with electrodes that deliver electrical pulses to brain tissue	Usually paddle-shaped, with different numbers of electrodes/contacts
Location of the lead (target)	Usually, the centromedian-parafascicular complex; the central thalamus is attracting increasing attention	The midline of the posterior epidural space of the spinal cord between C2 and C4
Main research teams	Most come from Europe and America	Most come from East Asia
Stimulation frequency	25 Hz–250 Hz; large differences between reports	5 Hz and 70 Hz most common
Total number of reported patients	78 patients	Hundreds of patients
Strictly designed studies with positive results	Schiff <i>et al.</i> [14]	None

MCS) selected from 49 DOC patients [32]. Three MCS patients regained consciousness after DBS, one VS patient improved to MCS, three VS patients died during follow-up, and the remaining patients did not recover. A larger study involving 21 VS patients reported the encouraging result that 8/21 of these patients showed long-lasting behavioral improvement after unilateral DBS of the centromedian-parafascicular thalamic nucleus or reticular formation on the less affected side [33].

There are still some practical difficulties in applying DBS for DOC treatment. The DBS-induced modulation depends on the exact physiological and geometric properties of the DBS target and the connectivity of the affected region [13]. Precise electrode implantation requires a relatively normal brain anatomy and clear mapping of nuclei, which are usually lacking in DOC patients. Brain connectivity is also impaired to varying degrees in these patients. As a result, the majority of DOC patients do not meet the minimal criteria of brain connectivity and tissue preservation that are required for attempting thalamic DBS [31]. Besides, in some reports, it is difficult to ascribe behavioral improvements to the exclusive effect of DBS since the implant was carried out within the period of possible spontaneous recovery and the lack of a control group.

Despite the many problems, DBS has received increasing attention for DOC treatment. The reports in the literature confirm that DBS can improve the clinical status of DOC patients. As spontaneous recovery from chronic DOC to the level of consciousness is very rare, DBS could be a treatment option in many situations [32]. Randomized double-blind controlled studies are lacking so far. Due to the highly heterogeneous etiology and clinical status of DOC patients, there are logistical and methodological difficulties associated with conducting placebo-controlled trials in this population [34]. More studies with larger numbers of patients are needed to develop selection criteria for surgical patients.

Spinal Cord Stimulation

SCS is a therapeutic technique that has been classically used for pain and spasticity management [35–39]. According to the literature, research groups in Japan have applied this technique in DOC patients [24, 40–46]. For DOC treatment, the lead is usually implanted at the midline of the posterior epidural space of the spinal cord between C2 and C4. Different electrode settings in the lead produce different electrical field configurations [36, 47]. Monopolar stimulation with only one cathode contact in the lead produces large electrical fields, while bipolar stimulation with oppositely-charged contacts in the lead produces more focal stimulation [36]. Besides the electrode settings, frequency and amplitude are the main parameters affecting the stimulation effect [13]. It has been reported that, in general, low-frequency electrical stimulation has an excitatory effect, whereas high-frequency stimulation produces neuronal inhibition in SCS [36, 48].

The mechanism underlying SCS for DOC treatment is still unknown. Cervical SCS might enhance firing to the cerebral cortex by a direct effect on the reticular formation through the ascending arousal system [49]. According to previous studies, SCS enhances $\alpha 1$ sympathetic activity, promoting neuroplasticity in the central nervous system and activating residual functional cortical areas [42]. Besides, increases of cerebral blood perfusion [50, 51] and catecholamines (dopamine and norepinephrine) in the cerebrospinal fluid after SCS have been reported, and superoxide free radicals are decreased after SCS [52].

Clinical experience with SCS for DOC treatment is limited to some prospective uncontrolled and nonrandomized observational studies. Altogether, we reviewed 12 studies on this topic. The two most influential reports are from Kanno's and Yamamoto's groups [42, 43]. Kanno *et al.* performed an observational study on the effect of SCS at 70 Hz in 214 VS patients of various etiologies. Positive results were obtained in 109 of 201 patients (54%),

with better responses in those aged < 35 years, those in a persistent vegetative state (PVS) of traumatic origin, and those with a regional cerebral blood flow > 20 mL/100 g per minute [42]. Yamamoto *et al.* reported an observational series of 10 MCS patients receiving SCS at 5 Hz, of whom 8 emerged from MCS over a 1-year follow-up period [43]. The preliminary results are encouraging, but it is still hard to make any rigorous assessment as the effect of SCS is difficult to distinguish from spontaneous recovery under the existing experimental design. Further evidence-based, randomized controlled trials are needed to confirm the efficacy of SCS. Unfortunately, we have not seen such a study yet. In addition, the programmed parameter settings (amplitude, frequency, pulse width, and duration of stimulation) were different from previous studies. As important factors affecting the therapeutic effect, the discussion of programming parameters is inadequate.

Since 2017, the mechanism underlying SCS for DOCs has been explored and programming parameters have been discussed [53–55]. Our research team measured the effects of SCS on the EEG of MCS patients and the frequency-specific effects of SCS on neurophysiological activity [53], and found that 70 Hz is a possible effective frequency for DOC treatment. Then we investigated the functional connectivity and network properties during SCS at 70 Hz in MCS patients [54]. The results showed that SCS at 70 Hz affects cortical gamma activity, including immediate global effects and long-lasting local effects. Besides the stimulation frequency, Zhang *et al.* discussed whether and how the inter-stimulus interval affects the SCS neuromodulation in DOC using functional near-infrared spectroscopy [55]. They found that a shorter inter-stimulus interval improves the blood volume in the prefrontal cortex. All these studies added to evidence that SCS can modulate brain function in DOC patients.

Non-Invasive Brain Stimulation

NIBS techniques deliver electrical or magnetic stimuli to the brain without the need for surgery. Invasive brain stimulation methods are associated with surgical risks (infection, acute inflammation, and/or seizures) [56]. Although the scope and accuracy of stimulation are limited, the non-invasive property makes them acceptable for the families of patients. They also have fewer ethical and procedural limitations than the invasive methods [29]. As a result, extensive developments have recently been made in approaches that deploy NIBS. Among all the NIBS methods, rTMS and tDCS have been widely adopted and used in both healthy and clinical samples.

Repetitive Transcranial Magnetic Stimulation

TMS is a safe, non-invasive, and painless technique that can be applied one stimulus at a time (single-pulse TMS), in pairs of stimuli separated by a variable interval (paired-pulse TMS), or in trains of repetitive stimuli (rTMS) [13]. TMS has been shown to have a neuro-modulatory effect when given repetitively [57, 58]. Despite the intra- and inter-individual variability of responses to rTMS [59], low-frequency rTMS (~1 Hz) is considered inhibitory whereas high-frequency stimulation is considered to have excitatory effects [60]. The terms “excitation” and “inhibition” refer to the balance between excitatory and inhibitory effects on different neural circuits [61].

The neuromodulatory effect of rTMS has been repeatedly verified by a variety of technical means in previous studies. Its modulation of distant brain networks was first demonstrated in neurophysiological studies that reported a modulation of M1 excitability induced by stimulation applied over the dorsal premotor cortex [62–64]. Neuroimaging data also showed changes of the blood-oxygen-level-dependent signal [65] and cerebral blood flow [66] after rTMS of the premotor or motor cortex. MCS patients showed significant increases in cerebral blood flow, which were temporally related to high-frequency rTMS [67]. Our recent studies also added evidence to the case for rTMS as an effective neuromodulation tool by quantitative EEG [68] and TMS-EEG analysis [69].

The clinical application of rTMS in patients with DOCs has a very short history. Clinical data on its efficacy as a neuromodulatory approach in DOC derive mainly from small open-label studies and case reports, with only a few cross-over, controlled studies. We reviewed 8 main clinical studies (listed in Table 2). The preliminary clinical results are intriguing and encouraging in most studies. A recent preliminary study carried out by our team also showed a modest therapeutic effect of rTMS for DOC patients, somewhat more in those with MCS than in most of the others with VS/UWS [70]. However, there are also reports of negative results. In particular, a randomized, sham-controlled study by Cincotta *et al.* showed no effect of rTMS at 20 Hz on the primary motor cortex in VS patients [71]. Multiple inherent defects in the experimental design (limited sample size and lack of a control group) have limited the power of the conclusions in most studies. Besides, stimulation protocols vary widely among studies. There is still no specific, unified criterion regarding rTMS for DOC treatment. Its clinical application still requires deep investigation. Clearly, a larger study is needed to include control subjects with rigorous inclusion and exclusion criteria, along with a carefully-defined protocol of consciousness evaluation.

Table 2 Main clinical studies of rTMS in DOCs.

Study	Design	Number of patients and diagnosis	Time from injury	Target	Stimulation protocols	Results
Louise-Bender Pape <i>et al.</i> [72]	Case report	1 VS	9 months	Right DLPFC	300 paired-pulse trains per session; 100 ms inter-pulse and 5 s inter-train intervals; 30 sessions in 6 weeks	Trend toward significant neurobehavioral gains temporally related to provision of rTMS
Piccione <i>et al.</i> [73]	Case report	1 MCS	60 months	Left M1	10 trains of 100 stimuli at 20 Hz; single session	Frequency of specific and meaningful behaviors increased after rTMS, along with absolute and relative power in the EEG δ , β , and α bands
Manganotti <i>et al.</i> [74]	Open-label	3 VS, 3 MCS	12 months–94 months	Left/right M1	Single session of 1000 stimuli delivered in 10 trains of 20 Hz rTMS; each train lasted 5 s with a 20 s inter-train pause	Long-lasting behavioral and neurophysiological modifications in only one patient in MCS
Cincotta <i>et al.</i> [71]	Randomized, sham-controlled study	11 VS	9 months–85 months	Left M1	10 trains of 100 stimuli at 20 Hz; five sessions	No evidence of therapeutic effect
Naro <i>et al.</i> [75]	Controlled study	10 post-anoxic UWS	4 months–15 months	Right DLPFC	Single session of 1000 biphasic pulses delivered in trains of 50 stimuli in 5 s (10 Hz) repeated every 20 s	Transient significant clinical improvement associated with a short-lasting reshaping of brain connectivity in 3 patients
Xie <i>et al.</i> [76]	Case control study	11 VS, 7 MCS and 2 in coma (10 in the treatment group)	NA	Right DLPFC	5 Hz; 28 sessions in 4 weeks	Changes in the neural electrophysiology and behavior after rTMS in 6 patients
Liu <i>et al.</i> [67]	Controlled study	5 VS, 5 MCS	1 months–28 months	Left M1	Single session of 1,000 stimuli delivered in 20 trains of 20 Hz with stimulus intensity equal to MT; each train lasted 2.5 s with a 28 s inter-train pause	No significant changes in CRS-R subscores of 10 patients after rTMS; MCS group exhibited significant increases in peak systolic velocity and mean flow velocity of left MCA
Xia <i>et al.</i> [70]	Prospective single-blinded study with selected subjects	11 VS/UWS, 5 MCS	3 months–35 months	Left DLPFC	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	CRS-R scores increased in all 5 MCS and 4 of 11 VS/UWS patients

DLPFC dorsolateral prefrontal cortex, *M1* primary motor cortex, *MCA* middle cerebral artery, *MCS* minimally conscious state, *MT* motor threshold, *rTMS* repetitive transcranial magnetic stimulation, *UWS* unresponsive wakefulness syndrome, *VS* vegetative state.

Transcranial Direct-Current Stimulation

tDCS can induce neuroplasticity and modulate cortical functioning by applying weak direct current over the scalp [77]. Similar to rTMS, tDCS also acts as an exciter or an inhibitor of brain activity in regions of interest. Anodal stimulation has excitatory effects, whereas cathodal stimulation has inhibitory effects on the underlying cortex [78, 79]. Neuromodulatory effects of tDCS can be long-lasting, and are related to the duration of stimulation and magnitude of the applied current [80].

tDCS is considered to have advantages over TMS in some aspects. TMS has been associated with the potential for causing seizures if applied inappropriately [81, 82], while no severe side-effects have been reported for tDCS. Further, tDCS is relatively low-cost, user-friendly, portable, and tolerable [83, 84].

The mechanisms underlying the cortical excitatory or inhibitory effect of tDCS have yet to be fully understood [85, 86]. Functional MRI studies have demonstrated that tDCS exerts distant actions by modulating different patterns of functional connectivity between cortical and

subcortical networks when applied over M1 [87, 88] or the dorsolateral prefrontal cortex (DLPFC) [89]. Recent electrophysiological evidence has revealed that tDCS effectively modulates cortical excitability in patients with DOCs [90, 91]. In terms of noninvasive intervention, tDCS has been widely used in the treatment of many diseases including drug addiction [92], stroke [93], epilepsy [94], Parkinson's disease [95], chronic pain [96], Alzheimer's disease [97], and depression [98]. Recently, some studies have explored the potential of tDCS to improve patients' consciousness. We reviewed 5 main studies regarding the therapeutic effect of tDCS for DOCs (Table 3). Clinical tDCS studies of DOC are fewer than those of rTMS, but the quality of experimental design is higher. Thibaut *et al.*

found that the left prefrontal tDCS transiently improved behavioral responsiveness, mostly in MCS patients, in a randomized double-blind sham-controlled crossover study [11]. In another sham-controlled randomized clinical trial, tDCS stimulation of the posterior parietal cortex was also found to improve the recovery of clinical signs of consciousness in some MCS patients, but the effects were weaker than prefrontal stimulation [99]. However, negative results have also been reported. In a double-blind crossover study, Estraneo *et al.* found that repeated tDCS did not have remarkable short-term clinical and EEG effects in patients with prolonged DOC [100].

Some beneficial results of tDCS protocols have been demonstrated in MCS patients. However, the reported

Table 3 Main studies on the therapeutic effect of tDCS for DOC.

Study	Design	Number of patients and diagnosis	Time from injury	Target	Stimulation protocols	Results
Thibaut <i>et al.</i> [11]	Randomized double-blind sham-controlled crossover study	25 UWS, 30 MCS	7 days–132 months	Left DLPFC	Anodal tDCS; 2 mA for 20 min; cathode over right supraorbital region; single session	Patients in MCS showed a significant treatment effect as measured by CRS-R total scores
Angelakis <i>et al.</i> [101]	Prospective, case-series trial	7 UWS, 3 MCS	6 months–120 months	Left primary sensorimotor cortex or left DLPFC	Anodal tDCS; 20 min/day, 5 days/week; sham tDCS week 1, 1 mA week 2, 2 mA week 3; cathode over right supraorbital region	All patients in MCS showed clinical improvement immediately after treatment. No patient in PVS/UWS showed immediate improvement after stimulation, but 1 patient in PVS/UWS for 6 years before treatment showed improvement and change of status to MCS at 12-month follow-up
Thibaut <i>et al.</i> [102]	Randomized double-blind sham-controlled crossover study	16 MCS	5 months–365 months	Left DLPFC	Anodal tDCS; 2 mA for 20 min; cathode over right supraorbital region; 5 sessions	Treatment effect at the end of active tDCS session and 1 week later
Estraneo <i>et al.</i> [100]	Randomized double-blind sham-controlled crossover study	7 VS, 6 MCS	3 months–84 months	Left DLPFC	Anodal tDCS; 2 mA for 20 min; cathode over right supraorbital region; 5 sessions	Repeated tDCS had no short-term clinical and EEG effects in patients with prolonged DOC
Huang <i>et al.</i> [99]	Randomized double-blind sham-controlled crossover study	37 MCS	> 1 month	Posterior parietal cortex	Anodal tDCS; 2 mA for 20 min; cathode over right supraorbital region; 5 sessions	Improved recovery of clinical signs of consciousness in some patients in MCS; weaker than prefrontal stimulation

DLPFC dorsolateral prefrontal cortex, *MCS* minimally conscious state, *PVS* persistent vegetative state, *tDCS* transcranial direct-current stimulation, *UWS* unresponsive wakefulness syndrome, *VS* vegetative state.

studies are still preliminary in small samples, with heterogeneous outcome measures, including either clinical or functional connectivity variables [103]. Further studies are needed to determine the long-term therapeutic effects of tDCS on different targets in DOC patients. The spatial accuracy of tDCS is poor. To compensate for this defect, a recent development is the introduction of high-definition tDCS [104], which allows for more focal stimulation than conventional tDCS and we can expect its application in DOC treatment.

Other Neuromodulatory Therapies

Besides the four main techniques of neuromodulation discussed above, other techniques have also been explored for the treatment of DOC. Naro *et al.* used transcranial alternating-current stimulation (tACS) to modulate brain oscillation patterns in the gamma band in order to evaluate the residual network connectivity in DOC patients [105]. tACS induced no significant CRS-R changes either during or after each experimental session, but there were some changes in EEG parameters. The same research group also compared cerebellar 5-Hz oscillatory tDCS to sham stimulation and found increased theta and gamma power and gamma coherence at up to 30 min after the stimulation, associated with transient CRS-R amelioration in MCS patients [106]. Electrical stimulation of the vagus nerve can also modulate functional brain activity. Recently, a study has demonstrated the therapeutic potential of surgical vagus nerve stimulation to modulate large-scale human brain activity and alleviate disorders of consciousness [107]. In the same year, another study showed that noninvasive transcutaneous auricular vagus nerve stimulation improved the clinical condition and functional network of the brain in a DOC case [108]. Stimulation of the right median nerve is a noninvasive neuromodulatory therapy which uses a pair of flat metal disc electrodes taped to the skin of the wrist to generate an electrical field and a current through the axons of the nerve. The procedure is very simple and suitable even for critical patients. As a result, median nerve stimulation is more common in acute-subacute consciousness disorders, whereas studies on chronic DOC are lacking [13].

All existing neuromodulation techniques have limitations. Invasive approaches can lead to complications tied to implantation. Noninvasive approaches such as rTMS and tDCS now have only superficial penetration and cannot modulate deep brain nuclei directly. New revolutionary techniques of neuromodulation are being developed to avoid these disadvantages. Low-intensity focused ultrasound pulsation modulates deep nuclei non-invasively without affecting the intervening tissues. A recent case

study reported its first use in an acute DOC patient recovering from severe traumatic brain injury [109]. Grossman *et al.* have described an experimental noninvasive strategy that specifically targets deeply-situated neurons without affecting the overlying cortex in the mouse [110]. This provides proof-of-concept that deep brain tissue can be specifically targeted by the exterior application of two electromagnetic fields of slightly different frequencies. Noninvasive deep brain stimulation, although not yet clinically achieved, seems possible [111].

Perspective

The content presented above suggests that neuromodulation therapies present an interesting means of treating DOC patients. The reports in the literature indicate that such therapies for DOC are not yet satisfactory. Few patients have achieved full recovery. Limited by small samples and defective experimental designs, the effects of modulation are indistinguishable from spontaneous recovery in some studies. Despite these shortcomings, great progress has also been made. Due to the combination of imaging and electrophysiological tools, our understanding of neuromodulation is becoming more profound. In recent years, many clinical studies have been carried out to verify the efficacy and to optimize the protocols. Among the current neuromodulation therapies, only tDCS has been validated to show good short-term effectiveness in MCS patients, but remains to be further explored in terms of persistence and effectiveness in chronic patients [9]. All other neuromodulation therapies still need further investigation with larger samples, properly controlling for spontaneous recovery. Revolutionary and exciting new approaches, such as low-intensity focused ultrasound pulsation and non-invasive DBS, are being developed. They are hopeful but await systematic assessment.

The judgment of efficacy and the stimulation paradigms are based more on clinical observation than on objective measurements for both invasive and non-invasive stimulation at present. In the future, further adjustments based on objective detection technology will be assessed. Based on in-depth studies of brain networks and DOC awareness mechanisms, different stimulation target areas will be explored to obtain better curative effects, or to identify different intervention sites specifically for different characteristics of DOC. Combined or sequential intervention with multiple modulation approaches is worth exploring. A closed-loop stimulation strategy will attract more attention as it could effectively avoid excessive adverse stimulation. The possibility of seizure induction will be reduced further. For invasive stimulation, the ability to detect the patient's sleep-wake cycle and give more or stronger stimulation in

the awake state may increase the efficacy of stimulation and effectively conserve battery life. The emergence of new detection technologies and new intervention methods is also expected.

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Compliance with Ethical Standards

Conflict of interest All authors claim that there are no conflicts of interest.

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