doi:10.1093/brain/awaa026 BRAIN 2020: 143; 1177–1189 | 1177

BRAIN
A JOURNAL OF NEUROLOGY

Prognosis for patients with cognitive motor dissociation identified by brain-computer interface

Jiahui Pan,[1,2,*] Qiuyou Xie,[3,4,*] Pengmin Qin,[5,*] Yan Chen,[4] Yanbin He,[4,6] Haiyun Huang,[1] Fei Wang,[1,2] Xiaoxiao Ni,[4] Andrzej Cichocki,[7,8] Ronghao Yu[4] and Yuanqing Li[1]

*These authors contributed equally to this work.

See Owen (doi:10.1093/brain/awaa056) for a scientific commentary on this article.

Cognitive motor dissociation describes a subset of patients with disorders of consciousness who show neuroimaging evidence of consciousness but no detectable command-following behaviours. Although essential for family counselling, decision-making, and the design of rehabilitation programmes, the prognosis for patients with cognitive motor dissociation remains under-investigated. The current study included 78 patients with disorders of consciousness who showed no detectable command-following behaviours. These patients included 45 patients with unresponsive wakefulness syndrome and 33 patients in a minimally conscious state, as diagnosed using the Coma Recovery Scale-Revised. Each patient underwent an EEG-based brain-computer interface experiment, in which he or she was instructed to perform an item-selection task (i.e. select a photograph or a number from two candidates). Patients who achieved statistically significant brain-computer interface accuracies were identified as cognitive motor dissociation. Two evaluations using the Coma Recovery Scale-Revised, one before the experiment and the other 3 months later, were carried out to measure the patients' behavioural improvements. Among the 78 patients with disorders of consciousness, our results showed that within the unresponsive wakefulness syndrome patient group, 15 of 18 patients with cognitive motor dissociation (83.33%) regained consciousness, while only five of the other 27 unresponsive wakefulness syndrome patients without significant brain-computer interface accuracies (18.52%) regained consciousness. Furthermore, within the minimally conscious state patient group, 14 of 16 patients with cognitive motor dissociation (87.5%) showed improvements in their Coma Recovery Scale-Revised scores, whereas only four of the other 17 minimally conscious state patients without significant brain-computer interface accuracies (23.53%) had improved Coma Recovery Scale-Revised scores. Our results suggest that patients with cognitive motor dissociation have a better outcome than other patients. Our findings extend current knowledge of the prognosis for patients with cognitive motor dissociation and have important implications for brain-computer interface-based clinical diagnosis and prognosis for patients with disorders of consciousness.

1 Center for Brain-Computer Interfaces and Brain Information Processing, South China University of Technology, Guangzhou, China
2 School of Software, South China Normal University, Guangzhou, China
3 Department of Rehabilitation Medicine, Zhujiang Hospital, Southern Medical University, Guangzhou, China
4 Centre for Hyperbaric Oxygen and Neurorehabilitation, Guangzhou General Hospital of Guangzhou Military Command, Guangzhou, China
5 Centre for Studies of Psychological Applications, Guangdong Key Laboratory of Mental Health and Cognitive Science, School of Psychology, South China Normal University, Guangzhou, China
6 Department of Traumatic Brain Injury Rehabilitation and Severe Rehabilitation, Guangdong Work Injury Rehabilitation Hospital, Guangzhou, China

Received June 4, 2019. Revised December 8, 2019. Accepted December 17, 2019. Advance access publication February 26, 2020
© The Author(s) (2020). Published by Oxford University Press on behalf of the Guarantors of Brain.
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

7 Skolkovo Institute of Science and Technology (Skoltech), Moscow 143026, Russia
8 Nicolaus Copernicus University (UMK), Torun 87-100, Poland

Correspondence to: Yuanqing Li, PhD
Center for Brain-Computer Interfaces and Brain Information Processing
South China University of Technology
Guangzhou, 510640, China
E-mail: auyqli@scut.edu.cn

Correspondence may also be addressed to: Ronghao Yu, MD
E-mail: gesund@21cn.com

Keywords: cognitive motor dissociation; brain-computer interface; disorders of consciousness; prognosis; unresponsive wakefulness syndrome

Abbreviations: BCI = brain-computer interface; CMD = cognitive motor dissociation; CRS-R = Coma Recovery Scale-Revised; GUI = graphical user interface; MCS = minimally conscious state; SSVEP = steady-state visual evoked potential; SVM = support vector machine; UWS = unresponsive wakefulness syndrome

Introduction

Much effort has been made over the past decade to detect residual brain function in patients with disorders of consciousness such as unresponsive wakefulness syndrome (UWS, also known as vegetative state) and minimally conscious state (MCS) (Fernandez-Espejo and Owen, 2013; Giacino *et al*., 2014; Noirhomme *et al*., 2017). Patients with UWS have no consciousness of the environment or themselves, while patients with MCS show inconsistent but reproducible signs of awareness through their behavioural responses (Giacino *et al*., 2004). In 2006, Owen and colleagues identified one UWS patient with clear consciousness by demonstrating command-following brain activation (Owen *et al*., 2006). Subsequent studies by that team showed that 20% of UWS patients had clear brain activation patterns in response to specific active tasks (Monti *et al*., 2010; Cruse *et al*., 2011). These findings led to a new clinical entity named cognitive motor dissociation (CMD), also known as functional locked-in syndrome; in this condition, patients show no detectable command-following behaviours, but there is clear neuroimaging evidence of command-following brain activities (Schiff, 2015; Boly and Laureys, 2018). More importantly, one recent study showed that there may be more patients with CMD in disorders of consciousness (21 of 28) than are currently recognized (Curley *et al*., 2018). With the detection of more CMD patients, the prognosis of these patients has drawn increasing interest because of its crucial impact on family counselling, decision-making and the design of rehabilitation programmes (Curley *et al*., 2018). However, the prognosis for CMD patients remains to be investigated.

Two methods are usually adopted to identify patients with CMD. One involves mental imagery tasks in which patients with disorders of consciousness are instructed to imagine playing tennis or other activities (Owen *et al*., 2006; Cruse *et al*., 2011; Goldfine *et al*., 2012; Claassen *et al*., 2019). The datasets are subjected to offline analysis to discover command-following brain activation patterns in patients with disorders of consciousness, from which patients with CMD are then identified. The other method is through a brain-computer interface (BCI) (Lulé *et al*., 2013; Gibson *et al*., 2016; Guger *et al*., 2018; Pan *et al*., 2018). BCIs are designed to restore the communication ability of patients; these tools involve real-time analysis and classification of brain responses to command-following tasks that could reflect the user's intention (Luaute *et al*., 2015). The command-following activation patterns are used to drive computer interfaces to enable communication without behavioural responses (Chatelle *et al*., 2012). EEG-based BCIs, which may rely on sensorimotor rhythms, P300, steady-state evoked potentials, or slow cortical potentials, have been used to detect command-following brain activation patterns in patients with severe brain injuries, and can effectively identify CMD patients (Gibson *et al*., 2016; Guger *et al*., 2018; Pan *et al*., 2018). Compared with offline EEG data analysis of mental imagery tasks, the online analysis-based feedback of a BCI has the advantage of allowing the patients to engage more directly with the tasks if they maintain awareness (Gibson *et al*., 2016).

To explore the prognosis of CMD patients, EEG-based BCIs were adopted in the current study to identify CMD patients from 78 patients with disorders of consciousness (45 UWS patients and 33 MCS patients). All patients were assessed using the Coma Recovery Revised-Scale (CRS-R) during the week before the experiment. None of the 78 patients showed detectable behavioural command-following abilities. Regarding the definition of CMD, the underlying assumption was that if the patients could follow the commands to perform a cognitive task (e.g. recognize and select a photograph) with significant accuracies using the BCI system, they were considered to be conscious and thus defined as CMD patients. Three BCI paradigms were carried out, including photograph, number and audiovisual tasks (see Fig. 1 for schemas of the experimental procedures). Each patient was enrolled in one experimental paradigm. A second

CRS-R assessment was performed for each patient 3 months after admission as an index of the patient's outcome. Finally, the outcomes of the CMD patients were compared with those of the other patients. Patients with CMD were hypothesized to show better recovery than non-CMD patients, given that they are likely to have more preserved high cognitive brain function and that such function is associated with better recovery (Giacino and Whyte, 2005).

Materials and methods

Subjects

This study involved 78 patients with disorders of consciousness (51 males and 27 females; 45 UWS and 33 MCS; mean age 37.87 ± 14.28 years; Supplementary Table 1) at the General Hospital of Guangzhou Military Command of People's Liberation Army, China, between October 2014 and August 2018. The following inclusion criteria were used: (i) a diagnosis of UWS or MCS, with no detectable command-following behaviours observed during the week of admission (Bruno *et al.*, 2011); (ii) more than 1 month since a traumatic brain injury (TBI), anoxic brain injury, or cerebrovascular disease; (iii) no history of impaired visual acuity before brain injury; and (iv) presence of a visual startle response according to the CRS-R scale, or intact visual evoked potentials when a visual startle response was not detected.

In addition, eight healthy volunteers with no history of neurological disease [seven males; mean age ± standard deviation (SD), 29.13 ± 4.67 years] were included to verify the performance of the BCIs (Chae *et al.*, 2012). The present study was approved by the Ethics Committee of the General Hospital of Guangzhou Military Command in Guangzhou and complied with the Code of Ethics of the World Medical Association (Declaration of Helsinki). Written informed consent was provided by each patient's legal surrogate for the experiments and for publication of the patient's individual details in this study.

Clinical evaluation

All patients were subjected to two CRS-R assessment periods: one during the week before the experiment and another 3 months later. For each patient, a minimum of two CRS-R assessments were performed by two experienced doctors (blinded to the BCI results) in each assessment period. No sedation was administered in the 24 h prior to CRS-R assessment and the BCI experiment. In general, increasing CRS-R scores indicate a trend towards an improvement in the level of consciousness (Bagnato *et al.*, 2015). CRS-R scores (Supplementary Table 1) at each period were based on the patient's best responses during the repeated CRS-R assessments. Considering the outcome of the patients, UWS patients with an upgrade in their level of consciousness (i.e. from UWS to MCS) were classified as 'improvement', while those without any upgrade were classified as 'no improvement'. For MCS patients, patients with an increase in their CRS-R scores were classified as 'improvement', while those without an increase in their CRS-R scores were classified as 'no improvement'.

Brain-computer interface experiments

BCI experiments were performed by several researchers who were blinded to the patients' CRS-R scores. In these BCI experiments, the participants were instructed to focus on the target stimulus and perform simple tasks. The BCI system was designed to detect the target stimulus based on EEG signal changes when participants performed the tasks. Patients with a BCI accuracy significantly higher than the chance level were operationally defined as CMD patients. Note that non-significant BCI accuracy could not be used as definitive evidence for a non-CMD state because false-negative findings in BCI experiments are possible in some patients with disorders of consciousness, and even in healthy subjects (Guger *et al.*, 2009; Allison *et al.*, 2010). Thus, patients without significant BCI accuracies could potentially be either non-CMD patients or CMD patients who were not detected with our BCI method; for this reason, they were labelled potential non-CMD patients. For BCI experiments, we used a NuAmps device (Compumedics, Neuroscan, Inc.) to collect EEG signals via a 30-channel cap (LT 37). EEG signals from all electrodes were referenced to the right mastoid and digitized at a sampling rate of 250 Hz. Electrode impedances were kept below 5 kΩ.

For each patient, the BCI experiment included a calibration session and an online evaluation session. In the calibration session, the patient performed 10 trials using the graphical user interface (GUI) shown in Fig. 1. An initial support vector machine (SVM) classifier for P300 detection was trained on these data. SVM models have been successfully applied for classification in various domains of pattern recognition (Lotte *et al.*, 2007), including EEG classification in disorders of consciousness (Goldfine *et al.*, 2012; Henriques *et al.*, 2014; Noirhomme *et al.*, 2017; Claassen *et al.*, 2019). In an SVM, an optimal hyperplane is found to separate two classes by maximizing the margin from the nearest training points (Kaper *et al.*, 2004; Salvaris and Sepulveda, 2009). SVMs often show an advantage over other classifier algorithms in generalization performance and in cases where only small training datasets are available (Yin and Hou, 2016). In the training data, a label of 1 was assigned to the photograph-related P300 feature vector of the target photograph, and a label of –1 was assigned to the feature vector of the non-target. These P300 feature vectors and labels were used to train a linear kernel SVM classifier implemented in the LibSVM toolbox. All parameters were set to their default values (Varoquaux *et al.*, 2016). Note that the steady-state visual evoked potential (SSVEP) detection did not require a calibration process.

The online evaluation session contained five blocks of 10 trials. The initial classification model was updated after each online evaluation block based on the data from the calibration session and the data collected online. Different blocks were conducted on separate days because the patients were easily fatigued and had a limited attention span. Each patient performed five blocks of the experiment in approximately 1 week. During each trial, the patient was carefully monitored by the researchers to ensure task engagement, as they would sometimes fall asleep (close their eyes). Trials in which the patient fell asleep were discarded, and the next trial started after the patient awoke. On average, 0.74 trials were discarded for each patient. Each patient completed 50 trials while awake.

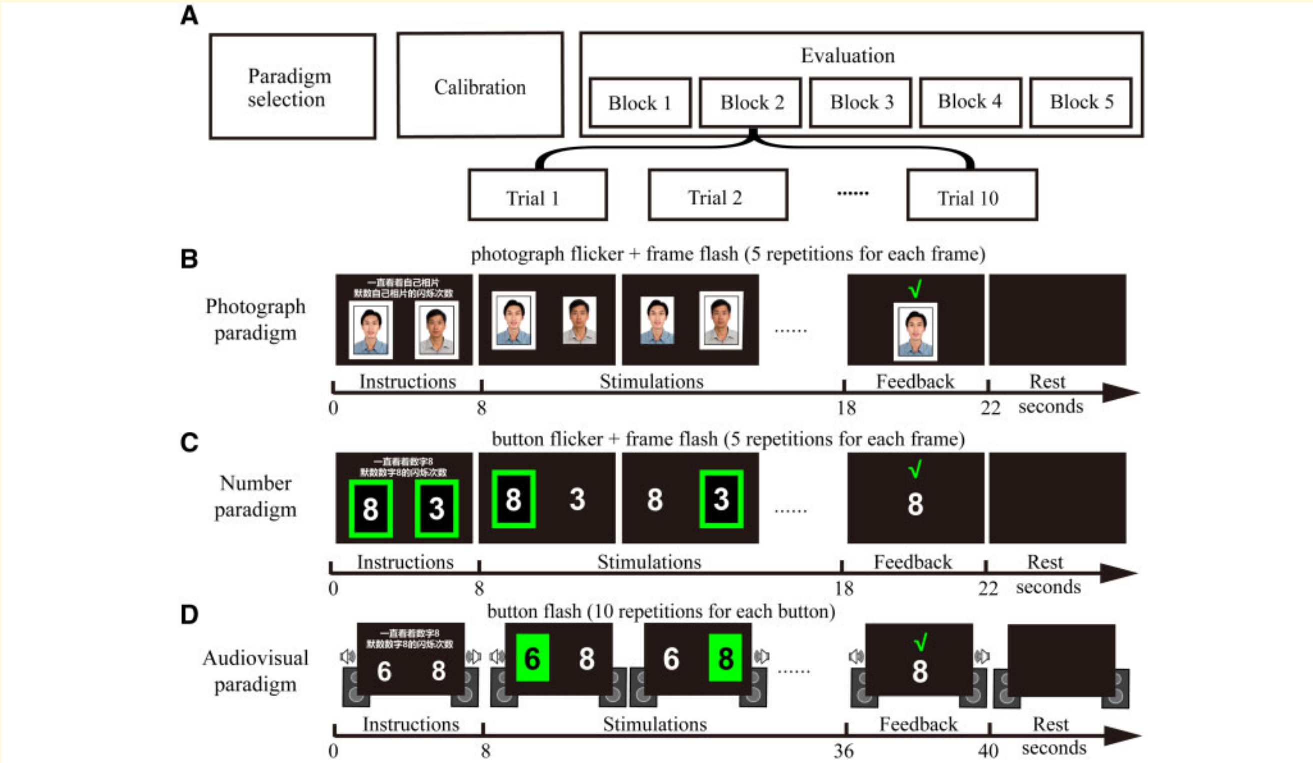

Figure 1 Illustration of the experimental design and procedure. (**A**) Experimental design. In this study, each patient participated in the BCI experiment based on the visual photograph paradigm, number paradigm, or audiovisual paradigm, as selected by his or her family members. To qualify for the audiovisual paradigm, patients needed to have both audition and vision. Before the online experiment, each patient performed a calibration run of 10 trials, from which we used the EEG data to train an initial P300 classification model. An online evaluation run contained five blocks, and each block was composed of 10 trials. Different blocks were conducted on separate days because the patients were easily fatigued and had limited attention span. The initial P300 classification model was updated after each block of online evaluation based on the online data. (**B**) Experimental procedure for the photograph paradigm in one trial, including the instructions (0–8 s), stimuli (8–18 s), feedback of classification results (18–22 s), and rest period (e.g. 22–32 s). Specifically, the patients were asked to focus on their own photographs or the photographs of strangers in a random order. Each trial started with audiovisual instructions in Chinese: 'Focus on your own photograph (or the stranger's photograph) and count the flashes of the photo frame', which lasted for 8 s and indicated the target photograph. Next, the two photographs appeared, one of which had a flashing frame. The flashing frame was chosen randomly and flashed five times. After 10 s, one of the two photographs identified by the BCI algorithm appeared in the centre of the GUI as feedback. If the result was correct, then a tick symbol, a positive audio feedback clip of applause, and the detected photograph were given for 4 s to encourage the patient; otherwise, an '×' symbol and the detected photograph were presented for 4 s. A short break of at least 10 s was provided between two adjacent trials, where the length of the break depended on the patient's level of arousal, i.e. the next trial began only when the patient was in a high level of arousal. (**C**) The experimental procedure for the number paradigm was similar to that for the photograph paradigm except that the photographs were replaced by two numbers. (**D**) The experimental procedure for the audiovisual paradigm was similar to that for the photograph paradigm except that audiovisual stimuli were used.

After the online session, classification accuracy was calculated as the ratio of the number of correct responses (hits) to the number of total trials. Statistical significance was assessed using χ^2 statistics. For a significance level of $P = 0.05$, we obtained a χ^2 value of 3.84, corresponding to 32 hits in 50 trials or a binary choice accuracy of 64%.

Three hybrid BCIs were used in this study, including a hybrid P300 and SSVEP BCI based on photograph stimuli (photograph paradigm), a hybrid P300 and SSVEP BCI based on visual number stimuli (number paradigm), and an audiovisual BCI based on audiovisual number stimuli (audiovisual paradigm). The rationale for using the three BCIs was 2-fold. First, the GUI for each of these BCIs was similar, in which the patients were instructed to focus on one of the two stimuli while ignoring the other, therefore producing the same chance level (50%). Second, using different stimuli may be beneficial to assess the prognostic value of the BCI method for different patients with disorders of consciousness. Some patients may be more interested in photographs, whereas numbers may be more attractive for other patients. Furthermore, audiovisual stimuli may be suitable for patients who have somewhat intact auditory and visual function, whereas single-modality visual stimuli may be more suitable for patients who lack auditory function but retain their visual abilities.

Each patient participated in the visual photograph paradigm, the number paradigm, or the audiovisual paradigm, as selected by their family members. Note that for the audiovisual paradigm, the patients also needed to show an auditory startle response according to the CRS-R scale or brainstem auditory evoked potentials when an auditory startle response was not detected. Thirty-five patients participated in the experiment based on the photograph paradigm, 13 in the experiment based on the number paradigm, and 30 in the experiment based on the audiovisual paradigm. The eight healthy subjects participated in all three of the experiments.

Photograph paradigm

The GUI and the experimental procedure of the photograph paradigm are illustrated in Fig. 1B. In each trial, two frontal-view facial photographs were presented, including a photograph of the patient's own face and a photograph of an age- and sex-matched stranger. One of the two photographs would be randomly chosen as the target in each trial.

Each trial started with audiovisual instructions along with the two photographs, each embedded in a static photo-frame. Instructions were shown in Chinese characters for 8 s: 'Focus on your own photograph (or the stranger's photograph) and count the flashes of the photo frame'. Following the instructions panel, a 10-s stimulation period started, with two photographs appearing on the screen at the same time. The two photographs continued flickering at different frequencies (6.0 Hz and 7.5 Hz for the left and right photographs, respectively) to evoke the left/right photograph-related SSVEP. A total of 10 flashes (appearing and disappearing) of the two photo frames would occur simultaneously with the flickering of the photographs, with only one frame appearing at a time. The order of the flashes was pseudorandom, with each frame flashing a total of five times. Each flash had a duration of 200 ms, and there was an 800-ms interval between flashes. These flashes of the left/right photo frame would evoke the corresponding left/right photograph-related P300.

A feedback period followed the stimulation, during which the BCI algorithm selected one of the two photographs as the predicted target by comparing the left and right photograph-related P300 and SSVEP patterns. If the photograph selected was the same as the target, then that photograph and a tick symbol would be presented in the output panel as positive visual feedback, along with a sound clip of applause, and a success was counted; otherwise, the selected photograph and an '×' symbol of would appear in the output panel as a negative visual feedback. Feedback in the output panel would last for 4 s. A break of at least 10 s was provided between two adjacent trials, where the length of the break depended on the patient's level of arousal; i.e. the next trial began only when the patient displayed a high level of arousal. After 50 trials for each patient, the BCI accuracy was calculated as the ratio of the number of successes to the total number of trials.

Photograph experiment processing algorithm

Attended stimuli have been found to evoke a stronger P300 and SSVEP than unattended stimuli (Bernat *et al*., 2001; Chatelle *et al*., 2012). Based on this, the BCI system was designed to detect the attended photograph by comparing the left and right photograph-related P300 and SSVEP patterns. The P300 and SSVEP detectors were designed separately, and the EEG data were fed into the two detectors simultaneously.

An example of the data processing procedure for a photograph paradigm trial can be seen in Fig. 2. For the left photograph-related P300, EEG signals were first filtered from 0.1 to 10 Hz. For each flash of the frame surrounding the left photograph, we obtained a segment of the EEG signal from each channel (0–600 ms after the frame flash) and down-sampled this segment by a rate of five. We then concatenated the down-sampled segments of 10 channels (Fz, Cz, P7, P3, Pz, P4, P8, O1, Oz and O2), to obtain a data vector per flash. These were then averaged to give a final left photograph-related P300 feature vector for each trial. The SVM classifier was then applied to the left photograph-related P300 feature vector, and an SVM score, called a P300 score in Fig. 2, was obtained for the left photograph. The same procedures were performed for the right photograph-related P300, except that the right photograph-related P300 feature vector was constructed based on the EEG segments of the five right photo-frame flashes.

For the left photograph-related SSVEP, EEG signals were first filtered from 4 to 20 Hz. Eight EEG signal segments were extracted from eight electrodes (P7, P3, Pz, P4, P8, O1, Oz and O2) during a 10-s period from the initial stimulus onset. A weighted sum of the eight segments was then calculated, where the weights were obtained using the minimum energy combination method designed to enhance EEG information and reduce nuisance signals (Pan *et al*., 2013). The power spectrum of the weighted EEG signal was obtained through a discrete Fourier transform. An SSVEP feature vector composed of two mean power values was obtained based on the flickering frequency (6 Hz) of the left photograph. One mean power value was calculated from a narrow band with a width of 0.1 Hz and a centre frequency of 6 Hz, and the other from a wide band with a width of 1 Hz and a centre frequency of 6 Hz. The ratio of the mean power from the narrow band to that from the wide band was calculated to give an SSVEP score for the left photograph. The same procedures were performed for the right photograph-related SSVEP, except that the right photograph-related SSVEP feature vector was constructed based on the flicker frequency (7.5 Hz) of the right photograph.

Joint scores for the left (Score 1) and right (Score 2) photographs were calculated by computing the sum of the respective P300 and SSVEP scores. A classification decision was made based on the following criterion: if Score 1 was higher than Score 2, then the left photograph was selected as the predicted target by the BCI system; otherwise, the right photograph was determined as the predicted target. Finally, the corresponding output was presented as the feedback.

Number paradigm

The GUI and the experimental procedure for the number paradigm (Fig. 1C) were similar to those of the photograph paradigm except that the two photographs were replaced by two randomly selected single-digit Arabic numerals from 0 to 9 (e.g. 8 and 3 in Fig. 1C). Patients were instructed to focus on the target number in each trial (e.g. 8) and count the number of flashes of the corresponding button frame. The detection algorithm was the same as that for the photograph paradigm described above.

Audiovisual paradigm

The GUI and the experimental procedure of the audiovisual paradigm are shown in Fig. 1D. Specifically, two buttons were located on the left and right sides of the GUI, on which two different randomly selected single-digit Arabic numbers from 0 to 9 (e.g. 6 and 8 in Fig. 1D) were displayed. The two number buttons flashed in an alternating pattern, where the colour of the

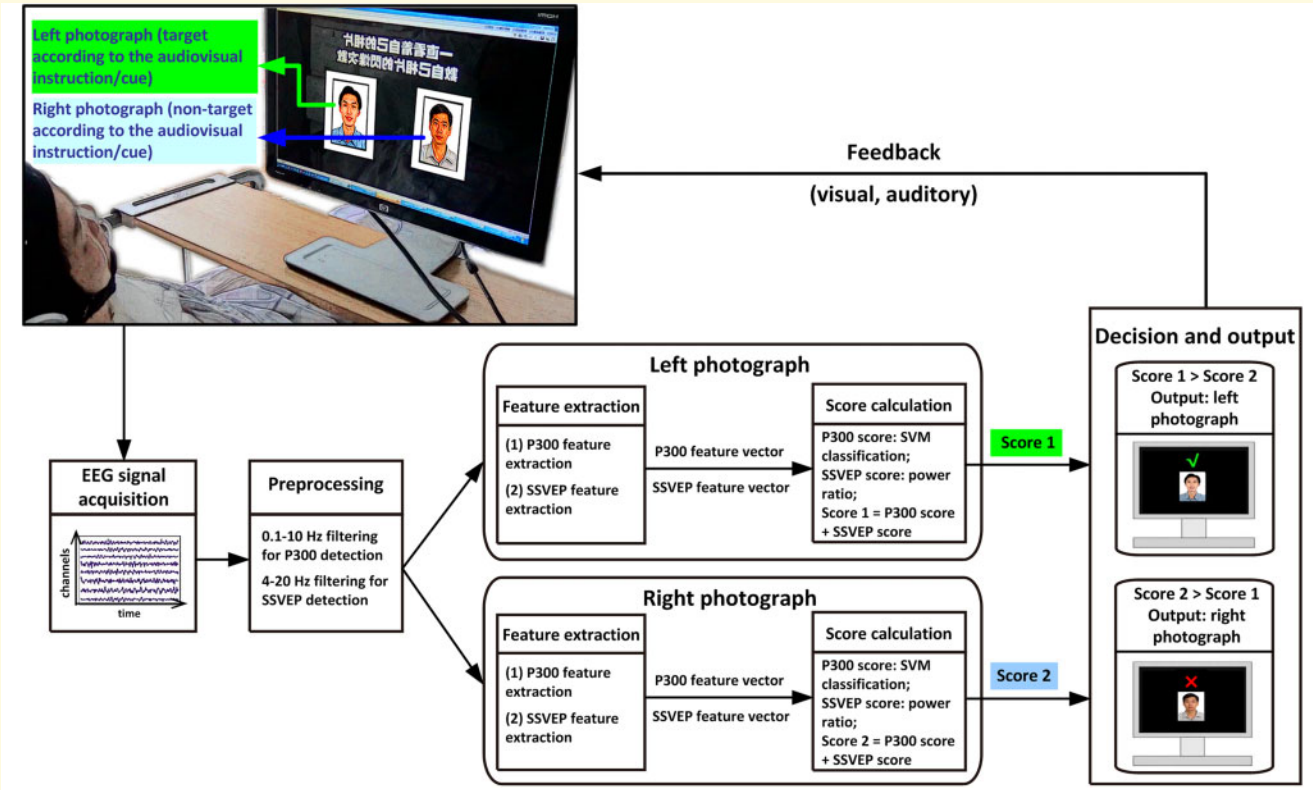

Figure 2 The data processing and decision-making procedure of a trial for the photograph paradigm. The patients were asked to selectively attend to the stimuli associated with one of the two photographs according to the audiovisual instructions/cues (i.e. voice in the headphone and sentence on the screen simultaneously; e.g. the left photograph is the target here), whereas the BCI system determined whether the patients were focusing on the target by detecting and comparing the left photograph-related and right photograph-related P300 and SSVEP patterns.

flashing button changed from green to black and the colour of the corresponding number changed simultaneously from black to white. The corresponding number was simultaneously read out from a speaker located on the ipsilateral side of the monitor. In this way, the subject was presented with temporally, spatially and semantically congruent audiovisual stimuli, each of which lasted for 300 ms, to evoke a P300 response. The P300 detection algorithm was similar to that for the photograph paradigm described above except that the EEG data of all 30 channels were used. The predicted target number was the number corresponding to the higher SVM score.

Offline event-related potential and spectral analyses

For each healthy subject and each patient, we calculated the event-related potential (ERP) waveforms using the EEG data from the online BCI experiment. Specifically, for each stimulus, after bandpass filtering (0.1–20 Hz), an EEG epoch of each channel was obtained from 50 ms prestimulus to 600 ms post-stimulus and was baseline-corrected based on the data from the 50-ms prestimulus interval. All epochs with voltage changes exceeding ±50 μV were automatically rejected. For each channel, we averaged the EEG epochs across all target stimuli and non-target stimuli to obtain two ERP waveforms.

Power spectrum analysis was performed on the EEG data collected from each healthy subject and patient who participated in the photograph or number paradigm-based BCI experiment. A spectrum was obtained for each trial using 10 s of EEG data from the eight electrodes (P7, P3, Pz, P4, P8, O1, Oz and O2) used for SSVEP detection. Averaged power spectrum curves across the trials with the target stimuli appearing on the left side (6 Hz) and right side (7.5 Hz) of the GUI were calculated.

Statistical analysis

Patients were first divided into two groups according to their BCI accuracies: patients with significant BCI accuracies (CMD patients) versus those without (potential non-CMD patients). The patients' demographic data were assessed using Student's *t*-test or the χ^2 test. Specifically, for the continuous variables of age and time since brain injury, Student's *t*-test was used to compare the two groups. Categorical variables, i.e. gender, aetiology, and clinical outcome (based on level upgrades of consciousness for UWS patients or CRS-R scores for MCS patients), were expressed as the numbers of patients, and the χ^2 test was applied to the data for the two groups (Bagnato *et al.*, 2016). All tests were two-sided, and a *P*-value < 0.05 [false discovery rate (FDR) corrected] was considered statistically significant (Benjamini and Yekutieli, 2001). Furthermore, we calculated the sensitivity and specificity to explore the prognostic value of the BCI accuracy index for clinical outcome based on level upgrades of consciousness or improvement of CRS-R scores at 3 months of follow-up.

Data availability

The data that support the findings of the current study are available from the corresponding author on request from qualified researchers for non-commercial research purposes. A material transfer agreement may be required.

Results

Healthy subjects

The average online accuracies of the eight healthy subjects for the photograph, number, and audiovisual paradigms were 96.0 ± 3.85%, 95.25 ± 4.13%, and 97.25 ± 3.99%, respectively. Each healthy subject achieved an online accuracy greater than the significance level of 64% ($P < 0.01$, χ^2 test) for all three paradigms.

Demographic information

Demographic information, clinical data and BCI accuracies for the patients with disorders of consciousness are presented in Supplementary Table 1. BCI accuracies were significant in 34 patients (CMD patients) and not significant in 44 patients (potential non-CMD patients). The average age or the average time since brain injury of the CMD patients was not significantly different from that of the potential non-CMD patients (Student's *t*-test, $P > 0.05$, FDR corrected). Considering gender and aetiology, there was no significant difference between the CMD patients and the potential non-CMD patients (χ^2 test, $P > 0.05$, FDR corrected).

Cognitive motor dissociation in unresponsive wakefulness syndrome

For the UWS patients, the criterion of consciousness recovery was based on an upgrade of consciousness from UWS to MCS. As shown in Fig. 3A, of the 20 UWS patients who regained consciousness, 15 of them belonged to the CMD group (sensitivity = 15/20 = 75%). By contrast, of the 25 UWS patients who remained at an unchanged level of consciousness, 22 of them belonged to the potential non-CMD group (specificity = 22/25 = 88%). For the UWS patients, those defined as CMD had better outcomes than potential non-CMD patients (χ^2 test, $P = 0.004$, FDR corrected). This observation still held for UWS patients who participated in the photograph paradigm (χ^2 test, $P = 0.008$, FDR corrected) or in the audiovisual paradigm (χ^2 test, $P = 0.03$, FDR corrected) but did not hold for the UWS patients who participated in the number paradigm (χ^2 test, $P = 0.08$, FDR corrected).

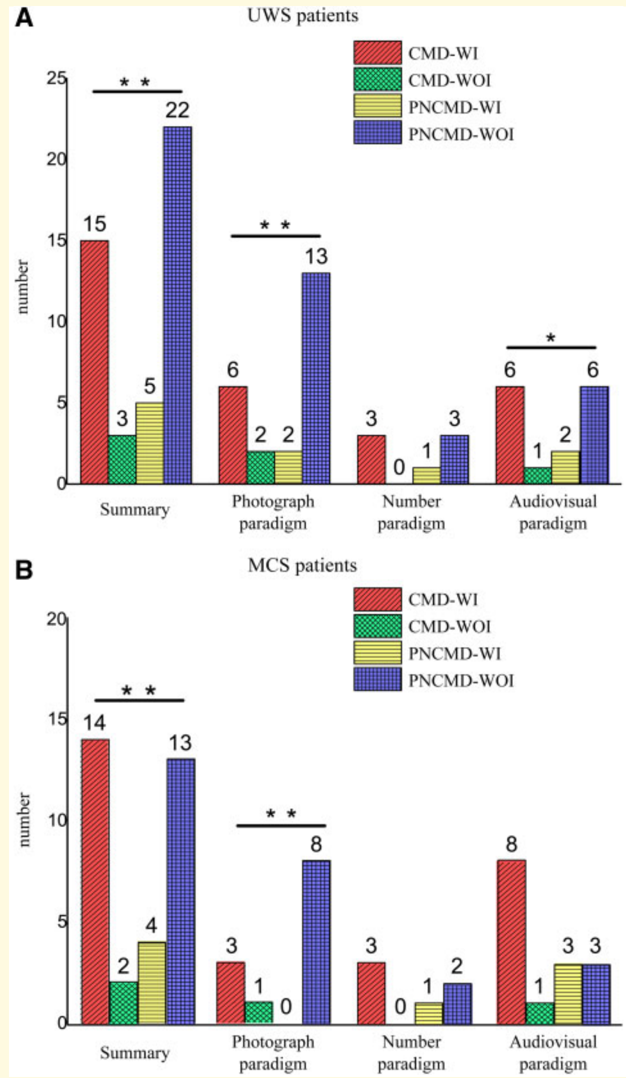

Figure 3 The behavioural improvement of patients. The comparison of the numbers of CMD patients with improvement (CMD-WI), CMD patients without improvement (CMD-WOI), potential non-CMD patients with improvement (PNCMD-WI), and potential non-CMD patients without improvement (PNCMD-WOI) for the UWS (**A**) and MCS patient groups (**B**). $^*P < 0.05$, FDR corrected. $^{**}P < 0.01$, FDR corrected. For UWS, patients with and without an upgrade in their level of consciousness were classified as 'improvement' and 'no improvement', respectively. For MCS, patients with and without an increase in their CRS-R scores were classified as 'improvement' and 'no improvement', respectively.

Cognitive motor dissociation in minimally conscious state

For the MCS patients, the criterion of consciousness improvement was based on an increase in CRS-R scores. As shown in Fig. 3B, of the 18 MCS patients who showed an improvement in CRS-R scores, 14 belonged to the CMD group (sensitivity = 14/18 = 77.78%). By contrast, of the 15

MCS patients who showed no CRS-R score improvement, 13 belonged to the potential non-CMD group (specificity = 13/15 = 86.67%). Statistically, the CMD patients had a better outcome than potential non-CMD patients (χ^2 test, $P = 0.004$, FDR corrected). This observation still held for MCS patients who participated in the photograph paradigm (χ^2 test, $P = 0.009$, FDR corrected); however, this observation did not hold for the MCS patients who completed the number paradigm (χ^2 test, $P = 0.094$, FDR corrected) or the audiovisual paradigm (χ^2 test, $P = 0.095$, FDR corrected).

Offline data analysis

To illustrate the effectiveness of our BCI detection approach further, we performed offline ERP and spectral analyses. P300-like components were clearly visible in the target curves for all the photograph, number, and audiovisual paradigms in healthy subjects and CMD patients, while no P300 responses were observed in either target or non-target curves for potential non-CMD patients (Fig. 4). Higher average spectral powers were obtained for target frequencies than for non-target frequencies for both the photograph and number paradigms in healthy subjects and CMD patients, but the same was not true in potential non-CMD patients (Fig. 5).

Discussion

Three EEG-based BCI paradigms were applied in the current study to detect patients with CMD and then investigate their clinical outcomes. We found a significant correlation between BCI accuracies and subsequent consciousness recovery. Specifically, within the UWS patient group, 15 of 18 CMD patients regained consciousness (based on their CRS-R scores) 3 months later, while only 5 of 27 potential non-CMD patients recovered consciousness. Furthermore, within the MCS patient group, 14 of 16 CMD patients showed improvements in their CRS-R scores, whereas 4 of 17 potential non-CMD patients showed improved CRS-R scores. Taken together, our results suggest that CMD patients have better outcomes than other patients.

Cognitive motor dissociation patient outcomes

The most important finding of the current study is that patients with CMD identified by BCI showed better recovery than other patients with disorders of consciousness. Although a few previous studies have investigated the outcomes of CMD patients (Owen *et al.*, 2006; Curley *et al.*, 2018), the current study is the first to show a statistically significant relationship between behaviourally defined consciousness recovery and the condition of CMD. To perform the BCI tasks, a patient needs many cognitive functions, including language comprehension (to understand the experimental instructions), working memory, object recognition, selective attention (to selectively attend to a photograph or number), and sustained attention (to focus on the target for a period of time). To verify this range of required processes, we performed a BCI experiment involving 10 healthy subjects. The details of this experiment are given in the Supplementary material. The results of the supplementary experiment indicated that if participants could not understand the instructions or did not pay selective attention, then their BCI accuracies were not different from chance level (Supplementary Table 2). Positive BCI results (i.e. BCI accuracies significantly higher than chance level) indicate that cognitive functions and residual awareness exist in these CMD patients. Such brain functions may indicate that CMD patients have a high chance of consciousness recovery (Giacino and Whyte, 2005). Our results enhance the value of BCI in rehabilitation programmes for patients without behavioural communication ability and are consistent with other studies suggesting that greater retained cognitive function may be associated with better clinical outcomes in disorders of consciousness (Faugeras *et al.*, 2018).

A significant BCI accuracy in the UWS group predicted the recovery of consciousness with 82% accuracy, 75% sensitivity and 88% specificity, according to behavioural responses. This finding indicates that our BCI is a good prognostic index relative to other potential indexes based on behaviour (Kavusipur *et al.*, 2013), functional MRI (Li *et al.*, 2015*a*; Qin *et al.*, 2015*b*), EEG (Logi *et al.*, 2011; Claassen *et al.*, 2019), and $GABA_A$ binding potential (Qin *et al.*, 2015*a*). More specifically, a previous study showed that an EEG-based index had a sensitivity of 68.7% and a specificity of 88.9% for consciousness improvement in coma and UWS patients (Logi *et al.*, 2011). For UWS patients, our previous study showed that two UWS patients with high $GABA_A$ binding potential regained consciousness, while five UWS patients with low $GABA_A$ binding potential remained unconscious as defined by behavioural responses (Qin *et al.*, 2015*a*). Combining UWS and MCS, a study based on a behavioural scale reported a sensitivity of 72% and a specificity of 50% for consciousness improvement (Kavusipur *et al.*, 2013). Li *et al.* (2015*a*) showed that the combination of functional MRI and EEG responses achieved a sensitivity of 70% and a specificity of 90.9% for consciousness improvement according to the behavioural response from patients with disorders of consciousness (UWS and MCS). Finally, a recent study (Claassen *et al.*, 2019) adopted motor imagery tasks and offline EEG data analysis to detect CMD patients. The results of that study showed that 8 of 16 CMD patients identified from 104 patients with disorders of consciousness and 23 of the remaining 88 patients without EEG activation improved before discharge. In conclusion, the current results strongly suggest the potential usage of BCI accuracy in predicting clinical outcomes for UWS patients.

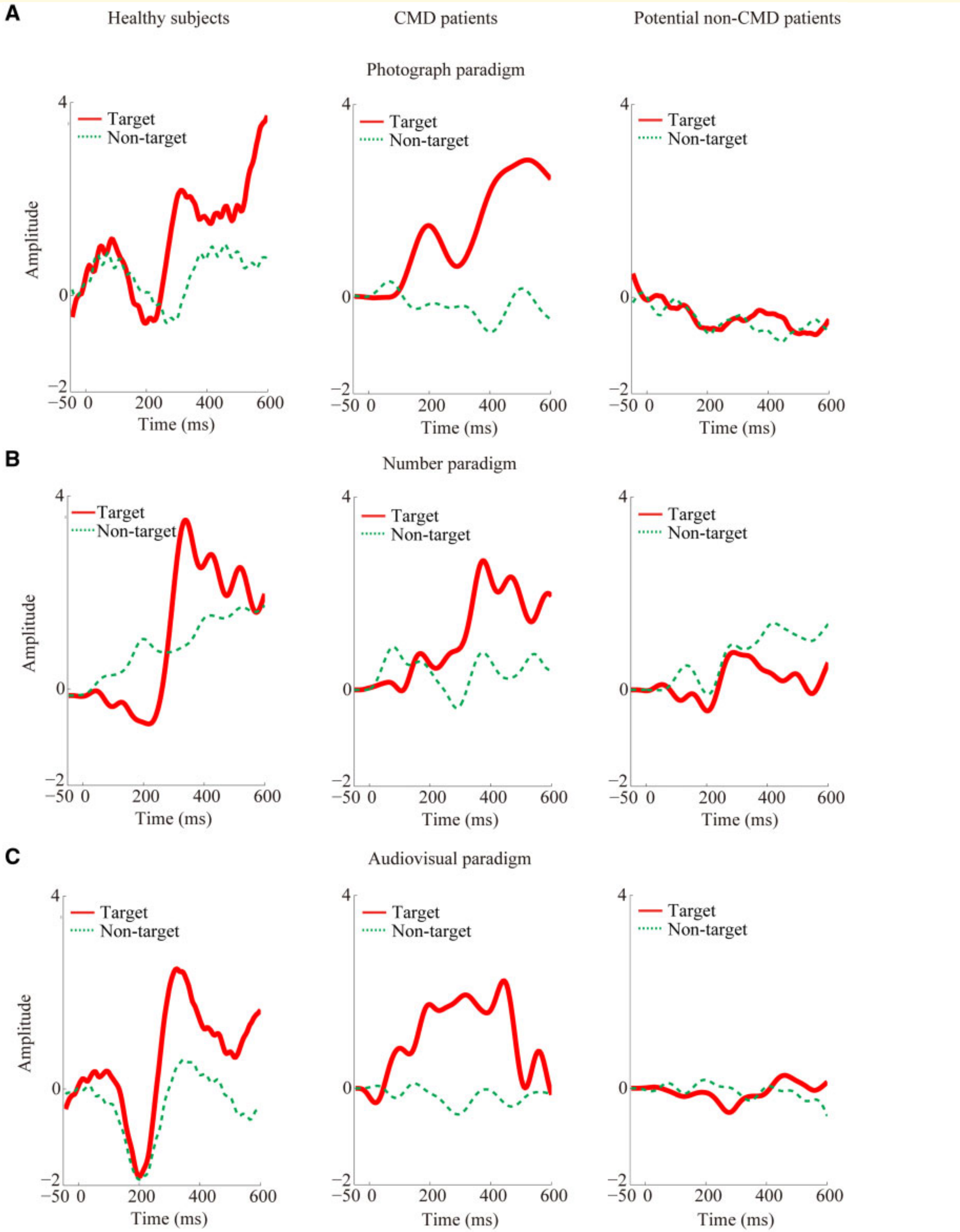

Figure 4 Average ERP waveforms at electrode 'Pz' across healthy subjects, across CMD patients, and across potential non-CMD patients. (**A**) Photograph paradigm. (**B**) Number paradigm. (**C**) Audiovisual paradigm. The solid red curves correspond to the target stimuli, and the dashed green curves correspond to the non-target stimuli. P300-like components are included in the target curves for patients with significant BCI accuracies.

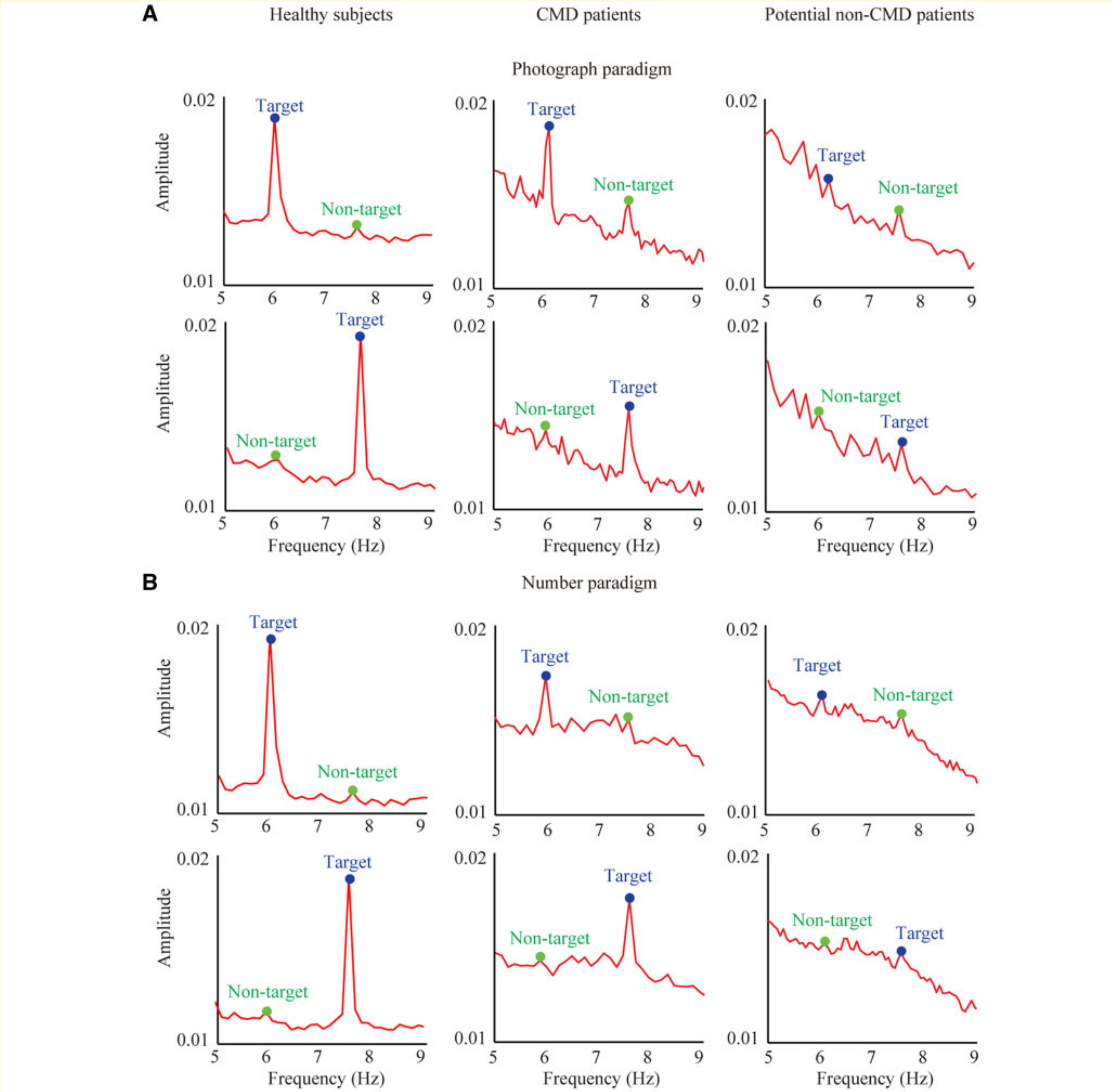

Figure 5 Average power spectrum curves of EEG signals across healthy subjects, across CMD patients, and across potential non-CMD patients. (**A**) Photograph paradigm. (**B**) Number paradigm. The blue and green points indicate flicker frequencies of the target and non-target buttons, respectively. The *top* and *bottom rows* in **A** and **B** refer to cases in which target buttons with a flicker frequency of 6 Hz/7.5 Hz appeared on the left/right sides of the GUI, respectively.

Proportion of cognitive motor dissociation patients among patients with disorders of consciousness

The current results showed that ~44% of the 78 patients with disorders of consciousness were CMD patients as defined by significant BCI accuracy. Two prior studies showed a higher proportion of CMD patients within disorders of consciousness patients than what we observed. Specifically, Curley *et al.* (2018) showed that 13 CMD patients were identified within 20 patients with disorders of consciousness (two of three UWS patients, 11 of 17 MCS patients) using motor imagery tasks. Schnakers *et al.* (2008) found nine CMD patients within 14 MCS patients using a name counting task. The main reason for the discrepancy between these studies and the current study may be that most of the patients in these two studies were MCS patients, while the current study included more UWS patients (45

UWS patients and 33 MCS patients, respectively). Another study showed a higher detection ratio of CMD within UWS patients (eight CMD patients of 12 UWS patients) than what we observed, which may be due to their relatively small sample size (Guger *et al.*, 2018). Meanwhile, several previous studies showed a lower proportion of CMD patients within disorders of consciousness patients than the current study (Naci *et al.*, 2012). Using functional MRI-based motor imaging tasks, Monti *et al.* (2010) found four CMD of 23 UWS patients, and another study observed four CMD patients of 26 patients with disorders of consciousness (Forgacs *et al.*, 2014). One possible reason is that the EEG methodology adopted in the current study may be more sensitive than functional MRI in detecting CMD patients (Curley *et al.*, 2018). However, several EEG studies adopting motor imagery tasks, a breath-controlling task, and other tasks showed low sensitivity to command-following brain activity (Cruse *et al.*, 2011; Lulé *et al.*, 2013; Charland-Verville *et al.*, 2014; Horki *et al.*, 2016; Claassen *et al.*, 2019). For example, using a 'yes/no'-induced brain activity pattern to test command following, only one CMD patient was identified among 16 patients with disorders of consciousness (13 MCS patients and three UWS patients) (Lulé *et al.*, 2013). This variability highlights the challenge of identifying a reliable technique for detecting CMD patients.

Clinical implications

The clinical significance of the current results lies in the fact that BCI accuracy could be used to effectively detect covert consciousness in CMD patients and to predict consciousness recovery. Many patients with disorders of consciousness may survive for years in either a chronic vegetative state or MCS. The proposed BCI method would allow carers and clinicians to predict the likelihood of improvement in these patients and to optimize their treatments. More importantly, a BCI could produce a tailor-made command-following brain activity template that could accommodate individual differences in brain activation patterns and brain injury severity (Bardin *et al.*, 2011; Curley *et al.*, 2018). Furthermore, a BCI provides easy-to-use real-time analysis where experimenters need only provide stimulus information; the data analysis is then performed automatically. These features support the usage of BCIs for future clinical application, where a standardized, automated and integrative BCI system for awareness detection and effective diagnosis of patients with CMD will be established and clinically tested across a large population.

None of the patients with UWS in this study showed visual fixation according to the first CRS-R assessment conducted before the BCI experiment. Several studies have presented gaze-independent P300- or SSVEP-based BCIs (Brunner *et al.*, 2010; Treder *et al.*, 2011; Lesenfants *et al.*, 2014). Generally, classification accuracies are lower for gaze-independent BCIs than for the gaze-dependent variety. In the GUI in this study, we used two large visual buttons containing photographs or numbers to facilitate the patients' employment of covert attention and to improve visual acuity in peripheral vision. Therefore, the BCIs in this study could be considered gaze-independent BCIs, and their effectiveness was demonstrated in the supplementary experiment (see Run 4 in Supplementary Table 2). Although our patients could not gaze at the target stimuli, the CMD patients could covertly attend to them and perform the experimental task using our BCIs.

Methodological limitations

The limitations of this study are as follows. First, we did not consider the various types of brain injuries among the patients or the different types of concurrent medical conditions (seizures, infections, metabolic disorders, etc.). Second, we did not consider the administration of specific therapeutic interventions for disorders of consciousness, such as psychoactive medications or neural stimulation. Future studies should seek to identify the effects of the above factors on the prognosis of CMD patients. Third, we performed only a 3-month follow-up in this study. Longer-term outcomes will be recorded and reported in the future. Fourth, the BCI classification accuracy needs to be further improved. In this study, 17 of 33 MCS patients showed no significant BCI accuracies. Based on the current accuracies, some of these patients might represent false negatives. Possible reasons for these false negatives are: (i) the paradigm and algorithm of a BCI may affect the user's performance; (ii) even among healthy users, a subset known as 'BCI illiterates' cannot use a BCI system (Guger *et al.*, 2009; Allison *et al.*, 2010); and (iii) the arousal level and brain functions might vary from moment to moment in patients with disorders of consciousness, which may lead to variable command-following abilities (Pokorny *et al.*, 2013). The limited brain functions of patients could also contribute to the phenomenon that none of the patients in our study achieved more than 80% accuracies, where accuracies are generally higher than 90% for healthy subjects. Further work is thus required to improve BCIs for use with patients with disorders of consciousness.

In conclusion, we used EEG-based BCIs to identify CMD in patients with disorders of consciousness. Our results showed that the hybrid BCIs could effectively identify CMD patients. More interestingly, our results showed that, among both UWS patients and MCS patients, those with CMD had a better chance of regaining consciousness on a behavioural level. Our findings extend the current knowledge regarding the outcomes of CMD patients and have important implications for BCI-based clinical diagnosis and prognosis in patients with disorders of consciousness.

Acknowledgements

We thank the patients and their families for participating in the study. We are also grateful to Dr Niall Duncan at Taipei Medical University for his help in improving the English in the manuscript.

Funding

This work was supported in part by the National Key Research and Development Program of China under Grant 2017YFB1002505, in part by the National Natural Science Foundation under Grants 61633010, 31771249, and 61876067, in part by the Guangdong Natural Science Foundation under Grants 2014A030312005 and 2019A1515011375, and in part by the Key R&D Program of Guangdong Province, China under Grant 2018B030339001.

Competing interests

The authors report no competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

References

Allison B, Luth T, Valbuena D, Teymourian A, Volosyak I, Graser A. BCI demographics: how many (and what kinds of) people can use an SSVEP BCI? IEEE Trans Neural Syst Rehabil Eng 2010; 18: 107–16.

Bagnato S, Boccagni C, Sant'Angelo A, Prestandrea C, Mazzilli R, Galardi G. EEG predictors of outcome in patients with disorders of consciousness admitted for intensive rehabilitation. Clin Neurophysiol 2015; 126: 959.

Bagnato S, Boccagni C, Sant'Angelo A, Prestandrea C, Virgilio V, Galardi G. EEG epileptiform abnormalities at admission to a rehabilitation department predict the risk of seizures in disorders of consciousness following a coma. Epilepsy Behav 2016; 56: 83.

Bardin JC, Fins JJ, Katz DI, Hersh J, Heier LA, Tabelow K, et al. Dissociations between behavioural and functional magnetic resonance imaging-based evaluations of cognitive function after brain injury. Brain 2011; 134: 769–82.

Benjamini Y, Yekutieli D. The control of the false discovery rate in multiple testing under dependency. Ann Stat 2001; 29: 1165–88.

Bernat E, Shevrin H, Snodgrass M. Subliminal visual oddball stimuli evoke a P300 component. Clin Neurophysiol 2001; 112: 159–71.

Boly M, Laureys S. Functional 'unlocking': bedside detection of covert awareness after severe brain damage. Brain 2018; 141: 1239–41.

Brunner P, Joshi S, Briskin S, Wolpaw JR, Bischof H, Schalk G. Does the 'P300' speller depend on eye gaze? J Neural Eng 2010; 7: 056013–9.

Bruno MA, Vanhaudenhuyse A, Thibaut A, Moonen G, Laureys S. From unresponsive wakefulness to minimally conscious PLUS and functional locked-in syndromes: recent advances in our understanding of disorders of consciousness. J Neurol 2011; 258: 1373–84.

Chae Y, Jeong J, Jo S. Toward brain-actuated humanoid robots: asynchronous direct control using an EEG-Based BCI. IEEE T Robot 2012; 28: 1131–44.

Charland-Verville V, Lesenfants D, Sela L, Noirhomme Q, Ziegler E, Chatelle C, et al. Detection of response to command using voluntary control of breathing in disorders of consciousness. Front Hum Neurosci 2014; 8: 1020.

Chatelle C, Chennu S, Noirhomme Q, Cruse D, Owen AM, Laureys S. Brain-computer interfacing in disorders of consciousness. Brain Inj 2012; 26: 1510–22.

Claassen J, Doyle K, Matory A, Couch C, Burger KM, Velazquez A, et al. Detection of brain activation in unresponsive patients with acute brain injury. N Engl J Med 2019; 380: 2497–505.

Cruse D, Chennu S, Chatelle C, Bekinschtein TA, Fernandez-Espejo D, Pickard JD, et al. Bedside detection of awareness in the vegetative state: a cohort study. Lancet 2011; 378: 2088–94.

Curley WH, Forgacs PB, Voss HU, Conte MM, Schiff ND. Characterization of EEG signals revealing covert cognition in the injured brain. Brain 2018; 141: 1404–21.

Faugeras F, Rohaut B, Valente M, Sitt J, Demeret S, Bolgert F, et al. Survival and consciousness recovery are better in the minimally conscious state than in the vegetative state. Brain Inj 2018; 32: 72–7.

Fernandez-Espejo D, Owen AM. Detecting awareness after severe brain injury. Nat Rev Neurosci 2013; 14: 801–9.

Forgacs PB, Conte MM, Fridman EA, Voss HU, Victor JD, Schiff ND. Preservation of electroencephalographic organization in patients with impaired consciousness and imaging-based evidence of command-following. Ann Neurol 2014; 76: 869–79.

Giacino J, Whyte J. The vegetative and minimally conscious states: current knowledge and remaining questions. J Head Trauma Rehabil 2005; 20: 30–50.

Giacino JT, Fins JJ, Laureys S, Schiff ND. Disorders of consciousness after acquired brain injury: the state of the science. Nat Rev Neurol 2014; 10: 99–114.

Giacino JT, Kalmar K, Whyte J. The JFK Coma Recovery Scale-Revised: measurement characteristics and diagnostic utility. Arch Phys Med Rehabil 2004; 85: 2020–9.

Gibson RM, Owen AM, Cruse D. Brain-computer interfaces for patients with disorders of consciousness. Prog Brain Res 2016; 228: 241–91.

Goldfine AM, Bardin JC, Quentin N, Fins JJ, Schiff ND, Victor JD. Reanalysis of "Bedside detection of awareness in the vegetative state: a cohort study". Lancet 2012; 381: 1701–2.

Guger C, Daban S, Sellers E, Holzner C, Krausz G, Carabalona R, et al. How many people are able to control a P300-based brain–computer interface (BCI)? Neurosci Lett 2009; 462: 94–8.

Guger C, Spataro R, Pellas F, Allison BZ, Heilinger A, Ortner R, et al. Assessing command-following and communication with vibro-tactile P300 brain-computer interface tools in patients with unresponsive wakefulness syndrome. Front Neurosci 2018; 12: 423.

Henriques J, Gabriel D, Grigoryeva L, Haffen E, Moulin T, Aubry R, et al. Protocol design challenges in the detection of awareness in aware subjects using EEG signals. Clin EEG Neurosci 2014; 47: 266–75.

Horki P, Bauernfeind G, Schippinger W, Pichler G, Muller-Putz GR. Evaluation of induced and evoked changes in EEG during selective attention to verbal stimuli. J Neurosci Methods 2016; 270: 165–76.

Kaper M, Meinicke P, Grossekathoefer U, Lingner T, Ritter H. BCI competition 2003-data set IIb: support vector machines for the P300 speller paradigm. IEEE Trans Biomed Eng 2004; 51: 1073–6.

Kavusipur S, Shirazi Ardekani RZ, Omidi Z. S. Prediction of consciousness recovery in coma after traumatic brain injury by disorder of consciousness scale (DOCS). Bull Emerg Trauma 2013; 1: 86–9.

Lesenfants D, Habbal D, Lugo Z, Lebeau M, Horki P, Amico E, et al. An independent SSVEP-based brain-computer interface in locked-in syndrome. J Neural Eng 2014; 11: 035002.

Li L, Kang XG, Qi S, Xu XX, Xiong LZ, Zhao G, et al. Brain response to thermal stimulation predicts outcome of patients with chronic disorders of consciousness. Clin Neurophysiol 2015; 126: 1539–47.

Logi F, Pasqualetti P, Tomaiuolo F. Predict recovery of consciousness in post-acute severe brain injury: the role of EEG reactivity. Brain Inj 2011; 25: 972–9.

Lotte F, Congedo M, Lécuyer A, Lamarche F, Arnaldi B. A review of classification algorithms for EEG-based brain–computer interfaces. J Neural Eng 2007; 4: R1–R13.

Luaute J, Morlet D, Mattout J. BCI in patients with disorders of consciousness: clinical perspectives. Ann Phys Rehabil Med 2015; 58: 29–34.

Lulé D, Noirhomme Q, Kleih SC, Chatelle C, Halder S, Demertzi A, et al. Probing command following in patients with disorders of consciousness using a brain-computer interface. Clin Neurophysiol 2013; 124: 101–6.

Monti MM, Vanhaudenhuyse A, Coleman MR, Boly M, Pickard JD, Tshibanda L, et al. Willful modulation of brain activity in disorders of consciousness. N Engl J Med 2010; 362: 579–89.

Naci L, Monti MM, Cruse D, Kubler A, Sorger B, Goebel R, et al. Brain-computer interfaces for communication with nonresponsive patients. Ann Neurol 2012; 72: 312–23.

Noirhomme Q, Brecheisen R, Lesenfants D, Antonopoulos G, Laureys S. "Look at my classifier's result": disentangling unresponsive from (minimally) conscious patients. Neuroimage 2017; 145: 288–303.

Owen AM, Coleman MR, Boly M, Davis MH, Laureys S, Pickard JD. Detecting awareness in the vegetative state. Science 2006; 313: 1402.

Pan J, Li Y, Zhang R, Gu Z, Li F. Discrimination between control and idle states in asynchronous SSVEP-based brain switches: a pseudo-key-based approach. IEEE Trans Neural Syst Rehabil Eng 2013; 21: 435–43.

Pan J, Xie Q, Huang H, He Y, Sun Y, Yu R, et al. Emotion-related consciousness detection in patients with disorders of consciousness through an EEG-based BCI system. Front Hum Neurosci 2018; 12:198.

Pokorny C, Klobassa DS, Pichler G, Erlbeck H, Real RG, Kübler A, et al. The auditory P300-based single-switch brain–computer interface: paradigm transition from healthy subjects to minimally conscious patients. Artif Intell Med 2013; 59: 81–90.

Qin P, Wu X, Duncan NW, Bao W, Tang W, Zhang Z, et al. $GABA_A$ receptor deficits predict recovery in patients with disorders of consciousness: a preliminary multimodal [(11) C]Flumazenil PET and fMRI study. Hum Brain Mapp 2015a; 36: 3867–77.

Qin P, Wu X, Huang Z, Duncan NW, Tang W, Wolff A, et al. How are different neural networks related to consciousness? Ann Neurol 2015b; 78: 594–605.

Salvaris M, Sepulveda F. Visual modifications on the P300 speller BCI paradigm. J Neural Eng 2009; 6046011: 046011.

Schiff ND. Cognitive motor dissociation following severe brain injuries. JAMA Neurol 2015; 72: 1413–5.

Schnakers C, Perrin F, Schabus M, Majerus S, Ledoux D, Damas P, et al. Voluntary brain processing in disorders of consciousness. Neurology 2008; 71: 1614–20.

Treder MS, Schmidt NM, Blankertz B. Gaze-independent brain–computer interfaces based on covert attention and feature attention. J Neural Eng 2011; 8: 066003.

Varoquaux G, Raamana PR, Engemann DA, Hoyos-Idrobo A, Schwartz Y, Thirion B. Assessing and tuning brain decoders: cross-validation, caveats, and guidelines. Neuroimage 2016; 145: 166–79.

Yin Z, Hou J. Recent advances on SVM based fault diagnosis and process monitoring in complicated industrial processes. Neurocomputing 2016; 174: 643–50.