Author’s response to reviews

Title: A Gaze-independent Audiovisual Brain-Computer Interface for Detecting Awareness of Patients with Disorders of Consciousness

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Responses to the Editor

The authors are highly grateful to the editors for coordinating the review of our manuscript. In light of your comments and suggestions, the paper has been revised. Please see our point to point responses in the following.

Technical Comments:

Editor Comments:

BMC Neurology operates a policy of open peer review, which means that you will be able to see the names of the reviewers who provided the reports via the online peer review system. We
encourage you to also view the reports there, via the action links on the left-hand side of the page, to see the names of the reviewers.

Response: According to your comments, we have carefully rewritten the related paragraphs in the present manuscript. Furthermore, we have checked editorial policies and formatting guidelines to ensure that our revised manuscript conforms to the journal style. Please see the following paragraph extracted from the present version.

“Brain-computer interfaces (BCIs) decode brain activities into computer control signals with the aim at providing a non-muscular communication pathway with external devices [1]. …For instance, the P300 speller described by Farwell and Donchin presented a selection of characters in a $6 \times 6$ matrix from a computer display [5]. The user was required to focus attention on the row and the column that contained the target character, while each row and column of the matrix flashed at random. In this case, the target character flashed with a probability of 0.167 (2/12). The visual P300 ERP elicited by the oddball was identified and translated into a character.” (p. 3, the first paragraph)

“The UWS is defined by the preservation of spontaneous or stimulus-induced arousal without self or environmental awareness, whereas the MCS is characterized by the presence of inconsistent but discernible behaviors. Keystones in diagnosis lies in recovering the voluntary response, such as the ability to follow commands and functional use two different objects, which indicates emergence from the UWS and the MCS, respectively [7].” (p. 3, the second paragraph)

“However, in recent years, electroencephalography (EEG), functional magnetic resonance imaging (fMRI) and other neuroimaging methods have shown that misdiagnosis of patients with DOC who display a severe lack of motor function is possible [9]. For instance, Cruse et al. tested a motor imagery-related BCI with a group of 16 patients with UWS. Three of these patients achieved offline accuracies ranging from 61% to 78% during the motor imagery tasks [10]. Monti et al. instructed 54 patients (23 with UWS and 31 with MCS) to “imagine playing tennis” and “walk through houses” during an fMRI experiment and found that five (4 with UWS and 1 with MCS) were able to modulate their sensorimotor rhythms [11]. Recently, many BCI paradigms have been proposed for patients with DOC [12-16]. Lule et al. [13] proposed an
auditory oddball EEG-based BCI paradigm based on data from 16 healthy subjects, 3 patients with UWS, 13 patients with MCS, and 2 patients with locked-in syndrome (LIS). One patient with MCS and one patient with LIS achieved significant offline accuracies over the chance level. In our previous study [17], we detected command following in eight patients with DOC (4 with UWS, 3 with MCS and 1 with LIS) using a visual hybrid P300 and SSVEP BCI, and successfully revealed that one UWS patient, one MCS patient and one LIS patient possessed residual awareness. However, the use of BCI for detecting awareness of patients with DOC remains in primary stage. These patients exhibit a generally weak BCI performance as they have a much lower cognitive ability than healthy individuals. Furthermore, substantial differences in EEG signals have been observed between patients with DOC and healthy individuals because of severe brain injuries in the patients. Therefore, many efforts should be taken for developing novel BCIs to enhance the performance of awareness detection.” (p. 4, the first paragraph)

“Belitski and colleagues compared different types of auditory-only, visual-only and audiovisual speller BCIs to assess their relative performance. Their experimental results involved 11 subjects reported that the positive effects of an audiovisual ERP-BCI paradigm compared with the corresponding visual-only and auditory-only variants [21]. Sellers and Donchin tested a P300-based BCI in the visual, auditory, and audiovisual modes, and reported that auditory mode exhibited a significantly worse classification accuracy compared with visual or audiovisual mode [22]. In our recent study [23], we designed an audiovisual BCI for detecting awareness of DOC patients, in which the audiovisual stimuli were semantically congruent visual and spoken numbers. The patients were required to give respond to target stimuli through following the instructions. According to the results regarding 8 healthy subjects, the use of the audiovisual BCI resulted in a better performance than the corresponding auditory-only or visual-only BCI, and multiple ERP components were strengthened by the audiovisual congruent target stimuli, which were useful for improving target detection.” (p. 4, the last paragraph)

“The experiment included ten healthy subjects (nine males; average age ± SD: 29 ± 2 years) and eight patients with severe brain injuries (seven males; five with UWS and three with MCS; mean age ± SD: 42 ± 12 years; Table 1) in a local hospital. The recruitment was conducted based on pre-arranged inclusion/exclusion criteria. There were five inclusion criteria: 1) the patient had not taken centrally acting drugs; 2) the patient had not accepted sedation in the past 48 hours; 3)
the patient should keep eye opening for a period; 4) the patient had not suffered impaired visual or auditory acuity; 5) the patient had been diagnosed with VS or MCS after anoxic brain damage, traumatic brain injury (TBI), or cerebrovascular disease. There are three exclusion criteria: 1) the patient had a documented history of brain injury; 2) the patient once suffered an acute illness; 3) the patient had accepted hospitalization for less than 2 consecutive months. This study was approved by the Ethical Committee of the General Hospital of Guangzhou Military Command of PLA.” (p. 6, the first paragraph)

“Point-wise running two-tailed t-tests were performed to evaluate the discriminative characteristics of target response and non-target response in the three conditions. From Fig.3(b), certain time windows, such as 300-500 ms, 500-700 ms, and 700-900 ms, could show more discriminative characteristics in audiovisual condition compared with the other two conditions.” (p. 13, the second paragraph)

“In our ERP analysis of healthy subjects, a stronger P300 response appeared in AV condition compared with A condition, and stronger responses for both N400 and LPC were detected in AV condition compared with A and V conditions. Furthermore, as shown in Fig. 3(b), in several time windows corresponding to the P300, N400 and LPC components, there was a greater difference between the target response and non-target responses for audiovisual condition compared with visual-only condition and auditory-only condition, which was helpful to improve the BCI performance (Table 2).” (p. 15, the last paragraph)

“As reported earlier, behavioral observation scales such as CRS-R can yield a relatively high misdiagnosis rate in patients with DOC. BCIs represent an auxiliary bedside tool for detecting residual awareness of patients. Specifically, if the ability to follow commands and the experimental task-related cognitive functions appear in a UWS patient in virtue of a BCI system, we may conclude that the patient possesses awareness and a misdiagnosis might occur. In the present study, one UWS patient (UWS4) could implement the BCI experimental task accurately, which well fit previous fMRI [11] and EEG [53] data showing that some patients who are diagnosed with UWS based on the behavioral scales possessed residual cognitive functions and even exhibited consciousness to some extents.” (p. 16, the second paragraph)
“Importantly, many cognitive functions, including the ability to understand instructions, selectively focusing on the target stimuli, and maintaining attentional focus on the target, are needed to perform the experimental tasks. One any abovementioned cognitive functions was missed, the experimental tasks may not be performed. Therefore, positive results in BCI experiments may indicate the existence of all these cognitive functions as well as residual awareness in these patients. However, negative results in BCI experiments should not be provided as final evidence for an absence of awareness, because even approximately 13% of healthy subjects exhibited BCI illiteracy, thus fail in effectively controlling a simple BCI [28].” (p. 17, the first paragraph)

Reviewer reports:

If improvements to the English language within your manuscript have been requested, you should have your manuscript reviewed by someone who is fluent in English. If you would like professional help in revising this manuscript, you can use any reputable English language editing service. We can recommend our affiliates Nature Research Editing Service (http://bit.ly/NRES_BS) and American Journal Experts (http://bit.ly/AJE_BS) for help with English usage. Please note that use of an editing service is neither a requirement nor a guarantee of publication. Free assistance is available from our English language tutorial (https://www.springer.com/gb/authors-editors/authorandreviewertutorials/writinginenglish) and our Writing resources (http://www.biomedcentral.com/getpublished/writing-resources). These cover common mistakes that occur when writing in English.

Response: We have sent this manuscript to a company (a professional editing website, http://www.aje.com) for improving the English.