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BRAIN COMPUTER INTERFACE BASED COMMUNICATION IN THE COMPLETELY LOCKED-IN STATE

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ABSTRACT: Patients in completely locked-in state (CLIS) are unable to communicate with the external world because of complete paralysis of the motor system. Brain computer interface (BCI) aims to restore communication in CLIS patient by bypassing the dysfunctional motor system. Electroencephalography (EEG) based BCI has been used successfully in patient in Locked-in state (LIS), but once the patient transition in CLIS EEG-BCI fails to provide communication. Recently we reported the first single case report of functional near infrared spectroscopy (fNIRS) based auditory BCI control by an ALS patient in CLIS. Here we report fNIRS-BCI based communication in four ALS patients in CLIS, two of them in permanent completely locked-in state (CLIS) and two entering the CLIS without reliable means of communication. Patients learned to answer personal questions with known answers and open questions all requiring a "yes" or "no" thinking using fronto-central oxygenation changes measured with fNIRS. Online fNIRS classification of personal questions with known answers and open questions, using linear support vector machine (SVM), resulted in an above-chance-level correct response rate over 70%. Electroencephalographic (EEG) oscillations and electro-oculographic (EOG) signals did not exceed the chance-level threshold for correct communication despite occasional differences between the physiological signals representing a "yes" or "no" response.

INTRODUCTION

Amyotrophic lateral sclerosis is a progressive motor disease of unknown etiology resulting eventually in a complete paralysis of the motor system but affecting sensory or cognitive functions to a minor degree [1]. There is no treatment available; patients have to decide to accept artificial respiration and feeding after the disease destroys respiratory and bulbar functions or to die of respiratory or related problems. If they opt for life and accept artificial respiration, the disease progresses until the patient loses control of the last muscular response, usually the eye muscles. If rudimentary voluntary control of at least one muscle is present, the syndrome is called locked-in state (LIS) [2]; ultimately as the disease progresses most of the ALS patients lose the control of all the muscles, the resulting condition is called completely locked-in state (CLIS) [2]. Patients in CLIS are unable to communicate with the external world because all assistive communication aids are based on some remaining motor control; hence there is a vital need for an assistive technology to help patients in CLIS to communicate their needs and feelings to their family members/caregivers. Brain computer interface (BCI) represents a promising strategy to establish communication with paralyzed ALS patients, as it does not need muscle control. BCI research includes invasive (implantable electrodes on or in the neocortex) and noninvasive means (including electroencephalography (EEG), magnetoencephalography (MEG), functional magnetic resonance imaging (fMRI), and near-infrared spectroscopy (NIRS)) to record brain activity for conveying the user's intent to devices such as simple word-processing programs. Non-invasive methods have been utilized more frequent than invasive methods for people with disabilities (such as those with ALS) [3-7].
For these conditions (LIS and CLIS) Brain-Computer-Interfaces were developed and tested extensively since the first publication of Birbaumer et al (1999) [8] of two LIS patients suffering from ALS. Patients select letters or words after learning self-regulation of the particular brain signal or by focusing their attention to the desired letter or a letter-matrix (Farwell & Donchin) [9] and the attention related brain signals allow the selection of desired letter. While healthy people and ALS patients up to the LIS showed successful BCI control and communication [10], completely paralyzed ALS patients in CLIS did not learn sufficient BCI control for brain communication (Kuebler & Birbaumer, 2008) [11]. A single case report by Gallegos Ayala et al., 2014 [12] suggested that a CLIS patient with ALS could achieve BCI-control and "yes" - "no" communication to simple questions with known positive answers or negative answers and some open questions over an extensive time period. NIRS was used to measure and classify cortical oxygenation and deoxygenation following the questions. The BCI methodology used in this report departed radically from the previous BCI-

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procedures: a more “reflexive” mode based on learning principles of classical conditioning to simple questions was used to train the classifier separating “yes” and “no” thinking of answers by the patient and instead of neuroelectric recording (EEG) functional NIRS (fNIRS) was used.

Hence, an extensive study was performed on four ALS patients in CLIS to train them to communicate “yes” and “no”. The fNIRS based BCI was employed successfully to train patients to regulate their fronto-central brain regions in response to auditorily presented questions. After training a classifier separating “yes” from “no” answer for several days the patients were given feedback of their affirmative or negative response to questions with known answers and open questions over weeks [13].

MATERIAL AND METHOD

The Internal Review Board of the Medical Faculty of the University of Tubingen approved the experiment reported in this study and the patients’ legal representative gave informed consent for the study with permission to publish the results and show the face of patients in the publication. The study was in full compliance with the ethical practice of Medical Faculty of the University of Tubingen. The clinical trial registration number is ClinicalTrials.gov Identifier: NCT02980380.

Patient

Patient F (Female, 68 years old, completely locked-in state) was diagnosed with bulbar sporadic ALS in May 2007, as locked-in in 2009, and as completely locked-in May 2010, based on the diagnosis of experienced neurologists. She has been artificially ventilated since September 2007, fed through a percutaneous endoscopic gastrostomy tube since October 2007, and is in home care. No communication with eye movements, other muscles, or assistive communication devices was possible since 2010.

Patient G (Female, 76 years old, CLIS) was diagnosed with bulbar ALS in 2010. She lost speech and capability to walk by 2011. She has been fed through a percutaneous endoscopic gastrostomy tube since September 2011, artificially ventilated since March 2012, and is in home care. She started using assistive communication devices employing one finger for communication in Feb 2013. Later she was diagnosed with degeneration of vision due to cornea defects in Sept 2013. After the failure of the finger communication device an attempt was made to communicate using eye tracking in early 2014. She stopped communicating with the eye in Aug. 2014 before the BCI was introduced and an attempt was made to communicate with the subtle twitch of eye lid which was not reliable. The husband and caretaker declared no communication with her since August 2014.

Patient B (Male, 61 years old, CLIS) was diagnosed with non-bulbar ALS in May 2011. He has been artificially ventilated since August 2011, fed through a percutaneous endoscopic gastrostomy tube since October 2011, and is in home care. He started communicating with a speech device in his throat from Dec. 2011 which ultimately failed and he started using MyTobii eye-tracking device in April 2012. He was able to communicate with MyTobii until Dec 2013 after which the family members attempted to communicate by training him to move his eyes to the right to answer “yes” and left to answer “no”, but the response was variable. No communications was possible since August 2014.

Patient (Female, 24 years old, locked-in state on the verge of CLIS) was diagnosed of juvenile ALS in Dec 2012. She was completely paralyzed within half a year after diagnosis and has been artificially ventilated since March 2013, fed through a percutaneous endoscopic gastrostomy tube since April 2013, and is in home care. She was able to communicate with eye-tracking from early 2013 to Aug 2014 but was unable to use the eye-tracking device after the loss of eye control in Aug 2014. After August 2014 family members were able to communicate with her by training her to move her eyes right to answer “yes” and left to answer “no” questions until Dec 2014. In Jan 2015 eye control was completely lost and she tried to answer yes by twitching the right corner of her mouth and that too varied considerably.

Instrumentation

A continuous wave (CW) based NIRS system, NIRSPORT (NIRX), which performs dual-wavelength (760 nm & 850 nm) CW near-infrared spectroscopic measurement at a sampling rate of 6.25 Hz, was used. The NIRS optodes were placed on the fronto central brain region.

During the BCI sessions the EEG was also recorded with a multi-channel EEG amplifier (Brain Amp DC, Brain Products) from ten Ag/AgCl passive electrodes mounted on the same cap. Six electrodes were used to acquire EEG signals based on the international 10-10 system and the selected channels were FC5, FC1, FC6, CP5, CP1 and CP6 while four electrodes were used to acquire the vertical and horizontal EOG. The signals were bandpass filtered using an FIR filter with a passband of 0.5 – 35 Hz. The EOG was filtered with different filters (3.5 Hz, 10 Hz, and 30 Hz) but none of the filters led to significant differences of neurophysiological patterns related either to the ocular activity or to their SVM-classification accuracies. Each channel was referenced to an electrode on the right mastoid and grounded to the electrode placed on the Fz location of the cap. Electrodes impedances were kept below 10 kΩ and the EEG signal was sampled at 500 Hz. During all BCI sessions the spontaneous EEG was visually controlled by one of the authors (NB or BX) to avoid longer periods of slow wave sleep. A BCI session was initiated only if the EEG was free of high amplitude slow activity below 3.5Hz.

Experiment Procedures

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An auditory based paradigm was employed to a) train patients on questions with known answers, b) give feedback on questions with known answers and c) answer open questions. Known questions are personal questions with known "yes" and "no" answer. Patients were asked to think yes or no and if possible also to use their previously successful eye movements. Open questions are general questions related to quality of life and questions of caretakers whose answer can only be known by the patient. The BCI study started with training sessions during which the patients were instructed to listen to 20 personal questions (with known answers) consisting of 10 true and 10 semantically equivalent false sentences, presented in random order. Patients were asked to think "ja, ja, …" (German for "yes") and "nein, nein, …" (German for "no") for 15 seconds, during the inter stimulus interval (ISI), until they heard the next sentence, as shown in Fig1. After the end of each training session the NIRS feature necessary to differentiate between "yes" and "no" answers during ISI was extracted and classified. If the classification accuracies across at least 3 consecutive training sessions were greater than 65% - 70% the patients were given online feedback after each question. During the online feedback sessions again the patients were presented the same sentences as described above but now at the end of the 15 sec answering period they were given auditory feedback, whether their answer was recognized as "yes" or "no". If the accuracy of online feedback was greater than 70% we presented the patient with open questions during which he/she was always given the auditory feedback of his/her answer. The validity of answers to open questions can only be estimated by a) face validity (i.e. questions of pain in the presence of an open wound), b) stability over time and c) external validity estimated by family members and caretakers and d) internal validity between questions (i.e. the concordance between the answers to semantically equivalent questions (e.g., "Berlin is the capital of France" and "Berlin is the capital of Germany"). Tab. 1 enumerates the total number of training, feedback and open questions sessions performed by each patient.

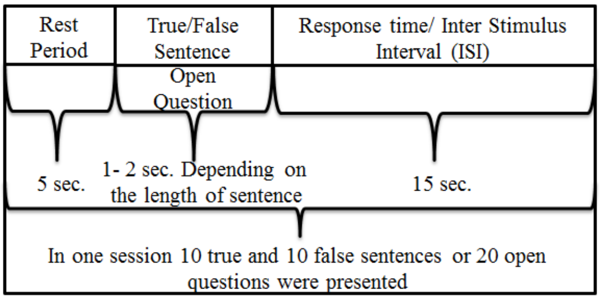

Figure 1: The auditory brain computer interface paradigm used for communication in CLIS patient.

Patient W received no open questions because of low classification accuracy which we and the parents attributed to her emotionality distracting her from concentrating on the responses due to the short time period of adaptation to the CLIS.

Table 1: Lists the total number of training, feedback, open question sessions performed by each patient

Patient / Sessions	Training Sessions	Feedback Sessions	Open Questions Sessions
Patient F	51	7	2
Patient G	51	6	2
Patient B	40	4	2
Patient W	16	4	0

Data Acquisition and Analysis

The schematic depicting the acquisition and analysis of NIRS and EEG data during the BCI sessions is shown in Figure 2. The NIRS data acquired online throughout all the sessions was normalized, filtered using a bandpass filter of 0.01 Hz – 0.3 Hz and processed using Modified Beer Lambert's law, as described in Cope et al. (1987) [14] and Chaudhary et al. (2011) [15], to calculate the relative change in concentration of oxy (O_2Hb) and deoxy hemoglobin (RHb). The relative change in O_2Hb, with respect to the baseline, calculated online during each training session was used to train a model and check the cross-validation classification accuracy. The offline classification procedure used the mean of relative change in O_2Hb across each channel as input feature to train a 5-fold linear support vector machine (SVM) classifier [16]. The SVM [16] model interpolates the data corresponding to true and false sentences' ISI in a two-dimensional space such that the two categories are divided by a hyperplane and the gap between them is as wide as possible.

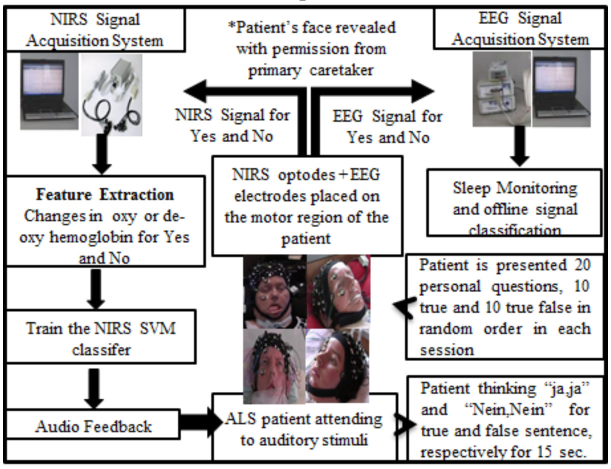

Figure 2: The setup and flow diagram of the brain computer interface for communication in ALS patients.

Firstly a model space was determined and the input feature, extracted from the recorded and processed NIRS signal, i.e., the relative change in O_2Hb, was mapped onto the model space to determine the side of the hyperplane the input feature fell on. For the NIRS signal the mean of the relative change in O_2Hb across all the channels was used as input feature to map onto

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model space, while for EEG and EOG signals temporal and power spectral features were used. The relative change in O_2Hb, EEG and EOG data acquired during BCI sessions from Patient F, G, B and W were processed off-line separately for each patient to determine:

1) The statistical difference in the particular physiological signal (O_2Hb, EEG and EOG) during the ISI of true (yes) and false (no) sentences.

T-tests between the averaged ISI of true and false sentences were performed to ascertain the significant difference, if any, between "yes" and "no" thinking. The t-test analysis was performed across all the channels in a session and for all the sessions of acquired O_2Hb, EEG and EOG signals. Furthermore t-test was also performed between the ISI of all the 10 true sentences and all the 10 false sentences across different channels in a session averaged over many sessions varying slightly between patients.

2) Classification accuracy, using SVM as described above, of O_2Hb, EEG and EOG signals across each session between the true and false sentences' ISI.

The shapes of the relative change in O_2Hb and EOG during ISI corresponding to true and false sentences from all the sessions were plotted in Figure 3 and Figure 5 respectively, while the power spectrum of the EEG signal, calculated using Welch's method [17], during the same ISIs is plotted in Figure 4.

RESULT

The t-test analysis performed using the relative change in O_2Hb showed a significant difference between the true and false sentences' ISI across all patients (not shown here). While, the same analysis performed using the EEG and EOG data across all the training sessions showed no significant differences ($p > 0.05$) between the true and false sentences' ISI across each. The relative change in O_2Hb in five channels over the fronto-central brain region of Patient F, G, B and W during the true and false sentence ISI is shown in Figure 3. Figure 3 illustrates that the shape of the change in O_2Hb during true sentence ISI is qualitatively different from false sentence ISI. Figure 3 also illustrates that the shape of the change in O_2Hb during a true or a false sentence ISI is not consistent between the patients even though within each patient the shape of the change in O_2Hb is stable. Figures 4 illustrates the power spectrum density (PSD) of EEG oscillations, in the frequency band 0 to 10 Hz, during the true and false sentence ISI from patient F, G, B and W respectively. The PSD of EEG signal shows that there was no significant difference between the true and false sentences ISI across all patients. The eye movements (vertical or horizontal, patients were free to use any direction) of patient F, G, B and W while they were performing the "ja (yes)" or "nein (no)" thinking task is shown in Figure 5. It illustrates that there was no significant difference in the eye movements between the true and false sentences ISI for all patients, confirmed by the t-test: Figures 6, 7, 8 and 9 depicts the SVM classification across all the sessions using the change in (a) O_2Hb, (b) EEG and (c) EOG in Patient F, G, B and W; respectively.

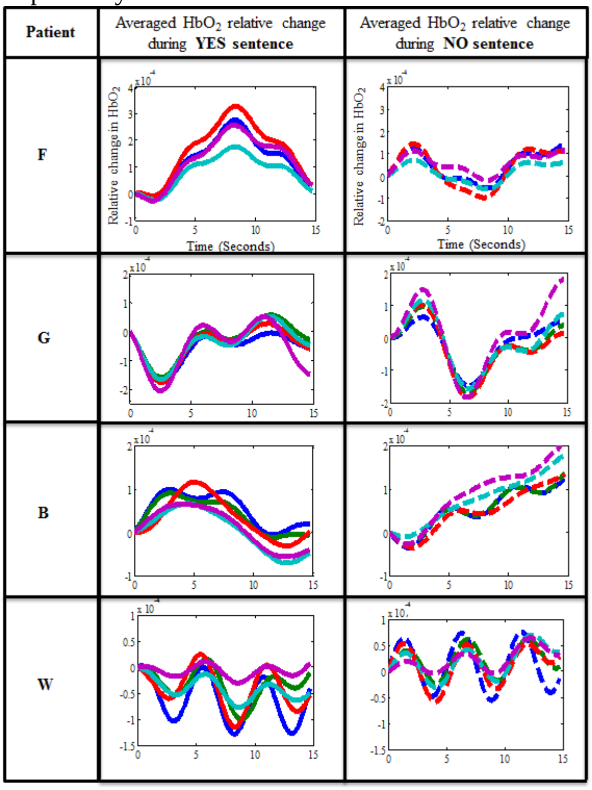

Figure 3: The averaged relative change in O_2Hb across 5 out of 20 channels corresponding to **YES and NO sentence** inter-stimulus interval (ISI) in Patient **F, G, B** and **W**. In each subplot; five different colored trace corresponds to relative change in HbO_2 across five different channels, x-axis is time in seconds and y-axis is relative change in HbO_2.

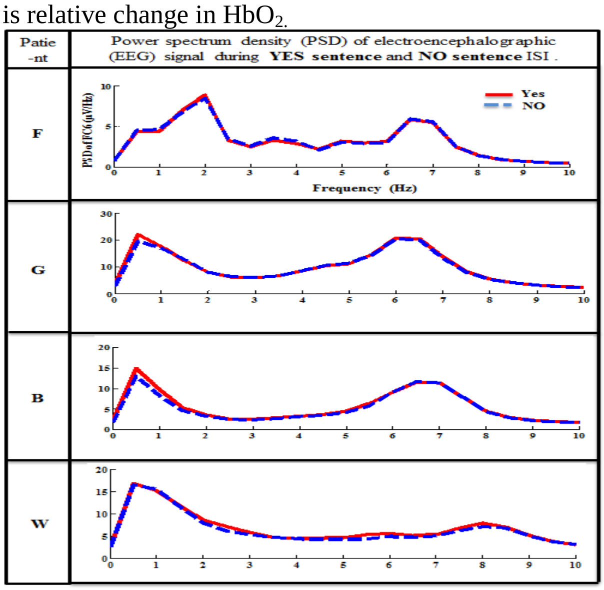

Figure 4: Power spectrum density (PSD) of electroencephalographic (EEG) signal corresponding to **YES** (red solid trace) and **NO** (blue dashed trace) sentence ISI acquired from channel FC6 in Patient **F, G, B** and **W**.

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A 65% cut off was used to define whether the classification accuracy was above or below the acceptable level [18].

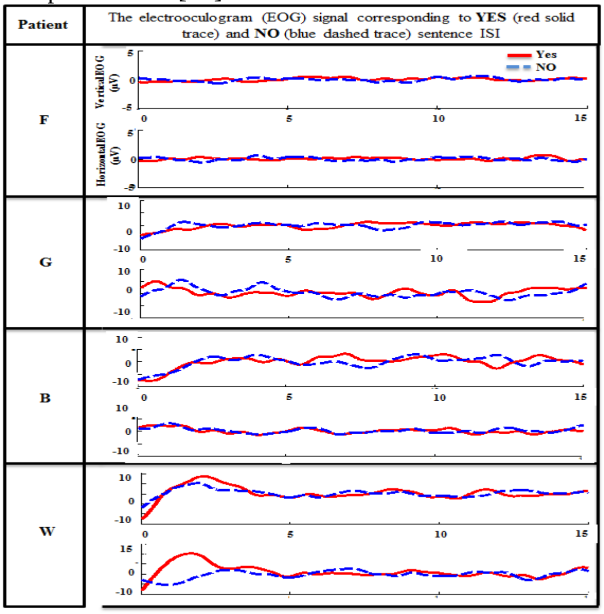

Figure 5: The electrooculogram (EOG) signal corresponding to **YES** (red solid trace) and **NO** (blue dashed trace) sentence ISI in Patient **F, G, B** and **W**. In each subplot x-axis is time in second and y-axis is EOG in micro volt (µV).

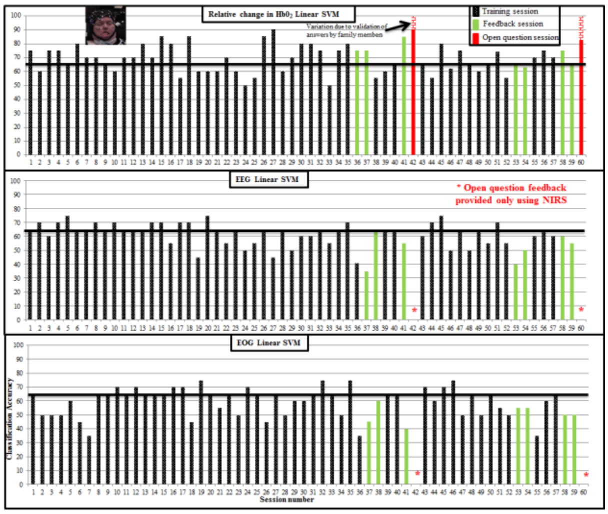

Figure 6 – ***Patient F***: Linear support vector machine (SVM) classification accuracy across all sessions 1) Training (bar plot in spotted black), 2) Feedback (bar plot in solid green) and 3) Open question (bar plot in solid red) obtained using **a)** Relative change in HbO_2, **b)** EEG and **c)** EOG data. In each histogram plot x-axis is the number of sessions and y-axis is classification accuracy. The black horizontal line represents the 65% classification accuracy.

The SVM results illustrates that highest classification accuracy was achieved using the change in O_2Hb for which more than 75% of the sessions yielded greater than 65% classification accuracy for all the patients with an average classification accuracy of 70%.

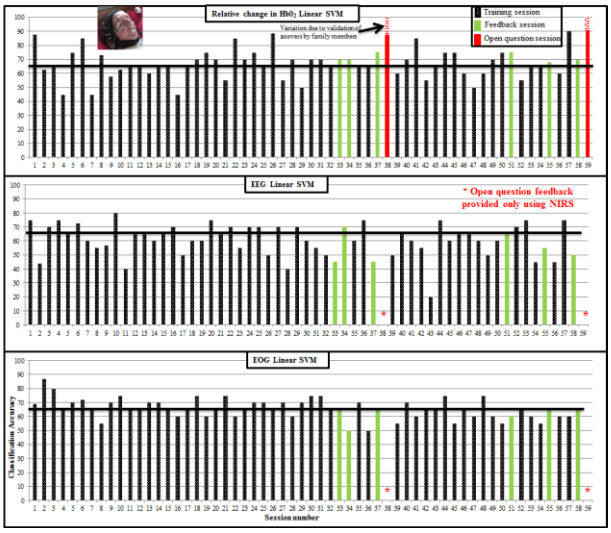

Figure 7 – ***Patient G***: The description of Figure is same as described in Figure 6.

Figure 8 – ***Patient B***: The description of Figure is same as described in Figure 6.

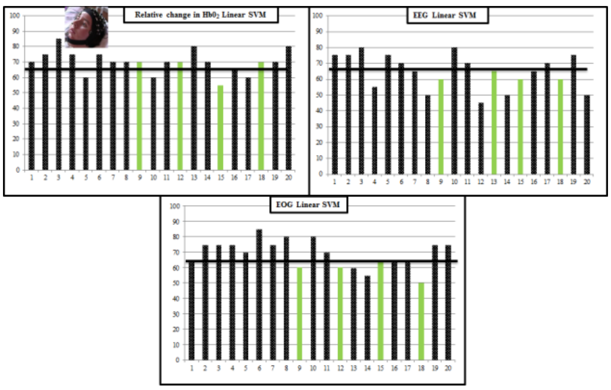

Figure 9 – ***Patient W***: The description of Figure is same as described in Figure 6.

While the SVM classification accuracy obtained using EEG and EOG data only few sessions yielded greater than 65% classification accuracy across all patients. Classification results using fNIRS for open question in

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patients F, B and G, using the criteria for correctness described above in paragraph 2.3 ranged between 75-90% “correct”. Patient W with 24 years of age suffering from juvenile ALS with an extremely rapid disease progression (2 years from diagnosis to CLIS) was not asked open questions at that early stage but continue to train the BCI at present.

DISCUSSION AND CONCLUSION

All in all, 4 patients in CLIS communicated with fronto-cortical oxygenation based BCI with an average correct response rate of 70% over a period of several weeks. Correct response rate for open questions as estimated by relatives exceeded even 75% in 3 of the 4 patients. Patient W, 24 years with juvenile ALS (completely locked-in within 2 years after diagnosis) is still in an emotional labile state which prevented us from asking her the difficult to validate open questions at the time of this study. Patient F, G and B answered open questions containing quality of life estimation with a yes response indicating a positive attitude towards the present situation and life in general as found in larger samples of ALS patients [19]. Correct classification of “yes” and “no” answers given mentally through fNIRS exceeded classification of EEG oscillations from 0-10 Hz (EEG frequencies in advanced ALS rarely show high frequencies) and vertical and horizontal EOG classification. However, despite the absence of reliable eye communication in all patients as the inclusion criteria in the study, EOG classification often was above chance despite the inability of the social environment to perceive them and eye tracker’s failure to use them for communication [10]**.** If replicated with ALS patients in CLIS, these positive results could indicate the first step towards abolition of complete locked-in states at least for ALS.

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