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Pathophysiological mechanisms of disorders of consciousness: From the perspective of the abnormal neural oscillations

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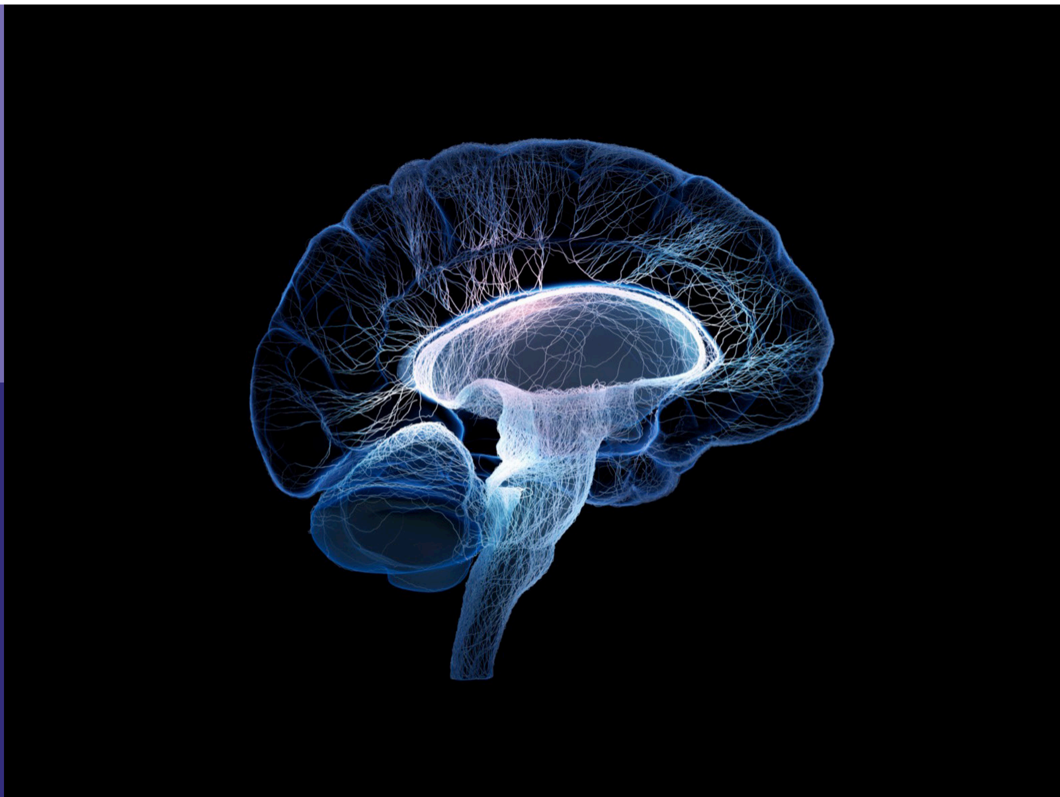

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Measure functional network and cortical excitability in post-anoxic patients with unresponsive wakefulness syndrome diagnosed by behavioral scales

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Background: Brain assessment shows great values in prognosis, treatment, resource allocation, and decision-making for patients with disorders of consciousness (DOC). However, less research focused on cortical conditions of patients with unresponsive wakefulness syndrome (UWS).

Methods: We recorded resting-state EEG and TMS-EEG from post-anoxic patients with UWS, diagnosed by repeated Coma Recovery Scale-Revised (CRS-R). Measurements of functional connectivity and networks were performed by phase lock value (PLV) and network parameters of graph theory (average path length, clustering coefficient, and small-world). Global cortical reactivity values (GCRV) were used to assess cortical excitability.

Results: The coefficient of variation (CV) presented marked inter-individual variations of PLV ($CV = 0.285$), network parameters ($CV > 0.2$), and GCRV ($CV = 0.929$) within these patients. The patients' PLV and network parameters at theta and alpha bands significantly correlated with their GCRV values. Patients with higher PLV ($r = 0.560$, 0.406), as well as better preserved network (lower average path length ($r = -0.522$, -0.483), higher clustering coefficient ($r = 0.522$, 0.445), and small-world ($r = 0.522$, 0.445) at theta and alpha bands, presented higher GCRV. The functional connectivity, which is significantly correlated with frontal GCRV, is also mainly located in the frontal region. These correlations were not significant at other frequency bands: Delta, beta, and gamma bands.

Conclusion: These findings suggested that the CRS-R-diagnosed post-anoxic patients with UWS had very different cortical conditions. Functional networks and cortical excitability measured by TMS-EEG could complement behavioral assessment to assess these patients' cortical conditions.

Significance: It provides a deeper understanding of neurophysiological dysfunction in patients with UWS and hints to the clinics that neural-electrophysiological assessment for such patients may be necessary to acquire their brain conditions, which may benefit stratified management for them.

KEYWORDS

functional connectivity, TMS-EEG, unresponsive wakefulness syndrome, global mean field amplitude, graph theory

Introduction

Brain assessment is crucial for the treatment strategy making of patients with disorders of consciousness (DOC) (Kondziella et al., 2020). Patients with different cortical conditions showed differentiated responses to treatment (Thibaut et al., 2015; Naro et al., 2016). In clinics, behavioral scales are always used to evaluate the conscious states of patients with DOC, especially the Coma Recovery Scale-Revised (CRS-R) (Giacino et al., 2004). However, it is always limited by the injured body function of patients in their expression (Schnakers et al., 2009; Gosseries et al., 2016), as it is based on behavioral responses to external stimulation or commands. It reported that ∼40% of patients with DOC may be misdiagnosed based on CRS-R assessment (American Congress of Rehabilitation Medicine, Brain Injury-Interdisciplinary Special Interest Group, Disorders of Consciousness Task Force, Seel et al., 2010; Gosseries et al., 2016). Therefore, CRS-R is not an effective and direct approach to assess the brain conditions of patients with DOC.

Recently, multiple neural-electrophysiological technologies, such as electroencephalography (EEG) (Lehembre et al., 2012a; Bai et al., 2017b), concurrent transcranial magnetic stimulation and EEG (TMS-EEG) (Casali et al., 2013; Formaggio et al., 2016), and event-related potential (ERP) (Cruse et al., 2011, 2014), have been used to improve brain assessment of patients with DOC. Studies using EEG features in assessing the brain of patients with DOC are challenging and exciting. A large body of research suggested resting-state EEG could effectively evaluate cerebral cortex activity for the diagnosis, prognosis, and treatment effect in patients with DOC (Bai et al., 2017b). Among the complicated EEG characteristics, the measurement of functional connectivity and networks reflects the information interaction between distributed brain regions and conforms to the concepts of "integration" in the information integration theory, which was proposed to be the foundation of consciousness (Tononi, 2004; van Vugt et al., 2018). In general, the levels of functional connectivity of patients with DOC were found to be consistent with their levels of consciousness (Pollonini et al., 2010). This consistency was proven by the correlation between connectivity measures and clinical assessments of consciousness (Lehembre et al., 2012b). Patients with higher levels of consciousness showed higher power functional connectivity and better-connected networks than those with lower levels of consciousness (Lehembre et al., 2012b). In addition, EEG functional networks could predict metabolism and complement systematic behavioral assessment in DOC diagnosis (Chennu et al., 2017). Therefore, EEG functional networks would be considered convincing features in assessing neural-electrophysiological states of patients with DOC.

Transcranial magnetic stimulation-EEG, as an emerging technology, shows practical prospect in the assessment of the brain of patients with DOC (Bai et al., 2016). TMS-EEG can measure the interaction between various brain areas at the millisecond level, thus revealing information on subjects' cortical excitability and reactivity (Sarasso et al., 2014). In patients with DOC, cortical excitability derived from TMS-EEG could effectively differentiate different consciousness states, for example, unresponsive wakefulness syndrome (UWS) formerly called vegetative state (VS), minimally conscious state (MCS), and locked-in syndrome (LIS) (Rosanova et al., 2012), and predict the consciousness recovery of patients with DOC (Bai et al., 2016). Patients with UWS show a simple, local cortical response to TMS, while patients with MCS and LIS have complex activations involving different brain areas and affecting large-scale cortex after TMS. Moreover, TMS-EEG could detect the immediate cortical responses to treatments, which would not be observed by clinical assessment (Bai et al., 2017a). Casali et al. (2013) quantified the cortical responses of TMS-EEG and proposed the perturbation complexity index to measure the level of consciousness. Several multi-modal studies also provided evidence verifying that the TMS-EEG characteristics correlate with the structural integrity (Bodart et al., 2018), metabolism (Bodart et al., 2017), and cortical injury (Gosseries

Abbreviations: TMS, transcranial magnetic stimulation; DOC, disorders of consciousness; UWS, unresponsive wakefulness syndrome; PLV, phase lock value; GCRV, global cortical reactivity values.

et al., 2015) of the patients with DOC. Therefore, because of its high sensitivity to conscious alteration and close correlation with the fundamental brain conditions, TMS-EEG would be a critical technique to assess the brain conditions of patients with DOC.

A large number of studies addressed EEG functional networks and cortical excitability in patients with DOC. Less of them, however, focus on exploring the brain conditions of patients with UWS. Both traumatic and non-traumatic injuries result in patients with UWS. Non-traumatic injuries, especially anoxia, produce widespread damage to cortical and thalamic neurons. However, patients with UWS after anoxia do not invariably show diffuse neocortical neuronal loss (Schiff, 2010). We hypothesize that the patients with UWS after anoxia, especially the ones diagnosed by behavioral scales alone, would have divergent cortical conditions. Brain assessment would facilitate the inhomogenous management of such patients. Therefore, this study used EEG and TMS-EEG to investigate the functional networks of cortical excitability in post-anoxic patients with UWS diagnosed by CRS-R and to improve our knowledge of the cortical conditions of those patients.

Materials and methods

Patient

The clinical characteristics of patients are shown in **Table 1**. All participants had suffered severe anoxia and showed no severe cerebral atrophy by MRI scans. They had no epileptic history or EEG epileptiform activity, pacemakers, aneurysm clips, neurostimulators, or brain/subdural electrodes. All patients received routine medication and rehabilitation courses but no consciousness-influenced treatment in at least 2 months before this study, including zolpidem, modafinil, midazolam, and baclofen. None of the participants had suffered fever or infections 1 week before the EEG and TMS-EEG recording. Written informed consent to participate in this study was obtained from patients' caregivers. This study was approved by the Ethics Committee of People's Liberation Army (PLA) Army General Hospital.

Behavioral assessment

Clinical assessment was carefully conducted by trained neurologists using repetitive Coma Recovery Scale-Revised (CRS-R) (Giacino et al., 2004). The CRS-R contains 23 items separated into six subscales (the visual, auditory, motor, and oromotor/verbal functions, communication, and arousal). Each patient received a minimum of three times of CRS-R assessment on the afternoon of a different day. The best result was kept as the behavioral diagnosis.

Transcranial magnetic stimulation

A single TMS-EEG data acquisition session took 10–15 min. Each patient received 200 single pulses of TMS tangentially at the left dorsolateral prefrontal cortex (DLPFC) under navigation (navigate by Brainsight system and mark the target site at the electrode cap using a marking pen). DLPFC as a stimulating target is widely used in DOC research (Rosanova et al., 2012; Bai et al., 2016, 2017a). We used a Magstim R^2 stimulator with a 70 mm figure-of-eight coil (Magstim Company Limited, Whitland, UK), which can produce a biphasic waveform with a pulse width of ∼0.1 ms. The TMS handle rotated posterior-laterally, approximately 45° to the middle line of the brain. Stimulation intensity for each patient was set as 120% of their resting motor threshold (RMT) (Ferreri et al., 2011). The RMT was defined as the lowest TMS intensity that can evoke at least 5 out of 10 EMG with an amplitude of $> 50\mu V$ peak to peak in the relaxed first dorsal interosseous muscle of the right hand. During the TMS-EEG recording, subjects were inserted earplugs, which continuously played a masking noise, to avoid TMS-evoked auditory potentials by the click associated with the TMS discharge. Bone conduction was attenuated by placing a thin layer of foam between the coil and scalp. Magnetic stimulation was administered in accordance with safety guidelines (Wassermann, 1998).

Electroencephalography recordings and pre-processing

Transcranial magnetic stimulation-EEG and 20 min of resting-state EEG were recorded on the same day for all the patients, with resting-state EEG first and TMS-EEG followed. The signals were acquired by a TMS-compatible EEG recorder with 62 channels (BrainAmp 64 MRplus, Brain Products), with positions of the international 10–20 system. The equipment used TMS-compatible sintered Ag/AgCl-pin electrodes, with the skin/electrode impedance maintained below 5 kΩ. We set a band-pass filtered at DC to 1,000 Hz in the recorder, while EEG signals were digitized at a sampling rate of 2.5 kHz.

Offline analysis was performed using EEGLAB 12.0.2.5b, running in a MATLAB environment (version 2013b, MathWorks Inc., Natick, USA). For the TMS-EEG processing (1) EEG signals were segmented into epochs starting from 300 ms before to 500 ms after the TMS pulse onset (Massimini et al., 2005; Ferrarelli et al., 2010; Ferreri et al., 2011). (2) Data from 10 ms before to 20 ms after the TMS pulse were replaced using the cubic interpolation function of MATLAB (Thut et al., 2011) to exclude the TMS artifacts. (3) The 50 Hz power-line artifact was removed from the remaining trials using a notch filter. (4) EEG signals were down-sampled to 500 Hz and band-pass filtered (1–80 Hz). (5) Independent component analysis (ICA) was used to identify the evoked artifacts (such as eye movement, muscle artifacts, decay, and recharge artifacts),

TABLE 1 Demographic details for the patients.

Patient	Age	Sex	Cause	Months post-injury	CRS-R						
					Auditory	Visual	Motor	Oro-motor	Comm	Arousal	Total
P1	30	F	Acute myocardial	7	1	0	2	1	0	2	6
P2	60	M	Cardiac arrest	8	1	0	2	1	0	2	6
P3	50	F	Cardiopulmonary arrest	8	1	0	2	1	0	2	6
P4	35	M	Cardiac arrest	9	0	0	2	1	0	2	5
P5	43	M	Cardiac arrest	13	1	0	2	1	0	2	6
P6	42	F	Cardiopulmonary arrest	8	0	0	2	1	0	2	5
P7	52	F	Cardiac arrest	6	1	0	2	1	0	2	6
P8	70	F	Cardiac arrest	30	1	1	2	1	0	1	6
P9	62	M	Cardiopulmonary arrest	12	1	0	2	1	0	1	5
P10	23	F	Respiratory infarction	8	1	1	2	1	0	2	7
P11	26	M	Respiratory infarction	11	1	0	2	1	0	2	6
P12	34	F	Respiratory infarction	9	1	1	2	1	0	1	6
P13	56	M	Respiratory infarction	5	1	0	2	0	0	1	4
P14	28	M	Cardiac arrest	6	1	1	2	1	0	1	6
P15	44	M	Cardiopulmonary arrest	12	1	0	2	1	0	1	5

Comm, communication; CRS-R, Coma recovery scale-revised; F, female; M, male; UWS, unresponsive wakefulness syndrome.

with visual inspection to assess scalp distribution, frequency, timing, and amplitude. The components deemed to be artifacts were removed using ICA (Casula et al., 2014). (6) Single trials were carefully inspected to remove residual TMS artifacts. (7) After the artifact reduction, at least 150 trials were preserved for each patient, and the baseline was corrected over 300 ms pre-stimulus. After processing, data were average-referenced; TMS-evoked EEG response was obtained by averaging over the trials.

For the resting-state EEG analysis (1) EEG signals were down-sampled to 500 Hz and band-pass filtered (1–45 Hz). (2) ICA was used to identify and remove the artifact-relevant components, such as eye movement and muscle activation. (3) The data were average-referenced and segmented into epochs of 10 s. Epochs with artifacts were removed by visual inspection.

Functional connectivity

Phase-locking value

In the present study, functional connectivity was measured by PLV, which has been used in several previous studies (Rudrauf et al., 2006; Holz et al., 2010; Fell and Axmacher, 2011). We measured PLV in different frequency bands: full band (1–45 Hz), delta (1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz), and gamma (30–45 Hz). In this study, we give a brief description of the calculation. For the resting-state EEG epochs, we evaluated the instantaneous phase $\varphi_x(t)$ and $\varphi_y(t)$ of the pairwise channel, based on the Hilbert transform. Then, the phase difference was defined by as follows:

$$\Delta\varphi_{xy}(t) = \varphi_x(t) - \varphi_y(t) \quad (1)$$

Several indices, based on the phase difference within the short term, can be used to indicate the phase synchronization between two series (Rosenblum et al., 2001). In this study, PLV based on the circular variance of the phase difference was applied as follows:

$$PLV_{xy} = \frac{1}{N}\left|\sum_{t=1}^{N} e^{j\Delta\varphi_{xy}(t)}\right| \quad (2)$$

This measure of PLV varies from 0 to 1, and the computation involves no parameter choices. In this way, the functional connectivity can be described by phase synchronization matrix C, with each element of PLV_{xy}.

Then, we used a surrogate method (the iterative amplitude-adjusted Fourier transform method) to correct the false coupling. In calculating the PLV between two channels, we randomly shuffled the phase of one signal and kept its spectrum unchanged. Then, a new surrogated PLV (PLV_{surro}) can be obtained. After surrogating over N_{sum} times ($N_{sum} > 50$), PLV values greater than 95% statistical threshold (mean plus 1.96 times the standard deviation) of PLV_{surro} will be preserved, and the other is set to zero.

Graph theoretical analysis

To further describe the functional connectivity, graph theoretical analysis was performed based on the PLV matrix. The nodes in the graph were represented by the electrodes, while the links were defined by the measures of association between the nodes in the study's PLV values.

Graphs can be characterized by various measures; in this study, synchronization matrix C was used to create weighted graphs. Average path length represented the average number of edges of the shortest path between the pairs of vertices. The clustering coefficient denoted the likelihood that neighbors of a vertex would also be connected to each other. Full definitions for the calculation of the clustering index (C_w) and path length (L_w) for the analysis of weighted networks have previously been described by Stam et al. (2009). To calculate the clustering index from weighted networks, the weights between node i and other nodes j should be symmetrical ($\omega_{ij} = \omega_{ji}$) and, $0 \leq \omega_{ij} \leq 1$ as proposed by Onnela et al. (2005). Indeed, both conditions are readily fulfilled when using PLV values as a weight definition. The weighted clustering index of vertex i was then defined as follows:

$$C_i = \frac{\sum_{k \neq i} \sum_{l \neq i, l \neq k} \omega_{ik}\omega_{il}\omega_{kl}}{\sum_{k \neq i} \sum_{l \neq i, l \neq k} \omega_{ik}\omega_{il}} \quad (3)$$

Note that in all sums, terms with $k = i$, $l = i$, or $k = l$ were skipped. The mean clustering of the total network was defined as follows:

$$C_w = \frac{1}{N} \sum_{i=1}^{N} C_i \quad (4)$$

The length of a weighted path between two vertices was then defined as the sum of the lengths of the edges of this path. The shortest path L_{ij} between two vertices i and j was the path between i and j with the shortest length. The averaged path length of the entire network was computed as follows:

$$L_w = \frac{1}{(1/N(N-1)) \sum_{i=1}^{N} \sum_{j \neq i}^{N} (1/L_{ij})} \quad (5)$$

In the aforementioned formula, the harmonic mean was used to handle disconnected edges resulting in infinite path lengths, that is, $1/\infty \rightarrow 0$ (Newman, 2003). The small-world was then calculated as $S = \frac{C_w}{L_w}$.

Cortical excitability

Global mean field power

To measure the TMS-evoked global response, a GMFP was used to describe the TMS-evoked potential (TEP). The GMFP can be expressed as follows:

$$GMFP(t) = \sqrt{\sum_{i=1}^{N} [V_i(t) - \bar{V}(t)]^2 / N} \quad (6)$$

where $V_i(t)$ is the signal averaged over trials measured on EEG channel i at time t, $\overline{V}(t)$ is the signal averaged over trials and channels at time t, and N is the number of channels. The GMFP identifies the maximum amplitude of the evoked field and is used to index the effect of TMS on global brain activities (Komssi et al., 2004). At each time of TEP peaks, we performed source modeling to investigate TMS-evoked cortical activation. Brainstorm software (Tadel et al., 2011)[1] was used to compute the cortex, skull, and scalp meshes and co-register these meshes with EEG sensor positions by rigid rotations and translations of anatomical landmarks (nasion, left tragus, and right tragus). Conductive head volume was modeled according to the 3-spheres BERG method. The inverse solution was calculated on TEP by using the weighted minimum norm constraint.

Global cortical reactivity value

A global cortical reactivity value was measured to quantify the cortical responses to TMS pulses. First, a bootstrap method was used to shuffle 1,000 times the time samples of pre-stimulus activity (from −300 to −10 ms) of GMFP time series at a single-trial level. The maximum value across all latencies was selected at each shuffling, and the maximum distribution was used to assess a threshold for determining the significance of GMFP with a significance level of $p < 0.01$ (McCubbin et al., 2008; Gosseries et al., 2015). Then, the significant voltage values in post-stimulus (20–500 ms) of each GMFP time series were cumulated as the global index of cortical reactivity (Rosanova et al., 2009).

Statistics

Inter-individual variations of the features were assessed by the coefficient of variation (CV) (ratio of the standard deviation to the mean). Correlational analyses of the functional network features (average PLV, average path length, cluster coefficient, and small-world) with the GCRV were measured using Kendall's tau coefficient. $P < 0.05$ is the threshold for significance.

Results

Functional network and cortical excitability

Figure 1 shows functional connectivity measured by PLV of four patients at the full band. It also shows different

1 http://neuroimage.usc.edu/brainstorm

strengths and patterns of connectivity within patients. Patients 8 and 6 showed marked and strong global connectivity (P8: average $PLV = 0.514$, standard deviation = 0.229; P6: average $PLV = 0.393$, standard deviation = 0.237). Patients 9 and 10 had a relatively weak connectivity pattern (average $PLV = 0.186$ and standard deviation = 0.142). For all the patients, CV is 0.285 (maximum value = 0.514, minimum value = 0.186, standard deviation = 0.097, and mean = 0.340).

To further describe the functional network, we calculated PLV and graphical network parameters at each frequency band. Table 2 gives mean values and standard variance values of the features at each frequency band. All the CV of the features are greater than 0.2 (Figure 2). Among them, small-world has the highest CV at each band, followed by the cluster coefficient.

TMS-evoked potential and corresponding GMFP were measured for all patients (Figure 3). Figure 3 gives four samples of patients (P5, P11, P9, and P4). It showed that the patients had very different cortical responses to TMS in both temporal and spatial domains. P5 and P11 show distinct evoked components and marked response power upper threshold, but the evoked patterns are different between P5 and P11. In temporal, the evoked components in TEP of P11 mainly appear within 300 ms following TMS. However, P5 has significant evoked peaks after 300 ms. In addition, P5 shows more complex evoked components and stronger evoked power ($GCRV = 99.71\ \mu V$) than P11 ($GCRV = 54.81\ \mu V$). On the contrary, P9 and P4 show less evoked components and low evoked power (P9: $GCRV = 3.62\ \mu V$; P4: $GCRV = 0.12\ \mu V$), as shown at the bottom of Figure 1. This distinct inter-individual difference could be found within all the 15 patients: $CV = 0.929$ (maximum value = 107.007, minimum value = 0.120, standard deviation = 41.284, and mean = 44.440).

Correlation between the functional network and the cortical excitability

As shown in Figure 4, the patients' GCRV had a significantly positive correlation with the average PLV of the global brain at theta ($r = 0.560$, $p = 0.005$) and alpha ($r = 0.406$, $p = 0.04$) bands. The patients with higher average PLV in functional connectivity measurement showed higher GCRV in TMS-EEG measurement. In addition, the connectivity, which significantly correlated with the GCRV, either at theta or alpha bands (bottom panel of Figure 4) was mainly located at the frontal region. There was no significant correlation between the average PLV and the patients' GCRV at other frequency bands.

Significant correlations were found between the network parameters and the patients' GCRV (Figure 5). Patients' GCRV had a negative correlation with the average path length (theta: $r = -0.522$, $p = 0.009$; alpha: $r = -0.483$, $p = 0.015$) and a positive correlation with the cluster coefficient (theta: $r = 0.522$, $p = 0.009$; alpha: $r = 0.445$, $p = 0.025$) and the small-world (theta: $r = 0.522$, $p = 0.009$ alpha: $r = 0.445$, $p = 0.025$) at theta and alpha bands. Table 3 shows that there was no significant correlation between the GCRV with network features at other frequency bands.

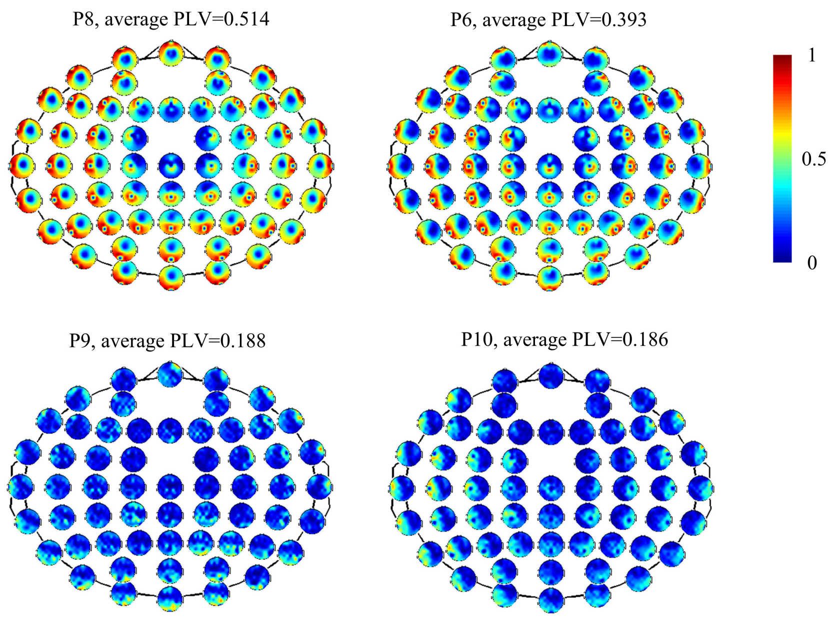

FIGURE 1
Functional connectivity measured by PLV of electrodes with overall brain in four patients (P8, P6, P9, and P10).

TABLE 2 Average PLV and graphical network parameters (mean value and standard variance) at each frequency band.

	Delta	Theta	Alpha	Beta	Gamma
Average PLV	(0.367, 0.089)	(0.359, 0.127)	(0.342, 0.121)	(0.306, 0.079)	(0.285, 0.061)
Average path length	(3.028, 0.722)	(3.178, 0.950)	(3.316, 0.979)	(3.519, 0.823)	(3.663, 0.748)
Cluster coefficient	(0.334, 0.091)	(0.325, 0.131)	(0.307, 0.123)	(0.265, 0.076)	(0.243, 0.055)
Small-world	(0.121, 0.059)	(0.124, 0.086)	(0.111, 0.077)	(0.083, 0.041)	(0.071, 0.026)

There was no significant correlation between the GCRV or functional network parameters with their clinical assessment (CRS-R), the patients' age, and months post-injury.

Discussion

The present study measured functional network features and cortical excitability features in post-anoxic patients with UWS. Big inter-individual variations of functional connectivity and cortical excitability were found in these patients. Some patients had markedly cortical responses to TMS and strong connectivity, whereas some patients showed relatively weak connectivity and low cortical excitability. In addition, the patients' GCRV showed a significant correlation with their functional connectivity and network parameters at theta and alpha bands. The correlation did not exist at other frequency bands, such as delta, beta, and gamma bands.

The functional connectivity can represent common inputs from other brain areas, while the GCRV depends explicitly on the influence that one neural system exerts over another at the population level (Friston, 2011). In addition, a good network showed more efficient configuration (small average path length, high cluster coefficient, and high small-world) within the brain regions: Each small cortical region was more willing to connect to its neighbors, and it took them fewer steps to communicate with each other. These features all reflect the "integration" of the patients' brains. They revealed very different cortical conditions among the patients in the present study. Furthermore, the residual brain network of patients with DOC correlated with their residual brain metabolism. A strong association has been demonstrated between functional connectivity and glucose metabolism (Chennu et al., 2017). TMS-EEG can measure cortical reactivity directly, and TEP presents the excitation changes in cortical circuits on a millisecond time scale (Ferreri et al., 2011; Bai et al., 2016). TMS-EEG study showed TMS triggered a simple local excitation change in patients with UWS, but TMS evoked MCS patients' local and large-scale cortical responses (Rosanova et al., 2012). In summary, TMS-EEG measures proved a clear-cut difference in cortical excitability between patients with UWS and MCS. In addition, TMS-EEG also showed congruent results with glucose metabolism in patients with DOC (Bodart et al., 2017). Therefore, for patients with DOC, the residual functional network and preserved cortical excitability may share a similar physiological basis: cortical metabolism. To some extent, these findings provide a possible explanation for the correlation results in the patients, and patients who preserved better metabolism showed better cortical excitability and functional networks. On the contrary, studies of neuromodulation also support the findings: The responses of DOC patients' brains to external stimulation depend on the residual brain network (Cavinato et al., 2015; Thibaut et al., 2015).

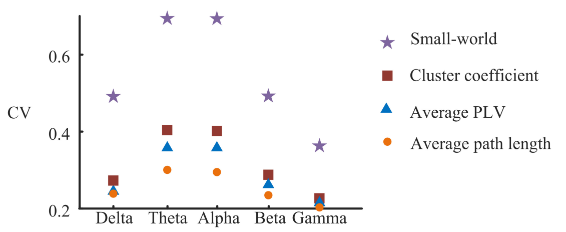

FIGURE 2
Relative coefficient of variation of functional network parameters.

The patients we addressed in the present study are rare in clinics, as most of them tend to die within the first 2 years after injury. Previous studies always tend to research the brain conditions or consciousness states among patients with various etiologies or just with a rough classification: TBI and non-TBI. Less of them focused on homogenous groups such as post-anoxic patients with UWS. In behavioral assessed post-anoxic patients with UWS, studies reported that no significant EEG responses were elicited by TMS, even when TMS was delivered at high intensity at multiple stimulation sites (Ragazzoni et al., 2013; Gosseries et al., 2015), but these studies only included a few cases. Nevertheless, in such patients, different cortical responses to stimulation were also reported in ERP research. In three behavioral assessed post-anoxic patients with UWS, one patient showed a distinct N1 component, while the other two showed no meaningful evoked component (Ragazzoni et al., 2013). The present study is the first to focus on the brain conditions within such homogenous patients with UWS. Consistent with our hypothesis, the inter-individual variations denote the very different cortical conditions within the patients. It was the first time found that some behavioral assessed post-anoxic patients with UWS preserved good cortical excitability.

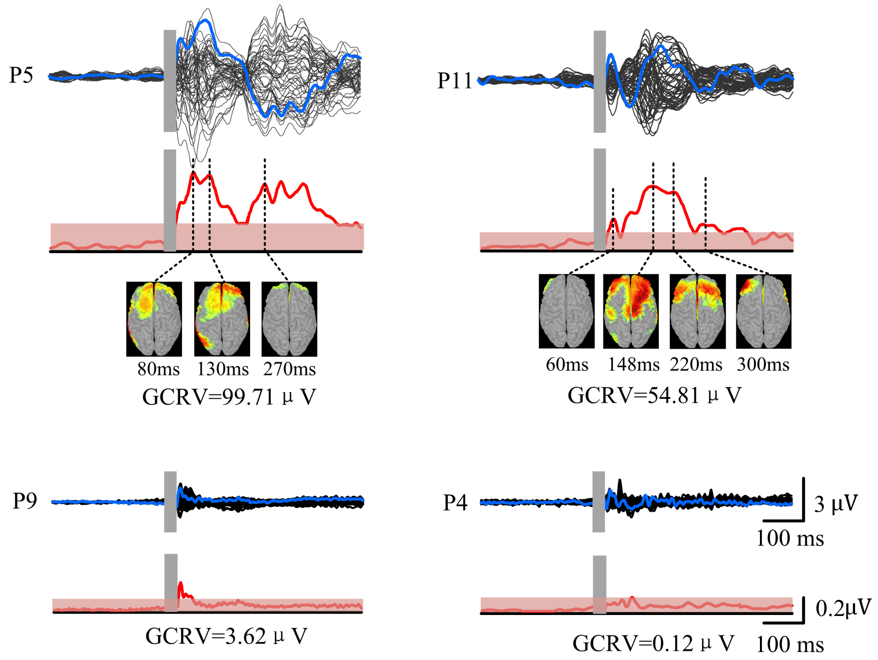

FIGURE 3
TMS-EEG of four patients (P5, P11, P9, and P4). Black curves show butterfly plots of TEP at all electrodes. Blue curves show TEP at F3 electrode (near target site). GMFP (red curves) was calculated based on the TEP. Red shadows show threshold values for determining significance of GMFP with significance level at $p < 0.01$. Source model was performed at each peak of TEP.

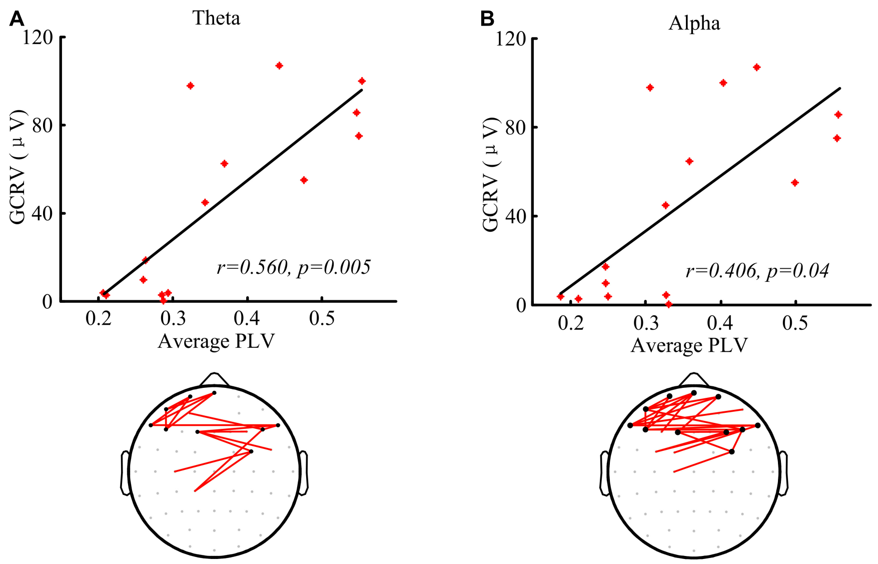

FIGURE 4
Functional connectivity measured by PLV and the correlation with the global cortical reactivity values (GCRV). **(A,B)** Correlation (Kendall's tau coefficient) of global averaged PLV at theta **(A)** and alpha **(B)** band with the patients' GCRV. Bottom panel shows the connectivity (red lines) that significantly correlate with the patients' GCRV. Black dots show electrodes associated with at least three red lines.

On the contrary, the strength of functional connectivity and cortical excitability is generally consistent with conscious levels of patients with DOC (Casali et al., 2013; Sitt et al., 2014). Especially, the functional connectivity measured by phase coupling at theta and alpha bands was demonstrated as an efficient feature for capturing consciousness levels of patients with DOC (Lehembre et al., 2012b). However, these findings were not the case in the patients with UWS of the present study:

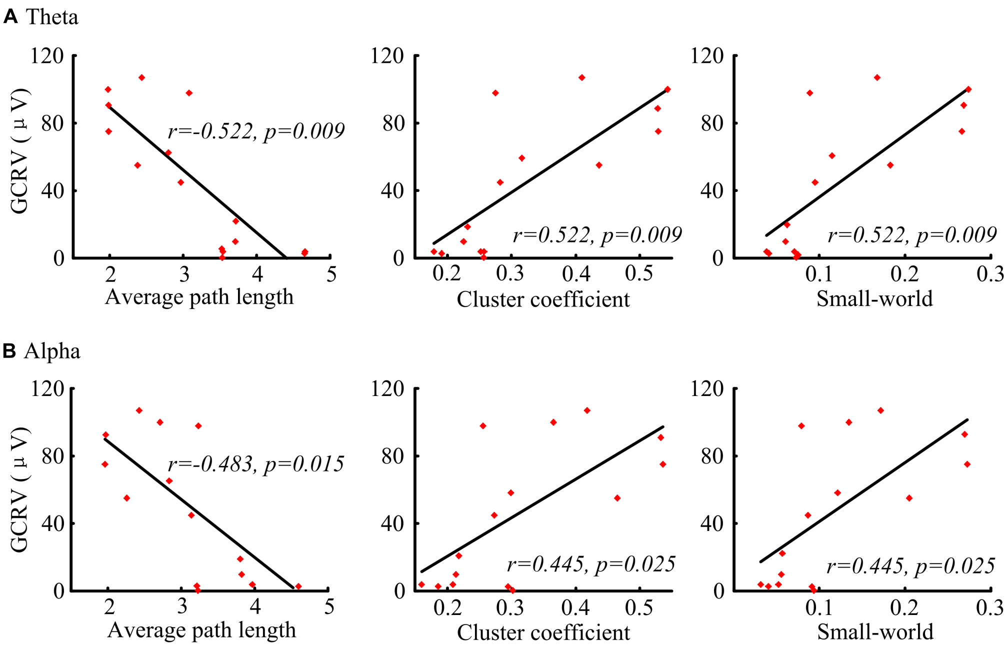

FIGURE 5
Correlation (Kendall's tau coefficient) of the graphical network parameters with the patients' GCRV. **(A)** Correlation of the average path length, cluster coefficient, and small-world at theta band with the patients' GCRV. **(B)** Correlation of the average path length, cluster coefficient, and small-world at alpha band with the patients' GCRV.

The functional networks showed no correlation with patients' CRS-R. Of course, considering the high rate of misdiagnosis when using CRS-R alone, there are enough reasons to speculate that the patients with better cortical excitability and functional networks may be actually in a better conscious state. Anyway, the findings of the present study revealed a necessity of depth assessment with the assistant of EEG or TMS-EEG. Acquiring more details about the brain conditions of the patients with UWS would raise diagnostic accuracy or improve stratified management of them in clinics.

Further study is needed to validate the findings of the present study. In the present study, the frontal region was selected as a target for detecting cortical excitability, as we considered that the frontal region is a crucial hub participating in the consciousness-related networks (Tononi, 2004, 2008; Alkire et al., 2008; Schiff, 2010). Frontal excitability would be very minded by non-invasive neuromodulation research (Angelakis et al., 2014; Thibaut et al., 2014; Naro et al., 2015; Cavaliere et al., 2016). In a way, it may lead to the results of frontal-located connectivity, which significantly correlates with GCRV. However, cortical excitability at other regions is still needed to validate the findings. Meanwhile, the analysis was conducted on UWS patients with the same cause (anoxia). More samples with various etiologies should be included to investigate whether the big inter-individual variations and correlations are ubiquitous in patients with UWS. Finally, future research should consider the relationship between the differences in cortical activity and the prognosis of post-anoxic patients with UWS.

TABLE 3 Correlation (Kendall's tau coefficient) of functional network features with the patients' global cortical reactivity values at delta, beta, and gamma bands.

	Delta	Beta	Gamma
Average PLV	$r = 0.309$, $p = 0.218$	$r = 0.382$, $p = 0.121$	$r = 0.236$, $p = 0.359$
Average path length	$r = -0.309$, $p = 0.218$	$r = -0.418$, $p = 0.087$	$r = -0.200$, $p = 0.445$
Cluster coefficient	$r = 0.319$, $p = 0.308$	$r = 0.309$, $p = 0.218$	$r = 0.164$, $p = 0.542$
Small-world	$r = 0.319$, $p = 0.308$	$r = 0.309$, $p = 0.218$	$r = 0.164$, $p = 0.542$

Conclusion

This is the first study which revealed that the post-anoxic patients with UWS, who were diagnosed by repeated CRS-R alone, had marked inter-individual variations of residual EEG networks and cortical excitability. The functional connectivity and cortical excitability showed significant correlations in those patients. These findings suggest us to measure functional networks and cortical excitability as complement assessments for such patients. It proved great values of neural-electrophysiological tools in assessing the brain conditions of patients with DOC.

Data availability statement

The original contributions presented in this 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 PLA Army General 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

CL and XX had full access to all the data in the study and takes responsibility for the integrity of the data. XX designed and conducted the study. YW and CL prepared the manuscript draft with important intellectual input from YY. YY and WL helped conduct the study, provided input, and helped with patient recruitment and consent. All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

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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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Frontal and parietal lobes play crucial roles in understanding the disorder of consciousness: A perspective from electroencephalogram studies

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Background: Electroencephalogram (EEG) studies have established many characteristics relevant to consciousness levels of patients with disorder of consciousness (DOC). Although the frontal and parietal brain regions were often highlighted in DOC studies, their electro-neurophysiological roles in constructing human consciousness remain unclear because of the fragmented information from literatures and the complexity of EEG characteristics.

Methods: Existing EEG studies of DOC patients were reviewed and summarized. Relevant findings and results about the frontal and parietal regions were filtered, compared, and concluded to clarify their roles in consciousness classification and outcomes. The evidence covers multi-dimensional EEG characteristics including functional connectivity, non-linear dynamics, spectrum power, transcranial magnetic stimulation-electroencephalography (TMS-EEG), and event-related potential.

Results and conclusion: Electroencephalogram characteristics related to frontal and parietal regions consistently showed high relevance with consciousness: enhancement of low-frequency rhythms, suppression of high-frequency rhythms, reduction of dynamic complexity, and breakdown of networks accompanied with decreasing consciousness. Owing to the limitations of EEG, existing studies have not yet clarified which one between the frontal and parietal has priority in consciousness injury or recovery. Source reconstruction with high-density EEG, machine learning with large samples, and TMS-EEG mapping will be important approaches for refining EEG awareness locations.

KEYWORDS

frontal, parietal, neural correlates of consciousness, electroencephalogram (EEG), disorder of consciousness (DOC)

1. Introduction

Researchers have long debated the origin of consciousness and the neural correlates of consciousness. Studies have demonstrated that the global workspace of the sensory areas, namely, the prefrontal and posterior parietal cortices, is highly correlated with the conscious activity of the brain (Giacino et al., 2014). The posterior cortex contains a posterior hot zone for the production of many conscious experiences such as vision, hearing, and touch (Boly et al., 2017; Koch, 2018), which serves as direct evidence that posterior brain regions are associated with human consciousness. Patients who have suffered severe prefrontal damage still retain arousal and awareness, suggesting that the prefrontal cortex should be excluded as a consciousness-dependent cortex (Koch, 2018). However, some researchers believe that damage to most frontal structures unrelated to consciousness does not lead to a loss of consciousness; key structures in the frontal lobe dominate human consciousness (Koenigs et al., 2007; Koch et al., 2016).

Disorder of consciousness (DOC) is an altered state of consciousness caused by damage or dysfunction in parts of the nervous system that regulate arousal and awareness (Schiff and Plum, 2000; Giacino et al., 2014). DOC patients have usually suffered severe brain damage owing to stroke, hypoxia, etc. (Gosseries et al., 2011b, 2014). Such patients can be in a vegetative state (VS) or a minimally conscious state (MCS). Both states feature high arousal levels; the MCS involves reproducible non-reflexive behavioral responses, whereas the VS [also called unresponsive wakefulness syndrome (UWS)] only involves reflexive behavioral responses to external stimuli. VS/UWS is a clinical syndrome describing patients who fail to show voluntary motor responsiveness under eyes-open wakefulness (Laureys et al., 2010). MCS patients cannot communicate with their environment; however, they show a fluctuating remnant of volitional behavior (Laureys et al., 2004). Furthermore, MCS could be divided into MCS + and MCS-, dependent on their ability to respond to commands, intentionally communicate, and so on (Chennu et al., 2017; Rizkallah et al., 2019). In addition, Thibaut et al. (2021) identified VS/UWS patients with brain activity similar to MCS as MCS*.

The frontal lobe is the control center of speech function and motor behavior; it is further thought to be involved in higher cognition, including memory and executive power (Chayer and Freedman, 2001). The global workspace theory hypothesizes that consciousness emerges by information processing, which propagates input information to the whole brain through two neuronal networks with centers at the frontal and parietal lobes (Koch, 2018). Neuroimaging studies have shown that an improved consciousness level is accompanied by changes in the metabolic rate of the parietal associative cortices (Laureys et al., 1999) as well as increased frontal-related neural connectivity (Jang and Lee, 2015). An electroencephalogram (EEG) is a non-invasive, highly compatible, and portable measure of brain function, and it allows the application of quantitative methods to better understand and interpret consciousness-related patterns (Kondziella et al., 2015). A variety of clinical and basic science studies have found a correlation between the level of consciousness and the EEG characteristics in frontal and parietal brain regions as well as fronto-parietal connections (Bai et al., 2017). However, the methodology and computation of EEG features are complex, and the abstraction of their neurophysiological interpretation limits their traceability to the neural correlates of consciousness. This makes it difficult for clinicians when they translate them into clinical practice.

2. Literature search

Literature searches were performed in four electronic databases: EMBASE, MEDLINE (*via* PubMed), Web of Science, and EBSCOAs. The retrieval time limit was set from the establishment of the database to 15 May 2022, and the language was limited to English. The search string was built as follows: EEG OR (Electroencephalogram) AND [(MCS) OR (minimally conscious state) OR (disorder of consciousness) OR (coma) OR (unresponsive wakefulness syndrome) OR (vegetative state) OR (disturbance of consciousness)]. The original search found 1,653 records, with 857 remaining after excluding duplicates. After the preliminary screening of article types, titles, and abstracts, 258 records were left. Ultimately, 43 records were included into our review after excluding literatures that did not explicitly involve specific brain regions. The key findings related to frontal and parietal brain regions were filtered to explore their electrophysiological role in the state of consciousness. **Figure 1** shows the defined frontal and parietal regions in EEG 10–20 electrode system and corresponding cortical lobes.

3. Evidence of frontal role in DOC

3.1. Frontal EEG characteristics in classification of DOC

The frontal lobes of DOC patients showed significantly different spectrum band powers compared with those of healthy controls. They have been proved to be able to distinguish DOC patients and to differentiate them into MCS and VS/UWS patients (**Supplementary Table 1**). The relative delta and alpha powers in the frontal area showed significant correlations with the revised version of the coma recovery scale (CRS-R) scores (Rossi Sebastiano et al., 2015). DOC patients exhibited a lower frontal delta source pattern compared with that of healthy controls (Naro et al., 2016a). The frontal area of VS/UWS patients showed a higher delta power but lower theta, alpha, and beta (not MCS*) powers than those of MCS* and MCS patients (Rossi Sebastiano et al., 2015; Piarulli et al., 2016;

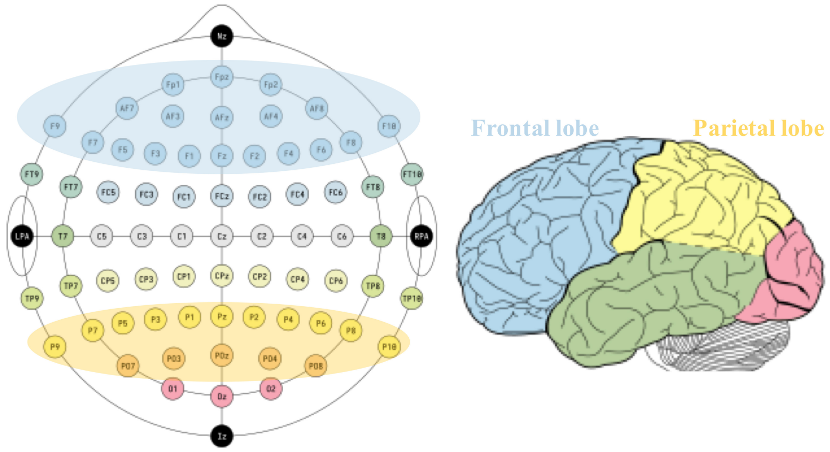

FIGURE 1
Defined frontal and parietal regions according to typical 10–20 EEG system **(left)** and the corresponding cortex **(right)**.

Naro et al., 2018; Thibaut et al., 2021). MCS patients showed lower source magnitudes of beta at frontal lobes than those seen with severe neurocognitive disorders (SNDs) (Leon-Carrion et al., 2008).

The functional network within the frontal area was significantly weaker in DOC patients than in healthy subjects (Naro et al., 2018). The participation coefficient of the frontal cortex positively correlated with the consciousness level (Chennu et al., 2017) and was significantly lower in MCS patients than in healthy controls (Rizkallah et al., 2019). Compared with the control group, the reduced participation coefficient of MCS- and MCS + differed in the frontal lobe and MCS- also showed lower integration in the parietal lobe but not MCS + (Rizkallah et al., 2019). The frontal lobe of DOC patients showed a lower node degree in the theta and alpha bands than in the case of healthy controls (Zhang L. et al., 2022). MCS patients had a higher degree of nodal values (Zhang L. et al., 2022), alpha band quadratic phase self-coupling (QPSC) (Bai et al., 2019), and multiplex clustering coefficients (Cai et al., 2020) at the frontal area than did VS/UWS patients. MCS* also has a higher alpha participation coefficient and alpha degree in the frontal lobe than VS/UWS (Thibaut et al., 2021). Moreover, time-varying gamma phase synchronization was only found in the frontal of MCS patients but not in VS/UWS patients (Naro et al., 2018). Transient states were demonstrated as novel self-constructed brain networks in spontaneous EEG. The anterior state is represented by the high delta power at frontal lobe and enhanced frontal connectivity. The fractional occupancy of the anterior state in DOC patients was significantly higher than that in healthy controls. Specifically, the anterior state occupied the most state expression time in VS/UWS patients and not in MCS patients (Bai et al., 2021).

Vegetative consciousness/unresponsive wakefulness syndrome patients always exhibited lower EEG complexity at the frontal than did MCS and healthy subjects (Thul et al., 2016). It has been revealed through the approximate entropy, amplitude coalition entropy and spectral entropy (Gosseries et al., 2011a; Piarulli et al., 2016; Liu et al., 2021; Visani et al., 2022).

The frontal scalp regions exhibited novel P300 (nP3) in MCS patients but not in VS/UWS patients (Risetti et al., 2013; Naro et al., 2016b). The frontal areas elicited a predictive value mismatch negativity (MMN) which showed a lower average amplitude in DOC patients than in healthy subjects (Hu et al., 2021). In addition, the frontal cluster showed increased delta modulation in command-following patients than in non-command-following patients during the early window of event-related potentials (Rivera-Lillo et al., 2021).

Transcranial magnetic stimulation-electroencephalography (TMS-EEG) could be conducted at the bedside as an advanced stimuli-response technique for improving the diagnostic accuracy of DOC. When TMS is targeted over the frontal region, VS/UWS patients showed simper neural responses and OFF periods, which differed from those of healthy subjects and MCS patients (Rosanova et al., 2012; Ragazzoni et al., 2013). The causal effects of TMS on the local cortical activity were shorter-lived in VS/UWS patients than in healthy awake controls (Rosanova et al., 2018).

3.2. Frontal EEG characteristics in outcome of DOC

The frontal functional network could be considered an effective characteristic for tracking consciousness recovery in DOC patients. The frontal QPSC in the theta band predicted patients who recovered their brain functions after 3 months (Bai et al., 2019). Frontal inter-hemisphere coherence in the delta band decreased in patients who recovered after tDCS treatment (Guo et al., 2019). A positive correlation was found between the fronto-central coherence and the motor item improvement of MCS patients (Naro et al., 2016c). Further, the event-related potential was commonly used to track the consciousness recovery of DOC patients (Gosseries et al., 2014). VS/UWS patients with a frontal distribution of nP3 topography recovered to MCS after 4.5 months (Risetti et al., 2013). After 2 weeks of HD tDCS treatment, alpha-beta activity in frontal lobe increased in patients with improved conscious representations (Zhang C. Y. et al., 2022).

4. Evidence of parietal role in DOC

4.1. Parietal EEG characteristics in classification of DOC

The parietal theta, alpha, and gamma powers were much lower in DOC patients than in healthy subjects (Naro et al., 2016a). The EEG of the parietal region showed a higher delta but lower theta, alpha, and gamma source patterns in VS/UWS patients than those in the healthy subjects (Lechinger et al., 2013; Sitt et al., 2014). Significant correlations exist between the CRS-R scores and the relative delta and relative alpha powers (Rossi Sebastiano et al., 2015). Compared with the parietal lobes of patients with SNDs, those of MCS patients showed a higher amplitude of beta and theta frequencies (Leon-Carrion et al., 2008). Moreover, the parietal gamma oscillatory activity correlates with the level of awareness of DOC patients (Naro et al., 2018). Regarding the difference between VS/UWS and MCS/MCS* patients, the parietal region showed increased delta power but decreased theta, alpha, and beta powers in the former relative to the latter (Naro et al., 2016a, 2018; Piarulli et al., 2016; Thibaut et al., 2021). The midline of the parietal region had a larger high-to-low frequency power ratio during the day-time than during the night-time in MCS patients, whereas no significant difference was seen in VS/UWS patients (Wislowska et al., 2017). In MCS patients, the parieto-occipital region showed some preserved topographical differentiation of alpha activity, whereas VS/UWS patients showed residual multifocal alpha activities in all regions (Rossi Sebastiano et al., 2015; Naro et al., 2018).

Consistent with the findings in the frontal region, the participation coefficient of the parietal lobe increased greatly with a higher consciousness level (Chennu et al., 2017). The parietal region showed time-varying gamma phase synchronization, higher mutual information, lower multiplex participation coefficient, and higher multiplex clustering coefficients in MCS patients than in VS/UWS patients (King et al., 2013; Naro et al., 2018; Cai et al., 2020). Additionally, MCS* also appeared higher participation coefficient and degree of alpha in the parietal region (Thibaut et al., 2021). Further, the parietal regions of VS/UWS patients showed the most extensive variation of beta bands with higher clustering coefficients compared with those of MCS patients (Cacciola et al., 2019). Furthermore, the fractional occupancy of the posterior transient state, which was characterized by a higher alpha power at parietal lobe and enhanced parietal connectivity, was significantly higher in healthy subjects than in DOC patients (Bai et al., 2021).

When TMS was applied over parietal cortices, VS/UWS patients showed simpler response patterns and OFF periods, unlike MCS patients. The duration of the causal effects of TMS on local cortical activity was shorter-lived in VS/UWS patients than in healthy awake controls (Rosanova et al., 2018). Higher complexity of parietal activities was found in MCS patients than in VS/UWS patients, which were revealed by spectral entropy and permutation entropy (Sitt et al., 2014; Piarulli et al., 2016). VS/UWS patients were found to lack nP3 and P300 components, unlike MCS or conscious patients (Risetti et al., 2013; Xiao et al., 2018).

4.2. Parietal EEG characteristics in outcome of DOC

Vegetative consciousness/unresponsive wakefulness syndrome patients exhibited nP3 with parietal scalp topography, and they recovered to MCS after 4.5 months (Risetti et al., 2013). The survivors of DOC showed stronger central-parietal negativity N1 than did the non-survivors (Meiron et al., 2021). The parietal region of patients showed a significant increase in the normalized theta power and an increase in the permutation entropy in the theta-alpha band after tDCS treatment (Hermann et al., 2020). Patients who had prominently parietal strong connections showed negative outcomes (Chennu et al., 2017). After HD-tDCS treatment, alpha-beta increasing and delta decreasing occurred in the parietal lobe (Cai et al., 2019; Zhang C. Y. et al., 2022).

5. Frontal-parietal connectivity in DOC

Studies revealed that the functional connectivity between the frontal and parietal brain regions was highly correlated with the state of consciousness of DOC patients (**Supplementary Table 1**). The fronto-parietal connectivity was impaired in DOC patients (Naro et al., 2020). When referring to behavioral response levels, the strength of the fronto-parietal connectivity in the theta (Lehembre et al., 2012) and alpha (Naro et al., 2018) bands increased with the consciousness level. The inter-hemispheric connectivity in the fronto-parietal cortex of VS/UWS patients was lower than that in MCS patients (Chennu et al., 2017; Cacciola et al., 2019). Although MCS + and MCS-cannot be distinguished from connectivity, MCS + showed a the strongest fronto-parietal focus of topographical pattern for, which is more pronounced in patients with high levels of consciousness (Chennu et al., 2017).

The association of gamma connectivity with consciousness levels was not consistent across studies. An increased fronto-parietal gamma coherence induced by noxious stimulation was reported in healthy subjects and MCS patients but not in VS/UWS patients (Cavinato et al., 2015). However, the gamma coherence decreased after tDCS in MCS patients but not in VS/UWS patients (Bai et al., 2018). Furthermore, a clear TMS-evoked neural response propagated from frontal to parietal in the MCS patients but not in the VS/UWS patients (Wang et al., 2022). In the analysis of transient states, DOC patients showed a break of coherence in the alpha band between the medial prefrontal cortex and posterior cingulate cortex in the anterior state (Bai et al., 2021).

The enhancement of the fronto-parietal connectivity was reported along with the recovery of consciousness. The patients with higher delta, theta, alpha, and beta coherence recovered from VS/UWS to MCS after 1 year (Schorr et al., 2016). Similarly, the fronto-parietal connectivity in the alpha and beta bands appears in patients with an improved state of consciousness after 3 months (Fingelkurts et al., 2013).

6. Discussion

The EEG contains consciousness information in different dimensions: rhythmic oscillations (spectrum), functional network, and dynamic non-linearity. In combination with the multi-dimensional information, the EEG features in the frontal and parietal showed a significant difference with different consciousness levels. The spectrum captures the rhythmic spontaneous activity of neuronal populations (Coleman et al., 2005). Impaired consciousness is usually accompanied by spectral abnormalities in the resting state. In either the frontal or parietal brain regions, VS/UWS patients always showed higher delta power and lower theta, alpha, and beta (not MCS*) powers than those of MCS and MCS* patients. Non-linear dynamic theory considers neural networks to be a complex non-linear system. Non-linear dynamics in the time or frequency domain are more straightforward to quantify the complexity of neural activities. Compared with VS/UWS, the non-linearity of MCS was generally more complex in MCS patients in both the frontal and parietal regions. The functional network, which captures the local integration and global synchronization relationships of the cortex, showed more intensity connections, with higher integration in MCS patients than in VS/UWS patients in both the frontal and parietal brain regions. The TMS-evoked neural responses in the frontal and parietal brain regions were highly abnormal in the case of injury of consciousness. VS/UWS patients showed a specific off-period and a shorter causal effect duration than those of healthy subjects (Rosanova et al., 2018).

The frontal and parietal still showed differences in distinguishing consciousness. Regarding the power spectrum, the frontal only showed a difference between MCS and VS/UWS for delta, theta, alpha, and beta. In the parietal area, high-frequency activity (gamma) was also considered a characteristic relevant to consciousness (Naro et al., 2016a, 2018). The indicator of the parietal gamma activity even exceeded alpha in the deterioration of consciousness (Srivas et al., 2016). Although the functional connectivity showed a decrease in both the frontal and parietal regions of DOC patients, most evidence for the frontal region came from the comparison of DOC and healthy subjects, while the parietal region showed clear differences between VS/UWS and MCS (Sitt et al., 2014; Chennu et al., 2017; Cacciola et al., 2019; Cai et al., 2020).

Overall, the reduction of consciousness is often accompanied by an enhancement of low-frequency rhythms, suppression of high-frequency rhythms, reduction of dynamic complexity, and breakdown of networks in the frontal and parietal brain regions. Although the current studies reported a difference in EEG characteristics between the frontal and parietal brain regions for the classification of consciousness levels, enough evidence is not available to clarify their priority in consciousness injury or recovery.

Literatures reported a significant correlation between the fronto-parietal network and residual consciousness of DOC patients. According to the current knowledge, the consciousness level of DOC patients depends on the strength of the large-scale connectivity between the frontal and parietal brain and is related to the neural activities within local regions. Consciousness impairment is often accompanied by the deterioration and heterogeneity of frontal and parietal connectivity within a certain frequency band (e.g., theta, alpha) (Lehembre et al., 2012; Chennu et al., 2017; Bai et al., 2018; Naro et al., 2018). This is consistent with the meso-circuit model in which the frontal and parietal cortices act as critical hubs and the fronto-parietal connection integrates consciousness-related information processing at the cortical level part of the consciousness circuit (Schiff, 2010; Giacino et al., 2014). The frontal cortex organizes goal-directed behavior (Schiff, 2010), adjusts the body's arousal levels in different states and alertness, and activates or cooperates with the central thalamus to adapt to higher cognitive needs by increasing activity (Paus et al., 1998; Nagai et al., 2004). The functional connectivity between the frontal and parietal lobes allows the two cortices to not only directly regulate the meso-circuit through feedback but also indirectly through the frontal cortical-striatopallidal-thalamocortical loop systems (Münkle et al., 2000; Werf et al., 2002) to maintain normal conscious pathways in the brain.

In the cross-sectional comparison of different states of consciousness in DOC, most comparisons between VS/UWS and MCS could not clearly exclude impacts from individual differences, such as age, etiology, treatment strategy, and care environment. The longitudinal tracking of DOC outcomes could help to identify the most important characteristics by focusing on the temporal correlation between consciousness levels and neural electrical activity in individuals. The follow-up studies highlighted the role of evoked potentials in the frontal and parietal regions in detecting consciousness. The nP3 topography changed as the patients recovered from VS/UWS to MCS. DOC survivors showed lateralization in the N1 component topography compared to non-survivors. The centers of the topography distribution indicated important information processing in the frontal and parietal regions (Risetti et al., 2013; Meiron et al., 2021). Simultaneous changes of delta, alpha and beta index the patients with signs of consciousness improvement (Cai et al., 2019; Zhang C. Y. et al., 2022). Furthermore, the enhancement of frequency coupling (QPSC) and phase synchronization (coherence) (Naro et al., 2016c; Bai et al., 2019; Guo et al., 2019) in the frontal region both indicated the functional recovery of DOC patients.

Most EEG studies made conclusions based on scalp-level observations, which would be biased by the effect of volume conduction. Although existing studies consistently highlight the role of the frontal and parietal regions in DOC, the accurate location of the NCC at the cortical level remains unclear. Source construction in combination with high-density EEG and individualized anatomy could technically improve the spatial accuracy of EEG characteristics by solving the volume conduction problem. In addition to the source construction, TMS-EEG can provide high cortical-spatial precision causal relationships between TMS targets and neural responses. Current TMS-EEG studies have provided considerable and detailed information for the diagnosis of DOC and cortical damage. However, studies to establish maps between target-evoked responses and consciousness are still needed. These could facilitate our understanding of the excitability and plasticity of the frontal and parietal regions in human consciousness. In EEG studies, source reconstruction of high-density EEG, machine learning with large samples, and TMS-EEG mapping should be important tools for refining EEG awareness locations and locating the smallest neural correlates of consciousness.

Author contributions

YB wrote the manuscript. YL and ZL reviewed the manuscript. 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

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2022.1024278/full#supplementary-material

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Opioid-induced short-term consciousness improvement in patients with disorders of consciousness

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Introduction: Effective treatment to facilitate recovery from prolonged disorders of consciousness is a complex topic for the medical community. In clinical practice, we have found that a subset of patients has a short-term improvement of consciousness after general anesthesia.

Methods: To determine the clinical factors responsible for the consciousness improvement, we enrolled 50 patients with disorders of consciousness who underwent surgery from October 2021 to June 2022. Their states of consciousness were evaluated before surgery, within 48 h after surgery, and 3 months after surgery. Clinical-related factors and intraoperative anesthetic drug doses were collected and compared between patients with and without consciousness improvement. Independent associations between selected factors and postoperative improvement were assessed using multivariate logistical regression analyses.

Results: Postoperative short-term consciousness improvement was found in 44% (22/50) of patients, with significantly increased scores of auditory and visual subscales. Patients with traumatic etiology, a preoperative diagnosis of minimally conscious state, and higher scores in the auditory, visual, and motor subscales were more likely to have postoperative improvement. This short-term increase in consciousness after surgery correlated with patients' abilities to communicate in the long term. Furthermore, the amount of opioid analgesic used was significantly different between the improved and non-improved groups. Finally, analgesic dose, etiology, and preoperative diagnosis were independently associated with postoperative consciousness improvement.

Discussion: In conclusion, postoperative consciousness improvement is related to the residual consciousness of the patient and can be used to evaluate prognosis. Administration of opioids may be responsible for this short-term improvement in consciousness, providing a potential therapeutic approach for disorders of consciousness.

KEYWORDS

disorders of consciousness, vegetative state, minimal conscious state, opioid analgesic, medical treatment

1. Introduction

Critical brain damage, such as traumatic brain injury (TBI), intracerebral hemorrhage (ICH), and anoxic brain injury (ABI), cause disorders of consciousness (DoC). Patients who remain in a state with preserved wakefulness and impaired awareness for >4 weeks are diagnosed with prolonged DoC (Scolding et al., 2021). Many studies have performed further diagnoses in DoC patients to better understand the natural recovery of consciousness (i.e., the ability to respond to external stimuli and to have internal feelings). Depending on the degree of wakefulness and awareness of the patients, DoC is divided into coma (unwakefulness, unawareness), unresponsive wakefulness syndrome/vegetative state (VS) (wakefulness, unawareness), and minimally conscious state (MCS; wakefulness, minimal but definite evidence of awareness) (Thibaut et al., 2019). The diagnosis of MCS is further divided into MCS+ and MCS− by presence or absence of language-related behaviors, respectively, as the functional impairments are different between these two groups of patients (Thibaut et al., 2020).

Despite the significant advances in understanding DoC over the last few decades, there are few valid interventions to promote recovery (Edlow et al., 2021). Several pharmacological treatments are tested for restoring cognitive function after severe brain injuries. Representative classes of drugs are dopaminergic stimulants (e.g., amantadine, methylphenidate, levodopa, bromocriptine, and apomorphine), gamma amino-butyric acid (GABA) receptor stimulants (e.g., zolpidem and baclofen), and antidepressants (e.g., Tricyclic antidepressants) (Pistoia et al., 2010; Ciurleo et al., 2013). However, amantadine is the only pharmacological treatment tested in randomized controlled trials to show benefit in accelerating functional recovery (although it does not improve final outcomes) from acute to subacute traumatic VS and MCS (Giacino et al., 2012). The efficacy of other drugs and treatments is ambiguous, with insufficient evidence and low positive response rates (Fridman and Schiff, 2014). With recent advances in neural arousal circuit research, multiple neuromodulation therapies [e.g., deep brain stimulation and spinal cord stimulation (SCS)], have been used to promote recovery in DoC patients (Xia et al., 2018).

Of interest, during clinical practice with these novel techniques and with more traditional surgical approaches (e.g., cranioplasty and cerebrospinal fluid shunt), we found that a large proportion of patients exhibited a temporary increase in consciousness after general anesthesia, regardless of the type of surgery they received. General anesthesia is the common intervention provided to all patients undergoing surgery. General anesthesia involves a reversible state of unconsciousness, amnesia, analgesia, and dyskinesia induced by a combination of medications, including anesthetics, analgesics, and muscle relaxants (Avidan et al., 2022). The mechanisms by which anesthetic agents induce and maintain the unconscious state, and how consciousness recovers after general anesthesia, are critical issues in neuroscience. Anesthetics can suppress consciousness by inhibiting arousal nuclei in the brainstem and diencephalon (e.g., locus coeruleus and pons reticular formation) or by activating sleep-promoting nuclei (e.g., preventral optic nucleus) (Mashour and Hudetz, 2017). However, opioids, which are the most commonly used analgesics, cause a central excitatory effect during anesthesia recovery (Dzikiti et al., 2016).

The present study examined the hypothesis that the medications used in general anesthesia induce improvements in consciousness in the short-term postoperative period. We retrospectively reviewed 50 DoC patients who underwent surgery and examined the changes in consciousness before and after the operation. Clinically related factors and intraoperative doses of anesthetic drugs were collected and analyzed. The overall aim of this study was to determine the medicines that were responsible for, and that affected the occurrence of short-term consciousness improvement. This information may provide important new information on potential treatments for DoC.

2. Materials and methods

2.1. Participants

Patients diagnosed with VS or MCS for ≥4 weeks scheduled to undergo surgery in Beijing Tiantan Hospital or the Seventh Medical Center of PLA General Hospital from October 2021 to June 2022 were enrolled in this study. We excluded participants with pre-existing neurological conditions, who took long-acting sedative drugs before the study, and those with liver and kidney failure or serious complications. The overall research protocol was approved by the Ethics Committee of Beijing Tiantan Hospital and the Seventh Medical Center of the Chinese PLA General Hospital. Informed consent was obtained from the legal representatives of the subjects.

2.2. Data collection

The demographic and clinical data of all included patients were recorded at baseline. The collected data included age, gender, weight, disease course, and etiology of DoC. Consciousness status was assessed by experienced raters using the revised JFK Coma Recovery Scale (CRS-R) (Kalmar and Giacino, 2005). The scores of six subscales of the CRS-R scale evaluating auditory, visual, motor, oromotor, communication, and arousal functions were recorded. Preoperative CRS-R scores were assessed at least five times within 2 weeks during awake and stable (without complications, including fever, and epilepsy) periods to avoid potential errors caused by fluctuations in responsiveness. The highest score was used to assess each patient's baseline consciousness level.

The operation methods, the classification of the American Society of Anesthesiologists (Kotake, 2016), and the anesthesia methods were documented. Intraoperative medications, including propofol, sevoflurane, remifentanil, sufentanil, and rocuronium, and their doses were recorded for further analysis. The doses of sufentanil and remifentanil were converted to the morphine dose (Arnold and Weissman, 2003) and added to analyze the total analgesic effect.

After awakening from anesthesia, two experienced physicians screened and recorded each patient's consciousness state for 48 h. Postoperative consciousness states were also evaluated by the CRS-R scale, and the highest scores were used to describe the patient's postoperative consciousness level. No treatments or drugs for cortical excitability were used during the first 2 days after surgery. Patients with improved postoperative diagnosis (VS to MCS or MCS− to MCS+) or those who reached the criterion of "localization to sound" or "visual fixation" [reflecting higher-order processing (Weaver et al., 2022)] were classified as the improved group. The remaining patients were classified as the non-improved group. The same assessment was also performed 3 months after surgery.

2.3. Statistical analysis

The difference between preoperative and postoperative CRS-R scores and subscores were analyzed with the Wilcoxon signed rank test. To determine the cause of postoperative improvement, explorative data analyses were performed between the improved and non-improved groups. Results are presented as proportions (%), medians and interquartile range, or arithmetic means and standard deviations depending on their scale. Tests for statistical significance were performed with Fisher's exact test, chi-square test, Wilcoxon–Mann–Whitney *U* test, or two-tailed Student's *t*-test. Multivariate logistic regression analysis was used to identify independent risk factors for postoperative improvement. A *p*-value < 0.05 was considered statistically significant.

3. Results

Fifty DoC patients (18 cases of traumatic brain injury, 16 cases of ICH, and 16 cases of ABI) were enrolled in the present clinical trial between October 2021 and June 2022. The characteristics of all patients are presented in Table 1. All patients suffered from DoC for > 1 month. The preoperative diagnosis was determined according to the CRS-R scores [12] and the diagnosis criteria of MCS+ [3]. The median CRS-R score was 7 (range, 4–13). All patients received surgical treatments under general anesthesia, including percutaneous SCS ($n = 35$), SCS ($n = 11$), cranioplasty ($n = 5$), ventriculoperitoneal shunt ($n = 4$), and skin dilator implantation ($n = 1$). Six patients underwent two operations at the same time. The surgical methods were summarized into minimally invasive operations ($n = 30$) and open operations ($n = 20$). There were no significant differences between the surgical techniques, the anesthesia methods, or the anesthetic time.

Postoperative consciousness improvement was found in 22 (44%) patients. The postoperative CRS-R scores of these patients significantly increased ($p < 0.01$) by 1–4 points compared with their preoperative scores (Supplementary Table 1). The scores of the auditory ($p < 0.01$) and visual ($p = 0.01$) subscales increased significantly, with no noticeable change in other subscales. However, this consciousness improvement only lasted 8–48 h after emergence from anesthesia.

3.1. Comparisons between the improved and non-improved groups

To analyze the causes and influencing factors of postoperative consciousness improvement, we divided DoC patients into improved and non-improved groups (Table 2). Patients with or without postoperative improvement were significantly different in etiology, preoperative diagnosis, and preoperative CRS-R score (mainly in the auditory, visual, and motor subscales) compared with the non-improved group. Patients with short-term postoperative consciousness improvement also performed better in long-term outcomes compared with the non-improved group. More importantly, patients with short-term postoperative improvement were more likely to regain the ability to communicate (28.6%, two accurate and four intentional) than those without postoperative improvement (7.1%, two intentional). However, the occurrence of postoperative improvement did not predict whether patients would benefit from other treatments (Supplementary Table 2).

TABLE 1 Baseline demographic and clinical characteristics of the patients.

	Group	Patients ($n = 50$)
Age, years		45.2 ± 15.0
Weight, kg		64.6 ± 8.9
Gender (Male)		30 (60%)
Disease course, months		4.0 [2.0–6.5]
Etiology	TBI	18 (36%)
	ICH	16 (32%)
	ABI	16 (32%)
Diagnosis on admission	VS	29 (58%)
	MCS−	16 (32%)
	MCS+	5 (10%)
CRS-R		7 [6–8]
Severity of surgery	II	4 (8%)
	III	22 (44%)
	IV	24 (48%)
Surgical method	Minimally invasive operation	30 (60%)
	Open operation	20 (40%)
Anesthetic method	Intravenous	14 (28%)
	Inhalation	12 (24%)
	Intravenous-inhalation	24 (48%)
Anesthetic time, minute	–	123 [80–180]

TBI, traumatic brain injury; ICH, intracerebral hemorrhage; ABI, anoxic brain injury; VS, unresponsive wakefulness syndrome/vegetative state; MCS, minimally conscious state; CRS-R, revised JFK coma recovery scale. Data are given as mean ± SD for normal distributed continuous variables, as median [IQR] for abnormal distributed continuous variables, and as count (percentages) for categorical variables.

We also found a significant difference in intraoperative opioid consumption between the two groups. Considering the similar pharmacologic effect of remifentanil and sufentanil, only the converted morphine dose was used in subsequent analyses. By contrast, there were no differences in the other intraoperative medications, surgical methods, anesthetic methods, and anesthetic times (Supplementary Table 2). We further investigated the relationship between the etiology, preoperative diagnosis, and analgesic dose. However, there were no differences in analgesics between patients with different etiologies or diagnoses.

3.2. Association with postoperative consciousness improvement

Multivariate logistic regression analysis for the endpoint of postoperative consciousness improvement (improved vs. non-improved) was adjusted for etiology (TBI and ICH vs. ABI), preoperative diagnosis (MCS+ and MCS− vs. VS), and analgesic dose (high vs. low). Because of the close relationship between the diagnosis and the CRS-R score (as well as the subscores), we only included the diagnosis in the multivariate logistic regression. To simplify the evaluation, the analgesic doses were divided into high

TABLE 2 Clinical characteristics between the improved and non-improved groups.

	Non-improved	Improved	χ^2/Z	*P*-value[#]
	n = 28 (56%)	*n* = 22 (44%)		
Etiology			6.37[b]	**0.04**
TBI	6 (21.4%)	12 (54.5%)		
ICH	10 (35.7%)	6 (27.3%)		
ABI	12 (42.9%)	4 (18.2%)		
Diagnosis			11.02[b]	**<0.01**
UWS/VS	22 (78.6%)	7 (31.8%)		
MCS−	5 (17.9%)	11 (50%)		
MCS+	1 (3.6%)	4 (18.2%)		
Preoperative CRS-R	6 [5–7]	8 [7–9]	−3.46[a]	**<0.01**
Auditory	1 [1–1]	1 [1–1]	−2.25[a]	**0.02**
Visual	0.5 [0–1]	1 [1–3]	−2.52[a]	**0.01**
Motor	2 [2–2]	3 [2–3]	−3.72[a]	**<0.01**
Oromotor	1 [1–1]	1 [1–1]	0.00[a]	1.00
Communication	0 [0–0]	0 [0–0]	−1.61[a]	0.11
Arousal	2 [2–2]	2 [2–2]	−0.62[a]	0.53
Long-term CRS-R	7 [6–10.5]	10 [8–19]	−2.901[a]	**<0.01**
Auditory	1 [1–2]	1 [1–4]	−1.621[a]	0.11
Visual	1 [0–3]	3 [1–5]	−2.749[a]	**<0.01**
Motor	2 [2–2]	3 [2–5]	−2.637[a]	**<0.01**
Oromotor	1 [1–1]	1 [1–1]	−1.952[a]	0.05
Communication	0 [0–0]	0 [0–1]	−2.045[a]	**0.04**
Arousal	2 [2–2]	2 [2–3]	−2.456[a]	**0.01**
Intraoperative medication				
Propofol, mg/kg	1.33 [0–6.22]	3.27 [0.43–10.22]	−1.196[a]	0.23
Sevoflurane,%	1.5 [0.2–2]	1.5 [0–2]	−0.253[a]	0.80
Sufentanil, μg	20 [10–30]	20 [15–22.5]	−0.359[a]	0.72
Remifentanil, μg/kg/min	0.03 [0–0.06]	0.05 [0.05–0.1]	−2.312[a]	**0.02**
Morphine (conversion), mg/kg	0.55 [0.25–1.21]	1.23 [0.61–1.65]	−2.424[a]	**0.02**
Rocuronium, mg	50 [30–50]	45 [30–57.5]	−0.119[a]	0.91

TBI, traumatic brain injury; ICH, intracerebral hemorrhage; ABI, anoxic brain injury; UWS/VS, unresponsive wakefulness syndrome/vegetative state; MCS, minimally conscious state; CRS-R, revised JFK coma recovery scale. Data are given as median [IQR] for abnormal distributed continuous variables, and as count (percentages) for categorical variables. [a]Wilcoxon–Mann–Whitney test was used to compare groups for continuous variables. [b]Fisher's exact test was used to compare groups for categorical variable. [#]Bold indicates data reaching the threshold of significance ($p < 0.05$).

and low groups using the median as the boundary. We found an 8.2-fold higher odds ratio (OR) for postoperative consciousness improvement with a higher analgesic dose [OR, 8.22; 95% confidence interval (95% CI), 1.56–43.23; $p = 0.013$]. Furthermore, etiology (TBI vs. ABI: OR, 10.77; 95% CI, 1.31–88.43; $p = 0.027$) and preoperative diagnosis (MCS− vs. VS: OR, 9.6; 95% CI, 1.63–56.73; $p = 0.013$; MCS+ vs. VS: OR, 12.26; 95% CI, 1.06–142.07; $p = 0.045$) were independently associated with postoperative consciousness improvement (**Figure 1**).

4. Discussion

In the present study, 22 of the 50 patients with DoC experienced a short-term postoperative consciousness improvement. Indeed, postoperative assessment with the CRS-R scale showed a clear and definite improvement in the auditory and visual function of those patients. Patients with traumatic etiology and those with preoperative diagnosis of MCS were more likely to have postoperative improvement. Furthermore, the scores of auditory, visual, and motor subscales were most predictive of postoperative improvement. Finally, this short-term increase in consciousness after surgery correlated with the patients' abilities to communicate in the long-term. To the best of our knowledge, this is the first clinical report demonstrating the phenomenon of short-term postoperative consciousness improvement in DoC patients. We suggest that opioid analgesics play a critical role in this phenomenon, and that opioids may be a novel therapeutic intervention to promote consciousness and functional recovery in DoC patients.

4.1. Relationship between residual consciousness and postoperative consciousness improvement

We found that differences in preoperative diagnosis and etiology of DoC were associated with the incidence of postoperative consciousness improvement. The preoperative CRS-R scores and the auditory, visual, and motor subscores differed between patients in the improved and non-improved groups. Moreover, the patients with short-term consciousness improvement had higher CRS-R scores and the scores of visual, motor, communication, and arousal subscales at 3 months after surgery. Finally, the probability of regaining communication ability was significantly higher in patients in the improved group.

A diagnosis of minimal conscious state was previously defined as reproducible evidence of environmental- or self-awareness (Bender et al., 2015), while a diagnosis of minimal conscious state plus was characterized by the presence of linguistically mediated behaviors (Thibaut et al., 2020). Both states indicated a better-preserved residual consciousness (Laureys et al., 2004). Compared with VS patients, MCS patients demonstrated more widespread brain activation following simple sudatory stimulation and had more robust functional connectivity between the secondary auditory cortex and the temporal and prefrontal auditory-related cortices (Boly et al., 2004). An imageology study also revealed that the dorsomedial body volume of the thalamus was significantly lower in DoC patients, and that this atrophy was more extensive in VS than MCS patients (Fernández-Espejo et al., 2010). Furthermore, significant differences in the N200 and P300 waves of event-related potentials were found between MCS and VS patients (De Salvo et al., 2015). It is generally accepted that traumatic etiology is associated with more favorable outcomes (Ní Lochlainn et al., 2013; Giacino et al., 2018), indicating more complete neural networks in traumatic DoC. The higher rate of postoperative consciousness improvement in patients with

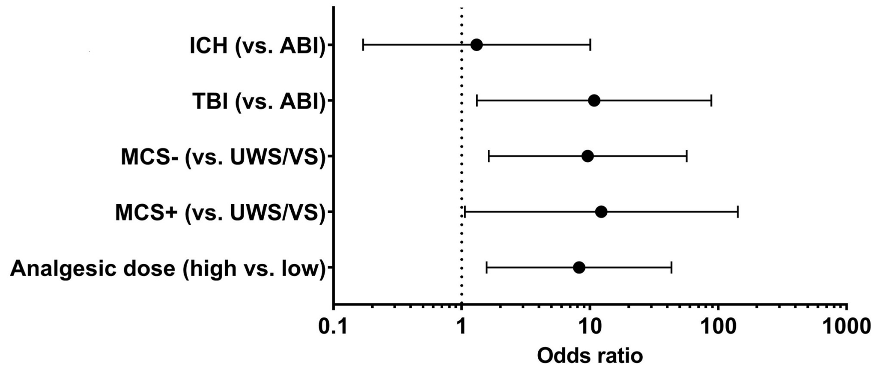

FIGURE 1
Relative factors of postoperative improvement in DoC patients. In multivariate logistic regression, the etiology (TBI vs. ABI: OR, 10.77; 95% CI, 1.31–88.43; $p = 0.027$), preoperative diagnosis (MCS− vs. VS: OR, 9.6; 95% CI, 1.63–56.73; $p = 0.013$; MCS+ vs. VS: OR, 12.26; 95% CI, 1.06–142.07; $p = 0.045$), and opioid analgesic dose (high vs. low: OR, 8.2; 95% CI, 1.56–43.23; $p = 0.013$) were independently associated with the postoperative improvement in DoC patients. TBI, traumatic brain injury; ICH, intracerebral hemorrhage; ABI, anoxic brain injury; UWS/VS, unresponsive wakefulness syndrome/vegetative state; MCS, minimally conscious state.

traumatic etiology, better preoperative diagnosis, and higher CRS-R scores suggest that short-term improvement may be correlated with better residual consciousness. Given that significant differences were only found in the auditory, visual, and motor subscales in the present study, these subscales may have better predictive power for residual consciousness, which is consistent with our previous findings (He et al., 2014).

We also found that the short-term consciousness improvement was related to the level of consciousness at 3 months after surgery. More importantly, patients in the improved group had significantly higher scores on the communication subscale at 3 months after surgery, and this group had a higher reestablishment rate of communication ability. Although it is unclear whether this long-term improvement was caused by the intraoperative opioid application, the appearance of short-term postoperative improvement may help predict outcomes in DoC patients and guide more aggressive treatments. Communication ability is the most concerning issue for doctors and families of DoC patients, with a great deal of work performed to detect residual consciousness and potential communication abilities (Owen and Coleman, 2008; Gui et al., 2020). Complex methods, including structural (Sattin et al., 2021) and functional (He et al., 2015; Aubinet et al., 2020) magnetic resonance imaging, electroencephalography (Bai et al., 2021; Porcaro et al., 2022), and brain–computer interfaces (Müller-Putz et al., 2013), are used to evaluate residual consciousness and prognosis. However, changes in patient performance can affect the assessment and prognosis accuracy in DoC (Murovec et al., 2020). Our findings raise the possibility that a short-term administration of opioids (or remifentanil) may improve patients' performance and assist in assessing residual consciousness.

4.2. Role of opioids analgesics in postoperative consciousness improvement

We found no significant differences in postoperative consciousness improvement for any intraoperative medications except remifentanil. When combining the doses of remifentanil and sufentanil by converting to the morphine dose, the difference was even more marked. The lack of a difference with sufentanil treatment between the two groups may be related to use of a similar dose to that for induction drugs by the anesthesiologists. However, in subsequent multivariate regression analysis, the dose of opioid analgesics was an independent factor affecting short-term postoperative improvement.

Both remifentanil and sufentanil are opioid agonists, which produce an analgesic effect by activating the μ-opioid receptor (MOR) (Ziesenitz et al., 2018). Opioid receptors are widely distributed in the central nervous system. MORs located in the dorsal horn of the spinal cord, a major center of pain information processing (Braz et al., 2014), are essential for both the analgesic effects and the sensory input potentiation of opioids (Sun et al., 2019). The opioid system also potently modulates the mesolimbic circuitry, limbic circuitry, cortical and hippocampal circuitry, and various brain regions underlying motivation, fear responses, and cognitive functions (Puryear et al., 2020). MORs are predominantly expressed on GABAergic inhibitory interneurons and exert a potent disinhibitory effect on excitatory neurons (Nam et al., 2021).

There is a paradoxical hyperalgesia response in patients receiving opioids for pain control, whereby some patients become more sensitive to painful stimuli (hyperalgesia) and have a painful reaction to innocuous stimuli (allodynia)—this is termed opioid-induced hyperalgesia (OIH) (Velayudhan et al., 2013). The mechanism of OIH is not fully understood but is generally considered related to sensitization of the pronociceptive pathway caused by peripheral and central neuroplastic changes (Lee et al., 2011). OIH has been widely reported after the perioperative use of opioid analgesia (Colvin et al., 2019). A meta-analysis of OIH after surgery comparing 1,494 patients from 27 studies found that a higher intraoperative opioid dose (mainly remifentanil) was correlated with higher postoperative pain intensity and morphine use (Fletcher and Martinez, 2014). A biphasic time-dependent effect of fentanyl was also reported (Célèrier et al., 2000), with a nociceptive threshold increase lasting 2–5 h after fentanyl injection, followed by a sustained descending nociceptive threshold for up to 5 days.

The degree of hyperalgesia is dose-dependent. The occurrence of postoperative consciousness improvement was only found in patients receiving higher doses of opioids. Moreover, the time points of the consciousness improvement (within 48 h post-operation) and OIH were similar. The pattern between the onset of hyperalgesia and opioid analgesia use was similar to that between the short-term postoperative consciousness improvement and the use of opioids found in the present study, suggesting a relationship between OIH and consciousness improvement. However, we found no difference between minimally invasive and open surgery, indicating that the incision pain was not responsible for the consciousness improvement. Sensitization of the pronociceptive pathway is achieved *via* sensitization of primary afferent neurons and second-order neurons, an increased concentration of excitatory neurotransmitters (through enhanced production and release and diminished reuptake), and activation of descending facilitation of the rostral ventromedial medulla (Lee et al., 2011). These mechanisms ultimately lead to enhanced sensory afferent signals, which cause algesia in conscious patients. However, in patients with DoC, the same physiological responses to opioids strengthen the external environmental stimulation, enhancing the signal input to the ascending reticular activating system. This activation maintains cortical neurons in a state of facilitation and excitation, leading to a better clinical manifestation in DoC patients. Although this side effect of opioids is unwanted by anesthesiologists, it has the potential to become a therapy to promote recovery of consciousness in DoC patients. Further studies assessing the mechanisms of hyperalgesia in DoC are required.

Another potential mechanism underlying the postoperative improvement in consciousness with opioids involves enhanced dopamine release caused by the disinhibitory effect of activated GABAergic neurons. Opioids can activate MORs in the reward circuitry of the brain, which suppresses inhibitory neurotransmission in the ventral tegmental area and reduces the inhibitory postsynaptic event frequency of GABAergic interneurons, further increasing the release of dopamine into the striatum and prefrontal cortex (Colvin et al., 2019). This opioid-mediated disinhibition of dopaminergic neurons in the ventral tegmental area and substantia nigra pars compacta is hypothesized to cause the arousing and rewarding effects of opioids (Steidl et al., 2017). Recently, the occurrence of forebrain dysfunction in DoC was found to be caused by death and disconnection of neurons as well as "circuit-level" functional disturbances, which could be modulated to promote the recovery of consciousness (Schiff, 2010). The "mesocircuit" hypothesis suggests that normal anterior forebrain function depends on activation of thalamocortical projections in the central thalamus, which is inhibited by globus pallidus internal tonic signals during DoC (Schiff, 2008). High levels of dopaminergic activity maintain striatal firing rates, which inhibits the tonic signals of the globus pallidus and further activates the central thalamus (Grillner et al., 2005). The only validated treatment for DoC, amantadine (Giacino et al., 2012), is an indirect dopamine agonist. Increased striatal D2 dopamine-receptor availability and prefrontal cortical metabolism were found after amantadine treatment (Kraus et al., 2005; Schnakers et al., 2008). The same pattern of dopaminergic neuron activation is also found after opioid administration.

There are a number of other potential mechanisms involved in the beneficial effects of opioids. The latest clinical guidelines recommend evaluating and treating pain in patients with DoC (Giacino et al., 2018). However, as a subjective experience, it is difficult to recognize pain in DoC patients when no self-report is available. Nevertheless, recent advances in neuroimaging techniques have provided the capacity to perceive pain in DoC patients (Schnakers and Zasler, 2015). The high prevalence of spasticity in DoC patients and the positive correlation between the level of spastic muscle overactivity and pain (Thibaut et al., 2015) suggest that a large proportion of these patients suffer pain. Persistent pain may affect patients' responses to the external environment, and pain relief *via* administration of analgesics may improve the clinical manifestations in DoC patients. Recent studies have shown that the pain-related brain circuit is incomplete in VS patients, with less evidence of painful conscious experiences. By contrast, MCS patients have sufficient cortical integration to process nociceptive stimuli, and the patterns of brain activation to painful stimulation in MCS patients were similar to those in healthy controls (Schnakers and Zasler, 2007). These differences in pain experience between VS and MCS patients may partly explain the different rates of postoperative improvement between these two groups.

4.3. Limitations

This preliminary study included a small sample of patients. Further studies with more patients and standardized within-group differences are required. Furthermore, we only assessed the level of consciousness during the first two postoperative days because additional treatments introduced more distractors on the following days. It should also be noted that because of the lack of responsiveness in DoC patients, a wide range of the anesthetic agents were applied to our patients. Standardized anesthesia protocols should be stipulated in future studies.

5. Conclusion

Short-term consciousness improvement is related to patients' residual consciousness and can aid estimation of long-term prognosis. Opioid analgesics may cause short-term improvements in consciousness *via* enhanced sensory afferent signals caused by (i) opioid-induced peripheral and central neuroplastic changes, (ii) increased striatal dopamine release caused by disinhibition of opioid-related GABAergic neuron activation, and (iii) relief of persistent pain in DoC patients. These findings suggest that opioids may be useful for determining prognosis and promoting recovery in DoC patients. However, further clinical and experimental studies are required to understand the utility of opioids in DoC patients, including opioid-related consciousness improvement.

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 and the Seventh Medical Center of the Chinese PLA General Hospital.

Written informed consent to participate in this study was provided by the participants or their legal guardian/next of kin.

Author contributions

JH, QG, and YW contributed to conception and design of the study. QG, YW, YZ, and QL organized the database. QG and YW performed the statistical analysis. QG wrote the first draft of the manuscript. YW wrote sections of the manuscript. 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/fnins.2023.1117655/full#supplementary-material

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A prediction model of clinical outcomes in prolonged disorders of consciousness: A prospective cohort study

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Objective: This study aimed to establish and validate a prediction model for clinical outcomes in patients with prolonged disorders of consciousness (pDOC).

Methods: A total of 170 patients with pDOC enrolled in our rehabilitation unit were included and divided into training (n = 119) and validation sets (n = 51). Independent predictors for improved clinical outcomes were identified by univariate and multivariate logistic regression analyses, and a nomogram model was established. The nomogram performance was quantified using receiver operating curve (ROC) and calibration curves in the training and validated sets. A decision curve analysis (DCA) was performed to evaluate the clinical usefulness of this nomogram model.

Results: Univariate and multivariate logistic regression analyses indicated that age, diagnosis at entry, serum albumin (g/L), and pupillary reflex were the independent prognostic factors that were used to construct the nomogram. The area under the curve in the training and validation sets was 0.845 and 0.801, respectively. This nomogram model showed good calibration with good consistency between the actual and predicted probabilities of improved outcomes. The DCA demonstrated a higher net benefit in clinical decision-making compared to treating all or none.

Conclusion: Several feasible, cost-effective prognostic variables that are widely available in hospitals can provide an efficient and accurate prediction model for improved clinical outcomes and support clinicians to offer suitable clinical care and decision-making to patients with pDOC and their family members.

KEYWORDS

disorder of consciousness, brain injury, minimally conscious state, vegetative state, cohort

1. Introduction

Disorders of consciousness (DOC) is a state in which an individual's consciousness has been severely affected due to massive brain injury. There are two essential elements of consciousness: arousal and content. Disruption of one or both of these elements may result in DOC. Prolonged disorder of consciousness (pDOC) is defined as a coma condition usually lasting more than 4 weeks (Giacino et al., 2018b). Approximately 10–15% of individuals (Andriessen et al., 2011) develop pDOC after acquiring brain injuries or experiencing nervous system dysfunction and remain in the vegetative state/unresponsive wakefulness syndrome (VS/UWS—patients open their eyes but show no clinical evidence of consciousness; Laureys et al., 2010) or in a minimally conscious state (MCS—patients showing minimal, inconsistent but clearly discernible intentional and non-reflexive behaviors such as fixation, visual pursuit, localization to noxious stimuli, reproducible movements to command, and automatic motor responses; Giacino et al., 2002).

In the United States, ∼100,000–300,000 patients are diagnosed with pDOC (Giacino et al., 2018a), whereas in Europe the prevalence ranges from 0.2 to 6.1 patients per 100,000 (van Erp et al., 2014). There are at least 300,000 to 500,000 patients with disorders of consciousness in China, with more than 70,000 new patients diagnosed every year and an annual cumulative medical expenditure of RMB ¥30 to 50 billion (Chen et al., 2020). Within a year after disorders of consciousness, 35% of the affected population faced mortality and only 40% had an improved consciousness (Nekrasova et al., 2021). With high morbidity and mortality, heavy economic burden, and uncertain clinical effects, disorders of consciousness bring many social and economic problems to clinical decision-making and heavy economic and spiritual burden to patients' families.

To the best of our knowledge, there are a few prognostic prediction models for patients with pDOC (Kang et al., 2022). Many previous studies aimed at identifying the risk factors affecting the prognosis of pDOC. Previous studies using functional connectivity analysis showed that the number and strength of cortical functional connections between EEG segments (Fingelkurts et al., 2013) and high frontoparietal theta and alpha coherence (Schorr et al., 2016) were associated with favorable outcomes in DOC patients. Bai et al. (2019) demonstrated that lower frontal quadratic phase self-coupling at the theta band indicated a higher probability of consciousness recovery. A study on sleep EEG indicated that the occurrence of sleep spindles was related to clinical improvement within 6 months (Cologan et al., 2013). The predictive value of the presence of mismatch negative (MMN; Kotchoubey et al., 2005), N400 (Steppacher et al., 2013), and P300 latency (Cavinato et al., 2011) on event-related potentials were found in patients with DOC. Moreover, low thalamocortical connectivity during functional magnetic resonance imaging (fMRI) (Chen et al., 2018) and low gray matter/white matter (GM/WM) ratio (Scarpino et al., 2018) are associated with poor neurological deficit in patients with pDOC. Although a number of studies identified several neurophysiologic or neuroimaging risk factors for patients with DOC, the above examinations are difficult to perform, relatively expensive, and time-consuming, which limits their wide applications.

Several previous studies showed that age, MCS diagnosis (Estraneo et al., 2019), and the presence of pupil reflex (Lee et al., 2010) were associated with better clinical outcomes. Young individuals have better neuroplasticity after brain injury, which may affect the development of DOC. In addition, patients diagnosed with MCS and pupil reflex have relatively mild brain damage after a traumatic or non-traumatic brain injury compared to those diagnosed with VS and absence of pupil reflex. Hypoalbuminemia is common in patients with DOC after severe brain injury (Morotti et al., 2017). Albumin, synthesized in the liver, plays important roles in maintaining normal metabolism functions, such as detoxification and maintaining plasma colloid osmotic pressure, which could avoid much accumulation of fluid in tissue spaces and can act as a carrier of drugs and hormones (Montalcini et al., 2015). Albumin is an indicator of protein nutrition status, and a low concentration of serum albumin is a sign of unstable clinical states (Montalcini et al., 2015). Serum albumin has been found to be a good predictor of the prognostication of cancer (Wang et al., 2022) and cognitive decline in Parkinson's disease (Shen et al., 2022). A cohort study of multiple sclerosis found that cerebrospinal fluid/serum albumin is an independent variable for the prognostication of multiple sclerosis (Berek et al., 2022). Low levels of serum albumin could aggravate the degree of brain edema and affect drug efficacy in patients after traumatic brain injury (Jungner et al., 2010). Albumin has been found to be associated with clinical outcomes in patients with traumatic brain injury (Wang et al., 2020) and ischemic stroke (Lu et al., 2022), but its predictive value of short-term clinical outcomes in patients with pDOC remains uncertain.

Thus, this prospective cohort study aimed to investigate a prognostic model based on clinical factors (i.e., clinical indices, repeated diagnosis, and serologic markers).

2. Methods

2.1. Participants and inclusion and exclusion criteria

For this prospective study, we screened patients with DOC who were consecutively admitted to a neurorehabilitation unit from January 2021 to June 2022. The inclusion criteria were as follows: (1) clinical diagnosis of VS/UWS or MCS according to the standard criteria (Giacino et al., 2004; Wannez et al., 2017); (2) age ≥ 18 years; (3) traumatic, vascular, or anoxic etiology; and (4) duration of DOC ranging from 1 to 3 months (Estraneo et al., 2020). The exclusion criteria were as follows: (1) nervous system dysfunction or unstable clinical condition (e.g., severe heart or respiratory failure); (2) previous history of brain injury or neurodegenerative diseases; and (3) patients with motor impairment and locked-in syndrome. Enrollment of the patients was carried out by three doctors involved in the study who were also responsible for patient management. During their hospital stay, comprehensive multidisciplinary rehabilitation care was offered to all patients. We divided the patients into two independent sets: 119 patients treated between January 2021 and December 2021 constituted the training set, whereas 51 patients treated between January 2022 and June 2022 constituted the validation set.

2.2. Sample size

We relied on an Events Per Variable criterion (EPV), notably EPV≥10, to determine the minimal sample size required (van Smeden et al., 2019). In our study, with four independent variables selected and 40% of patients with clinical improvement (Nekrasova et al., 2021), the minimal sample size calculated was 100. Allowing for a 20% dropout rate during the study, a minimum total of 120 participants were needed in the training set.

2.3. Data collection and clinical assessment

Upon study entry, the prehospital information about patients' clinical indices (CI), including demographic data (e.g., age, education, and sex) and medical history (e.g., pupillary light reflex, etiology, duration of DOC, hypertension, and diabetes), were collected. Pupillary light reflex was classified into two categories based on the presence or absence of bilateral light reflex. After study entry, the diagnoses were confirmed by repeated Coma Remission Scale-revised assessment (CRS-R) (at least five times a week), which is standardized by the clinical criteria for DOC. We also collected the serum albumin and hemoglobin concentrations of the patients upon study entry. Serum albumin and hemoglobin were measured from venous blood within the first 24 h of admission. The patients were followed up at 6 months after brain injury using repeated CRS-R evaluations that were performed by the same clinicians during their hospital stay. At the time of assessing the level of consciousness of patients with pDOC, drugs such as sedation, antiepileptics, and neuroexcitation were excluded.

2.4. Outcome definition

The primary outcome was defined by an improvement in clinical diagnosis, which was determined by repeated CRS-R assessment, the golden standard for the diagnosis of pDOC (Giacino et al., 2004; Wannez et al., 2017). While VS/UWS is a condition in which patients open their eyes but show no clinical evidence of consciousness (Laureys et al., 2010), the most frequent signs of consciousness in MCS patients are fixation, visual pursuit, localization to noxious stimuli, reproducible movements to command, and automatic motor responses (Giacino et al., 2002). Emergence from MCS is defined as the patient communicating with others (i.e., the family members or the doctors) exactly or the ability to use objects (Machado et al., 2010). The VS/UWS state is the lowest level of consciousness, while emergence from MCS is the highest level of consciousness in patients with DOC. We classified the primary outcome as improved if there was an improvement in clinical diagnosis upon follow-up compared to that upon diagnosis after study entry (e.g., patient in VS/UWS at study entry who improved to MCS or emergence from MCS and patient in MCS at study entry who emerged from MCS). We classified the clinical outcome as not improved if the clinical diagnosis did not improve (i.e., patient in VS/UWS at study entry who persisted or died and patient in MCS at study entry who worsened to VS/UWS or died or remains in MCS).

2.5. Statistical analysis

Continuous variables were expressed as mean ± standard deviation, and categorical variables were expressed as counts and/or frequencies. Continuous variables were subjected to the Shapiro–Wilk test for normality tests. As scores of several variables significantly varied from the norm, we compared the basic clinical characteristics between the training and validation sets by the nonparametric Mann–Whitney *U*-test for continuous variables (i.e., CRS-R and GCS total scores) and the Chi-square test for categorical variables. A univariate logistic regression analysis was performed to screen for statistically significant variables that were associated with the clinical outcomes. A multivariate logistic regression analysis was used to further analyze all statistically significant indicators in the univariate analysis. The independent prognostic variables were determined as significant if the p value was <0.05 in the multivariate analysis. We integrated these four independent variables into the nomogram model. The nomogram performance was quantified using the area under the curve (AUC) of the receiver operating curve (ROC) and the calibration curves in the training and validated sets. A decision curve analysis (DCA) was performed to evaluate the clinical usefulness of this nomogram model. The value of (true positive + true negative)/total was evaluated for accuracy. All the analyses were performed using the statistical package R (http://www.R-project.org, The R Foundation) and Empower (R) (www.empowerstats.com; X&Y Solutions, Inc). A two-sided p-value of <0.05 was considered to be statistically significant.

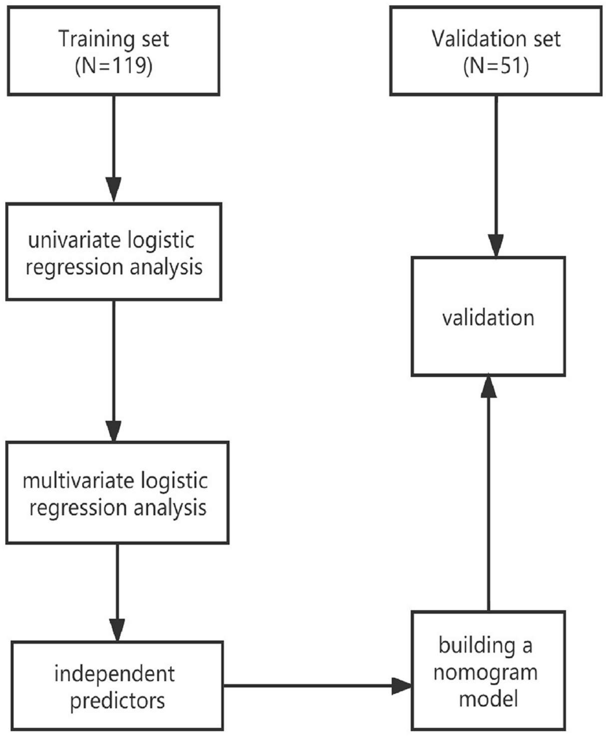

FIGURE 1
Study flowchart.

2.6. Protocol approvals

The study was performed with the approval of the First Affiliated Hospital of Nanchang University Ethics Committee (No. 2020-061-3). Written informed consent was obtained from the relatives or legal guardians of all patients.

3. Results

3.1. Description of the sample

The study flowchart is presented in Figure 1. The demographic and clinical basic characteristics of the training and the validation cohorts are presented (Table 1). Overall, 170 patients (mean age 54.32 ± 14.80 years, VS 90, and MCS 80) were included. In the development set, we included 119 consecutive patients with pDOC, of whom 60 (50.42%, mean CRS-R 7.3 ± 1.93) patients showed improved clinical outcomes and 59 patients (49.58%, mean CRS-R

TABLE 1 Demographic and clinical characteristics of patients with pDOC.

	Total	Validation set	Training set	*P*-value
N	170	119	51	
Age (y)	54.32 ± 14.80	53.09 ± 15.23	57.18 ± 13.44	0.099
Serum albumin (g/L)	35.34 ± 5.63	35.65 ± 6.00	34.64 ± 4.61	0.285
Hemoglobin (g/L)	100.92 ± 15.70	102.18 ± 15.16	97.98 ± 16.66	0.110
GCS	7.81 ± 1.95	7.68 ± 1.98	8.10 ± 1.87	0.202
CRS-R	6.75 ± 2.48	6.52 ± 2.00	7.27 ± 3.32	0.070
DOC duration (d)	49.86 ± 31.88	49.24 ± 22.42	51.31 ±35.38	0.698
Diagnosis				0.180
MCS	80(47.05%)	60 (50.42%)	20 (39.22%)	
VS/UWS	90(52.95%)	59 (49.58%)	31 (60.78%)	
Improved outcome				0.441
Yes	81 (47.65%)	59 (49.58%)	22 (43.14%)	
No	89 (52.35%)	60 (50.42%)	29 (56.86%)	
Pupillary reflex				0.131
Absent	59 (34.71%)	37 (31.09%)	22 (43.14%)	
Present	111 (65.29%)	82 (68.91%)	29 (56.86%)	
Sex				0.404
Female	62 (36.47%)	41 (34.45%)	21 (41.18%)	
Male	108 (63.53%)	78 (65.55%)	30 (58.82%)	
Job				0.041
No	70 (41.18%)	55 (46.22%)	15 (29.41%)	
Yes	100 (58.82%)	64 (53.78%)	36 (70.59%)	
Married				0.109
No	16 (9.41%)	14 (11.76%)	2 (3.92%)	
Yes	154 (90.59%)	105 (88.24%)	49 (96.08%)	
Education				0.001
Primary	91 (53.53%)	53 (44.54%)	38 (74.51%)	
Middle	58 (34.12%)	46 (38.66%)	12 (23.53%)	
High	21 (12.35%)	20 (16.81%)	1 (1.96%)	
Etiology				0.198
Traumatic	73 (42.94%)	49 (41.18%)	24 (47.06%)	
Vascular	75 (44.12%)	51 (42.86%)	24 (47.06%)	
Anoxic	22 (12.94%)	19 (15.97%)	3 (5.88%)	
Diabetes				0.961
No	147 (86.47%)	103 (86.55%)	44 (86.27%)	
Yes	23 (13.53%)	16 (13.45%)	7 (13.73%)	
Hypertension				0.263
No	99 (58.24%)	66 (55.46%)	33 (64.71%)	
Yes	71 (41.76%)	53 (44.54%)	18 (35.29%)	

5.73 ± 1.74) showed poor clinical outcomes. While in the validation set, 51 patients were screened, with 29 (56.86%, mean CRS-R 8.41 ± 3.78) patients showing improved outcomes and 22 patients (43.14%, 5.77 ± 1.73) presenting poor clinical outcomes compared to baseline characteristics. There were no significant differences between the two cohorts in terms of CRS-R, GCS, age, etiology, DOC duration, sex,

TABLE 2 Univariate and multivariate logistic regression analyses.

Variable	Univariable			Multivariable	
	Ref	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value
Age (y)	–	0.96 (0.94, 0.99)	0.002	0.94 (0.90, 0.98)	0.005
DOC duration (d)	–	1.01 (0.99, 1.02)	0.48		
CRS-R	–	1.61 (1.27, 2.04)	0.001	1.41 (0.90, 2.22)	0.134
GCS	–	1.47 (1.19, 1.83)	0.000	1.02 (0.61, 1.70)	0.936
Sex (f/m)	Female	0.95 (0.45, 2.03)	0.899		
Job (y/n)	No	1.91 (0.92, 3.96)	0.083		
Married (y/n)	No	1.41 (0.46, 4.35)	0.548		
Education					
Primary	Primary	1.0			
Middle		1.7 (0.8, 3.8)	0.184		
High		1.0 (0.4, 2.8)	0.983		
Etiology					
Traumatic	Traumatic	1.0			
Vascular		1.27 (0.58, 2.79)	0.548		
Anoxic		1.26 (0.43, 3.63)	0.673		
Diagnosis (VS/MCS)	MCS	0.09 (0.04, 0.22)	0.001	0.12 (0.04, 0.42)	0.000
Serum albumin (g/L)	–	1.09 (1.02, 1.17)	0.012	1.13 (1.03, 1.25)	0.012
Hemoglobin (g/L)	–	1.02 (0.99, 1.04)	0.146		
Pupillary reflex	Absent	4.22 (1.80, 9.88)	0.000	3.70 (1.00, 13.67)	0.049
Hypertension (y/n)	No	1.19 (0.58, 2.45)	0.637		
Diabetes (y/n)	No	0.98 (0.34, 2.81)	0.971		

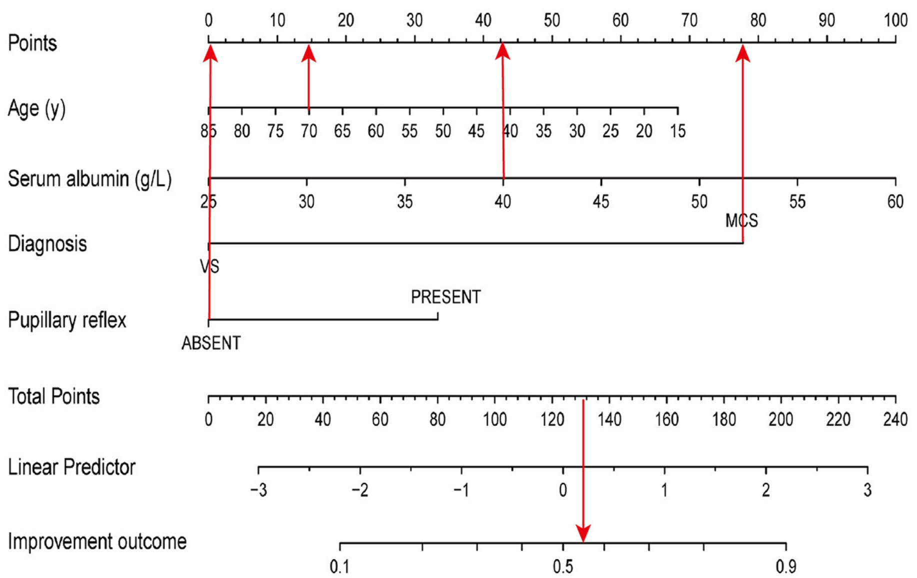

FIGURE 2
A nomogram model to predict the clinical outcomes. The red arrows present the calculation of total points of a 70-year-old patient diagnosed with MCS, absence of bilateral light reflex, and a serum albumin concentration of 40 g/L upon entry within 2 months of injury.

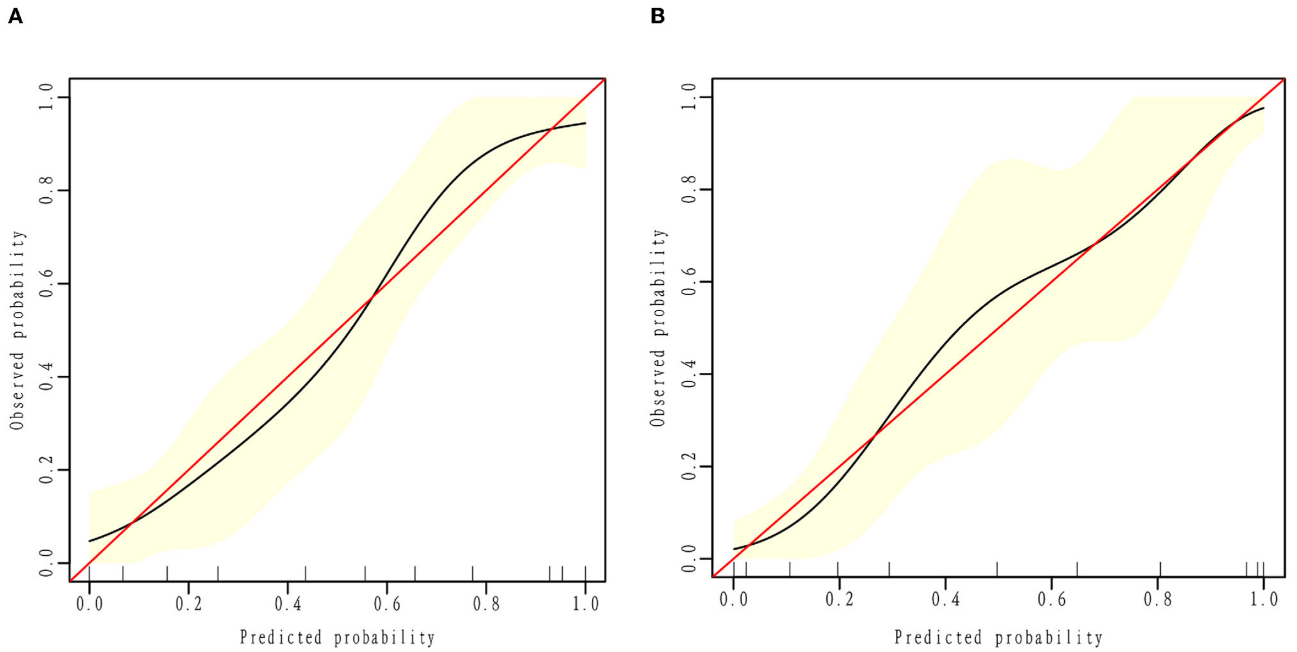

FIGURE 3
Calibration curve. The black calibration curve shows the predicted proportion of clinical outcomes against the actual probability of outcomes. The red line demonstrates the actual risk equal to the predicted risk. Calibration plots for estimating improved outcome probabilities are presented for the training **(A)** and validation cohorts **(B)**.

marital status, serum albumin level, hemoglobin level, hypertension, and diabetes.

3.2. Screening prognostic predictors

In the training cohort, univariate analysis showed that improved clinical outcomes were associated with the total scores of CRS-R, GCS, age, the concentration of serum albumin, entry diagnosis, and pupillary reflex. Multivariate logistic regression analysis of improved clinical outcomes indicated that age, pupillary reflex, entry diagnosis, and the concentration of serum albumin (g/L) were the prognostic predictors for patients with pDOC. A final logistic regression analysis including the four predictors was conducted to demonstrate the odds ratio (OR) of each predictor in the model (Table 2).

3.3. Development and validation of the model

According to the results of the multivariate logistic regression analysis, four predictive variables (age, entry diagnosis, serum albumin level (g/L), and pupillary reflex) were used to establish a 6-month outcome prediction nomogram model in patients with pDOC (Figure 2). The total risk points were calculated by summing the points of each predictor. The higher the total points, the higher the likelihood of an improved clinical outcomes. For example, consider a 70-year-old patient diagnosed with MCS showing the absence of bilateral light reflex and a serum albumin concentration of 40 g/L upon entry within 2 months after injury. The points for age, MCS diagnosis, absence of pupil reflex, and level of serum albumin level of 40 mg/L were 15, 77.5, 0, and 42.5, respectively. The total points added up to 135, which demonstrated about a 58% likelihood of an improved diagnosis 6 months after injury.

The validation was performed by using the other cohort of 51 patients with pDOC. In the validation cohort, the independent risk factors integrated into the nomogram were examined. The accuracy of the model is 0.745 [(true positive + true negative)/total]. The AUC values were 0.845 and 0.801 in the training and validation sets, respectively.

3.4. Calibration and decision curve

To evaluate the consistency of the actual and predicted risks by the model, a calibration curve was drawn to measure calibration, which is an important aspect of the prediction models. It is demonstrated that the actual risk (red line) was consistent with the predicted risk (black curve) in both the training and validation cohorts (Figures 3A, B). From the decision curve, it can be seen that the net benefit of the model (blue curve) was higher than that with all treatment at the same threshold probability (red curve) in both the training and validation sets (Figures 4A, B), which indicates that clinicians could benefit from this model for decision-making.

3.5. Comparison of age, pupil reflex, and diagnosis with our model

Previous studies reported the predictive value of age, pupil reflex, and diagnosis, but the value of serum albumin level

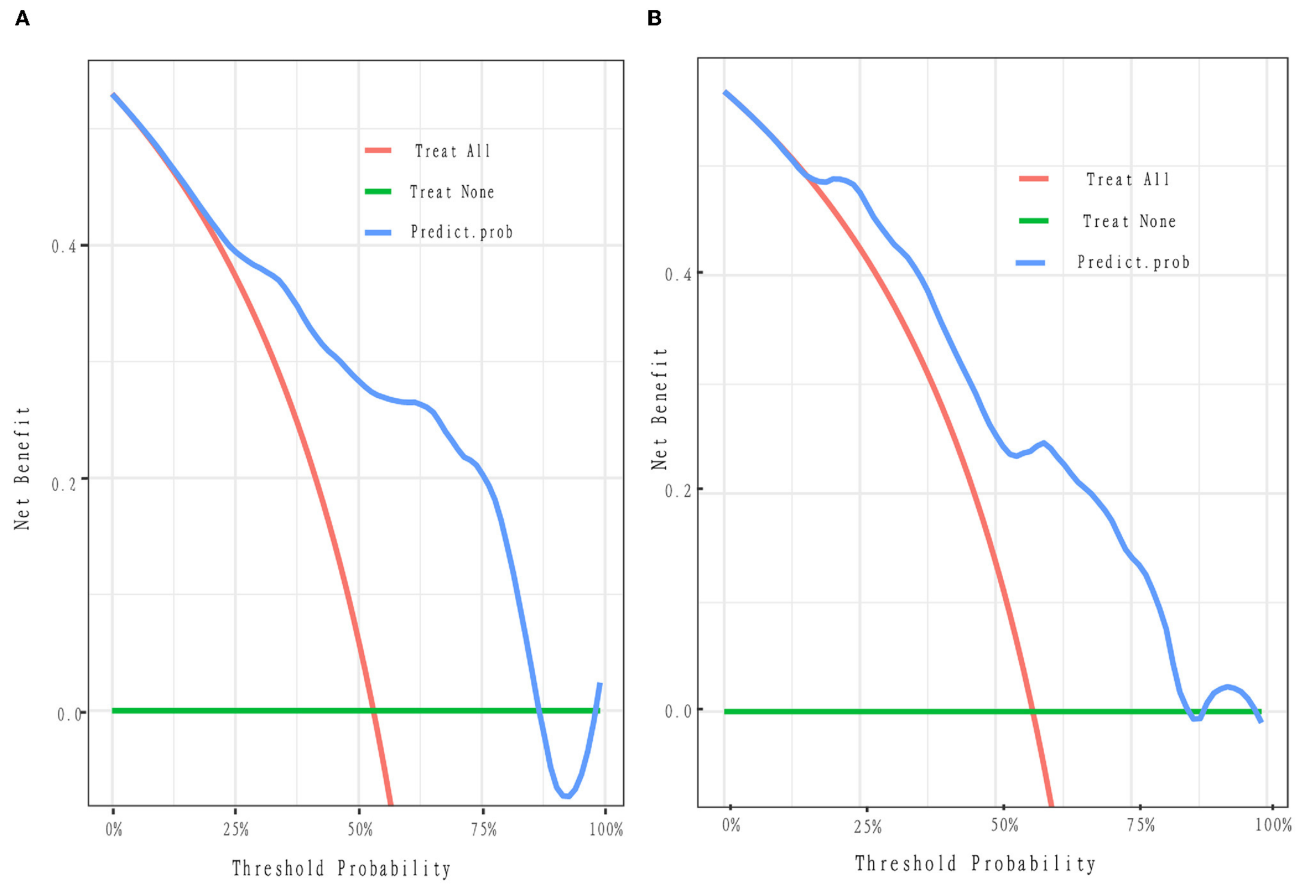

FIGURE 4
Decision curve. The y-axis represents the net benefit. The x-axis is the threshold probability. The blue curve represents the nomogram. The red oblique represents the hypothesis that all patients with pDOC have improved outcomes with all treatments. The green line represents the hypothesis that no patients will have improved outcomes. The threshold probability is where the expected benefit of the treatment is equal to the expected benefit of no treatment. For example, if the possibility of the improved outcome of a patient is over the threshold probability, then the patients with pDOC will not benefit from all the treatment strategy. **(A, B)** Depict the decision curves of the training and validation cohorts, respectively. Net benefit means the clinical efficacy of the treatment.

has rarely been reported. We compared the performance of our model by incorporating age, pupil reflex, diagnosis, and serum albumin level with those of clinical index (CI) predictors (age+pupil) and CI predictors plus diagnosis in predicting improved clinical outcomes. The AUC of the receiver operating curve was evaluated for CI predictors (age + pupil), CI + entry diagnosis, and our final model (CI + entry diagnosis + serum albumin). Our results demonstrated that the AUC of MODEL3 (CI + entry diagnosis + serum albumin) was the highest in both the training and validation sets (AUC = 0.845 and 0.801, respectively) (Figure 5). We adjusted the model by sex, marital status, job, etiology, education level, hypertension, diabetes, and DOC duration.

The formula for the final model in the validation set was as follows: −0.97443 – 0.02752 * age + 0.94099 * (pupil reflex = presence) – 2.19467 * (diagnosis = VS) + 0.08060 * serum albumin in the training set. The formula for the final model in the validation set was as follows: −3.84513 – 0.01792 * age – 2.02802 * (diagnosis = VS) + 1.15271*(pupilreflex = presence) + 0.10959 * serumablumin.

4. Discussion

Prolonged disorders of consciousness, which is often caused by severe brain injury, always lead to severe complications (e.g., pneumonia, hemorrhage of the digestive tract, and dysfunction of the liver), poor clinical outcomes, and high mortality. Predicting clinical improvement in patients with pDOC is very helpful in supporting clinicians to offer suitable clinical care and aiding in the decision-making of patients and their family members (Scarpino et al., 2020). Although several previous studies aimed at identifying the risk factors that affect poor clinical outcomes, severe neurological deficit, or awakening from coma, only one nomogram model was established to predict the severe neurological deficit outcomes of pDOC (Kang et al., 2022). Thus, our present study aimed to build and validate a nomogram model for predicting improved clinical outcomes in patients with pDOC.

Many factors are known to influence the prognosis of patients with pDOC (Formisano et al., 2019). Our findings showed that younger age, MCS diagnosis at entry, higher serum albumin level, and the presence of pupillary reflex were associated with improved

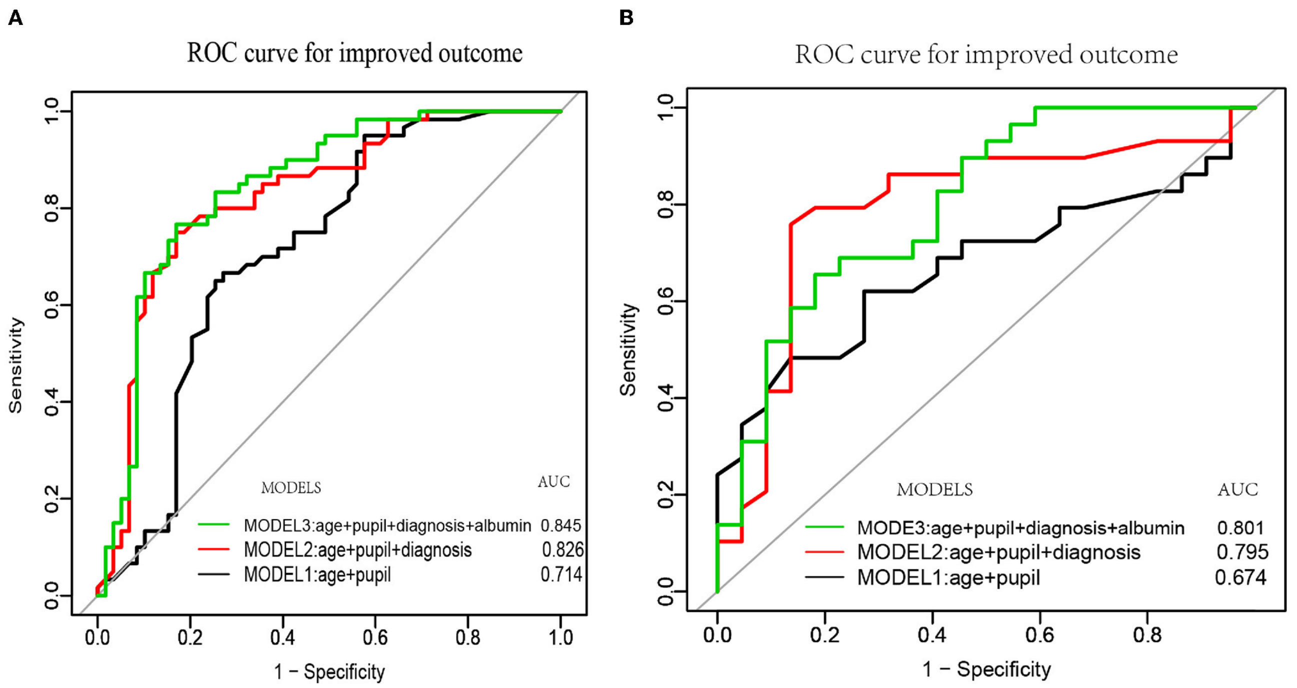

FIGURE 5
The ROC curves of age, pupil, diagnosis, albumin, and their combined models. MODEL 1 was constructed based on age and pupil reflex (black curve). MODEL 2 was established based on age, pupil reflex, and diagnosis (red curve). MODEL 3 was established based on age, pupil reflex, diagnosis, and serum albumin (green curve). **(A, B)** Depict the three ROC curves of the training and validation cohorts, respectively.

outcomes at 6 months after brain injury. Several studies showed that age, female sex (Estraneo et al., 2019), traumatic etiology (Whyte et al., 2009), and higher CRS-R (Portaccio et al., 2018; Foo et al., 2019) were related to better clinical outcomes. Whereas this predictive value of age was in line with our findings on patients with DOC, the value of female sex, traumatic etiology, and CRS-R were not. A study by Lucca et al. (2019) found that pDOC patients with CRS-R values >12 upon admission were associated with a favorable likelihood of emergence from DOC. In the current study, a majority of patients with CRS-R scores of <12 upon admission were presented, which may explain why CRS-R was not associated with improved outcomes in our study. Moreover, the results of the present study are consistent with those of a study (Estraneo et al., 2018), showing that a VS/UWS diagnosis was associated with a poor outcome and the total scores of CRS-R were not. In addition, a previous study by Lee et al. (2010) demonstrated that the presence of pupillary reflex had an effect on awakening from coma, which is consistent with our findings. They found that the AUC of pupil reflex in predicting severe neurological deficit in patients with coma was 0.744. One cause of DOC is damage to the ascending reticular activating system (ARAS) of the brainstem. The degree of brainstem damage is related to the level of consciousness, which has been known to clinicians. As pupillary light reflex is an important aspect of brainstem reflex, the bilateral absence of pupillary reflex indicates severe brainstem damage after injury. Therefore, we believe that pupil reflex is a good indicator to predict the outcomes in patients with pDOC.

Here, for the first time, we found that higher serum albumin level was associated with clinical improvement in patients with pDOC. A previous study (Chen et al., 2014) found that the concentration of serum albumin was associated with favorable outcomes in patients with traumatic brain injury. However, to the best of our knowledge, no research concerning the predictive value of serum albumin on clinical improvement in patients with pDOC has been reported until now. There are several reasons for the decrease in serum albumin levels in patients with DOC. First, the stress state leads to increased consumption of albumin. Second, intracranial hemorrhage and lung infection lead to albumin loss. In addition, the albumin from the blood passes into the cerebrospinal fluid (CSF) with the compromised blood–brain barrier (BBB) after severe brain injury (Kim et al., 2018). Finally, liver dysfunction in patients with pDOC results in decreased albumin synthesis. Therefore, a decrease in serum albumin implicates severe organ dysfunction, clinical instability, or severe brain injury, which may be the reason for poor clinical outcomes.

To the best of our knowledge, only one retrospective study established a nomogram model for predicting severe neurological deficit (including vegetate state and death) in patients with pDOC. Our present study would be the first prediction model for detecting the outcomes of patients with pDOC using a nomogram in a prospective study. The present prospective cohort study evaluated the prognostic value of clinical indices, entry diagnosis, and serologic markers that are easy to collect in patients with DOC 6 months after brain injury in grassroots hospitals. Therefore, we collected data on patients with pDOC within 1–3 months and established a simple, efficient, and accurate prediction model based on age, pupillary reflex, repeated diagnosis, and concentration of serum album. Considering the possible effect between clinical outcomes and the time of data collection, a covariate analysis of the time of data collection was performed. It showed that the time of data collection in our cohort study did not affect the clinical outcomes; OR 1.01 (95% CI 0.99–1.02; $p = 0.48$). Our cohort study demonstrated that the AUC of Model 3 (age + pupil + diagnosis + albumin) was the highest (AUC = 0.845) and was significantly higher than those of Model 1 (age + pupil) and Model 2 (age + pupil + diagnosis), the AUC values of which are 0.714 and 0.826, respectively. A retrospective prognostic model study (Kang et al., 2022) using age, diagnosis, GCS scores, and degree of brainstem auditory evoked potential (BAEP) demonstrated an AUC value of 0.815(29). Our final model (MODEL 3) showed an AUC value of 0.845. There are two reasons for the difference between the two models. First, GCS assessment is a good measure to evaluate the degree of brain damage of patients in the acute phase after severe brain injury rather than that of a patient in coma in the chronic phase (Bodien et al., 2021). Second, pupillary light reflex and BAEP examination are good indicators when evaluating brainstem injury, while the AUC value of pupil reflex (0.744) is good in predicting severe neurological deficits in patients with coma. Lee et al. (2010) stated that the AUC value was better in predicting awakening from coma (Fischer et al., 2004). Our study indicated that several feasible, cost-effective prognostic variables can provide an efficient and accurate prediction model for short-term clinical outcomes. However, the prognosis of pDOC is affected by many factors and remains a major clinical issue, especially as the prognostic values of the neuroimaging markers in predicting DOC are becoming a consensus among neurorehabilitation clinicians (Song et al., 2018; Yu et al., 2021). Thus, the values of other neurophysiologic or neuroimaging markers will be further investigated and integrated into the nomogram to improve the accuracy of the prediction model.

There are several limitations to our study. First, due to a small sample size, prognostic prediction was not allowed between the different diagnostic groups, which could underestimate the value of some predictors, such as CRS-R. Second, with the short follow-up time, identifying long-term prognostic markers was not sufficient as it has been found that prognostic markers may have different effects on each marker.

5. Conclusion

A higher concentration of serum albumin, higher consciousness level, young age, and presence of pupillary reflex could predict an improvement in pDOC 6 months after injury. These predictors are routinely measured in most hospitals, including grassroot rehabilitation units, and are not expensive and time-consuming. These feasible, cost-effective prognostic variables can provide an efficient and accurate prediction model for improved clinical outcomes and support clinicians by offering suitable clinical care and supporting the decision-making of patients and their family members.

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 First Affiliated Hospital of Nanchang University Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

Author contributions

QX conducted the experiment properly and prepared the manuscript. KL, YT, and XD are responsible for the management of patients. YZhon and YZhou performed repeated diagnoses and collected the data. YW performed the statistical analyses of the data. ZF secured funding for the project. All authors have read 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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Functional networks in prolonged disorders of consciousness

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Prolonged disorders of consciousness (DoC) are characterized by extended disruptions of brain activities that sustain wakefulness and awareness and are caused by various etiologies. During the past decades, neuroimaging has been a practical method of investigation in basic and clinical research to identify how brain properties interact in different levels of consciousness. Resting-state functional connectivity within and between canonical cortical networks correlates with consciousness by a calculation of the associated temporal blood oxygen level-dependent (BOLD) signal process during functional MRI (fMRI) and reveals the brain function of patients with prolonged DoC. There are certain brain networks including the default mode, dorsal attention, executive control, salience, auditory, visual, and sensorimotor networks that have been reported to be altered in low-level states of consciousness under either pathological or physiological states. Analysis of brain network connections based on functional imaging contributes to more accurate judgments of consciousness level and prognosis at the brain level. In this review, neurobehavioral evaluation of prolonged DoC and the functional connectivity within brain networks based on resting-state fMRI were reviewed to provide reference values for clinical diagnosis and prognostic evaluation.

KEYWORDS

prolonged DoC, network, functional connectivity, fMRI, neuroimaging

Introduction

The incidence of disorders of consciousness (DoC) has increased sharply due to the development of first-aid and intensive care techniques over the years. DoC is characterized as states of unconsciousness induced by severe brain injuries involving trauma (O'Donnell et al., 2019; Giacino et al., 2020), hemorrhage (Crone et al., 2014), or hypoxic–ischemic encephalopathy such as cardio-pulmonary resuscitation (Weng et al., 2017; Peran et al., 2020) or poisoning (De Paepe et al., 2012). The temporal division of DoC includes the acute phase from a few days or weeks after brain injury when patients get treated in the emergency room or intensive care unit, with the addition of subacute and chronic phases when patients spent time in a rehabilitation center, care facilities, or home (Edlow et al., 2021). Subsequently, prolonged DoC was used to describe subacute and chronic phases of patients ≥28 days following the primal brain injury (Giacino et al., 2018), including vegetative state (VS)/unresponsive wakefulness syndrome (UWS) and minimally conscious state (MCS; Schnakers, 2020). With an in-depth understanding and continuous evolution, the recognition of a locked-in syndrome (LIS) state (cognitively intact but complete or near-complete paralysis) and non-behavioral MCS (MCS star or MCS*, patients in the VS/UWS state who may preserve partial brain activities that resemble those in MCS) have provided a more precise distinction between patients in a comatose state and conscious-wakefulness (Hocker and Wijdicks, 2015; Thibaut et al., 2021).

It is generally accepted that the cumulative effect of differentiation of central thalamic neurons and active inhibition of neocortical and striatal neurons leads to extensive regression of synaptic activity and low cerebral metabolic rates, ultimately generating a range of unresponsive symptoms in patients with DoC (Thibaut et al., 2019; Edlow et al., 2021; Zheng et al., 2022). Meanwhile, the recovery of consciousness is regarded as closely relevant to the restoration connections within corticothalamic neuronal activity (Wagner et al., 2020; Edlow et al., 2021). Based on these theories, resting-state functional magnetic resonance imaging (fMRI) is recommended as part of the clinical multimodal evaluation and provides valuable information for brain networks to detect those possibly subtle transformations in brain activities (Snider and Edlow, 2020; Norton et al., 2023).

In this review, we discuss the clinical behavioral evaluations of prolonged DoC and target studies that investigated the correlation between prolonged DoC and separate brain networks. To explore their diagnostic and evaluation value in patients with prolonged DoC, we searched PubMed for articles published in English between 1 January 2012 and 31 October 2022 using the following search terms: "consciousness disorders[Mesh]," and "fMRI," "network," or "assessment." Seven major brain networks involved "default mode network," "salience network," "executive control network," "dorsal attention network," "auditory network," "visual network," and "sensorimotor network" (Raichle, 2011, 2015). We screened clinical trials, case reports, and review articles that included patients with prolonged DoC and were relevant to the topic. Additional references were collected and reviewed from the included articles' bibliographies.

Neurobehavioral evaluation of prolonged DoC

Accurate diagnosis of prolonged DoC is not only necessary for the medical teams to make prognosis estimation but also provides meaningful information and helps family members participate in valid clinical care support and clinical decision-making. However, a misdiagnosis rate of 30–40% was reported from consensus-based expert diagnoses (Schnakers et al., 2009), including misdiagnoses of those that have emerged from the vegetative state into a VS/UWS or LIS into a VS or an MCS (van Erp et al., 2015; Vanhaudenhuyse et al., 2018). Here are a few possible reasons. First, the performance of patients with prolonged DoC fluctuated incessantly, especially when some inconsistent responsiveness could only be elicited *via* certain stimulation or in specific situations. Second, measurement outcomes could be largely influenced by the patient's own disease or complications (e.g., cranial nerve palsies, quadriplegia, severe spasticity, and dystonia). In addition, the assessor's experience (lack of extended observation of patients or under training) may also have led to considerable reporting bias and error in the results (Childs et al., 1993). It follows that limited clinical examination may lead to an underestimation of consciousness levels in patients in a VS/UWS or an MCS, and the diagnostic accuracy of bedside qualitative examination needs to be enhanced.

The American Congress of Rehabilitation Medicine reviewed a number of neurobehavioral scales for DoC that have been applied to diagnose and predict functional outcomes (Seel et al., 2010). Of these, the most accepted and recommended was the Coma Recovery Scale-Revised (CRS-R), which includes six subscales—audition, vision, motion, mouth movement, communication, and arousal level—and is widely used to diagnose and classify different levels of consciousness owing to its reliable validity and reliability (Tamashiro et al., 2014; Binder et al., 2018; Han et al., 2018; Iazeva et al., 2018; Zhang et al., 2019). In addition, the Full Outline of Unresponsiveness Score (FOUR) showed substantial evidence of good interrater reliability and could reduce the misdiagnosis of locked-in syndrome and MCS for patients in the intensive care unit (Kondziella et al., 2020). The Sensory Modality Assessment Technique (SMART; da Conceicao Teixeira et al., 2021), Western Neuro Sensory Stimulation Profile (WNSSP; Cusick et al., 2014), Sensory Stimulation Assessment Measure (SSAM; Park and Davis, 2016), Wessex Head Injury Matrix (WHIM; Shiel et al., 2000), and Disorders of Consciousness Scale (DOCS; Pape et al., 2014) are recommended for assessing DoC with moderate reservations. Rather, the Coma/Near-Coma Scale (CNC; Weaver et al., 2021) may be suitable for patients with major reservations. Although standardized behavioral assessment scales might outperform clinical expert diagnosticians' bedside evaluation for signs of consciousness (Schnakers et al., 2009), even a single assessment of CRS-R might result in a misdiagnosis rate of 36% in patients with prolonged DoC (Wannez et al., 2017). The accuracy rating of these diagnosis scales is still limited due to the battery of confusion factors in patients' and assessors' experiences listed earlier.

Neuroimaging and electrophysiological assessment

To date, diverse auxiliary inspection tools have been used in the diagnosis and assessment of prolonged DoC. Positron emission tomography (PET) was first used to identify preserved but covert cortical processing evidence in patient in VS (Menon et al., 1998). The application of PET provides evidence for cortical activation in patients with prolonged DoC and helps to identify different unconsciousness states (Laureys and Schiff, 2012). By contrast, the electroencephalogram technology (EEG) method is widely applicable and could also provide objective information for the evaluation efficacy of patients with prolonged DoC, especially appropriate for bedside inspection (Chennu et al., 2017). EEG-derived neuronal signals including both speech-tracking responses and temporal dynamics of whole-brain neuronal networks were reported to be related to the behavioral diagnosis of consciousness and wakefulness prediction (Gui et al., 2020; Zhang et al., 2022). Continuous EEG and quantitative EEG could also provide effective value for diagnosis and initial consciousness recovery (Hwang et al., 2022; Lutkenhoff et al., 2022). In addition, functional near-infrared spectroscopy (fNIRS) is another non-invasive method to quantitatively detect brain function based on cerebral oxygen information in real time (Kempny et al., 2016).

Compared with EEG and fNIRS, fMRI has higher spatial resolution and better integration with structural lesions and is more available than PET (Ansado et al., 2021). Assessment during the resting state is particularly opportune for patients with prolonged DoC since patient interaction and application of possible experimental setups are mostly difficult and infeasible. Recent studies have measured the brain's spontaneous neural activities by resting-state fMRI (rs-fMRI), which used blood-oxygen-level-dependent (BOLD) contrast to reflect fluctuations and uncover the important process underlying consciousness (Palanca et al., 2015; Zhang et al., 2021). The BOLD signal was thought to provide an indirect measure of brain function that is closely related to ongoing neuronal events in the brain (Phillips et al., 2016) and could be used to forecast human behavior (Ward et al., 2020). The superiority of its sensitivity and technical simplicity have made other non-invasive imaging techniques of fMRI outshone (Jann et al., 2015). Of note, it has been suggested that spontaneous BOLD fluctuation is not random but specifically correlated with the spatially distinct systems and brain networks in the resting human brain (Keller et al., 2011). It is, thus, possible that functional connectivity, measured by the BOLD signal, is disturbed in brain networks in prolonged DoC.

The intrinsic activities of the brain are linked to multiple temporal and spatial-related functional networks through integrating structural or functional connections of different cortical regions. It has been reported that the brain networks of prolonged DoC changed from that when in a comatose state until they recovered consciousness (Cavanna et al., 2018; Threlkeld et al., 2018; Crone et al., 2020) and potentially predicted recovery (Wu et al., 2015; Zou et al., 2017; Zhang et al., 2018). Moreover, the detectable rate of intrinsic cortical activity in MCS seems higher than that in a coma or VS/UWS with resting-state fMRI (Kondziella et al., 2020). This suggests that the whole-brain dysfunction after brain injury may underlie the abnormal network connectivity of prolonged DoC, which is strongly correlated with the level of consciousness. Moreover, by calculating functional temporal correlations within spatially separated neurophysiologic activities from fMRI, functional connectivity could be used to identify covert signatures of consciousness in patients with prolonged DoC and reflect the inherent brain activities (Bodien et al., 2019; Snider and Edlow, 2020).

Functional networks in prolonged DoC

As we know, two primary positively correlated components are involved in consciousness, wakefulness, and awareness (Naro et al., 2017). In particular, awareness can be subdivided into two parts: environment (external) and self (internal) awareness (Demertzi et al., 2011). It has been identified that the default mode network (DMN) exhibits internal activities, also referred to as the "task-negative network" (Andrews-Hanna, 2012; Andrews-Hanna et al., 2014), whereas the lateral frontoparietal areas related to the network of dorsal attention (DAN; Mallas et al., 2021) and executive control (ECN; Martin-Signes et al., 2019) mediate task-driven stimuli (Xin et al., 2021; i.e., task-positive network). These two sets of regions are reported to be negatively correlated with healthy adults, anesthetic patients, or patients with prolonged DoC (He et al., 2014; Palanca et al., 2015), both under resting-state or attention-demanding processes (Lyu et al., 2021). In another case, according to the regulating function, the brain networks could be classified into higher order networks [the DMN, ECN, DAN, and salience network (SN)] and sensory-related (perceptual processing) lower order networks including the sensory input auditory network (AN; Braga et al., 2017), visual network (VN; Wang Y. et al., 2020), and sensorimotor network (SMN; Liang et al., 2015; Figure 1). Notably, altered functional brain networks have been observed in different types of unconsciousness states, such as in deep sleep (Samann et al., 2011; Boly et al., 2012; Houldin et al., 2021; Rue-Queralt et al., 2021; Tarun et al., 2021), anesthesia (Qiu et al., 2017; Golkowski et al., 2019; Malekmohammadi et al., 2019; Wang S. et al., 2020), pathological hypnosis (Cojan et al., 2015; McGeown et al., 2015; Jiang et al., 2017), and psychedelics (Tagliazucchi et al., 2016; Preller et al., 2019; Luppi et al., 2021a). As for patients with prolonged DoC, the functional connectivity in key regions of each network was reported to be correlated with CRS-R scores from different distributions and functions (Demertzi et al., 2015).

Default mode network (DMN)

The default mode network contains a set of brain regions that are more active during the resting state than when they focus on features of the external environment, such as attention-demanding tasks (Buckner and Krienen, 2013; Raichle, 2015). Compared with the regions of the cortex that is more directly constrained by extrinsically driven neural activity, the DMN took on roles that are both more complex and less directly influenced. This network is active in internally oriented mentation such as "mind-wandering," "daydreaming," or "self-referential processing" (Konishi et al., 2015; Yeshurun et al., 2021). To date, the DMN has been the most studied network in prolonged DoC, and its functional connectivity is not only critical for the detection of consciousness levels but also involved in the process of awareness emergence in these patients (Fernandez-Espejo et al., 2012; Norton et al., 2012; Crone et al., 2015; Qin et al., 2015a). The within-network correlations were recognized as positive DMN connectivity, and anti-correlations between networks were recognized as negative DMN connectivity (Di Perri et al., 2016). Functional connectivity within the DMN was found to be decreased in patients with DoC, ranging from those in an MCS and UWS to those in a coma state (Fernandez-Espejo et al., 2012; Norton et al., 2012; Crone et al., 2015; Hannawi et al., 2015; Coulborn et al., 2021), and remained intact in patients with locked-in syndrome (Vanhaudenhuyse et al., 2010).

Generally, there are three major fields in the DMN: the medial prefrontal cortex (mPFC), the posterior cingulate cortex (PCC), and the adjacent precuneus plus the lateral parietal cortex (LPC; Leech and Sharp, 2014; Raichle, 2015), which constitute the primary intrinsic functional connectivity in patients with DoC (Wu et al., 2015). The neuropathological basis of the DoC includes the interruption of connections within the DMN, which involves key regions, such as PCC and mPFC (Silva et al., 2015). The mPFC is a large, complex, and heterogeneous area with the highest baseline metabolic activity at rest (Gusnard et al., 2001) and could be broadly classified into distinct subregions along with the dorsal to the ventral axis: the medial precentral area, anterior cingulate cortex (ACC), prelimbic cortex (PL), and infralimbic cortex (IL; Xu et al., 2019). Among these regions, some researchers have suggested that the dorsal medial prefrontal cortex (dmPFC) contains the dorsal region of the ACC and the PL, while the ventral PL, IL, and dorsal peduncular cortex belong

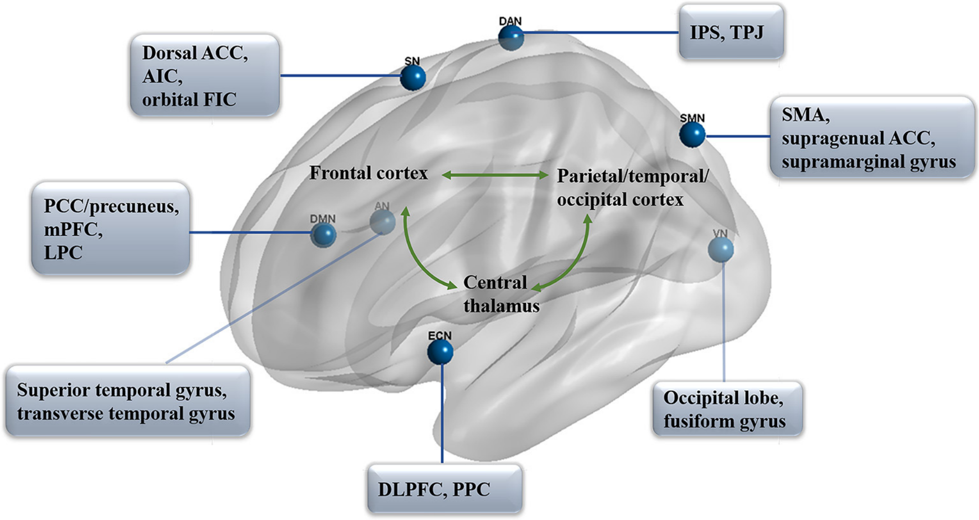

FIGURE 1
Functional networks in prolonged DoC. The distribution of seven primary networks that control the resting state of functional connectivity in prolonged DoC. DMN, default mode network; PCC, posterior cingulate cortex; mPFC, medial prefrontal cortex; LPC, lateral parietal cortex; DAN, dorsal attention network; IPS, intraparietal sulcus; TPJ, temporoparietal junction; ECN, executive control network; DLPFC, dorsolateral prefrontal cortex; PPC, posterior parietal cortex; SN, salience network; ACC, anterior cingulate cortex; AIC, anterior insula cortex; FIC, frontoinsular cortices; AN, auditory network; VN, visual network; SMN, sensorimotor network; SMA, supplementary motor area.

to the ventral medial prefrontal cortex (vmPFC; Jasinska et al., 2015). Resting-state activity in the mPFC was regarded as correlated with private self-consciousness (Huang et al., 2016). Of which, functional activation of the dmPFC subsystem was considered, specifically associated with rumination (Zhou et al., 2020) and perceptual memory (Schwiedrzik et al., 2018). By contrast, as the sensory-visceromotor component of the DMN, the vmPFC plays a role in theory-of-mind ability, processing self-relevant information, and greater extinction memory in humans' ability to modulate fear (Hebscher et al., 2016; Hiser and Koenigs, 2018; Nejati et al., 2021). Fast network oscillations are consistently larger in the dmPFC than in the vmPFC region in anesthetized animals (Gretenkord et al., 2017), which reflects possible different inputs to mPFC subregions in prolonged DoC.

Intrinsic functional connectivity strength in the PCC/precuneus was found to be significantly correlated with consciousness level, recovery outcome, and differential diagnosis (Bonfiglio et al., 2014; Palhano-Fontes et al., 2015; Flamand et al., 2018). The PCC serves as a main connector hub within functional neural distinct networks in the DMN and plays an important role in integrating the neural representations of self-location, body ownership, and internally directed thoughts (Leech et al., 2012; Guterstam et al., 2015). As sleep depth increased, contributions of the PCC and mPFC to the DMN seem to be decreased (Samann et al., 2011). In addition, it was suggested that the PCC is the only DMN node that interacts with most of the other DMN nodes and is strongly co-activated with the mPFC (i.e., dmPFC and vmPFC; Fransson and Marrelec, 2008; Supekar et al., 2010). This region is characterized by the BOLD signal time series during rest conditions and is distinguished from task-positive network regions (Yu et al., 2011). Notably, patients in VS showed significantly reduced self-inhibition and increased oscillations in the PCC compared with those of patients in MCS and healthy people (Crone et al., 2015). Furthermore, the DMN may be related to the prognosis prediction of patients with prolonged DoC. It was evident that PCC and left LPC connectivity differentiate patients with UWS who recovered consciousness after 3 months from those who did not (Qin et al., 2015a), and patients in coma exhibit significantly enhanced functional connectivity in the PCC/precuneus when they regained consciousness (Norton et al., 2012; Guo et al., 2019). These findings indicate that as a relatively independent network module, the functions of the brain regions within DMN are closely connected, and the PCC/precuneus and mPFC in DMN are found to be important brain network hubs in prolonged DoC (Silva et al., 2015; Wang et al., 2019).

Salience network (SN)

The salience network contributes to the identification of stimulus processing that guides behavior (Heine et al., 2012; Miyata, 2019), attention control (Peters et al., 2016), or interoceptive awareness/conscious perception (Chong et al., 2017; Ueno et al., 2020). This network could also be activated by interoceptive stimuli as part of a representation of all feelings from the body, such as pain (Veréb et al., 2020). The SN comprises the dorsal ACC, the bilateral anterior insula cortex (AIC), and the orbital frontoinsular cortices (FIC) and has connections to subcortical regions, including the amygdala, the substantia nigra/ventral tegmental area, the thalamus, and the limbic structures (Veréb et al., 2020). It was reported that AIC, especially the anterior and ventral (inferior) areas, are involved in the representation of all subjective feelings from both body and emotional awareness, such as self-recognition and time perception (Craig, 2009), and play a fundamental role in human awareness. The SN is non-uniformly impaired in unconsciousness states, such as in anesthetic (Bonhomme et al., 2016; Golkowski et al., 2019), psychedelic (Lebedev et al., 2015), or epileptic states (Lee et al., 2018). Similar to the DMN, the reduced functional connectivity in this key network is also correlated with the degree of impaired consciousness in prolonged DoC. Functional connectivity of the SN is reduced in patients in MCS but hardly identified in patients in VS/UWS (Demertzi et al., 2015). Moreover, the functional connectivity between the AIC and ACC may also play a fundamental role in awareness (Luo et al., 2014) and emotional feelings (Krach et al., 2015). Compared with MCS, patients in UWS showed significantly reduced functional connectivity between supragenual ACC and left AIC within the SN (Qin et al., 2015a).

In addition, the SN may also serve as a "switch" between the "task-positive" network and the "task-negative" network (Goulden et al., 2014). First, the SN and the "task-positive" network DAN are anti-correlated with DMN, including, the SN and DAN having an inhibitory influence on DMN regions, whereas the DMN in turn excites SN and DAN regions (Zhou et al., 2018). In addition, functional connectivity between the SN and another "task-positive" network ECN was observed to be positively elicited under hypnosis (Jiang et al., 2017), and it was reported that an anesthetic-induced unresponsive state generates small increases in bidirectional connectivity within the SN and ECN (Ihalainen et al., 2021). Moreover, the structural and functional integrity of the SN seems to be necessary for efficient regulation of the activity of the DMN. The structural damage in the SN may specifically predict abnormalities in DMN function (Bonnelle et al., 2012), and stimulus inherent salience could attenuate the deactivation BOLD responses of the PCC in the DMN, which could be offset by a sufficient level of glutamate in the dorsal ACC (von Düring et al., 2019). Therefore, it is reasonable to presume that the SN is a potential neural correlate of consciousness.

Executive-control network (ECN)

As stated, awareness is related to a large-scale frontoparietal network that comprises two distinct subsystems in processing the self and external-related components of awareness (Haugg et al., 2018). In the composition of awareness, except for the impaired DMN that is involved in internal awareness, the ECN acts more like a lateral and dorsal frontoparietal network involved in the awareness of the environment and related to externally guided awareness (Luppi et al., 2021b). It is centered on the dorsolateral prefrontal cortex (DLPFC) and the posterior parietal cortex (PPC), and also includes the frontal eye fields (FEF) and part of the dorsomedial prefrontal cortex (dmPFC) that coordinate executive function (Chen et al., 2013; Friedman and Robbins, 2022; Menon and D'Esposito, 2022). This network regulates behavioral measures of executive control (e.g., attention, working memory, and cognitive control), including the voluntary control of novel and complex situations (Martin-Signes et al., 2019). Moreover, the anterior ECN was reported to be involved in interference control, which modulates perceptual sensitivity and conscious perception (Colás et al., 2017). Previous studies suggested that there are neural correlates between executive control and conscious perception in frontal–parietal regions by functional connection analysis (Martin-Signes et al., 2019; Martín-Signes et al., 2021). Compared with the wake state, the within-network functional connectivity of the DMN, SN, and ECN was observed to be significantly reduced under unresponsive states (drug sedation or deep sleep; Guldenmund et al., 2017). In addition, fewer patients in MCS and VS/UWS showed components of neuronal origins for bilateral ECN compared with healthy controls (Demertzi et al., 2014). It could be speculated that the ECN constitutes a crucial neural substrate of the global workspace that enables consciousness control. Moreover, it has been suggested that the reduced functional connectivity between the DLPFC and precuneus enables the former a popular therapeutic target for non-invasive brain stimulation in prolonged DoC as to restore the disrupted balance between the ECN and DMN (Qin et al., 2015b; O'Neal et al., 2021).

Dorsal attention network (DAN)

The dorsal attention network (DAN) is a vital part of the "task-positive" network and typically modulates brain activity to exert control over thoughts, feelings, and actions during task performance (Humphreys and Sui, 2016; Lu et al., 2019). The DAN could be subdivided into endogenous and exogenous control components. The endogenous attention control components link the dorsal frontoparietal regions and cover the intraparietal sulcus (IPS), while exogenous components are associated with the ventral frontal and temporoparietal regions, including the temporoparietal junction (TPJ; Bourgeois et al., 2013; Ahrens et al., 2019). It was reported that functional connectivity within the DAN was reduced under anesthetic-induced light sedation (Wang et al., 2021). Moreover, the DAN is also negatively correlated with the DMN and constitutes negative DMN connectivity (Fox et al., 2005; Favaretto et al., 2022). In comparison, the DMN mediates the recurrence of thoughts experienced during past events, whereas the DAN may contribute to the visuospatial attention distribution of episodic memory features (Stawarczyk et al., 2018). As the anti-correlation between the spontaneous activity of the DMN and DAN increased, patients' behavioral performance became more consistent, and these negative correlations seem to be decreased proportionally under anesthesia (Boveroux et al., 2010). It was reported that the switching between these two networks is crucial for conscious cognition and might be a more credible marker for tracking alterations of consciousness even than the positive DMN connectivity in patients with prolonged DoC (Di Perri et al., 2016). In any event, the disruption in both positive DMN connectivity and negative DMN connectivity seemed always to be increased with the improvement of consciousness (i.e., from UWS, MCS, and emergence from MCS to healthy controls; Boly et al., 2009; Di Perri et al., 2016).

Auditory, visual, and sensorimotor networks

As is well-known, the direct clinical diagnosis of prolonged DoC is mainly based on the behavior responses reflected from auditory, visual, and sensorimotor cortices (Kondziella et al., 2020). The visual system consists of the primary, lateral, and occipital visual networks including the occipital lobe and the fusiform gyrus

(Heine et al., 2012; Wang Y. et al., 2020). Interestingly, there were studies suggesting that the activity and connectivity in lower order networks appear to be less affected under unresponsive states, while higher order brain networks are significantly weakened (Boveroux et al., 2010; Kirsch et al., 2017; Wang et al., 2021). For instance, the functional integrity of higher order networks was severely disrupted by light sedation when lower level networks were found to be globally preserved (Liang et al., 2015). Patients in MCS might also preserve large-scale cortical networks associated with language and visual processing (Giacino et al., 2006). However, other studies suggested that the functional activities of low-order networks in prolonged DoC are reduced, especially in patients in VS/UWS, and all these networks have a certain capacity to discriminate against patients with prolonged DoC (Demertzi et al., 2015; Medina et al., 2022). Specifically, decreased connectivity between visual and SMN (Amico et al., 2017) and ECN (Mikell et al., 2015) was observed in unresponsive patients, respectively. The exact reason is not clear, but we suspect that the inconsistent results may be partly due to different etiologies or inducements, as well as different analysis methods of brain networks.

In contrast, more studies have explored AN elicited by voice stimulation under task-state fMRI, which may be related to the prognosis of prolonged DoC (Di et al., 2007; Wang et al., 2015). Nevertheless, the functional connectivity of AN at the resting state could also be used to distinguish patients in an MCS from those in a VS/UWS, and the reduced connectivity between the auditory and visual cortices may be more sensitive to distinguish patients independently (Boveroux et al., 2010; Demertzi et al., 2015). This might be partly due to the disrupted anatomical connections in patients with DoC and the direct comparison between patients in MCS and VS/UWS among these networks. The regions of the AN encompassed the bilateral auditory cortices including the superior/transverse temporal gyrus and are associated with TPJ (Laureys et al., 2000; Demertzi et al., 2014). Auditory–visual functional connectivity is considered relevant to multisensory integration, which is indispensable in predicting forthcoming sensory events and differentiating patients with prolonged DoC (Boly et al., 2008). In particular, according to the analysis of network neuronal properties (neuronal vs. non-neuronal), the DMN and AN were thought to discriminate patients from healthy subjects with high accuracy (Demertzi et al., 2014).

Apart from the primary somatosensory and ventrobasal thalamic nucleus that transmits somatosensory cortical activity, and the primary motor cortex and the ventral lateral thalamic nucleus that carry motor control information (Kang et al., 2016), there is a higher order sensorimotor circuit of the brain's global functional network that supports consciousness in the sensorimotor processing. This circuit is constituted by the supplementary motor area (SMA), the supragenual ACC, the bilateral supramarginal gyrus, and the left middle temporal gyrus (Qin et al., 2021). Prior studies have shown abnormal activities or connectivity in higher order sensory and motor regions in patients in a UWS, healthy people who are asleep, or patients under anesthesia (Mitra et al., 2015; Qin et al., 2021), while the stimulus-evoked activity of primary sensory regions is largely preserved.

Discussion

As fMRI has been increasingly applied in the clinical utility and investigation of neurological diseases, its clinical values in prolonged DoC are increasingly significant (Albrechtsen et al., 2022). Previous studies have mainly applied fMRI to the baseline consciousness assessment and brain function exploration in prolonged DoC (Crone et al., 2014; Weng et al., 2017; Zhang et al., 2018), providing insights into the neural mechanisms of brain networks that have not been fully understood so far. In addition to brain injury, functional connectivity and network integrity are also disturbed to varying degrees in aging (Malagurski et al., 2020; Patil et al., 2021) and neurodegenerative disorders including mild cognitive impairment, Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (Zhu et al., 2021; Miao et al., 2022; Thome et al., 2022; Zhao et al., 2022). Of which, the DMN is highly vulnerable. The underlining mechanisms remain unclear so far, but some studies suggested that the DMN is especially vulnerable to amyloid deposition (Hampton et al., 2020; Guzman-Velez et al., 2022) and inconsistently activated across time (Malagurski et al., 2020).

Here, we focused on the major brain networks that have been identified as being associated with prolonged DoC in the last few years. Based on this research, it is determined that prolonged DoC is associated with severely impaired resting state network connectivity, especially in higher order (Demertzi et al., 2015; Kirsch et al., 2017). Notably, numerous studies have indicated that the impaired functional connectivity within the brain networks is present in a consciousness-level-dependent manner (Norton et al., 2012; Crone et al., 2015; Panda et al., 2022; Wang et al., 2022), even in linear correlation (Di Perri et al., 2016), and most networks seem to have a high discriminative capacity to separate patients in an MCS and VS/UWS (Demertzi et al., 2015). Of the seven networks we listed, the DMN is the most concerned brain network in prolonged DoC. The functional connectivity strength between the mPFC and PCC/precuneus has potentially significant value for the prediction of consciousness awakening (Norton et al., 2012; Guo et al., 2019). In addition, the negative DMN connectivity including the anti-correlation between the spontaneous activity of the DMN and DAN or ECN was also found to be impaired in prolonged DoC (Boly et al., 2009; Qin et al., 2015b; Di Perri et al., 2016), as well as the SN may play an important role in switching between "task-positive" and "task-negative" networks (Goulden et al., 2014; Zhou et al., 2018).

Apart from consciousness assessment and supportive diagnosis, recently, fMRI was applied as an evaluation tool to estimate the therapeutic efficacy of wake-promoting treatment such as transcranial direct current stimulation (Aloi et al., 2022), transcutaneous auricular vagus nerve stimulation (Yu et al., 2017), zolpidem (Rodriguez-Rojas et al., 2013), sensory stimulation (Pape et al., 2015), amantadine, and transcranial magnetic stimulation (Bender Pape et al., 2020). In particular, abnormal functional connectivity as assessed by resting-state fMRI is pivotal in personalized target identification in neuromodulation therapy (Ren et al., 2022). This means that fMRI may be an effective technique to assist in the treatment of prolonged DoC. However, this still needs a lot of research to confirm. In addition, given that DLPFC is one of the most commonly used targets for neuromodulation therapy in patients with prolonged DoC (O'Neal et al., 2021), ECN may also serve as an important network for efficacy evaluation as well as DMN.

Furthermore, although increasing research has been devoted to exploring the brain networks of prolonged DoC, few studies have delved into the different etiologies. A previous study analyzed the fMRI data of 29 patients with cardiac arrest and 14 patients with traumatic brain injury, the results indicated that posteromedial cortex disturbance was particularly found in patients with cardiac arrest, whereas cingulum architectural was found in traumatic patients (Peran et al., 2020). However, the relationship between functional networks and different pathological states of the brain remains poorly understood. Future studies are required to elucidate differences in functional connectivity between prolonged DoC of different etiologies, as well as between patients with prolonged DoC, medicated sedation, or in deep sleep states to facilitate more accurate diagnosis and the development of personalized treatment. Moreover, it is worth noting that there is a major challenge facing the application of fMRI in prolonged DoC, that is, most of these patients are inapposite for MRI scanning. Whether it is the intracranial metal, large areas of brain tissue deformation, or the unconscious head movement during the process, would all limit the clinical practice and data analysis of fMRI in prolonged DoC (Desai et al., 2015; Kirsch et al., 2017). Future compatible technologies and advanced algorithms are expected to overcome and improve this problem.

Conclusion

In recent years, the study of neurofunctional imaging in the field of DoC has evolved from small sample-based studies on areas-of-interest networks to multicenter across whole-brain network studies, which significantly advanced our understanding of the brain function in patients with prolonged DoC at the network level, allowing them to be dynamically modeled gradually. Meanwhile, due to the numerous analytical methods of fMRI, one or two reports are sometimes insufficient to be fully replicated. Further investigations might aim at larger samples of patients and provide more objective and cautious evidence.

Author contributions

HL designed and wrote the original draft. XZ, XS, and LD aided in literature retrieval and screening. HL and HZ were involved in writing-review and editing. SY and HZ supervised and administrated 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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Optimizing the modulation paradigm of transcutaneous auricular vagus nerve stimulation in patients with disorders of consciousness: A prospective exploratory pilot study protocol

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Background: Transcutaneous auricular vagus nerve stimulation (taVNS) is a non-invasive neuromodulation technique. Several studies have reported the effectiveness of taVNS in patients with disorders of consciousness (DOC); however, differences in the modulation paradigm have led to inconsistent treatment outcomes.

Methods/design: This prospective exploratory trial will include 15 patients with a minimally conscious state (MCS) recruited according to the coma recovery scale-revised (CRS-R). Each patient will receive 5 different frequencies of taVNS (1, 10, 25, 50, and 100 Hz); sham stimulation will be used as a blank control. The order of stimulation will be randomized, and the patients' CRS-R scores and resting electroencephalography (EEG) before and after stimulation will be recorded.

Discussion: The overall study of taVNS used in treating patients with DOC is still in the preliminary stage of exploration. Through this experiment, we aim to explore the optimal stimulation frequency parameters of taVNS for the treatment of DOC patients. Furthermore, we expect to achieve a stable improvement of consciousness in DOC patients by continuously optimizing the neuromodulation paradigm of taVNS for the treatment of DOC patients.

Clinical trial registration: https://www.chictr.org.cn/index.aspx, identifier ChiCTR 2200063828.

KEYWORDS

disorders of consciousness, transcutaneous auricular vagus nerve stimulation, minimally conscious state, coma recovery scale-revised, electroencephalography

Introduction

Following severe brain injury, consciousness can remain impaired for a long time, resulting in DOC (Wu et al., 2022), which can severely affect patients' quality of life, placing a huge burden on society and their families. DOC includes coma, unresponsive wakefulness syndrome/vegetative state (UWS/VS), and minimally conscious state (MCS) (Gosseries et al., 2014). In contrast to patients with UWS/VS, patients with MCS exhibit signs of recovery of consciousness, such as visual pursuit, object localization, or following verbal commands (Giacino et al., 2002).

Neuromodulation therapy has been widely used in treating patients with DOC, divided into invasive and non-invasive neuromodulation according to the need for surgical assistance (Edlow et al., 2021; Shou et al., 2021; Wu et al., 2021). Non-invasive neuromodulation mainly includes repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), and transcutaneous auricular vagus nerve stimulation (taVNS).

Although taVNS is still in the early stages of scientific research and clinical application, thus far, it has been recognized as safe, convenient, inexpensive, and easy to use, allowing patients to use it from home and thus reducing their daily expenses. Therefore, it has been gaining increasing interest from clinicians and researchers.

To date, relevant studies have shown that taVNS is feasible and safe for patients with DOC. In 2017, our team reported a case of a 73-year-old female patient with the recovery of consciousness from VS to MCS after 4 weeks of treatment with taVNS and CRS-R score increased from 6 to 13. Functional MRI (fMRI) results showed that the patient had increased functional connectivity directly between the posterior cingulate/precuneus, hypothalamus, thalamus, ventral medial prefrontal cortex, and superior temporal gyrus, and decreased functional connectivity between the posterior cingulate and precuneus and cerebellum (Yu et al., 2017). In our opinion, taVNS enhances functional connectivity in the default mode network of the patient's brain, which may be the main reason for the recovery of consciousness. Our previous study found that the retention of auditory stimuli was important for the response to taVNS in patients with DOC (Yu et al., 2021).

In their study, Hakon et al. (2020) treated 5 patients diagnosed with VS or MCS with taVNS for 8 weeks and found improvement in consciousness in 3 out of the 5 patients, with 2 patients progressing from VS and MCS to eMCS and 1 patient progressing from VS to MCS. In another study, 14 DOC patients (VS = 6, MCS = 8) received taVNS in the left ear for only 4 weeks. One of the MCS patients showed new signs of consciousness at the end of the 4-week stimulation, and the other four showed new signs of consciousness at the 4-week follow-up time point (Noé et al., 2020).

In the above study, only one patient experienced intermittent ear pruritus during stimulation; however, no significant relationship with taVNS was found, indicating that taVNS is a feasible and safe treatment for patients with DOC.

Although taVNS has shown positive results in studies of DOC, the overall effectiveness rate is low, and an understanding of the mechanisms of consciousness regulation is lacking. A growing body of evidence suggests that the optimal frequency of taVNS may vary across disorders. E.g., a clinical study of taVNS in therapeutic epilepsy showed that patients in the 25-Hz group had significantly lower seizure frequency compared to the 1-Hz group (Schnakers et al., 2008). In another clinical study of migraine patients, researchers found that although both 1 and 25 Hz taVNS improved the prognosis of patients with chronic migraine, a greater improvement was observed with 1 Hz taVNS (Schnakers et al., 2009). In their vagal cortical pathway model, Briand et al. (2020) suggested that brainstem activation may be critical for taVNS to lead to recovery of consciousness in patients with DOC. Several researchers evaluated brainstem fMRI responses to 2, 10, 25, and 100 Hz taVNS in healthy subjects and found that 100 Hz stimulation elicited the strongest brainstem response (Sclocco et al., 2020). Therefore, exploring the optimal stimulation frequency parameters for taVNS-treated should be addressed in order to improve the therapeutic efficacy of taVNS in patients with DOC.

We propose to preliminarily evaluate the optimal stimulation frequency parameters in patients with DOC treated with taVNS by changes in CRS-R and EEG before and after taVNS. The behavioral changes induced by taVNS can be measured by CRS-R, while changes in brain function brought about by taVNS can be measured by EEG. Based on previous studies, we believe that the increase in spectral power in the alpha and theta bands may represent an improvement in patient awareness (King et al., 2013; Chennu et al., 2014; Sitt et al., 2014). However, due to the small number of relevant studies, we mainly considered these two indicators but were not limited to them. Our previous study found that EEG changes were more pronounced in MCS patients than in VS patients before and after taVNS treatment (Yifei et al., 2022).

In this study, we will record the CRS-R scores and resting EEG of 15 MCS patients before and after five random taVNS at different frequencies (1, 10, 25, 50, and 100 Hz) and one sham stimulation. Changes in CRS-R scores will be used as the primary evaluation index, and the immediate effects of EEG will be used as a secondary index to assess the effects of different frequencies of taVNS on MCS patients. In this way, we will attempt to initially explore the optimal stimulation frequency parameters for taVNS treatment of DOC patients to optimize the neuromodulation paradigm and improve efficacy.

Methods

Patients

We plan to recruit 15 patients diagnosed with MCS at the Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University. Patients will be assessed for inclusion criteria at admission by the principal investigator and screened according to exclusion criteria. Patients' current state of consciousness will be determined using at least two CRS-R assessments. Inclusion and exclusion criteria are shown in **Table 1**.

Procedures

The pilot study will begin as early as day 30 after the patient's injury and will be completed within 1 year of the injury.

Written informed consent will be obtained from the patient's legal representative following an open discussion of the study objectives, methods, and potential risks. The patient's legal representative will be informed that the patient's legal representative has the right to ask the patient to withdraw from the study at any time during the course of the study and that each party will retain a copy of the signed informed consent form.

This is a prospective exploratory trial including 15 MCS patients, each receiving a total of five different frequencies of taVNS (1, 10, 25, 50, and 100 Hz) and a sham stimulus as a blank control for 20 min, where the order of stimulation is completely randomized. We chose these five frequencies to span the range used in previous taVNS studies, including our own. Patient's CRS-R scores will be recorded before and after each stimulation. Each CRS-R score will be performed by no fewer than two physicians with extensive clinical experience. Also, by using a bedside 32-channel EEG (Nicolet EEG V32, Natus Neurology, USA), a 10-min resting EEG will be recorded before and after each stimulation, respectively. The interval between stimulations will be at least 48 h. SDZ-IIB electronic stimulator (Suzhou Medical Supplies Factory) will be used to provide stimulation. The experimental flow is shown in Figure 1.

Consistent with our previous experiments, a pair of identical-looking clips will be placed on both ears. The clips are designed with three carbon-impregnated silicone tips, one of which serves as the common end for supporting the posterior surface of the auricle, and the other two tips are designed to stimulate two skin surface points, one in the outer ear and the other in the navicular bone, with the two silicone tips at the outer ear point placed in the Cymba conchae and the Cavum conchae, respectively, as these are the two areas where the vagus nerve is most densely distributed in the ear. As shown in Figure 2, the SDZ-IIB electronic stimulator provides electrical pulses and continuous waves with a current of 1–1.5 mA. Real stimuli with frequencies of 1, 10, 25, 50, and 100 Hz are used on five occasions throughout the experiment, while a sham stimulus with the turned-off stimulator will be used on one occasion.

Assignment of interventions: Blinding

Throughout the trial, subjects and their legal representatives, caregivers on the medical team, and all researchers involved in patient assessment and statistical analysis will be blinded to the assignment of the intervention. During the trial, six envelopes of the same color, texture, and size will be placed in a box that will only be opened on one side. The investigator will randomly select an envelope and give it to a clinically experienced physician who will adjust the stimulation parameters for the patient according to the envelope instructions, and the extracted envelope will not be placed back in the box. This physician will not have any communication (including written, email, or verbal communication) with the investigator, the subject and his or her legal representative, the entire medical team, or the research staff involved in patient assessment and statistical analysis.

TABLE 1 Study inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
(1) Meeting the diagnostic criteria for MCS	(1) Open craniotomy
(2) Aged between 19 and 65 years old	(2) Brainstem injury
(3) Responding to auditory stimuli	(3) Pacemaker
(4) 3–12 months after injury	(4) Pregnant women
(5) Skull defect area less than one-third	(5) Metallic brain implants
(6) Family members agreed to sign an informed consent form	(6) Serious medical conditions that may affect clinical diagnosis or EEG activity

EEG recording and processing

A total of 20 min of EEG signals will be recorded for each stimulation procedure, and 10 min will be acquired before and after taVNS. EEG will be acquired by 32 channels (Nicolet EEG V32, Natus Neurology, USA) at a sampling rate of 1000 Hz, and the device will have 32 Ag/AgCl electrodes based on the national standard 10–20 system setup. All electrodes will be used with FCz as the reference electrode and AFz as the ground electrode, and the skin/electrode impedance will be kept below 5 kΩ. Patients will be awake during the acquisition, and if they show signs of sleepiness, the CRS-R scale will be used to wake up the procedure, or the experiment will be paused. Thirty-two electrodes (Fp1, Fp2, F3, Fz, F4, F7, F8, FC1, FC2, FC5, FC6, C3, Cz, C4, CP1, CP2, CP5, CP6, Pz, P3, P4, PO3, PO4, PO7, PO8, O1, Oz, O2, T3, T4, T5, and T6) will be selected for offline EEG analysis, and the EEG display parameters will be set to trap 50 Hz and bandpass filtered to 1–40 Hz. The frontal, central, parietal, and occipital regions of the brain are shown in Figure 3.

EEG analysis

The relative power of oscillations will be used to assess the effect of different frequencies of taVNS stimulation on the EEG of MCS patients (Bai et al., 2017). The relative power will be calculated as follows:

$$Relative\ Power\ (f_1,f_2) = Power\ (f_1,f_2)/Power\ (1,40) \times 100\%,$$

where Power (f_1,f_2) indicates the absolute power between the low f_1 and high f_2 frequencies. Power (1,40) is the sum of power (1–40 Hz).

taVNS and sham stimulations

The stimulation is provided by the SDZ-IIB electronic stimulator (Suzhou Medical Supplies Factory), which stably delivers continuous wave taVNS in the range of 1–100 Hz. In taVNS studies, the stimulation current intensity is commonly set according to the patient's perception threshold, usually at 1–1.5 mA, depending on the patient's tolerance (Badran et al., 2018). Based on previous experimental studies, we consider that the absence of a significant increase in heart rate, decrease in blood pressure, and painful expressions during stimulation mean that the patient tolerates the stimulation. Two silicone tips of the SDZ-IIB electronic stimulator are placed in the patient's ear cavity and ear canal, and each patient

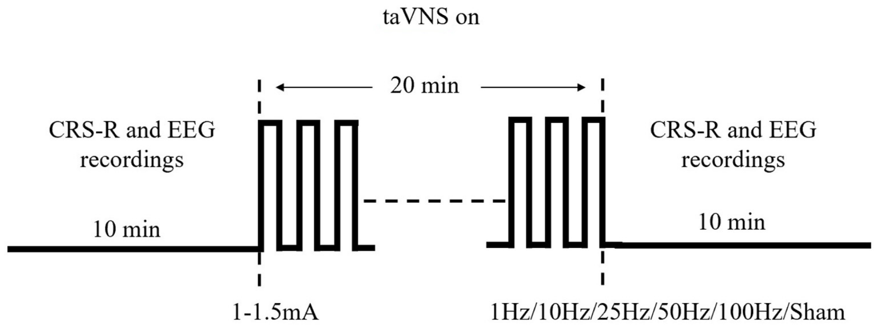

FIGURE 1
Single stimulation process and parameters used for stimulation.

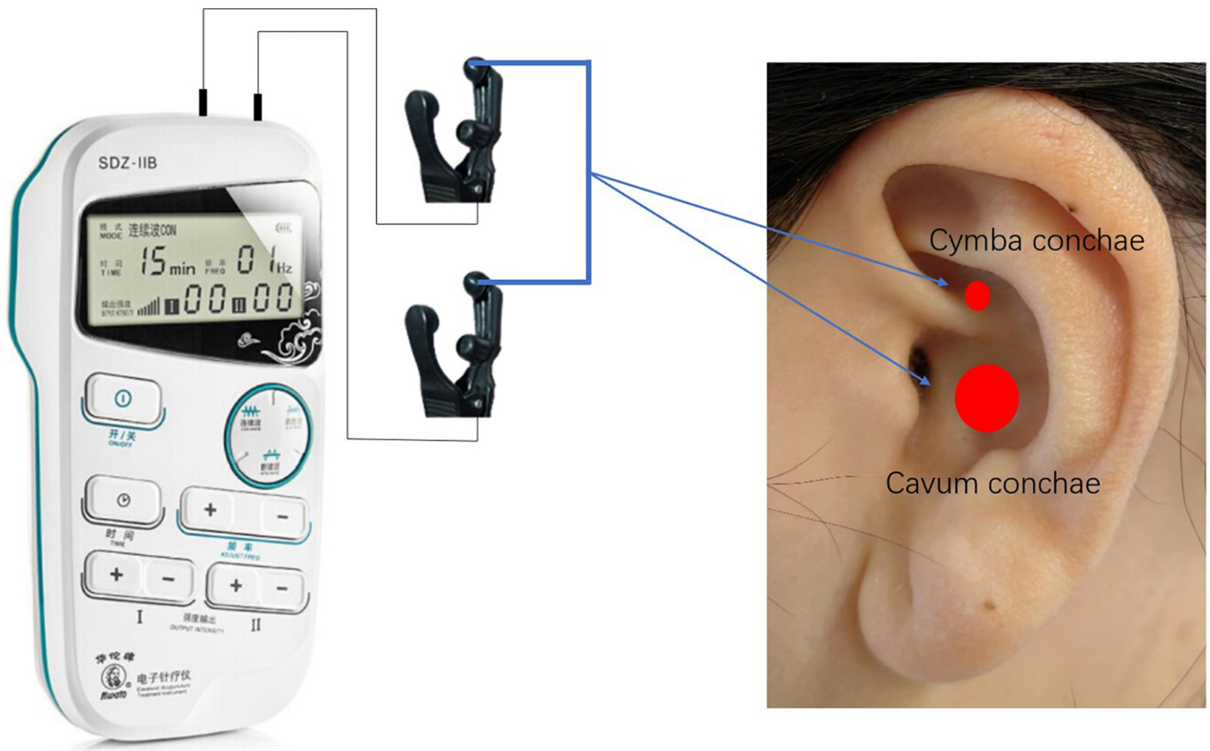

FIGURE 2
Stimulation sites of taVNS.

receives five different frequencies of taVNS and a sham stimulus in a randomized order. The technical parameters of the sham stimulation are identical, but no current is passed through.

Behavioral assessments

The CRS-R is the recommended method for classifying the level of consciousness (American Congress of Rehabilitation Medicine Brain Injury-Interdisciplinary Special Interest Group Disorders of Consciousness Task Force et al., 2010). The patient's level of consciousness is assessed using the CRS-R. This scale is the most valid and sensitive method for identifying behavioral signs of consciousness, leading to a better diagnosis of UWS/VS and MCS. It consists of six following subscales: auditory, visual, motor, oral-motor and verbal functions, communication, and arousal level. There are 23 items ordered by complexity, ranging from reflexive to cognitively mediated behaviors (Giacino et al., 2004).

Data collection and management

All information collected in this study will be kept confidential. All data will be stored using encryption measures, and paper copies will be stored electronically and encrypted. Subjects' legal representatives will be informed of the nature of the

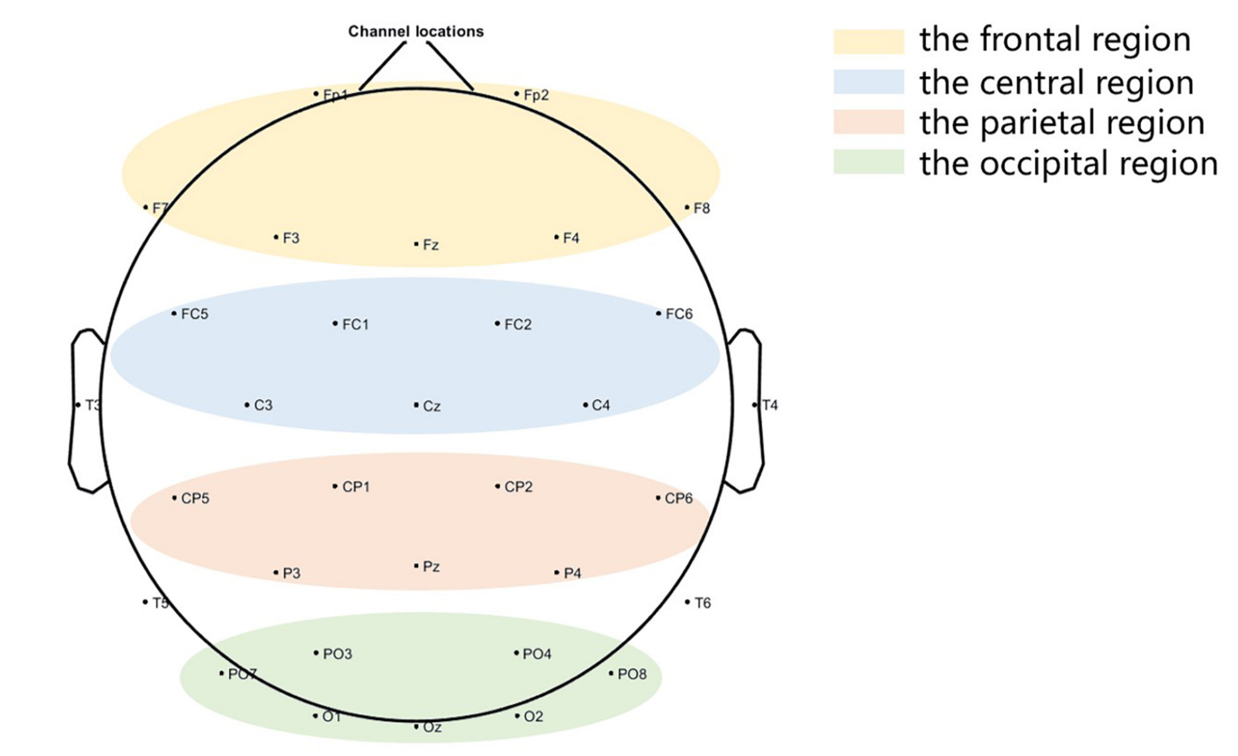

FIGURE 3
Brain local regions.

collected data and their rights to that same data through specific information sheets.

Statistical analysis

SAS 9.4 (SAS Institute, Cary, Cary, NC, USA) statistical software will be used, and data analysis will be completed by a third-party (Clinical Evaluation Center of the Chinese Academy of Traditional Chinese Medicine) statistician. Filling of missing values: multiple filling methods will be used. The regression filling method will be used for monotonic missing data of measures, and Monte Carlo filling method will be used for arbitrary missing data; the logistic regression filling method will be used for monotonic missing data of counts, and the FCS filling method will be used for arbitrary missing data; the regression analysis will be used for sensitivity analysis.

Discussion

Although previous studies have reported a positive effect of taVNS in the treatment of DOC patients, the efficacy is not stable due to different neuromodulation paradigms. Given the urgent therapeutic needs of DOC patients and the promising therapeutic prospects of taVNS, the scientific questions of optimal frequency parameters of taVNS should be urgently addressed.

The vagus nerve is the strongest parasympathetic nerve in the autonomic nervous system, consisting of 80% afferent and 20% efferent fibers, and serves as a bridge between the brain and the body in both directions (Butt et al., 2020). Vagus nerve stimulation is performed by electrically stimulating the vagus nerve to regulate brain activity (Shi et al., 2013). The distribution of the vagus nerve in the ear branch is mainly concentrated in the auricular region, including the Cymba conchae and the Cavum conchae (He et al., 2012). Therefore, electrical stimulation of the ear branch can produce similar effects to classical vagus nerve stimulation (Fang et al., 2016) without inducing perioperative risks.

The results of several previous studies have shown that taVNS modulates or activates cortical and subcortical areas associated with conscious control, including the locus coeruleus, nucleus accumbens, hypothalamus, medial prefrontal cortex, dorsolateral prefrontal cortex, anterior cingulate cortex, and posterior cingulate cortex (Kraus et al., 2007; Ruffoli et al., 2011; Cao et al., 2017; Corazzol et al., 2017).

In our previous study, we reported the effect of taVNS on cerebral hemodynamics in patients with DOC (Yu et al., 2021). Among 10 DOC patients included in the study, 5 responded to auditory stimulation and 5 showed no response. After 4 weeks of taVNS treatment, patients who responded to auditory stimulation had increased cerebral blood flow in several brain regions, a significant increase in CRS-R scores, and GOS scores indicating a good prognosis. In contrast, in patients who did not respond to auditory stimulation, the increase in cerebral blood flow with taVNS treatment was relatively weak, with a significant increase only in the left cerebellum and no significant changes in CRS-R scores or GOS scores. Therefore, our team suggests that the preservation of auditory function may be a key factor in response to taVNS in patients with DOC.

Our recent study focused on the EEG changes in 12 DOC patients before and after 14 days of taVNS treatment (Yifei et al., 2022), revealing a decrease in δ-band energy and an increase in β-band energy in the EEG of MCS patients after treatment, while no significant changes were observed in VS. Therefore, in this experiment, we used the diagnosis of MCS and preservation of auditory function as important screening criteria in order to improve the success rate.

By reviewing six studies on tavNS for patients with DOC, Jang and Cho (2022) found that four studies reported positive outcomes in patients with DOC treated with taVNS, including two EEG studies and two fMRI studies. However, in terms of stimulation frequency, 20–25 Hz was chosen by most studies, probably because there were no studies on the optimal stimulation frequency of taVNS in patients with DOC. Accordingly, the FDA-approved frequency range of 20–30 Hz for vagus nerve stimulation ensued.

The range of stimulation frequencies along the vagus nerve is clearly lacking in consideration for taVNS. We found that different stimulation frequencies may be appropriate for taVNS in different diseases. Also, different frequencies for the same disease produce different therapeutic effects. E.g., Marsal et al. (2021) innovatively boosted the taVNS stimulator to 2 kHz for the treatment of rheumatoid arthritis disease, and after 12 weeks of treatment, the mean DAS28-CRP significantly decreased in 27 patients compared to baseline, demonstrating that a 100-fold higher treatment frequency was more effective in patients with rheumatoid arthritis than the conventional 20 Hz. In another study, 24 patients with migraine were randomized into two groups, one of which was treated with 1 Hz, and the control group was treated with 20 Hz, both for 4 weeks. The results showed that after 4 weeks of treatment, the efficacy of 1 Hz was significantly due to 20 Hz (Cao et al., 2021).

In contrast to the previous study, we will eliminate the sparse wave treatment and replace it with a continuous wave treatment. This is because the experiment needs to control for a single variable frequency. Based on previous reports in the literature, we will use 1 Hz, 10 Hz, 25 Hz, 100 Hz, and sham stimuli as controls and 50 Hz as a supplement considering the large gap between the 25 and 100 Hz ranges. According to the existing literature (Sun et al., 2021), the retention effect of taVNS on the EEG lasts for about 1 h. Therefore, we will set a 48-h interval, i.e., a 48-h interval before the two stimuli, to ensure that the next stimulus does not receive the effects of the previous one.

In this study, we propose investigating the changes in behavior and brain function induced by taVNS in DOC patients using CRS-R and EEG measurements. In addition, the relative power of the oscillations will be used to assess the effects of different frequencies of taVNS on the EEG of MCS patients. Based on this, we will attempt to initially explore the selection of the optimal stimulation frequency parameters of taVNS for DOC patients through this experiment and to lay the foundation for subsequent experimental studies.

Data availability statement

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

Author contributions

WZ, HJ, JH, and PR contributed to the conception and design of the study. YZ, YY, JZ, and YFW reviewed the manuscript and suggested the changes. WZ wrote the first draft of the manuscript. YW, Y-NZ, and SZ embellished and revised the language of the manuscript. All authors participated in the revision of the manuscript, 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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EEG microstate changes during hyperbaric oxygen therapy in patients with chronic disorders of consciousness

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Hyperbaric oxygen (HBO) therapy is an effective treatment for patients with disorders of consciousness (DOC). In this study, real-time electroencephalogram (EEG) recordings were obtained from patients with DOC during HBO therapy. EEG microstate indicators including mean microstate duration (MMD), ratio of total time covered (RTT), global explained variance (GEV), transition probability, mean occurrence, and mean global field power (GFP) were compared before and during HBO therapy. The results showed that the duration of microstate C in all patients with DOC increased after 20min of HBO therapy ($p<0.05$). Further statistical analysis found that the duration of microstate C was longer in the higher CRS-R group (≥8, 17 cases) than in the lower group (<8, 24 cases) during HBO treatment. In the higher CRS-R group, the transition probabilities from microstate A to microstate C and from microstate C to microstate A also increased significantly compared with the probability before treatment ($p<0.05$). Microstate C is generally considered to be related to a salience network; an increase in the transition probability between microstate A and microstate C indicates increased information exchange between the auditory network and the salience network. The results of this study show that HBO therapy has a specific activating effect on attention and cognitive control in patients and causes increased activity in the primary sensory cortex (temporal lobe and occipital lobe). This study demonstrates that real-time EEG detection and analysis during HBO is a clinically feasible method for assessing brain function in patients with DOC. During HBO therapy, some EEG microstate indicators show significant changes related to the state of consciousness in patients with chronic DOC. This will be complementary to important electrophysiological indicators for assessing consciousness and may also provide an objective foundation for the precise treatment of patients with DOC.

KEYWORDS

disorders of consciousness, hyperbaric oxygen, electroencephalogram, microstate, clinical assessment

1. Introduction

Disorders of consciousness (DOC) are states of loss of consciousness caused by various severe brain injuries, such as coma, vegetative state (*VS*), and minimally conscious state (MCS). Prolonged DOC (pDOC) is defined as disorders of consciousness with loss of consciousness for more than 28 days (Giacino et al., 2018; Kondziella et al., 2020). One of the greatest difficulties in DOC graded diagnosis is identifying and differentiating patients who retain some degree of consciousness from those who do not. In the absence of a better way to assess a person's level of consciousness, physicians can only infer a patient's state based on the patient's ability to perform apparently voluntary actions that suggest consciousness. With the development of diagnostic techniques for the level of consciousness, the continuous revision of the Coma Recovery Scale-Revised (CRS-R), and the use of functional brain imaging techniques, which solve the problem of consciousness detection in patients after severe brain injury, our understanding of the classification of DOC is also advancing (Porcaro et al., 2022).

There are many clinical causes of DOC, including traumatic brain injury, cerebrovascular disease, hypoxic ischemic encephalopathy, brainstem injury, and many other causes (Pauli et al., 2020; Zhang et al., 2023). Clinical intervention treatment of DOC is very important for the recovery of consciousness. Insufficient appropriate intervention treatment may lead to a persistent vegetative state, which not only brings a heavy burden to society and families but also causes family members and medical staff to face ethical dilemmas (Schnakers et al., 2009). Accurate identification of UWS/*VS* and MCS is of great significance to the treatment of patients and the selection of medical resources. However, the current clinical misdiagnosis rate of MCS as UWS/*VS* is 41% (Schnakers et al., 2009; Ye et al., 2020). When the patient's level of consciousness shifts from UWS/*VS* to MCS, there is an inflection point in electroencephalography (EEG) features (Lei et al., 2022). An increasing number of studies have confirmed the role of hyperbaric oxygen (HBO) therapy in the process of awakening in patients with DOC (Ye et al., 2020; Porcaro et al., 2022), and quantitative EEG (qEEG) can be applied to evaluate the effect of the HBO therapy course or intervention time on the curative effect of patients with cerebral resuscitation (Ye et al., 2020). Then, as a therapeutic stimulus, HBO may help to accurately identify the patient's level of consciousness if the EEG changes during HBO therapy can be monitored, which in turn guides treatment without wasting medical resources or delaying patients' treatment. However, real-time EEG monitoring during HBO therapy in patients with impaired consciousness has not been reported.

EEG is a technology that analyzes the physiological electrical signal activity of each brain region by recording the electric potential of the scalp surface electrode and the electric field strength (von Wegner and Laufs, 2018). EEG, with a history of nearly a century, has the advantages of low price and high temporal resolution and can noninvasively evaluate the neural activity of brain regions (Plum and Posner, 1972). At present, there are some relatively mature methods to extract effective information from multichannel EEG data, and microstate analysis is one of them (Michel and Koenig, 2018). Lehmann et al. (1987) proved for the first time that the alpha frequency band (8–12 Hz) of the multichannel resting-state EEG signal could be decomposed into a series of quasi-steady states. These discrete states are defined as "microstates," and each microstate can be stable for 80–120 ms before switching between different microstates. Microstate analysis differs from other methods in that signals from all electrodes are considered simultaneously, taking the global functional state into account. Microstate time series have a rich syntax that enables a variety of new quantifications of neurophysiologically relevant EEG signals. At the same time, the study of Lehmann et al. (2010) showed that the time series of EEG microstates will change with changes in behavior, disease, etc.

In previous studies, microstates were usually divided into four categories. Some researchers found that different microstates correspond to different brain regions in the human brain and reflect changes in different brain networks. Microstate A is primarily associated with the bilateral superior and middle temporal gyri, which are associated with the auditory system. Some studies showed that this area is closely related to the auditory network, reflecting the input and processing of auditory information (Britz et al., 2010). Microstate B is related to brain areas related to visual processing and may be connected to the visual network. Changes in microstate B are the first to be noticed when the human visual system is damaged or changed (Khanna et al., 2015). Microstate C is related to the posterior part of the anterior cingulate cortex, the bilateral inferior frontal gyrus, and the right anterior insula. It corresponds to the salience network and plays an important role in switching between the central executive network and the default network (Khanna et al., 2015). Microstate D is associated with locations such as the right dorsal and ventral areas of the frontoparietal cortex and with the central executive network, which is responsible for higher-level tasks such as cognition and decision-making (Khanna et al., 2015).

There is no report on the real-time monitoring of EEG during HBO therapy in patients with DOC. We believe that some EEG indicators of DOC patients will change during HBO therapy, and the characteristics of these changes may be helpful for the assessment of clinical consciousness level. Therefore, the purpose of this study was to observe the electrophysiological changes in patients with DOC before and during treatment by using the microstate change indicators of EEG. By analyzing the microstate indicators of patients, the feasibility of real-time EEG detection in HBO therapy and its role in brain function evaluation are herein discussed. EEG microstate changes during HBO therapy are likely to become important electrophysiological indicators for consciousness assessment.

2. Materials and methods

2.1. Patients

For this study, 41 DOC patients were recruited at the Beijing Tiantan Hospital, Capital Medical University, from March 2021 to January 2022. The age of the 41 DOC patients ranged from 18 to 76 years (47.7 ± 16.3), including 28 male patients (age 47.3 ± 16.9 years) and 13 female patients (age 48.8 ± 15.5 years). The postinjury period was 1–16 months (4.2 ± 3.8), and the CRS-R score before HBO therapy was 3–15 (7.1 ± 2.9) (Table 1). All enrolled patients met the following inclusion criteria: (1) definitively diagnosed with DOC; (2) age 18–80 years; (3) onset time more than 1 month; (4) consciousness in a stable period, unconscious improvement or decline at least 4 weeks before enrollment; and (5) family members who agreed to receive HBO therapy and signed an informed consent form.

TABLE 1 Details of DOC patients participating in real-time EEG monitoring during HBO therapy.

Patient	Gender	Age (years)	Etiology	Post-injure (months)	CRS-R						
					Total	A	V	M	OM	C	Ar
1	M	76	T	1.0	5	0	1	1	1	0	2
2	F	36	A	2.0	7	1	1	2	1	0	2
3	M	33	S	4.0	5	1	0	1	1	0	2
4	M	35	S	2.0	10	1	3	3	1	0	2
5	M	56	S	1.0	3	0	0	2	1	0	0
6	M	22	T	1.0	8	1	1	3	1	0	2
7	F	58	T	3.0	9	1	3	2	1	0	2
8	F	31	T	8.0	10	1	3	3	1	0	2
9	M	32	S	4.0	4	0	0	2	1	0	1
10	M	65	T	7.0	4	0	1	0	1	0	2
11	F	62	T	4.0	6	1	1	1	1	0	2
12	F	52	S	12.0	5	1	0	2	1	0	1
13	M	35	T	2.0	8	1	1	3	1	0	2
14	F	53	S	1.8	7	1	3	2	1	0	0
15	M	39	S	3.0	5	0	0	2	1	0	2
16	M	47	A	1.0	7	1	1	2	1	0	2
17	F	39	T	1.0	15	3	4	5	1	0	2
18	F	65	T	2.0	5	1	1	2	1	0	0
19	M	43	T	4.0	5	0	0	2	1	0	2
20	M	46	T	5.0	5	0	1	1	1	0	2
21	F	34	T	2.0	14	3	4	4	1	0	2
22	M	30	S	1.0	5	1	0	2	1	0	1
23	M	72	S	2.0	8	1	1	3	1	0	2
24	M	58	S	3.0	7	0	3	1	1	0	2
25	M	33	T	4.0	7	1	1	2	1	0	2
26	M	53	T	2.0	11	2	3	3	1	0	2
27	M	64	S	7.0	8	1	3	1	1	0	2
28	M	56	T	6.0	10	1	3	3	1	0	2
29	F	56	T	12.0	4	0	0	2	0	0	2
30	M	34	A	1.0	6	1	0	2	1	0	2
31	M	71	S	4.0	8	2	1	2	1	0	2
32	M	56	S	2.0	12	1	3	4	1	0	3
33	F	18	T	1.7	9	1	3	2	1	0	2
34	M	21	T	3.0	4	0	0	1	1	0	2
35	F	62	T	11.0	3	0	0	2	1	0	0
36	M	59	S	13.0	7	1	1	2	1	0	2
37	M	67	S	1.7	3	0	0	1	1	0	1
38	M	34	A	2.0	11	1	3	3	2	0	2
39	F	68	S	6.0	10	1	3	3	1	0	2
40	M	67	T	2.0	5	0	1	1	1	0	2
41	M	19	S	16.0	8	1	1	2	2	0	2

Sex (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). Forty-one patients were included in the study, aged 18–76 years (47.7 ± 16.3), 1–16 months (4.2 ± 3.8) post-injury, and CRS-R score 3–15 (7.1 ± 2.9). Twenty eight male patients (age: 47.3 ± 16.9) and 13 female patients (age: 48.8 ± 15.5) were included in the study.

The exclusion criteria were as follows: (1) patients who could not tolerate HBO therapy, DOC caused by neurodegenerative diseases (Alzheimer's disease, Lewy body dementia) and malignant brain tumor surgery; (2) coma caused by exacerbation of systemic diseases or expected survival time; (3) duration of illness <3 months; (4) epileptic seizures that were difficult to control; (5) treatment with experimental drugs or equipment; and (6) untreated tension pneumothorax or other conditions that HBO physician deems inappropriate for treatment.

The study was conducted under the Declaration of Helsinki of the World Medical Association and approved by the Ethics Committee of Beijing Tiantan Hospital (No. KYSQ 2021–396-01). Before inclusion, the researcher fully informed each patient's legal guardians of the study protocol and obtained informed consent from them.

2.2. Clinical evaluation

During the period of HBO therapy, the level of consciousness of the patients was evaluated based on the CRS-R scale (Giacino et al., 2004). Each CRS-R score was performed independently by two trained clinicians. At least three assessments by CRS-R were performed 1 week before HBO therapy to clarify the patient's level of consciousness.

2.3. HBO

The HBO therapy in this study was completed in the intensive care cabin group of the Hyperbaric Oxygen Department of Beijing Tiantan Hospital, Capital Medical University. The treatment pressure was 0.2 MPa (normal environment 0.1 MPa), and a single treatment lasted for 2 h: 30 min boost–60 min stabilized oxygen inhalation–30 min decompression. The oxygen chamber was equipped with a ventilator, sputum suction device, etc. ECG monitoring was maintained, and medical staff accompanied the whole process to ensure the safety of patients. During the treatment, the oxygen and carbon dioxide concentrations in the cabin were monitored to maintain them within the normal range.

2.4. EEG recording

EEG recordings were collected by Nicolet EEG with 19 channels. Data were collected synchronously during HBO therapy. The sampling rate was 500 Hz. The impedance of all electrodes was kept within 5 kΩ. During data collection, the bilateral mastoid electrodes A1 and A2 were used as reference electrodes.

2.5. EEG processing

We preprocessed the data using the eeglab plugins in the MATLAB toolbox. First, the data were filtered. A 50 Hz notch filter and 1–45 Hz bandpass filter were applied to the data according to the acquisition situation, some unnecessary electrodes (including bilateral mastoid electrodes A1 and A2) were removed, and the data were divided into 3 s epochs. Then, we removed the artifacts from the signal. First, most of the artifacts were removed by visual inspection, and then an independent component analysis (ICA) algorithm was used for correction to retain the characteristics of the original EEG signal but remove the artifacts associated with electrooculographic, electromyographic, and ECG events.

2.6. EEG microstate

To analyze the microstate of the preprocessed data, we first calculated its global field power (GFP). GFP can reflect the instantaneous electric field strength of the brain, so it is often used to measure the brain's response to events or describe changes in brain activity (Khanna et al., 2015). The calculation formula of GFP is as follows:

$$GFP = \sqrt{\left(\sum_{i}^{K}\left(V_i(t) - V_{mean}(t)\right)^2\right) / K}$$

where K is the number of electrodes in the EEG data. $V_i(t)$ is the potential of the i-th electrode at a certain time point. $V_{mean}(t)$ is the average value of the instantaneous potential across electrodes, and the formula is as follows:

$$V_{mean}(t) = \left(\sum_{i}^{K} V_i(t)\right) / K$$

In the microstate analysis, the topographic map of the local maximum value of GFP is considered to represent the discrete state of EEG. Therefore, through the cluster analysis of the local maximum value of GFP, all topographic maps are divided into several types. K-means clustering is the most basic method employed in the MATLAB toolbox. The method starts with partitioning the EEG samples into a fixed number of clusters, to which the EEG samples are relocated in iterations, until an optimal cluster assignment has been achieved. The clustering results were four microstates, labeled A, B, C, and D, and most of the differences could be explained using the topographic maps of the four microstates. After clustering the microstate topography map, we calculated the microstate parameters of all patients, including mean microstate duration (MMD), ratio of total time covered (RTT), global explained variance (GEV), transition probability, mean occurrence, and mean GFP.

2.7. Statistical analysis

Microstate analysis was performed on the EEG of all patients before and after HBO therapy. We analyze patients from different perspectives: (1) all patients (41 cases); (2) CRS-R ≥ 8 (17 cases) and CRS-R < 8 (24 cases); (3) traumatic brain injury and non-traumatic brain injury (including anoxic and stroke); and (4) other factors: age, sex, and postinjury (months). This study compares the differences in EEG microstates between different clinical groups before and after HBO.

We used SPSS 25 software for statistical analysis. We tested the data for normality using the Shapiro–Wilk test. The Wilcoxon signed-rank test was used for non-normally distributed data. The paired sample t-test was used to compare the microstate differences before and after HBO therapy. $p < 0.05$ was considered statistically significant.

3. Results

3.1. HBO treatment in DOC patients

All 41 patients completed a single session of HBO therapy and EEG monitoring, and no adverse events, such as middle ear and pulmonary barotrauma, occurred. The patients were treated smoothly in the HBO chamber, and there was no sudden instability of respiratory and blood pressure, suffocation with excessive phlegm, epilepsy, fever, or other events.

3.2. Analysis of EEG microstates in DOC patients

According to our previous research, when oxygen is inhaled for 20 min in a hyperbaric chamber, changes in patients' EEG microstates can be observed, reflecting the impact of HBO on brain function (Yu et al., 2011, 2014). Referring to the research of Britz et al. (2010), we analyzed the EEG microstates of 41 patients with DOC by applying a clustering algorithm to fit four microstate topographic maps before HBO therapy and 20 min after HBO therapy; these microstates were designated A, B, C and D (Figure 1). The microstate class orientations were (A) right frontal left posterior; (B) left frontal right posterior; (C) anterior–posterior; and (D) frontocentral extreme (polarity is ignored in the microstate analysis).

Statistical analysis was performed on the changes in microstate parameters of 41 patients with DOC before and after HBO therapy. We found that the duration of microstate C in all patients at 20 min of HBO therapy was significantly increased compared with the corresponding pretreatment duration ($p = 0.021$) (Table 2 and Figure 2). The contribution, occurrence and mean GFP of all microstates did not change significantly. There was no significant change in the transition probabilities of the microstates in the 41 DOC patients (Table 3).

3.3. Analysis of EEG microstates in DOC patients with different levels of consciousness

We used the CRS-R scores to define the level of consciousness in DOC patients. We divided the patients into two groups by their CRS-R scores, namely, CRS-R ≥ 8 (17 cases) and CRS-R < 8 (24 cases), and performed a statistical analysis. The results showed that patients with CRS-R ≥ 8 had significant changes in microstates before and after HBO therapy (Figure 3), while those with CRS-R < 8 had no significant changes (Figure 4). The duration of microstate C in patients with CRS-R ≥ 8 at 20 min of HBO therapy was significantly increased compared with the pretreatment value ($p = 0.047$) (Table 4 and Figure 5). At the same time, the contribution of microstate D in these patients was lower at 20 min of HBO therapy than at pretreatment ($p = 0.030$). The results showed that the transition probability of microstates in patients with CRS-R ≥ 8 from microstate A to microstate C ($p = 0.035$) and microstate C to microstate A ($p = 0.032$) after 20 min of HBO therapy was significantly increased compared with the pretreatment probability. However, the transition probabilities among other microstates were not significantly different (Figure 6).

3.4. Analysis of EEG microstates in patients with DOC with different etiologies

From the perspective of etiology, we divided the patients into two groups: traumatic brain injury and nontraumatic brain injury (including anoxic and stroke), and the microstate parameters of each group of patients were statistically analyzed. The results showed that the duration of microstate C in nontraumatic brain injury patients after 20 min of HBO therapy was increased compared with the pretreatment duration. The mean GFP of patients with traumatic brain injury showed some decrease after 20 min of HBO therapy compared with pretreatment. There were no significant differences in the remaining microstate parameters between the two groups.

Statistical analysis showed that there was no significant difference in the microstate parameters of patients according to age, sex, or postinjury time either before or after they received HBO therapy (*t*-test, $p > 0.05$).

4. Discussion

With the continuous development of HBO medicine, comprehensive rehabilitation treatment based on HBO can clinically benefit patients with DOC. As an important electrophysiological technique, EEG detection is widely used in the evaluation of brain function in DOC patients. It is safe and feasible to carry out real-time EEG monitoring research under HBO therapy, which can not only provide an objective basis for precise HBO therapy but also enrich the clinical evaluation indicators of DOC. In this study, through the microstate analysis of EEG signals before and during HBO therapy, we found that some microstate indicators of DOC patients were significantly different.

Since the recovery of consciousness is not only a dynamic process but also one that involves interaction among various regions of the brain (Lei et al., 2022), the improvement of the brain functional network precedes the change in behavioral signs of awareness in DOC patients (Bareham et al., 2020). It is speculated that HBO therapy restored the function of some brain cells and enhanced the connections among different brain regions. If HBO therapy is used as a stimulating condition, the EEG changes during HBO can be monitored under this condition, which may help clinicians assess the patient's level of consciousness and formulate a more scientific clinical treatment plan.

In this study, we included 41 patients with different degrees of DOC, collected their baseline information, and completed real-time EEG monitoring during HBO therapy. Compared with previous DOC research (Stefan et al., 2018), our study included more patients with more extensive degrees of DOC, thus our results were more representative.

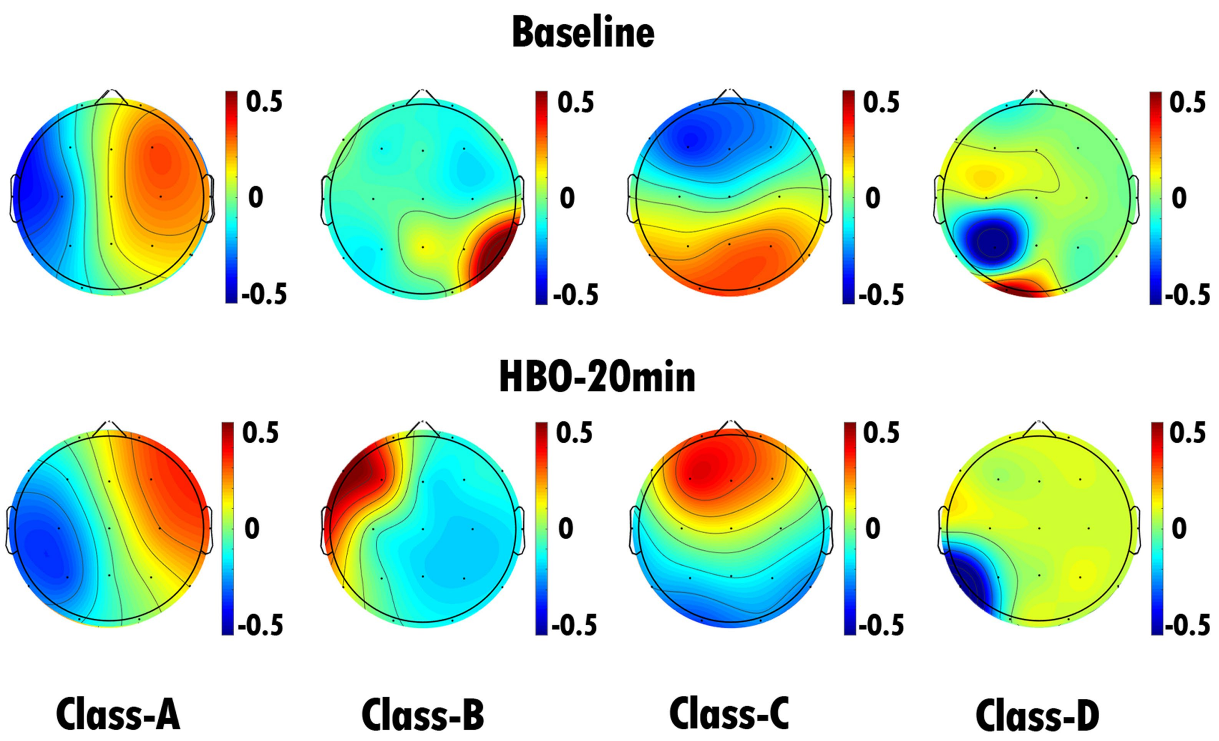

FIGURE 1
EEG microstate topography of all DOC patients (41 cases). The top row is the EEG microstate topography map of 41 DOC patients before HBO therapy, and the bottom row is the EEG microstate topography map of 41 DOC patients after 20min of HBO therapy. Through statistical analysis, we found that the duration of microstate C in patients significantly increased after 20min of HBO therapy compared with pretreatment (*p*<0.05).

TABLE 2 EEG microstate duration, occurrence, contribution and mean GFP analysis results of all DOC patients (41 cases).

	Class A		Class B		Class C		Class D	
	Baseline (Mean±SD)	HBO-20min (Mean±SD)	Baseline (Mean±SD)	HBO-20min (Mean±SD)	Baseline (Mean±SD)	HBO-20min (Mean±SD)	Baseline (Mean±SD)	HBO-20min (Mean±SD)
Duration (s)	0.048 ± 0.021	0.053 ± 0.025	0.047 ± 0.021	0.050 ± 0.022	0.043 ± 0.018	**0.051 ± 0.025**※	0.048 ± 0.024	0.047 ± 0.022
Occurrence (s^{-1})	6.614 ± 3.074	6.238 ± 2.793	6.417 ± 3.299	6.075 ± 2.401	6.783 ± 4.170	6.061 ± 2.497	6.558 ± 2.479	6.200 ± 2.880
Contribution (%)	0.258 ± 0.066	0.265 ± 0.077	0.248 ± 0.061	0.250 ± 0.065	0.236 ± 0.059	0.249 ± 0.065	0.259 ± 0.081	0.236 ± 0.051
Mean GFP (mV)	7.719 ± 3.206	8.018 ± 4.044	7.805 ± 3.343	7.994 ± 3.996	7.701 ± 3.427	8.002 ± 4.068	8.003 ± 3.314	7.967 ± 3.829

※Indicates the *t*-test result was significant ($p < 0.05$).
The duration of microstate C in 41 patients was significantly increased after 20 min of HBO therapy compared with the corresponding pretreatment duration ($p < 0.05$). Other microstate parameters did not change significantly.

4.1. Research status of the microstate in DOC patients

Recently, many studies have shown that the microstate indicators of patients with neurological and psychiatric diseases will change accordingly and may become potential biomarkers of certain types of diseases (de Bock et al., 2020; Wang et al., 2021; Sun et al., 2022). Microstate analysis can also be used as one of the indicators of drug treatment effects in patients with certain diseases (Serrano et al., 2018). In recent years, EEG microstate analysis of DOC patients has also developed rapidly. Representative studies have shown that microstate indicators can provide new anchor points for DOC patient evaluation and DOC patient prognosis assessment. For example, Stefan et al. (2018) analyzed 63 DOC patients' EEG, predicted the prognosis of 39 patients, and found that microstate A had significant differences. Guo et al. (2022) showed that DOC patients had significant changes in microstate C and microstate D after high-definition transcranial direct current stimulation (HD-tDCS) treatment. Zhang et al. (2022) performed microstate analysis on resting-state EEG data from DOC patients and identified seven microstates with distinct spatial distributions of cortical activation. There were significant differences in the microstate between the MCS group and the *VS* group. In existing research related to DOC, EEG data was collected from patients

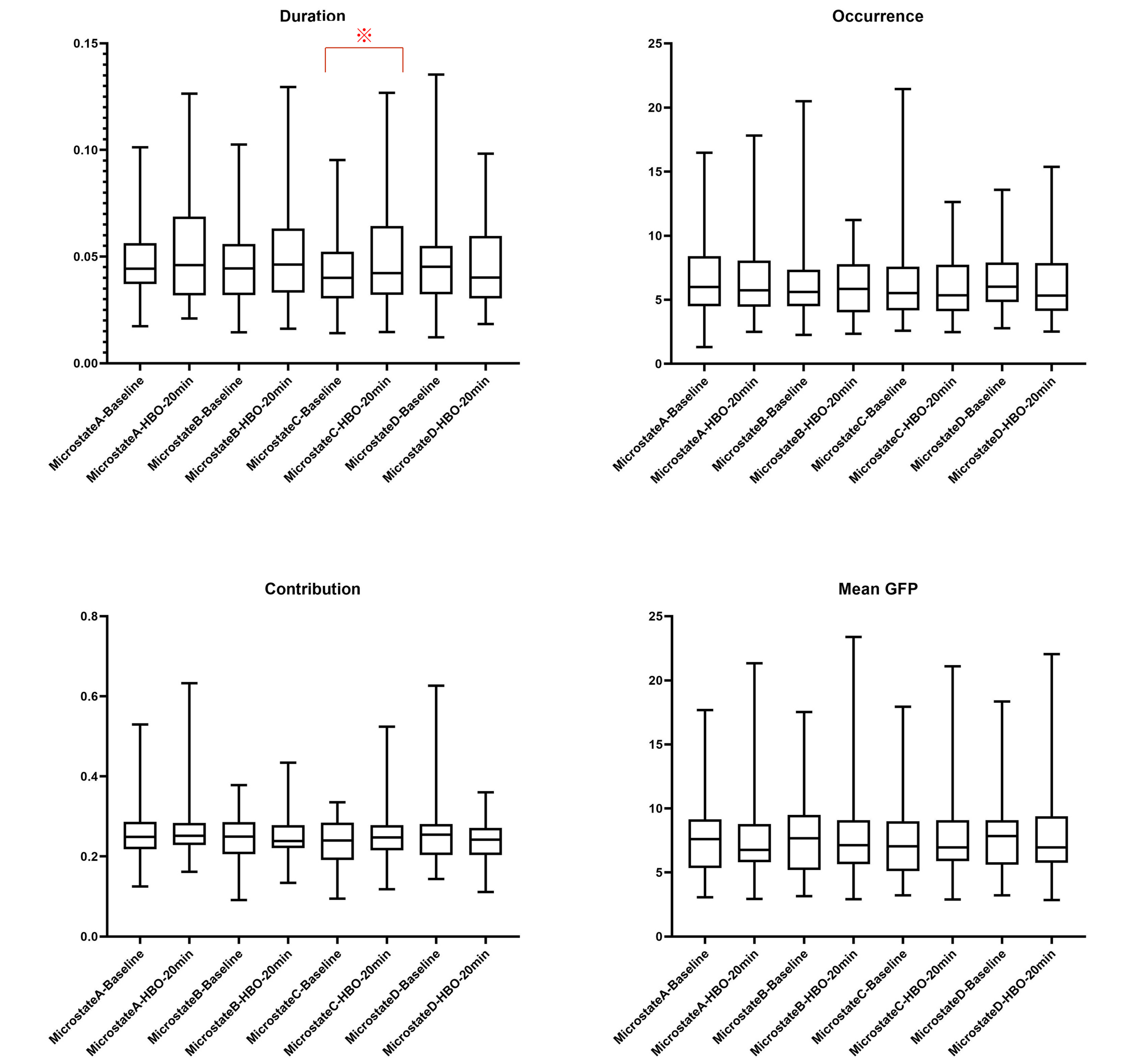

FIGURE 2
EEG microstate duration, occurrence, contribution and mean GFP analysis results of all DOC patients (41 cases). ※Indicates the *t*-test result was significant ($p<0.05$).

in the resting state for microstate analysis, but there is no related research on real-time EEG monitoring under special conditions. Our research on EEG real-time monitoring under resting-state and HBO conditions is of great significance for future studies on HBO treatment effects and disease indicators of DOC. Therefore, this study can not only greatly enrich real-time EEG monitoring in special environments but also provide new ideas for EEG research in DOC patients in an HBO environment.

4.2. Microstates of DOC patients during HBO therapy

Based on the EEG signals of all 41 DOC patients included in the study, we used a clustering algorithm to fit topographic maps to the microstates before and after 20 min of HBO therapy and divided them into four categories: A, B, C, and D (Figure 1). From the fitted topographic maps, we can see that microstate B and microstate D of DOC patients are quite different, while microstate A and microstate C conform to the classic microstate type compared with the four classic resting microstate topographic maps of normal people found by previous researchers (Britz et al., 2010). Through the statistical analysis of the microstate parameter results of all 41 DOC patients included in the study, we found that the duration of microstate C in patients after HBO therapy was generally significantly increased compared with the duration before treatment.

Microstate B is considered to be related to bilateral visual cortex regions. The topographic map of microstate B in DOC patients is quite different compared with that in normal individuals, which may

TABLE 3 EEG microstate transition probability and GEV analysis results of all DOC patients (41 cases).

	Class A		Class B		Class C		Class D	
	Baseline (Mean±SD)	HBO-20min (Mean±SD)	Baseline (Mean±SD)	HBO-20min (Mean±SD)	Baseline (Mean±SD)	HBO-20min (Mean±SD)	Baseline (Mean±SD)	HBO-20min (Mean±SD)
Class A (%)	–	–	0.079 ± 0.025	0.083 ± 0.020	0.082 ± 0.024	0.086 ± 0.021	0.090 ± 0.031	0.084 ± 0.020
Class B (%)	0.081 ± 0.025	0.083 ± 0.020	–	–	0.081 ± 0.028	0.081 ± 0.018	0.081 ± 0.023	0.084 ± 0.023
Class C (%)	0.083 ± 0.026	0.087 ± 0.024	0.081 ± 0.026	0.081 ± 0.020	–	–	0.085 ± 0.027	0.081 ± 0.015
Class D (%)	0.087 ± 0.031	0.084 ± 0.021	0.084 ± 0.024	0.084 ± 0.023	0.086 ± 0.027	0.081 ± 0.015	–	–
GEV (%)	0.721							

The transition probability of all DOC patients did not change significantly.

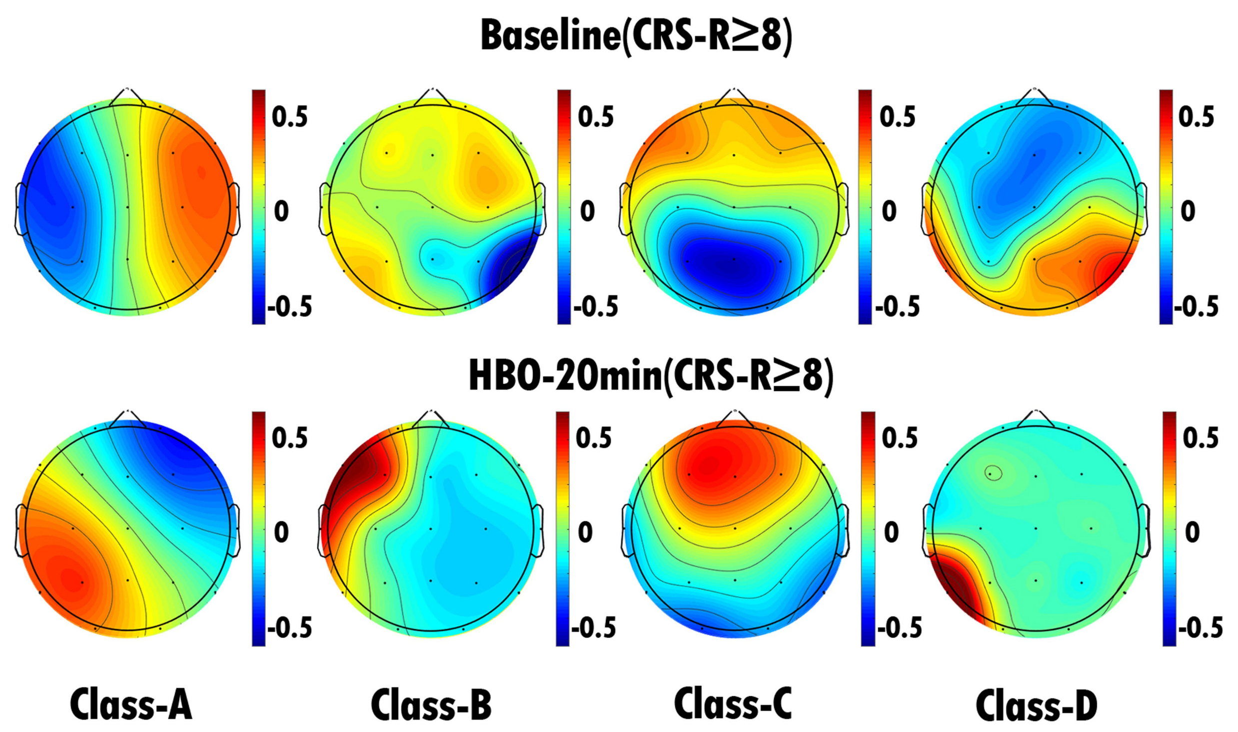

FIGURE 3
EEG microstate topography of DOC patients (17 cases) with CRS-R≥8. The top row is the EEG microstate topography map of the patients before HBO therapy, and the bottom row is the EEG microstate topography map of the patients after 20min of HBO therapy. We found that the duration of microstate C was significantly increased ($p<0.05$) and the contribution of microstate D was significantly decreased ($p<0.05$) after 20min of HBO therapy compared with the pretreatment value.

be related to the changes in the vision-related brain network in DOC patients (Britz et al., 2010). However, due to the different basic conditions of patients at admission, more research is needed to verify this hypothesis. Before and after a single HBO treatment, the parameters related to microstate B of the patients did not change significantly, which suggests that 20 min of HBO therapy is not enough to cause EEG changes in the relevant brain regions of the patients.

Compared with the microstate parameters of patients before and after 20 min of HBO therapy, the parameters related to microstate C increased significantly. Although the physiological basis of microstate C is still highly controversial, in the study of Britz et al. (2010), microstate C was considered to be part of the salience network, which mainly detected and responded to internal or external stimuli received by other brain networks. The salience network, which plays a key role in switching between central executive functions and default modes,

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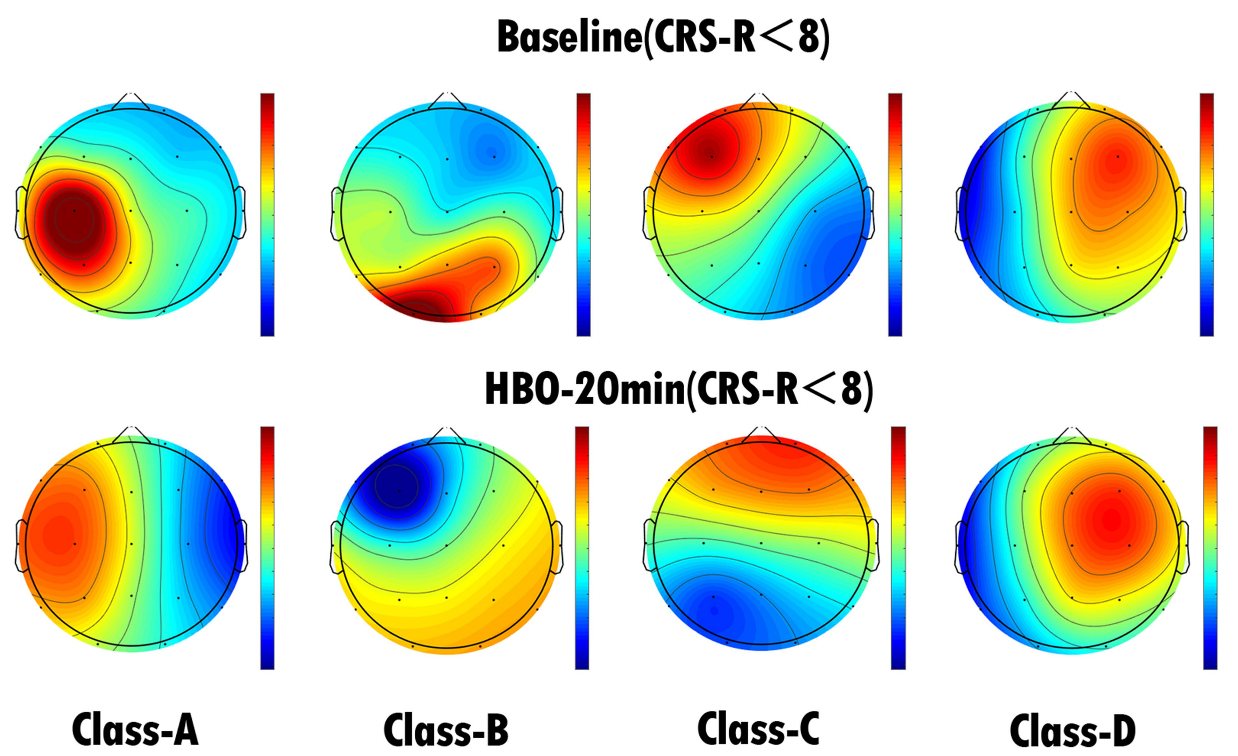

FIGURE 4
EEG microstate topography of DOC patients (24 cases) with CRS-R<8. The top row is the EEG microstate topography map of the patients before HBO therapy, and the bottom row is the EEG microstate topography map of the patients after 20min of HBO therapy.

TABLE 4 EEG microstate duration, occurrence, contribution and mean GFP analysis results of DOC patients (17 cases) with CRS-R≥8.

	Class A		Class B		Class C		Class D	
	Baseline (Mean±SD)	HBO-20min (Mean±SD)	Baseline (Mean±SD)	HBO-20min (Mean±SD)	Baseline (Mean±SD)	HBO-20min (Mean±SD)	Baseline (Mean±SD)	HBO-20min (Mean±SD)
Duration (s)	0.052 ± 0.022	0.060 ± 0.030	0.047 ± 0.020	0.049 ± 0.020	0.043 ± 0.018	**0.056 ± 0.029**※	0.055 ± 0.026	0.050 ± 0.025
Occurrence (s^{-1})	6.227 ± 2.840	6.070 ± 2.360	5.623 ± 2.358	5.653 ± 2.389	6.086 ± 3.460	5.937 ± 2.482	6.161 ± 1.929	5.741 ± 2.421
Contribution (%)	0.266 ± 0.091	0.289 ± 0.102	0.228 ± 0.058	0.226 ± 0.048	0.217 ± 0.062	0.259 ± 0.053	0.289 ± 0.101	**0.227 ± 0.053**※
Mean GFP (mV)	7.686 ± 2.587	9.304 ± 5.231	7.674 ± 2.539	9.121 ± 5.263	7.569 ± 2.963	9.324 ± 5.267	8.243 ± 2.782	9.162 ± 4.954

※Indicates the *t*-test result was significant ($p < 0.05$).
The bold values indicate the *t*-test result was significant ($p < 0.05$).
The duration of microstate C of 17 patients had significant increased after 20 min of hyperbaric oxygen therapy compared with pre-treatment ($p < 0.05$). And the contribution of microstate D had significant reduced ($p < 0.05$). Other microstate parameters did not change significantly.

can combine interoceptive information with emotional salience to form subjective representations of one's own body (Sun et al., 2022). As the "mediator" of the brain, the salience network plays an integral role in the processing of sensorimotor information, general cognition, and the coordination between emotion, pain, and body movement. The significant increase in the microstate C parameters of patients may indicate that brain areas related to high-level functions such as attention and cognition are activated during HBO therapy.

The microstate D of patients is also significantly different from the microstate map of normal people. In the current study, microstate D is considered to correspond to the central executive network of the brain, and the central executive network is related to functions such as task selection and decision-making and is responsible for high-level cognitive tasks. Through the analysis of the microstate, we found that the cognitive and decision-making-related cortical areas of DOC patients are in a state of inhibition, which is also consistent with the clinical diagnosis of DOC.

4.3. Microstates of DOC patients with CRS-R scores under HBO conditions

We fitted the microstate topographic maps of the 17 patients with CRS-R ≥ 8 before and after treatment (Figure 3). Similar to the results in Figure 1, the microstate B and microstate D of these 17 DOC

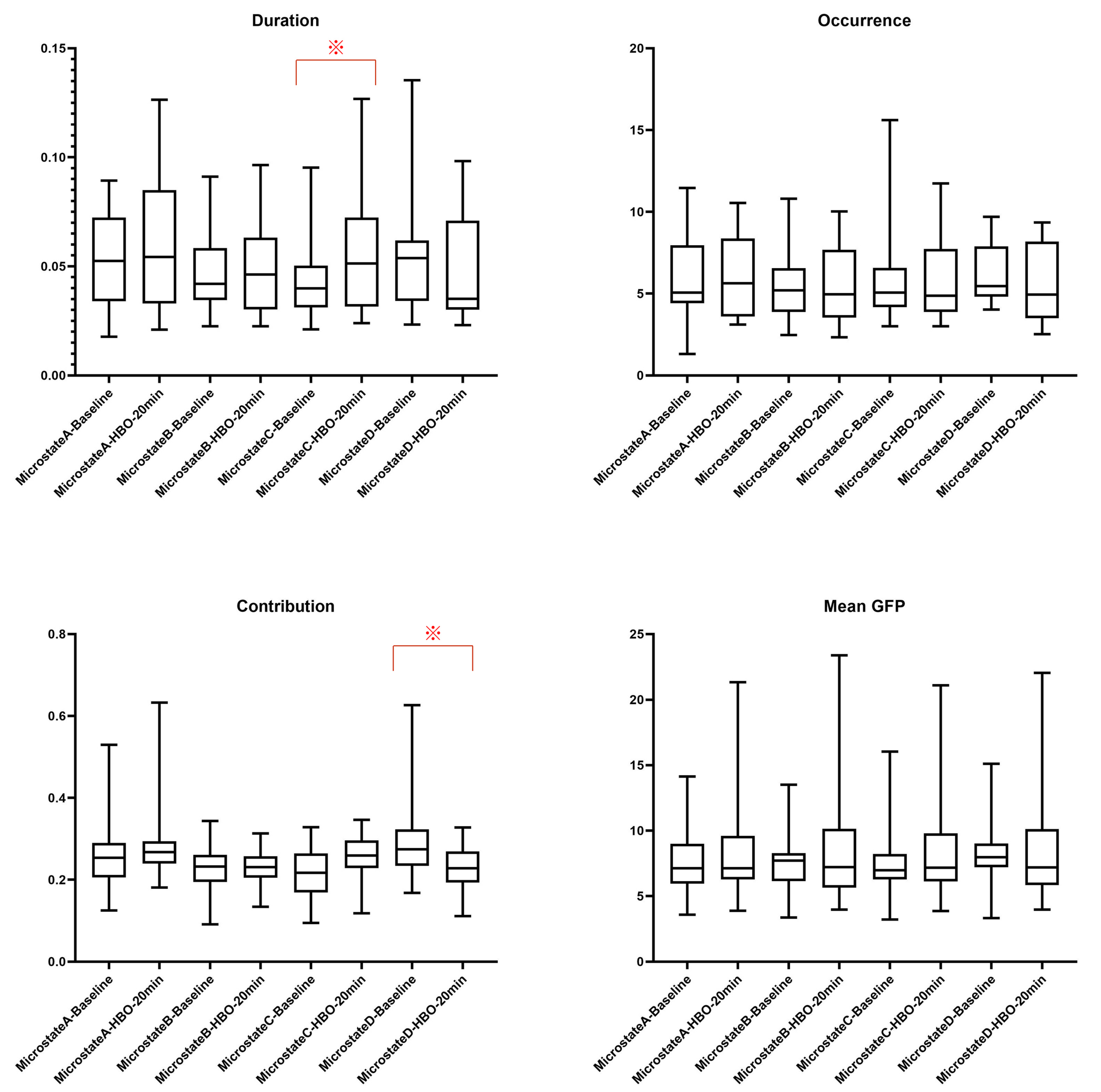

FIGURE 5
EEG microstate duration, occurrence, contribution and mean GFP analysis results of DOC patients (17 cases) with CRS-R≥8. ※Indicates the *t*-test result was significant (p <0.05).

patients were significantly different from those found by Britz et al. (2010). By analyzing the microstate parameters of 17 patients with CRS-R ≥ 8, we found that the duration of microstate C in patients with CRS-R ≥ 8 was increased significantly compared with the pretreatment duration; moreover, the contribution of microstate D decreased significantly, and the transition between microstate A and microstate C increased significantly compared with the pretreatment values.

In the current study, microstate A was thought to be associated with the activation of the bilateral superior and middle temporal gyri regions, which are associated with functions such as hearing. The transition probability between microstate A and microstate C in patients increased significantly, which may indicate that the input of auditory information in patients with CRS-R ≥ 8 became more active during HBO therapy than when they were not treated. This shows that HBO therapy may increase the information exchange between the auditory network and salience network in patients. Increased processing of auditory information may indicate some recovery from brain damage in patients. This type of result did not appear in patients with CRS-R < 8, which indicates that patients with a relatively better level of consciousness have better activation of the auditory network in response to HBO therapy. This is similar to recent findings by Guo et al. (2022), who reported that the probability of occurrence per second (OPS) of microstate D was positively correlated with CRS-R scores in *VS* and MCS patients before HD-tDCS treatment. Patients progress from *VS* to MCS when the OPS in microstate D increases. This may indicate that patients with higher CRS-R scores have better

A

	Class A			Class B	
	Baseline (Mean±SD)	HBO-20min (Mean±SD)		Baseline (Mean±SD)	HBO-20min (Mean±SD)
B (%)	0.081±0.028	0.082±0.018	A (%)	0.078±0.027	0.083±0.019
C (%)	0.078±0.023	**0.099±0.022↑***	C (%)	0.075±0.025	0.078±0.013
D (%)	0.091±0.036	0.083±0.015	D (%)	0.080±0.025	0.079±0.021

	Class C			Class D	
	Baseline (Mean±SD)	HBO-20min (Mean±SD)		Baseline (Mean±SD)	HBO-20min (Mean±SD)
A (%)	0.079±0.023	**0.096±0.017↑***	A (%)	0.093±0.033	0.085±0.015
B (%)	0.071±0.027	0.079±0.013	B (%)	0.082±0.026	0.078±0.021
D (%)	0.095±0.035	0.082±0.014	C (%)	0.091±0.033	0.080±0.012

*Indicates the t-test result was significant (p < 0.05)

B

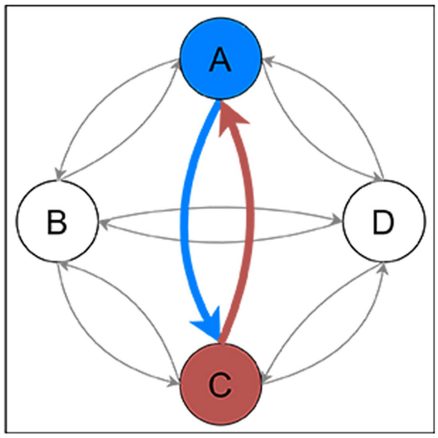

FIGURE 6
EEG microstate transition probability analysis results of DOC patients (17 cases) with CRS-R≥8. **(A)** Analytical results of the EEG microstate transition probability in DOC patients (17 cases) with CRS-R≥8. The transition probability from microstate A to microstate C and microstate C to microstate A was significantly increased after 20min of HBO therapy compared with pretreatment (p<0.05). **(B)** Schematic diagram of the mutual transition trends among the four microstates. The 4 solid circles represent 4 microstates, and the different arrows represent the transition trends between different microstates. The gray arrows represent that the transition trends between different microstates are not significant, and the bold colored arrows represent significant transition trends (p<0.05).

recovery of consciousness. Whether increasing the frequency of HBO therapy will affect similar changes in patients with CRS-R < 8 remains to be further studied.

5. Limitations

This study only analyzed the EEG detection data during a single session of HBO therapy. Some indicators were found to be significantly different in the EEG microstate, but the results were not enough to explain the effectiveness of HBO therapy, especially the superposition of multiple HBO therapy effects. Further research is still needed to confirm this hypothesis. In addition, this was an exploratory, single-center study with relatively large limitations, and the results should be interpreted with caution. The number of included samples is not sufficient, and the etiologies of the DOC cases are extremely heterogeneous. The results of EEG microstate changes under HBO are not sufficient to explain the brain network response of DOC patients' consciousness from the level of pathophysiological mechanism.

6. Conclusion

Real-time EEG detection in DOC patients during HBO therapy is safe and feasible. The results of this study show that HBO therapy has a specific activating effect on attention and cognitive control in patients and causes increased activity in the primary sensory cortex (temporal lobe and occipital lobe). This study demonstrates that real-time EEG detection and analysis during HBO is a clinically feasible method for assessing brain function in patients with DOC. During HBO therapy, some EEG microstate indicators show significant changes related to the state of consciousness in patients with prolonged DOC. This will be complementary to important electrophysiological indicators for assessing consciousness and may also provide an objective foundation for the precise treatment of patients with DOC, but more research is needed.

Data availability statement

The raw data supporting the conclusions of this article are available on request to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by IRB of Beijing Tiantan Hospital, Capital Medical University. The legal guardians of the patients with chronic disorders of consciousness provided their written informed consent to participate in this study.

Author contributions

JW, LX, QY, and XZ conceived and designed the research. LC, XG, XC, LX, YLL, and CW performed the experiments. YW, YL, and JW were responsible for the data analysis. QG, YZ, JW, LX, QY, JH, and XZ drafted the manuscript. All authors had a lot of contributions at all stages of preparing 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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Olfactory response is a potential sign of consciousness: electroencephalogram findings

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Objective: This study aimed to explore whether olfactory response can be a sign of consciousness and represent higher cognitive processing in patients with disorders of consciousness (DoC) using clinical and electroencephalogram data.

Methods: Twenty-eight patients with DoC [13 vegetative states (*VS*)/unresponsive wakefulness syndrome (UWS) and 15 minimally conscious states (MCS)] were divided into two groups: the presence of olfactory response (ORES) group and the absence of olfactory response (N-ORES) group according to behavioral signs from different odors, i.e., vanillin, decanoic acid, and blank stimuli. We recorded an olfactory task-related electroencephalogram (EEG) and analyzed the relative power and functional connectivity at the whole-brain level in patients with DoC and healthy controls (HCs). After three months, the outcomes of DoC patients were followed up using the coma recovery scale-revised (CRS-R).

Results: A significant relationship was found between olfactory responses and the level of consciousness ($\chi^2(1)=6.892$, $p=0.020$). For olfactory EEG, N-ORES patients showed higher theta functional connectivity than ORES patients after stimulation with vanillin ($p=0.029$; $p=0.027$). Patients with N-ORES showed lower alpha and beta relative powers than HCs at the group level ($p=0.019$; $p=0.033$). After three months, 62.5% (10/16) of the ORES patients recovered consciousness compared to 16.7% (2/12) in the N-ORES group. The presence of olfactory response was significantly associated with an improvement in consciousness ($\chi^2(1)=5.882$, $p=0.023$).

Conclusion: Olfactory responses should be considered signs of consciousness. The differences in olfactory processing between DoC patients with and without olfactory responses may be a way to explore the neural correlates of olfactory consciousness in these patients. The olfactory response may help in the assessment of consciousness and may contribute to therapeutic orientation.

KEYWORDS

disorders of consciousness, olfactory response, electroencephalogram, diagnosis, prognosis

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1. Introduction

Severe brain injuries may lead to varying stages of disorders of consciousness (DoC), such as coma, vegetative state (*VS*)/unresponsive wakefulness syndrome (UWS), minimally conscious state (MCS), and emergence from MCS (EMCS) (Giacino et al., 2002; Laureys et al., 2010). The clinical evaluation of consciousness is mostly dependent on the behavioral responses of DoC patients to external sensory stimuli. Patients with *VS*/UWS recover their arousal but continue to be insensitive to external stimuli and are unaware of themselves and their surroundings. Patients with MCS display nonreflex activities that indicate consciousness. In clinical practice, auditory and visual-based assessments are the most widely used modalities, which are also subscales in the coma recovery scale-revised (CRS-R) (Giacino et al., 2004; Jain and Ramakrishnan, 2020). However, there is no consensus on whether olfactory stimuli can be used for the behavioral evaluation of consciousness.

The olfactory system is unique because it lacks an obligatory thalamic relay that may provide direct conditions for inducing consciousness (Mori et al., 2013). Merrick et al. (2014) believed that the olfactory system could be used to distinguish between conscious and unconscious processing because, in addition to its anatomical characteristics, it has its own phenomenological, cognitive, and neurodynamic properties. The special phenomenon of olfaction is that it does not produce conscious processing when the concentration of odorants is very low or during sensory habituation to odorants (Walla, 2008). The emergence of consciousness in the olfactory system depends on the synchronization of high-frequency oscillations (beta and gamma) (Mori et al., 2013; Yang et al., 2022), that is, the synchronous integration of widely distributed cortical neuron activities. These high-frequency activities appear to be coupled with respiration, which is linked to slow-wave activities (theta and delta) (Fontanini and Bower, 2006; Kay et al., 2009). High and low oscillations play functional roles in olfactory perception. The primary olfactory cortex, the amygdala, is associated with emotions (Rolls, 2015), whereas the olfactory cortex connects to the hippocampus and is associated with memory (Zhou et al., 2021). The emotions involved in experiencing the external environment may persist in patients with DoC (Steinhoff et al., 2015). Emotional and memorial stimuli may potentially distinguish *VS*/UWS from MCS, or evoke patient consciousness. The uniqueness of the olfactory pathway and its functions make it an ideal system for testing consciousness (Keller and Young, 2014).

Central olfactory processing has been reported to show various degrees of preservation in patients with DoC and has a clear relationship with their consciousness (Nigri et al., 2016). Simultaneously, sniff responses induced by olfactory stimuli are highly predictive in *VS*/UWS patients. Some *VS*/UWS patients with sniff responses eventually transition to MCS (Arzi et al., 2020). When given emotional olfactory stimuli, the mean amplitude of skin conductance increased in DoC patients (Luauté et al., 2018). Based on these previous studies, we believe that olfactory stimuli can induce a conscious behavioral response and predict the recovery of consciousness. However, the effects of olfactory responses in patients with DoC have rarely been studied (Jain and Ramakrishnan, 2020). An objective assessment is needed to clearly define the olfactory response based on observations (Wang et al., 2022).

The purpose of this study was to investigate whether the olfactory response is a sign of consciousness and whether it can represent higher cognitive processing in DoC patients, using clinical and electroencephalogram data. We expect that patients with higher levels of consciousness will have clear responses to olfactory stimuli, and the presence or absence of an olfactory response will help predict the recovery of DoC patients.

Abbreviations: DoC, disorders of consciousness; MCS, minimally conscious state; *VS*/UWS, vegetative state/unresponsive wakefulness syndrome; CRS-R, Coma Recovery Scale-Revised; ORES, presence of olfactory response; N-ORES, absence of olfactory response; HCs, healthy controls; DOCS, the Disorders of Consciousness Scale; wPLI, weighted phase lag index.

2. Materials and methods

2.1. Study design and participants

Twenty-eight patients with DoC were recruited in this study. Thirteen patients were diagnosed with *VS*/UWS and 15 were diagnosed with MCS based on the CRS-R assessment (Giacino et al., 2004) (see Supplementary material for inclusion and exclusion criteria). We investigated the presence of an olfactory response in these patients and divided them into two groups: ORES group (the presence of olfactory response) and N-ORES group (the absence of olfactory response). Next, we collected the olfactory electroencephalogram (EEG) data from each patient along with data on healthy controls (HCs) (see Supplementary material; Supplementary Table S1). Finally, the patients were followed up for 3 months after the assessments. Written informed consent was obtained from the legally authorized representative of the patients. The ethics committee of Zhujiang Hospital approved all aspects of the study.

2.2. Behavioral and outcome data

Each patient was assessed at least three times by two experienced raters using the CRS-R. The best result was retained as the behavioral diagnosis. The olfactory response was assessed using vanillin (pleasant odor), decanoic acid (unpleasant odor), and a blank (see Supplementary material). The rating points of olfactory responses were rated according to the Disorders of Consciousness Scale (DOCS) guidelines (Pape et al., 2005): 0 = No Response, 1 = General Response, and 2 = Localized Response. At the group level, we classified patients into the ORES group (i.e., gained a general response to stimuli with two odorants, gained a general response with one stimulus, or gained a localized response with one stimulus) or the N-ORES group (i.e., no response to stimuli with any odorant). Patients were followed up for 3 months by conducting structured telephone interviews using the CRS-R, according to a previous study (Thibaut et al., 2021). The diagnosis of transition to MCS or EMCS in *VS*/UWS patients, based on CRS-R, was defined as improvement, and the diagnosis of transition to EMCS in MCS patients was also defined as an improvement.

We compared ORES and N-ORES patients with the HC group in terms of age and gender using one-way analysis of variance (ANOVA) and chi-square tests. We also compared the etiology and the duration of injury of ORES and N-ORES patients using Fisher's exact test and independent-sample *t*-test, and for age and gender using independent-sample *t*-test and Fisher's exact test. Differences between olfactory responses to the three stimuli were analyzed using McNemar's test. Statistical differences in the presence of olfactory responses between *VS*/UWS and MCS patients were examined using Fisher's exact test. Statistical differences in clinical improvement between patients with and without olfactory responses were assessed using the chi-square test.

2.3. EEG procedure and statistical analysis

2.3.1. Experimental procedure

The olfactory task was performed while the electrophysiological activity was recorded. We placed two pure odorants (vanillin and decanoic acid) and a blank presentation approximately 2 cm in front of the patients' nostrils. All the odorants have been used in previous studies (Gottfried et al., 2002; Arzi et al., 2020). Two odorants were presented with felt-tip pens, while one unfilled pen served as a blank (Hummel et al., 1997). We used a blank pen as the baseline to exclude the behavioral responses induced by visual stimuli. During the experiment, the odorant and blank pens were randomly presented to the patients for approximately 5 s. Each pen was presented approximately five times with 30 s intervals in a block design. There were two blocks with 2 min intervals. The protocol used was similar to that used in a previous study (Arzi et al., 2020). E-prime 3.0 (Psychology Software Tools Inc., Pittsburgh, PA, USA) was used to design the experiments. The total number of marks were recorded. All the participants received pleasant odor, unpleasant odor, and blank stimulation. The experiment was performed in a quiet room at an ambient temperature of 24°C and stable humidity.

2.3.2. EEG recording and processing

Brain activity was recorded using a 66 channel system (SynAmps2TM 8500; Neuroscan, USA) at a sampling rate of 2,500 Hz, following the International 10–20 System. The signals were amplified by bandpass filtering at a 1,000 Hz direct current. During the experiment, the electrode impedance was kept below 5 kΩ.

EEG preprocessing was conducted using the EEGLAB toolbox (13_0_0b) in MATLAB (version 2013b; MathWorks Inc., Natick, Massachusetts, USA). The EEG data were filtered between 0.5 and 45 Hz and down-sampled to 500 Hz. The EEG signals were segmented into 10 s epochs using the markers. Independent Component Analysis was used to eliminate the artifacts caused by muscle activity and eye movements. Epochs containing obvious artifacts were manually deleted via visual inspection. A semi-automated process was used to exclude epochs with activity exceeding ±100 μV. Artifact-free signals were used as the average reference. And a fixed number of epochs were used for each participant separately to match trial numbers across groups for further analysis.

2.3.3. EEG data analysis

The following frequency bands were used to analyze the EEG power spectra: delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), and beta (13–30 Hz). Mean connectivity at the whole-brain level was also estimated for the frequency bands and for each group using the weighted Phase Lag Index (wPLI) described in a previous study, see Supplementary material (Vinck et al., 2011). Mean relative power of the entire brain was estimated for each band and group. Absolute power was calculated relative to the total power across the entire frequency spectrum for each frequency band.

Statistical analyses were performed using repeated measures analysis of variance (ANOVA) with the group (HCs, ORES, and N-ORES) as the between-subject factor and type of stimulation (pleasant, unpleasant, and blank) as the within-subject factor. *Post hoc* Bonferroni correction for multiple comparisons was performed when statistically significant differences were observed. SPSS version 22.0 was used to conduct the statistical analysis.

3. Results

For patients with DoC, the ORES and N-ORES groups did not significantly differ in terms of age, gender, etiology, or time since injury. Age did not differ significantly among ORES, N-ORES, and HCs ($p = 0.128$), and neither did gender ($p = 0.437$). The demographic data of the patients and comparison of ORES and N-ORES behavioral data are reported in Table 1. Table 2 shows the clinical assessment of ORES patients (see Supplementary Table S2 for clinical data of patients with N-ORES).

3.1. Behavioral and outcome data

An olfactory response was present in 16 out of 28 patients (57%), 4 out of 13 patients with *VS*/UWS (31%), and 12 out of 15 patients with MCS (80%). A significant relationship was found between the presence of olfactory response and level of consciousness ($\chi^2(1) = 6.892$, $p = 0.020$, Figure 1A). Among all the patients, 15 showed olfactory responses to pleasant stimuli, 12 showed olfactory responses to unpleasant stimuli, 2 showed olfactory responses to blank stimuli, and 11 patients both showed olfactory response to pleasant stimuli and unpleasant stimuli. When compared to blank stimuli, the incidence of olfactory responses was significantly higher for pleasant and unpleasant stimuli ($\chi^2(1) = 14.275$, $p = 0.007$; $\chi^2(1) = 9.524$, $p = 0.001$). There was no significant difference between the use of pleasant and unpleasant stimuli ($\chi^2(1) = 0.644$, $p = 1.000$). The proportion of traumatic brain injury (TBI) patients (56%) who showed an olfactory response did not differ from nTBI patients (60%) ($\chi^2(1) = 0.052$, $p = 0.820$, Fisher's exact test: $p = 1.000$).

Outcome data were available for all patients. After three months, 62.5% (10/16) of the ORES patients regained some signs of consciousness compared to 16.7% (2/12) in the N-ORES group. Significant differences in consciousness improvement were found between patients with and without olfactory responses ($\chi^2(1) = 5.882$, $p = 0.023$, Figure 1B).

3.2. EEG results

A significant interaction was found between the groups (HCs, ORES, and N-ORES) and stimulations (pleasant, unpleasant, and blank) for functional connectivity in the theta band ($F = 3.093$,

TABLE 1 Demographic data summary of the patients and comparison of ORES and N-ORES of EEG.

	DoC patients			Behavioral data		
	Whole sample	MCS	VS/UWS	ORES	N-ORES	*p*-value
Participants	28	15	13	16	12	-
Age	48.0 ± 13.4	50.2 ± 12.3	45.5 ± 14.6	48.6 ± 13.2	47.2 ± 14.2	$p = 0.793$
Gender (F/M)	10/18	6/9	4/9	6/10	4/8	$p = 1.000$
Etiology (TBI/nTBI)	10/18	7/8	3/10	3/13	3/9	$p = 1.000$
Time since injury in months	5.4 ± 3.5	4.6 ± 2.3	6.2 ± 4.6	5.13 ± 3.5	5.7 ± 3.7	$p = 0.697$

DoC, disorders of consciousness; ORES, presence of olfactory response; N-ORES, absence of olfactory response; SD, standard deviation; TBI, traumatic brain injury; NTBI, non-traumatic brain injury.

TABLE 2 Demographical, clinical, and outcome data of the 16 patients with olfactory response.

Patient No./ gender/age (years)	Etiology	Post- injury (month)	CRS-R diagnosis	Vanillin (pleasant)	decanoic acid (unpleasant)	Blank	Outcome at 3months (CRS-R)
1/M/53	nTBI	1	MCS	LR	LR	NR	EMCS*
2/M/39	TBI	8	MCS	LR	LR	NR	VS/UWS
3/F/48	nTBI	4	MCS	LR	LR	NR	EMCS*
4/M/66	nTBI	15	VS/UWS	GR	NR	NR	MCS*
5/M/41	TBI	9	MCS	GR	LR	LR	MCS
6/M/38	nTBI	1	VS/UWS	LR	LR	LR	MCS*
7/M/41	nTBI	4	VS/UWS	LR	NR	NR	EMCS*
8/F/31	TBI	3	MCS	LR	NR	NR	EMCS*
9/M/25	TBI	4	MCS	GR	LR	NR	MCS
10/F/70	nTBI	8	MCS	GR	LR	NR	EMCS*
11/F/61	TBI	5	MCS	GR	NR	NR	MCS
12/F/67	nTBI	6	MCS	GR	LR	NR	EMCS*
13/M/56	nTBI	4	MCS	LR	LR	NR	EMCS*
14/M/52	TBI	2	MCS	GR	GR	NR	MCS
15/M/50	nTBI	5	MCS	NR	LR	NR	MCS
16/F/40	nTBI	3	VS/UWS	GR	GR	NR	EMCS*

CRS-R, coma recovery scale-revised; TBI, traumatic brain injury; NTBI, non-traumatic brain injury; NR, No Response, GR, General Response, and LR, Localized Response; *, improvement.

$p = 0.019$). No significant main effects were observed in either the group or stimulation. Further interaction analysis indicated that after pleasant stimulation, the N-ORES group showed a higher theta wPLI than the ORES group after Bonferroni correction ($p = 0.029$, Figure 1C). And after pleasant stimulation, the N-ORES group showed a higher theta wPLI than the HCs group after Bonferroni correction ($p = 0.027$, Figure 1C). No significant differences were observed between ORES patients and HCs. Figure 1D showed mean connectivity of the whole brain in three groups after pleasant stimulation.

When observed the difference, the pairwise comparisons of connectivity between every electrode were performed within two groups. The significantly altered connectivity was consistent with increased connectivity. The increased wPLI of the theta band was primarily observed in the central-parietal region in N-ORES patients compared to that in ORES patients and HCs group (Figure 1D, last two panels). There were no significant differences in other frequency bands between the groups and stimulations.

Power spectral analysis showed a significant main effect for factor 'group' in the alpha and beta band ($F = 4.299$, $p = 0.019$ and $F = 3.634$, $p = 0.033$ respectively). Multiple comparisons showed that the N-ORES group had lower alpha and beta relative powers than the HCs group ($p = 0.019$ and $p = 0.031$ respectively, after Bonferroni correction, Figure 2A). Figure 2B showed the power spectra in the top plot between different groups in the alpha and beta bands. No significant interaction or stimulatory effects were observed. The relative power did not differ between the groups and stimulation in other bands.

4. Discussion

In the current literature, olfactory stimuli are recommended for assessing the level of consciousness in some scales (Ansell and Keenan, 1989; Rappaport et al., 1992; Gill-Thwaites and Munday, 2004; Pape et al., 2005). However, there is no consensus on whether the olfactory response could be a conscious behavior. Here, we aimed to explore

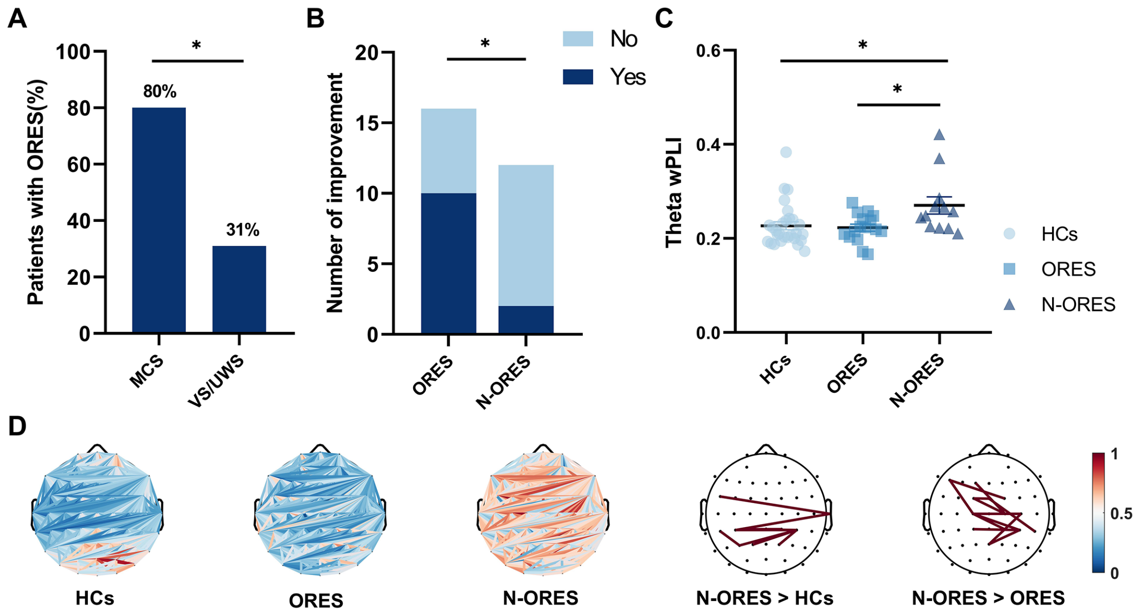

FIGURE 1
Behavioral results and global connectivity among HCs, ORES, and N-ORES. **(A)** The proportion of olfactory response among MCS and *VS*/UWS patients. A relationship was observed between the presence of olfactory response and level of consciousness (χ^2(1)=6.892, *p=0.020). **(B)** The consciousness improvement outcome in the ORES and N-ORES patients (at 3-month follow-up). Patients with olfactory response had higher improvement rates (at 3-month follow-up) than those without response (χ^2(1)=5.882, *p=0.023). **(C)** Scatter plot of global wPLI values in theta bands after pleasant stimulus. N-ORES patients showed higher theta connectivity measures compared to ORES patients and HCs (*p=0.029; *p=0.027, after Bonferroni correction). **(D)** The top panel shows average connectivity (the first three panels) and significantly altered connectivities in different groups. The red line means significantly increased connectivity (the last two panels).

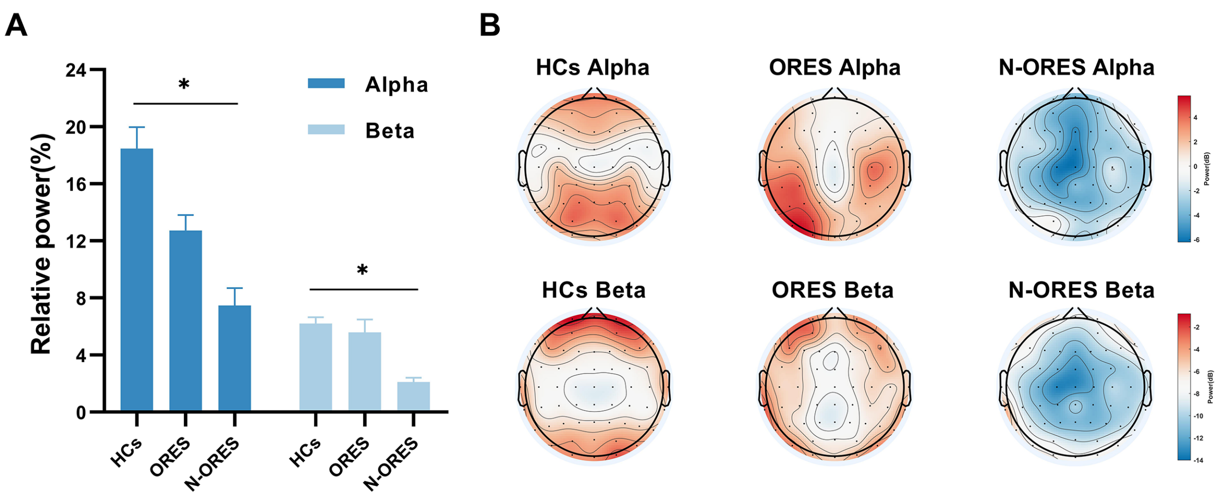

FIGURE 2
The result of the repeated measures of ANOVA showed that differences in EEG relative power at the group level (HCs, ORES, and N-ORES). **(A)** The relative power in alpha and beta frequency band. A marked decrease in alpha and beta relative power were observed in the N-ORES compared with the power in the HCs group (*p=0.019; *p=0.031, after Bonferroni correction). The data were expressed as the means± SEM. **(B)** The power distribution of the whole brain topographic in different groups was displayed.

whether the olfactory response is a conscious behavior and reflects a higher level of consciousness (using EEG). We found that the probability of observing an olfactory response increased with the level of consciousness, and that the olfactory response could predict the clinical outcome in patients with DoC. In addition, EEG indicated significant differences between ORES and N-ORES groups. At the whole-brain level, N-ORES patients showed higher theta functional connectivity after pleasant stimuli than ORES patients. N-ORES patients showed lower alpha and beta relative powers than HCs at the group level. Overall, the findings support our hypothesis that olfactory response is a conscious behavior and contributes to research on the importance of consciousness-related olfactory responses.

Clinically, the probability of olfactory responses increased in MCS than *VS*/UWS patients, which is consistent with a previous study that showed that the probability of behavioral response was higher in MCS patients than *VS*/UWS patients (Wang et al., 2022). The presence of an olfactory response in patients with DoC is associated with a higher level of consciousness. This result indicates that olfactory responses could help diagnose the consciousness of patients with DoC. We also showed that the presence or absence of an olfactory response can significantly predict the recovery of consciousness. The ORES patients had a higher improvement rate than the N-ORES patients. This result was inconsistent with that of a previous study in which olfactory behavior could not predict the outcome in DoC patients (Wang et al., 2022). This difference may be due to the different odors used in the study. We chose pure and emotional odors that were more effective and could induce different behaviors (Stevenson et al., 2007; Schriever et al., 2017). We further observed that the proportion of patients with olfactory responses in TBI and nTBI was not significantly different, indicating that the etiology may not affect olfactory function in patients with DoC. However, a previous study showed that patients with TBI and hemorrhage have greater olfactory preservation (Nigri et al., 2016). This inconsistency may be due to different groupings in the research (Marino and Whyte, 2022). In fact, a minority of people have olfactory dysfunction 1 year after TBI (Sigurdardottir et al., 2010). Both pleasant and unpleasant odorants elicited olfactory responses compared to blank. It has been shown that emotions or familiar senses linked to stimuli elicit much stronger responses (Gao et al., 2019; Jain and Ramakrishnan, 2020). Emotional olfactory stimuli may be more effective in awake DoC patients (Martinec Nováková et al., 2021).

At the whole-brain level, N-ORES patients showed a higher theta wPLI than ORES patients after pleasant stimuli. Over the past few years, slow-wave oscillations have been identified as key oscillations associated with olfactory perception and discrimination (Fontanini and Bower, 2006; Kay et al., 2009). Theta oscillations are also locked into the breathing rhythm (Kay, 2014). The association of the olfactory system with many brain regions (Mori et al., 2013) suggests that a robust pathway involving nasal breathing can generate rhythmic electrical activity. There is a distinct reduction in respiratory phase-locked oscillations in theta when the nasal airflow decreases (Zelano et al., 2016; Han et al., 2018). A previous study has shown that when given different olfactory stimuli, most MCS patients had a decrease in nasal airflow volume compared to UWS patients (Arzi et al., 2020). We speculated that the higher theta connectivity in N-ORES patients may be due to their inability to modulate nasal airflow when performing olfactory tasks. Patients with *VS*/UWS do not respond to breathing-based commands (Charland-Verville et al., 2014). Moreover, the level of consciousness may affect olfactory processing. The olfactory bulb receives fewer external inputs under deep anesthesia (Li et al., 2010). Thus, N-ORES patients who have lower consciousness levels might remain in a relatively high-theta connectivity state.

Another interesting finding of our study is the difference caused by pleasantness. Vanilla is a pleasant and familiar odor to the participants in our study. Connectivity differences may arise based on the different valences of the odorants (Callara et al., 2021), whereas motional or hedonic intensities would more strongly influence brain activation (Royet et al., 2003). Emotion involves one's experiences of external stimuli and is consequently considered "consciousness" (Turner and Knapp, 1995). Emotional stimuli are more likely to attract the attention of patients with DOC (Gao et al., 2019). The association between the limbic system (amygdala and hippocampus) and the primary olfactory cortex is related to emotion and memory in the brain. A previous study demonstrated that the majority of *VS*/UWS patients and all MCS patients showed significant odor-related activation within the amygdala (Nigri et al., 2016). Patients with DoC have various degrees of preservation of the limbic system (Di Perri et al., 2013; Cacciola et al., 2019). This may explain why the pleasant stimuli used in this study were more effective.

Regarding spectral power, the results indicated a lower relative power in the alpha and beta bands at the whole-brain level in N-ORES patients compared to HCs. Lower levels of consciousness have been linked to suppressed alpha activity (Chennu et al., 2014; Rossi Sebastiano et al., 2015). Such configurations in the alpha band are not present in N-ORES patients, demonstrating the importance of alpha power in arousal and awareness. Previous studies have also reported on the role of the alpha band in olfactory tasks. Alpha oscillation is used for concentration, helps classify emotional olfactory stimuli, and is related to odorant administration (Harada et al., 1996; Placidi et al., 2015; Raheel et al., 2019). Lower alpha power in N-ORES patients showed that they could not concentrate well enough to engage in olfactory tasks, even odorless tasks. Beta frequency bands have rarely been considered in patients with DoC (Bai et al., 2020). A previous study reported that lower beta power was present in populations with lower levels of consciousness, representing no thalamocortical activity (Edlow et al., 2021). These results are consistent with our behavioral findings that N-ORES patients have lower consciousness.

Our results suggest that olfactory response should be considered a conscious behavior. We compared the difference between the presence and absence of olfactory responses linked to EEG results and found that theta connectivity may be the neural correlate of olfactory consciousness. The strategy used to identify behavioral correlates of consciousness could relate to the underlying neural mechanisms (Koch et al., 2016). In our study, some *VS*/UWS patients who have olfactory responses transited to MCS or EMCS. If these findings are confirmed in further studies, patients diagnosed with *VS*/UWS who have an olfactory response may be considered as functional MCS (Schnakers et al., 2022). This study also has several limitations. The lack of time control of stimuli is a significant issue (i.e., without using an olfactometer). The olfactometer is a machine that can control the exact timing of olfactory stimuli. However, most olfactometers using large multichannel odorant banks provide limited delivery flexibility and can be expensive to build (Davison and Katz, 2007; Soucy et al., 2009; Tan et al., 2010). Therefore, we particularly analyzed frequency-domain indicators after stimuli to reduce the influence of stimulus time on olfactory perception. It has reported that a single-trail olfactory task without using olfactometer can dynamically reveal changes in hedonic olfactory network (Callara et al., 2021). We hypothesized that such differences would be negligible. Although the number of patients with DoC was limited, we conservatively concluded that some patients with DoC preserved olfactory processing. In addition, future research should follow the recovery of consciousness after olfactory assessments over a longer period. Future research should also include time-frequency indicators or olfactory evoked potentials, which would add to our understanding of olfactory processing.

5. Conclusion

Our results confirmed the hypothesis that olfactory response should be considered a sign of consciousness. We observed that olfactory response in patients with DoC had a significant relationship with consciousness level and could predict consciousness recovery. In addition, we observed differences in olfactory processing between patients with and without an olfactory response. Theta connectivity may be a neural correlation with olfactory consciousness in patients with DoC, which could help in the assessment of consciousness and contribute to therapeutic strategies.

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 authors.

Ethics statement

The studies involving human participants were reviewed and approved by ethics committee of ZhuJiang Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

WW, QXie, and XH contributed to conception and design of the study. WW, CX, XZ, and QXia organized the experiment. XH, QL, HZ, NC, and YL helped develop the study measures and data collection. WW performed the statistical analysis and wrote the first draft of the manuscript. CX and QL wrote sections of the manuscript. QXie and XH contributed to conceptualization, funding acquisition, resources, supervision, and writing–review and editing. 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/fnins.2023.1187471/full#supplementary-material

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The effect of neural pre-stimulus oscillations on post-stimulus somatosensory event-related potentials in disorders of consciousness

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Brain activity of people in a disorder of consciousness (DoC) is diffuse and different from healthy people. In order to get a better understanding of their cognitive processes and functions, electroencephalographic activity has often been examined in patients with DoC, including detection of event-related potentials (ERPs) and spectral power analysis. However, the relationship between pre-stimulus oscillations and post-stimulus ERPs has rarely been explored in DoC, although it is known from healthy participants that pre-stimulus oscillations predispose subsequent stimulus detection. Here, we examine to what extent pre-stimulus electroencephalography band power in DoC relates to post-stimulus ERPs in a similar way as previously documented in healthy people. 14 DoC patients in an unresponsive wakefulness syndrome (UWS, N=2) or a minimally conscious state (MCS, N=12) participated in this study. In an active oddball paradigm patients received vibrotactile stimuli. Significant post-stimulus differences between brain responses to deviant and standard stimulation could be found in six MCS patients (42.86%). Regarding relative pre-stimulus frequency bands, delta oscillations predominated in most patients, followed by theta and alpha, although two patients showed a relatively normal power spectrum. The statistical analysis of the relationship between pre-stimulus power and post-stimulus event-related brain response showed multiple significant correlations in five out of the six patients. Individual results sometimes showed similar correlation patterns as in healthy subjects primarily between the relative pre-stimulus alpha power and post-stimulus variables in later time-intervals. However, opposite effects were also found, indicating high inter-individual variability in DoC patients´ functional brain activity. Future studies should determine on an individual level to what extent the relationship between pre- and post-stimulus brain activity could relate to the course of the disorder.

KEYWORDS

disorder of consciousness, EEG frequency bands, EEG, somatosensory event-related potentials, unresponsive wakefulness syndrome, minimally conscious state

Introduction

Millions of people worldwide suffer severe brain injury each year and fall into coma or are put into a medically induced coma. Most of these patients awake from the coma and recover, some of them have consequential damage after awakening and some do not survive. Among the consequential damages resulting from severe brain injuries are disorders of consciousness (DoC), which can be divided into different stages such as the minimally conscious state (MCS; Giacino et al., 2002) and the unresponsive wakefulness syndrome (UWS), formerly known as vegetative state (Laureys et al., 2010). Because of reduced behavioral responses in both conditions (Giacino and Kalmar, 1997), it is challenging to make a correct diagnosis to differentiate between UWS and MCS, but these states are distinguishable by circadian rhythms and the presence of conscious awareness (Giacino and Kalmar, 1997; Giacino et al., 2002). In UWS, patients do not establish genuine sleep-wakefulness cycles, they show altered sleep patterns with a disturbed circulation of sleep over the day and night (Mertel et al., 2020). They also lost their speech production and show no signs of awareness of the self- or the environment (Jennett and Plum, 1972). In MCS, most patients have preserved sleep-wakefulness cycles and they appear to understand single words or short phrases and show minimal but definite evidence of self-awareness and/or awareness of the environment (Giacino et al., 2002, 2014).

Minimally conscious state can be further subdivided into MCS+ and MCS-depending on the complexity of the behavioral responses of the patient where MCS+ is diagnosed for patients with high-level (e.g., command following, intelligible verbalizations or gestural or verbal yes/no responses) and MCS- for patients with low-level responses (e.g., orientation of noxious stimuli, pursuit eye movements that occur in direct response to moving or salient stimuli, movements or affective behaviors that occur appropriately in relation to relevant environmental stimuli; Bruno et al., 2011). The prognosis for recovery from both, the MCS and UWS state can vary widely. They can become a permanent condition without changes of the cognitive status of the patient for years until ultimate death, but patients can also make progress towards recovery (Steppacher et al., 2016, 2020), whereby patients in MCS, and those who have reached MCS faster after injury and coma, seem to have a better chance to do so (Giacino and Kalmar, 1997; Giacino and Kalmar, 2005; Voss et al., 2006; Luauté et al., 2010; Hirschberg and Giacino, 2011).

Neuroimaging research using multiple methods such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET), electroencephalography (EEG) and magnetoencephalography (MEG) has been performed to study the brain activity in patients with DoC in attempts to get a better understanding of their cognitive processes and functions. These studies reveal that sometimes patients that are behaviorally diagnosed as UWS have brain activity that is indicative of higher-order cognitive processes and even resembles what is found in healthy people (e.g., Owen et al., 2006; Cruse et al., 2011). The outcomes of such studies may help to develop prognostic tools but also new treatment strategies and techniques, such as brain–computer interfaces (BCI) which may allow overtly unresponsive patients to get in touch with their environment. Although underlying brain injuries seriously affect the dynamics of brain activity, studies have demonstrated that some patients in UWS and MCS are capable of following commands and executing mental tasks such as motor imagery. This has been found in blood-oxygen-level-dependent (BOLD) responses from fMRI (e.g., Monti et al., 2010; Bardin et al., 2012; Stender et al., 2014; Bodien et al., 2017) or EEG spectral power analysis (e.g., Goldfine et al., 2011; Höller et al., 2013). Likewise, attention-related responses to specific events or stimuli that elicit event-related potentials (ERPs) in the EEG (e.g., Kotchoubey et al., 2005; Lulé et al., 2013; Spataro et al., 2018) have been identified. These findings suggest that some patients can be aware of their surroundings, but there is high interindividual (and perhaps also intraindividual) variability. Not all of the patients show reliably detectable brain responses in a given paradigm: Factors like disease duration and traumatic pathology are also related to performance (Kotchoubey et al., 2005). Since fMRI, PET and MEG are limited in their clinical use, EEG is a feasible alternative for bedside examinations and also for the detection of awareness, because ERPs and oscillations in EEG recordings have been suggested as relevant markers of consciousness that can predict the outcome of patients with DoC (Fischer et al., 2004; Kotchoubey, 2005; Luauté et al., 2005; Chennu et al., 2017; Steppacher et al., 2020).

EEG oscillations can be divided into several frequency bands with different spectral boundaries such as delta (<4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–30 Hz) and gamma (>30 Hz). Alpha is the dominant frequency band in the EEG of healthy adults (Klimesch, 1999) with an active role in information processing (Klimesch, 2012). In DoC-patients, the relative power of these frequency bands is highly abnormal, typically with decreased power in the alpha and increased power in the delta band. Relative delta band power is higher in UWS than in MCS patients, whereas alpha power is higher in MCS compared to UWS patients (Lehembre et al., 2012a).

In healthy people, pre-stimulus oscillatory activity in cognitive tasks has been shown to affect conscious perception in the auditory, visual and somatosensory modality (Linkenkaer-Hansen et al., 2004; Henry and Obleser, 2012; Weisz et al., 2014; Benwell et al., 2017). Especially the power and phase of the alpha-frequency band can predict subsequent conscious perception. Multiple studies showed that pre-stimulus activity affects post-stimulus ERPs, especially regarding the P300 (Jasiukaitis and Hakerem, 1988; Haig and Gordon, 1998; Ergenoglu et al., 2004; Mathewson et al., 2009; Roberts et al., 2014) which has often been linked to conscious stimulus perception, but also the N100, an index of sensory registration (Intriligator and Polich, 1995). So far, studies relating pre-stimulus EEG activity with post-stimulus ERPs were conducted with healthy volunteers and also mostly in the visual or auditory modality. A study from Ai and Ro (2014) also suggested a relationship between pre-stimulus alpha power and the stimulus detection rate in a tactile perception task (Ai and Ro, 2014). P100 and N200 somatosensory ERPs (sERPs) amplitudes increased in perceived trials and had an inverted U-shaped relationship with the pre-stimulus alpha power, indicating the existence of an optimal level of pre-stimulus alpha power for tactile perception (Ai and Ro, 2014).

In the present study we examined how pre-stimulus EEG activity relates to post-stimulus somatosensory responses in individuals in DoC. Therefore we analyzed pre-stimulus oscillations and post-stimulus sERP-data in response to an active somatosensory oddball paradigm. Scalp potentials evoked by sensory stimuli in oddball paradigms are for example the tactile N140, which is functionally analogous to the auditory and visual N100 component, and the P300, a positive deflection in averaged EEG data. Because of the

TABLE 1 Patients demographic information.

#	Sex	Age at m.d.	Clinical State	Duration of illness (years)	Etiology
01	F	29	MCS+	10	HBD
02	F	67	MCS−	9	CCT/HBD
03	M	27	MCS−	10	CCT
04	M	54	MCS−	11	CCT/HBD
05	M	47	UWS/MCS	15	HBD
06	F	63	MCS−	13	HBD
07	M	35	MCS+	17	HBD
08	F	54	MCS	5	TI
09	M	38	MCS	2	HBD
10	F	42	MCS	2	ICH
11	F	42	MCS+	4	HBD
12	M	22	MCS+	3	IS
13	M	46	MCS	13	HBD
14	M	54	UWS	1	CCT

F, female; M, male; M.d., measurement date; MCS, minimal conscious syndrome; UWS, unresponsive wakefulness syndrome; HBD, hypoxic brain damage; CCT, craniocerebral trauma; TI, thalamus infarct; ICH, intracerebral hemorrhage; IS, ischemic stroke.

heterogeneity of brain lesions and side in our patients, we first analyzed the post-stimulus epochs of standard and deviant stimuli to see at which electrodes and in which time-interval differences between the stimuli were statistically significant. After that the latency of the amplitude maximum, the amplitude maximum and also the area under curve (AUC) of the post-stimulus sERPs in the significant time interval were determined and the relative power of frequency bands in the pre-stimulus epochs of deviants were computed. We tested individually for each patient if the relative power of pre-stimulus frequency bands was correlated with post-stimulus variables to assess if pre-stimulus oscillation frequencies can predict the post-stimulus outcome in different stimulation conditions.

Patients and methods

Patients

Fourteen DoC-patients (6 female) who were stationary housed at the care facility “Haus Elim MeH,” Bethel, in Bielefeld from June to July 2018 participated in this study. The data sample consists of 13 MCS and 1 UWS patients (mean age-at measurement 44.29 years). Patients have been assessed through the early functional abilities (EFA) scale (Heck et al., 2000). Informed consent was obtained either from relatives or legal representatives for each patient. The research was approved by the ethics committee of the German Psychological Association. The individual demographic data for all patients are reported in Table 1.

Experimental procedure

The experimental paradigm of this study is similar to the study by Lindenbaum et al. (2021). Vibrotactile stimuli were presented through the inhouse developed BRIX2 prototyping system (Zehe, 2018) with an extension-module consisting of cell-type-vibration motors (ERM; 10 mm × 3 mm; see Figure 1).

The intensity and duration of each vibration motor can be modified in the Arduino sketch-based firmware separately. The user can choose a value between 0 and 255 to adjust the amplitude of the vibration, where 0 is no vibration at all and 255 is the maximum vibration of the motors (100%). A fixed stimulus sequence with associated stimuli was created for each experimental run in OpenSesame (Mathôt et al., 2012). When stimulating body parts with neighboring cortical representation within one hemisphere, these representations interact, reflecting intra-hemispheric interference (Lindenbaum et al., 2021). This interference leads to decreased post-stimulus brain responses in the ipsilateral condition, whereas the contralateral stimulation requires a more complex interhemispheric connectivity. Therefor we defined four blocks of where and how patients were stimulated (see Table 2; Figure 1) including two ipsilateral and contralateral conditions. Each block consisted of 200 standard and 40 deviant stimuli. In the ipsilateral stimulation condition, three motors for standard and deviant presentation were always attached to the index, middle, and ring finger on one body site (left or right). In addition to the three motors (e.g., left fingers) for standard presentation a single motor was attached at the index finger (e.g., right index) for deviant presentation in the contralateral condition. The motors were attached to the fingers using adhesive plasters. Patients sat in a wheelchair or lay in their nursing bed and were instructed to focus on the deviant stimuli and count their occurrences.

Stimuli

The characteristics and discriminability of stimuli presented in this study were previously tested with healthy subjects (Lindenbaum et al., 2021). Standard and deviant stimulus differed in their vibration-intensity but not in the duration of vibration. The duration of stimulus presentation was 150 ms. Standard stimuli had a peak frequency of 92.5 Hz and an intensity value of 75 (29.41% of the maximum vibration, magnitude 0.33 g) the deviant stimulus had a peak frequency of 175 Hz and an intensity value of 150 (58.85% of the maximum vibration, magnitude 0.8 g). The ratio of standard to deviant presentation was 5:1 and no two deviant stimuli followed consecutively. The inter-stimulus-interval (ISI) was 1,200 ms.

Electroencephalography recording and preprocessing

Electroencephalography signals were recorded using a BioSemi system with 32 active electrodes,[1] Cz as the recording reference and a

1 http://www.biosemi.com

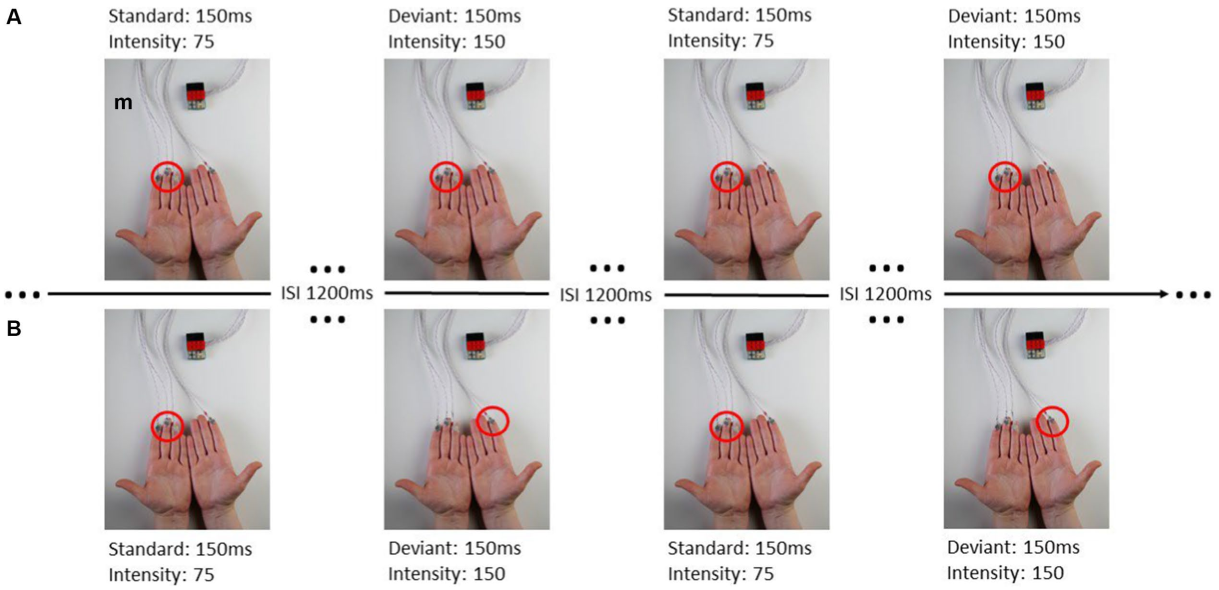

FIGURE 1
From Lindenbaum et al. (2021): **(A)** ipsilateral stimulation, **(B)** contralateral stimulation.

TABLE 2 Experimental setup and spots of stimulus presentation.

Laterality of stimuli presentation	Standard stimuli	Deviant stimuli
Ipsilateral	Left fingers	Left fingers
Ipsilateral	Right fingers	Right fingers
Contralateral	Left fingers	Right index finger
Contralateral	Right fingers	Left index finger

sampling rate of 2,048 Hz. Off-line, data were down-sampled to 1,024 Hz and re-referenced to the average reference.

For all types of analyses, EEG-Data were pre-processed in BESA® Research 6.0 using the automatic artifact rejection.

Preprocessing for single-subject-sERP-analyses

The EEG-Data were pre-processed using a high-pass filter of 0.30 Hz (forward) and a low-pass filter of 15 Hz (zero-phase). We segmented the Data into epochs from 100 ms before stimulus (baseline) onset to 800 ms after Stimulus onset. Artifact-free epochs were submitted to single subject analyses in EMEGS (Peyk et al., 2011).

Preprocessing for Fast Fourier Transformation

Artefact-free trials corresponding to deviant stimulation were segmented into epochs from 600 ms before stimulus to stimulus-onset (0 ms). The unfiltered data-epochs were then exported as BESA-text-files and converted to .txt-files using EMEGS (Peyk et al., 2011). The deviant epochs used for FFT-analysis were the same as in the single-subject-sERP-analyses.

Data analyses

Single-subject-sERP-analyses

The single-subject-analysis consisted of cluster-based permutation tests for each participant and condition. For each time-point and electrode, a two-sample *t*-test comparing the cortical response to the standard and deviant vibrotactile stimuli was calculated and compared against a distribution of 1,000 permutations and a cluster mass test (Maris and Oostenveld, 2007) as implemented in EMEGS (Peyk et al., 2011). This was done for two different pre-defined time-epochs, in which sERPs can typically expected (N140: 0–250 ms, P300: 250–750 ms) as well as across the entire epoch (0–800 ms) with all electrodes. The entire epoch of the whole post-stimulus interval (0–800 ms) was also included to test for any atypical processing differences between standards and deviants. T-tests were performed in EMEGS (Peyk et al., 2011). With the t-values of the t-test the cluster mass test with the three different time-epochs with all electrodes was computed. The significance criterium of the cluster mass test was set to $p < 0.05$ and values of significant time intervals with significant channel groups were saved for further analyses.

We then averaged the standard epochs for every patient and condition and subtracted the average standard epoch from every related single-trial deviant epoch. The difference epochs were then averaged across significant channel groups in the respective significant time interval. *Via* in-house python-based software the most positive peak (maximum), relating to the post-stimulus P300, and its latency was identified in the significant averaged difference epochs and the area under the sERP curve (AUC) was calculated.

FFT

In an in-house python-based script the unfiltered single-trial-files of pre-stimulus deviant-epochs were averaged across significant post-stimulus electrode clusters from the single-subject-analysis. Hereafter, the averaged data was filtered with a sixth order 100 Hz digital butterworth low-pass filter [cut-off frequency was normalized by dividing by half of the sampling frequency (Nyquist-frequency)]. A 50 Hz notch filter was also applied to filter out AC line noise. Filtered data epochs were then windowed using a Hanning taper and symmetrically zero-padded at both ends to 1,024 timepoints (1 s of data). After that the one-dimensional discrete Fourier Transformation for real input was calculated using the python library NumPy and the relative power of frequency bands was computed. The frequency bands and the defined spectral boundaries are listed in Table 3.

Statistical analysis of relationship between pre-stimulus power and post-stimulus brain response

For statistical analysis of the relationship between pre-stimulus frequency power and post-stimulus ERP parameters a correlation matrix was computed for every subject, condition, and time interval separately. Therefore, relative power of frequency bands in the pre-stimulus interval, the maximum and latency of the post-stimulus difference amplitude, and the AUC of the post-stimulus significant time interval for every deviant trial were used for the analysis. The correlation coefficients are reported as Spearman's rho. Given that a total of 15 correlations were calculated for each subject and condition, it is expected that some of them may be chance correlations.

Results

Single-subject-sERP-analysis

All results of the single-subject-sERP-analysis are listed in Table 4. In six out of 14 subjects time intervals with significant differences between brain responses to standard and deviant stimulation were found and the data were suitable for further analyses. Ipsilateral deviant stimulation at the left fingers and the contralateral deviant stimulation at the right index finger most often led to significant differences in brain responses. Two subjects had significant intervals in only one stimulation condition whereas three subjects had significant intervals in two conditions and one subject had significant intervals in three conditions. The results of the ipsilateral stimulation at the fingers are shown in Figures 2, 3 with significant electrode clusters in Figures 4, 5. The results of the contralateral stimulation are depicted in Figures 6, 7 and the significant cluster to contralateral stimulations are shown in Figures 8, 9. The grey background in the waveform illustrations displays the time interval in which the differences of deviant and standard stimuli were significant ($p < 0.05$). Please note that waveforms of different time intervals in the same condition can differ, because they are based on different significant electrode clusters. Subjects 04 and 08 showed very jagged ERP response time-courses to especially the ipsilateral stimulation (see Figure 2) whereas other subjects showed better-defined courses of post-stimulus amplitudes.

TABLE 3 Frequency band and the defined spectral boundaries.

Frequency band	Spectral boundaries
Delta	0–4 Hz
Theta	>4–8 Hz
Alpha	>8–12 Hz
Beta	>12–30 Hz
Gamma	>30–100 Hz

FFT-analysis

Averaged relative pre-stimulus frequency bands for deviant trials in patients who showed significant post-stimulus ERP differences between standard and deviants are listed in Table 5. The results of the ipsilateral stimulation at the fingers are shown in Figures 10, 11, results of the contralateral conditions are in Figures 12, 13. The power spectral densities (PSDs) of the significant electrode cluster in the significant time interval 0–250 ms are presented as black line, the time interval 0–800 ms as dashed black line and the 250–750 ms time interval as dotted black line. For the illustrations frequencies were cut at 50 Hz, because the gamma activity was so low in every subject that the PSD approaches zero. The percentage of frequency bands was the greatest in the delta range followed by the theta and alpha range for most of the subjects. One subject (#08) had a higher percentage of the theta than delta range whereas another subject (#04) had an almost similar percentage of delta and theta activity.

Correlation-analysis

The results of the correlation analyses are listed in Tables 6–9. Five out of the six subjects showed significant results in the correlation analyses. The results of subject 02 were not significant in the correlation analysis. Subject 04 showed multiple moderate and weak correlations between pre-stimulus frequency bands and post-stimulus variables in the ipsilateral as well as in the contralateral stimulation (see Tables 6, 9), which might be due to the jagged course of post-stimulus response. Subject 06 showed positive correlations with the theta band, AUC and maximum amplitude (see Table 9) of post-stimulus intervals for the contralateral stimulation with the deviant presented at the right index finger. Subject 08 had positive and negative correlations in the ipsilateral and contralateral stimulation (see Tables 6, 8). In the ipsilateral stimulation at the left fingers, delta activity correlated positively with the AUC in the significant electrode- and time cluster 0–250 ms. In both, the 0–800 ms and 250–750 ms time-interval pre-stimulus alpha activity correlated positively with the latency of the maximum amplitude in post-stimulus time interval. In the contralateral stimulation with the deviant at the left index, alpha power correlated negatively with the AUC, with the AUC being more negative when the relative alpha power increased. Subject 11 showed significant correlations in both time intervals in the ipsilateral stimulation at the left fingers (see Table 6). In the time interval 0–800 ms, where alpha band power correlated negatively with the

TABLE 4 Results of single-subject-sERP-analysis.

Subject #	Condition	Time interval in analyses	Significant time interval (ms)	Cluster mass p Value	AUC Ø	Ø Max amplitude (µV)	Ø Latency max. amplitude (ms)
02	Ipsilateral deviant left fingers	250–750	408–750	$p = 0.043$	−2498.92	13.22	489.12
04	Ipsilateral deviant left fingers	0–250	4–250	$p = 0.046$	−210.60	3.49	150.76
		0–800	4–663	$p = 0.038$	−402.24	4.38	352.01
	Contralateral deviant right index	0–800	33–677	$p = 0.029$	−744.78	3.95	428.71
06	Contralateral deviant left index	0–250	0–250	$p = 0.012$	168.22	6.90	114.17
		0–800	0–800	$p = 0.009$	879.75	13.70	447.52
		250–750	250–750	$p = 0.021$	513.96	12.07	492.24
	Contralateral deviant right index	0–250	95–250	p = 0.01	−687.35	2.33	167.52
		0–800	95–339	$p = 0.048$	−138.32	1.86	273.52
08	Ipsilateral deviant left fingers	0–250	53–187	$p = 0.032$	−107.51	2.53	119.09
		0–800	424–700	$p = 0.041$	−314.23	5.59	557.54
		250–750	424–700	$p = 0.022$	−314.23	5.59	557.54
	Contralateral deviant left index	0–250	14–250	$p = 0.042$	64.23	4.43	114.53
	Contralateral deviant right index	0–800	459–719	$p = 0.043$	−430.50	3.14	615.93
		250–750	459–719	$p = 0.017$	−430.50	3.14	615.93
11	Ipsilateral deviant left fingers	0–800	0–800	$p = 0.03$	214.72	6.08	363.56
		250–750	250–750	$p = 0.021$	−119.62	4.16	495.02
13	Ipsilateral deviant right fingers	0–250	77–250	$p = 0.024$	−721.50	4.66	140.78
		0–800	77–375	$p = 0.028$	−992.75	5.91	222.34
	Contralateral deviant right index	0–250	12–250	$p = 0.036$	−569.23	5.64	112.68
		0–800	12–799	$p = 0.009$	−1513.94	6.94	379.77
		250–750	250–750	$p = 0.009$	−1262.13	6.31	261.19

Averaged AUC, maximum amplitude from the difference epochs (deviant-standard) and latency of the maximum in the significant time interval. Rows with grey background refer to the same time interval and/or electrode-cluster.

AUC and maximum amplitude post-stimulus. Maximum amplitudes decreased whereas relative alpha activity increased. Also, delta activity correlated positively with the maximum amplitude. In the time interval 250–750 ms the relative alpha band power correlated negatively with the maximum amplitude, with amplitudes decreasing whereas the relative alpha power increased. Subject 13 showed significant correlations in the ipsilateral as well as in the contralateral condition (see Tables 7, 9). In the ipsilateral stimulation at the right fingers alpha activity correlated with the maximum amplitude in both time intervals. In the contralateral condition the 250–750 ms time interval showed a significant positive correlation between the pre-stimulus beta activity and the AUC of post-stimulus amplitudes.

Discussion

We investigated if pre-stimulus oscillation frequencies are related to post-stimulus cortical target differentiation in sERPs of patients in DoC. Fourteen DoC-patients participated in this study of whom six (42.86%) had significant differences between brain responses to standard and deviant stimulation in specific post-stimulus time intervals and electrode clusters. Thereof five subjects had multiple statistically significant correlations between pre-stimulus oscillations and post-stimulus variables. All of those were in MCS.

Single-subject-sERP-analysis

Eight patients showed no significant differences between brain responses to standard and deviant stimuli (see Table 4). This finding is consistent with other studies showing that oddball responses, especially the P300, are less frequently detected in patients with DoC than healthy individuals (Gott et al., 1991; Signorino et al., 1997; Kane et al., 2000). All of our patients had enough artifact free trials for the analysis, so this outcome cannot be reduced to insufficient data or artefacts such as excessive motion, although involuntary head and/or body movements are very common in DoC patients. The absence of significant results in these patients does not necessarily indicate a general absence of significant differences in brain responses to certain stimuli. It could be the case that the stimulation paradigm used in this

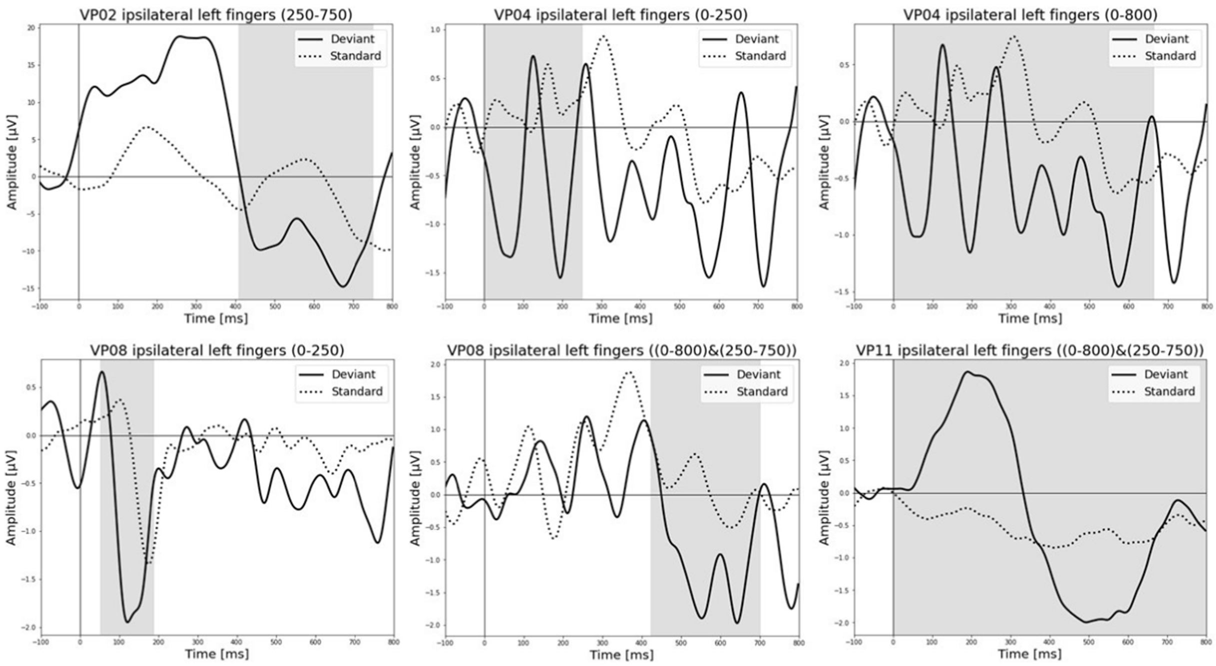

FIGURE 2
Grand-averaged event-related potential (ERP) waveforms of significant electrode cluster in response to the ipsilateral stimulation at the left fingers. The grey background shows the significant time-interval.

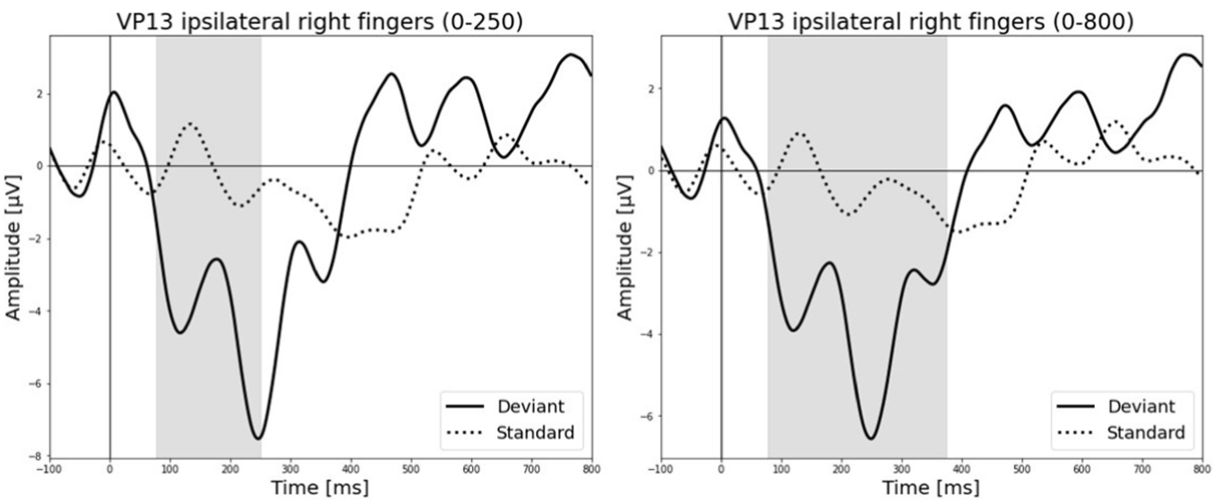

FIGURE 3
Grand-averaged ERP waveforms of significant electrode cluster in response to the ipsilateral stimulation at the right fingers. The grey background shows the significant time-interval.

study is not effective for all our patients and that a different type of stimulation (e.g., auditory) would have led to significant differences in these patients.

In a study of Rousseau et al. (2008) four patients in the persistent vegetative state were stimulated in a tri-modal design (auditory, visual and somatosensory) to elicit evoked potentials (EPs). One patient showed EPs in the auditory and somatosensory, but not in the visual paradigm; another showed neither auditory nor somatosensory EPs, but, somewhat abnormal, visual EPs; the third patient showed somatosensory evoked potentials, but only in the right hemisphere and small visual evoked potentials, but auditory EPs were missing; and the last patient showed somatosensory and abnormal visual EPs, but the auditory evoked potentials were absent. These results show that not all modalities lead to brain responses in every patient and that the stimulation paradigms may need to be chosen individually for patients in DoC. The same applies to our stimulation paradigm. No patient showed significant results in all stimulation conditions but it appears that for some of them (e.g., patient 06) the contralateral stimulation

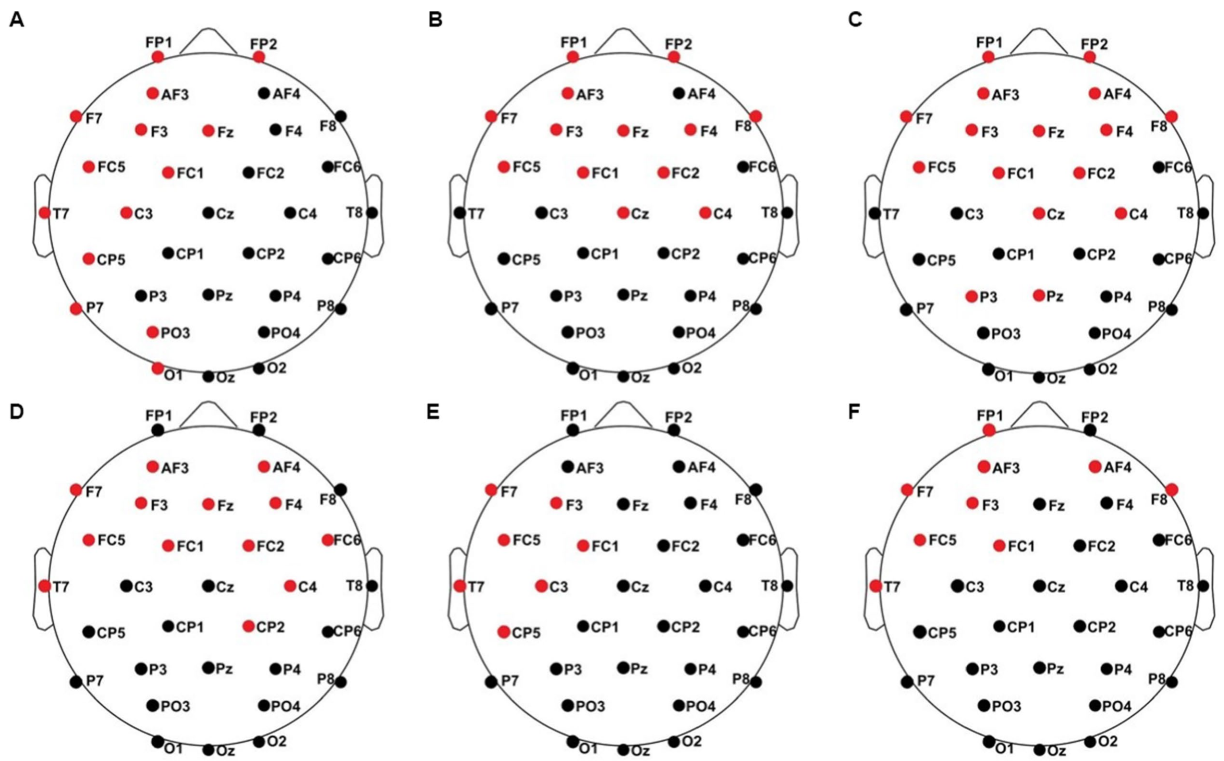

FIGURE 4
Significant electrode cluster (red) in response to the ipsilateral stimulation at the left fingers. **(A)** #02 (250–750ms), **(B)** #04 (0–250ms), **(C)** #04 (0–800ms), **(D)** #08 (0–250ms), **(E)** #08 (0–800ms and 250–750ms), **(F)** #11 (0–800ms and 250–750ms).

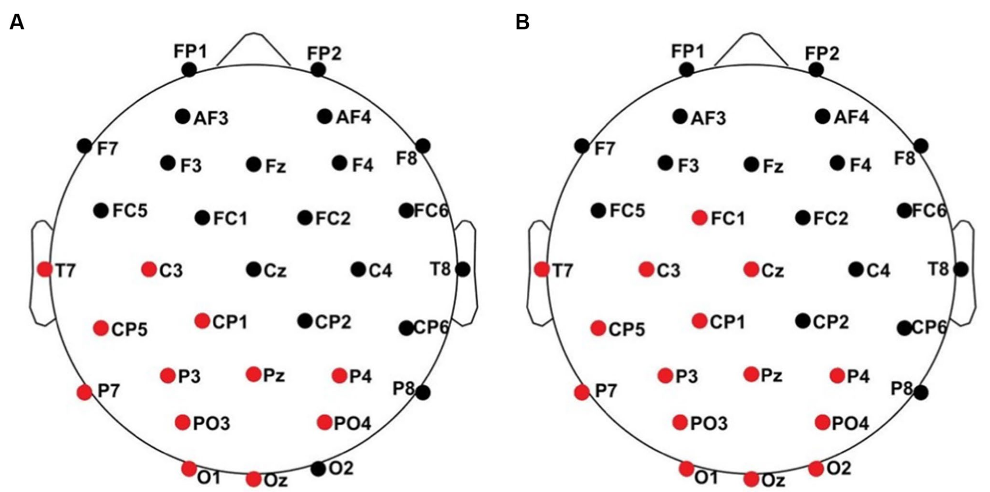

FIGURE 5
Significant electrode cluster (red) in response to the ipsilateral stimulation at the right fingers. **(A)** #13 (0–250ms), **(B)** #13 (0–800ms).

leads to significant results whereas the ipsilateral presentation does not. Moreover, a certain presentation side of stimuli (right vs. left) can be more effective (e.g., patient 13).

Also, other factors like fatigue or fluctuations in arousal could have led to the inability to find significant results in several patients. It might be that the recording session was performed during a time of decreased level of activity due to arousal fluctuations and therefor with the incapability of the patient to maintain attentive and distinguish between the stimuli (Neumann and Kotchoubey, 2004).

It is challenging to visually identify the presence and absence of post-stimulus sERPs in patients 04 and 08 because the waveforms of post-stimulus interval were very jagged in the ipsi—as well as in the contralateral conditions (see Figures 2, 6, 7) but the statistical analyses revealed that the brain responses to deviant stimuli were significantly

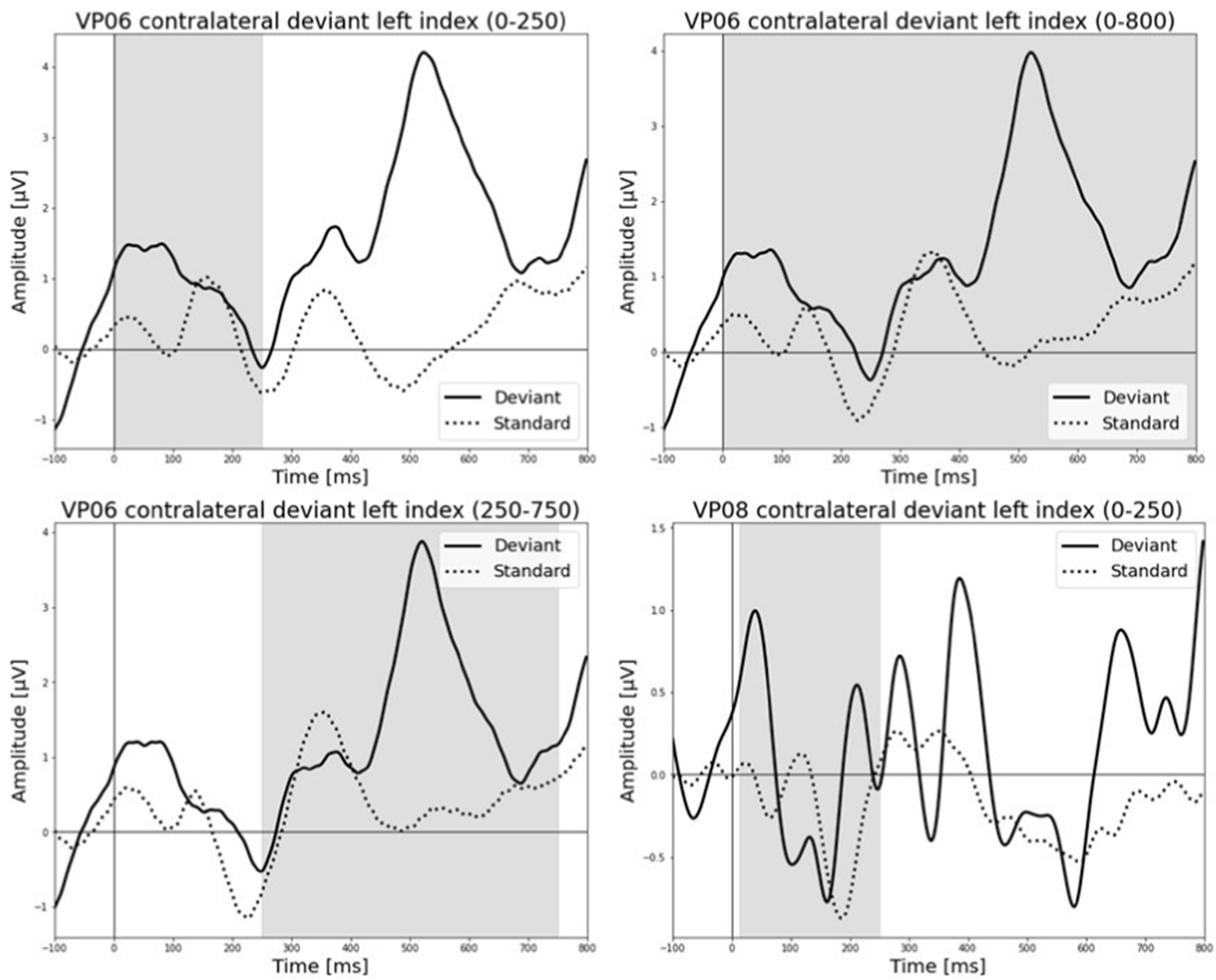

FIGURE 6
Grand-averaged ERP waveforms of significant electrode cluster in response to the contralateral stimulation with the deviant at the left index finger. The grey background shows the significant time-interval.

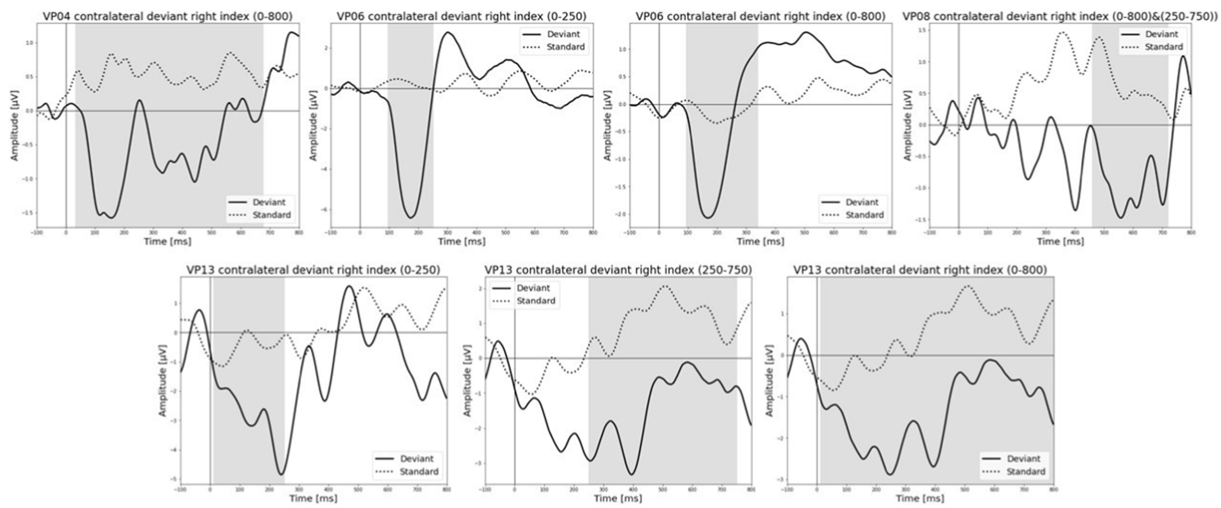

FIGURE 7
Grand-averaged ERP waveforms of significant electrode cluster in response to the contralateral stimulation with the deviant at the right index. The grey background shows the significant time-interval.

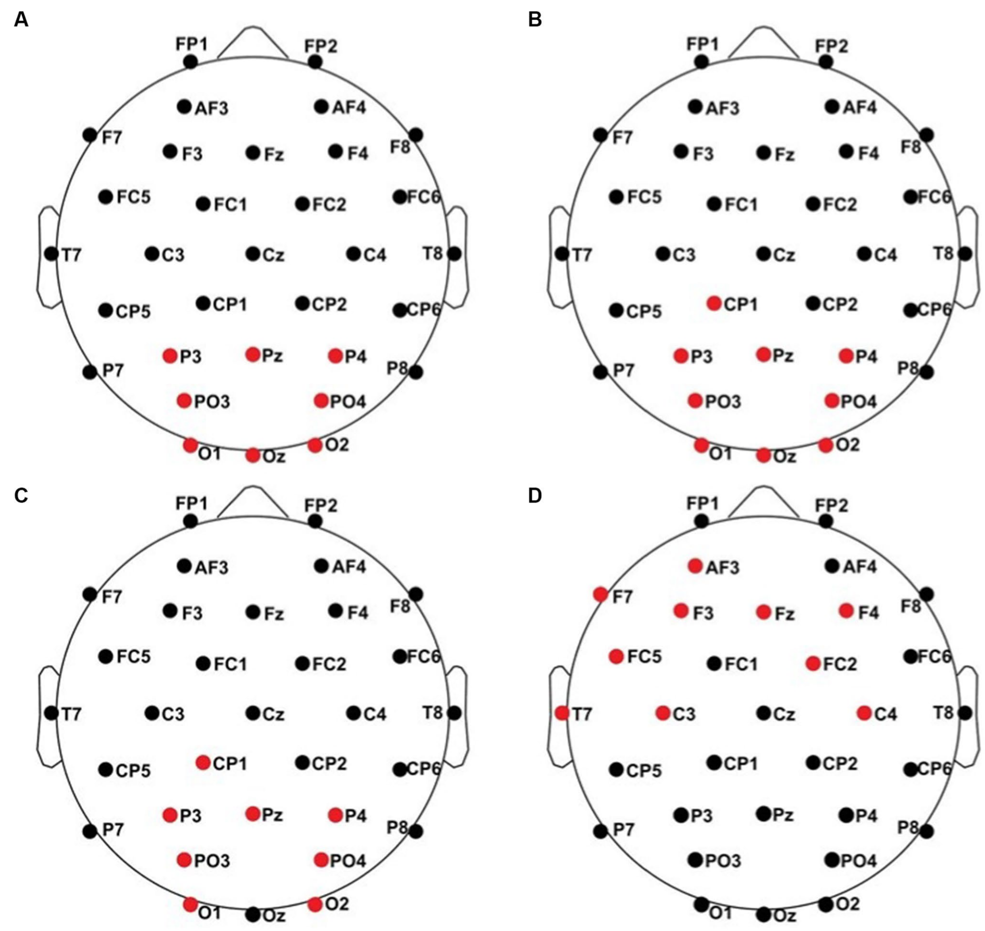

FIGURE 8
Significant electrode cluster (red) in response to the contralateral stimulation with the deviant at the left index finger. **(A)** #06 (0–250ms), **(B)** #06 (0–800ms), **(C)** #06 (250–750ms), **(D)** #08 (0–250ms).

different from standard ones in specific time intervals and electrode clusters. On the other hand, the sERP curves of patient 06 even showed well-defined ERP components (N140 and P300) to deviant stimuli in the contralateral stimulation at the right index with significant time intervals in the specific time domain of the N140, despite a rather abnormal pre-stimulus power spectrum. Our results are quite variable, this could be due to the underlying injury, current (asleep) or general (diagnosis) clinical condition.

FFT

Our results showed that in four of the six patients, in whom significant post-stimulus effects could be found, pre-stimulus relative power consisted predominantly of the delta frequency band (see Table 5; Figures 10–13). Patient 08 had a higher relative power of the theta than the delta band and patient 04 had an almost similar percentage of delta and theta activity. The order of the pre-stimulus relative power of frequency bands in these six DoC patients, ranked by percentage, was delta, theta, alpha, beta, and gamma.

Healthy awake adults show symmetric alpha rhythm at posterior electrodes at rest with a superimposed beta rhythm when they are attentive to their environment (Lehembre et al., 2012b). The theta rhythm is predominant when the individual is tired and the delta rhythm is predominant in deep sleep states (Lehembre et al., 2012b). The power of frequency bands is highly abnormal in DoC-patients with decreased power in the alpha and increased power in the delta band and also with differences in UWS compared to MCS patients (Lehembre et al., 2012a). Also, many abnormal patterns can be observed in the EEG of patients in DoC. Besides diffuse slowing activity continual focal polymorphic delta rhythm and epileptiform activity can be observed over damaged regions (Brenner, 2005). Our results are in line with previous findings (Nagata et al., 1989; Claassen et al., 2004; Fellinger et al., 2011) showing that the delta band power is predominant in DoC-patients.

Correlation-analysis

Several studies have investigated the relationship between pre-stimulus oscillations and post-stimulus outcomes in healthy participants. Pre-stimulus activity, especially in the alpha band, can affect the early and late post-stimulus ERPs with regard to the amplitude maximum and its latency (Jasiukaitis and Hakerem, 1988; Intriligator and Polich 1995; Haig and Gordon, 1998; Ergenoglu et al., 2004; Mathewson et al., 2009; Roberts et al., 2014). Moreover, lower

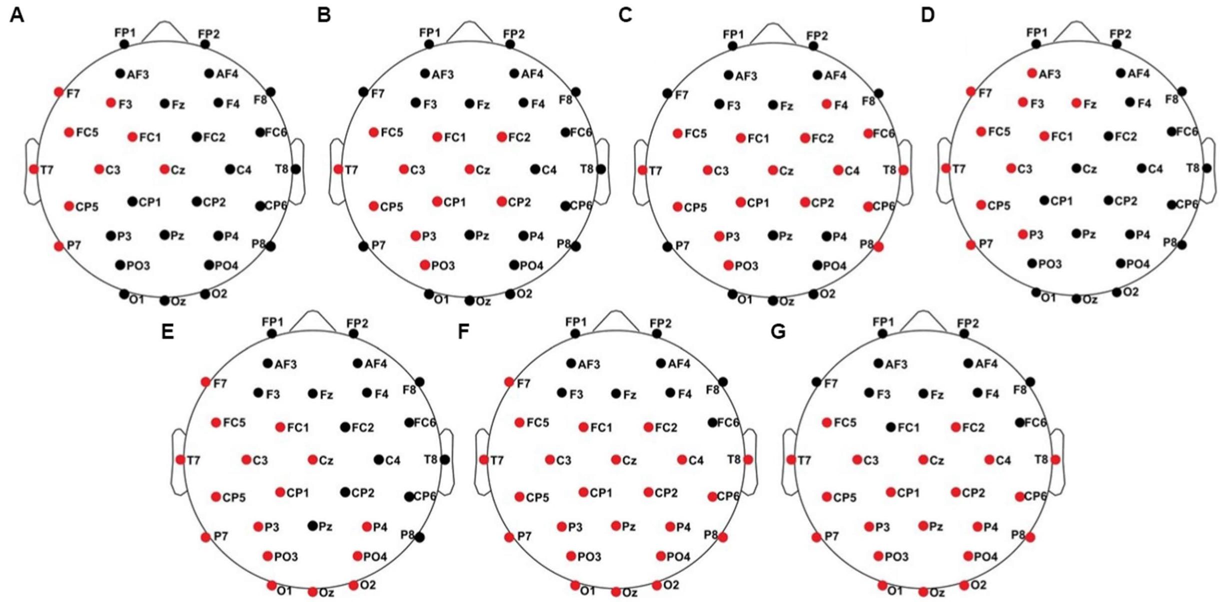

FIGURE 9
Significant electrode cluster (red) in response to the contralateral stimulation with the deviant at the right index finger. **(A)** #04 (0–800ms), **(B)** #06 (0–250ms), **(C)** #06 (0–800ms), **(D)** #08 (0–800ms and 250–750ms), **(E)** #13 (0–250ms), **(F)** #13 (0–800ms), **(G)** #13 (250–750ms).

frequency bands in pre-stimulus epochs have been found to affect post-stimulus ERPs and evoked potentials (EPs), especially early ones such as N100 and N200 (Romani et al., 1988; Intriligator and Polich, 1995).

Five out of the six patients, in whom significant differences between brain responses to standard and deviant stimuli in the single-subject-sERP-analysis could be found, showed significant correlations between the relative power of frequency bands in the pre-stimulus interval and various indices of post-stimulus responses to deviant stimuli (see Tables 6–9). The pre-stimulus frequencies and post-stimulus variables of patient 02 did not correlate significantly. Patient 04 had multiple moderate and weak correlations in the ipsilateral as well as in the contralateral stimulation condition (see Tables 6, 9). It is quite challenging to interpret this outcome, but it might be reduced to the jagged course of post-stimulus reaction especially in the ipsilateral condition. Interestingly, this person had a relatively normal pre-stimulus frequency spectrum. The results to the contralateral stimulation at the right index of patient 06 are listed in Table 9. We found two positive correlations between the pre-stimulus theta band and post-stimulus AUC and maximum in the early post-stimulus time interval (95–339 ms) referring to the N140. Intriligator and Polich (1995) conducted a study to examine the relationship between EEG spectral power and post-stimulus auditory ERPs (aERPs) in healthy young adults. They found a negative correlation between the theta band and the size of the auditory N100. Also, results by Romani et al. (1988) showed a relationship between pre-stimulus low-frequency amplitudes and post-stimulus auditory EPs. N1–P2 amplitudes were lower and N1 latencies longer with higher pre-stimulus low-frequency spectral power. Although results are very atypical and variable in patients in DoC, we could show that the post-stimulus ERPs of patient 06 are affected by pre-stimulus oscillations in a similar way as in healthy subjects.

Patient 08 also showed very diffuse courses in the post-stimulus interval but with shorter time-windows, where responses to standards and deviants differed. This pattern might be easier to interpret. In the ipsilateral condition (see Table 6) pre-stimulus relative delta power on patient 08 correlated positively with the AUC of post-stimulus interval. The course of the mean post-stimulus amplitude is shown in Figure 2 with significant differences in the N140 time-interval (53–187 ms). The higher the relative power of delta band in the pre-stimulus epoch, the less negative the AUC. This result is also in line with previous findings in healthy subjects (Romani et al., 1988) and implicates that the relative power of pre-stimulus frequencies also affects post-stimulus ERPs, at least in some patients in DoC. A positive correlation between the relative power of alpha band and latency of maximal amplitude in the later post-stimulus time interval, approximately referring to a delayed P300 time range (424–700 ms), which is also in line with previous findings of delayed ERPs in DoC (Perrin et al., 2006), was found. Multiple studies showed that the pre-stimulus alpha activity affects the post-stimulus P300 ERP component (e.g., Jasiukaitis and Hakerem, 1988; Haig and Gordon, 1998; Ergenoglu et al., 2004). The results of the study of Intriligator and Polich (1995) also showed a correlation between the resting state alpha frequency band and the latency of the P300 aERP component. The P300 latency reflects the stimulus-processing time, e.g., the time a person needs to evaluate the stimulus (Kutas et al., 1977). This result is in line with multiple studies which showed that the detection of a visual stimuli is more likely with less alpha power in the pre-stimulus epoch (e.g., Ergenoglu et al., 2004; Mathewson et al., 2009; Roberts et al., 2014). For patient 08, the contralateral condition with the deviant at the left index, the pre-stimulus alpha power at the significant frontal electrode cluster correlated negatively with the AUC of post-stimulus N140 time-interval (14–250 ms). The higher the alpha power, the more negative the AUC. The N100 or in the somatosensory

TABLE 5 Results of FFT-analysis.

Subject #	Condition	Significant time interval (ms)	Ø Delta (%)	Ø Theta (%)	Ø Alpha (%)	Ø Beta (%)	Ø Gamma (%)
02	Ipsilateral deviant left fingers	408–750	82.83	15.9	0.68	0.58	0.01
04	Ipsilateral deviant left fingers	4–250	38.6	34.59	13.87	9.94	2.78
		4–663	40.72	34.12	13.34	9.05	2.56
	Contralateral deviant right index	33–677	37.83	35.82	14.19	8.57	3.24
06	Contralateral deviant left index	0–250	88.48	9.38	1.32	0.74	0.08
		0–800	83.84	13.75	1.55	0.78	0.07
		250–750	81.62	15.77	1.73	0.81	0.07
	Contralateral deviant right index	95–250	64.77	29.7	3.31	2.01	0.2
		95–339	65.89	27.73	3.55	2.52	0.29
08	Ipsilateral deviant left fingers	53–187	17.31	51.57	19.52	11.28	0.30
		424–700	25.11	49.2	18.43	6.99	0.26
		424–700	25.11	49.2	18.43	6.99	0.26
	Contralateral deviant left index	14–250	21.38	50.59	18.41	9.19	0.40
	Contralateral deviant right index	459–719	29.32	41.22	18.72	9.15	1.48
		459–719	29.32	41.22	18.72	9.15	1.48
11	Ipsilateral deviant left fingers	0–800	86.41	8.63	2.05	2.02	0.82
		250–750	86.41	8.63	2.05	2.02	0.82
13	Ipsilateral deviant right fingers	77–250	66.36	27.11	5.42	1.07	0.04
		77–375	68.28	25.60	5.02	1.06	0.04
	Contralateral deviant right index	12–250	81.13	14.53	3.59	0.69	0.06
		12–799	82.94	13.65	2.69	0.65	0.07
		250–750	81.08	15.12	3.02	0.72	0.06

Averaged relative pre-stimulus frequency bands for deviants in significant electrode cluster. Rows with grey background means same time interval and/or electrode-cluster.

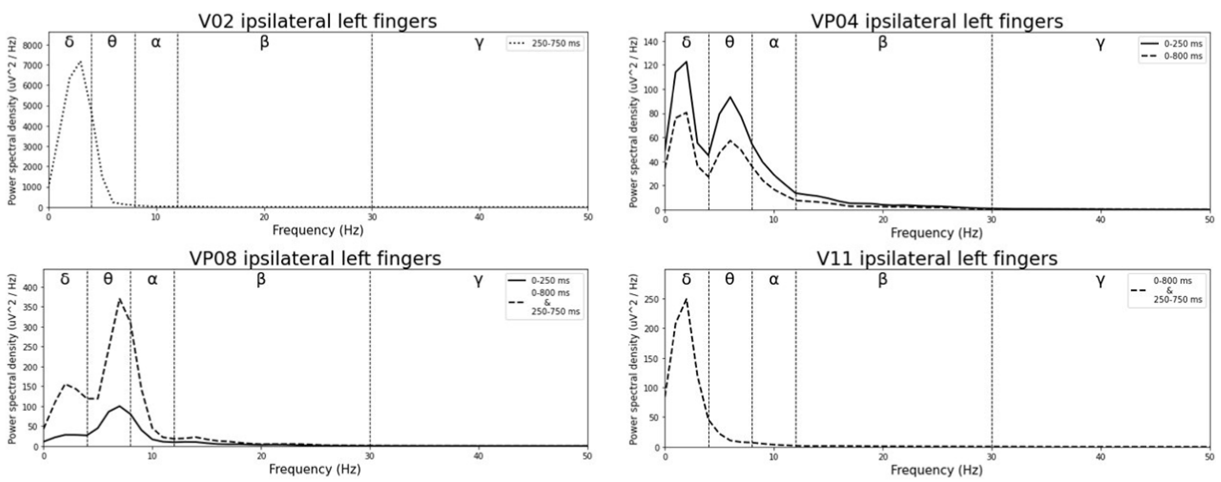

FIGURE 10
Averaged pre-stimulus frequency bands for ipsilateral stimulation at the left fingers.

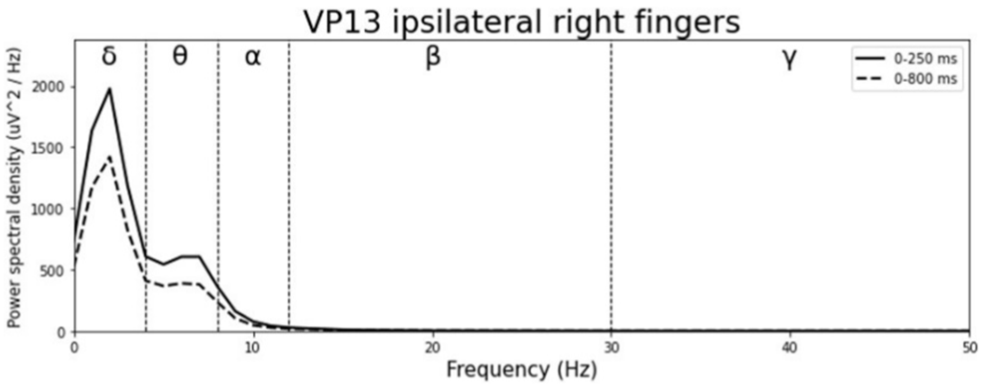

FIGURE 11
Averaged pre-stimulus frequency bands for ipsilateral stimulation at the right fingers.

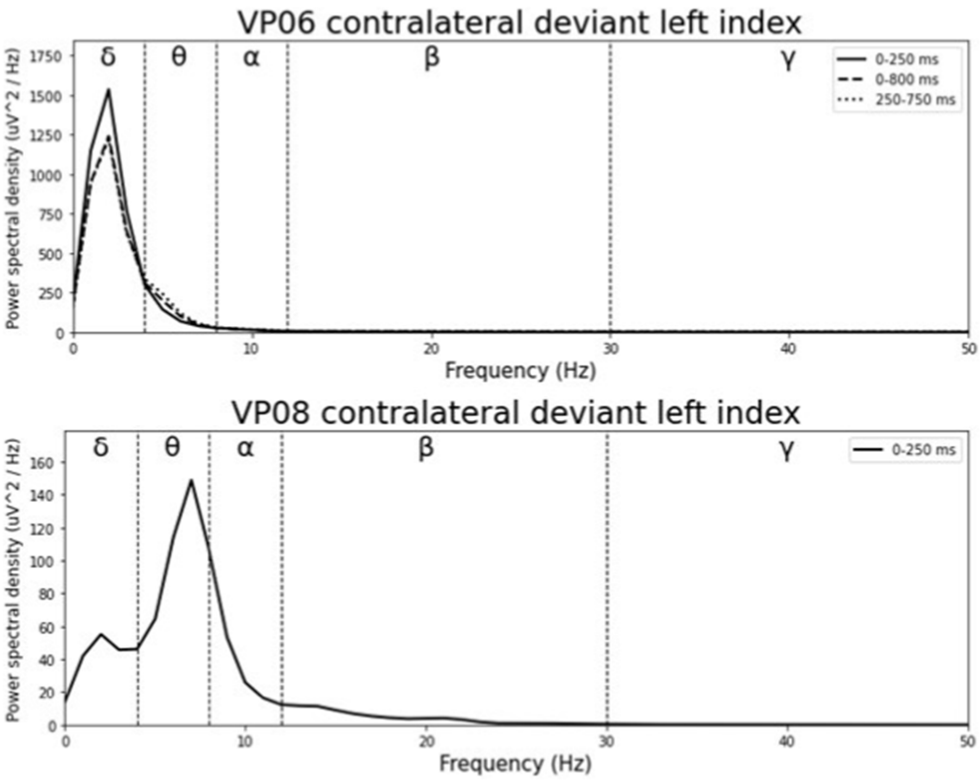

FIGURE 12
Averaged pre-stimulus frequency bands for contralateral stimulation with the deviant at the left index.

paradigm N140 reflects the discrimination process of stimuli. Roberts et al. (2014) found a relationship between pre-stimulus alpha-power and the N100 amplitude in a visual paradigm with more negative N100 amplitudes when pre-stimulus alpha power was low. Our findings suggest the opposite despite the fact that we computed the AUC of post-stimulus interval. The averaged N140 deflection of the patient (see Figure 6) does not show a single sharp peak instead it is more like a long trough, leading to a more negative AUC, which differs from the pattern in Roberts et al. (2014).

Patient 11 showed multiple significant correlations in the ipsilateral condition with stimuli presented at the left fingers (see Table 6) in two different time-intervals. We will focus on the later significant time-interval (250–750 ms), the expected time range of the P300, because the whole post-stimulus epoch (0–800 ms) was significant which makes the results of post-stimulus variables less meaningful. In the expected P300 interval the relative alpha band power correlated negatively with the maximal amplitude with more post-stimulus negative amplitudes when pre-stimulus

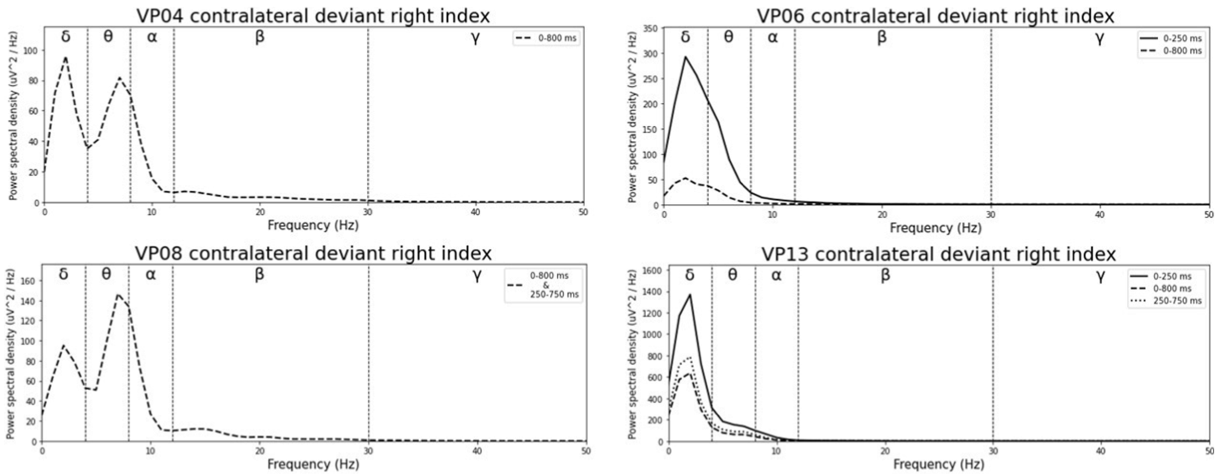

FIGURE 13
Averaged pre-stimulus frequency bands for contralateral stimulation with the deviant at the right index.

alpha power was higher. Jasiukaitis and Hakerem (1988) results showed a positive relationship between pre-stimulus spectral power in the alpha band and amplitude of the P300 in an auditory paradigm. Our finding is in line with the finding of Jasiukaitis and Hakerem (1988). The visual inspection of sERPs in the post-stimulus epoch (see Figure 2) shows inverse curves to expected courses of a healthy subject but with time-intervals where brain-responses to the stimuli are significantly different. The negative correlation can be reduced to the inverse amplitude of the P300. This outcome is not unusual. ERPs in DoC are different from ERPs of healthy participants. They are smaller, delayed and sometimes their polarity is inversed (Perrin et al., 2006; Pokorny et al., 2013).

The results of patient 13 are listed in Table 7 for the ipsilateral condition with stimuli presented at the right fingers and in Table 9 for the contralateral condition with deviants presented at the right index. In the ipsilateral condition results showed a positive correlation between pre-stimulus relative alpha power and the maximal amplitude in both significant time-intervals (77–250 ms & 77–375 ms). The more relative power of the alpha-band the less negative post-stimulus N140 amplitudes. This finding is in line with the results of Roberts et al. (2014). They could show that, in a visual stimulation paradigm, the N100 amplitude increases with decreased pre-stimulus alpha power. Although the post-stimulus sERP curves are unusual, we could show that the post-stimulus N140 of this patient is affected by pre-stimulus oscillations in a similar way as has been previously reported in healthy subjects. In the contralateral condition results showed a positive correlation between pre-stimulus relative power of the beta band and the post-stimulus AUC in the significant interval (250–750 ms). The grand-average of post-stimulus ERPs (see Figure 7) shows a continuous negativity of the ERP but the more beta activity in pre-stimulus epoch the more positive the ERP becomes. Still, the maximum amplitudes did not correlate with beta so this outcome is hard to interpret. It is known that, at least in healthy people, pre-stimulus alpha modulates post-stimulus P300 in the auditory and visual paradigm whereas beta modulates earlier ERPs such as P1, N1, and P2 (De Blasio and Barry, 2013).

Limitations and conclusion

We could show that pre-stimulus oscillations can be related to post-stimulus sERP also in patients in DoC. We found multiple correlations in the results of individuals which are in line with findings from studies with healthy volunteers. We only found significant differences between the standard and the deviant stimulus in six out of 14 subjects. This finding is consistent with other studies that have shown that not all patients in DoC who participated in an experiment had post-stimulus ERPs (e.g., Schoenle and Witzke, 2004; Kotchoubey et al., 2005). In most of the patients who had detectable sERPs, we were then also able to find a statistical relationship between pre-stimulus EEG power and post-stimulus deviant detection, although the direction did not always correspond to the direction previously described in healthy people. Given that we calculated 15 correlations for each patient, some chance correlations are to be expected. On the other hand, given the general changes in DoC patients' EEG spectra, some atypical, but still functional brain dynamics are also likely. Furthermore, it is challenging to interpret the correlative outcomes for longer time-intervals (e.g., 0–800 ms) in post-stimulus epochs due to the conflation of early and late ERPs. Of note, at present all patients who showed detectable sERPs and subsequent correlations between pre- and post-stimulus brain activity were diagnosed as MCS, leaving open whether similar relationships might be present in UWS This could be tested in further studies and because our results are quite variable, larger groups of DoC patients would be desirable. So far, most ERP-studies in DoC are primarily conducted with auditory paradigms because patients in UWS and MCS cannot always control their eye movements or maintain eye-opening and fixate to a specific point in their visual field. The somatosensory modality might be a good alternative to the visual and even auditory paradigm as it is a basic sensory modality for interaction with both the physical and social

TABLE 6 Spearman's rho of the correlation between pre-stimulus frequency band power and post-stimulus variables for the ipsilateral stimulation at the left fingers.

#02 (250–750ms)	α	β	γ	δ	θ
AUC	−0.286	−0.571	−0.607	0.071	−0.071
Max. Amp.	−0.107	−0.464	−0.429	−0.107	0.107
Lat. Max. Amp.	0.394	0.374	0.374	−0.236	0.236
#04 (0–250ms)	**α**	**β**	**γ**	**δ**	**θ**
AUC	**0.363***	**0.585*****	**0.330***	**−0.344***	−0.018
Max. Amp.	0.218	**0.359***	0.164	**−0.344***	0.013
Lat. Max. Amp.	0.290	**0.336***	0.163	−0.205	−0.154
#04 (0–800ms)	**α**	**β**	**γ**	**δ**	**θ**
AUC	**0.503****	**0.499****	0.283	−0.293	0.025
Max. Amp.	**0.377***	0.292	0.153	−0.194	−0.048
Lat. Max. Amp.	0.250	0.107	−0.010	−0.059	0.060
#08 (0–250ms)	**α**	**β**	**γ**	**δ**	**θ**
AUC	0.133	0.010	0.010	**0.342***	−0.281
Max. Amp.	0.118	−0.225	−0.175	−0.216	−0.028
Lat. Max. Amp.	−0.164	0.114	0.008	0.084	−0.206
#08 (0–800 and 250–750ms)	**α**	**β**	**γ**	**δ**	**θ**
AUC	0.138	0.092	0.047	−0.012	−0.140
Max. Amp.	0.039	0.054	0.008	0.056	−0.033
Lat. Max. Amp.	**0.334***	0.151	0.186	−0.114	−0.117
#11 (0–800ms)	**α**	**β**	**γ**	**δ**	**θ**
AUC	**−0.366***	−0.087	−0.151	0.219	−0.175
Max. Amp.	**−0.390***	−0.303	−0.233	**0.383***	−0.313
Lat. Max. Amp.	0.059	0.047	0.084	−0.053	−0.010
#11 (250–750ms)	**α**	**β**	**γ**	**δ**	**θ**
AUC	−0.314	0.001	−0.105	0.170	−0.180
Max. Amp.	**−0.345***	−0.221	−0.198	0.292	−0.224
Lat. Max. Amp.	0.104	0.147	0.010	−0.108	−0.061

*p < 0.05, ** $p < 0.01$, and *** $p < 0.001$. Significant correlations are highlighted in bold.

TABLE 7 Spearman's rho of the correlation between pre-stimulus frequency band power and post-stimulus variables for the ipsilateral stimulation at the right fingers.

#13 (0–250ms)	α	β	γ	δ	θ
AUC	0.368	0.277	0.116	−0.012	−0.112
Max. Amp.	**0.445***	0.232	0.062	0.019	−0.186
Lat. Max. Amp.	−0.024	0.158	0.157	−0.230	0.252
#13 (0–800ms)	**α**	**β**	**γ**	**δ**	**θ**
AUC	0.335	0.272	0.070	−0.048	−0.042
Max. Amp.	**0.411***	0.295	0.036	−0.008	−0.109
Lat. Max. Amp.	−0.132	0.102	0.087	−0.158	0.211

* $p < 0.05$. Significant correlations are highlighted in bold.

environment and covers large cortical representation areas. Therefore, it should be considered for further investigations in patients in DoC. Our findings suggest that pre-stimulus oscillations do affect post-stimulus sensory and cognitive processing, albeit in a highly individual manner. Determining such individual relationships might help determine optimal stimulation windows for DoC patients, thereby increasing the likelihood of stimulation being processed and helping patients along the way to recovery.

TABLE 8 Spearman's rho of the correlation between pre-stimulus frequency band power and post-stimulus variables for the contralateral stimulation with the deviant at the left index.

#06 (0–250ms)	α	β	γ	δ	θ
AUC	−0.268	−0.111	−0.178	0.147	−0.113
Max. Amp.	−0.231	−0.104	−0.220	0.081	−0.012
Lat. Max. Amp.	−0.151	−0.119	−0.046	0.080	−0.041
#06 (0–800ms)	**α**	**β**	**γ**	**δ**	**θ**
AUC	−0.281	−0.022	−0.116	0.080	−0.010
Max. Amp.	−0.177	−0.099	−0.127	0.020	0.004
Lat. Max. Amp.	−0.060	−0.075	0.043	−0.057	−0.003
#06 (250–750ms)	**α**	**β**	**γ**	**δ**	**θ**
AUC	−0.197	−0.055	−0.080	0.035	0.046
Max. Amp.	−0.149	−0.156	−0.118	0.018	0.000
Lat. Max. Amp.	0.140	0.054	0.143	−0.093	0.017
#08 (0–250ms)	**α**	**β**	**γ**	**δ**	**θ**
AUC	**−0.353** *	0.122	0.023	−0.196	0.275
Max. Amp.	−0.058	0.267	0.041	−0.168	0.029
Lat. Max. Amp.	−0.213	−0.104	−0.012	0.091	0.125

*$p < 0.05$. Significant correlations are highlighted in bold.

TABLE 9 Spearman's rho of the correlation between pre-stimulus frequency band power and post-stimulus variables for the contralateral stimulation with the deviant at the right index.

#04 (0–800ms)	α	β	γ	δ	θ
AUC	**−0.358***	−0.190	−0.265	**0.346***	**−0.333***
Max. Amp.	**−0.377***	**−0.354***	**−0.374***	0.284	−0.141
Lat. Max. Amp.	−0.089	−0.101	−0.102	0.022	0.073
#06 (0–250ms)	**α**	**β**	**γ**	**δ**	**θ**
AUC	−0.038	−0.014	−0.189	−0.050	0.041
Max. Amp.	−0.057	−0.037	−0.215	−0.251	0.266
Lat. Max. Amp.	0.078	−0.236	−0.143	−0.136	0.158
#06 (0–800ms)	**α**	**β**	**γ**	δ	**θ**
AUC	−0.163	−0.003	−0.021	−0.296	**0.349***
Max. Amp.	−0.089	0.055	−0.042	−0.321	**0.370***
Lat. Max. Amp.	0.288	0.270	0.006	−0.089	0.026
#08 (0–800ms and 250–750ms)	**α**	**β**	**γ**	δ	**θ**
AUC	0.045	−0.074	−0.263	−0.059	0.178
Max. Amp.	0.158	−0.030	−0.234	0.063	−0.024
Lat. Max. Amp.	−0.066	0.019	−0.085	−0.274	0.186
#13 (0–250ms)	**α**	**β**	**γ**	δ	**θ**
AUC	0.160	0.206	0.270	−0.248	0.231
Max. Amp.	−0.069	−0.004	0.036	−0.102	0.134
Lat. Max. Amp.	0.051	0.269	0.130	−0.151	0.199
#13 (0–800ms)	**α**	**β**	**γ**	δ	**θ**
AUC	0.220	0.294	0.290	−0.237	0.220
Max. Amp.	0.080	0.126	0.143	−0.073	0.066
Lat. Max. Amp.	−0.098	0.072	0.065	−0.019	0.059
#13 (250–750ms)	**α**	**β**	**γ**	δ	**θ**
AUC	0.247	**0.394***	0.351	−0.267	0.238
Max. Amp.	0.050	0.234	0.171	−0.110	0.085
Lat. Max. Amp.	−0.134	−0.148	−0.205	0.190	−0.182

*$p < 0.05$. Significant correlations are highlighted in bold.

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 Ethik-Kommission der Universität Bielefeld. The patients/participants provided their written informed consent to participate in this study.

Author contributions

LL and JK contributed to the conception and design of the study. LL, IS, and AM organized the database. LL performed the statistical analysis and wrote the manuscript. 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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Dysfunctional connectivity as a neurophysiologic mechanism of disorders of consciousness: a systematic review

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Introduction: Disorders of consciousness (DOC) has been an object of numbers of research regarding the diagnosis, treatment and prognosis in last few decades. We believe that the DOC could be considered as a disconnection syndrome, although the exact mechanisms are not entirely understood. Moreover, different conceptual frameworks highly influence results interpretation. The aim of this systematic review is to assess the current knowledge regarding neurophysiological mechanisms of DOC and to establish possible influence on future clinical implications and usage.

Methods: We have conducted a systematic review according to PRISMA guidelines through PubMed and Cochrane databases, with studies being selected for inclusion via a set inclusion and exclusion criteria.

Results: Eighty-nine studies were included in this systematic review according to the selected criteria. This includes case studies, randomized controlled trials, controlled clinical trials, and observational studies with no control arms. The total number of DOC patients encompassed in the studies cited in this review is 1,533.

Conclusion: Connectomics and network neuroscience offer quantitative frameworks for analysing dynamic brain connectivity. Functional MRI studies show evidence of abnormal connectivity patterns and whole-brain topological reorganization, primarily affecting sensory-related resting state networks (RSNs), confirmed by EEG studies. As previously described, DOC patients are identified by diminished global information processing, i.e., network integration and increased local information processing, i.e., network segregation. Further studies using effective connectivity measurement tools instead of functional connectivity as well as the standardization of the study process are needed.

KEYWORDS

disorders of consciousness, functional connectivity, disconnection syndrome, fMRI, EEG, neuromodulation

Introduction

Consciousness is frequently described as a compound phenomenon and still represents one of the major scientific challenges. In the beginning, many efforts have been made to find the neuroanatomical correlate of consciousness. Unfortunately, it is not that simple. Consciousness is a process rather than an object, and its main characteristic is "*one's sense of being a unified person despite being confronted with a diversity of sense impressions from different sense organs*" (Smythies et al., 2013). Among number of theories that have been suggested to elaborate the phenomenon of consciousness is neuronal oscillation theory (Seth and Bayne, 2022). It may be the one that provides the best description of the process itself. Vice versa, disrupting these processes, i.e., functional disconnection, plays a critical role the pathogenesis of disorders of consciousness (DOC) (Fernández-Espejo et al., 2012). In this systematic review, we gather evidence regarding patterns of dysfunctional connectivity in patients with disorders of consciousness.

Basically, consciousness represents the state of self-awareness and environment awareness (Laureys et al., 2010). Conscious behavior requires both wakefulness and content awareness, such as cognitive, affective, or sensory experience. Traumatic brain injury is a disastrous incident causing disruption of the brain's arousal and awareness systems, moderated by the brainstem and cortex. The severest injuries result in prolonged DOC consisting of the vegetative state (VS) and the minimally conscious state (MCS). In addition, VS is recently referred as post-coma unawareness or unresponsive wakefulness syndrome (UWS) (Laureys et al., 2010). Diagnosis of VS is based on "*no evidence of self or environment awareness, as well as absence of sustained, reproducible, purposeful, or voluntary behavioural response to visual, auditory, tactile, or noxious stimuli and language comprehension or expression*" (Multi-Society Task Force on PVS, 1994a,b). The MCS is presented by "*partial preservation of awareness of self and environment, responding intermittently but reproducibly to verbal command and demonstrating some degree of basic language comprehension*" (Giacino et al., 2002). Moreover, the MCS has been additionally classified in the MCS minus and MCS plus state, indicating MCS plus patients as one who can intelligibly or intentionally verbalize and communicate (Bruno et al., 2011a). The confusion in the diagnosis of MCS and VS could be done in patients with locked-in syndrome (Bruno et al., 2011b). The patients in locked-in syndrome are awake and conscious but selectively deafferented by lesion of corticospinal and corticobulbar pathways. They cannot speak, move limbs, or have facial movements (Bodart et al., 2013).

The possibility of consciousness recovery depends on the brain destruction degree and lesion etiology; still, after a year of unresponsive behavior, odds for recovery decrease (Multi-Society Task Force on PVS, 1994a,b; Giacino et al., 2014).

Over decades, a number of different clinical scales have been used to classify DOC patients. The latest scale to evaluate consciousness state nowadays is the JFK Coma Recovery Scale-Revised (CRS-R), based on the Disability Rating Scale (DRS) and the Coma Recovery Scale (CRS), including scoring of auditory, visual, motor, verbal functions, responsiveness, and arousal (Kalmar and Giacino, 2005). CRS-R total sum ranges from 0 (worst) to 23 (best), with specific subscores revealing MCS minus, MCS plus, or emergence MCS form. Similar to the DRS, the Coma/Near Coma (CNC) scale is associated with patients health status, course of treatment, outline and to the fundamental neurophysiological impairment (Rappaport, 2005).

Although effective treatment for this group of patients is not yet available, some progress has been made by introducing neuromodulation techniques, in the first-place deep brain stimulation (DBS). Historically, Morruzi and Magoun first showed brainstem reticular formation and thalamus stimulation of the anesthetized animals leading to desynchronization of low-frequency disorganized electroencephalograph (EEG) activity and background activity comparable to the patterns in wakeful states (Moruzzi and Magoun, 1949). Mentioned experiments, alongside other findings, aimed promote the concept of a reticular ascending activating system (RAAS) controlling sleep–wake cycle (Tapia et al., 2013). DBS emerged in 1960 as a potential therapeutical method and since then has been used in the thalamus, upper brainstem, high spinal cord, and associated targets in the basal ganglia (nowadays mainly in the central thalamic nucleus) in attempts to restore consciousness (Chudy et al., 2020).

In mentioned primary, as well as in later studies, the vast majority of patients manifest eye-opening and incomplete movements when receiving stimulation consistent with an arousal effect. Nevertheless, arousal effect occurrence did not predict any improvement. Furthermore, arousal effect, including eye-opening, autonomic function changes and EEG desynchronization characterize a fundamental and wide activation of the forebrain, brainstem, and spinal cord systems. It seems that apparent wakefulness and incomplete movements do not demonstrate higher integrative brain function recovery – it just gives evidence that DBS electrodes hit the target (Chudy et al., 2018).

Several research groups are continuously making efforts to improve patient selection criteria for DBS as well as neurostimulation protocols. The inclusion criteria for such procedures traditionally require the presence of multimodal evoked potentials (somatosensory, motor and visual evoked potentials), which are believed to be gross neurophysiological markers of cortical functional integrity.

Today, however, with the rapid advances in computing and neuroimaging techniques to test brain connectivity, we are faced with enormous amounts of data and novel mathematical modeling techniques. All this information might improve our understanding of underlying pathophysiological processes and lead us to better decision-making, but the careful interpretation is crucial.

Given that the estimated number of glia and neuronal cells in the human brain is around 10^{11} and there are roughly 10^{14} synaptic connections, it is impossible (and even pointless) to investigate disrupted connectivity patterns at a single neuron level (Dicke and Roth, 2016; von Bartheld et al., 2016). Therefore, the common goal is to make as precise as possible approximations of neuronal interactions while trying to avoid data overwhelming. Before even doing so, it is necessary to take a well-organized approach to different scale neuronal units within the appropriate space and time frame. Moreover, the fMRI's high spatial resolution and the EEG's high temporal resolution are complementary for understanding neural processes (Itthipuripat et al., 2019).

Therefore, the aim of this paper is a systematic review of conceptual framework derived from fMRI and EEG studies on

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DOC patients, current advances in the understanding of DOC pathophysiology and diagnostic role of neuromodulation protocols.

Methods

Search strategy

We have conducted a systematic review according to PRISMA guidelines (Page et al., 2021). The search was done on articles published up to January of 2023. We searched the PubMed and Cochrane databases for articles using the following keywords: "disorders of consciousness" and "functional connectivity," "vegetative state" and "functional connectivity," "unresponsive wakefulness syndrome" and "functional connectivity" and "minimally conscious state" and "functional connectivity."

After we applied appropriate filters, the search rendered 367 records. The studies were then selected based on the following inclusion and exclusion criteria (Figure 1). Articles were first screened by title and abstract, followed by full-text checking for their eligibility. Four authors selected the articles independently (PG, RM, CD, and DV), and final inclusion was done by agreement.

Inclusion and exclusion criteria

Studies accepted for inclusion were: (a) studies with patients diagnosed with DOC; (b) studies published up to January of 2023; (c) published in the English language; (d) published in indexed and peer-reviewed journals; and (e) evaluated consciousness using validated scales and scoring systems (usually by CRS-R scale).

Exclusion criteria include: (a) studies published in regional languages other than English, (b) examination in an acute state or during sedation/anaesthesia, and (c) no clear methodology or testing parameters described. Additionally, we excluded papers on basic research, brain-computer interfaces, machine learning, or pharmacological treatment response.

Studies were checked for quality, and finally, 89 studies were included (Figure 1).

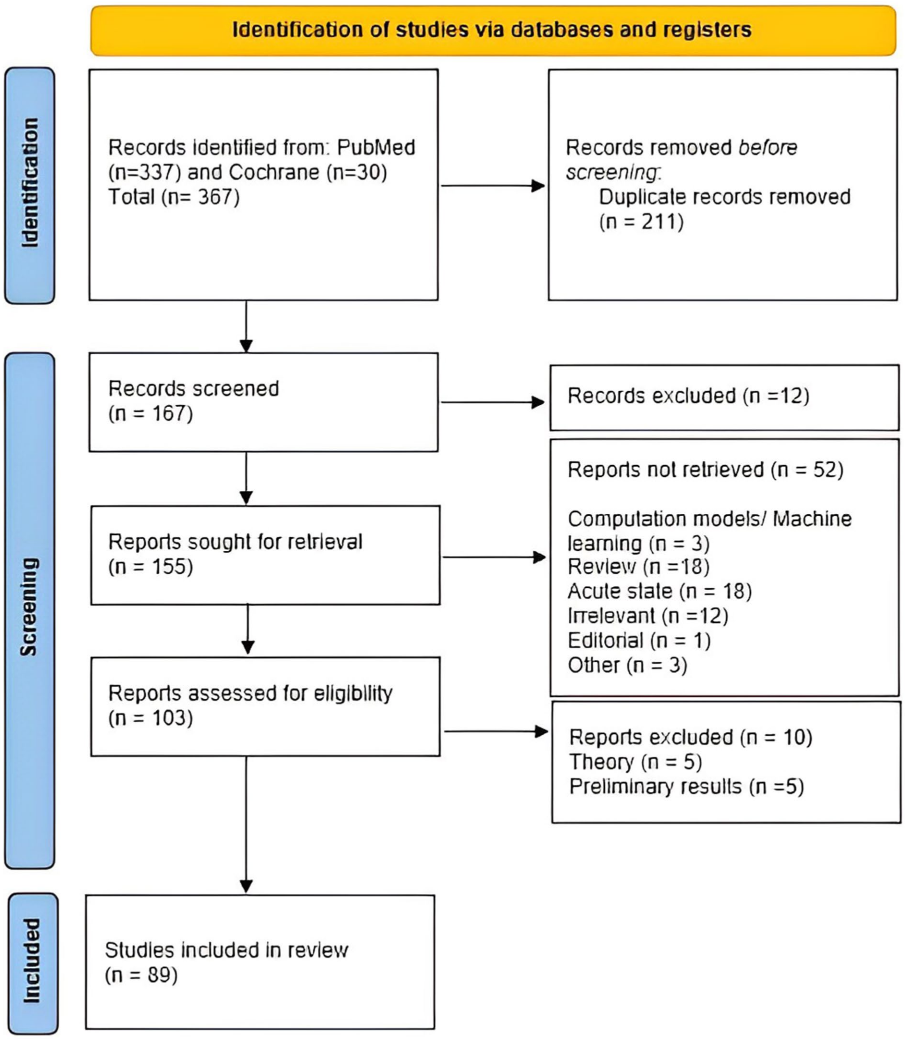

FIGURE 1
Prisma flow chart of the systematic review.

Conceptual frameworks for DOC research

We find increasing evidence linking DOC with interference in brain connectivity both locally and connecting remote brain areas. Disconnection generally indicates brain dysfunction following lesions to white matter connections (Catani and Ffytche, 2005). Theoretically speaking, consciousness has two different and separated components, both level and content (Laureys, 2005). While the consciousness level describes the extent of arousal or wakefulness, the content portray subjective experience or awareness. Anatomically, it is feasible to connect wakefulness with thalamocortical, vertical connectivity, while awareness rely on cortico-cortical, horizontal connectivity (Modolo et al., 2020). Wakefulness depends critically on thalamocortical connectivity, which is highly dependent on RAAS. Neurons of the human thalamic reticular nucleus (RT) are considered selectively vulnerable to ischemic neuronal damage following cardiac arrest (Ross and Graham, 1993) (Figure 2).

So, despite severe and irreversible damage of RT, cortical neurons and their connections with the thalamus may still be preserved. These pathological findings explain the fact that in some patients with severe DOC (VS and MCS), cortical somatosensory evoked potentials can still be elicited. RAAS bind together different cortical regions, and ischemic injury selectively lesson RAAS while leaving some cortical neurons intact, resulting in loss of consciousness of various degrees. On the other hand, awareness is mostly related to frontoparietal associative cortices. It is later subdivided into an internal awareness network (mostly midline regions), and an external awareness network (mostly lateral frontoparietal hemispheric regions).

In the last decades, an extraordinary flourishing of structural and functional imaging techniques, combined with mathematical models, offered us new ways for further advances in lesion mapping. Network theory is an umbrella term due to mathematical theory for the networks description. Therefore, a number of non-invasive novel techniques and methods analysis have provided whole-brain connectivity patterns inspection using electrical and magnetic brain activity (i.e., EEG, MEG), as well as cerebral blood flow changes as quantification of neural activity (fMRI) for network construction (Stephan et al., 2000). Thus, the network nodes are EEG electrodes, MEG sensors, and fMRI voxels or regions of interest, containing complex signal of the neurons activity (Figure 3).

To describe the relationship between pairs of network nodes, the term functional connectivity (FC) has been introduced. However, it is essential to point out that functional connectivity does not necessarily correspond to structural (anatomical) connections. Understanding the relationship between structural and functional organization represents one of the most critical challenges in neuroscience. In contrast to functional connectivity, effective connectivity includes information about the direction of the connection. Even so, present-day fMRI resting-state methods for causal connectivity are limited (Ramsey et al., 2014).

The network model is convenient for describing static brain properties, but another mathematical model is introduced, the so-called neuronal oscillations model, to evaluate dynamic interactions. Neural oscillations are widespread phenomena ranging from the microscopic level of individual neuron electric state oscillations to large neuronal ensembles macroscopic oscillations.

The recuring presynaptic neurons firing generates oscillatory activation, while the synchronized activity of several neurons generate macroscopic oscillations. Mentioned was first observed by Hans Berger in 1924 in EEG, leading to the brain rhythms classification into frequency bands. Rather than using single-neuron models, it is helpful to emerge a low-dimensional models to imitate the assembly of number of near-identical interconnected neurons with a preference to operate in synchrony. These neural mass models are composed out of state variables that track coarse-grained measures of the average membrane potential, firing rates, or synaptic activity (Ashwin et al., 2016).

> "*What fires together, wires together*" is a well-known (but simplified) Hebb's principle and, while mnemonic, could be very misleading: if neurons activations occur at the same time, the activation of one neuron cannot cause activation of the other. The actual ' 'Hebb's quote was: *"when an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is 'increased".*

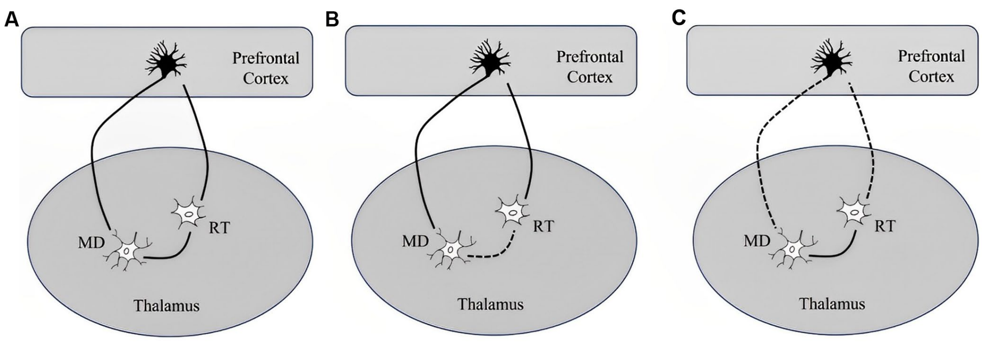

FIGURE 2
Simplified illustration of network including a thalamic relay neuron (MD), reticular neurons (RT), and a corticothalamic pyramidal neuron and their response to a short or long duration of cardiac arrest according to Ross and Graham study (Ross and Graham, 1993): **(A)** network segregation with intact RT and MD, **(B)** network integration with selective degeneration of RT following a short-term ischemia leaving cortico-thalamic reticular and thalamo-cortico-reticular innervation preserved, and **(C)** dysfunctional network organization in DOC characterized by impaired network integration, increased network segregation and topological reorganization with selective sparing of the RT following long-term complete ischemia causes the death of corticothalamic pyramidal neurons and thalamic relay neurons in the MD.

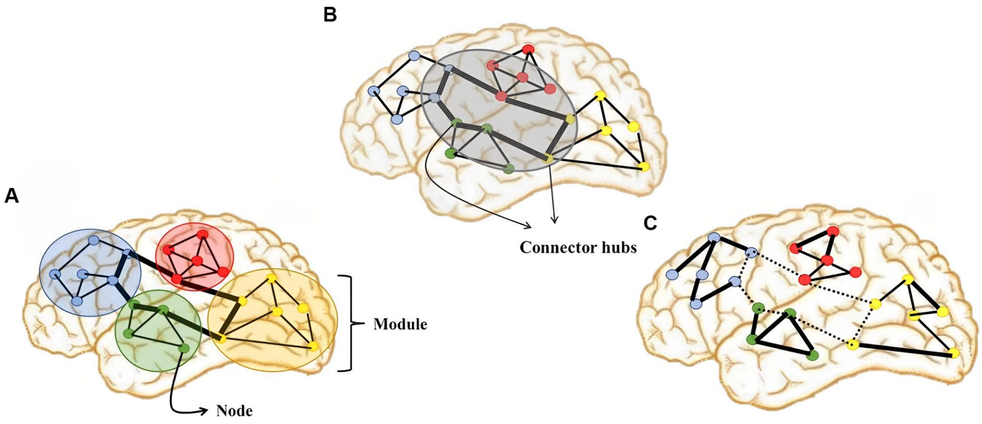

FIGURE 3
Illustration of graph-theoretic measures showing: **(A)** network segregation, **(B)** network integration, and **(C)** dysfunctional network organization in DOC which is characterized by impaired network integration, increased network segregation and topological reorganization.

> An attentive reveals the principle of causality and consistency (Keysers and Gazzola, 2014).

Results

Structural neuroimaging changes

Structural imaging approaches have not identified specific and consistent focal abnormalities, but there is evidence of diffuse irregularity in volume of both grey and white matter and connectivity in patients with disorders of consciousness (DOC) (Snider and Edlow, 2020). Diffusion MRI, usually processed with tractography, is widely used in DOC patients to investigate the integrity of white matter, i.e., structural connectivity (Snider and Edlow, 2020). Recently, ultra-high-field MRI at 7 Tesla in combination with Graph-theoretical analysis and network-based statistics was introduced to explore the structural network and white matter microstructure alterations (Tan et al., 2019). Network-based statistical analysis revealed significantly decreased structural connectivity, mainly in the frontal cortex, limbic system, occipital, and parietal lobes (Tan et al., 2019).

Functional neuroimaging changes

The signals obtained from PET, fMRI, and fNIRS rely on the detection of localized alterations in cerebral blood flow that are linked to neural activity. Functional neuroimaging investigations in DOC can be categorized into two types: resting-state studies and stimulus-based studies (Supplementary material). Resting-state functional connectivity, which does not require active participation, is especially convenient in this group of patients (Soddu et al., 2015).

The introduction of fMRI has brought significant advancements, with the majority of studies on patients with DOC relying on fMRI. While fMRI has limited temporal resolution (within a few seconds), it offers excellent spatial resolution (within millimeters). PET, despite being a more robust technique than fMRI, seems to be more sensitive than active fMRI in aiding the clinical diagnosis of DOC patients, although it may have led to a higher rate of false positives (Stender et al., 2014; Soddu et al., 2015).

Historically, the analysis of brain networks has focused on their anatomical organization. However, there is a recent emerging trend that highlights the importance of examining the topological aspects of these networks. Topological metrics allow us to understand the relationships between elements within a system, irrespective of their physical placement. In this section, we will first discuss the patterns of dysfunctional connectivity observed in the anatomical organization of brain networks, followed by an exploration of the subsequent topological reorganization. PET has been used to assess cerebral metabolic activity in DOC patients and has shown modified connectivity between intralaminar nuclei of the thalamus and prefrontal and anterior cingulate cortices in the VS, while not after consciousness recovery (Laureys et al., 2000). Hypermetabolism in the RAAS and impaired functional connectivity between the RAAS and the precuneus have also been reported (Boly et al., 2009).

Lacking cortico-thalamic and reduced cortico-cortical connectivity patterns were also described in fMRI studies (Boly et al., 2009), as well as a considerable decrease in both specific and nonspecific thalamic functional connections (Zhou et al., 2011).

Depending on the analysis method, there are several strongly connected resting state neural networks (RSNs) of sensory and cognitive relevance including the default mode network (DMN), somatomotor network, dorsal attention network, ventral attention network, limbic system network, fronto-parietal and visual network, that are widely accepted (Yeo et al., 2011). These networks are composed of anatomically separated, but functionally connected regions. Recently, a triple-network model including DMN, salience network, and executive control network has been proposed for further investigation (Wang et al., 2022). Numerous studies have recognized the importance of the DMN network in the pathogenesis of disorders of consciousness. This network is composed mostly of associative cortex in the midline including posterior cingulate cortex (praecuneus), medial prefrontal cortex, and medial, lateral and inferior parietal cortex (Broyd et al., 2009). In healthy subjects, the DMN shows increased activity at rest, in the absence of cognitive tasks (Greicius et al., 2003). Furthermore, the DMN is involved in self-referential processing (internal awareness) (Fingelkurts et al., 2016), while the associative cortex on the convexity (mostly frontoparietal network) is associated with external awareness (Laureys et al., 2004; Vanhaudenhuyse et al., 2011). Hypofunctional DMN is seen as a marker of impaired consciousness (Crone et al., 2011; Fernández-Espejo et al., 2012). Impaired internal DMN connectivity is accompanied by reduced connectivity with all other cortical regions and the mediodorsal thalamus, respectively (He et al., 2015).

However, there is evidence of globally impaired functional connectivity within multiple RSNs (Demertzi et al., 2014). Pathologic intrinsic connectivity is characterized by hypoconnectivity or hyperconnectivity patterns in different RSNs. Hypoconnectivity is observed mainly in DMN and frontoparietal associative networks (Cauda et al., 2009). These findings are supported by PET studies showing that preserving a certain level of brain metabolism in the fronto-parietal network can greatly enhance the likelihood of recovering behavioral indicators of consciousness in individuals diagnosed with UWS (Stender et al., 2014).

Moreover, intrinsic functional connectivity strength in many brain regions significantly correlates with consciousness level and recovery outcome (Qin et al., 2015). Among them, DMN and auditory networks have the highest precision in differentiating DOC patients from healthy controls (85.3%) and VS from MCS patients (>80%) (Demertzi et al., 2014, 2015). On the other hand, increased connectivity (hyperconnectivity) is observed in the brainstem areas, cerebellum, and some limbic structures (Di Perri et al., 2013; Chen et al., 2018). Not only that intrinsic connectivity (in specific RSNs) is disturbed, but there is also abnormal interaction between different RSNs. Different degrees of consciousness impairment are associated with specific connectivity patterns between RSNs clinical DOC symptoms of DOC changes between MCS and VS, followed by further weakness of the functional connectivity, and resulting in two connections systems becoming inhibitory altogether in VS (Di Perri et al., 2013; Chen et al., 2018). Dysfunctional connectivity in VS is characterized by changes in network correlations, appearance of pathological network correlations, and pathological imbalance between positive and negative correlations in network (Di Perri et al., 2018).

Another approach to global network analysis is connectome-based. Brain networks have a topological organization, consisting of nodes that are grouped into modules, while extensively connected nodes are called the "hubs" of the connectome. The hubs play a critical part in coordinating communication between distant parts of the brain (Rawls et al., 2022). The higher complexity of networks is associated with higher levels of consciousness (Varley et al., 2020). However, DOCs are characterized not only by lower system complexity but there is evidence of whole-brain topological reorganization (Coppola et al., 2022). The level of consciousness deterioration is associated to decrease of integration in sensory and cognitive related RSNs, segregation decreases and increases in centrality for sensory-related RSNs (Martínez et al., 2020).

Considering both local (intrinsic) and global network alterations, recent studies proposed that regions sensorimotor integration of high arrangement play a crucial part in supporting consciousness. The view is supported by evidence of a significantly reduced number of connections in the sensorimotor cortex and their correlation with levels of consciousness (Qin et al., 2021). Furthermore, stimulus-related fMRI studies using the auditory, visual, or somatosensory paradigm demonstrated activation in the primary sensory areas (lower-level), but without activation of higher-level associative zones that process external signals (Kotchoubey et al., 2013). This corroborates the hypothesis that loss of consciousness might correlate with the disruption of higher-order associative cortices (Amico et al., 2017).

EEG findings in DOC

Frequency band analysis provides valuable insights into assessing consciousness. Studies have revealed decreased alpha power and increased delta power in patients with the UWS compared to those in the MCS (Fingelkurts et al., 2012). Furthermore, research has linked specific frequency bands to brain network measures and their association with consciousness. Initial investigations focused on the alpha and beta bands, which are implicated in conscious interactions, self-referential thoughts, internal attention, and sensory-motor processing (Fingelkurts et al., 2012). Connectivity alterations within the DMN occur in the alpha and beta bands among patients with DOC (Fingelkurts et al., 2012). UWS patients exhibit reduced connectivity compared to MCS patients in these frequency bands, regardless of the etiology of brain damage (Fingelkurts et al., 2013). Notably, strong connectivity within alpha frontoparietal networks is correlated with the level of consciousness. In the ß1 band, UWS patients show decreased functional connectivity, particularly in the interhemispheric frontoparietal network (Cacciola et al., 2019). Additionally, UWS patients demonstrate smaller functional connectivity in the alpha and gamma bands, while gamma-band connectivity strength correlates with behavioral responsiveness (Naro et al., 2018). Conversely, MCS patients exhibit connectivity in both short- and long-range networks across different frequency bands (Cacciola et al., 2019). Theta and delta bands are less useful for differential diagnosis in DOC; however, higher cortical functional connectivity in the delta-theta band has been observed in MCS compared to UWS, serving as a robust indicator of conscious states (Rizkallah et al., 2019). In summary, frequency bands play a crucial role in assessing consciousness, with distinct connectivity patterns observed between UWS and MCS patients in different frequency bands (Supplementary material).

The absence of consciousness in patients in the VS is paralleled by impairment in the overall EEG operational architecture (Lehembre et al., 2012; Fingelkurts et al., 2013; Bourdillon et al., 2020). Neuronal assemblies in these patients become smaller, their lifespan is shortened, and they become highly unstable and functionally disconnected (desynchronized). On the other hand, patients in the MCS show a partial restoration of EEG operational architecture, with increased size, lifespan, and stability of neuronal assemblies, as well as an increased number and strength of functional connections among them (Fingelkurts et al., 2013).

Brain networks have traditionally been analysed in anatomical space, but recent research has highlighted the importance of considering the topological aspects of brain networks. Further studies explored even more detailed frameworks to evaluate functional connectivity, for example using multiplex and multilayer network analyses of frequency-specific and area-specific networks (Naro et al., 2021). Alterations in brain networks are not limited to global changes but also manifest in specific subnetworks or regions. It is found that the level of consciousness is associated with the DMN subnetwork.

Patients with UWS and MCS display decreased connectivity within the DMN, which is partly attributed to impaired structural connectivity and compromised white matter integrity (Fingelkurts et al., 2012). In addition to the DMN, the frontoparietal (FP) networks play a crucial role in behavioral responsiveness, as measured by the CRS-R, in patients with DOC (Cacciola et al., 2019). Selective disruptions in FP regions are observed in UWS patients compared to MCS patients, indicating a breakdown of long-range connections in favor of shorter connections. This disruption impairs multisensory integration and top-down control processes (Wu et al., 2022). The properties of EEG network topology can differentiate between patients with UWS and MCS at a group level (Cacciola et al., 2019). However, the correlation between network topology measures and behavioral responsiveness, as measured by the CRS-R, is generally weak (Cacciola et al., 2019). Furthermore, functional network switching in DOC occurs at multiple time scales. Cai et al. demonstrated that network switching in the alpha band shows a significant correlation with consciousness levels, particularly for transitions of community assignments (Cai et al., 2020). The DOC brain exhibits a dynamic balance between segregation and integration (Cai et al., 2020). Regarding sensorimotor areas, passive hand movements induce slight desynchronization over the contralateral motor cortex in patients with DOC, suggesting functional reactivity despite network disruption and isolation of the motor areas in UWS patients (Formaggio et al., 2020). Moreover, Zhang et al. conducted a microstate-based study and found that networks in DOC patients exhibit impaired global information processing (network integration) and increased local information processing (network segregation) compared to controls (Zhang et al., 2023). Decreased integration, which reflects functional connectivity between distant areas, is associated with lower levels of consciousness (Zhang et al., 2023).

Diagnostic role of neuromodulation protocols

Neuromodulation protocols could be used for diagnostic or therapeutic purposes. In this review, we will primarily discuss their diagnostic value. Several methods have been used to access functional connectivity after stimulation protocols. We can divide them into two categories: (a) non-invasive – which is transcranial magnetic stimulation (TMS), and (b) invasive: spinal cord stimulation (SCS) (Bai et al., 2017), vagus nerve stimulation (VNS), and DBS (Arnts et al., 2022; Dang et al., 2023).

The invasive techniques are used primarily for therapeutic reasons. Since it is the most common, non-invasive, and painless technique, we will discuss TMS in more detail. The main advantage of TMS-evoked EEG responses compared to resting-state FC is "active probing" of effective connectivity. In contrast to resting state EEG measurements, TMS-EEG measures and maps cortical excitability and reactivity. Three types of TMS can be distinguished: single-pulse activated once every few seconds, paired-pulse, where two pulses are activated out of phase to inhibit or excite neurons of one hemisphere or to inhibit in one while exciting in the other hemisphere, and repetitive TMS (rTMS), where pulses are sent in fast sequence (Galletta et al., 2011). It has been showed previously that high-frequency rTMS increases the excitability of cortical neurons, while low-frequency rTMS decreases their excitability. Mentioned effects continues throughout the stimulation period (Liu et al., 2018; Guo et al., 2019; Tian and Izumi, 2022). By researching the articles, we found 16 studies with TMS stimulation, including all types of stimulation protocols with different stimulation targets: left primary motor area (M1), supplementary motor area, prefrontal cortex, cerebellum, etc. (Naro et al., 2015, 2016c). Finally, research groups used different types of measurements after modulation protocols: involving clinical assessment (CSR-R) and EEG absolute power spectra and functional measurements (Bai et al., 2018; Han et al., 2022) or post-stimulus time histogram (Naro et al., 2016a), and even neuroimaging (fMRI and PET) in some studies (Lin et al., 2019).

The first observation a significantly different effect of TMS treatment comparing VS and MCS patients; there was an improvement in EEG functional connectivity and increases in power spectra in the majority of MCS patients but modest or no effect in VS patients (Carrière et al., 2020; Hermann et al., 2020; Peng et al., 2022). Therefore, the patients are also called responders and non-responders (Hermann et al., 2020; Peng et al., 2022). Second, some may probably have significant detachment between behavioral and neuroimaging because of serious motor deterioration, rather than a functional cortico-cortical connectivity malfunction (Naro et al., 2016b; Hermann et al., 2020). And third, improvement in EEG functional connectivity parameters correlated well with CRS-R clinical examination scores (Naro et al., 2015).

DBS has been shown to have significant effects on functional connectivity in patients with MCS (Arnts et al., 2022). A study by Arnts et al. found that DBS is associated with changes in functional connectivity and neural variability in MCS patients. The study demonstrated that DBS with a lower frequency and larger volume of activation was associated with a stronger increase in functional connectivity and neural variability (Arnts et al., 2022). This increase in functional connectivity was observed across all frequency bands and throughout the brain, suggesting a widespread reorganization of brain networks [1]. Additionally, Dang et al. showed that DBS improved EEG functional connectivity in patients with MCS, leading to enhanced brain networks and improved consciousness activities (Dang et al., 2023). These findings highlight the positive impact of DBS on functional connectivity in MCS patients. However, enhanced functional connectivity does not necessarily imply overall behavioral improvement (Dang et al., 2023).

However, these results must be interpreted cautiously because of the small patient samples (Zhang et al., 2020). Among other neuromodulation techniques, VNS acts in a bottom-up manner, as opposed to top-down manner techniques (like TMS) in DOC patients (Corazzol et al., 2017; Vitello et al., 2023).

Discussion

Functional connectivity studies in DOC have predominantly relied on neuroimaging techniques, with a particular focus on resting-state fMRI (Cauda et al., 2009; Crone et al., 2011; Vanhaudenhuyse et al., 2011; Fernández-Espejo et al., 2012; Demertzi et al., 2014; He et al., 2015). Resting-state fMRI has the advantage of being mature and widely available, making it a convenient choice for investigating functional connectivity in DOC patients (Demertzi et al., 2014; Qin et al., 2015). However, it is important to note that fMRI captures hemodynamic signals and cannot directly measure fast neural oscillations, which limits its ability to determine certain aspects of neural activity. Rhythmic neuronal interactions can be quantified using multiple metrics, each with their own advantages and disadvantages. The choice of which metric to use is challenging, as the literature provides numerous options with varying levels of accessibility and comparability between studies. This makes it challenging for researchers to select and justify the most appropriate metric for their study. Furthermore, the algorithmic implementation of a particular interaction metric can vary across research groups, leading to limited accessibility and comparability between studies. These factors contribute to the potential for over-interpretation of results. Additionally, determining causality in detecting true interactions is crucial, as it significantly impacts the interpretation of brain function (Fingelkurts et al., 2012; Kotchoubey et al., 2013; Amico et al., 2017; Qin et al., 2021). Despite these challenges, functional connectivity studies using fMRI have provided valuable insights into the neural mechanisms of DoC.

Initial fMRI studies revealed disruptions in functional connectivity in regions such as the basal ganglia, thalamus, and frontal cortex, shedding light on the structural basis of functional disconnection underlying these conditions. Specifically, using RSNs, studies have shown local hypoconnectivity within multiple RSNs, particularly in the DMN and frontoparietal associative networks, suggesting a breakdown in the coordination and communication between different brain regions critical for normal cognitive functioning (Cauda et al., 2009; Crone et al., 2011; Vanhaudenhuyse et al., 2011; Fernández-Espejo et al., 2012; Demertzi et al., 2014; He et al., 2015; Qin et al., 2015).

In addition to hypoconnectivity, DOC patients also exhibit local hyperconnectivity in certain regions, including limbic structures, brainstem areas, and the cerebellum. This abnormal increase in connectivity may reflect compensatory mechanisms or maladaptive processes in the brain. Abnormal interactions between different RSNs have also been observed, and these abnormal connectivity patterns have been correlated with levels of consciousness, providing valuable information about the severity of the condition and potential prognosis. Furthermore, fMRI studies have demonstrated whole-brain topological reorganization in DoC patients, particularly affecting sensory-related RSNs. This reorganization is characterized by diminished global information processing (network integration) and increased local information processing (network segregation).

In addition to fMRI, electrophysiological techniques (particularly EEG) have also been used to estimate functional connectivity in DoC (Fingelkurts et al., 2012, 2013; Naro et al., 2018; Cacciola et al., 2019; Rizkallah et al., 2019; Bourdillon et al., 2020). Although MEG has some advantages over EEG, we focus primarily on EEG studies because of limited research in DOCs. EEG offers high temporal resolution and is cost-effective, making it a promising tool in this field. Frequency band analysis shows altered power and connectivity in specific bands, such as decreased alpha power and increased delta power in patients with UWS compared to those in the MCS. Connectivity disruptions within the DMN occur in the alpha and beta bands among DOC patients, with strong connectivity within alpha frontoparietal networks correlating with the level of consciousness. It has been observed that patients in UWS exhibit impaired EEG operational architecture, with smaller and desynchronized neuronal assemblies, while MCS patients show a partial restoration of EEG operational architecture, with larger and more stable neuronal assemblies and increased functional connections (Lehembre et al., 2012; Bourdillon et al., 2020; Cai et al., 2020; Formaggio et al., 2020; Naro et al., 2021; Wu et al., 2022; Zhang et al., 2023). These alterations extend to specific brain networks, including the DMN and FP networks, and have an impact on network topology and functional connectivity. Impaired global and local information processing is observed in DOC patients, with decreased network integration and increased network segregation compared to controls.

These findings emphasize the importance of frequency-specific connectivity patterns, EEG organizational changes, and network dynamics in assessing consciousness and differentiating between DoC states. Future research aims to determine levels of functional connectivity as biomarkers for responsiveness to potential neuromodulatory interventions.

Conclusion

Connectomics and network neuroscience provide valuable quantitative frameworks for analysing dynamic brain connectivity, offering new insights into the pathophysiology of disorders of consciousness. By integrating neuroimaging and electrophysiological techniques, functional connectivity studies hold promise for enhancing diagnostic accuracy, guiding treatment approaches, and assessing prognosis in DOC patients. Functional connectivity studies, particularly those conducted using resting-state paradigms, have significantly contributed to our understanding of the underlying neural mechanisms in DOC. These studies have revealed disruptions in functional connectivity, abnormal interactions between networks, and whole-brain topological reorganization.

However, several challenges need to be addressed, such as accurately extracting real signals from artifacts and irrelevant data arising from complex mathematical algorithms. To mitigate these challenges, it is essential to maintain a grounded understanding of basic neuroanatomy and neurophysiology to avoid misinterpretation of the data.

Considering that a significant number of patients exhibit a higher degree of preserved consciousness than clinically classified, functional connectivity techniques can aid clinicians in avoiding misdiagnosis. Expanding research on EEG functional connectivity, given its low-cost and routine implementation, has the potential to become a new gold standard for evaluating cortical integrity, particularly due to its strong correlation with clinical CRS-R testing. However, it should be noted that improved functional connectivity observed after various neuromodulatory interventions does not necessarily imply the full restoration of consciousness levels.

In DOC both awakenees and awareness are significantly impaired. Thalamocortical as well as cortico-cortical dysconnectivity play important role in the pathogenesis of DOC. Furthermore, there is critical role of high-order sensorimotor integration in supporting consciousness. The evidence of preserved sensorimotor integration in the higher-order cortex may hint at the potential for brain recovery. Additional research is required to validate these assumptions.

Author contributions

GP designed the study and wrote the first version of the manuscript. GP, MR, VD, and DC conducted the literature research, contributed to the data analysis, study concept, and design. VD and

DC interpreted the results and revised the manuscript. All authors read and approved the final version of the manuscript as submitted.

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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/fnins.2023.1166187/full#supplementary-material

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A cross-subject decoding algorithm for patients with disorder of consciousness based on P300 brain computer interface

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Background: Brain computer interface (BCI) technology may provide a new way of communication for some patients with disorder of consciousness (DOC), which can directly connect the brain and external devices. However, the DOC patients' EEG differ significantly from that of the normal person and are difficult to collected, the decoding algorithm currently only is trained based on a small amount of the patient's own data and performs poorly.

Methods: In this study, a decoding algorithm called WD-ADSTCN based on domain adaptation is proposed to improve the DOC patients' P300 signal detection. We used the Wasserstein distance to filter the normal population data to increase the training data. Furthermore, an adversarial approach is adopted to resolve the differences between the normal and patient data.

Results: The results showed that in the cross-subject P300 detection of DOC patients, 7 of 11 patients achieved an average accuracy of over 70%. Furthermore, their clinical diagnosis changed and CRS-R scores improved three months after the experiment.

Conclusion: These results demonstrated that the proposed method could be employed in the P300 BCI system for the DOC patients, which has important implications for the clinical diagnosis and prognosis of these patients.

KEYWORDS

brain computer interface, P300, disorder of consciousness, cross-subject, EEG

1. Introduction

Coma, unresponsive wakefulness syndrome (UWS), also known as vegetative state (*VS*), minimally conscious state (MCS), and emergence from MCS are all considered disorders of consciousness (DOC) (Xiao et al., 2016). The patients with DOC are usually assessed clinically by a doctor based on a behavior scale [e.g., the Glasgow Coma Scale (GCS), the Coma Recovery Scale-Revised (CRS-R)], which is based on the doctor's empirical judgment and highly subjective (Sternbach, 2000; Kalmar and Giacino, 2005). In addition, the patients lack adequate and stable behavioral responsiveness, which leads to an extremely high percentage of vegetative state misdiagnoses by the scale's behavioral-based approach (Van Erp et al., 2014; Johnson and Lazaridis, 2018). In previous research in 2020, the researchers analyzed 137 patients with long-term DOC by using the CRS-R scale. The results showed a misdiagnosis rate of 24.7% in patients with MCS assessed by a single CRS-R scale and over 38% in patients with MCS assessed by repeated CRS-R assessments (Wang et al., 2020). Therefore, accurate clinical diagnosis of people with DOC is challenging.

To resolve these issues, several researchers have considered utilizing brain-computer interfaces (BCI) to assess the DOC patients' state. This approach can directly detect the brain's response to an external stimulus without requiring behavioral or verbal expression from the patients. In an early study (Cruse et al., 2011), a novel EEG experiment incorporating motor imagery was developed to identify command-following in the absence of obvious behavior. While assessing 16 *VS* patients, 3 of them could reliably and repeatedly produce suitable EEG responses to two different commands. This indicated that EEG technique can detect awareness in some *VS* patients. In recent years, researchers have worked more on the BCI system based on P300 and steady-state evoked potential (SSVEP) compared to other paradigms. These systems primarily utilize external stimuli to generate P300 signals or SSVEP signals from DOC patients, and then decode the signals to accomplish the assessment or communication with the patients. A visual hybrid BCI system incorporating P300 and SSVEP responses was developed to assess awareness in severely brain injured individuals by Pan et al. (2014). It could determine which photo the patient focuses on. Among 7 patients (4 *VS* and 3 MCS patients), 2 (one *VS* and one MCS patients) were able to selectively attend to their own or unfamiliar photos. Huang et al. (2021) applied a hybrid asynchronous BCI system that presents DOC patients with a new way to communicate. The patients were directed to pay attention to the squares bearing the words "Yes" and "No." Three (MCS patients) of 7 patients (3 *VS* and 4 MCS patients) could utilize their hybrid asynchronous BCI system to communicate, which demonstrates that both the P300-only and SSVEP-only systems underperformed the hybrid asynchronous BCI system. Xiao et al. (2022) developed an innovative audiovisual BCI system to model the evaluation of sound localization in CRS-R. Among 18 patients, 11 patients showed sound localization in the BCI system and 4 in CRS-R assessment. More and more efficient BCI systems begin to be applied to the auxiliary diagnosis and evaluation of the DOC patients.

While P300 is easier to stimulate compared to SSVEP, P300 signal can be stimulated in many ways, including using visual and auditory (Li et al., 2019). These make it more widely used in DOC patients. Therefore, a decoding algorithm that can accurately detect the patient's P300 signal may improve the diagnostic accuracy of the patient's current status. However, compared to healthy individuals, DOC patients have less pronounced P300 features and greater differences (Li et al., 2022). Meanwhile, DOC patients are easily fatigued, which makes data collection challenging (Wang F. et al., 2019). Most current systems basically adopt the intra-subject decoding (Murovec et al., 2020). These approaches require users to first undergo a period of calibration to train a reliable model, which largely affects the widespread adoption of BCI systems. Therefore, it would be beneficial to design an excellent cross-subject decoding algorithm for BCI on DOC patients.

In current researches, the cross-subject P300 decoding algorithms are based on healthy human data for analyzing, and convolutional neural network (CNN) is one of the most efficient decoding algorithms (Mijani et al., 2020). In 2010, Cecotti and Graser (2010) proposed a CNN-based P300 detection method, which won the 3rd BCI competition. The approach sequentially extracted channel features and temporal features using a four-layer CNN architecture, which showed CNNs could capture spatial features and potential sequence dependencies from EEG signals. However, while CNNs have increased detection precision to previously unheard-of levels, there are still obstacles to this approach. Its network accuracy depends on the training data's quantity and quality (Wang et al., 2021). Furthermore, due to the high cost of time and labor, the P300 task commonly has a little amount of high-quality data. EEGNet (Lawhern et al., 2018) was proposed as a generalized deep network, which was implemented by deeply separable convolution, and it produced satisfactory results in various EEG detections. By using original EEG information, the network can perform sequence learning directly and then generalize the acquired dependencies in the spatial domain. Abibullaev et al. (2022) used the leave-one-subject cross-validation method to test the cross-subject capability of several CNNs on four publicly available datasets. Their results indicated that EEGNet and ShallowConvNet (Schirrmeister et al., 2017) had better performance. Alvarado-Gonzalez et al. (2021) proposed a simple network, SepConv1D, which consists of a depth-separable one-dimensional convolutional layer and a fully connected Sigmoid classification neuron. And only four filters and a minimal set of parameters make up SepConv1D's convolutional layer, but its performance is competitive. Although the current P300 detection methods have achieved good results in normal individuals, these may be not suitable for DOC patients. DOC patients may not be able to process information effectively, or their level of consciousness may be reduced, resulting in delayed or weakened P300 signals and decreased occurrence rates (Zhang et al., 2017). Furthermore, as there are differences in the P300 signal between different DOC patients, it is difficult to achieve good results when training with other patients' data. Due to the difficulty of collecting a large amount of data from DOC patients who are easily fatigued and difficult to control, studying cross-subject algorithms for DOC patients can be beneficial for clinical application.

In this study, we proposed a domain adaptation-based cross-subject P300 decoding algorithm for DOC patients. This method used healthy subjects' data to train the model, and then used an adversarial approach to adapt the network. The experiment results show our approach achieved the same level of cross-subject accuracy in DOC patients as the traditional intra-subject approach.

2. Materials and methods

2.1. Subjects

This study involved data from 19 subjects (including 11 DOC patients and 8 healthy subjects). Prior to the experiment, all subjects (or patients' relatives) provided written informed consent that they all signed. All data were acquired with 36-conductor Greentech electrode caps and a SynAmps2 amplifier from Neuroscan. The sampling rate of the amplifier was set at 250 Hz. 10 channels of EEG data (O1, Oz, O2, P7, P3, Pz, P4, P8, Fz, and Cz) were acquired from each subject wearing electrode caps according to the Extended International 10–20 System standard. To ensure signal quality during collecting data, all electrodes' scalp contact impedances were kept below 5 kΩ. Healthy subjects need to be between 18–55 years old, right-handed, and have normal or corrected-to-normal vision. Eight healthy subjects were males between the ages of 23 and 33 (mean 26.38 years). For patients, they are between 18 and 70 years old, with a disease course of no more than 1 year, right-handed, and have no history of diseases that cause perceptual impairments such as visual or auditory impairments. They also have no history of neurological or psychiatric diseases, or severe psychiatric symptoms. In this experiment, the diagnosis of each patient was evaluated using the CRS-R, which is the gold standard for clinical behavioral diagnosis, to assess various aspects such as auditory, visual, motor, language, response, and level of consciousness. Each patient's CRS-R score was evaluated by the same doctor. In this study, a total of two CRS-R assessment results were obtained: one before the start of the experiment and the other 3 months after the end of the experiment. When evaluating the patient's CRS-R score, the doctor observed the patient's best state and chose one day to score multiple times, taking the best score as the final result. Table 1 shows the patients' details.

2.2. Experimental paradigm

The data in this study were collected through a P300-based audio-visual BCI system (Wang et al., 2015; Pan et al., 2020). Based on the patient's condition, data collection was conducted for 1–2 days each week, with 1–2 blocks collected per day. The BCI experiment for each patient lasted for approximately 2 weeks. As shown in Figure 1, two random numbers ranging from 0–9 (e.g., 6, 8) appear on each side of the screen. Two speakers are placed at the side and rear of each side of the display. First, the user was introduced to his task through a 6s Chinese audiovisual instruction. And then, the two digital buttons flash alternately between black and green. At the same time, the speaker on the same side as the flashing digit presents the corresponding voice digit. Finally, the results are displayed on the monitor and voice feedback is given. At the end of the experiment, healthy subjects are given a 2s rest period. In contrast, for DOC patients, there is at least a 10s rest period. Since the patients are easily fatigued and unable to persist in acquiring data from multiple blocks consecutively, the acquisition of patient data needs to be done in multiple sessions based on their physical and mental conditions, as suggested by the medical staff.

2.3. Algorithm description

The experiments were performed on a single PC with Linux Ubuntu 20.04.3 LTS, an Intel(R) Core (TM) i9-12900 K CPU @ 5.20 GHz, 96 GB in RAM, and an NVIDIA GeForce RTX 3090 GPU and 24 GB of RAM. The networks were implemented in Pytorch 1.12.0 (Paszke et al., 2019) as backend. Figure 2 reports the Deep Learning algorithm pipeline. The raw EEGs of patients and healthy subjects are collected after data preprocessing, and then the data of healthy subjects are selected by Wasserstein distance (WD) (Vallender, 1974) for training. And then based on the Adversarial Discriminative Domain Adaptation (ADDA) (Tzeng et al., 2017) algorithm, we proposed an WD-Adversarial Discriminative Spatio-Temporal Convolution Network (WD-ADSTCN) to adapt the feature extractor and classifier to obtain the final results.

2.3.1. Preprocessing

In this study, all channel EEG data within 1000ms after the subject was stimulated were extracted as samples, and baseline correction was performed using the 100ms EEG data before stimulation, followed by 0.1–20 Hz band-pass filtering to filter out signal noise that was not in this frequency interval.

2.3.2. Subject selection

Since the P300 signal of DOC patients is significantly different from that of healthy people, the P300 wave of patients is smaller and difficult to identify (Li et al., 2015). Therefore, the inclusion of some healthy subjects in the training may have side effects on 0the results. The subject selection method adopted in this study centers on the difference between the two distributions by metrics. In the current research, WD is somewhat superior to other metrics such as Jensen-Shannon Divergence (Menéndez et al., 1997), which are defined as follows:

$$W\left(p_s,p_t\right)=inf_{\gamma\in\Pi\left(p_s,p_t\right)}\mathbb{E}_{(x,y)\in\gamma}\left[\|x-y\|\right]$$

TABLE 1 The information and CRS-R scores for all DOC patients.

Patient	Age (years)	Gender	Etiology	Time since injury (months)	Before experiment		After 3 months	
					CRS-R score (subscores)	Diagnosis	CRS-R score (subscores)	Diagnosis
P1	29	M	ABI	8.5	4 (1-0-1-0-0-2)	UWS	4 (1-0-1-0-0-2)	UWS
P2	37	M	ABI	2	5 (0-0-2-1-0-2)	UWS	5 (0-0-2-1-0-2)	UWS
P3	38	M	TBI	1	7 (1-1-2-1-0-2)	UWS	7 (1-1-2-1-0-2)	UWS
P4	33	M	TBI	2	7 (1-0-2-2-0-2)	UWS	7 (1-0-2-2-0-2)	UWS
P5	48	M	ABI	4	7 (1-1-2-1-0-2)	UWS	18 (4-5-5-1-1-2)	MCS+
P6	19	M	CVD	2	7 (1-1-2-1-0-2)	UWS	15 (4-5-2-2-0-2)	MCS+
P7	38	M	TBI	2	10 (1-3-3-1-0-2)	MCS-	19 (3-5-6-1-1-3)	MCS+
P8	44	M	CVD	2.5	9 (1-3-2-1-0-2)	MCS-	20 (4-5-6-2-1-2)	MCS+
P9	17	M	TBI	2	8 (1-1-3-1-0-2)	MCS-	18 (4-5-3-1-2-3)	MCS+
P10	46	F	TBI	1.5	7 (1-0-3-1-0-2)	MCS-	19 (3-5-6-2-1-2)	MCS+
P11	46	M	CVD	2	9 (1-1-4-1-0-2)	MCS-	20 (4-5-6-2-1-2)	MCS+

ABI, anoxic brain injury; TBI, traumatic brain injury; CVD, cerebrovascular disease.

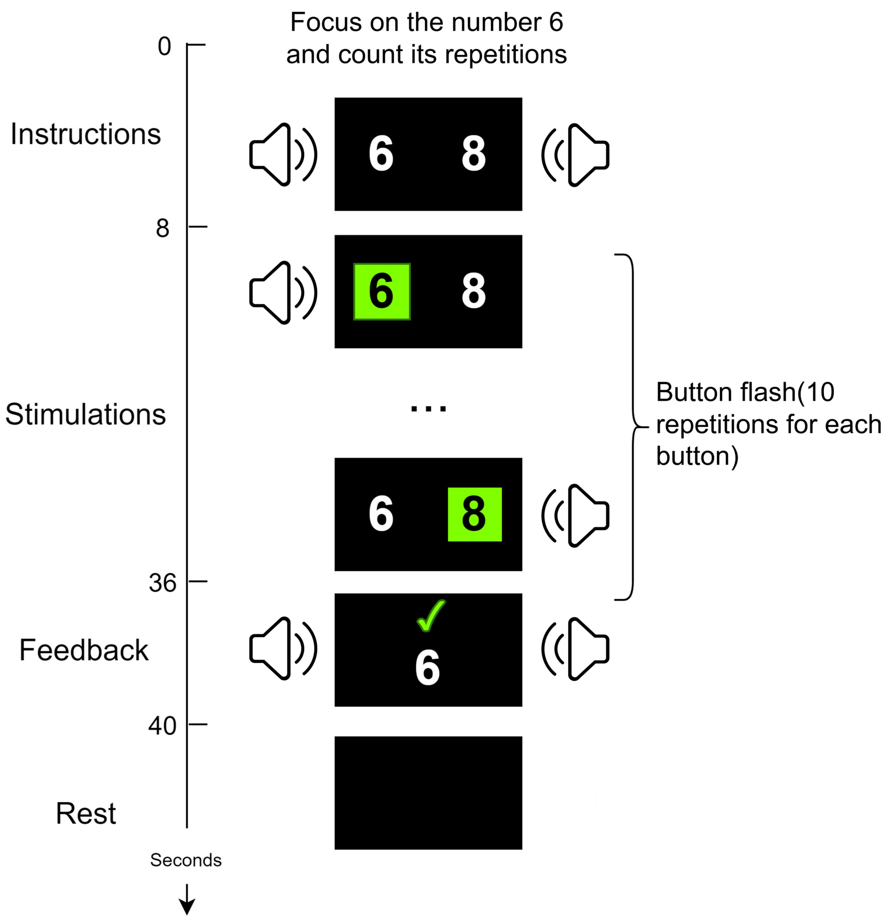

FIGURE 1
The P300-based audio-visual BCI system.

where p_s represents the source domain data distribution (healthy subjects data distribution) and p_t represents the target domain data distribution (DOC patients' data distribution). $\prod(p_s, p_t)$ denotes a set of joint distributions, which is the collection of all the possible joint probability distributions between p_s and p_t.

2.3.3. Domain adaptation and classification

As an integral part in transfer learning, domain adaptation is commonly applied to eliminate the differences in the feature distributions between different domains (Ren et al., 2022). The aim is to map the data into a feature space with distinct distributions for the source and target domains such that they are as close to one another as possible (Wang Z. et al., 2019). As shown in Figure 3, the source domain and the target domain with the same label space, but because of their different distributions, we cannot take the trained classifier in the source domain and utilize it to the classification of the target domain samples directly. After the domain adaptation, the trained classifier by source domain can also be employed to target domain and obtain the desired results.

The ADSTN algorithm will be adopted in this study. Its main structure is shown in Figure 4, which is mainly divided into three parts: pre-training, adversarial, and testing.

As in Figure 4A, in the pre-training phase, the feature extractor and classifier are trained by the source domain data. The loss of the network (cross-entropy loss) at this time can be noted as:

$$\min_{M_s, C} L_{cls}(X_s, Y_s) = -E_{(x_s, y_s) \sim (X_s, Y_s)} \sum_{k=1}^{K} 1_{[k=y_s]} \log C(M_s(x_s))$$

where X_s is the set of all samples in source domain, Y_s is the set of all labels in source domain, $M_s(x_s)$ is the extracted features from source domain feature extractor, and $C(x)$ is the output of the classifier.

Figure 4B, before adversarial, the feature extractor weights in the target domain are initialized to be the same as the source domain feature extractor after pre-training, and then the target domain data distribution after mapping is gradually approximated to the source mapping data distribution by loss gradient transfer, so that the source domain and the target domain cannot be distinguished by the domain discriminator. The loss in the discriminator can be written as:

$$\min_{D} L_{adv_D}(X_s, X_t, M_s, M_t) = -E_{x_s \sim X_s}\left[\log D(M_s(x_s))\right] - E_{x_t \sim X_t}\left[\log(1 - D(M_t(x_t)))\right]$$

where X_t is the set of all target domain samples, M_t is the set of target domain features, and $D(x)$ is the output of the domain discriminator. The prediction loss of the target domain after domain adaptation can be written as:

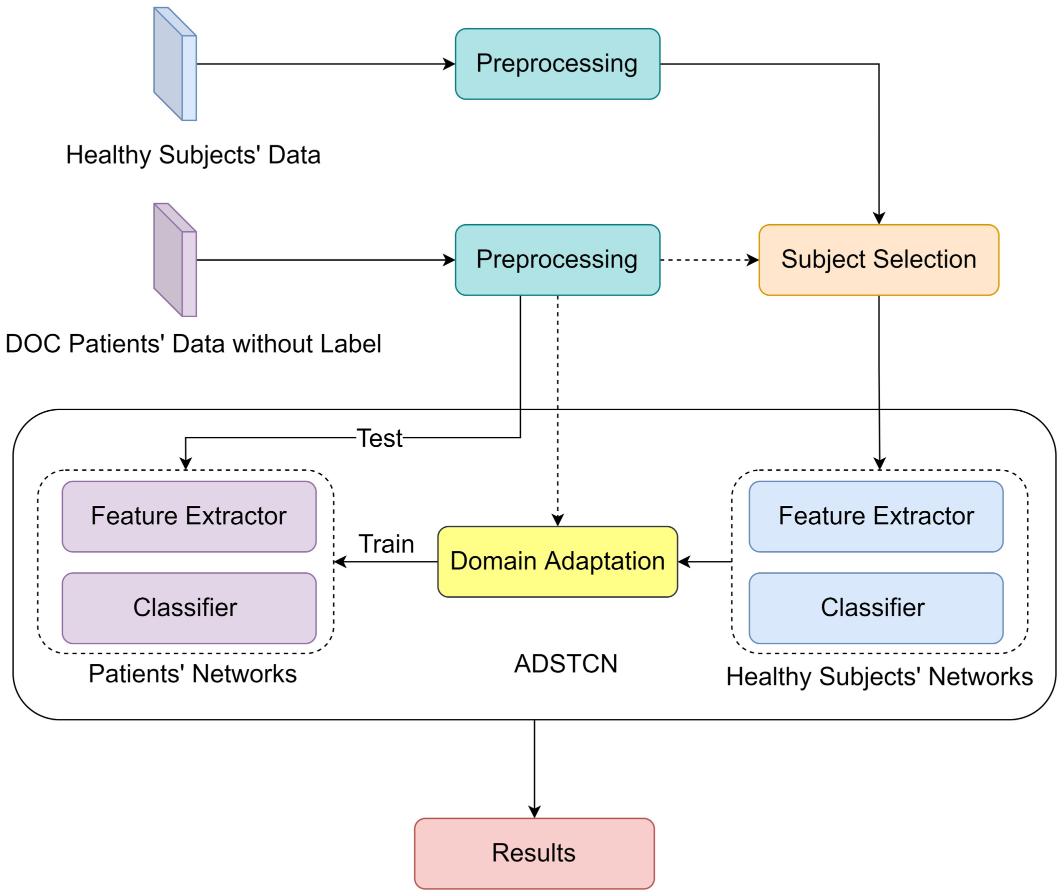

FIGURE 2
The framework of the proposed WD-ADSTCN.

$$\min_{M_s, M_t} L_{cls}(X_s, X_t, \mathrm{D}) = -E_{x_t \sim X_t}\left[\log D\left(M_t\left(x_t\right)\right)\right]$$

Figure 4C, testing the target domain feature extractor with the source domain classifier by using the target domain data.

In order to improve the extraction of temporal and spatial features from the P300 signal, we designed a CNN network named STCNN with a simple structure in this study. Its detailed structure of feature extractor is shown in Figure 5, the network includes 4 layers, labeled L1–L4.

L1——Input Layer: This layer was applied to load the P300 signal $(1 \times 150 \times 10)$.

L2——Spatial Convolution Layer: It consists of a convolution kernel of size 10, equal to the number of electrodes. This processing technique uses common space filtering and weighted superposition averaging. The S/N of the signal can be enhanced effectively while the spatial information of redundancy is further removed (Wang et al., 2021). The calculation process is as follows:

$$x^2 = f\left(I * k^2 + b^2\right)$$

where I is the input data, b is the additive bias, k is the second layer convolution kernel function, and f is the activation function (here is tanh).

L3——Temporal Convolution Layer: It consists of a convolutional kernel of size 4, which can effectively extract the temporal features from the P300 signal. The whole process can be expressed as:

$$x^3 = f\left(x^2 * k^3 + b^3\right)$$

As same as L2, Tanh is also applied as the activation function here.

L4——Feature Pooling Layer: Filter the superior features from the features obtained from L3 by the pooling operation. The pooling filter size used in this study is (2, 1). It contributes to reduce the computational complexity and to prevent overfitting with a small number of training samples.

In order to reduce network training time and model complexity, the label classifier of STCNN and the domain discriminator in this study both use the fully connected network, which can also obtain better classification results under the condition of matching with the feature extractor.

3. Results

3.1. The results in healthy subjects

To verify the validity of the healthy subjects' data, the most commonly used algorithm (SVM) as well as 3 CNN algorithms

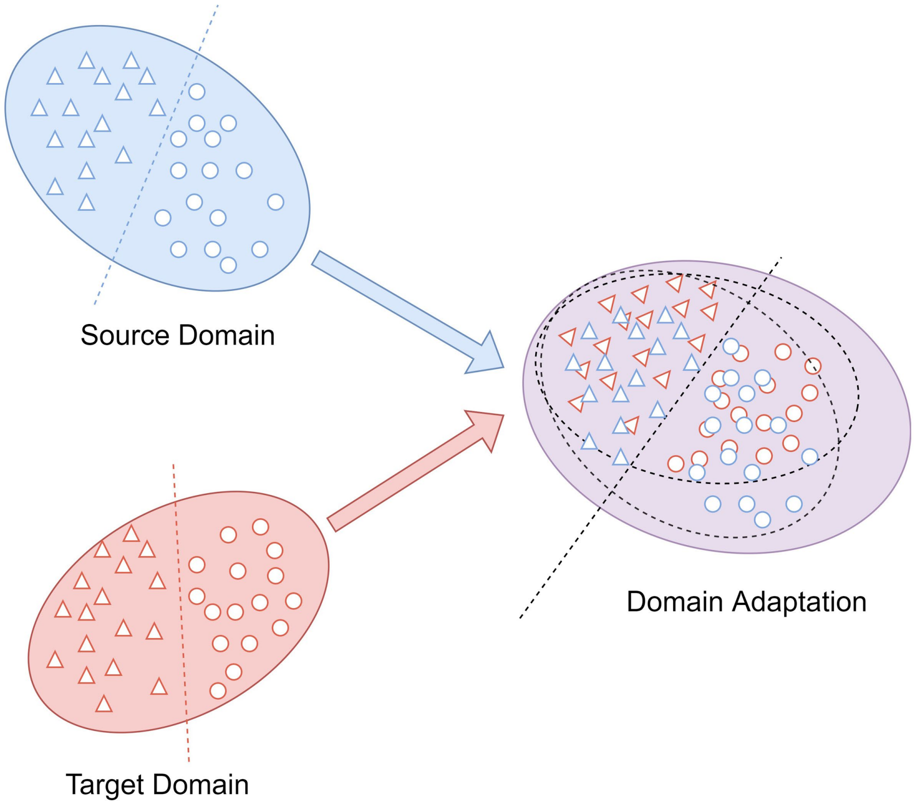

FIGURE 3
The main idea of domain adaptation.

(EEGNet, SepConv1D, STCNN) were employed to compare with the proposed WD-ADSTCN for the P300 cross-subject detection in 8 healthy subjects. As shown in Table 2, SVM is difficult to achieve effective results on cross-subject, with an average accuracy of only 64%. In contrast, the deep learning methods have an accuracy of over 70% except for individual subjects. The highest average accuracy of 75% was achieved by STCNN. The average accuracy of EEGNet was 73%. And the average accuracy of SepConv1D was only 72%, which was slightly lower than the other two deep learning methods. The cross-subject average accuracy of WD-ADSTCN on healthy subjects can reach 78%. A one-way repeated measures ANOVA showed that these classification algorithms had significant different results ($p<10^{-6}, F(4,35)=20.42$). Furthermore, the *post-hoc* ANOVA (Bonferroni-corrected) indicated that the average accuracy was significantly higher for the WD-ADSTCN than that for all other methods except STCNN ($p<0.05$ corrected).

3.2. The results in DOC patients

Patients were divided into two groups according to their improvement in CRS-R scores before and after the trial for 3 months: Group A were patients who did not improve significantly (P1, P2, P3, P4); group B were patients who improved significantly (P5, P6, P7, P8, P9, P10, P11). As shown in Tables 3, 4, the proposed algorithm was compared with the traditional SVM (within-subject and cross-subject) and other two cross-subject deep learning algorithms (EEGNet and SepConv1D). For patients in the group A, the accuracy in each algorithm was below 60% in each algorithm. For patients in the group B, the proposed algorithm and SVM-within achieved an average accuracy higher than 70%, while the accuracies in other algorithms were below 60%. We conducted a one-way repeated measures ANOVA on groups A and B separately, and found that there was no significant difference in results of the classification algorithms within group A ($p>0.05, F(4,16)=0.66$), while a significant difference in that within group B ($p<10^{-6}, F(4,30)=50.51$). Furthermore, the *post-hoc* ANOVA (Bonferroni-corrected) indicated that the average accuracy was significantly higher for the WD-ADSTCN in group B than for all other methods except SVM-within ($p<0.05$ corrected).

To further validate the relationship between P300 detection results and the detection of consciousness in patients with DOC, we compared the accuracy in Table 3 with the CRS-R scores (Table 1) in Figure 6. The accuracy curve of the proposed WD-ADSTCN algorithm is similar to the patients' CRS-R scores after the experiment. The proposed cross-subject WD-ADSTCN algorithm has achieved similar detection results with that of the within-subject algorithm. Also, the improvement in CRS-R scores of patients (P5, P10) was greater, when WD-ADSTCN accuracy was slightly higher than SVM-within. The results of other three cross-subject methods are different from those of CRS-R after the experiment.

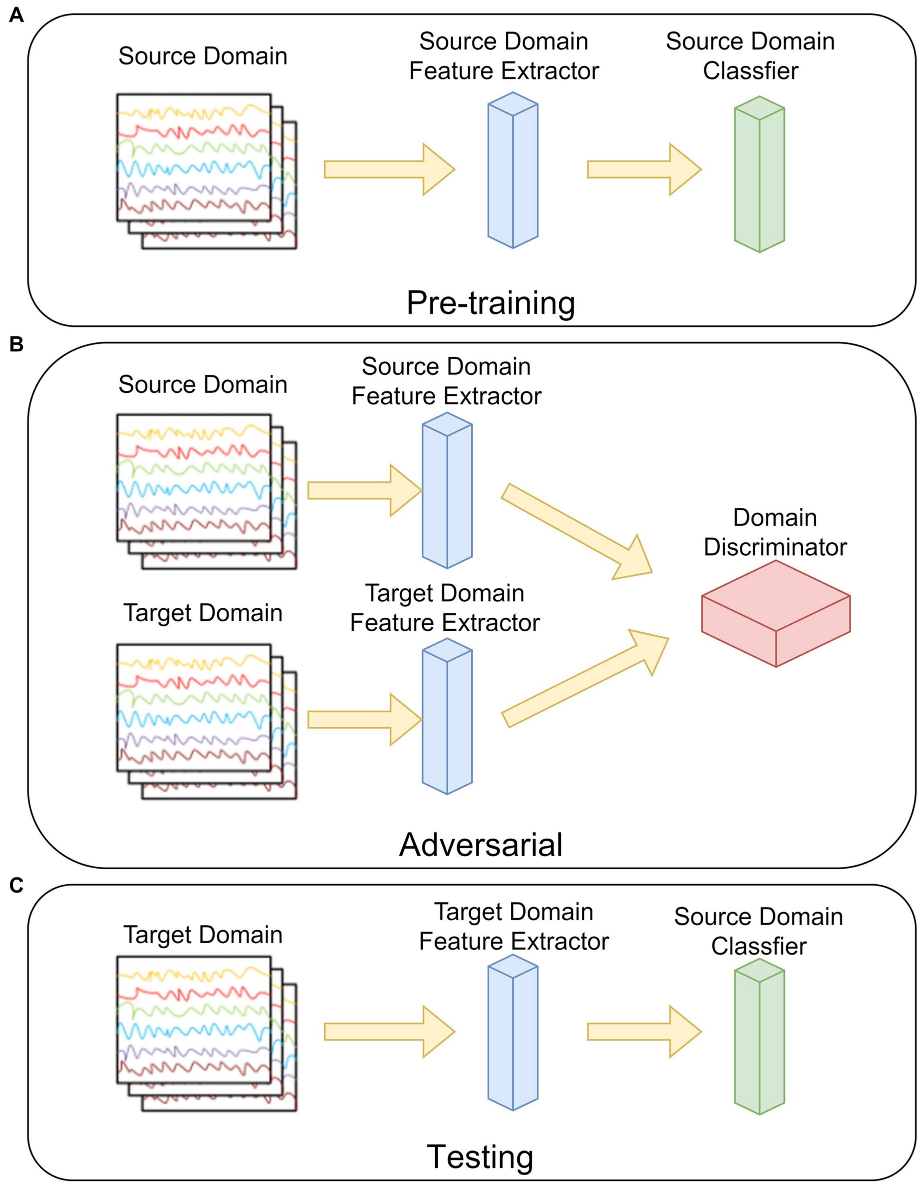

FIGURE 4
The steps of the ADSTCN network. **(A)** Pre-training. **(B)** Adversarial. **(C)** Testing.

3.2.1. The effect of domain adaptation

To verify the effect of domain adaptation in this study, we designed the following 3 experiments. STCNN_patient: Validate the effect of training STCNN on DOC patient data using a leave-one-out cross-validation; STCNN_healthy_subject: Training STCNN with healthy subjects and testing directly on DOC patients; ADSTCN_patient: Validate the effect of training ADSTCN on DOC patient data using leave-one-out cross-validation.

As shown in Figure 7, The results of STCNN_patient and STCNN_healthy_subject were extremely unsatisfactory and failed to achieve classification at all (below 64%). Although the average accuracy in ADSTCN_patient was lower than 64%, there were three subjects with good results (P5, P9, P11). The results show that ADSTCN can improve the cross-subject detection accuracy of P300 to some extent, but its enhancement effect is limited under the condition that the subject features are not obvious. Meanwhile, due to the large difference in P300 features between healthy subjects and the DOC patients, the patients could not directly apply the trained model from healthy subjects.

3.2.2. The effect of source domain

To investigate the effect of the source domain on the experimental results, we designed an additional set of experiments to compare with ADSTCN_patient (ADSTCN_healthy_subject: Transfer the healthy subjects training model to DOC patients by using ADSTCN). The source domain in ADSTCN_patient is other DOC patients, while ADSTCN_healthy_subject is healthy subjects.

The results are shown in Figure 8. The accuracy of using healthy subjects as the source domain was higher than using the other patients as the source domain on all patients. When using healthy subjects as the source domain, multiple patients (P8, P10, P11) had an accuracy rate of over 70%, with an average accuracy of 69.5%.

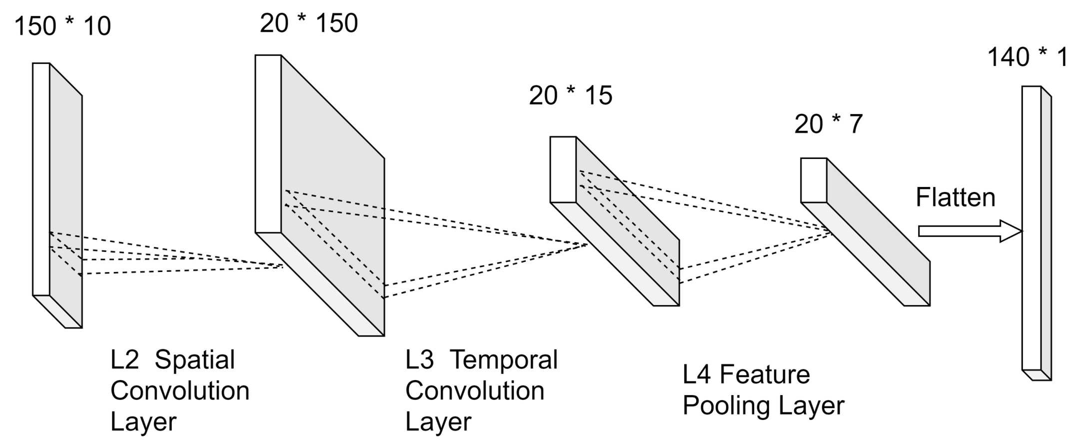

FIGURE 5
The structure of the feature extractor in the STCNN.

TABLE 2 The cross-subject accuracy comparison in healthy subjects.

Method	H1	H2	H3	H4	H5	H6	H7	H8	Mean	*p*-value (corrected)
SVM	0.67	0.58	0.65	0.61	0.66	0.61	0.67	0.69	0.64	3.58×10^{-9}
EEGNet	0.72	0.70	0.72	0.71	0.71	0.76	0.75	0.78	0.73	0.04
SepConv1D	0.70	0.67	0.70	0.70	0.76	0.74	0.74	0.76	0.72	0.01
STCNN	0.73	0.70	0.76	0.72	0.77	0.75	0.76	0.80	0.75	0.51
WD-ADSTCN	0.79	0.75	0.76	0.74	0.78	0.80	0.82	0.81	0.78	–

TABLE 3 The accuracy comparison of P300 detection in group A.

Method	P1	P2	P3	P4	Mean
SVM-within	0.46	0.56	0.58	0.54	0.54
SVM-cross	0.51	0.48	0.52	0.53	0.51
EEGNet	0.45	0.50	0.56	0.48	0.50
SepConv1D	0.55	0.49	0.50	0.47	0.50
WD-ADSTCN	0.52	0.53	0.53	0.50	0.52

3.2.3. The effect of subject selection

To confirm the contribution of WD subject selection, we compare the results of ADSTCN_healthy_subject (Without subject selection) with those in Table 3 (WD-ADSTCN). As shown in Figure 9, WD-ADSTCN had an average accuracy of 71.5%, which is better than ADSTCN_healthy_subject. The accuracy of the subjects fluctuated less after using WD, with an improvement in the otherwise poorer subjects (e.g., P5, P6, P7, P11), but a slight decrease in the better subjects (P8, P10). This indicates that WD does remove some of the subjects with side effects, but it may also remove useful ones when the overall effect is better. In this specific condition of DOC patients, WD subject selection has a certain effect.

4. Discussion

The BCI-based approach can directly evaluate DOC patients based on brain signals, and this approach may become a clinical tool to assist in the clinical setting. Currently, the researchers are mainly focused on the detection of EEG in DOC patients by using traditional SVM algorithms from intra-subject. This method requires the collection of patients' data to calibrate the system, which is rather inconvenient in clinical applications. In this regard, this study proposed a method based on a transfer model from healthy subjects to overcome the cross-subject problem of P300 detection in DOC patients. The results of our study show that all 7 patients whose prognosis improved had an accuracy of over 66%. This demonstrates the effectiveness of our algorithm on cross-subject of DOC patients and its possibilities for awareness detection and communication.

Before applicating in the patients, we first verified in the healthy subjects' data. We compared the proposed WD-ADSTCN algorithm with traditional SVM algorithm and some excellent deep learning networks (EEGNet, SepConv1D) on cross-subject (as shown in Table 2). The results show that the proposed algorithm has indeed some advantages, and demonstrate that the feature extractor of STCNN can extract suitable temporal and spatial features from the P300 signal. Under the condition of simplifying the structure as much as possible, STCNN still has excellent performance.

The experimental results show that other cross-subject methods (e.g., EEGNet and SepConv1D) performed poor, as shown in Tables 2, 3. Furthermore, the analysis of domain adaptation in Section 3.2.1 found that it is difficult to achieve results either directly in cross-subject on DOC patients or by using the model obtained from healthy subjects on DOC patients. These demonstrated a large difference in the P300 data between DOC patients and healthy subjects, and a similarly large difference between DOC patients. It may be due to the difference in the

TABLE 4 The accuracy comparison of P300 detection in group B.

Method	P5	P6	P7	P8	P9	P10	P11	Mean	Value of *p* (corrected)
SVM-within	0.66	0.70	0.66	0.66	0.78	0.78	0.74	0.71	1.00
SVM-cross	0.50	0.47	0.52	0.56	0.48	0.52	0.54	0.51	4.06×10^{-10}
EEGNet	0.55	0.51	0.56	0.58	0.51	0.49	0.57	0.54	8.91×10^{-9}
SepConv1D	0.49	0.53	0.57	0.56	0.54	0.56	0.52	0.54	8.91×10^{-9}
WD-ADSTCN	0.72	0.68	0.67	0.73	0.71	0.76	0.73	0.71	-

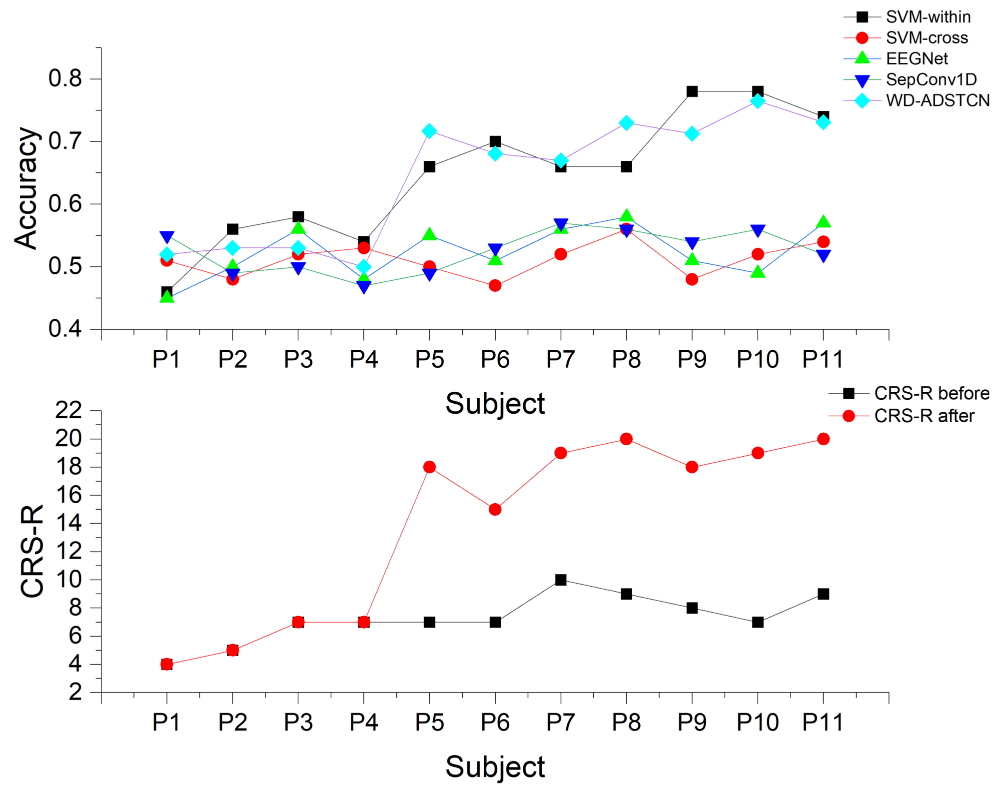

FIGURE 6
The accuracy and the CRS-R scores in each patient.

shifting of the wave peak and amplitude of P300. As shown in Figure 10, for healthy subjects H1, a clear P300 signal typically appears around 300ms after hearing or seeing an unexpected stimulus, with a clear difference in responses between target and non-target stimuli. In contrast, DOC patients do not show so obvious difference in responses as that of healthy subjects. The responses of patient P9 in group B are close to those of healthy subjects, while the target and non-target responses of patient P2 in group A are difficult to distinguish. These results may indicate DOC patients have different abilities to perform selective attention. Patients in group B could selectively pay attention to the target stimuli, but were still unable to completely ignore the non-target stimuli, resulting in some strong non-target responses. This difference may be due to impaired brain function in some DOC patients, leading to a decline in their cognitive ability [3]. In addition, the occurrence rate of P300 in some DOC patients may also decrease. Apart from impaired brain function, this may be due to the loss of consciousness and autonomy, making them unable to consciously respond to external stimuli.

In this study, 7 of 11 patients achieved P300 detection accuracy significantly higher than the chance level (i.e., 64% in Kübler and Birbaumer, 2008), using the proposed WD-ADSTCN algorithm. Furthermore, all the 7 patients showed the improved CRS-R scores after the experiment. These means that the classification accuracy of ADSTCN can be used as a prognostic judgment for DOC patients. Although, the SVM within subject got similar performance. Compared to SVM, ADSTCN can obtain similar results by utilizing easily collected healthy subject's data with unlabeled patient data. The problem of insufficient DOC patient data is solved to a certain extent.

In the Figure 8, we directly used ADSTCN within patients (other patients as source domain). However, the results have a significant gap compared with from healthy subjects to patients,

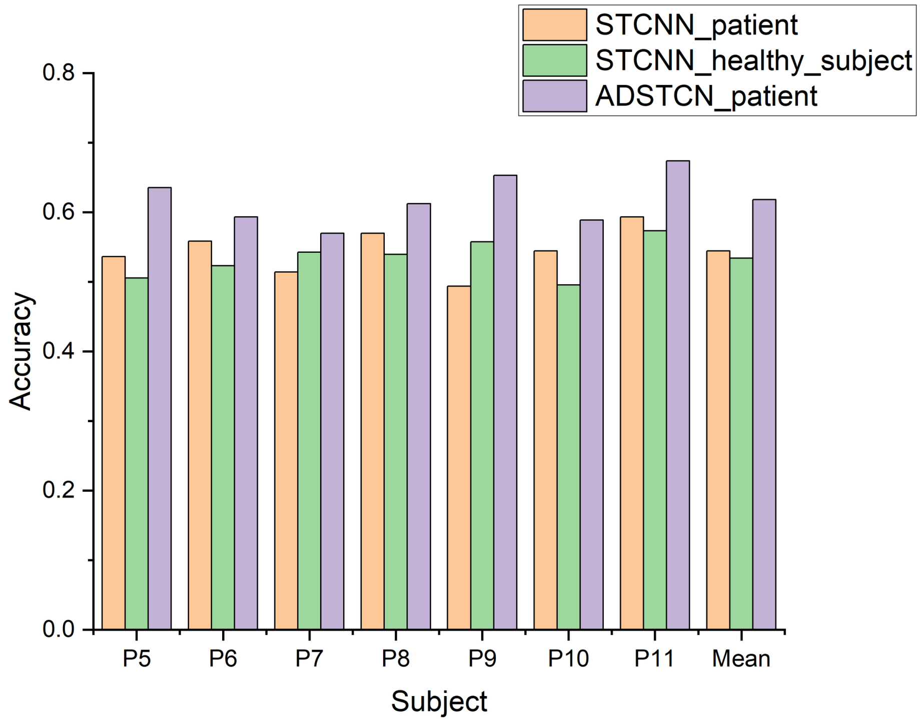

FIGURE 7
The accuracy of ADSTCN and STCNN for DOC patients in the group B.

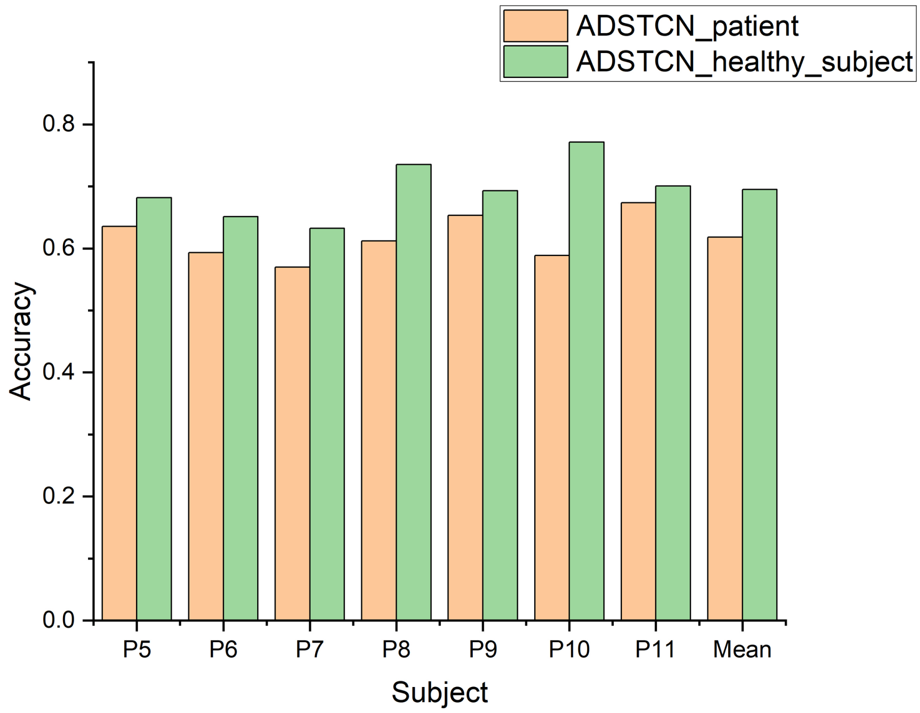

FIGURE 8
The accuracy of ADSTCN using different source domains for DOC patients in the group B.

which may be due to the fact that in the pre-training phase, the mixing of multiple patient data would not be able to get a better classifier, thus making the classifier ineffective even though the features obtained by the feature extractor in the adversarial phase are in the same feature space. And after we joined WD to select subjects, the patients' overall effect of P300 did improve, but there

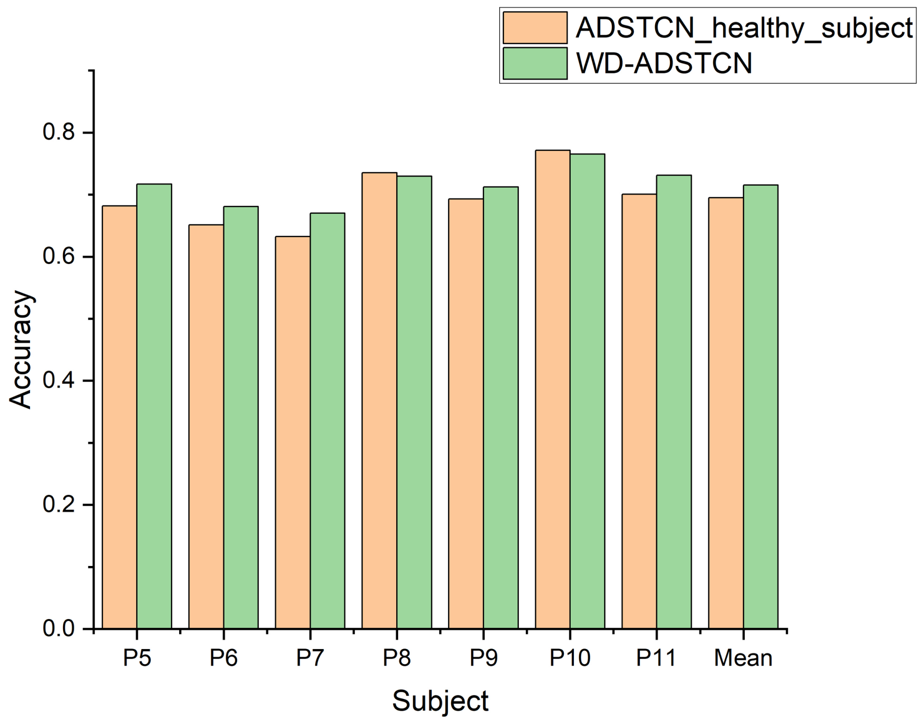

FIGURE 9
The accuracy of ADSTCN and WD-ADSTCN for DOC patients in the group B.

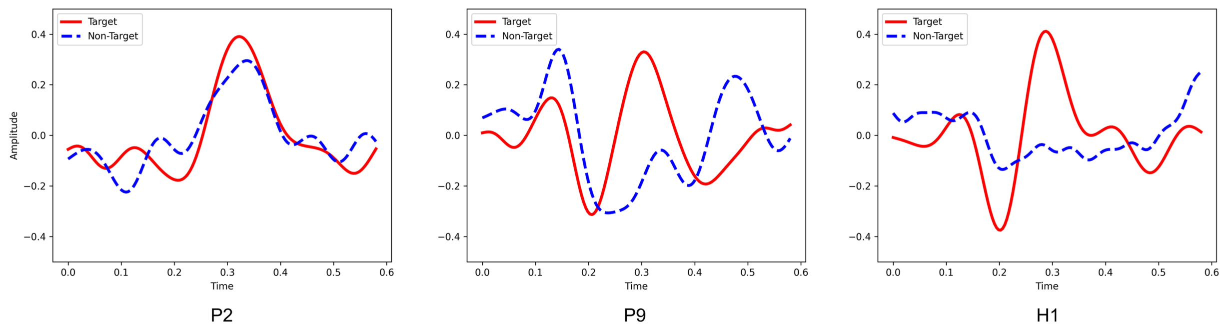

FIGURE 10
The P300 waveforms from patient P2, patient P9 and healthy subject H1.

is a decrease in individual subjects (as shown in Figure 9). Because the calculation of WD is more complicated, it is difficult to use it for selecting individual samples, and we will continue to work on more appropriate sample selection methods from relational networks and distance metric networks.

5. Conclusion

The current clinical approach to diagnosing patients with DOC by means of scales has a high rate of misdiagnosis. Although a P300-based BCI system can assist in diagnosis, there is no decoding algorithm that can detect P300 in DOC patients cross-subject. In this study, our proposed ADSTCN algorithm based on domain adaptation can train the initial model using data from the healthy subjects after selection by WD, and then adjusting it to achieve cross-subject effects by using patient data. The results showed that ADSTCN outperformed other methods in cross-subject testing of DOC patients, with the results approaching that of SVM in intra-subject. However, the subject selection module of ADSTCN may filter out useful subjects when the differences between subjects are small which could cause a slight decrease in accuracy. Moreover, the accuracy and stability of BCI technology are still limited due to issues such as signal noise and interference. At the same time, The CRS-R and other assessment scales remain the primary methods for evaluating DOC. Currently, BCI technology can be only served as an auxiliary diagnostic tool (Schnakers, 2020). In the future, we will further improve the subject selection and try to eliminate the differences between healthy subjects and DOC patient groups to obtain a generalized P300 classifier for DOC patients.

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 the General Hospital of Guangzhou Military Command. The patients/participants provided their written informed consent to participate in this study.

Author contributions

FW designed the system, experiment, and paradigm. FQ and FW collected the data. FW, YW, and ZL analyzed the data. FW, YW, and JL wrote the manuscript. 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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Stimulation of vagus nerve for patients with disorders of consciousness: a systematic review

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Purpose: The purpose of this study is to evaluate the efficacy and safety of stimulating the vagus nerve in patients with disorders of consciousness (DOCs).

Methods: A comprehensive systematic review was conducted, encompassing the search of databases such as PubMed, CENTRAL, EMBASE and PEDro from their inception until July 2023. Additionally, manual searches and exploration of grey literature were performed. The literature review was conducted independently by two reviewers for search strategy, selection of studies, data extraction, and judgment of evidence quality according to the American Academy of Cerebral Palsy and Developmental Medicine (AACPDM) Study Quality Scale.

Results: A total of 1,269 articles were retrieved, and 10 studies met the inclusion criteria. Among these, there were three case reports, five case series, and only two randomized controlled trials (RCTs). Preliminary studies have suggested that stimulation of vagus nerve can enhance the levels of DOCs in both vegetative state/unresponsive wakefulness state (VS/UWS) and minimally conscious state (MCS). However, due to a lack of high-quality RCTs research and evidence-based medical evidence, no definitive conclusion can be drawn regarding the intervention's effectiveness on consciousness level. Additionally, there were no significant adverse effects observed following stimulation of vagus nerve.

Conclusion: A definitive conclusion cannot be drawn from this systematic review as there was a limited number of eligible studies and low-quality evidence. The findings of this systematic review can serve as a roadmap for future research on the use of stimulation of vagus nerve to facilitate recovery from DOCs.

KEYWORDS

disorders of consciousness, vagus nerve stimulaiton, transcutaneous auricular vagus nerve stimulation, vagus nerve magnetic modulation, vegetative state/unresponsive wakefulness state, minimally conscious state, systematic review

Introduction

Disorders of consciousness (DOCs) refer to prolonged periods of impaired awareness following severe brain injuries or neurological impairments, such as traumatic brain injury (TBI), stroke, hypoxic–ischemic encephalopathy (HIE) and other related conditions (Dostovic et al., 2012; Eapen et al., 2017; Malone et al., 2019). The DOCs can be classified into four categories based on their neurobehavioral function: coma, vegetative state/unresponsive wakefulness state

(*VS*/UWS), minimally conscious state (MCS), and the emergence from MCS to higher consciousness level, namely eMCS (Cortese et al., 2023; Li et al., 2023). Comas are states of unconsciousness characterized by a lack of arousal and consciousness. In comas, spontaneous or stimulus-induced arousal is absent, and there is no opening of the eyes, as well as sleep–wake cycles are lost during EEG testing (Ardeshna, 2016). The term *VS*/UWS denotes the condition characterized by the preservation of fundamental brainstem reflexes and the sleep–wake cycle, accompanied by either spontaneous or induced eye opening, albeit without conscious awareness (Monti et al., 2010). The MCS referring to a severely altered state of consciousness in which there is minimal but definite evidence of awareness of self or surroundings, characterized by inconsistent but clearly discernible behavioral evidence of consciousness and can be distinguished from coma and *VS*/UWS by documenting the presence of specific behavioral features not found in either of these conditions (Giacino et al., 2002). MCS includes MCS+ and MCS−, MCS+ syndrome should be marked by reproducible evidence of any one of the following behaviors: command-following, intelligible verbalization, or intentional communication, while MCS− included automatic motor behaviors, object manipulation, localizing objects in space, localizing noxious stimuli, visual pursuit, and visual fixation, but no evidence of receptive or expressive language function (Thibaut et al., 2020).

There are currently alternative treatment options for DOCs, including pharmacological treatments such as amantadine, sensory stimulation, hyperbaric oxygen therapy, and neuromodulation (Septien and Rubin, 2018; Thibaut et al., 2019). Neuromodulation, encompassing non-invasive brain stimulation techniques like transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS), as well as invasive brain stimulation methods like deep brain stimulation (DBS) and spinal cord stimulation (SCS), holds significant potential as a therapeutic avenue for various neurological disorders, including drug-resistant epilepsy, depression, and DOCs (Perez-Carbonell et al., 2020; Marwaha et al., 2023).

In recent years, the utilization of stimulation of vagus nerve techniques, such as invasive vagus nerve stimulation (VNS), transcutaneous auricular vagus nerve stimulation (taVNS), and vagus nerve magnetic modulation (VNMM), has garnered significant interest among neuroscientists for the treatment of consciousness disorders. These techniques present a promising neuromodulatory therapeutic approach for the recovery of patients with DOCs. Nevertheless, a comprehensive systematic review evaluating the effectiveness and safety of stimulation of vagus nerve in the context of DOCs is currently lacking.

Hence, considering the significance of this matter and the dearth of empirical evidence substantiating the efficacy of any rehabilitative intervention for individuals with DOCs, the primary objective of this study was to investigate the effectiveness of stimulation of vagus nerve in treating DOCs. Furthermore, we aimed to ascertain any potential untoward consequences associated with this therapeutic approach.

Methods

The present systematic review was carried out following the guidelines specified in the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement (Moher et al., 2010).

Participants

Individuals of diverse age, gender, and ethnicity, who have been diagnosed with coma, unresponsive wakefulness syndrome/ vegetative state, minimally conscious state, extended minimally conscious state, and/or exhibit impaired consciousness as determined by assessment tools such as the Glasgow Coma Scale (GCS) or the Coma Recovery Scale-Revised (CRS-R), are included in this study. The scope of this study encompasses patients diagnosed with DOCs, focusing on clinical research and excluding animal-based experimental investigations.

Intervention

The stimulation of the vagus nerve, whether through implanted VNS or non-invasive taVNS, as well as other methods of vagus nerve stimulation such as VNMM by rTMS, is not dependent on the specific parameters employed (such as type of current, frequencies, amplitudes, and intensity) or the duration of treatment.

Outcome

The study primarily examined the impact of electrostimulation treatment on the level of consciousness, as measured by appropriate scales such as CRS-R and GCS. Secondary outcomes focused on potential adverse events, including changes in heart rate, blood pressure, respiratory rate, and/or saturation. Additionally, brain assessment techniques such as functional magnetic resonance imaging (fMRI), somatosensory evoked potentials (SEP), brainstem auditory evoked potentials (BAEP), and cerebral blood flow (CBF) were utilized.

Type of studies

We have exclusively incorporated clinical studies, for example, randomized controlled clinical trials (RCTs), case reports, case series, and other relevant sources. It should be emphasized that animal studies are not included.

Information sources

Adhering to the latest guidelines for updating systematic reviews, we have specifically opted for articles published after May 1, 2008, to ensure the provision of novel evidence based on necessity and priority. Our objective was to encompass studies from international English-language journals until July 10, 2023, pertaining to stimulation of vagus nerve in DOCs. The primary sources were acquired through comprehensive exploration of biomedical databases, gray literature, and meticulous examination of bibliographies of all deemed pertinent articles.

The biomedical databases examined in this study encompassed CENTRAL (Cochrane Central Register of Controlled Trials), MEDLINE (accessible through PubMed), EMBASE, and PEDro. Additionally, we conducted searches in databases containing clinical trial protocols, sought out unpublished or ongoing trials, and performed citation link searches using research bibliographies obtained from the aforementioned biomedical databases.

Search strategy

The search on Pubmed was: ("Consciousness Disorders" [Mesh] OR "Consciousness" [Mesh] OR Conscious* OR Unresponsive* OR Unconsciousness OR Coma* OR Unawareness OR Vegetative) AND ("Vagus Nerve" [Mesh] OR "Vagus nerve"). The search on CENTRAL was: (MeSH descriptor: [Consciousness] OR MeSH descriptor: [Consciousness Disorders] OR Coma* OR Conscious* OR Unresponsive* OR Unconsciousness OR Unawareness OR Vegetative) AND (MeSH descriptor: [Vagus Nerve] OR "Vagus nerve"). The search strategy on Embase was: (Conscious OR Unresponsive OR Unconsciousness OR Coma OR Unawareness OR Vegetative) AND "Vagus nerve." For PEDRo we used only the term "Vagus." An example of a PRISMA flow sheet is included, showing how the search strategy is put in place (Figure 1).

Study selection

The articles were selected by two authors (CV and FT) through a sequential analysis of the title, abstract, and full text, if accessible. Any conflicts arising between the two authors were resolved through comparison or, if necessary, the involvement of a third author (DF).

Data collection process

The data from the individual studies were obtained using a paper-based template created by two authors (CV and FD). Any discrepancies in the collected data were resolved through comparison or with the involvement of a third author (TI). Additionally, the variables extracted from each article included the participants' characteristics, intervention details, outcome measures along with their respective follow-up periods, and the obtained results.

Results

General aspects

A bibliographic research process was conducted, resulting in the identification of 1,268 studies. An additional study was found through citation chaining strategies. After removing duplicates, a total of 680, the title and abstract of 589 articles were screened. From this screening, 576 records were excluded, leaving 13 articles for further evaluation through reading the full text. Three papers were subsequently excluded, as one study involved animal experimentation and two studies were reviews. Ultimately, a total of 10 studies were selected. The study selection process is presented in the PRISMA flowchart depicted in Figure 1. The characteristics of each individual study have been extracted and summarized in Table 1.

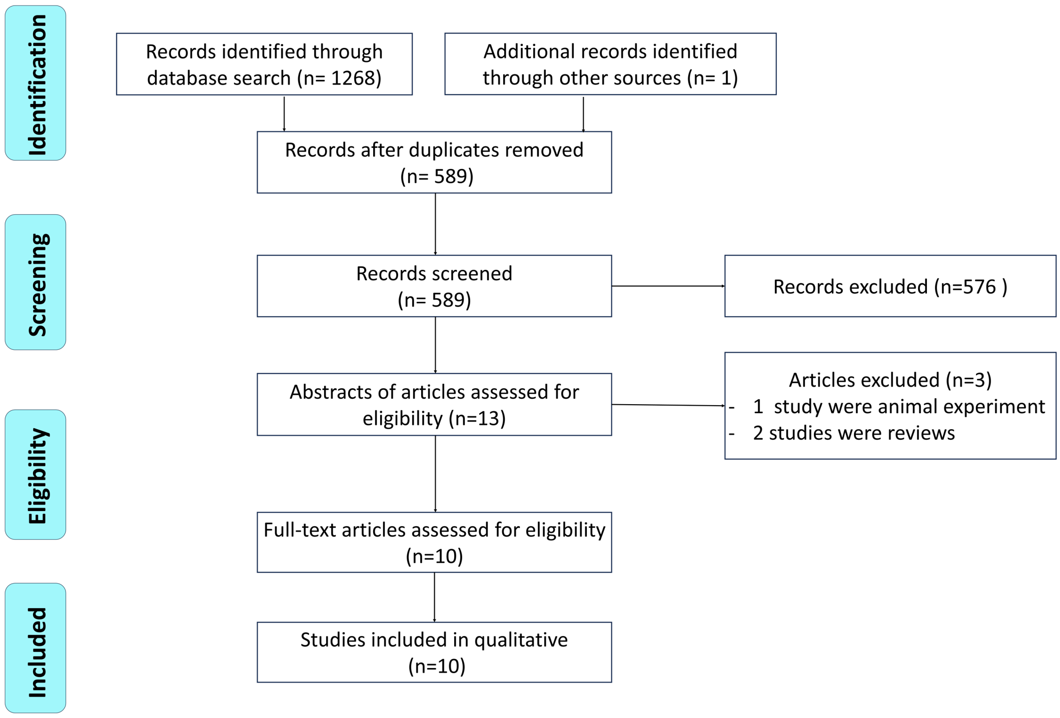

FIGURE 1
PRISMA flowchart.

TABLE 1 Characteristics of included studies.

Study	Type	Patients no.	Etiology	Stimulation devices	Stimulation side and site	Stimulation parameter	Data cycle	Clinical results	Side effect	Brain evaluation
Yu et al. (2017)	Case report	1	HIE	taVNS	Bilateral cymba	20 Hz, <1 ms, 4–6 mA	30 min, twice daily, 50 days	*VS* → MCS CRS-R: 6 → 13	–	fMRI: DMN connectivity↑
Corazzol et al. (2017)	Case report	1	TBI	VNS, Cyberonics Inc	Left surgical implantation of vagus nerve	30 Hz, 500 us, 0.25–1.5 mA	30s on/5 min off, 6 months	*VS* → MCS CRS-R: 5 → 10	–	EEG: theta band power ↑, wSMI: ↑, PET: activity in occipito-parieto-frontal and basal ganglia regions ↑
Hakon et al. (2020)	Case series	5	DAI after TBI	taVNS, Nemos®	Left cymba conchae	25 Hz, 250 us, 30s on/30s off, 0.5–1 mA	4 h, once a day, 8 weeks	2 MCS → EMCS 1 of 3 *VS* → MCS	Intermittent itching of the ear (1 patient)	–
Noe et al. (2020)	Case series	14	TBI: 7, HIE: 4, Hemorrhage: 3	taVNS, Parasym® CE	Left tragus	20 Hz, 250 us, 1.5 mA	30 min, twice daily, 5 days a week, 4 weeks	CRS-R: 5 of 8 MCS patients↑, 6 *VS*/UWS patients no changed	None	–
Xiang et al. (2020)	Case series	10	TBI: 4, HIE: 1, Hemorrhage: 5	VNS, G112, PINS Medical	Left surgical implantation of vagus nerve	20–30 Hz, 250–500 us, 0.1–3.5 mA	30s on/5 min off, 6 months	CRS-R: 9 of 10 patients↑	None	–
Yu et al. (2021)	Case series	10	HIE: 5, Hemorrhage: 3, TBI: 2	taVNS	Cymba conchae	20 Hz, 0.5 ms, 4–6 mA	30 min, twice daily, 4 weeks	CRS-R: 6 of 7 *VS* patients↑, 2 of 3 MCS patients↑	–	fMRI: CBF ↑ in auditory responded group
Osinska et al. (2022)	Case report	1	TBI	taVNS, Nemos®	Cymba conchae	25 Hz, 0.25 ms, 25 V, 30s on /30s off, 0.2–1.5 mA	4 h, once daily, 6 months	CRS-R: 4 → 13	–	EEG: alpha range ↑
Wang et al. (2022)	Case series	17	Hemorrhage: 9, HIE: 3, TBI: 5	VNMM, TMS (magneuro 60 stimulator)	Left mastoid	10 Hz	20 min, once daily, 5 days per week, 4 weeks	CRS-R: 7.88 ± 2.93 → 11.53 ± 4.94 GCS: 7.65 ± 1.90 → 9.18 ± 2.65	None	SEP: 1 patient improved from grade II to grade I. BAEP: grade I: 3 → 5, grade II: 8 → 9, grade III: 4 → 1, grade IV: 2 → 2
Yifei et al. (2022)	RCT	12	Stroke: 8, TBI: 2, Anoxic: 2	taVNS, Huatuo brand electronic acupuncture	Bilateral auricular concha	20 Hz, <1 ms, 4–6 mA	30 min, twice daily, 4 weeks	CRS-R: no significant improvement	–	EEG: delta band↑
Zhou et al. (2023)	RCT	57	Stroke: 30, TBI: 27	taVNS, Changzhou Rishena Medical Device	Left auricular concha	20 Hz, 200 us, intensity, 15	30 min, twice daily, 6 days per week, 4 weeks	CRS-R: significant improvement for MCS patients	None	–

DAI, diffuse axonal injury; TBI, traumatic brain injury; HIE, hypoxic ischemic encephalopathy; VNS, vagus nerve stimulation; taVNS, transauricular vagus nerve stimulation; VNMM, vagus nerve magnetic modulation; CRS-R, revised coma recovery scale; GCS, glasgow scale; minimally conscious state; VS/UWS, vegetative state/unresponsive wakefulness syndrome; EEG, electroencephalogram; DMN, default mode network; fMRI, functional magnetic resonance imaging; SEP, somatosensory evoked potentials; BAEP, brainstem auditory evoked potentials; CBF, cerebral blood flow.

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Study design and quality

All 10 articles consisted of prospective studies that examined the effects of vagus nerve stimulation on patients with DOCs, encompassing both *VS*/UWS and MCS. The evaluation of the articles' quality was conducted using the American Academy of Cerebral Palsy and Developmental Medicine (AACPDM) Study Quality Scale (Petrus et al., 2008) (refer to Table 2), the Clinical Relevance Tool for Case Studies, and the Quality, Rigor or Evaluative Criteria tool.

Two out of the 10 studies included in this analysis were randomized-controlled trials, which were categorized as level II evidence according to the AACPDM level of evidence scale (Yifei et al., 2022; Zhou et al., 2023). Five articles consisted of case series that lacked an active control group or sham group, resulting in their classification as level IV evidence (Hakon et al., 2020; Noe et al., 2020; Xiang et al., 2020; Yu et al., 2021; Wang et al., 2022). The remaining three articles were case reports that exhibited limited individual study quality, thus classified as level V evidence (Corazzol et al., 2017; Yu et al., 2017; Osinska et al., 2022).

Study samples

A total of 128 patients diagnosed with DOCs, encompassing both female and male individuals, were included in the various studies conducted. These studies focused on patients classified as either in a *VS*/UWS or in a MCS. One study exclusively examined MCS subjects (Xiang et al., 2020), while four case series reports (Hakon et al., 2020; Noe et al., 2020; Xiang et al., 2020; Wang et al., 2022) and two randomized controlled trials (Yifei et al., 2022; Zhou et al., 2023) included both *VS*/UWS and MCS patients. Furthermore, the etiology of DOCs encompassed conditions such as HIE, TBI, hemorrhage, and stroke.

Stimulation of vagus nerve protocols

The primary methods of stimulating the vagus nerve encompass invasive VNS, non-invasive taVNS, and VNMM. Among the articles reviewed, two employed VNS (Corazzol et al., 2017; Xiang et al., 2020), seven utilized taVNS (Yu et al., 2017; Hakon et al., 2020; Noe et al., 2020; Yu et al., 2021; Osinska et al., 2022; Yifei et al., 2022), and one employed VNMM through rTMS (Wang et al., 2022). The stimulation parameters for VNS included a sinusoidal waveform, pulse width ranging from 250 to 500 µs, a frequency of 20–30 Hz, and an amplitude ranging from 0.1 to 3.5 mA, targeting the left vagus nerve. For taVNS, the parameters consisted of a pulse width of 200–500 µs, a frequency of 20 to 25 Hz, an amplitude ranging from 0.1 to 6 mA, and targeting either the left or bilateral cymba conchae. In the case of VNMM, a frequency of 10 Hz was applied through rTMS to the left mastoid. In most studies, stimulation protocol lasted for 4 weeks, once or twice a day, for 30 min.

Consciousness assessment

The evaluation of consciousness disorders in these papers primarily encompasses behavioral assessments, such as the CRS-R and the GCS, as well as brain functional evaluations, including EEG, evoked potentials, fMRI, and positron emission tomography (PET). All of the studies employed the CRS-R as the primary outcome measure, with only one study utilizing the GCS as a secondary outcome measure (Wang et al., 2022). These studies reported significant improvements in CRS-R scores following intervention, except for Yifei's study, which did not demonstrate any significant improvement (Yifei et al., 2022). Several studies have reported alterations in the connectivity of the default mode network (DMN) (Yu et al., 2017) and CBF in patients, as observed through fMRI examinations (Yu et al., 2021). Furthermore, EEG (Corazzol et al., 2017; Osinska et al., 2022), evoked potentials (Wang et al., 2022) and PET (Corazzol et al., 2017) have also provided evidence of brain changes following stimulation.

Adverse effects

Out of the total of 10 studies examined, only one study conducted by Hakon et al. (2020) systematically addressed the adverse effects. This particular study reported that a single patient experienced intermittent itching of the ear during

TABLE 2 American Academy of Cerebral Palsy and Developmental Medicine (AACPDM) levels of evidence.

Levels of evidence	Study design
I	Systematic review of randomized controlled trials (RCT) Large RCT (with narrow confidence interval)
II	Smaller RCTs (with wider confidence intervals) Systematic reviews of cohort studies "Outcomes research" (very large ecologic studies)
III	Cohort studies (must have concurrent control group) Systematic reviews of case–control studies
IV	Case series Cohort study without concurrent control group (e.g., with historical control group) Case–control study
V	Expert opinion Case study or report Bench research Expert opinion based on theory or physiologic research Common sense/anecdotes

stimulation, although the severity of this symptom did not significantly impact the level of stimulation.

Discussion

The primary objective of this systematic review was to assess the efficacy of stimulation of vagus nerve in facilitating the recovery of consciousness among patients diagnosed with DOCs. Additionally, the secondary objective was to evaluate any potential adverse effects associated with this therapeutic intervention.

A total of 10 articles were gathered, comprising three case reports, five case series, and two RCTs (Table 1). In 2017, Yu et al. conducted a study in which they documented the case of a 73-year-old female patient who experienced respiratory and cardiac arrests (Yu et al., 2017). The patient exhibited partial recovery of impaired consciousness, transitioning from a *VS*/UWS to a MCS after undergoing taVNS for a duration of 4 weeks. The patient's level of consciousness improved from 6 points (*VS*/UWS) to 13 points (MCS) on the CRS-R following the 4-week taVNS intervention. Additionally, fMRI revealed an increase in the functional connectivity of the DMN after the taVNS treatment. In the same year, Corazzol et al. conducted an invasive VNS procedure on a patient with *VS*/UWS caused by lesions in multiple regions of the brain (Corazzol et al., 2017). This patient had been in a *VS*/UWS state for over 15 years. VNS was administered to the patient's left vagus nerve for a duration of 6 months following the onset of treatment. The application of VNS resulted in a significant increase in the patient's CRS-R scores, rising from 5 to 10 points. Furthermore, the patient's condition transitioned from *VS*/UWS to MCS.

In 2020, Hakon et al. conducted a study to examine the feasibility and safety of transcutaneous taVNS in patients with DOCs following TBI (Hakon et al., 2020). The study included three patients in a *VS*/UWS and two patients in a MCS who had experienced diffuse axonal injury more than 28 days prior. Following the 8-week taVNS intervention, three patients demonstrated improvement in the CRS-R, with two MCS patients transitioning to a higher level of consciousness and one *VS*/UWS patient progressing to MCS. Another study conducted by Noe et al. (2020) to examine the feasibility, safety and therapeutic effects of taVNS treatment in 14 patients (six with *VS*/UWS and eight with MCS) who had been diagnosed with DOCs for more than 6 months following brain injury (seven patients with TBI, four patients with anoxia, and three patients with hemorrhage). Throughout the 4 weeks leading up to taVNS treatment, there were no observed alterations in the CRS-R scores of the patients. However, at the conclusion of the one-month follow-up, there was a significant increase in the CRS-R scores. It is noteworthy that none of the patients diagnosed with *VS*/UWS exhibited any modifications in their CRS-R scores, whereas five out of the eight patients diagnosed with MCS displayed a progressive rise in their CRS-R scores over the course of this study. Xiang et al. (2020) conducted a study to examine the therapeutic effects of VNS on patients with MCS. The study included 10 MCS patients who had experienced TBI in four cases, hemorrhage in five cases, and HIE in one case. These patients were evaluated more than 5 months after their initial injury and had undergone VNS implantation on the left vagus nerve. Following 3 months of VNS, a notable disparity was detected in the overall CRS-R scores when compared to the initial measurements. Subsequently, after 6 months of VNS intervention, CRS-R evaluations consistently exhibited substantial enhancements, leading to the emergence of one patient from the MCS.

In 2021, Yu et al. conducted a preliminary study to examine the cerebral hemodynamic correlates of taVNS in the restoration of consciousness (Yu et al., 2021). The study included 10 patients with DOCs resulting from severe brain damage, specifically anoxia (five patients), hemorrhage (three patients), and traumatic brain injury (two patients). The patients who exhibited a response to auditory stimuli demonstrated a favorable outcome on the GCS following the four-week taVNS treatment. Conversely, the patients who did not respond to auditory stimuli experienced unfavorable outcomes. Simultaneously, taVNS increased CBF of multiple brain regions in the DOCs patients who responded to auditory stimuli.

In 2022, Osinska et al. documented a case study involving a patient who exhibited a restoration of impaired consciousness following 6 months of taVNS treatment (Osinska et al., 2022). The subject, a 28-year-old female, had been diagnosed with *VS*/UWS based on a four-point assessment on the CRS-R subsequent to a TBI that had occurred 6 years earlier. Notably, the patient's CRS-R score significantly improved from 4 to 13 points after approximately 100 days of taVNS therapy, suggesting a transition from *VS*/UWS to MCS or potentially even MCS+. Wang et al. conducted an evaluation on the impact of VNMM on a group of 17 patients diagnosed with DOCs (Wang et al., 2022). The patients were categorized as follows: 4 patients with *VS*/UWS, 11 patients with MCS, and 2 patients in a coma state. The underlying cause of the DOCs in these patients was acquired brain injury, with three patients experiencing HIE, nine patients with hemorrhage, and five patients with TBI. The results of both the CRS-R and the GCS demonstrated notable enhancements in patients with DOCs following 4 weeks treatment with VNMM. Additionally, improvements were observed in somatosensory evoked potentials and brainstem auditory evoked potentials. Yifei et al. (2022) investigated the effect of taVNS in 12 patients with DOCs (*VS*/UWS, seven patients and MCS, five patients) due to acquired brain injury (stroke, eight patients; anoxia, two patients and TBI, two patients). TaVNS was applied for 14 days and none of the patients exhibited notable advancements on the CRS-R scale; nevertheless, the resting state EEG power spectrum indicated a decline in the energy of the delta band and an elevation in the energy of the beta band among patients diagnosed with MCS, as opposed to those diagnosed with *VS*/UWS.

In 2023, Zhou et al. conduct a randomized controlled clinical trial to investigated the therapeutic efficacy and safety of taVNS in patients with DOCs (Zhou et al., 2023). The study included a total of 57 patients with DOCs, comprising 25 patients in a *VS*/UWS and 32 patients in a MCS, all of whom had acquired brain injuries, specifically 30 patients with stroke and 27 patients with TBI. The findings from this initial study offer preliminary evidence suggesting that taVNS could potentially serve as a safe and effective method for facilitating the restoration of consciousness in patients diagnosed with MCS, but not in those with *VS*/UWS.

In general, the utilization of stimulation of vagus nerve in individuals with DOCs demonstrated effectiveness, as evidenced by positive outcomes observed in 9 of 10 studies (Corazzol et al., 2017; Yu et al., 2017; Hakon et al., 2020; Noe et al., 2020; Xiang et al., 2020; Yu et al., 2021; Osinska et al., 2022; Wang et al., 2022; Zhou et al., 2023). Additionally, only one study reporting an itching sensation in the ear (Hakon et al., 2020). Moreover, seven studies investigating alterations in brain activity subsequent to stimulation of vagus nerve reported favorable results, employing various techniques such as fMRI, EEG, PET, and SEP. In terms of the application methods, the application site and time schedules of taVNS were found to be consistent across seven studies, with the cymba conchae being the chosen site, sessions lasting 30 min, and occurring twice daily. However, there was considerable variation in the treatment period, ranging from 4 weeks to 6 months. In relation to the electrical stimulation parameters, the frequency remained consistent across all studies at 20–25 Hz. However, there was variability in both the pulse width (ranging from 200 to 1,000 μs) and intensity (ranging from 0.1 to 6 mA). Furthermore, two studies employed an invasive method of VNS through left surgical implantation (Corazzol et al., 2017; Xiang et al., 2020), while one study utilized TMS on the left mastoid (Wang et al., 2022). Nevertheless, these publications are unable to yield a definitive conclusion due to the insufficiency of high-quality evidence. Primarily, the reporting quality of these studies is generally inadequate, as none of the included studies have provided a confidence interval or a measure of variance. This limitation has hindered the possibility of conducting a meta-analysis. Additionally, only two studies are RCTs, both with small sample sizes, encompassing 12 patients (Yifei et al., 2022) and 57 patients (Zhou et al., 2023), respectively. Hence, it is plausible to assert that the aforementioned studies may have lacked sufficient statistical power, thereby accounting for the limited occurrence of statistically significant outcomes. Additionally, it is worth noting that the longest duration of follow-up in these studies was merely 4 weeks post-incident, which presents a noteworthy constraint. This limitation becomes particularly significant when considering that a definitive diagnosis of *VS*/UWS necessitates a minimum period of 12 months following a non-traumatic event and 6 months following a traumatic event (Laureys et al., 2004; Roquilly et al., 2021).

However, the existing literature does not provide any evidence of level one support for a rehabilitation treatment aimed at enhancing consciousness recovery in patients with DOCs (Kondziella et al., 2020; Edlow et al., 2021). Consequently, it is justifiable to argue that, in light of the absence of reported adverse effects in the study conducted by Hakon et al. (2020) and the theoretical framework proposed in animal studies, stimulation of vagus nerve holds promise as a potential treatment for patients with DOCs, as supported by our own clinical experience with these individuals. Currently, there is an increasing number of reported study protocols for non-invasive taVNS in the context of DOCs (Cheng et al., 2023; Zhai et al., 2023). These protocols aim to design randomized controlled trials with large multicenter samples to assess the efficacy and safety of taVNS therapy for DOCs, as well as investigate the neural anatomy associated with taVNS during the process of consciousness recovery.

There have been a multitude of scholarly reports discussing the potential mechanisms through which the stimulation of the vagus nerve may augment wakefulness. Previous research conducted by our team has shown that VNS facilitates the restoration of consciousness in rats experiencing coma following TBI. Additionally, it has been observed that the upregulation of neurotransmitters, specifically orexin-A, in the prefrontal cortex may contribute to the wake-promoting effects of VNS (Dong et al., 2018; Dong and Feng, 2018). Meanwhile, it is plausible that VNS could mitigate brain damage following traumatic brain injury through the suppression of inflammation, oxidative stress, and apoptosis (Tang et al., 2020; Wang et al., 2021). Moreover, the spinoreticular segment of the vagus nerve pathway establishes connections with neurons of the ascending reticular activating system (ARAS), a pivotal structure responsible for sustaining wakefulness (Yuan and Silberstein, 2016). This observation implies the potential for VNS to exert an impact on the ARAS through vagus nerve stimulation. Furthermore, augmentation of CBF (Kunii et al., 2021), activation of neurotrophic factors, and modulation of synaptic plasticity (Follesa et al., 2007; Biggio et al., 2009) may also contribute to these effects.

The data presented in this systematic review hold significant importance in informing future research regarding the utilization of vagus nerve stimulation in patients with DOCs. Notably, a gap in the existing literature has been identified, necessitating the need for well-designed RCTs to address this gap. It is crucial to emphasize that forthcoming RCTs should strictly adhere to rigorous methodological standards, particularly in terms of selecting appropriate allocation concealment techniques and effectively managing missing data. Additionally, it is imperative that these trials adhere to the established reporting guidelines as outlined by Moher et al. (2012). It is also essential to incorporate the calculation of confidence intervals and the measurement of statistical variability to enhance the feasibility of future meta-analyses. In addition, it is recommended to employ alternative evaluation methods, such as evoked potentials, encephalogram, and functional near-infrared spectroscopy (fNIRS), in addition to the current use of the CRS-R in RCTs. Finally, subsequent studies should rigorously examine the potential negative consequences associated with vagus nerve stimulation, including but not limited to bradycardia, laryngismus, dyspepsia, dyspnea, heightened coughing, pain, voice modulation, paresthesia, headache, pharyngitis, infection, and others (Ben-Menachem, 2001; Wheless et al., 2018).

However, this systematic review is subject to certain limitations. The inclusion of studies with limited availability of information and poor methodological quality hinders the ability to establish conclusive findings. Additionally, we encountered challenges in obtaining the unpublished protocol of a substantial RCTs from a clinical trial protocol database. Despite attempts to contact the author for information regarding the study's publication date and access to raw data, no response was received.

Based on the findings of this systematic review, it is not feasible to establish conclusive recommendations regarding the application of vagus nerve stimulation as a treatment for patients with DOCs. This limitation arises primarily from the scarcity of studies available in the existing literature and their inadequate methodological rigor. Consequently, further research is necessary before definitive conclusions can be reached regarding the efficacy of VNS or taVNS in the management of DOCs. Further research is imperative, encompassing the key attributes of rigorous methodology, appropriate sample size selection, utilization of outcome measures with enhanced content validity for assessing consciousness levels, comprehensive investigation into potential adverse effects, and long-term monitoring of follow-up outcomes, while considering the prognosis of consciousness disorders.

Author contributions

XD: Conceptualization, Funding acquisition, Writing – original draft, Writing – review & editing, Formal analysis. YT: Methodology, Software, Investigation, Validation, Project administration, Resources, Writing – review & editing. YZ: Data curation, Investigation, Software, Validation, Writing – review & editing. ZF: Conceptualization, Resources, Supervision, Validation, Visualization, Data curation, Funding acquisition, Writing – review & editing.

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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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Current status and prospect of transcutaneous auricular vagus nerve stimulation for disorders of consciousness

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Disordered Consciousness (DOC) is among neurological disorders for which there is currently no admitted treatment. The pathogenesis of DOC is still unclear, covering a variety of indistinguishable types of diseases, high misdiagnosis rate and poor prognosis. Most treatments remain to be clarified in the future to provide adequate evidence for clinical guidance. Neuromodulation technology aims to regulate neural circuits to promote awakening more directly. At present, it is confirmed that the potential of transcutaneous auricular vagus nerve stimulation (taVNS) as a therapeutic tool is worth exploring in the context of consciousness disorders, as previously proposed for invasive forms of VNS, in which the means of stimulating the vagus nerve to change the brain areas related to cosciousness have also received widespread attention. In this paper, we review the literature on taVNS and DOC to better understand the current status and development prospect of taVNS treament as a non-invasive neuromodulation method with sensitivity and/or specificity at the single subject.

KEYWORDS

transcutaneous auricular vagus nerve stimulation, disorders of consciousness, neuromodulation, vagus nerve, treament

Introduction

Disorders of consciousness (DOC) refer to a persistent state of loss of consciousness that at least four weeks following sudden onset brain injury, including vegetative state/ unresponsive wakefulness syndrome (*VS* /UWS) and minimally conscious state (MCS) (Royal College of Physicians, 2020). *VS*/UWS is an unconscious awakening state in which there is sleep–wake cycles and a range of reflexive and spontaneous behavior. Whereas patients in MCS have emotional and directional behavioral responses such as following instructions, using objects, pain localization, sight tracking, or gazing at the target (Laureys et al., 2010). DOC can also cause a range of debilitating sequelae which require cognitive, motor, communication, emotional, or behavioral rehabilitation of varying intensity and duration. Currently there are about 100,000 new patients with DOC each year in China (Zhao, 2018), and the impact on people's quality of life and the problems brought to the society are becoming increasingly prominent. Effective treatment are urgent problems to be solved in clinical practice.

Behavioral, pharmacological, and neurostimulatory approaches are the most commonly therapeutic strategies for various neurological diseases (Mishra, 2017). Whether it is neurotransmitter-based drugs or neuromodulation therapy, individual effective case experiences cannot be successfully generalized to the population level (Monti et al., 2015; Sanz et al., 2019; Edlow et al., 2021). Neuroscientists are investigating ways to accelerate the improvement of consciousness in DOC patients while promoting functional recovery. Neuromodulation therapy has shown beneficial effects in promoting recovery after traumatic brain injury, but existing treatments such as transcranial magnetic stimulation, deep brain stimulation (DBS) and hyperbaric oxygen therapy still need further systematic studies to demonstrate their mechanisms of action (Rezaei Haddad et al., 2019; Chen et al., 2022; Huang et al., 2023). The brain function is mediated by the interaction between different neural circuits and neurons in brain regions. The brain, nerves and endocrine systems transmit impulses through neural circuits and regulate internal organ functions. Amantadine is the only intervention recommended by US practice guidelines for DOC (Giacino et al., 2012). Existing approaches all require large, double-blind, randomized controlled trials to confirm possible therapeutic effects. Surgical treatment based on implantation of medical equipment mainly includes invasive brain stimulation such as DBS, which achieve the role of neuroplasticity by sending electrical pulses to specific parts of the central nervous system (Rezaei Haddad et al., 2019). However, the high cost of implantation and the risk of postoperative infection limit its application in clinic to some extent. Therefore, developing new clinical approach that is both effective and safe is urgently needed for the treatment of DOC. Accordingly, we provide an overview of the current parameters, experimental settings and effects of taVNS, and expect the review can contribute to a clear summary of the current research progress of taVNS for DOC.

Vagus nerve electrical stimulation and neuroplasticity

In terms of the location in the brain where consciousness exists, the more recognised areas are the cerebral cortex, including sensory areas, motor areas and associative areas. The thalamus, situated in the centre of the brain, is implicated in consciousness. Specifically, the thalamocortical loop, entailing the interaction between the thalamus and cortical areas, is deemed crucial for consciousness (Shine et al., 2023). Based on the neurobiology of the vagus nerve and its effect on neural activity, a "bottom-up" therapeutic mechanism has been developed to activate the central nervous system by electrically stimulating the peripheral nerves (Yap et al., 2020). The Vagus nerve provides a major communication channel for brain-integrated, neural reflex regulation of physiological functions (Yuan and Silberstein, 2016). Neuroendocrine-immune network of the vagus nerve involved in maintaining metabolic homeostasis and regulating various pathological processes in the brain (Mravec, 2010).

Neurotransmitters or their metabolites, as well as the central nervous system's function, may be regulated by VNS to alleviate mental disorders (Akhtar et al., 2016). Previous research has established that VNS can effectively regulate motor response and promote motor learning through γ-aminobutyric acid-mediated neuromodulation mechanism (Fitchett et al., 2021). The nucleus tract solitary (NTS) enters the central nervous system and directly projects onto the parabrachial nucleus, thereby projecting to the locus ceruleus (LC) and the dorsal raphe nucleus (DRN) (Krahl et al., 1998). LC is subjected to perpetual stimulation from the prefrontal cortex, which is accountable for executive function. It then transmits to the brainstem, cerebellum, thalamus, hypothalamus, and amygdala. In the hypothalamus, central nervous system (CNS) incitement has been shown to amplify neuronal activity in the PVN, causing the activation of the HPA axis. DRN is the main source of serotonin (5-HT) (Manta et al., 2009). VNS increased the discharge activity of LC and DRN, while regulating basal forebrain activity. These regions are responsible for the release of NE, dopamine (DA), 5-HT and acetylcholine throughout the brain. Using positron emission tomography (PET), the researchers discovered that VNS activated the ventral tegmental area (VTA), which is one of two brain regions responsible for DA release (Val-Laillet et al., 2015). It has been reported that only dopamine metabolites experience an increase in the cerebrospinal fluid (CSF) following VNS therapy (Carpenter et al., 2004). VNS has a positive effect on disorders of consciousness and can regulate the activity of the human brain. The Food and Drug Administration (FDA) approved a prospective randomized cross-over trial to verify that VNS can objectively improve clinical manifestations in patients with severe craniocerebral trauma brain injury (TBI) (Wang et al., 2021). An awakening effect may result from increased cerebral blood flow and metabolic activity of the thalamus and reticular formation in response to the increased cerebral blood flow.

Traditional VNS requires surgery which implant an electrical device in the chest wall next to the cervical branch of the left vagus nerve with the attendant financial costs and risks to the patients (Yang and Phi, 2019). Furthermore, VNS surgery can cause potential adverse events including arrhythmias, hoarseness and other respiratory complications such as cough and nocturnal dyspnoea due to nerve damage, which limits dose regulation in clinical settings and patient tolerance (Goggins et al., 2022). VNS can also cause changes in breathing patterns during sleep, leading to an increase in the number of obstructive apnea and hypoventilation (Gurung et al., 2020). Simultaneously, a battery necessitates replacement every 3–5 years. Furthermore, post-implantation surgery, just 30% of patients exhibit clinical response (Downes et al., 2023).

Non-invasive brain stimulation (NIBS) has the potential to modify the circuit-level of neuronal signalling non-surgically. This can be achieved through manipulation of the relative levels of excitatory and inhibitory signalling, or via activation of the reticular activating system or thalamus-associated nuclei to heighten arousal levels. The procedure is free from side effects that are typically associated with invasive treatments (Zaghi et al., 2009).

Transcutaneous auricular vagus nerve stimulation (taVNS) in DOC

As a novel and non-invasive neuromodulation method, taVNS achieves therapeutic effects by stimulating the afferent branches of the vagus nerve distributed in the skin. It is discovered that vagus nerve has a branch of afferent projections at the auricular concha (Yuan and Silberstein, 2016). Unlike other non-invasive techniques of brain stimulation, taVNS does not make direct alterations to specific target areas of the cortex's neurons. Instead, it enhances the noradrenergic neurotransmission by indirectly stimulating the LC and thereby modulates brain functions in a systematic manner (Ruhnau and Zaehle, 2021).

It has been demonstrated that taVNS activated the vagal pathway, which suggests that taVNS is a promising form of VNS (Hilz, 2022; Hilz and Bolz, 2022).Thus, similar effects to those obtained with VNS may be achieved by superficial stimulation of the area in the ear that has vagus nerve innervation. Ventureyra first proposed taVNS in 2000 (Ventureyra, 2000). TaVNS is a non-invasive vagus nerve stimulation method, and its target is the vagus nerve branch of the external ear. After Fallgatter AJ et al. first observed taVNS in 2003 (Fallgatter et al., 2003), repeatable vagus nerve sensory evoking potentials were detected in the scalp, which confirmed that non-invasive vagus nerve stimulation was feasible. Animal studies have shown that taVNS activates cholinergic anti-inflammatory pathways in brain-injured regions, increases Ach levels, inhibits the secretion of inflammatory factors and thus mediates neuroprotection (Zhao et al., 2022).

Although non-randomized controlled trial studies and reviews are not particularly convincing, they do indicate that taVNS may have a role in the emergence from a coma. Yu[34]reported a patient in hypoxic encephalopathy treated with taVNS. In just 4 weeks of treatment, the patient's clinical score increased significantly with intensities of 4-6 mA and a frequency of 20 Hz twice a day. Blood oxygen level-dependent fMRI results indicate obvious activation of the posterior cingulate/anterior gyrus and thalamus, which play a vital role in awakening. Stefan Dietrich and colleagues demonstrated that taVNS can activate the left locus coeruleus, thalamus, left prefrontal cortex, postcentral gyrus, cingulate gyrus, left insular lobe, and other brain regions related to the vagus pathway (Dietrich et al., 2008). A recent fMRI study examining taVNS found that taVNS requires intact auditory function, and can enhance the response to auditory stimuli in patients with DOC (Yu et al., 2021). Potential side effects of taVNS on the brain include tingling caused by electrode stimulation and mild facial twitching with high intensity stimulation. In summary, taVNS is comparable to implanted vagus nerve stimulation, and several studies have demonstrated its safety, feasibility, and efficacy as a treatment option for patients with DOC (Hakon et al., 2020; Noé et al., 2020; Yifei et al., 2022).

The possible mechanisms of taVNS in DOC

Research into activating vagus nerve stimulation to promote arousal is currently at the feasibility stage (Table 1): Existing studies have gained validity through changes in functional brain networks, UWS/*VS* patients improve with MCS and show improved brain connectivity patterns. A suggested vagocortical pathway model, based on the mechanism of consciousness recovery, proposes that taVNS could offer a therapeutic benefit to patients with DOC by activating brainstem pathways associated with noradrenaline and serotonin (Briand et al., 2020).

Specifically, transcutaneous auricular vagus nerve stimulation results in the activation of NTS by stimulating the trigeminal spinal nucleus, which subsequently activates NTS. Activation of the associated nuclei promotes the release of NE (Zaehle and Krauel, 2021). Evidence suggests that NE is an important mediator of arousal (Ricci et al., 2020). Increasing the concentration of NE in the brain can promote the functional recovery after severe craniocerebral injury. Whether in coma, *VS* or MCS, the increase of DA and NE can improve the level of consciousness (Fukabori et al., 2020). A pooled mega-analysis confirmed that taVNS on salivary alpha-amylase as an indirect marker of noradrenergic activity (Giraudier et al., 2022). The activation of the LC-NE system may be the central mechanism of action of taVNS. The hypothesis that taVNS can enhance central NE release is supported by P300 event-related potentials, which serve as electrophysiological markers of the LC-NE system. A recent study found that taVNS caused pupil dilation and a concomitant decrease in occipital alpha activity in healthy individuals, indicating that taVNS may promote NE release and enhance attention (Chmielewski et al., 2017). Studies have consistently shown that reductions in central norepinephrine have a negative effect on attention. Conversely, increasing NE levels has shown to improve attention, affirming that NE facilitates the function of cortical circuits linked with alertness and attention (Smith and Nutt, 1996; Aston-Jones and Cohen, 2005).

TaVNS has been demonstrated to regulate attention and cognitive performance in healthy individuals, as well as through NTS activation, which may refers to cause changes in the concentration of neurotransmitters such as gamma-aminobutyric acid (GABA) through afferent vagal fiber activation of LC, thereby improving cognition, among other things (Van Leusden et al., 2015; Fischer et al., 2018). Capone et al. proposed that taVNS regulates cortical excitability in healthy subjects by regulating the GABA inhibitory loop (Capone et al., 2015). Amantadine treatment accelerates functional recovery in patients with post-traumatic disorders of consciousness, which may also involved in GABA neurotransmission system (Giacino et al., 2012). The plasticity of the cerebral cortex enables the healthy cortical area to take over some of the functions lost in the damaged area, and the mechanisms that regulate cortical plasticity are shared between the sensory and motor cortex. TaVNS stimulates Aβ-fibers to produce signal pulses that travel from the periphery to the brainstem nuclei and ultimately reach the cortex (Butt et al., 2020).

Increased cerebral blood flow may provide another mechanism by which taVNS operates. It is widely recognized that the rehabilitation of consciousness is correlated with the regeneration of the thalamus cortex (Laureys, 2005). fMRI results demonstrate that taVNS induces significant blood oxygen level-dependent (BOLD) signal changes in the prefrontal cortex of healthy participants. The signal intensity of the prefrontal lobe, thalamus, amygdala, and posterior cingulate gyrus was found to be elevated in the taVNS stimulation group, compared to the control group (Peng et al., 2018). The thalamus selectively transmits information to various parts of the cortex, which is closely related to sleep regulation and consciousness and even plays a key role in regulating wakefulness. Previous studies have found that emotional stimulation can activate the posterior cingulate cortex, which is part of the limbic system and mediates processes related to emotions and memory processing (Maddock et al., 2003).

It has also been suggested that preventing the inflammatory surge after a TBI may prevent systemic inflammatory response syndrome, sepsis, and multi-system organ failure (Johnson and Wilson, 2018). It may also be possible for taVNS to alleviate damages caused by TBI due to widespread neural inflammation. Regulation of cytokine expression by taVNS may provide significant therapeutic value in DOC. There is accumulating evidence to suggest that it can be used to help quell

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TABLE 1 Summary of studies on transcutaneous auricular vagus nerve stimulation in disorders of consciousness.

Authors	Patients	Brain pathology	Disease Duration			Data cycle			Clinical Results	Stimulation parameter			Brain evaluation
			acute	subacute	prolonged	Min/session	Time/d	Period		Hz	Pulse width (us)	Intensity (mA)	
Yu et al. (2017)	1	Anoxia	0	1	0	30	2	50 days	CRS-R: 6→13	20	1,000	4~6	fMRI
Noé et al. (2020)	14	TBI: 7 Anoxia: 4 Hemorrhage: 3	0	0	14	30	2	28 days	CRS-R: 62.5% MCS patients improved	20	250	1.5	-
Hakon et al. (2020)	5	TBI	0	3	1	240	1	56 days	All patients improves	25	250	0.5~1	-
Yu et al. (2021)	10	Anoxia: 5 Hemorrhage: 3 TBI: 2	2	4	4	30	2	28 days	Responded to auditory stimuli patients get improved	20	500	4~6	fMRI
Yifei et al. (2022)	12	Stroke: 8 Anoxia: 2 TBI: 2	0	0	12	30	2	14 days	CRS-R: no change	20	1,000	4~6	EEG

CBF, cerebral blood flow, CRS-R, Coma Recovery Scale-Revised, EEG, electroencephalography, fMRI, functional magnetic resonance imaging, DMN, default mode network, MCS, minimally consciousness state, NC, not commented, TBI, traumatic brain injury, taVNS, transcutaneous auricular vagus nerve stimulation, VS, vegetative state.

inflammation in a number of other autonomic or inflammatory disorders, which would make it useful for a wider range of patients suffering from disorders of conciousness as well (Falvey et al., 2022).

The enhanced basal metabolic level of the thalamus results in increased CBF in the cerebral cortex, encompassing the somatosensory cortex in the occipital lobe, superior temporal gyrus, and middle temporal gyrus, along with the executive control cortex in the prefrontal region via the intersensory system's ascending pathway (Rutecki, 1990; Craig, 2003). Simultaneously, enhancing the basal metabolic rate in the insula results in increased metabolism in the somatosensory cortex and prefrontal cortex, both of which play a role in the interoceptive system (Bourdillon et al., 2019). The interoceptive system plays a vital role in preserving a dynamic equilibrium in the body and potentially enhancing self-awareness, the foundation of human emotional well-being and consciousness. Among a variety of sensory pathways connecting to the brain, the vagus nerve is one of them. Consequently, taVNS might elicit the recovery of consciousness by activating the interoceptive system.

Neuroregulation is a physiological process that occurs in normal human life and involves changes in neurons and synaptic properties caused by neurons or substances they release. Nerve stimulation has ability to regulate how the central nervous system processes information, acting as a compensatory mechanism for the loss of normal function caused by disease or injury. While taVNS may not be recommended as a primary or solitary treatment for DOC, existing clinical data suggests that it may enhance brain plasticity and connectivity between the thalamus and cortical region associated with consciousness, thus potentially offering benefits for addressing consciousness disorders.

Limitations and prospects

Although much progress has been made in the treatment of DOC in recent years, there are still many problems to be solved in diagnosis, prognosis, treatment and rehabilitation of DOC. Patients may receive multiple stimulation methods or drug interventions simultaneously, so large-scale multicenter randomized controlled trials are lacking. The methodological quality of existing studies is low, such as limited simple numbers, high drop-out rates, and lacked proper randomization controls. Further high-quality evidence for the efficacy and safety of taVNS in a multicentre-trial to collect data with adequate sample size, and proper control trials is required. DOC have large differences in etiology and clinical manifestations, which makes it difficult to implement placebo controlled trials. Completely different lesions in the central nervous system can lead to the same clinical manifestations and limit the clinical inclusion criteria. Case reports of non-invasive brain stimulation techniques may be related to natural recovery or other treatments, to some extent, the effect of taVNS on awaking can be seen here. Due to the lack of standardization of methods and the diversity of experimental design, the improvement in clinical behavior is not enough to produce diagnostic changes in the revised version of the coma recovery scale, which may be related to the baseline differences of patients and small sample size. It may also be the source of biases in the results of existing studies, which makes it difficult to interpret the results, so further studies are needed to fully elucidate the mechanistic actions that explain potential role.

In the future, studies may focus on how stimulation affects brain networks and the possible mechanisms involved. It is necessary to design a more rigorous large sample randomized controlled trial, and classify the etiology, course of disease and level of consciousness of the patients in order to determine and verify the effectiveness of the treatment. Researchers are advised to summarize the clinical characteristics of patients who can benefit from the treatment, constantly improve the inclusion and exclusion criteria of the study and analyze cases of adverse reactions. There are many studies that provide inconsistent results on the efficacy of taVNS, either no effect or even the opposite effect. One reason for this may be the variability of the taVNS yield-enhancing parameters in use. There are many different stimulation frequencies (0.5–30 Hz), pulse widths (50-500 µs), intensities (0.5–50 mA) and stimulation positions. Few studies have aimed to assess the role of taVNS parameters on efficacy. This is not only a problem for taVNS, but also for the entire field of neuromodulation. They may do in-depth study of the therapeutic mechanism and constantly optimize the stimulation parameters such as stimulation target, stimulation frequency and stimulation duration to achieve more diversified and lasting clinical improvement.

Therefore, by combining various imaging techniques such as neuroimaging and neurophysiological assessment, we can better grasp the internal anatomical structure and network of the brain to determine the brain area mainly affected by the stimulation method. Neuromodulation and brain-computer interface technologies are cutting-edge hot development directions for future clinical research. According to the residual brain structure and function, we can better determine the beneficiary population and improve the curative effect. It also may be possible to link other physiological parameters associated with vagal stimulation to stimulation efficacy. Among these, the efficacy of taVNS in regulating heart rate and its coupling with neural activity deserves further investigation.

In addition, it has not been proven that taVNS is the decisive cause of changes in consciousness-related brain regions. Other stimulation methods apart from the vagus nerve may also be the causes of the observed results. Therefore, in basic experiments, it is necessary to further clarify the pathological basis of consciousness disorder, explore the physiological basis of the efficacy of taVNS, find suitable biomarkers for taVNS, metabolomics technology may be a biomarker to explore the response of taVNS. If patients can be detected by simple body fluids (blood, cerebrospinal fluid, urine, etc.), it will be an important breakthrough in precision diagnosis and treatment technology. There is an urgent need to seek responsive biomarkers to provide personalized treatment based on the patient's clinical characteristics and brain lesions. By the way, we may need optimized stimulation parameters such as pulse width, frequency, current intensity, amplitude, and duration to improve treatment efficiency, reduce side effects or adverse reactions, and establish standard procedures in clinical practice.

Conclusion

Consciousness comes from the brain. The brain can be studied at different but closely related levels, such as genes, proteins, synapses, neurons, neural loops to brain regions and the whole brain. There is no doubt that any single therapeutic approach has its own advantages and limitations and cannot solve all the problems associated with DOC. Meanwhile, any effective means of awakening must not be neglected. Despite clinical and scientific challenges, given that early post-injury period in DOC research is becoming increasingly important, as this is the most critical period for neuroplasticity and medical care decisions that have an undeniable impact on patient survival. Elucidating the mechanisms of consciousness based on existing models of DOC and establishing unique and clinically accurate identification techniques to improve clinical arousal rates remains a daunting task. It is precisely because cost is typically a major factor limiting access to medicines as well as limiting basic research, Ultimately, the potential of taVNS substantially increasing equity in medical care and use of basic science. This review shows that taVNS bears the prospect of being applied to DOC, however, more solid evidences are needed. TaVNS is a promising treatment method, and there are many studies in progress (Table 2). We look forward to the results of these studies can bring new hope to DOC patients.

TABLE 2 Summary of protocal on transcutaneous auricular vagus nerve stimulation in disorders of consciousness.

Authors	Patients	taVNS device	Data cycle			Stimulation parameter			Brain evaluation
			Min/ session	Time/d	Period	Hz	Pulse width (us)	Intensity (mA)	
Zhai et al. (2023)	15	SDZ-IIB	20	1	NC	1,10,25,50,100	NC	1 ~ 1.5	32- channel EEG
Vitello et al. (2023)	44	NEMOS/ tVNS®	45	1	5 days	25	200 ~ 300	3	EEG、EKG
Shou et al. (2023)	90	NC	NC	2	40 days	20 Hz output 7 s, 4 Hz output, and 3 s alternate cycle output	NC	NC	EEG、fMRI
Zhuang et al. (2023)	84	SDZ-IIB	30	2	4 weeks	4 ~ 20	30	1 ~ 1.5	EEG、MRI

CRS-R, Coma Recovery Scale-Revised, EEG, electroencephalography, fMRI, functional magnetic resonance imaging, NC, not commented, taVNS, transcutaneous auricular vagus nerve stimulation.

Author contributions

YiW: Writing – original draft. JZ: Project administration. WZ: Resources. YuW: Project administration. SL: Project administration. YY: Writing – review & editing. YZ: Resources. JH: Writing – review & editing. PR: Writing – review & editing.

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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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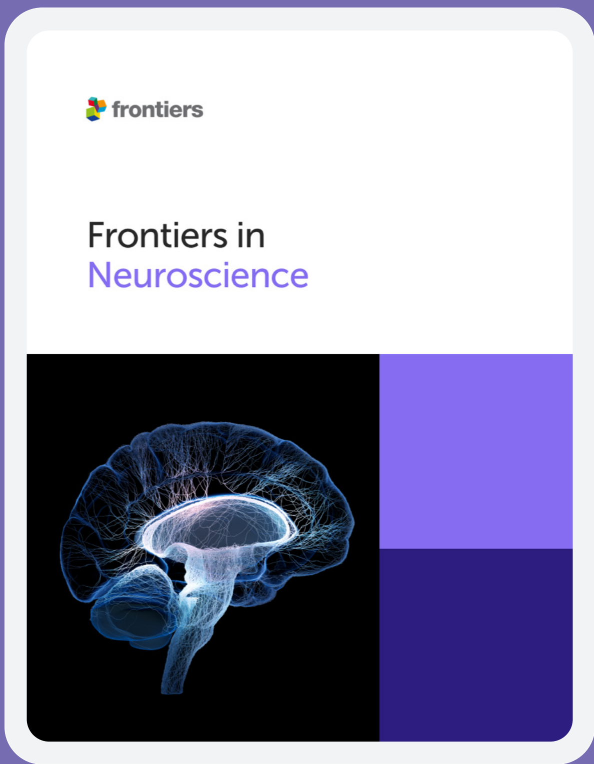

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