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Brain–Computer Interfaces for Awareness Detection, Auxiliary Diagnosis, Prognosis, and Rehabilitation in Patients with Disorders of Consciousness

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Abstract

In recent years, neuroimaging studies have remarkably demonstrated the presence of cognitive motor dissociation in patients with disorders of consciousness (DoC). These findings accelerated the development of brain–computer interfaces (BCIs) as clinical tools for behaviorally unresponsive patients. This article reviews the recent progress of BCIs in patients with DoC and discusses the open challenges. In view of the practical application of BCIs in patients with DoC, four aspects of the relevant literature are introduced: consciousness detection, auxiliary diagnosis, prognosis, and rehabilitation. For each aspect, the paradigm design, brain signal processing methods, and experimental results of representative BCI systems are analyzed. Furthermore, this article provides guidance for BCI design for patients with DoC and discusses practical challenges for future research.

Keywords
- ► disorders of consciousness
- ► brain–computer interfaces
- ► EEG-based BCIs
- ► unresponsive wakefulness syndrome
- ► minimally conscious state

Disorders of consciousness (DoC) are clinical conditions ranging from a coma to a vegetative state/unresponsive wakefulness state (VS/UWS) or a minimally conscious state (MCS).[1] After severe brain injury, patients may fall into a coma, appearing neither awake nor aware. Certain patients may progress to a VS/UWS, appearing awake but not aware of themselves or their environment. Other patients may improve to a MCS, showing inconsistent but reproducible evidence of self or environmental awareness.[2]

Currently, behavioral scales such as the Glasgow Coma Scale (GCS) and the JFK Coma Recovery Scale-Revised (CRS-R), which are highly dependent on the patient's motor ability, are still the traditional way to evaluate patients with DoC.[3] Because patients with DoC often lack the ability to perform normal physical movements and their reflexes and voluntary movement may be indistinguishable, this observation-based assessment appears to be insufficient. Thus, approximately 40% of patients in a MCS might be misdiagnosed as a VS/UWS.[4–6] Detecting signatures of consciousness (i.e., command-following or communication) in these patients is extremely challenging. Therefore, bedside tools that bypass the motor pathway to identify covert consciousness are warranted.

Since BCIs were first applied to the study of patients with DoC in 2005, their application in patients with DoC has expanded considerably. Advanced techniques based on neuroimaging and neurophysiological methods have been developed and applied to the assessment of residual

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consciousness and cognitive functions in patients with DoC. In recent years, brain–computer interface (BCI) technology has been rapidly developed; this technology has played an important role in the detection of cognitive motor dissociation (CMD) in patients who clinically appear to be VS/UWS in addition to restoring their communication abilities.[7–10] An increasing number of studies have strikingly demonstrated the presence of CMD in patients with DoC. Using noninvasive techniques, such as electroencephalography (EEG) and functional magnetic resonance imaging (fMRI), evidence of high levels of cognitive function and reliable compliance with commands was found in patients with CMD who behaviorally appeared unresponsive.

Compared with other advanced diagnostic techniques, EEG is more widely available, less expensive, and more practical for evaluating patients with DoC.[11] EEG-based BCIs may help in the development of relatively inexpensive and compact systems that can be readily deployed at the bedside. In support of this challenging population of patients with DoC, many studies on EEG-based BCI studies have been conducted over the past 20 years. Recent advances in the clinical application of BCIs may provide important breakthroughs in the diagnosis and treatment of patients with DoC.[12] The purpose of this article is to review the possible applications of BCIs to improve the quality of life for patients with DoC and their families. Notably, this article focuses on noninvasive EEG-based BCIs, as they may be applicable to the widest range of patients. The literature on invasive BCIs is not addressed here.

This review is structured as follows. First, the definitions and composition of EEG-based BCI are described, and literature related to their use in patients with DoC is discussed. Next, according to the applications of BCIs in the DoC population, the literature is divided into four aspects: awareness detection, auxiliary diagnosis, prognosis, and rehabilitation. Several studies on BCI systems are reviewed by analyzing their BCI paradigm designs, brain signal processing methods, and experimental results. Finally, this review concludes with suggestions for the design of BCIs for patients with DoC and provides an outlook on the key challenges for future research.

Methods

We searched the PubMed database in all fields using the keywords ((BCI) OR ("Brain-Computer Interface")) AND ((DOC) OR ("disorders of consciousness") OR ("vegetative state") OR ("unresponsive wakefulness syndrome") OR ("minimally conscious state") OR (coma)). We focused on the articles published in the past 20 years, with no language restrictions, related to the application of BCIs in patients with DoC. Excluding review articles, the number of relevant studies from 2002 to 2021 was 59. There were 13 articles that were excluded because they did not focus on BCIs in patients with DoC. Therefore, 46 studies were reviewed (►**Fig. 1**).

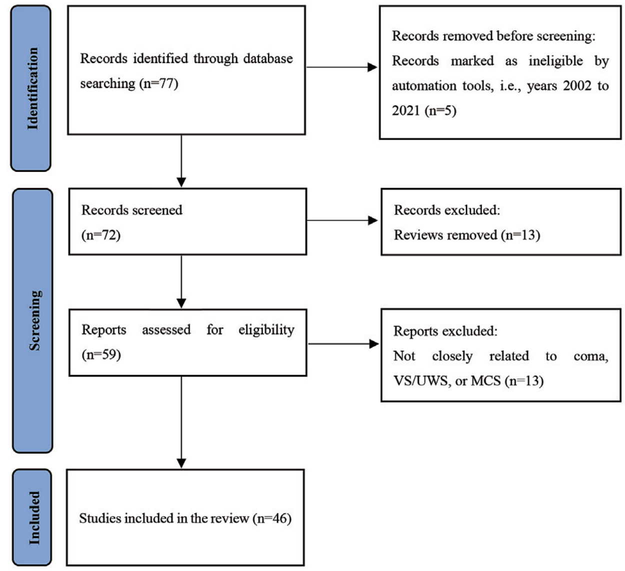

Fig. 1 PRISMA flow chart. MCS, minimally conscious state; VS/UWS, vegetative state/unresponsive wakefulness state.

BCIs in Patients with DoC

By definition, BCIs use brain activity to establish a nonmuscular communication pathway between the human brain and external devices,[13] making it possible for BCIs to provide evidence that patients with DoC may have movement-independent consciousness. A typical BCI system is shown in ►**Fig. 2**, which consists of four essential elements: signal acquisition, signal preprocessing, feature extraction, classification, and command translation to either external devices (e.g., smart home) or feedback (e.g., deep brain stimulation). Specifically, the first step is to acquire the patient's brain signals. Brain patterns, such as P300 event-related potentials (ERPs),[14] steady-state evoked potentials (SSEPs),[15] or sensorimotor rhythms (SMRs),[16] are induced and recorded in response to a task or a stimulus. The second step is to preprocess the brain signals to reduce artifact and extract discriminative features. The third step is to use machine learning algorithms for feature training and classification of new features. The final step is to translate the classification results into commands to control external devices (e.g., speller, wheelchair, prosthesis) or to detect command-following and functional communication. Unlike offline analysis based on fMRI and EEG, an important advantage of BCIs is that they can provide real-time detection results as a form of feedback, which has positive effects for patients if they possess awareness.[7]

The application of BCIs in patients with DoC to awareness detection, auxiliary diagnosis, prognosis, and rehabilitation is discussed in detail later.

BCI-Based Awareness Detection

Accurate awareness assessment for patients with DoC is vital to guide clinical treatment decisions and prevent premature withdrawal from life-sustaining therapies. EEG-based BCI systems can detect brain activation during command-following tasks in patients with severe brain injury, analyze and classify brain responses reflecting patients' thoughts in real time, and thus effectively identify patients with CMD. Compared with healthy individuals, patients with DoC have

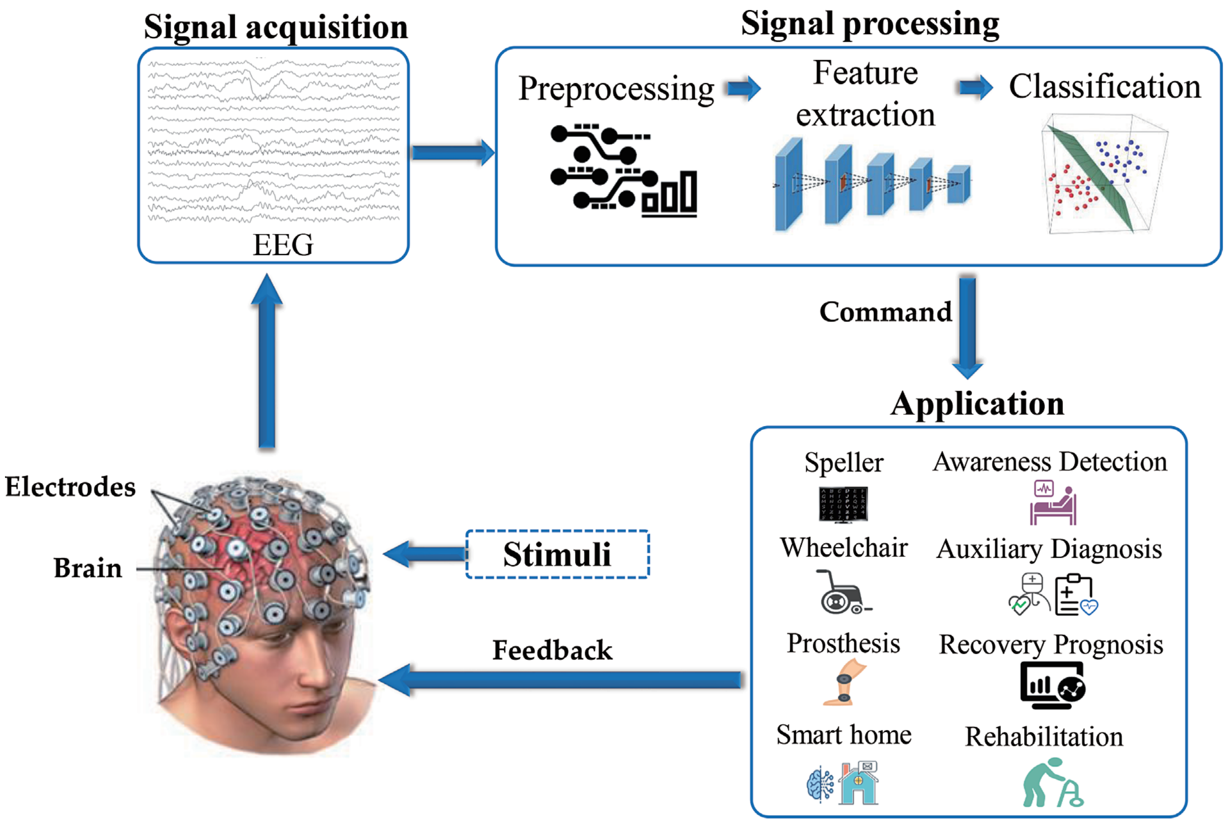

Fig. 2 A typical brain–computer interface framework, which includes signal acquisition, signal processing, application, and feedback. EEG, electroencephalography.

limited cognitive abilities. Therefore, BCIs developed for healthy individuals are often not applicable for these challenging populations. In recent years, many researchers have successfully used BCI technology to identify covert consciousness in patients with DoC through brain patterns, such as P300, steady-state visual evoked potential (SSVEP), and motor imagery. Several representative works on BCI-based awareness detection in patients with DoC are shown in ►**Table 1**.[17–26]

As the vision of most patients with DoC is commonly limited, researchers naturally considered using an auditory paradigm to detect awareness. Lulé et al first used an auditory P300 paradigm to detect awareness in patients with DoC.[17] In each trial, each of four stimuli ("yes," "no," "stop," and "go") appeared randomly 15 times, and the sound duration was 400 ms with a 600-ms break. The algorithm classified the subject's ERP responses based on spatiotemporal features. Experiments were conducted involving 16 healthy subjects and 18 patients with DoC (3 VS/UWS, 13 MCS, and 2 locked-in syndrome [LIS] patients). In an online experiment, subjects needed to answer 10 or 12 questions that were familiar to them (e.g., "Is your name Quentin?"), and the experimenter acquired their answer in a second and told the subject the result in each positive trial. The healthy subjects had a correct response rate of $73 \pm 23\%$. One LIS patient had a correct response rate of 60%. The other patients with DoC had a correct response rate of less than 40%. Therefore, the MCS and VS/UWS patients did not show a detectable response, but consciousness could be detected through the BCI system in one LIS patient. The experimental results show that the performance of a single auditory BCI for awareness detection in patients with DoC still needs to be improved.

Sensorimotor rhythm, as a stimulus-independent spontaneous signal, is widely used by many BCI researchers in various practical applications. Coyle et al proposed using a sensorimotor rhythm-based BCI with feedback to help patients with DoC actively participate in decision-making.[21] In the initial session, all patients were asked to imagine squeezing the right hand or wiggling the toes in six alternating blocks. Then, three patients participated in the training session with visual or auditory feedback. All patients in a MCS achieved classification accuracies significantly higher than 50% in the first session. Furthermore, the experimental results showed that after eight BCI training sessions, the training scores of all subjects improved significantly. Auditory feedback was found to be more suitable for patients in a MCS as experiments progressed. These experimental results indicated that patients in an MCS could modulate SMRs with feedback in a simple closed-loop BCI system.

Several studies in recent years have shown that multimodal/hybrid BCIs (or their variants) could result in better performance than single BCI systems in healthy subjects and patients with DoC.[7,27] Pan and colleagues developed a hybrid BCI combining P300 and SSVEP for awareness detection. In the online experiment, seven patients with DoC (4 VS/UWS and 3 MCS) were instructed to focus their attention on their own or unfamiliar facial photos in probing

Table 1 Studies on BCI-based awareness detection in patients with DoC

References	Study group	Paradigms	Results	Remarks	Limitations
Lulé et al[17]	3 VS/UWS, 13 MCS, and 2 LIS patients	P300	1 patient with LIS and 1 MCS patient showed functional communication with the auditory BCI	Auditory BCIs can provide a new channel of communication for patients with DoC	Low sensitivity
Pan et al[18]	4 VS/UWS, 3 MCS, and 1 LIS patients	P300 and SSVEPs	3 patients (1 VS/UWS, 1 MCS, and 1 LIS) could follow the instructions to selectively pay attention to the specified photo	Patients with DoC can simultaneously stimulate both P300 and SSVEP responses, and this hybrid BCI can be used for awareness detection for patients with DoC	N/A
Li et al[19]	6 VS/UWS, 3 MCS, and 2 EMCS patients	P300 and SSVEPs	2 VS/UWS, 1 MCS, and 2 EMCS patients had accuracies significantly above the chance level in the three digital tasks	Patients with DoC have the abilities to perform number processing, arithmetic, and command-following	Patients with visual impaired cannot use the system
Wang et al[20]	3 VS/UWS and 4 MCS patients	P300	1 VS/UWS and 4 MCS patients had significant responses using an audiovisual BCI paradigm.	This audiovisual BCI could be used to detect awareness in patients with DoC.	Patients with visual impaired cannot use the system.
Coyle et al[21]	4 MCS patients	Sensorimotor rhythms	4 MCS patients showed significant activations during the multiple assessments	The patients in an MCS could modulate sensorimotor rhythms with feedback in a simple BCI system	Limited number of patients, and each patient participated in small numbers of sessions
Xie et al[22]	5 VS/UWS and 3 MCS patients	P300	2 VS/UWS patients and 1 MCS patient showed the ability to recognize numbers according to instructions	The audiovisual paradigm can activate the responses of P300, N400, and late positive complex in patients with DoC	It requires a relatively high level of cognitive ability to understand task instructions
Curley et al[23]	4 VS/UWS, 15 MCS, and 9 EMCS patients	Motor imagery	21 patients in these groups had the capacity of command-following	A motor imagery–based BCI paradigm could be used for awareness detection, and fluctuations were found in EEG responses of patients with DoC	N/A
Guger et al[24]	12 VS/UWS patients	Vibrotactile P300	2 patients achieved significant accuracy of answering questions in the communication session	The chronic VS/UWS patients can follow command and answer questions with Yes or No	Low sample size
Huang et al[26]	2 VS/UWS patients, 5 MCS patients, and 1 EMCS patient	Emotion recognition	The BCI system recognized the evoked emotions in 2 MCS patients and 1 EMCS patient	BCI-based emotion recognition may be a reliable tool for consciousness detection in patients with DoC	Low sample size

Table 1 (*Continued*)

References	Study group	Paradigms	Results	Remarks	Limitations
Huang et al[25]	3 VS/UWS and 4 MCS patients	P300 and SSVEP	3 patients in an MCS achieved accuracies 64–70% higher than chance level	The efficiency of awareness detection in patients with DoC could be improved by an asynchronous hybrid BCI system	The types of communication questions were limited

Abbreviations: BCI, brain–computer interface; DoC, disorders of consciousness; EEG, electroencephalography; EMCS, emergence from minimally conscious state; LIS, locked-in syndrome; MCS, minimally conscious state; SSVEP, steady-state visual evoked potential; VS/UWS, vegetative state/unresponsive wakefulness state.

command-following.[18] Two patients successfully attended to their own or the unfamiliar photos with the accuracies of 66 and 74%, which is significantly higher than the chance level. Wang et al conducted a multimodal BCI study combining visual and auditory stimuli.[20] The authors designed an audiovisual BCI system based on the combination of visual and auditory stimuli, which was the same number and appeared simultaneously in the same orientation. In this BCI paradigm, two digits from 0 to 9 served as stimuli and appeared randomly on the left and right sides of the interface. The subjects needed to selectively pay attention to the target stimulus according to the cue and silently count the number of occurrences. In Experiment I, 10 healthy subjects interacted with three kinds of BCI systems (audiovisual, visual-only, and auditory-only BCI systems). The differences in EEG responses and the performance of the system under the three paradigms were analyzed and are presented in ►**Fig. 3A**. The results showed that ERP responses can be evoked in the three BCI paradigms and some ERP responses (such as P300) were higher under the visual-auditory paradigm than under the other two paradigms. Thus, the design of this paradigm is conducive to improving system performance.

The authors then applied this audiovisual BCI system to awareness detection in seven patients with DoC (three patients in a VS/UWS and four patients in an MCS). In Experiment II, the patients were asked to select the target number through the BCI system as instructed by the operator or family member. The experimental results found that five patients elicited ERP responses and achieved accuracies significantly higher than the chance level in multiple sessions. Compared with the single-modal system, the hybrid/multimodal system exhibits better recognition effect and stability. An increasing number of multimodal paradigms are likely to be applied in clinical practice for patients with DoC.

BCI-Based Auxiliary Diagnosis

In current clinical practice, behavioral scales, such as the CRS-R, is the "gold standard" for establishing the diagnosis of patients with DoC. However, behavioral assessment scales rely on patients' behavioral responses, and patients with DoC have motor impairments and lack behavioral responses leading to a relatively high misdiagnosis rate. Contrastingly, EEG-based BCIs directly detect brain responses to external stimuli and are not limited to clinicians' subjective observations of patients' behaviors. Therefore, to assist the CRS-R behavioral assessment, BCIs can provide an objective measurement and be used for auxiliary diagnosis of patients with DoC. ►**Table 2** lists the studies on BCI-based auxiliary diagnoses in patients with DoC in recent years.[28–34]

A novel oddball paradigm was designed specifically to mimic the assessment of auditory startles in the CRS-R,[29] in which the background noise (40 dB) and the sound of a clap (90 dB) were used as the standard and deviant stimuli, respectively. Four standard stimuli and one deviant stimulus were included in a stimulus round and were presented to the patients randomly. The deviant stimuli were used to evoke the related ERP components that could be detected by the proposed BCI. The ERP waveforms evoked by the deviant stimuli in selected channels and averaged scalp map of EEG response were analyzed and presented in ►**Fig. 3B**. From the results of the CRS-R and BCI in 19 patients with DoC, it was determined that 3 patients could not respond to the auditory stimuli behaviorally but generated a neural response that could be identified by the BCI system (significant ERP waveforms were elicited by the deviant stimuli).

The appearance of visual pursuit behavior in patients with DoC has been considered an early behavioral indicator of the transition from a VS/UWS to an MCS. To further expand the studies of BCIs supporting the CRS-R, a novel visual paradigm was designed to mimic the behavioral assessment of visual pursuit in the CRS-R.[32] Four buttons with face images were initially arranged in four directions of the graphical user interface (GUI). The BCI system randomly selected a target button and rearranged the target into the center of the GUI. Then, the target button, similar to the moving mirror in the CRS-R behavioral assessment, moved at a constant speed from the center to its initial direction, and the other three buttons did not move. Meanwhile, all four buttons flashed (changed from the subject's face image to the unfamiliar face image) randomly when the target moved. Based on the collected EEG data, the BCI system determined whether the patient selectively attended to the moving button (target). Of fourteen patients who completed the BCI and CRS-R assessment, seven who did not have any visual pursuit behavior were considered responsive to the moving button in the BCI assessment. Thus, the moving face–based BCI

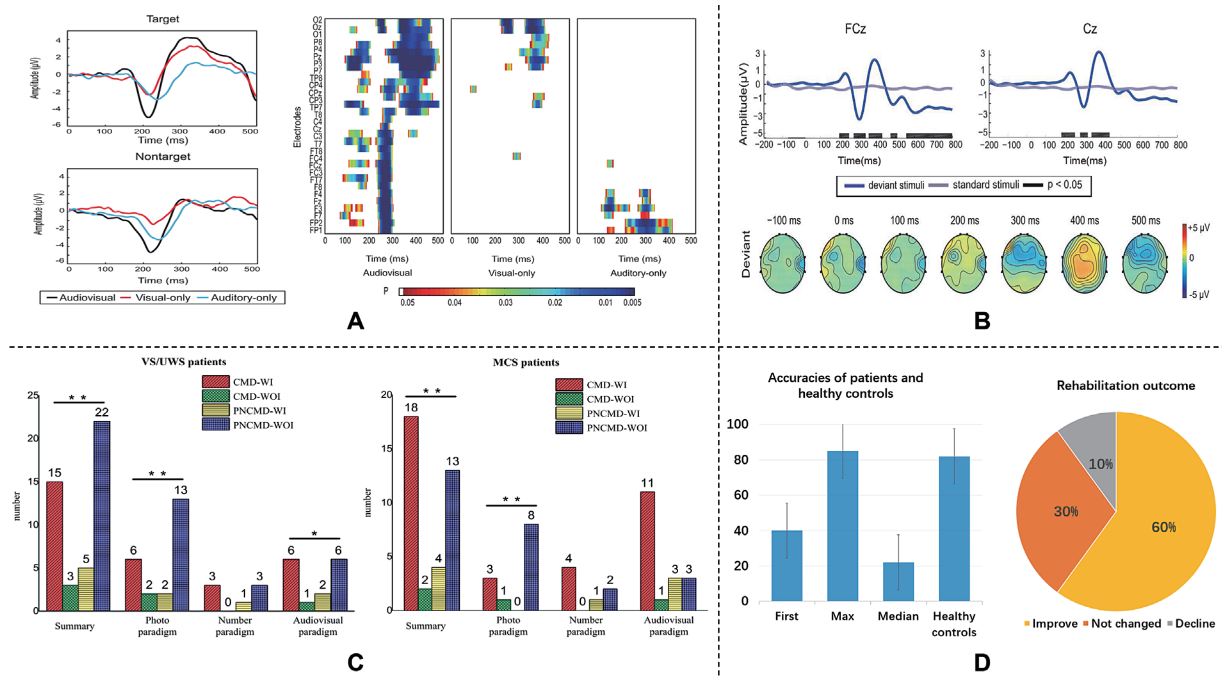

Fig. 3 Illustrations of the main types of BCI (awareness detection, diagnosis, prognosis, and rehabilitation). (**A**) This is an example of BCI-based awareness detection.[20] The ERP responses in the audiovisual, visual-only, and auditory-only paradigms from the "Pz" electrode for all subjects and the comparisons of the target and nontarget responses using the point-wise running *t*-test in the three paradigms across all subjects. (Modified from Fei Wang, Yanbin He, Jiahui Pan, Qiuyou Xie, Ronghao Yu, Rui Zhang, and Yuanqing Li. A novel audiovisual brain-computer interface and its application in awareness detection. Scientific Reports 2015(5):9962.) (**B**) This is an example of BCI-based auxiliary diagnosis.[29] The ERP waveforms evoked by the deviant stimuli in selected channels for all subjects and the averaged scalp map of EEG response across all subjects. (Modified from Jun Xiao, Qiuyou Xie, Yanbin He, Tianyou Yu, Shenglin Lu, Ningmeng Huang, Ronghao Yu, and Yuanqing Li. An auditory BCI system for assisting CRS-R behavioral assessment in patients with disorders of consciousness. Scientific Reports 2016(6):32917.) (**C**) This is an example of BCI-based prognosis.[42] The comparison of the numbers of CMD patients with improvement (CMD-WI), CMD patients without improvement (CMD-WOI), potential non-CMD patients with improvement (PNCMD-WI), and potential non-CMD patients without improvement (PNCMD-WOI) for the VS/UWS and MCS patient groups. (Modified from Jiahui Pan, Qiuyou Xie, Pengmin Qin, Yan Chen, Yanbin He, Haiyun Huang, Fei Wang, Xiaoxiao Ni, Andrzej Cichocki, Ronghao Yu, and Yuanqing Li. Prognosis for patients with cognitive motor dissociation identified by brain-computer interface. Brain 2020,143(4):1177–1189.) (**D**) This is an example of BCI-based rehabilitation.[43] Comparison of accuracies from patients and a healthy control group in the vibro-tactile BCI sessions and the rehabilitation outcome of the 20 patients with DoC. BCI, brain–computer interface; CMD, cognitive motor dissociation; EEG, electroencephalography; ERP, event-related potential; MCS, minimally conscious state; VS/UWS, vegetative state/unresponsive wakefulness state.

Table 2 Studies on BCI-based auxiliary diagnosis in patients with DoC

References	Study group	Paradigms	Results	Remarks	Limitations
Chennu et al[28]	9 VS/UWS and 12 MCS patients	A BCI paradigm based on word stimuli and distractor stimuli	3 patients with DoC showed a high level of attention independent of behavioral performance	Behaviorally unresponsive patients might retain dissociable attentional ability	Elucidating what content the patient might actually be conscious of in this experimental task remains challenging
Xiao et al[29]	14 VS/UWS patients, 4 MCS patients, and 1 EMCS patient	An auditory ERP-based oddball paradigm	3 out of 19 patients with no behavioral responses generated neural responses to auditory startle in assessments in which BCIs were used	Auditory BCIs may assist behavioral assessments of auditory startle in the CRS-R	Low sample size
Wang et al[30]	8 VS/UWS and 5 MCS patients	Audiovisual P300	7 patients were behaviorally unresponsive according	Audiovisual BCIs may provide a more reliable	Only one patient could proficiently use the system for

Table 2 (*Continued*)

References	Study group	Paradigms	Results	Remarks	Limitations
			to the CRS-R but could communicate with the external environment by BCI	approach to assess patients' communication ability than the CRS-R	communication in practice
Xiao et al[31]	8 VS/UWS patients, 5 MCS patients, 1 EMCS patients, and 1 lock-in patient	The P300 paradigm based on a moving colorful ball	1 patient exhibited no visual fixation behavior but was found to be responsive to visual fixation in a BCI assessment	The proposed BCI provides a promising way to assess visual fixation and complement behavioral observations	The online accuracies of responsive patients judged by the BCI system were relatively low
Xiao et al[32]	6 VS/UWS patients, 6 MCS patients, 1 EMCS patient, and 1 lock-in patient	A BCI based on moving face stimulation	7 patients with DoC who have no explicit visual pursuit behavior were considered to be responsive to the moving target in the BCI assessment	The BCI results of visual pursuit assessment can be a prognostic indicator in patients with DoC	The relatively small and abnormal responses in patients limited the BCI's performance to detect visual pursuit in DoC patients
Wang et al[33]	5 VS/UWS patients, 7 MCS patients, and 1 locked-in patient	Audiovisual P300 with a 3D stereo	6 patients with DoC without any behavioral expression in the CRS-R showed object recognition function in the BCI assessment	This BCI may provide a more sensitive method for evaluating the object recognition	Low sample size
Annen et al[34]	15 VS/UWS, 23 MCS, and 2 EMCS patients	Auditory and vibrotactile P300	P300 performance was dependent on clinical variables	Using multimodal assessments in patients with DoC can optimize the clinical diagnosis of patient's function	It requires a sufficient number of stimuli to draw valid conclusions

Abbreviations: BCI, brain–computer interface; CRS-R, Coma Recovery Scale-Revised; DoC, disorders of consciousness; EEG, electroencephalography; EMCS, emergence from minimally conscious state; ERP, event-related potentials; MCS, minimally conscious state; VS/UWS, vegetative state/unresponsive wakefulness state.

system proved to be more effective than the CRS-R behavioral assessment in tasks designed to identify visual pursuit function in patients with DoC. More importantly, five out of these seven patients recovered to an MCS or emergence from MCS (EMCS) shortly after the BCI experiment.

In recent years, multimodal approaches have been applied to the diagnosis of patients with DoC to optimize the assessment of patient's abilities. Annen et al proposed a P300-based paradigm with auditory and vibrotactile stimulation which was supposed to evoke auditory-evoked potentials and vibrotactile-evoked somatosensory potentials.[34] Forty patients with DoC and 12 healthy participants were separated into four groups (healthy participants, patients in an EMCS, patients in an MCS, and patients in a VS/UWS). The relationships between groups and "differentiated response" in none, either, or both paradigms were investigated, and a logarithmic regression model was then used to analyze the recorded P300 response data. The results showed no difference in the presence of a "differentiated response" between patients in a VS/UWS and patients in an MCS. Moreover, most patients in an MCS showed a "differentiated response" in both auditory and vibrotactile paradigms, but most patients in a VS/UWS showed a "differentiated response" in only one of auditory and vibrotactile paradigms. This result suggested that patients processed neither stimulus efficiently. Compared with structured behavioral assessments, multimodal approaches can reduce the risk of misdiagnosis of the consciousness level and the dependence on motor and language abilities.

Some important items in the behavioral scale, including visual fixation, visual pursuit, sound localization, communication, and object recognition, are considered evidence of consciousness at the behavioral level.[1] For example, visual pursuit has been regarded as a "milestone" in the recovery process of the DoC patient.[32,35] Furthermore, the reemergence of visual pursuit may predict good recovery outcomes of patients with DoC.[36] Experimental BCI and CRS-R results in patients with DoC suggested that BCIs might be effective for overcoming the subjective bias that usually exists in the behavioral observation and alleviating the misdiagnosis caused by motor disability. Therefore, BCI assessment may yield more sensitive and objective diagnostic results and be used to reduce the rate of clinical misdiagnosis. BCIs support more detailed and accurate information for the diagnosis and prognosis of patients with consciousness disorders.

BCI-Based Prognosis and Rehabilitation

Many patients with DoC survive for a prolonged period.[37] An accurate prediction of rehabilitation in patients with DoC is significant for the patient, the family, the clinicians, and caregivers.[38,39] Importantly, patients with DoC with minimal signs of consciousness are more likely to recover than patients without signs of consciousness. According to several previous studies,[40] the prognosis of VS/UWS and MCS patients could be evaluated by behavioral scales and neuroimaging techniques. However, the gathered behavior-based evidence is often insufficient to provide accurate prognostic information on these patients. Neuroimaging technique–based prediction of consciousness recovery in patients with DoC is still in its infancy with many opportunities and challenges.

In recent years, several BCI systems have been developed for recovery prognosis in patients with DoC, as shown in ►**Table 3**.[41–43] In one recent study,[43] we explored the prognostic value of BCIs in the recovery of consciousness in patients with DoC. Specifically, 78 patients with DoC (45 VS/UWS and 33 MCS patients) who showed no detectable behavioral command-following abilities were included. Each patient underwent a BCI experiment for awareness detection. Three BCI paradigms were used in the experiment, including photo, number, and audiovisual tasks. In each paradigm, patients were instructed to perform an item-selection task (i.e., select a facial photo or a number from two stimuli), while a machine learning classifier decoded their EEG response in real time to determine whether or not they were attending to the stimulus as requested. Patients who had statistically significant accuracies when using the BCI were identified as CMD. To measure the behavioral improvements of the patients, two CRS-R evaluations were performed: the first one was conducted before the experiment and the second was performed 3 months later. In this study, the authors found a high correlation between BCI accuracy and subsequent recovery results. Among the 78 patients with DoC, our results in ►**Fig. 3C** showed that within the VS/UWS patient group, 15 of the 18 patients with CMD (83%) regained consciousness according to the second CRS-R

Table 3 Studies on BCI-based recovery prognosis in patients with DoC

References	Study group	Paradigms	Results	Remarks	Limitations
Risetti et al[41]	8 VS/UWS and 3 MCS patients	Auditory ERP-based oddball paradigm	ERP components such as mismatch negativity and novelty P300 could be evoked under the passive BCI paradigm	ERPs detection could be a first step to follow up the clinical rehabilitation of patients with DoC	Paradigm is affected by concomitant factors, such as the longer stimulus duration, the complexity of its acoustic, and semantic salience
Claassen et al[42]	104 patients with DoC	Motor imagery, i.e., keep-opening and stop-opening commands	A GOS-E level of 4 or higher at 12 mo was found in 7 of 16 CMD patients (44%) with brain activation and 12 of 84 non-CMD patients (14%) without brain activation	Brain activation in response to spoken motor commands could be found in EEG signals	Did not consider the varied causes of brain injuries and the influence of life-sustaining therapies. Follow-up assessment was recorded by telephone
Pan et al[43]	45 VS/UWS and 33 MCS patients	P300-SSVEP BCIs based on photograph stimuli or visual number stimuli and an audiovisual BCI based on audiovisual number stimuli	15 of 18 VS patients with CMD regained consciousness. 5 of the other 27 non-CMD VS/UWS patients regained consciousness. 14 of 16 patients in an MCS with CMD improved in their CRS-R scores	Patients with CMD have a better outcome than other patients	Only a 3-mo follow-up was studied. Did not consider the types of brain injuries, medical conditions, etc.

Abbreviations: BCI, brain–computer interface; CMD, cognitive motor dissociation; CRS-R, Coma Recovery Scale-Revised; DoC, disorders of consciousness; EEG, electroencephalography; ERP, event-related potentials; GOS-E, Glasgow Outcome Scale-Extended; MCS, minimally conscious state; SSVEP, steady-state visual evoked potential; VS/UWS, vegetative state/unresponsive wakefulness state.

scores, while only 5 of the other 27 VS/UWS patients without significant BCI accuracy (19%) regained consciousness. As shown in ►Fig. 3C, 14 of the 16 patients with CMD (88%) showed improvement in the CRS-R scores for the MCS patient group, whereas only 4 of the other 17 patients in an MCS without significant BCI accuracy (24%) had improved CRS-R scores. The experimental results demonstrated that patients with CMD had a better outcome than the other patients with DoC. Thus, the BCI method could be considered a potential tool for predicting the likelihood of recovery in patients with DoC.

Claassen et al investigated brain responses to motor commands in predicting the prognosis of patients with DoC based on the functional results of the Glasgow Outcome Scale-Extended (GOS-E) after 12 months.[42] In this study, the motor execution–based BCI paradigm was employed in 104 patients with DoC. According to the verbal instructions, the patients were asked to keep opening and closing their right hands or stop opening and closing their right hands. For each patient, left-hand and right-hand blocks were recorded alternately six times, and the experiment lasted a total of 25 minutes. The power in the predefined frequency of each EEG was used as a feature to train a linear support vector machine (SVM) that aimed to distinguish the EEG response stimulated by two motor imagery commands. The results showed that 16 of 104 unresponsive patients (15%) had brain activity in response to spoken motor commands 4 days after injury. After 12 months, 7 of 16 brain-activated patients (44%) and 12 of 84 non–brain-activated patients (14%) had a GOS-E level of 4 or higher.

Compared with the diagnostic and prognostic methods, research on rehabilitation for patients with DoC is relatively sparse and preliminary. In one study,[44] a vibrotactile P300-based BCI (VT P300 BCI) paradigm was designed to explore rehabilitation in patients with DoC. Twenty patients with DoC participated in 10-session experiments over 10 days with 8 to 12 runs each day. Vibrotactile tactors were placed on two wrists and one foot of each patient. Patients wore ear buds and were asked to focus and silently count vibrotactile target stimuli on their left or right wrist and ignore the other stimuli. In the experiments over 10 days, the researchers investigated the changes in BCI classification performance in patients with DoC. The CRS-R score was used to measure the patients' consciousness before and after the 10 vibrotactile P300 sessions. As shown in ►Fig. 3D, patients achieved the classification accuracy of 40% in the first session, the maximum accuracy of 88% in the best session, and the median accuracy of approximately 21% for all sessions. Furthermore, significant improvement was found in CRS-R scores before and after the VT3 BCI experiments for all 20 patients. Twelve of 20 patients were found to improve the CRS-R score by 1 to 7 points after the experiments. Six patients did not show a change in the CRS-R scores, and two patients' scores declined by 1 point. Each patient had accuracy higher than 60% at least once, which indicated successful command-following. These findings demonstrated that the designed BCI paradigm is an important assessment tool and the corresponding CRS-R score improvement is a key indicator of outcomes in patients with DoC. A larger patient group should be included to investigate the therapeutic potential of vibrotactile BCI systems in future research.

Future Considerations

Currently, BCI studies in patients with DoC need to overcome many challenges to provide a more reliable clinical tool. Here, we offer several concluding remarks on the design principles of several important BCI components for patients with DoC.

Data Acquisition

For challenging populations, such as patients with DoC, on the one hand, their data quality is often suboptimal due to contamination by artifact caused by body and eye movements. On the other hand, such patients are prone to frequent fluctuations and prolonged fatigue, making it impossible to maintain adequate attention during experiments. These limitations can adversely affect the BCI-based classification results of patients with DoC. During the data acquisition, a break is thus encouraged to be provided depending on the patient's status. An experienced clinician or operator is needed to observe the patient carefully to ensure their engagement.

BCI Paradigm Design

The suitability of different BCI designs for individual patients varies widely and needs to be evaluated comparatively in each case. Studies have shown that some patients with DoC are able to consistently perform motor imagery tasks.[42,45] Compared with other BCI designs, the motor imagery–based BCI is relatively less hampered by the stimulus modality, requires fewer stimuli to be presented, and can be effectively delivered visually or auditorily. Others have demonstrated the ability to generate reliable P300 components.[24,46] P300 components can be elicited by meaningful stimuli that require only a limited amount of patient effort. Some of the most successful BCI systems are based on the visual P300. However, many patients with DoC suffer from gaze fixation disorder and cannot attend to visual stimuli. In fact, the BCI paradigm should be tested in healthy controls and adapted for the patients with DoC before being used in the clinical bedside. Furthermore, the paradigm design needs to consider the possibility of fluctuating arousal, rapid fatigue, and limited attention span of patients with brain injury.[47] In this regard, complexity and duration are important factors to be considered when designing a BCI paradigm.

Stimuli and Feedback

The design of stimuli and feedback is another important issue for BCI systems. Visual BCIs may be more effective than auditory or tactile BCIs in studies of healthy subjects, but the reliability of these BCIs deserves special attention in studies of patients with DoC, who may have sensory impairments, such as deafness, blindness, or oculomotor impairment. In fact, visual modalities are not feasible for some patients with DoC. The recent successful application of P300-based tactile BCI and auditory BCI in LIS patients will motivate researchers to design and develop more reliable BCI systems using a wider range of sensory stimuli (e.g., auditory, tactile) for patients with DoC in the context of a specific sensory impairment (e.g., vision).[34] Another option is to develop a BCI system based on multisensory modalities that provide stimulation, instructions, and feedback through multiple sensory channels. Different sensory modalities can be combined in one BCI system by different command-following tasks (e.g., counting an audiovisual number or focusing on a vibrotactile and auditory target). Compared with the single modal BCIs, the multimodal BCI provides much wider possibilities to gain entry to consciousness.

Decoding Algorithm

In the studies mentioned earlier, some patients with CMD achieved accuracies ($\sim$70%) that were significantly higher than the chance level but much lower than that of healthy subjects (usually higher than 90% in our experience).[19] For this problem, first, it is difficult to collect sufficient training data before online testing due to the rapid fatigue of patients, which may affect the performance of the classifier. Advanced machine learning technologies can improve this problem, where few-shot learning or cross-subject technology may be a potential solution. Second, we have shown that BCI performance can be improved by enhancing brain patterns through the presentation of multisensory stimuli or through the fusion of features from multiple brain patterns. Therefore, on the one hand, related studies of brain mechanisms should be conducted to ensure the effective fusion of these components in hybrid BCIs. On the other hand, further studies on fusion algorithms of multiple techniques are needed, including the fusion of multiple signal inputs, diverse brain patterns, multisensory modalities, or multiple intelligent systems.

Clinical Applications

In recent years, many BCI studies have improved the classification accuracy of DoC. In particular, bedside detection of EEG-based BCI can reduce the rate of misdiagnosis in patients who are unable to express conscious responses on behavioral assessments.[48] However, some BCI systems have low sensitivity and specificity for the diagnostic classification and prognostic determination of patients with DoC. The results of studies from different clinical centers vary widely. One possible reason for this outcome is the excessive heterogeneity of patients with DoC. Using the same BCI system for patients with different etiologies, different sites of damaged brain regions, or different levels of arousal and awareness, consciousness detection or auxiliary diagnosis is often unsatisfactory.[49] Therefore, in future research exploring the application of BCIs in patients with DoC, patients should be classified in increasing detail, and different categories of patients with DoC should use different categories of BCI systems for auxiliary diagnosis.

BCI systems can also help patients with DoC restore their ability to communicate with the outside world. It is important to note, however, that communication should be conducted with simple questions, as patients with severe brain damage may have difficulty answering complex or detailed questions accurately. In addition, complex approaches that combine multiple diagnostic methods, techniques, and tools may greatly improve the accuracy of diagnosis and prediction for patients with DoC. Such hybrid solutions (including noninvasive EEG, BCI, and fMRI) are considered important directions for further research in the clinical application of BCI in patients with DoC. At the same time, EEG-based BCI allows physicians to understand the neural response to a specific treatment. Pertinently, EEG-based BCI offers an opportunity to evaluate the efficacy of different treatments, as there are still limited effective treatments for patients with DoC.[50]

In summary, a BCI is currently suitable as a complementary tool for behavioral assessment but needs to effectively overcome the abovementioned highlighting issues before it can become the "gold standard" for awareness detection and aid in patient diagnosis and rehabilitation prediction. Current BCI technology requires significant time and effort to move from laboratory studies to bedside applications and to provide reliable clinical practice for improving the quality of life of patients with DoC. We believe that extensive collaboration between researchers from different disciplines, including multicenter-based data sharing, multidisciplinary paradigm design, and multidimensional data analysis, will enable us to achieve this goal.

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Conflict of Interest
None declared.

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