Title

Neuromodulation and Disorders of Consciousness: Systematic Review and Pathophysiology

Authors

Dutta, Rajeev R

Abdolmanafi, Sheila

Rabizadeh, Alex

et al.

Publication Date

2024-10-01

DOI

10.1016/j.neurom.2024.09.003

Neuromodulation: Technology at the Neural Interface

Received: May 23, 2024 Revised: September 9, 2024 Accepted: September 11, 2024

https://doi.org/10.1016/j.neurom.2024.09.003

Neuromodulation and Disorders of Consciousness: Systematic Review and Pathophysiology

Rajeev R. Dutta, BS[1]; Sheila Abdolmanafi, AS[2]; Alex Rabizadeh, BS[2]; Rounak Baghbaninogourani, BS[2]; Shirin Mansooridara, MD[3]; Alexander Lopez, MD, MS[4]; Yama Akbari, MD, PhD[3,4,5,6]; Michelle Paff, MD[4]

ABSTRACT

Introduction: Disorders of consciousness (DoC) represent a range of clinical states, affect hundreds of thousands of people in the United States, and have relatively poor outcomes. With few effective pharmacotherapies, neuromodulation has been investigated as an alternative for treating DoC. To summarize the available evidence, a systematic review of studies using various forms of neuromodulation to treat DoC was conducted.

Materials and Methods: Adhering to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for systematic literature review, the PubMed, Scopus, and Web of Science databases were queried to identify articles published between 1990 and 2023 in which neuromodulation was used, usually in conjunction with pharmacologic intervention, to treat or reverse DoC in humans and animals. Records were excluded if DoC (eg, unresponsive wakefulness syndrome, minimally conscious state, etc) were not the primary clinical target.

Results: A total of 69 studies (58 human, 11 animal) met the inclusion criteria for the systematic review, resulting in over 1000 patients and 150 animals studied in total. Most human studies investigated deep brain stimulation ($n = 15$), usually of the central thalamus, and transcranial magnetic stimulation ($n = 18$). Transcranial direct-current stimulation ($n = 15$) and spinal cord stimulation ($n = 6$) of the dorsal column also were represented. A few studies investigated low-intensity focused ultrasound ($n = 2$) and median nerve stimulation ($n = 2$). Animal studies included primate and murine models, with nine studies involving deep brain stimulation, one using ultrasound, and one using transcranial magnetic stimulation.

Discussion: While clinical outcomes were mixed and possibly confounded by natural recovery or pharmacologic interventions, deep brain stimulation appeared to facilitate greater improvements in DoC than other modalities. However, repetitive transcranial magnetic stimulation also demonstrated clinical potential with much lower invasiveness.

Keywords: Coma, deep brain stimulation, disorders of consciousness, functional neurosurgery, neuromodulation

INTRODUCTION

Disorders of Consciousness

Disorders of consciousness (DoC) are a group of conditions in which consciousness, a state of awareness of the self and environment, sentience, or being the subject of conscious states, is impaired.[1–3] DoC include coma, unresponsive wakefulness syndrome (UWS) (also known as the vegetative state), and the minimally conscious state (MCS). Coma is characterized by lack of arousal and awareness, UWS is characterized by some arousal but absent awareness, and MCS is characterized by some arousal with minimal or inconsistent awareness.[2] DoC are estimated to affect hundreds of thousands of people in the United States, many arising from traumatic brain injuries (TBIs) and strokes.[4]

Owing to the burden of DoC, numerous pharmacologic and nonpharmacologic interventions have been attempted. Pharmacologic

Address correspondence to: Rajeev R. Dutta, BS, School of Medicine, University of California Irvine, 101 The City Drive S, Orange, CA 92868, USA. Email: duttarr@hs.uci.edu

[1] School of Medicine, University of California Irvine, Irvine, CA, USA;
[2] University of California Irvine, Irvine, CA, USA;
[3] Department of Neurology, University of California Irvine, Orange, CA, USA;
[4] Department of Neurological Surgery, University of California Irvine, Orange, CA, USA;
[5] Department of Anatomy and Neurobiology, University of California Irvine, Irvine, CA, USA; and
[6] Beckman Laser Institute and Medical Clinic, University of California Irvine, Irvine, CA, USA

For more information on author guidelines, an explanation of our peer review process, and conflict of interest informed consent policies, please see the journal's Guide for Authors.

Source(s) of financial support: The authors reported no funding sources.

treatments have included amantadine (dopamine agonist and N-methyl-D-aspartate antagonist), modafinil, methylphenidate (thought to act as a dopamine and norepinephrine reuptake inhibitor), bromocriptine (D2 agonist), and zolpidem (GABA [γ-aminobutyric acid] agonist), among others, while nonpharmacologic treatments have included neurorehabilitation and neuromodulation,[4] among others. These interventions are directed at increasing excitatory signaling in the brain or stimulating neural plasticity. Even with a variety of available treatment modalities, recovery from DoC is far from guaranteed. A recent study suggested that under a third of patients with a DoC eventually emerge from an MCS, regaining full consciousness.[5] Other patients may remain in UWS or MCS or die. Given that DoC can be associated with high nursing care costs and numerous complications, such as infections and pressure ulcers, effective treatment options for DoC are needed.

Neuromodulation

While pharmacologic interventions for DoC are the standard of care, it is important to recognize that these interventions are not effective in reliably producing emergence or improvement from disordered states.[6] Accordingly, other interventions to supplement pharmacologic treatment of DoC are highly desirable. Six forms of neuromodulation have been reviewed in this study for the treatment of DoC: deep brain stimulation (DBS), spinal cord stimulation (SCS), low-intensity focused ultrasound (LIFU), median nerve stimulation (MNS), transcranial magnetic stimulation (TMS), and transcranial direct-current stimulation (tDCS).

DBS is an established intervention for the treatment of movement disorders, epilepsy, and certain psychiatric conditions, such as obsessive-compulsive disorder.[7] DBS involves implantation of multicontact electrodes into specific brain regions, with subsequent delivery of electric current, controlled with adjustable stimulation parameters.[8] Stimulation from DBS is thought to alter the activity and firing patterns of cell bodies and axons within the volume of activated tissue and may also modulate functionally connected neural networks.

SCS is commonly used in the treatment of refractory radiculopathy associated with persistent spinal pain syndrome.[9] Percutaneous or paddle electrodes are placed in the epidural space over the spinal levels corresponding to the painful regions of the body, and electrical current is delivered through the dura to the neural elements. The mechanism of analgesia is based on the gate theory of pain, which proposes that synaptic transmission of pain signals from slow-conducting pain fibers is blocked by electrical stimulation of the substantia gelatinosa, which closes the "presynaptic gate."[10]

LIFU is a relatively novel approach to neuromodulation that uses precise, high-frequency acoustic waves to alter brain activity (eg, in the central thalamus in the case of DoC). The exact mechanism of LIFU is currently unknown. The energy delivered by LIFU is believed to produce mechanical effects that may increase the permeability of membrane channels or plasma membranes, leading to alterations in membrane conductance and excitability.[11]

MNS is a less invasive intervention that has been suggested to improve nausea and vomiting, particularly after operations.[12] The mechanism is unknown but believed to be the same as that of acupuncture performed at the pericardium 6 (P6) point located on the ventral surface of the wrist. Accordingly, MNS is thought to modulate brainstem nuclei of the vagus nerve, the nucleus tractus solitarius, and the dorsal motor nucleus of the vagus, as suggested by alternative medicine systems.[13] MNS has also, more recently, been trialed to modulate olfactory perception and treat tic disorders.[13,14]

TMS is a noninvasive procedure that uses a magnetic field to induce transient currents in neural tissue according to Faraday's law of induction.[15] It is often used in the treatment of symptoms in major depressive disorder and less often implemented for epilepsy and Parkinson's disease.[16–18] Since TMS targets are superficial cortical areas, TMS is believed to elicit neurobehavioral changes in patients with DoC by inducing electrophysiological changes in the cortex.[19]

tDCS is another noninvasive modality, which uses scalp electrodes to emit and receive a small electrical current that passes through the soft tissues, skull, and presumably the brain.[20] Similarly to TMS, tDCS targets the cerebral cortex and is proposed to induce neurobehavioral changes in DoC through altering the excitability of cortical neurons.[21]

Neuromodulation for DoC

Herein, we systematically review DBS, SCS, LIFU, MNS, TMS, and tDCS interventions for DoC. Additionally, we discuss the relevant pathophysiology by which these modalities are hypothesized to achieve clinical efficacy (eg, improvements in connectivity, motor skills, cerebral blood flow, neurotransmitter release, etc).

MATERIALS AND METHODS

Systematic Search for Neuromodulation in Disorders of Consciousness: Animal and Human Trials

We queried the PubMed, Scopus, and Web of Science databases using the following search terms: (Neuromodulation OR Deep Brain Stimulation OR Stimulation) AND (Coma OR Disorders of Consciousness). Records between 1990 and 2023 describing randomized control trials, clinical trials, and case reports were sought.

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were followed,[22] including primary literature investigating the effects of neuromodulation in human or animal trials. One author (Rajeev R. Dutta) screened the articles, including randomized controlled trials, case studies, and case series that examined DBS, SCS, LIFU, MNS, TMS, and tDCS. Articles were excluded if the stimulation target was not identified, DoC were not the primary clinical interest (eg, articles focused on treating dystonia during a DoC were excluded), the article was unavailable in English, or the candidate literature was secondary (eg, a literature review). Owing to space constraints, several possible neuromodulation techniques were a priori excluded (eg, vagus nerve stimulation, electroconvulsive therapy, occipital nerve stimulation, sacral nerve stimulation, etc). Accordingly, this review is not comprehensive in scope, instead focusing on the six selected modalities.

Data including the number of participants, modality, etiology of DoC, clinical outcomes, and physiological outcomes were extracted from the records and reported descriptively (ie, without meta-analysis) owing to the variety of clinical and physiological measures. Four authors (Rajeev R. Dutta, Sheila Abdolmanafi, Alex Rabizadeh, and Rounak Baghbaninogourani) extracted data from the studies.

Quality and Certainty Assessment

The quality of all included studies was assessed using the ROBINS-I (Risk Of Bias In Non-randomised Studies - of Interventions) tool (Cochrane, London, United Kingdom).[23] A certainty assessment was conducted using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) framework.[24,25] The assessments were completed by one author (R.R.D.).

RESULTS

There were 970 records identified through the searches of PubMed, Scopus, and Web of Science. Duplicates were identified by Rayyan (Rayyan Systems Inc, Cambridge, MA) and excluded, resulting in 628 unique records.[26] Four records were excluded because they reported on the same patients reported in three other included studies. Finally, 69 articles met the inclusion criteria. In total, 58 human studies and 11 animal studies investigating neuromodulation for DoC were included.

The systematic review process is shown in Figure 1.

Neuromodulation Targets for DoC in Humans

A total of 48 human studies were reviewed, including those that investigated DBS (15 studies), SCS (6 studies), LIFU (2 studies), MNS (2 studies), TMS (18 studies), and tDCS (15 studies) (Table 1). Common targets included the primary motor cortex, dorsolateral prefrontal cortex (DLPFC), centromedian-parafascicular nucleus of the thalamus (CM-pf), central medial thalamus (CM), and mesencephalic reticular formation (MRF).

Of the DBS studies, 11 studies noted significant improvements in coma scale scores (eg, JFK Coma Recovery Scale – Revised [CRS-R]), and 4 of those studies observed emergence from DoC and return to some daily activities of living (often with assistance) for at least some of their participants (Table 1). Stimulation parameters varied widely; for example, Yang et al[41] performed 100-Hz stimulation for 15-minute on-off cycles for 12 hours a day for one year, while Yamamoto et al[29] performed 25-Hz stimulation in 30-minute installments every 2 to 3 hours for ten years. Overall, recoveries were observed more often in MCS than in UWS. The relationship between DoC etiology and successful therapy was unclear, although Tsubokawa et al[27] and Yang et al[41] suggested that patients with TBI or "cerebrovascular accidents" (including stroke) were more likely to benefit from DBS than patients with anoxia. By contrast, Chudy et al[34] found that three out of four patients

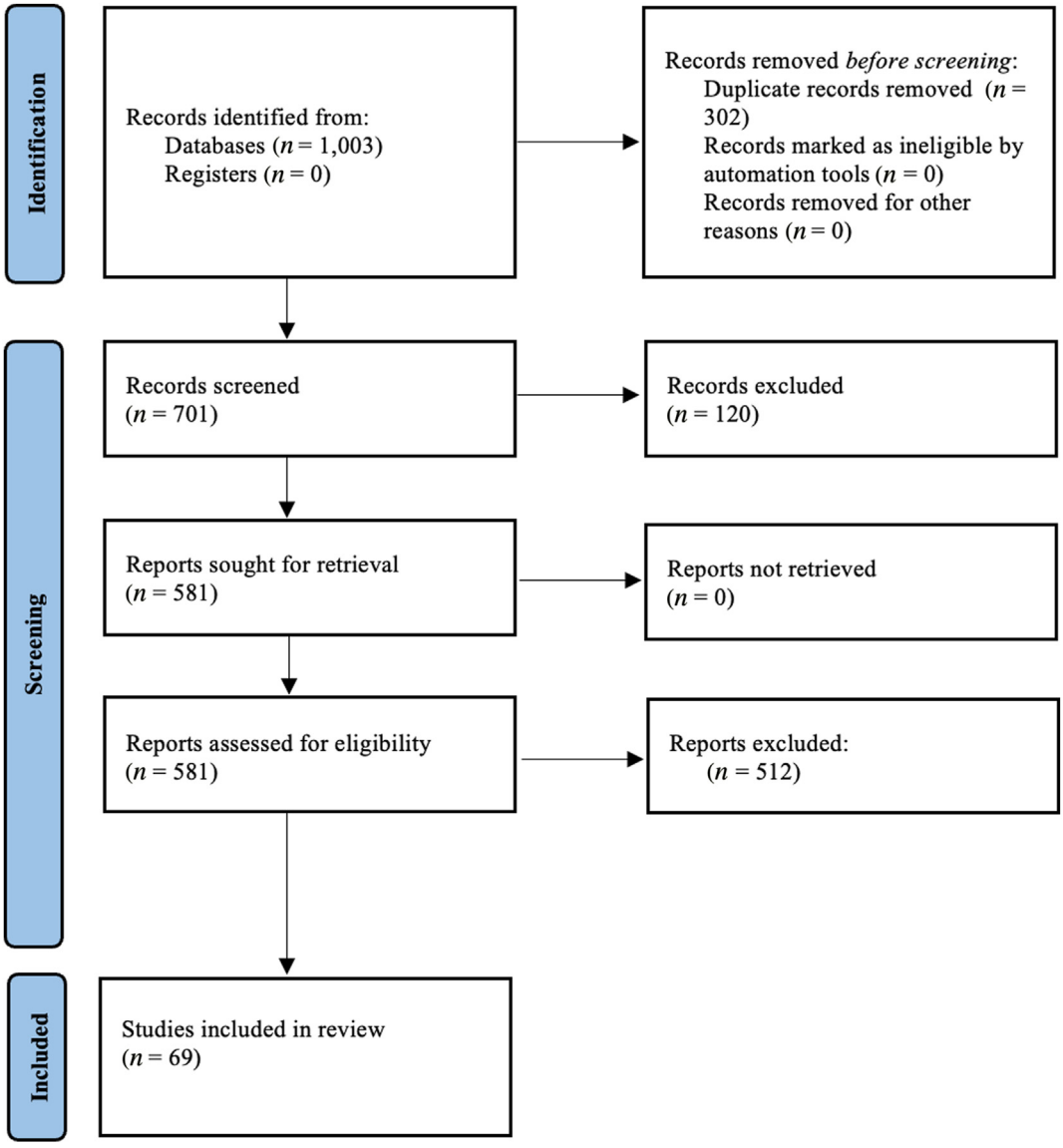

Figure 1. PRISMA flow diagram of the systematic review process. [Color figure can be viewed at www.neuromodulationjournal.org]

Table 1. Summary of Human Deep Brain Stimulation Studies.

Author, publication year	Sample size (DBS anatomical target)	Etiology — time since injury	Clinical outcomes	Physiological outcomes
Tsubokawa et al,[27] 1990	Eight patients with UWS (two MRF, six "non-specific" thalamus)	TBI (n = 4), "cerebrovascular accident" (n = 3), anoxia (n = 1) — each >six mo	NGS scoring showed complete recovery for three patients (one MRF, two thalamic), incomplete recovery for one patient (thalamic), and no improvement in four patients (one MRF, three thalamic)	EEG showed arousal pattern, increased rCBF, increased $rCMRO_2$, and increased rCMRGL in whole brain tissue for all patients during stimulation
Katayama et al,[28] 1991	19 patients with UWS (MRF and/or "non-specific" thalamus)	Unspecified — each >six mo	NGS scoring showed improvements for four patients, some responsive to verbal commands and capable of expressing language, only in chronic stimulation	EEG showed a transient increase of P_{250} in four patients by preceding stimulation of the MRF. Chronic DBS resulted in a persistent increase of P_{250} for the same patients.
Yamamoto et al,[29] 2005	26—21 patients with UWF (19 CM-pf, 2 MRF), 5 patients with MCS (CM-pf)	TBI (UWS, n = 9; MCS, n = 3), "cerebrovascular accident" (UWS, n = 9; MCS, n = 2), anoxia (n = 3) — each three mo	Four out of five patients with MCS experienced full recovery (resumed regular activities of living at home), 8 of 21 patients with UWS emerged from UWS—one resumed activities of living with wheelchair assistance, and seven could communicate but remained bedridden	A slight EEG desynchronization pattern was observed and was exacerbated in patients with MCS. EEG in the eight recovered patients with UWS showed a prolonged latency in the fifth wave of ABR and N20 of the SEP. P_{250} was recorded with an amplitude over 7 μV in both groups.
Schiff et al,[30] 2007	One patient with MCS (AIT-PR)	TBI — six y	CRS-R score improvements were significant ($p < 0.001$) in arousal, limb control, and oral feeding	N/A
Moll et al,[31] 2009	One anesthetized (GPi)	Anesthetized patient with tremulous cervical dystonia (27-y history)	While under general anesthesia for DBS to treat cervical dystonia, patient entered wakeful unawareness with bilateral eye opening in response to verbal commands	EEG showed a strong power change in the gamma band (>60 Hz) during stimulation In 6 out of 15 microelectrode positions, electrical stimulation resulted in significant autonomic activation and reproducible behavioral expressions of wakefulness
Wojtecki et al,[32] 2014	One patient (GCS 4, bilateral internal medullary lamina, and reticular nucleus)	TBI (subarachnoid hemorrhage) — seven y	Modulation of beta and theta waves within the central thalamus when presented with familiar-addressing speech, with local field potential oscillation recording suggesting involvement of CT	Theta phase was found to be coupled to the amplitude of gamma waves locally in the thalamus by scalp EEG. Thalamocortical coherence in the theta band increased in response to familiar-addressing speech.
Magrassi et al,[33] 2016	Three patients—two with UWS and one with MCS (AIT-PR)	TBI (n = 3; one UWS subdural hematoma, one UWS unspecified, one MCS subarachnoid hemorrhage) — each >six mo	Average increase of CRS-R scores after 18 mo was 2.33 ± 1.15. Two patients continued after 18 mo and increased CRS-R scores by 3.00 ± 0.00 for four y. None regained full consciousness.	EEG showed increased power of the theta and gamma bands after one mo of DBS. Overall spectral power increased in all patients (except alpha and beta in MCS) after full course of DBS.
Chudy et al,[34] 2018	14—10 patients with UWS and 4 with MCS (CM-pf)	TBI (UWS, n = 3; MCS, n = 1), hypoxic encephalopathy following cardiac arrest (UWS, n = 7; MCS, n = 3) — UWS range = 2.5–21.5 mo; MCS range = 65 d to 11.5 y	All patients experienced arousal reaction during stimulation (eye opening, changed facial expressions). Three out of four patients with MCS emerged to full awareness, able to interact and communicate—two of them live independently. One patient with UWS regained responsiveness. Three out of the four patients who showed improvements had hypoxic encephalopathy.	MRI showed progression of ischemic encephalopathy with marked brain atrophy in all patients

(Continues)

Table 1. *Continued*

Author, publication year	Sample size (DBS anatomical target)	Etiology — time since injury	Clinical outcomes	Physiological outcomes
Lemaire et al,[35] 2018	Five patients—one with UWS and four with MCS (bilateral medial pallidum and AIT-PR—cross-over, two in phase 1, three in phase 2)	TBI (UWS, n = 1; MCS, n = 2), hemorrhagic stroke (MCS, n = 2) — each ≥six mo (TBI ≥one y)	The patient with UWS and one patient with MCS had significantly increased average CRS-R scores following surgery ($p < 0.05$). Two additional patients with MCS experienced significantly increased average CRS-R scores when stimulation was turned on in a crossover phase ($p < 0.05$).	The two patients with significant CRS-R increases also experienced increased fluorodeoxyglucose metabolism of the medial cortices
Gottshall et al,[36] 2019	One patient with MCS (bilateral CT)	TBI — 21 y, five mo	Improvements in sleep electrophysiology, including re-emergence of alpha and delta waves after daytime stimulation. Significant decrease in CRS-R followed the end of stimulation ($p = 0.0116$).	Normalization of stage 2 sleep spindles, SWS, REM sleep, and waking alpha rhythms occurred during DBS. Spindle power was reduced after DBS. SWS delta power was significantly increased during and after DBS. SWS alpha power was significantly reduced during DBS and then rebounded after DBS ($p < 0.001$).
Raguž et al,[37] 2021	5—2 UWS patients and 3 MCS patients (CM-pf)	TBI (UWS, n = 1; MCS, n = 1), cardiac arrest (UWS, n = 1; MCS, n = 2) — range 2–14 months	All 5 patients raised to full awareness and were able to communicate and interact	Limbic and paralimbic cortices, the hippocampus, and the amygdala demonstrated significant increases in volume after 1 and 7 years after stimulation
Arnts et al,[38] 2022	One patient with MCS (CM-pf)	TBI — eight y	No significant changes in overall CRS-R scores, although eye dilation, head raising, increased respiratory rate, and visual tracking throughout the room were noticed	Lower stimulation frequency (50 Hz rather than 130 Hz) was associated with higher functional activity across all four MEG bands
Dang et al,[39] 2023	Nine patients with MCS (CM-pf — crossover; five in phase 1, four in phase 2)	TBI (n = 4), hemorrhage (n = 3), anoxia (n = 2)—range 6–12 mo	No significant overall changes in CRS-R scores, although three patients experienced increases ranging from 3 to 7 points	G_PCMI showed significantly increased functional connectivity in whole brain, frontal lobe, central lobe, frontal-central lobe, central-parietal lobe, and frontal-parietal lobe
Shu et al,[40] 2023	Ten patients—eight with UWS (five bilateral CM-pf, three right CM-pf) and two with MCS (one bilateral CM-pf and one right CM-pf)	TBI (UWS, n = 3; MCS, n = 1), hemorrhage (UWS, n = 3; MCS, n = 1), brainstem infarction (UWS, n = 2)—each ≥three mo (TBI ≥six mo)	Six patients showed increased CRS-R scores, while one patient (UWS bilateral) showed decreased CRS-R score. The remaining three patients (with brainstem hemorrhage or infarction) showed no change in CRS-R score.	The six patients showing increased CRS-R scores also showed increased functional connectivity by fNIRS in the frontal, parietal, and occipital lobes. The patient showing decreased CRS-R score showed decreased functional connectivity by fNIRS. The three remaining patients showed no change in fNIRS.
Yang et al,[41] 2023	37 patients—24 with UWS and 13 with MCS (CM-pf)	TBI (UWS, n = 2; MCS, n = 6), stroke (UWS, n = 15; MCS, n = 4), anoxia (UWS, n = 7; MCS, n = 3)—each >three mo	DBS patients showed significantly higher clinical improvement in CRS-R scores after one y ($p <$ 0.001). Patients with UWS showed significant subscale increases in communication ($p = 0.006$) and arousal ($p = 0.005$). Patients with MCS showed significant increases in all six subscales ($p < 0.001$).	N/A

MRF, mesencephalic reticular formation; CM-pf, centromedian-parafascicular thalamus; CM, central medial thalamus; AIT-PR, anterior intralaminar thalamic and adjacent paralaminar regions; GPi, globus pallidus internus; CT, central thalamus; UWS, unresponsive wakefulness (persistent vegetative state); MCS, minimally conscious state; TBI, traumatic brain injury; NGS, Nihon University Grading Scale for Persistent Vegetative State; CRS-R, JFK Coma Recovery Scale – Revised; rCBF, regional cerebral blood flow; $rCMRO_2$, regional cerebral metabolic rate of oxygen; rCMRGL, regional cerebral metabolic rate of glucose; P_{250}, cerebral evoked potential in response to painful stimulus (latency ~250 ms); SEP, somatosensory evoked potential; MEG, magnetoencephalography; G_PCMI, genuine permutation cross mutual information; fNIRS, functional near-infrared spectroscopy; ABR, auditory brainstem response; MRI, magnetic resonance imagining; REM, rapid eye movement; SWS, slow-wave sleep; N/A, not applicable.

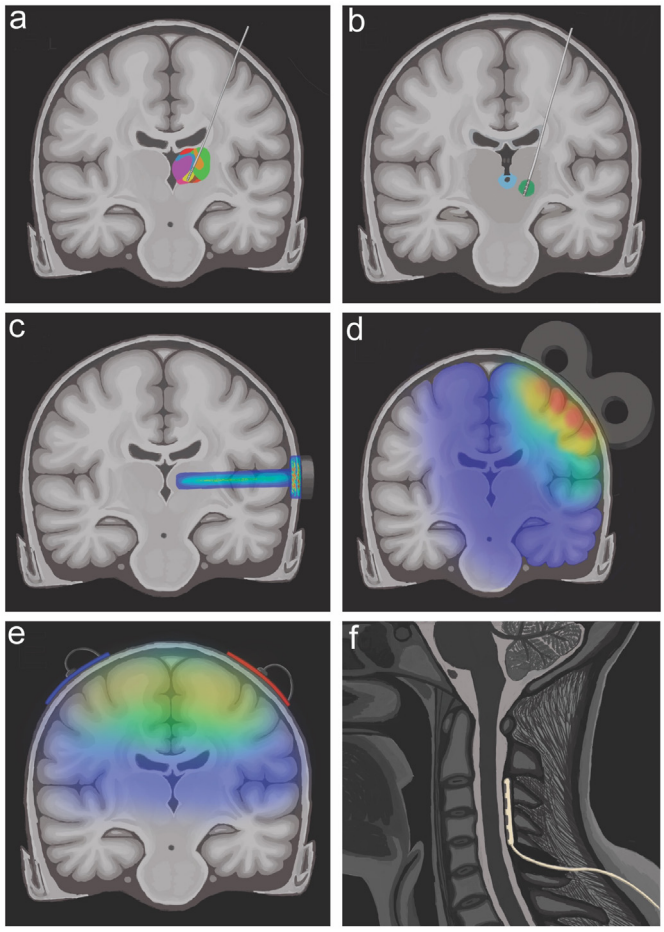

Figure 2. Neuromodulation techniques in human studies. Visual representation of (a) DBS of the centromedian nucleus of the thalamus, (b) DBS of the nucleus cuneiformis, target for the MRF, (c) LIFU of the left thalamus, (d) TMS in the left motor cortex, (e) tDCS in nonspecific frontal areas (anode, red; cathode, blue), and (f) SCS in the cervical spinal region. [Color figure can be viewed at www.neuromodulationjournal.org]

showing improvement from DoC had hepatic encephalopathy following cardiac arrest rather than TBI. Further, Shu et al[40] reported that no patients with brainstem hemorrhage or infarction showed improvement following CM-pf DBS (Fig. 2a), whereas patients with TBI and hemorrhage in other brain regions did. Although reported physiological outcomes were varied among DBS patients, physiological results were generally consistent across studies. For example, Dang et al[39] and Shu et al[40] both noted an increase in functional connectivity in similar brain regions (frontal and parietal regions) using genuine permutation cross mutual information with electroencephalography (EEG) data and functional near-infrared spectroscopy, respectively. Similarly, Tsubokawa et al[27] and Lemaire et al[35] reported an increase in markers of glucose metabolism following DBS. Other results include increases in regional cerebral blood flow, P_{250} amplitude (increased in MRF DBS [Fig. 2b]), and changes in EEG theta and gamma power.[27–29,32]

Similarly, studies implementing SCS all reported increases in coma scale points, with five of the six studies showing some clinical improvements (Table 2; Fig. 2f). Once again, stimulation parameters varied widely, with Zhuang et al[47] and Yamamoto et al[44] even varying stimulation parameters as an experimental variable (between 70 Hz and 5 Hz and between 25 Hz and 5 Hz, respectively) without significant clinical effects. Morita et al[42] and Kanno et al[43] noted "excellent" improvements to commands, speech, and oral ingestion, particularly in patients with TBI rather than patients with anoxia. Yamamoto et al[44] reported that seven patients emerged from a MCS. Of the four SCS studies reporting physiological outcomes, Kanno et al,[43] Yamamoto et al,[44] and Zhang et al[45] reported increases in cerebral blood flow, while Yang et al[46] observed increased functional connectivity between the anterior medial and dorsomedial prefrontal cortex, along with overall increased EEG activity.

Table 3 provides a summary of LIFU studies. Monti et al[48] reported the "first-in-man" LIFU study on a patient with TBI, demonstrating emergence from MCS after ten sonications with an average intensity of 720 mW/cm^2 for 30 seconds on/off aimed at the right thalamus. The LIFU study by Cain et al[49] reported significant increases in overall CRS-R scores one week after treatment (30 seconds on/off alternating for 10 minutes, 100-Hz pulse repetition frequency, squamous temporal bone [Fig. 2c]), along with reduced BOLD (blood oxygen level–dependent) signals (suggesting increased deoxyhemoglobin and a lack of overoxygenation) and variable changes in connectivity between certain brain regions.[50]

The two MNS studies both demonstrated significant increases in Glasgow Coma Scale (GCS) scores after treatment, with Wu et al observing full recoveries in almost three-quarters of their patients.[51,52] However, neither of the MNS studies reported physiological outcomes in addition to clinical outcomes. Cooper et al[51] stimulated the right median nerve at 20 mA with a pulse width of 300 μS at 40 Hz for two weeks, either 8 or 12 hours a day. Wu et al[52] stimulated the right median nerve at 15 to 20 mA with a pulse width of 300 μS at 40 Hz for two weeks, 8 hours a day. Table 4 provides a summary of the human MNS studies.

TMS showed mixed results for efficacy in treating DoC (Table 5; Fig. 2d). Around half of the studies reported some significant improvement in CRS-R scores, whereas the other half did not. Further, as reported by Piccione et al,[53] the effects of single-session TMS are likely transient. However, other studies, such as those of Bai et al,[57] Wu et al,[62] and Zhang et al,[67] noted sustained improvements, often associated with repeated TMS. The most common target for TMS was the unilateral (often left, sometimes right) dorsal prefrontal cortex (which tended to have more significant clinical improvements) and motor cortex areas (which tended to have fewer significant clinical improvements). Legostaeva et al[63] stimulated the angular gyrus and reported significant CRS-R increases in patients with MCS, but not those with UWS. Stimulation parameters varied widely, with length of stimulation ranging from a single session to repeated stimulations over several days.[56]

tDCS demonstrated mixed efficacy in treatment of UWS and MCS (Table 6; Fig. 2e). Thibaut et al[72] and Naro et al,[73] for example, found clinical improvements in patients with MCS, but not those with UWS. Most of the tDCS studies targeted the DLPFC (seven studies), which usually was associated with modest clinical improvements (five studies). Naro et al[73] targeted the middle cerebellum (anode placed half a centimeter below the inion), which led to significant improvements in CRS-R motor subscores, while Huang et al[76] stimulated the posterior parietal cortex, leading to temporary improvements in consciousness. As in TMS, stimulation parameters varied widely, although stimulation usually lasted several weeks with fixed parameters in each study.

Overall, the six therapeutic modalities reviewed in this article all demonstrated modest clinical coma scale score improvements. There was variability in the extent of score increases among studies

Table 2. Summary of Human SCS Studies.

Author, publication year	Sample size (SCS anatomical target)	Etiology — time since injury	Clinical outcomes	Physiological outcomes
Morita et al,[42] 2007	32 patients with UWS (DCS, C2-C4)	TBI (n = 21), hypoxic encephalopathy (n = 8), "cerebrovascular disorder" (n = 3) — not specified	Patients were categorized as "excellent" (reaction to orders, speech, and oral ingestion) or "positive" (changes in facial expressions, pursuit of gaze). Seven patients were labeled as "excellent" and five were labeled as "positive."	N/A
Kanno et al,[43] 2009	214 patients with UWS (DCS, C2-C4)	TBI (n = 106), anoxia (n = 50), "cerebrovascular disease" (n = 45) — each ≥three mo (TBI ≥one y)	Patients were categorized as "excellent" (reaction to orders, speech, and oral ingestion), "positive" (changes in facial expressions, pursuit of gaze), or "unchanged." Thirteen were lost to follow-up, 109 were labeled "excellent" or "positive," and 92 were labeled "unchanged." Stimulation was most successful in patients with TBI and least successful in patients with anoxia.	SPECT imaging showed more increases in rCBF for patients who underwent SCS, with a more consistent increase in rCBF for those with a preoperative rCBF above the mean of all the participants
Yamamoto et al,[44] 2017	31 patients—21 with UWS and 10 with MCS (DCS, C2-C4)	TBI (UWS, n = 4; MCS, n = 6), "cerebrovascular accident" (UWS, n = 13; MCS, n = 3), anoxia (UWS, n = 4), encephalomyelitis (MCS, n = 1) — range 3–51 mo	Eight of 21 patients with UWS showed wave V activity in ABR, 3 of whom emerged from UWS and were able to communicate through speech or "other responses," but remained bedridden. Nine of ten patients with MCS showed wave V activity in ABR, seven of whom emerged from MCS. One of the seven improved to moderate disability, while six required wheelchair assistance at one-y follow-up.	Average increase of 22.2% CBF observed during 5-Hz cervical SCS. During 5-Hz SCS, bilateral upper extremity muscle twitches were observed, while 25-Hz SCS induced bilateral upper extremity contractions.
Zhang et al,[45] 2018	Nine patients—seven with UWS and two with MCS (DCS, C2-C4)	TBI (UWS, n = 3) cerebral hemorrhage (UWS, n = 2), stroke (UWS, n = 1), hypoxic ischemic encephalopathy (UWS, n = 1; MCS, n = 2)—range 3–28 mo	Six of nine patients showed modest increases in CRS-R (ranging 1–3 points), while the remaining three patients were unchanged (UWS: one with TBI, one with cerebral hemorrhage, one with stroke). The highest increase (3 points) occurred in a 17-year-old female with UWS from TBI.	Shorter stimulation intervals (30 s) were shown to increase cerebral blood flow to the prefrontal cortex
Yang et al,[46] 2022	One patient with UWS	TBI—93 d	Increase in CRS-R score from a preoperative score of 7 to a score of 19 at four wk after treatment onset	EEG showed increased brain activity, amplitude, and rhythm. fMRI showed significant changes in functional connectivity in prefrontal cortex regions with a trend toward normal controls.
Zhuang et al,[47] 2022	31 patients—10 with UWS, 15 with MCS-, and 6 with MCS+	TBI (UWS, n = 3; MCS–, n = 6; MCS+, n = 1), stroke (UWS, n = 6; MCS–, n = 7; MCS+, n = 4;), anoxia (UWS, n = 1; MCS–, n = 1; MCS+, n = 1). One patient with MCS– of unspecified etiology — range 3–23 mo.	SCS significantly improved CRS-R scores at two wk after start of treatment and one wk after end of treatment ($p < 0.05$). Diagnostic improvements were observed in 62% of patients with MCS and 20% of patients with UWS. SCS for MCS- had significantly higher effective rates than rates for UWS or MCS+ ($p < 0.05$). No significant difference was observed in CRS-R scores for 5-Hz vs 70-Hz stimulation.	N/A

UWS, unresponsive wakefulness (persistent vegetative state); MCS, minimally conscious state; TBI, traumatic brain injury; CRS-R, JFK Coma Recovery Scale – Revised; DCS, dorsal column stimulation; SPECT, single-photon emission computed tomography; ABR, auditory brainstem response; rCBF, regional cerebral blood flow; fMRI, functional magnetic resonance imagining; N/A, not applicable.

Table 3. Summary of Human LIFU Studies.

Author, publication year	Sample size (LIFU anatomical target)	Etiology—time since injury	Clinical outcomes	Physiological outcomes
Monti et al,[48] 2016	One patient with MCS (GCS 7, right thalamus)	TBI—19 d	An increase in CRS-R score from 13 to 17 the day after sonication was noted. Emergence from MCS occurred.	N/A
Cain et al,[49] 2022	11 patients—5 with UWS, 1 with MCS–, 5 with MCS+ (central thalamus)	One glioma/stroke, ten TBI—each <six wk	LIFU showed a significant increase in maximal responsiveness based on CRS-R_{index} scores and total raw CRS-R scores at one wk after treatment. Changes in CRS-R scores immediately before and after LIFU were nonsignificant.	MRI showed significantly reduced BOLD signals in subcallosal and medial prefrontal cortex, anterior cingulate, and stratum after LIFU (ipsilateral to sonification). During LIFU, the thalamus increased connectivity with the central gyrus while decreasing connectivity with the ipsilateral frontal polar cortex.

GCS, Glasgow Coma Scale; UWS, unresponsive wakefulness (persistent vegetative state); MCS, minimally conscious state; TBI, traumatic brain injury; CRS-R, JFK Coma Recovery Scale – Revised; BOLD, blood oxygen level–dependent; N/A, not applicable; MRI, magnetic resonance imaging.

Table 4. Summary of Human MNS Studies.

Author, publication year	Right MNS sample size	Etiology—time since injury	Clinical outcomes	Physiological outcomes
Cooper et al,[51] 1999	Three patients with MCS (plus three controls)	TBI — each <one wk from admission	Three patients experienced an average improvement of 4.0 on GCS and average ICU stay of 7.7 d. Three controls experienced an average improvement of 0.7 on GCS and average ICU stay of 17.0 d.	N/A
Wu et al,[52] 2023	167 patients with "acute coma" (GCS 4–8) (plus 162 controls)	TBI from "road traffic incidence" (n = 101), "fallen injury" (n = 36), "violence" (n = 8), "others" (n = 22) — each 7–14 d	121 out of 167 patients with MNS and 92 out of 162 controls regained consciousness within six mo after TBI. MNS was associated with a higher conscious rate at six mo after injury. Glasgow Outcome Scale Extended scores were significantly higher in patients with MNS patients at three and six mo after TBI. Full Outline of Unresponsiveness scale scores were significantly higher in MNS patients at 28 d after injury.	N/A

MNS, median nerve stimulation; MCS, minimally conscious state; GCS, Glasgow Coma Scale; ICU, intensive care unit; TBI, traumatic brain injury; N/A, not applicable.

Table 5. Summary of Human TMS Studies.

Author, publication year	Sample size (TMS anatomical target)	Etiology—time since injury	Clinical outcomes	Physiological outcomes
Piccione et al,[53] 2011	One patient with MCS (primary motor cortex)	Right thalamic hemorrhage — >four y	CRS-R increased from 13 to 19 immediately following TMS; however, 7 h after stimulation, CRS-R reverted to 14	EEG pattern showed significant changes immediately after TMS: enhancement of alpha band activity, significant global increase in activation of delta band, and a more diffuse activation of the beta band. Similar patterns were observable for 6 h after TMS.
Manganotti et al,[54] 2013	Six patients—three with MCS and three with UWS (primary motor cortex)	TBI (UWS, $n = 1$; MCS, $n = 2$), hemorrhagic (UWS, $n = 2$; MCS, $n = 1$) — each >12 mo	An increase in CRS-R score from 10 to 18 was observed in one patient with MCS (hemorrhagic), which lasted for 6 h after stimulation. No other patients had clinically significant findings.	Immediately after TMS, the motor threshold significantly decreased and motor evoked potential significantly increased for all patients. In the patient with positive outcome, increases in all EEG rhythms, power increase in alpha and beta band, and increases in signal amplitude that were maintained for 38 min were noted.
Cincotta et al,[55] 2015	11 patients with UWS (primary motor cortex—sham-controlled crossover, 6 in phase 1; 5 in phase 2)	TBI ($n = 2$), anoxia ($n = 9$)—range 9–85 mo	No significant differences were found in CRS-R scores or subscores after 20-Hz rTMS. No significant differences were found in CGI-I scores.	No significant differences in the semiquantitative EEG parameters evaluated by the Synek scale and an ad hoc semiquantitative scale
Naro et al,[56] 2015	Ten patients with UWS (motor areas — sham-controlled for patients with UWS with higher CRS-R scores, ten healthy controls)	Acute myocardial infarction ($n = 5$), ventricular fibrillation ($n = 5$) — range 4–15 mo	Three patients experienced a transient, nonsignificant increase in CRS-R scores	Three patients showed a transient modulation of EEG motor evoked potential, short intracortical inhibition, and intracortical facilitation
Bai et al,[57] 2016	One patient with MCS (DLPFC)	Hypertensive cerebral hemorrhage (right basal ganglia)—nine mo	Increases in CRS-R score were observed from an initial score of 8 to a score of 13 after 20 d of rTMS	EEG TMS-evoked potentials showed increases in activated channels. The perturbational complexity index increased immediately after rTMS. Global Mean Field Power was uncorrelated with healthy controls until immediately after 20 d of rTMS treatment.
Xia et al,[58] 2017	16 patients—5 with MCS and 11 with UWS (DLPFC)	TBI (UWS, $n = 1$; MCS, $n = 1$), anoxia (UWS, $n = 4$; MCS, $n = 1$), intracranial hemorrhage (UWS, $n = 5$; MCS, $n = 3$), cerebral infarction (UWS, $n = 1$). All patients on at least amantadine — each ≥three mo.	Significant increases in CRS-R scores were observed in all 5 patients with MCS and 4 of the 11 patients with UWS ($p < 0.007$). Strong correlation was found between CGI-I and CRS-R scores (0.9191 Spearman's r value).	N/A
Xia et al,[59] 2017	18 patients—7 with MCS and 11 with UWS (DLPFC)	TBI (UWS, $n = 3$; MCS, $n = 1$), anoxia (UWS, $n = 4$; MCS, $n = 2$), intracranial hemorrhage (UWS, $n = 3$; MCS, $n = 3$), ischemic stroke (UWS, $n = 1$) — each ≥three mo	No significant change in CRS-R scores between patients following 1 d of rTMS or 20 d of rTMS	After 20 d of rTMS, patients with MCS experienced a significant decrease in delta EEG band and significantly increased beta band of the frontal and central regions. Patients with UWS experienced a significant delta band decrease in frontal and left hemisphere brain activity.
He et al,[60] 2018	Six patients—three with MCS and three with UWS (primary motor cortex—sham-controlled crossover, three in phase 1; three in phase 2)	TBI (UWS, $n = 2$; MCS, $n = 2$), hemorrhage (UWS, $n = 1$), "hypoxic-ischemic" (MCS, $n = 1$) — range 1–28 mo	No significant differences were observed in CRS-R scores following rTMS treatment. However, one patient with MCS showed an improvement in motor score.	No patients exhibited significant changes in EEG findings following rTMS except for the patient with improved motor function. This patient experienced good EEG reactivity in response to rTMS with a more significant increase in alpha and beta power than other channels.

(Continues)

Table 5. *Continued*

Author, publication year	Sample size (TMS anatomical target)	Etiology—time since injury	Clinical outcomes	Physiological outcomes
Liu et al,[61] 2018	Seven patients with DoC (unspecified MCS or UWS, primary motor cortex—randomized sham-controlled, plus 11 healthy controls)	TBI (n = 5), hemorrhage (n = 1), anoxia (n = 1) — range, one to six mo	No significant changes in CRS-R scores or brain FC following real or sham rTMS stimuli in the patients with DoC	Functional connectivity, measured by fMRI, was not significantly enhanced in the patients with DoC following rTMS. However, before stimulation, it was noted that patients with DoC had significantly altered functional connectivity compared with controls ($p < 0.001$) (eg, increased connectivity between the node of the right lateral prefrontal cortex and left precentral/postcentral gyrus)
Wu et al,[62] 2018	Eight patients—four with MCS and four with UWS (theta burst stimulation, DLPFC)	Unspecified	The CRS-R scores were increased in all four patients with MCS and three patients with UWS immediately after treatment. CRS-R scores at one wk after treatment remained higher than pretreatment levels.	Spontaneous changes in EEG (eg, increased alpha band power) were associated with behavioral changes immediately after and one wk after treatment, relative to baseline
Legostaeva et al,[63] 2019	38 patients—22 with MCS and 16 with UWS (angular gyrus)	TBI (UWS, n = 1; MCS, n = 11), anoxia (UWS, n = 15; MCS, n = 11) — each ≥three mo (TBI ≥one y)	CRS-R total scores significantly increased (p = 0.0001) after stimulation in the MCS subgroup (improvements observed in 19/22 patients with MCS). The greatest improvements were observed in the visual, auditory, and verbal scores. In the UWS subgroup, no significant differences were found.	N/A
Bender Pape et al,[64] 2020	Four patients—one with MCS and three with UWS (DLPFC)	TBI (n = 4) — range 1–15 y	Increases in Disorders of Consciousness Scale-25 and auditory-language change occurred most prominently in patients who had TMS treatment for four wk followed by TMS and amantadine treatment for four wk	Resting state functional connectivity (by blood oxygen level–dependent time series data) was increased in the language network for a patient with neurobehavioral gains, while default mode network irregularities were noted in all patients
Jang and Kwon,[65] 2020	One patient with UWS (DLPFC)	"Subarachnoid and intracerebral hemorrhages in the left fronto-parieto-temporal lobes" — multiple administrations at five and nine mo after injury	CRS-R score improved from 4 to 13, two mo after therapy, with the greatest subscore increases in visual and motor functions	Diffusion tensor tractography showed increases in tract volume of the right prefrontal lobe in the upper ascending reticular activating system, two mo after therapy
Ge et al,[66] 2021	15 patients with UWS (plus 17 UWS controls— DLPFC)	TBI (n = 8), intracerebral hemorrhage (n = 7) — each ≥two wk	All patients remained in a stable clinical state during routine medication and rehabilitation course. A significant increase in the CRS-R scores in the rTMS group was observed 20 d later. The median CRS-R score change in the rTMS group improved by 3 points, whereas the control group improved by 1 point.	N/A
Zhang et al,[67] 2021	24 patients with UWS (plus 24 UWS controls— DLPFC)	Unspecified — each ≥three mo	CRS-R scores underwent higher increases in the treatment group than in the control group before treatment (+0.04), 30 d after treatment (+1.54), and 60 d after treatment (+2.09)	The latency periods of each wave of the brainstem auditory evoked potentials in the treatment group were shorter than those in the control group after 30 and 60 d of treatment. EEG grading indices were lower for the treatment group compared with controls.

(Continues)

Table 5. *Continued*

Author, publication year	Sample size (TMS anatomical target)	Etiology—time since injury	Clinical outcomes	Physiological outcomes
Chen et al,[68] 2022	50 patients with unspecified DoC (DLPFC — randomized sham-controlled crossover)	TBI (n = 21), stroke (n = 19), anoxia (n = 10) — range, one to three mo	Significant improvements in CRS-R (p = 0.002) and GCS scores (p = 0.0018) occurred in both sham and treatment groups, although changes were significantly greater in the treatment group (CRS-R, p = 0.001 and GCS, p = 0.014)	Increases in somatosensory evoked potentials (N20-P25 amplitude, p = 0.011) were reported. Brainstem auditory evoked potentials normalized in both groups (p = 0.013), with greater effects in the treatment group.
Fan et al,[69] 2022	20 patients with unspecified DoC (DLPFC — plus 20 controls; randomized sham-controlled)	TBI (n = 6), stroke (n = 14) — μ = 54.15 ± 25.28 d	Significant improvements in CRS-R (p = 0.035) were associated with the active TMS group compared with the sham TMS group. No significant difference in awakening ratio or hospital stay was found.	N/A
Shen et al,[70] 2023	66 patients with UWS (33 primary motor cortex, 33 DLPFC — plus 33 controls; randomized sham-controlled)	TBI (n = 66) — range, one to three mo	Significant improvements in GCS ($p < 0.05$) and CRS-R ($p < 0.05$) occurred in all three groups after four wk of treatment (or sham treatment), but primary motor cortex patients experienced significantly higher improvements than both DLPFC and controls ($p < 0.05$)	Significant decreases in EEG reactivity and somatosensory evoked potentials index (level 1 = normal central conduction time) were found in the primary motor cortex and DLPFC groups ($p < 0.05$) but were significantly more pronounced in the primary motor cortex group ($p < 0.05$)

DLPFC, dorsolateral prefrontal cortex; UWS, unresponsive wakefulness (persistent vegetative state); MCS, minimally conscious state; TBI, traumatic brain injury; CRS-R, JFK Coma Recovery Scale - Revised; CGI-I, Clinical Global Impressions — Global Improvement scale; GCS, Glasgow Coma Scale; FC, functional connectivity; N/A, not applicable.

Table 6. Summary of Human tDCS Studies.

Author, publication year	Sample size (tDCS anatomical target)	Etiology—time since injury	Clinical outcomes	Physiological outcomes
Angelakis et al,[71] 2014	Ten patients—three with MCS and seven with UWS (primary sensorimotor cortex or DLPFC — sham for one wk followed by real stimulation for two wk)	TBI (UWS, *n* = 3; MCS, *n* = 2), anoxia (UWS, *n* = 4), "postoperative infarct" (MCS, *n* = 1) — range, six mo to ten y	All patients in an MCS showed clinical improvement immediately after treatment (within one wk after stimulation), according to CRS-R scores. One patient with UWS (TBI) changed status to MCS 12 mo after treatment.	N/A
Thibaut et al,[72] 2014	55 patients—30 with MCS and 25 with UWS (DLPFC — randomized sham-controlled crossover)	TBI (UWS, *n* = 6; MCS, *n* = 19), anoxia (UWS, *n* = 9; MCS, *n* = 4), subarachnoid hemorrhage (UWS, *n* = 4; MCS, *n* = 3), "cerebrovascular accident" (UWS, *n* = 5; MCS, *n* = 3), "mixed traumatic/anoxic" (UWS, *n* = 1; MCS, *n* = 1) — range, 7 d to 26 y	Thirteen patients in MCS showed a significant treatment effect as measured by CRS-R total scores. In patients with UWS, no treatment effect was observed.	N/A
Naro et al,[73] 2016	20 patients—10 with MCS and 10 with UWS (otDCS medial cerebellum — randomized sham-controlled crossover)	TBI (UWS, *n* = 6; MCS, *n* = 7), anoxia (UWS, *n* = 4; MCS = 3) — MCS: μ = 42 y; UWS: μ = 26 y	CRS-R scores showed improvement in MCS, significantly so in motor scores. Clinical improvements were not noted in patients with UWS.	Increased theta and gamma band functional connectivity was detected within fronto-parietal networks in patients with MCS
Bai et al,[74] 2017	16 patients—7 with MCS and 9 with UWS (DLPFC — sham-controlled crossover)	TBI (UWS, *n* = 2; MCS, *n* = 2), anoxia (UWS, *n* = 4; MCS, *n* = 3), hemorrhage (UWS, *n* = 2; MCS, *n* = 2), ischemic stroke (UWS, *n* = 1) — range 6–30 mo	N/A—patients received TMS-EEG immediately after tDCS	Patients with MCS and UWS had varied cortical excitability responses to TMS-EEG following tDCS. Patients with MCS experienced longer increases in global cortical excitability.
Estraneo et al,[75] 2017	13 patients—6 with MCS and 7 with UWS (DLPFC — randomized sham-controlled crossover)	TBI (UWS, *n* = 1), anoxia (UWS, *n* = 4; MCS, *n* = 2), vascular (UWS, *n* = 2; MCS, *n* = 4) — each ≥three mo	Five patients (three with MCS and two with UWS) demonstrated increases in CRS-R scores	EEG changes in background activity were only noted in patients with clinical improvement
Huang et al,[76] 2017	33 patients with MCS (posterior parietal cortex — randomized sham-controlled crossover)	TBI (*n* = 20), remaining unspecified — μ = six mo	A significant improvement in consciousness was measured by average CRS-R on the fifth day of tDCS ($p = 0.012$); however, these were diminished after the tenth day	N/A
Thibaut et al,[77] 2017	16 patients with MCS (prefrontal cortex — randomized sham-controlled crossover)	TBI (*n* = 11), "non-traumatic" (*n* = 5) — range 5–365 mo	Significant CRS-R improvements at day 5 ($p = 0.013$) and one wk ($p = 0.002$) after last stimulation were found. Nine patients were labeled "responders," meaning that they demonstrated a new sign of consciousness (eg, response to command, recognition of objects, etc).	N/A
Bai et al,[78] 2018	17 patients—8 with MCS and 9 with UWS (DLPFC — sham-controlled crossover)	TBI (UWS, *n* = 3; MCS, *n* = 4), anoxia (UWS, *n* = 4; MCS, *n* = 1), hemorrhage (UWS, *n* = 2; MCS, *n* = 3) — range 6–35 mo	No significant effect of tDCS was found on CRS-R scores	Functional connectivity, measured by EEG coherence, showed increased coherence in theta and gamma bands in the MCS group only
Martens et al,[79] 2018	22 patients with MCS (DLPFC — randomized sham-controlled crossover)	TBI (*n* = 10), cardiac arrest (*n* = 8), aneurysm (*n* = 3), anoxia (*n* = 1) — range 10–401 mo	Home-based tDCS induced a significant clinical improvement in consciousness at four wk compared with after each sham phase ($p = 0.043$). No correlation was found between etiology and clinical outcome.	N/A

(Continues)

Table 6. *Continued*

Author, publication year	Sample size (tDCS anatomical target)	Etiology—time since injury	Clinical outcomes	Physiological outcomes
Wu et al,[80] 2019	Ten patients (left DLPFC, three with MCS and two with UWS; right DLPFC, one with MCS and four with UWS) plus five controls (three MCS and two UWS) — randomized sham-controlled	TBI (n = 3), hemorrhage (n = 7) — controls TBI (n = 2), anoxia (n = 3) — range 42–631 mo	No significant CRS-R changes occurred in any of the three groups, either compared with baseline or with one another	Left DLPFC stimulation increased functional connectivity by EEG within and between the left frontal lobe and other cortical regions ($p < 0.05$). Right DLPFC stimulation increased connectivity only within the right frontal lobe ($p < 0.05$).
Carrière et al,[81] 2020	11 patients with MCS (DLPFC — randomized sham-controlled crossover)	TBI (n = 3), cardiac arrest (n = 3), aneurysm (n = 4), meningitis (n = 1) — range 3–25 mo	No significant CRS-R changes occurred at the group level. Three DLPFC patients and 1 sham patient showed some behavioral improvement.	Higher EEG power in alpha band (central regions) and theta band (frontal and posterior regions) were found. Higher weighted symbolic mutual information connectivity was found between left and right parietal regions.
Martens et al,[82] 2020	46 patients—23 with MCS, 17 with UWS, and 6 who emerged from MCS (DLPFC — randomized sham-controlled crossover)	TBI (n = 46) — median = 12 mo (range 5–47 mo)	No significant CRS-R changes occurred at the group level. Five patients had behavioral improvement only after real tDCS, contrasted with three patients with behavioral improvements only after sham tDCS.	After real tDCS, EEG complexity significantly increased in theta bands (p = 0.035) and delta bands (p = 0.002).
Zhang et al,[83] 2021	55 patients—26 with MCS and 29 with UWS (prefrontal area, left FTPC, right FTPC, DLPFC each for two wk) plus 50 historical controls (22 MCS and 28 UWS)	TBI (n = 27), hemorrhage (n = 28) — controls TBI (n = 19), hemorrhage (n = 31) — range, two to ten mo	CRS-R increased significantly in both treatment and control groups after eight wk ($p < 0.01$), but increases were significant in the tDCS group ($p < 0.05$). mGOS scores were significantly increased in the tDCS group ($p < 0.05$).	The tDCS group showed higher connectivity (via EEG) between central and frontal regions under painful stimulus compared with the control group ($p < 0.05$), which was associated with mGOS improvements
Barra et al,[84] 2022	12 patients—10 with MCS and 2 who emerged from MCS (left prefrontal tDCS and mastoid tPCS: randomized sham-controlled crossover)	TBI (n = 4), anoxia (n = 1), stroke (n = 7) — 8.8 ± 10.5 mo	No significant CRS-R changes occurred in any of the groups. tPCS and tDCS were both well-tolerated.	Significant differences in theta frontal functional connectivity by EEG activity were found between tDCS and [tPCS + sham] groups (p = 0.04)
Thibaut et al,[85] 2023	33 patients—17 with MCS and 16 with UWS (left prefrontal cortex) plus 29 controls (15 MCS and 14 UWS) — randomized sham-controlled	TBI (n = 13), "Non-TBI" (n = 20) — controls TBI (n = 10), "Non-TBI" (n = 19) — μ = 41 ± 23.5 wk (controls μ = 30 ± 15 wk)	Trial stopped for futility. Subgroup analysis at three mo showed significant improvement in patients with MCS with TBI etiology (p = 0.01).	N/A

otDCS, oscillatory transcranial direct-current stimulation; DLPFC, dorsolateral prefrontal cortex; UWS, unresponsive wakefulness (persistent vegetative state); MCS, minimally conscious state; TBI, traumatic brain injury; CRS-R, JFK Coma Recovery Scale - Revised; FTPC, fronto-temporo-parietal cortices; mGOS, Modified Glasgow Outcome Scale; tPCS, transcranial pulsed-current stimulation; N/A, not applicable.

of the same treatment and in the physiological outcomes measured. Furthermore, there were some common motifs across the articles, such as changes in cerebral blood flow, functional connectivity, and EEG patterns.

Neuromodulation Targets for DoC in Animals

Eleven animal studies were reviewed (Table 7), with nine studies focusing primarily on DBS, one using LIFU, and one using TMS. Within the DBS studies, nonhuman primates and rodents were stimulated in brain regions including the central lateral thalamus (CL), CM, pontine reticular nucleus, CM-pf, hippocampal CA1, lateral hypothalamic area, and secondary motor area. DBS elicited changes in physiological biomarkers of arousal across most studies (eg, arousal via EEG, awakening, neuronal activity). Redinbaugh et al[87] noted decreased arousal levels with both low (10-Hz) and high (200-Hz) frequencies of stimulation in the CL as measured with EEG. This observation highlights the complex effect of DBS on arousal depending on the frequency applied, emphasizing the need for a standardized DBS protocol for DoC. Of note, DBS procedures varied greatly among the animal studies. Some studies used clinical-grade DBS electrodes (particularly for nonhuman primates), with wide variations in stimulation patterns. For example, Quinkert and Pfaff used a random number generator to determine temporal patterns for stimulation in mice.[88,89]

Bian et al[95] studied the use of LIFU for DoC in mice. In this study, stimulation of the ventral tegmental area (40 minutes, 586 kPa) yielded arousal from isoflurane anesthesia–induced unconsciousness. An increase in c-Fos expression (immediate early gene expressed in neurons upon activation) was observed in the periaqueductal gray matter and locus coeruleus, and the administration of D1 antagonists significantly prolonged time to emergence from anesthesia in mice receiving ultrasound, reversing the effect of the stimulation.[95]

TMS was trialed in 34 adult male Wistar rats by Keck et al.[96] The authors reported an increase in mesolimbic and mesostriatal dopamine levels in urethane-anesthetized rats after repetitive TMS in the right dorsal hippocampus, right nucleus accumbens septi, and right dorsal striatum (although they did not report a correlation with emergence from coma).

Quality and Certainty Assessment

Overall, there was moderate to high risk of bias among the studies included in the present review. Most of the included studies were retrospective, rather than prospective, and reported on small cohorts of patients without controls or crossover phases (with exceptions, particularly in TMS and tDCS studies, which possessed relatively lower risk of bias).[39,86,91,93,95] In general, studies evaluating interventions for DoC face challenges in evaluating causal efficacy in changes to symptoms given the spontaneity of clinical and physiological changes observed in patients, including full recovery. Similarly, only moderate certainty was assessed owing to moderate risk of bias, relative imprecision (considering low sample sizes and lack of sham-controlled designs, especially in DBS and SCS studies), and the presumed publication bias typical for systematic reviews of this kind.[25] Wherever possible, randomization was achieved in studies (along with sham-controlled crossover designs in TMS and tDCS studies), but given the limited number of participants, the extent to which severity of disease, age, and other demographic characteristics are controlled for in studies with controls is notably limited. While age, gender, and disease severity were reported in studies before stimulation, it is still difficult to control for these factors, even in sham-controlled experiments, which constitutes another limitation for certainty. Further, stimulation parameters across modalities were generally varied, highlighting the need for unified guidelines concerning neuromodulation for DoC.

DISCUSSION

DoC: Pathophysiology and Neuromodulation

TBIs, strokes, and other cerebral insults can produce lesions that result in DoC, including coma, UWS, and MCS. While coma consists of both a lack of wakefulness and awareness, in which eyes are closed and no purposeful responses can be elicited, wakefulness and awareness can be dissociated in cases where wakefulness is spared while awareness is impaired, such as in MCS and UWS (vegetative states). Consciousness involves the intricate interplay of multiple brain areas and neurotransmitter systems, including the thalamus, cerebral cortex, amygdala, brainstem, and hippocampus.[97] While wakefulness appears to be primarily dependent on the integrity of the brainstem reticular activating system, awareness may be disrupted by lesions that compromise cortico-thalamic connectivity,[98] such as widespread bilateral cortical lesions or bilateral thalamic lesions. Indeed, the importance of connectivity between the thalamus and the cerebral cortex for awareness is highlighted by the tendency of diffuse axonal injury and thalamic damage to produce vegetative states (UWS).[99]

Ascending afferents from nuclei comprising the ascending reticular activating system (also referred to as the MRF) play a key role in facilitating wakefulness.[100] The ascending reticular activating system comprises multiple nuclei residing in the upper brainstem and midbrain tegmentum, including glutamatergic neurons of the reticular formation, cholinergic neurons of the pedunculotegmental nucleus, and cholinergic neurons of the laterodorsal tegmental nucleus. These neurons project to brain structures involved in arousal and consciousness, particularly the intralaminar thalamic nuclei, which in turn modulate cortical arousal.[101] A lesion analysis found that structural injuries within a small region of the rostral dorsolateral pontine tegmentum were significantly more often associated with coma compared with other brainstem lesions, underscoring the role of the pontine tegmentum in DoC.[102] The midline thalamic nuclei and rostral intralaminar nuclei are believed to be particularly important for cortical arousal, which is why they are often selected as targets for neuromodulation to treat DoC. Brainstem-thalamic connectivity in the ascending arousal network has been shown to increase in recovery from DoC, whereas persistent thalamic-temporal lobe disruption is present in patients who do not recover from DoC.[103]

Within the spectrum of available treatments for DoC, neuromodulation has emerged as a distinctive innovative therapeutic modality in the past few decades.[104] These therapeutic approaches use various techniques, including electrical or mechanical stimulation, to modulate brain activity. Neuromodulation can be achieved through either a noninvasive approach (eg, LIFU, TMS, tDCS) or a more invasive approach that directly targets specific pathways in the nervous system (eg, DBS, SCS, MNS). Given the relatively recent implementation of neuromodulation for a wider range of clinical disorders, including major depression and pain, neuromodulation has the potential to produce promising outcomes for treating DoC.[16,105,106] Especially considering that pharmacologic interventions have limited success in treating DoC, neuromodulation might offer better success by directly targeting the pathways involved in arousal and awareness.[107]

Table 7. Summary of Animal Studies Identified.

Procedure	Animal	Author, publication year	Sample size (anatomical target)	Outcomes
DBS	Macaques	Tasserie et al,[86] 2022	2 (right CM, plus 3 controls, ventrolateral thalamus)	DBS restored arousal from anesthesia-induced consciousness loss in both animals, supported by characteristic fMRI and EEG findings relative to controls.
		Redinbaugh et al,[87] 2022	2 (CL)	Thalamic DBS at 10 Hz and 200 Hz induced "perturbed" consciousness in anesthetized macaques, which was accompanied by a substantial increase in lower-frequency EEG and decreased consciousness.
	"Non-human primate"	Baker et al,[88] 2023	1 (right CL)	Real-time changes in ECoG of the cortex and thalamus were detected. Arousal from inattentive drowsiness was induced using episodic CT-DBS in a healthy control, associated with increased theta- and alpha-band power.
	C57BL/6J mice	Quinkert and Pfaff,[89] 2012	26 (bilateral-CT)	CT-DBS increased generalized arousal measured by EEG response and motor activity. A random number generator was used in an experimental group to vary temporal patterning of stimulation, but did not result in significant changes to EEG. However, exposure to daylight appears to increase EEG response to CT-DBS.
	Sprague Dawley rats	Pillay et al,[90] 2014	9 (PnO)	In isoflurane-anesthetized rats, PnO-DBS induced significantly reduced delta- and theta-band power and an increase in functional connectivity in the left nucleus basalis of Meynert and several paralimbic networks. No behavioral responses were observed.
	Wistar rats	Fernández-Cabrera et al,[91] 2017	7 (CM-pf, plus 6 control primary auditory and primary motor cortices)	PFn-DBS decreased NMDAR GluN1 gene expression in the prelimbic and nucleus cingulate cortices, suggesting that PFn-DBS modulates excitatory glutamate signaling in these regions.
	Sprague Dawley rats	Feng et al,[92] 2019	20 (hippocampal CA1)	In anesthetized rats, high-frequency ranges of 100 to 200 Hz of random inter-pulse-intervals (IPI) induced synchronized neuronal activity in the CA1 hippocampus, whereas constant IPI stimulation did not induce this activity.
	Sprague Dawley rats	Dong et al,[93] 2021	33 (LHA-DBS, plus 22 controls [sham DBS, no output], 11 with TBI)	Twenty-five (of 33) rats awakened from TBI, as opposed to 5 (of 11) TBI controls. Upregulation of alpha-1-adrenoceptor and orexin-receptor-1 with down-regulation of GABA-beta-receptor expression was observed in stimulated vs TBI control groups.
	C57BL/6J mice	Claar et al,[94] 2023	37 (10 MOs layer 2/3, 11 MOs layer 5/6, 8 SSp layer 2/3, 11 SSp layer 5/6)—10 received stimulation in multiple targets	On average, more neurons responded to deep-layer than to superficial stimulation, and more neurons outside of the stimulated cortical area will be modulated during deep-layer stimulation. Stimulation of deep layers evoked two event-related excitatory potentials during the awake period. Both anesthetized and wakeful mice were studied.

(Continues)

Table 7. *Continued*

Procedure	Animal	Author, publication year	Sample size (anatomical target)	Outcomes
Ultrasound	C57BL/6J mice	Bian et al,[95] 2021	6 (VTA plus 6 controls)	Ultrasound of VTA led faster arousal from isoflurane anesthesia, higher c-Fos expression, and decreased sensitivity to anesthesia compared with controls; the effect of VTA ultrasound was blocked by administering D1 antagonists.
TMS	Wistar rats	Keck et al,[96] 2002	34 (13 right dorsal hippocampus, 15 right nucleus accumbens septi, 6 right dorsal striatum plus 33 controls)	Acute rTMS of 20 Hz of the right dorsal hippocampus, right nucleus accumbens septi, and right dorsal striatum led to a significant rise in mesolimbic and mesostriatal dopamine levels in urethane-anesthetized rats.

CM, central medial thalamus; CL, central lateral thalamus; PnO, pontine reticular nucleus; CM-pf, centromedian-parafascicular thalamus; PFn, parafascicular nucleus; LHA, lateral hypothalamic area; MOs, secondary motor area; SSp, primary somatosensory area; VTA, ventral tegmental area; NMDAR GluN1, NMDA receptor subunit GluN1; EcoG, electrocorticography; N/A, not applicable.

Neuromodulation: Targets and Rationale

Deep Brain Stimulation

DBS delivers controlled electrical stimuli to specific brain regions, such as the CM-pf or MRF, key brainstem and thalamic nuclei that function in regulating consciousness. The CM-pf is the largest of the truncothalamic nuclei, thought to be involved in pain signaling, sensorimotor coordination, and consciousness.[108] Its connection to the reticular activating system may explain its efficacy in promoting arousal with DBS.[109] For example, Shu et al[40] demonstrated increased functional connectivity between frontal, parietal, and occipital areas, which was associated with increases in CRS-R scores after CM-pf DBS. Clinically, Yamamoto et al,[29] Chudy et al,[34] and Raguž et al[37] reported patients' emergence from MCS (and in some cases UWS) after CM-pf DBS, which represents a higher incidence of emergence from DoC compared with any other target. The MRF is known for its role in integrating many vital neural systems for survival, with its extensive connections to other neuroanatomical regions involved in arousal, making it an interesting target for DBS for DoC.[110] As Tsubokawa et al[27] observed, increases in functional connectivity with the MRF may play a role in ameliorating DoC pathophysiology, potentially promoting arousal, cerebral blood flow, cerebral oxygen metabolism, and cerebral glucose metabolism.

The studies reviewed on DBS for DoC suggested varied clinical outcomes and physiological responses. Noteworthy findings included improvements in neural response patterns, increased cerebral blood flow, and increased metabolic rates during stimulation. Significant enhancements in arousal, limb control, and oral feeding were observed in some cases. While some studies reported full recovery or emergence from DoC (in greater proportion from MCS than from UWS), most did not. This variability of outcomes illustrates the lack of standardized protocols among studies, the heterogeneous patient populations (eg, underlying pathology, age, sex), and the small sample sizes, both of which generate difficulty in drawing definitive conclusions about the efficacy of DBS for DoC. Additionally, the frequency of delivered stimulation may impact the efficacy of DBS for DoC. For example, high-frequency stimulation, such as that used for treatment of movement disorders, is known to produce clinical effects similar to those of creating a lesion (thalamotomy, pallidotomy). Conversely, DBS for pain produces analgesia using lower-frequency stimulation. Depending on the characteristics and location of the lesion causing DoC, the frequency of stimulation might be considered in future investigations.

Spinal Cord Stimulation

Typically used for back pain, SCS has also shown some potential in treating DoC.[111] SCS uses a surgically implanted electrode in the epidural space to stimulate the dorsal columns, but may also have an effect on the ascending reticular activating system. Studies have shown that SCS leads to increased cerebral blood flow and a change in cerebrospinal fluid neurotransmitter concentration; however, the exact mechanism by which this may help DoC has yet to be elucidated. The systematic review yielded a limited number of studies on SCS. Zhang et al[45] reported modest increases in CRS-R scores for six out of nine patients, accompanied by enhanced cerebral blood flow with shorter stimulation intervals. Yang et al[46] documented a substantial increase in CRS-R scores and improved brain activity, amplitude, and functional connectivity in a patient with UWS. Zhuang et al[47] found that SCS significantly improved CRS-R scores in a diverse patient sample, with diagnostic improvements more prominent among patients with MCS than

those with UWS. The efficacy of different stimulation frequencies remains an area of investigation. Overall, SCS demonstrates some limited potential in modulating consciousness-related outcomes.

Low-Intensity Focused Ultrasound

LIFU, a relatively novel technique, uses acoustic waves to alter brain activity. Functional ultrasound, or the therapeutic use of ultrasound, uses lower intensity than the ultrasound used for ablative lesioning.[112] LIFU excites or suppresses neuronal activity in the targeted areas, with neuromodulation effects that could help in DoC. The exact mechanism remains unknown (ultrasound produces mechanical effects, but it is unclear how neuronal function is impacted), with hypotheses involving thermal modulation and changes in membrane permeability.[11] Despite this uncertainty, studies have explored its effects on consciousness-related regions. Cain et al[49] studied LIFU in humans, and their results revealed a significant increase in behavioral responsiveness after LIFU relative to the patients' initial functioning levels. While immediate changes in neurobehavioral responsiveness were not observed, the study emphasizes the potential time-dependent nature of recovery following thalamic LIFU. Bian et al[95] used LIFU to arouse mice from anesthesia more quickly than controls. This effect was blocked by the administration of D1 antagonists, which the authors interpreted to suggest that dopamine D1 signaling promotes arousal from anesthesia. These few results indicate an immense complexity to the effect of ultrasound on DoC, emphasizing the need for future standardized, controlled studies to evaluate its effectiveness.

Median Nerve Stimulation

The mechanism of MNS with respect to DoC is poorly understood, but some authors have suggested that peripheral-to-central dopamine signaling in the consciousness network may be involved.[113,114] It is important to acknowledge that the rationale for MNS originates from early acupunctural attempts in traditional/alternative medicine.[13]

Cooper et al[51] reported significant recovery from coma following MNS in three young decerebrated comatose patients who experienced TBI compared with controls. Wu et al[52] reported accelerated improvement in consciousness and GCS, CRS-R, and Disability Rating Scale scores in over 100 patients with traumatic coma who received MNS. However, the lack of inclusion of any physiological data limits further understanding of the mechanism of MNS for DoC.

Transcranial Magnetic Stimulation

TMS is thought to affect the brain by evoking transient currents in neural tissue.[15] The DLPFC, which was stimulated by approximately half of the TMS studies in this review (and most of the tDCS studies), is thought to play a role in working memory, decision-making, and executive control.[115,116] Of note, the mesocircuit hypothesis of recovery after brain injury, introduced by Schiff[117], offers possible insight into the role of the DLPFC in recovery from DoC. The hypothesis emphasizes the interrelated roles of the thalamus, striatum, and the frontal cortex (in particular the DLPFC) in interventions and recovery related to DoC.[117,118] Thus, it is possible that electrical current generation in the dorsal prefrontal cortex could contribute to arousal from the states of DoC. However, the mechanism of TMS for DoC remains relatively underexplored, and changes are likely to be transient given the transient nature of TMS itself. Regardless, the noninvasive nature of TMS, paired with the possibility of longitudinal changes with repetitive TMS, presents a favorable risk-to-benefit ratio.

Because of a lack of understanding of the therapeutic mechanisms of TMS in treating DoC, physiological markers in the studies reviewed were varied. EEG changes, particularly in the alpha and delta frequency bands, were the most frequently reported physiological metrics. Changes in EEG activity were reported by Piccione et al,[53] Manganotti et al,[54] Bai et al,[57] Xia et al,[59] He et al,[60] and Wu et al.[62] Jang and Kwon,[65] by contrast, examined volume changes in the prefrontal cortex and found increases in white matter tract volume within regions associated with the ascending reticular activating system. In the rat study by Keck et al,[96] increases in mesolimbic and mesostriatal dopamine levels were found.

Despite some interesting clinical and physiological findings, stimulation parameters used in the identified studies varied substantially, from length of stimulation, frequency of stimulation, to periodicity of repetitions and other parameters. Thus, standardization with respect to TMS protocols for DoC is needed, at least for the purpose of enabling meaningful meta-analyses.

Transcranial Direct-Current Stimulation

Similar to TMS, tDCS is thought to impact the brain through electrical currents in neural tissue.[20] Most studies have targeted the DLPFC, suggesting that the role of this brain region in the mesocircuit was a focus of most of modulatory efforts.[118] As is the case with TMS, the therapeutic mechanism of tDCS in DoC is not fully understood.

Physiological indicators of the effects of tDCS were largely unreported by the studies reviewed. Naro et al[73] and Bai et al[78] measured changes in functional connectivity associated with tDCS. Naro et al[73] reported increases in theta and gamma band connectivity in frontoparietal areas while targeting the middle cerebellum, which was limited to patients with MCS. Bai et al[78] similarly observed increases in functional connectivity only among patients with MCS. This group also measured cortical excitability and found relatively sustained increases in global excitability following both tDCS and EEG-TMS in patients with MCS.[74] Overall, the interesting therapeutic implications of tDCS for DoC are countered by a need for a better understanding of its physiological effects.

Ethical Considerations and Indications

Given that the patient population affected by DoC is vulnerable, numerous ethical dilemmas arise in treating conditions such as coma, UWS, and MCS. The inability of the patient to communicate and consent to medical decision-making presents a challenge in initiating care, whether it involves end-of-life decisions, maintenance, or therapeutic options such as neuromodulation.[119] While the presence of relatives and durable power of attorney may ease the legal intricacies of determining care, ethical challenges remain in advocating for neuromodulation. For example, evidence concerning the efficacy of DBS, SCS, LIFU, MNS, TMS, and tDCS is limited and mixed with respect to DoC; thus, communicating realistic expectations is critical. However, given a dearth of effective options for treating DoC, with many patients facing poor prognoses, a medically conservative approach favoring life extension may allow attempting neuromodulation for DoC, particularly when other options have been exhausted.

In the interest of beneficence and restoring autonomy to patients with DoC, neuromodulation may be an ethical course of action, providing a possible route to improvement when others are

absent.[120] When considering whether to attempt neuromodulation, the likelihood of the patient's benefit is central to decision-making. Relevant factors may include likelihood and severity of disability if therapy is successful, comorbidities, wishes of the patient, and other clinical factors. For example, patients in MCS or UWS from trauma appear to show more benefit from neuromodulation than patients with systemic brain damage, likely in relation to relatively local distributions of cerebral injury.[41] Factors such as clinical outcomes, coma scales, and many others should be considered when weighing the risks and benefits of neuromodulation for treating DoC.

Limitations, Future Directions, and Conclusions

While these studies suggest potential in applying neuromodulation for DoC, they also underscore the need for more extensive, well-controlled trials. The identified studies exhibit a moderate risk of bias, often relying on retrospective analyses and small cohorts. Future studies should strive for prospective designs, larger sample sizes, and rigorous controls to enhance the reliability and generalizability of findings. Moreover, the heterogeneity in targets, stimulation parameters, and measured outcomes across studies complicates meta-analytic evaluation of these nascent data. Standardization of protocols through an evidence-based approach (eg, anatomical locations involved in the mesocircuit hypothesis, frequency and amplitude parameters, etc) for the modalities reviewed and a deeper understanding of individual variability are imperative for advancing the field and improving the effects and safety of neuromodulation for DoC. The long-term implications of neuromodulation, especially in terms of sustained benefits and potential adverse effects, warrant extensive investigation.

In line with the objectives of the Curing Coma Campaign, neuromodulation techniques applied to DoC, when deemed safe, should be carefully documented and shared with the broader research community to enhance the understanding of coma neurobiology, long-term recovery options, and care of comatose patients, and provide another potential therapeutic option for patients.[121] While the techniques discussed in this article can contribute to patient outcomes, they may also shed light on the pathophysiology of disordered states of consciousness, enabling further research and development in the future.

In conclusion, neuromodulation emerges as an interesting, unique, and potentially promising avenue in treating DoC such as UWS and MCS. Nuanced investigation of DBS, SCS, LIFU, MNS, TMS, and tDCS in the future could reveal breakthroughs, and these techniques (and potentially others heretofore unexplored) may offer hope for patients with impaired consciousness.

Authorship Statements

Rajeev R. Dutta, Yama Akbari, and Michelle Paff designed the study. Rajeev R. Dutta, Sheila Abdolmanafi, Alex Rabizadeh, and Rounak Baghbaninogourani conducted the study, including data collection and data analysis. Rajeev R. Dutta prepared the manuscript draft, with important intellectual input from Shirin Mansooridara, Alexander Lopez, Yama Akbari, and Michelle Paff. Rajeev R. Dutta created Figure 1, and Michelle Paff created Figure 2. Shirin Mansooridara, Alexander Lopez, Yama Akbari, and Michelle Paff provided editorial support during the preparation of this manuscript. All authors approved the final version of the manuscript.

Conflict of Interest

The authors reported no conflict of interest.

How to Cite This Article

Dutta R.R., Abdolmanafi S., Rabizadeh A., Baghbaninogourani R., Mansooridara S., Lopez A., Akbari Y., Paff M. 2024. Neuromodulation and Disorders of Consciousness: Systematic Review and Pathophysiology.
Neuromodulation 2024; ■: 1–21.

REFERENCES

1. Plum F, Posner JB. *The Diagnosis of Stupor and Coma*. Oxford University Press; 1982.
2. Giacino JT, Katz DI, Schiff ND, et al. Comprehensive systematic review update summary: disorders of consciousness. *Neurology*. 2018;91:461–470. https://doi.org/10.1212/WNL.0000000000005928.
3. Van Gulick R. Consciousness. In: Zalta EN, Nodelman U, eds. *The Stanford Encyclopedia of Philosophy*. Stanford University; 2022.
4. Eapen BC, Georgekutty J, Subbarao B, Bavishi S, Cifu DX. Disorders of consciousness. *Phys Med Rehabil Clin N Am*. 2017;28:245–258. https://doi.org/10.1016/j.pmr.2016.12.003.
5. Chen WG, Li R, Zhang Y, et al. Recovery from prolonged disorders of consciousness: a dual-center prospective cohort study in China. *World J Clin Cases*. 2020;8:2520–2529. https://doi.org/10.12998/wjcc.v8.i12.2520.
6. Cossu G. Therapeutic options to enhance coma arousal after traumatic brain injury: state of the art of current treatments to improve coma recovery. *Br J Neurosurg*. 2014;28:187–198. https://doi.org/10.3109/02688697.2013.841845.
7. Dougherty DD. Deep brain stimulation. *Psychiatr Clin North Am*. 2018;41:385–394. https://doi.org/10.1016/j.psc.2018.04.004.
8. Lozano AM, Lipsman N, Bergman H, et al. Deep brain stimulation: current challenges and future directions. *Nat Rev Neurol*. 2019;15:148–160. https://doi.org/10.1038/s41582-018-0128-2.
9. Garcia K, Wray JK, Kumar S. *Spinal Cord Stimulation*. StatPearls Publishing; 2023.
10. Eckermann JM, Pilitsis JG, Vannaboutathong C, Wagner BJ, Province-Azalde R, Bendel MA. Systematic literature review of spinal cord stimulation in patients with chronic back pain without prior spine surgery. *Neuromodulation Technol Neural Interface*. 2022;25:648–656. https://doi.org/10.1111/ner.13519.
11. Arulpragasam AR, van 't Wout-Frank M, Barredo J, Faucher CR, Greenberg BD, Philip NS. Low intensity focused ultrasound for non-invasive and reversible deep brain neuromodulation-a paradigm shift in psychiatric research. *Front Psychiatry*. 2022;13:825802.
12. Lee A, Fan LT. Stimulation of the wrist acupuncture point P6 for preventing postoperative nausea and vomiting. *Cochrane Database Syst Rev*. 2009;(2):CD003281. https://doi.org/10.1002/14651858.CD003281.pub3.
13. Maharjan A, Peng M, Cakmak YO. Non-invasive high frequency median nerve stimulation effectively suppresses olfactory intensity perception in healthy males. *Front Hum Neurosci*. 2019;12:533.
14. Iverson AM, Arbuckle AL, Song DY, Bihun EC, Black KJ. Median nerve stimulation for treatment of tics: a 4-week open trial with ecological momentary assessment. *J Clin Med*. 2023;12:2545. https://doi.org/10.3390/jcm12072545.
15. Siebner HR, Hartwigsen G, Kassuba T, Rothwell JC. How does transcranial magnetic stimulation modify neuronal activity in the brain? Implications for studies of cognition. *Cortex*. 2009;45:1035–1042. https://doi.org/10.1016/j.cortex.2009.02.007.
16. Rizvi S, Khan AM. Use of transcranial magnetic stimulation for depression. *Cureus*. 2019;11:e4736. https://doi.org/10.7759/cureus.4736.
17. Sun W, Fu W, Mao W, Wang D, Wang Y. Low-frequency repetitive transcranial magnetic stimulation for the treatment of refractory partial epilepsy. *Clin EEG Neurosci*. 2011;42:40–44. https://doi.org/10.1177/155005941104200109.
18. Kodama M, Kasahara T, Hyodo M, et al. Effect of low-frequency repetitive transcranial magnetic stimulation combined with physical therapy on L-dopa-induced painful off-period dystonia in Parkinson's disease. *Am J Phys Med Rehabil*. 2011;90:150–155. https://doi.org/10.1097/PHM.0b013e3181fc7ccd.
19. Xie Y, Zhang T. Repetitive transcranial magnetic stimulation improves consciousness disturbance in stroke patients: a quantitative electroencephalography spectral power analysis. *Neural Regen Res*. 2012;7:2465–2472. https://doi.org/10.3969/j.issn.1673-5374.2012.31.008.

20. Thair H, Holloway AL, Newport R, Smith AD. Transcranial direct current stimulation (tDCS): a beginner's guide for design and implementation. *Front Neurosci*. 2017;11:641. https://doi.org/10.3389/fnins.2017.00641.
21. Zaninotto AL, El-Hagrassy MM, Green JR, et al. Transcranial direct current stimulation (tDCS) effects on traumatic brain injury (TBI) recovery: a systematic review. *Dement neuropsychol*. 2019;13:172–179. https://doi.org/10.1590/1980-57642018dn13-020005.
22. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. https://doi.org/10.1136/bmj.n71.
23. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016;355:i4919. https://doi.org/10.1136/bmj.i4919.
24. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. *BMJ*. 2004;328:1490.
25. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336:924–926. https://doi.org/10.1136/bmj.39489.470347AD.
26. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. *Syst Rev*. 2016;5:210. https://doi.org/10.1186/s13643-016-0384-4.
27. Tsubokawa T, Yamamoto T, Katayama Y, Hirayama T, Maejima S, Moriya T. Deep-brain stimulation in a persistent vegetative state: follow-up results and criteria for selection of candidates. *Brain Inj*. 1990;4:315–327. https://doi.org/10.3109/02699059009026185.
28. Katayama Y, Tsubokawa T, Yamamoto T, Hirayama T, Miyazaki S, Koyama S. Characterization and modification of brain activity with deep brain stimulation in patients in a persistent vegetative state: pain-related late positive component of cerebral evoked potential. *Pacing Clinical Electrophis*. 1991;14:116–121. https://doi.org/10.1111/j.1540-8159.1991.tb04055.x.
29. Yamamoto T, Kobayashi K, Kasai M, Oshima H, Fukaya C, Katayama Y. DBS therapy for the vegetative state and minimally conscious state. *Acta Neurochir Suppl*. 2005;93:101–104. https://doi.org/10.1007/3-211-27577-0_17.
30. Schiff ND, Giacino JT, Kalmar K, et al. Behavioural improvements with thalamic stimulation after severe traumatic brain injury. *Nature*. 2007;448:600–603. https://doi.org/10.1038/nature06041.
31. Moll CKE, Sharott A, Hamel W, et al. Waking up the brain: a case study of stimulation-induced wakeful unawareness during anaesthesia. *Prog Brain Res*. 2009;177:125–145. https://doi.org/10.1016/S0079-6123(09)17710-5.
32. Wojtecki L, Petri D, Elben S, et al. Modulation of central thalamic oscillations during emotional-cognitive processing in chronic disorder of consciousness. *Cortex*. 2014;60:94–102. https://doi.org/10.1016/j.cortex.2014.09.007.
33. Magrassi L, Maggioni G, Pistarini C, et al. Results of a prospective study (CATS) on the effects of thalamic stimulation in minimally conscious and vegetative state patients. *JNS*. 2016;125:972–981. https://doi.org/10.3171/2015.7.JNS15700.
34. Chudy D, Deletis V, Almahariq F, Marčinković P, Škrlin J, Paradžik V. Deep brain stimulation for the early treatment of the minimally conscious state and vegetative state: experience in 14 patients. *J Neurosurg*. 2018;128:1189–1198. https://doi.org/10.3171/2016.10.JNS161071.
35. Lemaire JJ, Sontheimer A, Pereira B, et al. Deep brain stimulation in five patients with severe disorders of consciousness. *Ann Clin Transl Neurol*. 2018;5:1372–1384. https://doi.org/10.1002/acn3.648.
36. Gottshall JL, Adams ZM, Forgacs PB, Schiff ND. Daytime central thalamic deep brain stimulation modulates sleep dynamics in the severely injured brain: mechanistic insights and a novel framework for alpha-delta sleep generation. *Front Neurol*. 2019;10:20.
37. Raguž M, Predrijevac N, Dlaka D, et al. Structural changes in brains of patients with disorders of consciousness treated with deep brain stimulation. *Sci Rep*. 2021;11:4401. https://doi.org/10.1038/s41598-021-83873-y.
38. Arnts H, Tewarie P, Van Erp WS, et al. Clinical and neurophysiological effects of central thalamic deep brain stimulation in the minimally conscious state after severe brain injury. *Sci Rep*. 2022;12:12932. https://doi.org/10.1038/s41598-022-16470-2.
39. Dang Y, Wang Y, Xia X, et al. Deep brain stimulation improves electroencephalogram functional connectivity of patients with minimally conscious state. *CNS Neurosci Ther*. 2023;29:344–353. https://doi.org/10.1111/cns.14009.
40. Shu Z, Wu J, Li H, et al. fNIRS-based functional connectivity signifies recovery in patients with disorders of consciousness after DBS treatment. *Clin Neurophysiol*. 2023;147:60–68. https://doi.org/10.1016/j.clinph.2022.12.011.
41. Yang Y, He Q, Dang Y, et al. Long-term functional outcomes improved with deep brain stimulation in patients with disorders of consciousness. *Stroke Vasc Neurol*. 2023;8:368–378. https://doi.org/10.1136/svn-2022-001998.
42. Morita I, Keith MW, Kanno T. Dorsal column stimulation for persistent vegetative state. *Acta Neurochir Suppl*. 2007;97:455–459.
43. Kanno T, Morita I, Yamaguchi S, et al. Dorsal column stimulation in persistent vegetative state. *Neuromodulation Technol Neural Interface*. 2009;12:33–38. https://doi.org/10.1111/j.1525-1403.2009.00185.x.
44. Yamamoto T, Watanabe M, Obuchi T, et al. Spinal cord stimulation for vegetative state and minimally conscious state: changes in consciousness level and motor function. *Acta Neurochir Suppl*. 2017;124:37–42. https://doi.org/10.1007/978-3-319-39546-3_6.
45. Zhang Y, Yang Y, Si J, Xia X, He J, Jiang T. Influence of inter-stimulus interval of spinal cord stimulation in patients with disorders of consciousness: a preliminary functional near-infrared spectroscopy study. *NeuroImage Clin*. 2018;17:1–9. https://doi.org/10.1016/j.nicl.2017.09.017.
46. Yang Y, He Q, He J. Short-term spinal cord stimulation in treating disorders of consciousness monitored by resting-state fMRI and qEEG: the first case report. *Front Neurol*. 2022;13:968932. https://doi.org/10.3389/fneur.2022.968932.
47. Zhuang Y, Yang Y, Xu L, et al. Effects of short-term spinal cord stimulation on patients with prolonged disorder of consciousness: a pilot study. *Front Neurol*. 2022;13:1026221. https://doi.org/10.3389/fneur.2022.1026221.
48. Monti MM, Schnakers C, Korb AS, Bystritsky A, Vespa PM. Non-invasive ultrasonic thalamic stimulation in disorders of consciousness after severe brain injury: a first-in-man report. *Brain Stimul*. 2016;9:940–941. https://doi.org/10.1016/j.brs.2016.07.008.
49. Cain JA, Spivak NM, Coetzee JP, et al. Ultrasonic deep brain neuromodulation in acute disorders of consciousness: a proof-of-concept. *Brain Sci*. 2022;12:428. https://doi.org/10.3390/brainsci12040428.
50. Hillman EMC. Coupling mechanism and significance of the BOLD signal: a status report. *Annu Rev Neurosci*. 2014;37:161–181. https://doi.org/10.1146/annurev-neuro-071013-014111.
51. Cooper JB, Jane JA, Alves WM, Cooper EB. Right median nerve electrical stimulation to hasten awakening from coma. *Brain Inj*. 1999;13:261–267. https://doi.org/10.1080/026990599121638.
52. Wu X, Xie L, Lei J, et al. Acute traumatic coma awakening by right median nerve electrical stimulation: a randomised controlled trial. *Intensive Care Med*. 2023;49:633–644. https://doi.org/10.1007/s00134-023-07072-1.
53. Piccione F, Cavinato M, Manganotti P, et al. Behavioral and neurophysiological effects of repetitive transcranial magnetic stimulation on the minimally conscious state: a case study. *Neurorehabil Neural Repair*. 2011;25:98–102. https://doi.org/10.1177/1545968310369802.
54. Manganotti P, Formaggio E, Storti SF, et al. Effect of high-frequency repetitive transcranial magnetic stimulation on brain excitability in severely brain-injured patients in minimally conscious or vegetative state. *Brain Stimul*. 2013;6:913–921. https://doi.org/10.1016/j.brs.2013.06.006.
55. Cincotta M, Giovannelli F, Chiaramonti R, et al. No effects of 20 Hz-rTMS of the primary motor cortex in vegetative state: a randomised, sham-controlled study. *Cortex*. 2015;71:368–376. https://doi.org/10.1016/j.cortex.2015.07.027.
56. Naro A, Russo M, Leo A, Bramanti P, Quartarone A, Calabrò RS. A single session of repetitive transcranial magnetic stimulation over the dorsolateral prefrontal cortex in patients with unresponsive wakefulness syndrome: preliminary results. *Neurorehabil Neural Repair*. 2015;29:603–613. https://doi.org/10.1177/1545968314562114.
57. Bai Y, Xia X, Kang J, et al. Evaluating the effect of repetitive transcranial magnetic stimulation on disorders of consciousness by using TMS-EEG. *Front Neurosci*. 2016;10:473. https://doi.org/10.3389/fnins.2016.00473.
58. Xia X, Bai Y, Zhou Y, et al. Effects of 10 Hz repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex in disorders of consciousness. *Front Neurol*. 2017;8:182. https://doi.org/10.3389/fneur.2017.00182.
59. Xia X, Liu Y, Bai Y, et al. Long-lasting repetitive transcranial magnetic stimulation modulates electroencephalography oscillation in patients with disorders of consciousness. *NeuroReport*. 2017;28:1022–1029. https://doi.org/10.1097/WNR.0000000000000886.
60. He F, Wu M, Meng F, et al. Effects of 20 Hz repetitive transcranial magnetic stimulation on disorders of consciousness: a resting-state electroencephalography study. *Neural Plast*. 2018;2018:1–8. https://doi.org/10.1155/2018/5036184.
61. Liu X, Meng F, Gao J, et al. Behavioral and resting state functional connectivity effects of high frequency rTMS on disorders of consciousness: a sham-controlled study. *Front Neurol*. 2018;9:982. https://doi.org/10.3389/fneur.2018.00982.
62. Wu M, Wu Y, Yu Y, et al. Effects of theta burst stimulation of the left dorsolateral prefrontal cortex in disorders of consciousness. *Brain Stimul*. 2018;11:1382–1384. https://doi.org/10.1016/j.brs.2018.07.055.
63. Legostaeva L, Poydasheva A, Iazeva E, et al. Stimulation of the angular gyrus improves the level of consciousness. *Brain Sci*. 2019;9:103. https://doi.org/10.3390/brainsci9050103.
64. Bender Pape TL, Herrold AA, Livengood SL, et al. A pilot trial examining the merits of combining amantadine and repetitive transcranial magnetic stimulation as an intervention for persons with disordered consciousness after TBI. *J Head Trauma Rehabil*. 2020;35:371–387. https://doi.org/10.1097/HTR.0000000000000634.
65. Jang SH, Kwon YH. Effect of repetitive transcranial magnetic stimulation on the ascending reticular activating system in a patient with disorder of consciousness: a case report. *BMC Neurol*. 2020;20:37. https://doi.org/10.1186/s12883-020-1607-9.
66. Ge X, Zhang Y, Xin T, Luan X. Effects of 10 Hz repetitive transcranial magnetic stimulation of the right dorsolateral prefrontal cortex in the vegetative state. *Exp Ther Med*. 2021;21:206. https://doi.org/10.3892/etm.2021.9626.
67. Zhang XH, Han P, Zeng YY, Wang YL, Lv HL. The clinical effect of repetitive transcranial magnetic stimulation on the disturbance of consciousness in patients in a vegetative state. *Front Neurosci*. 2021;15:647517. https://doi.org/10.3389/fnins.2021.647517.
68. Chen JM, Chen QF, Wang ZY, et al. Influence of high-frequency repetitive transcranial magnetic stimulation on neurobehavioral and electrophysiology in patients with disorders of consciousness. *Neural Plast*. 2022;2022:7195699. https://doi.org/10.1155/2022/7195699.
69. Fan J, Zhong Y, Wang H, Aierken N, He R. Repetitive transcranial magnetic stimulation improves consciousness in some patients with disorders of consciousness. *Clin Rehabil*. 2022;36:916–925. https://doi.org/10.1177/02692155221089455.
70. Shen L, Huang Y, Liao Y, et al. Effect of high-frequency repetitive transcranial magnetic stimulation over M1 for consciousness recovery after traumatic brain injury. *Brain Behav*. 2023;13:e2971. https://doi.org/10.1002/brb3.2971.

71. Angelakis E, Liouta E, Andreadis N, et al. Transcranial direct current stimulation effects in disorders of consciousness. *Arch Phys Med Rehabil*. 2014;95:283–289. https://doi.org/10.1016/j.apmr.2013.09.002.
72. Thibaut A, Bruno MA, Ledoux D, Demertzi A, Laureys S. tDCS in patients with disorders of consciousness: sham-controlled randomized double-blind study. *Neurology*. 2014;82:1112–1118. https://doi.org/10.1212/WNL.0000000000000260.
73. Naro A, Russo M, Leo A, et al. Cortical connectivity modulation induced by cerebellar oscillatory transcranial direct current stimulation in patients with chronic disorders of consciousness: a marker of covert cognition? *Clin Neurophysiol*. 2016;127:1845–1854. https://doi.org/10.1016/j.clinph.2015.12.010.
74. Bai Y, Xia X, Kang J, Yang Y, He J, Li X. TDCS modulates cortical excitability in patients with disorders of consciousness. *NeuroImage Clin*. 2017;15:702–709. https://doi.org/10.1016/j.nicl.2017.01.025.
75. Estraneo A, Pascarella A, Moretta P, et al. Repeated transcranial direct current stimulation in prolonged disorders of consciousness: a double-blind cross-over study. *J Neurol Sci*. 2017;375:464–470. https://doi.org/10.1016/j.jns.2017.02.036.
76. Huang W, Wannez S, Fregni F, et al. Repeated stimulation of the posterior parietal cortex in patients in minimally conscious state: a sham-controlled randomized clinical trial. *Brain Stimul*. 2017;10:718–720. https://doi.org/10.1016/j.brs.2017.02.001.
77. Thibaut A, Wannez S, Donneau AF, et al. Controlled clinical trial of repeated prefrontal tDCS in patients with chronic minimally conscious state. *Brain Inj*. 2017;31:466–474. https://doi.org/10.1080/02699052.2016.1274776.
78. Bai Y, Xia X, Wang Y, et al. Fronto-parietal coherence response to tDCS modulation in patients with disorders of consciousness. *Int J Neurosci*. 2018;128:587–594. https://doi.org/10.1080/00207454.2017.1403440.
79. Martens G, Lejeune N, O'Brien AT, et al. Randomized controlled trial of home-based 4-week tDCS in chronic minimally conscious state. *Brain Stimul*. 2018;11:982–990. https://doi.org/10.1016/j.brs.2018.04.021.
80. Wu M, Yu Y, Luo L, et al. Efficiency of repetitive transcranial direct current stimulation of the dorsolateral prefrontal cortex in disorders of consciousness: a randomized sham-controlled study. *Neural Plast*. 2019;2019:7089543. https://doi.org/10.1155/2019/7089543.
81. Carrière M, Mortaheb S, Raimondo F, et al. Neurophysiological correlates of a single session of prefrontal tDCS in patients with prolonged disorders of consciousness: a pilot double-blind randomized controlled study. *Brain Sci*. 2020;10:469. https://doi.org/10.3390/brainsci10070469.
82. Martens G, Kroupi E, Bodien Y, et al. Behavioral and electrophysiological effects of network-based frontoparietal tDCS in patients with severe brain injury: a randomized controlled trial. *Neuroimage Clin*. 2020;28:102426. https://doi.org/10.1016/j.nicl.2020.102426.
83. 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. https://doi.org/10.3389/fnins.2021.641951.
84. Barra A, Rosenfelder M, Mortaheb S, et al. Transcranial pulsed-current stimulation versus transcranial direct current stimulation in patients with disorders of consciousness: a pilot, sham-controlled cross-over double-blind study. *Brain Sci*. 2022;12:429. https://doi.org/10.3390/brainsci12040429.
85. Thibaut A, Fregni F, Estraneo A, et al. Sham-controlled randomized multicentre trial of transcranial direct current stimulation for prolonged disorders of consciousness. *Eur J Neurol*. 2023;30:3016–3031. https://doi.org/10.1111/ene.15974.
86. Tasserie J, Uhrig L, Sitt JD, et al. Deep brain stimulation of the thalamus restores signatures of consciousness in a nonhuman primate model. *Sci Adv*. 2022;8, eabl5547. https://doi.org/10.1126/sciadv.abl5547.
87. Redinbaugh MJ, Afrasiabi M, Phillips JM, et al. Thalamic deep brain stimulation paradigm to reduce consciousness: cortico-striatal dynamics implicated in mechanisms of consciousness. *PLoS Comput Biol*. 2022;18:e1010294. https://doi.org/10.1371/journal.pcbi.1010294.
88. Baker JL, Toth R, Deli A, et al. Regulation of arousal and performance of a healthy non-human primate using closed-loop central thalamic deep brain stimulation. *Int IEEE EMBS Conf Neural Eng*. 2023;2023:10123754. https://doi.org/10.1109/NER52421.2023.10123754.
89. Quinkert AW, Pfaff DW. Temporal patterns of deep brain stimulation generated with a true random number generator and the logistic equation: effects on CNS arousal in mice. *Behav Brain Res*. 2012;229:349–358. https://doi.org/10.1016/j.bbr.2012.01.025.
90. Pillay S, Liu X, Baracskay P, Hudetz AG. Brainstem stimulation increases functional connectivity of basal forebrain-paralimbic network in isoflurane-anesthetized rats. *Brain Connect*. 2014;4:523–534. https://doi.org/10.1089/brain.2014.0254.
91. Fernández-Cabrera MR, Selvas A, Miguéns M, et al. Parafascicular thalamic nucleus deep brain stimulation decreases NMDA receptor GluN1 subunit gene expression in the prefrontal cortex. *Neuroscience*. 2017;348:73–82. https://doi.org/10.1016/j.neuroscience.2017.02.009.
92. Feng Z, Ma W, Wang Z, Qiu C, Hu H. Small changes in inter-pulse-intervals can cause synchronized neuronal firing during high-frequency stimulations in rat hippocampus. *Front Neurosci*. 2019;13:36. https://doi.org/10.3389/fnins.2019.00036.
93. Dong X, Ye W, Tang Y, et al. Wakefulness-promoting effects of lateral hypothalamic area–deep brain stimulation in traumatic brain injury-induced comatose rats: upregulation of α1-adrenoceptor subtypes and downregulation of gamma-aminobutyric acid β receptor expression via the orexins pathway. *World Neurosurg*. 2021;152:e321–e331. https://doi.org/10.1016/j.wneu.2021.05.089.
94. Claar LD, Rembado I, Kuyat JR, et al. Cortico-thalamo-cortical interactions modulate electrically evoked EEG responses in mice. *eLife*. 2023;12:RP84630. https://doi.org/10.7554/eLife.84630.
95. Bian T, Meng W, Qiu M, et al. Noninvasive ultrasound stimulation of ventral tegmental area induces reanimation from general anaesthesia in mice. *Research (Wash DC). 2021*. 2021:2674692. https://doi.org/10.34133/2021/2674692.
96. Keck ME, Welt T, Müller MB, et al. Repetitive transcranial magnetic stimulation increases the release of dopamine in the mesolimbic and mesostriatal system. *Neuropharmacology*. 2002;43:101–109. https://doi.org/10.1016/S0028-3908(02)00069-2.
97. Young GB, Pigott SE. Neurobiological basis of consciousness. *Arch Neurol*. 1999;56:153–157. https://doi.org/10.1001/archneur.56.2.153.
98. Laureys S. The neural correlate of (un)awareness: lessons from the vegetative state. *Trends Cogn Sci*. 2005;9:556–559. https://doi.org/10.1016/j.tics.2005.10.010.
99. Graham DI, Adams JH, Murray LS, Jennett B. Neuropathology of the vegetative state after head injury. *Neuropsychol Rehabil*. 2005;15:198–213. https://doi.org/10.1080/09602010443000452.
100. Yeo SS, Chang PH, Jang SH. The ascending reticular activating system from pontine reticular formation to the thalamus in the human brain. *Front Hum Neurosci*. 2013;7:416. https://doi.org/10.3389/fnhum.2013.00416.
101. Blumenfeld H. Neuroanatomical basis of consciousness. In: Laureys S, Gosseries O, Tononi G, eds. *The Neurology of Conciousness*. 2nd ed. Academic Press; 2016:3–29.
102. Fischer DB, Boes AD, Demertzi A, et al. A human brain network derived from coma-causing brainstem lesions. *Neurology*. 2016;87:2427–2434. https://doi.org/10.1212/WNL.0000000000003404.
103. Snider SB, Bodien YG, Frau-Pascual A, Bianciardi M, Foulkes AS, Edlow BL. Ascending arousal network connectivity during recovery from traumatic coma. *NeuroImage Clin*. 2020;28:102503. https://doi.org/10.1016/j.nicl.2020.102503.
104. Gildenberg PL. Neuromodulation: a historical perspective. In: Krames ES, Peckham PH, Rezai AR, eds. *Neuromodulation*. Academic Press; 2009:9–20.
105. Croarkin PE, MacMaster FP. Transcranial magnetic stimulation for adolescent depression. *Child Adolesc Psychiatr Clin N Am*. 2019;28:33–43. https://doi.org/10.1016/j.chc.2018.07.003.
106. Senatus P, Zurek S, Deogaonkar M. Deep brain stimulation and motor cortex stimulation for chronic pain. *Neurol India*. 2020;68(suppl):S235–S240. https://doi.org/10.4103/0028-3886.302471.
107. Edlow BL, Sanz LRD, Polizzotto L, et al. Therapies to restore consciousness in patients with severe brain injuries: a gap analysis and future directions. *Neurocrit Care*. 2021;35(suppl 1):68–85. https://doi.org/10.1007/s12028-021-01227-y.
108. Ilyas A, Pizarro D, Romeo AK, Riley KO, Pati S. The centromedian nucleus: anatomy, physiology, and clinical implications. *J Clin Neurosci*. 2019;63:1–7. https://doi.org/10.1016/j.jocn.2019.01.050.
109. Jang SH, Lim HW, Yeo SS. The neural connectivity of the intralaminar thalamic nuclei in the human brain: a diffusion tensor tractography study. *Neurosci Lett*. 2014;579:140–144. https://doi.org/10.1016/j.neulet.2014.07.024.
110. Mangold SA, Das JM. *Neuroanatomy, Reticular Formation*. StatPearls Publishing; 2023.
111. Piedade GS, Assumpcao de Monaco B, Guest JD, Cordeiro JG. Review of spinal cord stimulation for disorders of consciousness. *Curr Opin Neurol*. 2023;36:507–515. https://doi.org/10.1097/WCO.0000000000001222.
112. Baek H, Pahk KJ, Kim H. A review of low-intensity focused ultrasound for neuromodulation. *Biomed Eng Lett*. 2017;7:135–142. https://doi.org/10.1007/s13534-016-0007-y.
113. Cooper EB, Cooper JB. Electrical treatment of coma via the median nerve. *Acta Neurochir Suppl*. 2003;87:7–10. https://doi.org/10.1007/978-3-7091-6081-7_2.
114. Feng Z, Du Q. Mechanisms responsible for the effect of median nerve electrical stimulation on traumatic brain injury-induced coma: orexin-A-mediated N-methyl-D-aspartate receptor subunit NR1 upregulation. *Neural Regen Res*. 2016;11:951–956. https://doi.org/10.4103/1673-5374.184494.
115. Petrides M. The role of the mid-dorsolateral prefrontal cortex in working memory. *Exp Brain Res*. 2000;133:44–54. https://doi.org/10.1007/s002210000399.
116. Lee D, Wang XJ. Mechanisms for stochastic decision making in the primate frontal cortex: single-neuron recording and circuit modeling. In: Glimcher PW, Camerer CF, Fehr E, Poldrack RA, eds. *Neuroeconomics*. Academic Press; 2009:481–501.
117. Schiff ND. Recovery of consciousness after brain injury: a mesocircuit hypothesis. *Trends Neurosci*. 2010;33:1–9. https://doi.org/10.1016/j.tins.2009.11.002.
118. Thibaut A, Schiff N, Giacino J, Laureys S, Gosseries O. Therapeutic interventions in patients with prolonged disorders of consciousness. *Lancet Neurol*. 2019;18:600–614. https://doi.org/10.1016/S1474-4422(19)30031-6.
119. Rosenfeld JV, Mathiesen TI. The clinical and ethical challenges of treating comatose patients following severe brain injury. *Acta Neurochir*. 2023;165:829–831. https://doi.org/10.1007/s00701-022-05376-7.
120. Gillon R. Medical ethics: four principles plus attention to scope. *BMJ*. 1994;309:184–188.
121. Mainali S, Aiyagari V, Alexander S, et al. Proceedings of the second curing coma campaign NIH symposium: challenging the future of research for coma and disorders of consciousness. *Neurocrit Care*. 2022;37:326–350. https://doi.org/10.1007/s12028-022-01505-3.

COMMENT

This paper extensively explores the potential of neuromodulation technology in treating disorders of consciousness, systematically

analyzing emerging methods such as tDCS, DBS, and ultrasonic neuromodulation. While these technologies show promise in restoring consciousness and enhancing patients' quality of life, they face several key challenges. Firstly, the sample sizes and research designs of current clinical trials remain limited. Despite encouraging preliminary results, most studies are small-scale, single-center experiments lacking sufficient statistical power and long-term follow-up, thereby limiting comprehensive evaluation of long-term efficacy and safety. Future endeavors should prioritize larger, multicenter randomized controlled trials to validate these technologies across diverse populations. Secondly, the absence of standardized treatment protocols and evaluation methods is a significant concern in current research. Diverse parameters, treatment regimens, and assessment criteria utilized by different research teams lead to inconsistent and incomparable experimental outcomes. To advance clinical application and further research, establishing unified clinical guidelines and standardized assessment tools is imperative to harmonize findings and optimize treatment strategies. Additionally, developing personalized treatment strategies remains challenging. Given the varied etiologies and neural network impairments in disorders of consciousness, tailoring optimal treatment plans based on individual patient characteristics and medical histories is crucial. Future research should focus on constructing predictive models integrating neuroimaging and biomarkers to achieve precise and personalized medical interventions. While neuromodulation technology offers new hope for treating disorders of consciousness, addressing its current challenges is paramount. Overcoming limitations in experimental design, establishing uniform treatment standards, and advancing personalized treatment approaches will enhance the efficacy and durability of these technologies, thereby providing more effective and sustainable rehabilitation programs for patients. Looking ahead, the field of neuromodulation holds promising avenues for the treatment of disorders of consciousness. Advancements in technology and research methodologies are anticipated to address current limitations and expand therapeutic possibilities. Future studies could leverage innovative neuroimaging techniques, such as functional magnetic resonance imaging and EEG, to refine treatment protocols and personalize interventions based on real-time brain activity patterns. Integration of artificial intelligence and machine learning algorithms may enable predictive modeling for optimizing treatment outcomes and predicting patient responses more accurately. Moreover, ongoing collaborations among multidisciplinary teams, including neuroscientists, clinicians, engineers, and ethicists, will be pivotal in navigating ethical considerations and ensuring the responsible adoption of neuromodulation technologies. This collaborative approach will foster a robust framework for conducting larger-scale clinical trials with rigorous methodologies, thereby establishing evidence-based guidelines and enhancing clinical practice. In conclusion, while challenges persist, the evolving landscape of neuromodulation technology offers promising prospects for transforming the treatment landscape of disorders of consciousness. By harnessing interdisciplinary innovations and advancing personalized medicine, we can strive towards more effective, patient-centered care strategies and improve outcomes for individuals affected by these challenging conditions.

Yi Yang, PhD
Beijing, China