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A Gaze-Independent Audiovisual Brain-Computer Interface and its Application in Awareness Detection

Jiahui Pan[1,2], Yuanqing Li[1]

[1]School of Automation Science and Engineering, South China University of Technology, Guangzhou, China
[2]School of Software, South China Normal University, Guangzhou, China

E-mail: auyqli@scut.edu.cn

ABSTRACT: Awareness detection in patients with DOC is a challenging task, which is commonly addressed through behavioral observation scales. In this study, we proposed a gaze-independent audiovisual brain computer interface (BCI) for patients with disorders of consciousness (DOC). Semantically congruent and incongruent audiovisual number stimuli were presented one by one to evoke event-related potential (ERP) components. Subjects were instructed to selectively attend to the congruent audiovisual stimuli (target) whereas ignoring the incongruent audiovisual stimuli (nontarget). Ten healthy subjects first participated in the experiment to evaluate the system. The results demonstrated the audiovisual BCI system outperformed the corresponding auditory-only and visual-only systems. Multiple ERP components including the P300, N400 and LPC were observed in the audiovisual condition, which enhanced the discriminability between the brain responses for target and nontarget stimuli. This system was then applied to detect the awareness in eight patients with DOC. The results demonstrated the command following as well as number recognition in three of the eight patients. Therefore, this gaze-independent audiovisual BCI system might be used as a supportive bedside tool for awareness detection in patients with DOC.

INTRODUCTION

A potential application of Brain-computer interfaces (BCIs) is in awareness detection for patients with disorders of consciousness (DOC), such as vegetative state (VS) and minimally conscious state (MCS). Currently, the clinical diagnosis of DOC patients is generally based on behavioral scales such as the JFK Coma Recovery Scale-Revised (CRS-R), which rely on overt motor responses to external stimuli at the time of observation [1]. However, these patients are usually deprived of the capacity to make normal physical movements [2]. As a consequence, the clinical misdiagnosis rates have been relatively high, ranging from 37%-43% in VS and MCS patients [3]. Recently, several BCI paradigms have been presented for patients with DOC [4, 5, 6, 7]. In our previous study [7], we developed a visual hybrid BCI combining P300 and SSVEP to detect awareness in eight patients with DOC (4 VS, 3 MCS and 1 LIS) and successfully demonstrated command following in three patients (1 VS, 1MCS and 1 LIS). However, BCI-based awareness detection in patients with DOC is still in its infancy. The performance of the BCIs designed for these patients is generally poor because the patients' cognitive ability is considerably lower than that of healthy subjects. Furthermore, there existed big differences of EEG signals between the patients with DOC and healthy individuals because of severe brain injuries in these patients. One possible solution is to develop novel BCIs to improve awareness detection.

For BCI-based awareness detection, an important issue is the modality of stimulation. To date, most BCI studies have focused on unimodal (e.g., auditory-only or visual-only) stimuli. Compared to unimodal stimuli, congruent multisensory stimuli may cause additional neuronal activities and result in faster behavioral responses and more accurate perception/recognition [8]. However, multisensory stimulus paradigms have barely received attentions in the field of BCIs [9]. In this study, we focused on the potential benefits of audiovisual stimuli for the improvements of BCI performance. Since the patients with DOC lack the control of gaze movements, this study proposed a gaze-independent audiovisual BCI for their awareness detection. Specifically, the stimuli included semantically congruent and incongruent audiovisual numbers (25% congruent vs. 75% incongruent). Furthermore, all the audiovisual stimuli were presented one-by-one, this made the paradigm completely gaze-independent. With this study we aimed at (1) developing and validating a novel gaze-independent audiovisual BCI using semantically congruent and incongruent audiovisual stimuli; and (2) testing if this BCI system could serve as a supportive bedside tool for detecting covert conscious awareness in patients with DOC.

MATERIALS AND METHODS

Subjects Ten healthy subjects (nine males; mean age $\pm$ SD, 29 $\pm$ 2 years) and eight patients with severe brain injuries (seven males; five VS and three MCS; mean age $\pm$ SD, 42 $\pm$ 12 years; see Tab. 1) from a local hospital participated in this experiment. None of the patients had a history of impaired visual and auditory acuity. This s-

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tudy was approved by the Ethical Committee of the General Hospital of Guangzhou Military Command of People's Liberation Army, which complies with the Code of Ethics of the World Medical Association (Declaration of Helsinki). Written informed consent was obtained from the patients' legal surrogates. The eight patients attended a CRS-R assessments in the week before the experiment, with the CRS-R scores presented in Tab. 1.

GUI and audiovisual paradigm The GUI used in this study is illustrated in Fig. 1. A visual button was set at the center of a 22-inch LED monitor. Two loudspeakers were placed behind the monitor to present auditory stimuli. The visual stimuli consisted of 10 visual numbers $(0, 1, \cdots, 9)$, whereas the auditory stimuli included 10 spoken numbers ($(0, 1, \cdots, 9$; 22 kHz, 16 bit). The intensities of sounds were adjusted by equalizing the root mean square power across all sound files. Each stimulus presentation (300 ms) included a pair of the visual and spoken numbers which could be semantically congruent (such as a visual number 8 and a spoken number 8) or incongruent (such as a visual number 5 and a spoken number 6). Furthermore, there was a 700-ms interval between two consecutive stimulus appearances. Note that all the audiovisual stimuli are presented one-by-one with the visual stimuli appeared in the same location of the screen. This made the paradigm a gaze-independent one.

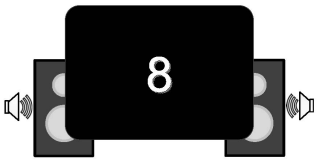

Figure 1: GUI of the audiovisual BCI.

Experimental procedures
The healthy subjects participated in Experiment I, whereas the patients with DOC participated in Experiment II. Experiment I contained three sessions in a random order, corresponding to the visual (V), auditory (A) and audiovisual (AV) stimulus conditions, respectively. In each session, there were first a calibration run of 10 trials for training the support vector machine (SVM) model and then a evaluation run of 40 trials. Note that we collected a small training data set for each subject, because this BCI system was designed mainly for patients with DOC who are easily fatigued during the experiment.
The experimental procedure of one trial of the audiovisual session is illustrated in Fig. 2. Four pairs of audiovisual stimuli were first constructed, in which one pair of audiovisual stimuli were semantically congruent and the other three pairs were semantically incongruent. Under the condition of semantic congruency/incongruency, these visual stimuli and auditory stimuli were pseudo-randomly chosen from the visual and spoken numbers $(0, 1, \cdots, 9)$. Each trial began with the visual and auditory presentation of the task instructions, which lasted 8 s. The instruction was "Count the number of times that the congruent audiovisual stimulus pairs appeared." Following the instruction, the four audiovisual stimulus pairs constructed as above were presented one by one for 8 times in a random order. Specifically, four number buttons flashed from appearance to disappearance in a random order. When a number button appeared, a spoken number was presented for 300 ms simultaneously. The subject was instructed to count the appearances of the congruent audiovisual stimuli (target) while ignoring the incongruent audiovisual stimuli (nontarget). After 32 s, a feedback result determined by the BCI algorithm appeared in the center of the monitor. If the result was correct, a positive audio feedback of applause was given for 4 s to encourage the subject. Otherwise, no feedback was presented and the screen was blank for 4 s.

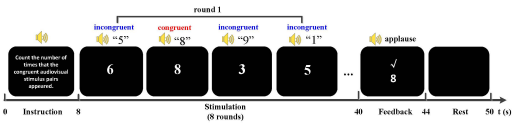

Figure 2: Procedure of one trial in the audiovisual condition.

For the visual and auditory sessions, the experimental procedure was similar to that for the audiovisual session with the following two exceptions. First, the instruction was "Focus on the target number (e.g., 8), and count the number of times that the target number is presented"; Second, there were visual-only stimuli for the visual session and auditory-only stimuli for the auditory session.
Experiment II contained an audiovisual session in which the procedure of each trial was the same as that for the audiovisual session of Experiment I. Eight patients participated in this experiment, which included a calibration run of 10 trials and an online evaluation run of 40 trials. Because the patients were subject to fatigue, the calibration and evaluation runs were divided into five blocks each of which contained 10 trials and was conducted on a separate days. Using EEG data from the calibration run, we trained a SVM classifier for the first evaluation block. For each of the later blocks, the classification model was updated using the data from the previous block. For example, we used the data from Block 2 to update the SVM model and then began the evaluation Block 3. During the experiment, the experimenters and families explained the instructions repeatedly so that the patient paid attention to the audiovisual target stimuli. The patient was carefully observed by an experienced doctor to ensure task engagement. Additionally, the break between two consecutive trials was extended to at least 10 s depending on the patient's level of fatigue.
Data acquisition A NuAmps device (Neuroscan, Compumedics Ltd, Victoria, Australia) was used to collect scalp EEG signals. Each patient wore an EEG cap (LT 37) with Ag-AgCl electrodes. The EEG signals were

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Table 1: Summary of patients' clinical status.

Patient	Age	Gender	Clinical Diagnosis	Etiology	Time Since Onset (months)	CRS-R score (subscores) Before the experiment
VS1	34	M	VS	ABI	2	5 (1-1-1-1-0-1)
VS2	55	M	VS	TBI	5	7 (1-1-2-2-0-1)
VS3	41	M	VS	CVA	1	6 (1-1-1-1-0-2)
VS4	48	M	VS	ABI	3	6 (1-1-2-1-0-1)
VS5	22	M	VS	TBI	18	5 (1-1-1-1-0-1)
MCS1	53	F	MCS	ABI	3	9 (1-3-2-1-0-2)
MCS2	37	M	MCS	TBI	4	8 (1-3-1-1-0-2)
MCS3	38	M	MCS	TBI	2	9 (1-3-2-1-0-2)

ABI, anoxic brain injury; CRS-R, coma recovery scale-revised; CVA, cerebrovascular accident; and TBI, traumatic brain injury; JFK CRS-R subscales: Auditory, visual, motor, oromotor, communication, and arousal functions.

referenced to the right mastoid. The EEG signals used for analysis were recorded from 32 electrodes placed at the standard positions of the 10-20 international system. The impedances of all electrodes were kept below 5 k Ω. The EEG signals were amplified, sampled at 250 Hz and band-pass filtered between 0.1 Hz and 30 Hz.

Data processing We performed the same online analysis for each session in Experiments I and II. In the following, we illustrated the online detection in an audiovisual session, as an example. For each trial of the calibration and evaluation runs, the EEG signals were first filtered between 0.1 and 20 Hz. We extracted an epoch (0-900 ms after the stimulus-onset) of the EEG signals for each channel and each stimulus appearance. This EEG epoch was down-sampled by a rate of 5 to obtain a data vector consisting of 45 data points. We concatenated the vectors from all 30 channels to obtain a new data vector, which corresponded to a stimulus appearance. Second, we constructed a feature vector for each audiovisual stimulus pair by averaging the data vectors across the 8 appearances in a trial. Third, we trained an SVM classifier using the feature vectors with labels from the calibration data. Finally, for each online trial, the SVM classifier was applied to the four feature vectors corresponding to the four audiovisual stimulus pairs, and four SVM scores were obtained. The detection result in this trial was determined as the audiovisual stimulus pair corresponding to the maximum of the SVM scores.

We performed ERP analysis using data from the evaluation run in each session of Experiment I. Specifically, for each trial, after band-pass filtering (0.1-20 Hz), the EEG epochs of each channel were extracted from 100 pre-stimulus to 900 ms post-stimulus, and baseline corrected using the data of the interval of 100 ms pre-stimulus. For artifact rejection, the epochs were discarded from averaging if the potential exceeded 60 μV in any one of channels. ERPs responses were extracted by time-locked averaging the EEG signal across 40 trials in the evaluation run for each of the stimulus conditions.

We also compared the ERPs for the target and nontarget stimuli to illustrate the effectiveness of our audiovisual BCI paradigm. Specifically, statistical analysis of the ERP components were conducted as follows [10]. First, based on the averaged ERP waveforms extracted above, the ERP components and their corresponding time windows were selected for all conditions. The width of the time window for each ERP component was 200 ms, referring to existing references such as [11]. Then, peak latency of each component was computed separately for each subject/condition individually. The latencies of maximum peaks were individually computed to ensure that each individual component's peak was enclosed in its corresponding time window. Next, mean amplitudes of these components were computed using a small window (50 ms in this study) surrounding the peak maximum. Finally, amplitude differences between targets and non-targets were tested with two-way repeated measures analyses of variance (ANOVA) on stimulus condition (the AV, V, and A conditions) and electrode site ("Pz", "Cz", and "Fz") as within-subjects factors for each of the ERP components. Post-hoc t-tests (Tukey-corrected for multiple comparisons) were further performed when necessary. Results were considered significant when p values were below 0.05.

For each session, the accuracy was calculated as the ratio of the number of all correct responses (hits) among the total number of presented trials. We used a binomial test based on Jeffreys' Beta distribution to calculate the significant level in a four-class paradigm as described below [12]:

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

where N is the number of trials, m is the expected number of successful trials, a is the expected accuracy (0.25 in this study), λ is the accuracy rate, and z is the z-score based on the standard normal distribution. Given a significance level of 0.05 for a one-sided test, z is 1.65. Using (1), we could obtain the accuracy rate λ corresponding to the significance level, which is 37.3% for 40 trials.

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RESULTS

Results for healthy subjects Ten healthy subjects participated in Experiment I. Tab. 2 summarized the online classification accuracies for all healthy subjects. Among the AV, V and A conditions, the A one exhibited the lowest online accuracy for each healthy subject. The audiovisual online accuracies for nine of the ten healthy subjects were better than or equal to the visual-only online accuracies. The average online accuracy across all subjects were 92%, 84.75%, and 74.75% for the AV, V and A conditions, respectively, as shown in Tab. 2. A one-way repeated measures ANOVA was conducted to test the effect of stimulus condition on the online accuracy. The analysis revealed that the stimulus condition exerted a significant effect ($F(2, 27) = 7.849$, $p \leq 0.01$). Furthermore, Post-hoc Tukey-corrected t-tests indicated that the online average accuracy was significantly higher for the AV condition than for the V or A condition (all $p \leq 0.05$ corrected).

Table 2: Online accuracies for healthy subjects.

Subject	Accuracy (%)		
	A	V	AV
H1	75	80	90
H2	70	85	85
H3	55	85	85
H4	87.5	87.5	92.5
H5	70	80	90
H6	82.5	90	100
H7	67.5	80	100
H8	80	90	85
H9	82.5	87.5	97.5
H10	77.5	82.5	95
Average	74.75±0.09	84.75±0.04	92±0.06

We compared the brain responses evoked by the target and nontarget stimuli in the AV, V and A conditions in our ERP analysis. The group average ERP waveforms from 0 to 900 ms post-stimulus at the "Fz", "Cz", and "Pz" electrodes are shown in Fig. 3(a). Three ERP components P300, N400, and LPC were observed. We further determined the time windows for these ERP components (P300 window: 300-500 ms; N400 window: 500-700 ms; and LPC window: 700-900 ms). A two-way ANOVA showed no significant interaction between factors of stimulus condition and electrode site on each of the ERP components. The electrode site had no significant effect for each of the ERP components. However, the analysis demonstrated a significant main effect of stimulus condition (the audiovisual, visual-only, and auditory-only conditions) on each of the ERP components (P300: $F(2,63)=7.928$, $p \leq 0.01$; N400: $F(2,63)=8.708$, $p \leq 0.01$; LPC: $F(2,63)=12.557$, $p \leq 0.01$). Furthermore, Post-hoc Tukey-corrected t-tests revealed the following: (i) For the P300 component, the amplitude differences between target and non-target were stronger in the AV condition than in the A condition ($p \leq 0.01$ corrected). (ii) For the N400 component, the amplitude differences between target and non-target were stronger in the AV condition than in the V or A condition (all $p \leq 0.05$ corrected). (iii) For the LPC component, the amplitude differences between target and non-target were stronger in the AV condition than in the V or A condition (all $p \leq 0.01$ corrected).

We further evaluated the discriminative features in the AV, V and A conditions using point-wise running t-tests (two-tailed) for target vs. nontarget responses. It follows from Fig. 3(b) that there were more discriminative features within certain time windows, such as 300-500 ms, 500-700 ms, and 700-900 ms, for the AV condition than for the V and A conditions.

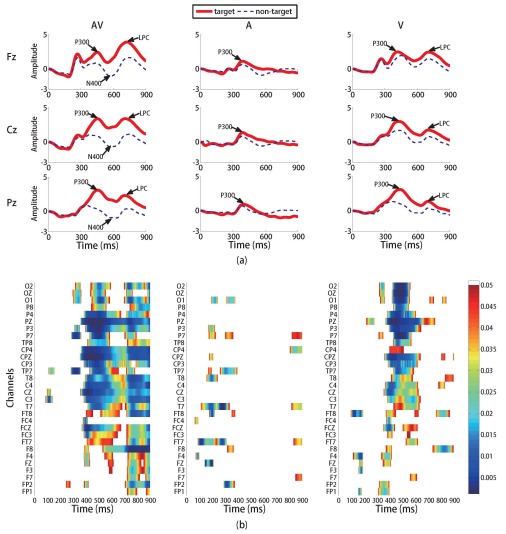

Figure 3: ERP waveforms and comparison results in the audiovisual (AV), visual-only (V) and auditory-only (A) conditions. (a) Average ERP waveforms of all healthy subjects from the "Fz", "Cz", "Pz" electrodes. The solid and dashed curves correspond to the target and nontarget stimuli, respectively. (b) Point-wise running t-tests compared target with nontarget responses across all healthy subjects for 30 electrodes. Significant differences were plotted when data points met an alpha criterion of 0.05 with a cluster size larger than seven.

Patients' results Eight patients participated in Experiment II, with the online results for the patients presented in Tab. 3. Three of the eight patients (VS4, MCS2, and MCS3) achieved accuracies (ranging from 40 to 45%) that were significantly higher than the chance level 25% (accuracy $\geq 37.3\%$ or $p \leq 0.05$, binomial test). For patients VS1, VS2, VS3, VS5, and MCS1, the accuracies were not significant (i.e., $\leq 37.3\%$; ranging from 22.5 to 35%).

For the eight patients with DOC, the ERP waveforms were calculated. Specifically, the ERP waveforms from 0 to 900 ms post-stimulus were obtained by averaging the EEG channel signals across all 40 trials. Fig. 4 shows the average EEG signal amplitudes of the electrodes "Fz", "Cz" and "Pz" for the eight patients; the solid red and the

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dashed blue curves correspond to the target and the nontarget stimuli, respectively. For the three patients (VS4, MCS2, and MCS3) whose accuracies were significantly higher than the chance level, a P300-like component is apparent in each target curve, whereas the N400 and LPC responses were not apparently evoked as in the healthy controls. For the other five patients (VS1, VS2, VS3, VS5, and MCS1), none of the P300, N400, and LPC components were observed.

Among the five patients who were determined to be entirely vegetative based on repeated behavioral JFK CRS-R assessments, two patients (VS2 and VS4) progressed to MCS during the experiment. Furthermore, the patient VS4 subsequently emerged from MCS after the experiment. The patients MCS2 and MCS3 subsequently emerged from their conditions and showed motor-dependent behavioral communication two months after the experiment. Other patients (VS1, VS3, VS5, and MCS1) remained clinically unchanged at follow-up.

Table 3: Online accuracy of each patient.

Subject	Trials	Hits	Accuracy	p-value
VS1	40	11	27.5%	$p = 0.7150$
VS2	40	9	22.5%	$p = 0.7150$
VS3	40	12	30%	$p = 0.4652$
VS4	40	16	**42.5%**	$p = 0.0106$
VS5	40	13	32.5%	$p = 0.2733$
MCS1	40	14	35%	$p = 0.1441$
MCS2	40	16	**40%**	$p = 0.0285$
MCS3	40	18	**45%**	$p = 0.0035$

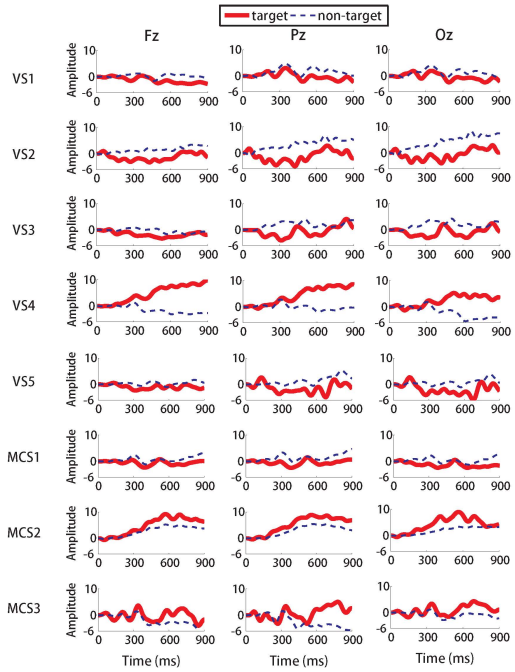

Figure 4: ERPs waveforms from the “Fz”, “Cz” and “Pz” electrodes for the eight patients with DOC. The solid red curves correspond to the target stimuli, and the dashed blue curves correspond to the nontarget stimuli.

DISCUSSION

In this study, we proposed a novel audiovisual BCI system using semantically congruent and incongruent audiovisual stimuli of numbers. All the audiovisual stimuli were presented in a serial manner, which made the BCI system gaze-independent. With respect to classification accuracy, the experimental results for ten healthy subjects demonstrated that the audiovisual BCI system outperformed the corresponding visual-only and auditory-only BCI systems. Furthermore, we applied the proposed audiovisual BCI for awareness detection in patients with DOC. Among the eight DOC patients (5 VS, 3 MCS) involved in the experiment, three (1 VS, 2 MCS) achieved accuracies significantly higher than the chance level (Tab. 3). To some extent, these results demonstrated both command following and residual number recognition ability in these three patients.

Here, our paradigm was different from the classic ‘oddball’ paradigms. The stimuli in our paradigm included semantically congruent and incongruent audiovisual numbers (25% congruent and 75% incongruent audiovisual stimuli), which were presented one by one. Using this paradigm, our experimental results for healthy subjects showed that two main ERP correlates of semantic processing (N400 and LPC) as well as the P300 were elicited in the audiovisual condition. As shown in Fig. 3(a), the ERP responses to semantic processing first included a negative shift (N400) with a latency of 500-700 ms at electrodes “Fz”, “Cz” and “Pz” for semantically incongruent stimuli (nontarget). Then, a following positive peak (LPC) during 700-900 ms was observed for semantically congruent stimuli (target) at electrodes “Fz”, “Cz” and “Pz”. These results are consistent with previous reports on semantic processing [13, 14]. In our ERP analysis for the healthy subject, a stronger P300 response was recorded in the AV condition than in the A condition, and both N400 and LPC responses were stronger in the AV condition than in the V and A conditions. Furthermore, as shown in Fig. 3(b), in several time windows corresponding to the P300, N400 and LPC components, the difference between the target and nontarget responses was greater for the AV condition than for the V and A conditions. This enhanced difference was useful for improving the performance of the BCI (see Tab. 2).

As previously mentioned, misdiagnosis rates based on behavioral observation scales such as CRS-R are relatively high. BCIs can be used as a supportive bedside tool to assess patients’ residual cognitions. For instance, if awareness is detected in a VS patient using a BCI system, we may conclude that the patient possesses the cognitive functions associated with the experimental task and that a misdiagnosis might occur. In this study, the experiment results showed that one VS patient (VS4) was able to perform the BCI experimental task with a significant accuracy. This result corroborates previous fMRI ([15]) and EEG ([16]) data that some patients who meet the behavioral criteria for VS might have residual cogni-

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tive functions and even consciousness. In fact, according to the behavioral CRS-R assessments, this VS patient progressed to MCS one month after the experiment and further emerged from MCS three months later. This behavioral observation supports our BCI assessment result for this VS patient.

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