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Detecting awareness in patients with disorders of consciousness using a hybrid brain–computer interface

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Abstract

Objective. The bedside detection of potential awareness in patients with disorders of consciousness (DOC) currently relies only on behavioral observations and tests; however, the misdiagnosis rates in this patient group are historically relatively high. In this study, we proposed a visual hybrid brain–computer interface (BCI) combining P300 and steady-state evoked potential (SSVEP) responses to detect awareness in severely brain injured patients. **Approach.** Four healthy subjects, seven DOC patients who were in a vegetative state (VS, $n = 4$) or minimally conscious state (MCS, $n = 3$), and one locked-in syndrome (LIS) patient attempted a command-following experiment. In each experimental trial, two photos were presented to each patient; one was the patient's own photo, and the other photo was unfamiliar. The patients were instructed to focus on their own or the unfamiliar photos. The BCI system determined which photo the patient focused on with both P300 and SSVEP detections. **Main results.** Four healthy subjects, one of the 4 VS, one of the 3 MCS, and the LIS patient were able to selectively attend to their own or the unfamiliar photos (classification accuracy, 66–100%). Two additional patients (one VS and one MCS) failed to attend the unfamiliar photo (50–52%) but achieved significant accuracies for their own photo (64–68%). All other patients failed to show any significant response to commands (46–55%). **Significance.** Through the hybrid BCI system, command following was detected in four healthy subjects, two of 7 DOC patients, and one LIS patient. We suggest that the hybrid BCI system could be used as a supportive bedside tool to detect awareness in patients with DOC.

Keywords: awareness detection, brain–computer interface, vegetative state, minimally conscious state, locked-in syndrome,

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1. Introduction

Patients suffering from a severe brain injury may fall into a coma and develop a variety of different clinical awareness states. Some patients may progress to a vegetative state (VS), in which they may awaken but show no awareness of

themselves or their environment (Jennett and Plum 1972). Other patients may improve to a minimally conscious state (MCS), in which they demonstrate inconsistent but reproducible signs of awareness (Giacino *et al* 2002). Currently, the clinical diagnosis of patients with disorders of consciousness (DOC) such as VS and MCS is based only on behavioral observations. Misdiagnosis rates in VS and MCS patients are relatively high, ranging from 37 to 43% (Childs *et al* 1993, Andrews *et al* 1996, Schnakers *et al* 2009a). Detecting signs of awareness in these patients is particularly challenging.

In recent years, functional magnetic resonance imaging (fMRI) and electroencephalographic (EEG) techniques have been proposed to examine the residual brain function in some DOC patients (see Chatelle *et al* 2012, Liberati and Birbaumer 2012, Noirhomme *et al* 2013 for review). These studies aimed to detect command-specific changes in fMRI or EEG signals and to provide motor-independent evidence of awareness. Using fMRI, several studies have objectively quantified patients' cerebral processing during the visual presentation of familiar faces to VS patients (Owen *et al* 2002) and during auditory presentation of the patients' own name to MCS patients (Laureys *et al* 2004, Di *et al* 2007). In one case study (Owen *et al* 2006), a VS patient was instructed to 'imagine playing tennis' or to 'imagine walking through her house' during an fMRI experiment. This VS patient displayed motor imagery-related brain activations similar to healthy controls during both tasks. In a follow-up study (Monti *et al* 2010), the potential of this paradigm was exploited to map imagery tasks to yes/no responses. Of 54 patients assessed (23 VS and 31 MCS patients), five (four VS and one MCS patients) were able to willfully modulate their brain activity. Unlike fMRI, EEG offers the potential for the development of a relatively inexpensive and portable system that can be used at the bedside (Naci *et al* 2012). For instance, Schnakers *et al* tested 22 patients (eight VS and 14 MCS patients) who were instructed to count the instances of their own names presented within an auditory sequence mixed with other names (Schnakers *et al* 2008). They found that five of the 14 MCS patients produced larger P300 responses to their own names during the actively counting condition than during the passively listening condition. Cruse *et al* instructed a group of 16 VS patients to imagine either squeezing their right hand or moving their toes. (Cruse *et al* 2012a). Three of the sixteen VS patients were able to modulate their sensorimotor rhythms, with cross-validated accuracies between 61–78%. However, the subsequent independent analysis illustrated the remaining challenges to propose reliable technologies for clinical use in DOC patients (Goldfine *et al* 2013).

Brain-computer interfaces (BCIs) are a relatively new technology that enable direct communication with an external device without the use of peripheral nerves and muscles (Wolpaw *et al* 2002). The potential use of BCIs for awareness detection and online communication with DOC patients has recently been demonstrated in a few studies (Lulé *et al* 2012, Müller-Putz *et al* 2012, Coyle *et al* 2012, Müller-Putz *et al* 2013). Lulé *et al* tested a four-choice auditory P300-

based BCI with 13 MCS, three VS, and two locked-in syndrome (LIS) patients (Lulé *et al* 2012). One LIS patient had a significant correct response rate of 60%, but no other patients could communicate through the BCI system. Coyle *et al* used an MI-based BCI system to determine if real-time feedback enhanced the system's ability to detect awareness in an MCS patient (Coyle *et al* 2012). The results indicated that the patient could perform the MI tasks using real-time feedback and achieved 80% online accuracy. Unlike fMRI and EEG-based ERP techniques, a key characteristic or advantage of BCIs in awareness detection is that the real-time detection result can be provided as a form of feedback. This real-time feedback has positive effects for the patients to use the BCI if they have awareness. However, the use of BCIs to detect awareness in DOC is still in its infancy, stronger BCIs are needed to improve brain activity detection.

For BCI-based awareness detection, an important issue is the modality of stimulation and feedback. To date, almost all of the existing studies focus on auditory stimuli due to the fact that most of the patients with DOC often suffer from gaze fixation impairment. However, it has been proven difficult to develop effective auditory BCIs that deliver promising performance (Kübler *et al* 2009, Halder *et al* 2010). This is because the brain signals evoked by the auditory stimuli are generally weaker than those evoked by the visual stimuli. Currently, the most robust BCIs enabling high accuracy in healthy subjects are based on visual stimuli and feedback (Sellers *et al* 2006, Bin *et al* 2009). Furthermore, ones have developed several gaze-independent P300- or SSVEP-based BCIs based on visual stimuli although for healthy subjects (Brunner *et al* 2010, Treder *et al* 2011, Lesenfants *et al* 2011).

Another issue is the choice of stimuli and feedback. Among the emotionally laden visual stimuli, face is a powerful one to gain entry to awareness. Lavie *et al* suggested that faces are special stimuli for attention because of their particular biological and social significance (Lavie *et al* 2003). It may be promising to use facial photos as visual stimuli to maximize our chances of awareness detection for the patients with DOC.

Recent studies have validated hybrid BCIs, which directly combine two or more different types of brain signals (Pfurtscheller *et al* 2010a). The performance, e.g., classification accuracy, of the BCIs could be improved by combining these brain signals (Allison *et al* 2010a, Pfurtscheller *et al* 2010b, Long *et al* 2012, Li *et al* 2013). In our previous study (Li *et al* 2013), a hybrid BCI combining the P300 and steady-state evoked potentials (SSVEPs) was developed for the detection of idle state in healthy subjects. We demonstrated that the performance of idle state detection was better for the hybrid BCI than for the P300- or SSVEP-based BCI. As an application, this method was used to produce a 'go/stop' command in real-time control of a wheelchair.

Considering the above factors, we proposed a visual hybrid BCI combining P300 and SSVEP, a variant of our previously established system (Li *et al* 2013), for the detection of awareness in DOC patients in this study. In the system, the visual stimuli and feedback were the patient's own facial photos, or unfamiliar facial photos. Specifically, through both

P300 and SSVEP detection, this system determined whether the patient focused on the instructed target, the patient's own facial photo, or an unfamiliar facial photo displayed on the graphical user interface (GUI). Using this system, the ability of the DOC patient to follow commands could be detected. Eight patients (four VS, three MCS, and one LIS patient) and four healthy subjects participated in our experiment; three patients (one VS, one MCS and one LIS patient) were able to follow commands using our hybrid BCI (classification accuracy 70–78%). These results implied that the three patients possessed residual cognitive function and conscious awareness, which were detected by our BCI system.

The remaining part of this paper is organized as follows. The methodology including the patients, experimental design, and data processing are presented in section 2. The experimental results are presented in section 3. Further discussions on the system and results are involved in section 4.

2. Methodology

2.1. Subjects

This study was undertaken at the Liuhuaqiao Hospital, Guangzhou, China, between October 2012 and July 2013. Brain activity was detected only when patients were free of centrally acting sedative drugs. Eight severely brain-damaged Chinese patients participated in this experiment (four males; four VS, three MCS, and one LIS; mean age \pm SD, 38 ± 19 years; see table 1). The study was approved by the Ethics Committee of Liuhuaqiao Hospital which complies with the Code of Ethics of the World Medical Association (Declaration of Helsinki). Written informed consent was obtained from each patient's legal surrogates. The VS and MCS clinical diagnoses were based on the JFK Coma Recovery Scale-Revised (CRS-R), which comprises six subscales that address auditory, visual, motor, oromotor, communication, and arousal functions (Giacino *et al* 2004). During the experiment, the eight patients underwent a CRS-R assessment every two weeks (the first CRS-R assessment happened within the week before the experiment). For each patient, the CRS-R scores presented in table 1 were based on his/her best responses of the repeated CRS-R assessments. No patient had a history of impaired visual acuity. In all eight patients, visual evoked potentials to flash stimulation showed preserved bilateral cortical responses. Additionally, four healthy subjects (HC1, HC2, HC3 and HC4) with no history of neurological disease (three males; mean age \pm SD, 29 ± 2 years) were included in our experiment as control group.

2.2. Experimental design

2.2.1. GUI and stimuli. The GUI used in this study is illustrated in figure 1. Facial photos were used as stimuli to capture the attention of unresponsive patients. Two full-face, frontal-view photos, the subject's own photo and an unfamiliar photo, were pseudo-randomly chosen from two sets of facial photos (ten photos of the subject and ten



Figure 1. GUI of the hybrid BCI, in which a subject's own facial photo and an unfamiliar facial photo are randomly displayed on the left and right side in each trial. The left and right photos flickered from appearance to disappearance on a black background at frequencies of 6.0 Hz and 7.5 Hz, respectively. Meanwhile, the two photo frames also flashed from appearance to disappearance in a random order. In this way, the SSVEP and P300 responses could be simultaneously elicited by the flickering target photo and the flashing target photo frame, respectively.

luminance- and contrast-matched unfamiliar photos of individuals of the same gender as the subject) and randomly displayed at the left and right side of the GUI. None of the subjects had facial hair or wore glasses. All photos were cropped to remove extraneous background, but the outlines of faces, including hairstyles, were preserved. In addition, all of the photos were modified using Adobe Photoshop 7.0 (Adobe, San Jose, CA) to produce identical overall luminance and contrast on a white background. Each 6.6 cm \times 9 cm facial photo was placed in the center of a white photo frame sized 8.6 cm \times 11 cm with a margin width of 2 cm. The horizontal distance between the two photo frames was 4 cm in the GUI. The ratios of the photo sizes (areas), the photo frame, and the GUI were matched for all stimuli and set at 0.06:0.1:1.

The two photos on the left and the right sides of the GUI flickered from appearance to disappearance on a black background at frequencies of 6.0 Hz and 7.5 Hz, respectively. Meanwhile, the two photo frames flashed in a random order, with each appearance lasting 200 ms and with an 800 ms interval between two consecutive appearances. The subject was instructed to focus on one or the other type of photo (e.g., the subject's own photo or the unfamiliar one) and to count the flashes of the corresponding photo frame. Using this hybrid BCI paradigm, SSVEP (i.e., stimulus frequency driven EEG responses (Allison *et al* 2010b)) and P300 (i.e., stimulus 'oddball' or novelty driven EEG responses (Guger *et al* 2009)) responses were simultaneously elicited by the flickering target photo and the flashing target photo frame, respectively.

2.2.2. Experimental procedures. During the experiment, each subject was seated in a comfortable wheelchair approximately 0.5 m from a 22 inch LED monitor. A preliminary screening was conducted before the experiment to explain the experimental procedure to the subject.

Table 1. Summary of patients' clinical status. ABI, anoxic brain injury; CRS-R, coma recovery scale-revised; CVA, cerebrovascular accident; and TBI, traumatic brain injury. Note that the clinical diagnosis and the CRS-R score for each patient were based on the best response of the repeated CRS-R assessments during the experiment.

Patient	Age	Gender	Clinical diagnosis	Etiology	Time since onset (months)	Best CRS-R score (subscores: auditory–visual–motor–oromotor–communication–arousal)
VS1	22	F	VS	ABI	6	6 (1-0-2-1-0-2)
VS2	19	M	VS	TBI	5	7 (1-1-2-1-0-2)
VS3	56	M	VS	CVA	7	5 (0-1-1-1-0-2)
VS4	36	F	VS	ABI	1	4 (1-1-0-0-0-2)
MCS1	47	M	MCS	TBI	18	10 (1-3-3-1-0-2)
MCS2	16	F	MCS	ABI	3.5	12 (1-3-5-1-0-2)
MCS3	36	F	MCS	TBI	4	10 (1-3-3-1-0-2)
LIS1	70	M	LIS	CVA	37	14 (4-5-0-0-2-3)

Before the online experiment, each subject performed a calibration run of ten trials with the GUI in figure 1. Specifically, for each trial, the left and right photos flickered for 10 s at frequencies of 6.0 Hz and 7.5 Hz, respectively. Simultaneously, the two photo frames flashed in a random order, with each photo frame flashing five times. The subject was instructed to pay attention to his/her own photo and to count the number of times that the corresponding photo frame was highlighted/flashed. We trained an initial P300 classification model using the EEG data from the calibration run. Furthermore, the P300 classification model was updated after each block of online evaluation based on the data from the calibration run and the collected online data. The rationale for training the P300 model in this manner was two-fold. First, because the patients were prone to be fatigue (inherent to DOC), the calibration procedure should be as short as possible, and a new calibration was not suitable before each evaluation block on a separate day. Second, due to the fluctuating level of consciousness in DOC patients, it was not appropriate to use a fixed model during the experiment lasting several days to weeks.

In the online evaluation, three experimental runs were conducted. Figure 2 illustrates the online experimental paradigm. Each run contained five blocks, and each block was composed of ten trials. Different blocks were conducted on separate days because the patients were easily fatigued and have limited attention span. Each trial began with the visual and auditory presentation of the task instructions (in Chinese), which lasted 6 s. Meanwhile, the two photos, the subject's own facial photo and an unfamiliar facial photo, were randomly displayed on the left and right sides of the GUI. The instruction for each trial of run 1 was 'focus on your own photo and count the number of times that your own photo frame is highlighted'; the instruction for each trial of run 2 was 'focus on the other person's photo and count the number of times that the other person's photo frame is highlighted'; the instruction for each trial of run 3 was the same as that of run 1 or 2. Specifically, the subject was instructed to focus on his/her own photo or the unfamiliar photo in a pseudo-random order in run 3. In each block of run 3, half of the trials corresponded to his/her own photos and the other half of the trials corresponded to the unfamiliar photos. After the instructions were presented, the two photos flickered while

the two corresponding photo frames flashed as in the calibration run. After 10 s, a feedback photo, determined by the BCI algorithm, appeared in the center of the GUI. If the result was correct, a positive audio feedback of applause was given for 4 s to encourage the subject. There was a short break of at least 10 s between two consecutive trials, depending on the subject's level of fatigue. Note that the tasks of runs 1, 2, and 3 were getting more and more difficult for a patient. Only if a subject successfully performed the tasks in runs 1 and 2, he/she was asked to perform run 3.

During the experiment, the patient was carefully observed by the examiner to ensure task engagement and to avoid that the patient would show decreased arousal (i.e., close his/her eyes) or continuous body movements (e.g., resulted by cough) during a testing trial. In this case, the trial was discarded, and the next trial would start after the patient again showed prolonged periods of spontaneous eye-opening or reawakened. For each trial of the experiment, in addition to the presented instructions, the doctor and the patients' relatives also told the patients to focus on the target photo.

2.3. Data processing

The procedures for the P300 and SSVEP detections have been described previously (Li *et al* 2013). Briefly, the P300 and SSVEP detectors were designed separately. The EEG data were copied and fed into the two detectors simultaneously. Figure 3 shows the data processing procedure for both P300 and SSVEP detections.

2.3.1. Data acquisition. A NuAmps device (Compumedics, Neuroscan, Abbotsford, Australia) was used to collect scalp EEG signals. Each subject wore an EEG cap (LT 37). The EEG signals were referenced to the right mastoid. Here we performed channel selection during data acquisition to keep the related neurological phenomenon intact as well as reduce the artifacts (Lan *et al* 2006). According to the standard 10–20 system (Jasper 1958), the EEG signals used for analysis were recorded from ten electrodes: 'Fz', 'Cz', 'P7', 'P3', 'Pz', 'P4', 'P8', 'O1', 'Oz' and 'O2' (Li *et al* 2013, Guger *et al* 2009, Friman *et al* 2007). The impedances of all electrodes were kept below 5 k Ω . The EEG signals are digitized at a sampling rate of 250 Hz.

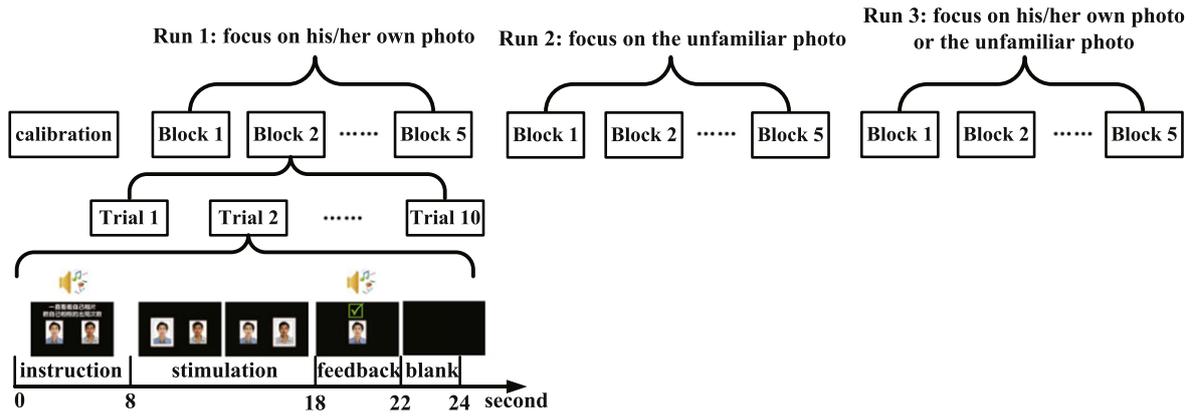


Figure 2. The experimental paradigm. Each run was divided into five blocks, and each block consisted of ten trials. Each trial began with the visual and auditory presentation of the task instructions. Then, two photos were randomly displayed on the left and right sides of the GUI. After the instruction, the two photos flickered, and the two corresponding photo frames were highlighted. After 10 s, an auditory (i.e., applause) and visual feedback (i.e., photo selected by the classification algorithm) was presented.

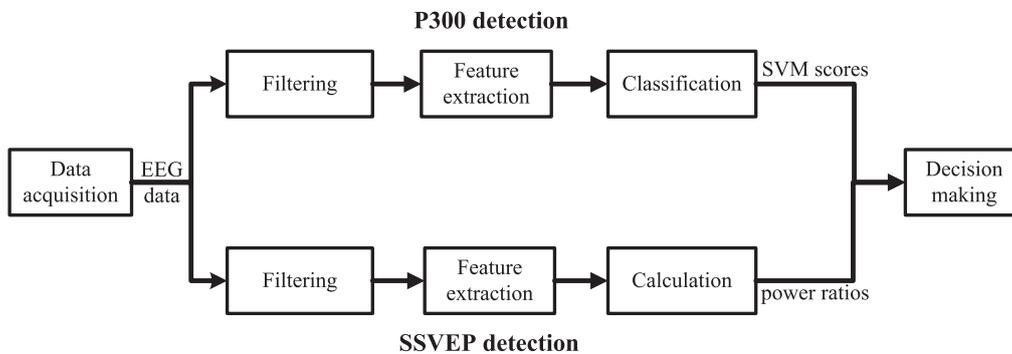


Figure 3. The data processing procedure for the P300 and SSVEP detections. In the hybrid BCI system, the EEG data were fed into two different data processing procedures simultaneously, one for P300 detection and the other for SSVEP detection. Next, the two detection outputs were merged to provide a weighted single decision.

2.3.2. P300 detection. Here, the EEG signals were filtered between 0.1 and 10 Hz. We extracted epochs (0–800 ms after a photo frame flash) of the EEG signal from each channel for each flash of a photo frame. This EEG epoch was downsampled by a rate of five to obtain a data vector consisting of 40 data points. We concatenated the vectors from all 10 channels to obtain a new data vector, which corresponded to a photo frame flash. Next, we constructed a feature vector for each photo frame by averaging the data vectors across the five flashes in a trial. Finally, a Support Vector Machine (SVM) classifier was applied to the two feature vectors corresponding to the two photos, and two SVM scores were obtained for each trial.

2.3.3. SSVEP detection. Here, the EEG signals were filtered between 4 and 20 Hz. After stimulus onset, we extracted the segment of the EEG signals from eight channels, ‘P7’, ‘P3’, ‘Pz’, ‘P4’, ‘P8’, ‘O1’, ‘Oz’ and ‘O2’, during a 10 s period (i.e., 2500 data points). Next, a weighted sum of the eight epochs was calculated by obtaining the weights through the application of the minimum energy combination method, which enhanced the EEG information and/or reduced the nuisance signals including EMG and EOG artifacts (Friman *et al* 2007). Using a discrete Fourier transformation, we

calculated the power density spectrum of this weighted signal. We calculated the power of this SSVEP response by integrating the power density spectrum of each flickering frequency and its second harmonic. The power ratio for each flickering photo was calculated as the ratio of the mean power in a narrow band (i.e., band width of 0.1 Hz) and in a wide band (i.e., band width of 1 Hz). In each trial, two power ratios were obtained for the two photos’ flickering frequencies.

2.3.4. Decision making algorithm and accuracy calculation. We summed the P300 detection SVM score and the SSVEP detection power ratio for each photo and determined the photo that corresponded to the maximum of the summed values as the trial feedback photo.

Accuracy was calculated as the ratio of the number of all correct responses (hits) among the total number of presented trials. To assess the accuracy’s significance, we calculated statistics as described below (Kübler and Birbaumer 2008):

$$\chi^2 = \sum_{i=1}^k \frac{(fo_i - fe_i)^2}{fe_i}, \quad (1)$$

where fo_i and fe_i are the observed and expected frequencies, respectively, of the i th class ($i = 1, 2, \dots, k$). In this study, the

Table 2. Online results for each subject. The results in the brackets are obtained based on the total number of trials (i.e. including the rejected trials). The accuracies significantly higher than the chance level ($\geq 64\%$, $p \leq 0.05$) are highlighted in bold. All subjects performed 50 trials in each of the three runs, with the exception of patient VS3.

Subject	Run 1			Run 2			Run 3		
	Number of trials	Accuracy	<i>p</i> value	Number of trials	Accuracy	<i>p</i> value	Number of trials	Accuracy	<i>p</i> value
VS1	50 (57)	76% (74%)	<0.001 (<0.001)	50 (60)	72% (70%)	0.002 (0.002)	50 (51)	68% (67%)	0.011 (0.017)
VS2	50 (58)	64% (62%)	0.048 (0.066)	50 (57)	50% (49%)	1.000 (0.895)			
VS3	50 (56)	48% (48%)	0.777 (0.789)	40 (46)	55% (54%)	0.527 (0.555)			
VS4	50 (56)	52% (52%)	0.777 (0.789)	50 (57)	52% (51%)	0.777 (0.895)			
MCS1	50 (56)	72% (70%)	0.002 (0.003)	50 (52)	70% (69%)	0.005 (0.006)	50 (55)	66% (64%)	(0.017) (0.043)
MCS2	50 (55)	68% (65%)	0.011 (0.022)	50 (55)	52% (53%)	0.777 (0.686)			
MCS3	50 (58)	46% (47%)	0.572 (0.599)	50 (58)	48% (48%)	0.777 (0.793)			
LIS1	50 (57)	78% (74%)	<0.001 (<0.001)	50 (55)	72% (71%)	0.002 (0.002)	50 (56)	76% (71%)	<0.001 (0.001)
HC1	50 (50)	84% (84%)	<0.001 (<0.001)	50 (50)	82% (82%)	<0.001 (<0.001)	50 (50)	94% (94%)	<0.001 (<0.001)
HC2	50 (50)	100% (100%)	<0.001 (<0.001)	50 (50)	100% (100%)	<0.001 (<0.001)	50 (50)	100% (100%)	<0.001 (<0.001)
HC3	50 (50)	94% (94%)	<0.001 (<0.001)	50 (50)	100% (100%)	<0.001 (<0.001)	50 (50)	96% (96%)	<0.001 (<0.001)
HC4	50 (50)	96% (96%)	<0.001 (<0.001)	50 (50)	96% (96%)	<0.001 (<0.001)	50 (50)	98% (98%)	<0.001 (<0.001)

observations fell into two classes (hit and miss). Specifically, f_{o1} and f_{o2} were the observed numbers of hits and misses, respectively, and f_{e1} and f_{e2} represented the respective expected numbers of hits and misses. The degree of freedom was 1 for our two-choice BCI. For example, when 50 trials of a two-choice paradigm were available for each run, 25 hits and 25 misses could be expected by chance. Using a significance level of $p = 0.05$, we obtained a value of 3.84 for χ^2 (with the degrees of freedom set at 1), which corresponded to 32 hits in 50 trials or an accuracy of 64%.

3. Results

Table 2 summarizes the experimental results obtained for each subject. In all the eight patients, accuracies for patients VS1, MCS1, and LIS1 were significant in runs 1 and 2. In run 1, five of the eight patients (patients VS1, VS2, MCS1, MCS2, and LIS1) achieved accuracies higher than chance level (i.e., $\geq 64\%$; ranging from 64 to 78%). In run 2, three patients (patients VS1, MCS1, and LIS1) achieved accuracies $\geq 64\%$ (ranging from 70 to 72%). The accuracies for patients VS2 and MCS2 were significant in run 1 but not run 2. This result may have occurred because emotional value or high familiarity makes one's own facial photo particularly likely to attract one's attention (Signorino *et al* 1995, Kircher *et al* 2000, 2001, Lavie *et al* 2003, Bindemann *et al* 2005),

similar to when a patient's own name is used as a stimulus (Perrin *et al* 2006). For patients VS3, VS4, and MCS3, the accuracies were not significant in either run 1 or run 2. The three patients VS1, MCS1, and LIS1 who successfully performed runs 1 and 2 still achieved accuracies higher than chance level in run 3 (i.e., $\geq 64\%$); ranging from 66 to 76%. Furthermore, four healthy subjects (HC1, HC2, HC3, and HC4) achieved accuracies $\geq 64\%$ (ranging from 82 to 100%) in runs 1, 2, and 3.

In this study, we used the chi-square test to determine statistical significance (i.e., *p* value) of the online accuracies. However, in chi-square statistics, the detection results are assumed to be independent (Lewis and Burke 1949, Satorra and Bentler 2001). This might not be suitable for our case. To account for independence among trials, we used a permutation test to re-evaluate the data for each subject as below (Goldfine *et al* 2012, 2013).

First, we calculated the leave-one-out cross-validated accuracy using the data of this subject (runs 1 and 2 for VS2, VS3, VS4, MCS2, and MCS3; runs 1, 2, and 3 for VS1, MCS1, LIS1, HC1, HC2, HC3, and HC4). Specifically, in each fold, one trial of data were used for test, and the other data were used for training. An SVM classifier was first obtained based on the training data, and then applied to the test data. After the leave-one-out cross-validation procedure, we obtained the classification accuracy. Next, we performed 1000 permutations, in each of which we generated a surrogate

Table 3. Results of the permutation test.

Subject	Number of trials (after manual rejection)	Accuracy based on the cross-validation of SVM classifier	p value by permutation test
VS1	150	0.673	<0.001
VS2	100	0.520	0.338
VS3	90	0.422	0.966
VS4	100	0.500	0.510
MCS1	150	0.653	<0.001
MCS2	100	0.560	0.068
MCS3	100	0.540	0.202
LIS1	150	0.747	<0.001
HC1	150	0.887	<0.001
HC2	150	0.993	<0.001
HC3	150	0.933	<0.001
HC4	150	0.833	<0.001

dataset by randomly relabeling the trials, and then calculated the leave-one-out cross-validated accuracy using the surrogate dataset. The p value was then determined as the fraction of the accuracies obtained by the 1000 permutations which were higher than the real accuracy. Table 3 shows the permutation test results, from which we can see that the accuracies were significantly higher than the chance level for the three patients VS1, MCS1, LIS1 and the four healthy subjects ($p \leq 0.05$).

For the subjects VS1, MCS1, LIS1, and HC1, the ERP waveforms and power spectra were calculated using the data collected in the three experimental runs. Specifically, for each trial, the EEG epochs of each channel were extracted from 200 pre-stimulus to 1000 ms post-stimulus, and baseline corrected using 200 ms pre-stimulus. The ERP waveforms were obtained by averaging the EEG channel epochs across 50 trials in runs 1, 2 and 3. Figure 4 shows the average EEG signal amplitudes of the electrodes 'Fz' and 'Pz' for subjects VS1, MCS1, LIS1, and HC1; the solid red and the dashed blue curves correspond to the target and the non-target photo frames, respectively. A P300-like component is apparent in each of the target curves.

For each run (run 1, 2 or 3) and each subject (VS1, MCS1, LIS1, or HC1), figure 5 shows two average power density spectrum curves of the EEG signals across the trials with the target photos appearing the left or right of the GUI. The power spectrum of each trial was calculated using 10 s of EEG signals from the eight selected channels ('P7', 'P3', 'Pz', 'P4', 'P8', 'O1', 'Oz' and 'O2'), as in the SSVEP detection. Figure 5 shows that higher average spectral powers were obtained in the target photo frequencies for all four subjects.

4. Discussions

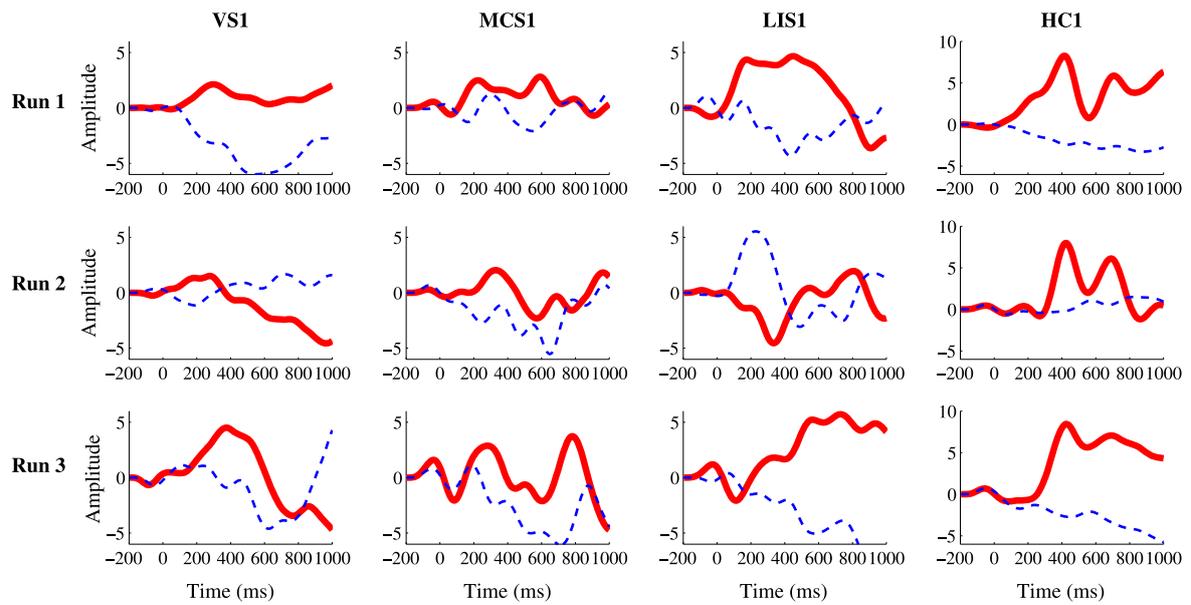
We here propose a hybrid P300- and SSVEP-based BCI to improve the detection of residual cognitive function and covert awareness in DOC patients. In this novel BCI paradigm, two flickering photos, the subject's own facial photo

and an unfamiliar facial photo, were randomly displayed on the left and right of the GUI, and each photo was embedded in a flashing photo frame. The BCI system determined which photo the subjects focused on (i.e., responded to command) through both the P300 and SSVEP detections.

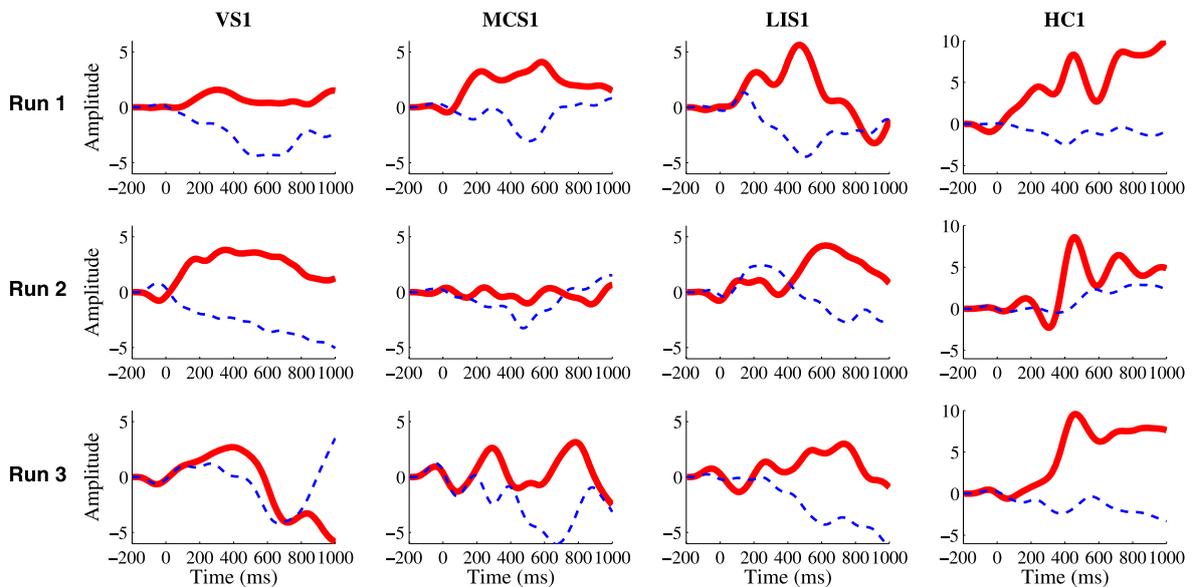
Using our hybrid P300- and SSVEP-based BCI, three experimental runs involving eight patients (five VS, three MCS, and one LIS) were conducted. In run 1, the patients were asked to focus on their own photo. Five of these patients (two VS, two MCS, and one LIS patients) achieved accuracies of greater than 64% (64–78%), which were considered significant accuracies. However, a correct response to the patient's own photo is not unequivocal evidence that a person is consciously aware. It has been argued that a P300 response evoked by one's own name does not necessarily reflect conscious perception and cannot be used to differentiate VS and MCS patients (Perrin *et al* 2006). Furthermore, Signorino *et al* who showed that emotional (as compared to neutral) stimuli increase the likelihood of obtaining a P300 response in comatose patients (Signorino *et al* 1995). To address this question, in the second run, where patients were instructed to focus on the unfamiliar photos, three of the five patients (i.e., patients VS1, MCS1, the LIS patient) achieved accuracies significantly higher than the chance level. Furthermore, in the third run, where patients were instructed to attend their own or the unfamiliar photos randomly, the three positive patients still achieved significant accuracies (66–76%), illustrating that the three patients were able to follow commands.

Among the eight patients involved in this study, one patient (VS1) who was clinically diagnosed as vegetative based on repeated behavioral standardized CRS-R assessments by trained and experienced clinicians was able to use the hybrid P300- and SSVEP-based BCI to choose the target photos. This result corroborates previous fMRI (e.g., Monti *et al* 2010) and EEG (e.g., Cruse *et al* 2012b) data that some patients who meet the behavioral criteria for VS might have residual cognitive function and even conscious awareness. The MCS patient (MCS1) who showed motor-independent BCI signs of command-following never showed any clinical motor sign of command-following for over a year prior to testing. The patient subsequently emerged from his condition and showed motor-dependent behavioral communication two months after the experiment-while patient VS1 remained clinically unchanged at follow-up.

It should be stressed that to perform the assessed experimental hybrid BCI tasks, many cognitive functions are needed, such as language comprehension (i.e., understanding the task instructions), object selection (i.e., attending to the left or right sided photo), working memory (i.e., remembering the instructions), and sustained attention (i.e., keeping attentional focus on the target photo). The absence of any of these cognitive functions could prevent success of performing the paradigm. Negative results can hence not be used as final evidence of a lack of awareness because false-negative findings in BCI studies are possible, even in healthy users (Allison *et al* 2010b, Guger *et al* 2009) and in some of the assessed VS (3 out of 4) and MCS (2 out of 3) patients included in our small convenience sample. However, positive



(A) Fz



(B) Pz

Figure 4. Grand-average P300 ERP waveforms of the ‘Fz’ and ‘Pz’ electrodes from 200 pre-stimulus to 1000 ms post-stimulus in runs 1 (upper panels), 2 (middle panels) and 3 (lower panels) for four subjects VS1, MCS1, LIS1, and HC1. The solid red curves containing P300 responses and the dashed blue curves without P300 responses corresponded to the target and non-target photo frames respectively.

results do indicate that all such cognitive functions exist in these patients, thus demonstrating their residual awareness.

Several previous studies examining P300 and SSVEP responses partially support our observations. The P300 response has been regarded as reflecting the cognitive potential that is dependent on attention and working memory (Linden 2005). Moreover, the modulation of the P300 response by manipulation of consciousness, such as in stimulus masking, attention manipulation, or anesthesia, highlight its possible usefulness as a marker of awareness (Naci *et al* 2012). Although the specific underlying mechanisms of

the SSVEP response are still not fully understood, its dependency to cognitive variables, such as attention, stimulus classification, and memory, has been observed (Muller *et al* 1998, Silberstein *et al* 1995). Both the P300 and SSVEP responses involve sequential activations of cortical networks and rely on higher-order cognitive abilities (Comerchero and Polich 1999, Pastor *et al* 2003, Kotchoubey *et al* 2005, Pastor *et al* 2007, Andersen *et al* 2011). In this study, the P300 (figure 4) and SSVEP responses (figure 5) were observed in 2/7 DOC patients who failed to show behavioral signs of command following. This observation suggests that these

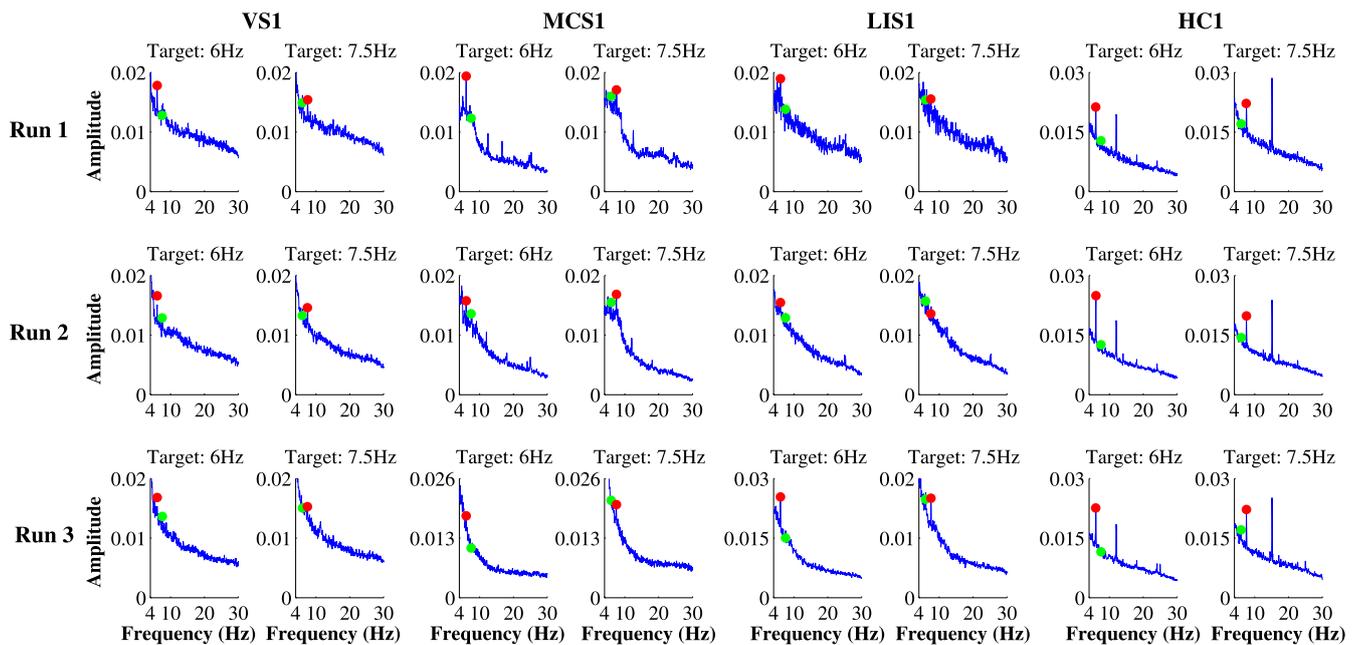


Figure 5. The average power density spectra of the EEG signals from the eight selected electrodes ('P7', 'P3', 'Pz', 'P4', 'P8', 'O1', 'Oz' and 'O2') in runs 1 (upper panels), 2 (middle panels) and 3 (lower panels) for four subjects VS1, MCS1, LIS1, and HC1. The red points indicate the flickering frequency of the attended target photo, and the green points indicate the flickering frequency of the non-attended non-target photo. The target frequencies of 6 Hz and 7.5 Hz imply that the target photos appeared in the left and the right of the GUI, respectively.

patients were able to voluntarily modulate their brain activities, and the evidence provided by EEG led to the conclusion that they possessed residual cognitive function.

One could argue that patients with DOC often lose the ability to fixate their gaze, which is generally necessary for the use of BCIs based on visual P300 and SSVEP responses. However, several studies have described gaze-independent P300- or SSVEP-based BCIs (Brunner *et al* 2010, Treder *et al* 2011, Lesenfants *et al* 2011, Zhang *et al* 2010), although the classification performances are typically lower for gaze-independent BCIs than for gaze-dependent ones. In the GUI used in this study, we used a few large visual elements instead of many small elements to ease the deployment of covert attention and to improve visual acuity in peripheral vision.

In our previous study (Li *et al* 2013), we proposed a hybrid BCI combining the P300 and SSVEP responses in healthy subjects. Our present experimental results demonstrate that the combined hybrid BCI achieved better classification accuracy than the corresponding separate P300- or SSVEP-based classification. In this study, the hybrid BCI, which was a variant of our previous system (Li *et al* 2013), was successfully used to detect awareness in two patients with DOC and a conscious LIS subject. This study is the first attempt to test a hybrid BCI in this challenging patient population. Our experimental results demonstrated that P300 and SSVEP responses could be elicited and recorded simultaneously in a clinical setting. Future studies should include the development of a simple 'yes/no' communication tool for patients with DOC or LIS based on the proposed hybrid BCI system.

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