Neuromodulatory therapies for patients with prolonged disorders of consciousness

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Abstract

Background: Reviving patients with prolonged disorders of consciousness (DOCs) has always been focused and challenging in medical research. Owing to the limited effectiveness of available medicine, recent research has increasingly turned towards neuromodulatory therapies, involving the stimulation of neural circuits. We summarised the progression of research regarding neuromodulatory therapies in the field of DOCs, compared the differences among different studies, in an attempt to explore optimal stimulation patterns and parameters, and analyzed the major limitations of the relevant studies to facilitate future research.

Methods: We performed a search in the PubMed database, using the concepts of DOCs and neuromodulation. Inclusion criteria were: articles in English, published after 2002, and reporting clinical trials of neuromodulatory therapies in human patients with DOCs.

Results: Overall, 187 published articles met the search criteria, and 60 articles met the inclusion criteria. There are differences among these studies regarding the clinical efficacies of neurostimulation techniques for patients with DOCs, and large-sample studies are still lacking.

Conclusions: Neuromodulatory techniques were used as trial therapies for DOCs wherein their curative effects were controversial. The difficulties in detecting residual consciousness, the confounding effect between the natural course of the disease and therapeutic effect, and the heterogeneity across patients are the major limitations. Large-sample, well-designed studies, and innovations for both treatment and assessment are anticipated in future research.

Keywords: Disorders of consciousness; Neuromodulation; Therapy

Introduction

Consciousness is defined as the state of being aware and responsive to one's surroundings and internal state, encompassing two levels: arousal and awareness. Disorders of consciousness (DOCs) are mostly caused by traumatic brain injury (TBI), cerebral hemorrhage, and hypoxic encephalopathy, with TBI being the most common cause of DOCs. Common types of DOCs include coma, vegetative state (VS)/unresponsive wakefulness syndrome (UWS), and minimally conscious state (MCS). VS/UWS refers to a special state of DOCs where the individual remains awake but lacks awareness.[1] However, both clinical treatment and nursing practice showed that some patients with DOCs retain a sleep-wake cycle and own limited but clear awareness of themselves and their surroundings as well. Furthermore, they have a better prognosis; therefore, more active therapeutic strategies should be adopted. This led to the formation of the concept and diagnostic criteria of MCS, where the individual shows functions of arousal, and clear functions of awareness.[2] The treatment of DOCs is a challenge that has yet to be overcome by current medicine. This not only causes physical and mental exhaustion in caregivers, but also places a heavy burden on society. Therefore, relevant research is highly significant for both medicine and society. Among the currently available treatment modalities, neuromodulatory therapy, which involves a series of techniques using electrical/magnetic stimulus to modulate cerebral activity either through a trancranial approach or via an afferent pathway, has been considered as a potential approach that may facilitate neural remodeling and consciousness restoration. In this review, we summarised the existing common neuromodulatory therapies in the

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000001377

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Chinese Medical Journal 2021;134(7)

Received: 01-12-2020 **Edited by:** Yan-Jie Yin and Xiu-Yuan Hao

field of DOCs and analyzed the major limitations of the currently available studies.

Methods

We searched the PubMed database, using the concepts of disorders of consciousness and neuromodulation. Search words included [(disorders of consciousness) OR (disorder of consciousness) OR (consciousness disorder) OR (minimally conscious state) OR (vegetative state) OR (unresponsive wakefulness syndrome)] AND [(DBS) OR (deep brain stimulation) OR (SCS) OR (spinal cord stimulation) OR (VNS) OR (vagus nerve stimulation) OR (TMS) OR (transcranial magnetic stimulation) OR (TBS) OR (theta burst stimulation) OR (tDCS) OR (transcranial direct current stimulation) OR (tACS) OR (transcranial alternating current stimulation) OR (tRNS) OR (transcranial random noise stimulation)], and the filed search was (title/abstract). Inclusion criteria were as follows: articles in English, published after 2002, and the inclusion of clinical trials of neuromodulatory therapies in human patients with DOCs. We emphasized the articles published in the last 20 years regarding the concept of MCS which was proposed in 2002; before, both the diagnosis and classification of DOCs only included coma and VS/UWS. Therefore, numerous conscious patients were misdiagnosed, according to the present criteria. Exclusion criteria were as follows: articles published before 2002, languages other than English, and having no report on the therapeutic effects of neuromodulation on consciousness in human patients with DOCs. The selected articles were included in this review.

Results

One hundred and eighty-seven published articles were selected, according to the inclusion criteria, 127 were excluded according to the exclusion criteria, and 60 that met the inclusion criteria were listed in Supplementary Table 1 and 2, http://links.lww.com/CM9/A462. The involved papers were classified in two groups: group 1 included papers regarding invasive approaches and group 2 included articles regarding non-invasive approaches. Each part is introduced below.

Invasive stimulation

Deep brain stimulation (DBS)

DBS, also known as brain pacemaker implantation, involves implanting electrodes in the brain that send electrical impulses to achieve targeted modulation of relevant brain nuclei.[3]

Since the 1960s, researchers targeted various nuclei in the midbrain reticular formation, globus pallidus, or the thalamus to treat patients with DOCs of different aetiologies, thus observing different degrees of consciousness recovery in patients[4-9]; however, most of these studies were pilot studies, using outdated diagnostic criteria and varying evaluations, and produced fairly ambiguous results. Schiff *et al*[10] performed a double-blinded, alternating crossover study demonstrating that the application of bilateral DBS to the central thalamus could significantly improve the consciousness of a patient who had remained in MCS for more than 6 years after TBI. As a result, the patient showed significant improvements in motor function and arousal level, and his communication ability improved to a certain extent.[10] This achievement attracted widespread attention to neuromodulation techniques as a treatment application for DOCs. Subsequently, Adams *et al*[11] used the same method as Schiff *et al*[10] to treat a patient who had remained in MCS for 21 years after TBI; however, they were unsuccessful. Comparing the two studies indicates that the former patient had a shorter disease duration; functional magnetic resonance imaging (fMRI) revealed that his language network was intact. This might constitute the decisive factor that distinguishes the results of the above two studies. Similarly, Magrassi *et al*[12] targeted the bilateral central thalamus; however, they introduced more detailed inclusion and exclusion criteria for the stringent evaluation of 40 DOCs cases; five cases that met the eligibility criteria were selected, and three patients underwent DBS therapy. The patients showed different levels of improvement in coma recovery scale-revised (CRS-R) scores, but none recovered their communication ability. Consequently, Chudy *et al*[13] strictly screened and selected 14 patients with DOCs who received DBS either of the left or right centromedian-parafascicular complex. Three patients with MCS and one with UWS gradually recovered from DOCs during treatment and follow-up; however, the disease duration of the four recovered patients was quite short (2–11 months), and the likelihood that the findings were confounded by spontaneous recovery is relatively high. Furthermore, Lemaire *et al*[14] performed simultaneous stimulation of the bilateral central thalamus and globus pallidus in five patients with DOCs, of whom one patient with UWS and one with MCS showed significant improvements in CRS-R scores after treatment. The disease durations of the patients enrolled in their study were relatively long (12–146 months), which, to a certain extent, reduces the likelihood of the findings being confounded by spontaneous recovery; nevertheless, the comparison between the cross-over periods failed to demonstrate that the effect during the DBS-on periods was stronger than the effect during the DBS-off periods. Although this may have been simultaneously affected by the carry-over effects of DBS and the adverse effects of surgery, it still highlights uncertain findings. In addition, a recent case showed that central thalamic DBS may be valuable for modulating sleep dynamics in patients with MCS; however, the patient showed no behavioral improvement either during or after the 7.5-year period of stimulation.[15]

The efficiency of DBS depends on many parameters, including the target sites, polarity and contacts, frequency, pulse-width, and stimuli intensity. Among intracranial targets, the thalamus (especially the central thalamus) was mostly used for DOC treatment in recent studies. This is because the deafferentation and active inhibition of neurons within the central thalamus are considered as causes of the low cerebral activity in patients with DOC, according to the mesocircuit model.[16] Nevertheless, the central thalamus is a complex structure, involving the anterior intralaminar thalamic nuclei and adjacent paralaminar regions of thalamic association nuclei, which may have distinct properties and connections in different patients.[17] This may account for the inconsistency in relevant studies, suggesting that more precise targets are worth exploring. As the origin of the ascent activation system, the brainstem was once commonly used as a DBS target; however, it is now rarely adopted because of the proposed crucial role of the thalamus. Furthermore, a study that used both the thalamus and brain stem as DBS targets suggested that brain stem stimulation had a relatively high probability of side effects.[6] It is known that different electrode polarities produce different effects. Specifically, monopolar stimulation produces a large, spherical electrical field, while bipolar stimulation produces a focal and elliptical electrical field; it is yet to be determined which polarity produces better therapeutic effects on DOCs. In addition, stimuli parameters may also affect DBS. The optimal stimulation frequency over the central thalamus was reportedly 50 to 100 Hz, while the 25 to 30 Hz frequency was more often used in the center median-parafascicular complex stimulation. The stimuli pulse-widths usually vary between 60 and 90 μs, while stimuli intensities were often within the threshold of inducing an arousal response.

The main risk of DBS, as an invasive treatment, is surgery-related hemorrhage and infection. The existing literature shows no fatal events directly associated with surgery among the abundance of patients with DOCs who were treated with DBS. A hematoma was found in the surgical path of one patient, but was resolved after a few days, thus continuing treatment.[12] Furthermore, the evoked arousal responses during DBS therapy included obvious eye-opening and mydriasis, which can be accompanied by different expression changes, as well as head, neck, and limb movements; vomiting may also occur in some patients.[6] Elevated facial and limb muscle tension was recorded in one patient, which was relieved after voltage reduction.[14] Another three patients developed seizures during the treatment phase; however, their symptoms were controlled after antiepileptic drugs were administered.[13] So far, no patient with DOCs has been reported fatal side effect due to DBS; nevertheless, DBS relies on surgery, posing greater risks and ethical dilemmas than other milder, non-invasive techniques. As patients with DOCs are unable to express themselves, they are more vulnerable to harm,[18,19] and recent studies are yet to consistently demonstrate a clear therapeutic efficacy of DBS. Developing stricter inclusion and exclusion criteria is, therefore, necessary to facilitate the selection of appropriate patients who are more likely to benefit from treatment. For example, patients whose neurophysiological tests reveal the presence of the N20 somatosensory evoked potential (SEP), unilateral or bilateral brainstem and cortical auditory and motor evoked potentials, and the P300 event-related potential (ERP), may have higher expected efficacy from DBS.[6,12,13]

Spinal cord stimulation (SCS)

SCS is an invasive neuromodulation that is used to send electrical signals to specific areas of the spinal cord (dorsal columns) for treating certain pain conditions and brain diseases.

Over the past few decades, numerous studies have investigated the SCS treatment of patients with DOCs, and have observed its potential boosting effects on behavior, neural activity, functional connectivity, and cerebral perfusion in patients with DOCs.[20-35] In these studies, electrodes were implanted in the C2–C4 segment of the spinal cord, producing an electrical field capable of directly stimulating the adjacent region of the brainstem, such as the reticular formation; then, it further affects a widespread region in the cerebrum by the projection of the ascending reticular activating system.[36] Consistent with DBS, the character of neurophysiology, such as the presence of the N20 of the SEPs may be a favorable factor of therapeutic efficacy.[33] Additionally, the polarity of the electrode, and the stimulation's frequency, pulse-width, and intensity may also affect. Monopolar stimulation generally produces a large electrical field, while bipolar stimulation produces a focal electrical field, and high/low frequencies induce excitatory/inhibitory effects, respectively. Frequencies of 5 and 70 Hz for SCS were widely used in DOCs patients; 70 Hz for SCS was recommended by recent studies because of its significant effect on cerebral hemodynamics and functional connectivity.[28,29,31] Stimulation intensity usually depended on the resting motor threshold (rMT) of the upper extremities.

Although some evidence indicated that SCS could be an effective method of DOCs treatment, current studies have not eliminated the effect of spontaneous recovery in patients who showed improvements in consciousness; therefore, whether SCS is definitively curative is still controversial. Well-designed controlled trials with larger samples are needed to verify the effects of SCS on restoring consciousness. In addition, because SCS is an invasive technique, it has a relatively high risk and is associated with a sensitive ethical dilemma. Research should balance the potential benefits against the risk of surgery and adopt strict inclusion and exclusion criteria.

Surgery vagus nerve stimulation (sVNS)

sVNS is an invasive neuromodulatory technique that stimulates the cervical vagus nerve, which carries somatic and visceral efferent and afferent fibers, through neck-implanted electrodes. The stimulation facilitates the activation of the nucleus tractus solitarii which is directly associated with the vagus nerve and other nuclei, such as the cholinergic basal forebrain and the noradrenergic locus coeruleus.[37] Moreover, other cerebral regions, including the dorsal raphe nuclei, thalamus, amygdala, and the hippocampus can also be affected.[38] Since VNS treatment accelerated the recovery of both motor function and cognition in animal models of TBI,[39] its therapeutic potential for human patients with DOCs has been discussed.

Corazzol *et al*[40] performed sVNS to a UWS patient who remained in this status for over 15 years. During the 6-month treatment protocol, behavioral improvements in arousal, attentive, and visual function, accompanied both by an enhanced cortical functional connectivity and strengthened metabolic activity in the thalamus were observed in this patient, suggesting that this surgical therapy may be effective for patients with DOCs. In this preliminary research, the long post-injury duration theoretically excludes the possibility of spontaneous recovery of consciousness; however, the patient only gained a partial behavioral increase without emerging from DOCs (a status that is unstable and fluctuant). It cannot be concluded that VNS had a beneficial therapeutic effect on patients with DOCs based on this uncontrolled trial that enrolled only one case. Therefore, further studies of VNS regarding DOCs treatment are needed.

Non-invasive stimulation

Transcranial magnetic stimulation (TMS)

TMS is a non-invasive neuromodulation technique involving the generation of external pulsed magnetic fields that can induce electrical currents in the cerebral cortex through electromagnetic induction, thus producing neural electrical activity. Repetitive TMS (rTMS) delivers either high (>5 Hz) or low-frequency (<1 Hz) electromagnetic pulses to the cortex, thus generating excitatory and inhibitory effects, respectively, that spread from the targeted area to a wider region via trans-synaptic effects and persist for a certain post-stimulation period.[41-43]

rTMS has a short history in this field of research. Louise-Bender Pape *et al*[44] attempted to treat a patient who remained in UWS 9 months after TBI, using rTMS to stimulate the patient's right dorsolateral prefrontal cortex (DLPFC). During the 6-week treatment protocol, the patient showed significant improvements in consciousness, was able to follow commands, vocalize single words, and achieve simple communication. Moreover, this improved state lasted for 1 year after the end of treatment. By targeting the right DLPFC, Naro *et al*[45] delivered 10 Hz pulses to stimulate ten post-anoxic patients with UWS and assessed their neurophysiology and cortical connectivity before and after stimulation. As a result, three patients showed a significant, but transient, increase in the connectivity of the cortical motor areas with relevant surrounding sites, as well as an improvement in CRS-R motor scores exceeding the MCS threshold; noticeably, this study also suggested the predictive potential of the N20 of the SEPs. In addition, a case report showed that the volume of the neural tract of a patient with DOCs was both temporally and spatially related to the rTMS over the right DLPFC.[46] Moreover, the left DLPFC has also been used as a therapeutic target, whereby screening was performed to select 16 patients with DOCs with a disease duration of more than 3 months, and in a stable condition, who, then, received 10 Hz rTMS therapy for 20 consecutive days. Among five MCS patients and 11 UWS patients, four patients showed improved consciousness and gained a certain level of communicational ability,[47] whereas the short disease duration increased the possibility of spontaneous recovery; however, this uncontrolled study provided limited confidence to its evidence. In other researches, a rTMS of the left DLPFC may improve the cortical activity or connectivity of patients with DOCs.[48-51]

Regarding therapeutic studies targeting the primary motor cortex (M1), the research team of Piccione and Manganotti [52] enrolled three MCS patients and three UWS patients, disease durations of more than 1 year, and delivered 20 Hz rTMS to the M1 side that produced better motor-evoked potentials. After a single treatment session, one patient who remained in MCS for five years after cerebral hemorrhage significantly improved, as shown by the ability to understand commands and correctly use objects. Nevertheless, this effect only lasted for a few hours after stimulation, and the remaining five patients did not show significant changes.[52,53] Subsequently, Cincotta *et al*[54] used the same stimulation parameters and performed a randomized sham-controlled cross-over study to verify the therapeutic effects of rTMS on the left M1; however, despite prolonging the treatment duration to five consecutive days, none of the 11 patients with UWS showed significant improvements. Our team also studied the therapeutic effects of delivering 20 Hz rTMS to the left M1. Whether stimulation was administered for one or five consecutive days, only one patient who remained in UWS for three months after cerebral hemorrhage showed increased CRS-R motor scores, whereas the other 15 patients with DOCs did not show any behavioral improvements.[55-57]

Both treatment parameters (frequency, intensity, pulse distribution, number of sessions, etc) and therapeutic targets of rTMS may affect its efficacy. Currently, there are limited studies with small sample sizes; therefore, it is not yet possible to form a uniform recommended paradigm. Regarding the number of sessions, single rTMS treatments often involve dividing a total hundreds of magnetic pulses into tens of trains and uniformly delivering them at a frequency of either 10 or 20 Hz. Stimulus intensity is determined based on the patient's rMT, given that it does not exceed 60% of its maximum output power. It is worth mentioning that our team has performed a preliminary study, using intermittent θ burst stimulation (iTBS) to treat eight patients with DOCs, of whom, three out of four patients with UWS and four patients with MCS gained behavioral improvements. Therefore, iTBS is a new rTMS model that could potentially be recommended for the treatment of DOCs.[49] In addition, other studies have also suggested that rTMS has an accumulative effect in the treatment of DOCs; therefore, the therapeutic efficacy of multiple consecutive stimulations may be superior to single treatments.[44,47,58] Either the right/left DLPFC or the right/left M1 are often chosen as the therapeutic targets of rTMS. When delivered to the M1 region of healthy brains, rTMS can produce remote effects on multiple regions of the frontal and parietal cortex, cingulate cortex, striatum, and thalamus.[59,60] Furthermore, the stimulation power, set according to the rMT, is safer, more accurate, and more reliable when applied to the motor cortex. Therefore, the M1 is an ideal stimulation site. The DLPFC is also closely related to the frontal and parietal cortex, thalamus, and brain stem, and may affect processes such as learning, memory, decision-making, and behavioral control.[61-63] More specifically, the right DLPFC is related to arousal and attention,[62] whereas the left DLPFC could be involved in cognition and emotion regulation.[64,65] Apart from these common sites, a therapeutic effect of rTMS over the left angular gyrus in patients with DOCs has been recently reported.[66] Future studies attempting therapeutic trials that combine the multiple targets above are needed. In addition, by combining TMS with electroencephalography (EEG) (ie, TMS-EEG techniques) we will be able to detect patterns of spatiotemporal changes in TMS-evoked EEG fluctuations across the entire cerebral cortex, thus allowing both the quantification and evaluation of the remote effects of TMS in specific patients, using specific targets and parameters.[67,68] Therefore, researchers can not only predict the rTMS effect prior to treatment, but can develop novel, individualized therapeutic targets based on multi-site TMS-EEG assessment as well.

The main risk of rTMS is seizures; however, all patients with DOCs (reported in the literature) who have undergone this technique have shown good tolerance, and no adverse reactions. As a painless, non-invasive neuromodulation technique, rTMS has several advantages over the aforementioned invasive techniques, including lower risk for complications and lower technical requirements. Therefore, it has recently become a popular topic. Nevertheless, the number of current studies on rTMS therapy for patients with DOCs is still small, with most of them being small-sample studies without a uniform paradigm. Moreover, there are also insufficient follow-up studies regarding the long-term effects of rTMS, with inconsistent conclusions of the various studies. Therefore, further investigation is needed to provide evidence for the effectiveness of this technique in the treatment of DOCs.

Transcranial direct current stimulation (tDCS)

tDCS is a non-invasive brain stimulation technique that involves the use of a weak direct current of 1 to 2 mA to stimulate the cerebral cortex, thereby producing an excitatory and inhibitory effect at the anodal and cathodal stimulation site, respectively.

Research regarding tDCS therapy for DOCs has recently been emerged. In general, the anode is placed on the scalp area, corresponding to the cortical target, while the cathode is placed either at the nasion or the periorbital region, thus inducing an excitatory stimulation of the cortical region of interest. In the study by Angelakis *et al*,[69] an anodal stimulation of the left DLPFC or M1 area increased the level of consciousness in three patients with MCS, one patient with the longest treatment time regained consciousness after treatment, and seven patients with UWS did not have any rapid improvements. Moreover, Thibaut *et al*[70] selected 30 and 25 patients with UWS and MCS, respectively, who received 2 mA of direct current stimulation to their left DLPFC. A double-blind randomized cross-over design was used to demonstrate that a single 20 min session of tDCS could transiently improve the CRS-R scores of 13 patients with MCS and two patients with UWS, and that the transient improvement in signs of consciousness in patients with MCS was significant. Subsequently, they once again enrolled 21 patients with MCS for a study that used the same stimulation parameters, but with the treatment duration extended to five consecutive days. Of the 16 patients who completed the treatment, four showed improvements on the first day of treatment, while another five gained improvements following subsequent treatments, with a significant therapeutic effect at 7 days following the end of the stimulation,[71] thus suggesting that tDCS may have accumulative and long-lasting effects. A number of other studies followed the one that involved the delivering of direct current stimulation to the DLPFC,[72-82] inferior/posterior parietal cortex,[83-87] and the M1.[88-91] Most of the studies reached a similar conclusion that tDCS can improve the consciousness of some patients with DOCs, and its therapeutic efficacy among patients with MCS is especially significant.

Nevertheless, although the published literature generally supports the significant therapeutic efficacy of tDCS for patients with MCS, there is still a large number of patients with MCS who did not individually respond well to tDCS, with even rarer responders in the UWS population. Some studies have shown that there may not be significant differences in the clinical features (ie, etiology, disease duration, age, etc) between responders and non-responders.[71,92] However, the group of MCS patients with better responsiveness to treatment may have greater grey matter volume and metabolic activity in the frontal, parietal, and temporal lobes, cingulate cortex, hippocampus, and thalamus, thus indicating that the residual activity of neural tissues in the attention and working memory network may be a factor influencing tDCS effectiveness.[92] Additionally, an elicited P300 of the ERPs may be relevant to a positive response to tDCS in patients with DOCs.[81] Therefore, fMRI and ERP assessments may be valuable in distinguishing the potential tDCS responders among patients with DOCs.[81,93]

Treatment parameters and stimulation targets may also affect therapeutic efficacy. Existing clinical studies on tDCS have all adopted a current intensity of 1 to 2 mA, and the same parameters have often been adopted for the same type of patients; however, studies have also found that applying currents with the same output intensity to different individuals may lead to differences in the actual current intensity generated by their neural tissues.[94] Therefore, it is worth exploring individualized treatment parameters. Currently, the left DLPFC is the most popular tDCS target in the treatment of DOCs, while M1, which is another common target in non-invasive neuromodulation, is also commonly used. According to an evidence-based guideline, clinical studies of other diseases have found that either the DLPFC or M1 areas are the sites where tDCS is most likely to be effective, which highlights the importance of these regions in therapeutic research.[95] Nevertheless, Huang *et al*[83] targeted the posterior parietal cortex in their treatment of patients with MCS and observed a certain level of therapeutic efficacy, thus suggesting the possibility of selecting other regions as potential therapeutic targets. Recently, researchers attempted to use high-definition tDCS (HD-tDCS) for the treatment of chronic DOCs. This technique alters the wide electric field distribution of traditional tDCS by modifying the electrodes, thus ensuring a higher spatial accuracy for targets of direct current stimulation. These studies have observed improvements both in the CRS-R scores and cortical functional connectivity of some patients.[84-86] Their preliminary results may provide insights into the basis for increasing the precision of therapeutic targets in relevant research; however, there is still little available information regarding the pathophysiological mechanisms of DOCs, there are numerous nuclei yet to be explored as potential targets. Therefore, at this stage, using conventional tDCS which stimulate a broader region is still the treatment of choice. In addition, both the widespread inhibition and interruption of neural connections in patients with DOCs may weaken the remote effects of tDCS, thereby affecting its therapeutic efficacy.[63,72,75,96-98] Consequently, multi-channel tDCS, which involves multiple simultaneous stimulation sites, may also provide a direction that is worth exploring in future studies.

The main risk of tDCS is epilepsy. Nevertheless, among the published studies regarding DOCs treatment, no adverse reactions have been reported except for temporary skin redness on the stimulation site. As with TMS, tDCS is a non-invasive neuromodulatory technique that has a low risk for complications and good tolerability. Furthermore, tDCS is easy to operate, can be administered at bedside, and is feasible for trained caregivers to implement during home therapy.[75] It is currently the most adaptable and easy technique to implement among existing neuromodulatory techniques.

Other forms of transcranial electrical stimulation

Transcranial alternating current stimulation (tACS) is a non-invasive neuromodulatory therapy that can induce neural plasticity due to its capacity to synchronize cortical oscillatory activity using an alternating low current.[99]

Naro *et al*[100] applied γ-band frequency (continuously and randomly ranging from 35 to 140 Hz) tACS over the right DLPFC in 26 patients with DOCs and 15 healthy individuals. The 10-min stimulation significantly strengthened the neural connectivity within the fronto- and temporoparietal networks in healthy individuals. Moreover, the same effects were partial in all patients with MCS and five out of 14 patients with UWS. Although the main purpose of this research was to identify the "hidden consciousness" in patients who were diagnosed with UWS, these results also indicated the therapeutic potential of tACS at the EEG level.

Notably, as a controlled condition, Naro *et al*[100] also applied transcranial random noise stimulation (tRNS) in the same research. tRNS is another type of transcranial electrical stimulation that applies an oscillatory multi-frequency spectrum of current in the form of white noise over the target cortex and is capable of inducing long-term enhancement of cortical excitability and brain function.[101] However, in this research, one session of tRNS with a frequency spectrum between 0.1 and 640 Hz was ineffective in modulating behavior and EEG properties in patients with DOCs.

In addition, Mancuso *et al*[102] included nine UWS patients in their study. They conducted a randomized sham-controlled trial to verify the therapeutic effects of tRNS. The results of both behavioral and neurophysiological assessments indicated that five consecutive days of high frequency (101–640 Hz) tRNS with a 2mA intensity did not rapidly improve the consciousness of patients with UWS, and only one patient evolved to an MCS right after multi-day tRNS. Research in this field is still new; therefore, recruiting more patients with DOCs (including those in an MCS) and adopting more evaluation methods, such as neuroimaging, may facilitate the applicability of this technique in the field of DOCs.

Transcutaneous auricular VNS (taVNS)

VNS can also be performed through a non-invasive approach. Recently, a novel form of VNS, named taVNS, which delivers electric current to the ear concha, was developed to modulate neural activity through auricular-vagal reflex. There are, currently, only a few pilot studies in this field. Researchers in China performed a twice daily, 4-week taVNS treatment on an aged female who had been in UWS for 50 days after cardiopulmonary resuscitation. The behavioral improvements as well as the increased functional connectivity between several cerebral regions indicated that the patient recovered a better conscious state after taVNS.[103] In addition, a case series reported that after a 4-week taVNS treatment and another 4-week follow-up, behavioral improvements were observed in five out of eight patients with MCS whose conscious state had been maintained for over 4 weeks before stimulation, thus proposing a long-lasting therapeutic potential of taVNS in patients with MCS.[104] Still, these studies failed to control the confounding effects of spontaneous recovery and fluctuant status of consciousness, and thus, only provided low confidence in its evidence. Nonetheless, it still introduced another low-risk, non-invasive neuromodulatory therapy into the treatment of DOCs. Further research studies with sham-controlled designs and a larger sample with more comprehensive etiology are worth being explored.

Discussion

Consciousness disorders can either be reversible or persistent; however, no treatments have been currently proven to be effective interventions. In this literature review, neuromodulatory techniques were used as trial therapies where both their curative effect and their potential mechanisms of consciousness restoration are largely unknown.

The ways in which consciousness arises is an unsolved scientific question; to date, only hypotheses exist. A widely accepted conception is that consciousness encompasses two main dimensions: (1) the "level" of consciousness, or the arousal level, is controlled by the ascending activation systems of both the brainstem and basal forebrain and reflects the background conditions for being conscious, and (2) the "content" of consciousness, that includes particular phenomenal components both within the experiences and the neural substrates that support these experiences and is thought to largely depend on the thalamocortical system.[105,106] Conscious content may originate from small cortical-thalamo-cortical networks and further organize the activities of larger cortical-cortical

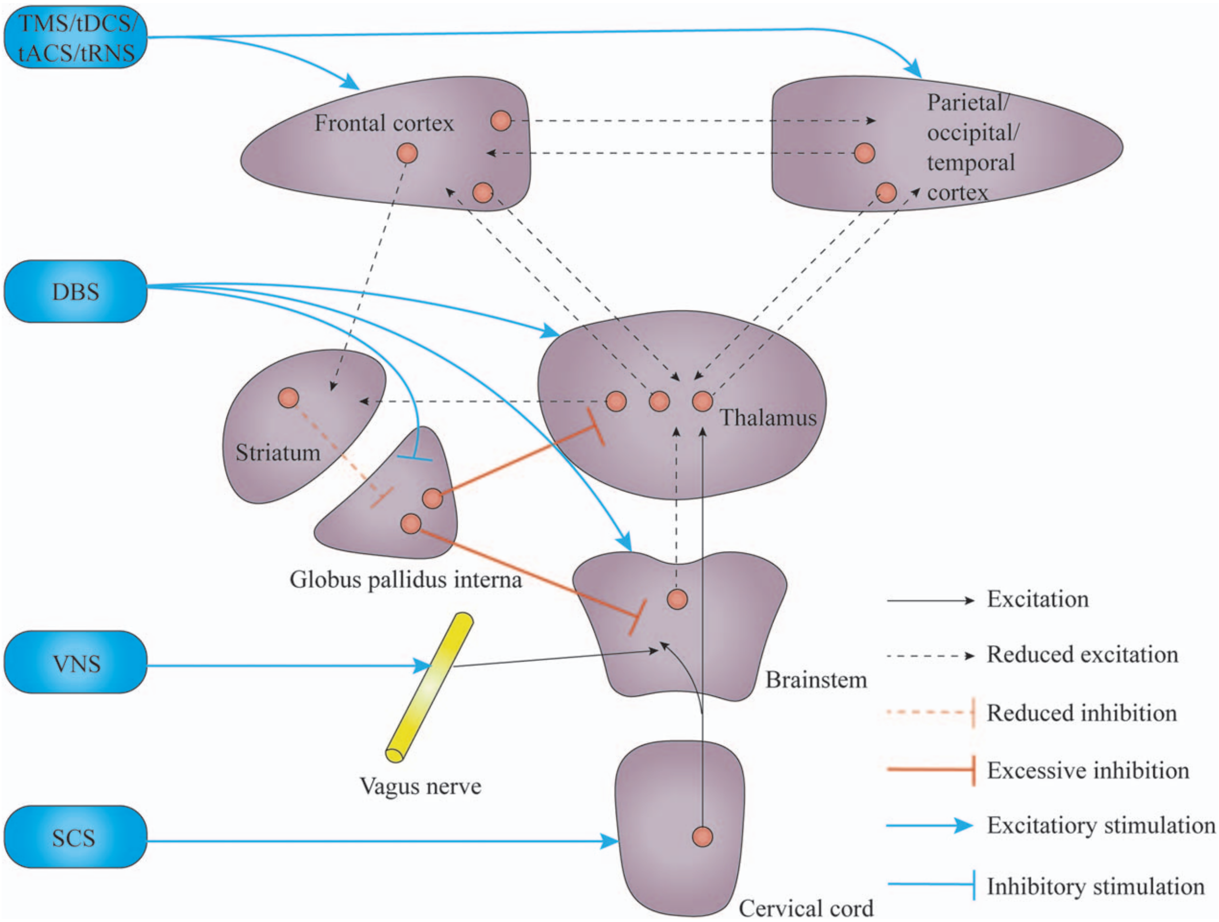

Figure 1: Mesocircuit model: reduced outflows within corticothalamus system decreased the active inhibition from the medium spiny neurons of the striatum to the globus pallidus interna, allowing excessive inhibitions to the relay neurons of the central thalamus and the projection neurons of the pedunculopontine nucleus, thus producing broad reductions in global cerebral synaptic activity. Neuromodulatory therapies can induce excitatory or inhibitory effects on both the stimulation site and over the widespread distant regions, and, therefore, modulate the activity and outflow of the mesocircuit either directly or via the ascending activating system. DBS: Deep brain stimulation; SCS: Spinal cord stimulation; TMS: Transcranial magnetic stimulation; tDCS: Transcranial direct current stimulation; tACS: Transcranial alternating current stimulation; tRNS: transcranial random noise stimulation; VNS: Vagus nerve stimulation.

and thalamo-cortical loops. The brain activities both within the frontal-parietal network and neocortical associative regions are proposed to support the cognitive process.[107,108] In patients with DOCs, both deafferentation and neural loss due to severe brain injury are widespread in the thalamocortical system, resulting in a broad reduction of corticostriatal, thalamocortical, and thalamostriatal outflow. This withdraws the afferent activation to the striatum's medium spiny neurons, allowing excessive active inhibitions from the globus pallidus interna to the relay neurons of the central thalamus and the projection neurons of the pedunculopontine nucleus, further producing broad reductions in global cerebral synaptic activity.[16,109] Neuromodulatory therapies are capable of inducing either excitatory or inhibitory effects on both the stimulation site and over the widespread distant regions, thus potentially directly modulating the activity and outflow of the cortical-thalamo-striatal-cortical circuit [Figure 1]. Moreover, both the electrical and magnetic stimulation over the neural substrates may modulate the calcium ion flow, increase the serum level of brain-derived neurotrophic factor and dopamine, as well as their receptor affinity (ie, TrkB and D1 receptors) that regulate the plasticity-relevant signaling pathway; these alterations induce long-term potentiation in the cerebral synaptic activity.[110,111]

Therefore, neuromodulatory therapies are currently considered as promising approaches for restoring consciousness in patients with DOCs. Indeed, the improvement in either consciousness levels or recovery in some patients can be regarded as promising for resolving the treatment problem of patients with DOCs. Nevertheless, a major problem is the substantial difference in the therapeutic efficacy of neuromodulatory techniques, either among different or the same study.

To deal with this problem, we must consider possible errors in evaluation efficacy. First, some patients' poor evaluation may be due to the insufficiency of existing technologies in detecting residual consciousness. Presently, the main evaluation method of states of consciousness involves searching for evidence of consciousness in the patient's behaviors, and CRS-R assessment is the existing diagnostic gold standard. However, since such patients often have sensory, motor, language, and cognitive impairments, their true level of consciousness cannot be easily detected by behavioral assessments alone.[98,112,113]

Due to the shortcomings of behavioral assessments, researchers have begun to introduce more objective neuroelectrophysiological and imaging indicators. For example, the TMS-EEG assessment indicates that the perturbational complex index has the potential for diagnosing states of consciousness.[67,68,114] The event-related potentials suggest that the mismatch negative, N1, P300, and other indicators may be related to consciousness.[115-117] fMRI findings reveal that the strength of the default mode network connectivity can be used as an evaluation indicator of consciousness.[118,119] In addition, the advancement of brain–computer interface technology will enable the effective expression of the conscious brain by "cybrain" (an intelligence based on interfaced human brain and computer), which can substantially improve the accuracy of consciousness assessment. The use of multi-indicator assessments related to neurophysiology and imaging in clinical studies can facilitate the enrichment of information to make more reliable judgements while also clarifying the therapeutic mechanisms underlying neuromodulation. Nevertheless, there is still a lack of reliable indicators that can replace the existing diagnostic gold standard. Hence, at present, neuroimaging and electrophysiological techniques can only serve as supplementary measures to the CRS-R assessment in efficacy evaluations.

Second, the confounding effect between the natural course of disease and therapeutic effect makes it difficult to distinguish positive results from spontaneous recovery. To avoid this confounding effect, some researchers have recommended selecting patients with longer disease durations (UWS for more than 6 months or MCS for more than 1 year) and low probability of spontaneous recovery.[3,120] Nonetheless, the lower probability of spontaneous recovery in patients with long disease durations may also be accompanied by the lower probability of their treatment benefit, thus increasing the risk/benefit ratio of participating in the study. Another way to reduce the interference of spontaneous recovery is to design controlled comparisons. As existing studies generally have small sample sizes, a self-controlled, randomized cross-over study is a typical design used in such studies. Nonetheless, such experimental protocols also present inherent defects, as the trials are more susceptible both to the natural course of disease and to the interference of simultaneous treatments. Generally, this type of study design often needs a relatively long "washout" period between the two test periods to minimize the carry-over effects. Therefore, such research studies are, in fact, possibly introducing instability in the comparison between the different courses of DOCs. Therefore, the results are more likely to be influenced by spontaneous recovery, deterioration, or any clinical event that requires changes in medications. A randomised, grouped, sham-controlled study is another common choice. However, such research studies need a quite large sample size to diminish inter-group heterogeneity.

In addition, the diversity of treatment protocols, other medications, and the individual differences among patients are also potential factors leading to inconsistencies in therapeutic efficacy. The patients with DOCs show a high level of heterogeneity regarding age, etiology, disease duration, lesion site, degree of injury, neurophysiological characteristics, and residual consciousness levels. There are currently no large sample studies with a high level of homogeneity in these features. Furthermore, therapeutic targets, stimulation parameters, treatment duration, and other simultaneous treatments may also affect therapeutic efficacy, while a uniform treatment paradigm for each stimulation is yet to be formed. Moreover, studies have shown that, in healthy individuals, significant differences can be observed in the responses of the cerebral cortex to TMS for different arousal levels (awake, asleep, anesthetized, etc).[121-123] All these highlight the importance of controlling for differences in treatment, individual characteristics, and different conditions for the same individual. Studies with more detailed classifications are necessary to explore which types of patients are more likely to benefit from treatment based on conditions, and what treatment paradigms can optimize the therapeutic efficacy without increasing the risk. This further emphasizes the importance of large samples in future research.

In conclusion, the application of neuromodulatory techniques in the field of DOCs has significant research value and room for progress. To facilitate progress at this stage, improvements in both experimental design and stimulation manner are necessary. For experimental design, the future direction of research should involve performing large sample, randomized controlled trials using comprehensive behavioral, electrophysiological, and imaging assessments with detailed classifications based on treatment protocols and patient heterogeneity. Available relevant studies are often limited to single or a few treatment centere. Therefore, a multi-center collaboration will provide researchers with more possibilities of finding further breakthroughs. Regarding the stimulation manner, developing safer and more efficient techniques may facilitate the production of more detectable efficacy. Recently, a non-invasive DBS approach, θ burst TMS pattern, and novel forms of transcranial electrical stimulation, such as HD-tDCS, tACS, and tRNS, have either been described or practiced in this field.[49,84-86,97,100,102] More innovations are worth exploring.

Funding

This work was supported by grants from the National Natural Science Foundation of China (No. 81870817) and the Fundamental Research Funds for the Central Universities (No. 2019-XZZX-001-01-02) and the Key Realm R&D Program of Guangzhou (No.202007030005).

Conflicts of interest

None.

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How to cite this article: Wu YH, Yu J, Hong LR, Luo BY. Neuromodulatory therapies for patients with prolonged disorders of consciousness. Chin Med J 2021;134:765–776. doi: 10.1097/CM9.0000000000001377