Published in final edited form as:

Clin Neurophysiol. 2018 August ; 129(8): 1519–1525. doi:10.1016/j.clinph.2018.04.747.

Feasibility of an EEG-based brain-computer interface in the intensive care unit

Camille Chatelle^{a,b,c}, Camille A. Spencer^{a,b}, Sydney S. Cash^{a,b}, Leigh R. Hochberg^{a,b}, and Brian L. Edlow^{a,b,d}

^aCenter for Neurotechnology and Neurorecovery, Massachusetts General Hospital, 175 Cambridge Street, Suite 300, Boston, MA, 02114, USA

^bDepartment of Neurology, Massachusetts General Hospital, Harvard Medical School, 175 Cambridge Street, Boston, MA, 02114, USA

^cComa Science Group, GIGA Consciousness, University and University Hospital of Liège, avenue de l'Hôpital 11, 4000 Liège, Belgium

^dAthinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Harvard Medical School, 149 13th St, Charlestown, MA, 02129, USA

Abstract

Objective—We tested the feasibility of deploying a commercially available EEG-based brain-computer interface (BCI) in the intensive care unit (ICU) to detect consciousness in patients with acute disorders of consciousness (DoC) or locked-in syndrome (LIS).

Methods—Ten patients (9 DoC, 1 LIS) and 10 healthy subjects (HS) were enrolled. The BCI utilized oddball auditory evoked potentials, vibrotactile evoked potentials (VTP) and motor imagery (MoI) to assess consciousness. We recorded the assessment completion rate and the time required for assessment, and we calculated the sensitivity and specificity of each paradigm for detecting behavioral signs of consciousness.

Results—All 10 patients completed the assessment, 9 of whom required less than 1 hour. The LIS patient reported fatigue before the end of the session. The HS and LIS patient showed more consistent BCI responses than DoC patients, but overall there was no association between BCI responses and behavioral signs of consciousness.

Conclusions—The system is feasible to deploy in the ICU and may confirm consciousness in acute LIS, but it was unreliable in acute DoC.

Corresponding Author: Camille Chatelle, PhD, Coma Science Group – GIGA Consciousness, Avenue de l'Hôpital, 11, 4000 Liège, Belgium, camille.chatelle@uliege.be.

Conflict of Interest Statement

The research was supported by a grant from Guger Technologies OG (g.tec). After receiving initial technical assistance from g.tec to optimize use of the mindBEAGLE system, the study was conducted, data were analyzed, and the manuscript draft was written solely by the authors. A final draft of the manuscript was provided to g.tec for the purpose of confirming accuracy of the system description. BLE, CC, CAS, LRH, and SSC declare that they have no personal conflict of interest.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Significance—The accuracy of the paradigms for detecting consciousness must be improved and the duration of the protocol should be shortened before this commercially available BCI is ready for clinical implementation in the ICU in patients with acute DoC.

Keywords

brain-computer interface; disorders of consciousness; coma; locked-in syndrome; intensive care unit

1. Introduction

Clinicians may fail to detect early signs of consciousness in patients with acute severe brain injuries. Several studies have reported a misdiagnosis rate of approximately 40% when using assessments tools such as the Glasgow Coma Scale to assess a patient's level of consciousness in the intensive care unit (ICU), as compared to comprehensive behavioral evaluations with the Coma Recovery Scale-Revised (CRS-R; (Andrews et al., 1996, Giacino et al., 2004, Schnakers et al., 2009b)). However, even the CRS-R has limitations, as it relies on motor and language abilities, which makes accurate diagnosis challenging in patients with motor impairment, aphasia (Majerus et al., 2009) or fluctuation of vigilance (Giacino et al., 2002, Piarulli et al., 2016). Moreover, the reliability of the diagnosis has been shown to depend on examiner experience (Lovstad et al., 2010). Because of these confounding factors, up to 20% of patients who are believed to be unconscious based on the CRS-R show evidence of consciousness with neuroimaging and electrophysiological tools (Monti et al., 2010, Cruse et al., 2011, Edlow et al., 2017). These findings provide both a clinical and an ethical imperative for the development of diagnostic tools to detect signs of consciousness when no response can be observed at the bedside (Owen et al., 2006, Monti et al., 2010, Cruse et al., 2011, for a review, Gosseries et al., 2016).

Brain-computer interfaces (BCI) could potentially address this clinical challenge. Portable EEG-based BCIs have been used to improve detection of consciousness (De Massari et al., 2013) in some patients with chronic disorders of consciousness (DoC; (Lule et al., 2013, Pokorny et al., 2013); for a review (Chatelle et al., 2015)). Although these studies have reported limited reliability of such assessments in this population, a potential advantage of BCIs is that they are “online” systems, meaning that the data pertaining to detection of consciousness and facilitation of communication are processed at the point of care and immediately available upon completion of the test. This immediate feedback, if reliable, could inform time-sensitive decisions about continuation of life-sustaining care and provision of rehabilitation services.

Despite the potential role for BCIs in the ICU (Mayaud et al., 2016) and the initial evidence supporting their use in patients with chronic DoC, the feasibility of using BCIs in the ICU for patients with acute DoC has not been tested. In this study, we tested the feasibility of using a commercially available EEG-based BCI (mindBEAGLE, Guger Technologies OG) in the ICU to detect consciousness, as defined by command following, in patients with acute DoC and locked-in syndrome (LIS). We also sought to determine whether such assessment correlated with behavioral signs of consciousness.

2. Methods

2.1. Subject Selection and Study Design

We identified patients admitted to the Neurosciences ICU at a single academic hospital between April 2016 and December 2016. Inclusion criteria for DoC were: 1) severe acquired brain injury with loss of consciousness; and 2) diagnosis of coma, vegetative state/unresponsive wakefulness syndrome (VS/UWS), or minimally conscious state (MCS). Inclusion criteria for LIS were: 1) ability to maintain wakefulness for at least 30 minutes; 2) ability to remain off intravenous sedative medication for at least 60 minutes; 3) absence of cerebral cortical injury on brain imaging; and, 4) a clinical diagnosis of LIS by an attending neurologist based upon the presence of quadriplegia or severe quadriparesis with preserved volitional eye movements, eye blinks, or other limited movements allowing functional communication. Exclusion criteria for all patients were: 1) history of developmental, neurologic, or major psychiatric disorder resulting in functional disability; 2) uncontrolled seizure disorder; 3) contraindication to scalp EEG leads; 4) contraindication to surface factors on the hands or ankle; and 5) no fluency in English prior to the injury.

Healthy subjects (HS) with no history of neurological disease were also enrolled. HS provided written informed consent. For DoC and LIS patients unable to provide consent, surrogate decision-makers provided written informed consent in accordance with a research protocol approved by the Institutional Review Board. Patient assent was also obtained when possible. The protocol was registered on ClinicalTrials.gov (NCT02772302).

2.2. Neurobehavioral Assessment

The CRS-R was used to define each patient's level of consciousness (LoC) as coma (i.e., absence of eye opening or signs of consciousness), VS/UWS (i.e., presence of eye opening without signs of consciousness), MCS (i.e., presence of eye opening and minimal signs of consciousness such as command-following, object recognition or localization, visual pursuit or fixation, automatic non-reflexive motor response, object manipulation, localization to noxious stimulation, intelligible verbalization and/or intentional communication), or emergence from the MCS (i.e., full recovery of consciousness as illustrated by functional object use and/or functional communication). Patients with quadriplegia or severe quadriparesis and limited facial movements were diagnosed as LIS if brain imaging (e.g. head CT and/or brain MRI) did not show cortical injury and if consciousness was confirmed via bedside testing by an attending neurologist experienced in the evaluation of patients with DoC or LIS (e.g. with eye movements, eye blinks, or other limited movements allowing functional communication). The CRS-R was performed immediately prior to BCI system testing.

2.3. Neurophysiological Assessment

2.3.1. EEG data acquisition—We used the mindBEAGLE system during the period from April 2016 to December 2016 (Guger Technologies OG, Austria). The BCI paradigms included are based on the P3 for auditory evoked potentials (AEP) (Schnakers et al., 2008, Schnakers et al., 2009a) and vibrotactile evoked potentials (VTP; (Lugo et al., 2014)), and on sensorimotor rhythms for motor imagery (MoI; (Pfurtscheller et al., 2010, Cruse et al.,

2011, Cruse et al., 2012)). The P3 is a positive deflection in the EEG that is time-locked to salient stimuli presented in an oddball paradigm, occurring between 200 and 500 ms after stimulus onset (Sutton et al., 1965). At the end of each paradigm, the classification accuracy and observed response is displayed on the BCI screen (Figure 1A). An overview of the BCI protocol is shown in Figure 1B.

EEG data were recorded at a sampling rate of 256 Hz with a gUSBamp, using 16 passive electrodes placed by EEG technicians based on the international 10-10 electrode system (reference: right ear lobe; ground: FPz). Electrode positions for AEP, VTP2 and VTP3 were Fz, C3, Cz, C4, CP1, CPz, CP2, Pz and for MoI FC3, FC4, C5, C1, C2, C6, CP3 and CP4 were also used. For patients with intracranial pressure monitors or external ventricular drains, the electrodes were placed as close as possible to the proper electrode location while maintaining standard precautions for avoiding contamination of the percutaneous device. Administration of sedative, anxiolytic, and/or analgesic medications was allowed for patient safety or comfort, at the discretion of the treating clinicians.

2.3.2. Oddball auditory evoked potentials—Four auditory sequences, each consisting of 15 target stimuli (i.e., 500 Hz; 100 ms) and 105 non-target stimuli (i.e., 1000 Hz; 100 ms) with an inter-stimulus interval (ISI) of 900 ms, were presented (total number of targets = 60, total number of non-targets = 420). The subject was verbally instructed to mentally count the number of times the target stimuli appeared in the sequence.

2.3.3. Vibrotactile evoked potentials—Stimuli were delivered using mechanical vibrating tactors fixed to the subject's left and right wrists. The tactors were placed by study staff in coordination with clinical nursing staff to ensure that nearby intravenous and intra-arterial catheters were not disrupted or otherwise affected by the tactors. The tactors were powered by a g.STIMbox that translates the stimulus command from the paradigm into voltage outputs that activate the tactors.

Two different paradigms were administered, the first using two tactors (VTP2), and the second using three tactors (VTP3). For both VTP2 and VTP3, four tactile sequences, each consisting of 15 target stimuli and 105 non-target stimuli (i.e., frequency = 250 Hz, duration = 110 ms, ISI = 300 ms), were presented (total number of targets = 60, total number of non-targets = 420). In VTP2, the tactor delivered nontarget stimuli, e.g. on the left wrist, whereas the tactor on the right wrist delivered target stimuli. The target (i.e., left or right) was randomly selected in the 4 sequences and the participant was informed about the target through the headphones. The subject was instructed to mentally count the number of times the target stimuli appeared in the sequence.

During VTP3, a third tactor was placed on the right ankle. The tactor on the left and right wrists each produced target stimuli, and the patient was asked to concentrate on one (specified, verbally instructed) wrist or the other in a randomized order. The third tactor on the right foot produced the nontarget stimuli (total n = 360; 250 Hz; 110 ms). If the subject achieved a classification accuracy of $\geq 60\%$ the subject was asked two questions taken from the visual (i.e., am I touching my nose right now?) or auditory set (i.e., am I clapping my hands right now) of the CRS-R communication protocol (Giacino et al., 2004)) using the

classifier (see below) built during the assessment. For each question, a sequence was presented (38 sec) and the subject was asked to concentrate on the stimuli on the right wrist to answer “yes” and the stimuli on the left wrist to answer “no”. The BCI provided immediate feedback at the end of the trial. Questions with known answers were selected.

2.3.4. Motor imagery—The subject was instructed to *imagine* opening and closing the left or right hand (see below for motor action) for 6 seconds. One trial started with an attention beep followed by two seconds of silence before the command was played. The subject then had to follow the Left/Right command for six seconds, after which a “relax” command was played, meaning that the trial was over. After a one-second pause, the next trial started. A total of 30 left and 30 right hand trials were presented to the patient in a randomized order. If the subject achieved a classification accuracy of $\geq 64\%$, the subject was asked two questions taken from the visual or auditory CRS-R communication protocol using the classifier built during the assessment. The subject was asked to imagine opening and closing the left hand to answer “yes” or the right hand to answer “no” (8 sec). As with VTP3 communication, the BCI provided immediate feedback at the end of the trial.

2.3.5. Motor action—To assess the reliability of the system to detect sensorimotor rhythms during MoI, we added a paradigm in which the investigator asked the subject to physically open and close the right or left hand (i.e., using the same sequence as MoI) for 6 seconds. This motor action (MoA) paradigm was hypothesized to possibly lead to higher classification accuracies than for the MoI paradigm.

One BCI session was composed of four paradigms (AEP, VTP2, VTP3, MoI, not counting the additional MoA paradigm). When time allowed (maximal time for study administration was 2 hours for the whole session), a second run was administered immediately after the first one, using classifiers built during the first session.

2.4. Classification

For AEP, VTP2 and VTP3, data segments of -100 to 600 ms surrounding each stimulus were extracted. For this period of 700 ms, an average was performed on every 12 samples for each EEG channel, resulting in 15 new sample points. These 120 features (15 new samples $\times$ 8 channels) were classified using linear discriminant analysis (LDA) to distinguish target from non-target stimuli. Trials were grouped in cycles containing 7 nontarget and 1 target trial each. Those cycles were randomly shuffled and 50% were used for training and 50% for testing. Within the pool of testing cycles, the following procedure was performed: the LDA distance is determined between each testing trial and the average of the training target trials; the maximal LDA distance across the 8 testing trials is classified as the ‘target’. If the classified target trial is the trial in which the target was presented, the cycle is considered to be classified correctly (score +1); otherwise, the cycle is considered to be classified incorrectly (no score). Since a cycle contains 7 nontarget trials and one target trial, the chance level of classification is $1/8 = 12.5\%$. Cycles are added using the above method until one reaches the full number of cycles ($n = 30$) in the pool of test-data. The scores are summed up to provide the classification accuracy (e.g., $0/30 = 0\%$, $30/30 = 100\%$). The shuffling and classification were then repeated 10 times and results were

averaged to obtain the assessment accuracy, which is 100% if target and non-target stimuli can be separated perfectly.

To calibrate the system for communication testing, all the data are used to develop a subject-specific classifier. For MoI, the data window 3–5 sec after the instruction were filtered (8–30 Hz) and used to train a common spatial patterns algorithm to automatically weight each electrode based on its contribution to discrimination accuracy. Then the variance of a 1.5 sec time window was calculated, log-transformed and normalized. The classification accuracy was calculated with a 10-fold cross-validation. All the data were used to train a LDA classifier to establish calibration data for future communication runs (Guger et al., 2017).

2.5. Statistical Analyses

To assess the feasibility and safety of deploying bedside EEG-based BCI in the ICU, we recorded 1) adverse events; 2) technical problems; and 3) time required for completion of one session. To investigate the relationship between BCI responses and behavioral signs of consciousness, we calculated the sensitivity (Se) and specificity (Sp) of each paradigm to detect signs of consciousness in DOC using the CRS-R diagnosis as the reference (i.e. unconscious [coma, VS/UWS] vs. minimally conscious [MCS]), and the sensitivity for HS. We did not calculate sensitivity in the one patient with LIS.

A differentiated EEG response (i.e. a positive response), as detected by the BCI, was defined as a classification accuracy exceeding the chance threshold calculated based on a binomial distribution. We calculated the p value and considered a response to be significantly different from chance if it was associated with $p < .05$ ($n = 30$ trials for AEP and VTP; $n = 60$ for MoI and MoA; chance success rate = $1/8$ for AEP and VTP; $1/2$ for MoI and MoA (Combrisson and Jerbi, 2015)). We used a Wilcoxon signed-rank test to compare the MoI and MoA responses. Finally, descriptive statistics were used for basic assessments of communication. We also looked at the association between the level of consciousness (i.e., clinical diagnosis) and BCI responses using Mann-Whitney U tests.

3. Results

3.1. Patient Demographics and Clinical Characteristics

Ten patients were enrolled: 4 in coma, 1 VS/UWS, 4 MCS, 1 LIS; median age = 56 [range 37–72] years; 8 men, median days post-injury 15 [range 3–38]. Two patients received pharmacologic sedation, anxiolysis or analgesia before or during the EEG, similar to the clinically indicated administration of these medications prior to study initiation.

Demographic and clinical data are summarized in Table 1. Ten HS were also enrolled (median age = 34 [range 20–70] years; 6 women) (see Table A.1 in the Appendix). The HS learned about the research through electronic postings.

3.2. Feasibility

A full session was completed in nine patients and all HS. The LIS patient reported tiredness during the session, after completion of VTP3. The average time needed to complete a session (including communication testing, if indicated) was 54 ± 15 minutes for HS and

44±13 minutes for patients. There were no adverse events during the study. In one patient, technical problems (software crash) prevented administration of the MoI paradigm.

3.3. BCI-based responses and behavioral signs of consciousness

In the analyses below, the CRS-R classification is considered “ground truth”. The possibility of the BCI system correctly detecting a level of cortical processing or consciousness greater than that determined by the CRS-R examination is addressed in the discussion.

3.3.1. Oddball auditory evoked potentials—A differentiated EEG auditory oddball response – that is, a difference in the evoked EEG following the target and nontarget stimuli as classified by the LDA method described above, reaching a classification accuracy above chance level– was observed in 3 of 5 unconscious patients (2 coma, 1 VS/UWS) but none of the 4 MCS patients (Se = 0%; Sp = 40%). The LIS and all 10 HS had a differentiated EEG response (HS Se = 100%; see Figure 2 and Table A.1 in the Appendix).

3.3.2. Vibrotactile—For VTP2, 1 of 5 unconscious patients showed a differentiated response (VS/UWS), as did 1 of 4 MCS patients (Se = 25%; Sp = 80%). The LIS patient and all 10 HS had a differentiated EEG response (HS Se = 100%). For VTP3, none of the unconscious patients and none of the MCS patients showed a differentiated EEG response (Se = 0%; Sp = 100%). The LIS patient and 9 of 10 HS had a differentiated EEG response (HS Se = 91%).

3.3.3. Motor imagery—No differentiated response was observed in unconscious patients (both coma) or in MCS patients (Se = 0%; Sp = 100%). The LIS patient did not show a differentiated EEG response; only 2 of 10 HS showed a differentiated response with MI (HS Se = 20%).

3.3.4. Motor action—No differentiated response was observed in the unconscious patients or MCS patients during MoA (Se = 0%; Sp = 100%). Five of the eight HS who completed MoA had differentiated responses (Se = 62.5%). Statistically, the difference between MoI and MoA responses was not significant for patients ($p = 0.89$) or HS ($p = 0.16$). However, four additional HS achieved responses with MoA as compared with MoI (increase in Se from 20% to 62.5%). We did not find a difference in BCI responses between UWS and MCS for any of the paradigms.

A second session was partly administered in nine patients (9 AEP, 8 VTP2, 3 VTP3, 7 MoI, 6 MoA) and six HS (6 AEP, 6 VTP2, 2 VTP3, 3 MoI; see Table A.2 in the Appendix). Completion of the second session was not possible due to time constraints ($n = 13$), technical problems ($n = 9$), technician error ($n = 8$) or patient level of arousal ($n = 1$; the LIS patient requested early discontinuation due to fatigue). Responses during the second session were heterogeneous in both HS and patients, more so in the patient group (Table A.2 in the Appendix). Higher classification accuracies were only observed in one HS during the second session in VTP3 and in one during MoI.

3.4. BCI for Communication in ICU Patients

Using VTP3, 2 of 8 HS who reached a threshold sufficient for communication testing correctly answered both questions. The LIS patient and 4 of 8 HS who reached a threshold sufficient for communication testing correctly answered one of two questions. For the other question, the system provided the wrong response for 4 subjects (LIS and HS), and no response for 1 HS. For the remaining 2 HS, the system provided the wrong response to the first question, and a technician error prevented testing of the second question. None of the unconscious or minimally conscious patients reached a threshold sufficient for communication testing. During the second session, the system indicated the correct answer for one out of two questions for one of the two HS assessed for communication. For the other HS assessed for communication, the system provided the wrong response to the first question and no response to the second question.

Using MoI, 2 HS reached the threshold for communication testing. For 1 HS, the system provided the correct response to both questions. For the other HS, the system provided the correct response to one question and the wrong response to the other question. Neither the DoC patients nor the LIS patient reached a threshold for communication testing using MoI.

4. Discussion

In this study, we examined the feasibility of using a commercially available EEG-based BCI to assess command following in patients with DoC and LIS in the ICU. BCI implementation in the ICU was achieved with assessment of cortical responses to four different tasks in under an hour. The advantage of implementing such a system in the ICU is that it is portable and less expensive (Chatelle et al., 2015) than other techniques that are currently used to detect cortical function, such as fMRI or PET (Laureys and Schiff, 2012). In addition, the “online” BCI system theoretically could provide immediate feedback to the clinician about the patient’s responses and does not require expertise in BCI data processing or analysis, which makes it a candidate for use in a clinical setting.

Overall, the system detected differentiated EEG responses in the HS and the acute LIS patient. Specifically, the oddball AEP, VTP2 and VTP3 paradigms provided a high sensitivity for detecting consciousness in fully conscious subjects (at least 9/10 HS and the LIS patient, $Se = 90\text{--}100\%$). However, the sensitivity of the MoI task was low, as only two out of ten HS had differentiated responses ($Se = 20\%$). In pooled analysis of unconscious and minimally conscious patients (i.e. in the analysis of patients for whom the presence of previously undiscernible communication ability is important to assess), the BCI system had limited sensitivity and specificity for detecting behavioral evidence of consciousness. For example, only one behaviorally responsive MCS patient showed a differentiated response to a paradigm whereas three unconscious patients showed a response.

These findings suggest that the current system could help confirm consciousness in patients with preserved cognitive abilities (i.e. acute LIS), but it is currently not sensitive or specific enough to reliably detect consciousness in severely brain-injured patients with acute DoC. While the low detection rate of differentiated EEG responses in DoC patients without behavioral evidence of consciousness (i.e. coma, VS/UWS) is not surprising, the low

sensitivity observed in minimally conscious DoC patients lowers confidence in the current paradigm and/or classifier's ability to detect consciousness. Restated, given the inconsistency of results across the patient sample, we cannot conclude that the current algorithms provide a robust indicator of consciousness in patients where the pre-test probability of consciousness is low. Alternative hypotheses – that the BCI system was either detecting cortical processing where the CRS-R unknowingly failed, or that the BCI system was refuting consciousness (due to either the absence of EEG response or to the algorithm's determination of EEG non-responsiveness) when the CRS-R demonstrated behaviors consistent with consciousness – would require alternative evidence, such as fMRI.

While reflective of a representative population of people with *acute* DoC, our observations should be considered in light of the specific patient conditions. For example, one MCS patient did not have behavioral signs of language function (i.e. MCS minus (Bruno et al., 2012)). Given that the system relies on language comprehension (i.e. following auditory instructions) to detect consciousness, the system might not be able to detect a differentiated brain response in a low-level MCS patient. Nevertheless, for the 3 MCS patients who did show behavioral evidence of language function (i.e. MCS plus (Bruno et al., 2012)) it remains unclear why the system did not detect evidence of consciousness. A confounding factor could be the administration of dexmedetomidine and oxycodone in one patient diagnosed as MCS, which may have reduced cortical responses, thereby reducing the sensitivity of the system for detecting consciousness. Also, results from the second session demonstrated heterogeneous responses in patients, which could reflect vigilance fluctuation, fatigue, or decreased effort over time (Piarulli et al., 2016). This is supported by the self-reported fatigue expressed by the LIS patient after the three first runs and suggest the need for multiple, shorter testing sessions to decrease the cognitive demand. Fluctuating arousal might not only limit the sensitivity of the system but could also undermine its consistency between sessions because a classifier built based on cortical responses during one session might not be applicable to the same patient in another session. Our findings therefore highlight the importance of considering the complete pattern of responses in an entire BCI session, rather than basing a diagnosis of consciousness on responses during any single paradigm (Fazel-Rezai et al., 2012). Importantly, the majority of the paradigms were based on oddball tasks that do not distinguish between active versus passive cortical responses. This property of oddball paradigms could explain the low specificity observed in DoC patients, as a previous study also reported differentiated brain responses to passive auditory stimuli during oddball paradigms in unconscious patients such as VS/UWS (Perrin et al., 2006).

Our data also provide initial evidence about the types of ICU patients who are most likely to use the device successfully to communicate, and the types of paradigms that might be most effective. Like the majority of HS (8 of 10), the LIS patient achieved results allowing for communication *testing* with VTP. The LIS patient and 6 of 8 HS tested for communication used VTP3 to answer at least one of two yes-or-no questions correctly. However, of these 7 subjects, the system provided the wrong answer to a second question in 5 subjects (LIS and 4 HS) and an inconclusive answer in 1 HS. Only 2 HS reached results allowing for communication *testing* with MoI. One of them correctly answered both questions whereas the other provided one correct and one incorrect answer. Overall, these VTP and MoI

communication results suggest that the system's accuracy for communication in conscious subjects, at least as tested under the time constraints of this ICU-feasible protocol, is currently limited.

None of the DoC patients with behavioral signs of consciousness (i.e. MCS) met the thresholds for communication testing. The difference observed in the LIS patient's ability to use VTP3 versus MoI to communicate may be explained by the fact that the VTP3 is based on a brain response triggered by exogenous stimulation whereas MoI, which is based on sensorimotor rhythms modulation, relies on the patient's ability to modulate his/her brain responses. Our data are consistent with previous studies suggesting that paradigms based on the P3 response, such as VTP3, are more appropriate for short-term assessment and communication than the EEG-recorded signals collected during a MoI paradigm. Prior studies have shown that P3-based paradigms do not require subject training and offer stable performance rates over time in motor disabled populations (Nijboer et al., 2008), whereas sensorimotor rhythms modulation has to be learned in a majority of subjects (Guger et al., 2003, Guger et al., 2009, Nijboer et al., 2010).

The main limitations of this study are its small sample size and single-center design, which limit its generalizability. Furthermore, the heterogeneity in responses detected by EEG-BCI – both between subjects with the same LoC and between paradigms in individual subjects – underscores the need for future studies to elucidate the mechanisms underlying response variability in patients with DoC and LIS. Since we aimed to test the feasibility of completing a single BCI session, we were not able to assess the effect of training on responses detected by BCI, which may be particularly helpful for the MoI paradigm (Guger et al., 2017). Given the time constraints inherent to diagnostic testing in the ICU, we only administered 2 questions to test for communication, which may be insufficient for a comprehensive assessment of a patient's potential for communication. Administration of additional questions would likely have provided a more accurate estimate of each patient's potential for communication using these paradigms. Finally, we used a binomial test as we thought it is the best option to define significant responses in these data, though it provides an optimistic lower bound of significance levels (Combrisson and Jerbi, 2015). A critical question that remains to be answered is how to choose an optimal statistical threshold for defining a BCI response as being consistent with volitional brain activity, and hence consciousness.

5. Conclusions

A commercially available EEG-based BCI is feasible to deploy for the assessment of severely brain-injured patients in the ICU, with most patients being able to complete BCI testing in less than one hour. The BCI system tested here may confirm consciousness in acute LIS, but the system was not reliable for assessing consciousness in acute DoC. Implementing multiple, briefer assessment sessions in future studies may help to avoid the effects of fluctuating arousal, which can confound the ability of EEG-based BCI to detect command-following in critically ill patients with acute severe brain injuries. Additional technical developments, paradigm optimization, and statistical threshold assessments are needed before such systems can be considered for clinical use.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank Damien Lesenfants and David Brandman for helpful statistical advice and Joseph Cohen and Courtney Michell for placing EEG leads on the patients and healthy subjects. We are grateful to the patients and their families for participating in the study. This research was supported by a clinical research grant from Guger Technologies OG (Austria) to Massachusetts General Hospital. The study was also supported by the NIH National Institute of Neurological Disorders and Stroke (K23NS094538), American Academy of Neurology/American Brain Foundation, James S. McDonnell Foundation, Massachusetts General Hospital Department of Neurology and Division of Neurocritical Care and Emergency Neurology.

Abbreviations

AEP	Auditory evoked potentials
BCI	Brain computer interface
CRS-R	Coma Recovery Scale-Revised
DoC	Disorders of consciousness
HS	Healthy subjects
ICU	Intensive care unit
LIS	Locked-in syndrome
LoC	Level of consciousness
MCS	Minimally conscious state
MoI	Motor imagery
VS/UWS	Vegetative state/unresponsive wakefulness syndrome
VTP2	Vibrotactile evoked potentials – 2 tactors
VTP3	Vibrotactile evoked potentials – 3 tactors

References

- Andrews K, Murphy L, Munday R, Littlewood C. Misdiagnosis of the vegetative state: retrospective study in a rehabilitation unit. *BMJ*. 1996; 313:13–6. [PubMed: 8664760]
- Bruno MA, Majerus S, Boly M, Vanhaudenhuyse A, Schnakers C, Gosseries O, et al. Functional neuroanatomy underlying the clinical subcategorization of minimally conscious state patients. *J Neurol*. 2012; 259:1087–98. [PubMed: 22081100]
- Chatelle C, Lesenfants D, Guller Y, Laureys S, Noirhomme Q. Brain computer interface for assessing consciousness in severely brain-injured patients. In: Rossetti A, Laureys S, editors *Clinical Neurophysiology in Disorders of Consciousness* Wien Springer; 2015
- Combrisson E, Jerbi K. Exceeding chance level by chance: The caveat of theoretical chance levels in brain signal classification and statistical assessment of decoding accuracy. *J Neurosci Methods*. 2015; 250:126–36. [PubMed: 25596422]

- Cruse D, Chennu S, Chatelle C, Bekinschtein T, Fernández-Espejo D, Junqué C, et al. Bedside detection of awareness in the vegetative state. *The Lancet*. 2011; 378:2088–94.
- Cruse D, Chennu S, Chatelle C, Fernandez-Espejo D, Bekinschtein TA, Pickard JD, et al. Relationship between etiology and covert cognition in the minimally conscious state. *Neurology*. 2012; 78:816–22. [PubMed: 22377810]
- De Massari D, Ruf CA, Furdea A, Matuz T, van der Heiden L, Halder S, et al. Brain communication in the locked-in state. *Brain*. 2013; 136:1989–2000. [PubMed: 23625062]
- Edlow BL, Chatelle C, Spencer CA, Chu CJ, Bodien YG, O'Connor KL, et al. Early detection of consciousness in patients with acute severe traumatic brain injury. *Brain*. 2017; 140:2399–414. [PubMed: 29050383]
- Fazel-Rezai R, Allison BZ, Guger C, Sellers EW, Kleih SC, Kubler A. P300 brain computer interface: current challenges and emerging trends. *Front Neuroeng*. 2012; 5:14. [PubMed: 22822397]
- Giacino JT, Ashwal S, Childs N, Cranford R, Jennett B, Katz DI, et al. The minimally conscious state: definition and diagnostic criteria. *Neurology*. 2002; 58:349–53. [PubMed: 11839831]
- Giacino JT, Kalmar K, Whyte J. The JFK Coma Recovery Scale-Revised: measurement characteristics and diagnostic utility. *Arch Phys Med Rehabil*. 2004; 85:2020–9. [PubMed: 15605342]
- Gosseries O, Pistoia F, Charland-Verville V, Carolei A, Sacco S, Laureys S. The Role of Neuroimaging Techniques in Establishing Diagnosis, Prognosis and Therapy in Disorders of Consciousness. *Open Neuroimag J*. 2016; 10:52–68. [PubMed: 27347265]
- Guger C, Daban S, Sellers E, Holzner C, Krausz G, Carabalona R, et al. How many people are able to control a P300-based brain-computer interface (BCI)? *Neurosci Lett*. 2009; 462:94–8. [PubMed: 19545601]
- Guger C, Edlinger G, Harkam W, Niedermayer I, Pfurtscheller G. How many people are able to operate an EEG-based brain-computer interface (BCI)? *IEEE Trans Neural Syst Rehabil Eng*. 2003; 11:145–7. [PubMed: 12899258]
- Guger C, Spataro R, Allison BZ, Heilinger A, Ortner R, Cho W, et al. Complete Locked-in and Locked-in Patients: Command Following Assessment and Communication with Vibro-Tactile P300 and Motor Imagery Brain-Computer Interface Tools. *Front Neurosci*. 2017; 11:251. [PubMed: 28529473]
- Laureys S, Schiff ND. Coma and consciousness: paradigms (re)framed by neuroimaging. *Neuroimage*. 2012; 61:478–91. [PubMed: 22227888]
- Lovstad M, Frosli KF, Giacino JT, Skandsen T, Anke A, Schanke AK. Reliability and diagnostic characteristics of the JFK coma recovery scale-revised: exploring the influence of rater's level of experience. *J Head Trauma Rehabil*. 2010; 25:349–56. [PubMed: 20142758]
- Lugo ZR, Rodriguez J, Lechner A, Ortner R, Gantner IS, Laureys S, et al. A vibrotactile p300-based brain-computer interface for consciousness detection and communication. *Clin EEG Neurosci*. 2014; 45:14–21. [PubMed: 24415400]
- Lule D, Noirhomme Q, Kleih SC, Chatelle C, Halder S, Demertzi A, et al. Probing command following in patients with disorders of consciousness using a brain-computer interface. *Clin Neurophysiol*. 2013; 124:101–6. [PubMed: 22920562]
- Majerus S, Bruno MA, Schnakers C, Giacino JT, Laureys S. The problem of aphasia in the assessment of consciousness in brain-damaged patients. *Prog Brain Res*. 2009; 177:49–61. [PubMed: 19818894]
- Mayaud L, Cabanilles S, Van Langenhove A, Congedo M, Barachant A, Pouplin S, et al. Brain-computer interface for the communication of acute patients: a feasibility study and a randomized controlled trial comparing performance with healthy participants and a traditional assistive device. *Brain-Computer Interfaces*. 2016; 3:197–215.
- Monti MM, Vanhaudenhuyse A, Coleman MR, Boly M, Pickard JD, Tshibanda L, et al. Willful modulation of brain activity in disorders of consciousness. *N Engl J Med*. 2010; 362:579–89. [PubMed: 20130250]
- Nijboer F, Birbaumer N, Kubler A. The influence of psychological state and motivation on brain-computer interface performance in patients with amyotrophic lateral sclerosis - a longitudinal study. *Front Neurosci*. 2010; 4:doi: 10.3389/fnins.2010.00055 [PubMed: 20582258]

- Nijboer F, Sellers EW, Mellinger J, Jordan MA, Matuz T, Furdea A, et al. A P300-based brain-computer interface for people with amyotrophic lateral sclerosis. *Clin Neurophysiol.* 2008; 119:1909–16. [PubMed: 18571984]
- Owen AM, Coleman MR, Boly M, Davis MH, Laureys S, Pickard JD. Detecting Awareness in the Vegetative State. *Science.* 2006; 313:1402. [PubMed: 16959998]
- Perrin F, Schnakers C, Schabus M, Degueldre C, Goldman S, Bredart S, et al. Brain response to one's own name in vegetative state, minimally conscious state, and locked-in syndrome. *Arch Neurol.* 2006; 63:562–9. [PubMed: 16606770]
- Pfurtscheller G, Allison BZ, Brunner C, Bauernfeind G, Solis-Escalante T, Scherer R, et al. The hybrid BCI. *Front Neurosci.* 2010; 4:30.
- Piarulli A, Bergamasco M, Thibaut A, Cologan V, Gosseries O, Laureys S. EEG ultradian rhythmicity differences in disorders of consciousness during wakefulness. *J Neurol.* 2016; 263:1746–60. [PubMed: 27294259]
- Pokorny C, Klobassa DS, Pichler G, Erlbeck H, Real RG, Kubler A, et al. The auditory P300-based single-switch brain-computer interface: paradigm transition from healthy subjects to minimally conscious patients. *Artif Intell Med.* 2013; 59:81–90. [PubMed: 24076342]
- Schnakers C, Perrin F, Schabus M, Hustinx R, Majerus S, Moonen G, et al. Detecting consciousness in a total locked-in syndrome: an active event-related paradigm. *Neurocase.* 2009a; 15:271–7. [PubMed: 19241281]
- Schnakers C, Perrin F, Schabus M, Majerus S, Ledoux D, Damas P, et al. Voluntary brain processing in disorders of consciousness. *Neurology.* 2008; 71:1614–20. [PubMed: 19001251]
- Schnakers C, Vanhaudenhuyse A, Giacino J, Ventura M, Boly M, Majerus S, et al. Diagnostic accuracy of the vegetative and minimally conscious state: clinical consensus versus standardized neurobehavioral assessment. *BMC Neurol.* 2009b; 9:35. [PubMed: 19622138]
- Sutton S, Braren M, Zubin J, John ER. Evoked-potential correlates of stimulus uncertainty. *Science.* 1965; 150:1187–8. [PubMed: 5852977]

Highlights

- We tested a commercial EEG-based brain-computer interface in the intensive care unit.
- The system confirmed consciousness in an acute locked-in patient.
- The system was unreliable in patients with acute disorders of consciousness.

Figure 1. EEG-based brain-computer interface assessment in the intensive care unit

(A) Photo of patient 1 (P1) undergoing EEG-based BCI assessment in the intensive care unit. (B) Schematic of a session. Abbreviations: EVD = external ventricular drain; A-line = arterial line.

Figure 2. Classification accuracies (%) in patients and healthy subjects

For patients, bars represent the classification accuracy obtained for a paradigm. In healthy subjects, the bar represents the mean classification accuracy observed for the group with the standard deviation. The horizontal red line represents the threshold used to determine communication testing (i.e., 60% for VTP3 and 64% for MoI).

Table 1

Demographics, clinical information and classification accuracies observed for each patient during each paradigm.

ID	Age	Sex	Mechanism of injury	Days since injury	Invasive Catheters, Lines, Tubes	Sedation	CRS-R Subscale Scores	LoC	AEP	VTP2	VTP3	MoI	MoA
P4	57	M	Hemispheric ICH with uncal herniation	5	ETT, OGT, CVC, a-line	none	A0V0M0O0C0Ar0	Coma	0.0%	10.0%	20.0%	52.3%	54.3%
P6	71	M	Brainstem ICH	15	Trach, NTG, CVC	none	A0V1M1O0C0Ar0	Coma	25.0%	10.0%	10.0%	61.7%	37.0%
P10	37	F	HIE	15	Trach, NGT, CVC, a-line	none	A0V0M1O1C0Ar0	Coma	100% ***	0.0%	0.0%	61.2%	-
P8	71	M	Cerebellar ICH with brainstem compression, IVH, hydrocephalus	6	EVD, ETT, OGT, CVC, a-line	none	A0V0M1O1C0Ar0	Coma	30.0% **	0.0%	20.0%	56.0%	49.0%
P1	72	M	Cerebellar ICH with brainstem compression, IVH, hydrocephalus	38	EVD, Trach (vent), PEG, CVC, PICC, a-line	none	A1V1M0O1C0Ar2	VS/UWS	30.0% **	70.0% ***	0.0%	-	0.0%
P5	49	M	TBI	6	EVD, ETT, OGT, CVC, a- line	Dexmedetomidine 0.4 mcg/kg/hr, fentanyl 1/5 mcg/hr	A0V0M3O0C0Ar0	MCS	5.0%	0.0%	10.0%	44.5%	55.8%
P2	56	M	PRES, Hypoxia	22	Trach, PEG, PICC, a-line	none	A3V0M3O2C0Ar2	MCS	10.0%	10.0%	0.0%	48.0%	45.3%
P7	57	M	Hypoxia, multifocal bihemispheric ischemic strokes	28	Trach, PEG, PICC, a-line	none	A3V2M4O2C0Ar2	MCS	10.0%	55.0% ***	20.0%	59.8%	49.3%
P9	41	M	TBI	19	Trach, NGT, PICC	Dexmedetomidine 1.2 mcg/kg/hr, oxycodone 5 mg	A3V3M5O3C1Ar1	MCS	15.0%	0.0%	20.0%	39.5%	61.3%
P3	56	F	Brainstem ischemic stroke	3	ETT, OGT, CVC, a-line	none	A4V5M-O2C2Ar3	LIS	80.0% ***	100% ***	100% ***	41.7%	48.3%

Numbers highlighted in bold represent classification accuracies above chance level (* = p < .05, ** p < .01, *** p < .001).

Abbreviations: CRS-R = Coma Recovery Scale-Revised; subscales for the CRS-R are Auditory Function (A), Visual Function (V), Motor Function (M), Oromotor Function (O), Communication (C), and Arousal (Ar). F = female; M = male.

LoC = Level of Consciousness

Mechanism of injury: ICH = intracerebral hemorrhage; HIE= hypoxic-ischemic encephalopathy; IVH= intraventricular hemorrhage; TBI= traumatic brain injury; PRES = posterior reversible encephalopathy syndrome.

Paradigms: - = Paradigm not administered.