Trends in BCI Research I: Brain-Computer Interfaces for Assessment of Patients with Locked-in Syndrome or Disorders of Consciousness

Christoph Guger, Damien Coyle, Donatella Mattia, Marzia De Lucia, Leigh Hochberg, Brian L. Edlow, Betts Peters, Brandon Eddy, Chang S. Nam, Quentin Noirhomme, Brendan Z. Allison and Jitka Annen

1 Introduction

Brain-computer interface (BCI) technology analyzes brain activity to control external devices in real time. In addition to communication and control applications, BCI technology can also be used for the assessment of cognitive functions of patients with disorders of consciousness (DOC) or locked-in syndrome (LIS) [1, 2, 3]; (Ortner et al., in press). The top-right corner of Fig. 1 reflects healthy persons with normal motor responses and cognitive functions. On the bottom-left corner are coma patients without these functions. Patients in the unresponsive wakefulness

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C. Guger (✉) · B.Z. Allison
g.tec Guger Technologies OG, Herbersteinstrasse 60, 8020 Graz, Austria
e-mail: guger@gtec.at

D. Coyle
Faculty of Computing and Engineering, School of Computing and Intelligent Systems,
Magee Campus, Ulster University, Northland Road, Derry, Northern Ireland BT48 7JL, UK

D. Mattia
Neuroelectrical Imaging and BCI Lab, Fondazione Santa Lucia, IRCCS, Via Ardeatina, 306,
00179 Rome, Italy

M. De Lucia
Laboratoire de Recherche en Neuroimagerie (LREN), Department of Clinical Neurosciences,
Lausanne University Hospital (CHUV) and University of Lausanne, chemin de Mont-Paisible
16, 1011 Lausanne, Switzerland
e-mail: marzia.de-lucia@chuv.ch

L. Hochberg · B.L. Edlow
Department of Neurology, Massachusetts General Hospital, 175 Cambridge Street, Boston,
MA 02114, USA

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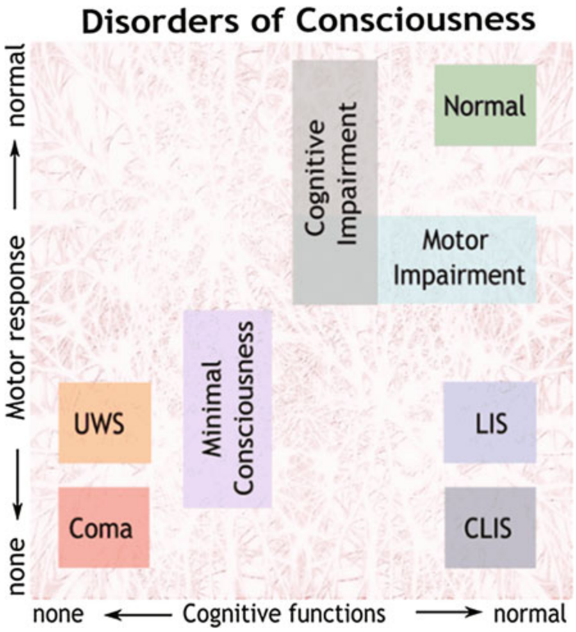


Fig. 1 Motor responses and cognitive functions for coma, unresponsive wakefulness state (UWS), minimally consciousness state (MCS), locked-in syndrome (LIS), complete locked-in syndrome (CLIS)

state (UWS) and minimally consciousness state (MCS) may have conscious awareness but no way to convey their awareness through any kind of movement. These patients should be carefully assessed to make sure that physicians, families and caregivers are aware of their cognitive functions. Cognitive assessment is also important for individuals with LIS, particularly CLIS (complete LIS), to understand which cognitive functions are remaining. Assessment may reveal whether patients understand instructions and conversations, and whether they may be able to communicate.

B. Peters · B. Eddy
Oregon Health & Science University, 707 SW Gaines St, #1290,
Portland, OR 97239, USA

C.S. Nam
Brain-Computer Interface (BCI) Lab, North Carolina State University,
Raleigh NC 27695, USA

Q. Noirhomme · J. Annen
Coma Science Group, GIGA Research and Neurology Department, University
Hospital of Liège, Liège, Belgium

People with locked-in syndrome (LIS) exhibit quadriplegia and anarthria, but may retain some voluntary movement of the eyes, eyelids, or other body parts. LIS is not a DOC, as persons with LIS are both conscious and aware. However, people with CLIS have no voluntary motor function and are thus unable to communicate or respond to behavioral testing, leading to frequent and often prolonged misdiagnosis [2, 4]. While people with CLIS may retain relatively normal cognitive functioning, shown in Fig. 1, their cognitive abilities and conscious awareness may also be impaired for various reasons. Furthermore, since people with CLIS cannot move or communicate, they may be unable to inform doctors, family and friends that they are in fact able to understand them and wish to play an active role in decisions affecting their lives.

The potential of BCI technology to support more accurate and detailed differential diagnosis among DOC and LIS patients is also apparent from the strong recent interest from the BCI community. In addition to numerous publications from different groups (reviewed in 2), there was considerable interest in this topic at the Sixth International BCI Meeting in 2016, including a workshop and day-long Satellite Event that presented the latest advances. In 2017 alone, this topic has been or will be presented in at least a dozen major conferences to our knowledge, including the Seventh International BCI Conference, Society for Neuroscience annual conference, and Human-Computer Interaction International (HCII) annual conference. This research direction was also recognized in our most recent book in this series [3].

Thus, the use of BCI technology for improved diagnosis and related goals for persons with DOC and LIS has become a prominent trend within the BCI research community. The primary goal of this article is to summarize new research results from several top groups in this field, along with commentary and future directions. First, we describe a commonly used platform for DOC assessment and communication called mindBEAGLE.

2 DOC Assessment and Communication Platform from g.tec

Some of the results presented here used the mindBEAGLE system. mindBEAGLE is an electro-physiological test battery for DOC and LIS patients that can use four approaches to assess conscious awareness: (i) auditory evoked potentials (AEP); (ii) vibro-tactile evoked potentials with 2 tactors—VT2; (iii) vibro-tactile evoked potentials with 3 tactors—VT3 and (iv) motor imagery (MI). The system consists of a biosignal amplifier, an EEG cap with active electrodes, the BCI software that analyzes the data in real-time, in-ear phones for the auditory stimulation, and 3 vibro-tactile stimulators (tactors). In the AEP approach, a sequence of low (non-target) and high (target) tones is presented to the patient and evoked potentials are calculated. The BCI classifier attempts to identify the target tone based on EEG data, leading to accuracies between 0 and 100%. Chance accuracy in this task is 12.5%, and the threshold for significant communication depends on the number of trials, but high accuracy may reflect conscious awareness. In the VT2 approach, one tactor is mounted on the right hand (target) and receives 10% of the stimuli and one tactor is mounted on the left hand and receives 90% of the stimuli (non-target). Then the patient has to silently count the right hand stimuli to elicit a P300 response that the BCI system can detect. In the VT3 approach, one tactor is mounted on the left hand (10% of stimuli), one tactor is mounted on the right hand (10% of stimuli) and one tactor is mounted on the spine or leg (80% of the stimuli) [5, 6]. Now the patient can count the stimuli on the left hand to say YES and can say NO by counting right hand stimuli. The motor imagery paradigm verbally instructs the patient to imagine either left or right hand movements and the BCI system classifies the data [7].

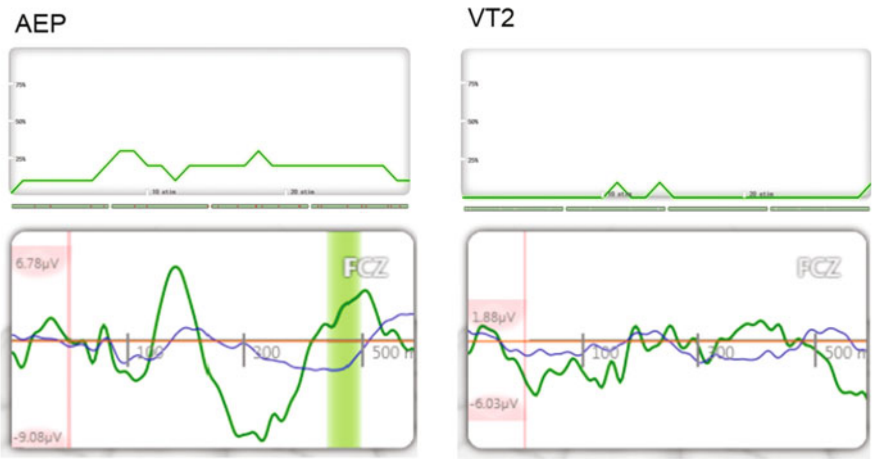
The top of Fig. 2 shows results for an UWS patient with no reliably discriminable Evoked Potentials (EPs) and a very low BCI accuracy for AEP and VT2 testing. Although this patient shows some differences in the EPs, the intertrial variability was very high. The bottom of Fig. 2 shows the results for an MCS- patient, which look like results from a healthy control. These results indicate that this MCS- patient could follow the experimenter's instructions, and thus is able to understand conversations.

After a successful assessment run, mindBEAGLE can also be used for communication. In this case, the patient is asked a question and can answer YES or NO by attending to vibrations of either the left or right tactor. Similarly, the patient can use the MI approach by imagining a left or right hand movement to say YES and NO.

The testing battery gives important information about a patient's cognitive functions and ability to follow conversations. Furthermore, it can allow communication and identify fluctuations in cognitive function. Of special importance is that mindBEAGLE provides a standardized approach for testing patients. Currently the system is being validated in 10 centers in China, Germany, Austria, Italy, Belgium, France, Spain and the USA.

One related direction that was very recently published extended mindBEAGLE technology to provide communication for persons with complete locked-in syndrome (CLIS). We showed that two of three patients with CLIS could communicate using the mindBEAGLE system [8]. This is an exciting development, because BCI technology had not yet been well validated with persons with CLIS. Consistent with the results presented above, the MI approach was not effective in the CLIS patients, but vibrotactile approaches were. We are now working with additional patients and considering new paradigms to improve communication.

UWS patient



MCS patient

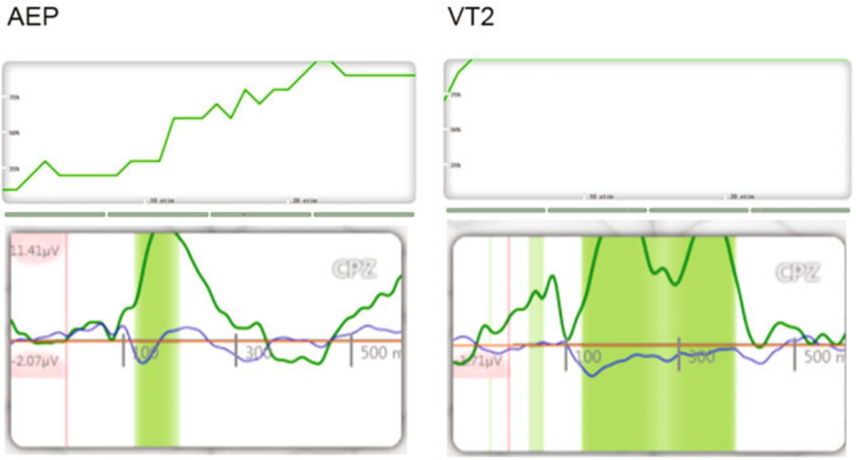


Fig. 2 AEP and VT2 results for one UWS (unresponsive wakefulness state) and one MCS (minimally conscicousness state) patient. The top curve shows the classification accuracy on the y-axis and the number of target stimuli on the x-axis. The bottom curve shows the EPs for target (*green*) and non-target (*blue*) stimuli. *Green* shaded areas reflect a significant difference between target and non-target EPs

3 DOC Assessment at Ulster

Initial research at Ulster [9] reported successful results with BCI-based motor imagery (MI) training in a patient who had MCS using sensorimotor rhythm (SMR) feedback. This result suggested that feedback could raise patients' awareness about the potential for BCI technology to impact their conditions, and could be effective in a detection of awareness protocol involving motor imagery BCIs. Subsequently, four MCS patients (3 male; age range, 27–53 yr; 1–12 yr after brain injury) participated in multiple sessions with sensorimotor rhythm (SMR) feedback, to determine whether BCI technology can be used to increase the discriminability of SMR modulations [10, 11]. The study had three objectives: (1) To assess awareness in subjects in MCS (initial assessment); (2) To determine whether these subjects may learn to modulate SMR with visual and/or stereo auditory feedback (feedback sessions) and (3) To investigate musical feedback for BCI training and as cognitive stimulation/interaction technology in disorders of consciousness (DOC). Initial assessment included imagined hand movement or toe wiggling to activate sensorimotor areas and modulate SMR in 90 trials, following the protocol described in [12]. Within-subject and within-group analyses were performed to evaluate significant brain activations. A within-subject analysis was performed involving multiple BCI training sessions to improve the user's ability to modulate sensorimotor rhythms through visual and auditory feedback. The sessions took place in hospitals, homes of subjects, and a primary care facility. Awareness detection was associated with sensorimotor patterns that differed for each motor imagery task. BCI performance was determined from mean classification accuracy of brain patterns using a BCI signal processing framework with a leave-one out cross-validation [10]. All subjects demonstrated significant and appropriate brain activation during the initial assessment without feedback. SMR modulation was observed in multiple sessions with auditory and visual feedback. Figure 3 shows results for subject E (19 sessions), showing that accuracy improves over time with auditory but not visual feedback.

In conclusion, the EEG-based assessment showed that patients who had MCS may have the capacity to operate a simple BCI-based communication system, even without any detectable volitional control of movement. All EEG-based awareness detection studies prior to this research did not provide real-time feedback to the patient during the assessment. This research was the first to demonstrate stereo auditory feedback of SMR in MCS patients, allowing the patient to hear the target and feedback, which could be useful in patients who cannot use visual feedback. As many DOC patients have limited eye gaze control and/or other visual system impairments, visual feedback is often unsuitable for them. We used musical auditory feedback in the form of a palette of different musical genres. This enabled us to open a dialogue with the care teams/families on musical preference, discussed in the presence of the patient, to enhance attentiveness and engagement. Anecdotal evidence indicates that musical feedback could help engage DOC sufferers during BCI training and improve BCI performance. A quote from one of the families of participants in our study is published in a recent report [13].

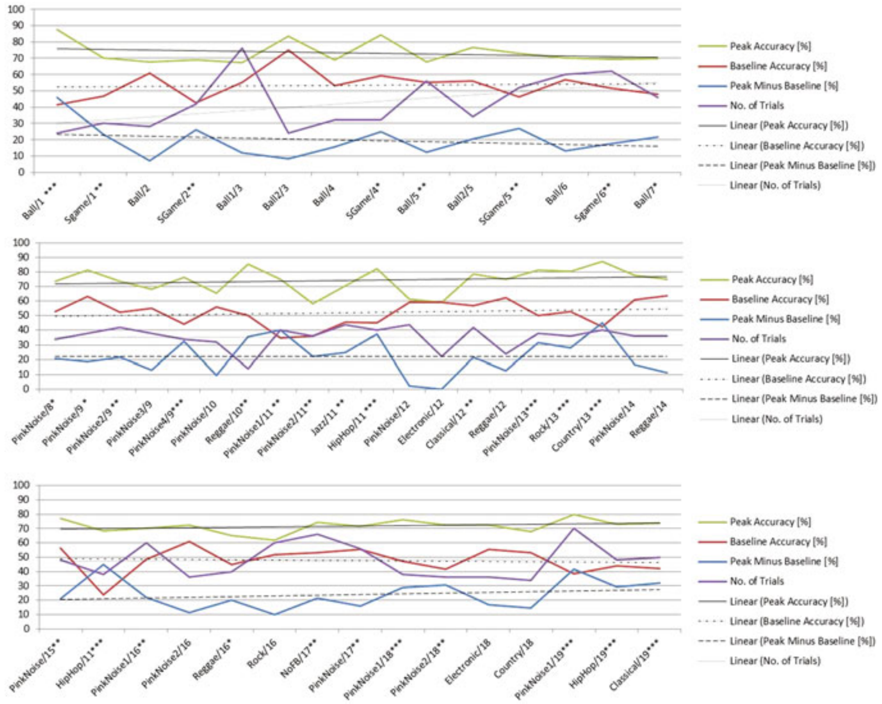


Fig. 3 BCI accuracy for patient E with MCS. *Top row* BCI accuracy with visual feedback (moving ball or computer game) and baseline accuracy without feedback. *Middle and bottom row* BCI accuracy with auditory feedback (pink noise, reggae, jazz, hip hop, electronic music, classical music, rock, country,…) and baseline accuracy without feedback. The number of trials in each run after artifact rejection are indicated after the type of feedback (*pink* noise, hip hop,…). Significant differences between baseline and feedback is indicated with the following notation: ***$P \leq .005$; **$P \leq .05$; *$P \leq .1$

4 DOC Neurophysiological Assessment at FSL

The stability of Event-Related Potentials (ERPs) is essential for efficient and effective ERP-based BCI systems, especially when BCIs is applied in a challenging clinical condition such as DOC. In this regard, there are several factors that can limit (if not prevent) the use of BCI technology in patients diagnosed with DOC such as fluctuations of vigilance, attention span and abnormal brain activity due to brain damage (Giacino et al. [21]) to name few. In a recent study conducted at Fondazione Santa Lucia (Rome), Aricò and colleagues [14] showed a significant correlation between the magnitude of the jitter in P300 latency and the performance achieved by healthy subjects in controlling a visual covert attention P300-based BCI. In particular, the higher the P300 latency jitter, the lower the BCI accuracy. We speculated that the covert attention modality increases the variability of the time needed to perceive and categorize the visual stimuli.

Currently, we are conducting a neurophysiological (EEG) screening in patients with DOC or functional looked-in syndrome (LIS) who are consecutively admitted at the Post-Coma Unit of the Fondazione Santa Lucia for their standard care rehabilitation. As part of this neurophysiological screening, patients are presented with a simple auditory P300 oddball paradigm, which consists of a binaural stream of 420 standard high tones (440 + 880 +1760 Hz) and 60 deviant complex low tones (247 + 494 + 988 Hz) pseudo-randomly interspersed (50 ms stimulus duration; 850 ms inter stimulus interval). Stimuli are first presented in a passive condition (just listening to auditory stimuli) and then in an active condition (mentally counting the deviant tones). EEG signals are recorded from 31 electrode positions (512 Hz sample rate) with a commercial EEG system. A preliminary (retrospective) analysis of the morphological features (amplitude and latency) of the main ERP waveforms (on Cz) was performed on a convenient sample of 13 admitted DOC patients (9 males; mean age = 47 ± 16; mean time from event = 24 ± 33.5; 5 unresponsive wakefulness state - UWS; 8 Minimally Conscious State - MCS) in their subacute and chronic stages. A wavelet transform method was applied to identify the P300 waveform peak in single trials and thus to assess the magnitude of latency jitter phenomenon [14]. We found significantly higher values of P300 jittering in UWS and MCS patients compared to a control (12 healthy subjects; 6 males; mean age = 30.3 ± 6.5) data set ($p < .01$), for both active and passive paradigms. Moreover, UWS patients showed significantly higher jitter values compared to MCS patients ($p < .01$) and to the control group ($p < .001$) in the active condition. The MCS data also exhibited a significantly higher jitter ($p < .05$) compared to control data set. A representative case is illustrated in Fig. 4. These preliminary findings prompted us to apply this analysis in a larger cohort of DOC patients to validate this measurement as indicative of different DOC states.

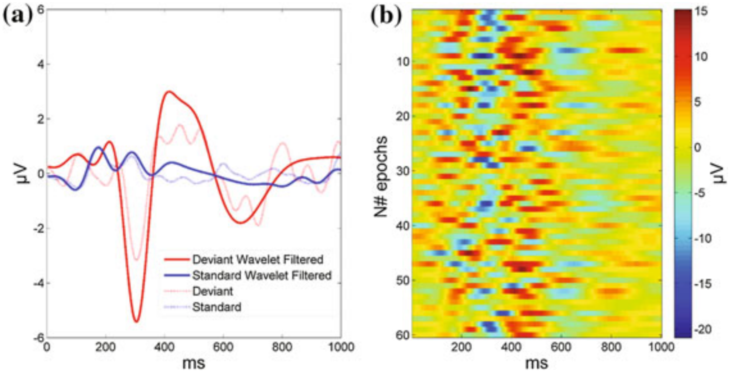


Fig. 4 Data from a representative MCS patient (male, 54 years old, 11 months after a traumatic brain injury). **a** Average of epochs related to deviant (*red*) and standard (*blue*) stimuli. *Solid lines* and *dotted lines* reflect the wavelet filtered and non-filtered potentials, respectively. **b** Single trial epochs associated with deviant stimuli filtered with the wavelet based method. In this case, the P300 peaks exhibited a range of latencies between 350 and 500 ms

Promisingly, we also found a significant negative correlation ($r = -.055$, $p < .05$) between the jitter values observed during the active listening condition in both UWS and MCS patients and the relative JFK Coma Recovery Scale-Revised (CRS-r) scores, that is, patients with lower CRS-r scores had higher jitter values [15].

5 DOC Prediction CHUV

Early prediction of comatose patients' outcome is currently based on a battery of clinical examinations that are repeatedly performed during the first days of coma (Rossetti et al., 2010). This includes the evaluation of brain stem reflexes, the motor response, and the electroencephalographic recordings while stimulating patients with arousing stimuli. All these examinations are highly predictive of poor outcome, i.e. death or vegetative state. In this context, the development of markers identifying patients with good outcomes remains challenging. Recently, the neural responses to auditory stimuli as measured by electroencephalography (EEG) over the first days of coma provided promising results for predicting patients' chance of surviving (Tzovara et al., 2013). This test consists of recording EEG responses to auditory stimuli during the first and second days of coma using a classic mismatch negativity (MMN) paradigm, in which a sequence of identical sounds is rarely (30% of the time) interrupted by a sound that differs from the standard stimulus in terms of pitch, location or duration. The differential response to standard and deviant sounds is measured via a single-trial decoding algorithm, and its performance is evaluated using the area under the Receiver Operating Characteristic (AUC) (Tzovara et al., 2012). The higher the value of the AUC, the more accurate the auditory discrimination between standard and deviant sounds. The test showed that an improvement in auditory discrimination between the first and second days of coma is only observed in survivors. Remarkably, the auditory discrimination per se during the first or second recording was not as predictive as the progression. The test has been extensively validated in a cohort of postanoxic comatose patients treated with therapeutic hypothermia, including 94 individuals (Tzovara et al., 2016). Results (see Fig. 5) showed a positive predictive power of 93%, with 95% confidence interval 5 0.77–0.99 when excluding comatose patients with status epilepticus either during the first or the second day of coma.

In addition to the prediction of awakening, recent results revealed that the progression of auditory discrimination during coma provides early indication of future recovery of cognitive functions in survivors (Juan et al., 2016). Current validation is ongoing in other comatose patients treated with different therapeutic strategies and at multiple hospital sites. This test will be further used in a longitudinal study targeting patients who exhibit an improvement in auditory discrimination but do not wake up within the first days or weeks after coma onset. These patients could first regain a minimal level of consciousness before waking up, and

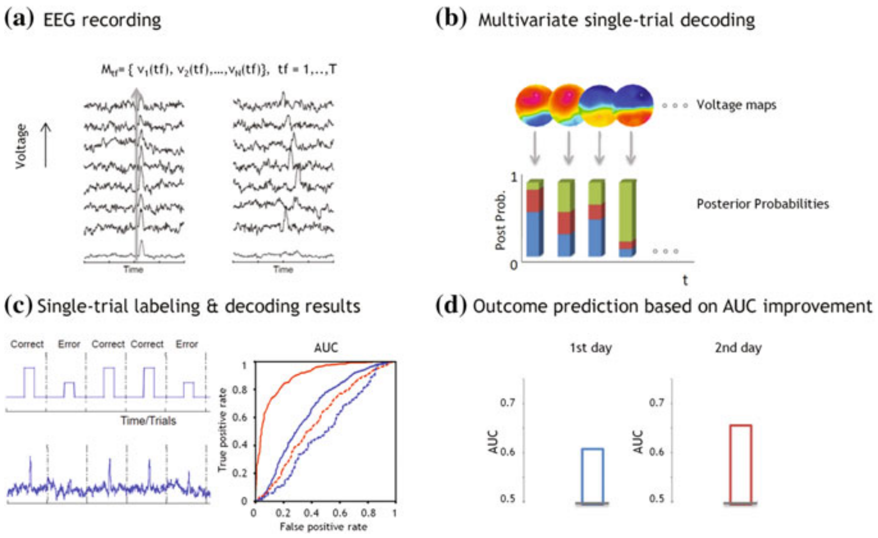


Fig. 5 Schematic representation of the EEG based test for predicting comatose patients' chance of awakening. **a**. Neural responses to standard and deviant sounds during an MMN paradigm are recorded through a clinical EEG at comatose patient's bedside. EEG measurements are represented as a vector of voltage measurements across the whole electrode montage. **b**. Time-point by time-point voltage topographies are modeled based on a mixture of Gaussians distribution, and the corresponding posterior probabilities are used for labeling EEG single-trials as belonging to standard or deviant sounds' responses. **c**. The performance of the decoding algorithm is quantified using the area under the Receiver Operating Characteristic (AUC), performed separately for each recording and patient. The AUC value is indicative of the auditory discrimination at a neural level. **d**. Based on the decoding performance obtained from the two recordings of the first two days of coma, one can compute the progression of the auditory discrimination and predict patients' chances of awakening, as an improvement is typically observed in survivors (positive predictive power 93%, with 95% confidence interval 5 0.77–0.99)

could be considered for further EEG based evaluation using the MindBEAGLE system and related experimental protocols.

6 Acute DOC Assessment at Massachusetts General Hospital (MGH)

Researchers at MGH have launched a pilot study to test the feasibility of using the mindBEAGLE BCI device in the Neurosciences Intensive Care Unit (NeuroICU). In addition to demonstrating the feasibility of implementing BCI in the acute NeuroICU setting, this pilot study (ClinicalTrials.gov Identifier NCT02772302) aims to determine if mindBEAGLE neurophysiological markers of cognitive function correlate with bedside behavioral assessments of consciousness. The MGH team recently enrolled its first patient (MGH1), a 72-year-old man with a history of hypertension who was admitted to the NeuroICU with a cerebellar hemorrhage that caused brainstem compression and coma. His NeuroICU course was complicated by intraventricular hemorrhage and hydrocephalus requiring bilateral external ventricular drains, as well as renal failure requiring hemodialysis. At the time of the BCI study, which was performed on his 39th day in the NeuroICU, his Glasgow Coma Scale score was 6T (Eyes = 4, Motor = 1, Verbal = 1T) and his behavioral evaluation with the CRS-R indicated a diagnosis of UWS (Auditory = 1, Visual = 1, Motor = 0, Oromotor/Verbal = 1, Communication = 0, Arousal = 2). EEG electrodes were placed manually since the presence of a left frontal external ventricular drain and a right frontal surgical wound from a recent endoscopic third ventriculostomy prevented application of an EEG cap. During the study, which was performed without complication and without any increase in intracranial pressure, the patient remained on mechanical ventilation via tracheostomy. No sedation was administered during or prior to the study.

The mindBEAGLE device detected P300 responses with 70% accuracy during the VT2 paradigm, an observation that suggests that the patient was able to attend to salient stimuli. Although this VT2 result may not definitively prove conscious awareness, it suggests that the patient may be cable of higher-level cognitive processing. Notably, the mindBEAGLE device detected only 30% accuracy during the AEP task, 0% during the VTP3 task, and chance accuracy during a motor task, suggesting the possibility that the patient's level of responsiveness may have been fluctuating. Within one month of the mindBEAGLE NeuroICU evaluation, the patient began to track visual stimuli, indicating transition from UWS to MCS.

7 LIS Assessment at Oregon Health and Science University (OHSU)

Researchers at OHSU conducted a small pilot study (N = 2) investigating the effects of custom MI prompts on assessment and communication accuracy with the mindBEAGLE MI paradigm for people with LIS. It was hypothesized that custom prompts based on well-rehearsed movements [16], using a first-person perspective, and incorporating visual, auditory, and tactile sensations associated with the movement [17], would improve performance compared to a generic prompt.

Patient P1 had incomplete LIS secondary to a brainstem stroke, and could communicate using eye movements. P2 had CLIS or possible DOC secondary to advanced amyotrophic lateral sclerosis. Both completed 12 weekly mindBEAGLE MI sessions, each including a 60-trial assessment run and a communication trial of 10 yes/no questions with known answers (e.g. "Is your name Bob?"). In a multiple-baseline AB design, participants were given a generic MI prompt (imagine touching the fingers to the thumb on the left or right hand, as described in the mindBEAGLE manual) in the first 6 or 7 sessions, and a custom prompt (e.g.

imagine picking guitar strings with the right hand and moving between chord positions with the left) in the remaining sessions. Custom prompts were based on activities participants had enjoyed when able-bodied, as reported by the participant himself (P1) or a family member (P2), and consisted of a guided imagery script with sensory elements (e.g. the feel of the guitar strings or the sound of the notes). During assessment, participants were given auditory prompts to imagine either the left- or right-sided movement for each trial. To answer questions, they were instructed to imagine the left-sided movement for YES and right-sided for NO.

Results are presented in Fig. 6. Participants' assessment accuracy stayed near chance levels and was similar for the generic (P1: mean = 51.8 ± 4.15%, P2: mean = 41.7 ± 17.22%) and custom (P1: mean = 51.2 ± 4.92%, P2: mean = 50.0 ± 10.95%) prompt conditions. Neither participant demonstrated a significant assessment accuracy level ($\geq$ 66.2%) in any session, and performance did not significantly improve with repeated practice. Accuracy in responding to YES/NO questions was more variable, perhaps due to the smaller number of trials, and again stayed near chance levels. Interestingly one patient reached 90% accuracy in one YES/NO run which shows awareness during this experiment. The custom prompt did not appear to improve performance on either task, as accuracy scores under that condition remained within the expected range based on scores achieved with the generic prompt.

The small sample size in this study precludes generalization of results to other potential BCI candidates. The poor performance of P1, who is known to be

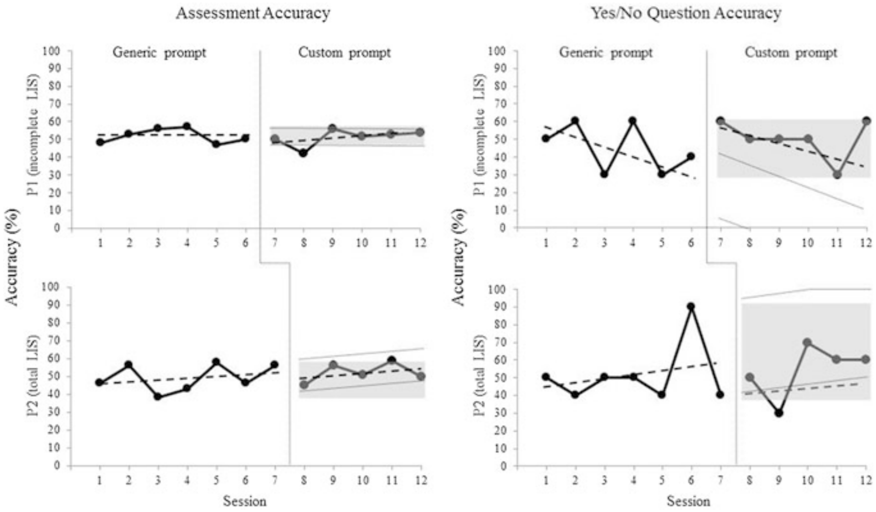


Fig. 6 Results for two participants with LIS using the mindBEAGLE MI paradigm for assessment (*left*) and answering yes/no questions (*right*). *Dashed lines* represent calculated trendlines within each condition. *Shaded* areas represent the degree of data overlap from the generic prompt phase. Small *dotted lines* represent the expected range of responses using the custom MI prompt based on performance with the generic prompt

conscious and cognitively intact, reminds us that a negative result on a BCI-based assessment is not conclusive evidence of impairment. Additional research with larger participant samples is necessary to determine the utility and appropriateness of MI BCI as a means of assessment and communication for individuals with LIS.

8 DOC Assessment at North Carolina State University (NCSU)

The research team at North Carolina State University (NCSU, Raleigh, USA) took a tactile-based hybrid BCI approach to assess consciousness and establish communication with behaviorally non-responsive patients. Tactile-based BCIs are a relatively new and upcoming research topic in the BCI area, which have the potential to help visually-impaired and blind groups. Steady-State Somatosensory Evoked Potentials (SSSEPs) can be elicited on the contralateral areas of the brain with vibrational stimuli [18]. Only recently have tactile-based BCIs been hybridized with SSSEP and tactile-P300 to increase the number of usable classes and improve BCI classification accuracy [19, 20]. In this study, we investigate how different spatial attention affects recorded brain signals, and which spatial patterns provide better SSSEP responses.

The stimulation equipment used was the same solenoid tactor setup presented in our previous study [20]. Five healthy volunteers were subjects for the experiment. Vibrational stimuli were presented on subjects' fingertip, wrist, forearm, and elbow of the dominant side. One tactor presented random pulses on one of four positions, with SSSEP stimulation presented on the other three positions (see Fig. 7a). Each subject conducted 100 pseudo-randomly distributed trials by locations and pulse patterns. To generate a random pulse, a 100 Hz sine wave was presented for 250 ms, while SSSEP stimulation was generated by modulating a 27 Hz square wave atop a 100 Hz sine wave. Each trial consisted of a 5 s rest period, 2 s reference period, and 8 s stimulation period, during which the subjects were asked to focus only on counting the number of random pulses. EEG signals were recorded with a g.USBamp biosignal amplifier using a large Laplacian montage around sites C3 and C4. BCI2000 was used for data acquisition and stimulus presentation, and EEG signals were sampled at 512 Hz and band-pass filtered between 20 Hz and 56 Hz, then analyzed using Canonical Correlation Analysis (CCA) from 20–29 Hz. The average CCA values showed higher Pearson's correlation (r-value) on the contralateral brain area for 27 Hz, while there were no differences on the ipsilateral brain area at the same SSSEP stimulus frequency (see Fig. 7b). ANOVA of different positions at 27 Hz on C3 for each subject showed that S1 had a significantly higher r-value on the fingertip than other positions ($p < .0001$), while S2 showed a significantly lower r-value on the fingertip than other positions ($p < .0001$) (see Fig. 7c). S3 ($p = .0619$) and S4 ($p = .0763$) showed marginal significance, and the r-value of fingertip was lower than that of the elbow for S3. There were no

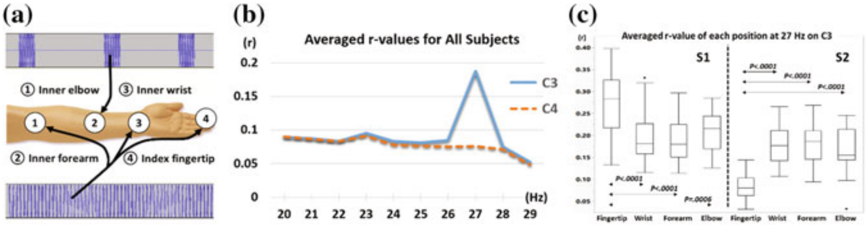


Fig. 7 **a** Conceptual diagram for tactor positions and stimuli when presenting random pulse **b** Averaged r-values of C3 and C4 areas for all subjects **c** Averaged r-value of each position at 27 Hz on C3 for S1 and S2

significant differences for S4 in post hoc Tukey tests. S5 showed no significant difference on positions.

The CCA value showed that unattended flutter sensation can elicit SSSEPs in the contralateral brain area by simply attending to random pulses presented on the same nerve pathway. Moreover, there were individually different effects of spatial-selective attention on the nerve pathway.

We have validated a new approach that evokes SSSEP through off-site attention, which may be used to reduce the mental workload needed to focus on SSSEP stimulation with random pulses and could be combined with P300 stimulation for a hybrid BCI system. In addition, these results can potentially improve the performance of a tactile-based BCI system by utilizing user-specific stimulation sites for improved SSSEP responses. These SSSEP features will be used for future research to develop a hybrid BCI for behaviorally non-responsive patients. SSSEP BCI technology could complement other emerging BCI technologies for these patients.

9 DOC Assessment and Communication in Liege

Correct diagnosis of patients with DOC is vital for realistic perspectives on revalidation and outcome. The gold standard for diagnosis is still behavioral bedside assessment, preferably using the Coma Recovery Scale-revised, as it has been proven to be the most sensitive tool that can detect the smallest non-reflexive signs of consciousness [21]. Patients could perform worse than their mental function permits during this kind of testing due to motor dysfunction, aphasia, sensorimotor deficits and other causes. Metabolism as measured with glucose positron emission tomography, and functional connectivity of the default mode network as measured with functional MRI during resting state, are objective ways to assess if consciousness is remaining in DOC patients (see Fig. 8). Active functional magnetic resonance imaging (fMRI) paradigms can be employed to assess command following via MI of playing tennis or navigating through a house, which, if used successfully, can be employed for BCI-based communication.

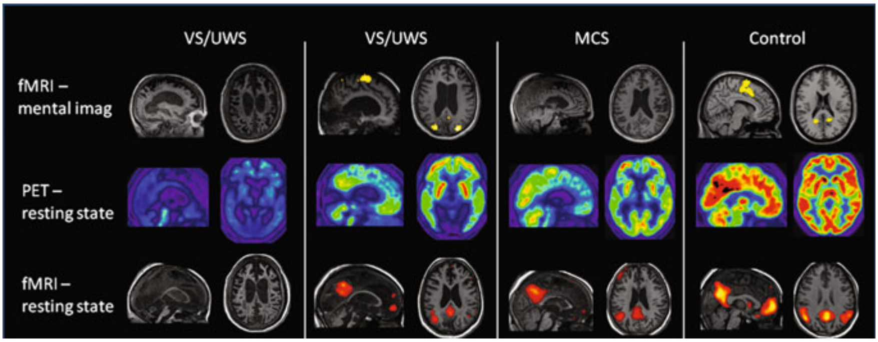


Fig. 8 From [31]. Glucose metabolism as measured with FDG positron emission tomography, BOLD resting state default mode network activity and BOLD mental imagery as measured with functional MRI in different states of consciousness. The UWS patient on the *left* shows the neuroimaging of a typical UWS patient with minimal residual brain function. The next panel shows a UWS patient who was unconscious on the behavioral level but who revealed signs of consciousness during the neuroimaging tests, such as command following during the active MRI paradigm. The next panel presents an MCS patient who shows residual metabolism and default mode network connectivity, albeit less than in a healthy subject. The *rightmost* column depicts normal brain function

Relative to MRI-based assessments, EEG-based BCIs have the advantages of being more affordable, portable and more robust to movement artifacts and metal implants. The tests are easily repeatable, making them very suitable for in clinical practice and during rehabilitation. Previous EEG based BCIs have proven useful to assess awareness and command following in this patient group. Auditory [22, 6] P300 oddball paradigms, and MI experiments [12] have been used successfully.

Ethical considerations play an important role for the use of BCIs in this patient population. The outcome of the BCI assessment might influence the medical team and the patient’s loved ones [23]. If the test results show less cognitive function than expected, the patient’s family might cope better with the decision to withdraw life supporting treatment, or lose hope. If the tests show more cognitive abilities than with neurological examination, the clinical management of the patient should be improved so that the chance of recovery increases, but this outcome could also give false hope to families. If the tests show the same level of cognitive abilities as the behavioral assessments, this affirms the decision of the medical team.

The patient’s physical and mental disabilities might make it hard to believe that patients can have a good quality of life, whereas healthcare professionals mainly aspire to help their patients attain and maintain a good quality of life. DOC patients cannot communicate whether they feel their life is enjoyable. LIS patients are classically able to communicate by means of eye movement, and when they compare their current well-being to the best and worst periods in their lives, the majority of patients is rather happy [24]. The feeling of well-being in the LIS subjects is comparable to the normal population, indicating that the level of physical (and possibly mental) disability does not significantly influence quality of life.

Furthermore, a BCI could give the patient a level of autonomy that would be life changing and most likely increase their quality of life.

10 Alternative Approaches and Directions

As alternatives to neuroimaging and electrophysiological paradigms, non-brain-based approaches, such as measurement of subclinical electromyography signals (Bekinschtein et al., [25, 26], pupil dilation during mental calculation [27], changes in salivary pH [28, 29] or changes in respiration patterns [30] have been proposed to identify covert voluntary cognitive processing in patients with disorders of consciousness. Recently, an electromyographic paradigm detected muscle activations in response to 'move your left/right hand' command in 14 patients with MCS (Lesenfants et al., submitted A). Six of them only behaviorally responded to commands on the day of the recording, while all of them showed behavioral responses to commands while assessed repeatedly on multiple days. This approach could be an alternative to BCI inspired paradigms in patients with some residual voluntary muscle control. These results open the door to the development of hybrid paradigms, looking jointly for subclinical electromyography signals and voluntary brain function in response to motor command.

Monitoring fluctuations of the level of vigilance can improve the detection of residual signs of consciousness by helping to select the best recording time and by tracking changes across a recording session. Attention itself can also serve as a marker of voluntary cognitive process. Tracking attention during a BCI task in 6 patients with LIS, Lesenfants and colleagues (submitted B) showed that they could track changes in attention with the EEG. They showed that the patients increased their attention during each trial in comparison to the resting periods between trials. While only two patients were successful with the BCI task, all six patients showed fluctuations of attention that could be distinguished from a rest period with more than 90% accuracy.

11 Discussion

The promising results with BCI technology for patients with DOC exhibit several trends. First, results show that new paradigms are emerging that are initially promising, but generally require broader validation with more patients over longer periods. The mindBEAGLE system could make such validation faster and easier while facilitating standardization. The system has standardized paradigms, is used in multi-center studies, is tested with VS, MCS, LIS, CLIS and healthy persons, is used at home, research centers, care facilities and intensive care units and has a standard approach to evaluation. Second, results support the hybrid BCI concept, in which one type of BCI is combined with another BCI and/or another means of communication to provide improved performance and move flexibility for users.

Results have shown that different paradigms, including MI, MMN, and visual and auditory P300 s, can be effective assessment and/or communication tools for these patients, and that SSSEPs could potentially provide another type of BCI for patients. FSL showed that the P300 jitter is larger for VS than MCS and for healthy control subjects, which could further facilitate new improvements.

Furthermore, the jitter was negatively correlated with the CRS-R. In some patients, non-EEG signals based on eye, muscle, or other activity could also be useful. Providing a suite of different assessment and communication options could lead to more decisive and detailed assessment and more effective communication while providing users some choice in the approach they wish to use. Third, results with MI BCIs are mixed. MI training can be effective with MCS patients, whereas MI training without feedback did not lead to effective communication in two ALS patients who explored different mental strategies. Interestingly, MCS patients could learn to modulate their SMR with auditory feedback. Fourth, persons with CLIS resulting from ALS, and perhaps other causes, could also benefit from BCI technology that has until now been focused on DOC patients. Fifth, there is a strong trend toward non-visual BCIs, which are often needed for this target group. Sixth, the joint workshops at different major conferences with different groups, and the very nature of this book chapter, show a trend toward dissemination and collaboration among researchers from different regions, disciplines, and sectors.

However, this is still a new technology that requires substantial further research, development, and validation with patients in field settings. Future systems could improve existing approaches based on MI, P300 s, and other paradigms, and add additional EEG and non-EEG based tools. New software could improve classifier accuracy, facilitate user interaction, and allow improved communication and control of devices such as fans or music players. New hardware could provide better quality data in noisy settings via more comfortable and practical electrodes. Additional background research is needed to better interpret data from this challenging population, develop and test new paradigms, explore improved classifier algorithms, and explore different patient groups. Research could also explore related tools to help target patients, such as methods to predict recovery (such as the new method from CHUV) or systems for cognitive and motor rehabilitation.

Another important future direction is public awareness—very few medical experts are aware of BCI-based options for DOC and other patients. Although very extensive work is still needed to develop methods and systems that are more informative, precise, flexible, and helpful, the results presented here show that BCI for consciousness assessment and communication has advanced beyond laboratory demonstrations, with successful validations of different approaches in different settings. The next several years should see significant improvements in this technology, improved quality of life for many patients, and more informative and reliable assessment tools that will help provide options and crucial information to medical staff, patients, and families.

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Author Biographies

Christoph Guger is actively running international research projects in the BCI domain, and is the CEO of g.tec medical engineering GmbH, Guger Technologies OG, g.tec neurotechnology USA Inc. and g.tec medical engineering Spain SL.

Damien Coyle is professor at the University of Ulster and active in BCI research for many years. He is a specialist for signal processing and has experience with DOC patients.

Donatella Mattia MD, PhD, Neurologist, Neurophysiologist. Lab. Director. Her main research interests are EEG-based BCI design and validation in neurorehabilitation and advanced signal processing methods for feature extraction and outcome measure.

Marzia De Lucia is principal investigator at the Laboratoire de Recherche en Neuroimagerie of Lausanne University Hospital and the Faculty of Biology and Medicine at the University of Lausanne, Switzerland. Her research focuses on consciousness detection and comatose patients' outcome prediction.

Leigh Hochberg is a vascular and critical care neurologist and neuroscientist. His research focuses on the development and testing of novel neurotechnologies to help people with paralysis and other neurologic disorders, and on understanding cortical neuronal ensemble activities in neurologic disease. Dr. Hochberg has appointments as Professor of Engineering, School of Engineering and Institute for Brain Science, Brown University; Neurologist, Massachusetts General Hospital, where he attends in the NeuroICU and on the Acute Stroke service; Director, VA Center for Neurorestoration and Neurotechnology, Providence VAMC; and Senior Lecturer on Neurology at Harvard Medical School. He also directs the Neurotechnology Trials Unit for MGH Neurology, where he is the IDE Sponsor-Investigator and Principal Investigator of the BrainGate pilot clinical trials (www.braingate.org) that are conducted by a close collaboration of scientists and clinicians at Brown, Case Western Reserve University, MGH, Providence VAMC, and Stanford University. Dr. Hochberg is a Fellow of the American Academy of Neurology and the American Neurological Association. Dr. Hochberg's BrainGate research, which has been published Nature, Science Translational Medicine, Nature Medicine, Nature Neuroscience, the Journal of Neuroscience, and others, is supported by the Rehabilitation R&D Service of the U.S. Department of Veterans Affairs, NCMRR/NICHD, NIDCD, and NINDS.

Brian L. Edlow received his B.A. from Princeton University and M.D. from the University of Pennsylvania School of Medicine. He completed an internal medicine internship at Brigham and Women's Hospital, followed by neurology residency and neurocritical care fellowship at Massachusetts General Hospital and Brigham and Women's Hospital. He is currently a critical care neurologist at Massachusetts General Hospital, where he is Associate Director of the Neurotechnology Trials Unit and Director of the Laboratory for NeuroImaging of Coma and Consciousness. Dr. Edlow's research is devoted to the development of advanced imaging techniques for detecting brain activity and predicting outcomes in patients with severe traumatic brain injury. The goals of this research are to improve the accuracy of outcome prediction and to facilitate new therapies that promote recovery of consciousness. Dr. Edlow receives support from the National Institutes of Health, Department of Defense, and American Academy of Neurology/American Brain Foundation.

Betts Peters is a speech-language pathologist specializing in augmentative and alternative communication, and works on BCI research with REKNEW Projects at Oregon Health & Science University.

Brandon Eddy is a clinical fellow in speech-language pathology at the Oregon Health & Science University Child Development and Rehabilitation Center in Portland, Oregon.

Chang S. Nam is currently an associate professor of Edward P. Fitts Industrial and Systems Engineering at North Carolina State University (NCSU), USA. He is also an associated professor of the UNC/NCSU Joint Department of Biomedical Engineering, as well as Department of Psychology. He is director of BCI Lab at NCSU. His research interests center around brain-computer interfaces and neurorehabilitation, smart healthcare, neuroergonomics, and adaptive and intelligent human-computer interaction. Currently, Nam serves as the Editor-in-Chief of the journal Brain-Computer Interfaces.

Quentin Noirhomme is senior scientist at Brain Innovation BV, where he works on the development of BCIs for clinical applications. He collaborates with the University of Maastricht and the University of Liege.

Brendan Z. Allison PhD was a Senior Scientist with g.tec and is a Visiting Scholar with the UCSD Cognitive Science Department. He has been active in BCI research for over 20 years, and is active with mindBEAGLE research for different groups.

Jitka Annen Jitka Annen is interested in multimodal analysis of consciousness and BCI applications in patients with DOC, and is PhD student in the Coma Science Group headed by Steven Laureys.