Review Article

Archives of Anesthesiology and Critical Care (In Press); x(x): xx-xx.

Available online at http://aacc.tums.ac.ir

Neurorecovery and Cerebral Hemodynamics in Patients Undergoing Transcranial Direct Current Stimulation with Disorders of Consciousness (DoC): A Systematic Review

*Masood Zangi, Mohammadreza Hajiesmaeili, Majid Mokhtari, Reza Goharani, Neda Tajaldin, Mahdi Amirdosara**

Critical Care Quality Improvement Research Center, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

ARTICLE INFO

Article history:
Received 25 December 2024
Revised 16 January 2025
Accepted 30 January 2025

Keywords:
Disorders of consciousness;
Non-invasive brain stimulation;
Transcranial direct current stimulation;
Cerebral hemodynamics

ABSTRACT

Background: Disorders of consciousness (DoC), encompassing coma, vegetative state/unresponsive wakefulness syndrome (VS/UWS), and minimally conscious state (MCS), result from severe brain injuries that disrupt neural networks responsible for arousal and awareness. Non-invasive brain stimulation (NIBS) techniques, including transcranial direct current stimulation (tDCS) and its variants, such as high-definition tDCS (HD-tDCS) and transcranial alternating current stimulation (tACS), offer promising therapeutic strategies. This review synthesizes evidence on the efficacy of NIBS, focusing on its impact on brain hemodynamics, neurophysiology, and clinical outcomes.

Methods: To this end, we searched the international databases (Web of Science, PubMed, Scopus) and extracted studies using the appropriate keywords. The Newcastle-Ottawa Scale (NOS) was used to assess the methodology and quality of the studies.

Results: Research demonstrates that tDCS and its advanced forms improve EEG patterns, including alpha and theta band power, reduce P300 latency, and enhance cortical-cortical and thalamocortical connectivity, correlating with better behavioral outcomes, as measured by the Coma Recovery Scale-Revised (CRS-R). Moreover, personalized protocols based on MRI simulations and multimodal therapies, such as combining NIBS with music stimulation or robotic rehabilitation, further optimize outcomes by targeting specific brain areas and enhancing network reconfiguration. The dual application of HD-tDCS with transcutaneous auricular vagus nerve stimulation (taVNS) has also shown synergistic effects on EEG microstate dynamics and CRS-R scores in MCS patients.

Conclusion: Overall, NIBS presents a promising approach for enhancing consciousness recovery, though challenges in protocol optimization and understanding the mechanisms of action remain. Future research should continue to explore these techniques' full potential, particularly through personalized, multi-target stimulation strategies.

The authors declare no conflicts of interest.
*Corresponding author.
E-mail address: dr.amirdosara@gmail.com

Introduction

Disorders of consciousness (DoC), including coma, vegetative state/unresponsive wakefulness syndrome (VS/UWS), and minimally conscious state (MCS), represent a spectrum of severe brain impairments characterized by varying levels of arousal and awareness [1]. These conditions typically result from traumatic brain injury (TBI), cerebrovascular events, hypoxic-ischemic encephalopathy, or other neurological damage that disrupts the complex brain networks responsible for consciousness [2]. Despite advances in medical care, treatment options for patients with DoC remain limited, with rehabilitation and pharmacological interventions showing limited efficacy in promoting meaningful recovery [3].

Recent research has increasingly focused on non-invasive brain stimulation (NIBS) techniques, particularly transcranial direct current stimulation (tDCS), as promising interventions for DoC [4]. tDCS and its advanced variations, such as high-definition tDCS (HD-tDCS) and transcranial alternating current stimulation (tACS), are non-invasive neuromodulation methods that use weak electrical currents to modulate neuronal excitability and promote neuroplasticity [5]. These techniques can potentially enhance brain function by targeting specific cortical regions and facilitating communication between critical neural networks for arousal, awareness, and cognitive processing. This approach has garnered attention due to its safety, ease of use, and ability to produce long-lasting effects on brain activity [6-7].

One of the key areas of focus in research on NIBS for DoC is the investigation of neurophysiological outcomes and hemodynamic changes induced by these interventions [8]. Studies suggest that NIBS can restore functional connectivity within disrupted brain networks, particularly the thalamocortical and fronto-parietal circuits, essential for consciousness and cognitive functions [9]. Moreover, emerging evidence highlights the impact of NIBS on cerebral blood flow (CBF) and oxygen metabolism, key hemodynamic indicators that reflect neuronal activity. Changes in these parameters may signal the restoration of neuronal excitability and the re-establishment of vital brain functions, potentially leading to improved behavioral outcomes in DoC patients [10].

The importance of understanding the brain's hemodynamic responses to neuromodulation in DoC cannot be overstated. Cerebral hemodynamics, including regional CBF and oxygen metabolism, are closely linked to neuronal activity and brain function [11]. In individuals with DoC, impaired cerebral blood flow and disrupted metabolic processes contribute to these conditions' diminished responsiveness and awareness [12]. NIBS interventions, such as tDCS, have been shown to modulate these hemodynamic parameters, promoting neurovascular coupling and enhancing oxygen delivery to the brain. This restoration of cerebral hemodynamics may, in turn, support the recovery of brain activity and facilitate improvements in clinical assessments of consciousness, such as the Coma Recovery Scale-Revised (CRS-R) and Glasgow Outcome Scale (GOS) [13].

However, despite the growing body of evidence supporting the use of NIBS in DoC, challenges remain in optimizing stimulation protocols and understanding the mechanisms underlying these interventions. The diversity of patient populations, ranging from acute to chronic cases, and the heterogeneity of the underlying causes of DoC complicate the interpretation of findings across studies. Furthermore, variations in stimulation parameters, including the intensity, duration, and electrode placement, may contribute to discrepancies in clinical outcomes. There is also a need to explore the synergistic effects of combining NIBS with other therapeutic modalities, such as music stimulation, robotic rehabilitation, and personalized protocols based on advanced neuroimaging techniques [14].

This systematic review aims to synthesize the current evidence on the efficacy of NIBS, particularly tDCS and its variations, in improving neurophysiological outcomes and brain hemodynamics in patients with DoC.

Methods

The present study used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist [15].

Search Strategy

A comprehensive literature search was conducted in multiple electronic databases, including PubMed, Scopus, and Web of Science, to identify studies investigating the use of NIBS in DoC patients. The following key terms were used: "disorders of consciousness," "coma," "vegetative state," "minimally conscious state," "non-invasive brain stimulation," "transcranial direct current stimulation," "transcranial alternating current stimulation," "tDCS," "tACS," "neurophysiology," and "brain hemodynamics." We also included relevant studies published in languages other than English through translation.

Study selection

After eliminating the duplicate studies, the titles and abstracts of the remaining articles were checked to find eligible studies based on the following inclusion and exclusion criteria. Inclusion criteria included studies involving adult patients diagnosed with DoC (coma, VS/UWS, or MCS) resulting from traumatic brain injury (TBI), cerebrovascular events, or hypoxic-ischemic encephalopathy; studies that used NIBS techniques, such as tDCS, HD-tDCS, or tACS, as the primary intervention; articles that reported neurophysiological outcomes (e.g., EEG, P300 latency) and/or brain hemodynamic parameters (e.g., CBF, oxygen metabolism); and randomized controlled trials (RCTs), cohort studies, and case-control studies with either pre-post intervention measures or comparisons between NIBS and placebo/control groups. Also, studies involving pediatric populations or those with comorbidities that significantly affect brain function (e.g., neurodegenerative diseases), studies where NIBS was combined with other therapies unrelated to DoC rehabilitation (e.g., deep brain stimulation), and studies focusing on NIBS for conditions other than DoC, such as psychiatric disorders or chronic pain, were excluded from the study.

Data extraction and quality assessment

Data were extracted from the selected studies using a standardized form by two independent reviewers. The extracted information included authors' names, study location, publication date, sample size, patient demographics (age, gender, etiology of DoC), type of intervention (e.g., tDCS, HD-tDCS, or tACS), stimulation parameters (e.g., intensity, duration, frequency), hemodynamic brain parameters (e.g., cerebral blood flow, oxygen metabolism), neurophysiological outcomes (e.g., EEG measures, P300 latency), and clinical outcomes (e.g., Glasgow Outcome Scale [GOS], Brainstem Auditory Evoked Potential [BAEP]). Additionally, details of the control group (sham treatment) and EEG analysis were also recorded.

Other authors independently reviewed the extracted data for potential biases, and final confirmation was obtained through consensus. To assess the methodology and quality of the studies, the Newcastle-Ottawa Scale (NOS) was used [16]. This scale evaluates studies based on selection, comparability, and outcome. Studies with NOS scores of 0-3 were classified as low quality, those with scores of 4-6 were classified as medium quality, and studies with scores of 7-9 were considered high quality. Studies with NOS scores less than 4 were excluded from further analysis (Table 1).

Results

867 records were identified through database searches: 315 from PubMed, 436 from Scopus, and 116 from Web of Science. After removing 257 duplicate records and 189 for various stated reasons (non-English language, 43; lack of full text, 12; irrelevant title/abstract, 134 records), 421 records remained for screening. During the screening process, 266 studies were excluded due to insufficient data (56), non-relevant populations (68), and non-relevant interventions (142). Of the 155 reports assessed for eligibility, an additional 147 studies were excluded, including animal studies (39), review articles (78), and studies conducted in non-critical care units (30). Ultimately, 8 studies were included in the final review and analysis (Figure 1) (Table 2).

The outcome of DoC includes consciousness disorders, which range from coma to VS/UWS and MCS. These illnesses are characterized by arousal, awareness impairment, and disrupted clinical circumstances. They are typically caused by alterations in thalamocortical and cortical-cortical connectivities that follow either traumatic or non-traumatic brain damage. The therapy options for these individuals are limited despite the significant advancements in medical care; as a result, there is a growing need for novel therapies. Enhancing neuronal connection, raising consciousness levels, and speeding up recovery are among the potential benefits of NIBS techniques, particularly tDCS and its variations. This systematic review aims to synthesize results from recent research on the effectiveness of neuromodulation in DoC with an emphasis on neurophysiological outcomes and brain hemodynamic effects.

Patient Demographics

With a mean age distribution of 35 to 50 years, the enrolled patients in the included studies ranged in age from 18 to 75 years. Male participants comprised 55% and 65% of the included cohorts, indicating a relatively balanced gender distribution. Although there were other causes of DoC, TBI accounted for the largest percentage, followed by cerebrovascular events and hypoxic-ischemic encephalopathy. The trials included acute and chronic DoC instances, and the individuals' duration since injury ranged from one month to more than a year. This diversity, which includes both early and long-term stages of consciousness impairment, reflects the complexity of the population being studied.

Intervention Methods

The neuromodulation techniques used in the analyzed research examined numerous stimulation parameters and adjunct therapies. Intensities of 1 to 2 mA were usually employed in standard tDCS protocols, administered for 5 to 30 days at 20 to 30 minutes per session. tACS and high-definition tDCS (HD-tDCS) were used to target particular brain regions essential for awareness, such as the parieto-occipital areas and precuneus. They left the dorsolateral prefrontal cortex (DLPFC). These areas are crucial for arousal and understanding and are part of the thalamocortical and fronto-parietal networks.

Table 1- Quality assessment of the included studies

Authors	Selection	Comparability	Outcome/Exposure	Total Score
De Koninck, (2024) [17]	3	2	3	8
Yan, (2024) [18]	4	2	3	9
Yoon, (2023) [19]	3	2	3	8
Zhang., (2021) [6]	3	1	3	7
Gangemi, (2024) [20]	4	2	3	9
Hermann, (2020) [21]	4	2	3	9
Zhuang, (2023) [22]	3	2	3	8
Li, (2019) [23]	4	2	4	9

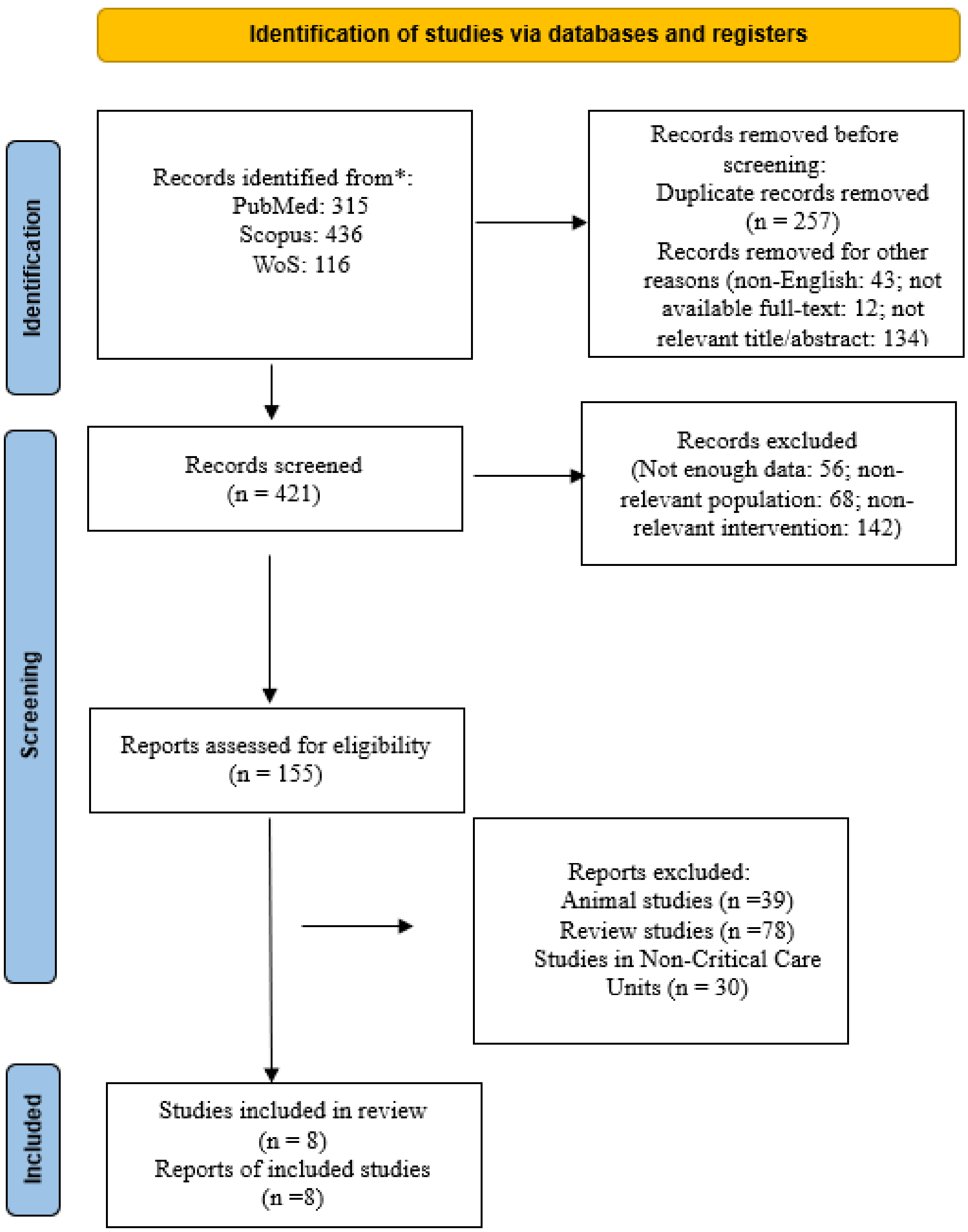

Figure 1- PRISMA flow diagram illustrating the selection of articles

Table 2- Characteristics of included studies

First Author, Year	**Li, (2019) [23]**	**Hermann, (2020) [21]**	**Gangemi, (2024) [20]**	**De Koninck, (2024) [17]**
Country	China	France	Italy	Canada
Number of Patients	80 patients (40 active, 40 sham)	60 patients (24 VS/UWS, 32 MCS, 4 exit-MCS)	24 patients (12 experimental, 12 control)	138 patients (69 active, 69 sham)
Age of Participants	18–65 years	18–80 years	Experimental: 59.66 ± 8.33; Control: 60.08 ± 11.06	Adults aged 18 or older
Intervention Type	tDCS + Rehabilitation	tDCS	tDCS + Robotic Verticalization	tACS
Stimulation Parameters	Intensity: 1–2 mA; 20 min/session, 6 days/week for 4 weeks	Intensity: 2 mA; Duration: 20 min/session (anode over DLPFC, cathode over right supraorbital cortex)	Intensity: 2 mA; Duration: 20 min before 45-min robotic verticalization sessions	Frequency: 10 Hz; Intensity: 1 mA; Duration: 20 minutes/session, 5 days
Hemodynamic Brain Parameters	Increased CBF and CBV in DLPFC; enhanced connectivity between DLPFC and thalamus.	Increased theta-alpha connectivity in centro-parietal regions; enhanced P300 response in responders.	P300 latency was reduced from 432.67 ms (T0) to 379.01 ms (T1) in the experimental group.	Increased alpha oscillations in 8–13 Hz; improved thalamocortical connectivity.
Outcome Metrics	Weekly GOS: The intervention group showed significant recovery.	CRS-R improvements: 20% transitioned to higher states of consciousness.	P300 latency, Level of Cognitive Functioning (LCF), Functional Independence Measure (FIM).	Glasgow Coma Scale (GCS), CRS-R, actigraphy, long-term recovery.
Control Group (Sham)	40 sham participants	No sham group	12 sham participants	69 sham participants
EEG Analysis	Pre- and post-tDCS monitoring of brain activity.	ERP-P300 focused on theta-alpha spectral connectivity.	ERP-P300 analysis pre- and post-tDCS.	High-density EEG; alpha-band functional connectivity.
Glasgow Outcome Scale (GOS)	Weekly GOS improvements were observed in the intervention group compared to sham.	CRS-R showed marked improvements in responders (R+).		GCS improvements were measured at multiple intervals.
Brainstem Auditory Evoked Potential (BAEP)	BAEP showed improved latency and amplitude post-tDCS.	Enhanced auditory novelty detection in responders post-tDCS.		
First Author, Year	**Yan, (2024) [18]**	**Yoon, (2023) [19]**	**Zhang., (2021) [6]**	**Zhuang, (2023) [22]**
Country	China	South Korea	China	China
Number of Patients	90 patients (30 per group: active, active+music, sham)	24 patients (cross-over trial with P-tDCS and sham)	105 patients (57 UWS, 48 MCS)	84 patients (21 per group: SJS, sham, taVNS only, HD-tDCS only)
Age of Participants	18–75 years	19–80 years	16–83 years	18–60 years
Intervention Type	HD-tDCS + Music Stimulation	Personalized tDCS based on simulation	Multi-target and Multi-session tDCS	Simultaneous taVNS and HD-tDCS (SJS)
Stimulation Parameters	HD-tDCS: 2 mA, 20 min/session, 5 days/week, over 2	P-tDCS: 2 mA, 30 min/session, 5 days/week for 2 weeks; sham: 2 mA	80 sessions; 2 mA, 20 min/session for the prefrontal area and	Travis: 1–1.5 mA, 4–20 Hz, 20 min/session; HD-

	weeks; Music: 20 min/session, 40–70 dB	ramp-up and down only for the 30s at start and end	bilateral FTPCs; 1.2 mA for left DLPFC	tDCS: 2 mA, 20 min/session, Pz as central electrode
Hemodynamic Brain Parameters	Changes in spectral power and functional connectivity observed with EEG; increased MMN amplitude	Simulated electric field based on personalized MRI segmentation; areas of stimulation modeled and optimized	Improved cortical connections between M1 and frontal cortex; enhanced prefrontal-parietal and temporoparietal networks	Restoration of thalamocortical connectivity; enhanced frontoparietal network interactions
Outcome Metrics	CRS-R and GOS scores improved; EEG changes included increased slow-wave power and enhanced connectivity	Primary: K-CRS-R score changes at 2 weeks; Secondary: EEG power/connectivity, exploratory: fMRI and FDG-PET changes	Significant improvement in CRS-R scores (from 10 to 16 median in tDCS group); better mGOS outcomes	Primary: CRS-R score improvement; Secondary: EEG microstate metrics and adverse events
Control Group (Sham)	30 sham HD-tDCS participants	Sham P-tDCS participants with identical protocols except for no sustained stimulation	50 historical controls with standard therapy	Sham stimulation group with identical devices
EEG Analysis	64-channel EEG; monitored spectral power, MMN latency, and frequency band changes pre- and post-intervention	Theta-alpha band spectral power, phase connectivity; changes measured via high-resolution EEG	Non-linear EEG analysis; C-ApEn indices for local and remote cortical network interconnections	Microstate analysis: duration, occurrence, coverage, and probability of microstates A–D
Glasgow Outcome Scale (GOS)	Improved GOS scores post-intervention; follow-up assessments at 1 week and 3 months		Improved mGOS score from 2 to 4 in the tDCS group and 3 in the control group	
Brainstem Auditory Evoked Potential (BAEP)				

Adjunct therapy further enhanced the effectiveness of the tDCS procedures. Using music's rhythmic and emotive involvement to improve brain activity, music stimulation in conjunction with HD-tDCS produced considerably higher CRS-R ratings than single-modality therapies. RVT with tDCS added demonstrated enhanced cortical connection and better cognitive results. Significant improvement was also seen in the electrophysiological measures, such as a decrease in P300 latency. In addition, customized tDCS protocols based on MRI-based electric field simulations enhanced cortical network reconfiguration and further adjusted stimulation settings to specific lesion patterns. [18, 20].

Lastly, a novel approach that addressed both thalamic-cortical and cortical-cortical pathways, simultaneous tAVNS, and HD-tDCS improved EEG microstate dynamics and CRS-R scores, demonstrating synergistic effects on MCS patients' recovery of consciousness. Increased functional EEG connectivity and better behavioral outcomes showed that the multitarget and multisession tDCS procedures, which involve sequential stimulation of multiple brain areas, restored general connectivity [6, 22].

Brain Hemodynamic Neurophysiological Outcomes

Clinically, behavioral aspects, as determined by the CRS-R score, improved in the included studies. Increased alpha and theta EEG band power, decreased P300 delay, and enhanced functional connectivity were all linked to these improvements in neurophysiology. EEG-based evaluations demonstrated the recovery of cortical-cortical connections and thalamocortical communication. Furthermore, multi-target stimulation procedures showed that these networks were more coherent and that global and regional connections had significantly improved. Although less common, hemodynamic effects were observed in a few investigations. The increased neuronal excitability brought on by neuromodulation was linked to increased rCBF and oxygen metabolism in some cortical regions. The restoration of hemodynamic parameters was made possible by optimal targeting, as demonstrated by the specific benefits that personalized protocols showed in disturbed networks [17, 19, 22].

Mechanisms of Neuromodulation and Brain Hemodynamics

Neuromodulation can restore hemodynamic parameters linked to awareness. In fact, by altering neuronal excitability and network connectivity, HD-tDCS and tACS improve rCBF and oxygen metabolism. For instance, 10-Hz tACS demonstrated enhanced alpha-band power and parieto-occipital cortical functional connectivity, which is thought to enhance thalamocortical communication crucial for arousal. According to CRS-R scores [17, 19, 22], these effects correlate with higher EEG connectivity measurements, which are linked to better behavioral outcomes.

Combined Multi-Modal Methods

The hemodynamic effects of combined therapy with tDCS have been improved. For example, the hemodynamics of the thalamocortical networks were improved in research combining HD-tDCS with music stimulation. The music further enhanced cortical-cortical communication by activating reward and self-referential networks. Similarly, EEG analysis utilizing P300 latencies showed enhanced cognitive processing, and the combination of tDCS and robotic verticalization training strengthened brain connections in motor and prefrontal regions [18, 20].

Customized Neuromodulation

Customized tDCS regimens based on MRI simulations found improved regional connectivity in lesioned areas. Modifying stimulation parameters based on lesion architecture improved cortical activity, hemodynamic indicators, and functional connectivity in the prefrontal and temporoparietal areas. Globally restoring connection across the frontal, motor, and parietal cortices with multi-target tDCS procedures that involve sequential stimulation of critical nodes reflects better rCBF and metabolic recovery in these networks [6, 21].

HD-tDCS and taVNS concurrently

Transcutaneous auricular vagus nerve stimulation (taVNS) in conjunction with HD-tDCS resulted in notable hemodynamic improvements targeting the thalamic and cortical-cortical pathways. Dynamic changes in brain activity were detected by EEG microstate analysis, especially in areas linked to the thalamic regulation of consciousness. This dual-stimulation strategy highlighted its potential for treating complex neural disturbances in MCS patients by improving thalamocortical connections and CRS-R scores [22].

Discussion

This systematic review aimed to synthesize the effectiveness of tDCS in patients with DoC, such as coma, vegetative state/unresponsive wakefulness syndrome (VS/UWS), and minimally conscious state (MCS). The review included studies published from 2000 to 2023, focusing on neurophysiological outcomes like EEG, P300 latency, and brain hemodynamics (e.g., cerebral blood flow (CBF) and oxygen metabolism) as measures of treatment efficacy.

The findings across these studies suggest that NIBS techniques hold promise as therapeutic interventions for DoC patients when applied appropriately. Notably, tDCS, HD-tDCS, and tACS have shown efficacy in enhancing cortical connectivity, improving neurophysiological markers, and yielding behavioral improvements, such as increased CRS-R scores. These interventions, particularly when combined with adjunct therapies like music stimulation or robotic verticalization training (RVT), enhanced clinical and neurophysiological outcomes more effectively than single-modality treatments.

The studies included in this review consistently demonstrated improvements in electrophysiological markers, including P300 latency and EEG parameters, such as increased alpha and theta band power. These changes suggest that NIBS can help restore cortical-cortical and thalamocortical connectivity, which is crucial for consciousness and awareness. Several studies have decreased the P300 latency, an important measure of cognitive processing, suggesting that neuromodulation may help re-establish processing pathways involved in attention and awareness. Similarly, EEG analysis showed a recovery of cortical connectivity, which is essential for global brain function. These findings align with previous research, indicating that increased EEG connectivity correlates with better behavioral outcomes, such as improved consciousness levels [24-25].

The CRS-R scores, which assess consciousness recovery in DoC patients, were also improved following NIBS interventions, reinforcing that NIBS can facilitate consciousness recovery [17, 22]. The CRS-R is particularly valuable in tracking changes in awareness, and its improvement indicates that neuromodulation might influence arousal and cognitive awareness by enhancing underlying neural connectivity [26].

NIBS techniques exert their effects primarily by modulating neuronal excitability and network connectivity, often disrupted in DoC patients due to brain injury. The review highlighted how HD-tDCS and tACS enhance parieto-occipital functional connectivity, a region critical for maintaining consciousness and attention. tACS, particularly at 10 Hz, has been shown to improve alpha-band power, which is thought to facilitate thalamocortical communication, a key pathway involved in the regulation of consciousness [19, 27].

Moreover, hemodynamic improvements observed in several studies point to the potential of NIBS in restoring regional cerebral blood flow (rCBF) and oxygen metabolism. These improvements suggest that neuromodulation affects neuronal activity at the synaptic level and induces physiological changes that can further enhance neural functioning [6, 21]. The correlation between improved rCBF and P300 latency or EEG connectivity provides strong evidence for the dual action of NIBS in both neurophysiological and hemodynamic domains [28].

A significant contribution of this review is the exploration of multimodal and personalized neuromodulation strategies, which have shown considerable promise in improving both neurophysiological outcomes and clinical recovery. Combined therapies, such as tDCS paired with music stimulation or RVT, have enhanced cortical and subcortical network activity, especially in motor and prefrontal areas. Music, with its rhythmic and emotive components, enhances brain activity by stimulating reward and self-referential networks, improving cognitive processing and functional connectivity. These adjunct therapies likely synergize with NIBS to enhance recovery [18, 20].

The notion of personalized neuromodulation also emerged as a key finding in this review. Customizing stimulation parameters based on MRI-guided electric field simulations enables more precise targeting of brain regions disrupted by injury. This individualized approach not only maximizes the efficacy of NIBS but also facilitates the restoration of regional connectivity in lesioned areas. Such customized protocols are essential in DoC rehabilitation, given the complex and individualized nature of brain damage in these patients. By adjusting stimulation to the specific lesion patterns, interventions can better align with the brain's unique needs, enhancing both neurophysiological recovery and behavioral outcomes.

The review also highlighted the potential benefits of combining HD-tDCS with transcutaneous auricular vagus nerve stimulation (taVNS). This dual-modality approach targets the thalamic-cortical and cortical-cortical pathways, essential for regulating consciousness. By improving thalamocortical communication, this combination therapy may profoundly affect consciousness recovery in MCS patients. The EEG microstate dynamics observed in these studies further support the idea that multi-target stimulation can facilitate more global brain network reorganization [29].

Challenges and Limitations

Despite the promising findings, several limitations must be considered. One challenge is the heterogeneity of the included studies. Variations in patient demographics, stimulation protocols, and outcome measures make it difficult to draw definitive conclusions. For instance, the duration of DoC varied widely across studies, which may influence the effectiveness of NIBS. Patients in the acute phase of DoC might respond differently to neuromodulation than those in chronic stages, and this variation needs to be addressed in future studies.

Additionally, while multimodal approaches have shown efficacy, further research is needed to determine the optimal combination of therapies. The need for consensus on standardized treatment protocols for DoC patients complicates the interpretation of results. It suggests additional randomized controlled trials (RCTs) are needed to confirm these findings and optimize treatment regimens.

Conclusion

In conclusion, NIBS techniques, particularly tDCS, HD-tDCS, and tACS, represent a promising avenue for enhancing consciousness recovery in DoC patients. These interventions restore neural connectivity, improve EEG and P300 latency, and increase cerebral blood flow and oxygen metabolism. Furthermore, multi-modal and personalized approaches, including combinations of NIBS with therapies like music stimulation and robotic verticalization, have shown synergistic effects in promoting recovery. However, the heterogeneity of current studies underscores the need for more rigorous, well-designed trials to validate these findings and determine the most effective treatment protocols for this complex patient population.

Acknowledgment

The authors thank the Clinical Research Development Unit (CRDU) of Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran, for their support and cooperation.

Funding

This study was supported by the Clinical Research Development Unit (CRDU) of Loghman Hakim

Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

References

[1] Hermann B, Sangaré A, Munoz-Musat E, Salah AB, Perez P, Valente M, et al., Importance, limits and caveats of the use of “disorders of consciousness” to theorize consciousness. Neurosci Conscious. 2022; 2021(2):niab048.

[2] Bagnato S, D'Ippolito ME, Boccagni C, De Tanti A, Lucca LF, Nardone A, et al., Sustained axonal degeneration in prolonged disorders of consciousness. Brain Sci. 2021; 11(8): 1068.

[3] Barra ME, Edlow BL, Brophy GM. Pharmacologic Therapies to Promote Recovery of Consciousness. Semin Neurol. 2022; 42(3):335-347.

[4] Hu Y, Hu L, Wang Y, Luo X, Zhao X, He L. The effects of non-invasive brain stimulation on disorder of consciousness in patients with brain injury: A systematic review and meta-analysis of randomized controlled trial. Brain Res. 2024; 1822:148633.

[5] Wu YH, Yu J, Hong LR, Luo BY. Neuromodulatory therapies for patients with prolonged disorders of consciousness. Chin Med J (Engl). 2021; 134(7):765-776.

[6] Zhang X, Liu B, Li Y, Duan G, Hou J, Wu D. Multi-Target and Multi-Session Transcranial Direct Current Stimulation in Patients With Prolonged Disorders of Consciousness: A Controlled Study. Front Neurosci. 2021; 15:641951.

[7] Dong L, Li H, Dang H, Zhang X, Yue S, Zhang H. Efficacy of non-invasive brain stimulation for disorders of consciousness: a systematic review and meta-analysis. Front Neurosci. 2023; 17:1219043.

[8] Straudi S, Antonioni A, Baroni A, Bonsangue V, Lavezzi S, Koch G, et al. Anti-Inflammatory and Cortical Responses after Transcranial Direct Current Stimulation in Disorders of Consciousness: An Exploratory Study. J Clin Med. 2023; 13(1):108.

[9] Hallett M, Di Iorio R, Rossini PM, Park JE, Chen R, Celnik P, et al. Contribution of transcranial magnetic stimulation to assessment of brain connectivity and networks. Clin Neurophysiol. 2017; 128(11):2125-2139.

[10] Hong KS, Khan MNA, Ghafoor U. Non-invasive transcranial electrical brain stimulation guided by functional near-infrared spectroscopy for targeted neuromodulation: a review. J Neural Eng. 2022; 19(4).

[11] Smith KJ, Ainslie PN. Regulation of cerebral blood flow and metabolism during exercise. Exp Physiol. 2017; 102(11):1356-1371.

[12] He Z, Lu R, Guan Y, Wu Y, Ge J, Liu G, Cet al. Brain Metabolic Connectivity Patterns in Patients with Prolonged Disorder of Consciousness after Hypoxic-Ischemic Injury: A Preliminary Study. Brain Sci. 2022; 12(7):892.

[13] Bourdillon P, Hermann B, Sitt JD, Naccache L. Electromagnetic Brain Stimulation in Patients With Disorders of Consciousness. Front Neurosci. 2019; 13:223.

[14] Zhang Y, Song W. Transcranial direct current stimulation in disorders of consciousness: a review. Int J Neurosci. 2018; 128(3):255-261.

[15] Vrabel M. Preferred Reporting Items for Systematic Reviews and Meta-Analyses. Oncol Nurs Forum. 2015; 42(5):552-4.

[16] Lo CK, Mertz D, Loeb M. Newcastle-Ottawa Scale: comparing reviewers' to authors' assessments. BMC Med Res Methodol. 2014; 14:45.

[17] De Koninck BP, Brazeau D, Deshaies AA, Briand MM, Maschke C, Williams V, et al. Modulation of brain activity in brain-injured patients with a disorder of consciousness in intensive care with repeated 10-Hz transcranial alternating current stimulation (tACS): a randomised controlled trial protocol. BMJ Open. 2024; 14(7):e078281.

[18] Yan J, Zha F, Zhou J, Zhou J, Zhao J, Zhang Q, et al. Combining HD-tDCS with music stimulation for patients with prolonged disorders of consciousness: Study protocol for an RCT trial. NeuroRehabilitation. 2024; 54(3):495-504.

[19] Yoon MJ, Oh HM, Kim T, Choi SJ, Choi WH, Jung HS, et al. Safety and therapeutic effects of personalized transcranial direct current stimulation based on electrical field simulation for prolonged disorders of consciousness: study protocol for a multi-center, double-blind, randomized controlled trial. Front Neurol. 2023; 14:1184998.

[20] Gangemi A, De Luca R, Fabio RA, Bonanno M, Cardile D, Mignacca MR, et al. Cognitive Effects of Transcranial Direct Current Stimulation Plus Robotic Verticalization in Minimally Conscious State. Biomedicines. 2024; 12(10): 2244.

[21] Hermann B, Raimondo F, Hirsch L, Huang Y, Denis-Valente M, Pérez P, et al., Combined behavioral and electrophysiological evidence for a direct cortical effect of prefrontal tDCS on disorders of consciousness. Sci Rep. 2020. 10(1): 4323.

[22] Zhuang Y, Zhai W, Li Q, Jiao H, Ge Q, Rong P, et al. Effects of simultaneous transcutaneous auricular vagus nerve stimulation and high-definition transcranial direct current stimulation on disorders of consciousness: a study protocol. Front Neurol. 2023; 14:1165145.

[23] Li S, Dong X, Sun W, Zhao N, Yu G, Shuai L. Effects of transcranial direct current stimulation on patients with disorders of consciousness after traumatic brain injury: study protocol for a randomized, double-blind controlled trial. Trials. 2019; 20(1):596.

[24] Bareham CA, Roberts N, Allanson J, Hutchinson PJA, Pickard JD, Menon DK, et al. Bedside EEG predicts longitudinal behavioural changes in disorders of consciousness. Neuroimage Clin. 2020; 28:102372.

[25] Boly M, Massimini M, Garrido MI, Gosseries O, Noirhomme Q, Laureys S, et al. Brain connectivity in disorders of consciousness. Brain Connect. 2012; 2(1):1-10.

[26] Vatrano M, Nemirovsky IE, Tonin P, Riganello F. Assessing Consciousness through Neurofeedback and Neuromodulation: Possibilities and Challenges. Life (Basel). 2023; 13(8):1675.

[27] Clancy KJ, Andrzejewski JA, You Y, Rosenberg JT, Ding M, Li W. Transcranial stimulation of alpha oscillations up-regulates the default mode network. Proc Natl Acad Sci U S A. 2022; 119(1):e2110868119.

[28] Wörsching J, Padberg F, Ertl-Wagner B, Kumpf U, Kirsch B, Keeser D. Imaging transcranial direct current stimulation (tDCS) of the prefrontal cortex-correlation or causality in stimulation-mediated effects? Neurosci Biobehav Rev. 2016; 69:333-56.

[29] Zheng RZ, Qi ZX, Wang Z, Xu ZY, Wu XH, Mao Y. Clinical Decision on Disorders of Consciousness After Acquired Brain Injury: Stepping Forward. Neurosci Bull. 2023; 39(1):138-162.