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Research Progress in Neuromodulation Techniques for Promoting Awareness in Patients with Disorders of Consciousness

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Abstract

Disorders of consciousness (DOC) are among the common and complex severe complications in patients with craniocerebral injury, significantly increasing the difficulty of prognosis recovery. As an emerging treatment method, neuromodulation technology is one of the most promising means of intervention in DOC at present. Common neuromodulation techniques include vagus nerve stimulation (VNS), deep brain stimulation (DBS), spinal cord stimulation (SCS), transcranial magnetic stimulation (TMS), and transcranial direct current stimulation (tDCS). This article reviews the research background of DOC, neuromodulation treatment methods, and future development directions, with the aim of providing references for clinical diagnosis and treatment.

Keywords

Disturbance of Consciousness, Neuromodulation Techniques, Deep Brain Stimulation, Electrical Stimulation of the Vagus Nerve

1. Introduction

Disorders of consciousness (DOC) refer to a state of unconsciousness resulting from severe brain injury. Patients with DOC often present with complex, rapidly changing clinical conditions, accompanied by high rates of disability and mortality, as well as generally poor quality of life, placing a substantial economic burden on families, society, and the nation. Therefore, facilitating the recovery of consciousness, reducing the risk of disability, improving quality of life, and supporting the reintegration of these patients into their families and communities have become issues of significant clinical and social importance. In conventional phar-

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macological treatment, dopamine agonists and similar agents are commonly used to alleviate clinical symptoms by modulating the balance of neurotransmitters. Although some small-sample studies and case reports suggest that pharmacological interventions may lead to improvements in neurological function or levels of consciousness, there is still a lack of systematic, high-quality evidence-based medical data to confirm their efficacy due to limitations such as small sample sizes and inadequate control groups [1]. In recent years, neuromodulation techniques have emerged as a major advancement in the treatment of DOC by directly regulating neural circuits and networks, effectively promoting cerebral metabolism and restoring cerebral blood flow. Currently employed techniques include vagus nerve stimulation (VNS), deep brain stimulation (DBS), spinal cord stimulation (SCS), and transcranial magnetic stimulation (TMS), among others. This review summarizes the background of DOC, neuromodulation-based treatment strategies, safety concerns, and future directions, aiming to provide a theoretical foundation and reference for clinical practice.

2. Research Background

Disorders of consciousness (DOC) represent a frequent clinical consequence of severe brain injury, most commonly observed in patients with prolonged coma or significantly impaired awareness [2]. In China, the large population base, high incidence of traumatic brain injury and stroke, coupled with uneven distribution of medical resources and variations in diagnostic and treatment standards across regions, contribute to a substantial number of DOC cases in clinical practice. Influenced by traditional culture and family values, many relatives opt for aggressive life-sustaining treatments, leading to a considerable accumulation of DOC patients and highlighting a pronounced need for long-term management and rehabilitation. According to studies primarily based on European data, the estimated incidence of DOC ranges from 0.2 to 6.1 per 100,000 people. Extrapolating these figures, the annual number of new cases in China is projected to be between 70,000 and 150,000, with associated medical costs potentially exceeding 30 billion RMB per year. From a clinical perspective, promoting recovery of awareness, reducing disability, improving functional outcomes, and enhancing quality of life in DOC patients are critical not only for individual rehabilitation but also for alleviating the caregiving burden on families and facilitating social reintegration, underscoring their broader practical significance.

Based on the duration of impaired consciousness, disorders of consciousness (DOC) can be classified into acute and chronic phases, with the latter also referred to as prolonged disorders of consciousness (pDOC). pDOC primarily includes the vegetative state (VS)/unresponsive wakefulness syndrome (UWS) and the minimally conscious state (MCS) [3]. The clinical management of DOC often involves a combination of pharmacological and nonpharmacological interventions. Pharmacological arousal therapy represents a key component of early-stage management, playing a significant role in facilitating the recovery of consciousness and improving neurological function. Currently, commonly used awakening agents include dopaminergic drugs (such as levodopa and amantadine), NMDA receptor antagonists, GABAergic modulators, and certain calcium channel blockers. In recent years, zolpidem, a non-benzodiazepine sedative-hypnotic, has attracted clinical attention due to its unexpected awakening effects in some DOC patients. For instance, one study involving 60 MCS patients treated with low-dose zolpidem reported restored functional communication in all participants, suggesting its potential utility in selected populations, though further clinical evidence is required to standardize its application [4]. To date, clinical evidence supporting the efficacy of most awakening medications remains largely derived from small-sample studies, non-randomized controlled trials, or case reports. There is still a lack of high-quality randomized controlled trials (RCTs), resulting in an incomplete evidence-based framework for their use [1]. Therefore, the clinical application of these agents warrants further validation through rigorously designed, large-scale clinical studies to establish more reliable and effective treatment guidelines for DOC patients. However, pharmacological interventions are characterized by significant interindividual variability and a lack of target specificity. In recent years, neuromodulation techniques have emerged as a pivotal therapeutic strategy for DOC, leveraging their ability to directly engage neural circuits and networks, thereby regulating cerebral metabolism and blood flow. These techniques not only offer a promising alternative to pharmacotherapy but may also produce synergistic effects when combined with specific pharmacological agents. These techniques can be categorized into invasive and non-invasive methods: invasive approaches include surgically implanted methods such as deep brain stimulation (DBS), spinal cord stimulation (SCS), and vagus nerve stimulation (VNS); non-invasive techniques comprise transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), among other external modulation modalities [5].

3. Neuromodulation Therapy Techniques

3.1. DBS

Deep brain stimulation (DBS) involves the surgical implantation of electrodes into specific brain regions, combined with subcutaneous placement of a pulse generator in the chest wall. It delivers electrical pulses to thalamic nuclei to achieve neuromodulation [6]. Although DBS is widely used in Parkinson's disease and epilepsy, it has increasingly been applied in recent years to promote recovery in patients with DOC [7], with a growing number of clinical cases reported. In arousal therapy, the central thalamus is a commonly targeted region, largely due to its potential to compensate for thalamic dysfunction. Stimulation is thought to facilitate depolarization along thalamocortical and thalamostriatal pathways, thereby promoting large-scale neural network reactivation and functional integration [8]. As early as the 1990s, DBS was attempted for arousal in patients with persistent vegetative state (PVS). In a study including 21 PVS patients, the centromedian-parafascicular complex was targeted in 19 individuals, while the midbrain reticular formation was stimulated in the other two. All patients received low-frequency stimulation at 25 - 30 Hz. Two years after treatment, eight patients in the DBS group regained the ability to follow simple verbal commands, whereas no significant improvement was observed in the control group [9]. In another case reported by Schiff's team [10], a patient who had been in a minimally conscious state (MCS) for six years showed clear command-following and recovered verbal communication after six months of central thalamus DBS, as demonstrated in a double-blind alternating stimulation paradigm. These outcomes suggest that DBS holds clinical potential for promoting arousal in selected patients. Based on current understanding of consciousness networks, DBS may help restore neural electrophysiological activity after severe brain injury by modulating key nodes such as the thalamus, offering a promising therapeutic direction for patients with prolonged disorders of consciousness (pDOC). Subsequent studies have continued to report consciousness-improving effects of DBS in DOC patients. In recent years, clinical exploration and mechanistic investigations in this field have continued. A study by Yang *et al.* [11] described outcomes in 24 chronic DOC patients (15 in VS and 9 in MCS) who underwent DBS treatment. One-year follow-up showed that 10 patients (7 MCS and 3 VS) had regained full consciousness or demonstrated consistent command-following. Current evidence indicates that patients in a MCS exhibit better responses to DBS compared to those with unresponsive wakefulness syndrome (UWS). This discrepancy is primarily attributable to the relatively preserved architectural integrity of the thalamocortical neural networks in MCS patients. The maintained functional connectivity and structural continuity within thalamocortical circuits allow neuromodulatory stimuli to be effectively integrated and transmitted to higher-order cortical regions, such as the prefrontal and posterior parietal cortices, thereby facilitating the reactivation of global conscious pathways. In contrast, UWS patients often suffer from extensive structural disruption within these networks, which considerably constrains the neuromodulatory efficacy of DBS [12]. However, the evidence-based recommendation level for DBS in DOC remains limited. On the one hand, the efficacy of DBS highly depends on accurate electrode placement. DOC patients often present with cerebral deformation or atrophy, which increases the risk of targeting errors and affects the reproducibility and stability of outcomes. On the other hand, most existing clinical studies suffer from methodological limitations, such as small sample sizes, lack of randomized controlled designs, and insufficient blinding, leading to weak conclusions and a high risk of bias. Therefore, DBS for DOC arousal is still considered an experimental treatment, and further large-sample, multicenter, high-quality randomized controlled trials are urgently needed to establish more reliable evidence.

3.2. SCS

Spinal cord stimulation (SCS) involves the implantation of electrodes into the epidural space at the C2 - C4 level to deliver electrical stimulation with specific intensity and frequency, thereby enhancing spinal neural excitability. With the development of permanently implantable epidural stimulation systems, SCS has gained increasing attention as a potential treatment for chronic DOC. In a study by Jian *et al.* [13], 27 DoC patients undergoing SCS were evaluated using the Coma Recovery Scale-Revised (CRS-R), event-related potentials (ERP), and EEG power spectral analysis. Among the 15 patients who completed follow-up, postoperative EEG spectra showed favorable changes, and parameters of the P300 wave—including amplitude, peak latency, and morphology—were significantly improved. Another analysis by Yuan Bangqing *et al.* [14] of 11 chronic DOC patients (5 in VS and 6 in MCS) revealed that among the 6 who received SCS, 4 regained consciousness, whereas none of the 5 untreated patients showed recovery. In a larger case series reported by Xia Xiaoyu *et al.* [15], 110 chronic DoC patients treated with SCS were assessed six months postoperatively through neurological examination and CRS-R. The overall effectiveness rate was 34.5%, with age, disease duration, preoperative CRS-R score, and surgical indications identified as major factors influencing outcomes. Current evidence suggests that SCS may facilitate arousal through multiple mechanisms: modulating cervical sympathetic ganglion activity to enhance cerebral blood flow, increasing cerebral glucose metabolism, promoting the release of neurotransmitters such as dopamine (DA) and norepinephrine (NE), and delivering electrical pulses to the origin of the ascending reticular activating system, thereby strengthening consciousness-related signaling and improving electrophysiological activity [16]. Overall, SCS represents a promising clinical strategy for promoting recovery in DOC. However, from an evidence-based perspective, several limitations remain: most studies are small-scale, single-center, and non-randomized, lacking high-level clinical evidence; treatment effects show considerable heterogeneity influenced by factors such as patient age, disease duration, baseline severity, and patient selection; and proposed mechanisms are largely derived from animal studies or theoretical models, requiring further validation in human subjects.

3.3. VNS

With the growing emphasis on precision and individualized treatment for DOC, the development of novel interventions to improve cognitive and functional outcomes in both acute and chronic stages has become a major research focus. The vagus nerve, which is widely distributed throughout the central nervous system and plays a key role in regulating somatic and visceral afferent and efferent signaling, can directly modulate brainstem activity. Studies indicate that vagus nerve stimulation (VNS) enhances metabolic activity in consciousness-related regions such as the forebrain, thalamus, and brainstem reticular formation. Technically, VNS typically involves coiling an electrode around the vagus nerve and implanting a pulse generator subcutaneously in the chest to deliver intermittent electrical stimulation. In addition, as the auricular branch is the only superficial projection of the vagus nerve, non-invasive transcutaneous auricular vagus nerve stimulation (taVNS) has recently been introduced into DOC arousal research. Beyond DOC, both VNS and taVNS have also been used in the treatment of neurological and psychiatric disorders such as epilepsy and treatment-resistant depression [17]. Yu *et al.* [18] were among the first to investigate the effects of taVNS in patients with DOC. Their study found significant activation in the thalamus—a region closely linked to arousal and awareness—as well as enhanced functional connectivity within the default mode network (DMN) following treatment. Another clinical report described improved CRS-R scores in a patient with severe traumatic brain injury after a three-week taVNS intervention [19]. Corazzol *et al.* [20] reported the case of a patient who had been in a chronic DOC state for 15 years following brain injury and showed improvements in alertness, limb movement, and visual tracking after taVNS treatment. Mechanistically, VNS is believed to facilitate cortical signaling and enhance neural metabolic activity. In 2020, Briand *et al.* [21] proposed a vagus-cortical pathway model integrating multiple potential mechanisms to explain how taVNS modulates brain activity and promotes recovery of consciousness. Animal studies [22] have further demonstrated that VNS upregulates the expression of excitatory neurotransmitters such as dopamine (DA) and its receptors, as well as norepinephrine receptors, while reducing GABA receptor levels in the rat brain. These neurochemical changes may contribute to the arousal effects of VNS [23]. Although the mechanisms of VNS/taVNS are physiologically plausible and the techniques are considered relatively safe, current evidence supporting their efficacy is largely derived from small case series, individual reports, and a limited number of before-and-after studies. Thus, VNS and taVNS remain exploratory treatment options that warrant further validation through larger, controlled trials.

3.4. TMS

Non-invasive neuromodulation techniques, particularly transcranial magnetic stimulation (TMS), have gained increasing attention in the treatment of prolonged disorders of consciousness (pDOC) in recent years due to their non-invasive nature and adjustable parameters, demonstrating considerable potential in facilitating the recovery of consciousness [24]. TMS was first developed in the mid-1980s by Barker *et al.* [25] based on the principle of electromagnetic induction. It modulates neural activity by applying external magnetic fields to localized brain regions, thereby inducing electrical currents and influencing neural function. Initially used in the treatment of depression, TMS has since been extended to various other neuropsychiatric conditions [26]. In recent years, a growing number of studies have systematically evaluated the clinical utility of TMS in patients with DOC. For instance, a study involving 48 patients in a vegetative state [27] demonstrated that repetitive TMS (rTMS) not only aids in assessing brain functional status but also promotes the recovery of consciousness, highlighting the unique advantages of this technique in the management of pDOC. From a mechanistic perspective, TMS may facilitate consciousness recovery through multiple pathways: modulating neuronal excitability and synaptic transmission, enhancing synaptic plasticity, improving cerebral blood flow and metabolic distribution, and promoting functional reorganization of impaired neural networks [28]. However, the therapeutic efficacy of TMS is influenced by various factors, including stimulation target, frequency, intensity, and individual patient differences. To date, no unified protocol for stimulation parameters has been established, underscoring the need for further research to standardize and personalize treatment protocols. To improve outcomes, combined neuromodulation strategies have emerged as a promising research direction. Several researchers have attempted to integrate rTMS with other neurostimulation techniques to achieve synergistic effects. For example, one study reported that combined median nerve stimulation (MNS) and rTMS led to more significant improvements in consciousness levels and neurobehavioral function compared to either intervention alone [29]. Another exploratory study [30] applied transcranial alternating current stimulation (tACS) synchronized with rTMS to precisely modulate stimulation timing and evoke specific neural oscillations, thereby enhancing the stability of brain activity and offering a novel approach for neuromodulation in DOC. Additionally, clinical observations [31] have indicated that a three-month course of rTMS combined with electroacupuncture significantly improved coma scale scores and overall neurological function, suggesting that multimodal combined interventions may further enhance arousal outcomes. In summary, TMS represents a promising non-invasive technique for the treatment of chronic disorders of consciousness. However, several challenges remain, including the optimization of stimulation protocols, long-term maintenance of therapeutic effects, and the development of individualized treatment strategies. Future large-scale, high-quality clinical studies are essential to validate and refine these approaches, facilitating the transition of TMS from an experimental therapy to routine clinical application.

3.5. tDCS

Transcranial direct current stimulation (tDCS) is a non-invasive technique that modulates cortical neural activity using weak direct electrical currents [32]. By applying low-intensity current through two electrodes—an anode and a cathode—tDCS can enhance cortical excitability under the anode while typically suppressing neural activity under the cathode [33]. The neuromodulatory effects of tDCS are influenced by multiple parameters, including current intensity, stimulation duration, and electrode placement. Originally applied in the rehabilitation of neuropsychiatric disorders such as post-stroke cognitive impairment, Alzheimer's disease, and depression [34], tDCS has more recently been explored as a therapeutic intervention for patients with prolonged disorders of consciousness (pDOC), particularly those in a minimally conscious state (MCS), showing tentative clinical potential. Several studies suggest that tDCS may enhance cortical excitability and functional integration. For example, Bai *et al.* [35] used TMS-EEG to demonstrate improved cortical excitability following tDCS intervention. Martens *et al.* [36], in a systematic review, proposed the left dorsolateral prefrontal cortex as a key target for optimizing behavioral responses. Similarly, Zhao Jingpu *et al.* [37] reported that tDCS enhanced endogenous functional connectivity within major brain networks, including the sensorimotor, frontoparietal, and default mode networks [38]. Despite these promising findings, current evidence supporting tDCS for DOC treatment remains limited. Many studies are constrained by small sample sizes, heterogeneous experimental designs, inconsistent assessment criteria, and a lack of long-term follow-up, which collectively undermine the reliability and generalizability of the results. Thus, although tDCS is mechanistically plausible for modulating neural excitability and network connectivity, its true clinical value and optimal protocol parameters require further validation through larger, well-designed, multicenter randomized controlled trials.

4. Conclusions and Future Perspectives

Neuromodulation techniques are emerging as a promising direction in clinical arousal therapy for DOC. This review systematically summarizes various neuromodulation strategies, including non-invasive and invasive approaches such as transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), vagus nerve stimulation (VNS), deep brain stimulation (DBS), and spinal cord stimulation (SCS). Studies suggest that these techniques may improve consciousness and behavioral responses in some patients through multiple mechanisms, including modulation of consciousness-related neural networks, thalamocortical circuits, and the default mode network, enhancement of neural metabolism and cerebral perfusion, and promotion of the release of arousal-related neurotransmitters such as dopamine and norepinephrine. In particular, patients in a minimally conscious state (MCS) tend to show better responses to various interventions compared to those with unresponsive wakefulness syndrome/vegetative state (UWS/VS). From a clinical perspective, different neuromodulation techniques are suited to distinct clinical scenarios based on their mechanisms and stimulation characteristics. In acute DOC, non-invasive techniques such as tDCS and TMS are often preferred for early intervention due to their ease of application and favorable safety profile. For chronic patients, especially those in MCS, invasive approaches like DBS or SCS may be considered to achieve sustained and precise modulation of deep neural nuclei. Etiology also plays a critical role in selecting the appropriate intervention: for example, patients with traumatic brain injury often retain relatively intact corticothalamic pathways and may respond better to TMS or tDCS, whereas those with hypoxic brain injury typically exhibit widespread neural network impairment, making techniques such as VNS or SCS—which modulate brainstem arousal systems—potentially more beneficial. Thus, clinical practice should incorporate disease duration, etiology, level of consciousness, and neuroimaging biomarkers to guide individualized treatment selection.

However, the field still faces challenges such as a lack of standardized treatment parameters, significant clinical heterogeneity, and insufficient high-level evidence-based medical data. Future research should focus on developing patient stratification strategies based on neuroimaging and electrophysiological biomarkers, promoting the development of personalized stimulation protocols, and conducting large-scale multicenter randomized controlled trials. These efforts will help establish the efficacy and applicability standards of neuromodulation in DOC arousal therapy, ultimately facilitating the development and implementation of evidence-based clinical guidelines.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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