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Coma and disorders of consciousness: An overview

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Coma and disorders of consciousness: An overview

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Editorial: Coma and disorders of consciousness: an overview

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Editorial on the Research Topic
Coma and disorders of consciousness: an overview

The exploration of coma and disorders of consciousness (DoC) remains a significant frontier in neurology, characterized by its complex challenges and the critical need for innovative therapeutic interventions. This Research Topic stems from the Curing Coma Campaign and its World Coma Day. The Curing Coma Campaign is the first global public health initiative to unify the concept of coma as a treatable medical entity with the goal of promoting recovery of consciousness through early intervention and long-term support. The assemblage of 13 scholarly articles in this Research Topic provides a broad perspective on the contemporary state of research and clinical practice pertaining to this field. Collectively, these studies shed light on the complicated, dynamic, and progressive nature of DoC, providing an overview of cutting-edge research that underscores novel treatment approaches, the critical timing and methodologies of rehabilitation, recent advancements in diagnostic tools, and the multifaceted ethical considerations necessary in clinical care.

Improving the diagnosis of patients with DoC is of paramount importance given the high rate of behavioral misdiagnosis. The critical importance of accurate diagnosis and assessment in DoC is explored in "*Clinical application of recommendations for neurobehavioral assessment in disorders of consciousness: an interdisciplinary approach.*" This review by Murtaugh et al. advocates for the use of standardized neurobehavioral rating scales to improve diagnostic accuracy, thereby facilitating more effective treatment planning and management. The article highlights the challenges of diagnosing DoC and the potential for improved outcomes through more precise assessment methodologies. Next, two studies of this Research Topic used auditory paradigms and EEG to improve diagnosis and prognosis at the bedside. Ferré et al. investigate the preservation of self-recognition capabilities in DoC patients in their original work "*Self-processing in coma, unresponsive wakefulness syndrome and minimally conscious state.*" This novel research on 112 DoC patients (acute and subacute, >3 months) suggests that the ability to process self-referential

auditory stimuli may serve as an early indicator of potential consciousness recovery, offering a new perspective on the assessment and prognostication of DoC patients. On their side, Binder et al. explore the evoked auditory responses to the chirp-modulated auditory stimulation as a potential biomarker for assessing awareness in prolonged DoC patients ($n = 62$) in their paper "*Diagnosing awareness in disorders of consciousness with gamma-band auditory responses.*" This pioneering approach offers a promising new method for evaluating consciousness, enhancing the diagnostic capabilities in the field of DoC research.

In addition to enhancing diagnosis and prognosis, it is crucial to improve the management and therapeutic intervention for DoC patients. The indispensable role of specialized rehabilitation is emphasized in "*Specialized intensive inpatient rehabilitation is crucial and time-sensitive for functional recovery from disorders of consciousness.*" This study by Zhang et al. on 137 DoC patients (acute, subacute and chronic stages) advocates for the timely initiation of rehabilitation interventions, highlighting the window of opportunity in which these treatments can have the most significant impact on recovery outcomes. The research underscores the need for early, active management and intensive therapies to maximize the therapeutic benefits for DoC patients. Zandalasini et al. synthesized the available research on the impact and management of neurogenic bowel dysfunction (NBD) in patients with acute brain injury ($n = 1.507$) in their scoping review titled "*Bowel dysfunctions after acquired brain injury: a scoping review.*" It reveals that oral laxatives are commonly used for treatment, yet there is a notable gap in instrumental assessment methods for incontinence. Highlighting the challenge of managing overlapping symptoms of NBD, the authors advocate for a collaborative strategy between the fields of rehabilitation and gastroenterology to enhance the diagnosis and treatment of NBD.

The utilization of neuromodulation techniques is gaining interest in both scientific and clinical communities working with DoC. In their work "*Effectiveness on level of consciousness of non-invasive neuromodulation therapy in patients with disorders of consciousness: a systematic review and meta-analysis,*" Liu et al. offers a comprehensive meta-analytical review of the efficacy of non-invasive neuromodulation therapies, such as transcranial Direct Current Stimulation (tDCS) and Transcranial Magnetic Stimulation (TMS), for prolonged DoC patients. By synthesizing data from multiple studies on a total of 345 patients, this review identifies key factors that influence treatment effectiveness, providing guidance for future research and clinical practice in developing more targeted and personalized therapeutic interventions.

The efficacy of repetitive transcranial magnetic stimulation (rTMS) is meticulously examined by Xu et al. in "*Repetitive transcranial magnetic stimulation over the posterior parietal cortex improves functional recovery in nonresponsive patients: A crossover, randomized, double-blind, sham-controlled study.*" This investigation shows that 10 Hz rTMS targeting the posterior parietal cortex significantly enhanced functional recovery in 20 unresponsive patients (>28 days and <1-year post-insult), suggesting a promising non-invasive approach to treating DoC. Although a small-scale study, the thoughtful study design supports the need for further exploration of rTMS as a therapeutic tool in the neurorehabilitation of DoC patients.

Three studies within this Research Topic investigate spinal cord stimulation (SCS) as a potential therapy for DoC. The manuscript "*Short-term spinal cord stimulation in treating disorders of consciousness monitored by resting-state fMRI and qEEG: The first case report*" by Yang et al. introduces a pioneering case where SCS was employed to treat a patient 3 months after a severe traumatic brain injury. This study is particularly notable for its use of advanced imaging techniques to monitor the effects of the intervention, demonstrating significant improvements in the patient's consciousness levels. The successful application of short-term SCS in this case highlights the potential of neuromodulation therapies in enhancing neural activity and promoting recovery in DoC patients. Further exploring this neuromodulation technique, "*Effects of short-term spinal cord stimulation on patients with prolonged disorder of consciousness: A pilot study*" by Zhuang et al. extends the investigation to a larger cohort including 31 patients with DoC (3–23 months post-injury), providing valuable insights into the safety, efficacy, and the specific modulation characteristics of different SCS frequencies. This research emphasizes the importance of tailoring neuromodulation therapies to individual patient needs, potentially leading to more effective and personalized treatment strategies for prolonged DoC. Finally, "*Clinical effect of short-term spinal cord stimulation in the treatment of patients with primary brainstem hemorrhage-induced disorders of consciousness*" by Huang et al. focuses on a specific subset of DoC patients ($n = 14$, 1–1.7-month post-injury), those with primary brainstem hemorrhage-induced conditions. The findings indicate that short-term SCS can lead to significant improvements in this particularly challenging group, suggesting that neuromodulation therapies may offer new hope for patients with brainstem hemorrhage.

Additionally, two neuromodulation protocols have been proposed. The innovative study protocol outlined by Yoon et al. in "*Safety and therapeutic effects of personalized transcranial direct current stimulation based on electrical field simulation for prolonged disorders of consciousness: study protocol for a multi-center, double-blind, randomized controlled trial*" present a novel approach to tDCS treatment, incorporating individual brain lesion characteristics to tailor interventions. This approach aims to enhance the safety and efficacy of tDCS, representing a significant step toward personalized neuromodulation therapies for DoC patients. The second protocol, entitled "*A protocol for a multicenter randomized and personalized controlled trial using rTMS in patients with disorders of consciousness*" by Vitello et al., presents a detailed evaluation plan for 20 Hz rTMS applied to different key brain regions. This work aims to elucidate the most effective stimulation sites and to characterize responder profiles, thereby also contributing to the development of more personalized and effective treatment strategies for DoC.

Finally, addressing the ethical landscape of severe brain injury management, Kreitzer et al. delve into the challenges of prognostication and communication with patients' families. In their brief research report "*Prognostic humility and ethical dilemmas after severe brain injury: Summary, recommendations, and qualitative analysis of Curing Coma Campaign virtual event proceedings,*" the authors call for a multidisciplinary approach

to patient care, emphasizing the importance of transparency, empathy, and collaboration in addressing the ethical dilemmas faced by healthcare professionals in this field.

In conclusion, the collection of articles reviewed provides an overview of current advancements in the diagnosis, management and treatment of coma and DoC. The studies collectively address the complex nature of DoC, assess new therapeutic interventions, and emphasize the importance of precise diagnostic techniques and ethical considerations in patient care. As the field evolves, these articles offer a substantive framework that informs ongoing scientific inquiry and clinical practice, aiming to improve the understanding and management of patients with coma and DoC.

Author contributions

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Effects of short-term spinal cord stimulation on patients with prolonged disorder of consciousness: A pilot study

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Background: Spinal cord stimulation (SCS) can improve the level of awareness of prolonged disorder of consciousness (pDOC), but its application is restricted due to damage of invasive operation. Short-term spinal cord stimulation (st-SCS) in a minimally invasive manner will better balance the benefits and risks.

Objectives: This study focuses on the safety and efficacy of st-SCS for pDOC and reveals the modulation characteristics of different frequencies of SCS.

Methods: 31 patients received 2-week st-SCS treatment and 3-months follow-up. All patients were divided into two types of frequency treatment groups of 5 Hz and 70 Hz according to the postoperative electroencephalography (EEG) test. The efficacy was assessed based on the revised coma recovery scale (CRS-R).

Results: The results showed a significant increase in CRS-R scores after treatment ($Z = -3.668$, $p < 0.001$) without significant adverse effects. Univariate analysis showed that the minimally conscious state minus (MCS−) benefits most from treatment. Furthermore, two frequency have a difference in the time-point of the CRS-R score increase. 5 Hz mainly showed a significant increase in CRS-R score at 2 weeks of treatment ($p = 0.027$), and 70 Hz additionally showed a delayed effect of a continued significant increase at 1 week after treatment ($p = 0.004$).

Conclusion: st-SCS was safe and effective in improving patients with pDOC levels of consciousness, and was most effective for MCS−. Both 5 Hz and 70 Hz st-SCS can promote consciousness recovery, with 70 Hz showing a delayed effect in particular.

KEYWORDS

disorder of consciousness, minimally conscious state, short-term spinal cord stimulation, frequency, neuromodulation

Introduction

pDOC refer to the state of awakening and not recovering consciousness for more than 28 days after severe brain injury, which is mainly classified into two diagnoses: vegetative state or unresponsive wakefulness syndrome (VS/UWS) and minimally conscious state (MCS). The former is characterized by the presence of a sleep-wake cycle but lack of consciousness, while the latter is characterized by the presence of fluctuating and reproducible signs of consciousness (1). In 2011, Bruno et al. identified heterogeneity in the MCS and further divided it into minimally conscious state minus (MCS–) and minimally conscious state plus (MCS+), with the former having signs of low-level consciousness responses and the latter with language-related cognitive abilities (2).

In the treatment field of pDOC, non-invasive neuromodulation such as transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS) have been widely used in clinical practice for their safety, simplicity, and non-invasiveness (3). In recent years, the mesocircuit model has suggested that loss of consciousness after severe brain injury may be due to disruption of cortico-thalamic and cortico-cortical connections (4). The principle of treatment of the non-invasive neuromodulation determines its scope of effect to modulate only the cortico-cortical connections. Deep Brain Stimulation (DBS) (5), spinal cord stimulation (SCS) (6), and vagus nerve stimulation (VNS) (7), can directly modulate the neural circuit and are expected to be an effective means to solve "disorders of consciousness (DOC)." DBS has been found to be an modulation for the thalamocortical and thalamostriate loops (8–10), but indications of DBS for DOC includes no significant lesions of thalamus and displacement of deep nuclear cluster to ensure accurate implantation of electrodes. Therefore, the strict indications make it impossible to perform in many pDOC.

SCS has become an important and valid surgical therapy for DOC because its operation procedure is relatively easy, safe, and has a wide range of indications. Kanno et al. (11) first proposed the application of SCS to pDOC and achieved promising results. Subsequently, DellaPepa et al. summarized multiple SCS studies and found that 51.6% patients with pDOC showed recovery of consciousness and inferred the treatment effect is that SCS activates the thalamocortical pathway and increases cerebral blood flow through the ascending reticular activating system (12). Our research team also reported that 31.8% patients showed improvement in consciousness (6), and the above findings suggest that SCS can effectively promote the recovery of consciousness. The overall effective rate of SCS ranges from 20 to 40% (13).

A study on factors influencing the efficacy of SCS found that pDOC patients with a short duration of disease had a better chance of recovery of consciousness (14). Yamamoto et al. have the same findings. All 10 pDOC patients who recovered consciousness underwent the operation of SCS within 9 months after brain injury (13). However, the disadvantages of SCS, such as the significant injuries caused by invasive operations and the potential risk of implant rejection, prevented its early application in DOC like TMS and tDCS. Therefore, SCS is usually used to treat pDOC patients with a duration of disease of more than 3 months to avoid the spontaneous high-speed recovery of consciousness (15). But, excessive waiting time may result in missing the golden window to receive treatment.

More broadly, the treatment of spinal cord stimulation includes SCS and st-SCS whose electrodes are placed percutaneously to the spinal epidural for 2 weeks. st-SCS was firstly used clinically to ease pain (16, 17), and it also used as experimental treatment to test for response of patients with pain to SCS. If there is significant analgesia, electrodes of SCS will be permanently implanted a few weeks later to maintain control of pain symptoms (18). It is now accepted that early stage pain patients are particularly suitable for this therapy (19).

According to clinical experience, we have found that different frequencies of SCS have caused various effects on different patients with pDOC. However, immediate behavioral change after single stimulation of SCS is hard to detect at bedside, which makes it difficult to adjust parameters after operation. Recently, different frequency activities of EEG have been found to play an important role in the assessment of intervention efficacy (20), of which enhanced delta activity and down-regulated alpha activity are now generally considered to be consistent markers of low levels of consciousness (21). A previous study by our team found that the relative power in the delta band was significantly lower in pDOC patients with single stimulation of SCS at 5 and 70 Hz compared to pre-stimulation (22).

Given the minimally invasive, simple, and low-risk advantage and the proven experience in the application of pain. We attempted to treat pDOC patients with st-SCS, aiming to minimize the injuries caused by operation, expand the beneficiary population of SCS and advance the time of intervention as much as possible, balancing to some extent the contradiction between the earlier time of spinal cord stimulation intervention and spontaneous high-speed recovery in the first three months of onset. Meanwhile, to exclude the possibility of unsuitable frequency for individuals leading to ineffective st-SCS treatment and reveal the characteristics of clinical modulation of different frequencies of SCS, the present study has two different frequencies treatment groups and individualized treatment frequency of st-SCS is selects by EEG.

Abbreviations: pDOC, Prolonged disorders of consciousness; tDCS, transcranial direct current stimulation; rTMS, repetitive transcranial magnetic stimulation; DBS, Deep Brain Stimulation; SCS, spinal cord stimulation; VNS, vagus nerve stimulation; RMANOVA, repeated measures ANOVA.

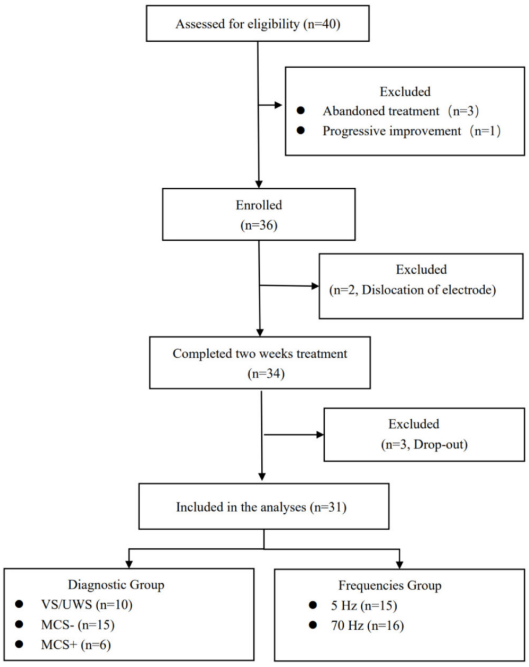

FIGURE 1
Study flow diagram. Diagnosis VS/UWS, vegetative state or unresponsive Wakefulness Syndrome; MCS−, minimally conscious state minus; MCS+, Minimally Conscious State plus.

Materials and methods

Study subjects

Forty patients with pDOC were recruited for this study at Beijing Tiantan Hospital, Capital Medical University, from November 2021 to March 2022. 9 patients finally were excluded and the details is showed in Figure 1. 31 included patients were aged 18–67 years (45.19 ± 15.33), with the duration of disease of 3–23 months (7.78 ± 5.49), preoperative CRS-R score of 3–15 (8.52 ± 3.05), and gender (25 male/6 female). Their etiologies were 10 traumatic brain injury (TBI), 18 stroke, and 3 ischemia and anoxia (IAA). They were divided into three clinical diagnostic subgroups according to the CRS-R scale, including 10 VS/UWS, 15 MCS−, and 6 MCS+ (Table 1).

All enrolled patients met the following inclusion criteria: (1) definitive diagnosis as DOC; (2) age 18–70 years; (3) duration of disease more than 3 months; (4) consciousness was in a stable phase for at least 4 weeks before enrollment and (5) patient's family members agreed to undergo the operation of st-SCS and had signed an informed consent form. Exclusion criteria included (1) neurodegenerative diseases such as Alzheimer's disease and Lewy body dementia; (2) coma caused or complicated by the deterioration of systemic diseases, or those who were not expected to survive long; (3) seizures that were difficult to control; (4) normal spine and spinal canal structure, no history of spinal cord injury, no cervical cone fracture or significant spinal stenosis, or other contraindications to operation; (5) those who are undergoing experimental drug or instrumentation trials.

Surgical procedure

The st-SCS operation is performed under general anesthesia as follows: (1) cervical MRI was performed before the operation to locate the target segment and spinal cord condition; (2) intraoperatively, the patient was placed in a prone position, with the neck flexed forward, and 8 contacts stimulation electrode (3777; Medtronic, Minneapolis, USA) was placed into the epidural space at the T7/8 level by skin puncture, and the tip of the electrode was implanted along the midline of the spinal cord to the C2 level under X-ray fluoroscopic guidance within the epidural space gap (Figure 2A); (3) the electrode extension was connected to an external pulse generator and battery (37022; Medtronic, Minneapolis, USA); (4) the puncture needle was withdrawn and the electrode leads were sutured and secured to the dorsal skin.

Cervical CT was reexamined within 24 h after the operation to observe the electrode position. The electrode was removed 2 weeks after the stimulation was turned on, and the cervical CT was reexamined within 24 h before the electrode removal to reconfirm the electrode position (Figure 2B) to ensure that this treatment process is an effective stimulation.

EEG recording

EEG signals were recorded online at the bedside at a sampling rate of 500 Hz using an EEG acquisition device (Nicolet EEG V32, Natus Neurology, USA) with 32 Ag/AgCl electrodes based on the international standard 10–20 system setup. All electrodes were set with FCz as the reference electrode and AFz as the ground electrode. The impedance between the electrodes and the patient's skin was always kept below 5 kΩ. Patients were kept awake during EEG monitoring. 19 electrodes (Fp1, Fp2, F3, Fz, F4, F7, F8, Cz, C3, C4, Pz, P3, P4, O1, O2, T3, T4, T5, T6) were selected for off-line visual EEG, and the EEG display parameters were set to trap 50 Hz, band-pass filtered to 1–40 Hz, reference to average reference, sensitivity to 70 uV/cm, and paper walking speed to 30 mm/s.

Stimulation protocol

The uppermost contact of the st-SCS was used for the stimulation contact cathode (0–1+2+). The stimulation pulse width was set to 120 us, the stimulation intensity ranged from 1.0

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TABLE 1 Demographic details for patients.

Patient	Gender	Age	Etiology	Post-injure (months)	CRS-R						
					Total	A	V	M	OM	C	Ar
VS/UWS											
P1	F	53	S	18	5	1	0	1	1	0	2
P2	M	36	A	3	7	1	1	2	1	0	2
P3	F	32	S	4	7	1	1	2	1	0	2
P4	M	55	S	3	3	0	0	2	1	0	0
P5	F	67	T	5	6	1	1	2	1	0	1
P6	M	54	T	12	7	1	1	2	1	0	2
P7	F	20	S	13	4	1	0	1	1	0	1
P8	F	64	T	7	4	1	0	1	1	0	1
P9	F	59	S	5	7	1	1	2	1	0	2
P10	F	30	S	12	7	1	1	2	1	0	2
MCS–											
P1	F	63	T	6	11	2	3	3	1	0	2
P2	F	59	S	14	9	1	3	2	1	0	2
P3	F	48	S	23	10	1	0	5	2	0	2
P4	F	45	T	7	6	0	3	1	0	0	2
P5	F	21	T	5	8	0	3	2	1	0	2
P6	F	52	S	4	9	1	3	2	1	0	2
P7	F	18	A	6	8	1	3	1	1	0	2
P8	M	49	S	9	8	0	3	2	1	0	2
P9	F	64	S	8	8	1	3	1	1	0	2
P10	F	18	T	3	8	0	3	2	1	0	2
P11	F	61	T	5	11	0	3	1	1	0	2
P12	F	58	S	3	7	0	3	1	1	0	2
P13	F	56	S	4	8	1	3	2	1	0	2
P14	F	35	T	3	8	1	1	2	1	1	2
P15	F	34	H	4	8	1	1	3	1	0	2
MCS+											
P1	F	28	S	8	14	3	4	4	1	0	2
P2	M	31	T	9	15	3	4	5	1	0	2
P3	M	56	S	9	15	3	4	5	1	0	2
P4	F	40	A	5	12	3	4	3	0	0	2
P5	F	36	S	23	11	3	3	1	2	0	2
P6	F	59	S	4	13	3	3	2	2	1	2

Gender (F, female; M, male); Etiology (A, anoxic; T, traumatic brain injury; S, stroke); CRS-R, Coma recovery scale-revised (A, auditory function; V, visual; M, motor; OM, oromotor; C, communication; Ar, arousal).

to 3.0 V, and the individualization stimulation intensity was set according to the Previous clinical study of SCS in the treatment of pDOC: 5 Hz stimulation induces bilateral upper limb tremors (13), and 70 Hz stimulation just did not induce significant limb movements (6).

Our prior study showed that frequency selection is crucial for the efficacy of spinal cord electrical stimulation (22). Therefore, in this study, patients were individually selected for appropriate frequencies based on the postoperative EEG test. The EEG test proceeded as follows: all patients received continuous stimulation at a single frequency of 5 or 70 Hz for 15 mins, and resting EEG was monitored for 30 mins before and after stimulation. The two frequency tests were at least 24 h apart to elute the residual effect of the last stimulus, and their sequences were performed in a pseudo-randomized manner. The test was completed 2 days after the operation (see Figure 3).

Two experienced electrophysiologists were offline and each independently visually observed changes in EEG background activity before and after stimulation, both without knowledge of the entire study. An increase in alpha rhythm (8–13 Hz) or a

decrease in delta rhythm (1–4 Hz) was taken as an improvement in EEG activity. The treatment frequency was eventually set to the frequency that caused the best improvement in EEG after stimulation (Figure 4).

On-stimulation time was less than the off-stimulation time to reduce neuronal fatigue or damage (15). Therefore, the stimulation cycle was chosen to be 5 min ON/15 min OFF. To meet the patients' normal sleep requirements, stimulation was turned on at 8 am and off at 8 pm for a total of 2 weeks of on-stimulation treatment.

All patients underwent routine rehabilitation: passive limb training and swallowing function training throughout the study. In order to attribute the efficacy to stSCS as much as possible, the enrolled patients not underwent non-invasive neuromodulation treatments such as TMS and tDCS.

Clinical assessments and follow-up

Changes in the patient's state of consciousness were assessed based on the CRS-R scale (1) in three phases: before treatment (2 weeks before operation, T0), treatment (1 week, T1, 2 weeks, T2), and post-treatment follow-up (1 week, T3, 3 months, T4) (Figure 5A). At least three times assessments by CRS-R were performed 2 weeks before the operation to clarify the patient's level of consciousness and clinical diagnosis before treatment. Effective clinical outcomes of st-SCS is that patients showed a clinical diagnostic improvement.

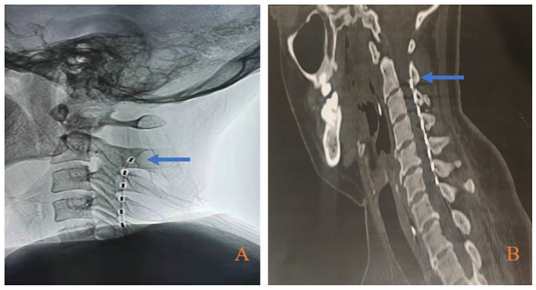

FIGURE 2
Electrode placement position. **(A)** Electrode position during operation; **(B)** Electrode position before electrode extraction. Bule arrow indicate the second cervical vertebra (C2) level.

Statistical analysis

IBM SPSS Statistics 26 software was used for statistical analysis. The effect of the time factor on the CRS-R score was analyzed by one-way repeated measures ANOVA (RMANOVA), and the effect of the frequency grouping factor and the time factor was analyzed by two-way RMANOVA. The *post hoc* test was adopted as the Least significant difference t-test; The difference in CRS-R scores before and after treatment was tested by Wilcoxon signed-rank test. And the difference between groups was tested by Mann-Whitney test for measurement data and were tested by the chi-square test or Fisher exact test for count data. The rate of change of subscale between pre-treatment and post-treatment [(mean post-treatment CRS-R − mean pre-treatment CRS-R)/(mean pre-treatment CRS-R + mean post-treatment CRS-R)] (23).

Results

Feasibility and safety

Fifiteen patients with pDOC of whom received 5 Hz stimulation and 16 of whom received 70 Hz stimulation. There were no epidural hematoma formation during electrode placement, and no seizures or intracranial infections during stimulation.

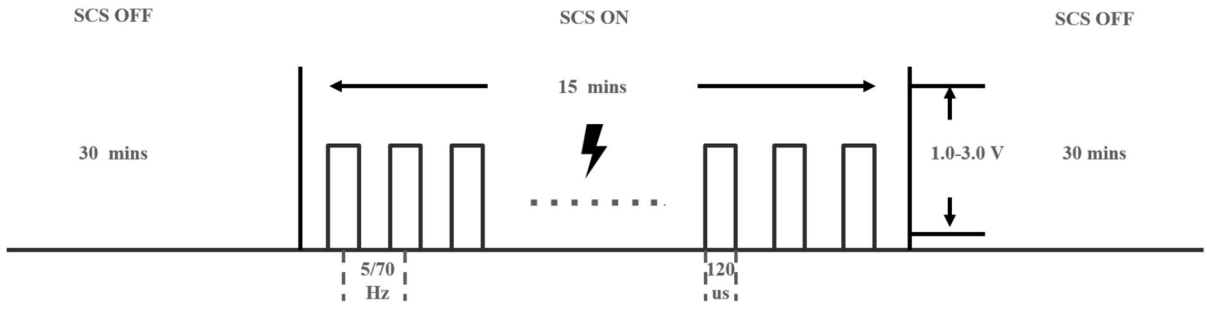

FIGURE 3
The stimulation paradigm of st-SCS.

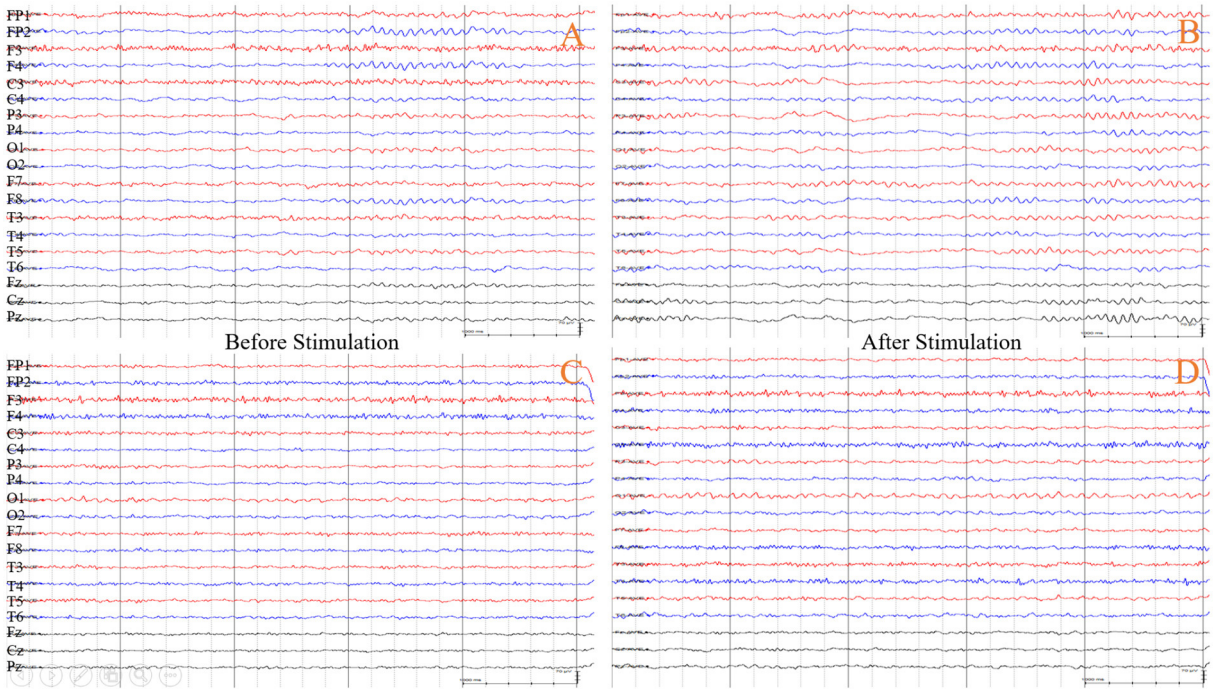

FIGURE 4
EEG responsiveness to different stimulation frequencies of st-SCS in a patient (he chose 5 Hz as the treatment frequency). **(A)** Before the stimulation at 5 Hz, the waking EEG background activity showed all lead is characterized by low-medium wave amplitude 9–10 Hz alpha rhythm activity, no obvious dominant rhythm in the occipital region, and poor modulation amplitude. **(B)** After stimulation at 5 Hz, the waking EEG background activity shows an increase in frequency to 11–12 Hz compared to the **(A)**, with improved modulation and higher amplitude. **(C,D)** Before and after stimulation at 70 Hz, the waking EEG background activity did not change significantly.

Clinical effect of st-SCS treatment

Diagnostic improvement was found in 15 patients at 3 months of follow-up with an overall effective rate of 48% (15/31) (Table 2).

The MCS had an effective rate of 62% (13/21), while the VS/UWS is 20% (2/10), however, there was no significant difference in effectiveness between the two diagnostic groups (2 × 2 Fisher exact test, $p = 0.054$). Further subdivision of the MCS diagnostic revealed a statistical difference between the effective and ineffective groups for the three diagnostic subgroups (2 × 3 Fisher exact test, $p = 0.002$) (Table 3). The MCS– had an effective rate of 80% (12/15) and the MCS+ is 17% (1/6). Further *post hoc* revealed that st-SCS for MCS– had significantly higher effective rate than VS/UWS (OR = 16, 95% CI: 2.165–118.27; $p = 0.005$) and MCS+ (OR = 20, 95% CI: 1.655–241.723; $p = 0.014$), while there was no statistically significant difference between MCS+ and VS/UWS with similar effective rate ($p > 0.05$). Specifically, 20% VS/UWS improved to MCS+, 75% MCS– improved to MCS+ But, only 25% MCS– improved to EMCS, and similarly only 17% MCS+ improved to EMCS (Figure 6). As for the CRS-R subscale (Figure 7), except for arousal function ($Z = -1.613$, $p = 0.107$), st-SCS significantly improved the other five functions (Wilcoxon signed-rank test, $p < 0.05$), with the greatest improvement in visual function (31%) and communication function (78%).

In addition, although the effective rate of the 70 Hz was higher than the 5 Hz [56% (9/16) vs. 40% (6/15)], there was no statistically significant difference in the frequency between the effective and ineffective groups ($X^2 = 0.366$, $p = 0.479$) (Table 3). Similarly, although the median duration of disease (5 vs. 7.5 months) and age (48 vs. 51 years) were lower in the effective group than in the ineffective group, there was no statistically significant difference between the two groups ($p > 0.05$) (Table 3).

Regulation characteristics of different frequencies of stSCS

st-SCS significantly improved CRS-R scores (T0:8.00 vs. T1:11.00, $Z = -3.668$, $p < 0.001$) (Figure 8A). One-way RMANOVA revealed a statistically significant main effect of Time (T0, T1, T2, T3, T4) [$F_{(2.005,60.163)} = 15.210$, $p < 0.001$)]. *Post hoc* revealed that the CRS-R score failed to improve significantly at 1 week of treatment (T0: 8.52 ± 3.054 vs. T1: 9.19 ± 3.66, $p = 0.103$), while a significant increase in CRS-R score could be seen at 2 weeks of treatment (T1: 9.19 ± 3.66 vs.

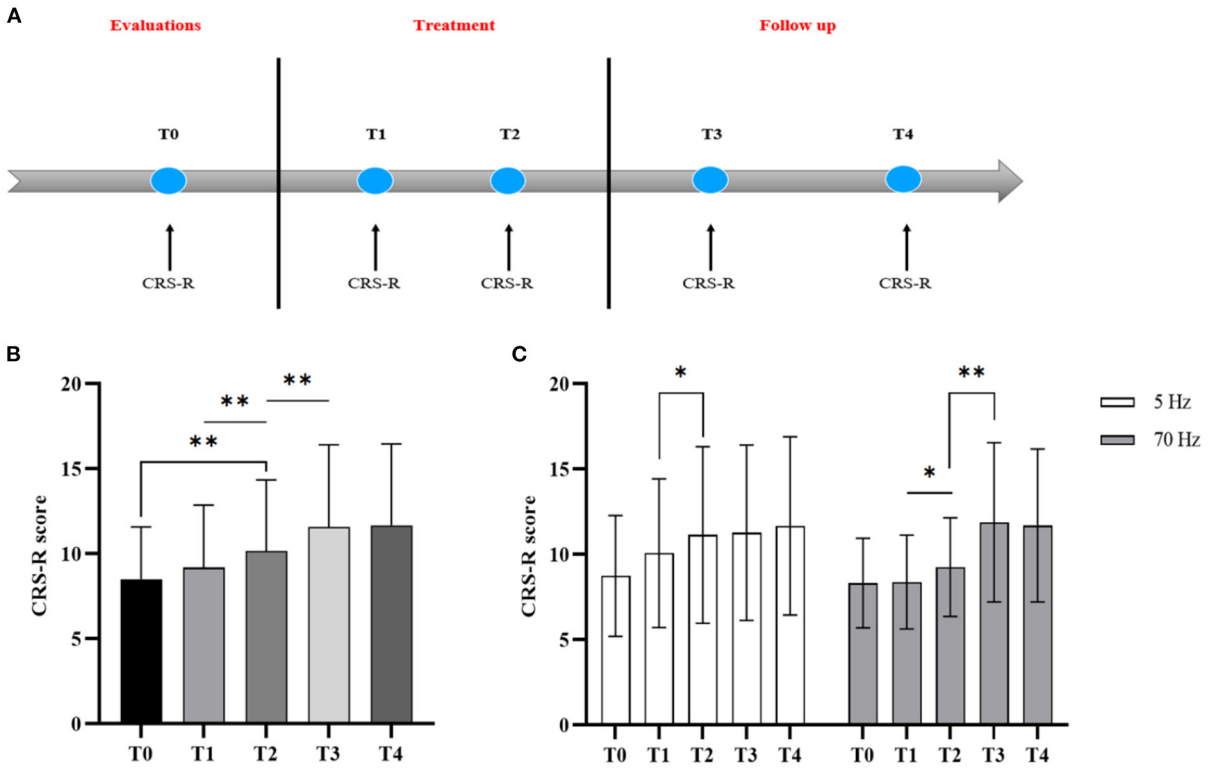

FIGURE 5
CRS-R changes with treatment going at five-time points: before the treatment (T0), treatment of 1 week (T1), treatment of 2 weeks (T2), 1 week after treatment (T3), and 3 months follow-up (T4). **(A)** Study protocol timeline showing treatment effects of stSCS evaluated with CRS-R, **(B)** CRS-R changes at five-time points, **(C)** CRS-R changes of different frequency groups at five-time points. Asterisk indicates significant differences based on One-way RMANOVA (*$p < 0.05$; **$p < 0.01$).

T2: 10.16 ± 4.19, $p = 0.001$) and a further significant increase in CRS-R score at 1 week after treatment (T2: 10.16 ± 4.188 vs. T3: 11.58 ± 4.82, $p = 0.004$), but the CRS-R score stabilized at 3 months of follow-up without a further increase (T3: 11.58 ± 4.82 vs. T4: 11.68 ± 4.78, $p = 0.742$) (Figure 5B).

As for the frequency subgroup (Figure 8B), regarding the time (T0, T4) ∗ frequency (5 Hz, 70 Hz) RMANOVA suggested a statistically significant effect of time [($p = 0.002$), $F_{(1, 14)} = 13.6$]. However, there was no statistical difference in the effect of frequency [($p = 0.979$), $F_{(1, 14)} = 0.001$]. One-way RMANOVA showed statistically significant effects of different frequencies respective time factors (T0, T1, T2, T3, T4) [5 Hz: $F_{(2.017,28.243)} = 5.623$, $p = 0.009 < 0.05$, 70 Hz: $F_{(1.212,18.183)} = 12.438$, $p = 0.002$]. *Post hoc* showed different clinical modulation characteristics between 5 and 70 Hz (Figure 5C). 5 Hz showed a significant increase in CRS-R score mainly at 2 weeks of treatment (T1: 10.07 ± 4.367 vs. T2:11.13 ± 5.167, $p = 0.027$), while 1 week after treatment (T2: 11.13 ± 5.167 vs. T3: 11.27 ± 5.133, $p = 0.334$), and 3 months follow-up (T2: 11.13 ± 5.167 vs. T4:11.67 ± 5.233, $p = 0.486$) did not continue to increase. In contrast, 70 Hz was able to significantly increase CRS-R score at 2 weeks of treatment (T1: 8.37 ± 2.754 vs. T2:9.25 ± 2.887, $p = 0.025$) and CRS-R scores continued to significantly increase after 1 week of treatment (T2: 9.25 ± 2.887 vs. T3: 11.88 ± 4.66, $p = 0.004$), but CRS-R scores stabilized during 3 months of follow-up (T3: 11.88 ± 4.66 vs. T4:11.69 ± 4.48, $p = 0.383$).

Discussion

Our work demonstrates the safety and feasibility of st-SCS in the treatment of pDOC, with an overall effective rate of 48%. At the same time, we found that although there was no difference in the effective rate of st-SCS between 5 and 70 Hz, there were different clinical modulation characteristics, and especially 70 Hz showed a significant delayed effect.

To verify the effectiveness of st-SCS and exclude the interference of natural recovery as much as possible, the study chose the same time of enrollment (3 months after onset brain injury) as conventional SCS (6, 15). And, we adopted a self-controlled design. The stable level of consciousness in pre-treatment and post-treatment may attribute the improvement of CRS-R to the treatment of st-SCS.

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TABLE 2 Changes in CRS-R at different time-points.

Patient	T0	T1	T2	T3	T4	Changes of diagnosis
	CRS-R: Total (A V M OM C Ar)					
VS/UWS						
P1[b]	5 (101102)	5 (101102)	6 (102102)	6 (102102)	5 (101102)	Remained VS/UWS
P2[a]	7 (112102)	5 (002102)	5 (002102)	5 (002102)	4 (002002)	Remained VS/UWS
P3[b]	7 (112102)	7 (112102)	9 (132102)	11 (332102)	11 (332102)	VS/UWS improved to MCS +
P4[a]	3 (002100)	4 (102100)	4 (102100)	4 (102100)	4 (102100)	Remained VS/UWS
P5[b]	6 (112101)	4 (102100)	5 (012101)	6 (012102)	6 (012102)	Remained VS/UWS
P6[b]	7 (112102)	7 (112102)	7 (112102)	7 (112102)	7 (112102)	Remained VS/UWS
P7[a]	4 (100102)	4 (100102)	4 (100102)	4 (100102)	4 (100102)	Remained VS/UWS
P8[b]	4 (101101)	5 (101102)	6 (111102)	8 (311102)	8 (311102)	VS/UWS improved to MCS +
P9[a]	7 (112102)	7 (112102)	7 (112102)	7 (112102)	7 (112102)	Remained VS/UWS
P10[b]	7 (112102)	7 (112102)	7 (112102)	7 (112102)	8 (112202)	Remained VS/UWS
MCS–						
P1[a]	11 (233102)	18 (346113)	18 (346113)	18 (346113)	14 (244112)	MCS– improved to MCS+
P2[b]	9 (123102)	9 (123102)	9 (123102)	18 (456102)	15 (345102)	MCS– improved to MCS+
P3[b]	10 (105202)	11 (105302)	12 (105312)	14 (305312)	14 (305312)	MCS– improved to MCS+
P4[a]	6 (031002)	8 (032102)	9 (132102)	11 (133202)	13 (133202)	Remained MCS–
P5[b]	8 (032102)	9 (132102)	9 (132102)	18 (453123)	18 (453123)	MCS– improved to EMCS
P6[b]	9 (132102)	8 (032102)	11 (332102)	16 (452122)	16 (452122)	MCS– improved to EMCS
P7[a]	8 (131102)	13 (343102)	15 (345102)	15 (345102)	18 (455112)	MCS– improved to MCS+
P8[b]	8 (032102)	8 (032102)	8 (032102)	8 (032102)	8 (032102)	Remained MCS–
P9[b]	8 (132101)	8 (132101)	8 (132101)	11 (332102)	11 (332102)	MCS– improved to MCS+
P10[b]	8 (032102)	9 (132102)	14 (333302)	20 (453323)	20 (453323)	MCS– improved to EMCS
P11[b]	11 (233102)	11 (233102)	11 (233102)	14 (343202)	14 (343202)	MCS– improved to MCS+
P12[a]	7 (031102)	9 (231102)	10 (232102)	10 (232102)	10 (232102)	Remained MCS–

(Continued)

TABLE 2 (Continued)

Patient	T0	T1	T2	T3	T4	Changes of diagnosis
	CRS-R: Total (A V M OM C Ar)					
P13[a]	8 (113102)	10 (313102)	10 (313102)	10 (313102)	16 (315322)	MCS– improved to MCS+
P14[a]	8 (112112)	15 (345102)	17 (453112)	17 (453112)	17 (453112)	MCS– improved to MCS+
P15[a]	8 (113102)	8 (113102)	11 (313112)	11 (313112)	11 (313112)	MCS– improved to MCS+
MCS+						
P1[a]	14 (344102)	14 (344102)	14 (344102)	14 (344102)	14 (344102)	Remained MCS+
P2[a]	15 (345102)	15 (345102)	21 (456123)	21 (456123)	20 (456122)	MCS+ Improved to EMCS
P3[b]	15 (345102)	15 (345102)	15 (345102)	15 (345102)	15 (345102)	Remained MCS+
P4[a]	12 (343002)	8 (231002)	9 (331002)	9 (331002)	9 (331002)	Remained MCS+
P5[b]	11 (331202)	11 (331202)	11 (331202)	11 (331202)	11 (331202)	Remained MCS+
P6[a]	13 (332212)	13 (332212)	13 (332212)	13 (332212)	14 (332213)	Remained MCS+

Clinical diagnosis (VS/UWS, vegetative state or unresponsive wakefulness syndrome; MCS−, minimally conscious state minus; MCS+, minimally conscious state plus; EMCS, emerged from MCS); Frequencies ([a]5 Hz; [b]70 Hz); CRS-R, Coma recovery scale-revised (A, auditory function; V, visual; M, motor; OM, oromotor; C, communication; Ar, arousal).

It is now generally accepted that VS/UWS and MCS have significant structural differences, with autopsies of VS/UWS patients revealing extensive death of neurons throughout the thalamus, subcortical white matter leading to widespread disconnections between different cortical regions (14), which makes the functional brain regions unable to work together, and information cannot be efficiently integrated and processed. Hence, This Cortico-cortical connectivity in VS/UWS is less likely to enhance through ascending impulses by SCS to reproduce the consciousness network. In contrast, MCS has relatively more intact brain structures, higher plasticity, and higher sensitivity to external stimuli. A series of studies also confirmed that there is a higher therapeutic value of SCS among MCS patietns compared to VS/UWS (6, 13). However, the study found no significant difference in effective rate of st-SCS between MCS and VS/UWS, and we found similar effective rate of st-SCS between MCS+ and VS/UWS with p values close to 1. We further subdivided MCS into MCS– and MCS+. The analysis revealed there is significant higher effective rate of st-SCS among MCS patients compared with the VS/UWS and the MCS+. Unlike previous SCS studies, st-SCS was not effective for the MCS+. The findings suggest that st-SCS is difficult to enable pDOC to break through the MCS+ and recover full consciousness.

Patients with emerging from MCS (EMCS) have higher cognitive functions and motor coordination. Both the global neuronal workspace theory (24) and the integrated information theory (25), suggest that consciousness arises from the interaction and integration of information by different neural networks or cognitive modules. The thalamocortical and cortical-cortical connections of the brain network are the core neural loops for the generation and maintenance of consciousness. The frontoparietal cortical network is considered to be the "hub" network of consciousness and is connected *via* the central thalamus. Recent anesthetized macaques studies have found that 50 Hz stimulation of the central thalamus can promote its project to frontoparietal cortex and further strengthens the interconnections between the frontoparietal cortex (26). In the study of the mechanisms of down-up modulation of cortico-cortical connectivity by SCS, our team found significant changes in connectivity within the frontal cortex and across frontal-parietal and frontal-occipital brain regions during SCS stimulation, but only stimulation effects in the frontal cortex remained after cessation of stimulation, while stimulation effects across brain regions returned to pre-stimulation baseline levels (27). Another study also found that only an increase in frontal EEG complexity after SCS stimulation was associated with higher levels of consciousness in pDOC. This shows that the frontal cortex plays a central role in SCS for the regulation of brain activity. We hypothesize that SCS give priority to increasing the level of frontal cortex activity and then recreates the consciousness network through its strengthening

TABLE 3 Clinical variables comparisons between improvement and unimprovement.

Variables	Improvement ($n = 15$)	Unimprovement ($n = 16$)	Statistic value	*P*
Gender			NA[a]	0.172
Male	14	11		
Female	1	5		
Age	48 (31.0, 61.0)	51 (36, 57.5)	113.5[b]	0.8
[M(P_{25},P_{75})]				
Etiology			1.588[c]	0.208
TBI	7	4		
NTBI	8	12		
Post-injure [M (P_{25},P_{75}), months]	5 (4.0, 8.0)	7.5 (4.5, 12.0)	217.5 [b]	0.379
CRS-R onset [Mean (min, max)]	8.80 (4.0, 15.0)	8.25 (3.0, 15.0)	86 [b]	0.188
Frequencies			0.819 [c]	0.479
5 Hz	6	9		
70 Hz	9	7		
Diagnosis			11.335[a]	0.002*
VS/UWS	2	8		
MCS–	12	3		
MCS+	1	5		

[a]Fisher exact test; [b]Mann-Whitney U test; [c]Chi-square test; *$p < 0.05$; Etiology (TBI, traumatic brain injuries; NTBI, not traumatic brain injuries); Clinical diagnosis (VS/UWS, Vegetative state or Unresponsive Wakefulness Syndrome; MCS−, minimally conscious state minus; MCS+, minimally conscious state plus; EMCS, emerged from MCS).

of frontal-parietal and frontal-occipital cortical connections. In conclusion, st-SCS may cause an initial restoration of brain regions and connectivity in the consciousness loop by enhancing frontal cortical activity, leading to a substantial improvement in consciousness in MCS– with low levels of consciousness, but consciousness improvement caused by st-SCS stops at MCS+ probably because short-term stimulation does not sufficiently activate the frontoparietal functional network to cause effective connectivity of multiple cognitive modules and prolonged neural remodeling. Our study also found that the delayed effect lasted only 1 week, which corroborates this idea.

The stimulation frequency is one of the most critical parameters for SCS treatment. low-frequencies SCS activate neurons, while high frequencies (>60 Hz) produce inhibitory effects in the field of treatment for pain (28). However, positive recovery of consciousness effects of low-frequency and high-frequency SCS both have been reported in the field of treatment for DOC (6, 12, 13, 15, 29). However, there is no direct clinical study for comparison differences in treatment between low and high-frequency SCS for pDOC. In this regard, this study presents the first EEG-based preferential treatment frequency and compares the difference between 5 and 70 Hz modulation. However, We did not directly find a significant difference of effective rate of st-SCS, which may be limited by the sample size. In addition, we found an additional delayed effect of 70 Hz. In a previous study, functional near-infrared spectroscopy studies found significant increases in hemodynamic responses after a single high-frequency SCS. Especially, significant enhancement of functional connectivity between frontal-occipital lobes occurred after 70 Hz modulation. But no significant post-stimulation effects were found with low-frequency stimulation (30). Our team further found that there was a significant post-effect of 70 Hz SCS based on EEG which showed a significant decrease in path length and a significant increase in small-world effect and tended to the normal control, as well as a strengthening of connectivity between frontal and posterior brain region (31). In conclusion, the sustained improvement of consciousness after high-frequency long-term

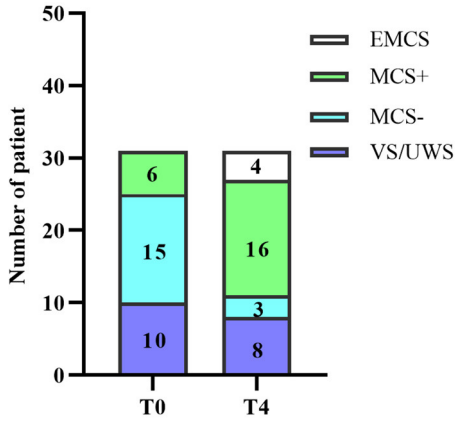

FIGURE 6
Changes in clinical diagnosis before and after treatment. T0: before the treatment; T4: 3 months follow-up.

stimulation may be a result of enhanced neuronal plasticity, allowing for the gradual enhancement of functional connectivity and information interaction in the thalamus-frontal nerve loop, which is closely related to conscious activity, and the recovery of sustained remodeling of functional networks throughout the brain.

The results should be interpreted with caution. Firstly, the study is an exploratory small sample study, and spontaneous recovery could not be completely excluded. Furthermore, small sample study has weak comparability between groups due to the great heterogeneity of pathological damage among individuals of pDOC, which preventing the set of controls group in this study. The relationship between duration of disease and the efficacy was not found in this study. On the one hand, the sample size was insufficient. On the other hand, restricted inclusion for early patients due to the consideration of mitigating the effect of spontaneous recovery on the outcome, which made the overall duration of disease in this study large. Therefore, there is a need to conduct future studies on ultra-early pDOC whose duration of disease is <3 months. In addition, in this study, we only used the CRS-R to quantify the efficacy of st-SCS, and future studies using more objective neuroimaging and neurophysiological assessment techniques to further understand the mechanisms of neuromodulation. Finally, our work indicates that st-SCS has limited efficacy. The combined activation of multiple brain regions by non-invasive neuromodulation techniques and st-SCS is also a promising therapy for the future.

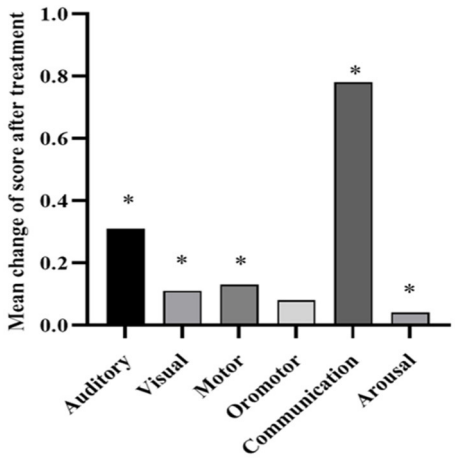

FIGURE 7
CRS-R subscale change rate before and after treatment. Wilcoxon signed-rank test indicates significant differences (*$p < 0.05$).

Conclusions

In this study, we found for the first time that st-SCS is a safe and effective therapy for patients with pDOC, and it is particularly suitable for MCS–. In addition, we found the modulation characteristics of the two types of frequencies 5 Hz and 70 Hz differed, with the former improving consciousness mainly during stimulation and the latter showing additional post-stimulation delay effects. Although we did not find a significant effect of age and duration of disease on the efficacy of st-SCS, we found that the two factors in the effective group

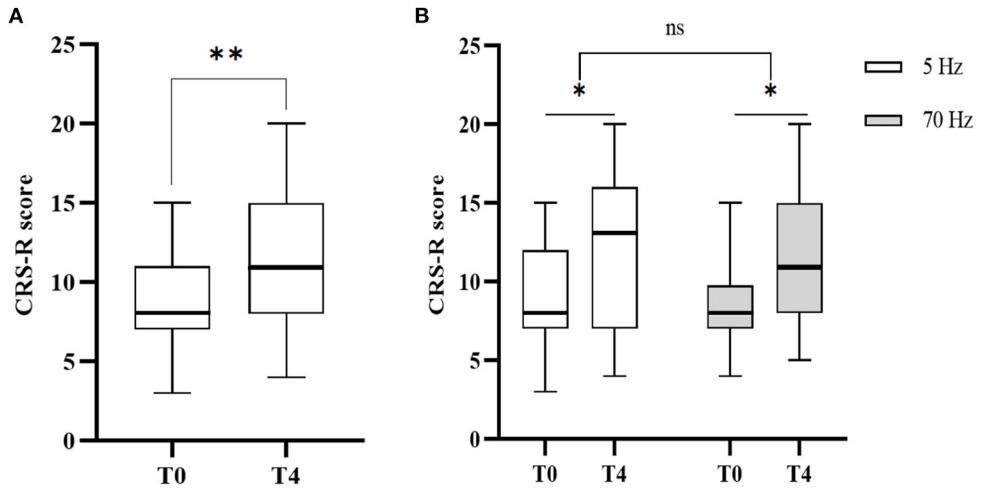

FIGURE 8
CRS-R changes before the treatment (T0) and 3 months follow up (T4). **(A)** CRS-R changes before and after the treatment. Wilcoxon signed-rank test indicates significant differences (**$p < 0.01$). **(B)** CRS-R changes in different frequency groups before and after the treatment. Two-way RMANOVA indicates significant differences (*$p < 0.05$), ns not statistically significant.

were lower than those in the ineffective group, which may need to be verified with a larger sample size, especially with the inclusion of pDOC patients with duration of diseases <3 months. In conclusion, this study provides a new perspective on the treatment of pDOC patients with SCS and provides a basis for the selection and modulation of postoperative stimulation parameters.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The study protocol was registered at the Chinese Clinical Trial Registry (ChiCTR2200061278) and was approved by the Ethics Committee of Beijing Tiantan Hospital, Capital Medical University (No. KYSQ 2021-396-01). The verbal and written informed consents were obtained prior to the study. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Conceptualization: YZ and JH. Methodology: YZ and YY. Data curation: XC and XG. Formal analysis, investigation, and writing—original draft preparation: YZ. Writing—review and editing: JH and JZ. Funding acquisition: JH and LX. Resources: XC. Supervision: JH. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Short-term spinal cord stimulation in treating disorders of consciousness monitored by resting-state fMRI and qEEG: The first case report

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Disorders of consciousness (DOC) are one of the most frequent complications in patients after severe brain injury, mainly caused by trauma, stroke, and anoxia. With the development of neuromodulation techniques, novel therapies including deep brain stimulation (DBS) and spinal cord stimulation (SCS) have been employed to treat DOC. Here, we report the case of a DOC patient receiving short-term SCS (st-SCS) treatment and showing improvement monitored by resting-state fMRI (rs-fMRI) and quantitative EEG (qEEG). A 35-year-old male with severe traumatic brain injury remained comatose for 3 months. The patient was evaluated using JFK coma recovery scale—revised (CRS-R) and showed no improvement within 1 month. He received st-SCS surgery 93 days after the injury and the stimulation was applied the day after surgery. He regained communication according to instructions on day 21 after surgery and improved from a vegetative state/unwakefulness syndrome to an emergence from a minimally conscious state. To our knowledge, this report is the first published case of st-SCS in a patient with DOC. These results shed light that st-SCS may be effective in treating certain patients with DOC, which may reduce patients' suffering during treatment and lessen financial burden.

KEYWORDS

spinal cord stimulation, disorders of consciousness, fMRI, EEG, treatment

Introduction

Disorders of consciousness (DOC) are one of the most frequent complications in patients after severe brain injury, mainly caused by trauma, stroke, and anoxia (1). Besides drugs, clinicians have tried some non-invasive and invasive neuromodulation technologies, but few of them were proven to improve patients' consciousness levels (2, 3). Patients with DOC impose a burden on medical resources and raise ethical issues. Therefore, it is necessary to develop effective and economic interventions for DOC.

With the development of neuromodulation techniques, novel therapies including deep brain stimulation (DBS) and spinal cord stimulation (SCS) have been employed to treat DOC. In cervical SCS, electrodes were implanted at the midline of the posterior epidural space of C2-C4 level and delivered electric stimulation to the dorsal column. The SCS technology was classically used for pain management, based on the concept of gate control theory (4). Kanno et al. firstly applied this technique to patients with DOC and showed encouraging results (5). However, the previous studies were based on permanent SCS (39286, Medtronic, USA) techniques, which present certain limitations, such as permanent foreign body implantation, high costs of batteries, and difficulty in maintenance. Based on our previous work, SCS with the percutaneous electrode (3777, Medtronic, USA) may also have a positive effect on the rehabilitation of patients with DOC (6–9). The characteristics of SCS with percutaneous electrodes are non-invasive, low cost, and early intervention making it more widely used. Here, we report the first case of percutaneous short-term SCS (st-SCS) in the treatment of a patient with DOC.

Case description

Patients

A 35-year-old male presented with severe traumatic brain injury. On admission, he was evaluated using the JFK coma recovery scale—revised (CRS-R, Table 1). He could open his eyes autonomously with no signs of attention or visual tracking and expressed an auditory panic and abnormal posture from pain stimulation. The CRS-R score was 7 points (1-1-2-1-0-2) and was diagnosed as vegetative state/unwakefulness syndrome (VS/UWS). Within 1 month before admission, no improvement in consciousness was observed.

Surgical procedures

Relatives gave consent to the st-SCS treatment. On the 93 days after the injury, after general anesthesia, the patient was placed in a prone position, and the T7/8 intervertebral space was positioned under C-arm as the puncture point. The electrode (3777, Medtronic, USA) was placed at the C2 level and fixed (Supplementary Figure S1). The day after the st-SCS operation, electric stimulation was applied to the patient's dorsal column with a voltage of 2.5 V, and a frequency of 70 Hz with 120us wave width. The stimulation was performed in 15-min on/15-min off cycles from 8 AM to 8 PM. The overall stimulation lasted for 21 days and then the electrode was removed.

Postoperative evaluation

Three physicians, who were not in charge of the st-SCS treatment, individually assessed the consciousness level repeatedly. The average of CRS-R was recorded as the final score. Data preprocessing and calculation were consistent with our previous studies and were shown in Appendix S1. Cervical CT scan and VRT reconstruction after SCS implantation are shown in Supplementary Figure S2. On the third day postoperatively (T2), the consciousness level of the patient was slightly improved, mainly manifesting as auditory localization. Then the patient showed visual localization and pain stimulation localization after 7 days. Compliance movement and visual tracking also appeared repeatedly, and he could grasp objects after 14 days. On day 21, he regained the ability to use motor movement expressing whether he ate or urinated. During the final evaluation on day 28, he could communicate according to instructions and was diagnosed as minimally conscious state (MCS). The specific scores are shown in Table 1.

Imaging results

To test the recovery process in the brain function, we performed fMRI and qEEG examinations before and after the st-SCS treatment. The level of preoperative fMRI or qEEG results were considered the baseline level. The preoperative upper limb sensory evoked potential and auditory brainstem response were shown in Supplementary Figure S3. After st-SCS treatment, the patient underwent fMRI and qEEG examinations, and the specific methods are shown in Appendix S1. We found brain area features of the anterior medial pre-frontal cortex (aMPFC) and posterior cingulated cortex (PCC) in the default mode network (DMN), and the dorsal medial prefrontal cortex (DMPFC) in the executive control network (ECN) represented a trend toward the functional connection pattern of normal controls. Functional connectivity between aMPFC in the DMN and DMPFC in the ECN was also changed significantly (Figure 1A). We also found brain activity, amplitude, and rhythm in EEG increased (Figure 1B), and the whole brain ordering entropy changes of patients were compared by the topographic map (Figure 1C). The results showed that the whole brain permutation entropy (PE) increased after treatment, and the change rates of frontal, central, and occipital brain areas were close, while the parietal brain area changed the most significantly. Finally, we found the channel information interaction increased after treatment (Figure 1D). The results indicate that the effect of the new surgical approach of st-SCS in this patient is similar to that of traditional long-term SCS implantation.

TABLE 1 Patient's CRS-R.

	T0 Admission	T1 Preoperative	T2 Day3	T3 Day7	T4 Day14	T5 Day21	T6 Day28
Auditory function scale							
4–Consistent movement to command *							
3–Reproducible movement to command *							
2–Localization to sound							
1–Response to auditory stimulation							
0–None							
Visual function scale							
5–Object recognition *							
4–Object localization: reaching *							
3–Visual pursuit *							
2–Fixation *							
1–Response to visual stimulation							
0–None							
Motor function SCALE							
6–Functional object use							
5–Automatic motor response *							
4–Object manipulation *							
3–Localization to noxious stimulation *							
2–Flexion withdrawal							
1–Abnormal posturing							
0–None							
Verbal function scale							
3 Understandable language *							
2 Vocalization/oral movement							
1 Oral reflex movement							
0–None							
Communication scale							
2–Functional: Accurate							
1–Non-functional: intentional							
0–None							
Arousal scale							
3–Attention							
2–Eye opening without stimulation							
1–Eye opening with stimulation							
0–Unarousable							
Total score	6	7	8	10	14	17	19

*The scale consists of 6 parts, separately representing auditory, visual, motor, verbal, communication, and arousal functions. The total score at each time point is listed. CRS-R, coma recovery scale-revised.

Discussion

Previous literature suggested DOC are the loss of function in certain eloquent brain areas, and the remaining brain functional areas lack sufficient connection or integration to support arousal or awareness. It was generally believed that direct stimulation to the dorsal column could improve such conditions, in ways such as enriching functional communication, motor performance, food intake, and object naming (10). The mechanism of SCS in the treatment of DOC has not yet been fully elucidated, and some studies suggested that the increase of cerebral blood flow and the changes in the expression of neurotransmitters played important roles (11–13). The positive results of fMRI and quantitative EEG indicate that the short-term effect of percutaneous puncture electrodes can activate the key regions and connections of the brain network. Our results

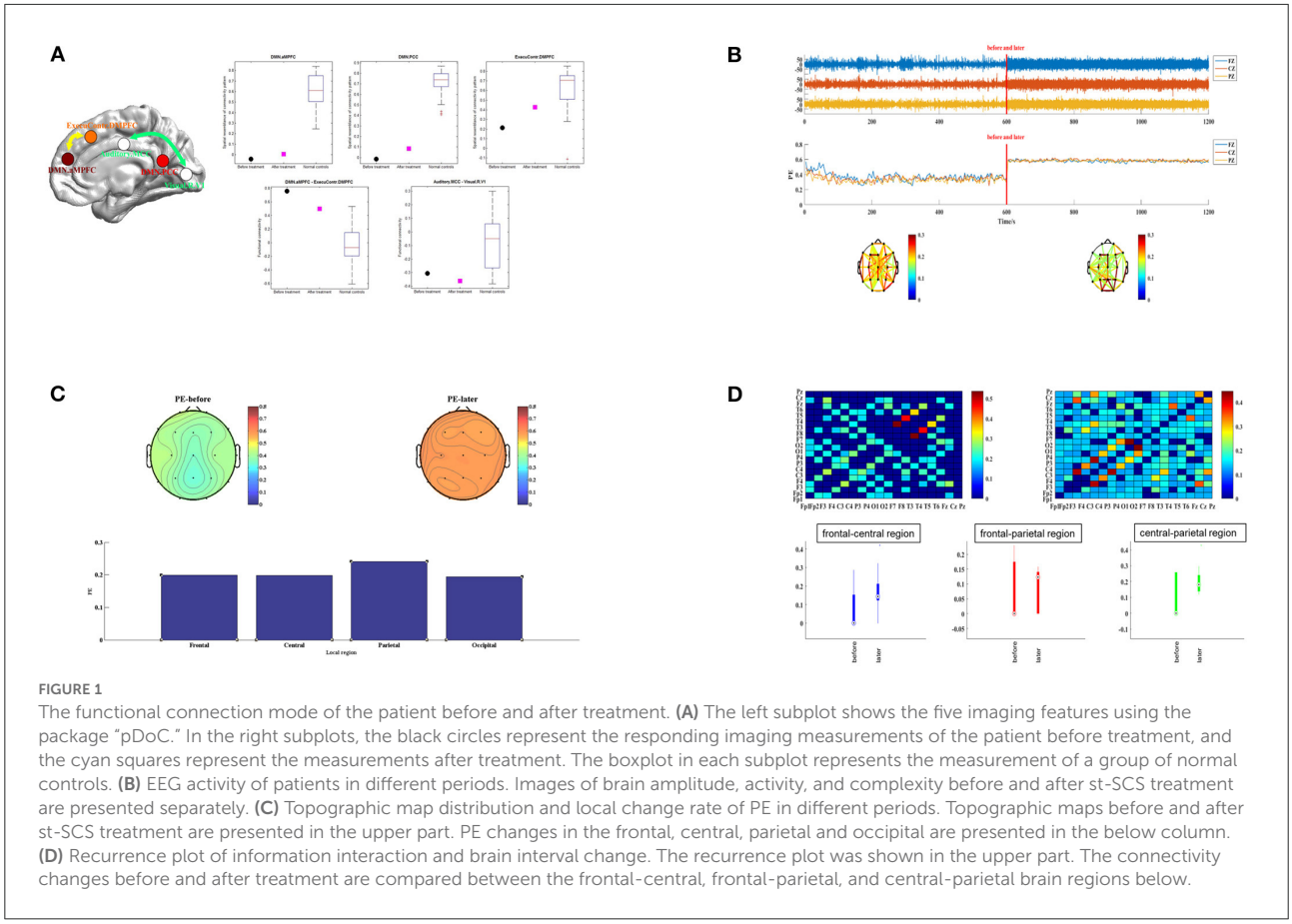

FIGURE 1
The functional connection mode of the patient before and after treatment. **(A)** The left subplot shows the five imaging features using the package "pDoC." In the right subplots, the black circles represent the responding imaging measurements of the patient before treatment, and the cyan squares represent the measurements after treatment. The boxplot in each subplot represents the measurement of a group of normal controls. **(B)** EEG activity of patients in different periods. Images of brain amplitude, activity, and complexity before and after st-SCS treatment are presented separately. **(C)** Topographic map distribution and local change rate of PE in different periods. Topographic maps before and after st-SCS treatment are presented in the upper part. PE changes in the frontal, central, parietal and occipital are presented in the below column. **(D)** Recurrence plot of information interaction and brain interval change. The recurrence plot was shown in the upper part. The connectivity changes before and after treatment are compared between the frontal-central, frontal-parietal, and central-parietal brain regions below.

indirectly elucidate the mechanism of SCS in treating DOC. The improvement suggests a significant therapeutic effect in an early stage such as st-SCS, which differ from the costly, invasive, and permanent electrode implantation. The surgical approach of temporary electrodes requires no cervical vertebra biting, and the skin incision position is relatively low at T7/8 intervertebral space, reducing the risk and invasiveness of the surgery. Therefore, the st-SCS can be activated the day after implantation while SCS permanent electrode implantation requires a 7–21-day surgical recovery period. Meanwhile, the morphology of the temporary electrode is much simpler than the permanent electrode, so the position of electrode pads can be closer to the midline and less prone to deviation, which is a direct factor affecting the effect of electrical stimulation. The outcome of this case suggests the positive therapeutic effect of st-SCS and short-term electric nerve stimulation for patients with DOC. In this way, the maximal clinical benefit can be obtained while avoiding those resulting side effects.

In this study, the possibility of spontaneous recovery could not be completely ruled out as there was only a single patient and no controls. However, according to previous studies, patients can achieve a better outcome as SCS performed earlier during the course of DOC. Meanwhile, there was no progressive increase or worsening of consciousness during the 4 weeks before the surgery, and a sudden spontaneous recovery after the surgery is considered less likely. Therefore, we considered that it is likely due to st-SCS given the possibility of natural evolution and improvement in this single patient study.

To our knowledge, this is the first case of st-SCS in a patient with DOC. The current case study sheds light on that st-SCS may potential be an effective way of treatment for certain patients with DOC, which may reduce patients' suffering during treatment and release the financial burden. Large-scaled randomized controlled trials are needed to confirm the preliminary findings.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of Beijing Tiantan Hospital, Capital Medical University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

YY designed the study. QH wrote the manuscript. JH supervised the study. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.968932/full#supplementary-material

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Repetitive transcranial magnetic stimulation over the posterior parietal cortex improves functional recovery in nonresponsive patients: A crossover, randomized, double-blind, sham-controlled study

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Background: Recent studies have shown that patients with disorders of consciousness (DoC) can benefit from repetitive transcranial magnetic stimulation (rTMS) therapy. The posterior parietal cortex (PPC) is becoming increasingly important in neuroscience research and clinical treatment for DoC as it plays a crucial role in the formation of human consciousness. However, the effect of rTMS on the PPC in improving consciousness recovery remains to be studied.

Method: We conducted a crossover, randomized, double-blind, sham-controlled clinical study to assess the efficacy and safety of 10 Hz rTMS over the left PPC in unresponsive patients. Twenty patients with unresponsive wakefulness syndrome were recruited. The participants were randomly divided into two groups: one group received active rTMS treatment for 10 consecutive days ($n = 10$) and the other group received sham treatment for the same period ($n = 10$). After a 10-day washout period, the groups crossed over and received the opposite treatment. The rTMS protocol involved the delivery of 2000 pulses/day at a frequency of 10 Hz, targeting the left PPC (P3 electrode sites) at 90% of the resting motor threshold. The primary outcome measure was the JFK Coma Recovery Scele-Revised (CRS-R), and evaluations were conducted blindly. EEG power spectrum assessments were also conducted simultaneously before and after each stage of the intervention.

Result: rTMS-active treatment resulted in a significant improvement in the CRS-R total score ($F = 8.443$, $p = 0.009$) and the relative alpha power ($F = 11.166$, $p = 0.004$) compared to sham treatment. Furthermore, 8 out of 20 patients classified as rTMS responders showed improvement and evolved to a minimally conscious state (MCS) as a result of active rTMS. The relative alpha power also significantly improved in responders ($F = 26.372$, $p = 0.002$) but not in non-responders ($F = 0.704$, $p = 0.421$). No adverse effects related to rTMS were reported in the study.

Conclusions: This study suggests that 10 Hz rTMS over the left PPC can significantly improve functional recovery in unresponsive patients with DoC, with no reported side effects.

Clinical trial registration: www.ClinicalTrials.gov, identifier: NCT05187000.

KEYWORDS

repetitive transcranial magnetic stimulation, disorders of consciousness, unresponsive wakefulness syndrome/vegetative state, randomized control trial, EEG

Introduction

Disorders of consciousness (DoC) resulting from severe brain injury are among the most challenging conditions encountered in clinical practice (1). They encompass a wide spectrum of conditions ranging from coma to vegetative stage/unresponsive wakefulness syndrome (VS/UWS) (2) to minimally conscious state (MCS) (3). Patients with VS/UWS exhibit reflexive behavior and are unable to perceive themselves or their surroundings (4). In contrast, MCS is characterized by the presence of non-reflexive, cortex-mediated behavior, and there is limited but discernible evidence of self-awareness or environmental awareness (5, 6). The long-term hospitalization of these patients leads to a significant increase in treatment costs, which places enormous pressure on individuals and society in terms of both economic and emotional suffering and raises a host of ethical and legal issues (7). Currently, the available treatments for patients with DoC are limited. However, neuromodulation technology, a non-pharmacological treatment, has been successfully applied to various neurological and psychiatric conditions and holds promise for the treatment of DoC (8).

Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive brain stimulation technique (NIBS) for the human brain. Compared to other NIBS, rTMS can be combined with neuronavigation to excite or inhibit some specific cerebral cortex areas of the brain below the coil (such as the M1 area) (9, 10). Similarly, it has a natural advantage in exploring more complicated domains of other cerebral functions (11). Recently, the rTMS guideline (12) has identified rTMS treatments as having Level A or B clinical evidence for neuropathic pain, depression, the post-acute stage of stroke, and Parkinson's motor function, proving that rTMS can modulate cortical excitability.

Several studies have successfully applied rTMS to treat patients with DoC in recent years. Most studies selected the intervention target of the left dorsal lateral prefrontal cortex (DLPFC). They believed that stimulating the DLPFC can strengthen thalamocortical and cortico-cortical connections and improve behavioral performance, EEG power spectrum, and estradiol levels, particularly in patients in MCS (13–20). However, according to Integrated Information Theory (IIT), consciousness is connected primarily with the posterior cortical areas (21), of which the posterior parietal cortex (PPC) has been demonstrated as the most critical consciousness-associative cortical region (22). It includes the superior marginal gyrus, the angular gyrus, and the precuneus, and it plays a key role in sensory and motor integration and is involved in various cognitive functions (23). Lin et al. (24) found that 14 sessions of rTMS treatment on the bilateral PPC improved clinical scores in one patient in MCS. Meanwhile, EEG and fMRI showed that the directional transfer function (DTF) of the posterior gamma band was significantly increased, and the activity of the inferior parietal lobule was recovered. Legostaeva et al. (25) applied 20 Hz rTMS on the left angular gyrus to 38 patients with DoC and showed improvement in the total CRS-R score in patients in MCS. Auditory and verbal scores improved the most, but there were no effects in patients in VS/UWS. Taken together, neuromodulation with rTMS is a promising way to regulate cortical activity and promote the recovery of behavioral consciousness in patients in MCS, but the effect is unclear for patients in VS/UWS (26), and further pertinent research is needed.

What is consciousness? What are the neuronal correlates of consciousness (NCC)? When scientists registered brain activity in healthy people using a magnetic scanner, they found some active cortical regions, collectively known as "the posterior hot zone" (27). These regions are located in the parietal, occipital, and temporal regions of the posterior cortex and play a crucial role in making up human consciousness. However, significant progress still needs to be made in identifying the true nature of the NCC. Patients with DoC provide a natural model for studying human consciousness. Recent studies revealed that structural and functional connectivity in the default mode network (DMN) correlates with the level of behavioral responsiveness in patients with DoC (28, 29). Decreased activation in the cortical (the middle frontal gyrus and the angular gyrus) and subcortical regions (the thalamus, the cingulate gyrus, and the caudate nucleus) has been observed in patients with DoC, especially in the DMN (30) and the frontal-parietal network (FPN) (31) areas. Furthermore, functional connectivity and structural integrity in the DMN are proportionally related to the index of conscious behavior, especially the posterior cingulate cortex (PCC)/precuneus, which are significantly correlated with the consciousness level and prognosis in patients with DoC (28–30, 32, 33). A cross-sectional study with 72 patients in VS/UWS and 36 patients in MCS indicated that DMN functional connectivity strength decreased in those in VS/UWS compared to those in MCS and positively correlated with CRS-R (34). It was also found that DMN activity was relatively preserved in a small subset of patients in VS/UWS, who eventually evolved to MCS. Therein, the PPC is an important hub of the DMN that plays a central role in multisensory integration (35), environmental-spatial cognition (36), various forms of high-order non-spatial cognition, and so on (37). Furthermore, the PPC is located on the surface of the precuneus cortex near the skull and thus would be an ideal target for rTMS.

Currently, rTMS can increase awareness levels in patients with DoC (38). However, the published results were based on a small sample size or pilot studies (8, 12, 39). In this study, we propose a crossover, randomized, double-blind, sham-controlled rTMS treatment study that uses the left PPC (P3 electrode site) as the target for an intervention program for patients in VS/UWS. CRS-R and EEG were used to evaluate the treatment effects.

Materials and methods

Patients

A total of 24 patients in VS/UWS were recruited from the Department of Rehabilitation Medicine, Zhujiang Hospital of Southern Medical University (SMU), Guangzhou, China from November 2021 to July 2022. All patients met the following inclusion criteria: (1) patients aged between 18 and 70 years with acquired brain injuries <1 year and more than 28 days in VS/UWS; (2) patients with no medical history of neuropsychiatric diseases; (3) patients who have not used any sedatives or other drugs that might interfere with brain stimulation, such as Na^{+} or Ca^{2+} channel blockers or NMDA receptor antagonists; (4) patients with a stable state of disease and vital signs; (5) voluntary agreement given by the families of the patients for the patient's participation in

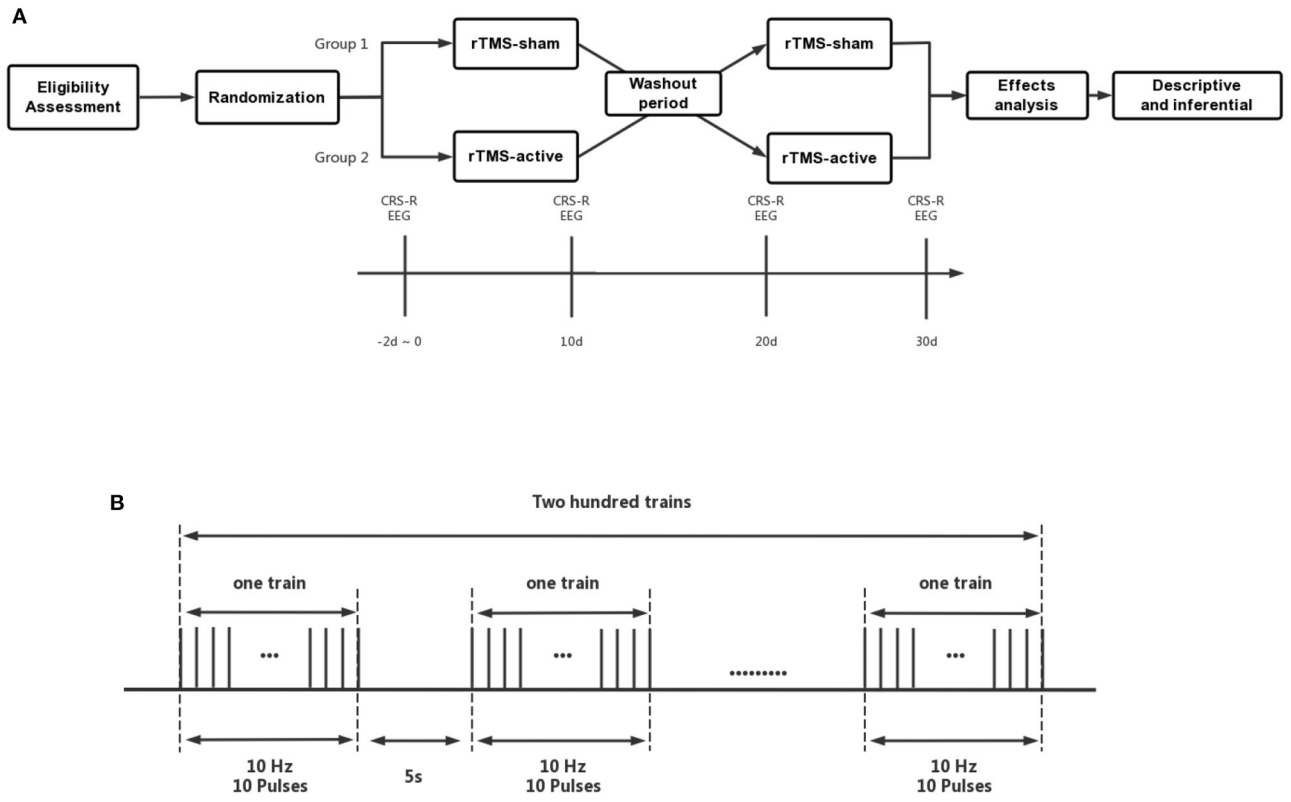

FIGURE 1
(A) The crossover, randomized, double-blind, sham-controlled study protocol, **(B)** Details of rTMS parameters. CRS-R, Coma Recovery Scale-Revised; EEG, Electroencephalogram; rTMS-a, rTMS-active; rTMS-s, rTMS-sham.

this study with signed informed consent provided; and (6) MRI used to verify the integrity of the left PPC. The exclusion criteria were as follows: (1) patients in other noninvasive or invasive neuroregulation trials; (2) patients with uncontrolled epilepsy or seizure within 4 weeks before enrollment; and (3) patients with contraindications for rTMS or EEG, such as metallic implants in the skull, pacemakers, craniotomies under the stimulated site, and implanted brain devices.

Study design

This study employed a crossover, randomized, double-blind, sham-controlled design. Participants received 10 sessions of intervention with 10 Hz rTMS-active targeting the left PPC and 10 sessions of rTMS-sham. Ten days' washout period was set between active and sham treatment (Figure 1A). CRS-R (40) total scores after two-stage treatments were considered the primary efficacy outcome. EEG relative spectral power was used as the secondary efficacy outcome.

The study was registered with ClinicalTrials.gov (NCT05187000) and approved by the Ethical Committee of the Zhujiang Hospital of SMU. Patients or their legal guardians who signed informed consent forms (ICF) followed the Declaration of Helsinki. In clinical research, we fully considered the unique characteristics of patients with DoC and their families, such as autonomy, respect for people, and informed consent (41).

Randomization, blinding, and allocation

Before the baseline period, patients were recruited and divided into two groups in a 1:1 ratio according to computer-generated randomization using the Random Numbers Function of the statistical software SPSS 23.0 (IBM, USA). Randomization was performed blindly by one staff member working under the control of the Data Monitoring Committee (DMC) of Zhujiang Hospital. He was the only person allowed to manage the electronic coding of the randomization to assign the individuals. All patients were assigned a code which was hidden from the allocation process to ensure proper blinding. To perform the allocation concealment process, the blind-coded groups were placed in a closed, opaque envelope and kept by DMC staff. It was opened only during the time of allocation. Both patients and clinic staff (researchers, outcome assessors, caregivers, nurses, physical therapists, statistical analysts, etc.) remained blind to group allocation. The study did not disclose whether the intervention was rTMS-active or rTMS-sham. The rTMS coil was wrapped in a white, opaque plastic paper and labeled as A and B. The rTMS physical therapist (responsible for administering the intervention) was not aware of the group allocation and was instructed by the DMC staff to use Surface A or B first.

TABLE 1 Demographic and clinical information of participants.

ID	Age (sex)	Etiology	Post-injury (months)	Treatment Allocation	CRS-R presham	CRS-R postsham	Δ rTMS-s	CRS-R preactive	CRS-R postactive	Δ rTMS-a	rTMS responder
1	34 (M)	TBI	0.9	Sham/Active	7 (1-1-2-1-0-2)	7 (1-1-2-1-0-2)	0	7 (1-1-2-1-0-2)	13 (2-1-6-2-0-2)	6	Responder
2	43(M)	Hemorrhage	11	Active/sham	7 (1-0-2-2-0-2)	7 (1-0-2-2-0-2)	0	7 (1-0-2-2-0-2)	7 (1-0-2-2-0-2)	0	Non-responder
3	40 (M)	HIE	2.2	Sham/Active	7 (1-0-2-2-0-2)	7 (1-0-2-2-0-2)	0	7 (1-0-2-2-0-2)	11 (2-3-2-2-0-2)	4	Responder
4	26 (M)	TBI	1.7	Sham/Active	6 (1-0-2-1-0-2)	6 (1-0-2-1-0-2)	0	6 (1-0-2-1-0-2)	10 (1-3-2-2-0-2)	4	Responder
5	58 (M)	TBI	4.4	Active/sham	9 (1-1-3-2-0-2)	9 (1-1-3-2-0-2)	0	5 (1-0-1-2-0-1)	9 (1-1-3-2-0-2)	4	Responder
6	56 (M)	HIE	1.8	Sham/Active	4 (0-0-1-1-0-2)	8 (2-1-1-2-0-2)	4	8 (2-1-1-2-0-2)	11 (2-3-2-2-0-2)	3	Responder
7	36 (F)	HIE	2.1	Active/sham	6 (1-0-2-1-0-2)	6 (1-0-2-1-0-2)	0	6 (1-0-2-1-0-2)	6 (1-0-2-1-0-2)	0	Non-responder
8	67 (F)	Hemorrhage	2.4	Sham/Active	4 (0-0-2-1-0-1)	5 (1-0-2-1-0-1)	1	5 (1-0-2-1-0-1)	8 (1-3-2-1-0-1)	3	Responder
9	32 (F)	HIE	2.5	Sham/Active	6 (1-0-2-1-0-2)	6 (1-0-2-1-0-2)	0	6 (1-0-2-1-0-2)	6 (1-0-2-1-0-2)	0	Non-responder
10	57 (M)	HIE	2.7	Sham/Active	4 (1-0-0-1-0-2)	4 (1-0-0-1-0-2)	0	4 (1-0-0-1-0-2)	4 (1-0-0-1-0-2)	0	Non-responder
11	66 (F)	HIE	3.6	Sham/Active	7 (1-0-2-2-0-2)	7 (1-0-2-2-0-2)	0	7 (1-0-2-2-0-2)	7 (1-0-2-2-0-2)	0	Non-responder
12	57 (F)	HIE	10.5	Sham/Active	5 (0-0-2-1-0-2)	5 (0-0-2-1-0-2)	0	5 (0-0-2-1-0-2)	5 (0-0-2-1-0-2)	0	Non-responder
13	35 (F)	HIE	2	Active/sham	7 (1-0-2-2-0-2)	7 (1-0-2-2-0-2)	0	7 (1-0-2-2-0-2)	7 (1-0-2-2-0-2)	0	Non-responder
14	67 (M)	Hemorrhage	9.8	Sham/Active	6 (0-0-2-2-0-2)	8 (1-1-2-2-0-2)	2	8 (1-1-2-2-0-2)	7 (1-0-2-2-0-2)	−1	Non-responder
15	43 (M)	TBI	4.5	Active/sham	6 (1-0-2-1-0-2)	5 (1-0-2-1-0-1)	−1	6 (1-0-2-1-0-2)	8 (2-1-2-1-0-2)	2	Non-responder
16	22 (M)	TBI	3.5	Active/sham	7 (1-1-2-1-0-2)	7 (1-1-2-1-0-2)	0	6 (1-1-2-1-0-1)	7 (1-1-2-1-0-2)	1	Non-responder
17	58 (M)	Hemorrhage	3.5	Active/sham	5 (1-0-2-1-0-1)	5 (1-0-2-1-0-1)	0	5 (1-0-2-1-0-1)	5 (1-0-2-1-0-1)	0	Non-responder
18	59 (M)	TBI	2.9	Active/sham	7 (1-1-2-1-0-2)	7 (1-1-2-1-0-2)	0	6 (1-0-2-1-0-2)	9 (1-3-2-1-0-2)	3	Responder
19	61 (M)	TBI	2.1	Active/sham	10 (1-3-2-2-0-2)	10 (1-3-2-2-0-2)	0	8 (1-1-2-2-0-2)	10 (1-3-2-2-0-2)	2	Responder
20	50 (M)	HIE	1.1	Active/sham	4 (0-0-1-1-0-2)	4 (1-0-1-1-0-2)	0	4 (0-0-1-1-0-2)	4 (0-0-1-1-0-2)	0	Non-responder

CRS-R scores are described as follows: Total score (Auditory subscore–Visual subscore–Motor subscore–Oromotor/Verbal subscore–Communication subscore–Arousal subscore); F, Female; M, Male; HIE, hypoxic-ischemic encephalopathy; TBI, Traumatic Brain Injury; CRS-R, Coma Recovery Scale-Revised; Δ, post–pre. In the last column, Responder, patients showing new signs of consciousness after rTMS; Non-responder, patients not showing any new sign of consciousness, taking into account the 4 CRS-R assessments (pre and post-rTMS-active and rTMS-sham) conducted during the study period.

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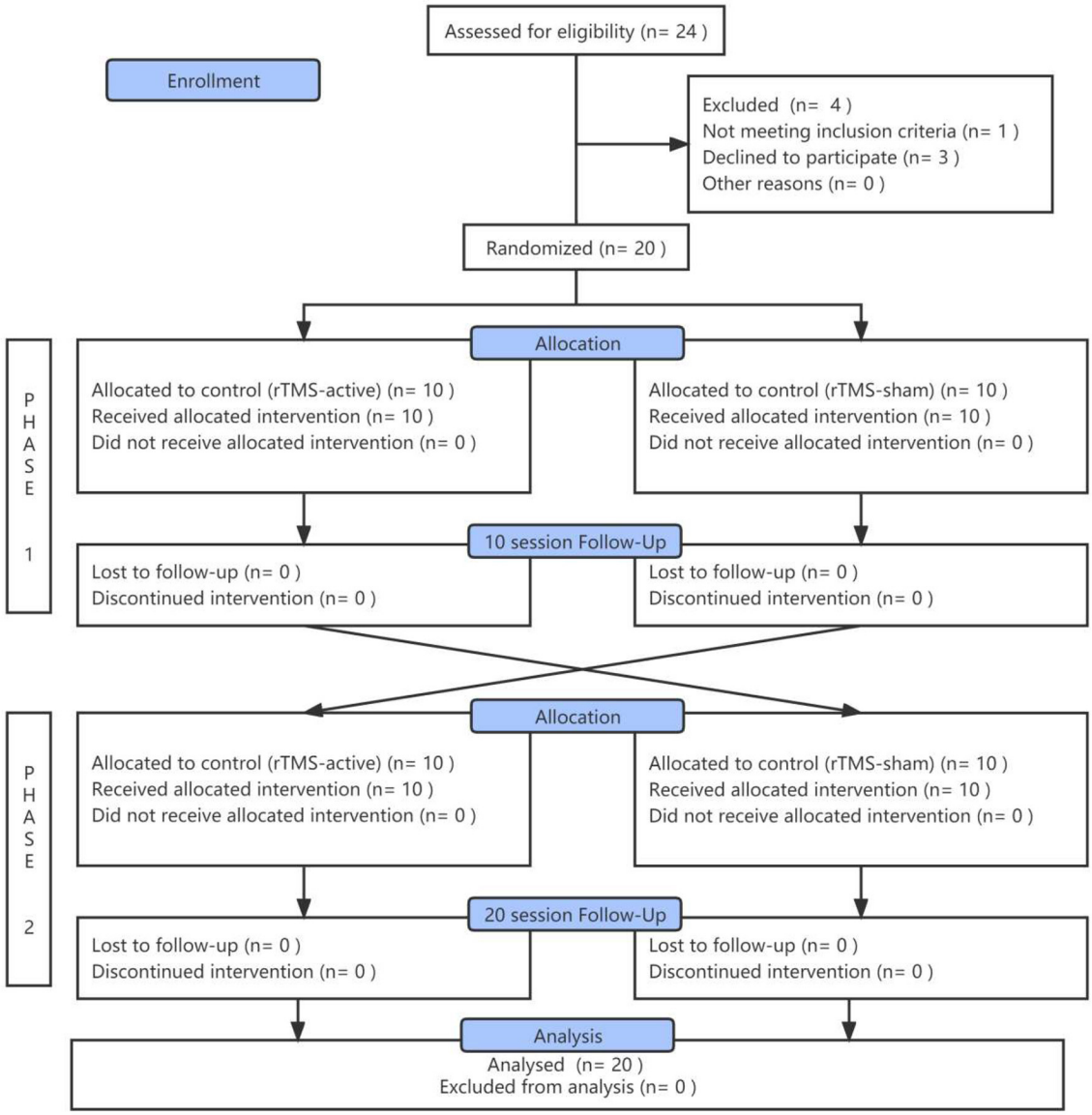

FIGURE 2
Flow diagram.

rTMS procedures

Across the experiment, stimulation intensity varied and was determined by the resting motor threshold (RMT), which is defined as the minimum intensity of TMS applied to the M1 region. It could evoke electromyography (EMG) with an amplitude of $>50\ \mu V$ peak-to-peak in the hands' relaxed first dorsal interosseous muscle in more than five out of 10 pulses. The researchers were trained to use the coil surface which was positioned at a tangent angle of 45° to the scalp (42) over the left PPC of the patient to perform rTMS interventions. The rTMS pulses were delivered using an NTK-TMS-II300 stimulator with an IIB502 97-mm figure-of-eight coil (surface A sents active pulses, while surface B sents sham pulses). There were two identical surfaces in this coil; one output rTMS-active pluses, and the other output rTMS-sham pluses (Brain Modulation Technology Development CO, LDT, JiangXi, CHN). A biphasic waveform with a pulse width of ∼0.32 ms would be produced.

During the active stage of rTMS treatment, patients received 10 consecutive sessions (one session daily) of stimulation. They were seated in a semi-reclined position on either an ABS bed or a wheelchair, and each session lasted 20 min with a frequency of 10 Hz, delivered over the left PPC (train duration: 1s; inter-train interval: 5s; 200 effective stimulation series; 2,000 pulses at 90% of RMT). An EEG cap marked with the international 10–20 positioning system was used to identify the P3 (left PPc) stimulation site. The rTMS treatment was administered in accordance with safety guidelines (43) (Figure 1B).

During the sham stage of rTMS, patients received 10 consecutive sessions (one session daily) of stimulation. The sham coil was designed to mimic the appearance of the active coil; however, it did not produce a magnetic field and delivered only noise and vibration

to mimic the feedback of the active coil. The sham coil was used to control for the placebo effect (44).

Behavioral assessment

CRS-R (45), as a generally accepted standard, is widely used to define the level of consciousness and assess neurobehavioral recovery in patients with DoC (1). In this study, CRS-R was evaluated by two experienced physicians at four time points: before and after the treatment of the first rTMS stage, after the washout period, and after the second rTMS stage. The CRS-R assessment was conducted between 3 and 5 pm Beijing time. rTMS responders were defined as patients showing new signs of MCS or EMCS in CRS-R (e.g., visual pursuit, pain location, or functional object use).

EEG recording and preprocessing

EEG was used to evaluate the brain function of patients with DoC (46). In this study, we collected and analyzed the EEG data of patients with DoC at four time points: before the experiment, after the first rTMS stage, after the washout period, and after the second rTMS stage. EEG was acquired from 66 channels (SynAmps^{2TM} 8500; Neurscan, USA) with positions of the 10–20 International EEG system. The equipment used an Ag/AgCl pin electrode with band-pass filtering at DC to 1,000 Hz in the recorder. The EEG sampling rate was set at 2,500 Hz. During the recording period, electrode impedance was maintained below 5 kΩ. We ensured that patients' eyes remained open during all recordings. We used the standard arousal method for CRS-R whenever the eyes of the patients were closed and suspended the assessment if the eyes remained closed.

Offline analysis was conducted using EEGLAB 14_1_1b, running in a MATLAB environment (version 2016a; Math Works Inc., Natick, Massachusetts, USA). The original EEG data were downsampled to 500 Hz and filtered between 1 and 45 Hz. Then, EEG data were divided into epochs of 10 s with 5 s of overlap for each patient, and the noisy segments were manually removed (no more than 20%). The independent component analysis (ICA) was used to eliminate non-neural activities such as blinking and muscle activation. After analyzing the data, the participants' relative power spectral density (RPSD) was calculated using the selected artifact-free EEG epochs across five frequency bands: δ (1–4 Hz), θ (4–8 Hz), α (8–13 Hz), β (13–30 Hz), and γ (30–45 Hz). The investigators calculated RPSD using offline analysis.

Basic treatments and routine rehabilitation

Qualified rehabilitation therapists at Zhujiang Hospital of Southern Medical University's Department of Rehabilitation Medicine administered various routine rehabilitation programs, including passive limb range-of-motion training, electrical limb stimulation, barometric therapy, respiratory therapy, swallowing therapy, gastrointestinal rehabilitation, and hyperbaric oxygen therapy.

TABLE 2 Univariate general linear model ANOVA for the CRS-R behavioral results.

Behavioral results (CRS-R total scores)					
	Type III Sum of Squares	df	Mean Square	*F*	*P*
Intercept	2016.400	1	.	.	.
Subject	124.700	18	6.928	4.062	0.002
Stage(2)	4.900	1	4.900	2.873	0.107
Treatment(rTMS-s)	14.400	1	14.400	8.443	0.009

Treatment, rTMS-a; rTMS-s, rTMS-sham; stage, 1 (the first period, the other level is 2).

Statistical analysis

SPSS 23.0 statistical software was used to analyze the results. All the statistical hypotheses were tested by a two-sided test, with the statistically significant level set at 0.05 and the confidence interval of the parameters set at 95%. The independent samples *t*-test and chi-square test were used to analyze and compare the baseline characteristics and the carryover effect between the two sequences. The main effects comparison between treatments, stages, and subjects were performed by the univariate general linear model ANOVA. Considering the crossover of this study, we assessed the carryover effect (i.e., the effect of the first treatment on the second treatment period) at the baseline of the first and second stages. The difference in baseline (measured CRS-R total scores) between the two periods was calculated separately for each patient in two sequence groups for this purpose. If the carryover effect was not significant at the 0.1 level, the different stages were excluded. EEG data were Ln transformed before analysis.

Result

A total of 24 inpatients were initially screened; one patient had suffered a stroke, and three patients' family members did not agree to sign the ICF. Twenty patients in VS/UWS completed rTMS treatment successively and were included in the final analysis (Figure 2). Their demographic and clinical characteristics are demonstrated in Table 1. There were no significant differences in age ($t = -0.574$, $p = 0.573$), gender (χ^2=0.952, $p = 0.329$), time since injury ($t = -0.142$, $p = 0.944$), or baseline CRS-R score ($t = 0.210$, $p = 0.836$) between the two sequence groups (rTMS-active – rTMS-sham vs. rTMS-sham – rTMS-active). There were no adverse events associated with the study.

Primary outcome: Behavioral assessment

The overall CRS-R score showed no significant difference between the first and second stages of treatment ($t = -0.969$, $P = 0.346$). Therefore, the carryover effect was excluded. At the group level, there was a significant rTMS treatment effect ($F = 8.443$, $P = 0.009$). Compared to the rTMS-sham treatment, the rTMS-active treatment exhibited a significant improvement in CRS-R total scores

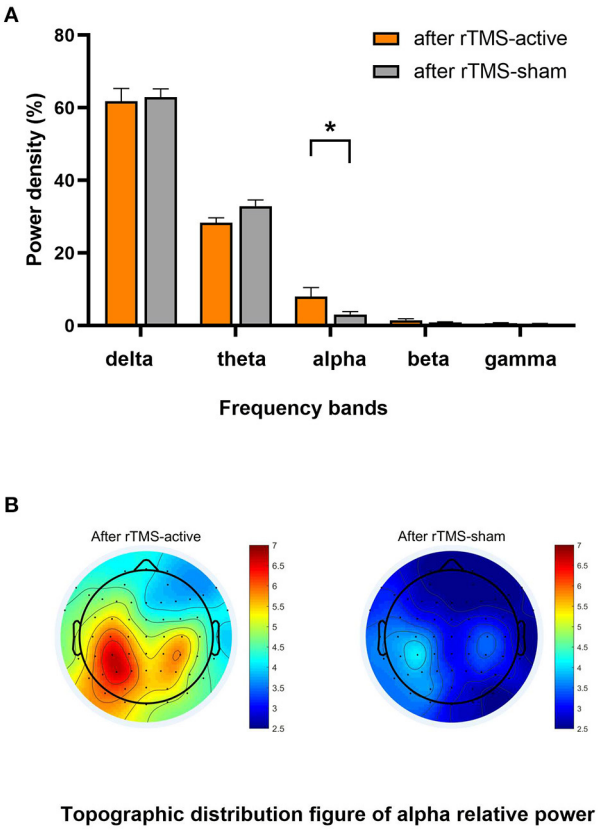

FIGURE 3
Result of the general linear model ANOVA showed differences in EEG relative power between-group levels (after rTMS-active and after rTMS-sham). **(A)** The relative power in five frequency bands. A statistical significance was only found in the relative alpha power (*$p <$ 0.01). The data were expressed as the means ± SEM. **(B)** There was a difference in whole-brain topographic distribution figure of relative alpha power. Left column: group of after rTMS-active; right column: a group of after rTMS-sham.

in the patients. The CRS-R details of the univariate general linear model ANOVA are summarized in Table 2.

Regarding single subjects, eight patients gained new signs of consciousness following rTMS activation and were defined as rTMS responders. Two patients improved in the motor subscore (functional object use and pain location, respectively), and six patients improved in the visual subscore (visual pursuit). Furthermore, three patients showed improvement in auditory, visual, or arousal functions but did not gain any sign of consciousness. Notably, one patient (P18) gained a visual pursuit after receiving the rTMS-active treatment but lost it in the second stage, only receiving a reserved visual shock. There were no significant differences between responders and non-responders in age ($p > 0.05$), sex ($p > 0.05$), time since injury ($p > 0.05$), or baseline CRS-R score ($p > 0.05$).

EEG assessment: Relative power and spectral density

The univariate general linear model ANOVA revealed that, when compared to rTMS-sham, the rTMS-active treatment demonstrated significantly higher alpha relative power of the whole brain at the group level ($F = 11.166$, $p = 0.004$) (Figures 3A, B; Table 3). For responder patients, the relative alpha power was significantly higher after rTMS-active than after rTMS-sham ($F = 26.372$, $p = 0.002$) (Figure 4A; Table 4). There were no significant differences in non-responder patients ($p>0.05$) (Figure 4B; Table 4). There were no statistical differences in other bands. We did not observe any evidence for EEG carryover effects or a difference in baseline (see Supplementary materials 1, 2).

TABLE 3 Univariate general linear model ANOVA for EEG relative alpha band power.

EEG results (Relative Alpha Band Power)					
	Type III Sum of Squares	df	Mean Square	*F*	*P*
Intercept	40.240	1	.	.	.
Subject	21.929	18	1.218	1.126	0.001
Stage(2)	0.010	1	0.010	0.039	0.845
Treatment(rTMS-s)	2.850	1	2.850	11.166	0.004

Treatment, rTMS-a; rTMS-s, rTMS-sham; stage, 1 (the first period, the other level is 2).

Discussion

In this crossover, randomized, double-blind, sham-controlled clinical study, we demonstrated the safety, feasibility, behavioral, and electrophysiological effects of using rTMS over the left PPC for the first time in patients in VS/UWS. The crossover design has the advantage of eliminating individual subject differences from the overall treatment effect and is suitable for chronic diseases such as DoC. Therefore, this study's behavioristics and EEG results make a significant clinical observation, which helps explore the target selection of rTMS (even other NIBS treatments) for DoC and improve its clinical diagnosis and treatment (8).

Safety is one of the most important issues of rTMS clinical treatment, especially for seizures. Past literature has reported 20 Hz rTMS-induced seizures in patients with DoC (47). Many situations or complications can contribute to the risk of seizures, such as metabolic abnormalities, fever, and sleep deprivation, which are common in patients with DoC (48). Given that the risk of seizures increases with higher frequency stimulation, our study chose a 10 Hz, 90% RMT stimulus, which is in line with the latest evidence-based guidelines (12) and safety guidelines (43), to ensure the safety of the treatment while effectively activating the target area. As expected, there were no adverse events related to rTMS by the end of the study. This study not only demonstrated the feasibility of this protocol in patients in VS/UWS but also showed the effectiveness of rTMS in combination with other rehabilitation techniques (passive limb range-of-motion training, swallowing therapy, hyperbaric oxygen therapy, etc.).

In this study, our primary results demonstrated for the first time that the left PPC is a highly promising rTMS target for improving functional recovery in unresponsive patients. Compared to rTMS-sham, the CRS-R total score at the rTMS-active level increased significantly, suggesting that rTMS above the left PPC increases awareness levels in unresponsive patients. It shows that the left

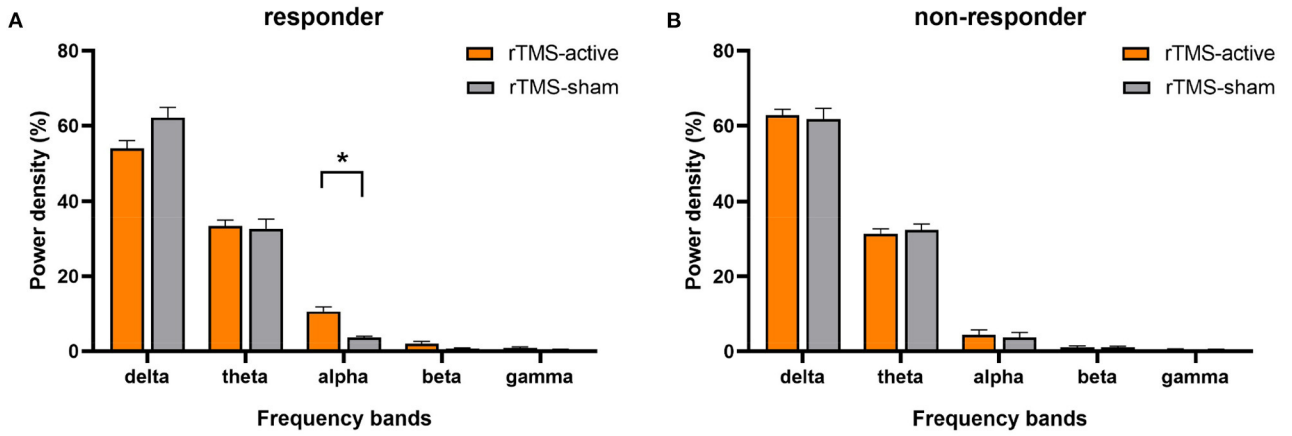

FIGURE 4
The result of the general linear model ANOVA showed changes in EEG relative power in five frequency bands for responders and non-responders, respectively (rTMS-active and rTMS-sham). **(A)** Statistical significance in responders was found in the relative alpha power (*$p < 0.01$). The data were expressed as the means ± SEM. **(B)** No significant difference was found for non-responders in any bands.

PPC is a key hub of the DMN, and increasing its activity plays a crucial role in the recovery of consciousness (49). Among these patients, eight were rTMS responders; seven progressed into MCS (4 TBI, 2 HIE, 1, and hemorrhage) after being rTMS-active, and one entered EMCS (P1, TBI). The CRS-R subscales showed that these responders regained consciousness at the visual and motor levels (six visual pursuits, one functional object use, and one pain location), which is consistent with the improvement of subscale items in responders in former studies of rTMS for DoC (14, 17, 25, 50). Our results may indicate that the residual expression of consciousness is more preserved in the visual and motor pathways in unresponsive patients (51, 52). This is consistent with a recent study that found that the regulation of PPC plays an important role in the alerting and maintenance of visuospatial attention (27), as well as in the recovery of consciousness. Thus, we need to devote more attention to observational and intervention studies in this field in the future. It is crucial to aid in the functional recovery of patients with DoC and establish a correct prognosis (53, 54).

EEGs, which provide objective, widely applicable, direct, and immediate information, are essential in DoC research (55). Compared with patients with MCS, patients with VS/UWS have decreased alpha power (56). The improvement of alpha and its source power as a prognostic measure in the parieto-occipital lobe is closely associated with the probability of consciousness recovery in patients with VS/UWS (57). Specifically, in patients with a DoC of <1 year, alpha power and its variability are vital predictors for functional recovery (26). In healthy adults, EEG activity during the awake resting state is typically dominated by the alpha rhythm, which is distinct from that of patients with disorders of consciousness (DoC) (58). Our findings support this conclusion: compared to rTMS-sham, the relative alpha power was increased after ten sessions of rTMS-active treatments, particularly at the left PPC stimulation target. Furthermore, eight responders had significantly higher relative alpha power after rTMS-active at the group level, but there was no significant change in non-responders. This suggests that the increase in relative alpha power may be a signature of response to 10 Hz rTMS in responders and may also be a characteristic of covert consciousness in unresponsive patients. Overall, the EEG analysis in this study supports the conclusion that 10 Hz rTMS over the left PPC may improve brain function.

TABLE 4 Univariate general linear model ANOVA for EEG relative alpha band power of responders and non-responders.

EEG results (Relative Alpha Band Power of responders)					
	Type III Sum of Squares	df	Mean Square	*F*	*P*
Intercept	13.188	1	.	.	.
Responders	5.542	6	0.924	1.126	0.034
Stage(2)	0.173	1	0.173	1.201	0.367
Treatment(rTMS-s)	4.786	1	4.786	26.372	0.002
EEG results (Relative Alpha Band Power of non-responders)					
Intercept	23.919	1	.	.	.
Non-responders	15.797	10	1.580	14.609	0.001
Stage(2)	0.081	1	0.081	0.745	0.408
Treatment(rTMS-s)	0.076	1	0.076	0.704	0.421

Treatment, rTMS-active; rTMS-s, rTMS-sham; stage, 1 (first period, the other level represents 2).

Due to the brain's sensitivity to ischemia and hypoxia, patients with DoC and HIE who suffer from cardiac arrest (CA) usually have a poor prognosis (40). In the study by Legostaeva et al., no change was observed after rTMS treatment in the VS/UWS subgroup. This may be due to the fact that the majority of patients (93%) are caused by HIE. Previous research showed that only 16.1% of patients in VS/UWS caused by HIE respond to rTMS treatment (8). A recent study that used a single session of rTMS for patients with DoC and HIE did not observe any behavioral or EEG changes and suggested that rTMS should not be recommended for these patients (18). However, in this study, two of the eight patients with HIE (25.0%) progressed from VS/UWS to MCS after treatment (P3 and P6). For a patient whose P3 stimulation site was caused by electrical damage, gender was male, and the time since injury was 2 months, the CRS-R score improved to MCS (1-3-2-1-0-2) and relative alpha

power significantly increased after 10 sessions of rTMS treatment. For a patient whose P6 stimulation site was caused by CA lasting for a minute, gender was male, time since injury was 3 months, the CRS-R score improved to MCS (2-3-2-2-0-2) and the relative alpha power significantly increased after 10 sessions of rTMS treatment. This suggests that patients with HIE still have the opportunity to recover consciousness from VS/UWS with timely and continuous rTMS treatment.

In addition, we have another important consideration. A growing body of literature indicated that the misdiagnosis rates remain high (30–40%) (59, 60). Some patients with residual consciousness are considered to be unresponsive (59, 61), suggesting that some patients in VS/UWS may be in MCS or may even be fully conscious (62, 63), such as with cognitive motor dissociation (CMD) (64) or locked-in syndrome (LIS) (65). In our study, two experienced physicians evaluated CRS-R two times to determine the patient's level of consciousness and to reduce the rate of misdiagnosis during the eligibility assessment stage. However, we still have to acknowledge the limitation that the methods currently available, such as behavioral tests and task-free or task-based measures for DoC, cannot provide evidence for the complete absence of consciousness (66). Once a patient has been clinically diagnosed to be in a VS/UWS, those possible errors can result in a poor prognosis and ineffective decision-making (61). They will not have the chance to receive active treatment, which may lead to the withdrawal of water and food (i.e., the termination of life support) (67). This can be a tragedy for their families. As treatments for patients in VS/UWS are currently limited, our results suggest that 10 sessions of rTMS should be used for nonresponsive patients with or without covert functional activities of consciousness. As a diagnostic treatment, it may be more significant for nonresponsive patients than neural measures. This is why we focused on nonresponsive patients in this study.

However, there are still several limitations to this study. First, we did not use rTMS combined with MRI navigation technology but instead used the P3 electrode of the 10–20 international EEG system to locate the left PPC, which cannot ensure precise locations of the stimulus. This method is more clinical as it is less expensive and less complicated, and there are fewer hospitals and institutions equipped with a navigation system. Therefore, our results can provide direct guidance for rTMS treatment for patients with DoC. Second, there are relatively few objective evaluation methods used in this study. Future studies should focus on TMS-evoked potential (TEP), perturbational complexity index (PCI) (68), or EEG source localization analysis induced by TMS-EEG (69).

Theta burst stimulation (TBS) is a new form of TMS in which rapid bursts of 50 Hz are delivered within slow-wave theta (5Hz) oscillations (70). Recently, TBS has been increasingly used as a therapeutic intervention for psychiatric and neurologic diseases (71). Wu et al., in their exploratory study, used intermittent thetic-burst stimulation (iTBS) over the left DLPFC in eight patients with DoC, of which seven of them showed an increased CRS-R score and increased EEG power of alpha (15). Compared to traditional rTMS, the biggest advantage of TBS is that completing its standard stimulation protocol only takes 3 min and it has a lower stimulation pulse intensity (72, 73). This not only saves time for patients' clinical treatment but also improves patients' compliance and increases treatment quality. In short, TBS is a promising avenue for DoC research in the future.

In conclusion, this crossover, randomized, double-blind, sham-controlled clinical study provides new evidence for the clinical application of rTMS in patients with VS/UWS. The results indicate that 10 Hz rTMS on the left PPC can improve functional recovery and significantly increase the relative alpha power of the whole brain, indicating that the treatment may be potentially considered to assist in the timely recovery of consciousness.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethical Committee of Zhujiang Hospital of Southern Medical University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

CX, YB, and QXe conceived and designed the study protocol and contributed to the draft of the manuscript. CX, WW, and XZ wrote the manuscript and participated in the coordination and implementation of the study. YB and QXe revised the study protocol and wrote several sections of the manuscript. XH, QL, QXa, HZ, and YL helped develop the study measures and data collection. All authors contributed to the manuscript's draft and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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Clinical effect of short-term spinal cord stimulation in the treatment of patients with primary brainstem hemorrhage-induced disorders of consciousness

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Objective: Recently, short-term spinal cord stimulation (st-SCS) has been used in neurorehabilitation and consciousness recovery. However, little is known about its effects on primary brainstem hemorrhage (PBSH)-induced disorders of consciousness (DOC). In this study, we examined the therapeutic effects of st-SCS in patients with PBSH-induced DOC.

Methods: Fourteen patients received a 2-week st-SCS therapy. Each patient's state of consciousness was evaluated using the Coma Recovery Scale-Revised (CRS-R). CRS-R evaluation scores were recorded at the baseline (before SCS implantation) and 14 days later.

Results: Over 70% (10/14) of the patients (CRS-R score increased to ≥2 points) responded to the SCS stimulation after 14 days of st-SCS treatment. All items included in the CRS-R exhibited a significant increase post-treatment compared with pretreatment. After 2 weeks of st-SCS treatment, seven patients showed diagnostic improvement, resulting in a 50% (7/14) overall effective rate. Approximately 75% (3/4) of patients with minimally conscious state plus (MCS+) improved to emergence from MCS (eMCS), and 50% (1/2) of patients with vegetative state or unresponsive wakefulness syndrome (VS/UWS) improved to MCS+.

Conclusion: In PBSH-induced DOC, st-SCS is a safe and effective treatment. The clinical behavior of the patients improved significantly following the st-SCS intervention, and their CRS-R scores markedly increased. This was most effective for MCS+.

KEYWORDS

short-term spinal cord stimulation, primary brainstem hemorrhage, disorder of consciousness, minimally conscious state, neuromodulation

1. Introduction

Primary brainstem hemorrhage (PBSH) is a hemorrhagic stroke subtype that occurs in the pons in the vast majority of cases and accounts for ∼5%−10% of intracerebral hemorrhage cases (1–3). This disease is characterized by an abrupt onset of symptoms, rapid neurological decline, poor prognosis, and high mortality (30%−90%) (4–6). Currently, the main therapeutic options for PBSH are conservative treatments, but surgical interventions have become increasingly attractive as treatment options (7, 8). Surgical removal of hematomas can achieve hemostasis, relieve brainstem pressure, and prevent secondary damage (9–11). However, abnormal rupture of blood vessels in brainstem-induced brain injuries can result in severe disorders of consciousness (DOC), often with a serious impact on postoperative recovery (12). Thus, the development of effective strategies targeting PBSH-induced DOC would be beneficial in clinical treatment.

Interest has increased concerning DOC, which is caused by severe brain injuries that cause loss or partial loss of consciousness (13, 14). The term disorders of consciousness summarize the vegetative state or unresponsive wakefulness syndrome (VS/UWS), minimally conscious state (MCS), and then emergence from the minimally conscious state (eMCS) (15, 16). VS/UWS is a severe DOC, defined as a state of unresponsiveness in which the patient shows spontaneous eye opening without any behavioral evidence of awareness of either the self or environment (17). MCS is defined as a state of severely impaired consciousness with minimal behavioral evidence of self or environmental awareness, manifested as the presence of non-reflexive behaviors (visual pursuit, appropriate motor response to a painful stimulus) or even intermittent command following cortical integration (16, 18). Thus, patients in MCS usually show a stronger level of awareness than those in VS/UWS, and the Coma Recovery Scale-Revised (CRS-R) has been recommended as the assessment scale (19, 20). Furthermore, with increasing research on MCS, it has been possible to divide MCS into minimally conscious state minus (MCS–) and minimally conscious state plus (MCS+) (21). The difference between the two is that the former displays low-level consciousness responses, whereas the latter demonstrates language-related cognitive abilities (22). Patients with MCS+ show high-level behavioral responses (i.e., command following, intelligible verbalizations, or non-functional communication), and patients with MCS– have low-level behavioral responses (i.e., visual pursuit, localization of noxious stimulation, or contingent behavior such as appropriate smiling or crying to emotional stimuli) (23). In addition, patients are classified as emerging from MCS (eMCS) when the patient can communicate functionally or show proper functional objects (24, 25).

The treatment of DOC still lacks a curative strategy. Several new non-invasive neuromodulation treatments have been developed in recent years, including transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS) (26–28). According to recent studies, loss of consciousness after severe brain injury is closely related to the disruption of neural circuits (such as cortico-thalamic and cortico-cortical connections) (29). According to its principles, non-invasive neuromodulation therapy does not directly modulate the neural circuit, particularly the cortico-thalamic connection. Thus, spinal cord stimulation (SCS) has become an essential and valid surgical treatment for DOC because of its relative ease of operation, safety, wide range of indications, effectiveness, and direct modulation of neural circuits (30). However, there are many difficulties in applying SCS to the clinical treatment of DOC, such as significant injuries caused by invasive operations and potential implant rejection. Therefore, SCS is usually used to treat patients with DOC with a disease duration of more than 3 months to avoid spontaneous high-speed recovery of consciousness (31). A previous study found that early rehabilitation was crucial for patients with DOC (32). Therefore, short-term spinal cord stimulation (st-SCS) has been developed. Another study already applied this method for the recovery from DOC (33, 34), but it was unclear whether it affected PBSH-induced DOC.

In this study, we hypothesized that st-SCS would improve the recovery of consciousness in patients with PBSH. We studied 14 patients with PBSH-induced DOC, diagnosed using the CRS-R test, and treated with st-SCS.

2. Materials and methods

2.1. Participants

Fourteen patients (nine men and five women; mean age, 55.79 ± 8.29 years) with MCS or VS/UWS who underwent st-SCS treatment in our hospital from November 2021 to July 2022 were enrolled. Ten of the 14 patients underwent minimally invasive stereotactic puncture therapy (MISPT) before st-SCS treatment. The average time since injury was 1.27 ± 0.31 months and ranged from 1 to 1.7 months. Detailed clinical information for each patient is presented in Table 1. We recruited patients who met the following inclusion criteria: (1) age ≥18 years with the onset of PBSH; (2) at least one neurological examination consistent with DOC defined by the CRS-R test; and (3) written informed consent obtained from legal surrogates. The exclusion criteria were as follows: (1) other intracerebral hemorrhage conditions; (2) age <18 years; (3) disagreement of relatives or their legal representative with MCS treatment; and (4) poor condition (other vital organ dysfunction or severe infection) and surgical inoperability. The Ethics Committee of Ganzhou People's Hospital approved the study protocol.

2.2. SCS implantation

Before SCS implantation, all patients underwent the following preoperative routine examinations: medical history, imaging examinations, and routine laboratory tests. Following the screening, all eligible patients were included in the study to receive SCS system (Medtronic Inc., Minneapolis, USA) implantation, as previously described (33, 34). Following general anesthesia, the patients were placed in a prone position and their necks were flexed forward. An 8-contact stimulation electrode (3777; Medtronic, Minneapolis, MN, USA) was inserted into the epidural spaces of T7 and T8. Next, the test stimulation lead was placed under X-ray fluoroscopy, and the electrode was flattened on the upper edge of the cervical-2 vertebral body (Figure 1). Finally, the electrode

TABLE 1 Clinical patient information.

No.	Gender	Age (years)	Cause	MISPT (yes/no)	Post-injury (months)	Diagnosis
1	Male	48	PBSH	No	1	MCS–
2	Male	42	PBSH	No	1.5	MCS+
3	Female	66	PBSH	Yes	1.7	MCS+
4	Male	48	PBSH	Yes	1	MCS–
5	Male	53	PBSH	No	1.3	MCS–
6	Female	51	PBSH	No	1.7	MCS–
7	Male	64	PBSH	Yes	1	MCS–
8	Male	68	PBSH	Yes	1.3	MCS–
9	Female	69	PBSH	Yes	1	VS/UWS
10	Female	58	PBSH	Yes	1.6	MCS–
11	Male	49	PBSH	Yes	1	VS/UWS
12	Male	54	PBSH	Yes	1	MCS–
13	Female	56	PBSH	Yes	1.7	MCS+
14	Male	55	PBSH	Yes	1	MCS+

MISPT, minimally invasive stereotactic puncture therapy; PBSH, primary brainstem hemorrhage; VS/UWS, vegetative state or unresponsive wakefulness syndrome; MCS–, minimally conscious state minus; MCS+, minimally conscious state plus; eMCS, emerged from MCS.

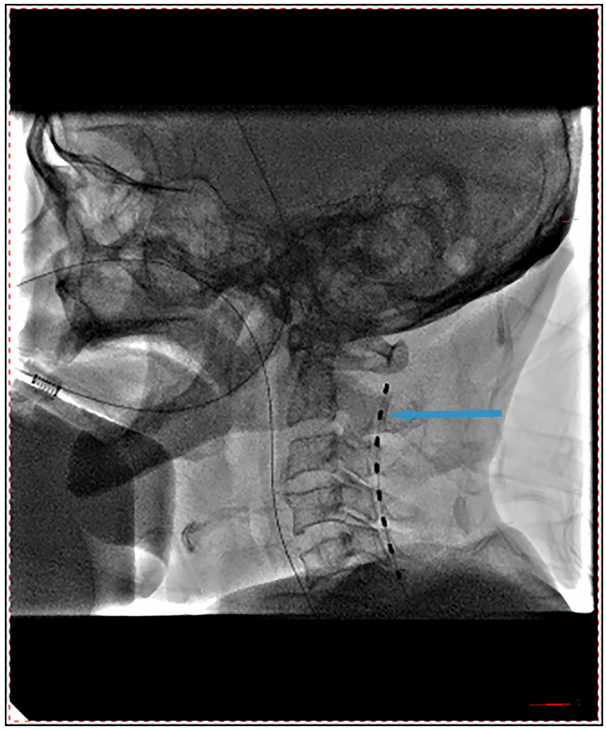

FIGURE 1
Electrode position during the operation.

was properly fixed, the multi-lead trialing cable was connected, an external neurostimulator was connected to the assembly, and test stimulation was performed intraoperatively to maintain the best state of the machine.

2.3. Adjustment of st-SCS parameters

After the st-SCS operation, the electrical stimulation of the spinal cord lasted for 14 days, and the electrode was removed. From 8 a.m. to 8 p.m., 5-min on/15-min off cycles were performed. The machine was turned on with the following parameters: voltage, 2.0 V; frequency, 70 Hz; and pulse width, 210 μs.

2.4. Behavioral assessment

The Chinese version of the CRS-R scale was used to assess the patient's state during the entire st-SCS treatment protocol (35, 36). The CRS-R consists of six subscales with total scores ranging from 0 to 23. The scoring standards for the CRS-R scale are presented in Table 2.

The CRS-R assessments were administered by clinicians who were not responsible for the st-SCS treatment. A minimum of six CRS-R assessments were recorded before the operation and 14 days after st-SCS therapy (35). The CRS-R scores for each patient in this study were based on their best responses to repeated CRS-R assessments (37). The effective clinical outcome of st-SCS was that patients showed a CRS-R score improvement. Patients with positive st-SCS responses exhibited an increase of $\geq$2 points in the CRS-R. In irresponsive patients, the total CRS-R scores remained unchanged or increased by $<$2 (38). Safety was primarily assessed by analyzing treatment-emergent adverse events (TEAEs).

2.5. Statistical analysis

Statistical results were demonstrated using an online scientific analysis platform, SPSSAU (version 20.0; Beijing, China, https://

TABLE 2 Description of items included in the CRS-R.

Item	CRS-R	Diagnosis
Auditory	4-Consistent movement to command	MCS+
	3-Reproduction movement to command	MCS+
	2-Sound localization	
	1–1 Auditory startling	
	0-None	
Visual	5-Object recognition	MCS+
	4-Object localization (reaching)	MCS–
	3-Visual pursuit	MCS–
	2-Fixation (>2 s)	
	1-Visual startle (startle reaction)	
	0-None	
Motor	6-Functional object use	eMCS
	5-Automatic motor response	MCS–
	4-Object manipulation	MCS–
	3-Flexion to noxious stimulation	MCS–
	2-Flexion withdraw	
	1-Abnormal posturing	
	0-None	
Oromotor	3-Intelligible verbalization	MCS+
	2-Vacalization	
	1-Oral reflexive movement	
	0-None	
Communication	2-Functional (accurate)	eMCS
	1-Non-functional	MCS+
	0-None	
Arousal level	3-Attention	
	2-Eye opening	
	1-Eye opening with stimulation	
	0-None	

CRS-R, Coma Recovery Scale-Revised; MCS+, minimally conscious state plus; MCS–, minimally conscious state minus; eMCS, emerged from MCS.

www.spssau.com). Categorical data and univariate analysis results were analyzed using Fisher's exact test, Mann–Whitney *U*-test, and Wilcoxon matched-pairs signed-rank test. A significant difference was defined as a p-value of <0.05. The statistical parameters for each analysis can be found in the relevant figure legends.

3. Results

3.1. Feasibility and safety

Fourteen patients (nine men and five women; mean age, 55.79 ± 8.29 years) with DOC who underwent st-SCS were enrolled in this study. The average time since injury was 1.27 ± 0.31 months and ranged from 1 to 1.7 months. All cases of consciousness in this study were due to PBSH (Table 1). Of all 14 patients, 10 were treated with minimally invasive stereotactic puncture therapy (MISPT) before SCS implantation. Notably, we did not record any severe adverse events (such as seizures or intracranial infections) associated with st-SCS implantation or programming.

TABLE 3 Clinical data of patients with disorders of consciousness treated by short-term spinal cord stimulation.

No.	CRS-R (T0)	CRS-R (T2)	Changes of diagnosis
1	8 (0–3–2–1–0–2)	20 (4–4–5–1–2–3)	MCS– improved to eMCS
2	14 (3–3–3–1–1–3)	23 (4–5–6–3–2–3)	MCS+ improved to eMCS
3	15 (3–3–4–1–1–3)	19 (4–5–6–1–1–3)	MCS+ improved to eMCS
4	4 (0–3–1–0–0–0)	6 (0–3–1–1–0–1)	Remained MCS–
5	6 (1–3–0–0–0–2)	8 (1–3–2–0–0–2)	Remained MCS–
6	8 (1–3–2–1–0–1)	10 (2–3–2–1–0–2)	Remained MCS–
7	8 (1–3–2–0–0–2)	23 (4–5–6–3–2–3)	MCS– improved to eMCS
8	8 (1–3–2–1–0–1)	8 (1–3–2–1–0–1)	Remained MCS–
9	5 (1–2–0–1–0–1)	11 (3–3–2–1–0–2)	VS/UWS improved to MCS+
10	8 (1–3–2–0–0–2)	14 (3–3–3–1–1–3)	MCS– improved to MCS+
11	5 (1–0–2–0–0–2)	5 (1–0–2–0–0–2)	Remained VS/UWS
12	8 (1–3–2–1–0–1)	8 (1–3–2–1–0–1)	Remained MCS–
13	19 (4–5–5–1–1–3)	21 (4–5–5–2–2–3)	MCS+ improved to eMCS
14	17 (3–3–5–1–1–3)	17 (3–3–5–1–1–3)	Remained MCS+

T0, time before SCS surgery; T2, 2 weeks after SCS surgery; VS/UWS, vegetative state or unresponsive wakefulness syndrome; MCS–, minimally conscious state minus; MCS+, minimally conscious state plus; eMCS, emerged from MCS; CRS-R, Coma Recovery Scale-Revised.
CRS-R includes six subscales addressing auditory, visual, motor, oromotor, communication, and arousal functions, which are summed to yield a total score ranging from 0 to 23.

3.2. Clinical diagnostic changes after st-SCS treatment

After 2 weeks of st-SCS treatment, seven patients had improved diagnostic results, with an overall effectiveness rate of 50% (7/14) (Table 3). An effective rate of 50% (6/12) was found in the patients with MCS, and a 50% (1/2) effective rate was also found in the patients with VS/UWS. After analyzing the clinical sample information, we found that 75% (3/4) of patients with MCS+ improved to eMCS, 50% (1/2) of those with VS/UWS improved to MCS+, 25% (2/8) of those with MCS– improved to eMCS, and only 12% (1/8) of those with MCS– improved to MCS+ (Table 3 and Figure 2).

3.3. CRS-R score changes after st-SCS therapy

Short-term spinal cord stimulation (st-SCS) treatment not only improved the clinical diagnosis of patients but also significantly

improved their CRS-R scores. After 14 days of electrical stimulation, over 70% (10/14) of the patients were classified into the efficacy group (CRS-R score increased by ≥2 points), and below 30% (4/14) were classified into the inefficacy group (CRS-R score unchanged or increased by <2 points; Figure 3A). In particular, 36% (5/14) of the patients showed an over 4-point increase, 36% (5/14) showed an increase between 2 and 4 points, and 28% (4/14) showed an increase of <2 points (Figure 3B).

Statistical analysis of the obtained results was then performed. The statistical results showed that patients had a marked increase in their CRS-R scores after 2 weeks of st-SCS therapy ($p = 0.005$). More excitingly, all six subscales included in the CRS-R scores exhibited a significant post-treatment increase when compared with the pretreatment values (Table 4).

In addition, clinical data from the effective and ineffective treatment groups were collected and analyzed. We assessed factors such as age, sex, and previous history of hypertension or MISPT for similarities and differences among the groups. As shown in Table 5, there were no significant differences between the two groups. Similarly, further subdivision of the MCS diagnostic revealed no significant difference between the effective and ineffective groups for the three diagnostic subgroups (VS, MCS–, and MCS+).

4. Discussion

Short-term spinal cord stimulation (St-SCS) was first used for pain relief and has become an indispensable treatment means for patients with early-stage pain (39–41). In recent years, with more extensive st-SCS investigations, it has been used in the recovery of consciousness. Our study demonstrated the safety and feasibility of st-SCS in treating PBSH-induced DOC, and it was the most effective treatment for patients with MCS+. After st-SCS treatment, over 70% of the patients showed improvement in the CRS-R score, and each item included in the CRS-R test exhibited a significant increase. Approximately 50% (7/14) of the patients showed improved neurological behavior. These results are promising for future applications of st-SCS in PBSH-induced DOC.

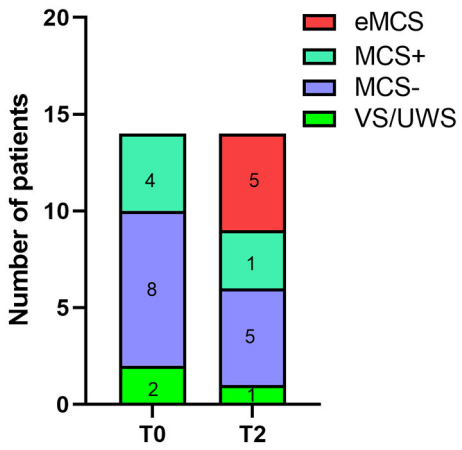

FIGURE 2
Changes in clinical diagnosis before and after treatment. T0, before the treatment; T2, 2 weeks of follow-up.

TABLE 4 Statistical analysis (*p*-value) of behavioral assessment by the CRS-R test.

	T2 vs. T0
Total CRS-R score	0.005**
Auditory function	0.017*
Visual function	0.038*
Motor function	0.017*
Oromotor	0.039*
Communication	0.038*
Arousal	0.014*

CRS-R, Coma Recovery Scale-Revised; T0, time before spinal cord stimulation surgery; T2, 2 weeks after spinal cord stimulation surgery.
Wilcoxon matched-pairs signed-rank test was used for all statistical analyses shown in this table.
*p < 0.05.
**p < 0.01.

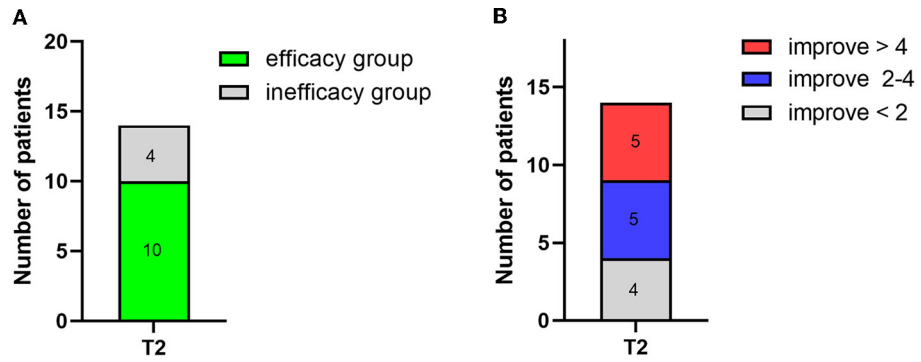

FIGURE 3
Number of patient changes in CRS-R score after 2 weeks of treatment (T2). **(A)** The number of patient changes for the efficacy group (CRS-R score increased by ≥2) and the inefficacy group (CRS-R score unchanged or increased by <2). **(B)** Detailed number of patients and the corresponding change in CRS-R score.

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TABLE 5 Clinical variable comparisons between improvement and unimprovement.

Variables	Improvement ($n = 10$)	Unimprovement ($n = 4$)	Statistic value	p-value
Sex				
Male	5	4	NA[a]	0.221
Female	5	0		
Age (years)				
40–60	7	3	12.780[a]	0.560
>60	3	1		
Hypertension				
Yes	8	3	NA[a]	1.000
No	2	1		
MISPT				
Yes	6	4	NA[a]	0.251
No	4	0		
Post-injure [*M* (P25, P75), days]	39.9 (30, 50)	42 (30, 38)	10.500[b]	0.149
CRS-R onset [mean (min, max)]	9.5 (4, 19)	9.5 (5, 17)	19.500[b]	0.947
Diagnosis				
VS/UWS	1	1	0.977[a]	1.000
MCS–	6	2		
MCS+	3	1		

MISPT, minimally invasive stereotactic puncture therapy; VS/UWS, vegetative state or unresponsive wakefulness syndrome; MCS–, minimally conscious state minus; MCS+, minimally conscious state plus.
[a]Fisher exact test.
[b]Mann–Whitney U-test.
*$p < 0.05$.

To the best of our knowledge, this is the first case in which st-SCS was used to treat PBSH-induced DOC. Therefore, st-SCS stimulation strategies were drawn from others reported for DOC. According to previous reports, the CRS-R score significantly increased after 2 weeks of DOC treatment at 70 Hz (33, 34); we selected this frequency for this study. According to previous studies, neuronal fatigue or damage was reduced if the stimulation time was shorter than the off-stimulation time (31). Therefore, the stimulation cycle was chosen as 5-min ON/15-min OFF. Finally, the treatment period started at 8 a.m. and ended at 8 p.m. for a total of 2 weeks to meet the patients' sleep demands. To further improve the outcome of st-SCS, future studies should consider other treatment protocols, including selected 5 Hz or prolonged treatment periods. Furthermore, non-invasive neuromodulation techniques combined with st-SCS are promising therapies for the future because they activate many brain regions simultaneously.

Furthermore, clinical data such as age, sex, and history of the disease are important for clinical treatment (42). There was no significant difference between the efficacy and inefficacy groups in terms of age, sex, hypertension, or MISPT history in our study; this result is similar to that reported in the literature (33). In addition, a subdivision of the MCS diagnosis did not reveal any significant differences between the two groups, contrary to previous research. This could be because PBSH-induced DOC may have other unclear mechanisms; moreover, the limit of sample size leading to statistical validity was not sufficient.

Finally, there were many limitations to our study, and future study is warranted. First, we used the CRS-R to diagnose DOC; however, there was also a need for neuropsychological measurements in these patients. Future studies should utilize neuroimaging and neurophysiological assessment techniques that provide objective feedback on patients' clinical performance. Second, the sample size of this study was small. The small sample size limited us from analyzing the factors that affect the therapeutic efficacy of st-SCS. Then, 3 months of follow-up were not available for some patients, limiting further statistical analysis of follow-up information. Finally, further studies are required to fully explore the mechanisms underlying st-SCS therapy.

5. Conclusion

In this study, we provided preliminary data suggesting that st-SCS is a safe and effective clinical therapy to facilitate the recovery of consciousness in patients with PBSH. As measured by the CRS-R score, st-SCS intervention significantly improved patients' clinical manifestations. It is worth noting that st-SCS seemed to be more applicable to patients with MCS+. Between the effective and ineffective groups, age, sex, duration of illness, and history of hypertension or MISPT had no significant effect. Further studies are required to explore whether these factors affect st-SCS therapy.

The results of this study provide a new perspective on the treatment of PBSH-induced DOC with st-SCS and a reference for treating other cerebrovascular diseases.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Ganzhou People's Hospital. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

DW: conceptualization and supervision. HZ and ZT: methodology. LL and JT: data curation. WH and QC: formal analysis, investigation, and writing original draft preparation. DW and JL: writing, review, and editing. DW and TL: funding acquisition. QJ: resources. All authors contributed to the writing of the article and approved the final version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Prognostic humility and ethical dilemmas after severe brain injury: Summary, recommendations, and qualitative analysis of Curing Coma Campaign virtual event proceedings

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Background: Patients with severe acute brain injuries (SABI) are at risk of living with long-term disability, frequent medical complications and high rates of mortality. Determining an individual patient's prognosis and conveying this to family members/caregivers can be challenging. We conducted a webinar with experts in neurosurgery, neurocritical care, neuro-palliative care, neuro-ethics, and rehabilitation as part of the Curing Coma Campaign, which is supported by the Neurocritical Care Society. The webinar discussed topics focused on prognostic uncertainty, communicating prognosis to family members/caregivers, gaps within healthcare systems, and research infrastructure as it relates to patients experiencing SABI. The purpose of this manuscript is to describe the themes that emerged from this virtual discussion.

Methods: A qualitative analysis of a webinar "Prognostic Humility and Ethical Dilemmas in Acute Brain Injury" was organized as part of the Neurocritical Care Society's Curing Coma Campaign. A multidisciplinary group of experts was invited as speakers and moderators of the webinar. The content of the webinar was transcribed verbatim. Two qualitative researchers (NK and BM) read and re-read the transcription, and familiarized themselves with the text. The two coders developed and agreed on a code book, independently coded the transcript, and discussed any discrepancies. The transcript was analyzed using inductive thematic analysis of codes and themes that emerged within the expert discussion.

Results: We coded 168 qualitative excerpts within the transcript. Two main themes were discussed: (1) the concept of prognostic uncertainty in the acute setting, and (2) lack of access to and evidence for quality rehabilitation and specialized continuum of care efforts specific to coma research. Within these

two main themes, we found 5 sub-themes, which were broken down into 23 unique codes. The most frequently described code was the need for clinicians to acknowledge our own uncertainties when we discuss prognosis with families, which was mentioned 13 times during the webinar. Several strategies were described for speaking with surrogates of patients who have had a severe brain injury resulting in SABI. We also identified important gaps in the United States health system and in research to improve the care of patients with severe brain injuries.

Conclusion: As a result of this webinar and expert discussion, authors identified and analyzed themes related to prognostic uncertainty with SABI. Recommendations were outlined for clinicians who engage with surrogates of patients with SABI to foster informed decisions for their loved one. Finally, recommendations for changes in healthcare systems and research support are provided in order to continue to propel SABI science forward to improve future prognostic certainty.

KEYWORDS

severe brain injury, caregiver, comfort care, prognosis, disorders of consciousness

Introduction

Approximately 258 per 1,00,000 patients per year in the United States sustain a severe acute brain injury (SABI), including traumatic and non-traumatic etiologies (Kondziella et al., 2022). Patients with severe neurologic insults such as these have the highest rates of long-term disability when compared to any other disease process (Murray et al., 2013; Gooch et al., 2017; WHO, n.d.). When SABI occurs, decisions of whether life sustaining measures should be maintained or discontinued are often left to surrogate decision makers such as family members/caregivers, a durable power of attorney or a guardian (Keating et al., 2010; Barclay et al., 2011; Fins, 2015). In order for surrogates to make treatment decisions on a patient's behalf, they must understand the diagnosis and prognosis as it relates to SABI from the patient's healthcare team. However, it is difficult to predict which patients will have long term severe disability, which patients may achieve functional improvement and which ones will be able to adapt to a new health state and regain a good quality of life. In addition, it may be important to consider the patient's support system and environment and consider how well they will adapt and or be able to support their loved one with a new level of disability (Wilson and Gilbert, 2008; Creutzfeldt and Holloway, 2012). In most cases of SABI, patients have not previously provided written, explicit wishes for continued care within an advance directive (AD) (Alonso et al., 2017; Sutter et al., 2020; Rutz Voumard et al., 2021). Thus, families are often left to assume the responsibility of making life or death treatment decisions for their loved one (Thompson et al., 2003; Adelman and Zahuranec, 2012; Sutter et al., 2020). Although many patients with SABI improve significantly over months and years post-injury, early mortality is high, and most patients who die do so after a decision to withdraw life-sustaining treatments (Zahuranec et al., 2010; Turgeon et al., 2011; Kowalski et al., 2021). Because of the complexities related to prognostic uncertainty, the term "prognostic humility" has been used to describe gaps in knowledge, understanding, and communication of prognostic uncertainty after SABI (Fins, 2020, 2022).

In order to better understand issues related to prognosis, family/caregiver engagement and systems of care for patients with SABIs, we conducted a webinar through the Neurocritical Care Society's Curing Coma Campaign (**Supplementary Table 1**). The Curing Coma Campaign began in 2019, and is a "public health initiative designed to develop and implement coma treatment strategies that improve human lives" (Curing Coma, n.d.). The Community of Collaborators (CoC) is a module of the Curing Coma Campaign with the goal of discussing issues that are pertinent to families, caregiving, and follow-up. This webinar was the first in a series of planned webinars designed to integrate the discussion of numerous aspects of caregiving after a SABI. The purpose of the webinar and subsequent qualitative analysis was to obtain qualitative responses from experts in the fields of neurosurgery, neurocritical care, palliative care, ethics, and rehabilitation in a virtual focus group environment. The authors describe the major themes and discussion points of this educational webinar. We report the findings that emerged from this expert discussion, which include best practice recommendations to clinicians who are speaking to surrogates of patients with SABI, suggestions for change in healthcare systems to support SABI survivors across the continuum of care, and important gaps in research to improve SABI care.

Materials and methods

This manuscript is a qualitative analysis of a webinar "Prognostic Humility and Ethical Dilemmas in Acute Brain Injury" that took place as part of the Neurocritical Care Society's Curing Coma Campaign on September 28, 2021, and was aired on October 5, 2021.

This webinar was designed by the Curing Coma Campaign "Community of Collaborators" module as a panel discussion between known experts in the field, all included as authors, with two moderators presenting open ended structured questions with no formal presentations. A multidisciplinary group of experts were invited as speakers and moderators of the webinar. Content experts involved in the webinar represented the fields of adult neurosurgery, Neuroethics, rehabilitation, neurocritical care, and neuro-palliative care from throughout the United States (**Supplementary Table 2**). The moderators (NK and BM) were trained in Neurocritical Care and Neurological Rehabilitation. Panel questions to facilitate coma prognostic discussion were developed by the core members of the CoC, and the final draft of questions were approved by the group. All questions were designed to be open-ended, and to spark a dialogue among all members of the group. Follow up questions were developed to go in depth on certain topics. It was anticipated that the discussion amongst the group would bring out rich, unplanned commentary. The webinar was recorded through Zoom© virtual platform and transcribed verbatim.

Analysis

The content of the transcript was analyzed using inductive thematic analysis after the recorded webinar was listened to, transcripts were made, read, re-read, and the coders had familiarized themselves with the text. Inductive analysis is a data-driven process of coding the data without attempting to fit it into an existing coding framework or the researcher's own analytic preconceptions (Braun and Clarke, 2006). All discussion components mentioned by participating speakers and moderators were included in the analysis. A list of themes and codes identified through this discussion from the group of content experts were initially developed, with a code book describing the definition of each code. This was edited multiple times by two investigators (BM and NK), and a final code book was agreed upon. The transcript was coded by the two investigators, and codes were discussed among the two authors to resolve disagreements. In the case that the final codes and themes could not be resolved by discussion among these two authors, a third author would have been appointed to resolve any discrepancies. Results were brought back to the author (and presenter) group, and their feedback solicited as a "member check" (Taylor and Bogdan, 1998).

Results

The webinar was aired on October 5, 2021. It was 1 h in length, followed by a 30-min Q and A session. Two main themes were identified: (1) the concept of prognostic uncertainty, and (2) lack of access to and evidence for quality rehabilitation and specialized continuum of care efforts specific to coma research. Within these two main themes, we identified 5 sub-themes, which we further broke down into 23 unique codes (**Table 1**). We coded 168 total unique excerpts from the discussion. The two coders (NK and BM) initially agreed on 137/(82%) of codes after independent review of the transcript, prior to discussion. After discussion, there were no discrepancies between the two coders. The most commonly coded transcript extracts fell into the codes of "healthcare systems do not exist or access to care is limited" (n = 21), describing issues with long-term rehabilitation not existing or not being available to patients in all geographic areas of the United States; "biases" (n = 19) which describes conscious and unconscious biases such as nihilism, the self-fulfilling prophecy, disability biases, or other biases, and ways clinicians should evaluated our own biases; and "acknowledging our own uncertainty" (n = 14), which describes uncertainties that clinicians have with prognosis (**Supplementary Table 2**).

Theme 1: Prognostic uncertainty

Sub-theme 1: Problems with prognosis that we need to understand as clinicians/researchers

Several challenges were discussed related to prognostic discussions within groups of interdisciplinary professionals and between interdisciplinary healthcare professionals and surrogates. These included the type of communication and language used by healthcare providers, which may not meet the healthcare literacy needs of individual families/caregivers. In many cases, healthcare professionals may not be using consistent language themselves to describe SABI or coma, which further complicates discussions with surrogates. Further, organizations such as the American Medical Association have called for increased awareness of patient literacy when discussing healthcare matters (Ad Hoc Committee on Health Literacy, 1999). These issues were highlighted with the quote: "*One of the things I think we have to be familiar with, and recognize is the language we use. Coma, vegetative state, minimally conscious state. You know, even stroke. People don't know what we're talking about.*"

Biases that influence prognostication such as nihilism defined as skepticism of treatment, (Merriam-Webster, n.d.) the self-fulfilling prophecy, defined as "an erroneous belief or expectation that leads to its fulfillment," (Merton, 1948) the disability paradox, defined as those patients with disabilities who report a good quality of life despite the fact that those externally may report an imagined poorer quality of life (Albrecht and Devlieger, 1999; Ubel et al., 2005), or other biases were brought up as an issue that arises in discussions with surrogates. It is important to recognize our own ingrained cultural beliefs and how they may differ from surrogates' cultural beliefs related to treatment preferences and decision-making. "*We as clinicians have a very different view of what a good outcome is, versus what a family has as a good outcome. And we need to spend more time talking to families about what their perspective of outcome is.*"

Sub-theme 2: Communication strategies to help with uncertainty

The second sub-theme focused on communication strategies to help with uncertainty as clinicians speak to surrogates about prognosis after SABI. Several strategies were discussed that may be beneficial. The healthcare team should ideally view surrogates as partners. As such, it is important to clearly convey to surrogates early after SABI that prognostic information changes over time. Although some aspects of prognoses after SABI may be uncertain, healthcare providers should highlight to surrogates the aspects of

TABLE 1 Theme, sub-theme, and coding structure.

Codes	Description/Definition of codes	Number of times code was used
Theme 1: Prognostic uncertainty		
Subtheme 1: Problems with prognosis that we need to understand as clinicians/researchers		
Language, communication, and health literacy	Clinicians have inconsistency among ourselves with the language and terminology we use. Families may not understand medical language. "*One of the things I think we have to be familiar with, and recognize is the language we use. Coma, vegetative state, minimally conscious state. You know, even stroke. People don't know what we're talking about*," "*If there are inconsistencies and a lack of consensus within the medical field, how do we even begin to help families understand if we're even struggling to purely understand and define this population*."	6
Only have limited information	The patient is generally in the early time course, so information is often limited. "*We are forced to make all these moral choices before we have all the facts.*"	4
Patient variability	Each patient is unique in terms of prognosis, making brain injury prognostication challenging: "*This is not a stereotypic disease. Everyone has their own injury. And everyone is going to behave differently and they're going to have comorbidities. And there's a lot of uncertainty*."	4
Biases	There are many biases clinicians may have. These include nihilism, self-fulfilling prophecy, disability bias, and others. Clinicians have conscious and unconscious biases that we should evaluate within ourselves so that we can improve. *"For a long time in neurocritical care, it seems we have been riddled with nihilism."*	19
Culture	Describes the cultural ways clinicians think about unconsciousness and the right to die after brain injury. "*We as clinicians have a very different view of what a good outcome is, versus what a family has as a good outcome. And we need to spend more time talking to families about what their perspective of outcome is*."	7
Subtheme 2: Communication strategies to help with uncertainty as we are communicating to families		
Information changes	It is important to convey to families that information about prognosis changes over time after a brain injury. This information may pertain to comorbidities and their interplay with the patient's initial brain injury. This may also involve proving psychological support/counseling for families to manage changing expectations. *And (decisions) are going to need to be made with information that is going to change and evolve even over a patient's time with us as well as while they are in a rehabilitation setting, or continuing to recover in a long-term care facility*	4
Need for clinical caregiver partnership	Clinicians need to see ourselves as partners with patients and surrogates. The partnership should be open, transparent, and clinicians should recognize that family/caregivers knows the patient as a human. "*I often tell families that I might be an expert in what I'm doing, but you are the expert in the person, the human being we are seeing in front of us.*"	6
Trajectories	Approach prognosis from the stance of trajectories, milestones, and a positive uncertainty. Describe short- and long-term milestones. Recognize uncertainty decreases over time. This information pertains to individual trajectories of acute brain injury. *"We talk about the cone of uncertainty, and how it gets narrower and narrower over time."*	13
New normal	Talk to families about what a new normal is like after severe brain injury. Psychological support/counseling regarding preparing for the new challenges expected through short- and long-term care of SCH patients. *"(It's important to) prepare the loved ones, the family members, for this new state of normal. It's not going to be who this person was before they became our patient. It's not going to be different; it's not going to be bad, or it's not going to be better, it's just going to be different."*	3
Certainty	Explain to families the things we can be certain about. "*I do think there are some times, certain things we can be relatively certain about. As an example, I am certain that this is going to be a very long road*."	3
Sub-theme 3: Strategies in managing ourselves as healthcare providers in the face of uncertainty		
Acknowledge our own uncertainty	Recognize that we have uncertainties ourselves, that this job is a humbling responsibility. "*I've seen enough people that I thought would do well that didn't and people that I thought would do terrible that didn't, that I really stopped prognosticating. So, I think it's a delicate walk that we do with families*."	14

(Continued)

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TABLE 1 (Continued)

Codes	Description/Definition of codes	Number of times code was used
Making peace and learning	We need to make peace with decisions and continue learning more. "*When we go back to the same decision, a year or more, we're probably going to make a different decision. So, we have to make our peace with that.*"	3
Incorporate science	Clinicians must incorporate scientific discoveries into our practice. Recognize that in many cases, early withdrawal of care is inconsistent with science. "*There is a remarkable emerging literature about how injured brains recapitulate the developmental process with sprouting and pruning of axons.*"	10
Theme 2: Systems approach: Healthcare and research issues		
Sub theme 1: Absence of, or too little support from health systems		
Healthcare systems do not exist or access to care is limited	The system of care necessary to help patients with severe brain injuries is absent. It is hard to partner with patients and families when many features such as long-term rehabilitation do not exist everywhere, since even when some systems exist, they are not available to everyone. "*If you live in the middle of the country, where are you going to go? There's nowhere to go. There's no heart in the heartland.*"	21
Fiscal Issues	There is too little of a fiscal investment in severe brain injuries. Caring for these patients requires years of expensive care that is unmet. "*We make a moral and fiscal investment in these people, and if we aren't going to pay for the tail of the injury, the first 6 weeks, and the next 20 years probably cost the same thing.*"	6
Lacking coma science	More research is needed, more dissemination of research is needed. "*In these diseases (cancer) where we have so much more data and we can understand outcomes better, and we have a lot more biomarkers to know where we are on that course and that journey.*"	4
Siloed by diagnosis	Patients are siloed based on diagnosis, rather than functional status, and this may get in the way of rehabilitation. Health systems focused on patients with similar spectrum of disability despite having a different etiology might benefit from shared resources. e.g., post-acute care rehabilitation tends to focus on ischemic stroke or traumatic brain injury. *"We have to be less obsessed with the diagnosis and more concerned with the functional status."*	5
Sub-theme 2: Solutions to healthcare or research related issues		
Agree on outcomes and timing	We need to define outcomes as a neurological care continuum, and determine when outcomes should be assessed. Current outcomes research and healthcare systems are heterogeneous in terms of timeline and outcome definition. *"But brains recover by biologic mechanisms, not reimbursement criteria."*	10
Optimize short term care	We should provide optimal care in the short term to prevent common complications of brain injuries. Short term care targets should not be biased or held back by prognostication discussions. *"I think it's important that we don't cause iatrogenic deaths either through the avoidable urinary tract infection and bed sore or pneumonia."*	2
Education interventions that target informed families	Systems must be in place that appropriately inform families, such that withdrawal of care is only considered after properly informing a family/caregivers. Such level of being informed should be considered at the same level as informed consent. *"Speaking of the goals and wishes for the patient who can't speak for themselves. If it's a life well lived, and they would not want to take that chance to see what would happen next, in that moment in time, our role as being those facilitators of a dignified death is also as important as being a facilitator of a dignified life."*	8
Civil rights	We may want to look at prognosis after severe brain injury through a civil rights violation lens. Civil rights, guarantees of equal social opportunities and equal protection under the law, regardless of race, religion, or other personal characteristics. *"This is not just an economic thing. This is about civil rights. This is about the rights of people who have severe brain injury to fully engage in society."*	4
Team	Systems should assure that a healthcare team should be on the same page and supportive of one another when discussing with families. *"The most important thing we do before we meet with families is to have the pre-meeting huddle. We don't share our confusion and our conflict. We try to reach a consensus about where this patient is."*	6
Need for research	There is a need for continued research into coma science, entailing precise outcomes, better prognostication tools, and an understanding of the timeline for patients with severe acute brain injuries. *"And so we need to kind of learn more about the biology to harmonize the financing to go with the science."*	6

Heat map color configuration: 1–5: orange; 6–10: aqua; 11–15: purple; 15–19: green; 20, and over: red.

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their care and prognosis that are more certain. In doing so, it is important to also describe to surrogates that the prognostic trajectory after SABI may become clearer over time in some cases, and that this may improve the ability to better understand prognosis. This trajectory can be augmented with short- and long-term milestones expected for the patient. Since the trajectory of many patients with SABI in prior literature is unknown due to withdraw of life sustaining treatments, serial monitoring and communication of an individual patient's trajectory may provide useful information to families/caregivers in understanding prognosis (Hammond et al., 2021). This serial monitoring requires the use of multidisciplinary professionals to work cohesively together along the continuum of care. One speaker said "*And (decisions) are going to need to be made with information that is going to change and evolve even over a patient's time with us as well as while they are in a rehabilitation setting, or continuing to recover in a long-term care facility.*"

Sub-theme 3: Strategies that clinicians can use to educate ourselves in the face of uncertainty

The third sub-theme described strategies clinicians can use to educate ourselves and improve our ability to care for surrogates of patients who face prognostic uncertainty. It was discussed that over time, it is important that healthcare providers reflect on past decisions, learn the emerging science in SABI prognosis, and make peace with prior decisions, so that we can better care for patients in the future. The most commonly discussed concept related to this was the need for us to acknowledge our own uncertainties about prognosis at times. One speaker said "*I've seen enough people that I thought would do well that didn't and people that I thought would do terrible that didn't, that I really stopped prognosticating. So, I think it's a delicate walk that we do with families.*"

Theme 2: A systems approach to healthcare and research issues

Sub-theme 4: Absence of, or too little support in healthcare systems

The fourth sub-theme describes the phenomenon that there are problems when caring for patients with SABIs in the United States related to the lack of resources within healthcare systems, rehabilitation facilities, and outpatient and community-based services. This may mean that systems do not exist, may be geographically sparse such that they are not widely available to a large portion of the United States population, or that ongoing care and rehabilitation needs are fiscally unattainable for many SABI survivors. The panel mentioned that patients may receive excellent emergency stabilization and acute care, only for funding in post-acute care to be lacking. Oyesanya et al. (2021) previously described this phenomenon in a Medicare database study in which they noted significant differences in rehabilitation outcomes following TBI based on geographical location within the United States. In addition, more research is needed to best understand how to optimize patients' rehabilitation needs. These issues were highlighted with the quote, "*If you live in the middle of the country, where are you going to go? There's nowhere to go. There's no heart in the heartland.*"

Sub-theme 5: Solutions to healthcare and research related issues

The final sub-theme described strategies for improvements within healthcare systems and within coma research. In addition to optimizing short term care and preventing complications in the acute period after SABI, it is important that healthcare systems have plans in place to make sure families are well-informed during this time. The utilization of a team-based approach to coma care can facilitate this. One example of a way to make sure families are well-informed and have not heard differing messages from members of the care team was to institute a "huddle," or a discussion within the healthcare team prior to meeting with family or caregivers (Hammond et al., 2021).

Lastly, we discussed the critical need for more research and dissemination of coma science in general. This encompasses a need for the scientific community studying coma outcomes to agree on the types of outcomes and timing after SABI of when to measure these outcomes. This was highlighted with the quote, "*there needs to be a plug for funding more research. Because we don't know. We need to say what we do know, and we realize what we don't know. We need to explore people's values knowing how well they are going to recover and adapt in the future. There's just so much we need to learn and systematically research.*"

Discussion

This qualitative study highlighted numerous issues related to prognostic uncertainty and healthcare systems after a SABI. There are numerous challenges related to prognostication of patients with SABI, particularly during the early ICU course of the injury. Although many patients with SABI may regain consciousness, functional independence, and even experience late improvements in outcomes, many others may not do well or would not want to live with SABI, making prognostication challenging (Whyte et al., 2013; Giacino et al., 2020; Kowalski et al., 2021). The panel discussed important solutions such as identifying our own biases as clinicians that lead to premature withdrawal of life-sustaining treatment, such as nihilism, the self-fulfilling prophecy, or the disability paradox. Additionally, the panel discussed that the family or caregivers may have inaccurate pre-conceived notions that withdrawal of life sustaining treatment may not be possible after the ICU course of illness, sometimes described as a "missed opportunity (Cochrane, 2009)."

This webinar focused extensively on discussions of prognostic uncertainty between clinicians and family surrogate decision makers. Some solutions have been described previously in published literature, such as assuring that clinicians understand current evidence as well as gaps in research related to coma science before conducting education and counseling with families. Clinicians need to be intentional to update discussions with surrogates using advanced tools, tailored predictions and meaningful long term endpoints to portray an accurate prognosis (Hammond et al., 2021). Family or caregiver discussions should specify both the predictions and level of confidence in predictions (Hammond et al., 2021). The disorders of consciousness practice recommendations describe best practices for counseling families about prognosis, and recommends that clinicians avoid statements

that indicate a universally poor prognosis in the first days and weeks post-injury (Giacino et al., 2018). A recent NIH workshop discussed recommendations similar to those that were brought up in our webinar, which included, (1) ways to communicate more clearly and consistently, (2) better assistance with navigating resources and access to places for families to care for themselves, and (3) opportunities for families to remain connected with their loved ones, social support networks and clinical team (Muehlschlegel et al., 2022). New solutions for discussions with surrogates focusing on prognosis were identified in the webinar. One example was the suggestion to approach prognosis as a trajectory, with short- and long-term milestones. As more time passes, the level of uncertainty may decrease, and surrogates may gain a better understanding of prognosis.

Although numerous problems related to prognosis and the healthcare system after SABIs were discussed, this webinar also discussed targets for improvement of care. There were two systemic issues discussed that require urgent action plans for optimizing SABI recovery. The first issue is the need for effective healthcare systems and infrastructure to care for patients who have sustained a SABI. Currently, a care continuum after SABI is not available to much of the population in the United States. The second issue is the need for more research in coma science, such as how and when to determine outcomes after SABI, and how to provide the optimum continuum of care to patients with SABI. Specifically, a unified type and time point to measure outcomes across research in SABI was deemed important by expert panelists, as well as the need for dissemination of research findings. Future work that builds from this qualitative work may investigate how the codes and themes that emerged in this work are related with one another, or even converge with one another, and how this plays a role in discovering targets for improvement of care.

Without healthcare systems support such as publicly funded long term care insurance, a budget for home health assistance, and with expensive co-pays for rehabilitation or novel treatments, and support for family caregivers, it is challenging to counsel families and to conduct research in this realm (Caplan, 2017; Sattin et al., 2014, 2017). Additionally, reports of variation in referral to rehabilitation among clinicians indicate there may be opportunities to standardize post-acute care (Swaine et al., 2018).

Limitations

As with any small qualitative study, it is noted that findings are affected by the experience and perceptions of the participating research team as well as the composition and experiences of the participants. To limit this bias in the analysis of this webinar, we utilized expertise in qualitative methods and analysis, and we followed a systematic process. This improved the credibility and dependability of findings. An additional limitation is only two authors (NK and BM) identified and coded themes and sub-themes. Recruiting additional reviewers of the webinar transcript to identify themes, sub themes and code those themes may have identified additional salient, yet important themes related to prognostic humility. We did not have representation in the panel from neonatal or pediatric SABI, so results cannot be extrapolated into the pediatric population. A final limitation is the webinar captured the knowledge, opinions and editorials of those experts involved in the webinar. There is a wide depth and breadth of evidence and experience-informed clinicians involved in care and prognosis of patients with SABI. Other experts or family members/caregivers could have brought additional insights and views that could have impacted the identification and coding of themes within the analysis. We hope that this initial work incites further investigation using a broader survey of community members that play roles in the issues pertinent to families, caregiving, and follow-up. Further webinars exploring these perspectives are underway. We have also requested a position paper from experts to address priorities prognostic humility and ethical dilemmas with data to support those thoughts/ideas.

Conclusion

This qualitative analysis identified and coded themes and sub-themes of an expert discussion focused on prognostic humility when approaching coma and SABI in the acute phases of care. Key themes related to acknowledging prognostic uncertainty when approaching patient care and family counseling were identified. Current approaches of prognosis as well as gaps in knowledge, comfort, and health systems create barriers to effective prognostication and support of families. It is imperative for the neurological care community to continue to engage in scientific processes to address the gaps discussed to improve prognostic discussion and advocacy for the patient with SABI and their families.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

CC, GM, and JF participated as expert panelists in the webinar. NK, AS, ND, and BM conducted the planning and moderating of the webinar. NK and BM drafted the manuscript and conducted the analyses. All authors revised and contributed to the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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Specialized intensive inpatient rehabilitation is crucial and time-sensitive for functional recovery from disorders of consciousness

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Background: Disorders of consciousness (DoCs) after severe brain injury are considered to be conditions with dire prognosis. Despite the accumulating evidence, inpatient rehabilitation is often denied by payers referring to the Medicare/Medicaid criteria, under the assumption that such patients will not *"actively"* participate in therapy or make *"measurable improvements."*

Objective: This study aimed to report on the effectiveness and efficiency of a specialized inpatient DoC rehabilitation program based on measurable clinical parameters.

Methods: A retrospective cohort study was conducted. The cohort comprised 137 patients with DoC admitted to a specialized acute inpatient rehabilitation program between January 2014 and October 2018. Patients were categorized as having been admitted at the acute stage (<=28 days post-injury), subacute stage (29–365 days following a traumatic brain injury (TBI) or 29–90 days following a non-TBI), or chronic stage (>365 days following a TBI or >90 days following a non-TBI). Outcomes included changes in level of consciousness (based on the Coma Recovery Scale–Revised (CRS-R), while also acknowledging scenarios beyond those captured by the CRS-R *via* Individualized Qualitative Behavioral Assessment and team consensus); Functional Independence Measure (FIM) levels; achievements in decannulation and initiation of oral diet; and time to those achievements.

Results: The rates of emergence from a minimally conscious state were 90, 62, and 18% among patients admitted at the acute, subacute, and chronic stages, respectively. Among patients who emerged, 100, 85, and 67%, respectively, had measurable FIM scores. Approximately 60 and 20% of patients at the acute and subacute stages, respectively, required moderate assistance or less in transfer/communication/eating/grooming/upper body dressing by the time of discharge from Phase I admission. The decannulation rates were 94, 67, and 17%. The oral diet initiation rates were 70, 23, and 6%. The time to reach these achievements lengthened as chronicity increased. There was a weak positive correlation ($r_s = 0.308$) in the case of decannulation and a strong positive correlation ($r_s = 0.606$, both $p < 0.01$) in the case of oral diet between days since injury on admission and days to the achievement after admission. Patients with

TBI and hypoxic brain injury had comparable recovery rates when admitted at the acute and subacute stages.

Conclusion: Specialized intensive inpatient rehabilitation is crucial and time-sensitive for functional recovery from DoC caused by TBI and hypoxic–ischemic brain injury. Specific goals and different outcome measures need to be developed to appraise the benefits of acute inpatient rehabilitation for DoC.

KEYWORDS

disorders of consciousness (DOC), inpatient rehabilitation, severe brain injuries, emergence, decannulation, oral diet, effectiveness and efficiency, outcome measures

Introduction

Disorders of consciousness (DoCs) after severe traumatic or non-traumatic brain injury (TBI or non-TBI) are commonly considered to be conditions with dire prognosis. The spectrum of DoCs includes coma, unresponsive wakefulness syndrome/vegetative state (UWS/VS), and minimally conscious state (MCS) (1). Recently, covert consciousness (a condition also recognized as "cognitive motor dissociation" or "functional locked-in syndrome") has been identified using advanced neuroimaging or electrophysiologic technologies in behaviorally unresponsive patients, which adds another dimension to the disease spectrum (2–4). Numerous studies worldwide have consistently shown that a continuous recovery process occurs in persons with DoC, even over a 10-year time span (5–11). The long-term outcomes in some of these patients have been surprisingly more favorable than presumed, especially among those with a traumatic etiology. A considerable proportion of those patients were able to achieve independence in at least one basic cognitive function (e.g., language/communication) and/or domain of activities of daily living (e.g., transfer, eating, dressing) over the course of 10 years post-injury (6, 7).

The road leading to recovery meanders, which is partly related to the severity of the brain injury and our limited understanding of the brain, but also arises from factors relating to healthcare access and nihilistic beliefs regarding treatments. Ten years ago, Katz et al. (11) provided evidence to support the recommendation of active and higher-intensity rehabilitation for patients with severely impaired consciousness after brain injury (11). Despite the accumulation of evidence over the years (6–11), such benefits are not commonly supported by insurance payers. The argument is that these patients do not meet the criteria of being able to "*actively* participate in 3 h of therapy per day at least 5 days per week" and are unable to make "*measurable* improvements"; therefore, they will not benefit from such a level of service (12). The prejudice regarding futility of treatments for DoCs in the minds of healthcare professionals, insurance payers, and the general population prevents these patients, who cannot advocate for themselves, from receiving opportunities for meaningful recovery, especially at an early stage after brain injury. Another contributing factor is that current regulatory measurement scales fail to capture patients' functional improvements as a result of inpatient rehabilitation services. Consequently, many patients may be misdiagnosed as having DoC or suboptimally treated due to lack of access to proper assessments and management (13, 14). Our preliminary analysis identified financial factors as the main barrier to accepting a DoC referral, and also identified a high rate of misdiagnosis in those referrals who were admitted (13). In the 2018 AAN/ACRM/NIDILRR DoC guidelines, the importance of referring a patient with DoC who is medically stable to a specialized inpatient rehabilitation program was emphasized as the top recommendation (Level B; "should be done") (15). Overall, implementation of these guidelines remains limited. With more standardized assessment paradigms, current inpatient rehabilitative interventions have seldom been described in detail in the literature. Recent guidelines have also provided care standards and minimum competencies for rehabilitation programs providing care for persons with DoC (16). In addition, there are a limited number of such programs accepting these patients nationwide. The barriers are multifactorial and intertwined.

While the field has seen major advancements in the detection of consciousness and in standardization of assessments (2, 15), we hope to contribute by providing guidance for effective clinical rehabilitation and advocating for increased rehabilitative access for these patients. Recently, we summarized and proposed clinical approaches in the assessment of reversible causes, confounders, and mimics of DoC (17), spasticity management (18), and the application of GABAergic medication trials (19). It is notable that meaningful improvements can be observed out of the scope of commonly used scales, such as achievement of decannulation and initiation of oral diet, thereby facilitating remaining voluntary motor control, etc. A primary focus of the present study was to report on the effectiveness of specialized intensive rehabilitative services for DoC related to TBI and non-TBI at various stages post-injury based on measurable clinical parameters. Furthermore, as indicated in rehabilitation for stroke and other types of non-progressive brain injuries, time is a sensitive matter for neurorecovery, since the greatest pace of recovery is usually expected in the first 3–6 months post-injury. Therefore, the current study also aimed to report on the efficiency of specialized intensive rehabilitative services for functional recovery in DoC.

Methods

This was a single-institution retrospective study. The cohort consisted of 137 patients; it was was derived from an established

cohort of 146 patients, which included all patients with DoC admitted to a specialized DoC rehabilitation program from January 2014 to October 2018. Nine patients who were found to have emerged from DoC on initial evaluation upon admission were excluded from the cohort, as the study was intended to evaluate the outcomes of the DoC rehabilitation program, including improvements in level of consciousness.

Operation of the DoC rehabilitation program

The admission criteria and screening process have previously been described in detail (17). In brief, pre-admission screening was performed to determine the appropriateness of admission to the specialized DoC program (i.e., to triage potential misdiagnosis of DoC). The program accepts all patients with DoC who are either in a USW/VS or in a MCS with or without ventilation support. Beyond this criterion, a patient needs to be medically stable for the transfer to take place.

Each patient's level of consciousness was assessed on admission and periodically (every 3–7 days) until discharge using standardized protocols, i.e., the Coma Recovery Scale–Revised (CRS-R) and the Individualized Qualitative Behavioral Assessment. It should be noted, however, that emergence from MCS (eMCS) was determined not solely by performance on these tests but also by close clinical observation and evaluation during daily encounters by the entire team and families, as some of the behavioral evidence of consciousness occurred outside of the testing scheme or was not assessed by the standardized tests [several case scenarios are reported in Zhang et al. (19)]. The assessments were performed by a dedicated group of experienced professionals. The management philosophy included addressing reversible causes of DoC (17); identifying confounders and mimics (17); managing neurological complications and general medical conditions (17, 18); improving arousal and awareness (e.g., sleep optimization, environmental enrichment, verticalization with sitting and standing schedules, mobilization, minimization of sedating or cognitive-impairing medications, use of neurostimulants, and sensory stimulation including tactile, music, and median nerve stimulation); and trialing GABAergic medications (e.g., zolpidem and/or lorazepam) for potential paradoxical stimulating responses (19). General medical management was undertaken with a systemic approach, including (but not limited to) domains such as the cardiovascular (e.g., storming), pulmonary (e.g., airway access and secretion management, ventilation/oxygenation, infection prevention), gastrointestinal (e.g., nutritional access and optimization, elimination), genitourinary (e.g., voiding, infection prevention), integumentary (e.g., skin breakdown), neuromuscular (e.g., spasticity, contracture prevention), and pain. All patients participated in at least 3 h of therapy daily, including physical, occupational, and speech therapy (provided by PT/OT/SLP), 5 days per week, with goals of identification of signs of consciousness, facilitation of the emergence of consciousness, and cardiopulmonary and neuromuscular conditioning. PT/OT provided modalities for maintenance of body mobility and joint range of motion, and helped to identify potential voluntary movements which a patient could use to answer yes/no questions (e.g., sometimes these were only trace movements of the fingers or head/neck). Physiatrists assisted PT/OT in spasticity management using injections, intrathecal baclofen, or spasmolytic medications. Respiratory therapists collaborated with SLP to work toward decannulation. SLP collaborated with OT to work on oropharyngeal exercises and oral diet initiation. Neuropsychologists communicated with the entire team and families to collate observed evidence, assessed contingent motoric and affective behaviors, collaborated with PT/OT/SLP to incorporate salient behaviors into assessment paradigms and treatments, collaborated with physiatrists on the use of neurostimulants and psychoactive agents, and provided further feedback to the team to consolidate all information and promote rehabilitative efficacy. Once a patient was noted to have emerged, the next important focus was to establish a communication system, minimize pain/discomfort, and improve quality of life. There was ongoing daily communication with nursing/caregivers and weekly family meetings were convened for updates, education, counseling, and care planning. Specialists were consulted when needed, e.g., neurosurgery for hydrocephalus and ENT for difficulty in decannulation.

A patient's first admission to the DoC program was defined as Phase I rehabilitation admission. Subsequent planned admissions were defined as Phase II, and so on. Subsequent admissions to a general brain injury rehabilitation service may occur if the patient has emerged and their level of functioning makes this appropriate. Unplanned transfer/return for medical emergencies did not constitute a new phase of admission in the study.

Data retrieval and analysis

Basic demographic information, admission status, instances of acute unplanned transfer, and other functional information were obtained from electronic medical records (EMRs). The case mix index (CMI) is presented here as a reflection of overall medical complexity, although no designated diagnosis of DoC is involved in its calculation.

Acuity and chronicity were defined as suggested by the AAN/ACRM/NIDILRR DoC guidelines (15). "Acute stage" referred to cases <=28 days following a TBI or a non-TBI; "subacute stage" referred to cases 29–365 days following a TBI or 29–90 days following a non-TBI; and "chronic stage" referred to >365 days following a TBI or >90 days following a non-TBI. In subsequent analyses, all patients were categorized according to these three stages.

Measurable clinical outcomes included improvements in diagnostic category in terms of level of consciousness, Functional Independence Measure (FIM) scores, achievement of decannulation, and oral diet initiation. Level of consciousness was collected on admission and at final discharge (at the end of the last discharge if there were multiple phases of rehabilitation admission). The date the order was placed for decannulation (which was executed on the same day) was considered to represent

the timing of achievement of decannulation. The date the order was placed for a dysphagia diet was considered to represent the timing of achievement of oral diet initiation, even if a patient might still require modifications or supplementary tube feeding. The number of patients who advanced to a regular diet was also collected. The time taken to achieve these functional goals was obtained by calculating the differences between the exact dates. FIM scores were obtained by the end of Phase I inpatient DoC rehabilitation. Measurable FIM indicated that a patient scored above 1 on any one of the items. FIM subtotal was the sum of scores on self-care, transfer, locomotion, communication, and social cognition (no sphincter control data was available), with a lowest possible score of 12 and a highest possible score of 84. The self-care domain contained five items (eating, grooming, bathing, upper body dressing, and lower body dressing), with a lowest possible score of 5 and a highest possible score of 35. The bed/chair transfer domain consisted of one item with a lowest possible score of 1 and a highest possible score of 7. The locomotion domain consisted of one item measuring walking or mobility using a wheelchair, whichever was ranked higher, with a lowest possible score of 1 and a highest possible score of 7. The communication domain contained two items (compression and expression) with a lowest possible score of 2 and a highest possible score of 14. Finally, the social cognition domain contained three items (social interaction, problem-solving, and memory) with a lowest possible score of 3 and a highest possible score of 21. The percentages of patients who required moderate assistance or less (scores $\geq$ 3) in bed-to-chair transfer, communication, and self-care are presented as meaningful outcomes, indicative of a meaningful reduction in care burden.

Data were analyzed in Microsoft 365 Excel and SPSS 20.0. Numerical variables are presented in the form mean±SD. In cases where the data did not follow a normal distribution, the median and interquartile are provided. Categorical variables are presented as numbers or percentages. Only data for patients admitted in the acute and subacute stages were included in the correlation analysis, as the recovery trajectory varied widely in the chronic stage. The correlations between time since injury on admission and time to achieve certain functional outcomes since admission were examined using Spearman's rank correlation. Statistical significance was set at $p < 0.05$.

Results

The demographics and status of the patients admitted at the acute, subacute, and chronic stages are presented in Table 1. The average age at the time of injury was ∼35 years; this was similar in all three groups. Patients were predominantly male. More patients with TBI (60–70%) were admitted in the acute and subacute stages, while more patients with non-TBI (67%) were admitted in the chronic stage. The program accepted patients from diverse ethnic groups. The proportion of MCS was higher than the proportion of VS in the acute and subacute stages, and lower in the chronic stage, based on CRS-R on admission. CMI was on average ∼2.4, which is significantly higher than average CMI in the institution's general brain injury services (1.7–1.8) and the national score (1.3–1.4) in 2014–2018 (Supplementary Figure 1) (20). Most patients (91%) received 1–2 phases of inpatient rehabilitation. Specifically, most patients received 2–3 months' Phase I specialized DoC inpatient rehabilitation (on average 86.4 ± 69.1 days) and a total of 3–4 months' inpatient rehabilitation (on average 105.8 ± 86.2 days) when subsequent admissions were included. Those admitted in the acute stage had the shortest average length of stay for Phase I and for total inpatient rehabilitation. Acute unplanned transfer for emergencies occurred in 30–50% of the patients, with the highest incidence and acuity rates found in patients admitted in the subacute stage.

Functional recovery rates of patients with DoC admitted at different stages post-injury

Functional recovery rates of patients with DoC admitted at different stages post-injury are presented in Figure 1 and Table 2. Almost all patients admitted at the acute stage achieved eMCS, as did over half of patients admitted at the subacute stage. Most patients exhibited measurable improvement on FIM items by the time of discharge from Phase I inpatient rehabilitation. Additionally, 18% of patients admitted at the chronic stage achieved emergence, and two-thirds of this group exhibited measurable improvement on FIM items. Among patients who achieved emergence, by the end of Phase I inpatient rehabilitation, ∼60% of patients admitted at the acute stage and 20% of patients admitted at the subacute stage required moderate assistance or less in bed-to-chair transfer, communication, eating, grooming, and upper body dressing. Patients admitted at the chronic stage were very motorically impaired; however, 50% of this group were able to comprehend with moderate assistance or less.

Almost all patients admitted at the acute stage were decannulated. This was achieved on average 1.5 months after admission and ∼2 months after the initial injury. Approximately 67% of patients admitted at the subacute stage were decannulated. This was achieved on average 2 months after admission and ∼4 months after the initial injury. Finally, ∼17% of patients admitted at the chronic stage achieved decannulation, while an additional 14% had the potential to be decannulated (when including those undergoing capping trials and tolerating a speaking valve by the time of discharge). This was achieved on average 3.5 months after admission and nearly 1.4 years after the initial injury. There were wide variations among individual cases in the time needed to achieve decannulation. A weak positive correlation was found between days since injury on admission and days to achieve decannulation after admission ($r_s = 0.308$, $p = 0.009$).

Approximately 70% of patients admitted at the acute stage achieved initiation of an oral diet. This was achieved on average 1 month after admission and ∼2 months after the initial injury. Nearly two-thirds of this group achieved a regular diet by the time of final discharge. Approximately 23% of patients admitted

TABLE 1 Demographics and status of all patients admitted at the acute, subacute, and chronic stages.

	Full cohort ($N = 137$)	Acute ($N = 20$)	Subacute ($N = 84$)	Chronic ($N = 33$)*
Age at the time of injury (years)	35.8 ± 15.0	35.8 ± 18.0	35.7 ± 14.4	36.3 ± 15.3
Gender [male (%); female (%)]	103 (75.2%); 34 (24.8%)	17 (85.0%); 3 (15.0%)	60 (71.4%); 24 (28.6%)	26 (78.8%); 7 (21.2%)
Etiology [TBI (%); non-TBI (%)]	81 (59.1%); 56 (40.9%)	12 (60.0%); 8 (40.0%)	58 (69.0%); 26 (31.0%)	11 (33.3%); 22 (66.7%)
Ethnicity (*N*, %)				
White/Caucasian	74 (54.0%)	9 (45.0%)	45 (53.6%)	20 (60.6%)
Hispanic	24 (17.5%)	7 (35.0%)	15 (17.9%)	2 (6.1%)
African-American	22 (16.1%)	3 (15.0%)	14 (16.7%)	5 (15.1%)
Middle Eastern	10 (7.3%)	0	4 (4.8%)	6 (18.2%)
Asian	4 (2.9%)	1 (5.0%)	3 (3.6%)	0
Pacific Islander	2 (1.5%)	0	2 (2.4%)	0
Mixed	1 (0.7%)	0	1 (1.2%)	0
Days since injury on admission	241.4 ± 538.0	19.4 ± 5.9	78.9 ± 65.2	789.5 ± 899.7 Median: 428 (IQR: 211, 1036)
Diagnosis on admission [MCS (%); UWS/VS(%)]	74 (54.0%); 63 (46.0%)	14 (70.0%); 6 (30.0%)	46 (54.8%); 38 (45.2%)	14 (42.4%); 19 (57.6%)
Case Mix Index (CMI)	2.4 ± 0.3 Min 1.6 Max 3.1	2.5 ± 0.3 Min 1.6 Max 3.1	2.4 ± 0.3 Min 1.8 Max 3.1	2.3 ± 0.3 Min 1.7 Max 2.8
Admission phases (*N*)				
Phase I	92	14	52	26
Phase II	32	5	22	5
Phase III	8	0	7	1
Phase IV	3	1	1	1
Phase V	1	0	1	0
Phase VI	1	0	1	0
Total inpatient rehab. days	105.8 ± 86.2	75.8 ± 35.3	117.3 ± 87.9	94.6 ± 99.0 Median: 67 (IQR: 38, 112)
Phase I inpatient days	86.4 ± 69.1	65.3 ± 29.6	91.7 ± 64.6	85.8 ± 92.8 Median 58 (IQR 33, 92)
Acute unplanned transfer (N, %)	57 (41.6%)	7 (35.0%)	38 (45.2%)	12 (36.4%)
Among unplanned transfers, required ICU level of care (N, %)	25 (18.2%)	1 (14.3%)	19 (50.0%)	5 (41.7%)

*Including 20 patients who were admitted 1 year after their initial brain injuries.

at the subacute stage achieved initiation of an oral diet. This was achieved on average 3 months after admission and ~5 months after the initial injury. Nearly half of this group achieved a regular diet by the time of final discharge. Only two patients (6%) who were admitted at the chronic stage achieved initiation of an oral diet; they did so over 2 months and 8 months after admission, which was nearly 1.3 years after their initial brain injuries. A strong positive correlation was found between days since injury on admission and days to achieve initiation of an oral diet after admission ($r_s = 0.606$, $p < 0.001$).

Functional achievements of patients with DoC related to TBI and non-TBI

Changes in the level of consciousness following specialized acute inpatient rehabilitation among patients with different etiologies and admitted at different stages post-injury are presented in Figure 2. As mentioned earlier, among all etiology groups, almost all patients admitted at the acute stage underwent emergence. The emergence rate decreased significantly with increasing chronicity among all etiology groups. For TBI, the rate decreased from 83.3%

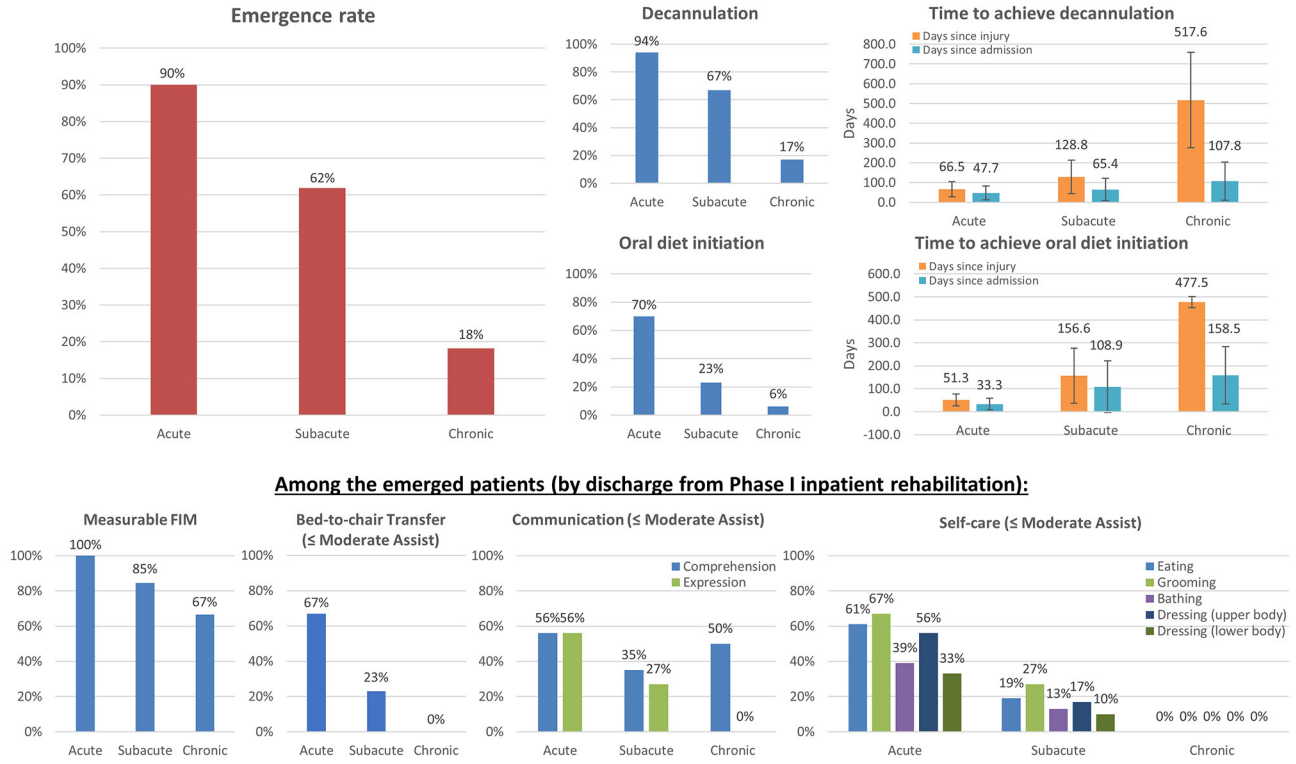

FIGURE 1
Functional recovery among patients with DoC admitted at different stages post-injury. The total numbers of patients included at the acute, subacute, and chronic stages were 20, 84, and 33, respectively. The left upper panel shows the overall emergence rates (N=18, 52, and 6, respectively). The four right upper panels show the overall decannulation and oral diet initiation rates and corresponding time to those achievements after injury and after admission. The four bottom panels show the percentages of patients undergoing meaningful improvements in transfer, communication, and self-care among emerged patients, requiring only moderate assistance or less (by the end of Phase I inpatient rehabilitation). The results demonstrate that specialized intensive inpatient rehabilitation is crucial for functional recovery from DoC with measurable and meaningful gains.

(10/12) among those admitted at the acute stage to 69.0% (40/58) among those admitted at the subacute stage, and to 27.3% (3/11) among those admitted at the chronic stage. For hypoxic brain injury (also referred to as anoxic brain injury, ABI), the rate decreased from 100.0% (6/6) among those admitted at the acute stage to 45.5% (10/22) among those admitted at the subacute stage, and to 10.5% (2/19) among those admitted at the chronic stage. For stroke, the rate decreased from 100.0% (2/2) among those admitted at the acute stage to 50.0% (2/4) among those admitted at the subacute stage, and to 33.3% (1/3) among those admitted at the chronic stage. Another significant proportion of patients admitted at the chronic stage improved from UWS/VS to MCS, especially in the ABI group.

Comparisons of decannulation rates and time to achieve decannulation among patients with different etiologies and admitted at different stages post-injury are presented in Figure 3. Among all etiology groups, almost all patients admitted at the acute stage achieved decannulation. Decannulation rates decreased significantly with increasing chronicity among all etiology groups. For TBI, the rate decreased from 90.0% (9/10) among those admitted at the acute stage to 78.3% (36/46) among those admitted at the subacute stage, and to 11.1% (1/9) among those admitted at the chronic stage. For ABI, the rate decreased from 100.0% (5/5) among those admitted at the acute stage to 45.5% (10/22) among those admitted at the subacute stage, and to 23.5% (4/17) among those admitted at the chronic stage. For stroke, the rate decreased from 100.0% (1/1) among those admitted at the acute stage to 50.0% (2/4) among those admitted at the subacute stage, and to zero (0/3) among those admitted at the chronic stage. The time to achieve decannulation was similar for TBI and ABI patients who were admitted at the acute stage, on average ∼1.5 months after admission and 2 months after injury. The same pattern was found among patients admitted at the subacute stage when comparing only TBI and ABI patients with the same post-injury period of 29–90 days: the achievement was made on average ∼1.5–2 months after admission and 3 months after injury. Only one TBI patient and two ABI patients admitted at the chronic stage achieved decannulation, at significantly different periods since admission but at a similar amount of time (approximately 1.4 years) post-injury.

Comparisons of oral diet initiation and the time to achieve oral diet initiation among patients with different etiologies and admitted at different stages post-injury are presented in Figure 4. Most of the TBI patients and half of the ABI patients admitted at the acute stage achieved initiation of an oral diet. The oral diet initiation rate decreased significantly with increasing chronicity among all etiology groups. For TBI, the rate decreased from 75.0% (9/12) among those admitted at the acute stage to 22.4% (13/58) among those admitted at the subacute stage, and to 9.1% (1/11) among

TABLE 2 Functional recovery among patients with DoC admitted at different stages post-injury.

	Acute ($N = 20$)	Subacute ($N = 84$)	Chronic ($N = 33$)
Emergence rate	**90.0% (18/20 [a])**	**61.9% (52/84)**	**18.2% (6/33)**
Among emerged patients (by the time of discharge from			
Phase I inpatient rehabilitation):			
Measurable FIM*	100.0% (18/18)	84.6% (44/52)	66.7% (4/6)
FIM (subtotal)	33.2 ± 15.2	20.8 ± 11.1	14.7 ± 2.7
FIM (bed/chair transfer)	3.1 ± 1.8	1.7 ± 1.2	1.0 ± 0.0
FIM (locomotion)	3.1 ± 2.1	1.8 ± 1.5	1.0 ± 0.0
FIM (communication)	6.1 ± 3.4	4.7 ± 2.4	3.7 ± 1.5
FIM (social cognition)	7.5 ± 4.1	4.9 ± 2.6	4.0 ± 1.3
FIM (self-care)	13.5 ± 7.2	7.9 ± 5.3	5.0 ± 2.0
Required moderate assistance or less (FIM score ≥ 3) by the end of			
Phase I inpatient rehabilitation):			
Bed-to-chair transfer	66.7% (12/18)	23.1% (12/52)	0% (0/6)
Locomotion**	55.6% (10/18)	17.3% (9/52)	0% (0/6)
Comprehension	55.6% (10/18)	34.6% (18/52)	50% (3/6)
Expression	55.6% (10/18)	26.9% (14/52)	0% (0/6)
Eating	61.1% (11/18)	19.2% (10/52)	0% (0/6)
Grooming	66.7% (12/18)	26.9% (14/52)	0% (0/6)
Bathing	38.9% (7/18)	13.5% (7/52)	0% (0/6)
Dressing (upper body)	55.6% (10/18)	17.3% (9/52)	0% (0/6)
Dressing (lower body)	33.3% (6/18)	9.6% (5/52)	0% (0/6)
Decannulation rate	**94.1% (15/16 [b])**	**66.7% (48/72 [c])**	**17.2% (5/29 [d])**
Potential rate***	100% (16/16)	73.6% (53/72)	31.0% (9/29)
Days since injury (min, max)	66.5 ± 38.5 (30, 179)	128.8 ± 85.0 (39, 515)	517.6 ± 241.5 (199, 871)
Days since admission (min, max)	47.7 ± 35.3 (17, 153)	65.4 ± 57.0 (3, 314)	107.8 ± 96.1 (30, 267)
Oral diet initiation rate	**70.0% (14/20)**	**22.6% (19/84)**	**6.1% (2/33)**
Achieved adult regular diet	45.0% (9/20)	9.5% (8/84)	3.0% (1/33)
Achieved dysphagia diet	25.0% (5/20)	13.1% (11/84)	3.0% (1/33)
Days since injury (min, max)	51.3 ± 25.6 (29, 124)	156.6 ± 120.4 (43, 549)	460.0 and 495.0
Days since admission (min, max)	33.3 ± 24.9 (11, 107)	108.9 ± 112.4 (5, 487)	247.0 and 70.0

[a]One of the non-emerged patients emerged after discharge per note, which brings the rate up to 95.0%. [b]Three patients were extubated before admission; one patient was not intubated. [c]Twelve patients were extubated before admission. [d]Four patients were extubated before admission. *Measurable FIM indicates that a patient scored above 1 on any one of the FIM items. FIM subtotal score range: 12–84; self-care score range: 5–35; bed/chair transfer score range: 1–7; locomotion score range: 1–7; communication score range: 2–14; social cognition score range: 3–21. **Walking or at wheelchair level, whichever scores better. ***Including those undergoing capping trials and tolerating a speaking valve by the time of discharge. The bold values were intended to show/distinguish the hierarchy.

those admitted at the chronic stage. For ABI, the rate decreased from 50.0% (3/6) among those admitted at the acute stage to 18.2% (4/22) among those admitted at the subacute stage, and to 5.3% (1/19) among those admitted at the chronic stage. For stroke, the rate decreased from 100.0% (2/2) among those admitted at the acute stage to 50.0% (2/4) among those admitted at the subacute stage, and to zero (0/3) among those admitted at the chronic stage.

Interestingly, the time to achieve oral diet initiation appeared to be shorter in ABI than in TBI patients among those admitted at the acute and subacute stages. Only one TBI patient and one ABI patient admitted at the chronic stage achieved an oral diet; these patients did so after significantly different periods following admission but after a similar amount of time (approximately 1.3 years) post-injury.

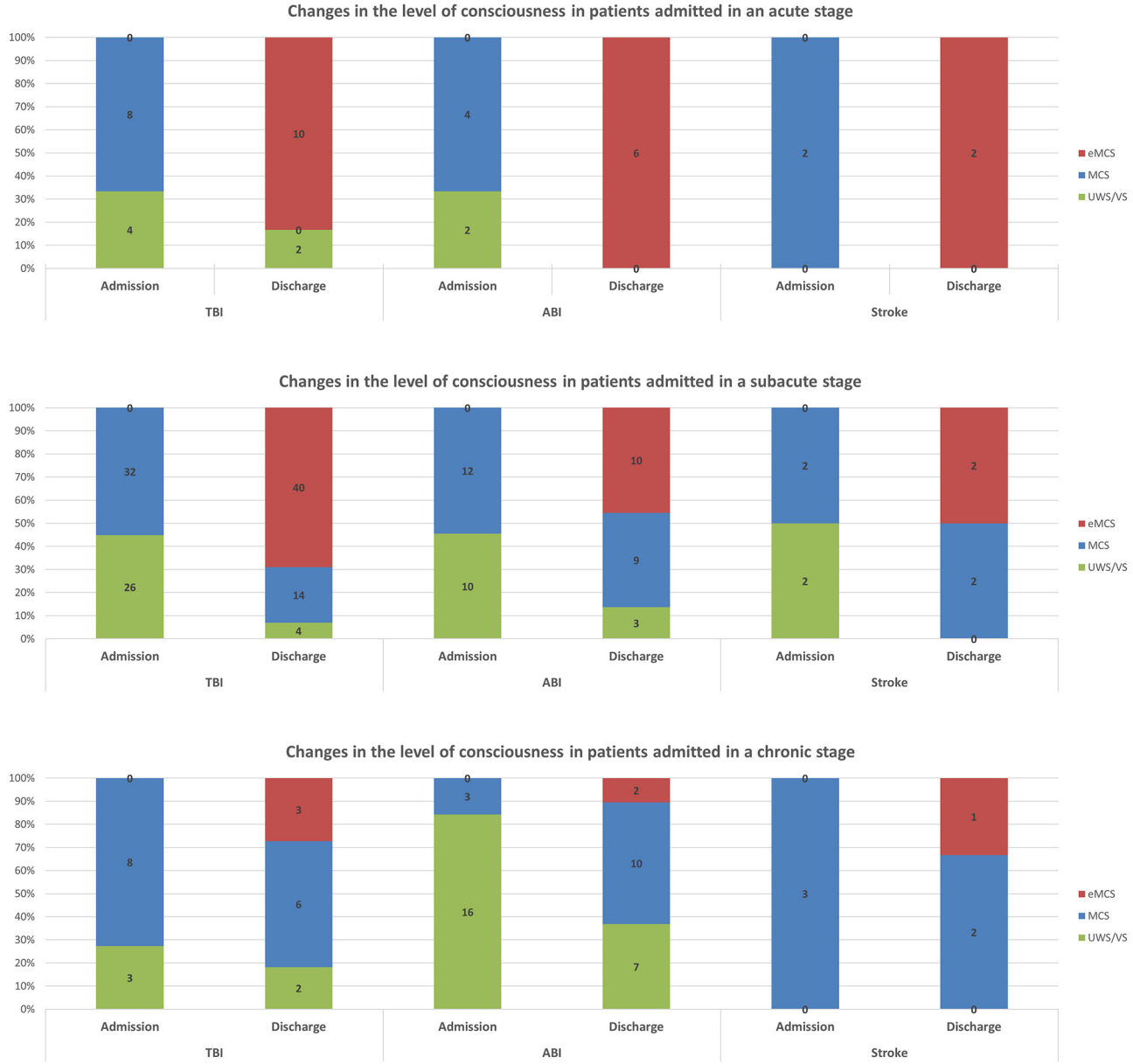

FIGURE 2
Changes in level of consciousness following specialized acute inpatient rehabilitation among patients with different etiologies and admitted at different stages post-injury.

Discussion

The results objectively demonstrate functional recovery among persons with DoC following active management and intensive therapies in an acute inpatient rehabilitation program. Almost all patients admitted at the acute stage achieved eMCS (90%) and decannulation (94%); 70% achieved an oral diet; and, ∼60% only required moderate assistance or less in bed-to-chair transfer, communication, and self-care using the upper limbs by the end of Phase I inpatient rehabilitation. Rates of functional achievement decreased, and more time was required for these achievements, with increasing chronicity. This was observed in all functional domains and in each etiology group. In this program, patients with TBI and ABI had comparable recovery rates when admitted at the acute or subacute stage. It is also worth noting that a small proportion of persons with chronic DoC made a meaningful functional recovery. The results demonstrate the effectiveness and efficiency of a specialized inpatient DoC rehabilitation program. In concert with the 2018 AAN/ACRM/NIDILRR practice guidelines for DoC, the results support the utility of inpatient rehabilitation for persons with DoC, as evidenced by their functional improvements measured by and beyond the FIM. The results justify the claim that persons with DoC meet the medical necessity requirements for inpatient rehabilitation services regulated by the Centers for Medicare and Medicaid Services (12), specifically regarding "*active*" participation in a sufficient amount of therapy and undergoing

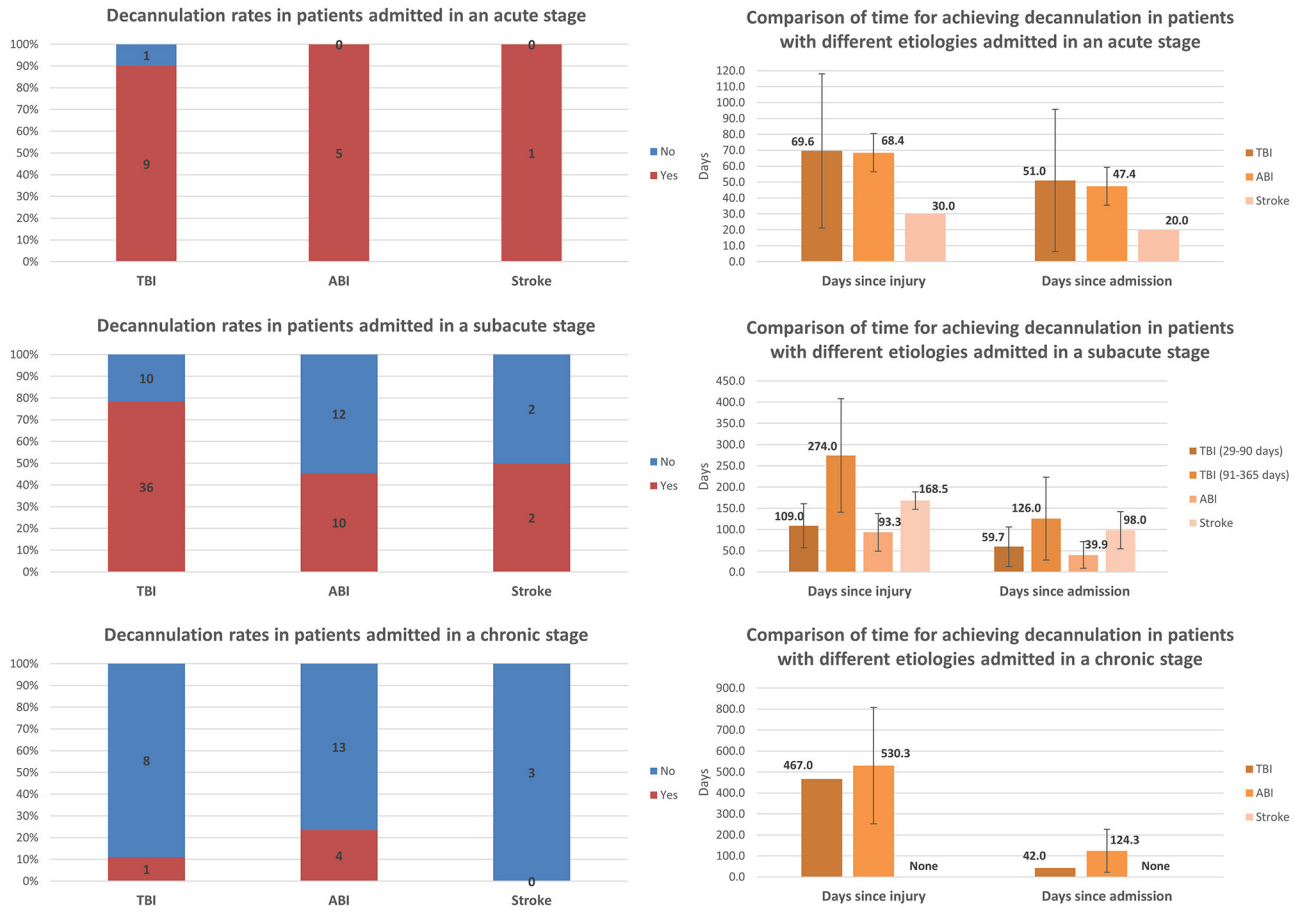

FIGURE 3
Comparison of decannulation rates and time to achieve decannulation among patients with different etiologies and admitted at different stages post-injury (error bars represent standard deviations).

significant "*measurable improvements*" as a result of the intensive rehabilitation program.

Furthermore, initiation of oral diet and/or decannulation is indicative not only of improved swallowing and respiratory status, but also of improved voluntary secretion management, airway protection, and reduced risk of aspiration and subsequent pulmonary complications; these improvements carry implications for prognosis as well as healthcare costs. Requiring moderate assistance or less in functional tasks is significantly meaningful to caregivers and could be viewed as a meaningful reduction in care burden. The functional items on which data were collected in the study represent different goals and outcome measures that need to be developed to appraise the rehabilitative benefits of this type of program for patients with DoC. The corresponding clinical results could be used as benchmarks for updated appraisal mechanisms. The study adds practical value and actionable suggestions to the proposed minimum competency recommendations for DoC rehabilitation programs (16).

For recovery, time is a critical factor. Patients admitted at the acute stage had a higher likelihood of achieving emergence, decannulation, and oral diet initiation than those admitted at the subacute and chronic stages. This was the case among patients with DoC related to TBI, ABI, and stroke. Our results showed that it took longer to achieve decannulation and initiation of an oral diet as chronicity increased. The durations of Phase I inpatient rehabilitation stay and total inpatient rehabilitation stay were also noted to be significantly shorter in patients admitted at the acute stage. Therefore, as suggested earlier (11, 15), specialized intensive inpatient rehabilitation is as crucial and time-sensitive for functional recovery in these cases as it has been indicated to be in cases of other types of less severe brain injuries. It is important to emphasize that persons with chronic DoC should not be overlooked under the current healthcare system, as some may be misdiagnosed or suboptimally treated in the acute or subacute stages (21). They may possess the potential to make meaningful improvements under appropriate care (22, 23). Our results revealed a small subset of patients who were found to be fully conscious and made significant functional gains beyond the standard measures used for regulation. In addition, our results present a possible clinical scenario of disproportionate recovery between the mind and the body in the chronic stage, raising concerns about negligence in clinical care and covert suffering.

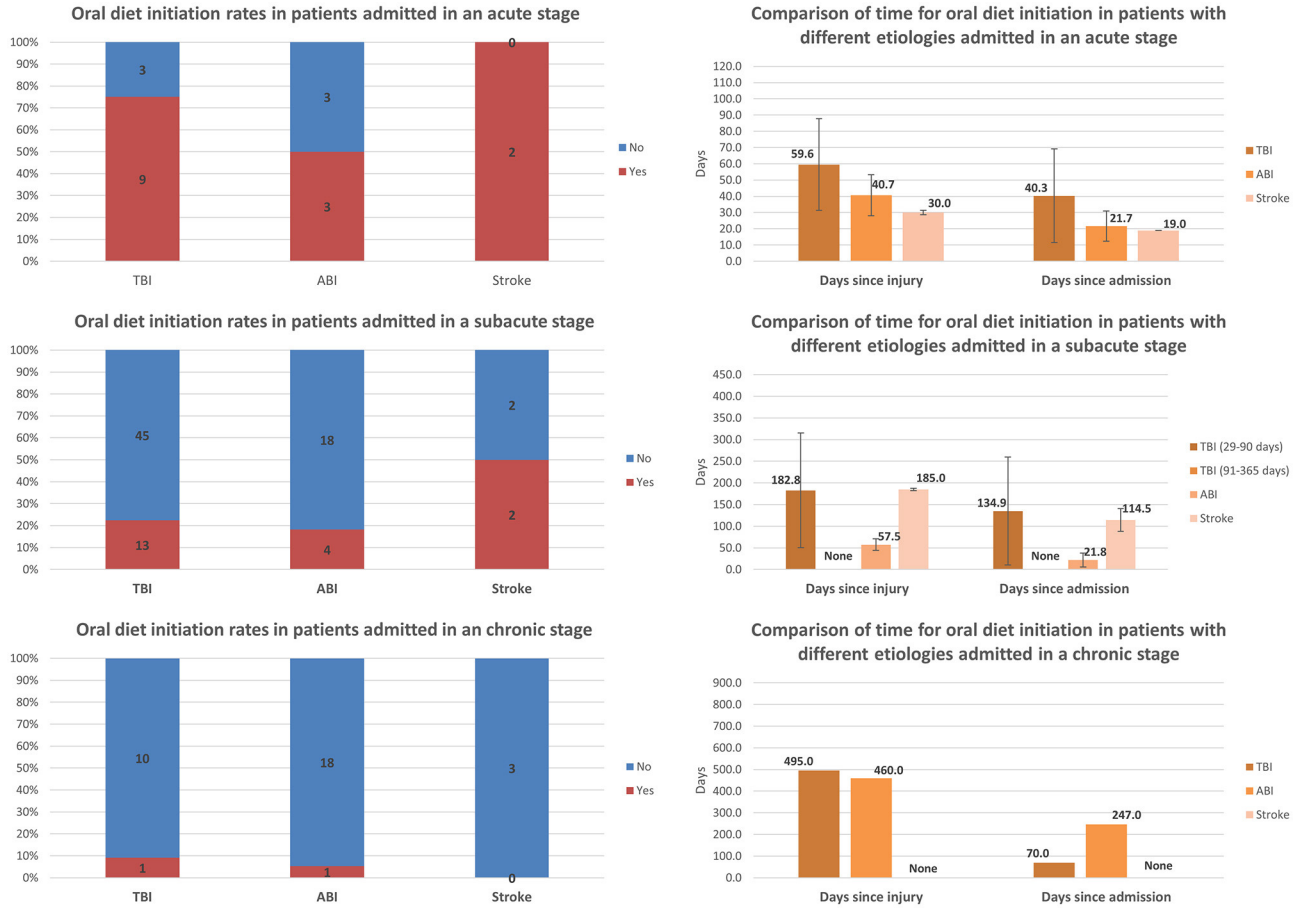

FIGURE 4
Comparison of rates of oral diet initiation and the time to achieve oral diet initiation among patients with different etiologies and admitted at different stages post-injury (error bars represent standard deviations).

Providing intensive rehabilitation services is equally important for DoC caused by any etiology. In this study, the time to achieve decannulation was similar in cases of TBI and ABI for patients admitted at both the acute and the subacute stages (in the latter case, when pairing on number of days post-injury). Interestingly, the time to achieve oral diet initiation was shorter for ABI patients than for TBI patients at both the acute and the subacute stages (again, in the latter case, when pairing on number of days post-injury). This finding is distinct from the existing impression of the prognosis of ABI-related DoC.

Our results also support the view that the outcomes of persons with a DoC are not universally poor, and prognostic information should be given cautiously within the first 28 days post-injury (15). Acute inpatient rehabilitation should be provided to patients who still have a DoC following acute care but have achieved medical stability. A delay in providing, or the absence of, this type of care is likely to reduce the chance of functional recovery or prolong the recovery process. It is unclear whether it is the initial severity of the brain injury itself or the delay in rehabilitative interventions that leads to an arrest in recovery in the chronic stage. Delay in care will also increase the risk of medical and musculoskeletal complications, increase the financial burden, and potentially bring with it other ethical and legal challenges. In our previous preliminary study, financial barriers (including insurance denial, a lack of covered benefits, and out-of-network care) accounted for over 40% of denials of referral to an acute inpatient DoC rehabilitation program (13). There is an urgent need to update acute inpatient rehabilitation admission criteria and outcome measures to provide appropriate rehabilitative care to these patients and to avoid undue complications resulting from misdiagnosis and negligence of care. More studies from a clinical rehabilitation perspective are needed.

Limitations

Even though the data adopted in the study were objective in nature, several limitations must be mentioned. First, without a control group, spontaneous recovery could be a confounding factor, especially in the acute and subacute stages. However, improvements observed in the chronic stage supported the effectiveness of inpatient rehabilitation management. Second, it is possible that the patients were unable to be admitted earlier due to the severity and acuity of their medical conditions. In our preliminary study, nearly 25% of referrals were deferred due to medical instability (for example, a patient was medically stable when the initial referral was placed, but their condition subsequently changed

within days while the referral was being processed) (13). Therefore, patients who were admitted at the acute stage may have less severe medical conditions compared to those admitted in a subacute stage, thus resulting in better functional outcomes. This may be indirectly reflected in the acute unplanned transfer data in Table 1. Third, as this study was limited to the information obtained *via* chart review, it is unclear whether patients, especially those admitted at the chronic stage, received rehabilitation services at other facilities. The quality and quantity of rehabilitation services accessed at other facilities were also unmeasurable. This may affect the validity of the conclusions drawn in the study. Fourth, the scope of our study may be skewed by the fact that only a very small percentage of patients with DoC are referred and accepted to receive acute inpatient rehabilitation services—the "tip of the iceberg"—as the majority of these patients are more likely to be discharged to long-term care facilities under "custodial care," without any rehabilitative interventions. Therefore, our scope may be subject to survivorship bias. Beyond these issues, the sample size became smaller after stratification, which means that the findings warrant further investigation with a larger sample size or a systemic national registry.

Conclusion

Specialized intensive inpatient rehabilitation is crucial and time-sensitive for functional recovery from DoC. Providing such a level of rehabilitative care is equally important for DoC caused by TBI and by hypoxic–ischemic brain injury. Specific goals and different outcome measures (e.g., consciousness level, decannulation, and oral diet initiation) need to be developed to appraise the benefits of acute inpatient rehabilitation for DoC.

Author's note

The results of this study were partially submitted as an abstract to AAP 2023 and IBIA 2023.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the University of Texas Health Science Center at Houston Committee for the Protection of Human Subjects (HSC-MS-18-0198). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

Conceptualization, project administration, and methodology: BZ, KO'B, and SL. Data acquisition: BZ, BC, and CR. Formal analysis: BZ and BC. Writing–original draft preparation: BZ, KO'B, and JW. Writing–review and editing: BZ, KO'B, JW, BC, CR, SL, and SK. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1126532/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Case Mix Index for the institution's general brain injury services (blue lines; average = 1.7–1.8) and national brain injury services (green lines; average = 1.3–1.4) in 2014–2018.

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Self-processing in coma, unresponsive wakefulness syndrome and minimally conscious state

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Introduction: Behavioral and cerebral dissociation has been now clearly established in some patients with acquired disorders of consciousness (DoC). Altogether, these studies mainly focused on the preservation of high-level cognitive markers in prolonged DoC, but did not specifically investigate lower but key-cognitive functions to consciousness emergence, such as the ability to take a first-person perspective, notably at the acute stage of coma. We made the hypothesis that the preservation of self-recognition (i) is independent of the behavioral impairment of consciousness, and (ii) can reflect the ability to recover consciousness.

Methods: Hence, using bedside Electroencephalography (EEG) recordings, we acquired, in a large cohort of 129 severely brain damaged patients, the brain response to the passive listening of the subject's own name (SON) and unfamiliar other first names (OFN). One hundred and twelve of them (mean age±SD=46±18.3years, sex ratio M/F: 71/41) could be analyzed for the detection of an individual and significant discriminative P3 event-related brain response to the SON as compared to OFN ('SON effect', primary endpoint assessed by temporal clustering permutation tests).

Results: Patients were either coma (n=38), unresponsive wakefulness syndrome (UWS, n=30) or minimally conscious state (MCS, n=44), according to the revised version of the Coma Recovery Scale (CRS-R). Overall, 33 DoC patients (29%) evoked a 'SON effect'. This electrophysiological index was similar between coma (29%), MCS (23%) and UWS (34%) patients (p=0.61). MCS patients at the time of enrolment were more likely to emerged from MCS (EMCS) at 6months than coma and UWS patients (p=0.013 for comparison between groups). Among the 72 survivors' patients with event-related responses recorded within 3months after brain injury, 75% of the 16 patients with a SON effect were EMCS at 6months, while 59% of the 56 patients without a SON effect evolved to this favorable behavioral outcome.

Discussion: About 30% of severely brain-damaged patients suffering from DoC are capable to process salient self-referential auditory stimuli, even in case of absence of behavioral detection of self-conscious processing. We suggest that self-recognition covert brain ability could be an index of consciousness recovery, and thus could help to predict good outcome.

KEYWORDS
disorders of consciousness, coma, self-processing, event-related potentials, P300

Introduction

The assessment of coma and other disorders of consciousness (DoC), following severe brain injury, is extremely challenging. The central issue is both the evaluation of sensory-motor and cognitive functions but also awareness of self and the environment. The latter are currently inferred on the basis of the patient's behavioral reactivity and is the backbone of the diagnostic classification (Giacino et al., 2004). Coma is a state of profound unawareness from which the patient cannot be aroused and is defined by an absence of eye opening and adapted motor response even after nociceptive stimuli (Plum and Posner, 1983). Following a coma, a patient regaining an eye-opening/closing cycle and reflexive motor activity, devoid of any voluntary interaction with the environment, is diagnosed in a unresponsive wakefulness syndrome (UWS, formerly known as vegetative state; Laureys et al., 2010). The diagnosis of minimally conscious state (MCS) is proposed for patients who are able to produce reproducible but inconsistent non-reflexive behaviors (e.g., visual pursuit, reproducible movement to command; Giacino et al., 2004; Giacino, 2005; Laureys et al., 2009; Rohaut et al., 2013, 2019). The emergence from MCS (EMCS) is established if the patient is capable of accurate communication or functional use of objects (Giacino et al., 2002).

The diagnosis of UWS, MCS and EMCS requires the practical use of the revised version of the Coma Recovery Scale (CRS-R), which is now considered as the gold standard (Giacino et al., 2004, 2018; Schnakers et al., 2008a; Kondziella et al., 2020). However, it is now well known that the behavioral description of these patients does not systematically reflect their residual brain or cognitive functions (Fernandez-Espejo and Owen, 2013; Schnakers et al., 2022). Dissociations between behavior and brain activity have been observed repeatedly, both with fMRI and Electroencephalography (EEG) methodologies, in various very simple or complex protocols. The most popular study is undoubtedly that of Owen and colleagues in which they showed that a UWS patient showed brain activity comparable to that of control subjects during mental imagery and command-following tasks (Owen et al., 2006). This observation is exceptional probably because the cognitive functions of interest are complex (Monti et al., 2010). Nevertheless, by measuring lower-level cognitive processes, it has been also shown that a larger number of DoC patients, probably around 15% of them (Kondziella et al., 2016; Schnakers et al., 2020), may exhibit such dissociations. For example, studies using passive language and/or music stimuli have shown that some patients with DoC demonstrate association cortex responses despite absent behavioral evidence of language comprehension [Coleman et al., 2009; Okumura et al., 2014; Edlow et al., 2017; for a systematic review of residual implicit language abilities during passive language listening tasks in patients with DoC, see Aubinet et al. (2022)]. Taken together, these studies are extremely important since they suggest that brain activities associated with cognitive functions, and sometimes probably with consciousness, can be observed in patients for whom the behavior rather suggests its failure.

In the context of non-communicative patients, it is useful to know whether they respond (cerebrally and/or behaviorally) to their own name. Indeed, the presence of such a response means that he/she can detect or discriminate a self-referential stimulus, i.e., an item of the environment that refers to her/him (Fingelkurts and Fingelkurts, 2023). Its presence suggests not only the preservation of one aspect of the self but also a possible perspective taking, i.e., meta-representations of mental and bodily states as one's own mental and bodily states (Vogeley and Fink, 2003). Dissociations between brain and behavior responses to the own name have been reported in patients with DoC. Note that these observations are possible because the EEG cerebral response to one's own name is strong enough to be studied at the individual level. For example, Perrin et al. (2006) had shown that the cerebral response to one's own name (versus unfamiliar other first names) was observed in 3/5 of UWS patients (and 6/6 MCS) while they had no behavioral response to this stimulation (Perrin et al., 2006). Its presence in UWS and MCS patients has been confirmed in other studies, but always in small cohorts of patients (Perrin et al., 2006; Castro et al., 2015; Heine et al., 2021). Thus, no cohort study has investigated the percentage of UWS or MCS patients who show this response and whether it is also observable in comatose patients.

The electrophysiological response to one's own first name is observed in different states of unconsciousness, in sleep (Perrin et al., 1999) and using subliminal presentation (Doradzinska et al., 2020). Thus, it may not reflect self-awareness but rather a self-processing, i.e., the ability to probe an autobiographical memory. If it is true, this response should be observable in DoC, including coma, i.e., regardless of the patient's behavioral ability and with a similar probability of occurrence regardless of diagnosis (coma, UWS and MCS).

If the brain response to the subject's own name is not a sign of awareness, it could rather reflect the persistence of a mechanism that is essential for the recovery of consciousness. Indeed, it is often admitted empirically that self-processing would be a prerequisite for consciousness: "Experience is impossible without an experiencer" (Damasio, 2003; Lane, 2020). Interestingly, Damasio investigated minimal forms of self that he coined 'mental or core self' stipulating that they are required in the making of consciousness (Damasio, 1999). If self is necessary for consciousness, then the presence of a cerebral response to the patient's own name should be associated with a very high rate of favorable evolution (whereas its absence could indicate nothing since the response could reappear later). In line with this hypothesis, Castro et al. (2015) observed a link between patients with a brain response to their own name and a favorable patient outcome, but the authors could not conclude because of the small cohort of patients (Castro et al., 2015).

Through the study of electrophysiological marker of auditory discrimination of the subject's own name in a large cohort of coma, MCS and UWS patients with a documented outcome, we made the

assumption that a P3 (aka P300) response could be identified independently of their behavioral status, and that its presence would be associated with a favorable outcome.

Materials and methods

Population

Electrophysiological data (i.e., ERPs induced by the subject's own name (SON) auditory task) from 22 healthy subjects (mean age 34.5 years (± 14.7), sex ratio (M/F): 14/8, right-handed, postgraduate) were recorded from February 2017 to June 2018. Coma, MCS and UWS patients hospitalized in the Critical Care Unit of the University Hospital of Purpan (Toulouse, France) between December 2017 and October 2019 or hospitalized in the Critical Care Unit or in the Post-Critical Care Neurological Rehabilitation Unit of the Pierre Wertheimer Hospital (Hospices Civils de Lyon, Bron, France) during the 2011–2022 period were included in the present study. During their stay, several evaluations and exams were performed when indicated including neurological clinical assessment, brain CT scan and structural brain MRI, clinical EEG, and ERPs induced by the subject's own name (SON) auditory task. The study was approved by the ethics committees "CPP Sud-Est II (2012–036-2)" and "CPP Nord-Ouest II (69LHCL19_0672)." Written consent was obtained from healthy participants and all patients' close relatives. All experiments were conducted in accordance with the guidelines of the Declaration of Helsinki.

Clinical assessment of behavioural diagnosis and outcome

Diagnosis

The state of coma of acute severely brain-damaged patients was determined using both of the following criteria: GCS ≤ 8 and absence of eye opening and adapted motor response even after nociceptive stimuli at the time of enrolment (Rohaut et al., 2019). The UWS or MCS behavioral states of consciousness were determined by neurologists or intensivists (FF, EN, FG, FD, WB, BS, BR, JL, and SS) who were trained users of the French version of the CRS-R (Giacino et al., 2004; Schnakers et al., 2008a). We used the CRS-R score measured immediately before the SON task ERP recording. In case of discrepancy with previous CRS-R scores, a consensus-based diagnosis was applied. Interruption of any sedative agent for at least 48 h (for propofol, ketamine, clonidine, morphine, dexmedetomidine) or 72 h (for benzodiazepines) was a prerequisite for the ERPs recording.

Outcome

The primary outcome was patient status assessed 6 months after the brain injury and was collected by trained users of the CRS-R during an in-person neurological clinical assessment realized by neurologists or specialists of neurorehabilitation (for patients still in rehabilitation centers), or by one of the study investigators through a dedicated in-person visit (when appropriate) or, alternatively, through a structured phone interview with patient's relatives who were questioned about items derived from the CRS-R (motor, visual, auditory, oromotor and communication functions scale) and items of the daily life. An item was considered as present only when the corresponding behavior was univocal. Two measures of recovery have been evaluated: conscious state and behavioral improvement. Patients were considered to have recovered consciousness if they were categorized EMCS (i.e., univocal functional use of object or accurate communication; Giacino et al., 2004) at 6 months. Behavioral improvement was stipulated for patients who were in a coma at the inclusion and were MCS or EMCS at 6 months, for patients who were in a UWS at the inclusion and were MCS or EMCS at 6 months, and for patients who were in a MCS at the inclusion and were EMCS at 6 months. The Glasgow outcome scale (GOS) defining 5 categories (from 1 = death to 5 = good recovery) of possible outcomes after a brain injury was also collected at the same time (Jennett and Bond, 1975).

Subject's own name paradigm: Stimuli and procedure of ERPs recordings

From 2011 to 2022, three different versions (v1, v2, and v3; please see supplementary Text for details) of the SON paradigm were developed and tested, and part of these data were previously published (Castro et al., 2015; Heine et al., 2021). The common main aim of these protocols was to investigate the cerebral discriminative response to the SON against 7 (v1) or 6 (v2 and v3) irrelevant stimuli (other unfamiliar first names; OFN). The SON (or nickname if relevant) was selected for each subject. Irrelevant OFN were selected by asking participants or representatives to indicate on a predefined list if any were familiar or not. All OFN were disyllabic (1.05 s, SD = 0.05 s). All names were pronounced by a female voice (v1) or by voice(s) created using text to speech software with a neutral intonation (Natural Reader, NaturalSoft Ltd.). All stimuli were equalized to the same A-weighted sound level, and presented binaurally during the experiment at a sound pressure level of approximatively 65 dBA SPL. In patients, if environmental noise was high, the presentation level was slightly increased to a level that was clearly audible but not painful.

Ten sequences of 64 equiprobable first names (v1), or 24 sequences (v2) or 12 sequences (v3) of 42 first names, were created and presented in a pseudo-random order (with no repetition of a same name and with a homogeneous temporal distribution of the first names). The mean stimulus onset asynchrony was 1,414 ± 137 ms (v1) and was between 1,400 and 1,500 ms, with random steps of 100 ms (v2 and v3). The three versions also varied by the presence (or not) of excerpt of music that preceded each sequence of first name, and we decided to average the first names after music and its control condition (neutral sound) to enhance the signal to noise ratio (and because very minor differences exist between the averages after all contexts, music + control, and the averages after music).

Finally, all subjects were instructed as follows: "You will hear a series of names […]. You will hear them passively but you must pay attention. The experiment lasts about [x] minutes"; [x] depending on the version of the protocol.

EEG recording and preprocessing

EEG signals were acquired in v1 from 13 Ag/AgCl electrodes referenced to the nose, as well as a bipolar EOG (below and above the right eye) and amplified using SystemPlus EEG amplifier (Micromed®) and in v2 and v3 from 128 electrodes referenced to the vertex and amplified using geodesic sensor net (EGI®, Philips) system.

All raw data were resampled at 250 Hz and visually inspected to identify bad channels. Any channels with huge continuous outliers were indicated as bad, interpolated (using spherical spline method) but taken out of the analysis. Data were bandpass filtered between 0.1 and 40 Hz using a FIR zero-double filter and a notch at 50 Hz. For patients, a second analysis was done with data filtered between 1 and 40 Hz [as previously motivated in (Sergent et al., 2017; Heine et al., 2021)] and an effect was suggested if one of the two analyses showed an effect. All electrodes signal were calculated from an average reference. Cz was interpolated for EGI recordings. For any subject where data were affected by eye-blinks, an ICA (*fastICA*) was performed to remove the blink components from the signal. Trials were then segmented (epochs) from −200 ms to +1,000 ms relative to the onset of the stimulus and a baseline correction (−200 to 0 ms) was applied. To further clean the data, an automatic rejection function was used where bad trials are either interpolated or rejected based on trial-wise assessment of individual sensor thresholds (Jas et al., 2018). All these processing stages were performed using MNE-Python version 19.2.

Event-related individual analyses

Averaged responses to SON and OFN preceding it (for comparisons with similar signal-to-noise ratio) were computed for each individual and for each of the 13 electrodes common to the Micromed® and EGI® acquisition systems. Statistical differences between SON and OFN were tested at the individual level (for healthy participants and DoC patients), using temporal clustering permutation tests, with one sided *t*-tests and 10,000 permutations (Maris and Oostenveld, 2007). Cluster level alpha was set to 0.01 with a cluster forming threshold of 0.05. To reduce the risk of false discovery rate by making multiple comparisons on 13 electrodes, a 'SON effect' (defined as the statistical difference between ERP elicited in SON and OFN conditions) was deemed present if a temporal cluster was identified on at least 2 electrodes (whether they were contiguous or not) from 200 ms after stimulus onset to the end of epoch. This criterion was determined on the basis of the large time window effect observed between SON and OFN in previous studies (Perrin et al., 2006). The minimal duration for a significant temporal cluster was measured at 48 msec.

Comparison between ERPs effect and outcome

The normality of quantitative data was verified using the Shapiro–Wilk test. Quantitative data were expressed as median (25th–75th percentile) or mean (± standard deviation) as appropriate. Qualitative variables were expressed as number (%). Categorical variables were compared using Chi2 or McNemar tests. Frequentist approach was used to compute sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), positive (LR+), negative (LR-) likelihood ratio, and area under the receiver operating characteristic curve (AUC). Statistical analysis was performed using MedCalc software (version 12.6.1, MedCalc Software bvba, Ostend, Belgium; 2013). A value of $p < 0.05$ was considered statistically significant.

Results

During the 2011–2022 period, 129 non-communicating patients were recorded with ERPs acquisition during the SON paradigm. Seventeen patients were excluded because of insufficient electrophysiological data quality. The final cohort consisted of 112 patients, age 46.0 (±18.3) years, of whom 71 (63%) were males (Table 1).

Among these 112 patients, 38 (34%), 30 (27%) and 44 (39%) were in a state of coma, MCS or UWS, respectively (Table 1). The most common etiology was traumatic brain injury (TBI; 49%), then anoxia (29%). The delay between the brain lesion and the evaluation was ≤3 months for 99 patients (88%; Table 1).

Event-related potentials to SON

Seventeen of the 22 healthy subjects (77%) had a significant effect between SON and OFN. Illustration of the statistically significant P3 event-related potential in response to SON versus OFN at the group level is available in Supplementary Figure.

Thirty-three patients (29%) had a statistically significant different brain response between SON and OFN conditions. Interestingly, no difference in the incidence of this SON effect was found between coma (11/38, 29%), MCS (7/30, 23%) and UWS patients (15/44, 34%; $p = 0.61$ for comparison between groups). Furthermore, the effect was more frequently observed in non-traumatic brain patients (23/57, 40%) than in traumatic brain patients (10/55, 18%; $p = 0.01$ for comparison between groups). Cases of patients with and without a SON effect are illustrated in Figure 1.

Outcome of DoC patients

Overall population of DoC patients

Among the 109 patients with a documented outcome, 85 patients (78%) survived 6 months after the brain damage. Concerning their behavioral evolution, 48 patients (44%) were EMCS, 20 patients (18%) were MCS, and 17 patients (16%) were UWS at 6 months (Table 1). MCS patients at the time of enrolment were more likely to recover consciousness at 6 months (20/30, 67%) than coma (13/36, 36%) and UWS patients (15/43, 35%; $p = 0.013$ for comparison between groups). The median (25th–75th percentile) GOS was 3 (2–3). The global outcome of traumatic brain patients was better than

TABLE 1 Clinical and demographics characteristics of patients with disorders of consciousness (overall population).

	Patients (n=112)
Age (years)	46 ± 18.3
Age ≥ 45 years	62 (55.4%)
Sex ratio (M/F)	71/41
Diagnosis	
Coma	38 (33.9%)
MCS	30 (26.8%)
UWS	44 (39.3%)
Etiology	
TBI	55 (49%)
Others	57 (51%)
Anoxia	32
ICH	14
Metabolic	5
Ischemic	4
Tumoral	1
Encephalitis	1
Delay since brain injury (days)	23 [14–49]
Acute (≤ 1 month)	71 (63.4%)
Acute and subacute (≤ 3 months)	99 (88.4%)
Patients with a SON effect	33 (29.5%)
Outcome at 6 months (n = 109)	
GOS (/5)	3 [2–3]
EMCS, MCS, UWS, dead	48, 20, 17, 24
Recovery of consciousness (i.e., EMCS)	48 (44%)

Data are expressed as n (%), mean (± SD) or median [25th–75th percentile] as appropriate. M = male; F = female; MCS = minimally conscious state; UWS = unresponsive wakefulness syndrome; TBI = traumatic brain injury; ICH = intracerebral hemorrhage; ERP = event-related potential; SON = subject's own name; GOS = Glasgow outcome scale; EMCS = emergence of MCS

non-traumatic brain one [respectively 33 patients (62%) vs. 15 patients (26%) were EMCS at 6 months, $p = 0.0002$].

Survivors

The analyses of the predictive power of a SON effect were conducted on survivors to mitigate the impact of withdrawing of life-sustaining therapies in potentially conscious but extremely impaired patients (Perez et al., 2020). Hence, the behavioral outcome at 6 months regarding the presence/absence of a SON effect has been studied in the 72 survivors' patients for whom the delay between brain injury and EEG recording was ≤ 3 months ('acute and subacute patients'; Figures 2, 3). Among them, 45 (63%) were EMCS at 6 months. Concerning the 16 (22%) patients with a SON effect, 75% of them were EMCS at 6 months, while 59% of the 56 (78%) patients without a SON effect were EMCS at 6 months. In other words, the false positive (percentage of unconscious patients at 6 months among patients with a SON effect) and false negative (percentage of conscious patients at 6 months among patients without a SON effect) rates were 25 and 59%, respectively. The prognostic value (Se, Sp, PPV, NPV, LR +, LR – and AUC) of the SON effect in DoC patients are reported in Supplementary Table 1 (for recovery of consciousness) and Supplementary Table 2 (for behavioral improvement).

Focus on coma patients

The characteristics of the 38 coma patients are detailed in Table 2. Individual analyses showed 11/38 patients (29%) with a SON effect. Among the 36 coma patients with a documented outcome, 24 of them (67%) were alive at 6 months among whom 13 (54%) were EMCS (Table 2; Figure 2). Concerning the 6 (25%) survivors' patients with a SON effect, 67% of them were EMCS at 6 months, while 50% of the 18 patients (75%) without a SON effect were EMCS at 6 months. In other words, the false positive and false negative rates were 33 and 50%, respectively. The prognostic value (Se, Sp, PPV, NPV, LR +, LR– and AUC) of the SON effect in coma patients are reported in Supplementary Table 3 (for recovery of consciousness) and Supplementary Table 4 (for behavioral improvement).

Discussion

The neurological outcome following severe brain injury is a daily interrogation for the caregivers and family members of (acute) non-communicating patients. Clinicians specializing in the care of severely brain-damaged patients are well acquainted with the clinical features of DoC. Notably, coma and UWS patients are characterized by the complete absence of behavioral signs of self and environmental awareness, the likelihood of withholding life-sustaining therapies or denying rehabilitative services increasing substantially with the persistence of this behavioral status. In this context, we reported new evidence about covert abilities to discriminate self-relevant words in this specific population of patients. Interestingly, we demonstrated, in a large series of comatose and other DoC patients, that the presence of a bedside differential brain response to the SON could help to predict behaviorally overt consciousness recovery, questioning the role of this cerebral index as potentially being a key-cognitive function to consciousness emergence (Lane, 2020).

The use of personally relevant stimuli has been promoted in recent years for investigating severely brain damaged DoC patients with the aim of identifying their ability to categorize self-related stimuli (Perrin et al., 2006; Castro et al., 2015; Perrin et al., 2015). In this context, it has been demonstrated that hearing one's own first name, presented within other unfamiliar first names, evoked a P3 potential in some patients (Perrin et al., 2006). In our study, we demonstrated that coma, MCS and UWS patients were able to discriminate their own name (compared to unfamiliar first names) as a significant P3 was individually observed in about 30% of them. Interestingly, this SON effect has no added value in clarifying the diagnosis of an altered state of behavioral awareness. Indeed, whereas several published articles supposed that it should be mainly found in MCS patients in which definite behavioral evidence of self-awareness is demonstrated (Perrin et al., 2006; Schnakers et al., 2008b, 2015; Hauger et al., 2015; Sergent et al., 2017)—for a review, see (Wutzl et al., 2021)—a P3 response to SON was indifferently observed in all the phenotypes of patients. This result paves the way of a potentially existing dissociation between electrophysiological evidence of self

FIGURE 1
Illustrative cases. Event-related potentials (ERP) at Pz and global field power (GFP) from two patients are represented: one COMA patient without SON effect **(A)**, and one COMA patient with SON effect **(B)**. Temporal clustering permutation tests, with one sided *t*-tests and 10,000 permutations. Significance threshold: alpha cluster was set to 0.01; value of $p \leq 0.05$ for SON (orange curve) and OFN (blue curve) comparison at each sample. Abbreviations: SON=subject's own name; OFN=other first names.

and environmental processing and the complete absence of its behavioral signs, notably in the acute stage of coma and in UWS patients. In the early 2000s, functional neuroimaging studies suggested that cognitive processing capacity might be underestimated in MCS patients (Hirsch et al., 2001; Schiff et al., 2005). Based on our results, we assume that cortical brain activity that is dissociated from behavior is possible in patients with UWS (Edlow et al., 2017), but also in the acute stage of coma. The pattern of residual neural activity of a self-related stimulus perceptive discrimination we identified for the first time in such individuals suggest that EEG paradigms are required to complement behavioral assessment in patients without command following at the bedside (Kondziella et al., 2020). Definitely, behavior is an indirect and thus incomplete measure of brain functions leading to interpretative errors in these patients. Consequently, standardized clinical evaluation and neuroimaging-based measures (including bedside EEG-based techniques) should be integrated for multimodal evaluation of patients with DoC in accordance with the guidelines of the European and American Academies of Neurology on the diagnosis of coma and other DoC (Giacino et al., 2018; Kondziella et al., 2020).

Current conceptual models of consciousness, such as the global neuronal workspace theory (GNWT; Dehaene and Changeux, 2011) and the information integration theory (Tononi, 2004), propose that consciousness requires the integrated activity of association cortices. However, such activation is likely necessary but not sufficient for consciousness. Here, we do not assert that higher-order cortex motor dissociation is indicative of covert consciousness. In contrast, the preservation of self-recognition could reflect the ability to use first-person perspective and could be considered as a key-cognitive prerequisite to consciousness emergence. Indeed, one of our main results was the good positive predictive value attributed to the presence of a P3 component in response to SON: this self-recognition electrophysiological pattern could predict an improvement of consciousness until its behaviorally overt emergence. This specific brain reactivity to the own name alludes to Zeman's fourth sense of self-consciousness referring as self-recognition, i.e., our ability to recognize our own bodies as our own, for example in mirror (Zeman, 2001, 2005). From a conceptual point of view, Northoff assumes self-referential processing, accounting for distinguishing stimuli related to one's own self from those that are not relevant to one's own

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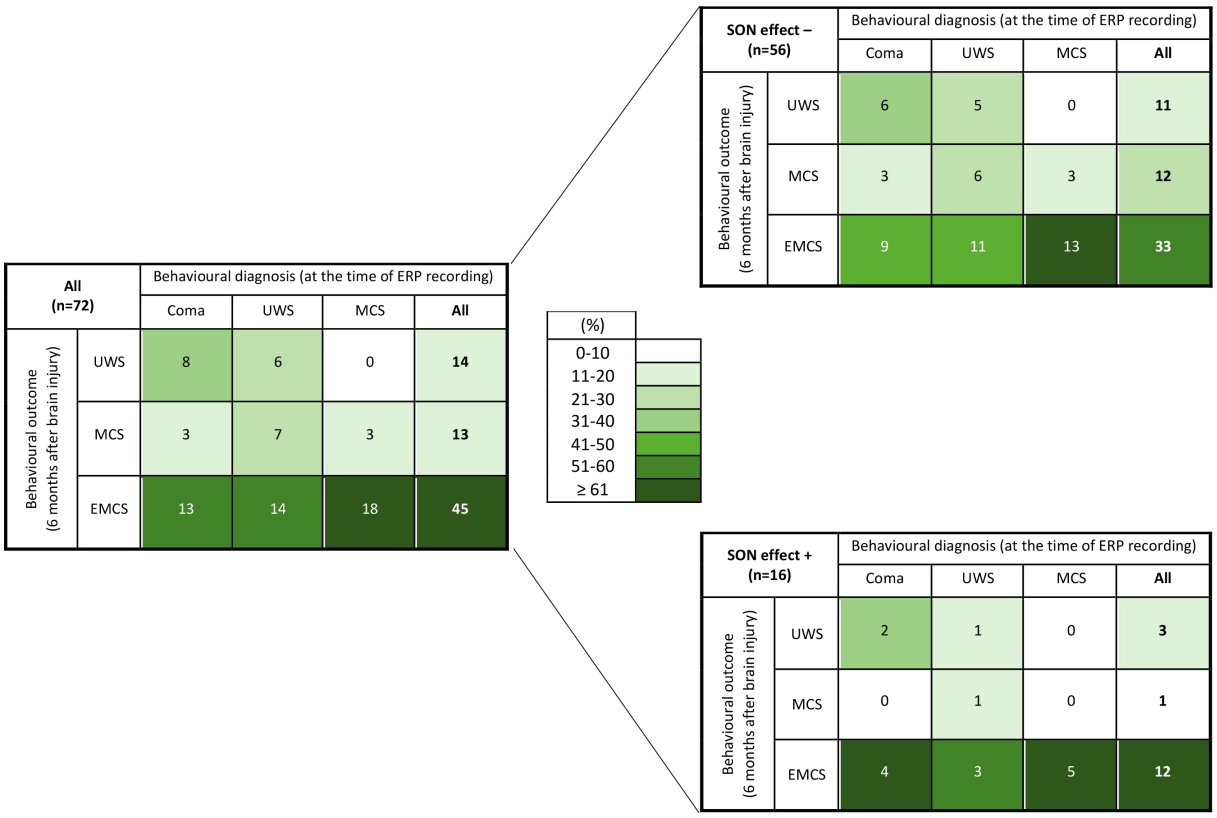

FIGURE 2
'Heat maps' illustrating 6months behavioral outcome of survivors' patients with disorders of consciousness according to their behavioral state of consciousness at the time of ERP recording and the absence/presence of a SON effect at the acute stage of brain injury. Background color coding indicates density of patients (%) within a diagnostic category, suggesting clusters of observations. UWS=unresponsive wakefulness syndrome; MCS=minimally conscious state; EMCS=emergence of minimally conscious state; SON=subject's own name; SON effect –/+=absence/presence of a SON effect.

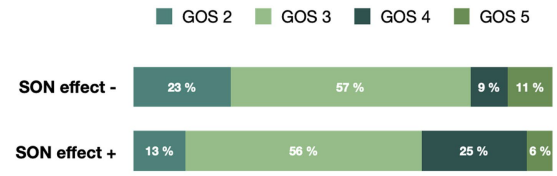

FIGURE 3
Glasgow Outcome Scale of survivors' patients with disorders of consciousness 6months after their brain injury according to the absence/presence of a SON effect at the time of ERP recording. GOS=Glasgow outcome scale; SON=subject's own name; GOS 2/3/4/5: persistent vegetative state/severe disability/moderate disability/good recovery.

concerns, to be at the core of the self (Northoff and Bermpohl, 2004; Northoff et al., 2006). Furthermore, Damasio investigated minimal forms of self that he coined 'mental or core self' stipulating that they are required in the making of consciousness (Damasio, 1999). In this setting, minimal self could be considered as the bifurcation point between conscious and unconscious states (Lane, 2020), and might constitute the basis for higher-level, cognitive forms of self, as well as the understanding of other minds (Limanowski and Blankenburg, 2013).

TABLE 2 Clinical and demographics characteristics of coma patients.

	Coma patients
(*n* = 38)	
Age (years)	49.6 ± 19.9
Age ≥ 45 years	25 (65.8%)
Sex ratio (M/F)	21/17
Etiology	
TBI	15 (39.5%)
Others	23 (60.5%)
Delay since brain injury (days)	14.5 [10–24]
Acute (≤ 1 month)	33 (86.8%)
Acute or sub-acute (≤ 3 months)	38 (100%)
Patients with a SON effect	11 (28.9%)
Outcome at 6 months (*n* = 36)	
GOS (/5)	2 [1–3]
EMCS, MCS, UWS, dead	13, 3, 8, 12
Recovery of consciousness (i.e., EMCS)	13 (36.1%)

Data are expressed as *n* (%), mean (± SD) or median (25th–75th percentile) as appropriate. M = male; F = female; TBI = traumatic brain injury; SON = subject's own name; GOS = Glasgow outcome scale; EMCS = emergence of MCS; MCS = minimally conscious state; UWS = unresponsive wakefulness syndrome.

Finally, we assert that this covert brain ability to correctly categorize self-referential ecological stimulation from outside could be both an index of self-processing and a prerequisite for consciousness recovery. This brain ability observed in up to 30% of coma patients suggests that coma is not a passive state of sensory isolation, but rather a transient and active state that could benefit from a rich sensory stimulation regimen in which, from instance, music—and its autobiographical characteristics—could have a role to play through cortical arousal and/or awareness enhancement [in agreement with "the arousal and mood hypothesis" (Janata et al., 2007; Zatorre, 2013; Castro et al., 2015)].

Our results must be interpreted with caution and a number of limitations should be borne in mind. Firstly, the proof of a potential for consciousness recovery (or not) using electrophysiological biomarker of self-processing is forcefully being challenged at the individual level by the very weak negative predictive strength—meaning that its absence was not a reliable predictor of negative outcome–, the low sensitivity and also the wide PPV confidence interval we noticed. It is worth noting that the sensitivity for all cognitive evoked potentials is known to be low (i.e., with a high rate of false negative), even in healthy subjects (Perrin et al., 2006; Schnakers et al., 2008b; Fischer et al., 2010; Faugeras et al., 2011, 2012; Sergent et al., 2017). Nonetheless, a SON effect was detected in 17 of the 22 healthy subjects (77%) enrolled in our study. This relatively low rate of false negative could be due to the extreme salience of being presented one's own name and might be associated to the enhancement of top-down and/or arousal mechanisms (Chennu and Bekinschtein, 2012). However, even if personal and emotional significance increases the probability to observe a brain response in DoC patients—P3 to SON is elicited more frequently as compared to P3 to rare tone (Cavinato et al., 2011)—the high rate of false negative (59%) in our cohort of patients underscores the need for caution in interpreting negative findings on EEG and encourages finding ways to improve the sensitivity of the SON paradigm (Castro et al., 2015). In this setting, we think that the very weak predictive strength of a negative effect could encourage to repeat the electrophysiological evaluation (longitudinal follow-up), the late recovery of a discriminative response to SON being theoretically possible. Whether the SON effect recovery is strongly associated with consciousness emergence would deserve to be studied. Moreover, complementary pattern of predictive power would be interesting. For instance, the 'local effect' (i.e., MMN/P3a obtained to local deviant sounds during the local–global auditory task) could be used as a surrogate marker of low-level perceptive function therefore reflecting the preservation of a local cortical network and playing as a necessary but insufficient condition to consciousness recovery (Baars, 1988; Dehaene and Naccache, 2001; Dehaene and Changeux, 2011). To go further, the use of a multifaceted ERP battery exploring more distinct cognitive processes to provide a more nuanced cognitive profile, from low-level perceptive (e.g., echoic memory) to higher-order cognitive abilities, would be promising (Sergent et al., 2017). Secondly, we were surprised to find a higher incidence of the P3 response to SON in non-traumatic (40%) than traumatic brain (18%) patients, while the latter had a more favorable neurological outcome. These findings could support the notion of brain cortical modularity in P3 generation to target stimuli. Theoretically, global forms of brain injury (e.g., cerebral hypoxia, diffuse axonal injury) could sever the connections between each module without destroying the module itself (Giacino, 2005). Under these circumstances, the functional integrity of a particular module (e.g., the module generating a P3 to self-relevant stimuli) may be spared. Thirdly, an accurate categorization of MCS patients into MCS + and MCS – subgroups and their respective SON effect would deserve to be investigated. Based on our results, we assume that no difference would be expected between these 2 categories of patients because we believe that the preservation of a (minimal) self-processing is independent of the behavioral impairment of consciousness. The minimal self almost certainly depends on brain processes and an ecologically embedded body, but one does not have to know or be aware of this to have an experience that still counts as a self-experience (Gallagher, 2000). Finally, modules that remain active but become isolated may produce higher-order cortical response that occur in the absence of conscious experience (please, see the intriguing possibility of 'words without mind' suggesting activity of isolated 'islands of cortex' described by Schiff et al. in a patient suffering from UWS (Schiff et al., 1999). Conversely, traumatic brain injury could produce a focal lesion of a specific cognitive module that may become underactive while connections between modules are spared. It would seem therefore interesting to confront our assumption with the topography of the traumatic brain lesions. Lastly, the calculation of the predictive strength of the SON effect on consciousness recovery was focused on long-term survivors in order to discard the impact of withdrawing of life-sustaining therapies in potentially conscious but extremely impaired patients. However, this methodological choice is not transposable to the management of patients and their family in real-time clinical practice.

To conclude, about 30% of severely brain-damaged patients suffering from DoC are capable to discriminate salient self-referential auditory stimuli, even in case of absence of behavioral detection of conscious processing. We suggest that this covert brain ability, detected for the first time in coma patients, could be both an index of self-processing and a prerequisite for consciousness recovery. Guide the research on the attentional modulation of the cortical discriminative response to the SON of non-communicating patients would contribute to enriching the discussion regarding neural correlates of access to pre-conscious and conscious content.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by CPP Sud-Est II (2012-036-2) and CPP Nord-Ouest II (69LHCL19_0672). The patients' relatives/participants gave a written informed consent to participate in this study.

Author contributions

FP contributed to conception and design of the study. FF, LH, AC, and FP contributed to analyses. FF, LH, SS, and FP contributed to interpretation of the results. FF wrote the first draft of the manuscript. All authors have contributed to data acquisition. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2023.1145253/full#supplementary-material

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Effectiveness on level of consciousness of non-invasive neuromodulation therapy in patients with disorders of consciousness: a systematic review and meta-analysis

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Background: Disorders of consciousness (DoC) commonly occurs secondary to severe neurological injury. A considerable volume of research has explored the effectiveness of different non-invasive neuromodulation therapy (NINT) on awaking therapy, however, equivocal findings were reported.

Objective: The aim of this study was to systematically investigate the effectiveness on level of consciousness of different NINT in patients with DoC and explore optimal stimulation parameters and characteristics of patients.

Methods: PubMed, Embase, Web of Science, Scopus, and Cochrane central register of controlled trials were searched from their inception through November 2022. Randomized controlled trials, that investigated effectiveness on level of consciousness of NINT, were included. Mean difference (MD) with 95% confidence interval (CI) was evaluated as effect size. Risk of bias was assessed with revised Cochrane risk-of-bias tool.

Results: A total of 15 randomized controlled trials with 345 patients were included. Meta-analysis was performed on 13 out of 15 reviewed trials indicating that transcranial Direct Current Stimulation (tDCS), Transcranial Magnetic Stimulation (TMS), and median nerve stimulation (MNS) all had a small but significant effect (MD 0.71 [95% CI 0.28, 1.13]; MD 1.51 [95% CI 0.87, 2.15]; MD 3.20 [95%CI: 1.45, 4.96]) on level of consciousness. Subgroup analyses revealed that patients with traumatic brain injury, higher initial level of consciousness (minimally conscious state), and shorter duration of prolonged DoC (subacute phase of DoC) reserved better awaking ability after tDCS. TMS also showed encouraging awaking effect when stimulation was applied on dorsolateral prefrontal cortex in patients with prolonged DoC.

Conclusion: tDCS and TMS appear to be effective interventions for improving level of consciousness of patients with prolonged DoC. Subgroup analyses identified the key parameters required to enhance the effects of tDCS and TMS on level of consciousness. Etiology of DoC, initial level of consciousness, and phase of DoC could act as significant characteristics of patients related to the effectiveness of tDCS. Stimulation site could act as significant stimulation parameter related to the effectiveness of

TMS. There is insufficient evidence to support the use of MNS in clinical practice to improve level of consciousness in patients with coma.

Systematic review registration: https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=337780, identifier: CRD42022337780.

KEYWORDS

disorders of consciousness, coma, non-invasive neuromodulation therapy, transcranial Direct Current Stimulation, Transcranial Magnetic Stimulation, median nerve stimulation

Introduction

During the past several years, with the development of resuscitation techniques and intensive care, the mortality rate of patients after traumatic brain injury (TBI), cerebral vascular accident (CVA), hypoxic-ischemic encephalopathy (HIE), or other severe neurological injury has decreased gradually (Stein et al., 2010; Fugate et al., 2012; Mensah et al., 2017; Jiang et al., 2019). However, patients who have survived may still suffer from a range of cognitive, emotional, and behavioral sequelae secondary to the injury (Howlett et al., 2022). Disorders of consciousness (DoC), as one of these sequelae, are characterized by the reduction of wakefulness and/or awareness (Sergi and Bilotta, 2020). The former refers to the state of consciousness, which is characterized by individual eyes-opening readiness to respond to stimuli in such a way as to favor continued health (Sergi and Bilotta, 2020). The latter refers to the content of consciousness, which is characterized by a serially time-ordered, organized, and reflective awareness of self and the environment (James, 1894). Coma, as the most severe stage of DoC, is characterized by the complete loss of wakefulness and awareness (Sergi and Bilotta, 2020). Such patients commonly exhibit eyes-closing and lack a normal sleep-wake cycle. Coma typically lasts only a few hours, days, or weeks and transitions into either a vegetative state/unresponsive wakefulness syndrome (VS/UWS) or a minimally conscious state (MCS). The fundamental difference between VS/UWS and MCS is whether the patient has inconsistent but clearly discernible behavioral evidence of self or environmental awareness, including simple command-following, gestural or verbal "yes/no" response, and purposeful motional or affective behaviors that occur concerning relevant environmental stimuli (Giacino et al., 2002; Porcaro et al., 2021). Although some patients with MCS may follow commands to a certain extent, functional communication remains challenging, which causes severe distress to their families. Furthermore, the cost of lifetime rehabilitation care for patients with DoC places heavy economic load on individuals and society (Adan Ali and Farah Yusuf Mohamud, 2022).

Although there are various treatments for DoC currently, only a small part of them have demonstrated a strong level of evidence (Thibaut et al., 2019). Regarding medical therapy, amantadine is the only medicine that has been recommended as effective treatment for patients with DoC after TBI between 4 and 16 weeks in American guidelines (Giacino et al., 2018b). However, its efficacy is still limited by specific population and duration of DoC, and cannot be extended to a broader group of patients with DoC at present. As for neuromodulation therapy, it can be further divided into invasive neuromodulation therapy and non-invasive neuromodulation therapy (NINT). The former usually applies direct stimulation of the brain or nerves through invasive approaches such as implanted electrodes. A recent open-label study of central thalamic deep brain stimulation in patients with DoC reported that four out of fourteen patients with VS/UWS or MCS showed positive effects on clinical recovery (Chudy et al., 2018). However, given the high risk of invasive operation and high surgery cost, NINT has shown unique advantages because of convenience, safety, and economics.

Among different types of non-invasive interventions, the most common one that is applied in clinical practice is non-invasive brain stimulation which includes transcranial Direct Current Stimulation (tDCS) and Transcranial Magnetic Stimulation (TMS). Both tDCS and TMS have the effect of regulating functional connectivity between different brain regions by modulating cortical excitability and neuroplasticity (Cirillo et al., 2017). In addition, non-invasive peripheral neuromodulation therapy such as median nerve stimulation (MNS), and transcutaneous auricular vagus nerve stimulation (taVNS) is also proposed for awaking therapy. In contrast to non-invasive brain stimulation, peripheral neuromodulation commonly regulates functional brain activity by modulating the impulses sent from peripheral nerves to the central nerve and indirectly adjusting the electrophysiological activity of cortical neurons (Briand et al., 2020).

Several systematic reviews and meta-analyses have examined whether tDCS, rTMS, or MNS can be applied as an effective awaking therapy in patients with DoC (Zaninotto et al., 2019; Feng et al., 2020; Feller et al., 2021; O'Neal et al., 2021). A recent meta-analysis on twelve trials indicated that tDCS could be expected to improve the level of consciousness in patients with DoC whereas TMS had no clear evidence (Feng et al., 2020). Remarkably, the conclusion of this review was limited to the effectiveness of tDCS but lacked further exploration for optimal stimulation parameters and characteristics of patients. Meanwhile, the conclusion for TMS was based on only two TMS studies. As a result, a high risk of bias of this conclusion induced by the limited number of studies could exist. In addition, a review conducted by Feller et al. (2021) only reported a qualitative result and drew an indefinite conclusion about the effectiveness of MNS. As a result, the objective of this review was to explore the effectiveness of different NINT and find out their optimal stimulation parameters and characteristics of patients with DoC.

Methods

The systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework (Page et al., 2021) and was registered with PROSPERO (CRD42022337780).

Eligible criteria

The Patient-Intervention-Comparison-Outcome-Study Design (PICOS) framework was used to organize the inclusion criteria.

(P) Studies recruited patients diagnosed with DoC by coma recovery scale-revised (CRS-R) or Glasgow coma scale (GCS). (I) Studies using tDCS, TMS, MNS, or any other type of NINT to investigate its effectiveness on level of consciousness in patients with DoC. (C) Studies adopting control conditions such as sham stimulation, no stimulation, or any active control intervention. (O) Studies adopted at least one of the clinical behavioral scales, neurophysiology evaluation, neuroimaging evaluation, or any other measures to assess level of consciousness. (S) Randomized controlled trials (RCTs) with parallel or cross-over design.

In addition to the above criteria, we only included studies reported in English. Review articles, conference abstracts, expert opinion papers, and editorials were excluded. Meanwhile, studies reporting on less than five patients or providing only one session intervention were excluded.

Information sources

Electronic databases were searched from their inception through November 2022, including PubMed, Embase, Web of Science, Scopus, and Cochrane central register of controlled trials. Meanwhile, we searched the reference lists of included studies to identify further studies. The search was performed using the following keywords: ("disorders of consciousness" OR DoC OR Coma OR "Vegetative State" OR VS OR "unresponsive wakefulness syndrome" OR UWS or "minimally conscious state" OR MCS) AND (neuromodulation OR "non-invasive brain" OR "transcranial electrical current stimulation" OR TES OR "transcranial Direct Current Stimulation" OR tDCS OR "transcranial alternating current stimulation" OR tACS OR "transcranial random noise stimulation" OR tRNS OR "transcranial magnetic stimulation" OR TMS OR "theta burst stimulation" OR TBS OR "low-intensity focused ultrasound" OR LIFU OR "transcutaneous auricular vagus nerve stimulation" OR taVNS OR "Near-infrared laser stimulation" OR N-LT OR "focused shock wave therapy" OR F-SWT OR "median nerve stimulation" OR MNS). The detailed searching strategies were shown in Appendix S1.

Selection process

After removing duplicates, two authors (B.B.Y, and J.Y.W.) independently screened all eligible articles and cross-checked the information. In a case where the eligibility of inclusion was conflicted, a third senior author (X.L.) was consulted to solve the dispute, and a final decision was made by consensus.

Data collection process

Two authors (Z.Y.L. and X.T.Z.) independently extracted data using a standardized form for each eligible study. This form includes information concerning general information (e.g. title, first author, year of publication), methodology (e.g. study design, duration of the study), demographics (e.g. age, gender, time from injury to intervention), interventions (e.g. type of intervention, stimulation parameter), outcomes (e.g. outcome measures, evaluation timepoint) and adverse events. Disagreements between the two authors were resolved by discussion with a third senior author (X.L.).

Study risk of bias assessment

We assessed the risk of bias in all included studies using revised Cochrane risk-of-bias tool (ROB version 2.0) (Sterne et al., 2019). Aspects of randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcomes, and selection of the reported result were evaluated. Bias arising from period and carryover effects were additionally evaluated for cross-over studies. Each domain was assessed as "low risks", "some concerns", or "high risks". Two authors (Z.Y.L. and X.T.Z.) independently accomplished assessment and resolved any discrepancy through discussion with a third senior author (X.L.).

Effect measures

With the assistance of R statistical software, library "meta" was used to perform meta-analysis if at least two studies assessed one specific outcome. For outcomes based on continuous data obtained at the end of the intervention, we adopted mean difference (MD) with 95% confidence interval (CI) as effect size. For dichotomous outcomes obtained at the end of the intervention, we adopted risk ratio (RR) with 95% CI. For ordinal outcomes, if there was a cut-off point that could be obtained, we transformed the data into dichotomous data. Otherwise, it was calculated as continuous data.

Synthesis methods

Meta-analyses were calculated following the methods suggested by the Cochrane Review (Higgins et al., 2011). Combined design meta-analytic formula, using the methods suggested by Elbourne et al. (Curtin et al., 2002; Elbourne et al., 2002), were used to combine parallel and cross-over trial results. With no carry-over effects in cross-over studies, trial results were combined with parallel studies by the combined design meta-analytic formula or included in qualitative analysis, depending on whether the study reported the order of crossover and individual specific different

time-point results. Otherwise, only data from the first phase in cross-over studies was included and combined with parallel studies.

Statistical heterogeneity of included trials was evaluated with I^2 statistic and between-study variance (τ^2) (Higgins and Thompson, 2002). Studies with an I^2 of 0 to 24% were considered as low heterogeneity; I^2 of 25% to 49% as moderate heterogeneity; I^2 of 50%-74% as substantial heterogeneity and 75%-100% as high heterogeneity (Higgins et al., 2003). When I^2 was greater than 50%, it was assumed that there was considerable heterogeneity between studies, therefore random-effects model was applied. Sensitivity analyses were conducted by the "leave-one-out" method and omitting studies with high risk of bias.

To examine the differential effects of confounders, pre-planned subgroup analyses were conducted by certain parameters if data was available, including etiology of Doc (TBI, CVA or HIE), initial level of consciousness (Coma, VS/UWS or MCS), phase of DoC (Acute, Subacute or Chronic), and stimulation site (primary motor cortex, dorsolateral prefrontal cortex or others).

Moderator effects were examined by meta-regression using stimulation parameters as predictor variables. For tDCS, these parameters included number of total sessions and total stimulation time. For TMS, these parameters included frequency of stimulation, number of sessions, number of pulses per session, and total stimulation number of pulses.

Reporting bias assessment

Reporting biases were assessed by a contour-enhanced funnel plot (Peters et al., 2008). Based on the effect sizes and standard errors of included studies, the significance of any effect size could be calculated and relevant study could be distributed to special color regions representing different significance levels. An asymmetrical appearance of the plots represents the existence of bias. When bias was detected through funnel plot, we used a trim and fill algorithm to adjust (Duval and Tweedie, 2000). The adjusted results obtained by the algorithm could balance the bias in the overall results of studies that were unpublished due to insignificant effects. Adjusted results combined with primary results were used to determine whether the bias remarkably affected effect size estimation.

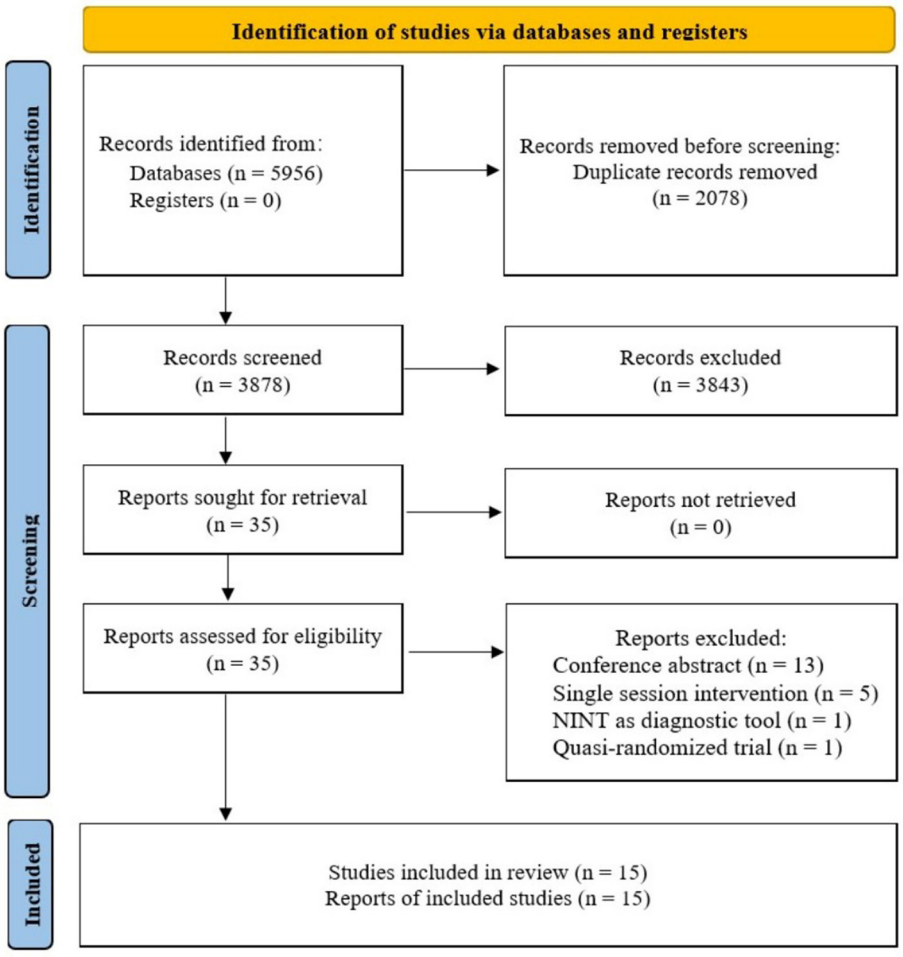

FIGURE 1
Flowchart summarizing study selection process. NINT, non-invasive neuromodulation therapy.

Results

Study selection

Process of study selection was summarized in Figure 1. A total of 5,956 studies were retrieved from the databases. After duplication elimination, 3,878 studies were obtained. Fifteen studies met the eligibility criteria and were finally included in the systematic review. Two studies were excluded from quantitative synthesis due to lack of sufficient data for obtaining effect sizes. A PDF document of the comprehensive search results including all the records was shown in Appendix S2.

Study characteristics

Table 1 summarized characteristics of studies included in this review. A total of 15 randomized controlled studies with sample size ranging from 6 to 50 patients were included in this review. Regarding patients' initial level of consciousness, three studies included only patients with coma, four included patients with VS/UWS, three included patients with MCS, and the remaining five did not specify the type of DoC in their eligibility criteria.

As for the intervention of studies, seven studies used tDCS. Five studies used TMS. The remaining three studies used MNS. In addition, in terms of the design of studies, we included seven randomized cross-over controlled studies and eight randomized parallel controlled studies.

tDCS studies

Seven tDCS studies enrolled 154 patients with VS/UWS or MCS. Clinical behavioral scales like CRS-R, Western Neurosensory Stimulation Profile (WNSSP), or neurophysiology evaluation like electroencephalogram (EEG), event-related potential (ERP) were evaluated as the outcome. Among them, Huang et al. (2017) and Thibaut et al. (2017) reported significant effects ($p < 0.05$) on CRS-R in patients with MCS. Both studies used a unilateral monopolar montage protocol and selected right supraorbital region as the reference cathode. It is worth noting that the former selected posterior parietal cortex (PPC) as the anodic stimulation site, whereas the latter chose the left dorsolateral prefrontal cortex (DLPFC). Cavinato et al. (2019) reported that only a proportion of patients with MCS had significant effects on WNSSP when the left DLPFC and the right deltoid muscle were selected as the anode and cathode respectively ($p < 0.05$). None of the remaining four studies reported any significant effects (Estraneo et al., 2017; Zhang et al., 2017; Martens et al., 2018; Wu et al., 2019).

TMS studies

Five TMS studies recruited 155 patients with VS/UWS or MCS. CRS-R was the only commonly used outcome. In addition, neurophysiological evaluation such as EEG, somatosensory evoked potential (SEP), or brainstem auditory evoked potential (BAEP) was also used to assess patients' level of consciousness. Cincotta et al. (2015) and He et al. (2018) applied TMS on left primary motor cortex (M1) and reported no significant effect on CRS-R and EEG. Zhang et al. (2021) investigated the effects of TMS with left DLPFC on CRSR, EEG, and BAEP in patients with DoC and reported a significant effect ($p < 0.05$). Similarly, Chen et al. (2022) and Fan et al. (2022) selected left DLPFC as stimulation target and showed significant effects ($p < 0.05$) of TMS on CRS-R either.

MNS studies

Three MNS studies enrolled 36 patients with coma. Cooper et al. (1999) and Nekkanti et al. (2016) both applied MNS on right median nerve and reported significant effects on GCS. However, Peri et al. (2001) used MNS on unilateral median nerve according to patients' injured brain hemisphere and reported no significant effect on GCS.

Risk of bias in studies

Results from assessment of bias using revised Cochrane risk-of-bias tool for parallel and cross-over studies were presented in Figures 2, 3. Only three studies were assessed as "low risks" (Peri et al., 2001; Chen et al., 2022; Fan et al., 2022). In addition, the majority of included studies ($n = 7$) were assessed as "some concerns" because of indistinct illustration of randomization process or other relatively rare reasons (Cooper et al., 1999; Huang et al., 2017; Thibaut et al., 2017; Zhang et al., 2017; He et al., 2018; Martens et al., 2018; Wu et al., 2019). Five studies were assessed as "high risks" on account of significant bias in at least one domain (Cincotta et al., 2015; Nekkanti et al., 2016; Estraneo et al., 2017; Cavinato et al., 2019; Zhang et al., 2021).

Synthesis of results

Thirteen studies were included in the meta-analysis. CRS-R was the only commonly used outcome in six tDCS studies and five TMS studies. Similarly, GCS was the only outcome that could be extracted from two MNS studies. Separate meta-analyses were conducted for tDCS, TMS, and MNS studies.

Effectiveness of tDCS on level of consciousness

Meta-analysis of effectiveness of tDCS on CRS-R of six studies was presented in Figure 4. There was a small but significant effect size (MD 0.71 [95% CI 0.28, 1.13], $p < 0.01$) without significant heterogeneity ($I^2 = 0.0\%$, $p = 0.53$). Furthermore, result was stable when we adopted sensitivity analysis (Table 2). The contour-enhanced funnel plot (Figure 5) with the trim and fill method did not show evidence of reporting bias (MD 0.68 [95% CI 0.26, 1.11], $p < 0.01$).

TABLE 1 Characteristics of included studies.

References	Country	Study design	Sample size	Intervention	Target	Stimulation parameter (intensity/duration/total sessions/pulses)	Control	Outcome
Estraneo et al. (2017)	Italy	Cross-over	13	tDCS	LDLPFC	2 mA * 20 min/session * 5 sessions	Sham tDCS	CRS-R EEG
Huang et al. (2017)	Belgium	Cross-over	33	tDCS	PPC	2 mA * 20 min/session * 5 sessions	Sham tDCS	CRS-R
Thibaut et al. (2017)	Belgium	Cross-over	16	tDCS	LDLPFC	2 mA * 20 min/session * 5 sessions	Sham tDCS	CRS-R
Zhang et al. (2017)	China	Parallel	26	tDCS	LDLPFC	1 or 2 mA * 20 min/session * 20 sessions	Sham tDCS	CRS-R ERP
Martens et al. (2018)	Belgium	Cross-over	27	tDCS	LDLPFC	2mA * 20 min/session * 20 sessions	Sham tDCS	CRS-R
Cavinato et al. (2019)	Italy	Cross-over	24	tDCS	LDLPFC	2 mA * 20 min/session * 10 sessions	Sham tDCS	EEG CRS-R WNSSP
Wu et al. (2019)	China	Parallel	15	tDCS	LDLPFC or RDLPFC	2 mA * 20 min/session * 10 sessions	Sham tDCS	CRS-R EEG GCS-E
Cincotta et al. (2015)	Italy	Cross-over	11	TMS	LM1	90% RMT * 1000pulses/session * 5sessions Frequency: 20 Hz	Sham TMS	CRS-R CGI-I EEG
He et al. (2018)	China	Cross-over	6	TMS	LM1	100%RMT * 1,000pulses/session * 5 sessions Frequency: 20 Hz	Sham TMS	CRS-R EEG
Zhang et al. (2021)	China	Parallel	48	TMS	LDLPFC	80% RMT * 2,000 pulses/session * 40 sessions Frequency: 5 Hz	Sham TMS	CRS-R EEG
Chen et al. (2022)	China	Parallel	50	TMS	LDLPFC	90%RMT * 1,000 pulses/session * 30sessions; Frequency: 10Hz	Sham TMS	CRS-R GCS SEP BAEP
Fan et al. (2022)	China	Parallel	40	TMS	LDLPFC	100%RMT * 2,000 pulses/session * 20sessions Frequency: 20 Hz	Sham TMS	CRS-R
Cooper et al. (1999)	USA	Parallel	6	MNS	RMN	20mA * 8 or 12 h/session * 14sessions Frequency: 40 Hz Waveform: asymmetric biphasic	Not mentioned	GCS Days spent in ICU GOS
Peri et al. (2001)	USA	Parallel	10	MNS	LMN or RMN	15-20 mA * 8h/session * 14 sessions. Frequency: 40Hz Waveform: asymmetric biphasic	Sham MNS	Time out of coma GCS GOS FIM
Nekkanti et al. (2016)	India	Parallel	20	MNS	RMN	20 mA * 30 min/session * 30 sessions Frequency: 40 Hz. Waveform: asymmetric biphasic	Regular medication	GCS

tDCS, transcranial Direct Current Stimulation; LDLPFC, left dorsolateral prefrontal cortex; min, minute; CRS-R, coma recovery scale-revised; EEG, electroencephalography; PPC, posterior parietal cortex; ERP, event-related potential; WNSSP, Western Neurosensory Stimulation Profile; RDLPFC, right dorsolateral prefrontal cortex; GCS-E, Glasgow coma scale-extended; TMS, Transcranial Magnetic Stimulation; LM1, left primary motor cortex; RMT, resting motor threshold; CGI-I, clinical global impression scale-improvement; GCS, Glasgow coma scale; SEP, somatosensory evoked potential; BAEP, brainstem auditory evoked potential; USA, United States of America; MNS, median nerve stimulation; RMN, right median nerve; h, hour; GOS, Glasgow outcome scale; LMN, left median nerve; FIM, function independent measure.

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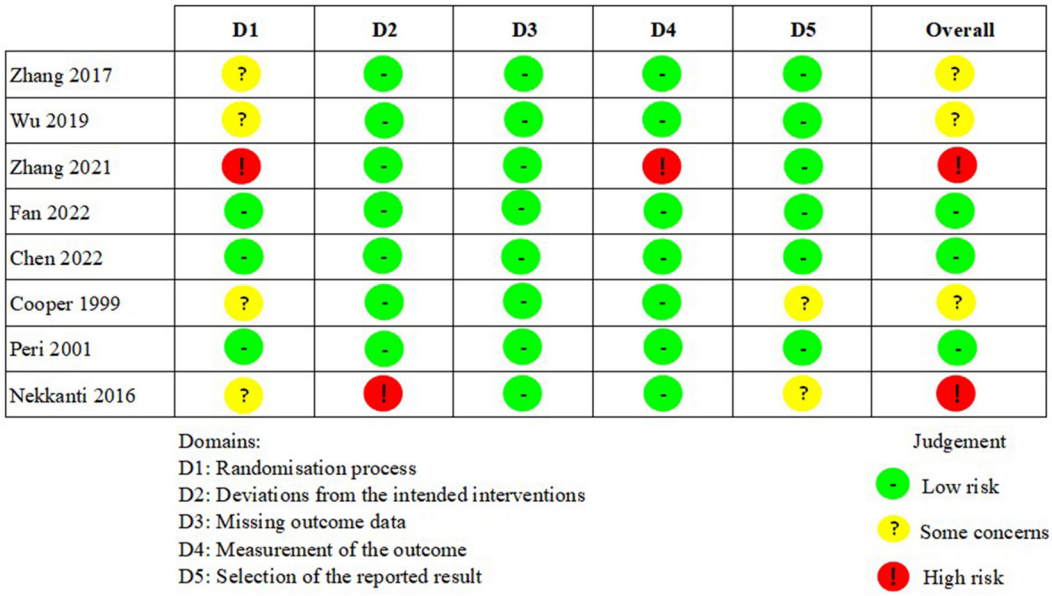

FIGURE 2
The risk of bias in parallel studies.

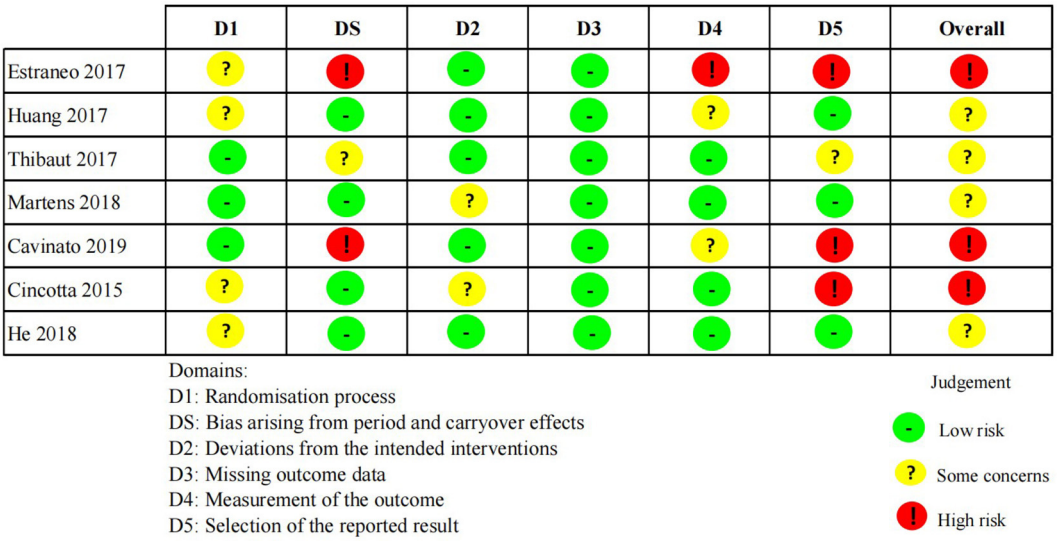

FIGURE 3
The risk of bias in cross-over studies.

To examine the differential effects of confounders, subgroup analyses were conducted. As shown in Table 3, the subgroup analysis by the etiology of DoC revealed that among patients with TBI, tDCS showed a positive and significant effect size on CRS-R (MD 1.09 [95%CI 0.37, 1.82], $p = 0.003$), while patients with CVA had a positive but insignificant effect size (MD 0.53 [95%CI−0.10, 1.163], $p = 0.10$) and patients with HIE only showed a negative and insignificant effect size (MD−0.30 [95%CI−1.50, 0.91], $p = 0.63$).

Factors that showed a significant effect size favoring tDCS include initial level of consciousness among patients with MCS (MD 1.08 [95%CI 0.40, 1.77], $p = 0.004$), subacute phase of DoC (MD 0.97 [95%CI 0.13, 1.81], $p = 0.02$) and DLPFC as the stimulation target (MD 0.92 [95%CI 0.20, 1.64], $p = 0.01$).

As shown in Table 4, the meta-regression analysis showed that none of the between-study variables significantly predicted the effects of tDCS (number of total sessions: $\beta = 0.01$, $p = 0.71$; total stimulation time: $\beta = 0.00$, $p = 0.71$).

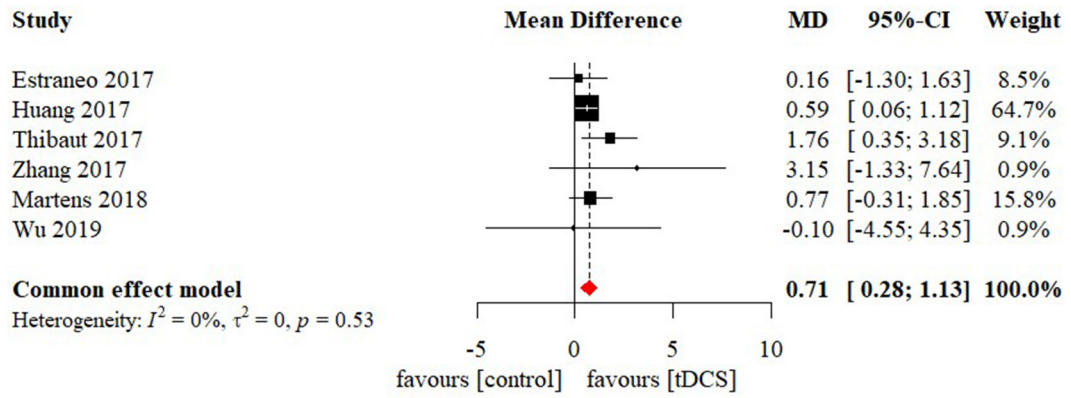

FIGURE 4
Statistical summary and forest plot of effect of tDCS studies. tDCS, transcranial Direct Current Stimulation; MD, mean difference; CI, confidence interval.

TABLE 2 Sensitivity analyses in tDCS and TMS studies.

Studies omitted	MMD	95% CI	*P* value	Weight in total synthesis
tDCS studies				
Estraneo et al. (2017)†	0.76	0.31–1.20	<0.01	8.50%
Huang et al. (2017)	0.92	0.20–1.64	0.01	64.70%
Thibaut et al. (2017)	0.60	0.15–1.05	<0.01	9.10%
Zhang et al. (2017)	0.68	0.25–1.11	<0.01	0.90%
Martens et al. (2018)	0.69	0.23–1.16	<0.01	15.80%
Wu et al. (2019)	0.71	0.28–1.14	<0.01	0.90%
High risks	0.76	0.31–1.20	<0.01	8.50%
TMS studies				
Cincotta et al. (2015)†	1.74	1.11–2.37	<0.01	14.40%
He et al. (2018)	1.59	0.99–2.19	<0.01	6.20%
Zhang et al. (2021)†	1.65	0.82–2.48	<0.01	50.50%
Chen et al. (2022)	1.51	0.87–2.15	<0.01	16.30%
Fan et al. (2022)	1.51	0.88–2.13	<0.01	12.50%
High risks	2.03	1.04–3.02	<0.01	64.90%

† Studies with a high risk of bias.
tDCS, transcranial Direct Current Stimulation; TMS, Transcranial Magnetic Stimulation; MMD, modified mean difference; CI, confidence interval.

Effectiveness of TMS on level of consciousness

Meta-analysis of effectiveness of TMS on CRS-R of five studies was presented in Figure 6. There was a small but significant effect size (MD 1.59 [95% CI 1.01, 2.18], p < 0.01). Non-significant level of heterogeneity (I^2 = 0.0%, p = 0.71) was found. The result was further confirmed by using sensitivity analysis (Table 2). The contour-enhanced funnel plot (Figure 7) with the trim and fill method did not show evidence of reporting bias (MD 1.51 [95% CI 0.96, 2.06], p < 0.01).

To examine the differential effects of confounders, subgroup analyses were conducted. None of the four included TMS studies specified subjects from their etiology, initial level of consciousness, and duration of DoC. Individual patient data related to the above variables could not be extracted either. As a result, subgroup analysis was only conducted for stimulation site. As shown in Table 3, only patients who applied TMS on DLPFC showed a positive and significant effect size (MD 1.75 [95%CI 1.09, 2.40], p < 0.01), while patients who applied TMS on M1 had a small but insignificant effect size (MD 1.01 [95%CI−0.28, 2.30], p = 0.13).

As shown in Table 4, the meta-regression analysis showed that none of the between-study variables significantly predicted the effects of TMS (frequency of stimulation: β = −0.01, p = 0.88; number of sessions: β = 0.01, p = 0.63; number of pulses per session: β = 0.00, p = 0.74; total stimulation number of pulses: β = 0.00, p = 0.80).

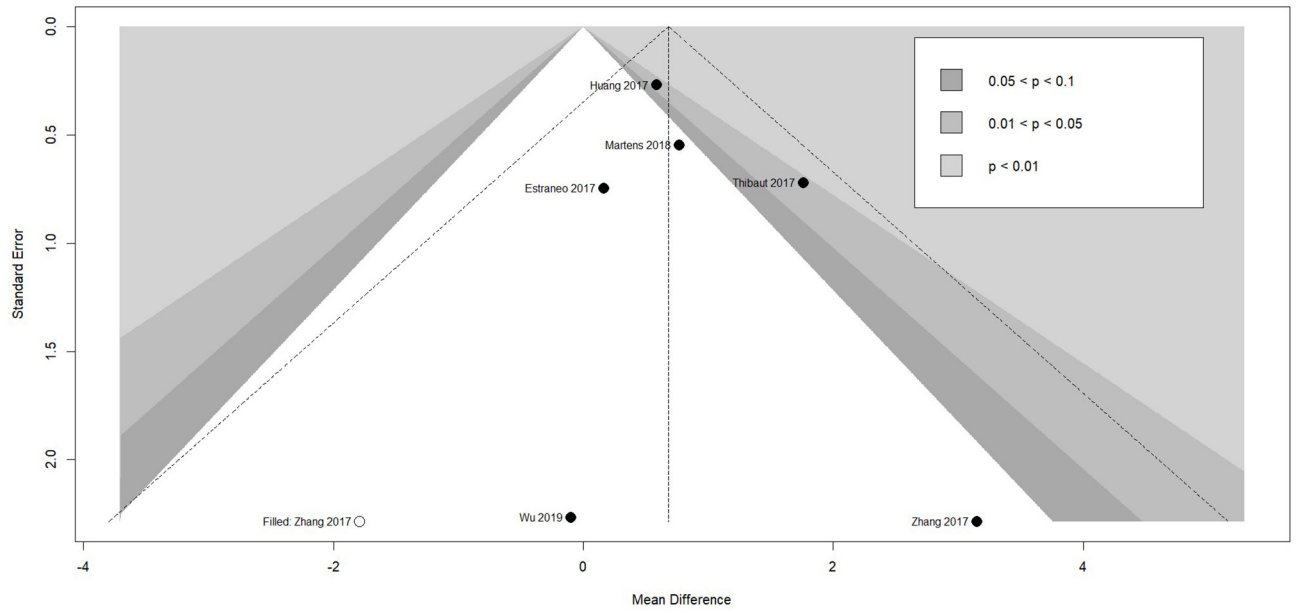

FIGURE 5
Funnel plot of the reporting biases in tDCS studies. tDCS, transcranial Direct Current Stimulation.

TABLE 3 Subgroup analyses for tDCS and TMS studies on CRS-R.

Subgroup analyses	Category	Studies	MD	95% CI	P value	I^2
tDCS studies						
Etiology of DoC	TBI	5	1.09	0.37–1.82	<0.01	21.50%
	CVA	3	0.53	−0.10–1.16	0.10	0.00%
	HIE	3	−0.30	−1.50–0.91	0.63	0.00%
Initial level of consciousness	MCS	6	1.08	0.40–1.77	<0.01	50.30%
	VS/UWS	4	−0.10	−1.45–1.24	0.88	0.00%
Phase of DoC	Subacute	3	0.97	0.13–1.81	0.02	43.90%
	Chronic	6	0.55	−0.03–1.13	0.06	41.80%
Stimulation site	DLPFC	5	0.92	0.20–1.64	0.01	0.00%
	PPC	1	0.59	0.06–1.12	N/A	N/A
TMS studies						
Stimulation site	DLPFC	3	1.75	1.09–2.40	<0.01	0.00%
	M1	2	1.01	−0.28–2.30	0.13	0.00%

tDCS, transcranial Direct Current Stimulation; TMS, Transcranial Magnetic Stimulation; CRS-R, coma recovery scale-revised; MD, mean difference; CI, confidence interval; DoC, disorders of consciousness; TBI, traumatic brain injury; CVA, cerebral vascular accident; HIE, hypoxic-ischemic encephalopathy; MCS, minimally conscious state; VS/UWS, vegetative state/unresponsive wakefulness syndrome; DLPFC, dorsolateral prefrontal cortex; PPC, posterior parietal cortex; M1, primary motor cortex.

Effectiveness of MNS on level of consciousness

Meta-analysis of effects of MNS on GCS was presented in Figure 8. Only two MNS studies were included in the meta-analysis of effects of MNS on GCS. There was a significant effect size in GCS (MD 3.20 [95%CI: 1.45, 4.96], $p < 0.001$) favoring the MNS group. Sensitivity analysis, reporting bias, subgroup analysis, and meta-regression were not conducted due to the limited number of studies.

Discussion

The current study evaluated the effect of NINT on various neurobehavioral or electrophysiological evaluation in patients with DoC. Compared to sham intervention, the synthesized results

TABLE 4 Results from meta-regression analyses examining the effects of stimulation parameters.

Study type/predictor variable	Beta	95% CI	*P* value	I^2
tDCS studies				
Number of total sessions	0.01	−0.06–0.09	0.71	0.00%
Total stimulation time	0.00	−0.01–0.01	0.71	0.00%
TMS studies				
Frequency of stimulation	−0.01	−0.09–0.08	0.88	0.00%
Number of sessions	0.01	−0.03– 0.05	0.63	0.00%
Number of pulses per session	0.00	−0.01–0.01	0.74	0.00%
Total stimulation number of pulses	0.00	−0.01–0.01	0.80	0.00%

CI, confidence interval; tDCS, transcranial Direct Current Stimulation; TMS, Transcranial Magnetic Stimulation.

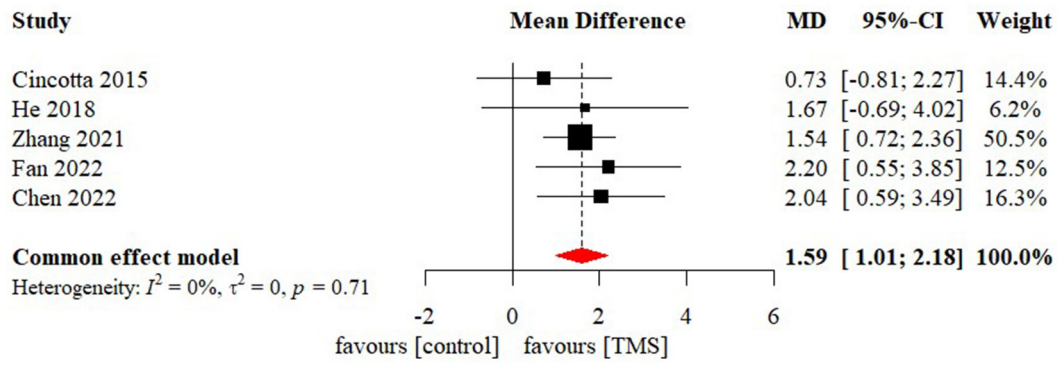

FIGURE 6
Statistical summary and forest plot of effect of TMS studies. TMS, Transcranial Magnetic Stimulation; MD, mean difference; CI, confidence interval.

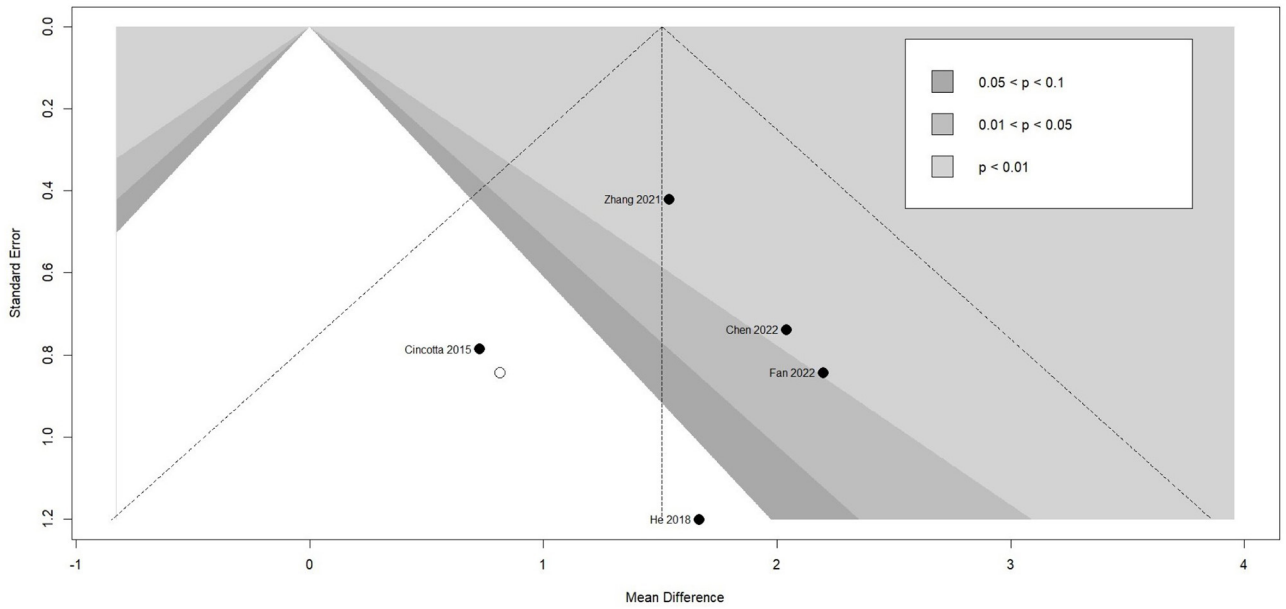

FIGURE 7
Funnel plot of the reporting biases in TMS studies. TMS, Transcranial Magnetic Stimulation.

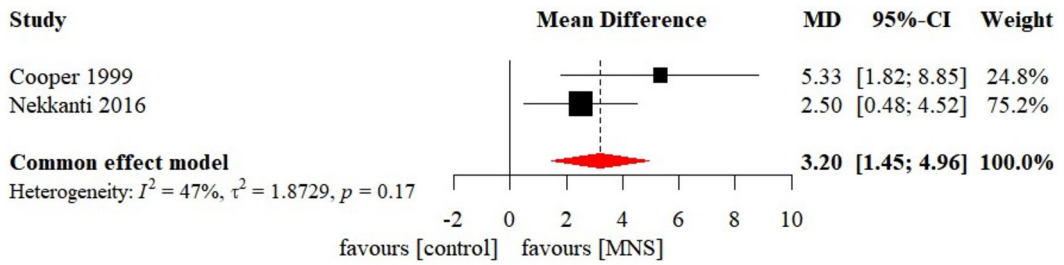

FIGURE 8
Statistical summary and forest plot of effect of MNS studies. MNS, median nerve stimulation; MD, mean difference; CI, confidence interval.

revealed small but significant effects in favor of tDCS, TMS, and MNS. Notably, the mechanisms of recovery of consciousness among different phases of DoC are distinct. Based on the current cellular and circuit hypothesis, the recovery of consciousness depends on the recovery of neural activities of cortex, thalamus, and striatum and the re-emergence of dynamic interactions between multiple cerebral networks, such as the mesocircuit, frontoparietal network, and ascending reticular activating system (ARAS) (Edlow et al., 2021). A common pathophysiological mechanism of coma is widespread impairment of cortical neuronal excitatory activity, which may stem from structural lesions of cerebral cortex and/or insufficient input from the ARAS to the mesocircuit and frontoparietal network (Steriade et al., 1993; Timofeev et al., 2000). With the recovery of condition, patients with coma gradually transition into prolonged DoC (i.e., VS/UWS and MCS), which refers to any DoC that has lasted for more than 4 weeks following sudden brain injury of any cause (Giacino et al., 2018b; Physicians, 2020). The pathophysiology of prolonged DoC is typically characterized by functional recovery of ARAS, whereas the connectivity between functional networks critical for processing intrinsic thoughts and extrinsic stimuli remains disjointed (Steriade, 1996; Silva et al., 2010). In addition, the variability of stimulation parameters across different protocols may also contribute to the difference in awaking effect. Therefore, considering the difference in patients and stimulation parameters of these included studies, the effectiveness of any single intervention cannot be simply extended to the entire population of patients with DoC. This further highlights the necessity to conduct subgroup analysis and meta-regression to explore the optimal characteristics of patients and stimulation parameters.

Effectiveness of tDCS on level of consciousness

The meta-analysis of the effect of tDCS on level of consciousness in patients with prolonged DoC indicated a positive, albeit, small significant effect size. Subgroup analyses revealed that only patients with TBI presented significant improvement in the level of consciousness compared to patients with CVA or HIE. Moreover, we also found that higher initial level of consciousness (MCS) and shorter duration of prolonged DoC (Subacute phase of DoC) may be associated with better clinical awaking effects.

Regarding the stimulation parameter, almost all studies adopt the same stimulation intensity and stimulation time per session. The results of meta-regression also showed a non-significant "dose-dependent" correlation between total stimulation duration and effectiveness. A possible explanation for this might be that the current result was based only on the short-term effects. Whether the benefit of tDCS in long-term effects improves with an increasing number of sessions remains to be discussed in future studies. As for the stimulation sites, five studies selected DLPFC as the anodic stimulation site and only one study selected PPC. As a result, only the effectiveness of tDCS applied on DLPFC could be confirmed. The effectiveness of tDCS applied on other sites remains to be explored.

Compared to previously published reviews (Zaninotto et al., 2019; Feng et al., 2020), our finding was consistent with that of Feng et al. who reported a positive effect of tDCS in patients with MCS. In addition to specific initial level of consciousness of patients, we found that etiology and phase of DoC could be significant factors for effectiveness of tDCS. This finding was also consistent with the current consensus that patients with MCS or TBI had a better prognosis compared to other diagnostic or aetiologic subtypes (Giacino et al., 2018a). Our results, while preliminary, suggested that the above characteristics of patients could contribute to the effectiveness of tDCS.

Effectiveness of TMS on level of consciousness

The meta-analysis of the effect of TMS on level of consciousness in patients with prolonged DoC indicated a small but significant effect size. Regarding the stimulation parameter, the result of meta-regression showed no linear relationship between stimulation frequency, stimulation duration, or number of stimulation pulses and effectiveness. One reason for this result might be that all included studies utilized high-frequency (5–20 Hz) TMS. Similar excitatory effect on the cortex was produced with the long-term potentiation induced by high-frequency stimulation (Pascual-Leone et al., 1994). On the other hand, the absence of "dose-dependent" correlation might also be attributed to the lack of long-term follow-up data. Whether the benefit of TMS in long-term effects improves with an increasing

number of sessions or pulses remains to be discussed in future studies.

Subgroup analysis revealed that only patients who applied TMS on DLPFC presented significant improvement in the level of consciousness compared to patients who applied TMS on M1. Interestingly, this finding was partly consistent with that of Feng et al. A non-significant awaking effect was found by two studies that applied TMS on M1 (Feng et al., 2020). Compared to this previous review, the reason that caused the difference stemmed from three newly included TMS studies in our study. Given the results of subgroup analysis and meta-regression, the main factor for the opposite conclusions might be attributed to the different stimulation sites of TMS. As compared to M1, it seems that TMS has an awaking effect via DLPFC. A possible explanation for this hypothesis could be linked to the function of different cerebral networks. DLPFC, as a critical component of executive control network (ECN), plays a vital role in mediating environmental awareness and repairing the imbalance between the ECN and default mode network (DMN) (Seeley et al., 2007). Therefore, it can be assumed that stimulation of DLPFC could modulate internetwork connectivity between ECN and DMN via salience network and accelerate patients' transition from VS/UWS to MCS. However, this assumption needs to be verified further. Future work is required to determine whether DLPFC is the most optimal stimulation site for TMS.

Effectiveness of MNS on level of consciousness

The meta-analysis of the effect of MNS on level of consciousness in patients with coma indicated a small but significant effect size. Notably, the results should be interpreted cautiously, considering the high risk induced by the limited number of available studies. In contrast to previous studies, one systematic review reported qualitative results and expressed concerns about the effectiveness of MNS (Feller et al., 2021). Currently, the mechanism regarding the awaking effect of MNS remains unclear. One possible mechanism is that MNS enhances ARAS activity by stimulating the locus coeruleus and dorsal raphe nucleus, which represents the origins of the noradrenergic and serotonergic neurotransmitter systems, respectively (Kayama and Koyama, 1998). Whether MNS has an awaking effect in patients with prolonged DoC also lacks evidence from research. Nonetheless, the convenience and economics of MNS allow caregivers to provide beside therapy without the assistance of medical staff. As a result, the effectiveness of MNS on level of consciousness remains to be explored in future studies.

Discernible effects of NINT on level of consciousness

Our finding, while preliminary, further supported the validity of the cellular and circuit mechanism (Edlow et al., 2021). Both central neuromodulation applied on the DLPFC (e.g., tDCS and TMS) and peripheral neuromodulation applied on the median nerve were involved in the reorganization of dynamic interactions between multiple cerebral networks. Notably, as consciousness was dominated by complex cerebral networks, the stimulation of a single neural circuit might not extend to other neural networks. Therefore, compared with the single NINT commonly used in clinical research, whether the combination of multiple neuromodulation therapies can achieve better awaking effects by activating widespread functional connectivity between brain regions remains to be further investigated.

Limitation

Our review cannot be ruled out with limitations. Firstly, although most studies applied assessments other than neurobehavioral evaluation as outcomes, it is difficult to combine these results into synthesis analysis because of their varying collection and analysis methods. Therefore, our meta-analyses were based only on CRS-R and GCS. Secondly, due to few studies reported follow-up results, our finding was only applied to short-term effects. Future studies need to further explore the effectiveness of NINT in long-term awaking effects. Thirdly, limited by the fact that included tDCS studies and TMS studies had only one common outcome, as well as the lack of direct comparison between tDCS and TMS, it is difficult to conduct a network meta-analysis. As a result, it is hard to draw a definite ranking list of the superiority of the two interventions. Finally, although several new studies of NINT such as taVNS, low-intensity focused stimulations (LIFUS), and focused shock wave therapy (F-SWT) have been published in recent years and both have reported encouraging results in awaking therapy (Hesse et al., 2016; Cain et al., 2021, 2022). Most of them are still case series and need further validation through more high-quality randomized controlled trials. Therefore, only tDCS, TMS, and MNS were included in our review.

Conclusion

In light of the findings of this review, based on the limited neurobehavioral outcomes measured by CRS-R or GCS, the existing evidence shows that tDCS and TMS may be advantageous to the recovery of consciousness in patients with prolonged DoC. Etiology of DoC, initial level of consciousness, and phase of DoC could act as significant characteristics of patients related to the effectiveness of tDCS. Stimulation site could act as significant stimulation parameter related to the effectiveness of TMS. In addition, there is limited evidence to suggest that MNS may improve level of consciousness in patients with coma. Considering the convenience and better tolerability, MNS may also have a promising role in awaking therapy in the future. Further research should investigate the optimal parameters and ranking list of different NINT through more high-quality randomized controlled trials.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

XL was responsible for conception and design of the study. ZL and XZ were responsible for data extraction and data analysis and drafted the manuscript. BY and JW were responsible for trial screening. All authors contributed to manuscript revision, read, and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2023.1129254/full#supplementary-material

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Safety and therapeutic effects of personalized transcranial direct current stimulation based on electrical field simulation for prolonged disorders of consciousness: study protocol for a multi-center, double-blind, randomized controlled trial

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Background: Disorders of consciousness (DOC) resulting from acquired brain injury (ABI) increase the mortality rate of patients, complicate rehabilitation, and increase the physical and economic burden that DOC imposes on patients and their families. Thus, treatment to promote early awakening from DOC is vital. Transcranial direct current stimulation (tDCS) has shown great potential for promoting neuro-electrochemical activity. However, previous tDCS studies did not consider structural damage or head and brain lesions, so the applicability of the results to all DOC patients was limited. In this study, to establish a patient-specific tDCS treatment plan considering the brain lesions of and damage sustained by DOC patients, we considered the electric field calculated by a the "finite electric" three-dimensional brain model based on magnetic resonance images. This protocol was developed to aid tDCS treatment of actual patients, and to verify its safety and effectiveness.

Methods/design: Twenty-four patients with DOC after ABI will be enrolled in this cross-over trial. All participants will receive typical rehabilitation combined with sham tDCS and typical rehabilitation plus personalized tDCS (P-tDCS). Each interventional period will last 2weeks (30min/day, 5days/week). The primary outcome [score on the Korean version of the Coma Recovery Scale-Revised

(K-CRS-R)] will be assessed at baseline and the end of the first day of the intervention. Secondary outcomes (K-CRS-R at 1week and 2weeks after experimental session and quantitative EEG changes quantitative electroencephalography changes) will be measured at baseline and the end of week 4. Adverse events will be recorded during each treatment session.

Discussion: For patients with neurological disorders, tDCS has served as a painless, non-invasive, easily applied, and effective therapy for several decades, and there is some evidence that it can improve the level of consciousness of patients with DOC. However, variability in the effects on consciousness among subjects have been reported and personalized strategies are lacking. This protocol is for a randomized controlled trial designed to validate the effectiveness and safety of P-tDCS combined with typical rehabilitation for DOC.

Clinical trial registration: https://cris.nih.go.kr, identifier KCT0007157.

KEYWORDS

non-invasive brain stimulation, DOC, consciousness, transcranial direct current stimulation, neuromodulation, clinical trial, minimal consciousness state, vegetative state

Introduction

Acquired brain injury can result in prolonged disorders of consciousness (DOC) including coma, "unresponsive wake syndrome" (UWS; also called vegetative state [*VS*]) (1) and a minimally conscious state (MCS) (2). Several studies have attempted to determine the effectiveness of brain stimulation techniques, such as deep brain stimulation (DBS) (3), transcranial magnetic stimulation (4), and transcranial direct stimulation (tDCS), for improving the level of consciousness of patients with DOC (5). In particular, tDCS therapy is emerging as a non-invasive treatment, with no side effects such as seizures (6).

tDCS is a form of cortical stimulation in which anode and cathode electrodes are attached to the scalp or forehead and continuous direct current is applied. Several studies have reported that anodal stimulation of the damaged cortical area in DOC patients improves the function of the stimulated area. The dorsolateral prefrontal cortex (DLPFC) is the most important target region to improve consciousness in DOC patients. One study showed that a single session of tDCS over the left DLPFC improved the level of consciousness in 43% of patients in an MCS (7) In a study of UWS and MCS patients, tDCS was used to activate the left DLPFC and restore consciousness, and all MCS patients showed immediate clinical improvement after the tDCS intervention. Patients who received a second tDCS treatment 3 months after the first showed additional clinical improvement and the emergence of consciousness (8). In another study, consciousness was restored in chronic MCS patients through repeated tDCS treatment, and a significant change in the Coma Recovery Scale-Revised (CRS-R) score was seen compared with a sham tDCS treatment. Moreover, recovery of consciousness was maintained for up to 1 week after the end of tDCS treatment (9). tDCS has also been applied in clinical settings, as it can easily be customized by varying the position, size, number, and current of electrodes without any major adverse events.

Several studies have attempted to improve the effectiveness of tDCS for patients with DOC. The retrospective study described above divided patients with DOC into groups that did and did not recover consciousness (9). In that study, left DLPFC tDCS correlated with less metabolic impairment in distant brain regions, as well as in regions presumably stimulated by tDCS. Studies have begun to explore why tDCS treatment is not effective in all patients; differences in the severity of the disability, location or size of the brain lesion, and structural characteristics of the brain around the lesion have all been implicated.

tDCS has emerged as a major research interest. However, studies have only been performed retrospectively; no actual patients have been recruited and personalized tDCS (P-tDCS) has not been performed. Precise modeling and simulation are often precluded by the patient's surgical history, a pre-existing implant device, or a skull defect. Datta (10) performed a simulation study to test the effect of a pre-existing device on the tDCS-induced electrical field and reported no significant interference. We will apply P-tDCS to patients with DOC, with a focus on safety. The goal is to provide evidence that tDCS can be applied as a new treatment method other than medication or existing physical therapy for DOC patients who have been excluded from several previous studies, considering that it may not be safe to receive tDCS treatment due to skull defects or medical history. To achieve that goal, this study will consider the electric field values generated in the target area for consciousness recovery with a simulation-based P-tDCS method and perform a tDCS simulation. This clinical trial aims to develop P-tDCS programs to restore consciousness in DOC patients in a *VS*/UWS or MCS. Sham tDCS will serve as the control. Whether P-tDCS treatment based on brain magnetic resonance imaging (MRI)-optimized tDCS is safer and more effective than sham tDCS will be assessed.

Materials and methods

Trial design

A prospective, randomized placebo-controlled cross-over double-blind multicenter phase 2 feasibility study will be performed (Figure 1;

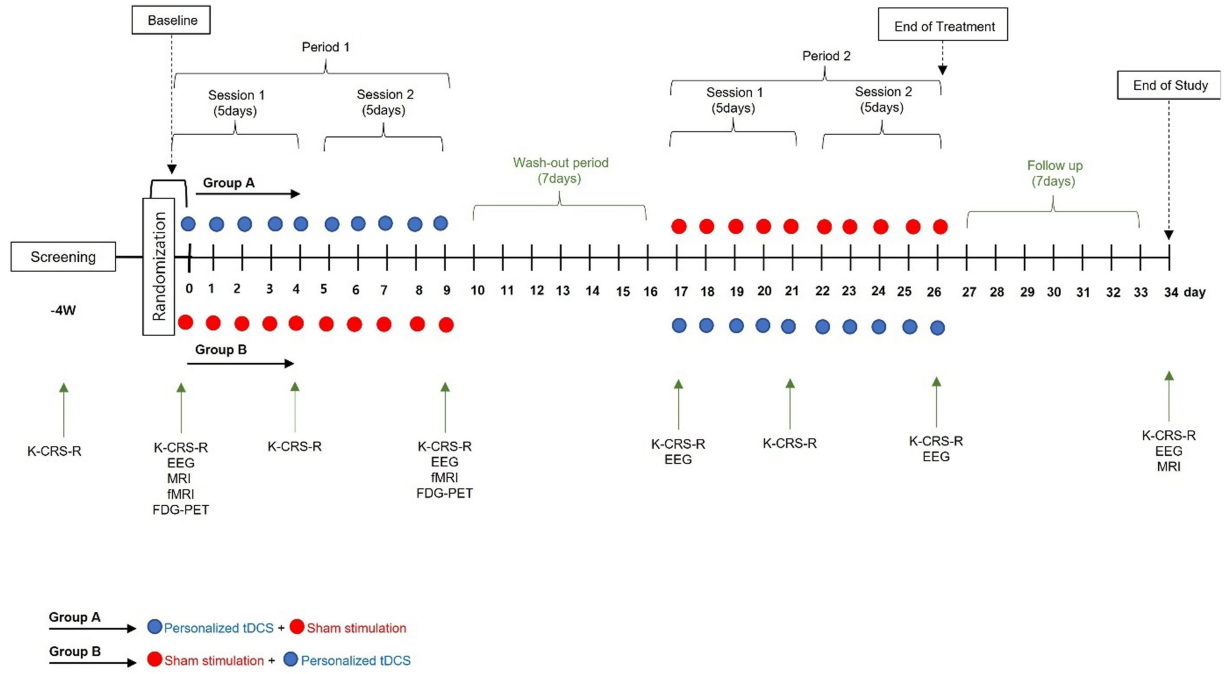

FIGURE 1
The study protocol.

Table 1). P-tDCS will be compared to sham tDCS in patients in a *VS*/UWS or MCS (8, 11). Typical rehabilitation will also be applied, such as physical or occupational therapy for 1–2 h per day (5 days per week). The therapies will be performed passively, i.e., not in a goal-oriented manner, due to the debilitating nature of DOC.

Participants involvement and ethics approval

This protocol was approved by the Korean Ministry of Food and Drug Safety and complied with the ethical standards of the Declaration of Helsinki. The final protocol was approved by the Ethics Review Boards of St. Vincent's Hospital and Bucheon St. Mary's Hospital (Catholic University of Korea; approval number: XC21DDDS0158), as well as the National Traffic Injury Rehabilitation Hospital (approval number: NTRH-21027). Written informed consent will be obtained from each participant's legal guardian.

Recruitment

Participants will be screened and recruited from three hospital in the Republic of Korea: St. Vincent's Hospital, Bucheon St. Mary's Hospital, and the National Traffic Injury Rehabilitation Hospital.

Inclusion and exclusion criteria

The inclusion criteria that will be applied in the study are as follows: aged 19–80 years; acquired brain injury patients diagnosed with *VS*/UWS or MCS based on the results of the Korean version of the Coma Recovery Scale-Revised (K-CRS-R), administered at least twice within 1 week (12); stable, without any change in medication or other treatments for underlying diseases at least 1 week before the screening date, and scheduled to receive medication or treatment during the study period.

The exclusion criteria that will be applied are as follows: alcohol and drug induced change of consciousness; brain tumor; degenerative disease such as Parkinson's syndrome; unable to undergo tDCS due to scalp disease; a pre-existing implant device in the brain or skull with a location corresponding to the tDCS electrode attachment sites; use of a stimulation device similar to the medical devices used in this study within the last 1 year or experience participating in related clinical trials; clinically unstable vital signs; unsuitable for tDCS due to surgery that caused structural changes in the brain (e.g., lobectomy or extensive cranial defects), and a medical condition that may affect consciousness.

Enrollment and randomization

Participants will be assigned a random number at baseline and randomized to either Group A or Group B. As this trial uses a cross-over design, the only difference between the two groups is the order of the intervention [Group A: P-tDCS (period 1), washout period (> 2 weeks), and sham tDCS (period 2); Group B: sham tDCS (period 1), washout period, P-tDCS (period 2)].

All participants will be randomly assigned to the groups at a 1:1 ratio according to the order of registration by the investigator. The statistician for this clinical trial will use the latest version of SAS statistical software (SAS Institute, Cary, NC, USA) to issue random

TABLE 1 Study design.

	Screening	Baseline	Period 1		Outcome	Wash-out period	Period 2		End of study
			Session 1	Session 2			Session 1	Session 2	
Visit	V1	V2	V3 ~ V6	V7 ~ V11	V11	2 weeks	V12 ~ V16	V17 ~ V21	V22
ENROLLMENT									
Informed consent	V								
Eligibility screen	V	V							
Randomized allocation		V							
Taking a clinical photo	V								
MRI-based simulation and planning for tDCS		V							
INTERVENTIONS									
Personalized tDCS Sham-tDCS		V	V	V			V	V	
ASSESSMENTS									
Outcome variables		V							
Vital signs	V	V	V	V	V	V	V	V	V
Physical examination	V	V							
K-CRS-R		V			V				V
EEG		V							V
NCS-R		V	V	V	V	V	V	V	V
MRI, fMRI, and PET scan		V							V
Other variables Adverse events		V	V	V		V	V	V	V

numbers. A stratified block randomization method will be used with a predefined block size; institution will be a stratification factor. Envelopes containing the study numbers will be provided to the "investigational device manager" (IDM) before the participants are registered.

To maintain blinding of the IDM, an unblinded investigator will be assigned to each institution, and will provide the participants with devices according to their group assignments. The unblinded investigators will not participate further in the study.

This parallel randomized controlled trial uses a cross-over design given the clinical needs of the DOC patients. There is no gold standard treatment for DOC, although tDCS may be useful. However, use of tDCS is prohibited in Korea, except in clinical trials, and the treatment options for DOC patients are limited. Benefits of tDCS have been reported in some cases of DOC (13). Because sham group patients would not receive any of the benefits of tDCS due to the parallel study design, a cross-over design is used so that all participants will have the same opportunity to receive tDCS.

tDCS treatment, simulation, and blinding

After being assigned a study number, the IDM will take photographs with a digital camera to determine the condition of the participant's scalp and forehead; redness or burns caused by the medical device will be checked, and changes will be recorded. This process will help minimize side effects. After unblinding, the IDM will select electrode positions based on simulations performed using Neurophet tES Lab (ver. 3.0; Neurophet, Seoul, South Korea); the electrodes will then be attached. P-tDCS will be performed using Neurophet tES Lab; three-dimensional (3D) T1 MRI images of the participants will be imported into the software, brain tissue will be segmented, and a mesh will be generated. Brain tissue will be divided into eight layers: skin, skull, cerebral and cerebellar white matter, gray matter, cerebrospinal fluid, and affected tissue (14). A 3D brain model will be created based on the segmentation and mesh. Points in front of both ears, the nasion, and the inion will serve as landmarks in the brain model, which will be optimized using the software. To optimize the P-tDCS, $5 \times 5\,cm^2$ electrodes will be deployed in a representative area of the left DLPFC, which is the target area for stimulation to recover consciousness. The simulation parameters for determining the optimal electrode position include the initial positions of the anode electrode (F3) and cathode electrode (Fp2), which are based on the international 10–20 electroencephalography (EEG) system. The simulation will begin after inputting these parameters. After completing the simulation, the IDM will check the results and positions of the electrodes, and prepare for the actual tDCS intervention.

tDCS device

The tDCS treatment will be applied using a battery-driven, portable tDCS device (Neurophet innk; Neurophet) and two

sponge-coated $5 \times 5\,cm^2$ electrodes. The stimulation parameters will be set using the bundled software. The parameters in Group A will be as follows: tDCS mode, current intensity of 2 mA, and simulation time of 30 min. In Group B (sham tDCS), the sham mode of the software will be used; the stimulation time will be the same as in Group A, while the current will be increased to 2 mA over the first 30 s and then decreased to 0 mA over the next 30 s (15). The current will then be maintained at 0 mA for the next 28 min, increased to 2 mA over 30 s, and finally decreased to 0 mA over the next 30 s.

The tDCS device can check impedance in real time. If the impedance is >13 kOhm, the stimulation will be stopped and the IDM will check the condition of the patient's skin to prevent adverse events.

Each tDCS intervention will be performed 10 times over 2 weeks. Then, the other tDCS intervention will be performed depending on the group assignment. Any rehabilitation programs in which the participants are enrolled can be continued during the study. The electrode locations will be the same in the sham tDCS and P-tDCS groups.

P-tDCS

The P-tDCS process consisted of four steps: MRI segmentation, 3D brain modeling, personalized tDCS planning based on the simulation of E-field, and the treatment. The whole process is going to be conducted using NEUROPHET tES LAB. All participants undergo baseline MRI scans before enrollment. On MRI scans, if a skull bone defect (such as a burr hole) is detected in patients with a history of surgery, or if an implant such as a cable or coils is found, the principal investigator will discuss it with a neurology and neurosurgery specialist to decide whether the patient can participate in the study. After confirming that, as the first step for planning tDCS, the MR image segmentation will be semi-automatically labeled into eight layers: skin, skull, cerebral and cerebellar white matter, gray matter, cerebrospinal fluid, and affected tissue (14). If a patient has a pre-existing implant, their MRI will be segmented manually based on computed tomography scans and X-rays. The second process is brain modeling. Based on the labeled images and segmented data, a 3D model of tetrahedron meshes is generated. Third, P-tDCS planning is based on the simulation of the E-field. The tDCS-induced E-field in the 3D head and brain model is computationally simulated based on the finite element method (FEM). For computational simulation, the electrical conductivity was assigned to a head and brain tissue; scalp = 0.465, skull = 0.01 CSF = 1.65, ventricle = 1.65, white matter = 0.126, gray matter = 0.276, affected tissue = 0.8087, all in S/m (16) To plan P-tDCS in NEUROPHET tES LAB, the Left DLPFC is localized according to a widely used method, in which F3 on the 10–20 electroencephalogram (EEG) system is selected as the anode placement site (center of anode electrode over F3). The method for the P-tDCS plan is a built-in tES LAB feature to determine the optimized position of an anode electrode among several candidate positions around F3, based on the E-field of the Lt DLPFC region.

Outcomes

K-CRS-R: The CRS is a neurobehavioral assessment instrument used to evaluate the state of consciousness of patients with severe brain injury; it is able to predict the treatment outcome with high accuracy. The CRS-R was released in 2004 and reflects the diagnostic criteria for MCS developed by the Aspen Workgroup in 2002 (2); it is the most effective tool for assessing long-term DOC patients and is recommended by the American Congress of Rehabilitation Medicine (17). The CRS-R distinguishes MCS from *VS* based on six sub-domains (auditory, visual, motor, oral movement/language, communication, and arousal). Total scores range from 0 to 23; higher scores indicate a higher level of function. The validity of the K-CRS-R was established through comparison with the CRS-R (18).

EEG: EEG is a reliable, non-invasive modality to examine the state of consciousness of patients with DOC (18). The spectral power, complexity, and functional connectivity of the theta and alpha bands are related to the state of consciousness, and combining behavioral measures with and EEG is optimal for evaluating the possibility of improving a patient's consciousness. Brain function changes after tDCS will be evaluated in this study *via* power spectral analysis of the brain region of interest. Interactions and connectivity will be evaluated based on the correlations of EEG phase and amplitude (19, 20).

Functional magnetic resonance imaging (fMRI): fMRI can reveal blood flow changes in response to brain activation by various stimuli. An increase in activity in the brain region associated with mental imagery in a patient with a consciousness disorder imagining performing a specific task indicates that the task instructions are being followed. Because it will be difficult to perform fMRI as a routine examination due to the characteristics of the patients in this clinical trial, it will only be used where available as an exploratory analysis.

Fluorodeoxyglucose-positron emission tomography (FDG-PET): PET measures the activity in a brain area within a short period of time. Hypometabolism is particularly severe in the bilateral frontoparietal cortex of patients with long-term unconsciousness, and metabolic recovery in this area is correlated with the recovery of consciousness (21). In this clinical trial, FDG-PET will be conducted only when it is judged as feasible by the investigator and is thus considered as an exploratory endpoint.

Nociception Coma Scale-Revised (NCS-R): The NCS is used to detect pain in patients with impaired consciousness (22, 23). It consists of four subscales that evaluate facial expressions and motor, verbal, and visual responses to noxious stimuli; total scores range from 0 to 12 points. The NCS-R only evaluates motor, verbal, and facial responses, and total scores thus range from 0 to 9 points (24).

Primary and secondary outcomes

The primary outcome will be the change in total K-CRS-R score 2 weeks after the baseline assessment. The secondary outcomes will be changes in the total K-CRS-R score after 1 and 2 weeks, and at the end of the study. Score changes in the auditory, visual, motor, oral motor/linguistic function, communication, and arousal domains will be assessed, along with changes in EEG activity. The exploratory endpoints are fMRI and FDG-PET changes after 2 weeks. The safety endpoints are the NCS-R score, vital signs, and concomitant drug use.

Sample size estimates

The purpose of this study is to validate the feasibility of P-tDCS for consciousness recovery in patients with PDOC. The effect size f of P-tDCS is expected to be at least 0.25 and the power 0.80, so this study should enroll 22 participants, assuming a drop-out rate of 10%, a total of 24 participants will be enrolled, which is G-Power (version 3.1.9.7)

software was used to calculate. The sample size is larger than a previous study of MCS patients (9) and is considered as an appropriate basis for pivotal trial design (25).

Statistical analyses

As stated above, the primary outcome is the change in total K-CRS-R score 2 weeks after the baseline assessment. Repeated-measures analysis of covariance (ANCOVA) will be performed to compare the groups, with the baseline K-CRS-R score included as a covariate. The first secondary outcome to be evaluated will be the change in total K-CRS-R score 1 week after the baseline assessment and at the end of the study. Repeated-measures ANCOVA will be performed to compare the groups, with the baseline K-CRS-R score included as a covariate. The second secondary outcome will be the changes in K-CRS-R subscale scores at 1 week, 2 weeks, and the end of the study compared to the baseline. Repeated-measures ANCOVA will be performed to compare the groups, with the baseline K-CRS-R score included as a covariate. The third secondary outcome will be the changes in EEG 2 weeks after the baseline assessment and at the end of the study. Repeated measures ANCOVA will be performed, with the baseline EEG results included as a covariate. Finally, repeated-measures analysis of variance will be performed to compare the groups at each time point in terms of changes in fMRI and FDG-PET results relative to baseline. Descriptive statistics (mean ± standard deviation and median and range) will be generated for each outcome. A p-value <0.05 will be considered significant.

Discussion

This randomized, multicenter clinical trial will investigate the immediate and delayed effects of tDCS on the level of consciousness and EEG activity of patients with prolonged DOC. Although previous studies have reported improvements in the level of consciousness after applying tDCS to the F3 region of *VS*/UWS and MCS patients, no clear conclusions were drawn due to methodological limitations and differences in effects among studies and individuals. In addition, most previous studies excluded patients with a history of brain surgery. This trial is being performed to overcome these limitations; it is expected to have relatively high internal validity because participants will be randomly assigned to groups, randomization concealment will be implemented, and raters, participants, and the IDM will be blinded.

Although the neurophysiological and electrophysiological effects of tDCS have been confirmed, and safety has been demonstrated (19, 26), its clinical utility remains to be verified. This clinical trial will aim to determine the effects of P-tDCS treatment in UWS and MCS patients, and the role of simulated electric fields. If tDCS can be proven to provide clinical benefits, it could serve as an important treatment for patients with cognitive impairments.

In closing, this trial has been designed to validate the safety and effectiveness of P-tDCS developed based on each participant's T1-weighted MRI scans and the results of simulations. The aim is to determine whether P-tDCS is a viable therapy for DOC patients with a surgical history, skull defects, or pre-existing implantable device. Recently developed simulation technologies and Neurophet tES LAB software will be used to this end; in particular, the latter will be used for segmentation and 3D brain modeling.

Trial status

Recruitment of participants started in May 2022 and will be completed in December 2023. This manuscript reports protocol version 2.1 (December 2, 2022).

Ethics statement

This study protocol was approved by the Korean Ministry of Food and Drug Safety and complies with ethical standard based on the Declaration of Helsinki. Case report forms will be stored where only researchers can access them, and electronic documents are stored with secure, limited access. Data transmission will be encrypted and information that identifies individuals will be removed. The authors plan to disseminate the results in peer reviewed journals and related scientific conferences. The study protocol was approved and reviewed by Institutional Review Board of Catholic University, College of Medicine, St. Vincent's Hospital, Bucheon St. Mary's hospital (approval number: XC21DDDS0158). The study protocol was also approved and reviewed by Institutional Review Board of National Traffic Injury Rehabilitation Hospital (approval number. NTRH-21027). The patients/participants' legal guardians provided their written informed consent to participate in this study.

Author contributions

M-JY, HO, TK, and S-JC: making concept, making protocol, and writing draft. WC, HJ, SuL, YY, HP, BH, and G-YP: making protocol. DK, T-WK, SI, and SeL: making concept, writing draft, review and finalize of draft. TK and DK: funding. All authors contributed to the article and approved the submitted version.

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Conflict of interest

Neurophet Inc. provided the tDCS equipment used for investigational use. DK has equity in Neurophet, Inc. TK is employed by Neurophet, Inc.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Clinical application of recommendations for neurobehavioral assessment in disorders of consciousness: an interdisciplinary approach

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Accurate diagnosis, prognosis, and subsequent rehabilitation care planning for persons with Disorders of Consciousness (DoC) has historically posed a challenge for neurological care professionals. Evidence suggests rates of misdiagnosis may be as high as 40% when informal beside evaluations are used to determine level of consciousness. The presence of myriad medical, neurological, functional (motor, sensory, cognitive) and environmental confounds germane to these conditions complicates behavioral assessment. Achieving diagnostic certainty is elusive but critical to inform care planning, clinical decision making, and prognostication. Standardized neurobehavioral rating scales has been shown to improve accuracy in distinguishing between coma, unresponsive wakefulness syndrome/vegetative state and minimally consciousness state as compared to informal assessment methods. Thus, these scales are currently recommended for use as the informal "gold standard" for diagnostic assessment in DoC. The following paper will present an evidence-based approach to neurobehavioral assessment for use in clinical practice. Strategies for optimizing assessment and aiding in identification and management of confounds that can limit diagnostic accuracy will be provided. Finally, clinical application of an interdisciplinary approach to identifying and managing confounds will be discussed and how assessment results can be used to identify trends in performance and guide prognostic counseling with families.

KEYWORDS

brain injury, consciousness disorders (MeSH), diagnosis, prognosis, assessment practices

Introduction

Impairments in arousal and awareness after severe brain injury are ubiquitous to disorders of consciousness (DoC) which include coma, unresponsive wakefulness syndrome (UWS)/vegetative state (VS), and the minimally conscious state (MCS). MCS is a clinically heterogeneous category; as it is further stratified into MCS plus (+) and MCS minus (−).

MCS+ is applied when observed behavioral responses demonstrate some level of preserved language functioning, as evidenced by the ability to follow commands, discriminate objects, or attempts to communicate (Bruno et al., 2011b; Giacino et al., 2022). Subtle behavioral differences that distinguish between these conditions are not easily detected on informal non-standardized bedside evaluation. For example, the re-emergence of spontaneous eye opening without evidence of purposive behavior is considered the hallmark of transition from coma to UWS/VS, yet even patients in MCS+ may demonstrate poor sustained arousal and highly inconsistent purposive behaviors. Conversely, reflexive vocalizations, eye, and limb movements are all commonly seen in UWS/VS, and may be misinterpreted as purposive responses to stimuli. Expected variability and ambiguity of behavioral responses further complicates the clinical phenotype and limits diagnostic certainty at the individual level. Consequently, informal bedside assessment and team consensus carries a 40% misdiagnosis rate (Schnakers et al., 2009; Wang et al., 2020). The potential consequences of misdiagnosis are great, as one's level of consciousness plays a central role in driving important care decisions such as withdrawal of life sustaining treatments and access to specialty post-acute and rehabilitation services.

This paper will present a structured approach to evidence-based assessment of DoC to apply clinically to improve diagnostic accuracy across the continuum of care. An overview of practice guidelines and program recommendations will be provided, which include the use of standardized neurobehavioral rating scales to reduce diagnostic error. Common confounds germane to DoC will be discussed along with strategies to help address and mitigate their impact on behavior responsiveness and optimize diagnostic certainty. The clinical strategies to neurobehavioral assessment highlighted in this paper were included based on published evidence including the American Academy of Neurology (AAN) DoC Practice Guideline Recommendations (Giacino et al., 2018) and European Academy of Neurology Guidelines for Diagnosis of Coma and DoC (Kondziella et al., 2020) in conjunction with various evidence-informed recommendations such as the American Congress of Rehabilitation Medicine's DoC Minimal Competency Recommendations (Giacino et al., 2020a). Specifically, published Guidelines and Recommendations underwent intensive expert investigation, systematic review, data analysis, application of the Grading Recommendation Assessment, Development and Evaluation (GRADE) process. Additionally, the AAN DoC Guideline development applied the AAN Clinical Practice Guideline Process Manual to direct the methods of creating the 2018 Practice Recommendations.

Abbreviations: AAN, American academy of neurology; CLOCS, Comprehensive Levels of Consciousness Scale; CMD, cognitive motor dissociation; CNC, Coma Near Coma Scale; CRS-R, Coma Recovery Scale-Revised; DoC, disorders of consciousness; DOCS, Disorders of Consciousness Scale; EAU, European academy of neurology; FOUR, Full Outline of UnResponsiveness; GCS, Glasgow Coma Scale; LOEW, Loewenstein Communication Scale; MCS(-), minimally conscious state minus; MCS(+), minimally conscious state plus; NCS-R, Nociception Coma Scale-Revised; RLS85, Swedish Reaction Level Scale-1985; SMART, sensory modality assessment technique; UWS, unresponsive wakefulness syndrome; VS, vegetative state; WHIM, Wessex Head Injury Matrix; WNSSP, Western Neuro Sensory Stimulation Profile.

Neurobehavioral assessment: DoC practice guidelines and recommendations

Published American and European DoC practice guidelines and American minimal competency recommendations for rehabilitation programs support the use of valid and reliable standardized neurobehavioral rating scales as the "gold standard" for assessment of persons with DoC (Giacino et al., 2018, 2020a; Kondziella et al., 2020). Their superior diagnostic accuracy as compared to team-based consensus has been supported through the past published evidence (Schnakers et al., 2009; Wang et al., 2020). Patient performance on these scales can assist in identifying level of consciousness within the DoC spectrum, facilitate detection of diagnostic confounds and guide development of strategies aimed at accessing latent cognition to maximize rehabilitation potential and functional outcomes. Moreover, serial assessments can be used to identify trends in the rate and trajectory of recovery that can help inform prognosis and degree of long term disability (Giacino et al., 2018, 2020a). **Tables 1**, **2** present a complete list of practice guidelines and program recommendations related to diagnostic assessment.

Overview of standardized neurobehavioral assessments for DoC

There are several evidence-supported standardized behavior scales that can be employed in clinical practice, at all levels of care, to aid diagnosis, prognosis and family counseling for DoC. Irrespective of specific scale used, assessment of persons with DoC typically evaluates behavioral responsiveness in the common domains of sensory process and function including: auditory, visual, motor, oral motor, communication and arousal (Kalmar and Giacino, 2005; Pape et al., 2009, 2014; Morrissey et al., 2018). Often responses are graded based on a hierarchy of behaviors that demonstrate neurological functioning at either a brainstem, subcortical or cortical level (Giacino et al., 2022). Seel et al. (2010) conducted a review of available behavioral DoC assessment scales and provided recommendations for use based on the psychometric qualities (validity and reliability) of each scale and other criteria. The Coma Recovery Scale-Revised (CRS-R) was the only tool recommended for clinical use with minor reservations secondary to its strong reliability, validity, standardized administration and scoring procedures, interpretative scoring guidelines, and ease of accessibility for clinicians. Five additional scales were recommended for practice with moderate reservations including the SMART, WNSSP, SSAM, WHIM, and DOCS. One scale, the CNC, was recommended, however, with major reservations. Four scales were specifically not recommended for bedside assessment of DOC due to poor validity, reliability or a lack of standardization. These included the RLS85, LOEW, and CLOCS (Seel et al., 2010). See **Table 3**.

Since the review Seel et al. (2010), the CRS-R has undergone further extensive investigation. Bodien et al. (2016) performed sensitivity and specificity analyses using CRS-R derived diagnoses

to determine that a total cut-off score of eight or higher reliably distinguishes between patients in UWS/VS and MCS in 93% of cases (Bodien et al., 2016). Collective evidence evaluating the utility of the CRS-R, compared to other behavior rating scales, diagnostic modalities, and neurophysiological studies, demonstrates the superiority of the CRS-R as a sensitive and reliable tool to accurately

TABLE 1 American (AAN) and European (EAU) DoC practice guideline recommendations addressing neurobehavioral assessment.

Recommendations to improve diagnostic accuracy	• Use standardized serial assessment deemed reliable by American Congress of Rehabilitation Medicine (See Seel et al., 2010; AAN; Also see **Table 2**).
	• Reassessment intervals dependent upon patient presentation (AAN)
	• Optimize patient arousal prior to assessment, especially when observed to be diminished (AAN)
	• Use of mirror to diagnose visual pursuit (EAN).
	• Observe for spontaneous motor behaviors to diagnose signs of consciousness (EAN).
	• Use of FOUR consciousness assessment in ICU (EAN).
	• Use of CRS-R for consciousness assessment in subacute and ICU (EAU).
Recommendations to mitigate diagnostic confounds	• Use multi-modal assessment tools when bedside assessment results are unclear (AAN).:
	• Utilize serial assessment results to identify and address complications (AAN).
	• Use of PET, FMRI, EEG to identify covert consciousness and differentiate between UWS/MCS (EAN).
Recommendations related to prognosis	• Utilize serial standardized assessment inform prognosis (AAN).
	• Use CRS-R to inform prognosis with non-traumatic vegetative state presentation (AAN).
	• EAU does not provide Guidelines addressing prognosis.

Adapted from Giacino et al. (2018), Kondziella et al. (2020).

TABLE 2 Minimal competency recommendations for programs serving DoC population: recommendations related to neurobehavioral assessment.

Recommendations to improve diagnostic and prognostic accuracy	• Specialized programs should adopt a systematic approach to diagnostic and prognostic assessment. • Protocols should be in place to reduce misdiagnosis and mitigate confounds Validated measures should be used to monitor recovery trajectory from baseline assessment
Recommendations to mitigate diagnostic confounds	• Upon admission, a comprehensive neurosensory exam should be conducted to identify any unidentified auditory, visual, motor or somatosensory deficits Address environmental factors that may influence arousal and patient performance

Adapted from Giacino et al. (2020b).

TABLE 3 Recommended behavioral assessment scales: Pros & Cons comparison of utilization.

Assessment Scale	Pros	Cons	Recommendation of use
CRS-R	• Freely available	• Unstudied prognostic validity	Minor reservations
	• Valid and reliable for VS/MCS/EMCS		
	• Standardized administration and scoring		
	• Reasonable time to administer		
SMART	• Defined administration and scoring	• Requires purchase	Moderate reservations
	• Content validity for VS/MCS/EMCS	• Completion of 5 day training course	
	• 60 min to complete		
WNSSP	• Excellent internal consistency	• Approx. 45 min to administer	Moderate reservations
	• Content validity for VS/MCS/EMCS	• Unproven prognostic validity	
SSAM	• Defined administration and scoring	• Absent diagnostic validity studies	Moderate reservations
	• Reasonable time to administer	• Lacks evidence for test-retest reliability and internal consistency	
	• Content validity for VS/MCS/EMCS		
WHIM	• Defined administration and scoring	• Requires purchase	Moderate reservations
	• Content validity for VS/MCS/EMCS	• Approx. 60 min to administer	
DOCs	• Defined administration and scoring	• Unproven inter-rater reliability and test-retest reliability	Moderate reservations
	• Reasonable time to administer		
	• Acceptable content validity.		

Adapted from Seel et al. (2010).

identify and discriminate among the levels of DoC (Lechinger et al., 2013; Annen et al., 2019; Formisano et al., 2019a; da Conceição Teixeira et al., 2021). Additional evidence focusing on the utility of the CRS-R identifies the benefit of serial use of the CRS-R to improve accuracy of identifying behavioral presentation of DoC (Wannez et al., 2017; Yang et al., 2021). Further evaluation and investigation of the CRS-R has produced development of a CRS-R index to improve total score interpretation and translation of the CRS-R into multiple languages for international use (Lombardi et al., 2007; Tamashiro et al., 2014; Binder et al., 2018; Annen et al., 2019; Zhang et al., 2019). Moreover, research also supports the use of the CRS-R to help inform the trajectory of DoC recovery and prognosis at the individual level (Bodien et al., 2016, 2022; Giacino et al., 2018, 2020a).

Assessment of consciousness in the intensive care unit

Standardized behavior rating scales such as the CRS-R are rarely utilized in the intensive care unit (ICU) for diagnostic assessment of Doc after severe brain injury (Chaturvedi et al., 2021). Time demands imposed by these tools, along with use of sedation, paralytics, mechanical ventilation and movement restricting equipment all serve as practical barriers to the implementation of standardized assessment of consciousness in DoC patients (Chaturvedi et al., 2021). Consequently, physicians in the neurological ICU routinely perform non-standardized bedside evaluations to determine level of consciousness.

The Glasgow Coma Scale (GCS) is the most widely known and utilized tool for assessing brain injury severity and level of coma in ICU/acute care settings due to its feasibility and time efficient implementation required at this level of care (Formisano et al., 2019b; Helbok et al., 2022). However, the GCS is an observational scale and lacks sensitivity to distinguish among different levels of consciousness, and to identify salient features of MCS (−/+) in particular (Bodien et al., 2021). Bodien et al. (2021) compared GCS score combinations to CRS-R scores and found great variability and diagnostic error rates when the GCS is used to identify consciousness. Specifically, they found that GCS total scores did not differentiate among DoC subtypes and that when GCS scoring criteria are used, many persons in MCS were erroneously classified as being "comatose." The Full Outline of UnResponsiveness (FOUR) is an additional neurological assessment implemented in the ICU that is recommended by the European (EU) DoC guidelines for assessment of level of consciousness in the ICU (Kondziella et al., 2020). The EU recommends the use of the FOUR over the GCS in light of its convenience of serial use by clinicians and nurses. Additionally, the FOUR is more sensitive in capturing certain MCS and locked-in syndrome behaviors involving eye movement which decreases the risk of misdiagnosis (Bruno et al., 2011a; Kondziella et al., 2020; Bodien et al., 2021). Although the FOUR is a recommended assessment for this patient population, there are currently efforts underway to develop and validate an abbreviated version of the CRS-R and other standardized rating scales adapted for DoC patients in the ICU (Aubinet et al., 2021; Bodien et al., 2021; Sanz et al., 2021).

Neurobehavioral assessment across care settings: impact of confounds on diagnostic accuracy

Notably, even standardized behavioral rating scales are limited in their ability to differentiate a subset of ICU patients at risk for being misidentified as having a DoC due to the presence of related clinical features such as complete motor paralysis or language impairment (Kondziella et al., 2020). Recent research has found approximately 15–20% of persons classified as having a DoC in the ICU actually have cognitive motor dissociation (CMD), a condition of covert consciousness characterized by the retained capacity for volitional thought in the absence of overt behavioral manifestations or motoric output (Schiff et al., 2005; Owen et al., 2007; Owen and Coleman, 2008). CMD can only be detected with the use of advanced technologies such as functional MRI and electroencephalograph (EEG). These modalities have demonstrated the ability to identify cases of higher-order cortex motor dissociation by eliciting accurate responses to language and music based tasks in persons behaviorally presenting as UWS/VS (Edlow et al., 2017; Claassen et al., 2019; Kondziella et al., 2020; Thibaut et al., 2020). Active and passive paradigms in using fMRI and EEG have demonstrated utility in identifying CMD in behaviorally unresponsive patients. However, it has been found that passive paradigms have a greater likelihood of capturing preserved consciousness (Kondziella et al., 2016; Aubinet et al., 2022). The scientific understanding of CMD is evolving, but current evidence suggests it is likely a distinct phenomenon separate from the DoC spectrum (Kondziella and Stevens, 2022), more akin to a functionally locked-in syndrome. Evidence suggests those who are identified as CMD while in the ICU have an improved functional recovery as compared to those unresponsive patients who demonstrate no evidence of consciousness with advanced neuroimaging (Edlow et al., 2017, 2021). This is a critical issue, given detection of consciousness, or lack thereof, can have significant impact on surrogate decisions regarding withdrawal of care while in ICU (Giacino et al., 2018; Graham et al., 2018; Naci and Owen, 2022; Pruvost-Robieux et al., 2022).

Beyond CMD, persons with DoC present with a wide range of overlying complications and comorbidities that can exacerbate the complexity of the clinical picture (Majerus et al., 2009; Schnakers et al., 2015; Bodien et al., 2022). US practice guidelines recommend that prior to making a final determination regarding level of consciousness, efforts be made to identify and treat confounding conditions that impede accurate diagnosis and directly impact the ability to actively participate and interact with others (Giacino et al., 2018). Similarly, minimal competency recommendations (Giacino et al., 2020b) state that rehabilitation programs should have a protocol in place to detect and treat confounds that can mask evidence of conscious awareness and lead to misdiagnosis. For purposes of the present paper, the authors conceptualize these confounds within three primary categories: medical/neurological issues, overlying functional (motor/sensory/cognitive) impairments, and adverse environmental influences on behavior responsiveness (see **Table 3**). Some confounds may be present in the acute/ICU setting, whereas others may not develop or become apparent until the post-acute setting.

Medical confounds

Patients with DoC are at risk of developing medical complications with a frequency that contributes to high rates of re-hospitalization (Whyte and Nakase-Richardson, 2013). Common medical and neurological confounds include secondary complications such as hydrocephalus, seizures, secondary hemorrhage or intracranial fluid collection, cerebral edema, increased intracranial pressure, infections (pneumonia, urinary tract infections, sepsis), sleep disorders, metabolic/endocrine disturbances and other systemic comorbidities (Ganesh et al., 2013; Whyte and Nakase-Richardson, 2013). The occurrence of one or more medical complications may suppress a person's level of responsiveness during standardized assessment. Additionally, an increased number and frequency of comorbid conditions and complications has been associated with a protracted trajectory of recovery and worse long-term outcomes (Whyte and Nakase-Richardson, 2013).

Functional confounds

Functional confounds include impairments that negatively affect the patient's ability to demonstrate motor output, integrate sensory information, or otherwise provide appropriate responses to test stimuli. Beyond conditions like CMD, common motor confounds to consider include spasticity and joint contracture. Spasticity is a frequent confound that many patients with DoC experience; reported incidence rates are as high as 90% (Martens et al., 2017; Zhang et al., 2021b). Other motor confounds include hemiplegia/hemiparesis, concomitant spinal cord injury, myopathies, neuropathies, dystonia and other central nervous system movement disorders. Sensory and perceptual confounds such as vision, hearing, or other impairments may occur due to damage to the peripheral sensory nerves, cranial nerves, thalamus, primary sensory cortices, or cortico-sensory pathways. Cognitive confounds include overlying aphasia, apraxia, agnosia, problems with higher level auditory or visual processing, as well as disorders of diminished drive and motivation (Lancioni et al., 2010, 2012).

Environmental confounds

Environmental confounds are controllable factors that should be systematically evaluated for their impact on patient arousal and overall level of responsiveness. Sleep-wake cycle and concomitant arousal disturbances are intrinsic to DoC, but can be exacerbated by inappropriate lighting, ambient noise, or the sedating effects of commonly used medications for seizures, pain and spasticity. Other potential variables include conditions such as time of day, patient positioning, and the presence of physical restraints (e.g., splints, casts, braces) that may impede the ability to demonstrate purposive motor responses. In addition, pain and discomfort, extreme room temperature, excessive stimulation, and the presence of distracting or competing stimuli may limit attention capacity and ultimately impact validity and reliability of assessment (Giacino et al., 2020a; Bodien et al., 2022) (see **Table 4**).

Practical strategies for optimizing neurobehavioral assessment across care settings

Interdisciplinary assessment

Effective neurobehavioral assessment begins with an interdisciplinary approach that promotes coordination, collaboration and communication among professionals across care specialties including medical, nursing and rehabilitation. Baseline measures of performance on behavior rating scales should be obtained by multiple disciplines, in different environments at different times of day, and under different conditions to establish trends in arousal and response patterns and aid in comparing and analyzing any scoring inconsistencies. Assessment schedules can become more individualized over time once conditions of optimal arousal and responsiveness are identified. Standardized neurobehavioral assessment can be administered by a variety of care specialists including physicians, neuropsychologists, speech, occupational and physical therapists across the care continuum. A general rule, assessments should be performed by clinicians who have experience working with persons with DoC and received specialized training in the tool being utilized. Findings from a physician survey suggest lack of knowledge and skill are practical

TABLE 4 Common possible confounds seen in DoC population.

Aphonia
Concomitant spinal cord injury
Contractures
Excessive stimulation
Fractures
Hemiplegia/Paresis
Hydrocephalus
Intracranial complications
Illness/Infection
Lighting
Medication side effects
Myopathies
Movement disorders
Neuro-endocrine dysfunction
Neuropathies
Noise
Paroxysmal autonomic hyperactivity
Patient positioning
Presence of restraints
Seizures
Sleep disorders
Spasticity
Temperature
Time of day

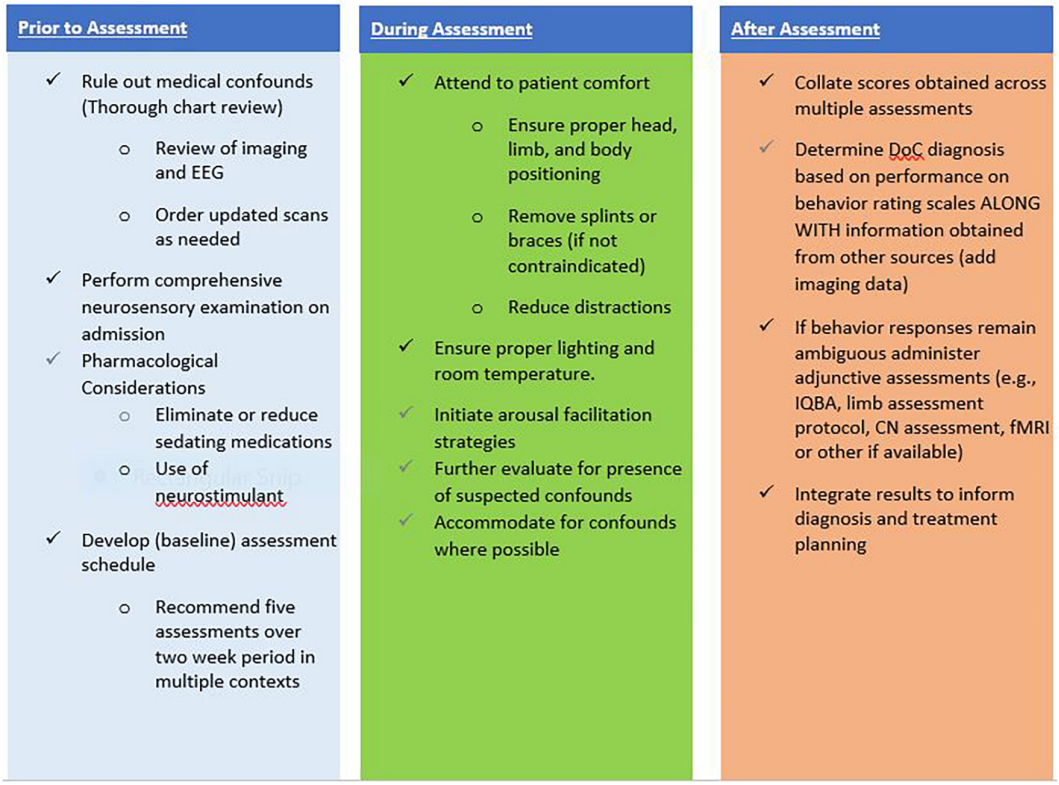

FIGURE 1
Checklist suggested for optimizing neurobehavioral assessment.

difficulties contributing to poor implementation of the CRS-R (Chaturvedi et al., 2021). In contrast, a study by Løvstad et al. (2010) found that increased experience administering the CRS-R increased the reliability of assessment results, emphasizing the importance of providing systematic interdisciplinary education and training in DoC assessment. A staff training curriculum should include an overview of DoC, introduction to neurobehavioral assessment of DoC, and hands-on training to ensure a consistent standard of care and implementation across disciplines (Giacino et al., 2020a). Clinical training and mentorship should also provide clinicians ample opportunities to practice test administration and scoring on a wide range of DoC patients with varying behavioral presentations.

Medical confounds

Promoting medical stability is key to optimizing neurobehavioral assessment. Systematic medical monitoring helps ensure early detection and treatment of comorbidities or complications that may arise (Zhang et al., 2021a). Brain imaging studies, including CT and MRI, should be performed and reviewed on admission to a post-acute setting to screen for potential neurological confounds or complications (Giacino et al., 2020a). Efforts should be made to reduce or eliminate the use of potentially sedating medications where possible at any level of care when standardized neurobehavioral assessment is implemented. Additionally, nursing initiating systematic sleep monitoring can facilitate timely management of sleep wake issues including introducing the strategic use of medications to promote improved nighttime sleep and daytime arousal to optimize assessment (Giacino et al., 2020a; Gottshall and Rossi Sebastiano, 2020). A comprehensive neurosensory examination can identify the presence of previously unrecognized overlying motor, sensory, or cognitive impairments. This may involve testing of reflexes, cranial nerve assessment, and/or the use of sensory evoked potentials to evaluate the integrity of primary sensory systems, peripheral nerves, and to obtain information about cortical signaling and processing (De Salvo et al., 2015). Pain perception may be difficult to identify in persons with DoC, yet pain should be treated for patient comfort (Fins and Bernat, 2018; Giacino et al., 2018). The EU guidelines include a recommendation of the use of the Nociception Coma Scale-Revised (NCS-R) to monitor for signs of pain and discomfort in persons with DoC (Kondziella et al., 2020). The NCS-R is a behavior assessment tool that was developed to assess pain perception in patients with DoC (Schnakers et al., 2010; Chatelle et al., 2012, 2016b) and can be used to aid prompt utilization of pain management strategies.

Functional confounds

Functional confounds may first be suspected during initial assessment by neuropsychology, occupational or speech therapy. Development of adaptation strategies to functional confounds requires collaboration and application across disciplines in

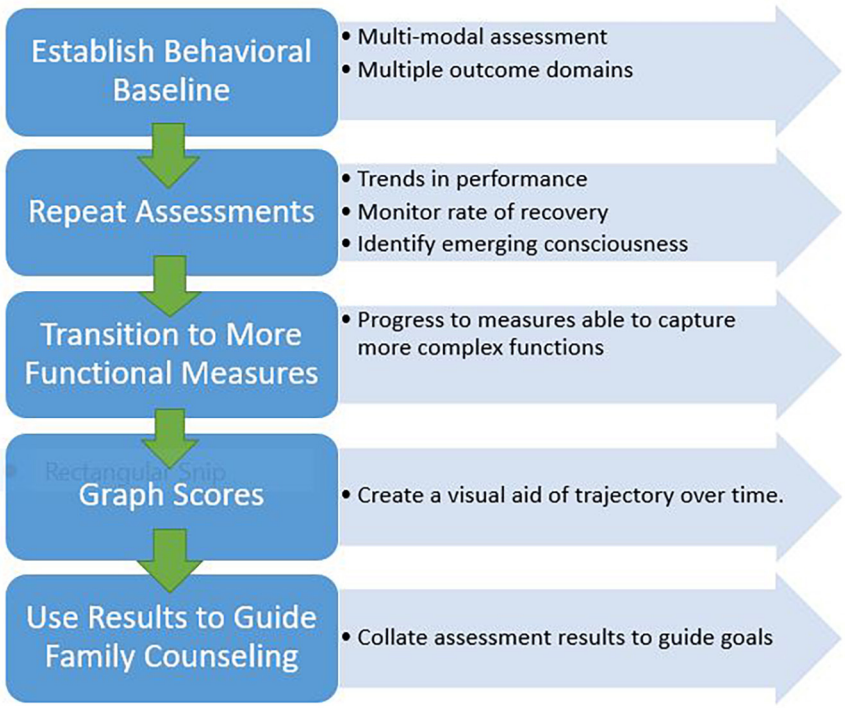

FIGURE 2
Recommended sequential approach to serial assessment application and outcome monitoring.

order to be effective. For example, a combination of nursing, rehabilitation, pharmacologic and surgical interventions may be required to maintain joint integrity and assuage spasticity, pain or contractures to support enough range of motion to elicit active movement. Some motor impairments may benefit from adapting test administration procedures to facilitate the ability to respond. Suspected hemiparesis on the affected side would warrant presentation of stimulus on the unaffected side. Providing proximal support at the elbow to help a person compensate for limb weakness and perform functional object use. Similarly, presenting visual stimuli in a vertical format to one side of a patient's visual field to help accommodate for a gaze deviation, suspected hemispatial neglect, or visual field loss as an adaptation for vision changes. Another common adaptation is determining the best compensatory response mode (e.g., head/mouth control switch or eye gaze) for a person with severe motor limitations, and subsequently implementing an augmentative technology to aid communication and environmental control. Finally, offering increased time to respond may facilitate detection of command following in persons with slow speed of auditory processing, sensory or perceptual impairments, or suspected drive state disorders.

As a supplementary tool, the updated CRS-R manual (Giacino et al., 2020b) includes a test completion coding system to help clinicians identify and characterize factors that may have impacted response validity during any given assessment. These codes allow for the documentation of suspected or known patient specific confounds of the patient as well as extraneous factors that may have affected a patient's score in a specific sub-scale or the total CRS-R score. In addition, Chatelle et al. (2016a) identified nine impossible and 36 improbable CRS-R sub-score combinations that can be used to aid response interpretation and ensure accuracy of obtained CRS-R scores. Each improbable sub-score combination is accompanied by a list of possible contributing factors to consider when scoring errors are ruled out (Chatelle et al., 2016a).

Environmental confounds

Environmental adaptation, based on individual need can enhance the ability to participate with interpersonal interactions. Attempts to increase arousal should be undertaken prior to initiating an assessment and anytime arousal is observed or suspected to be diminished throughout the evaluation (Giacino et al., 2018, 2020a). The CRS-R administration manual includes a structured arousal facilitation protocol that provides a good model for eliciting and promoting sustained arousal during assessment (Kalmar and Giacino, 2005). Prior to initiating the assessment, ensure proper head and limb positioning, remove splints or braces if feasible, and observe the patient for any signs of pain or discomfort. Accommodate for any other potential limiting environmental conditions such as timing of assessment as it relates to medication dosing, lighting, temperature, and noise levels.

Serial assessment

Serial monitoring over time, using recommended neurobehavioral assessment tools, can facilitate early detection of behaviors that may indicate emerging awareness and guide development of individualized rehabilitation strategies. Collated

results from repeat assessments performed over time, can assist in ensuring accuracy of initial diagnosis, monitoring trends in recovery and maximizing detection of the patient's highest level of function over time (Bagnato et al., 2017; Lee et al., 2020; Nekrasova et al., 2021; Bodien et al., 2022). One-time use of standardized neurobehavioral assessment can fail to capture purposive behaviors demonstrated infrequently. Current practice guidelines and recommendations do not specify how often serial examination should be performed. Rather, they state that the frequency of reassessment should be determined based on individual circumstances (e.g., extent of variability in arousal and responsiveness, the presence of confounds), but be sufficient to address individual specific questions of interest (Giacino et al., 2018, 2020a). Emerging research exemplifies how the number of repeated administrations of the CRS-R can significantly influence the clinical diagnosis. Wannez et al. (2017) performed the CRS-R on a sample of 123 patients with chronic DoC at least six times within a 10-day period. They found that diagnoses made based on a single CRS-R led to a misdiagnosis rate of 36% as compared to diagnoses constructed on multiple CRS-R trials. Based on these results, the authors recommend performing at least five assessments within a short time interval (e.g., 2 weeks) to boost diagnostic certainty, even in persons with chronic DoC (Wannez et al., 2017). A similar study by Yang et al. (2021) developed statistical formulas to estimate the probability of positive response with use of the CRS-R in relation to the minimal number of successive examinations. Yang et al. (2021) identified that a minimum of five assessments is needed for patients with non-traumatic DoC and six assessments for traumatic DoC (Yang et al., 2021).

Multimodal assessment

A multimodal approach to assessment should be employed to improve sensitivity and specificity of assessment results, thereby improving diagnostic accuracy (Majerus et al., 2005; Giacino et al., 2006; Owen et al., 2007; Coleman et al., 2009). If available and feasible, the use of advanced technologies can help enhance diagnostic certainty, especially in cases where behavioral responses remain ambiguous or infrequent despite serial behavior assessment, or when confounds to valid assessment are identified (Giacino et al., 2018, 2020a). Functional MRI, positron emission tomography, single photon-emission computed tomography, electroencephalography and evoked potentials have all demonstrated utility in detecting cover evidence of awareness not demonstrated on serial bedside behavior exam such as in cases of CMD mentioned earlier (Edlow et al., 2017, 2021; Claassen et al., 2019; Kondziella et al., 2020; Thibaut et al., 2020). While advances in these technologies hold promise for improving diagnostic certainty, especially in cases of CMD, unfortunately these tools are not readily available for routine clinical use as it stands today. Additional elements of a multimodal approach to neurobehavioral assessment include: results of objective tests, performance on standardized behavior scales, family and staff reports. Individualized Quantitative Behavioral Assessment (IQBA) is an adjunctive assessment strategy that may be helpful in cases where observed behavior and performance on standardized rating scales are ambiguous. IQBA can be used to address specific questions in a standardized manner to assist in identifying and improving confidence in determining level of consciousness (Whyte et al., 1999; Day et al., 2018; Giacino et al., 2020a).

As patients progress through the DoC continuum toward emergence, a range of validated measures should be used to monitor progress across multiple domains (e.g., arousal, mobility, communication, participation). As performance reaches a ceiling on standardized behavior rating scales such as the CRS-R, measures capable of capturing more complex abilities should be employed (Giacino et al., 2020a). Although outside the scope of this paper, there are tools available for assessing agitation, confusion, attention, orientation, language and communication in persons with DoC demonstrating MCS+ or emergence behaviors. These assessments can include the Confusion Assessment Protocol, Agitated Behavior Scale, Orientation Log and the Loewenstein Communication Scale (Bogner et al., 1999; Sherer et al., 2005; Frey et al., 2007; Spiteri et al., 2021; Aubinet et al., 2022). **Figure 1** presents an overview of recommended strategies to optimize the patient and environment to ensure accuracy of assessment results.

Neurobehavioral assessment informing prognosis and guiding family counseling

Serial monitoring over time, using recommended neurobehavioral assessment tools, can facilitate early detection of behaviors that may indicate emerging awareness and thus guide development of individualized rehabilitation strategies. Collated results from repeat assessments can help identify trends in recovery that can inform long-term prognosis for persons with DoC. A compendium of evidence supports the prognostic utility of CRS-R scores and the trajectory of those scores over time to predict recovery of consciousness and functional outcome (Pignat et al., 2016; Portaccio et al., 2018; Annen et al., 2019; Lucca et al., 2019; Hamilton et al., 2020; Boltzmann et al., 2021). Ultimately, when results are to be used to help inform prognosis, serial CRS-R scores must be considered along with other significant factors such as patient age, premorbid conditions, injury comorbidities and severity, frequency of complications and effective acute management (Estraneo et al., 2018; Steppacher et al., 2020; Kowalski et al., 2021; Nekrasova et al., 2021; Siegert et al., 2022). **Figure 2** presents a recommended structured approach to applying serial assessment to outcome monitoring.

Ongoing tracking of scores over time provides objective data that can be used to help guide family education and counseling efforts regarding clinical care decisions and long term care planning. When communicating diagnosis and prognosis with family caregivers, rely on use of simple language that is easy to understand, and provide periodic updates (Giacino et al., 2020a). Counseling should include education about their loved one's behavioral assessment results, information about the assessment tools used and how obtained results relate to expectations for recovery. Presenting a graph of scores on the CRS-R and other measures throughout the course of care is a useful tool to visually demonstrate a person's recovery trajectory and areas of progress (or lack thereof). This approach to counseling is aimed at helping

family caregivers understand their loved one's condition and care needs so they can develop realistic expectations for recovery and collaboratively establish an appropriate short- and long-term plan of care (Giacino et al., 2020a).

Future of DoC assessment

Assessment of Doc is rapidly evolving. As previously mentioned, there are efforts underway to develop and validate consciousness screens and short-form versions of existing scales to facilitate expedient, accurate assessment in critical care settings. Additionally, a valid and reliable DoC assessment in young children is needed. Slomine et al. (2019) have developed the Coma Recovery Scale for Pediatrics (CRS-P) to evaluate DoC in children 12 months and older. The CRS-P is undergoing continued investigation related to strength of psychometric properties and utility of use in the pediatric DoC population (Slomine et al., 2019). Ongoing exploration into ways to expand the use of neuroimaging and electrophysiological technologies to aid detection of consciousness and to identify CMD early post injury is a high priority to better inform medical decision-making (e.g., withdrawal of care) and overall care planning. Brain Computer Interface (BCI) is an additional modality that has been studies extensively as an assessment tool to identify consciousness or CMD through "cerebral communication" (Farisco et al., 2014; Ortner et al., 2017; Wang et al., 2017). BCI is evolving through research and ideally will become a clinical tool feasible for utilization at the bedside. Evaluating the comparative sensitivity, specificity, cost, and overall ease of implementation among these technologies will help direct future efforts to make these tools more accessible. There is a significant need to develop a prognostic algorithm where neurobehavioral assessment results, in combination with evidence-based biomarkers (e.g., neuroimaging, electrophysiological studies, etc.) can be applied to promote diagnostic accuracy and enhance the precision of prognostic estimates to support informed care decisions (Hammond et al., 2021; Mainali et al., 2022; Olson et al., 2022). Finally, operationalizing an interdisciplinary education, training, and mentorship methods can help ensure reliability and validity of assessment results and enhance clinical application of results to guide quality DoC care.

Conclusion

Standardized neurobehavioral assessment is a primary feature of quality DoC care essential to ensuring diagnostic accuracy, appropriate rehabilitation planning, and outcome monitoring. Given the high prevalence of medical, neurological, functional and environmental confounds in persons with DoC, it is imperative to have tools that facilitate accurate bedside assessment of consciousness. Evidence-based neurobehavioral rating scales are widely available and accessible tools for bedside use across the continuum of care. Serial and multimodal assessment can improve diagnostic certainty, identify trends in recovery over time, and guide prognostic counseling with families. As technology continues to advance through future funding and research, the application of multimodal assessment tools will likely continue to evolve and play an increasingly important role in supporting DoC assessment and overall care planning for this population.

Author contributions

BM and AS equally contributed to the development and completion of manuscript content, including review of the literature, manuscript prose, development of tables and figures, and the editing process. They completed the final review of the manuscript together over various virtual meetings and achieved consensus on final manuscript and submission. Both authors contributed to the article and approved the submitted version.

Conflict of interest

AS was employed by Brainmatters Neuropsychological Services, PLLC.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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A protocol for a multicenter randomized and personalized controlled trial using rTMS in patients with disorders of consciousness

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Background: Improving the functional recovery of patients with DoC remains one of the greatest challenges of the field. Different theories exist about the role of the anterior (prefrontal areas) versus posterior (parietal areas) parts of the brain as hotspots for the recovery of consciousness. Repetitive transcranial magnetic stimulation (rTMS) is a powerful non-invasive brain stimulation technique for the treatment of DoC. However, a direct comparison of the effect of TMS treatment on the front versus the back of the brain has yet to be performed. In this study, we aim to assess the short- and long-term effects of frontal and parietal rTMS on DoC recovery and characterize responders phenotypically.

Methods/design: Ninety patients with subacute and prolonged DoC will be included in a two-part multicenter prospective study. In the first phase (randomized controlled trial, RCT), patients will undergo four rTMS sessions in a crossover design over 10 days, targeting (i) the left dorsolateral prefrontal cortex (DLPFC) and (ii) the left angular gyrus (AG), as well as (iii & iv) their sham alternatives. In the second phase (longitudinal personalized trial), patients will receive personalized stimulations for 20 working days targeting the brain area that showed the best results in the RCT and will be randomly assigned to either active or sham intervention. The effects of rTMS on neurobehavioral and neurophysiological functioning in patients with DoC will be evaluated using clinical biomarkers of responsiveness (i.e., the Coma Recovery Scale-Revised; CRS-R), and electrophysiological biomarkers (e.g., power spectra, functional and effective connectivity, perturbational complexity index before and after intervention). Functional long-term outcomes will be assessed at 3 and 6 months post-intervention. Adverse events will be recorded during the treatment phase.

Discussion: This study seeks to identify which brain region (front or back) is best to stimulate for the treatment of patients with DoC using rTMS, and to characterize the neural correlates of its action regarding recovery of consciousness and functional outcome. In addition, we will define the responders' profile based on

patients' characteristics and functional impairments; and develop biomarkers of responsiveness using EEG analysis according to the clinical responsiveness to the treatment.

Clinical Trial Registration: https://clinicaltrials.gov/ct2/show/NCT04401319, Clinicaltrials.gov, n° NCT04401319.

KEYWORDS

coma, vegetative state, unresponsive wakefulness syndrome, minimally conscious state, dorsolateral prefrontal cortex, angular gyrus, non-invasive brain stimulation, treatment

Introduction

Disorders of consciousness

Severe brain injury may result in disorders of consciousness (DoC) (1). Such neurological conditions range from coma (i.e., no wakefulness and reflex behaviors only), to the unresponsive wakefulness syndrome (UWS/*VS*) (i.e., recovery of wakefulness with reflex behaviors) (1), and the minimally conscious state (MCS) (i.e., reproducible and purposeful behaviors, such as visual pursuit and responses to commands) (2). Moreover, MCS can be subcategorized into MCS- and MCS+ depending on the presence or absence of language processing. MCS- patients can show visual fixation and pursuit, localization of noxious stimuli or emotionally contingent behavior, while MCS+ patients show reproducible command-following, intelligible verbalization or intentional communication (2). Patients are thought to have emerged from MCS when they display functional communication or functional use of two objects in two consecutive assessments (3).

Therapeutic options in DoC

In the last decade, few studies have investigated treatment options for patients with DoC (4). Recently, some RCTs have been performed, focusing on pharmacological [e.g., amantadine (5), zolpidem (6)] and non-pharmacological interventions to improve patients' neurobehavioral functioning. Regarding the latter, a recent meta-analysis studying the effect of non-invasive brain stimulation found evidence for left dorsolateral prefrontal cortex (DLPFC) transcranial direct current stimulation efficacy against sham on behavioral measures in MCS patients with low to moderate effect sizes (7).

Among neuromodulation techniques, repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation tool that can modulate cortical excitability, enhance neural plasticity, and induce strong neuromodulatory effects that outlast the period of stimulation (8, 9), especially when applied repeatedly. Thus, it is now established that TMS holds an important role in promoting and monitoring functional recovery in severe brain injury (10). In the field of DoC, some studies have investigated rTMS-induced changes on behavior (11) and electrophysiology (12) or both in patients with severe brain damage (12–17). However, these protocols usually differ in several experimental parameters (e.g., stimulation site, stimulation intensity, number of sessions delivered), making it difficult to draw any conclusion on an effective stimulation protocol at this stage.

To date, most studies have investigated the effects of high-frequency (20 Hz) primary motor cortex stimulation to elicit recovery in DoC patients, showing poor to null clinical improvement at the group level (18–20). However, one RCT comparing the effects of 20 Hz stimulation over the motor cortex and the prefrontal cortex to sham stimulation demonstrated improvement in all groups, but of highest magnitude in the motor cortex group (16).

Regarding other target locations, some RCTs recently reported significant clinical changes in patients (i.e., increased behavioral total scores after intervention) when targeting the left prefrontal regions using multiple sessions (i.e., between 10 to 30 sessions) of high-frequency (i.e., 10–20 Hz) rTMS (21–23).

Eventually, two recent open label studies exploring the effect of rTMS over the left parietal cortex found improved behavioral total scores in MCS patients (24) and even in some UWS/*VS* patients (15). Hence, from these studies, it becomes evident that rTMS is feasible in DoC patients, and that some protocols involving specific target parameters may elicit clinical as well as physiological changes (25), especially in the prefrontal and anterior parietal regions (i.e., DLPFC and angular gyrus, AG). However, to our knowledge, although these two stimulation sites seem relevant, there is currently no study comparing the effect of DLPFC versus AG rTMS in DoC patients.

Consciousness theories to support the role of frontal and parietal rTMS as therapeutic candidates

Despite their indisputable core importance in the dynamic brain processes that are essential in consciousness circuitry, studies trying to isolate the role of frontal versus posterior cortical regions in the emergence of consciousness show contrasting evidence (26). However, it is well established that DoC are caused by widespread dysfunctions preventing the interaction between these areas (27). A common model accounting for post-comatose DoC is the fronto-parietal mesocircuit model (28, 29). This model supports the idea that deafferentation and loss of neurons due to a severe brain injury could induce a reduction of thalamo-cortical and thalamo-striatal functional connectivity from the central thalamus, and consequently, further decreases the activity of the central thalamic and the fronto-parietal networks (30). Figure 1 illustrates the mesocircuit model and the hypothetical changes induced by therapeutic rTMS. Beside this model, the integrated information theory (IIT) postulates that the response of the brain to perturbation needs to be integrated and differentiated – as indexed by the perturbational complexity index (PCI), a proxy for the degree of these

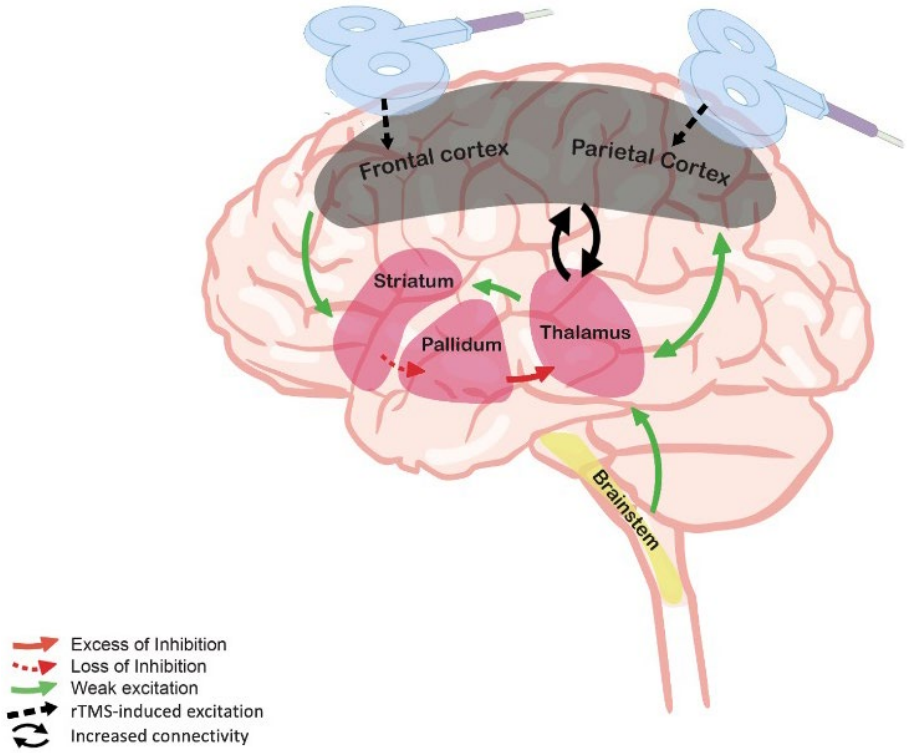

FIGURE 1
Mesocircuit model and rTMS. The deafferentation of thalamostriatal and corticostriatal outflows following widespread neuronal disruption leads to reduced activity of the striatum, resulting in an inhibition of thalamic activity and decreased thalamo-cortical connectivity and cortical activation. By stimulating the frontal or the parietal cortex, rTMS may hypothetically supply for the missing thalamic excitatory inputs through the reestablishment of cortico-subcortical connectivity. Adapted from Giacino et al. (28).

components in response to an external perturbation (31). IIT suggests that the posterior part of the brain is the hotspot of consciousness as an experimental hypothesis (26, 27, 32). In contrast, the global neuronal workspace theory suggests that the hotspot of consciousness is located at the front of the brain, and that consciousness arises from ignition (33, 34). In parallel with their theoretical implications, these different models can also guide therapeutic perspectives aimed at restoring consciousness functioning. Thus, approaches acting over these critical structures could hypothetically restore the loops between the central thalamus, the cortex, the striatum and the globus pallidus interna. The loops within and between frontal and parietal cortex can be indexed by EEG-based functional connectivity (35).

In the light of the above theories, we here propose to investigate the effects of rTMS over the frontal and the parietal areas of the brain to promote recovery of consciousness in patients with DoC. More specifically, we here propose to target the DLPFC, as it is involved in a number of higher-level behaviors and cognitive processes (36, 37) as well as the AG, that occupies a key neuroanatomical position within the parietal structures of the default mode network, a specific network that has been shown to correlate with the level of responsiveness in DoC patients (38, 39).

Study objectives and hypotheses

Although the choice of stimulation site is becoming an increasingly important issue in the neurostimulation community, no clinical RCT has been performed to determine which stimulation site might be associated with the best clinical outcomes after severe brain injury. Hence, this is the study's main objective. In a second phase, we will provide a patient-tailored individualized therapy approach through a personalized medicine design. We aim to (1) improve the functional recovery of patients with DoC using either frontal or parietal rTMS, (2) investigate the neurophysiological effects of rTMS interventions in these two distinct brain areas using resting state electroencephalography (EEG) and TMS-EEG, (3) determine the phenotype of clinical responders (i.e., that is, any patient who displayed new sign(s) of consciousness following stimulation that was never displayed during the screening phase nor at baseline), and (4) assess the long-term efficacy of the rTMS interventions in terms of functional outcomes through follow-up assessments.

Our primary hypothesis for the RCT crossover is that a significant portion of our patient sample will show increased responsiveness (i.e., overall CRS-R scores and signs of consciousness) following a single session of DLPFC or AG rTMS (responders). We also expect some patients to show stronger EEG connectivity at the whole brain level, especially in frontoparietal regions (20) compared to sham stimulation.

As for the second phase of the study, as a primary outcome, we hypothesize that patients stimulated over the left DLPFC or the left AG for 20 consecutive sessions will show higher levels of behavioral improvement compared to patients in the sham stimulation group.

Moreover, as secondary hypotheses, we expect that these changes in responsiveness will be associated with modifications in brain complexity and functional connectivity. We postulate that the EEG

resting state metrics (e.g., spectral power metrics, connectivity) in the frequencies of interest (i.e., delta, theta and alpha bands) and the TMS-EEG derived measures of brain responses (e.g., PCI) will be modulated by the rTMS intervention and associated with behavioral responses to therapy.

As exploratory hypotheses, we also expect that MCS patients will be more likely to respond to the treatment than patients in UWS/VS. We also expect patients who received the active treatment to obtain better outcome at 3 and 6 months following the end of the intervention period compared to the sham group. No adverse event is expected in any of the three study arms.

Methods

Design

This multicenter study consists of two parts: a within-subject, four-arm crossover double-blind RCT and a three-arm parallel double-blind personalized & randomized controlled trial. Both parts will be conducted at the neurological rehabilitation centers William Lennox (Ottignies-Louvain-la-Neuve Belgium), Therapiezentrum Burgau (Burgau, Germany), and Schön Klinik Bad Aibling-Harthausen (Bad Aibling, Germany). A pilot has already been conducted to assess our methods and the protocol as well as our ethical committee have been adapted based on that early testing phase. Therefore, the trial will be preceded by a new pilot phase on a minimum of two patients with the current study design to re-assess feasibility as well as tolerability of our protocol.

Population and recruitment

Ninety patients with DoC after severe brain injury will be included in the study. Written informed consent will be obtained from patients' legal surrogates and the patients themselves if they recover functional communication. The study will be conducted in accordance with the Declaration of Helsinki in its latest form. The study protocol was approved by the University Hospital of Liege Ethics Committee under the reference number 2019/277 (BE021921888) and the Ethics Committee of the Medical Faculty at Ludwig-Maximilians-University Munich under the reference number 20–0873 (Therapiezentrum Burgau and Schön Klinik Bad Aibling-Harthausen) and registered on Clinicaltrials.gov (identifier NCT04401319).

Eligibility will be derived from medical records and clinical visits. Inclusion criteria will be the following: patients with DoC due to acquired brain injury classified according to international guidelines as UWS/*VS* or MCS with at least two repeated behavioral assessments with the CRS-R within 10 days prior to inclusion; ≥ 18 years old; > 28 days post-injury; and stable vital parameters. As for exclusion criteria, they will be the following: no previous neurological deficits prior to the brain lesions; no pregnancy; no contraindication for TMS (e.g., uncontrolled epilepsy, that is, seizure within 4 weeks prior to enrollment, metallic implant in the skull, pacemaker, craniotomy under the stimulated site, peri-ventricular shunting device, sensitive skin); no sedative drugs or drugs thought to interfere with brain stimulation such as Na or Ca channel blockers (e.g., carbamazepine) or NMDA receptor antagonists (e.g., dextromethorphan); no drugs or substances which have strong potential of seizure induction (imipramine, amitriptyline, doxepine, nortriptyline, maprotiline, chlorpromazine, clozapine, foscarnet, ganciclovir, ritonavir, phencyclidine, ketamine, gamma-hydroxybutyrate, alcohol, and theophylline); and no current enrollment in other therapeutic clinical trial for the whole duration of the treatment protocol and follow-up. Patients will still receive all the standard medical and para-medical care from their facilities such as sensory stimulation or physical therapy. Table 1 summarizes all inclusion and exclusion criteria. In the present study, we will not exclude patients with lesions at the stimulation site (i.e., over the DLPFC or the AG) as it will enable us to document if patients with this structural profile show a lower rate of clinical responders compared to patients with healthy brain tissue at the target location.

Procedure

Screening phase & enrollment

The study procedure will start at the earliest on the 28th day post-injury. All patients will be evaluated repeatedly (i.e., at least twice within 10 days prior to inclusion) with the CRS-R to confirm DoC diagnosis before enrollment. Existing CT or MRI-scans will be used to document structural lesions for neuronavigation-based targeting within 28 days before inclusion. Following screening phase, the legal surrogate of each eligible patient will be contacted for oral and written informed consent. After inclusion, every patient will first be enrolled in the crossover RCT protocol and will thus undergo four rTMS sessions. Based on the analysis of the patient's best behavioral or electrophysiological response to either left DLPFC or left AG

TABLE 1 Study inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
• Age ≥ 18 years old	• Previous neurological deficits prior to the brain lesions
• Acquired cerebral damage of known etiology	• Pregnancy
• Diagnosed in UWS/*VS* or MCS as defined by at least two CRS-R assessments performed during the screening period • Time since injury >28 days	• Contra-indication for TMS (e.g., uncontrolled epilepsy, that is, seizure within 4 weeks prior to enrollment, metallic implant in the skull, pacemaker, craniotomy under the stimulated site, implanted brain device)
• Informed consent given by the legal surrogate	• Sedative drugs or drugs thought to interfere with brain stimulation such as Na or Ca channel blockers or NMDA receptor antagonists • Concurrent enrollment in any other therapeutic experimental trial

stimulation, the personalized protocol (4 weeks) will be started up to a week later.

Randomized crossover trial

Within 10 days, all patients will undergo four rTMS sessions that will be administered in a randomized order and separated by a 72 h washout period: (i) one real stimulation over the left DLPFC, (ii) one real stimulation over the left AG, (iii) one sham stimulation over the left DLPFC, and (iv) one sham stimulation over the left AG. In this study, we chose to stimulate the left hemisphere because it tends to be more often targeted in non-invasive brain stimulation trials with DoC patients than the right hemisphere and because it was shown to have more promising results in other top-down electromagnetic-based techniques such as transcranial direct current stimulation (40). Randomization of the sequence of the four stimulation sessions will be stratified for gender, etiology, time post-injury, and diagnosis using computerized random number generator. Standardized behavioral assessments will be performed by experienced clinicians who will be blind to the nature of the sessions. The CRS-R will be performed before and after each stimulation session. Fifteen minutes of resting state high-density EEG will be performed directly before and after the stimulation (i.e., after the behavioral evaluation pre-stimulation and before the behavioral evaluation post-stimulation). Together with the EEG, electrooculogram (EOG) and electrocardiogram (ECG) will be recorded. See Figure 2 for the randomized crossover trial protocol.

Personalized parallel trial

This trial will include three arms (i.e., DLPFC rTMS, AG rTMS and the sham-controlled condition). After a 1 week washout period following the randomized crossover study, the personalized parallel trial will be conducted. Based on their behavioral (primary) or electrophysiological (secondary) responses to either the left DLPFC or left AG treatment in the crossover RCT, patients will be assigned to one of two groups (i.e., DLPFC group if the patient was a responder to the DLPFC stimulation; AG group if the patient was a responder to the AG stimulation). If no behavioral response nor EEG change from the RCT could be obtained regarding the best stimulation hotspot or if the patient is a responder to both sites, the patient will be randomized into one of the two stimulation hotspots in a 1:1 ratio. Then, all patients will be randomized between the experimental condition and the sham condition following a 2:1 ratio by a randomized order generator. Only the investigator in charge of the randomization will be aware of the patients' group allocation. The assigned intervention (i.e., active stimulation versus sham stimulation) will be concealed from the patient, the family, the care providers and all investigators involved in the patient's assessment for the whole duration of the treatment phase. The evaluator will stay blind from the sequence as well as from the stimulation group during treatment and follow-up. Moreover, analyses will be conducted in a triple blind fashion (see *rTMS device* point for more information about blinding methods). All patients included in the trial will undergo 4 weeks (i.e., 20 working days) of stimulation. Behavioral effects will be assessed with the CRS-R at baseline and once a week during the 4 weeks stimulation protocol. Fifteen minutes of high-density EEG resting state will be performed right before and right after the first session as well as before and after the last session. Eventually, TMS-EEG acquisitions will be performed the first and last day of the 4 weeks protocol. As we will assess the effects following a single session (first stimulation session) and after 4 weeks of rTMS, we will be able to compare the effect of a single versus repeated sessions of stimulation. Figure 3 depicts an overview of the two studies.

Assessment of adverse events & follow-up phase

Throughout both trials, all observed adverse events will be reported, described, and graded on a scale from 1 to 5 (1. mild, 2. moderate, 3. severe, 4. life-threatening, and 5. death referred to as severe adverse event). We will evaluate the proportion of patients who had adverse events and confront them with available adverse effect rates reported in the literature. Following the end of the 4 weeks treatment period, all patients will undergo behavioral (i.e., CRS-R) and neurophysiological (i.e., resting-state EEG) assessments 1 and 2 weeks after treatment to monitor immediate aftereffects. At 3 and 6 months timepoints following the end of the treatment, patient's functional outcome will be collected. These evaluations will be carried out by means of structured phone interviews with the patient's relatives/caregivers using the Disability Rating Scale (DRS) (41) and the Glasgow Outcome Scale-Extended (GOS-E) (42).

Instruments

rTMS device

Each stimulation session from the crossover and the longitudinal studies will last 20 min with a frequency of 20 Hz (train duration: 4 s; inter-train interval: 26 s; 3,200 pulses at 120% of the resting motor threshold – RMT, or sham stimulation), adapted from the parameters reported by Legostaeva and colleagues (24) who performed rTMS over the AG in patients with DoC. The RMT (i.e., the minimum stimulus intensity that generated a motor evoked potential response of at least 50 μV at rest for 5 out of 10 trials) will be calculated using single pulses on the corresponding hemisphere of the patient's dominant hand and reported by a visually detectable twitch in the abductor pollicis brevis muscle. The RMT will be determined at the beginning of each week of treatment with a dedicated round coil, to account for potential changes in the RMT. If a patient presents a high degree of spasticity, or is plegic in the dominant hand, or for any other reason resulting in abnormal corticospinal excitability [which has been described in DoC patients (43)], the other hemisphere will be used for RMT assessment as the RMT calculation is not thought to significantly differ from one hemisphere to the other (44, 45). If the RMT assessment is not conclusive at all, we will rely on RMT data in DoC patients arising from Lapitskaya et al. (43). The associated mean value reported in this article as the mean percentage (%) of maximal stimulator output will be used (i.e., 60%). For the rTMS sessions at both sites, a biphasic stimulator with a capacity up to 100 Hz stimulation will be used (DEYMED diagnostic s.r.o., Hronov, Czech Republic). Stimulations will be delivered through a figure-eight coil with active liquid-cooling (at the Belgian recruiting site) or air-cooling (at the German recruiting sites). Depending on the experimental condition, different coils are used: active stimulation will be delivered via an active rTMS coil, whereas sham stimulation will be delivered via a dedicated sham coil, using the very same parameters. This coil uses a particular shielding mechanism so that no vertical magnetic field is induced. In addition to blocking of magnetic field, the construction of the sham coil makes it suitable for double-blind protocols: since the coil looks the same as the active coil, neither the

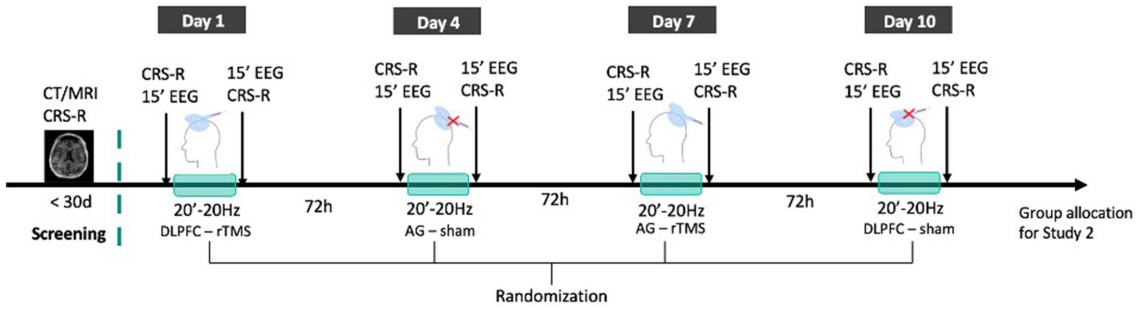

FIGURE 2
rTMS crossover RCT protocol. Patients' state of consciousness will be repeatedly assessed with the CRS-R to confirm DoC diagnosis and existing MRI or CT images will be collected. All patients included will then receive 4 sessions (frontal rTMS; parietal rTMS; frontal sham: parietal sham) of 20 min 20 Hz rTMS administered in a double-blind and randomized order within 10 days and separated by a 72 h washout period. Each session will be directly preceded and followed by CRS-R assessments and 15 min resting state EEG recordings. Patients will then be allocated to one of the groups of Study 2.

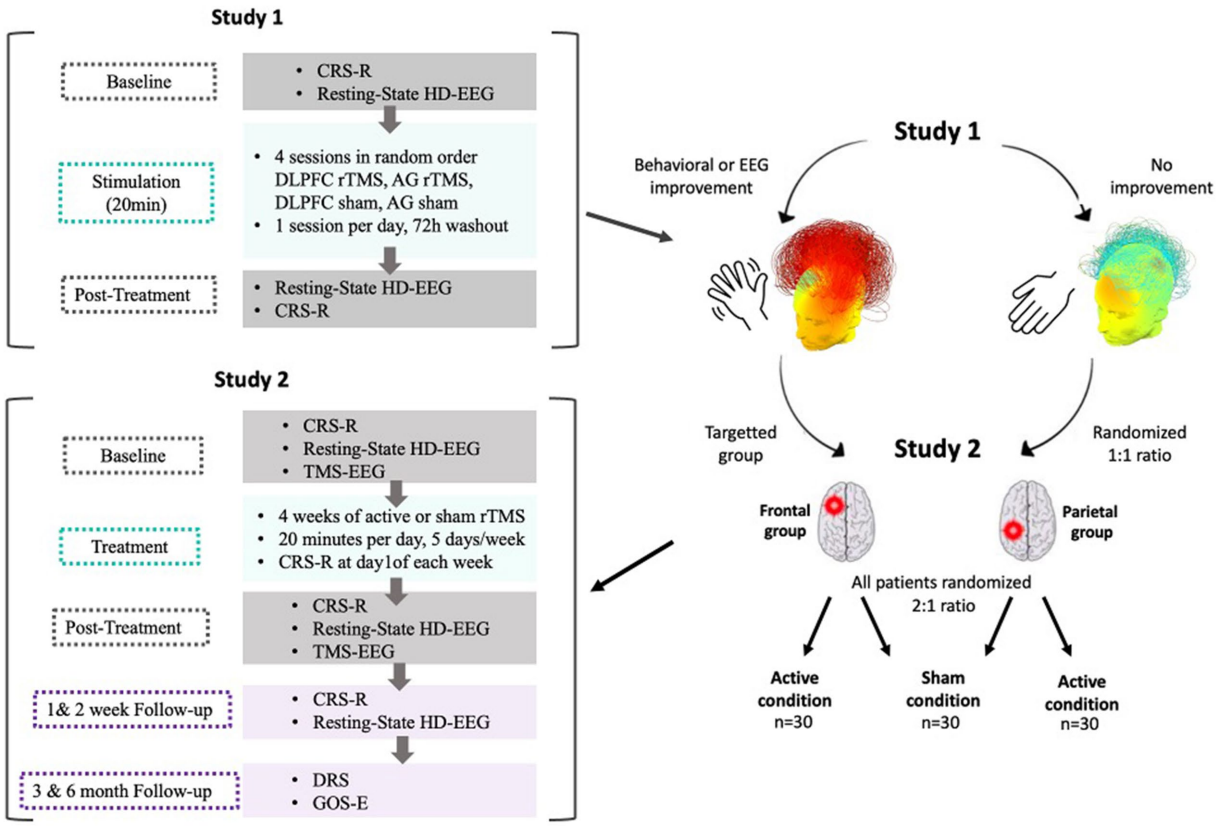

FIGURE 3
Overall protocol overview. After Study 1, patients who showed behavioral or EEG improvements following stimulation (either frontal or parietal) will be attributed to the corresponding group in Study 2. Patients who showed no improvement following either stimulation types will be randomized between the frontal and the parietal stimulation group in a 1:1 ratio. All patients will then be randomized between active and sham conditions in a 2:1 ratio. In Study 2, patients will be randomly assigned to either the active or the sham condition and will receive a longitudinal treatment protocol. The treatment phase will consist of stimulation sessions applied 20 min per day, 5 days a week during 4 weeks for a total of 20 stimulations sessions. Baseline (first day of stimulation, before the session) and post-treatment (last day of stimulation, after the session) assessments will include the CRS-R, 15 min resting state EEG and TMS-EEG to compute PCI. Follow-up measures (CRS-R and resting state EEG) will be collected at +1 and + 2 weeks following the end of the treatment phase. At 3 and 6 months following the end of the treatment phase, functional outcomes will be collected.

experimenter nor the patient can see a difference between the coils. The same applies for the acoustic and sensory effect, as there is no difference in the click sound nor in the somatosensory effects. For blinding purposes, a number will be attributed to each coil by the investigator in charge of the randomization. Only the investigator who generated the number assignment will be aware of the allocation and will then disclose the assigned coil number to the investigator in charge of the stimulation the day of the first session.

Structural MRI scans will be used in the crossover RCT to accurately localize the DLPFC and AG (46), using a neuronavigation system that will be connected to the rTMS device (Polaris Vega ST, NDI, Ontario, Canada). In patients without a structural MRI scan, neuronavigation will be performed using a CT scan. In case neuronavigation is not available (e.g., if CT or MRI images could not be obtained), we will target the stimulation area using the 10–20 EEG system electrode positions. The left DLPFC (BA9) can be reached by placing the coil over F3 while the AG has been reported to correspond to BA39, which is under electrode position P3 (47). The cortical structures normally lie within 2 cm of the positions, resulting in 90% accuracy of hotspot detection (48).

Patients are expected to be awake (eyes open) during the rTMS stimulation sessions. If a patient falls asleep, the stimulations will be paused, and the patient will be aroused by auditory or tactile stimulation first. If the patient is still not opening the eyes, the arousal facilitation protocol will be applied according to the CRS-R guidelines (49). The stimulation will resume when the patient opens the eyes again and stimulation time will be adapted accordingly. The patient's state of arousal will be reported in the Case Report Form for each stimulation session.

Behavioral assessments

The CRS-R consists of 23 items arranged hierarchically and divided into six subscales (auditory, visual, motor, oromotor/verbal, communication, and arousal) that test for arousal and awareness in DoC patients (49). The score is based on the presence or absence of behavior in response to stimuli. The total quantitative score is calculated in addition to the best response observed in each subscale. The diagnosis is based on the nature of the best responses observed overall. To overcome the limitation of overlapping total scores for two different diagnoses, the CRS-R index score will be used as well for statistical purposes (50). The validated version for German and French speaking patients will be used accordingly in the study sites (51, 52). The Disability Rating Scale (DRS) is a tool for the quantitative assessment of the severity of brain injuries. It consists of four categories: arousal and awareness, cognitive abilities, physical and psychosocial independence (41). The Glasgow Outcome Scale – Extended (GOS-E) is an interview tool rating the severity of the cognitive, physical, and psychosocial consequences after severe brain injury in the form of an interview with the primary caregiver. It rates the functionality of the patient from death to complete remission (42).

EEG

High-density resting state EEG will be recorded using a BrainVision device (BrainAmp, BrainProducts, GmbH, Gilching, Germany). EEG signals will be measured in microvolts, sampled at 500 Hz and referenced to the vertex (Cz) using 64-channels TMS-compatible EEG nets. During the 15 min of recordings in Study 1 and 2, patients will be kept awake (e.g., eyes open) by the experimenter. EEG signals are sensitive to movements and DoC patients are often unable to comply with the instruction to stay still during the recordings. Therefore, in case of agitation or heavy artifacts, recording times will be adapted to obtain enough data to perform the analyses. The resting state data will be used to obtain spectral power and brain connectivity using the graph theory, which have proven to correlate with behavioral recovery of patients with DoC (35).

TMS-EEG

The simultaneous use of TMS with EEG implies the perturbation of the brain with a magnetic pulse while recording brain activity electrophysiologically in response to the stimulation. TMS-EEG has become a promising tool in assessing different brain states and functionality (e.g., neural plasticity) over the past two decades (46, 53). The PCI is a mathematical index that expresses the complexity of the brain response to the magnetic perturbation and can successfully discriminate between different brain states (31, 54, 55). In the present protocol, the PCI will be used as a secondary outcome to determine the neurophysiological effects of the 4 weeks rTMS intervention. For TMS-EEG measurements, the coil will be positioned over the premotor area and the precuneus using neuronavigation based on the individual's T1-weighted MRI or CT images. The stimulation will be individualized depending on the brain responses (first peak-to-peak around 10 μV, and 0.4–0.5 Hz frequency). The jittering of the perturbation (2–2.3 s) should avoid patients building up habituation effects regarding the repetitive stimulation. Once a spot has been found to give appropriate responses as displayed by the general user interface of the machine, a total of 300 pulses will be applied per area (i.e., premotor area and precuneus), which results in a protocol duration of approximately 10 min per area. Noise-masking will be applied via in-ear headphones to avoid auditory late cognitive potentials due to the magnetic stimulation. Moreover, if somatosensory artifacts were to be detected, a thin foil would be placed between the coil and the scalp to reduce skin movement induced by the field.

Power calculation

There are currently no RCTs available in the literature simultaneously testing the effects of DLPFC and AG rTMS in patients with DoC. As no clear-cut information could be drawn from the literature, a dedicated power analysis was done using G*Power software (56). Assuming a medium effect size of $f = 0.5$ at an alpha error level of 0.05 and a power of 0.8 with ANOVA or multiple regression analysis, 74 patients need to be recruited to detect meaningful differences in the primary outcome (CRS-R) between the real versus sham stimulation groups. Considering a 20% dropout ratio, the number of patients to be recruited adds up to 90.

Electronic data collection and management

All data collected during this study will be processed and anonymized by an identification number which code will only be known by the researchers involved in the study and will therefore be handled confidentially. Electronic data will be protected by firewall. The researcher in charge will keep the personal data in a file dedicated to the study. All data will be stored and shared between institutions onto Research Space RSpace© – an online secured server providing database security and protection against

malicious use. These case report forms (CRF) will be filled out in print and safely stored in lockers inside the clinic and only accessible to the research staff. Patient data will be pseudonymized in all CRF files. These data will be the subject of presentation and scientific publications, in which the identity of the participating patients will be anonymized.

Data analysis

Primary outcomes

For both crossover and longitudinal trials, primary analyses will focus on the detection of behavioral changes (i.e., enhanced behavioral total scores and/or changes in the level of consciousness as defined by the CRS-R) at the group level, comparing the sham interventions to the active interventions; and at the individual level, comparing post treatment to pre-treatment data. Along the same lines, analyses will also offer a comparison of the effects of frontal and parietal active rTMS on patients' behavioral scores following one session of stimulation for the crossover RCT, and 4 weeks of stimulation for the longitudinal trial. Behavioral CRS-R total scores and subsequent index scores (50) will be defined as our primary outcome. Group treatment effects will be assessed with calculation of the difference between each group post-treatment and pre-treatment score means. Furthermore, we will identify clinical responders to (1) a single session of rTMS in the crossover trial and (2) the 4 weeks treatment protocol of the longitudinal trial as patients who will display new sign(s) of consciousness following treatment that was not present at baseline nor during the screening phase. In that context, further subgroup analyses will also be conducted along age, etiology, time since injury and diagnosis at inclusion.

Secondary outcomes

In the RCT, the change in EEG metrics between post and pre stimulation of each session will be estimated and will stand as our secondary outcome. More specifically, analyses will focus on changes in whole brain connectivity markers as well as on power spectrum for each frequency band and brain response complexity. The alpha-band participation coefficient will be used to determine the response of a patient to the stimulation in the crossover stimulation protocol by means of pre and post stimulation differences. The same metrics will be computed and compared for the longitudinal trial before and after the 4 weeks treatment period. Additionally, for the latter study, TMS-EEG derived PCI will be computed and compared using the same method. TMS-EEG data will be analyzed with EEGLAB,[1] FieldTrip,[2] Brainstorm,[3] MNE-Python[4] and in-house MATLAB (SSP BioMedical Data Analysis Package; SiSyPhus Project; Version 2.5e) and Python scripts. The resting state data will be analyzed with a dedicated analysis pipeline (35). Continuous EEG resting state data will be filtered between 0.5 and 45 Hz and segmented into 10 s epochs. Then, data will be thresholded to remove clear-cut artifacts. EOG and ECG will be used to inform the removal of artifactual data epochs. An independent component analysis (ICA) will be used to remove remaining artefactual components from the EEG signal. Data will be used to compute spectral connectivity in the frontal and parietal areas in the delta, theta and alpha frequencies and expressed in graph theorem-based metrics (e.g., participation coefficient in the alpha band). Further, a set of these graph-theoretic parameters will be extracted from the network analyses and used to train and test a machine-learning model. We will analyze the parameters' capacity to inform and predict treatment outcome independently (univariate regressions) and combined (multivariate pattern analysis and machine learning).

Data analysis will be carried out using RStudio (57). Analyses will be based on means ± standard deviations (SDs) for normally distributed quantitative variables, and as median and interquartile range (P25 – P75) for the skewed distributed variables. Numeric outcomes (e.g., the number of responders to the 4 weeks rTMS programme) will be summarized using count and proportion (%). Results will be considered significant at the 5% critical level ($p < 0.05$) and will be corrected using Holm correction for multiple comparisons. The Cohen's d effect size will be calculated from the difference in means and standard deviations between baseline and post-treatment comparing active with sham interventions.

Dissemination of results

Results of this clinical trial will be published in peer-reviewed open-access journals as original research articles and will be presented at various scientific conferences. The first publication will cover the clinical (CRS-R) and electrophysiological (connectivity markers) results of the RCT. The second publication is planned to report the clinical (CRS-R) and electrophysiological (connectivity markers and PCI) results of the personalized clinical trial and the follow-up period. A third publication is reserved for a detailed description of the machine-learning classifier developed to determine the features of treatment responders.

Discussion

The current state of experimental science and medicine only offers few adequate therapeutic options for patients with prolonged and chronic DoC and their long-term management is becoming a public health concern (4). Moreover, the absence of clear consensus regarding a patients' prognosis coupled with the lack of therapeutic opportunities may play a critical role in medical care decisions having an undeniable impact on patient's survival. Because of these issues, it is crucial that more resources be put in place to further verify the potential effect of new therapies in robust settings and define who they might benefit to the most. In that context, some patients with DoC after severe brain injury can be successfully treated with non-invasive therapeutic interventions (7), among which rTMS seems to be the most effective option (25). However, there is currently a debate on whether recovery is mostly supported by the frontal or the posterior networks and structures (26, 58). While there seems to be evidence for the efficacy of targeting both regions with rTMS in promoting behavioral and/or electrophysiological recovery in patients with DoC (13, 17, 24, 59,

1 https://sccn.ucsd.edu/eeglab/
2 http://www.fieldtriptoolbox.org/
3 https://neuroimage.usc.edu/neuro/BrainStorm
4 https://mne-tools.github.io

60), this protocol describes, to the authors' knowledge, the first study investigating a direct comparison of the frontal versus parietal theories of stimulation hotspots (26). This clinical trial could help to understand which stimulation hotspot for non-invasive brain stimulation with rTMS is best suited for a patient. While the best research designs to support treatment efficacy in a given population are indisputably RCT, it becomes more and more evident that the field of therapeutic management of DoC patients is guided towards the direction of a personalized treatment approach instead of systematic randomization (61–63). Indeed, as described earlier, significant positive results are rarely observed in all DoC patients following non-pharmacological interventions. This suggests that not all patients can benefit from all types of interventions, thus supporting the clinical approach which pays particular attention to each patient characteristics and potential positive response to treatment in order to design a treatment plan. Thus, by positioning itself in that direction, this protocol acts as a major step in the pioneering approach of the development of patient-fitted tailored interventions. Although there is already existing evidence regarding certain endotype markers that may allow for response to brain stimulation treatments, the field is still at its debuts and needs massive joint efforts to provide conclusive guidelines for the clinical setting. In that sense, our personalized approach might help to increase the number of responders as compared to previous RCTs in the literature. Consequently, such increased number of responders will allow us to extract and define a possible phenotype regarding the effectiveness of transcranial magnetic brain stimulation.

The overall goal of this personalized trial is to improve the functional recovery at the clinical level. At the electrophysiological level, this study offers the opportunity to test different models of consciousness: anterior stimulation will allow to study the effect on consciousness recovery (32) according to the fronto-parietal mesocircuit model (28, 29) and the global neuronal workspace theory, suggesting that the hotspot of consciousness is located at the front of the brain (33, 34). Posterior stimulation – on the contrary – will allow for the testing of IIT claiming that the posterior part of the brain is the hotspot of consciousness (26, 27). We will use neurophysiological assessments as well as neurobehavioral exams to test the hypothesis that rTMS can modulate the neural network of the severely injured brain to promote the recovery of both consciousness at the clinical level, and functional thalamocortical network integrity at the neurobiological level. As such, this trial will bring direct evidence to challenge the above-mentioned models and will shed new light on the use of frontal and parietal rTMS as a therapeutic candidate to treat DoC.

A potential pitfall of this protocol might be the challenging timeframe of investigation. Indeed, full completion of the procedure of both trials should add-up to a total of 9 weeks. This is a particularly challenging feature since as we mentioned earlier, DoC patients are a very fragile population prone to complications and management issues. Safety precautions will be taken to avoid potential harm to the patients during the study, especially during the rTMS stimulation sessions, and to allow patients to complete the protocol.

This protocol stands as an important milestone in the development of new patient-tailored therapeutic options in the field of DoC. Our findings could usher in a new era of research for a challenging patient population in desperate need of medical solutions.

Ethics statement

The studies involving human participants were reviewed and approved by University Hospital of Liège Ethics Committee, William Lennox Neurological Hospital Ethics Committee (Belgian identifier B0201941888), Ethics Committee of the medical faculty of the Ludwig-Maximilians-University Munich (identifier 20-0873). The patients/participants will provide their written informed consent to participate in this study.

Author contributions

MV, MR, MN, AB, and OG were involved in conception and methodology design of the study, ethical and trial registration procedures, and manuscript writing. MV, MR, OG, and AB lead the implementation and the coordination of the trials. PC, LW, NL, and AT participated in trial methodology design and provided technical expertise regarding the clinical trial materials and settings. AT, SL, AB, and OG participated in study conception and helped defining its theoretical framework. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Bowel dysfunctions after acquired brain injury: a scoping review

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Bowel dysfunction is a common consequence of neurological diseases and has a major impact on the dignity and quality of life of patients. Evidence on neurogenic bowel is focused on spinal cord injury and multiple sclerosis; few studies have focused on patients with acquired brain injury (ABI). Neurogenic bowel dysfunction is related to a lifelong condition derived from central neurological disease, which further increases disability and social deprivation. The manifestations of neurogenic bowel dysfunction include fecal incontinence and constipation. Almost two out of three patients with central nervous system disorder have bowel impairment. This scoping review aims to comprehend the extent and type of evidence on bowel dysfunction after ABI and present conservative treatment. For this scoping review, the PCC (population, concept, and context) framework was used: patients with ABI and bowel dysfunction; evaluation and treatment; and intensive/extensive rehabilitation path. Ten full-text articles were included in the review. Oral laxatives are the most common treatment. The Functional Independence Measure (FIM) subscale is the most common scale used to assess neurogenic bowel disease (60%), followed by the Rome II and III criteria, and the colon transit time is used to test for constipation; however, no instrumental methods have been used for incontinence. An overlapping between incontinence and constipation, SCI and ABI increase difficulties to manage NBD. The need for a consensus between the rehabilitative and gastroenterological societies on the diagnosis and medical care of NBD.

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KEYWORDS

bowel dysfunction, brain injury, constipation, fecal incontinence, rehabilitation

1. Introduction

Neurogenic bowel dysfunction (NBD) is defined as a loss of voluntary control of bowel function due to central nervous system (CNS) disease (Hinds et al., 1990; Edwards et al., 1992), leading to a spectrum of bowel symptoms, mainly fecal incontinence (FI; Hinds et al., 1990; Harari et al., 2003) and/or constipation (Hinds et al., 1990; Glickman and Kamm, 1996; Stocchi et al., 2000). The CNS plays a key role in gastroenteric control in terms of motor, sensory storage, and excretory functions (Camilleri, 2021). There is a complex and continuous interaction between the CNS and the enteric nervous system (ENS), nervous ganglia present within the gastroenteric wall, mainly through the sympathetic prevertebral ganglia, pelvic, and vagus nerve pathways (Furness et al., 2014). The CNS centers directly control contractile/secretive activity

in the upper gastrointestinal tract, but they are also involved in lower tract motility, blood flow, electrolyte transport by reflex circuits expressed by ENS neurons, and control defecation through spinal cord lumbosacral centers (Furness et al., 2014). Brain control, along with anatomical structures and somatic and visceral peripheral innervation, ensures the physiological function of the anorectal system. Unlike the relatively well studied literature on spinal and peripheral innervation, the cerebral mechanisms regulating anorectal continence are still poorly understood (Bittorf et al., 2006). The rectum serves as a reservoir for solid and liquid feces, as well as gases produced by the small and large intestines, and it must ensure efficient emptying. The smooth and striated muscular sphincteric apparatus ensures fecal continence. The mechanisms of fecal continence and fecal evacuation are partly under the control of the same cerebral structures that ensure urinary continence (Drake et al., 2010).

The physiological sequence, under voluntary control, between filling and emptying depends on the information that reaches the brain from the periphery. Any situation that disrupts the perception, transmission or processing of this information at the cerebral level can lead to dysfunction of the lower intestinal tract (Hinds et al., 1990; Weber et al., 1990; Nakayama et al., 1997; Lotze et al., 2001; Cardozo and Staskin, 2022).

Advancements in imaging have allowed for the development of understanding regarding the cerebral areas responsible for the control of anorectal continence. Rectal distension, a situation comparable to the arrival of fecal bolus caused by a high-amplitude propagated contraction (HAPC; Mertz et al., 2000; Hobday et al., 2001; Lotze et al., 2001; Bernstein et al., 2002; Kern and Shaker, 2002; Verne et al., 2003) evokes bilateral activation of the insula, anterior cingulate gyrus, secondary somatosensory cortex and thalamus. Activation of motor areas (M1, Supplementary Motor Area, and cerebellum) occurs exclusively during anal stimulation and is likely a reflex response to rectal distension, with a latency of approximately 6 s (Lotze et al., 2001). Reflex motor activity forms the basis of passive fecal continence, ensuring the containment of fecal bolus within the rectal ampulla (Lotze et al., 2001). Voluntary contraction of the external anal sphincter activates the motor cortex of the supplementary motor area, as well as the primary somatosensory cortex and insula, if repeated (Kern and Shaker, 2002).

Recent studies have also shown co-activation of cortical areas controlling the external anal sphincter and the control areas of the long flexor of the hallux (Rana et al., 2015). This ability to integrate various functions at the cerebral level, such as continence, lower limb movement, and respiration, demonstrates the complexity of the control systems involved in continence at the brain level and seems to be connected to the need to maintain continence under physiological condition (Hodges et al., 2007; Rana et al., 2015).

The overlap control of intestinal and bladder functions is confirmed by the control pathways in the brainstem and spinal cord, as well as the peripheral innervation provided by the pudendal nerve, which is common to both functions (Mackel, 1979).

There is evidence supporting the concept that a pontine defecation center (analogous to the Pontine Micturition Center – PMC) controls the distal colon, rectum, and internal anal sphincter; the external anal sphincter is controlled by the Pontine Continence Center (PCC), which ensures fecal continence (Holstege and Tan, 1987; Rouzade-Dominguez et al., 2003).

The true distinctive element in the control of intestinal function is the ENS, a network composed of approximately half a million neurons spread in the Meissner's plexus (which regulates intestinal secretions) and the Auerbach's plexus (responsible for the motor activity of the entire intestine; Furness et al., 2014).

This complex neuronal system is capable of integrating, with excitatory or inhibitory functions, all the reflex activity present in the digestive tract, thereby demonstrating its autonomy from both the central nervous system and the peripheral nervous system. This situation allows us to rightly define it as the "brain in the gut" (Lotze et al., 2001; Lamberti and Biroli, 2020).

The alternation between the filling phase and the emptying phase is under the control of the ENS which ensures propulsion in a proximal-distal direction (but also distal-proximal, a fundamental phenomenon for mixing and nutrient absorption; Bazzocchi et al., 1991); the activation of reflex mechanisms underlying propulsion is determined by the intestinal content, thus making its dimensions crucial (Costa et al., 2015). The propulsion of the food bolus and, in the final segment of the intestine, of the fecal bolus, is ultimately the result of the distension of the intestinal wall (Huizinga et al., 2014). Furthermore, a central feature of intestinal function research is the gut microbiota, which contributes to homeostasis in the human body.

The human body hosts a diverse array of microorganisms forming the microbiome, which plays a crucial role in influencing various physiological processes, including brain health and function. Communication between the brain and the gut microbiota happens through multiple pathways and in a bidirectional manner, involving microbial metabolites, the vagus nerve, the endocrine and the immune systems (Carloni and Rescigno, 2023).

The gut microbiota-brain axis is controlled by the systemic circulation, which is provided with various epithelial and vascular barriers, including: gut-vascular barrier (GVB), blood–brain barrier (BBB), choroid plexus vascular barrier (PVB), blood-cerebrospinal fluid barrier (B-CSF) and intestinal epithelial barrier (IEB; Carloni and Rescigno, 2022).

There is an increased interest in secondary enteric inflammatory bowel disease and dysbiosis, which could result in severe ABI induced neuropathology and neurobehavioral deficits. Microbiome and ABI studies have revealed alterations in the composition of gut microbiota following ABI leading to a state of dysbiosis (Hanscom et al., 2021).

Disruption of the gut barrier integrity, leading to increased permeability and consequent translocation of microbial output into circulation, contributes to systemic immune activation and neuroinflammation (Carloni and Rescigno, 2023). Additionally microbial metabolites, as short chain fatty acids (SCFAs) and neurotransmitter precursors have been implicated in neuroprotection and neuronal repair processes following ABI (Hanscom et al., 2021).

Advancing research in the field of microbiome and acute brain injury requires personalized medicine approaches, identification of microbiome based biomarkers, and well designed clinical trials. Ethical considerations and regulatory frameworks must also be addressed to ensure the safe and responsible application of microbiome based interventions. The microbiome plays a critical role in ABI, influencing pathogenesis, neuroinflammation, and therapeutic responses (Arya and Hu, 2018; Hanscom et al., 2021). Exploring the complex interconnections between microbiome and acute brain injury holds promise for the development of innovative diagnostic-tools and targeted treatments. Continued research efforts are needed to unravel the underlying mechanisms and facilitate the translation of findings into clinical practice, ultimately improving outcomes for individuals

affected by ABI. Emerging evidence suggests a relationship between stroke and alterations in the gut microbiota composition (Arya and Hu, 2018; Yamashiro et al., 2021). Dysbiosis may affect stroke outcomes through various mechanisms, including modulation of immune responses, production of metabolites (such as trimethylamine-N-oxide), and disruption of the gut barrier, leading to systemic inflammation. Targeting the microbiome gut-brain axis presents a promising avenue for stroke prevention and management (Yamashiro et al., 2021). CNS damage may result in a loss of voluntary anorectal control (Bharucha and Rao, 2014), with additional social disability for patients (Joan Roach et al., 2000; Camilleri, 2021). Moreover, in patients with ABI, impaired consciousness and memory loss can complicate the assessment of bowel continence (Lim et al., 2012; Emmanuel, 2019). In intensive care units (ICUs), enteral nutrition is associated with diarrhea, one of the most common causes of FI, often a side effect of other treatments (antibiotics, osmolar compounds, and *C. difficile* infection; Reintam Blaser et al., 2015). Drug treatment can also lead to the onset of dysbiosis, which can lead to worse constipation or FI (Weiss and Hennet, 2017). For example, alteration of the gut microbial profile can be caused by using GABA B receptor agonists to treat spasticity (Blackshaw, 2001) or reduction of colon transit time during opioid treatment (Poulsen et al., 2016; Berry et al., 2020).

A broad spectrum of conditions has been extensively studied in NBD epidemiology, including Parkinson's disease (Stocchi et al., 2000; Awad, 2011), multiple sclerosis (Preziosi et al., 2018; Carotenuto et al., 2021), spinal cord injury (SCI; Emmanuel, 2019; Johns et al., 2021), spina bifida (Emmanuel, 2019), stroke (Harari et al., 2003; Li et al., 2017), and cerebral palsy (Wright et al., 2016).

Neurogenic gut has been extensively studied and investigated in SCI (Stiens et al., 1997; Brading and Ramalingam, 2006). The algorithms and protocols for neurogenic bowel management presented in the literature were aimed at patients with SCI and analyzed intestinal dysfunction according to the reflexia/areflexia of the colon (Stiens et al., 1997; Brading and Ramalingam, 2006). However, in recent years, other factors, such as the microbiota and observations of the enteric system itself, have changed the way neurogenic intestinal problems are treated (Hamilton and Sampson, 2022; Valido et al., 2022).

The assessment of NBD includes descriptions of bowel habits preceding injury or neurological disease, bowel diary, and analysis of current symptoms, including stool consistency (e.g., Bristol stool form scale; O'Donnell et al., 1990) and frequency of bowel movements. In addition, episodes of urgency or flatus/FI, time spent toileting, maneuvers required for evacuation (digital anorectal stimulation, splinting), and use of laxatives or drugs can be assessed.

Rating scales, such as the St. Mark's incontinence score and Cleveland Clinic constipation score, may be used to quantify symptoms specifically. The precise NBD score has been improved for spinal cord injury and in children with spina bifida (Emmanuel, 2019).

The most common investigation recommended in NBD was the colon transit time (CTT), an abdominal radiograph obtained after ingesting radiopaque markers on a fixed day. Patients with neurological disorders showed delayed transit. Electrophysiological tests and invasive manometry have also been used; their use may be suitable, especially in the presence of past anorectal surgery, obstetrics-gynecology history, and pelvic organ prolapse (POP). Finally, colon imaging and colonoscopy should be carry out in the existence of "red flag" manifestation or patient >50 years (Emmanuel, 2019).

NBD treatment is mainly based on conservative strategies [dietary modifications, laxatives and anti-diarrheal drugs, and trans anal irrigation (TAI)]; however, surgical strategies can also be used, such as antegrade irrigation according to Malone, stoma formation, and sacral neuromodulation (Emmanuel, 2019).

Despite scarce literature, conservative treatment options have been studied in patients with multiple sclerosis and SCI, including conservative measures such as diet (Spinal Cord Medicine Consortium, 1998), antibiotic drugs (Emmanuel, 2010), and TAI (Hultling, 2020) reaching preliminary evidence.

Due to the scarcity of literature and heterogeneity of existing data on ABI NBD (Coggrave et al., 2014; Valbuena Valecillos et al., 2022), a scoping review was planned. The present scoping review aimed to underline the type and entity of evidence regarding bowel dysfunction after brain injury and to present treatment options (except surgery).

The objectives of this study were to understand the number of bowel symptoms in patients with ABI, map assessment tools used in the evaluation of symptoms, and explore the management options for bowel symptoms.

2. Methods

This scoping review was conducted according to the PRISMA Extension for Scoping Reviews (PRISMA-ScR; Tricco et al., 2018; Peters et al., 2020); the search protocol was recorded in the Open Science Framework on August 16, 2022.[1] Reviewers elaborated on search queries following PCC (population, context, and concept) framework as follows:

- Population: patients with bowel dysfunction following ABI, no filter on the trauma mechanism has been added;
- Context: inpatient/outpatient rehabilitation departments;
- Concept: evaluation and treatment of bowel symptoms.

Our research question was developed to better understand the extent of literature about evaluation and treatment of bowel dysfunction in patients with ABI in rehabilitation settings.

Regarding data collection, no time limits were specified for eligible articles; all quantitative study articles, e.g., randomized controlled trials (RCTs), controlled trials without randomization, pre/post studies, quasi-experimental cohorts, and suspended time-series studies, were included. In addition, analytical observational studies, including analytical cross-sectional studies, case–control studies, and retrospective and prospective cohort studies, will be included. Gray literature articles were also considered suitable for review. The Congress Act and extract of the textbooks were excluded.

2.1. Inclusion criteria

Studies have been carried out in a rehabilitation setting involving adults diagnosed with bowel dysfunction due to ABI.

1 https://doi.org/10.17605/OSF.IO/NEQMA

TABLE 1 PubMed search string.

Domain	Search keywords
Population	Brain injury OR acquired brain injury OR cerebrovascular trauma OR brain injuries, traumatic OR Brain injury OR brain concussion OR Consciousness Disorders OR cognition disorders OR vegetative state OR coma OR unresponsive wakefulness state) AND (neurogenic bowel OR neurogenic bowel dysfunction OR fecal incontinence OR constipation)
Context/Concept	AND (therapeutic use OR physical therapy modalities OR therapy OR Rehabilitation OR assessment, outcome)

2.2. Exclusion criteria

Population: studies involving children, spinal cord injury, multiple sclerosis, stroke, Parkinson's disease and any other conditions determining bowel dysfunction not related to ABI.

Context: home-based rehabilitation setting.

Concept: evaluation/rehabilitation strategies focused on motor/walking function.

2.3. Search strategy and data charting

We searched the following databases Cinhal, Medline (Ovid), Pedro, PubMed, Scopus (Elsevier), Cochrane Library, Web of Science, PROSPERO (NIHR), and sources of unpublished studies/gray literature (open dissertation, clinical trials, Directory of Open Access Journals, and Directory of Open Access Scholarly Resources). For PubMed publications, a specific search string was built, directly derived from PCC, and for other databases, a simple textual search was carried out. The entire search strategy is presented in Table 1. After the removal of duplicates, all data were organized using the Rayyan platform (Ouzzani et al., 2016), an automated online abstraction tool. Two authors (MZ and PS) independently performed the process of evidence screening to obtain at least a double judgment for each article; a first filter by title and abstract was employed. In case of disagreement, a third author (LP) resolved the issue. Includible articles were retrieved in full text for a more in-depth text analysis and the last review round was performed; no critical evaluation was performed on the included articles. A summary data chart was drawn, including all selected articles; for each included article authors and year, sample, intervention and outcome were extracted; the summary of extracted information following the PCC framework was shown in Figure 1.

3. Results

The electronic database search recognized 2,580 plausible studies after elimination of duplication. Following a preparatory examination of keywords, abstracts and titles, 2,432 articles were excluded, and 49 studies were further examined. Although seven studies were not retrieved, 42 studies were checked for eligibility. Based on exclusion criteria, 32 studies were rejected and, finally, 10 full-text articles were included in the review. The publication dates ranged from 2003 to 2022. 1,507 participants were included in the reviewed articles. The most common study model was retrospective 4/10 (40%). A summary of these results is presented in Table 2.

Regarding the population (patients with ABI with bowel dysfunction), the incidence of FI ranged from 41 to 68% during admission to rehabilitation, dropped to 12–36% at discharge, and reached 5% 1 year after discharge. The incidence of constipation ranges from 32 to 41%, with an index at discharge of approximately 20%. Only one study reported a patient with a double diagnosis of SCI and ABI (Valbuena Valecillos et al., 2022).

Regarding the context (inpatient/outpatient rehabilitation departments), most of the studies involved hospitalized patients, and only one study analyzed outpatient ABI (Matsumoto-Miyazaki et al., 2019).

Regarding the concept (evaluation and treatment of bowel symptoms), the analysis used the Functional Independence Measure (FIM) instrumental subscale (60%; Foxx-Orenstein et al., 2003), followed by the Rome II and III criteria, to assess bowel symptoms in patients with ABI. Instead, to map the assessment tools, only two studies have performed CTT to assess constipation (Lim et al., 2012; Enevoldsen et al., 2018). The CTT study correlates constipation with other neurovegetative parameters such as heart rate variation (HVR), lesion site, and slowest colonic transit area. Finally, to examine management alternatives for bowel symptoms, only one study proposed a trial for constipation using acupuncture (Matsumoto-Miyazaki et al., 2019). Oral laxatives have been proposed as the most common treatment. More than 50% of the articles did not propose specific treatments, focusing on the incidence in the population.

4. Discussion

This scoping review distinguished 10 main studies addressing NBD in ABI during rehabilitation. In the management of neurogenic bowel dysfunction, we have to consider the etiopathogenetic mechanisms that contribute to it. There are concurrent alterations in the central nervous system as well as intestinal and microbiota dysfunctions (Carloni and Rescigno, 2023). The gut-brain axis should be understood as a bottom-up interaction: dysbiosis can affect the permeability of the intestinal barrier and, consequently, the blood–brain barrier, leading to processes of cerebral neuroinflammation. However, it should also be understood as a top-down interaction: damage to the CNS system causes oxidative stress and the production of neurotransmitters, which can alter the intestinal bacterial flora (Carloni and Rescigno, 2023). This implies the impossibility of standardizing the extent and type of intestinal dysfunction based on the specific brain localization and the type of damage to the central nervous system. Given the multiple factors involved,

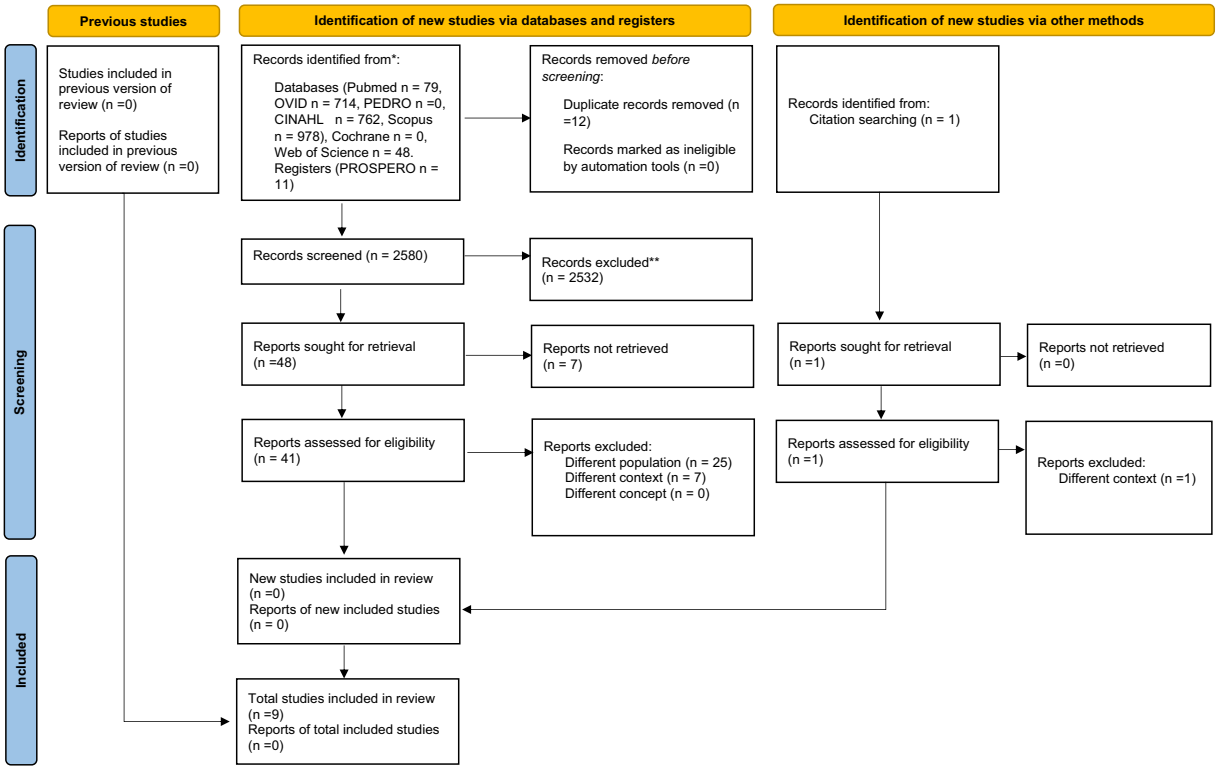

FIGURE 1
PRISMA 2020 flow diagram of updated systematic reviews which included search of database, register, and other sources. *Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers). **If automation tools were used, indicate how many records were excluded by a human and row many were excluded by automation tools. From Page et al. (2021) (for more information, visit: http://www.prisma-statement.org/).

management should be comprehensive and encompass both neurological damage and intestinal dysbiosis, as well as nutritional aspects.

4.1. Clinical assessment

The most common diagnostic method for constipation diagnosis reported in the literature is the ROME II and III criteria (Drossman and Corazziari, 2000; Drossman, 2016). Table 3 highlights the evolution from ROME II to ROME IV criteria (Drossman and Corazziari, 2000; Longstreth et al., 2006; Drossman, 2016). This method, commonly employed for constipation not associated with neurological issues, is utilized and referenced in the majority of identified articles even for ABI.

The instrument used for the clinical assessment of fecal incontinence, on the other hand, is the FIM scale; FIM bowel management subscale less than 5 was considered FI (Foxx-Orenstein et al., 2003), but this was not constantly used in the various authors analyzed. The most common indirect clinical method to assess stool transit was the Bristol scale (O'Donnell et al., 1990; Lewis and Heaton, 1997), that present high reliability (Chumpitazi et al., 2016).

In addition to being a reliable and routinely used tool, also practical to use in the intestinal diary, the Bristol scale could be a simple indirect indicator of potential dysbiosis, as feces vary in shape and color in cases of dysbiosis (Benno et al., 2019).

4.2. Instrumental assessment

CTT was reported as the gold standard for instrumental detection of constipation; however, two protocols, Western (Abrahamsson et al., 1988; Evans et al., 1992) and Asian (Park et al., 2004), were used in clinical practice. Although CTT is a useful tool for constipation, it can only be used in patients without dysphagia due to the shape of the marker. Although CTT was reduced in healthy females (Mugie et al., 2011), no association with sex has been reported in patients with ABI (Dourado et al., 2012; Lim et al., 2012). Despite the absence of an international standardized protocol, CTT has been proposed as a first-level instrumental examination for the assessment of constipation (Arhan et al., 1981). However, future investigations are crucial to test the safety of markers in percutaneous endoscopic gastrostomy to extend examinations in patients with dysphagia.

4.3. Management of NBD

The conservative management of NBD in the literature finds limited evidence; indeed, the 2014 Cochrane review (Coggrave et al., 2014) highlights how techniques for bowel management are supported by scarce evidence. Nevertheless, our findings reported only one RCT, which was based on complementary medicine such as acupuncture (Matsumoto-Miyazaki et al., 2019). In this study, 25 patients with chronic disorders of consciousness were treated for constipation using

TABLE 2 Result.

Authors and year	Number of patients	Diagnosis	Intervention	Main Outcome
Aadal et al. (2019)	76	Incontinence / Constipation	Laxative	Setting inpatient rehabilitation; On admission the incidence of fecal incontinence is 68 and 32% of fecal constipation. 90% received laxatives in the first month. 35% received combinations of laxatives. After 1 month, the use of laxatives persist in 20% of the patients.
Valbuena Valecillos et al. (2022)	SCI + TBI	Neurogenic Bowel Dysfunction	Suppository, digital stimulation	Setting rehabilitation. Dual diagnosis SCI and TBI from 7 to 74.2%. Rehabilitation goals: regularize fecal evacuation, avoid diarrhea and bowel incontinence, and manage autonomic dysfunction.
Lim et al. (2012)	55	Constipation	Colon transit time (CTT)	Setting inpatient rehabilitation. No correlation between localization brain damage and total CTT or constipation score. CTT of the left colon delay in pontine lesions ($p < 0.05$). The constipation group have increased constipation scores and lower Bristol stool form scale, with delay CTT of total, left, and right colon.
Matsumoto-Miyazaki et al. (2019)	25	Constipation	Acupuncture 2\week for 10 weeks	Setting outpatient rehabilitation. Increase defecation 16.7%, reduction of laxative use.
Kushner and Johnson-Greene (2014)	9	Incontinence	/	Setting inpatient rehabilitation. Improvement of cognitive function follows improvement of continence, maybe due to the prefrontal cortex pathway.
Enevoldsen et al. (2018)	25	Constipation	Laxative occasional	Setting inpatient rehabilitation. Patients with mild to moderate ABI have increase CTT but no related to the heart rate variation (HRV)
Foxx-Orenstein et al. (2003)	1,013	Incontinence	/	Setting inpatient rehabilitation. On admission the incidence of fecal incontinence is 68%, drop out to 12.4% at rehabilitation discharge, and 5.2% at 1-year follow-up
Leary et al. (2006)	238	Incontinence	/	Setting inpatient rehabilitation. On admission 50% of patients reduced bladder/bowel FIM sub scores. At discharge, 36% of patients still had impairment. Although more than 90% of patients set goals on self-care and mobility, only 3.5% patients set goals regarding bladder and bowel function.
New Zealand Guidelines Group (2006)	/	Constipation	/	Recommendations: "verify sufficient fluid intake; use natural laxatives/simple bulk laxatives; perform exercise and standing. Prevent medications reducing gut motility. Increase privacy and comfort during defecation; maintain evacuation routine in a sitting up. If rectum is full, a daily rectal stimulation can be used; if the rectum is empty for 3 days running, the use of an osmotic laxative/ stimulant can be evaluated."
Dourado et al. (2012)	66	Constipation/ Incontinence	/	Setting inpatient rehabilitation. Prevalence of constipation 27%, fecal incontinence (FI) 24%. IF associated with motor, communicator and memory impairment.

acupuncture sessions twice a week for 10 weeks. There was an increase in defecation frequency from three to 3.5 times a week ($p < 0.05$), with a significant reduction in the use of suppositories. In the study, a single acupuncture point was employed, selected from various points documented in the literature for constipation, known to alter intestinal transit time in an animal study (Iwa et al., 2006). The assessment of constipation improvement relied on clinical parameters, without, however, incorporating intestinal transit time as a measure of efficacy. Moreover, a detailed evaluation of fecal consistency and volume was not conducted.

From a pharmacological perspective, despite the heterogeneity of the population, suppositories and digital stimulation have been reported as constipation treatment options in patients with a double diagnosis of ABI and SCI (Valbuena Valecillos et al., 2022) and these can be regarded as first-line therapeutic choices.

Trans anal irrigation (TAI), as an invasive method, can manage constipation and/or fecal retention and incontinence. Using water to induce the rectal reflex of the colon, TAI can be used in chronic conditions with low side effects (Emmanuel, 2019). TAI is usually well tolerated, can reduce FI, low urinary infection, and improve quality of life (Emmanuel et al., 2016).

The utilization of TAI also enables us to hypothesize significant benefits, particularly considering the operational modes of more recent devices (Bardsley, 2020). Additionally, employing TAI in this phase allows us to address the typical consequences of dysbiosis in these patients (Catanzaro et al., 2019), thus aiming to prevent a

TABLE 3 Difference between Rome II vs. Rome III vs. Roma IV (Rome II: Drossman, 1999, Rome III: Longstreth et al., 2006, Rome IV: Drossman, 2016).

Diagnostic Criteria	Rome II (1999) Two or more of the following for at least 12 weeks (not necessary consecutive) in the preceding 12 months:	Rome III (2006) at least two of the following criteria are met for the last 3 months with symptom onset at least 6 months prior to diagnosis	Rome IV (2016) Diagnostic criteria* Must include two or more of the following:**
	Straining during (25%) of bowel movement	Straining on >25% of defecations	Straining during more than ¼ (25%) of defecations
	Lumpy or hard stools for >25% of bowel movements	Lumpy or hard stools on >25% of defecations	Lumpy or hard stools (Bristol Stool Form Scale 1–2) more than ¼ (25%) of defecations
	Sensation of incomplete evacuation for >25% of bowel movement	Sensation of incomplete evacuation on >25% of defecations	Sensation of incomplete evacuation more than ¼ (25%) of defecations
	Sensation of anorectal blockage for >25% bowel movement	Sensation of anorectal obstruction/blockage on >25% of defecations	Sensation of anorectal obstruction/blockage more than ¼ (25%) of defecations
	Manual maneuvers to facilitate more than 25% of bowel movement (e.g., digital evacuation, support of the pelvic floor)	Manual maneuvers on >25% of defecations (e.g., digital evacuation, support of the pelvic floor)	Manual maneuvers to facilitate more than ¼ (25%) of defecations (e.g., digital evacuation, support of the pelvic floor)
	Three bowel movement per week	Fewer than 3 defecations per week.	Fewer than three SBM per week
	Loose stools not present	Loose stools must be rarely present without the use of laxatives	Loose stools are rarely present without the use of laxatives
	Insufficient criteria for irritable bowel syndrome met	Insufficient criteria for irritable bowel syndrome	Insufficient criteria for irritable bowel syndrome

*Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.
**For research studies, patients meeting criteria for opioid-induced constipation (OIC) should not be given a diagnosis of FC because it is difficult to distinguish between opioid side effects and other causes of constipation. However, clinicians recognize that these two conditions may overlap.

worsening of the intestinal neuroinflammatory condition (Sundman et al., 2017; Rice et al., 2019).

4.4. Non-conventional therapy

An interesting line of research by Enevoldsen et al. analyzed the correlation between NBD and autonomic dysfunction using heart rate variation (HRV), trying to identify correlations between this and intestinal transit time. However, any correlation between CTT and HVR was shown (Enevoldsen et al., 2018). The Italian ABI minimal protocol (Lavezzi et al., 2022) attempt to analyze autonomic dysfunction in patients with ABI reporting a scale to evaluate the autonomic system with the paroxysmal sympathetic hyperactivity assessment measure (PSHAM; Baguley et al., 2014). It's interesting to note that autonomic dysfunction is not typically considered in patients with ABI, whereas in patients with SCI, autonomic dysfunction is always taken into account and analyzed, as we can see in the autonomic function after spinal cord injury book (ISAFSCI; Wecht et al., 2021). At the moment, there are no specific targeted treatments for the autonomic nervous system in ABI.

An interesting approach using an osteopathic mesenteric lift to increase bowel movement was proposed for ABI in the ICU (Ward, 2003; Berry et al., 2020). The researchers reported that 77% experienced bowel movements compared to 36% in the control group ($p = 0.01$). This technique has some contraindications, such as severe abdominal pain, infections, metastatic lesions, internal hemorrhage, abdominal aortic aneurysm, recent visceral surgery, and lack of tolerance to treatment (Chila, 2011).

Another original approach was to perform local magnetic stimulation (A-FMS) in a stroke patient with constipation. After the treatment with A-FMS the authors report a 50% reduction in CTT in the left colon and an increase of 50% in the frequency of defecation compared to the sham group (Yun et al., 2019) has been reported.

4.5. Consequence of NBD

Fecal incontinence is generally accompanied by the use of laxatives (Aadal et al., 2019), older age (Foxx-Orenstein et al., 2003), memory and communication impairment (Dourado et al., 2012), and damage to the frontal or prefrontal cortex (Foxx-Orenstein et al., 2003). In addition, FI can be used as a marker for the severity of disability (Foxx-Orenstein et al., 2003) and as a predictor of nursing home replacement in the stroke population (Granger et al., 1989). The direct consequences of FI include dermatologic diseases (skin irritation, pressure ulcers, infection) and social problems (reduced activity and participation; Gibson, 1990).

Only one study reported a patient with a double diagnosis of SCI and ABI that increased from 7 to 74% according to different criteria (Valbuena Valecillos et al., 2022). The dissociation between parasympathetic and ENS can contribute to NBD in patients with SCI or traumatic brain injury (TBI; Blanke et al., 2021).

The dysautonomic framework resulting from severe acquired brain injury leads to the disruption of the brain-gut axis, contributing to secondary events related to gastrointestinal disorders, including altered motility, dysbiosis, and increased mucosal permeability. Intestinal disruptions may give rise to heightened systemic inflammation, further exacerbating neuropathological consequences,

particularly concerning behavioral symptomatology (Hanscom et al., 2021).

Furthermore, dysbiosis and increased intestinal permeability are linked to heightened blood–brain barrier permeability, leading to a state of neuroinflammation associated with central neurological damage (Carloni and Rescigno, 2022).

Retrospective studies have shown that bowel and urinary management is not well integrated into rehabilitation programs (Leary et al., 2006) and this results in an increase in healthcare and assistance costs for patient management. Indeed an education program during rehabilitation has been suggested to reduce nursing time and as part of a specific rehabilitation program (Cotterill et al., 2018).

4.6. Conclusion

NBD is a common consequence after stroke and brain injury (Bracci, 2007; Coggrave et al., 2014). The authors have analyzed the possible mechanisms involved in the pathogenesis of neurogenic bowel dysfunction and the proposed strategies for managing NBD.

This scoping review underlines the need to establish a clearer understanding of potential correlations between the locations of cerebral lesions and the extent of NBD (Turnbull et al., 1999; Kern and Shaker, 2002), particularly given the frequent overlap of constipation and fecal incontinence and their evolution over time (Hakim et al., 2022).

The currently available evidence also highlights how, beyond cerebral localizations, there can be many factors influencing the onset of NBD, such as diet, medication, secondary motor and cognitive difficulties resulting from neurological damage, and alterations in the microbiota; it has also not been possible to identify therapeutic protocols applied early on to prevent the onset of the problem.

The need for a consensus between the rehabilitative and gastroenterological societies on the diagnosis and medical care of bowel dysfunction, particularly in patients with ABI, could be a way to implement patient care and quality of life. In an effort to standardize intestinal management and expand knowledge on the topic the authors advocate the development of an international consensus to deliver bowel management after ABI.

4.7. Limitation

This study had several limitations. First, the characteristics of ABI population are unknown in most of the article.

Second, the sample of patients with NBD in ABI has been briefly studied in the literature. Regarding the sample size, most of the samples were from a single US database.

Data availability statement

The original contributions presented in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author.

Author contributions

GC, MG, GL, and MZ designed the study. MZ, GC, and LP interpreted the data, and wrote the first draft of the manuscript. MZ organized the database and collected the data. MZ, SP, and LP performed the analytical evaluation of articles. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Diagnosing awareness in disorders of consciousness with gamma-band auditory responses

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Introduction: The prolonged disorders of consciousness (pDOC) describe a group of neurological conditions characterized by severe impairment of consciousness resulting from the injury of the central nervous system. As the behavioral diagnosis of pDOC remains challenging, the methods based on observing brain activity appear as promising alternatives. One of these methods is electroencephalography, which allows for noninvasive assessment of brain function.

Methods: In this study, we evaluated evoked auditory responses to the chirp-modulated auditory stimulation as a potential biomarker of awareness in pDOC. Chirp-modulated stimulation is based on the repetitive presentation of auditory stimuli with a changing frequency over time. Two protocols were tested: amplitude-modulated narrow-band chirps (frequency range 25–55 Hz) and click-based wide-band chirps (30–100 Hz). The studied pDOC patient group included 62 patients (19 females and 43 males, mean age 40.72 years) diagnosed with Coma Recovery Scale-Revised. Envelope-following responses to stimulation were examined using the intertrial phase clustering coefficient.

Results: For both types of stimulation, the strength of the response in the low-gamma range (around 40 Hz) was related to the diagnosis of pDOC. Patients diagnosed with unresponsive wakefulness syndrome exhibited diminished responses, while more favorable diagnoses, suggesting awareness (minimally conscious state or emergence from the minimally conscious state), showed elevated responses. The variations in the integrity of the auditory pathway and the etiology of brain injury altered the observed response strength. Narrow-band stimulation yielded a more systematic relationship between low-gamma response and pDOC diagnosis.

Discussion: The results suggest the potential role of low gamma-band responses to chirp-modulated stimulation as the supportive diagnostic tool to detect awareness in the pDOC patient group.

KEYWORDS

disorders of consciousness, consciousness, EEG, auditory stimulation, auditory steady-state responses, envelope following response, Coma Recovery Scale-Revised

1 Introduction

The prolonged disorders of consciousness (pDOC) include the group of neurological conditions that result from extensive damage to the neuronal tissue of the central nervous system. The causes of such disorders vary, with traumatic brain injury (TBI) and anoxia being the most frequent ones (Estraneo and Trojano, 2018). pDOC include conditions, such as unresponsive wakefulness syndrome (UWS, also known as vegetative state; Laureys et al., 2010) and minimally conscious state (MCS; Giacino et al., 2002), which is divided into subdiagnoses of minimally conscious state minus (MCS-) and minimally conscious state plus (MCS+; Thibaut et al., 2020). MCS+ is recognized when a patient displays signs of communication skills (e.g., command following), and MCS- when only non-verbal symptoms of consciousness can be observed (e.g., visual pursuit). The pDOC patients who have regained consciousness are diagnosed with emergence from a minimally conscious state (EMCS; Giacino et al., 2002).

Even though various diagnostical tools exist, they lack sufficient diagnostic accuracy, as approximately 40% of patients with UWS are misdiagnosed (Schnakers et al., 2009). In recent years, various methods based on observation of brain activity were proposed to tackle that issue, including, among others, functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and electroencephalography (EEG), used in isolation or with concurrent transcranial magnetic stimulation (TMS-EEG technique; Giacino et al., 2018; Kondziella et al., 2020). Among those techniques, the potential diagnostical role of auditory steady-state response (ASSR) has been evaluated (Binder et al., 2017; Górska and Binder, 2019). This method seems a suitable alternative for DOC patients, being relatively cheap, robust, and technically less challenging than fMRI PET or TMS-EEG. It might be especially beneficial when clinical scales such as Coma Recovery Scale–Revised give ambiguous results due to an extensive motor or visual dysfunction. The ASSRs were analyzed as trains of clicks or amplitude-modulated sounds with constant stimulation frequency and as trains of periodic stimuli with chirp-modulated variable frequency (Binder et al., 2020). The latter solution allows for inducing oscillations in broader spectra of frequencies. In stimulations spanning the range of at least 30–100 Hz, two peaks of heightened responsitivity are often detected (Artieda et al., 2004; Pipinis et al., 2018). The first is centered around 40 Hz (labeled as the low-gamma band response), and the second is around 80–100 Hz (labeled as the high-gamma band response). The evoked activity in both of these frequency ranges has a different distribution of primary sources, with low-gamma response mainly originating in cortical, thalamic, and brainstem sources, while the high-gamma response predominantly generated by the brainstem sources with a lesser contribution from the higher levels of the auditory pathway (Herdman et al., 2002; Farahani et al., 2017, 2019, 2021). Applying ASSR-based protocols to pDOC patients revealed the promising correlation between the level of consciousness and the phase-locking index (PLI) in the low-gamma range (Binder et al., 2017, 2020; Górska and Binder, 2019). However, those studies were based on relatively small groups of patients, thus requiring further research to confirm the initial results.

The current study aimed to explore responses to chirp-modulated sounds in the low and high gamma ranges as potential biomarkers of awareness in pDOC on a larger patient sample. The response to two types of chirp stimulation was evaluated, and the intertrial phase clustering coefficient (ITPC) was analyzed for the chosen ranges of the responses. The Polish version of the Coma Recovery Scale–Revised (CRS-R; Giacino et al., 2004; Binder et al., 2018) was used as a reference for the pDOC diagnosis. In the previous study (Binder et al., 2020), we found that the low-gamma response to periodic auditory stimulation displays sensitivity to the condition of the pDOC patients as measured with CRS-R.

2 Materials and methods

2.1 Subjects

The convenience sample of pDOC patients consisted of 62 subjects, 19 females and 43 males (31% females and 69% males), with a mean age of 40.72 (SD = 12.91, range from 18 to 74 years old); one subject was left-handed, and one was ambidextrous. The sample of healthy control (HC) consisted of 20 subjects, 9 females and 11 males (45% females and 55% males), mean age of 29.45 (SD = 9.1, range from 20 to 55 years old), two subjects were left-handed. The mean ages in groups were compared using two-tailed t-test for unequal variances and received p-value < 0.0001, indicating that mean age differed significantly between the patient and control groups. The gender ratios were compared between the control and patient groups using the Fisher's Exact Test, which resulted in an insignificant result of $p = 0.283$, indicating that gender ratios did not differ significantly between the groups.

The control group was studied between February 2020 and September 2021, and the patient group between December 2020 and February 2023. For each subject, an informed consent was acquired. In the case of the participants from the pDOC group, the consent was given by their legal surrogates. The study design was approved by the local review board at the Institute of Psychology, Jagiellonian University, Kraków, Poland, and followed the provisions of the Declaration of Helsinki. The patients who took part in our study received a standard clinical treatment for patients diagnosed with prolonged disorders of consciousness, which involved physical therapy, pharmacotherapy, speech therapy, and general patient care treatment. The specific regimen of those clinical interventions depended on each patient's individual needs.

For the control group, the exclusion criteria were the presence of mental or neurological problems and pharmacological treatment with psychoactive medications. Inclusion criteria involved passing the audiological screening test set.

For the pDOC patient group, the inclusion criteria included: diagnosis of the prolonged disorder of consciousness (unresponsive wakefulness syndrome, minimally conscious state ±, emergence from the minimally conscious state), age 16–80 years, acquired severe brain injury, and passing the audiological screening test set (the details of screening procedure are described below). The exclusion criteria included: severe somatic conditions influencing pDOC diagnosis and EEG activity (e.g., severe hepatic or renal insufficiency, seizure activity during EEG acquisition) and schizophrenia before the incident causing pDOC. Patient studies were conducted in the rehabilitation centers located in Poland:

PCRF "Votum" centers in Kraków and Sawice, COiR "Zdrowie" Center in Częstochowa, and Fundacja "Światło" Center in Toruń.

Both groups underwent an audiological screening test set with the use of Titan device v. 3.4.1 (Interacoustics A/S, Middelfart, DK), testing integrity of the inner ear with otoacoustic emissions and integrity of the auditory pathway with auditory brainstem responses. The chosen screening protocols for otoacoustic emissions included Transient Evoked Otoacoustic Emissions (TEOAE) testing, based on a repeated broad-band click stimulus, activating a wide area of the basilar membrane, and Distortion Product Otoacoustic Emissions (DPOAE), which use the simultaneous presentation of two pure- tones to evoke and measure the distortion that occurs in various places along the cochlea. The hearing of 1000, 1500, 2000, 3000, and 4000 Hz frequencies was investigated using two TEOAE protocols. Two DPOAE protocols were used: the first examined the hearing of 500, 594, 707, 840, and 1000 Hz frequencies, and the latter focused on 500, 1000, 1500, 2000, 3000, 4000, 5000, 6000, 7000, 8000, 9000, and 10000 Hz frequencies. A threshold was set for at least three frequencies per protocol to meet the "pass" criterion for a protocol to be considered passed. The only exception was made for the second DPOAE protocol, in which 7 out of 12 measured frequencies were required to meet the "pass" criterion for the protocol to be considered passed. The screening test for the integrity of the auditory pathway was based on ABR (auditory brainstem response) measurement. It involved the proprietary CE-Chirp® ABRIS screening test protocol with 35 dBnHL sound intensity with the standard mastoid montage, two electrodes placed on mastoids, and one on the forehead of the participant. The response was displayed as "pass" or "refer." The final inclusion screening criterion required for participants to be included in the study was passing at least one of the otoacoustic emission tests and/or passing the ABR screening test. Only patients who passed this criterion were included in EEG data analysis. Datasets of some of the patients were further discarded during preprocessing due to low signal quality or technical problems encountered during signal acquisition. The final sizes of patient groups included in the data analysis are provided in **Table 1**. The tables containing detailed information about controls and patients can be found in the **Supplementary Table 1** (controls) and **Supplementary Table 2** (patients).

All patients were assessed using the Polish version of the CRS-R scale (Binder et al., 2018) for the pDOC diagnosis. Each patient was evaluated by at least two different examiners. Five CRS-R assessments per patient were done within a week. The total score, subscale scores, and the diagnosis were noted for each assessment. During the evaluation, patients were either seated in a wheelchair or raised in their beds to be in an upright position. The background noises, such as TV or radio, were muted for the time of the administration.

TABLE 1 The number of observations/subjects included in final analyses in both experimental conditions, split by the most frequent diagnosis.

Condition	UWS	MCS-	MCS+	EMCS	Total
NBC	28	15	6	5	54
WBC	27	11	3	5	46

NBC, narrow-band chirp condition; WBC, wide-band chirp condition; UWS, unresponsive wakefulness syndrome; MCS, minimally conscious state minus; MCS+, minimally conscious state plus; EMCS, emergence from the minimally conscious state.

2.2 Stimuli

The auditory stimuli were designed in the MATLAB environment (The MathWorks, Inc.). Two types of auditory stimuli were created: narrow-band chirp-modulated and wide-band chirp-modulated sounds. Each individual narrow-band chirp-modulated stimulus consisted of 1000 Hz carrier tone 100% amplitude modulated with a linear chirp that decreased in frequency from 55 to 25 Hz during 500 ms time (see **Figure 1A**). Stimulus duration was 500 ms, with 10 ms onset/offset linear ramps to avoid onset and offset clicks. Wide-band chirp-modulated stimuli were a series of single clicks 1 ms white-noise bursts distributed in a logarithmic manner, which decreased in frequency from 100 to 30 Hz during 1000 ms time (see **Figure 1B**). Both types of stimuli were presented at the sound intensity of 60 dB.

An acoustic calibration procedure was conducted to ensure an accurate and stable sound pressure level (SPL) is present. The performed test was prepared to verify two factors: firstly, the stability of the acoustic output measured inside the ear, and secondly, the repeatability of the measured SPL regarding the in-ear pads used with the consideration of difference for trials on put on and put off inside the ear.

The acoustic measurement test was conducted in an anechoic chamber of AGH University of Kraków with the Bruel and Kjaer type 4128-C Head and Torso simulator (HATS) with artificial ear and built-in microphones connected to two SVAN 912E sound meters. Each stimulus was measured five times after the calibration to verify if it was possible to achieve stable SPL. The LAeq sound level was measured within the 10-s time frame. Previous work defined proper binaural stimuli testing level as 65 dB SPL (Neher et al., 2017) or 60 dB SPL with EEG testing (Ignatious et al., 2021). In this work, the base level was set as 60 dB with the active weighting curve A (dBA) as it better reflects the actual human hearing mechanism and was proved to be the proper level of long-term brain stimuli testing (Kasprzak, 2011). The results of the acoustic testing procedure are presented in the **Supplementary Table 3**.

All stimuli levels were properly calibrated around 60 dBA. The standard deviation from the five measurement trials in all cases was lower than 1 dB, which was the result claiming good repeatability between measured subjects (Engel, 2001).

2.3 Experimental procedure

Each participant was presented with 300 repetitions of wide-band chirp-modulated sounds with 2220–3020 ms variable inter-stimulus intervals (in 200 ms steps) in the wide-band chirp condition (hence labeled WBC) and 300 narrow-band chirp-modulated sounds stimulus repetitions with 1220–1520 ms variable inter-stimulus intervals (in 100 ms steps) in the narrow-band chirp condition (hence labeled NBC), in a fixed order. Control subjects were evaluated in the sleep laboratory while seated on the bed, with eyes open, alone in a separate room with dimmed lights.

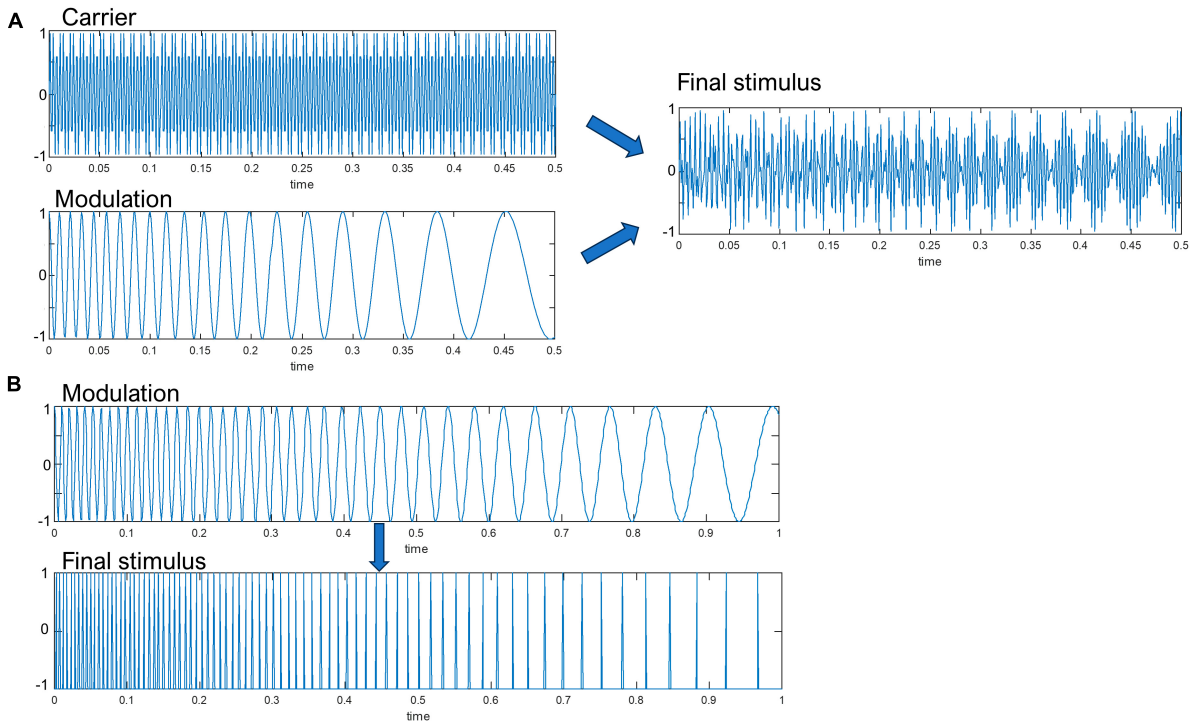

FIGURE 1
A schematic representation of the **(A)** narrow-band amplitude-modulated, **(B)** wide-band click-based chirp stimulus. Note that the white-noise bursts were emitted at the zero-crossings of the modulation waveform. The *Y*-axis represent sound pressure level in arbitrary units.

During patient studies, all participants were placed in a wheelchair or remained in their beds in an upright position. Recording occurred in a separate room or the patient room, with only the patient and two experimenters present. Ambient noise levels were not monitored at either recording session. EEG acquisition was performed when patients had their eyes open to ensure they were awake. Experimenters were blind to the results of the final CRS-R diagnoses at the time of recording and data processing.

2.4 Apparatus

Auditory stimuli were delivered using ER-3C insert earphones (Etymotic Research, Elk Grove Village, IL, USA) and a headphone amplifier Millenium HP1. EEG recordings were conducted using a 64-channel Active Two system (BioSemi, Amsterdam, Netherlands), with a 10–20 system head cap and four additional leads located above and below the right eye and in the external canthi of both eyes. Two added reference electrodes were placed on mastoids and recorded in parallel. CMS and DRL electrodes were placed between POz and PO3 and POz and PO4, respectively. Data were sampled at 1024 Hz. Stimulus presentation was controlled by Presentation software (Neurobehavioral Systems, Berkeley, CA, USA). The audio signal was recorded concurrently with EEG data using Analog Input Box (Biosemi, Amsterdam, NL, USA) and stored in a single dataset. The synchronization between the onset of the auditory stimulation and temporal markers in the EEG data indicating the start of the stimulation was verified off-line before data preprocessing steps.

2.5 Data processing

The initial preprocessing steps were performed using Brain Vision Analyzer 2.2 (Brain Products, Gilching, DE, USA). During the first step, data were filtered using an IIR high-pass filter (Zero phase shift Butterworth filter, eight order) and notch filter (at 50 Hz). Then, data were re-referenced to a common average reference and downsampled to 512 Hz. Noisy channels (e.g., muscle artifacts, loss of contact) were rejected and further interpolated. Eye movement correction was performed using the ICA ocular correction module (Independent Component Analysis) implemented in Brain Vision Analyzer 2 software and a semi-automatic module for blink detection. For further analysis, seven frontocentral channels were selected (FC1, FC2, C1, C2, Fz, FCz, Cz), as these regions display the most robust response to periodic auditory stimulation (Schwarz and Taylor, 2005; Spencer et al., 2008; Voicikas et al., 2016) and are less susceptible to artifacts. The continuous EEG data from the selected datasets were segmented into −700, 1200 ms epochs in the narrow-band chirp condition and into −700, 1700 ms epochs in the case of the wide-band chirp condition. In the next step, all individual epochs in both conditions were baseline-corrected using a pre-onset period −699, −200 ms. After that, segments containing artifacts were rejected using semi-automatic mode with the following criteria: amplitude limits −200 μV to 200 μV; 200 μV maximum allowed difference in intervals over 200 ms; maximal voltage step of 150 μV/ms. Using custom MATLAB (The MathWorks, Inc.) scripts employing FieldTrip functions (Oostenveld et al., 2011), the number of epochs across subjects was equalized using the following rule: the

minimum number of epochs necessary for further analysis was set to 200 epochs, and if the number of epochs exceeded 240, this number of epochs was randomly selected from the available set. This step resulted in the rejection of some datasets, and the final group sizes are shown in **Table 1**.

In the next step, time-domain data were decomposed into time-frequency representation using FieldTrip function ft_freqanalysis, with short-term Fourier transformation and Hanning taper (using mtmconvol option with Hanning taper), with the following transformation settings: time-window 500 ms, bandwidth 2–120 Hz, with 2 Hz steps, output temporal resolution 9.765625 ms. Using a custom MATLAB script, the TF data were then used to calculate the ITPC (also known as a phase-locking index, PLI). The ITPC was calculated using the following formula (based on Delorme and Makeig, 2004 and FieldTrip documentation):

$$ITPC\left(f,t\right) = \left|\frac{1}{n}\sum_{k=1}^{n}\frac{F_k\left(f,t\right)}{\left|F_k\left(f,t\right)\right|}\right|$$

Where $F_k(f,t)$ is the spectral estimate of trial k at frequency f and time t, and n is the number of trials.

2.6 Data analysis

The curve representing time-frequency points corresponding to the progression of chirp-modulated stimulation across time and frequency was used to estimate responses to chirp-modulated sounds. As we used periodic auditory stimuli that change their modulation frequency in time and consequently their envelope, we decided to use the term "envelope following response" (EFR; Dolphin, 1997) instead of "auditory steady-state response" to describe the observed evoked changes in the time-frequency domain of the EEG signal. Envelope following response is defined as the gross changes in the EEG signal caused by the populations of neurons that respond synchronously (phase-locked) to the envelope of an acoustic stimulus (Encina-Llamas et al., 2021), and in contrast to the ASSR definition, it does not assume the constant frequency of stimulation (Ross, 2013). The envelope following the frequency response curve (hence labeled EFR curve) was constructed using the MATLAB formula used previously to generate the stimulation. In order to estimate the prestimulus and post-stimulus level of the EEG signal, the envelope curve was extrapolated before onset and after the offset of the stimulus (see **Figures 2**, **5**) and spanned the period −400, 800 ms for the narrow-band chirps and −160, 1190 ms for the wide-band chirps. To account for temporal smoothing due to the used method of time-frequency decomposition and the delay in sensory pathways, for each time-frequency point belonging to the envelope curve, the ITPC value was calculated at each frequency step as a mean of temporal window covering 50 ms before the stimulation and 100 ms after the onset of the stimulation (see the dashed lines in **Figures 2**, **5**).

The individual CRS-R diagnoses of the patients were transformed into a single final diagnosis based on the most frequent diagnosis obtained by a patient during five assessments (the variable hence labeled FreqDiag). We did not choose to use the criterion of the best diagnosis to determine the patient's condition during the study period because it is probable that such an approach may amplify the diagnostic error made during a single examination.

Due to the small and unequal sizes of MCS-, MCS+, and EMCS groups, exploring data for each diagnosis was impossible. To equalize the patient group size, MCS-, MCS+, and EMCS patients were combined to constitute the group of all pDOC patients who can be considered aware. This group was labeled "MCSe" (MCS "extended" group). Ultimately, two groups of participants were compared: UWS (presumably unaware subjects) and MCSe (presumably aware patients), with the HC group not included since it was used for identifying the shape and the localization of the EFR response.

To compare EFR response curves between these groups while effectively controlling the type I error in a situation involving multiple comparisons, we used a non-parametric cluster-based permutation procedure implemented in FieldTrip software (Oostenveld et al., 2011), using the same settings as the previously described analysis. We chose the ft_statfun_indepsamplesT function to estimate the statistical effects of that comparison. Samples that survived the initial test (i.e., the uncorrected *p*-value was less than 0.005) were clustered based on the temporal proximity. Cluster-level statistics were obtained by summing the sample statistics within each cluster. The maximum of these was used to evaluate the significance of the results against a randomization distribution. This distribution was obtained by randomly permuting the original data, taking the maximum cluster-level statistic (labeled as clusterstat in the section "3 Results"), and repeating this process 30,000 times. The probability of obtaining a statistic from this distribution larger than the actual cluster statistic was tested at a p-level set less than 0.001. We performed the one-sided test because our earlier studies provided evidence for higher ITPC responses in groups with more favorable CRS-R results (Binder et al., 2017, 2020).

To test for more specific effects based on the mean ITPC scores sampled from the frequency ranges of the suprathreshold clusters, we used the robust aligned rank transform ANOVA test where appropriate (with the p-level set at 0.05). These statistical analyses were conducted using jamovi software (Version 2.2.5; The Jamovi Project, 2022).

3 Results

3.1 Narrow-band chirp condition—Effects of diagnosis

The grand mean responses in the time-frequency domain and the grand mean EFR curves in the healthy control group and the patient group are shown in **Figure 2**. In both groups, the maximum ITPC response was observed between 40 and 50 Hz (see **Figures 2B, D**). The representative topoplots for the frequency range 32–50 Hz in **Figure 2** (the right panel) show the maximum response at the frontocentral channels in the control group and in the representative case with MCS+ diagnosis, yet this response is barely visible in the representative patient from the UWS group.

Before further analysis, one outlier was removed from the NBC dataset due to an excessively high ITPC response. The outlier detection analysis was based on the interquartile range method

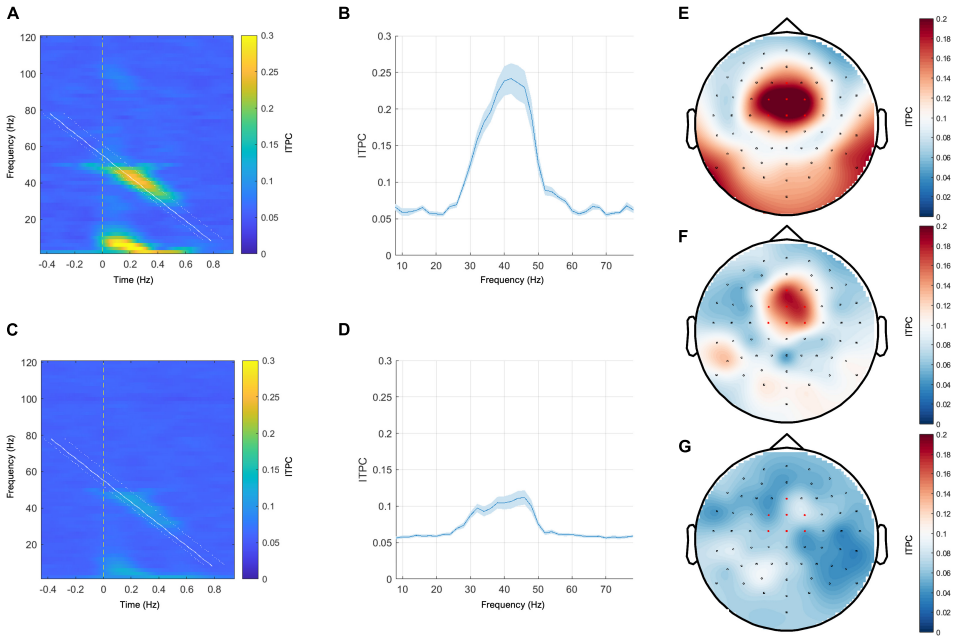

FIGURE 2
Left panel: grand mean responses to narrow-band chirp-modulated stimulation on the time-frequency plane in the healthy control group **(A)** and in the patient group **(C)**. Middle panel: grand mean EFR curves over frequency in the healthy control group **(B)** and the patient group **(D)**. The blue ribbons represent the standard error of the mean. Right panel: topoplots for the narrow-band chirp condition ITPC response sampled from the range of 32–50 Hz. **(E)** Grand mean response of the control group, **(F)** representative subject with the MCS+ diagnosis and the positive ABRIS result, **(G)**—representative subject with UWS diagnosis and the positive ABRIS result. Red-colored dots indicate channels that were included in calculating EFR responses.

applied to the whole envelope responses in the patient and control groups. We also included the control group in the outlier detection procedure since we expected that some responses, especially in the patients with EMCS diagnosis, might be comparable to the responses of healthy patients while being much higher than responses in the group of patients with UWS diagnosis.

The unaware group (UWS) consisted of 28 patients with the most frequent UWS diagnosis, and the aware group (MCSe) included 26 patients with the most frequent MCS-, MCS+, or EMCS diagnosis. We compared these two groups using a non-parametric cluster-based permutation procedure (see **Figure 3A**). We found a significant difference corresponding to a cluster at 36–50 Hz frequency range (clusterstat = 27.64, cluster significance $p < 0.001$), with higher response in the MCSe group (see **Figure 3B**). The distributions of individual ITPC scores (see **Figure 3C**) in both groups indicate that in the UWS group results are clustered from 0.05 to 0.01 scores with three cases above 0.1 level. The results of the MCSe group are on average higher, with several observations below 0.1 level. See **Table 2** for the mean ITPC scores for both patient groups in this condition.

3.2 Narrow-band chirp condition—Effects of auditory pathway integrity

Our inclusion criteria allowed for patients with negative ABRIS screening test results. Such results indicate possible functional or structural disruptions of the brainstem part of the auditory pathway. There is evidence that such disruptions can decrease the strength of ASSR in the low-gamma band (Johnson and Brown, 2005) and thus introduce bias on the observed relation between pDOC diagnosis and EFR responses. First, to eliminate the factor of the integrity of the auditory pathway on the relation between EFR response and pDOC diagnosis, we repeated the non-parametric cluster-based analysis on the subset of the ABRIS-positive patients (i.e., those who have passed the ABR screening test). We found a significant difference in the same direction, corresponding to the single cluster at the 36–48 Hz frequency range ($N = 40$, clusterstat = 24.52, cluster significance $p < 0.001$), confirming that the observed relation is not dependent on the injuries of the brainstem part of the auditory pathway.

To further explore the relation between ABRIS results and the narrow-band EFR response in its part that displayed the highest difference between the groups, we conducted an ANOVA test with factors of ABRIS result (negative–"refer" or positive–"pass") and FreqDiag score. We chose a 2 x 2 between-subjects robust aligned rank transform test ANOVA due to violations of normality and non-homogeneity of variances in the untransformed data. We observed the significant ABRIS x FreqDiag interaction $F_{(1,50)} = 5.57$, $p < 0.05$. The marginal means plot is depicted in **Figure 4A**. The main effect of FreqDiag was absent $F_{(1,50)} = 1.69$, $p = 0.2$, but there was a significant main effect of ABRIS result $F_{(1,46)} = 7.69$, $p < 0.01$. Note that the validity of results is constrained by the strongly unbalanced design with only three observations of MCSe patients with negative ABRIS results (other subgroups MCSe/ABRIS-positive–23 subjects, UWS/ABRIS-negative–11 subjects, UWS/ABRIS-positive–17

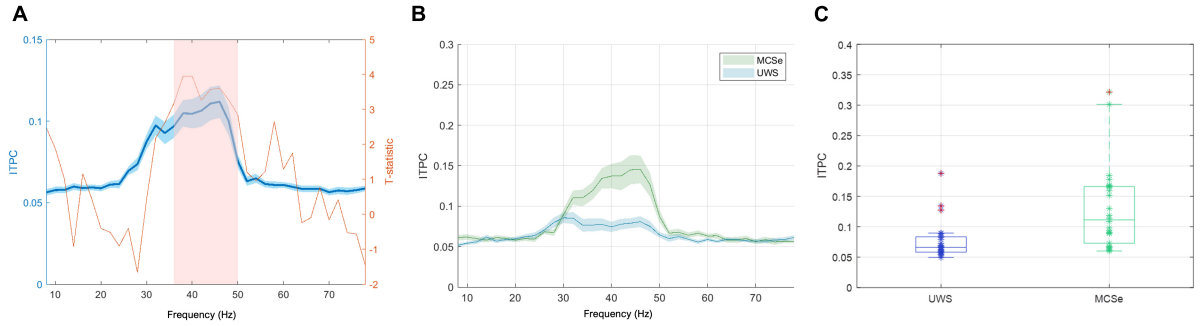

FIGURE 3
The narrow-band chirp condition results indicating differences in low-gamma response between aware and unaware groups (FreqDiag variable). **(A)** Results of the non-parametric cluster-level statistical analysis for the differences between MCSe and UWS groups, blue plot: grand average EFR response with overlaid T-statistic scores (red plot), the pink box represents the suprathreshold cluster, **(B)** mean EFR curves for both FreqDiag groups, **(C)** box-plots of group FreqDiag results with individual data, extreme values indicated in red. Ribbons on panels **(A,B)** represent the standard error of the mean.

TABLE 2 Mean ITPC scores and standard deviations (in parentheses) for the suprathreshold clusters for the patient groups in all conditions.

Condition	UWS	MSCe
NBC	0.0749 (0.0296)	0.1199 (0.0606)
WBC	0.0749 (0.0324)	0.1322 (0.0549)

NBC, narrow-band chirp condition; WBC, wide-band chirp condition; UWS, the unaware group; MCSe, the aware group.

subjects). The inspection of the plot indicates that the ABRIS result did not have an influence on UWS results and, in accordance with our suspicions, it probably had an impact on the MCSe group, substantially decreasing ITPC levels in the negative ABRIS subgroup to the level obtained by the UWS group (note, however, the previous remark on the number of subjects, and extensive CI range for the MCSe/ABRIS negative group).

3.3 Wide-band chirp condition—Effects of diagnosis

The grand mean responses for the wide-band chirp stimulation condition for the control group and the patients are shown in Figure 5. The highest ITPC response can be observed around 40 Hz (low-gamma band) in both groups. The peak around the high-gamma band can be readily observed in the control group, while it is much smaller in the patient group. The response topographies in the low-gamma (range 40–50 Hz) in Figure 5 (the right panel) indicate that the response was most pronounced in the frontocentral channels and was visible in controls and the representative patient from the aware group and was barely visible in the representative case from the unaware group. The outlier detection procedure did not exclude any patients in the wide-band chirp condition.

The non-parametric cluster-based permutation procedure with FreqDiag as the independent variable did not reveal any suprathreshold cluster at $p < 0.001$. However, at a more relaxed threshold $p < 0.005$, a significant difference in wide-band EFR response between both patient groups was revealed, corresponding to the cluster at a low gamma range (40–50 Hz, clusterstat = 24.06, $p < 0.005$). The plots depicting statistical scores, the comparison of the EFR responses range, and the individual ITPC scores are depicted in Figure 6. Similarly to the previous condition, the individual results in the UWS group are concentrated between 0.05–0.01, with three cases above 0.1 level. The individual results of the MCSe group display a much greater spread, with higher responses on average and several observations below 0.1 level. See Table 3 for the mean ITPC scores for both patient groups in this condition.

3.4 Wide-band chirp condition—Effects of auditory pathway integrity

In order to remove the influence of the factor of auditory pathway integrity, we conducted the non-parametric cluster-based analysis constrained to the subjects with positive ABRIS results. Again, there was not any significant difference at $p < 0.001$. Still, a significant difference was observed at the relaxed $p < 0.005$ threshold, corresponding to the suprathreshold cluster spanning the 42–50 Hz range ($N = 35$, clusterstat = 19.08, $p < 0.005$).

To obtain a more detailed view of the possible interaction between the factor of auditory pathway integrity and pDOC diagnosis, we analyzed mean ITPC scores aggregated from the suprathreshold cluster data. Similarly to the narrow-band stimulation, we performed the aligned rank transform test ANOVA (due to violations of the ordinary ANOVA assumptions) using a 2 × 2 design. The interaction of ABRIS results and FreqDiag group was insignificant $F_{(1,42)} = 1.90$, $p = 0.176$, and at the same time, both the main effect of ABRIS result and FreqDiag diagnosis were significant [$F_{(1,42)} = 6.07$, $p < 0.05$ and $F_{(1,42)} = 5.70$, $p < 0.05$, respectively]. The marginal means plot is shown in Figure 7A. Similarly to the results in the narrow-band chirp condition, the current result must be interpreted with caution because of the non-balanced design (MCSe/ABRIS-positive–17 subjects, MCSe/ABRIS-negative–2 subjects, UWS/ABRIS-positive–18 subjects, UWS/ABRIS-negative–9 subjects). Nevertheless, the current results show that negative ABRIS result decreases the response in the MCSe group and has lesser influence in the UWS group, though it is more pronounced than in the previous

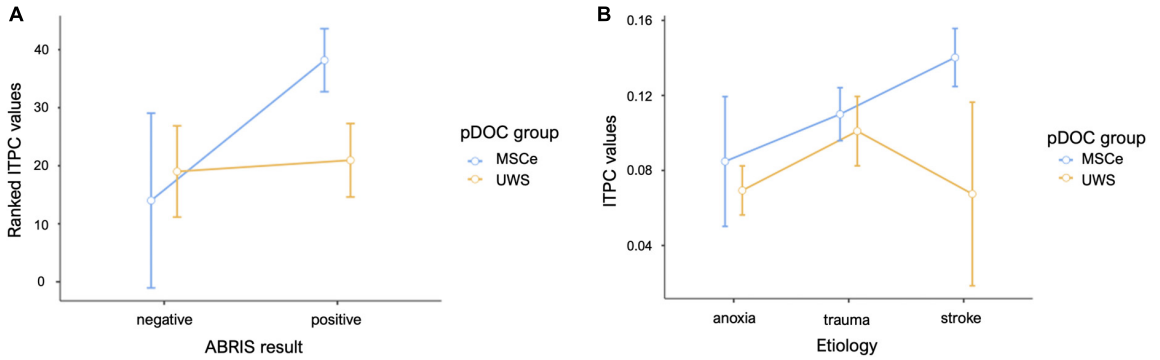

FIGURE 4
Mean plots for the data sampled from the suprathreshold cluster in the narrow-band chirp condition. **(A)** Mean results for the FreqDiag groups split by ABRIS screening test results. **(B)** Mean results for the FreqDiag groups split by etiology category. Error bars represent 95% confidence intervals.

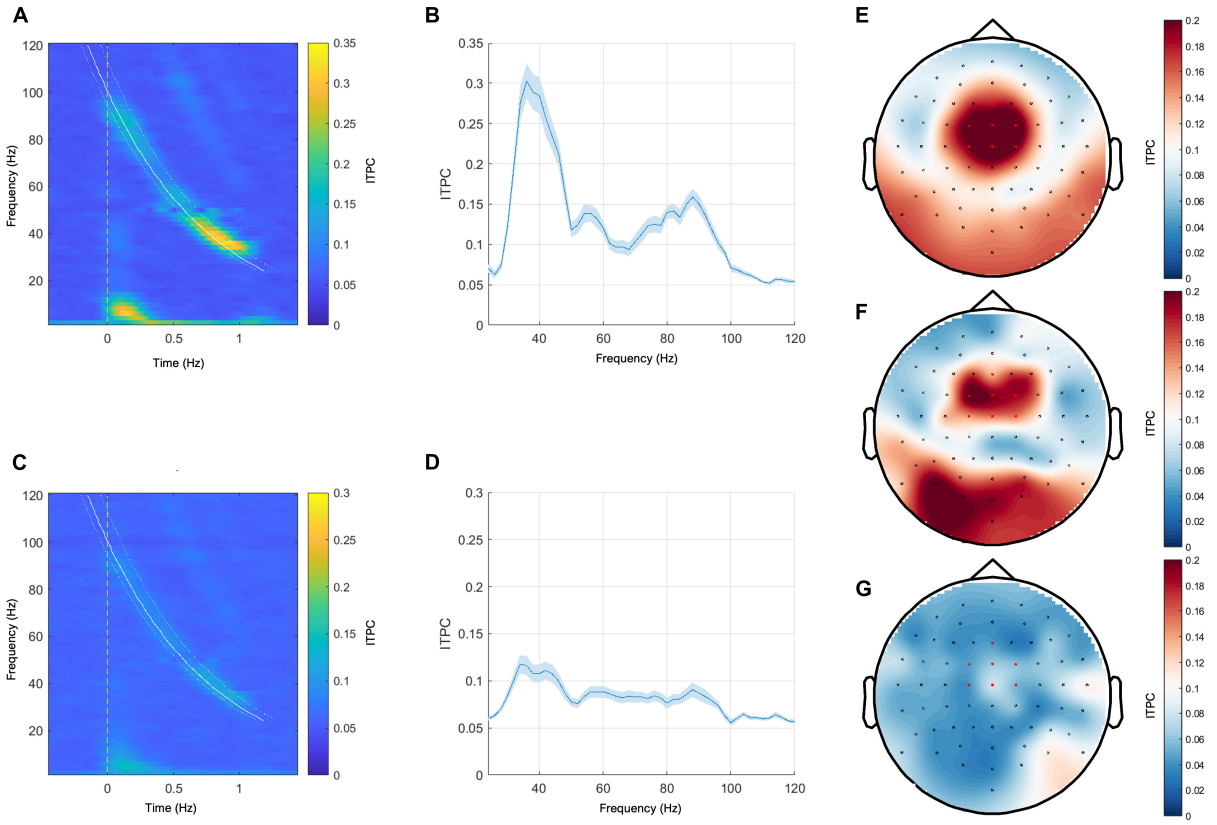

FIGURE 5
Left panel: grand mean responses to wide-band chirp-modulated stimulation on the time-frequency plane in the healthy control group **(A)** and in the patient group **(C)**. Middle panel: grand mean EFR curves over frequency in the healthy control group **(B)** and the patient group **(D)**. The blue ribbons represent the standard error of the mean. Right panel: topoplots for the wide-band chirp condition ITPC response sampled from the range of 40–50 Hz. **(E)** Grand mean response of the control group, **(F)** representative subject with the MCS+ diagnosis and the positive ABRIS result, **(G)** representative subject with UWS diagnosis and the positive ABRIS result. Red-colored dots indicate channels that were included in calculating EFR responses.

condition and reduces the interaction effect. The results for the wide-band stimulation show a less systematic relationship between evoked EFR response to wide-band stimulation and the pDOC diagnosis. Nevertheless, just as for the narrow-band chirp condition, the low-gamma response appears as the most sensitive part of the response to the most frequent diagnosis.

3.5 Narrow-band chirp condition—Effects of etiology

We also attempted to examine the potential effects of the cause of brain injury on the EFR responses in the studied group of pDOC patients. Table 3 shows the sizes of patient

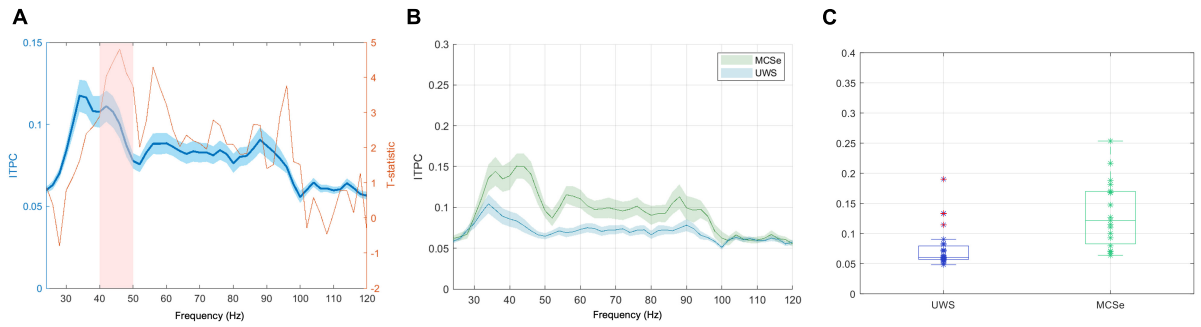

FIGURE 6
The wide-band chirp condition results indicating differences in low-gamma response between aware and unaware groups (FreqDiag variable). **(A)** Results of the non-parametric cluster-level statistical analysis for the differences between MCSe and UWS groups, blue plot: grand average EFR response, with overlaid T-statistic scores (red plot), the pink box represents the suprathreshold cluster, **(B)** mean EFR curves for both FreqDiag groups; **(C)** box-plots of group FreqDiag results with individual data, extreme values indicated in red. Ribbons on panels **(A,B)** represent the standard error of the mean.

TABLE 3 **Number of observations across etiology categories, split by the FreqDiag group assignment.**

Etiology	UWS	MCSe
Anoxia	14	2
Trauma	7	12
Anoxia and trauma	4	0
Stroke	1	10
Stroke and anoxia	1	0
Other etiology	1	1

UWS, the unaware group; MCSe, the aware group.

subgroups in the etiology categories we have distinguished. We have compared responses across the etiologies with the highest numbers of included observations, namely, anoxia, trauma, and stroke. We have compared average ITPC values sampled from the suprathreshold cluster obtained for the FreqDiag analysis described previously. The results showed that the most pronounced difference between FreqDiag groups was observed within the stroke group, with other groups having smaller differences between groups (see **Figure 4B**). Notably, within the etiology category of trauma, the differences between both groups were reduced, seemingly due to the heightened ITPC response in the UWS subgroup.

3.6 Wide-band chirp condition—Effects of etiology

For the wide-band chirp condition we had, as for the previous type of stimulation, the unbalanced size of subgroups prevented performing strict statistical tests (see **Table 3**). As for the previous stimulation type, we focused on the three etiologies with the highest group sizes. We compared responses in the low-gamma cluster identified by the non-parametric cluster test for the FreqDiag independent variable (see **Figure 7B**). Similarly to the previous simulation, the trauma group showed the smallest difference between pDOC groups, this time this reduction was due to lowered responses in the MSCe group. In other etiology groups, MCSe patients on average displayed higher ITPC responses in the low-gamma band.

Overall, despite the unbalanced group size, the results suggest that the etiology of the brain injury may have considerable influence on the responsitivity to the chirp-based auditory stimulation in the studied pDOC group. Three points can be inferred. The first is a relatively stable and high response in the group of MCSe stroke patients for both types of stimulation. On the other extreme, UWS patients with anoxic etiology showed systematically virtually absent response to stimulation. The third point is related to the results obtained in the trauma group for which the difference between the UWS and MCSe was least pronounced. These issues will be further discussed in the section "4 Discussion" of the paper.

4 Discussion

The aim of this study was to assess the sensitivity of EFR response to chirp-modulated stimulation in a group of patients with prolonged Disorders of Consciousness. We have chosen two types of chirp-modulated stimulation—narrow-band stimulation centered around 40 Hz and based on amplitude modulation and wide-band stimulation, covering both low-gamma and high-gamma frequency ranges, based on a series of clicks. The pDOC diagnosis, representing the level of consciousness, was based on the repeated CRS-R evaluation (Seel et al., 2010; Giacino et al., 2018). CRS-R is regarded as a "gold standard" in the assessment of pDOC, and multiple administration has been proven to lower the risk of misdiagnosis (Wannez et al., 2017). As there is no consensus in the literature concerning the integration of multiple CRS-R assessments into a single diagnostic score, we chose a way of parametrizing the diagnosis of pDOC based on the dominant diagnosis across five measurements. This approach emphasizes the potential of the diagnosed patient to manifest behavioral markers of the respective diagnostic entity. We decided not to choose the parameter based on the best diagnosis, as we see it as posing the risk of amplifying a single misdiagnosis over the whole assessment series if it happens to be the best one.

We used a 25–55 Hz frequency range in the first condition to explore the low-gamma response. We chose it as it is known

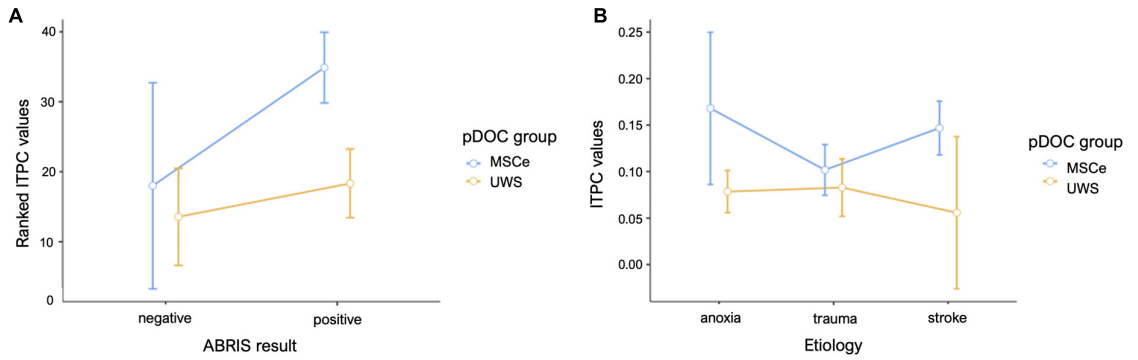

FIGURE 7
Mean plots for the data sampled from the suprathreshold cluster in the wide-band chirp condition. **(A)** Mean results for the FreqDiag groups split by ABRIS screening test results, **(B)** mean results for the FreqDiag groups split by etiology category. Error bars represent 95% confidence intervals.

that the maximum response frequency in the low-gamma range is subject to some individual variation (Mockevičius et al., 2023), and thus using many frequencies instead of a single one may create an opportunity to capture the maximal low-gamma response in all studied subjects. We decided to represent the evoked response by the EFR curve because it accurately represents the dynamic changes in the sensitivity of the ITPC response across time and frequency. The grand average response in a group of 20 healthy subjects was represented by the gradual increase in ITPC with a maximal response at around 40 Hz. The topographic plot of the response around its maximum (range 32–50 Hz) shows that the maximal response was observed in the frontocentral channels. Such topographic distribution has been reported in other studies employing chirp-modulated stimulation involving low-gamma (Pipinis et al., 2018), and the studies involving constant 40 Hz stimulation (Ross, 2013). This supports the conjecture that the observed response has been generated in the auditory cortex and probably other sources that are involved in 40 Hz ASSR generation (Farahani et al., 2017, 2019, 2021). A similar profile, as well as the maximal frequency of response, was observed in the pDOC patient group (see **Figure 2B** for the healthy control group and **Figure 2D** for the patient group), albeit the consistency of the response was notably lower than in the control group.

In the case of the wide-band stimulation, we were interested in the effects of the sensitivity to the stimulation frequencies beyond low gamma, focusing primarily on high gamma as the other potential source of meaningful differences among pDOC patient groups. We decided not to include lower frequencies, firstly, because they coincide with high-amplitude physiological oscillations that may substantially lower signal-to-noise ratio, and secondly, because the appropriate estimation of lower frequencies requires longer inter-stimulus intervals and would make our protocol considerably longer and thus harder to implement, especially in the challenging conditions of pDOC patient measurement. The control group results showed the dominant EFR response within the low-gamma range (see **Figures 5A, B**). In the case of pDOC patients, the low-gamma response was greatly diminished (see **Figures 5C, D**). The topography of the low-gamma was centered around the frontocentral channels, just as in the case of narrow-band stimulation (see **Figure 5**, the right panel).

The analysis of the narrow-band chirp condition results revealed the low-gamma cluster that was also visible in the same location in the reduced group with positive ABRIS results. This result corroborates the conclusion that the low-gamma response depends on the response originating in the upper parts of the auditory system whose function is somehow connected to the pDOC status. The ANOVA analysis testing for interaction between the FreqDiag group factor and ABRIS result, on the other hand, suggests that the negative ABRIS results (indicating disruption of the brainstem parts of the auditory pathway) may substantially reduce the EFR low-gamma response in the MCSe group. Observations not aligned with the central tendency suggest that factors other than brainstem integrity may influence response variability in the pDOC group. One of them may be the changed topography of the response caused by changed dipole orientation resulting from structural damage to the neural tissue. In this case, the highest response will be observed beyond the seven channels we have selected. Indeed, analysis of the influence of etiology on the effect of the narrow-band stimulation suggested that trauma etiology may change the pattern of results within the group, where the diagnosis of pDOC did not differentiate between EFR response. The structural damage and the dipole orientation reflected in the changed topography may at least partly explain that result.

The wide-band chirp condition analysis of EFR response revealed a low-gamma cluster both in the analysis including all suitable patients and in the analysis limited to the group of the ABRIS positive patients, though using a more lenient significance threshold. The influence of etiology on the results obtained in this cluster was similar to the narrow-band chirp condition, with the traumatic group not showing a clear relationship between the FreqDiag score and the ITPC result. As in the previous condition, in the most numerous Etiology subgroups (despite lack of balance), in the anoxia group, low FreqDiag scores coincided with low ITPC, and reversely, in the stroke group, high FreqDiag scores coincided with high ITPC scores.

In conclusion, the results of both stimulation conditions suggest that the low-gamma response to periodic auditory stimulation measured from the frontocentral channels exhibits

sensitivity to the ability of pDOC patients to manifest signs of awareness as measured with multiple CRS-R administration. On the one hand, this sensitivity manifested as a very diminished response in all patients with unfavorable FreqDiag scores. On the other hand, the patients that scored higher had elevated EFR responses, yet they displayed some variability, which at least in part can be accounted for by the etiology of their brain injury with less meaningful responses from the subjects with traumatic brain injury.

The response in other frequency bands showed no significant relationship with the awareness diagnosis. The preliminary data from other experiments with broad-band stimulations (Górska and Binder, unpublished data) suggest higher ITPC at the high-gamma band in conditions of low arousal (NREM sleep, general anesthesia), which is probably caused by disinhibition of that response, yet they may be related to other brain mechanisms. The lack of a systematic relationship in other frequencies suggests that the low-gamma response cannot be attributed to generalized changes in auditory cortex responsitivity to auditory stimulation across all stimulation frequencies but suggests a more selective type of response—pointing to the specific mechanism that may become severely disrupted in the unaware pDOC patients.

As to the possible account for the observed effects, there is evidence that the disruption of low-gamma response can be treated as the marker of disrupted excitation-inhibition balance (E/I balance) across the cortical mantle (Tada et al., 2020; Ahmad et al., 2022). According to Tada et al. (2020), the entrainment hypothesis of 40 Hz stimulation is based on the endogenous oscillatory activity in the gamma range based on the interaction between GABAergic interneurons and pyramidal excitatory neurons or based mainly on the inhibitory PV+ networks activity. Low-gamma responses to auditory stimulation are widely seen as the selective marker of the ability to maintain this E/I balance, which is crucial for the efficient functioning of the cortex. Although this account has been mainly used to explain differences in 40 Hz ASSR responses in neuropsychiatric disorders, predominantly schizophrenia, which are relatively small in comparison to the effects observed in the current study, it may nevertheless point to the meaningful connection between the E/I capacity and the networks underlying awareness. In this light, the proposed protocols can be utilized as the perturbational markers of the E/I balance.

Another explanation, which does not exclude the previous one, is based on the general disruption of the arousal networks that are supplied by the centers in the dorsal brainstem and central thalamus (Schiff, 2010). The low-gamma responses are known to depend on the cholinergic system (Zhang et al., 2016) and glutaminergic NMDA receptors (Sivarao, 2015; Sivarao et al., 2016). Disruptions of those systems may also be present in pDOC and play a significant role in influencing the strength and consistency of the low-gamma response in the studied group of pDOC patients.

Unfortunately, we could not obtain balanced sizes in all etiology categories. Such distribution stems from the fact that different etiologies tend to co-occur with specific pDOC diagnoses, which is caused by the fact that depending on the etiology, the brain injury associated with it disrupts the structure and the function of the central nervous system in an unequal way, and in case anoxic etiology usually the extent of the damage is more extensive than in the case of stroke or traumatic injury. This effect is strengthened in time, following several months after the incident, because different etiologies also differ with respect to the rate of recovery. From the statistical point of view, this size imbalance makes it impossible to perform a strict statistical analysis of the effects of etiology. Thus, the conclusions are tentative.

The main limitation of the current study is the size of the studied patient sample, which needs to be bigger to perform a statistically sound comparison of the groups depending on their etiology. The imbalance of the group sizes is also because our subjects were patients with prolonged DOC, which means that the different recovery rates depending on the cause of brain injury were reflected in the availability of subjects across different etiology groups, e.g., patients with anoxic etiology prevailing in the UWS group. Nevertheless, the observed tendencies represent a reliable indication of the effects of etiology and thus set up a good starting point for a follow-up study exploring in a more systematic way low-gamma responses across various types of brain injury.

5 Conclusion

In this study, we examined the responsiveness of the auditory system using the Envelope Following Response in a group of patients with prolonged Disorders of Consciousness with differing diagnoses and etiologies of brain injury. We applied two types of periodic chirp-modulated auditory stimulation: amplitude-modulated narrow-band stimulation (25–55 Hz) and click-based wideband stimulation (30–100 Hz). We used the temporal-frequency changes in the intertrial phase clustering coefficient following frequency changes as a response parameter, which was presented as an EFR curve.

For both types of stimulation, we observed variations in the strength of the response in the low-gamma range, which were related to the prevailing diagnosis of pDOC. We observed diminished responses in patients diagnosed with unresponsive wakefulness syndrome, while patients with more favorable diagnoses showed more pronounced responses. The integrity of the auditory pathway and the etiology of brain injury exerted a modifying influence on the observed response strength, with negative ABR results and traumatic etiology associated with decreased responses in the low-gamma range in the aware group. Narrow-band stimulation yielded a more systematic relationship between low-gamma response and pDOC diagnosis.

The results of the study suggest that measuring EFR responses in the low-gamma range can be used as a supportive tool for diagnosing pDOC. Detection of low or absent responses may suggest an unaware state of the brain, while higher responses may indicate an aware state. However, due to the observed variability of results, caution should be exercised when interpreting negative effects (risk of false negatives, low specificity), while positive effects may have diagnostic value.

Auditory responses observed in our study may provide the basis for constructing a relevant set of features for the machine learning models that can be used for improved diagnosis and prediction of patients' outcomes (Mofatteh, 2021; Liuzzi et al., 2022). Our approach could prove particularly advantageous in large-scale studies, where it is highly suitable for integration.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: https://osf.io/xq485/?view_only=e67da8690c36483e84e8bccdb5737e1d.

Ethics statement

The studies involving humans were approved by the Research Ethics Review Board, Institute of Psychology, Jagiellonian University. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

MB: conceptualization, methodology, software, formal analysis, investigation, data curation, writing–original draft, writing–review and editing, visualization, supervision, project administration, and funding acquisition. JP: investigation, data curation, writing–original draft, and writing–review and editing. IG-B: conceptualization, methodology, formal analysis, and writing–review and editing. SF: investigation, data curation, writing–original draft, and writing–review and editing. BC: methodology, resources, and writing–original draft. UG-K: conceptualization, methodology, and writing–review and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2023.1243051/full#supplementary-material

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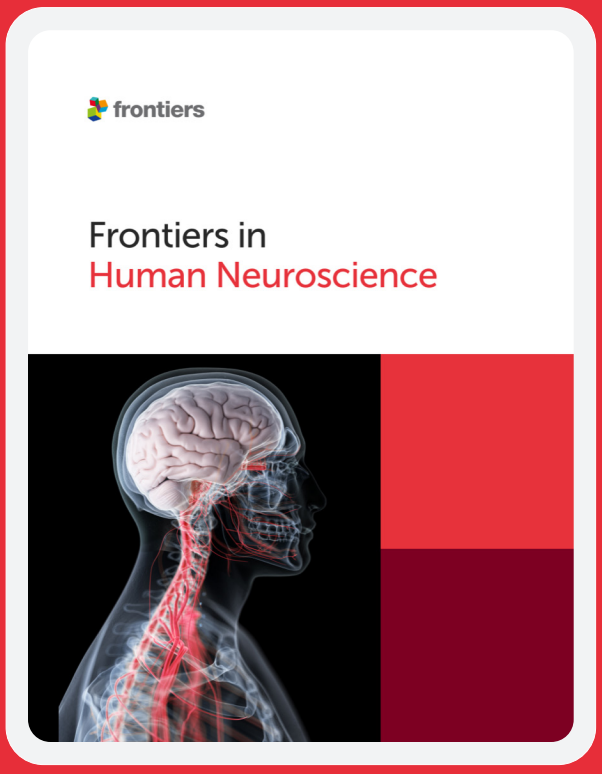

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