Toward Assessment of Sound Localization in Disorders of Consciousness Using a Hybrid Audiovisual Brain–Computer Interface

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***Abstract*— Behavioral assessment of sound localization in the Coma Recovery Scale-Revised (CRS-R) poses a significant challenge due to motor disability in patients with disorders of consciousness (DOC). Brain-computer interfaces (BCIs), which can directly detect brain activities related to external stimuli, may thus provide an approach to assess DOC patients without the need for any physical behavior. In this study, a novel audiovisual BCI system was developed to simulate sound localization evaluation in CRS-R. Specifically, there were two alternatively flashed buttons on the left and right sides of the graphical user interface, one of which was randomly chosen as the target. The auditory stimuli of bell sounds were simultaneously presented by the ipsilateral loudspeaker during the flashing of the target button, which prompted patients to selectively attend to the target button. The recorded electroencephalography data were analyzed in real time to detect event-related potentials evoked by the target and further to determine whether the target was attended to or not. A significant BCI accuracy for a patient implied that he/she had sound localization. Among eighteen patients, eleven and four showed sound localization in the BCI and CRS-R, respectively. Furthermore, all patients showing sound localization in the CRS-R were among those detected by our BCI. The other seven patients who had no sound localization behavior in CRS-R were identified by the BCI assessment, and three of them showed improvements in the second CRS-R assessment after the BCI experiment. Thus, the proposed BCI system is promising for assisting the assessment of sound localization and improving the clinical diagnosis of DOC patients.**

***Index Terms*— Hybrid brain-computer interface (hBCI), event-related potential (ERP), disorders of consciousness (DOC), sound localization, behavioral assessment.**

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I. Introduction

DISORDERS of consciousness (DOC), including coma, vegetative state (VS, also known as unresponsive wakefulness syndrome) and minimally conscious state (MCS), usually result from a variety of acute brain injuries. DOC patients may lack perceptual awareness and self-related awareness due to disorders in associated neural networks of injured brain regions [1]. Accurate assessment of the residual function in patients with DOC is of critical importance in establishing prognosis, promoting revival from coma and treatment interventions. The current clinical methods to assess DOC patients are dependent mainly on behavioral scales, of which the Coma Recovery Scale-Revised (CRS-R) has shown good validity and reliability in distinguishing MCS from VS patients [2], [3]. The CRS-R assesses DOC patients in terms of auditory, visual, motor, oromotor, communication and arousal functions, and the maximal CRS-R total score is 23. Each functional scoring is performed from the highest score item to the lowest score item, i.e., from the cognitive-mediated behaviors to the reflexive activity. Some important items in CRS-R, including visual fixation, visual pursuit and sound localization, are considered to be the evidence of consciousness at the behavioral level. The presence of sound localization represents relative integrity of the linguistic processing structure and also the patient's recovery from VS to MCS [4], [5]. In the standard behavioral assessment of sound localization, the clinician presents an auditory stimulus lasting 5 s (e.g., voice, bell ring) from the right and left sides, respectively. Then, the clinician repeats the above procedure for a total of 4 trials, 2 on each side. The assessment criterion is that the patient's head or eyes orient toward the direction of the stimulus at least two trials. Scoring of items in the CRS-R relies on the presence or absence of specific behavioral responses to given stimuli for DOC patients.

Clinical studies have suggested that the generation of consciousness is closely related to the joint action of various sensations in the cortex of the brain, and the auditory cortex is a vital part of the brain cortex [6], [7]. Probing of residual auditory perceptual abilities in DOC patients may provide a potential way to predict their clinical evolution. Therefore, auditory function tests such as auditory startle and sound localization included in behavioral scales play a key role in DOC patients' diagnosis, prognosis and recovery of consciousness [8], [9]. Sound localization has been investigated by several clinical groups [10]–[12]. Cheng *et al.* investigated sound localization in DOC patients through different types of auditory stimulation. Eighty-six DOC patients' results indicated that the patient's own name elicited the sound localization behaviors more easily than other auditory stimuli [10]. Heine *et al.* studied four items including auditory localization in 13 DOC patients. They suggested that preferred auditory stimuli contributed to the expression of residual function and could improve the diagnostic accuracy [11]. The assessment of sound localization in the CRS-R relies mainly upon observed specific behaviors. However, detecting the behavioral response in these patients remains a major challenge since their motor disabilities might result in false-negative for a DOC patient who has the ability of sound localization. This problem also exists in the other items in the CRS-R such as visual fixation and visual pursuit, which is the origin of a high rate of clinical misdiagnosis (approximately 40%) [13], [14]. The limitations of behavioral scales have highlighted the need for additional tools to achieve accurate and objective assessments in DOC patients.

Brain computer interfaces (BCIs), which can directly detect command following-specific changes or brain activities related to external stimuli from electroencephalography (EEG), may thus provide a reliable approach to assess DOC patients without the need for any physical behavior. BCIs used to assess covert cognition in patients and improve the clinical diagnoses of DOC patients have been extensively studied [15]–[20]. Claassen *et al.* studied the EEG response to spoken command in 104 patients with cognitive motor dissociation (CMD). The results showed that 16 of 104 CMD patients exhibited command-following brain responses detected by EEG. In addition, 8 of these 16 patients (50%) demonstrated command-following behaviors before discharge [21]. Pan *et al.* investigated 78 DOC patients who showed no detectable command-following behaviors. Their results showed that 15 of 18 patients with CMD (83.33%) in the unresponsive wakefulness syndrome (UWS) group regained consciousness and 14 of 16 patients with CMD (87.5%) in the MCS group showed improvements in their CRS-R scores [22]. Xie *et al.* proposed a BCI based on an audiovisual stimulation sequence consisting of congruent and incongruent stimuli to detect the awareness of DOC patients [23]. These findings have important implications for the application of BCI in clinical diagnosis and prognosis for DOC patients. BCIs based on auditory or vibrotactile paradigms have also been the main modalities used to evaluate the consciousness levels of DOC patients [24]. Lulé *et al.* proposed an oddball auditory EEG-BCI to test the communication abilities of DOC patients and observed that a few of these patients could conduct functional interactive communication with a BCI [25]. Ortner *et al.* designed a hybrid BCI for two applications: assessing the residual cognitive function and establishing a communication channel for DOC patients [26]. Annen *et al.* investigated the difference in P3 performance between auditory and vibrotactile stimulation. They supported that multimodal methods could optimize the evaluation of DOC patients' abilities [27].

The aforementioned BCIs focused on DOC patients' overall consciousness and required that the patients retain higher level language comprehension ability than required for the behavioral assessment [16]. Actually, BCIs furnish direct measures of brain responses to external stimuli based on EEG signals, which have advantages than behavioral scales such as CRS-R [28]. BCI studies that assisted behavioral item assessments in DOC patients based on the CRS-R were reported in our previous study [29]–[33]. For instance, Wang *et al.* designed a 3D stereo audiovisual BCI to mimic the evaluation of object recognition item in the CRS-R [33]. DOC patients determined the target by comprehending the instructions and then selectively attending to the target stimuli. Regarding the evaluation of auditory function [29], we applied BCIs to assess the auditory startle in the auditory subscale, which represents reflexive activity in auditory function. We found that some DOC patients who did not show behavioral responses to external stimuli could generate related brain activity that could be detected by BCI systems.

The aforementioned studies showed that the BCI detection is independent of the behaviors of DOC patients and therefore can reduce clinical misdiagnosis caused by motor disabilities. Our previous studies indicated that BCIs can be used to assess the awareness of DOC patients and have advantages over behavioral scales such as CRS-R. On the other hand, sound localization behavior is an important item of the CRS-R and represents the degree of rehabilitation of DOC patients. However, to our knowledge, an effective BCI system for sound localization assessment in DOC patients has not yet been reported.

In this study, we mimicked the sound localization assessment in the CRS-R and devised an EEG-based BCI that directly detected the brain responses of DOC patients to the directional audiovisual stimuli cued by the auditory stimuli, which could be a potential solution to sound localization assessment. In the BCI assessment, our BCI system first presented a bell sound from the left or right side to the patient to prompt the target direction. Next, two buttons on the left and right sides of the GUI alternately flashed at random intervals, while the auditory stimuli were presented only in the target direction and synchronized with the target button flashing. Specifically, an experimental trial contained ten stimulation rounds, in each of which the auditory stimuli were presented unilaterally only in the target direction. If a DOC patient had sound localization ability, he/she could determine the target according to the auditory stimuli and was continuously

TABLE I
SUMMARY OF PATIENTS' CLINICAL STATUS

Patient.	Age	Clinical Diagnosis	Etiology	Interval Post-ictus (months)	CRS-R Score
Patient 1	37	VS	NTBI	3	3 (0-1-0-0-0-2)
Patient 2	31	VS	TBI	5	6 (1-0-2-1-0-2)
Patient 3	47	VS	TBI	72	6 (0-1-2-1-0-2)
Patient 4	27	VS	NTBI	9	6 (1-0-1-2-0-2)
Patient 5	40	VS	TBI	14	6 (1-0-2-1-0-2)
Patient 6	50	VS	NTBI	20	6 (1-0-2-1-0-2)
Patient 7	61	VS	NTBI	15	7 (1-0-2-2-0-2)
Patient 8	52	VS	TBI	24	7 (1-0-2-2-0-2)
Patient 9	22	VS	TBI	19	7 (1-1-2-1-0-2)
Patient 10	63	VS	NTBI	6	7 (1-0-2-2-0-2)
Patient 11	38	MCS	TBI	93	8 (1-3-1-1-0-2)
Patient 12	45	MCS	TBI	7	9 (1-1-4-1-0-2)
Patient 13	35	MCS	NTBI	20	9 (1-3-2-1-0-2)
Patient 14	30	MCS	TBI	36	10 (1-3-2-2-0-2)
Patient 15	36	MCS	NTBI	10	11 (2-3-3-1-0-2)
Patient 16	61	MCS	TBI	9	12 (2-3-4-1-0-2)
Patient 17	42	MCS	NTBI	7	15 (3-3-4-2-0-3)
Patient 18	61	MCS	NTBI	4	16 (3-4-5-1-1-2)

The CRS-R scores in bracket are the subscale scores, of which the first column is the score of the auditory function scale. Auditory Function Scale: 4-Consistent Movement to Command; 3-Reproducible Movement to Command; 2-Localization to Sound; 1-Auditory Startle; 0-None.

attracted by the repetitive auditory stimuli to selectively attend to the audiovisual stimuli in this direction. In this case, the corresponding ERPs could be evoked in the patient and a significant BCI accuracy could be achieved. For those DOC patients without sound localization ability, the target could not be determined and no significant accuracy could be obtained in the BCI assessment. The experimental results showed that the BCI system was superior to the behavioral method in sound localization assessments for DOC patients.

II. MATERIALS AND METHODS

A. Subjects

Ten healthy subjects (mean age ± SD: 27.8 ± 6.6 years) were recruited for the initial experiment based on audiovisual and auditory-only paradigms to ensure the feasibility of the BCI system. A total of twenty DOC patients from Guangdong Provincial Work Injury Rehabilitation Hospital, with an age range of 22-63, took part in our experiments. Two of the twenty patients were excluded from further analysis due to excessive expectoration and psychomotor agitation. The remaining eighteen patients' clinical information is presented in Table I, which includes the CRS-R scores for each function (auditory, visual, motor, oromotor, communication, arousal).

The experiment was approved by the Ethics Committee of Guangdong Provincial Work Injury Rehabilitation Hospital (approval number: AF/SC-07/2020.03) and it was also conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). Written informed consent was obtained from both the healthy subjects and the patients' legal surrogates.

B. Experimental Design

We used a Neuroscan SynAmps2 amplifier (Compumedics, Australia) and a 30-channel EEG cap (GreenTek, China) to collect scalp EEG signals at a sampling rate of 250 Hz, and kept the impedances below 5 kΩ for all electrodes during the recording. Notch filtering at 50 Hz and 0.05-100 Hz bandpass filtering were applied before further processing.

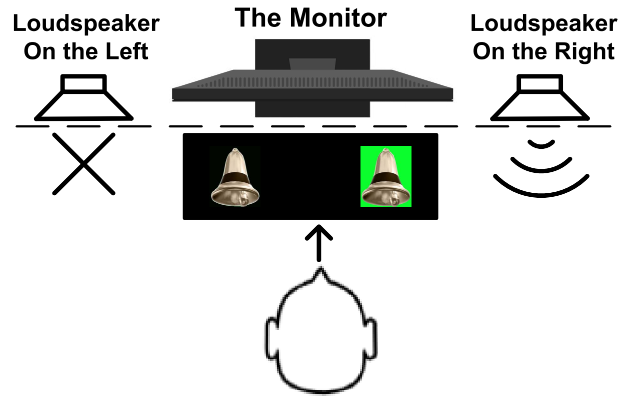

Fig. 1. GUI of the audiovisual BCI and the locations of loudspeakers. If the target direction is the right, the auditory stimulus is presented by the right loudspeaker accompanied by a flash of the right button.

Fig. 1 illustrated the graphical user interface (GUI) of the audiovisual paradigm and the locations of loudspeakers. Two flash buttons (size of 10*12 cm) were placed on the left and right parts of the screen, and the two corresponding loudspeakers were placed on the right and left sides of the monitor. The horizontal distance between the center points of the two buttons was 31 cm, and the corresponding visual angle was 17.2°. The foreground images of the two buttons were bell images, whereas the background was green. The auditory stimuli of a bell ring sound with a sound-pressure level (SPL) of approximately 65 dB were presented only in the target direction and were synchronized with the target-side visual stimuli.

The paradigm of our audiovisual BCI system was designed to simulate the behavioral assessment of sound localization in the CRS-R, as shown in Fig. 2. Each experimental trial began with an instruction in Chinese, which lasted for 7 s. The instruction was "Please pay attention to the direction of the bell sound and count its repetitions silently". Then, one of the two directions (right and left) was pseudo-randomly chosen as the target direction, and a bell sound with a duration of 3 s was presented by the loudspeaker in the target direction, which guided the subject to pay attention to the sound's direction. Subsequently, there were 10 stimulation rounds (35 s). In each stimulation round, the two buttons flashed once for each in a random order (changing between the foreground and the background), with a 200-ms onset time for each flash and an inter stimulus interval (ISI) randomly chosen from 900, 1000, 1100, 1200, 1300 or 1400 ms. Meanwhile, the corresponding bell sound auditory stimulus was simultaneously presented by the ipsilateral loudspeaker during the flashing of the target button. The auditory stimulus onset duration was set to 200 ms to be consistent with the visual stimulus. Note that there was no corresponding auditory stimulus when the nontarget button flashed. In this way, the auditory stimuli might also maintain patients' attention and enhance the neural responses to target

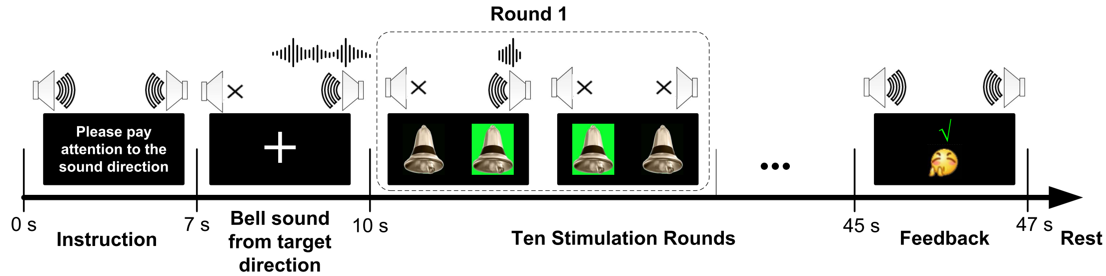

Fig. 2. Experimental paradigm. Each trial included instruction (7 s), presentation of a bell sound from the target direction (3 s), ten stimulation rounds (35 s) and feedback (2 s).

stimuli during the whole trial. There was a short break of variable time duration between the two consecutive rounds to ensure that the period of each round was fixed at 3.5 s. If the subject had sound localization, he/she would selectively attend to the audiovisual stimuli in the target direction cued by the auditory stimuli, and the ERPs could be evoked by the target stimuli and detected. Otherwise, he/she could not selectively attend to the target stimuli and produce corresponding ERPs. At end of the online trial, the trained classifier output the predicted target to which the subject was paying attention. If a correct result was obtained for this trial, a pleasant dynamic picture showing positive feedback was presented for 2 s, along with a sound clip of applause. No feedback was displayed for an incorrect result. The online positive feedback was used to encourage the subjects and to enhance their sustained attention to stimuli [34]. There was a varying break time following each trial, depending on the subject's status. During each trial, the patient was carefully observed and verbally encouraged by an experienced doctor to ensure participation and to avoid fluctuations in arousal levels. If the patient showed decreased arousal or continuous movements in a trial, the trial was rejected to ensure the reliability of the BCI assessment. In addition, ten healthy subjects also participated in the experiment based on the auditory-only paradigm, in which only the repeated auditory stimuli were randomly presented and the corresponding visual stimuli were removed.

The BCI experiment consisted of two sessions and a total of 40 trials. Each session comprised a calibration subsession and an online subsession, including 10 trials for each. The calibration subsession was first performed to train a classifier, and the online subsession was conducted to assess the sound localization response. Ten healthy subjects completed the BCI experiments for a total of 4 sessions: 2 sessions based on the audiovisual paradigm and 2 sessions based on the auditory-only paradigm. Eighteen DOC patients completed two sessions of the BCI experiments based on the audiovisual paradigm and were evaluated by the CRS-R before and after the BCI experiment. Specifically, all patients were subjected to two CRS-R assessment periods: one during the week before the experiment and another two months after the experiment. For each CRS-R assessment period, the CRS-R assessments were performed twice per week by two experienced doctors for each patient. The best behavioral response observed during the week of the recording was noted.

C. EEG Data Analysis

1) Data Processing: Scalp EEG signals recorded during both calibration and online subsessions were first fed into a 0.1-20-Hz bandpass minimum-phase filter. The channel-wise filtered data were then segmented into many 600-ms epochs, i.e., 30 by 150 data matrices in our 30-channel recording and 250-Hz sampling rate setting, according to stimulus onset. Each epoch was further 1/6 temporally down-sampled and flattened into a 750-dimensional feature vector. Feature vectors constructed from the 10 repeated epochs for the same stimulus in a trial were averaged to produce a final feature vector. These feature vectors were labeled $+1$ if they were from epochs for the target stimuli (direction with auditory stimulus) or -1 otherwise in the calibration subsessions. We then trained a support vector machine (SVM) with the labeled feature vectors. Thereafter, in a trial of our online subsessions, two feature vectors corresponding to the stimuli in the two directions were classified by the trained SVM into target and nontarget classes. In this way, the overall online accuracy of the BCI assessment for each subject could be calculated after the experiments.

Binomial test was performed on the online accuracy to verify whether the achieved accuracy value lay significantly above the chance level. For two-class paradigm in this study, the binomial test was calculated using Jeffreys' Beta distribution as follows:

$$\lambda \approx \left\{a + \frac{2(N-2m)z\sqrt{0.5)}}{2N(N+3))}\right\} \pm z\sqrt{\frac{a(1-a)}{N+2.5}} \qquad (1)$$

where N and m are the numbers of total and correct trials, respectively. a is the estimated accuracy of 0.5 in our study. Here, we focus on the accuracies greater than the chance level of 0.5, therefore, z is the z-score of 1.65 for a one-sided test with $p < 0.05$. Based on (1), the accuracy rate of 67% was considered to be significant for 20 trials, which was equivalent to more than 13 correct trials. A subject was considered to be responsive to sound localization if a significant BCI online accuracy higher than 67% was achieved. For each patient, a two-fold cross-validation using the 40 trials of all training and testing datasets was performed to obtain the offline classification accuracies.

2) ERP Analysis: The physiological consistency of the BCI results was confirmed by ERP analysis. The ERP analysis focused on the oddball event-related potentials of mismatch negativity (MMN) and P300 [35]–[37]. It is known that MMN is typically distributed throughout frontal-central brain regions and occurs in the latency range of 250-350 ms. In addition, P300 is a broad, positive component that is primarily distributed throughout the central-parietal regions, and its latency can range from approximately 250 to 1000 ms.

The individual ERP waveforms were calculated for each subject's target and nontarget averages across 40 trials. Moreover, ERPs were calculated at the group level for healthy subjects and patients who obtained negative results in both the BCI and CRS-R assessments. Specifically, for each stimulus, after bandpass filtering (0.1-20 Hz), an EEG epoch in each channel was obtained from the period of 100 ms pre-stimulus to 600 ms post-stimulus. For each channel, we averaged the EEG epochs across all target stimuli and across all nontarget stimuli to obtain two ERP waveforms (EEG responses). In addition, scalp topographies of subjects' EEG responses to target and nontarget stimuli were plotted to observe the spatial distribution of the differences between the two stimuli conditions. For each subject and channel, the EEG responses to different stimuli were averaged in 100-ms windows.

3) Time-Frequency Analysis: Compared with traditional ERP analysis, time-frequency analysis provides information about different aspects of neural activity, such as phase relationships. Among many methods of time-frequency analysis, the event-related spectral perturbation (ERSP) reflects the extent to which the power at different frequencies in EEG signals is altered in relation to a stimulation onset. The ERSP is defined as:

$$ESRP(f,t) = \frac{1}{n}\sum_{k=1}^{n}(F_k(f,t)^2) \quad (2)$$

where n is the number of trials/epochs, and $F_k(f,t)$ is the spectral estimation of the kth trial/epoch at frequency f and time t.

The inter-trial phase coherence (ITPC) can be seen as complementary to the ERSP and measures the event-related phase locking across trials/epochs in EEG response. Specifically, a high ITPC indicates that the signal in a given frequency band is in phase on different trials, and an ITPC of zero indicates that there is no relationship between phases from one trial to the next. It is defined as follows:

$$ITPC(f,t) = \frac{1}{n}\left|\sum_{k=1}^{n}\frac{F_k(f,t)}{|F_k(f,t)|}\right| \quad (3)$$

The dynamic features of ERSP and ITPC were used for the analysis of auditory evoked EEG responses in a recent study [38], the results of which showed that the ERP components were associated with significant phase locking in particular frequency bands and latency windows.

III. Results

A. Healthy Subjects

For ten healthy subjects, the averaged online accuracies of BCI experiments based on audiovisual and auditory-only paradigms were 98±4.5% and 64±12.4%, respectively. The accuracies of the audiovisual paradigm were significantly greater than those of the auditory-only paradigm ($p < 0.001$, t-test), mainly because visual stimulation generated stronger ERP responses compared to auditory stimulation. It is concluded that the visual responses in the audiovisual paradigm make a larger contribution to the classification. Heathy subjects' results verified that the proposed BCI system was effective in detecting EEG responses to sound localization.

Comparisons of ERPs and scalp maps between the audiovisual paradigm and auditory-only paradigm were conducted as shown in Fig. 3. The responses to auditory-only stimuli (negative component) were distributed mainly in the frontal-central and central regions, and the responses to audiovisual stimuli (positive component) were distributed primarily in the vision-associated areas, including the parieto-occipital and lateral-occipital areas.

B. Patients With DOC

Eighteen DOC patients were included in this study. Both the BCI and two sets of CRS-R results for these patients are shown in Table II. First, we found that four of these patients, i.e., patients 15-18, were classified as responsive due to their positive results on both the BCI-based and behavioral evaluations. Specifically, the average online accuracy of the BCI for these four patients was 82.5±6.4%, which was much higher than the significance threshold of 67%. In addition, their auditory subscale scores (before the experiment) were equal to or greater than 2, which indicated that the patients exhibited sound localization behavior in CRS-R. Second, seven of the 18 patients, including patients 1, 3, 6, 8, 10, 11 and 13, were classified as nonresponsive because of their negative results in the two types of assessments. Their average online accuracy (48±9.5%) was at the chance level of 50%. Moreover, these seven nonresponsive patients did not show any improvement in the second behavioral assessment. Third, and most importantly, we classified the remaining seven patients, i.e., patients 2, 4, 5, 7, 9, 12 and 14, into the inconsistent group because their results were not consistent in both the BCI and CRS-R assessments. Specifically, the average online accuracy of 78±8% for the inconsistent group was much higher than the chance level, indicating that these patients were considered to be sound localization responsive in the BCI assessment. However, their auditory assessment scores, which were less than 2 in the first clinical CRS-R assessment, meant that they might be behaviorally nonresponsive. Interestingly, three of these seven patients, including patients 7, 9 and 12, showed a CRS-R score improvement in the second clinical assessment. Meanwhile, the average offline accuracies of the responsive, nonresponsive and inconsistent groups were 87.5±8.7%, 50±5.8% and 82.9±9.9%, respectively. The offline accuracies of DOC patients were consistent with their online accuracies, as shown in Table II.

As shown in Fig. 4, patients 16, 17 and 18 exhibited a negative component in a latency range between 300 and 400 ms at "FCz" or "Cz". Following this negative component, a P300-like component, which peaked between 450 ms to 550 ms, was widely distributed over the temporal-parietal and occipital areas in the target scalp topographies. Unlike these three patients, patient 15 exhibited only a marked positive peak within 300-400 ms at "Cz". This positive component was

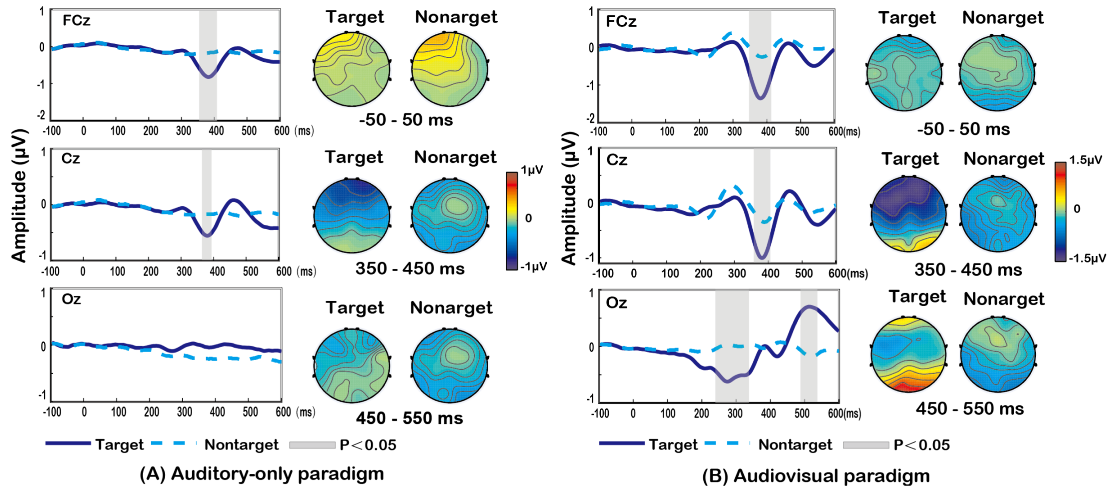

Fig. 3. The averaged ERPs at "FCz", "Cz" and "Oz" and scalp topography in the three time windows (i.e., −50-50, 350-450 and 450-550 ms) of ten healthy subjects. (A) Auditory-only paradigm. (B) Audiovisual paradigm. The target and nontarget waveforms are denoted by the solid and dashed lines, respectively. Significant differences between the two stimulus conditions (t-test, $p < 0.05$) are denoted by gray shaded areas.

TABLE II
BCI AND CRS-R RESULTS OF DOC PATIENTS

Group	Patient.	Clinical Diagnosis	Hits/Trials	BCI online accuracy (%)	P value	BCI offline accuracy (%)	P value	CRS-R Score before experiment	CRS-R Score after experiment
Responsive	Patient 15	MCS	15/20	**75**	0.0089	**75**	0.0089	11 (2-3-3-1-0-2)	13 (3-4-3-1-0-2)
	Patient 16	MCS	16/20	**80**	0.0022	**90**	<0.0001	12 (2-3-4-1-0-2)	12 (2-3-4-1-0-2)
	Patient 17	MCS	18/20	**90**	<0.0001	**90**	<0.0001	15 (3-3-4-2-0-3)	15 (3-3-4-2-0-3)
	Patient 18	MCS	17/20	**85**	<0.0005	**90**	<0.0001	16 (3-4-5-1-1-2)	16 (3-4-5-1-1-2)
Nonresponsive	Patient 1	VS	10/20	50	0.5	45	0.3176	3 (0-1-0-0-0-2)	3 (0-1-0-0-0-2)
	Patient 3	VS	12/20	60	0.1714	50	0.5	6 (0-1-2-1-0-2)	6 (0-1-2-1-0-2)
	Patient 6	VS	9/20	45	0.3176	40	0.1714	6 (1-0-2-1-0-2)	6 (1-0-2-1-0-2)
	Patient 8	VS	11/20	55	0.3176	50	0.5	7 (1-0-2-2-0-2)	7 (1-0-2-2-0-2)
	Patient 10	VS	10/20	50	0.5	55	0.3176	7 (1-0-2-2-0-2)	7 (1-0-2-2-0-2)
	Patient 11	MCS	6/20	30	0.0289	50	0.5	8 (1-3-1-1-0-2)	8 (1-3-1-1-0-2)
	Patient 13	MCS	10/20	50	0.5	40	0.1714	9 (1-3-2-1-0-2)	9 (1-3-2-1-0-2)
Inconsistent	Patient 2	VS	16/20	**80**	0.0022	**80**	0.0022	6 (1-0-2-1-0-2)	6 (1-0-2-1-0-2)
	Patient 4	VS	14/20	**70**	0.0289	**70**	0.0289	6 (1-0-1-2-0-2)	6 (1-0-1-2-0-2)
	Patient 5	VS	17/20	**85**	<0.0005	**95**	<0.0001	6 (1-0-1-2-0-2)	6 (1-0-1-2-0-2)
	Patient 7	VS	14/20	**70**	0.0289	**80**	0.0022	7 (1-0-2-2-0-2)	9 (1-0-4-2-0-2)
	Patient 9	VS	16/20	**80**	0.0022	**75**	0.0089	7 (1-1-2-1-0-2)	9 (1-3-2-1-0-2)
	Patient 12	MCS	14/20	**70**	0.0289	**90**	<0.0001	9 (1-1-4-1-0-2)	15 (4-1-6-1-1-2)
	Patient 14	MCS	18/20	**90**	<0.0001	**100**	<0.0001	10 (1-3-2-2-0-2)	10 (1-3-2-2-0-2)

Note: The BCI online accuracies higher than the significance level of 67% ($p = 0.05$ binomial-test) are highlighted in bold.

observed in most brain regions, as shown in patient 15's target scalp map. It can be inferred from the latency and distribution of these components that the negative and positive components were very likely to be MMN and P300, respectively. Furthermore, the rehabilitation results of the responsive group showed that patient 15 had behavioral improvements in his CRS-R scores after the BCI experiment, especially on the auditory and visual subscale scores. The other three patients' clinical states (patients 16, 17 and 18) remained unchanged before and after the BCI experiment.

Seven patients in the nonresponsive group, namely, patients 1, 3, 6, 8, 10, 11 and 13, neither exhibited sound localization behavior nor achieved significant online accuracy. Their group average ERPs indicated that the target waveforms were highly similar to the nontarget waveforms in "FCz" and "Cz" (Fig. 5(A)). Significant differences between target and

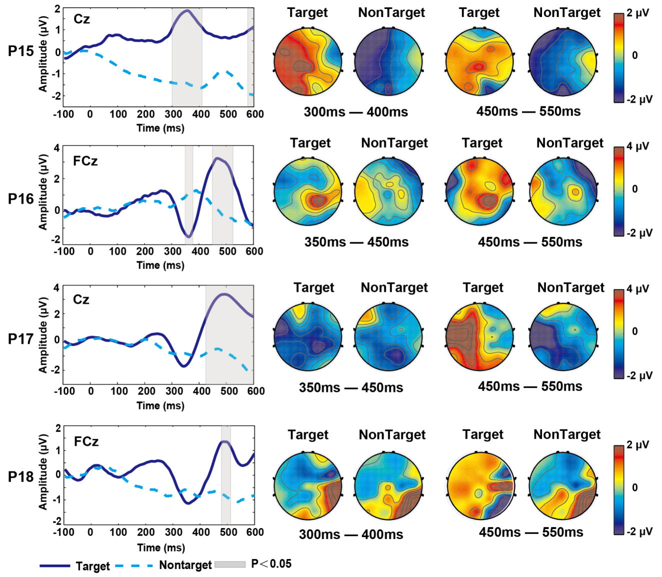

Fig. 4. The individual ERP waveforms and scalp topographies of the responsive patients (15, 16, 17 and 18). The target and nontarget waveforms are denoted by the solid and dashed lines, respectively. Significant differences between the two stimulus conditions (t-test, $p < 0.05$) are denoted by gray shaded areas. The scalp topographies showed that the negative and positive responses were distributed throughout different brain regions in specific time windows.

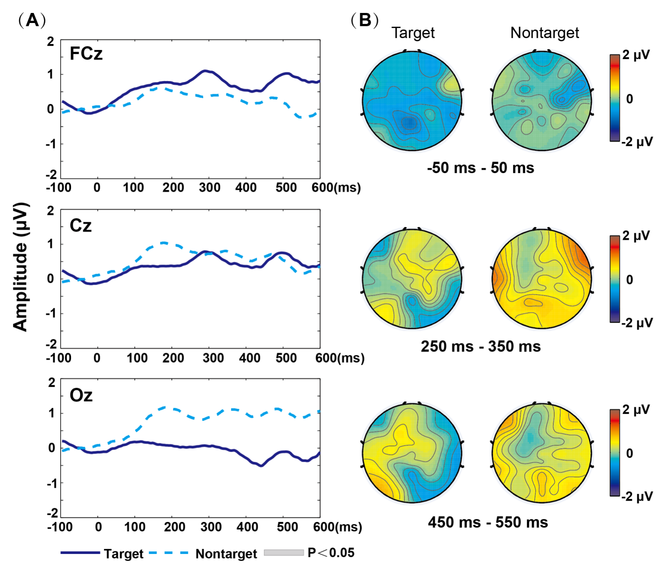

Fig. 5. The averaged ERP waveforms and scalp topographies of the seven patients in the nonresponsive group. (A) ERP waveforms in “FCz,” “Cz” and “Oz.” Significant differences between the two stimulus conditions were not observed. (B) Scalp topography in the three time windows (i.e., −50-50, 250-350 and 450-550 ms).

nontarget stimuli conditions were not observed in the selected channels (t-test, $p < 0.05$). There was only a small positive component evoked by nontarget stimuli in channel “Oz” after 100 ms post-stimulus. Correspondingly, there was no obvious change evoked by the audiovisual stimuli in the target direction over the scalp map, as shown in Fig. 5(B).

Above all, the remaining seven patients, who may be behaviorally nonresponsive in the first CRS-R evaluation, achieved the significance threshold of the BCI online accuracy (see Table II) and thus were diagnosed as being sound localization-responsive by BCI. In contrast to the findings that MMN- and P300-like components were both evoked by the audiovisual stimuli in healthy subjects, most patients in the inconsistent group showed only one negative or positive component, as shown in Fig. 6. Specifically, patients 2, 4, 5, 9 and 14 revealed only a P300-like component in selected channels of the ERP waveforms; i.e., for patient 2, a P300-like component in the time range of 250-380 ms was observed in “FCz” and was located mainly at the frontal-central sites. Patients 7 and 12 exhibited a remarkable negative component (MMN-like) in “FCz” or “Cz”, and patient 12 exhibited a positive component, as shown in Fig. 6. Interestingly, patients 7, 9 and 12 had improved CRS-R scores in the second behavioral evaluation. From the results of patient 12, a marked, negative peak appeared at approximately 320 ms, and the negative component was observed in asymmetrical frontal-central scalp areas between 250 and 350 ms in his target scalp. Furthermore, patient 12 showed improvements in his CRS-R scores in the second behavioral measurement (after the BCI experiment), and the score of the auditory subscale increased from 1 to 4.

In addition, ERSP and ITPC values were calculated on bandpass-filtered (0.1-50 Hz) target epochs at the major electrode of FCz related to the ERPs. There were 400 epochs corresponding to target stimuli across 40 trials for each selected subject, including both healthy subjects and patients in the different groups. As shown in Fig. 7, the time-frequency colormaps were plotted against time (x-axis) from −100 ms to 800 ms and frequency (y-axis) between 0.1 and 50 Hz. These plots reflected the change in the power spectrum with the stimulation and the homogeneity of the instantaneous phase across different trials/epochs. In Fig. 7, the first panel showed ERSP and ITPC of H3 in the healthy group, where H3’s ERSP showed a substantial increase in power between 250 ms and 650 ms, mainly in the delta, theta and alpha bands, associated with similar phase locking in the ITPC in time ranges of 250-500 ms and 550-650 ms. The second panel showed ERSP and ITPC values of P16 in the responsive patient group, with power increasing within the period of 250 to 500 ms, primarily in the beta band and extending into the delta, theta and alpha bands, even in frequency bands higher than 40 Hz. Additionally, this power increase was accompanied by significant phase locking in the frequency band of 1-20 Hz with a time range of 250-500 ms. The third panel of P12 in the inconsistent patient group showed obvious evoked power increases in time segments of 200-350, 400-500 and 650-700 ms, mainly in frequency bands below 20 Hz and above 40 Hz. Moreover, the phenomenon of phase locking is consistent with H3 and P16. The last panel for P13 in the nonresponsive patient group revealed that there was little evoked power increase in the ERSP, while the ITPC was close to zero at different times and frequencies. Obviously, the ERSP and ITPC values of the signal with the ERP component for H3, P16 and P12 in the time period of 250-450 ms, mainly in the frequency band less than 20 Hz, were larger than those without these components for P13 in the nonresponsive group. This result implied that the activity evoked by the audiovisual

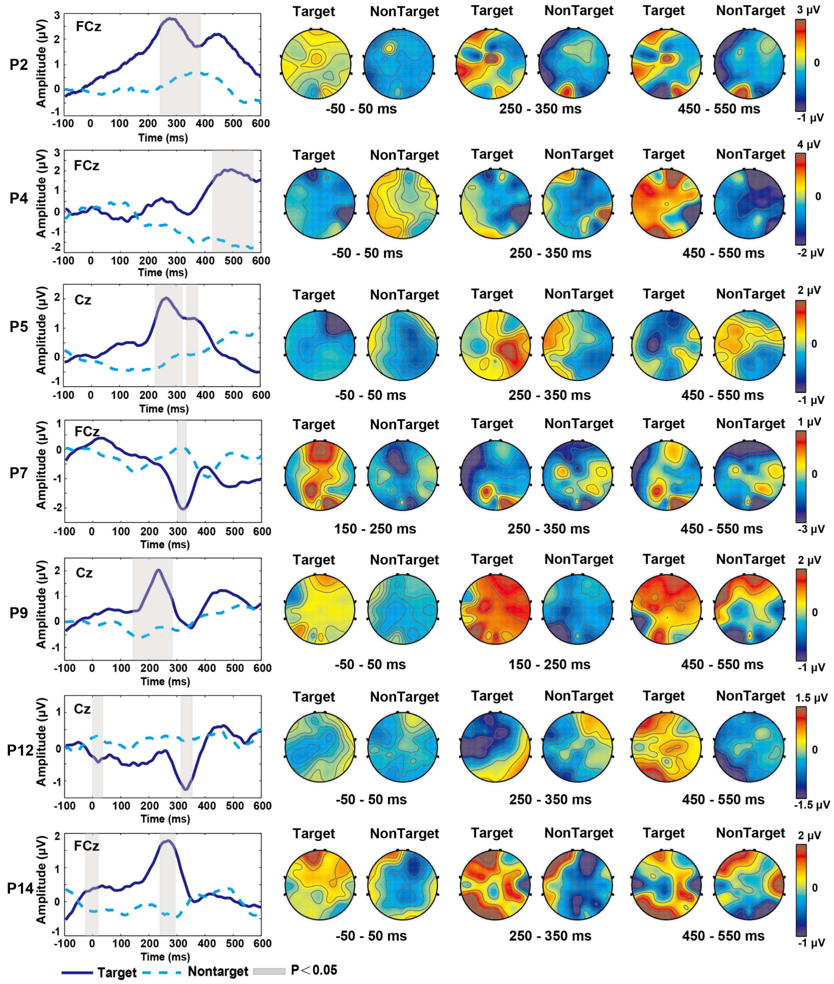

Fig. 6. The individual ERP waveforms and scalp topographies of the seven patients in the inconsistent group. The target and nontarget waveforms are denoted by the solid and dashed lines, respectively. Significant differences between the two stimulus conditions (*t*-test, $p < 0.05$) are denoted by gray shaded areas. The scalp topographies of patients' EEG responses to target and nontarget stimuli were plotted to observe the spatial distribution in the different time windows.

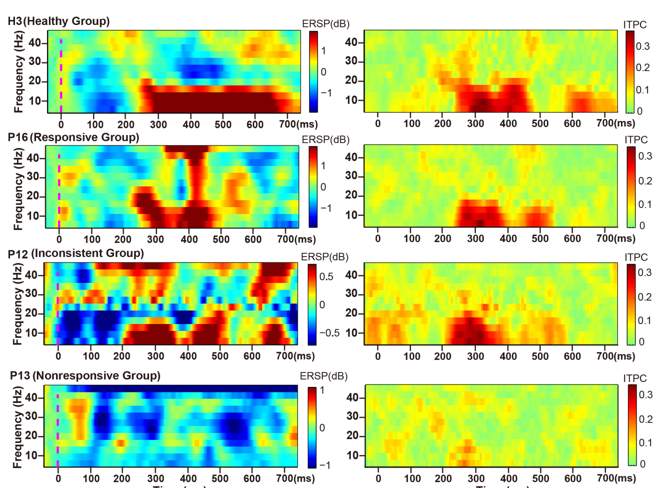

Fig. 7. Time-frequency analysis of the target audiovisual task from four selected subjects at the major electrode of FCz. The four panels show ERSP and ITPC colormaps of H3, P16, P12 and P13, respectively.

target stimuli can reflect the response of sound localization and further demonstrated the efficacy and reasonability of the BCI assessment.

IV. Discussion

A hybrid audiovisual BCI system that simulates the assessment of sound localization in the CRS-R was developed to assist in the clinical diagnosis of DOC patients. In the experimental procedure, the auditory stimuli induced the patients to pay attention to the flashing button and ipsilateral synchronous bell sound in the target direction. The recorded EEG responses were analyzed in real time to provide output as feedback. Among the 18 DOC patients, four and seven patients were classified as sound localization-responsive and nonresponsive, respectively, in both the BCI and CRS-R assessments. Crucially, the remaining seven patients who might be behaviorally nonresponsive were identified by the BCI assessment as sound localization responsive.

A. Identification of Patients With Cognitive Motor Dissociation

Severe lack of behavioral expression caused by motor impairment in DOC patients poses a challenge for behavioral assessments in clinical practice [39]. In fact, behavioral assessments, which are heavily dependent on motor abilities, could lead to a high rate of misdiagnosis for these DOC patients.

For instance, the scoring criterion for sound localization in CRS-R is whether or not the patient oriented his/her head or eyes toward the stimulus direction. However, this subtle sign of sound localization (head or eye movements) can be imperceptible to examiners and frequently missed. Previous studies have noted that a subset of DOC patients with no behavioral responsiveness have shown neuroimaging or electrophysiological evidence of preserved cognitive ability, which has been termed cognitive motor dissociation (CMD) [40], [41]. At the same time, the proportion of CMD patients among DOC patients has varied greatly. Specifically, Pan *et al.* showed that 44% of 78 DOC patients were CMD patients as defined by significant BCI accuracy [22]. Curley *et al.* identified 13 CMD patients among 20 DOC patients using motor imagery tasks [42]. Moreover, Monti *et al.* found four CMD patients among 23 UWS patients using functional magnetic resonance imaging (fMRI)-based motor imaging tasks [43]. For instance, Wang *et al.* verified that five of seven (71%) DOC patients exhibited command following using a number recognition task [44]. This variability highlights the challenge as well as importance of distinguishing the CMD patients from the DOC patients. Generally, EEG-based BCIs showed advantages over other neuroimaging techniques in being automatic, objective, and effective in the identification of CMD patients [14], [45].

Our previous studies presented several audiovisual BCIs for DOC patients [22], [23], [32], [33], [44]. The BCI in this study and previous BCIs differed substantially in the following aspects: (i) The BCI in this study was to assess sound localization function, while the BCIs in the previous studies were used to detect awareness, to assess communication or to assess object recognition function; (ii) These studies differed in the presentation and role of the auditory stimuli. In this study, the auditory stimuli were presented only in the target direction as a cue and continuously attracted the subjects' attention to the target side. However, the auditory stimuli in the previous BCIs [22], [23], [32], [33], [44] were presented on both target and nontarget sides and were synchronized with visual stimuli to enhance ERPs for detection, whereas the target was cued by the instructions and thus the patients needed to understand the instructions to determine the target; (iii) In the previous BCIs, high-level language understanding and memory functions, in addition to corresponding cognitive functions related to the tasks, were necessary for the patients to use the BCIs effectively. However, in this study, high-level language understanding and memory functions were not necessary for the patients because the auditory stimuli prompted patients to selectively attend to the target button. In conclusion, the special design in this study enabled the realization of sound localization assessment in the CRS-R, which could not be achieved by the BCIs presented in the previous studies.

As seen from our experimental results, sound localization behaviors were observed in only four of the 18 patients using the CRS-R, and all four patients were detected by the BCI system. However, other patients without behavioral expression of sound localization might include patients with CMD. Seven patients in the inconsistent group, who failed to show a sound localization behavior in the first CRS-R assessment, were found to have an averaged BCI accuracy of 78%, which significantly exceeded the chance level. The significant online accuracy obtained in BCI assessment reflects that the patient could selectively attend to the target cued only by the auditory stimuli, i.e., possessing sound localization ability. It could also mean that the patient had normal visual function and selective attention. These seven patients' ERPs and rehabilitation results further confirmed the BCI results. The remaining seven patients were assessed as nonresponsive to directional auditory stimuli in both the BCI and CRS-R assessments, implying that these seven patients are indeed nonresponsive or could be responsive but were missed by both the BCI and the CRS-R. Four patients who exhibited sound localization behaviors in the CRS-R assessment were among those detected by the BCI in this study. This validated our BCI-based assessment. More importantly, seven patients who had no sound localization according to the CRS-R assessment showed sound localization in our BCI assessment, which implied that BCI could be a promising technique for assisting sound localization assessment in clinical diagnosis. Incorporating tactile stimuli [46], [47] into our paradigm might improve the performance of the sound localization BCI. In addition, fine tuning a general model that learn from a large patient group could greatly shorten the calibration time without performance degeneration [48], [49] and improve the feasibility of our system in clinical applications in future work.

B. Clinical Implication of Auditory Assessment in DOC Patients

Auditory stimulation can enrich the environment and facilitate the recovery of consciousness in DOC patients. It is an experimental awakening method that exhibits superior efficacy over other noninvasive methods. Recent studies have used auditory ERPs to predict the likelihood of recovery for DOC patients [35]. Reliable evidence has indicated that auditory cortical activation was very important for recovery of consciousness in the VS patients [50]. A study by Wijnen *et al.* showed that the amplitude of MMN elicited by auditory stimuli increases with recovery from VS to normal consciousness [36]. Therefore, the auditory assessments have important implications for clinical prognosis in DOC patients [51].

In our study, the hybrid BCI could provide a method to assess sound localization in DOC patients. Eleven patients, including four in the responsive group and seven in the inconsistent group, were considered to be sound localization responsive by the BCI assessment. In contrast to the findings that MMN- and P300-like components were simultaneously evoked by the audiovisual stimuli in healthy subjects, most of these eleven patients showed either only a negative or a positive component, as shown in Fig. 4 and Fig. 6. The results might be due to the brain injury-related factors (e.g., injury locations) in these patients. Although the ERP patterns of DOC patients were different from those of healthy subjects, the proposed BCI could detect the ERPs evoked by attending to the target stimuli in DOC patients. Interestingly, three of seven patients in the inconsistent group, namely patients 7, 9 and 12, showed improvements in their CRS-R scores in the second assessment after the BCI experiment. Most notably, patient 12, with both MMN- and P300-like components recovered to EMCS and showed sound localization behavior in the second CRS-R assessment. His CRS-R score greatly improved from 9 to 15, and his auditory subscale score increased from 1 to 4. The BCI results of sound localization assessment could provide a new clinical basis for subsequent interventional treatment. Long-term tracking of the rehabilitation results further confirmed the BCI results of DOC patients with a short disease duration.

C. Hybrid Audiovisual BCI System

We utilized an audiovisual paradigm for two reasons. First, the auditory stimuli were employed to prompt the target direction for the patient. The patient had to determine the target direction according to the auditory stimuli. Moreover, patients could do it only based on the auditory stimuli even if they did not have the ability of language comprehension of the instructions. Second, when patients attended to the target cued by the auditory stimuli, ERPs including P300 could be evoked by the audiovisual stimuli, where the visual stimuli played a major role according to our experimental results of healthy subjects. The BCI algorithm could determine whether the target was attended to or not by detecting the evoked ERPs.

If a patient obtained significant accuracy in our BCI assessment, it implies that he/she could selectively attend to the target cued only by the auditory stimuli, indicating that he/she had sound localization ability. On the other hand, if a patient (e.g., with an auditory deficit) did not have sound localization, he/she was unable to determine the target according to the auditory stimuli (cues). As a consequence, ERPs could not be reliably evoked by the target audiovisual stimuli, and the online BCI accuracy was at a random level. Hence, the BCI results were informative for the assessment of sound localization ability. As seen from our results, seven patients were classified as nonresponsive to sound localization by the online BCI accuracy that approached the chance level. However, the other eleven patients were classified as responsive to sound localization by the significant online BCI accuracy. Only four of these eleven patients showed sound localization behavior in the CRS-R assessment. The results indicated that the proposed BCI could identify more patients with sound localization ability than the CRS-R. In the behavioral scale-based assessment of sound localization, overt attention was required, e.g., head or eyes movement. However, it is difficult for DOC patients with substantial head or ocular motor impairments to pay overt attention in the CRS-R. As we know, ERPs could be evoked by attending overtly and covertly to target stimuli in the BCI [52]. The proposed BCI could provide a promising way to detect the sound localization responses for DOC patients with motor impairments.

V. Conclusion

We investigated a hybrid BCI system to facilitate the clinical assessment of sound localization in DOC patients. The proposed BCI system could detect brain responses to sound localization so as to assist in identification of CMD among DOC patients. Although encouraging results were obtained, much effort should be exerted to improve this study. First, patients with brain injuries other than TBI and NTBI, as well as different types of concurrent medical conditions, have not yet been considered. For instance, the ERP components were not consistent with each other, and brain injury-related factors (e.g., injury locations) have been shown to influence ERPs in DOC patients. Further studies should be conducted to identify the effects of these factors on the brain responses in DOC patients. Second, there was a long time interval from the brain injury to the BCI experiment, including a period of more than 12 months, for 9 of the 18 DOC patients involved in our experiment; however, the literature has shown that the clinical significance of sound localization assessment is more relevant to the prognosis of DOC patients with shorter disease durations. Future studies should consider the disease durations of patients with DOC. Third, a 2-month clinical follow-up was not sufficient. Longer term tracking should be performed in future studies.

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