11

Brain-Computer Interface for Assessing Consciousness in Severely Brain-Injured Patients

Camille Chatelle, Damien Lesenfants, Yelena Guller,
Steven Laureys, and Quentin Noirhomme

Contents

Abstract

Brain-computer interfaces (BCIs) are tools that allow overcoming motor disability in patients with brain injury, allowing them to communicate with the environment. This chapter reviews studies on BCI applications in patients with disorders of consciousness, including EEG and fMRI applications, with a critical appraisal regarding false-positive and false-negative results. The role of steady-state visually evoked potentials and of the cognitive evoked potential P3 (or P300) will be highlighted. Future research has to overcome several challenges limiting current BCI application in routine practice and provide more reliable tools for diagnosis. Alternative protocols might be of interest in the development of easy-to-use systems for caregivers.

11.1 Introduction

Motor disability poses a significant challenge for clinicians working with patients with severe brain injury and especially disorders of consciousness (DOC), in terms of diagnosis, care, and rehabilitation (Schnakers et al. 2009; Cruse et al. 2011; Owen et al. 2006; Monti et al. 2010). Indeed, behavioral assessment, which remains the traditional way to evaluate consciousness (i.e., command-following and/or communication) in these patients, is highly dependent on motor

---

C. Chatelle (✉)
Coma Science Group, Cyclotron Research Centre
and Neurology Department, University and
University Hospital of Liège,
Sart-Tilman B30, Liège 4000, Belgium

Department of Physical Medicine and Rehabilitation,
Spaulding Rehabilitation Hospital,
Harvard Medical School, Boston, MA, USA
e-mail: Camille.chatelle@ulg.ac.be

D. Lesenfants • S. Laureys, MD, PhD
Q. Noirhomme, PhD
Coma Science Group, Cyclotron Research Centre,
University and University Hospital of Liège,
Sart-Tilman B30, Liège 4000, Belgium

Y. Guller
Department of Physical Medicine and Rehabilitation,
Spaulding Rehabilitation Hospital,
Harvard Medical School, Boston, MA, USA

A.O. Rossetti, S. Laureys (eds.), *Clinical Neurophysiology in Disorders of Consciousness: Brain Function Monitoring in the ICU and Beyond*, DOI 10.1007/978-3-7091-1634-0_11,

abilities. In this context, paraclinical tools to detect signs of consciousness that bypass the motor pathway are needed. Brain-computer interface (BCI) constitutes an interesting approach as it allows direct recording of the brain activity without requiring behavioral responses (Wolpaw et al. 2002). Recent studies show that there are command-specific changes in signals recorded with electroencephalography (EEG) or functional magnetic resonance imaging (fMRI) in patients with severe motor disabilities and that about 18 % of the patients being diagnosed as unconscious at the bedside might actually be able to follow a command by modulating their brain activity with respect to the relevant task (Schnakers et al. 2008a, 2009; Cruse et al. 2011; Monti et al. 2010; Chatelle et al. 2012; Goldfine et al. 2011; Lulé et al. 2013). These techniques could help improve the diagnosis of patients with DOC. However, poor performance (Lulé et al. 2013; Kubler et al. 2009), motor dependence (Kubler and Birbaumer 2008; Combaz et al. 2013; Piccione et al. 2006), and the need for time-consuming user training (Kubler and Birbaumer 2008; Birbaumer 2006; Neuper et al. 2003) are well-known limitations of BCI for detecting command-following and communication in conscious brain-injured patients. Furthermore, the high rate of false negatives (patients showing command-following at the bedside but not detected with BCI; 22–94 % (Monti et al. 2010; Schnakers et al. 2008b; see also Chatelle et al. 2014)) and the issue of false positives (patients detected as showing command-following with BCI who are actually unconscious (Cruse et al. 2013; Goldfine et al. 2013)) highlights the current need to develop more reliable tools for the diagnosis of patients with DOC. Indeed, having reliable systems would have a real impact on providing care such as treatment (in particular, pain and anxiety) and rehabilitation, as well as on quality of life (Kubler et al. 2006).

Here we review the studies on BCI applications for detecting response to command in patients with DOC. We then highlight the main challenges that will need to be overcome in future research and suggestions from studies conducted in healthy controls and motor-disabled patients that may be applied to the severely brain-injured population.

11.2 Brain-Computer Interfaces and Diagnosis in Disorders of Consciousness

A BCI is a system allowing for communication between the brain and the external environment. It is therefore independent from any peripheral neural or muscular activity (Wolpaw et al. 2002). This system is based on cerebral activity that can be measured using techniques such as EEG, fMRI, implanted electrodes (electrocorticography – EcoG (Hochberg et al. 2006)), or functional near-infrared spectroscopy (fNIRS; (Sorger et al. 2009)). The primary function of a BCI is to provide the subject a virtual keyboard where each covert “key press” constitutes a choice of an item from a set of items. This choice is made through the control of neuroelectrical activity (Sellers and Donchin 2006; Sellers et al. 2006). A specific algorithm translates the extracted features into commands that represent the users’ intent (see Fig. 11.1). These commands can control effectors to select items such as words, images, or devices. Recent development has shown the usefulness of BCIs for controlling motor prosthesis and cursors, providing a means of communication, and accessing the Internet (Hochberg et al. 2006; Citi et al. 2008; Yoo et al. 2004; Mugler et al. 2010; Sellers et al. 2010; Lee et al. 2009).

In the context of DOC, the first goal of a BCI is to detect command-specific changes in brain signals as evidence of conscious thoughts. Then, if the patient is able to reproducibly follow a command using the system, the software and hardware can be extended to test communication. The acquisition of voluntary responses such as command-following and functional communication is keystones in diagnosis as defined by behavioral criteria (Giacino et al. 2002; Plum and Posner 1966; Laureys et al. 2010). The presence of command-following indicates emergence from the vegetative/unresponsive wakefulness

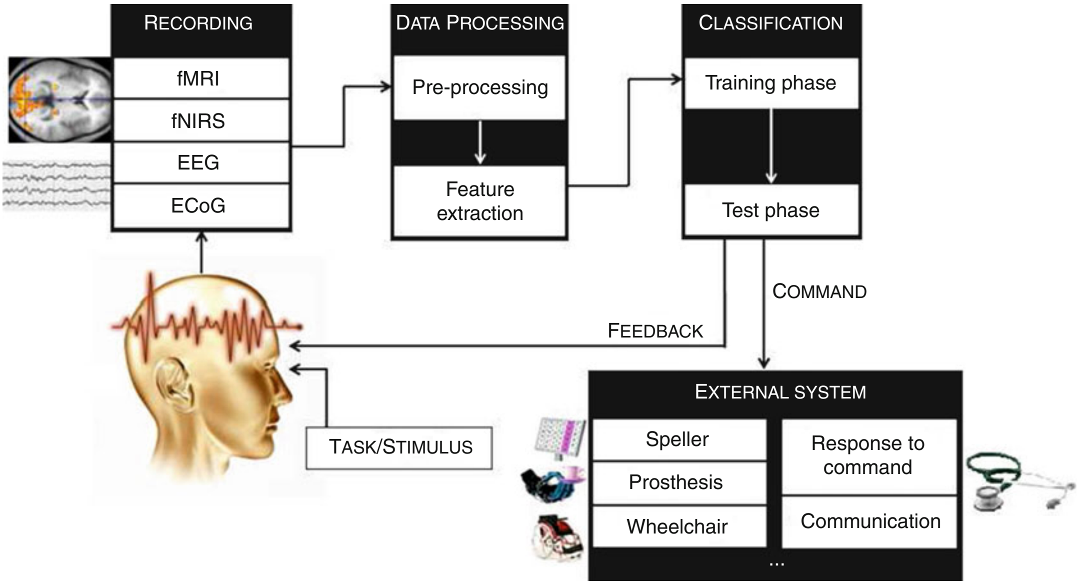

Fig. 11.1 A typical brain-computer interface schema. Modifications of brain activity due to a task/stimulus are recorded with fMRI, fNIRS, EEG, or ECoG. These neural data are pre-processed before discriminative features are extracted. Machine learning techniques are then used to train classifiers to detect statistical patterns in the features that are reliably associated with prespecified (supervised) volitional states of the user. The trained classifier is then used to classify new features corresponding to states now selected by the user to communicate choices. Finally, the result of the classification is fed back to the user to help him/her train themselves in the use of the BCI and to control external devices (e.g., word spelling, control of a wheelchair, a robotic prosthesis) or to help clinicians detect a response to command or functional communication

state (VS/UWS; (Laureys et al. 2010)) or recovery of a minimally conscious state (MCS; (Giacino et al. 2002; Bruno et al. 2012)). The recovery of functional communication indicates the emergence from MCS (EMCS; (Giacino et al. 2002)). Command-following and functional communication also distinguish locked-in syndrome (LIS) (Plum and Posner 1966) from VS/UWS patients. Because a better outcome for MCS versus VS/UWS patients has been reported (Luauté et al. 2010), patient access to rehabilitation is likely to be influenced by the clinical diagnosis. In addition, a recent study of 108 patients with traumatic brain injury reported that 56–85 % of patients showing command-following before discharge from the acute inpatient rehabilitation were functioning independently by 5 years post-injury, as compared to 19–36 % of patients who did not show command-following at discharge (Whyte et al. 2013). It remains unclear whether it was the presence of command-following, the quality of rehabilitation treatment (e.g., duration, hours of therapy, etc.), or both that contributed to better outcomes for command-followers. For LIS patients, the difficulty to recognize unambiguous signs of consciousness in the acute stage often results in the diagnosis being delayed or even missed (Laureys et al. 2005), with potentially catastrophical implications. Conversely, an early diagnosis allows clinicians to start developing a communication tool tailored to the patients' residual abilities.

To benefit from a BCI, the patient would need to first understand the task and repeat it several times, then to be able to attend to stimuli/questions while retaining task information in working memory. However, current BCIs require that the patient have much more capacity than required by behavioral testing, leading to undetectable command-following in many patients. When looking at the results obtained in studies of patients with DOC, we therefore need to take into account the number of patients showing command-following with the system, and how many of them were able to follow a command at bedside that could not be detected by the system (i.e., false negatives; see Table 11.1). False-positive rate should also be considered, but will not be discussed here as it is difficult to determine the level of consciousness of patients diagnosed unconscious but showing response to command with a BCI.

11.3 Absence of Motor Responses and Brain-Computer Interfaces

The first study showing the possibility of detecting response to command with BCI was conducted by Owen et al. in 2006 and reported that one patient diagnosed as being in VS/UWS was able to follow the instruction to "imagine playing tennis" and "walking through her house" during an fMRI session (Owen et al. 2006). The paradigm consisted of several sessions of mental imagery followed by a resting period, both lasting 30 s. This patient displayed similar brain activation as compared to healthy volunteers for both tasks. In addition, the patient behaviorally evolved into MCS a few months after the study. In a follow-up study (Monti et al. 2010) including 54 patients (23 VS/UWS and 31 MCS), five (four VS/UWS) showed ability to willfully modulate their brain activity according to the task. One of them was also able to answer simple questions, e.g., "Is your father's name Alexander?" using one task for "yes" and the other for "no." However, out of 18 patients showing command-following at the bedside, only one could be identified with the system (false-negative rate: 94 %). Bardin et al. (Bardin et al. 2011) investigated the use of a different imagery task instructing patients to imagine themselves swimming or playing tennis with their right hand, using a similar protocol to the one used by Owen et al. (2006) and Monti et al. (2010). Out of six patients (three MCS, two MCS/emerging MCS, one LIS), three were able to follow commands with the system (one MCS, one MCS/emerging MCS, one LIS). However, of the five patients who were able to follow commands at the bedside, two of them could not be identified with the system (false-negative rate: 40 %). Similarly, using an active task in fMRI task (counting a target-neutral monosyllabic word in an auditory sequence of nontargets words), Monti et al. reported preserved working memory abilities in a MCS patient exceeding that which could be observed with standard behavioral assessment (Monti et al. 2009). This patient was able to follow a command and communicate non-functionally at the bedside. Finally, three patients (one VS/UWS, two MCS) were instructed to either count the occurrences of a target word ("yes" or "no") or to simply relax and passively listening to a sequence of "yes" and "no" presented in a random series of numbers (Naci and Owen 2013). Command-following could be detected in all of the patients, and two patients (one VS/UWS and one MCS) were able to focus their attention to communicate correct answers to two different binary ("yes" or "no") questions such as "are you in a supermarket?" or "is your name Steven?" Because the latter two studies included few patients, and the results have not been replicated yet, interpretation of false-negative rates has not been conducted.

These first BCI studies showing response to command in DOC patients were conducted using fMRI, a technique that has many limitations preventing it from being applied universally to the DOC population. First, ferrous metallic implants are a contraindication to MRI, preventing many patients from undergoing this procedure. Even if implants are nonferrous, metal in the head can cause significant image artifact, making the analysis of the results difficult or impossible. Second, fMRI is sensitive to motion, which can result from reflexive movement in the scanner, general restlessness, or decreased patient cooperation. Images that are affected by significant motion artifact cannot be interpreted. Specifically, over three years of the European FP7 project DECODER during which the fMRI active sport/navigation paradigm described above was used in clinical settings at the Centre Hospitalier Universitaire de Liège, 169 patients were elected for the fMRI procedure. From this cohort, only

Table 11.1 Studies using brain-computer interfaces (BCIs) and alternative systems in patients with disorders of consciousness for assessing response to command and communication with false-negative ratios (patients showing command-following at the bedside, but not detected by the BCI)

References	Technique used – brain response	Task	Total number of patients included	False-negative ratio (%)
BCI applications				
Owen et al. (2006) and Monti et al. (2010)	fMRI – motor imagery	Playing tennis vs. walking through your house (command-following and communication)	55 (24 VS/UWS; 31 MCS)	17/18 (94 %)
Bardin et al. (2011)	fMRI – motor imagery	Swimming (command-following and communication)	6 (3 MCS; 2 exit MCS; 1 LIS)	2/5 (40 %)
Monti et al. (2009)	fMRI – P3	Count a target word – neutral (command-following)	1 (MCS)	0/1 (0 %)[a]
Naci and Owen (2013)	fMRI – P3	Count a target word – neutral (command-following and communication)	3 (1 VS/UWS; 2 MCS)	0/1 (0 %)[a]
Schnakers et al. (2008a, 2009)	EEG – P3	Count a target word – subject's own name (command-following)	23 (8 VS/UWS; 14 MCS; 1 LIS)	2/8 (25 %)
Lulé et al. (2013)	EEG – P3	Count a target word (communication)	18 (3 VS/UWS; 13 MCS; 2 LIS)	5/6 (83 %)
Goldfine et al. (2011b)	EEG – motor imagery	Swimming vs. walking through your house (command-following)	3 (1 MCS, 1MCS/exit MCS, 1 LIS)	1/3 (33 %)
Cruse et al. (2011, 2012a)	EEG – motor imagery	Squeeze your right hand vs. move your toes (command-following)	39 (16 VS/UWS; 23 MCS)	13/15 (87 %)
Cruse et al. (2012b)	EEG – motor imagery	Squeeze your right vs. left hand (command-following)	1 (VS/UWS)	Not applicable
Pokorny et al. (2013)	EEG – P3	Count the number of deviant tones (command-following and communication)	12 (1 VS/UWS, 10 MCS, 1 exit MCS[b])	1/3 (33 %)[b]
Chennu et al. (2013)	EEG – P3 (20 patients also seen with fMRI active task used in (Owen et al. 2006; Monti et al. 2010))	Count the number of target word (command-following)	21 (9 VS/UWS; 12 MCS)	EEG: 7/7 P3b (100 %), 5/7 P3a (71 %); fMRI: 3/7 (43 %)
Alternative systems				
Bekinschtein et al. (2008)	EMG – muscle activity	Move your right hand (command-following)	10 (8 VS/UWS, 2 MCS)	0/1 (0 %)[a]
Stoll et al. (2013)	Infrared camera – pupil dilation	Perform arithmetic problem (communication but command-following with the MCS patient)	13 (12 LIS; 1 MCS)	0/1 (0 %)[a] when used for command-following, but 9/12 (69 %) when used for communication

The ratio percentage is calculated by dividing the number of patients who responded to command at the bedside, but did not show response to command with the system by the total number of patients' response to command at bedside

[a] Not interpretable as only one patient showing command-following has been tested with this system

[b] Based on CRS-R data obtained from Pokorny et al. Note that for four patients, subscales scores were not available, preventing the current analysis in terms of false negatives

60 studies yielded active paradigm data that were interpretable, outlining the difficulties in generalizing this approach. The main reason for data rejection was artifact caused by head motion in the scanner. Finally, many clinical settings do not have access to MRI because it is an expensive technique to implement. Furthermore, fMRI requires executing complicated data processing methods, which necessitates involvement of personnel with expertise in this area. Given these limitations, EEG may be better suited for assessing DOC patients as it is not contraindicated by metallic implants and is less sensitive to motion. EEG is relatively inexpensive, and compact systems can be readily deployed at the bedside. In recent years researchers have been developing EEG-based BCI to assess response to command in DOC.

As suggested by fMRI studies, BCI using imagination of movement may be a reasonable supplement to observation of actual movement during standard behavioral assessment. EEG studies have shown that motor imagery is associated with a power decrease (event-related desynchronization) in the sensorimotor or mu rhythm (8–15 Hz; (Pfurtscheller et al. 1997; Neuper et al. 2005)), focused in the motor region that is implicated in the movement being imagined (Pfurtscheller and Lopes da Silva 1999). Goldfine and colleagues (2011) recorded EEG from three patients showing command-following at the bedside (MCS, MCS/emerging MCS, and LIS), while they were involved in motor imagery and spatial navigation tasks. The session alternated eight 15-second periods of mental imagery with 15-second periods of rest. All of the patients demonstrated the capacity to generate mental imagery on the same tasks on independent fMRI studies. With univariate comparisons (individual frequencies), these investigators showed evidence of significant differences between the frequency spectra accompanying the two imagery tasks in one MCS patient (however, results were not stable between the two runs) and one LIS patient (false-negative rate: 33 %).

In another study from Cruse and colleagues, motor imagery tasks were investigated in 16 VS/UWS (Cruse et al. 2011) and in 23 MCS patients (Cruse et al. 2012a). Eight (three VS/UWS, five MCS) were able to voluntarily control their brain activity in response to a command ("imagine squeezing your right hand" versus "imagine moving all your toes"). Out of 15 patients showing command-following, 13 could not be identified by the system (false-negative rate: 87 %). In order to decrease the cognitive load required to complete the task (e.g., minimize task switching and the duration of the session), the latter study used a block design with instructions to perform motor imagery following each of 15 subsequently presented tones. However, in this population block design may be problematic because changes in the EEG signal across and within blocks may be influenced by vigilance and motor artifacts leading to lack of independence between trials. For this reason, these results should be interpreted cautiously because dependence between trials was not accounted for in the statistical analyses. This issue is specifically relevant for the severely brain-injured population, and BCI studies in the future will need to take it into account (Cruse et al. 2013; Goldfine et al. 2013).

In an attempt to circumvent the statistical pitfalls of block design, an alternate paradigm has been investigated. In this paradigm, each trial is started with one of three instructions (i.e., "try to move your right hand," "try to move your left hand," and "and now, relax") that are presented through sounds in a randomized order. Because the instructions are presented before each trial as oppose to at the beginning of a block, significantly less working memory capacity is required to carry out the task. In addition, this method is technically less challenging and more efficient as it requires the use of only four electrodes. The utility of this paradigm as a diagnostic tool has been reported in a single patient diagnosed as being in a VS/UWS at bedside (Cruse et al. 2012b). However, this type of protocol still requires higher-level cognitive abilities, such as sustained attention and task switching, as compared to behavioral assessment.

Several studies have suggested that motor imagery cannot be reliably used in motor-disabled patients (Kasahara et al., 2012; Fiori et al., 2013). Instead of motor imagery, Nijboer et al. has recommended the preferential use of the P3-based BCI in patients with severe motor impairment (Nijboer et al. 2010) (see also Chap. 8). The P3 response (also called P300) is a positive deflection in the EEG appearing around 200–500 ms following a target stimulus (see also Chaps. 7 and 9). The advantage of the P3 is that it can be elicited by meaningful stimuli and requires a limited working memory load from the patient. Some of the earliest EEG-based BCI systems were based on the P3 component (Farwell and Donchin 1988; Donchin et al. 2000). The successful use of P3-based BCIs by a larger population of healthy users versus the sensorimotor rhythm has also been reported by Guger et al. (Guger et al. 2009; Guger et al. 2003). Moreover, many studies have shown that this system is feasible and practical for patient groups (see, e.g., Sellers et al. 2006; for a review, Hoffmann et al. 2008; Manyakov et al. 2011) and offers a stability of the performance over time in this population (Sellers et al. 2010; Nijboer et al. 2008; Silvoni et al. 2009). Consequently, auditory P3 responses are more likely to be usable by a greater number of patients (Chatelle et al. 2012). However, some of the most successful P3-based BCI systems are based on visual P3 responses which may be difficult to elicit in brain-injured patients as they frequently present with gaze fixation impairments (Lew et al. 2009; Alvarez et al. 2012) preventing them from attending to visual stimuli. Schnakers et al. proposed using an auditory P3 for detecting command-following using EEG (Schnakers et al. 2008a). They used a paradigm instructing patients to count the number of times a name (subject's own name or unfamiliar name) was presented within an auditory sequence of random names in 22 patients (eight VS/UWS, 14 MCS) (Schnakers et al. 2008a). Results showed that five out of 14 MCS patients showed significantly larger P3 responses when actively counting the occurrence of their own name as compared to when only passively listening to it. In addition, four other MCS patients showed a response only when they were asked to count an unfamiliar name as compared to passive listening. These results suggest that fluctuation of vigilance may play a role in task performance in this population. The eight VS/UWS patients did not show any response to the active task. The same paradigm has been used in a patient behaviorally diagnosed as being comatose, who showed a significant difference between the passive and the active task (Schnakers et al. 2009). Following this finding, this patient was reassessed and diagnosed with complete LIS. This extreme case illustrates the clinical utility of BCI as a supplement to behavioral assessment. Using this paradigm, two out of eight patients showing command-following at bedside could not be detected with the system (false-negative rate: 25 %). Similar results have been replicated in a recent study including patients with DOC (Risetti et al. 2013).

When the data were analyzed offline, one LIS patient reached 79 % accuracy. Out of six patients showing command-following at bedside (four MCS, two LIS), five could not be detected with the system (false-negative rate: 83 %). However, these results should be interpreted cautiously because the offline analysis used data from both the command-following and communication sessions to determine the presence of command-following.

A study by Lulé et al. used a four-choice auditory-based paradigm for communication with three VS/UWS, 13 MCS, and two LIS patients (Lulé et al. 2013). After a command-following training phase (four runs of counting "yes" or "no's"), each patient was asked to communicate by answering 10 questions (counting "yes" or "no's" depending on the answer). When using the system online, no patient could achieve performances allowing communication (>70 % accuracy (Kubler and Birbaumer 2008)). When the data were analyzed offline, one LIS patient reached 79 % accuracy. Out of six patients showing command-following at bedside (four MCS, two LIS), five could not be detected with the system (false-negative rate: 83 %). However, these results should be interpreted cautiously because the offline analysis used data from both the command-following *and* communication sessions to determine the presence of command-following.

Pokorny et al. tested a different auditory P3-based paradigm based on tone stream segregation allowing for binary decisions in 12 patients (10 MCS, one VS/UWS, one emerging MCS[1]). Two tone streams with infrequently and randomly appearing deviant tones were presented to the patient. This paradigm is suggested to be simpler than the previous ones as only two classes of stimulation are used. The patients were asked to count the number of deviants in one stream and thus modulate the P3 response in the attended stream. Only five patients could achieve results above chance level, and none of them achieved performances allowing communication with the system. In addition, response to command could be detected in nine patients after averaging all the responses obtained, although in two of them the response duration was very short (between 30 and 60 ms). Finally, out of three patients showing response to command at bedside (two MCS, one emerging MCS[1]), two could be detected with this paradigm. Note that command-following in the emerging MCS patient could not be detected with BCI. It is important to highlight that this paradigm was first used in healthy controls and had to be adapted to be usable with patients with DOC, reflecting the difficulty of applying a BCI paradigm efficient in non-neurologically impaired samples to brain-injured patients. Modifications to the paradigm included using fewer electrodes, adding a simple paradigm to habituate the patient to the task and to test the presence of a P3 response, using blocks of five consecutive trials with the same target stream instead of a randomized order to decrease the cognitive load, and adding additional auditorily presented instructions at the beginning of each run (Pokorny et al. 2013).

Finally, extensive research on attention involving healthy subjects has suggested that the P3 response should be deconstructed into separable subcomponents represented by the P3a and P3b. The relatively early frontally centered novelty P3a is thought to reflect exogenous attention, triggered by "bottom-up" stimulus novelty that may be task irrelevant. The later, parietally focused target P3b, on the other hand, is seen as a marker of "top-down" or volitional engagement of endogenous attention to task-relevant targets to be consolidated into working memory and made available for conscious access (Polich 2007). Based on this idea, Chennu et al. (2013) used a task designed to engender exogenous or endogenous attention, indexed by the P3a and P3b components, respectively, in response to a pair of word stimuli presented auditorily among distracters. They included 21 patients (nine VS/UWS; 12 MCS). Among these patients, three of them (MCS) generated only early non-discriminative responses to targets, suggesting that involuntary bottom-up attentional orienting might be preserved in a greater proportion of patients. In addition, one patient in VS/UWS generated a P3a as well as a P3b response, suggesting a preserved "top-down" or volitional engagement of endogenous attention. Out of the seven patients showing command-following at bedside, none of them generated a P3b (false-negative rate: 100 %), and only two of them showed a P3a (false-negative rate: 71 %). Interestingly, 20 of these patients were also administered the fMRI paradigm developed by Owen et al. (Owen et al. 2006; Monti et al. 2010). In six patients in whom a discernible P3a/P3b response could be elicited, a response to command using fMRI tennis imagery task could be detected. This discrepancy may be explained by vigilance fluctuation, as the paradigms were completed at different times. These results also suggest that the level of difficulty required by this attention task is too high to enable a good rate of detection of conscious patients. However, the VS/UWS patient who showed P3a/P3b responses did also show a response to command with the fMRI, supporting that the presence of a P3a and P3b may highlight a preserved volitional attention process.

11.4 Systems to Detect Response to Command at Bedside

BCI research has classically focused on systems using sophisticated EEG or fMRI techniques, which may be practical for clinical diagnosis, but

---

[1] Based on CRS-R data obtained from Pokorny et al. Note that for four patients, subscales scores were not available, preventing the current analysis in terms of false negatives.

become challenging in daily use. For this reason, other tools have also been developed and tested in patients with DOC to detect motor-independent response to command at bedside.

Bekinschtein et al. studied 10 patients with DOC (eight VS/UWS, two MCS) using electromyography (EMG; recording of muscle activity) (Bekinschtein et al. 2008). They auditorily presented four different 30 s blocks of commands to the patient: "Please try to move your right hand" and "Please try to move your left hand." At the end of the block, the instruction was "Please do not move, stay still." Two control auditory phrases were used: "Today is a sunny day" and "It is raining outside today." They reported that one VS/UWS patient and both MCS patients demonstrated an increased EMG signal specifically linked to the command, suggesting that electromyography could be used to objectively detect residual motor responses in this population. One MCS patient could follow command at bedside and showed increased EMG activity with the system.

Stoll et al. (2013) investigated the applicability of an alternative physiological signal, the pupil dilation, that can be readily and noninvasively measured with robust, inexpensive, easy-to-use equipment, to communicate with motor-disabled patients and patients with DOC. Pupil dilation has been related to a variety of cognitive functions and is a response that could be used to circumvent the challenges associated with the practical use of traditional BCI approaches. Twelve LIS patients (seven typical LIS and four severely brain-injured LIS with supratentorial lesions) and one MCS patient were included in the study. They reported that three out of seven LIS patients showed significantly higher performances than chance when answering yes-no questions using pupil dilation. However, none of the severely brain-injured LIS patients reached significance. Interestingly, they also used pupil response to detect command-following in one MCS patient following command at bedside. In this study, nine out of 12 patients could communicate at bedside, but could not use the system (false-negative rate: 69 %).

Although preliminary results suggest that these tools may provide simpler bedside methods of detecting command-following and communication with the potential to assist the clinician and improve the accuracy of diagnosis, some limitations prevent their use in patients with DOC. First, EMG still necessitates the preservation of some residual voluntary muscle activity which would prevent its use in patients with severe paralysis or chronic spasticity. Second, pupil response can be altered by the use of centrally acting drugs. Finally, as in fMRI and EEG, restlessness can lead to non-interpretable results. However, future studies should start using these alternative systems in conjunction with EEG and/or fMRI to investigate the integrity of cognitive function in this population.

11.5 Guidelines for Future Research

The high false-negative rate achieved with current BCIs highlights the need to develop more accurate paraclinical diagnostic tools for the DOC population (see Table 11.1). Indeed, a system that is not sensitive to detecting patients diagnosed as conscious at the bedside could not be reliably used in patients with unclear diagnoses. Similarly, a system which is very sensitive and detects signs of consciousness in all patients behaviorally diagnosed as conscious but also a majority of unconscious patients would not be specific enough to be reliable for clinicians. Currently, research on BCI in patients with DOC will have to overcome a number of challenges:

1. Brain-injured patients are likely to present arousal fluctuation, fatigue, and limited attention span, especially in MCS (Giacino et al. 2002). For this reason, paradigm complexity (stimulus, instructions) and duration are important factors to consider when evaluating BCI applications. Moreover, multiple repetitions of the BCI session must be considered to ensure a reliable diagnosis and account for fluctuation. In terms of communication, evaluation should be assessed with simple questions as severely brain-damaged patients may have difficulty giving accurate answers to

trivial yes/no questions (Nakase-Richardson et al. 2009).

2. Brain injury can be associated with sensory deficits (such as cortical deafness, blindness, or oculomotor impairments (Lew et al. 2009; Alvarez et al. 2012; Pogoda et al. 2012; Rowe et al. 2013)). While BCI research in healthy participants seems to highlight better performance with a visual as compared to auditory or tactile BCIs (Kubler et al. 2009; Halder et al. 2010; Pham et al. 2005), the key challenge here will be to develop reliable systems offering stimuli, instruction, and/or question presentation through multiple domains. A recent study reporting the applicability of a vibrotactile P3-based BCI in LIS patients might enable us to provide systems using a wider range of modalities taking into account various sensory deficits (Lugo et al. 2014).
3. A certain amount of cerebral reorganization and neuroplasticity might occur in several cases resulting in the recruitment of other brain areas during the performance of a given cognitive task, limiting a direct comparison with results observed in healthy controls (Chennu et al. 2013; Nam et al. 2012). In addition, future studies should take into account the topographic and latency variability observed in healthy subjects to interpret patients' data (Kaufmann et al. 2011; Bianchi et al. 2010).
4. Suboptimal data quality due to movement, ocular, and respiration artifacts in these challenging populations may also be confounding factors that need to be overcome with the assistance of appropriate statistical analyses. It also needs to be pointed out is that, in EEG, the classification accuracy achieved with a BCI naturally depends on the quality and inter-trial consistency of the data used to train the classifier (Goldfine et al. 2011, 2013; Cruse et al. 2013). This is problematic for most patients with DOC, particularly those in MCS, who are prone to frequent and prolonged bouts of fatigue and fluctuation of vigilance preventing them from paying attention for sufficiently long periods. For many patients, this limitation will adversely affect the classification results (e.g., dependency). It is therefore important to design protocols accordingly (i.e., avoid using blocks of the same stimulation and long-lasting sessions; assess the patient at different time periods (Cruse et al. 2013; Goldfine et al. 2013)), in order to decrease the number of false negatives. In addition, this will help us to take care of the false positives (patients detected as "responders" with the system who are actually unconscious (Goldfine et al. 2013)).
5. The success of active paradigms relies on the patient's willingness to do the task, which might be decreased in case of loss of motivation (Nijboer et al. 2010; Kleih et al. 2010) or akinetic mutism (Giacino 1997; Royal College of Physicians, 1996). These factors must be considered with care as we cannot distinguish a patient lacking motivation to do the task from one who is unconscious.
6. Finally, negative findings should be interpreted cautiously, as significant variability in brain responses are observed in control subjects. For example, some healthy participants lack expected ERP and fMRI responses (Lulé et al. 2013; Guger et al. 2003, 2009; Logie et al. 2011; Cui et al. 2007).

Among the different designs developed in healthy controls and tested in DOC, motor imagery BCIs are relatively less hindered by problems of stimulation modality. There is relatively little stimulation that needs to be presented, and this can be effectively delivered with sounds. Studies on their use in some patients with DOC have produced promising results (Monti et al. 2010; Goldfine et al. 2011). This knowledge, along with the fact that motor imagery (e.g., playing tennis vs. spatial navigation imagery) in fMRI has already allowed a patient to communicate when he was unable to do so at bedside (Monti et al. 2010), bodes well for similar BCI paradigms. However, motor imagery usually requires training of the participant before reliable performance can be achieved, which poses a significant challenge in a population of DOC, as illustrated by the high rate of false negatives achieved in previous studies on imagery tasks (Monti et al. 2010; Goldfine et al. 2011; Cruse et al. 2012a). A recent study suggested that imagery of complex and familiar actions may result in EEG responses that are more reliably classified as compared with simpler or unfamiliar actions in healthy volunteers (Gibson et al. 2014). Tailoring those paradigms to the patient's previous habits may help increase the sensitivity of these systems.

In this context, P3-based BCI designs could also be of interest since they rely on "automatic" responses of the brain to salient stimuli and hence require relatively little explicit user training. As highlighted earlier, previous findings by Schnakers et al. (2008a), Chennu et al.(2013), Monti et al. (Monti et al. 2009), and Naci and Owen (2013) have shown that some patients with DOC can generate consistent changes in EEG and fMRI when asked to selectively attend to task-relevant stimuli. Moreover, the P3 paradigm seems to be the most sensitive in terms of false-negative rates as compared to the other designs studied recently (see Table 11.1). Eventually, if successful with a patient, a P3-based BCI for spelling words and sentences using a predictive language support program could provide a true, multiclass system with relatively high efficiency. Moreover, a study using a visual P3 in healthy subjects has reported that 89 % of the participants were able to use the system with an accuracy between 80 and 100 % (Guger et al. 2009), as compared to another study showing only 20 % of the users achieving those performances with motor imagery-based BCI (Guger et al. 2003). Since we know that the most successful P3-based BCI is visually based, it may also be possible to adapt a visually based BCI for patients with eye control disabilities using individually presented rather than presenting multiple stimuli on the same screen. This approach has been successfully tested in LIS by Hoffman et al. (2008), but has not yet been applied in DOC.

Other kind of BCIs were only studied in healthy controls and LIS but can be of interest for patients with DOC. Steady-state visually evoked potentials (SSVEPs; (Vialatte et al. 2010; Regan 1989)) are the oscillatory electrical responses of neurons in the visual cortex to stimuli that are repeatedly presented (or flashed) at frequencies above 6 Hz. SSVEPs are easy to detect, as their frequency content is completely determined by the visual stimuli used to elicit them. The advantage of this response is that it has a high signal-to-noise ratio and EMG artifacts (Regan 1966; Gray et al. 2003). However, systems developed and successfully tested in healthy subjects and motor-disabled patients (Combaz et al. 2013; Parini et al. 2009) are highly dependent on eye motor control movement, which may prevent its use in patients with DOC. An alternative approach based on covert attention will therefore need to be tested in DOC (Lesenfants et al. 2011).

Finally, Birbaumer and colleagues (Birbaumer et al. 1999, 2000; Elbert et al. 1980) have worked on the development of slow cortical potentials-based BCIs (SCPs). SCPs are slow voltage changes generated in the cortex that occur over periods of 0.5–10.0 s. Usually, negative SCPs are associated with motor movement and other functions involving increased cortical activation, while positive SCPs are associated with reduced cortical activation (Birbaumer 1997). This system has been tested in patients with late-stage amyotrophic lateral sclerosis and has been shown to be capable of providing basic communication capacities (Kubler et al. 1999). However, the main problem is again that the most successful system uses visually based feedback (Pham et al. 2005; Birbaumer et al. 2000), and a relatively long period of training is needed (Birbaumer 2006). On the other hand, SCPs have the advantage of being the most stable over long periods (Chatelle et al. 2012).

Altogether, BCI applications may offer many possibilities for patients with DOC, but further work must be done before BCI can be used as a supplemental tool to the current behavioral "gold standard" for assessment of consciousness. We think that an extensive collaborative project between researchers, including data sharing to enable comparison between paradigms, analyses, and patient's demographic and clinical data is needed to efficiently answer the issues highlighted here. In addition, studies will need to focus not only on the decrease of false negatives, but also on the decrease of false positives in order to develop reliable tools for clinicians.

In the future, BCI could help us detect cognitive impairment at an early stage, using a binary communication code (Schnakers et al. 2008b) with such systems (Müller-Putz et al. 2013), and guide rehabilitation programs accordingly. In addition, BCI could also be used for motor rehabilitation in patients with DOC, as previous literature has suggested that motor imagery training could induce a modification of cortical activity in healthy volunteers and stroke patients ((Pichiorri et al. 2011; Page et al. 2009; Santos-Couto-Paz et al. 2013; Dickstein et al. 2014) for a review, see (Teo and Chew 2014)). In addition, studies have shown its interest to help in the recovery of motor function of the paralyzed limb in stroke patients (Jackson et al. 2001; Prasad et al. 2010; Page et al. 2007) as well as in patients with traumatic etiology (Sacco et al. 2011; Oostra et al. 2012). Given evidence that injured brain regions retain the ability to generate motor imagery of actions they cannot perform (Cruse et al. 2011; Owen et al. 2006; Monti et al. 2010; Goldfine et al. 2011; Cruse et al. 2012a), motor imagery-based BCIs could be an ideal candidate for early motor rehabilitation (Bruno et al. 2011) in patients with severe motor disabilities. However, we will need to investigate whether this is still possible for patients with chronic severe motor disabilities (Birbaumer et al. 2012).

Finally, it is important to note that, in order to use any of the paradigms presented above, the patient needs to be able to understand the task requirements, and therefore we need to be cautious as these systems will not be sensitive to detect patients suffering from language impairments (which is very likely to be the case for many patients, as shown in (Majerus et al. 2009)). In that case, language-independent paradigms will be needed (e.g., (Casali et al. 2013; Phillips et al. 2011; Malinowska et al. 2013; Faugeras et al. 2011; King et al. 2013) for a review, see (Boly and Seth 2012)).

11.6 Conclusion

In this chapter, we reviewed the current stage of the development of BCI and other alternative tools for the diagnosis of patients with DOC. We highlighted the great impact that these systems could have on rehabilitation strategies, quality of life, and prognosis. Currently, results obtained in patients with DOC will need to be interpreted with caution. Indeed, results from these studies show that the likelihood that a covertly aware patient might go undetected (i.e., the false-negative rate) is likely to vary significantly across different paradigms. In addition, the suitability of different BCI designs for single patients is variable and will need to be assessed on a case-by-case basis. While some patients have been shown to be able to generate reliable P3 responses to task-relevant stimuli, others have demonstrated the ability to consistently perform mental imagery in response to command. Hence, none of these tests applied individually to look for command-following can currently be used to interpret negative results, without combining findings from multiple testing methods to mitigate against the level of uncertainty. Similarly, we think that positive findings should not be taken as clear evidence of consciousness but should rather be used as an opportunity to discuss clinical findings.

Future research will need to overcome several challenges limiting current BCI application in DOC in order to provide more reliable tools for diagnosis. Studies on BCIs in healthy participants could be used as a basis for the development of new paradigms, but there is a need to conduct extensive testing with patients likely to benefit from various BCI systems in their daily lives (Kubler et al. 2006), since we know that often results from controls do not generalize well to patient groups (Pokorny et al. 2013; Hill et al. 2006). Alternative systems such as EMG or pupil dilation might also be of interest especially in the development of easy-to-use systems for caregivers.

Acknowledgment We gratefully acknowledge Martin Monti, Christoph Pokorny, and Audrey Vanhaudenhuyse for their collaboration on the patients' data information. This study was supported by the National Funds for Scientific Research (FNRS), Action de Recherche Concertée, Fonds Léon Fredericq, James S. McDonnell Foundation, Mind Science Foundation, University of Liège, the Belgian American Educational Foundation (BAEF), the Fédération Wallonie Bruxelles International

(WBI), and the Belgian Interuniversity Attraction Pole. CC is funded by the BAEF and WBI; SL is an FNRS research director. The text reflects solely the views of its authors.

References

Alvarez TL et al (2012) Concurrent vision dysfunctions in convergence insufficiency with traumatic brain injury. Optom Vis Sci 89(12):1740–1751

Bardin JC et al (2011) Dissociations between behavioural and functional magnetic resonance imaging-based evaluations of cognitive function after brain injury. Brain 134(Pt 3):769–782

Bekinschtein TA et al (2008) Can electromyography objectively detect voluntary movement in disorders of consciousness? J Neurol Neurosurg Psychiatry 79(7):826–828

Bianchi L et al (2010) Which physiological components are more suitable for visual ERP based brain-computer interface? A preliminary MEG/EEG study. Brain Topogr 23(2):180–185

Birbaumer N (1997) Slow cortical potentials: their origin, meaning, and clinical use. In: van Boxtel GJM, Böcker K (eds) Brain and behavior past, present, and future. Tilburg University Press, Tilburg, pp 25–39

Birbaumer N (2006) Breaking the silence: brain-computer interfaces (BCI) for communication and motor control. Psychophysiology 43(6):517–532

Birbaumer N et al (1999) A spelling device for the paralysed. Nature 398(6725):297–298

Birbaumer N et al (2000) The thought translation device (TTD) for completely paralyzed patients. IEEE Trans Rehabil Eng 8(2):190–193

Birbaumer N et al (2012) Ideomotor silence: the case of complete paralysis and brain-computer interfaces (BCI). Psychol Res 76(2):183–191

Boly M, Seth AK (2012) Modes and models in disorders of consciousness science. Arch Ital Biol 150(2–3):172–184

Bruno MA et al (2011) From unresponsive wakefulness to minimally conscious PLUS and functional locked-in syndromes: recent advances in our understanding of disorders of consciousness. J Neurol 258(7):1373–1384

Bruno MA et al (2012) Functional neuroanatomy underlying the clinical subcategorization of minimally conscious state patients. J Neurol 259(6):1087–1098

Casali AG et al (2013) A theoretically based index of consciousness independent of sensory processing and behavior. Sci Transl Med 5(198):198ra105

Chatelle C et al (2012) Brain-computer interfacing in disorders of consciousness. Brain Inj 26(12):1510–1522

Chatelle C, Laureys S, Noirhomme Q (2014) BCI and diagnosis. In: Gerd Grübler, Elisabeth Hildt (ed) Brain-computer-interfaces in their ethical, social and cultural contexts. Springer, Dordrecht

Chennu S et al (2013) Dissociable endogenous and exogenous attention in disorders of consciousness. Neuroimage Clin 3:450–461

Citi L et al (2008) P300-based BCI mouse with genetically-optimized analogue control. IEEE Trans Neural Syst Rehabil Eng 16(1):51–61

Combaz A et al (2013) A comparison of two spelling Brain-Computer Interfaces based on visual P3 and SSVEP in Locked-In Syndrome. PLoS One 8(9):e73691

Cruse D et al (2011) Bedside detection of awareness in the vegetative state. Lancet 378(9809):2088–2094

Cruse D et al (2012a) The relationship between aetiology and covert cognition in the minimally-conscious state. Neurology 78(11):816–822

Cruse D et al (2012b) Detecting awareness in the vegetative state: electroencephalographic evidence for attempted movements to command. PLoS One 7(11):e49933

Cruse D et al (2013) Reanalysis of "Bedside detection of awareness in the vegetative state: a cohort study" – Authors' reply. Lancet 381(9863):291–292

Cui X et al (2007) Vividness of mental imagery: individual variability can be measured objectively. Vision Res 47(4):474–478

Dickstein R et al (2014) Motor imagery group practice for gait rehabilitation in individuals with post-stroke hemiparesis: a pilot study. NeuroRehabilitation 34(2):267–276

Donchin E, Spencer KM, Wijesinghe R (2000) The mental prosthesis: assessing the speed of a P300-based brain-computer interface. IEEE Trans Rehabil Eng 8(2):174–179

Elbert T et al (1980) Biofeedback of slow cortical potentials. I. Electroencephalogr Clin Neurophysiol 48(3):293–301

Farwell LA, Donchin E (1988) Talking off the top of your head: toward a mental prosthesis utilizing event-related brain potentials. Electroencephalogr Clin Neurophysiol 70(6):510–523

Faugeras F et al (2011) Probing consciousness with event-related potentials in the vegetative state. Neurology 77(3):264–268

Fiori F et al (2013) Exploring motor and visual imagery in Amyotrophic Lateral Sclerosis. Exp Brain Res 226(4):537–547

Giacino JT (1997) Disorders of consciousness: differential diagnosis and neuropathologic features. Semin Neurol 17(2):105–111

Giacino J et al (2002) The minimally conscious state: definition and diagnostic criteria. Neurology 58(3): 349–353

Gibson RM et al (2014) Complexity and familiarity enhance single-trial detectability of imagined movements with electroencephalography. Clin Neurophysiol 125(8):1556–1567

Goldfine AM et al (2011) Determination of awareness in patients with severe brain injury using EEG power spectral analysis. Clin Neurophysiol 122(11):2157–2168

Goldfine AM et al (2013) Reanalysis of Bedside detection of awareness in the vegetative state: a cohort study. Lancet 381(9863):289–291

Gray M et al (2003) Cortical neurophysiology of anticipatory anxiety: an investigation utilizing steady state probe topography (SSPT). Neuroimage 20(2):975–986

Guger C et al (2003) How many people are able to operate an EEG-based brain-computer interface (BCI)? IEEE Trans Neural Syst Rehabil Eng 11(2):145–147

Guger C et al (2009) How many people are able to control a P300-based brain-computer interface (BCI)? Neurosci Lett 462(1):94–98

Halder S et al (2010) An auditory oddball brain-computer interface for binary choices. Clin Neurophysiol 121(4):516–523

Hill NJ et al (2006) Classifying EEG and ECoG signals without subject training for fast BCI implementation: comparison of nonparalyzed and completely paralyzed subjects. IEEE Trans Neural Syst Rehabil Eng 14(2):183–186

Hochberg LR et al (2006) Neuronal ensemble control of prosthetic devices by a human with tetraplegia. Nature 442(7099):164–171

Hoffmann U et al (2008) An efficient P300-based brain-computer interface for disabled subjects. J Neurosci Methods 167(1):115–125

Jackson PL et al (2001) Potential role of mental practice using motor imagery in neurologic rehabilitation. Arch Phys Med Rehabil 82(8):1133–1141

Kasahara T et al (2012) The correlation between motor impairments and event-related desynchronization during motor imagery in ALS patients. BMC Neurosci 13:66.

Kaufmann T et al (2011) ERPs contributing to classification in the P300 BCI. In: Proceedings of the 5th International Brain-Computer Interface Conference. Graz University of Technology, Austria

King JR et al (2013) Information sharing in the brain indexes consciousness in noncommunicative patients. Curr Biol 23(19):1914–1919

Kleih SC et al (2010) Motivation modulates the P300 amplitude during brain-computer interface use. Clin Neurophysiol 121(7):1023–1031

Kubler A, Birbaumer N (2008) Brain-computer interfaces and communication in paralysis: extinction of goal directed thinking in completely paralysed patients? Clin Neurophysiol 119(11):2658–2666

Kubler A et al (1999) The thought translation device: a neurophysiological approach to communication in total motor paralysis. Exp Brain Res 124(2):223–232

Kubler A et al (2006) BCI Meeting 2005–workshop on clinical issues and applications. IEEE Trans Neural Syst Rehabil Eng 14(2):131–134

Kubler A et al (2009) A brain-computer interface controlled auditory event-related potential (p300) spelling system for locked-in patients. Ann N Y Acad Sci 1157:90–100

Laureys S et al (2005) The locked-in syndrome: what is it like to be conscious but paralyzed and voiceless? Prog Brain Res 150:495–511

Laureys S et al (2010) Unresponsive wakefulness syndrome: a new name for the vegetative state or apallic syndrome. BMC Med 8:68

Lee JH et al (2009) Brain-machine interface via real-time fMRI: preliminary study on thought-controlled robotic arm. Neurosci Lett 450(1):1–6

Lesenfants D et al (2011) Design of a novel covert SSVEP-based BCI. In: Proceedings of the 5th International Brain-Computer Interface Conference. University of Technology Publishing House, Graz, Austria

Lew HL et al (2009) Auditory and visual impairments in patients with blast-related traumatic brain injury: Effect of dual sensory impairment on Functional Independence Measure. J Rehabil Res Dev 46(6):819–826

Logie RH et al (2011) Low and high imagers activate networks differentially in mental rotation. Neuropsychologia 49(11):3071–3077

Luauté J et al (2010) Long-term outcomes of chronic minimally conscious and vegetative states. Neurology 75(3):246–252

Lugo ZR et al (2014) A vibrotactile P300-based brain-computer interface for consciousness detection and communication. Clin EEG Neurosci 45(1):14–21

Lulé D et al (2013) Probing command following in patients with disorders of consciousness using a brain-computer interface. Clin Neurophysiol 124(1):101–106

Majerus S et al (2009) The problem of aphasia in the assessment of consciousness in brain-damaged patients. Prog Brain Res 177:49–61

Malinowska U et al (2013) Electroencephalographic profiles for differentiation of disorders of consciousness. Biomed Eng Online 12(1):109

Manyakov NV et al (2011) Comparison of classification methods for P300 brain-computer interface on disabled subjects. Comput Intell Neurosci 2011:519868

Monti MM, Coleman MR, Owen AM (2009) Executive functions in the absence of behavior: functional imaging of the minimally conscious state. Prog Brain Res 177:249–260

Monti MM et al (2010) Willful modulation of brain activity in disorders of consciousness. N Engl J Med 362(7):579–589

Mugler EM et al (2010) Design and implementation of a P300-based brain-computer interface for controlling an internet browser. IEEE Trans Neural Syst Rehabil Eng 18(6):599–609

Müller-Putz GR et al (2013) A single-switch bci based on passive and imagined movements: toward restoring communication in minimally conscious patients. Int J Neural Syst 23(2):1250037

Naci L, Owen AM (2013) Making every word count for nonresponsive patients. JAMA Neurol 70(10):1235–1241

Nakase-Richardson R et al (2009) Emergence from minimally conscious state: insights from evaluation of post-traumatic confusion. Neurology 73(14):1120–1126

Nam CS, Woo J, Bahn S (2012) Severe motor disability affects functional cortical integration in the context of brain-computer interface (BCI) use. Ergonomics 55(5):581–591

Neuper C et al (2003) Clinical application of an EEG-based brain-computer interface: a case study in a patient with severe motor impairment. Clin Neurophysiol 114(3):399–409

Neuper C et al (2005) Imagery of motor actions: differential effects of kinesthetic and visual-motor mode of imagery in single-trial EEG. Brain Res Cogn Brain Res 25(3):668–677

Nijboer F et al (2008) A P300-based brain-computer interface for people with amyotrophic lateral sclerosis. Clin Neurophysiol 119(8):1909–1916

Nijboer F, Birbaumer N, Kubler A (2010) The influence of psychological state and motivation on brain-computer interface performance in patients with amyotrophic lateral sclerosis – a longitudinal study. Front Neurosci 4:55

Oostra KM et al (2012) Motor imagery ability in patients with traumatic brain injury. Arch Phys Med Rehabil 93(5):828–833

Owen AM et al (2006) Detecting awareness in the vegetative state. Science 313(5792):1402

Page SJ, Levine P, Leonard A (2007) Mental practice in chronic stroke: results of a randomized, placebo-controlled trial. Stroke 38(4):1293–1297

Page SJ et al (2009) Cortical plasticity following motor skill learning during mental practice in stroke. Neurorehabil Neural Repair 23(4):382–388

Parini S et al (2009) A robust and self-paced BCI system based on a four class SSVEP paradigm: algorithms and protocols for a high-transfer-rate direct brain communication. Comput Intell Neurosci 864564

Pfurtscheller G, Lopes da Silva FH (1999) Event-related EEG/MEG synchronization and desynchronization: basic principles. Clin Neurophysiol 110(11):1842–1857

Pfurtscheller G et al (1997) EEG-based discrimination between imagination of right and left hand movement. Electroencephalogr Clin Neurophysiol 103(6):642–651

Pham M et al (2005) An auditory brain-computer interface based on the self-regulation of slow cortical potentials. Neurorehabil Neural Repair 19(3):206–218

Phillips CL et al (2011) “Relevance vector machine” consciousness classifier applied to cerebral metabolism of vegetative and locked-in patients. Neuroimage 56(2):797–808

Piccione F et al (2006) P300-based brain computer interface: reliability and performance in healthy and paralysed participants. Clin Neurophysiol 117(3):531–537

Pichiorri F et al (2011) Sensorimotor rhythm-based brain-computer interface training: the impact on motor cortical responsiveness. J Neural Eng 8(2):025020

Plum F, Posner J (1966) The diagnosis of stupor and coma, F.A. Davis Co., Philadelphia

Pogoda TK et al (2012) Multisensory impairment reported by veterans with and without mild traumatic brain injury history. J Rehabil Res Dev 49(7):971–984

Pokorny C et al (2013) The auditory P300-based single-switch brain-computer interface: paradigm transition from healthy subjects to minimally conscious patients. Artif Intell Med 59(2):81–90

Polich J (2007) Updating P300: an integrative theory of P3a and P3b. Clin Neurophysiol 118(10):2128–2148

Prasad G et al (2010) Applying a brain-computer interface to support motor imagery practice in people with stroke for upper limb recovery: a feasibility study. J Neuroeng Rehabil 7:60

Regan D (1966) Some characteristics of average steady-state and transient responses evoked by modulated light. Electroencephalogr Clin Neurophysiol 20(3):238–248

Regan D (1989) Human brain electrophysiology: evoked potentials and evoked magnetic fields in science and medicine. Elsevier, New York

Risetti M et al (2013) On ERPs detection in disorders of consciousness rehabilitation. Front Hum Neurosci 7:775

Rowe FJ et al (2013) A prospective profile of visual field loss following stroke: prevalence, type, rehabilitation, and outcome. Biomed Res Int 2013:719096

Royal Collage of Physicians. The permanent vegetative state (1996). Review by a working group convened by the Royal College of Physicians and endorsed by the Conference of Medical Royal Colleges and their faculties of the United Kingdom J R Coll Physicians Lond 30(2):119–121

Sacco K et al (2011) A combined robotic and cognitive training for locomotor rehabilitation: evidences of cerebral functional reorganization in two chronic traumatic brain injured patients. Front Hum Neurosci 5:146

Santos-Couto-Paz CC, Teixeira-Salmela LF, Tierra-Criollo CJ (2013) The addition of functional task-oriented mental practice to conventional physical therapy improves motor skills in daily functions after stroke. Braz J Phys Ther 17(6):564–571

Schnakers C et al (2008a) Voluntary brain processing in disorders of consciousness. Neurology 71:1614–1620

Schnakers C et al (2008b) Cognitive function in the locked-in syndrome. J Neurol 255(3):323–330

Schnakers C et al (2009) Detecting consciousness in a total locked-in syndrome: an active event-related paradigm. Neurocase 4:1–7

Sellers EW, Donchin E (2006) A P300-based brain-computer interface: initial tests by ALS patients. Clin Neurophysiol 117(3):538–548

Sellers EW, Kubler A, Donchin E (2006) Brain-computer interface research at the University of South Florida Cognitive Psychophysiology Laboratory: the P300 Speller. IEEE Trans Neural Syst Rehabil Eng 14(2):221–224

Sellers EW, Vaughan TM, Wolpaw JR (2010) A brain-computer interface for long-term independent home use. Amyotroph Lateral Scler 11(5):449–455

Silvoni S et al (2009) P300-based brain-computer interface communication: evaluation and follow-up in amyotrophic lateral sclerosis. Front Neurosci 3:60

Sorger B et al (2009) Another kind of ‘BOLD Response’: answering multiple-choice questions via online decoded single-trial brain signals. Prog Brain Res 177:275–292

Stoll J et al (2013) Pupil responses allow communication in locked-in syndrome patients. Curr Biol 23(15):R647–R648

Teo WP, Chew E (2014) Is motor-imagery brain-computer interface feasible in stroke rehabilitation? A narrative review. PM R 6(8):723–728

Vialatte FB et al (2010) Steady-state visually evoked potentials: focus on essential paradigms and future perspectives. Prog Neurobiol 90(4):418–438

Whyte J et al (2013) Functional outcomes in traumatic disorders of consciousness: 5-year outcomes from the National Institute on Disability and Rehabilitation Research Traumatic Brain Injury Model Systems. Arch Phys Med Rehabil 94(10):1855–1860

Wolpaw JR et al (2002) Brain-computer interfaces for communication and control. Clin Neurophysiol 113(6):767–791

Yoo SS et al (2004) Brain-computer interface using fMRI: spatial navigation by thoughts. Neuroreport 15(10):1591–1595