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Chapter 11

# Brain-computer interfaces for consciousness assessment and communication in severely brain-injured patients

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**Abstract**

Patients with disorders of consciousness (DOC) suffer from awareness deficits. Comorbidities such as motor disabilities or visual problems hamper clinical assessments, which can lead to misdiagnosis of the level of consciousness and render the patient unable to communicate. Objective measures of consciousness can reduce the risk of misdiagnosis and could enable patients to communicate by voluntarily modulating their brain activity. This chapter gives an overview of the literature regarding brain-computer interface (BCI) research in DOC patients. Different auditory, visual, and motor imagery paradigms are discussed, alongside their corresponding advantages and disadvantages. At this point, the use of BCIs for DOC patients in clinical applications is still preliminary. However, perspectives on the improvements in BCIs for DOC patients seem positive, and implementation during rehabilitation shows promise.

## INTRODUCTION

### Disorders of consciousness and clinical guidelines

Patients with disorders of consciousness (DOC) experience trouble perceiving themselves and their surroundings after a comatose period following severe acquired brain injury. Between coma and full recovery of consciousness, a number of clinical entities exist that exhibit various levels of arousal and awareness, the two pillars on which consciousness is based. During physiologically and pharmacologically altered states of consciousness, arousal and awareness usually go hand in hand (with the exception of dreaming), while this is not the case in DOC (Laureys, 2005). The lowest level of consciousness in the DOC spectrum is coma. Coma patients are unaware and do not arouse spontaneously or after intense external stimulation (Laureys et al., 2004). Patients with unresponsive wakefulness syndrome (UWS) are awake but completely unaware, showing solely reflexive behaviors (Laureys et al., 2010). This condition is also referred to as a vegetative state (Monti et al., 2010a). Patients in a minimally conscious state (MCS) are to some extent aware of themselves or the environment (Giacino et al., 2002), and they present a wide range of behavioral manifestations. Signs of awareness in MCS are most often expressed by reproducible visual pursuit or fixation, automatic motor reactions, responses to commands, and localization of nociceptive stimulation (Wannez et al., 2017b). Patients who show behavior independent of language comprehension, such as visual pursuit or automatic motor reactions, can be subcategorized as MCS minus (MCS−). Patients who show signs of preserved language processing are considered MCS plus (MCS+) (Bruno et al., 2011). These patients are able to respond to commands and they could potentially use these responses as a means of communication. For example, if a patient can consistently look at a green or red card when asked, these colors could be coupled to “yes” and “no,”

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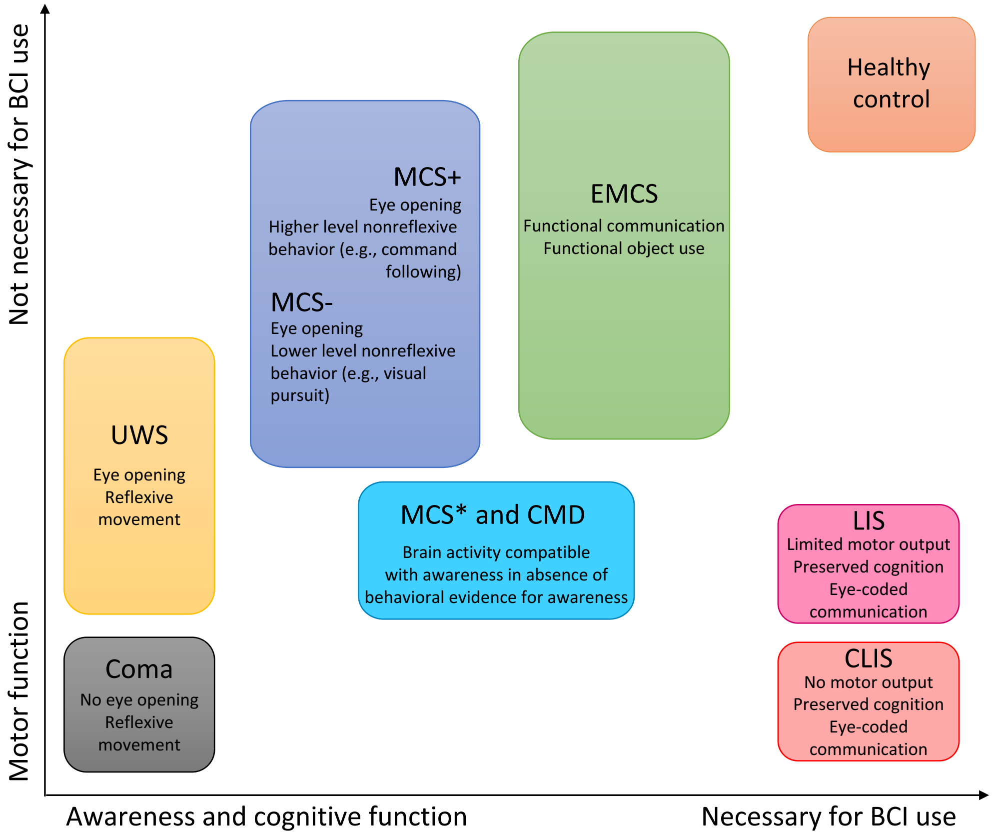


**Fig. 11.1.** Motor and cognitive functions in DOC (UWS and MCS), EMCS, and LIS patients. The distinction between the different clinical entities can be represented on the axes of motor function (not necessary for BCI use), cognitive function (necessary for BCI), and arousal (not represented here). At the bottom left, comatose patients are characterized by absence of motor and cognitive function. UWS patients may show limited motor function and no cognitive function. MCS minus and plus patients have residual cognitive function and motor function, of which the MCS + patients are likely to have more preserved motor and cognitive function than MCS − patients. EMCS patients regained more cognitive and motor function, as presented by functional communication or object use. The largest dissociation between cognitive function and motor function is present in CLIS/LIS patients, who have normal cognitive function and no/extremely limited motor function. The biggest challenge for BCI research in DOC patients is to find a means of interaction with the environment for patients whose motor abilities are too limited to show signs of higher cognitive abilities. *CLIS*, complete locked-in syndrome; *EMCS*, emergence from the minimally conscious state; *LIS*, locked-in syndrome; *MCS (−/+)*, minimally conscious state (minus/plus); *UWS*, unresponsive wakefulness syndrome.

enabling the patient to communicate in a nonverbal binary manner. Patients who are able to reliably communicate or who are able to use objects in a functional manner are said to have emerged from the MCS (EMCS) (Giacino et al., 2002). A similar, yet very different, group of patients consists of those with locked-in syndrome (LIS). These patients are fully conscious but have no (or very limited) muscle control due to a disruption of the brainstem's corticospinal pathways (Patterson and Grabois, 1986). Some LIS patients have additional brain lesions outside the brainstem that may cause cognitive deficits (Schnakers et al., 2008a). Most often, LIS patients have minimal recovery of motor function over time, while patients in complete LIS (CLIS) have no residual voluntary muscle control. In this chapter, LIS patients who have experienced a period of coma and classically suffered from a bilateral ventral pontine lesion are considered. If studies concern patients suffering from neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS), it is specifically mentioned. Fig. 11.1 summarizes the different clinical conditions and illustrates possible dissociations between motor and awareness function in patients with DOC (i.e., UWS and MCS), EMCS, and LIS.

The gold standard for diagnosis is by means of clinical assessment, preferably using the Coma Recovery Scale-Revised (Giacino and Kalmar, 2004). Clinical tests look for subtle signs of consciousness in different modalities such as auditory, visual, and motor functions. However, often the patients' deficits are not limited to consciousness alone. Deafness, blindness, aphasia, attention deficits, and motor disabilities are a nonexhaustive list of possible causes for misdiagnosis (Giacino et al., 2009). Indeed, misdiagnosis rates based on clinical consensus (without the use of standardized behavioral scales) range between 32% and 41% (Schnakers et al., 2008b; Stender et al., 2014). Erroneously diagnosing patients as unconscious can have serious medical and ethical consequences. Treatment perspectives also differ per diagnosis. For example, transcranial direct current stimulation (tDCS) helps to recover a new sign of consciousness in about half of MCS patients, but in UWS patients no treatment effects have been observed (Thibaut et al., 2014; Zhang et al., 2017). Patient diagnoses also have different implications for the patient's family and for legal issues regarding potential treatment withdrawal. For example, medical doctors find it more acceptable to stop treatment for UWS patients than for MCS patients (Demertzi et al., 2013).

Brain-computer interfaces (BCIs) can be useful for UWS and MCS patients in potential awareness detection and command following, while the EMCS and LIS patient groups can also greatly benefit from BCI applications for communicating and controlling their surroundings with assistive technologies (e.g., computer, wheelchair, communication device; Fig. 11.2). These latter applications could give users their autonomy back and improve their quality of life.

The attitude of a patient's family toward assistive technologies is also an important ethical consideration (Jox et al., 2012). Both overestimation and underestimation of a patient's capabilities can have both beneficial and harmful effects. On the one hand, family members may cope better with treatment withdrawal if the assistive technology affirms the bad prognosis of the clinical evaluation, but on the other hand they may lose hope for the patient if the results are worse than expected, or may nurture false hope if the results are much better than expected (for more ethical considerations regarding BCI, please refer to Chapter 24 on ethics).

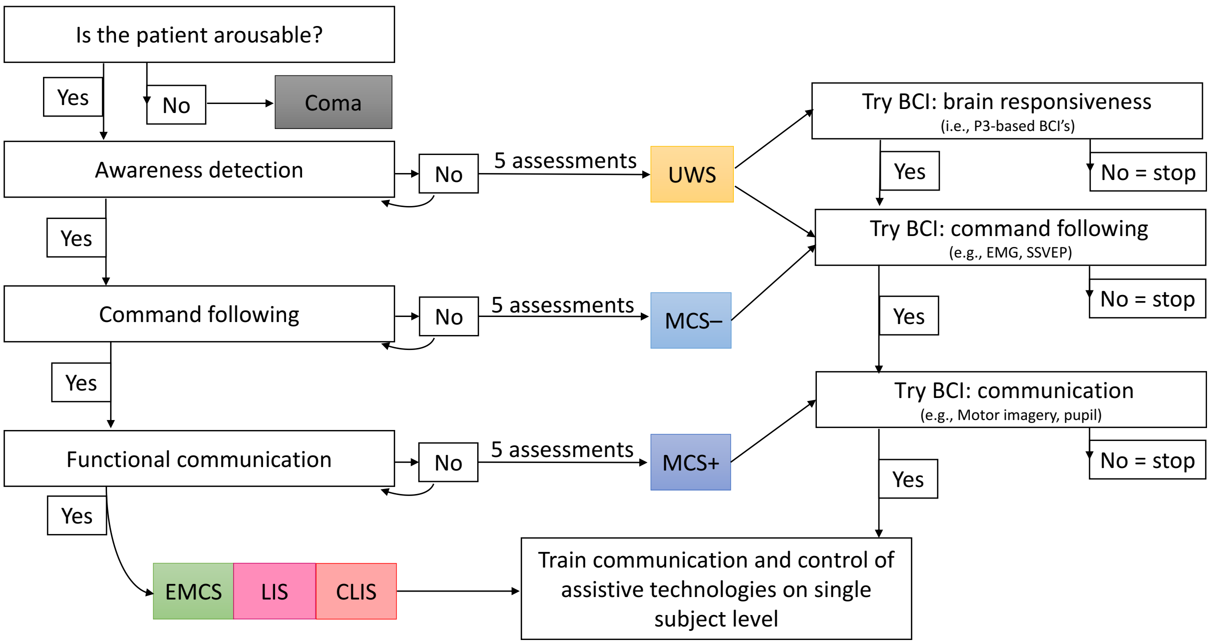


**Fig. 11.2.** Schematic representation of awareness detection and BCI use in DOC patients. Given that BCIs have been used successfully in healthy volunteers, they can be tested in DOC and severely motor-disabled patients. If the results are negative during any of the stages, it is recommended to repeat the assessment at least five times, to avoid arousal fluctuations hampering the assessments. Awareness testing and BCI use is not recommended in unarousable patients and should be postponed until eye opening is observed. If behavioral measures of awareness have not been observed for at least five assessments, the patient is likely to be UWS. However, BCI applications could be used to see if overt signs of awareness can be detected. If there are clinical signs of awareness, the patient is MCS, and testing should determine whether the patient can follow commands. If the patient does not follow commands on the behavioral level, the patient could be diagnosed as MCS −, but BCI applications could be used to test neural signs for command following. If the patient does follow commands overtly but does not communicate, the patient is MCS* or CMD. In this case, communication by means of a BCI could be attempted and, if successful, could identify candidates for the use of assistive technologies. Patients who are able to communicate (or follow commands) on the behavioral level could use assistive technologies to facilitate communication or control the environment. Please note that the proposed schedule is merely an aid to clinical assessment and diagnosis and is not intended to replace clinical assessment. *CLIS*, complete locked-in syndrome; *EMCS*, emerged from the minimally conscious state; *LIS*, locked-in syndrome; *MCS (−/+)*, minimally conscious state (minus/plus); *UWS*, unresponsive wakefulness syndrome.

*Table 11.1*

| Type of BCI | Awareness, command following, communication | Potential problems | Advantages |
|---|---|---|---|
| *fMRI* | | | |
| Motor imagery | Command, communication | Deafness, contraindications, not easily repeatable | Sensitive, independent from voluntary muscle control |
| *EEG based* | | | |
| Auditory P3 | Awareness, command, communication | Deafness, startle responses, requires neural response before testing command following | Flexible |
| Visual P3 | Awareness, command, communication | Blindness, requires neural response before testing command following | Flexible |
| Vibrotactile P3 | Awareness, command, communication | Spasticity, somatosensory issues, requires neural response before testing command following | Flexible |
| SSVEP | Command, communication | Blindness | Gaze independent, can be used for multiple choices |
| Motor imagery | Command, communication | False negatives (also in healthy controls) Deafness | Can be adapted to other imagery tasks |
| *Alternatives* | | | |
| fNIRS | Command, communication | Less commonly available than EEG | Sensitive |
| EMG | Command, communication | Requires residual motor function Deafness | Objective measure for (subthreshold) motor responses |
| Pupil/saliva | Command, communication | Limited application possibilities Deafness | Independent from voluntary muscle control |
| Intracranial BCI | Command, communication | Invasive, might cause infection, contraindication for implantation | No need to set up EEG acquisition, independent from voluntary muscle control |

In this chapter, we will review studies on detection of awareness, command following, and communication in patients with DOC (i.e., UWS and MCS), EMCS, and LIS (Table 11.1). Ideally, the BCI should first be used to detect consciousness through response to commands; in responsive patients, the BCI can then be used to establish a means for communication. The main focus will be on electroencephalography (EEG)-based BCI, including oddball paradigms, motor imagery, steady-state visually evoked potentials, and spelling devices. Future perspectives on rehabilitation research will also be discussed.

## The beginnings of BCI research in DOC patients

Owen et al. (2006) were the first to use functional magnetic resonance imaging (fMRI) as a means to probe the ability of DOC patients to follow commands (2006). In this seminal paper, a patient who was diagnosed as UWS was asked to imagine playing tennis, navigating through her house, and rest without particular thought in blocks of 30 s while lying in the MRI scanner. This block design ensured that the observed test response was not simply a result of passive processing of verbal instructions, and that the response was absent when the instruction not to perform a task was given. Imagining playing tennis activated the supplementary motor area, while navigation imagery activated the parahippocampal gyrus, enabling measurement of specific command following, as observed in healthy subjects. In a subsequent study, this command-following fMRI paradigm was successful in 5 out of 54 DOC patients, including 2 patients who clinically seemed UWS. In one MCS patient, these two commands were coupled to “yes” and “no,” which allowed the patient to answer five out of six autobiographic questions correctly (Monti et al., 2010b). This proof of concept led to further BCI research in DOC patients (Bodien et al., 2017; Edlow et al., 2017; Haugg et al., 2018) and highlighted one important possible pitfall of BCI approaches: negative results can never be interpreted as the absence of consciousness. Aphasia, apraxia, vigilance fluctuations, or even the patient’s unwillingness to participate might all negatively affect the assessment results. Thus negative findings in an active paradigm can never exclude the possibility that the patient is (minimally) conscious (Comte et al., 2015). The technical limitations of functional MRI for a BCI are rather obvious: e.g., it is expensive, sensitive to movement, not easy to repeat, has contraindications for patients with metal implants, and only a minority (about 10%) of DOC patients are able to positively respond to this approach (Monti et al., 2010b). EEG-based BCIs are portable and affordable and might therefore be more promising in the clinical setting of DOC patients.

## AWARENESS DETECTION, COMMAND FOLLOWING, AND COMMUNICATION

A hierarchical scheme should be followed when developing and implementing BCIs for DOC patients (Fig. 11.2). The first challenge is to detect awareness using objective and quantifiable measures. Assistive technologies could contribute to identifying subtle signs of consciousness. For example, some DOC patients only exhibited visual pursuit and fixation using BCI technology using a moving target stimuli and EEG recordings (Xiao et al., 2018a,b). However, there is currently no consensus about which objective electrophysiological measure proves (and disproves) awareness without doubt. Finding this neural measure is clinically relevant for diagnosis, as it could indicate that the patient is MCS but perhaps not able to show signs of consciousness due to physical limitations; that the patient presents with a "cognitive motor dissociation" (CMD; Schiff, 2015), or that the patient possibly should be classified as "nonbehavioral MCS" (MCS*) (Gosseries et al., 2014). A recent study even suggests that up to 75% of DOC patients show evidence of command following using EEG (Curley et al., 2018). It is important to identify these patients as candidate BCI users. A typical method for demonstrating awareness in a DOC patient using a BCI is to measure the patient's brain responses at rest or during passive paradigms and then compare them to the responses to some command-following tasks. If consistent covert command following as measured with brain objective responses (including specific event-related potentials (ERPs) or increased amplitude) is present during the command-following period, the patient should be considered MCS* or CMD (Cruse et al., 2011, 2012); however, see Goldfine et al. (2013) and Forgacs et al. (2014).

Once we know a patient is (minimally) conscious, the second challenge is to find a way to communicate. During behavioral assessments, communication can be established using binary auditory or visually oriented questions ("Am I clapping my hands/touching my nose?"), or simple autobiographic questions (e.g., "Is your name John?"). These kinds of questions can also be used in BCI assessments of communication using covert command following. If the patient is able to answer these questions consistently, only then can questions about wishes and feelings be asked.

## P3-based BCIs

In oddball paradigms, a sequence of two or more different (auditory) stimuli with a low and high probability are presented in a random fashion. In the ongoing EEG the P3 can be measured as a positive deflection after the onset of a salient stimulus, occurring typically 300 ms after the stimulus onset (Chapman and Bragdon, 1964). The P3 can, however, range between 200 and 500 ms after onset. Longer latencies should be accounted for in classification algorithms and are related to worse clinical status (Schettini et al., 2015). Two different P3 responses can be distinguished, the P3a and P3b (Comercherom and Polich, 1999). The bottom-up P3a is elicited by an unpredicted stimulus, strongest over frontal electrodes, and irrelevant to task performance. Providing further evidence for the insensitivity of the P3a to consciousness, the P3a can also be present during sleep and sedation when arousal and awareness are absent (for further reading, see Chennu and Bekinschtein, 2012). The P3b is a top-down response and occurs when a task is performed, such as counting the number of deviant stimuli. The P3b latency is slightly longer than that of the P3a and is strongest over posterior electrodes. The P3b has been related to conscious processing (Dehaene and Changeux, 2011), and hence this ERP is the one of interest for BCIs. In this chapter, we refer to the P3b when the P3 response is mentioned (for further reading regarding the P3, please refer to Chapter 18 on EEG).

### Active P3 tasks

The presence of the P3 in the postacute state (>1 month after injury) has been related to regaining of consciousness (Cavinato et al., 2009). Somatosensory discrimination as measured with the P3 in postacute and chronic UWS patients correlated with clinical outcome (as measured with the CRS-R) at 6 months (Spataro et al., 2018). However, compared to other EEG measures, such as band power and complexity or connectivity, the auditory P3 seems to provide less information regarding the presence of consciousness (Sitt et al., 2014). The P3 response is not limited to auditory stimuli, but also occurs with visual and sensory stimulations. In the latter case, a P3 response can be observed over the sensorimotor cortex contralateral to the limb that received the deviant stimulation (Fig. 11.3A).

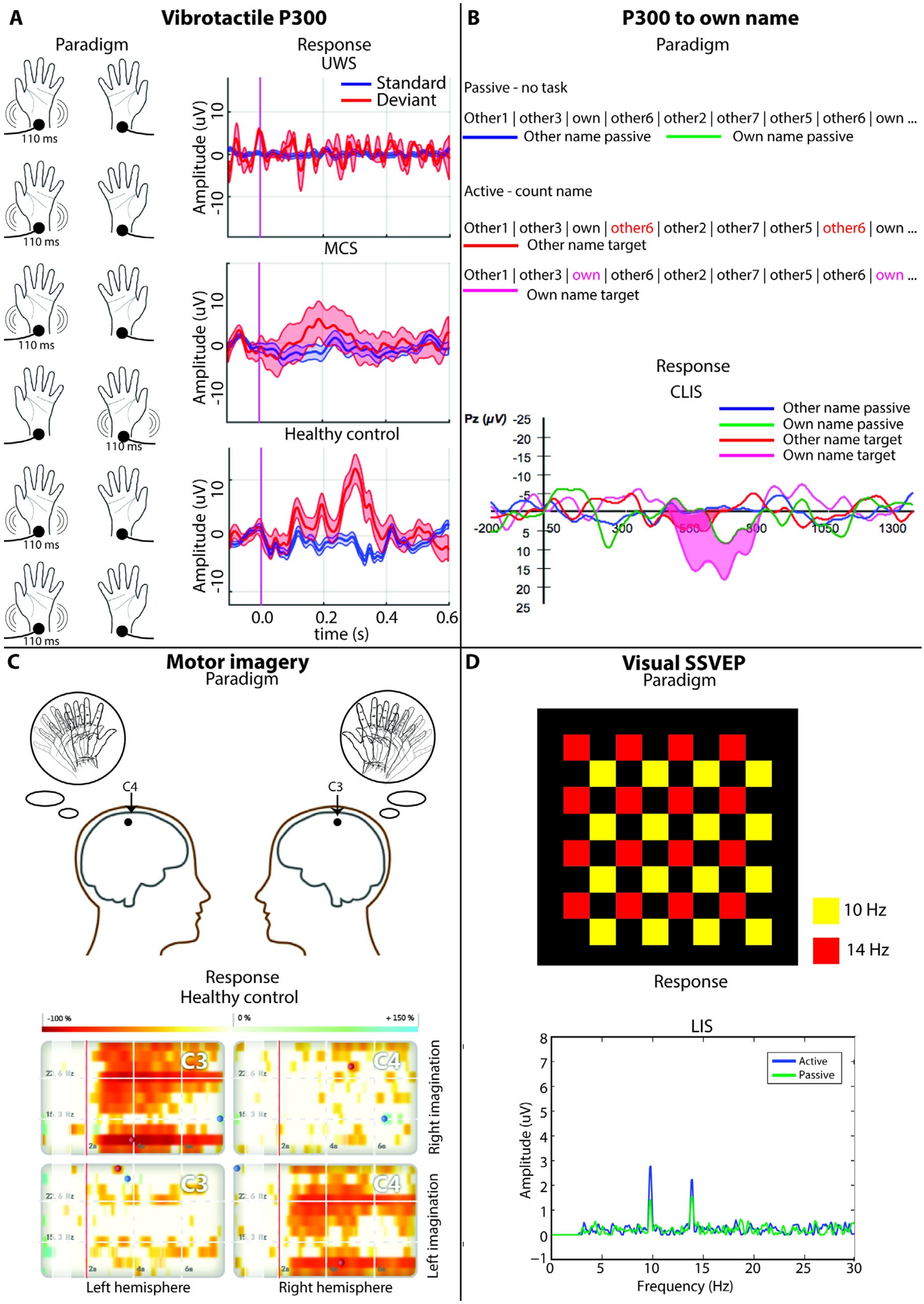


**Fig. 11.3.** See legend on opposite page.

By attention to vibrations on the left or right wrist, command following was detected in 1 MCS patient (Annen et al., 2016) and 4 out of 6 LIS patients, for whom one could use this code to functionally communicate (Lugo et al., 2014). In 1 patient diagnosed as MCS−, the presence of a distinctive P3 response to the deviant stimulus in an actively attended deviant tactile stimulus was marked by preserved glucose uptake in the whole (left lateralized) language network, typically preserved in MCS+ patients (Annen et al., 2018). This supports the BCI finding of (covert) command following in this patient. Some preliminary evidence suggests that a minority of patients behaviorally diagnosed as UWS could use such BCIs (Guger et al., 2018). A special case of the P3 is use of the patient's own name presented alongside other names, because self-related information may increase responsiveness (Fig. 11.3B). In DOC patients, this responsiveness could be indicative of preserved semantic processing (Perrin et al., 2006). Similar to that of healthy controls, the P3 response in MCS patients seems larger when the patient's own name is counted than when no active task is performed, but this is not the case for UWS patients (Schnakers et al., 2009a,b). These results suggest that active processing of specific stimuli is partially preserved in MCS patients, but not in UWS patients. Contrary to these early studies, later work reported that only half of the MCS patients showed signs of volitional top-down attention as a response to their own name (Schnakers et al., 2014; Hauger et al., 2015). So, it seems that the sensitivity (true positive rate) and specificity (true negative rate) for detection of consciousness with the P3 are rather low and therefore the P3 response to one's own name cannot be used to differentiate UWS from MCS patients.

A more complex P3 paradigm permits testing of the detection of local (within a trial/short time span) and global (across trials/within a long time span) violations of predicted tones. This more sophisticated "local–global" paradigm was initially tested on eight DOC patients and seems promising, since neural processing of the global violations was only observed in patients with residual consciousness (Bekinschtein et al., 2009). Hence, detection of these global effects seems to be a specific marker of consciousness. These results were confirmed in 49 DOC patients (Faugeras et al., 2012). Later, using single trial analysis, it was found that the global response was present in 14% of the UWS patients and in only 31% of the MCS patients (King et al., 2013). The apparent lack of sensitivity points out the limitations of that paradigm in clinical practice.

While P3 BCI testing usually presents two different items (one with a high probability of presentation and one deviant stimulus), more than two items can be presented. Apart from tones, various words can be employed to elicit P3 responses. A four-choice ("yes," "no," "stop," "go") auditory P3 BCI was successfully used with healthy volunteers attending to the desired word and in 1 out of 2 LIS patients, while in DOC patients no typical signs of command following and communication were observed (Lulé et al., 2013).

## P3 FOR PREDICTION OF RECOVERY IN THE ACUTE STAGE

Detecting patients with a high likelihood of recovery in the early stage after brain injury is important for treatment perspectives and end-of-life debates. In a CLIS patient, the P3 to the own name was observed prior to any behavioral recovery, and thus could be valuable in the absence of neuroimaging (Fig. 11.2B, Schnakers et al., 2009a,b). Indeed, the presence of the P3 in the acute stage after severe brain injury might be predictive of a good outcome in nonanoxic etiologies, as concluded from the metaanalysis of Daltrozzo et al. (2007). A recent study suggests that the auditory and vibrotactile P3 paradigm developed in a commercially available BCI (along with motor imagery) has not shown any correlation with behavioral responses in brain-injured patients in the intensive care unit, and is thus not (yet) reliable in the acute DOC population (Chatelle et al., 2018). Therefore, one should keep in mind that the heterogeneity in the studied samples is large and therefore hard evidence is still lacking for the prognostic value of the P3 in the acute phase after brain injury (Vanhaudenhuyse et al., 2008). However, a more complicated version of the P3 to the own name with two different P3 responses was reported

**Fig. 11.3.** Paradigm and brain responses for different BCI paradigms. (A) The vibrotactile P300 paradigm presents vibration on the wrists, where the *left wrist* is the standard stimulation and the *right wrist* is the deviant stimulation. Representative P3 responses are depicted for UWS patients, MCS patients, and normal in control subjects. (B) The P3 responses to the own name compared to the P3 to another name and to passive listening are presented in a CLIS patient. The differences in response between the passive and active own name sessions are presented in pink and this indicates that the patient is performing the task successfully. (C) The motor imagery task is a mental task where the subject is asked to imagine left and right hand movements. When commands are followed consistently, event-related synchronization in the mu band over the contralateral sensorimotor cortex can be observed. (D) The SSVEP paradigm presents *red and yellow lights* flickering at 10 and 14 Hz, respectively, in a checkerboard pattern. The frequency decomposition shows a peak in amplitude for both frequencies, with a higher amplitude for the active condition when the subject attends a specific color/frequency. Panel A: Annen et al. (2016); Panel B: Schnakers et al. (2009a,b); Panel C: Cruse et al. (2011); Panel D: Lesenfants et al. (2014).

to be specific to MCS patients and UWS patients who awakened (Li et al., 2015a). Recently, the local–global paradigm was tested in acute postanoxic comatose patients, where the authors reported the presence of the global effect in 78%–93% of comatose patients (Tzovara et al., 2015a, 2016). However, differences in the paradigm and targeted patients might impede a direct comparison between the results in chronic and comatose patients (Piarulli et al., 2015; Tzovara et al., 2015a,b). In summary, it seems that advances have been made, but conclusive evidence for an objective predictor of recovery is still lacking.

#### Considerations regarding P3 paradigm

There are some important considerations regarding the P3 paradigm. First, before testing DOC patients, it is of paramount importance to have a BCI that is highly reliable in healthy volunteers in order to be able to interpret the results in patients in a meaningful way. Second, there are some indications that the current P3 techniques are not sensitive enough to detect command following as measured by EEG activity, leading to high false negative rates in DOC patients. For instance, in a study combining results from the P3 and fMRI mental imagery task, 1 UWS patient was identified to follow commands in both tasks while 6 DOC patients showed signs of command following only in the fMRI task but not with the EEG-based BCI (Chennu et al., 2013). The P3 is also less reliable in LIS patients than in healthy volunteers (Lugo et al., 2016). Last, the auditory oddball paradigm can elicit startle responses and was therefore proposed as an aid for clinical assessment of behavioral startle (Xiao et al., 2016). At the same time, these startle responses may cause noise, influencing the performance of the auditory BCI, and should therefore be avoided.

### Motor imagery-based BCIs

A similar approach to the fMRI-based BCI (i.e., using motor and spatial imagery to assess command following and binary communication) can be employed for EEG-based BCIs. Before and during the movement of a hand or foot, event-related desynchronization of the sensorimotor rhythms (in the beta band, 13–35 Hz) is observed over the contralateral motor cortex (Pfurtscheller and Lopes, 1999). Right after the movement, event-related synchronization is observed in the same frequency band. This (de)synchronization is not only observed after a real movement, but also after imagined movement, giving opportunities for BCI use (Jeon et al., 2011). In principle, movement of the left and right hand/foot could then be coupled to a “yes” or “no” response in order to communicate. Evidence for covert awareness as measured by motor imagery (e.g., imagine squeezing your hand) was found in 19% of UWS patients (Cruse et al., 2011) (Fig. 11.3C). A slightly higher percentage of MCS patients (22%) showed covert response to command with the same paradigm (Cruse et al., 2012). Note that these patients were of traumatic etiologies and that none of the non-TBI patients showed command following. The data of the motor imagery task in UWS patients were, however, later reanalyzed using a different methodology, after which no evidence for command following was found (Goldfine et al., 2013), indicating that the motor imagery results should be interpreted with caution. One smaller and later study showed that command following could be reliably detected with only three electrodes in all four MCS patients assessed (mixed etiologies) (Coyle et al., 2015), yet given the sample size of the study, these results may not be representative of the MCS population. The EEG-based mental imagery paradigm seems sensitive to false negative, as it does not work for all healthy individuals. For example, only 2 out of 10 healthy subjects were able to use this technique after two sessions of imagined hand/foot movement (Müller-Putz et al., 2013). Nevertheless, another study found above change level classification for 19 out of 20 healthy control subjects after 60 min of training, suggesting that these subjects could potentially use this BCI for communication, yet actual communication was not attempted (Ortner et al., 2015). One consideration regarding the motor imagery-based approach is that the sensorimotor function (and pathways) of many DOC and LIS patients is affected. Therefore, it might be more sensible to target other imagery tasks, such as spatial navigation. This task is, however, less sensitive to picking up command following than motor-related EEG tasks (Horki et al., 2014). When higher-level cognitive functions were probed, it was possible to decode in 5 late-state ALS patients whether they were thinking about self-referential memories or whether they were doing a nonmemory related task with similar accuracy to that in the 14 healthy controls (Hohmann et al., 2016).

### Steady-state visually evoked potentials (SSVEPs)

SSVEPs are the neural responses to visual stimulation at specific frequencies (Regan, 1977). The visual cortex shows electric activity in the same frequency band (and harmonic frequencies) at which the retina is stimulated (for a review, see Vialatte et al., 2010). If multiple items are presented in an overlapping checkerboard pattern, the subject can attend anywhere in the grid without affecting the response, making this protocol gaze independent (Lesenfants et al., 2014). This is particularly interesting for patients without voluntary muscle control. By attending to the desired item (related, for example, to "yes" or "no"), the BCI can decode the answer using the frequency observed in the visual cortex. In a study including 14 healthy controls, about half of the subjects were able to achieve effective, online communication (Allison et al., 2008). A similar approach was implemented for LIS patients and healthy controls, with good results in two-thirds of the healthy controls and one of the four LIS patients (Fig. 11.3D) (Lesenfants et al., 2014). A four-choice SSVEP, with four different frequencies, giving the opportunity for faster communication, was also used successfully in five LIS patients (Hwang et al., 2016). Measures of spectral entropy during the periods of attention (concentrating on a specific frequency) as compared to the passive viewing condition increased significantly for LIS patients but not for UWS patients, suggesting that the SSVEP protocol could be used as a diagnostic and communication tool for consciousness (Lesenfants et al., 2016b).

## Spelling devices

Apart from the detection of awareness, the P3 has been proven useful for spelling. The P3 response can be employed for selecting letters and characters presented in a grid in which the rows and columns are flashing repeatedly. To spell, the user has to attend to the desired item and count how many times the character flashes. In a mixed group of LIS patients (ALS and patients who suffered from acquired brain injury), the overall accuracy for a visual P3-spelling BCI was 70%, while healthy subjects reached an accuracy of 90% (Ortner et al., 2011). This suggests that results from healthy subjects cannot always be extrapolated to patients. In the case of visual impairment or gaze fixation problems, the visual P3-spelling protocol is challenging. However, it can be adjusted to an auditory protocol as well, with only slightly worse results than with the visual spelling paradigm in healthy subjects (Furdea et al., 2009). On the other hand, in patients with late-stage ALS, the auditory speller performed significantly worse than the visual speller (Kübler et al., 2009). Another study found congruent results, with only three out of seven LIS patients able to achieve above-chance level accuracies using the auditory P3-based speller, compared to all seven patients with the SSVEP-based BCI (Combaz et al., 2013). When comparing an auditory P3- and SSVEP-based spelling BCI, it seems that the SSVEP version is easier to use with LIS patients. However, future adjustments might improve the system for patients who do not have voluntary gaze control. Results obtained in healthy volunteers are encouraging and suggest that, with sufficient training, the auditory P3 speller might work as efficiently as the visual version (Klobassa et al., 2009).

In a very innovative fMRI study using different mental tasks and task delays, hemodynamic responses were measured and decoded to select letters (Sorger et al., 2012). The paradigm enables spelling in real time on a single trial basis and does not require pretraining. It seems that fMRI is a powerful tool for communication purposes and it would be beneficial for these techniques to be tried with DOC patients (Sorger et al., 2009). For further reading on this topic, please refer to Chapter 21 on real-time fMRI for brain-computer interfacing.

## Alternatives to brain activity-based BCIs

As alternatives to BCI functioning through brain activity, other physiological activity can be used to probe command following and communication. One out of 14 MCS patients was able to stop the ongoing music to command by breathing vigorously (using a sniffing tool), but this patient was not able to show command following with motor output (Charland-Verville et al., 2014). This assistive device was also used in LIS patients who were asked to actively sniff to control a speller, with similar speed and accuracy to a P3-based speller (Plotkin et al., 2010). Another objective way to detect voluntary behavioral command following is offered by electromyography (EMG), even when responses are subthreshold for behavioral recognition. Suprathreshold EMG activity related to command following (e.g., "move your left hand," "move your right hand") was observed in two MCS patients (one MCS− and one MCS+) and in one of eight UWS patients (Bekinschtein et al., 2008). In a following study on a bigger cohort of patients, only 1 out of 10 UWS and 3 out of 20 MCS+ patients (and none of the 8 MCS− patients) showed signs of command following (Habbal et al., 2014). This suggests that a high false negative rate is associated with the EMG technique, perhaps because it is challenging to know which command the patient could react to best. However, when patients are presented with more trials, 2 out of 8 MCS−, all MCS+ ($n=14$), EMCS ($n=3$), and LIS ($n=2$) patients showed signs of suprathreshold command following (Lesenfants et al., 2016a,b). Interestingly, only 6 of the 14 MCS+ patients showed behavioral signs of command following on the day of the EMG assessment, suggesting that the technique might contribute to more sensitive clinical diagnosis.

The aforementioned methods all require some, albeit minimal, level of residual voluntary motor control. In CLIS patients, pupil reactions could be measured after (non-)command following. Subtle pupil dilation can be related to a variety of mental functions. Indeed, about 50% of the LIS patients were able to reliably communicate by performing a complex arrhythmic task associated with a "yes" response (and "no" was associated with rest) (Stoll et al., 2013). Employing this method, even one MCS patient was able to follow commands (Stoll et al., 2013). Also, salivary pH can be used to communicate. When imagining the taste of lemon, the pH of saliva decreases, and it increases when imagining the taste of milk. This method, which does not require any voluntary muscle control, was tested and used successfully in one late-stage ALS patient (Wilhelm et al., 2006). Assistive technologies based on minimal muscle control and other physiological reactions that do not require muscle control are appealing solutions, as they are robust, simple, and allow for a huge variety of applications. This makes them promising tools for clinical practice, as compared to fMRI-based communication and EEG-based BCIs, which usually require more training and concentration and are more sensitive to noise.

## FUTURE DIRECTIONS OF BCI RESEARCH FOR DOC PATIENTS

Since the field of BCI research specifically for DOC patients is relatively limited, there are many future directions. The patient population is relatively small, so it is important to study the needs of every single patient. Based on that research, the BCI with the highest a priori success rate could be investigated further, possibly leading to patient-tailored BCI systems. In this section, the various future directions of BCI research in DOC patients are discussed further, in terms of both BCI setup and data analysis. General recommendations for BCI research in DOC patients are provided.

### Future directions for existing BCI approaches

BCI applications targeting more than one sense might be valuable extensions of the ordinary paradigms that target one modality. The discriminatory power between target and nontarget stimuli increases with a simultaneous audiovisual P3 task, compared to the auditory-only and visual-only task, in healthy volunteers and DOC patients (Wang et al., 2015). The functionality of audiovisual integration was also shown in a case study with one clinical MCS patient who was able to communicate with 86.5% accuracy by focusing on audiovisually presented "yes" and "no" (Wang et al., 2016). Taking it a step further, hybrid BCI systems aim to combine a BCI with another BCI or with a different kind of physiological input, such as an eye tracker or heart rate monitor (for further reading, see Pfurtscheller et al., 2010). The possibilities for application are much wider than for a single BCI system, because different modalities can be combined in one system serving different actions, such as focusing on an item and selecting it. The combination of an SSVEP and P3 experiment to attend familiar but not unfamiliar photos was successful in probing command following in two DOC patients who were unable to show command following at the behavioral level (Pan et al., 2014). Importantly, the combination of the SSVEP and P3 task was more successful than the separate paradigms. In a similar experiment, combining SSVEP and P3 responses for number recognition, number comparison, and mental calculation was tested (Li et al., 2015b). One-third of the UWS and MCS patients showed above-chance level accuracies, which suggests that command following and arrhythmic abilities could be evaluated through this hybrid BCI system. The literature on hybrid BCI use in DOC patients is still limited, but in the near future it is likely that new advances will be made to facilitate BCI use in DOC patients, increasing the number of patients who might profit from BCIs. Moreover, attention deficits, gaze problems or visual deficits, and auditory deficits could become less problematic when multiple strategies are used at once.

Another interesting future direction for BCI research in DOC patients is the assessment of cognition. An inventive application of the P3 paradigm combined flashes of the standard and deviant stimuli with emotional movie clips (i.e., crying and laughing), which were correctly recognized and attended upon request by three out of eight DOC patients (Pan et al., 2018). Another study employed fNIRS to assess arithmetic capabilities of DOC patients, unfortunately with limited success (Kurz et al., 2018). Still, the evaluation of cognitive capabilities in DOC patients is a line of research worth pursuing. Practically speaking, for any kind of BCI, it is crucial to bring the patient into the best possible state before starting the BCI session. The patient should be aroused when perceived as becoming drowsy, or the session should be discontinued. A more active way of increasing the level of the patient's awareness is to apply low-intensity transcranial electrical current stimulation over the frontoparietal cortex, which increases awareness in about half of MCS patients (Thibaut et al., 2014) and which could easily be applied before BCI use or during BCI use in a closed loop system. tDCS might increase cortical excitability in DOC patients and therefore could increase the detectability of changes in brain states used by the BCI (Bai et al., 2017). However, it is challenging to predict what the specific interactions between tDCS and BCI would be. Evidence exists for the loss of language network integrity in MCS – patients (Bruno et al., 2012), and therefore these patients are likely to have troubles perceiving and producing language when prompted. BCIs that are language independent, such as those using symbols instead of letters (Koul et al., 1998; Müller et al., 2009), could be developed to specifically target MCS – and aphasic patients. Invasive BCIs, where the recording probes are implanted in the patient's head or body, have the advantage of being less sensitive to noise. A late-state ALS patient (see Chapter 7 about communication for more information regarding BCI communication technologies) had electrodes implanted in the motor cortex and could spell letters by imagining hand movements (Vansteensel et al., 2016). This and successful case might open a door for future LIS and DOC patients. Especially in DOC patients, who typically present lower levels of brain activity that could easily be lost in noise, invasive BCIs could be used to pick up a more stable and stronger signal. Recent applications in other patient populations have shown that BCIs can be used to decode phonemes in the sensorimotor cortex (Ramsey et al., 2017) and the ventral motor cortex (Ibayashi et al., 2018). Even if speech-decoding BCIs are challenging to implement and use (Martin et al., 2018), they might give a voice to otherwise noncommunicating DOC, EMCS, or LIS patients. A drawback for noncommunicative DOC patients is that it is difficult to obtain the patient's consent to implementation. Yet the study of a patient described by Wilhelm et al. (2006) proves that consent for surgery can be given by using another noninvasive BCI, in this case through pH-based BCI.

DOC patients often suffer from severe spasticity, and thus have no or limited motor control (Thibaut et al., 2015). Assistive technologies could be designed for regaining some level of motor control. Some tetraplegic patients could control a robotic arm with an EEG-based BCI (Onose et al., 2012). Patients with spinal cord injury were able to walk and complete tasks in a virtual reality environment by controlling an EEG-based BCI. Once such a system worked reliably, it could be combined with an exoskeleton to restore the patient's motor control (King et al., 2012). However, this kind of assistive technology needs more development before it can be applied in DOC, EMCS, or LIS patients.

### Advances in data processing

More sophisticated data processing and analysis techniques could contribute to improvements in BCIs for DOC patients. One of the major challenges regarding BCIs for DOC patients is the low certainty performance of the subjects (i.e., the subjects are likely to perform close to chance level). Involving more sophisticated machine-learning techniques might help to overcome this problem (see Chapter 23 on machine learning for more details). Indeed, the application of sparse dictionaries before the feature selection step increased the classifier performance levels in healthy volunteers, with hope for future application in DOC patients (Victorino et al., 2015). As mentioned earlier in the chapter, auditory-based BCIs do not depend on gaze, but they have the disadvantage of decreased performance and achieve lower accuracy rates as a consequence. More complex analysis techniques such as Bayesian approaches could overcome this issue by defining the *a priori* accuracy as a function of the signal-to-noise ratio (Lopez-Gordo et al., 2012). These kinds of improved analysis techniques might offer patients with visual difficulties the possibility of using BCIs based on other modalities in the future. However, it is important to bear in mind that classification techniques other than those used for healthy subjects might be better suited for DOC patients (Höller et al., 2013), hampering the translation from healthy subject research to DOC patients.

## General guidelines for BCIs in DOC patients

There are some general guidelines to take into account for successful BCI applications in DOC patients. Foremost, the BCI should reach a high accuracy in control subjects and should obtain negative results in control trials (passive listening/instructing the subject not to perform the task). The signal should be robust to noise, or at least have a very good signal-to-noise ratio. To use a BCI, different cognitive functions are required, which might not always be the case in (DOC) patients. Language comprehension needs to be intact (to understand the task); the patient must be able to select the correct object/target and keep it in working memory (in order to remember the task instructions); and the patient must be able to pay continuous attention to/focus on the target. Whenever one of these elements is lacking, the BCI assessment is likely to fail. For these reasons, it is important to realize that negative results are not evidence for the absence of awareness or command following (Sanders et al., 2013). Indeed, negative results can also occur in healthy volunteers (Guger et al., 2009; Allison et al., 2010). Patients who show signs of consciousness often show them in a fluctuating fashion, as demonstrated in the resting-state EEG in MCS patients (Piarulli et al., 2016). These arousal fluctuations also affect behavioral diagnosis, which is only reliable after five CRS-R assessments within a two-week period (Wannez et al., 2017a). BCI results tend to vary across sessions and conditions (Pokorny et al., 2013), and it is likely that multiple BCI sessions will be required before consistent conclusions can be drawn. Therefore, it is essential that the acquisitions are fast and reproducible in order to obtain reliable results. Rehabilitation centers are an ideal environment for BCI use in this population, as time for multiple assessments is limited in the acute hospital setting soon after the injury. Most BCI tasks are of complex nature and repeated sessions may help the patient to train in order to learn the task and increase performance in the long term. Alternatively, repetitive measurements of arousal fluctuations could be implemented in the BCI to determine the best moment to attempt BCI use, as in a closed-loop setup.

More than half (62%) of LIS patients use assistive technologies, indicating that for this population technologies are made widely available (Lugo et al., 2015). LIS patients suffer from changes in experienced identity due to their paralyzed body (Nizzi et al., 2012). As these technologies could help to overcome limitations related to paralysis, the quality of life might be improved. Indeed, one late-stage ALS patient has been using a P3-speller BCI for a study period of over 2.5 years, enabling the patient to continue his scientific career and contributing to a good quality of life (Sellers et al., 2010). On the other hand, a metaanalysis of EEG-based BCIs used in 35 ALS-LIS patients found that, in the 7 CLIS patients, communication by means of BCI was never established (Kübler and Birbaumer, 2008). Perhaps EEG signals are not sensitive enough to detect mental command following and communication, and other techniques such as fNIRS may be more hopeful for the future (Chaudhary et al., 2016). It is challenging to extrapolate these findings to see how BCI might affect the population of DOC patients, but the availability of assistive technologies in the LIS population is very promising for the improvement of quality of life in DOC patients. Associations for DOC and LIS patient groups, such as the Association of Locked-in Syndrome (ALIS) in France (http://www.alis-asso.fr), could be key organizations for updating patients on the newest developments and possibilities, and they could help to minimize the gap between research and real-life applications. Even if it seems that BCIs used during rehabilitation are still in their infancy stage, so far at least two commercial systems are available that can be used during rehabilitation: mindBEAGLE from g.tec (Annen et al., 2016, 2018; Guger et al., 2017; Chatelle et al., 2018; Spataro et al., 2018) and the C-Eye system from AssisTech.

## CONCLUSION

DOC patients not only suffer from awareness deficits, but often also experience auditory, visual, and language-processing problems, arousal fluctuations, and muscular deficits. Therefore, BCI research for DOC patients is a challenging field. Prior to probe communication or use of assistive technologies, awareness and consistent command following must be detected. Since the first fMRI-based BCI, which enabled seemingly unconscious patients to follow commands and communicate, various EEG and other portable approaches have been employed. Different P3 paradigms, visually evoked potentials, motor imagery tasks, and motor independent tasks have been used with varying success. Further research employing hybrid systems and more complex analysis techniques are promising for the future use of BCI in DOC patients.

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### References

Allison BZ et al. (2008). Towards an independent brain–computer interface using steady state visual evoked potentials. Clin Neurophysiol 119: 399–408. https://doi.org/10.1016/j.clinph.2007.09.121.

Allison B et al. (2010). BCI demographics: how many (and what kinds of ) people can use an SSVEP BCI? IEEE Trans Neural Syst Rehabil Eng 18: 107–116.

Annen J et al. (2016). MindBEAGLE: an EEG-based BCI developed for patients with disorders of consciousness. In: BCI meeting proceedings.

Annen J et al. (2018). BCI performance and brain metabolism profile in severely brain-injured patients without response to command at bedside. Front Neurosci 12: 1–8. https://doi.org/10.3389/fnins.2018.00370.

Bai Y et al. (2017). TDCS modulates cortical excitability in patients with disorders of consciousness. Neuroimage Clin 15: 702–709. https://doi.org/10.1016/j.nicl.2017.01.025.

Bekinschtein TA et al. (2008). Can electromyography objectively detect voluntary movement in disorders of consciousness? J Neurol Neurosurg Psychiatry 79: 826–828. https://doi.org/10.1136/jnnp.2007.132738.

Bekinschtein TA et al. (2009). Neural signature of the conscious processing of auditory regularities. Proc Natl Acad Sci U S A 106: 1672–1677. https://doi.org/10.1073/pnas.0809667106.

Bodien YG, Giacino JT, Edlow BL (2017). Functional MRI motor imagery tasks to detect command following in traumatic disorders of consciousness. Front Neurol 8: 688. https://doi.org/10.3389/fneur.2017.00688.

Bruno M-A 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: 1373–1384. https://doi.org/10.1007/s00415-011-6114-x.

Bruno MA et al. (2012). Functional neuroanatomy underlying the clinical subcategorization of minimally conscious state patients. J Neurol 259: 1087–1098. https://doi.org/10.1007/s00415-011-6303-7.

Cavinato M et al. (2009). Post-acute P300 predicts recovery of consciousness from traumatic vegetative state. Brain Inj 23: 973–980. https://doi.org/10.3109/02699050903373493.

Chapman RM, Bragdon HR (1964). Evoked responses to numerical and non-numerical visual stimuli while problem solving. Nature 203: 1155–1157.

Charland-Verville V et al. (2014). Detection of response to command using voluntary control of breathing in disorders of consciousness. Front Hum Neurosci 8: 1020. https://doi.org/10.3389/fnhum.2014.01020.

Chatelle C et al. (2018). Feasibility of an EEG-based brain–computer interface in the intensive care unit. Clin Neurophysiol 129: 1519–1525. https://doi.org/10.1016/j.clinph.2018.04.747.

Chaudhary U, Birbaumer N, Ramos-Murguialday A (2016). Brain-computer interfaces in the completely locked-in state and chronic stroke. In: Progress in brain research, first edn. Elsevier B.V. https://doi.org/10.1016/bs.pbr.2016.04.019.

Chennu S, Bekinschtein TA (2012). Arousal modulates auditory attention and awareness: insights from sleep, sedation, and disorders of consciousness. Front Psychol 3: 1–9. https://doi.org/10.3389/fpsyg.2012.00065.

Chennu S et al. (2013). Dissociable endogenous and exogenous attention in disorders of consciousness. Neuroimage Clin 3: 450–461. https://doi.org/10.1016/j.nicl.2013.10.008.

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: 1–14. https://doi.org/10.1371/journal.pone.0073691.

Comercherom DM, Polich J (1999). P3a and P3b from “novel” and “typical” stimuli. Psychophysiology 110: 24–30.

Comte A et al. (2015). On the difficulty to communicate with fMRI-based protocols used to identify covert awareness. Neuroscience 300: 448–459. https://doi.org/10.1016/j.neuroscience.2015.05.059.

Coyle D et al. (2015). Sensorimotor modulation assessment and brain–computer interface training in disorders of consciousness. Arch Phys Med Rehabil 96: S62–S70. https://doi.org/10.1016/j.apmr.2014.08.024.

Cruse D et al. (2011). Bedside detection of awareness in the vegetative state: a cohort study. Lancet 378: 2088–2094. https://doi.org/10.1016/S0140-6736(11)61224-5. Elsevier Ltd.

Cruse D et al. (2012). Relationship between etiology and covert cognition in the minimally conscious state. Neurology 78: 816–822. https://doi.org/10.1212/WNL.0b013e318249f6f0.

Curley WH et al. (2018). Characterization of EEG signals revealing covert cognition in the injured brain. Brain 141: 1404–1421. https://doi.org/10.1093/brain/awy070.

Daltrozzo J et al. (2007). Predicting coma and other low responsive patients outcome using event-related brain potentials: a meta-analysis. Clin Neurophysiol 118: 606–614. https://doi.org/10.1016/j.clinph.2006.11.019.

Dehaene S, Changeux JP (2011). Experimental and theoretical approaches to conscious processing. Neuron 70: 200–227. https://doi.org/10.1016/j.neuron.2011.03.018. Elsevier Inc.

Demertzi A et al. (2013). Pain perception in disorders of consciousness: neuroscience, clinical care, and ethics in dialogue. Neuroethics 6: 37–50. https://doi.org/10.1007/s12152-011-9149-x.

Edlow BL et al. (2017). Early detection of consciousness in patients with acute severe traumatic brain injury. Brain 140: 2399–2414. https://doi.org/10.1093/brain/awx176.

Faugeras F et al. (2012). Event related potentials elicited by violations of auditory regularities in patients with impaired consciousness. Neuropsychologia 50: 403–418. https://doi.org/10.1016/j.neuropsychologia.2011.12.015. Elsevier Ltd.

Forgacs PB et al. (2014). Preservation of electroencephalographic organization in patients with impaired consciousness and imaging-based evidence of command-following. Ann Neurol 76: 869–879. https://doi.org/10.1002/ana.24283.

Furdea A et al. (2009). An auditory oddball (P300) spelling system for brain–computer interfaces. Psychophysiology 46: 617–625. https://doi.org/10.1111/j.1469-8986.2008.00783.x.

Giacino JT, Kalmar K (2004). Coma recovery scale revised administration and scoring guidelines, Solaris Health System.

Giacino JT et al. (2002). The minimally conscious state: definition and diagnostic criteria. Neurology 58: 349–353. https://doi.org/10.1212/WNL.58.3.349.

Giacino JT et al. (2009). Behavioral assessment in patients with disorders of consciousness: gold standard or fool’s gold? Prog Brain Res 177: 33–48. https://doi.org/10.1016/S0079-6123(09)17704-X. Elsevier.

Goldfine AM et al. (2013). Reanalysis of "Bedside detection of awareness in the vegetative state: a cohort study". Lancet 381: 289–291. https://doi.org/10.1016/S0140-6736(13)60125-7. Reanalysis.

Gosseries O, Zasler ND, Laureys S (2014). Recent advances in disorders of consciousness: focus on the diagnosis. Brain Inj 28: 1141–1150. https://doi.org/10.3109/02699052.2014.920522.

Guger C et al. (2009). How many people are able to control a P300-based brain–computer interface (BCI)? Neurosci Lett 462: 94–98. https://doi.org/10.1016/j.neulet.2009.06.045.

Guger C et al. (2017). Complete locked-in and locked-in patients: command following assessment and communication with vibro-tactile P300 and motor imagery brain–computer interface tools. Front Neurosci 11: 1–11. https://doi.org/10.3389/fnins.2017.00251.

Guger C et al. (2018). Assessing command-following and communication with vibro-tactile P300 brain–computer interface tools in patients with unresponsive wakefulness syndrome. Front Neurosci 12: 1–9. https://doi.org/10.3389/fnins.2018.00423.

Habbal D et al. (2014). Volitional electromyographic responses in disorders of consciousness. Brain Inj 28: 1171–1179. https://doi.org/10.3109/02699052.2014.920519.

Hauger SL et al. (2015). Neurophysiological indicators of residual cognitive capacity in the minimally conscious state. Behav Neurol 2015: 1–12. https://doi.org/10.1155/2015/145913.

Haugg A et al. (2018). Do patients thought to lack consciousness retain the capacity for internal as well as external awareness? Frontiers Neurol 9: 492. https://doi.org/10.3389/fneur.2018.00492.

Hohmann MR et al. (2016). A cognitive brain–computer interface for patients with amyotrophic lateral sclerosis. Prog Brain Res 228: 221–239. https://doi.org/10.1016/bs.pbr.2016.04.022.

Höller Y et al. (2013). Comparison of EEG-features and classification methods for motor imagery in patients with disorders of consciousness. PLoS One 8: e80479. https://doi.org/10.1371/journal.pone.0080479.

Horki P et al. (2014). Detection of mental imagery and attempted movements in patients with disorders of consciousness using EEG. Front Hum Neurosci 8: 1009. https://doi.org/10.3389/fnhum.2014.01009.

Hwang H-J et al. (2016). Clinical feasibility of brain–computer interface based on steady-state visual evoked potential in patients with locked-in syndrome: case studies. Psychophysiology 54: 444–451. https://doi.org/10.1111/psyp.12793.

Ibayashi K et al. (2018). Decoding speech with integrated hybrid signals recorded from the human ventral motor cortex. Front Neurosci 12: 221. https://doi.org/10.3389/fnins.2018.00221.

Jeon Y et al. (2011). Event-related (De)synchronization (ERD/ERS) during motor imagery tasks: implications for brain–computer interfaces. Int J Ind Ergon 41: 428–436. https://doi.org/10.1016/j.ergon.2011.03.005. Elsevier Ltd.

Jox RJ et al. (2012). Disorders of consciousness: responding to requests for novel diagnostic and therapeutic interventions. Lancet Neurol 11: 732–738. https://doi.org/10.1016/S1474-4422(12)70154-0. Elsevier Ltd.

King CE et al. (2012). Operation of a brain–computer interface walking simulator by users with spinal cord injury. J Neuroeng Rehabil 10: 1–14.

King JR et al. (2013). Single-trial decoding of auditory novelty responses facilitates the detection of residual consciousness. Neuroimage 83: 726–738. https://doi.org/10.1016/j.neuroimage.2013.07.013. Elsevier Inc.

Klobassa DS et al. (2009). Toward a high-throughput auditory P300-based brain–computer interface. Clin Neurophysiol 120: 1252–1261. https://doi.org/10.1016/j.clinph.2009.04.019.

Koul RK et al. (1998). Comparison of graphic symbol learning in individuals with aphasia and right hemisphere brain damage. Brain Lang 62: 398–421. https://doi.org/10.1006/brln.1997.1908.

Kübler A, Birbaumer N (2008). Brain–computer interfaces and communication in paralysis: extinction of goal directed thinking in completely paralyzed patients? Clin Psychol 119: 2658–2666. https://doi.org/10.1016/j.clinph.2008.06.019.

Kübler 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. https://doi.org/10.1111/j.1749-6632.2008.04122.x.

Kurz E et al. (2018). Towards using fNIRS recordings of mental arithmetic for the detection of residual cognitive activity in patients with disorders of consciousness (DOC). Brain Cogn 125: 78–87. https://doi.org/10.1016/j.bandc.2018.06.002. Elsevier.

Laureys S (2005). The neural correlate of (un)awareness: lessons from the vegetative state. Trends Cogn Sci 9: 556–559. https://doi.org/10.1016/j.tics.2005.10.010.

Laureys S, Owen AM, Schiff ND (2004). Brain function in coma, vegetative state, and related disorders. Lancet 3: 537–546.

Laureys S et al. (2010). Unresponsive wakefulness syndrome: a new name for the vegetative state or apallic syndrome. BMC Med 8: 1–4. https://doi.org/10.1186/1741-7015-8-68. BioMed Central Ltd.

Lesenfants D, Habbal D, Lugo Z et al. (2014). An independent SSVEP-based brain–computer interface in locked-in syndrome. J Neural Eng 11: 035002. https://doi.org/10.1088/1741-2560/11/3/035002.

Lesenfants D et al. (2016a). Electromyographic decoding of response to command in disorders of consciousness. Neurology 87: 2099–2107. https://doi.org/10.1212/WNL.0000000000003333.

Lesenfants D et al. (2016b). Toward an attention-based diagnostic tool for patients with locked-in syndrome. Clin EEG Neurosci 49: 122–135. https://doi.org/10.1177/1550059416674842. Nov.

Li R et al. (2015a). Connecting the P300 to the diagnosis and prognosis of unconscious patients. Neural Regen Res 10: 473–480. https://doi.org/10.4103/1673-5374.153699.

Li Y et al. (2015b). Detecting number processing and mental calculation in patients with disorders of consciousness using a hybrid brain–computer interface system. BMC Neurol 15: 259. https://doi.org/10.1186/s12883-015-0521-z.

Lopez-Gordo MA et al. (2012). An auditory brain–computer interface with accuracy prediction. Int J Neural Syst 22: 1250009. https://doi.org/10.1142/S0129065712500098.

Lugo ZR et al. (2014). A vibrotactile P300-based brain–computer Interface for consciousness detection and communication. Clin EEG Neurosci 45: 14–21. https://doi.org/10.1177/1550059413505533.

Lugo ZR et al. (2015). Beyond the gaze: communicating in chronic locked-in syndrome. Brain Inj 9052: 1–6. https://doi.org/10.3109/02699052.2015.1004750.

Lugo ZR et al. (2016). Cognitive processing in non-communicative patients: what can event-related potentials tell us? Front Hum Neurosci 10: 569. https://doi.org/10.3389/fnhum.2016.00569.

Lulé D et al. (2013). Probing command following in patients with disorders of consciousness using a brain–computer interface. Clin Neurophysiol 124: 101–106. https://doi.org/10.1016/j.clinph.2012.04.030.

Martin S et al. (2018). Decoding inner speech using electrocorticography: progress and challenges toward a speech prosthesis. Front Neurosci 12: 422. https://doi.org/10.3389/fnins.2018.00422.

Monti M, Laureys S, Owen AM (2010a). The vegetative state. Br Med J 341: 292–296. https://doi.org/10.1136/bmj.c3765.

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

Müller IM, Buchholz M, Ferm U (2009). Text messaging with picture symbols—possibilities for persons with cognitive and communicative disabilities. Assist Technol Res Ser 25: 879. https://doi.org/10.3233/978-1-60750-042-1-879.

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: 1250037. https://doi.org/10.1142/S0129065712500372.

Nizzi MC et al. (2012). From armchair to wheelchair: how patients with a locked-in syndrome integrate bodily changes in experienced identity. Conscious Cogn 21: 431–437. https://doi.org/10.1016/j.concog.2011.10.010. Elsevier Inc.

Onose G et al. (2012). On the feasibility of using motor imagery EEG-based brain–computer interface in chronic tetraplegics for assistive robotic arm control: a clinical test and long-term post-trial follow-up. Spinal Cord 50: 599–608. https://doi.org/10.1038/sc.2012.14.

Ortner R et al. (2011). Clinical EEG and neuroscience accuracy of a P300 speller for people with motor impairments: a comparison. Clin EEG Neurosci 42: 214–218. https://doi.org/10.1177/155005941104200405.

Ortner R et al. (2015). How many people can control a motor imagery based BCI using common spatial patterns? In: 7th annual international IEEE EMBS conference on neural engineering, pp. 22–24.

Owen AM et al. (2006). Detecting awareness in the vegetative state. Science 313: 1402. https://doi.org/10.1126/science.1130197.

Pan J et al. (2014). Detecting awareness in patients with disorders of consciousness using a hybrid brain–computer interface. J Neural Eng 11: 056007. https://doi.org/10.1088/1741-2560/11/5/056007. IOP Publishing.

Pan J et al. (2018). Emotion-related consciousness detection in patients with disorders of consciousness through an EEG-based BCI system. Front Hum Neurosci 12: 1–11. https://doi.org/10.3389/fnhum.2018.00198.

Patterson JR, Grabois M (1986). Locked-in syndrome: a review of 139 cases. Stroke 17: 758–764. https://doi.org/10.1161/01.STR.17.4.758.

Perrin F et al. (2006). Brain response to one's own name in vegetative state, minimally conscious state, and locked-in syndrome. Arch Neurol 63: 562–569. https://doi.org/10.1001/archneur.63.4.562.

Pfurtscheller G, Lopes FH (1999). Event-related EEG/MEG synchronization and desynchronization: basic principles. Clin Neurophysiol 110: 1842–1857. https://doi.org/10.1016/S1388-2457(99)00141-8.

Pfurtscheller G et al. (2010). The hybrid BCI. Front Neurosci 4: 4–30. https://doi.org/10.3389/fnpro.2010.00003.

Piarulli A, Charland-Verville V, Laureys S (2015). Cognitive auditory evoked potentials in coma: can you hear me? Brain 138: 1129–1137. https://doi.org/10.1093/brain/awv041.

Piarulli A et al. (2016). EEG ultradian rhythmicity differences in disorders of consciousness during wakefulness. J Neurol 263: 1746–1760. https://doi.org/10.1007/s00415-016-8196-y. Springer Berlin Heidelberg, June.

Plotkin A et al. (2010). Sniffing enables communication and environmental control for the severely disabled. Proc Natl Acad Sci U S A 107: 14413–14418. https://doi.org/10.1073/pnas.1006746107.

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: 81–90. https://doi.org/10.1016/j.artmed.2013.07.003. Elsevier B.V.

Ramsey NF et al. (2017). Decoding spoken phonemes from sensorimotor cortex with high-density ECoG grids. Neuroimage 180: 301–311. https://doi.org/10.1016/j.neuroimage.2017.10.011. Elsevier Ltd, (April).

Regan D (1977). Steady-state evoked potentials. J Oct Soc Am 67: 1475–1489.

Sanders RD et al. (2013). Unconsciousness ≠ unresponsiveness. Anesthesiology 116: 946–959. https://doi.org/10.1097/ALN.0b013e318249d0a7.

Schettini F et al. (2015). P300 latency Jitter occurrence in patients with disorders of consciousness: toward a better design for brain computer interface applications. In: Proceedings of the annual international conference of the IEEE engineering in medicine and biology society, EMBS, 2015-November, pp. 6178–6181. https://doi.org/10.1109/EMBC.2015.7319803.

Schiff ND (2015). Cognitive motor dissociation following severe brain injuries. JAMA Neurol 72: 1413–1415. https://doi.org/10.1001/jamaneurol.2015.2899.

Schnakers C et al. (2008a). Cognitive function in the locked-in syndrome. J Neurol 255: 323–330. https://doi.org/10.1007/s00415-008-0544-0.

Schnakers C et al. (2008b). Voluntary brain processing in disorders of consciousness. Neurology 71: 1614–1620. https://doi.org/10.1212/WNL.0b013e3181bd68bc.

Schnakers C, Perrin F et al. (2009a). Detecting consciousness in a total locked-in syndrome: an active event-related paradigm. Neurocase 15: 271–277. https://doi.org/10.1080/13554790902724904.

Schnakers C, Vanhaudenhuyse A et al. (2009b). Diagnostic accuracy of the vegetative and minimally conscious state: clinical consensus versus standardized neurobehavioral assessment. BMC Neurol 9: 35. https://doi.org/10.1186/1471-2377-9-35.

Schnakers C et al. (2014). Preserved covert cognition in noncommunicative patients with severe brain injury? Neurorehabil Neural Repair 29: 308–317. https://doi.org/10.1177/1545968314547767.

Sellers EW, Vaughan TM, Wolpaw JR (2010). A brain–computer interface for long-term independent home use. Amyotroph Lateral Scler 11: 449–455. https://doi.org/10.3109/17482961003777470.

Sitt JD et al. (2014). Large scale screening of neural signatures of consciousness in patients in a vegetative or minimally conscious state. Brain 137: 2258–2270. https://doi.org/10.1093/brain/awu141.

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. https://doi.org/10.1016/S0079-6123(09)17719-1. Elsevier.

Sorger B et al. (2012). A real-time fMRI-based spelling device immediately enabling robust motor-independent communication. Curr Biol 22: 1333–1338. https://doi.org/10.1016/j.cub.2012.05.022. Elsevier Ltd.

Spataro R, Heilinger A, Allison B et al. (2018). Preserved somatosensory discrimination predicts consciousness recovery in unresponsive wakefulness syndrome. Clin Neurophysiol 129: 1130–1136. https://doi.org/10.1016/j.clinph.2018.02.131.

Stender J et al. (2014). Diagnostic precision of PET imaging and functional MRI in disorders of consciousness: a clinical validation study. Lancet 6736: 8–16. https://doi.org/10.1016/S0140-6736(14)60042-8.

Stoll J et al. (2013). Pupil responses allow communication in locked-in syndrome patients. Curr Biol 23: R647–R648. https://doi.org/10.1016/j.cub.2013.06.011. Elsevier.

Thibaut A et al. (2014). tDCS in patients with disorders of consciousness. Neurology 82: 1–7. https://doi.org/10.1212/WNL.0000000000000260.

Thibaut FA, Chatelle C, Wannez S et al. (2015). Spasticity in disorders of consciousness: a behavioral study. Eur J Phys Rehabil Med 51 (4): 389–397. Epub 2014 Nov 6. PMID: 25375186.

Tzovara A et al. (2015a). Neural detection of complex sound sequences in the absence of consciousness. Brain 138: 1160–1166. https://doi.org/10.1093/brain/awv041.

Tzovara A et al. (2015b). Reply: neural detection of complex sound sequences in the absence of consciousness? Brain 138: 1160–1166. https://doi.org/10.1093/brain/awv041.

Tzovara A et al. (2016). Prediction of awakening from hypothermic postanoxic coma based on auditory discrimination. Ann Neurol 79: 748–757. https://doi.org/10.1002/ana.24622.

Vanhaudenhuyse A, Laureys S, Perrin F (2008). Cognitive event-related potentials in comatose and post-comatose states. Neurocrit Care 8: 262–270. https://doi.org/10.1007/s12028-007-9016-0.

Vansteensel MJ et al. (2016). Fully implanted brain–computer interface in a locked-in patient with ALS. N Engl J Med 375: 2060–2066. https://doi.org/10.1056/NEJMoa1608085. Nov.

Vialatte FB et al. (2010). Steady-state visually evoked potentials: focus on essential paradigms and future perspectives. Prog Neurobiol 90: 418–438. https://doi.org/10.1016/j.pneurobio.2009.11.005.

Victorino J et al. (2015). Improving EEG-BCI analysis for low certainty subjects by using dictionary learning, IEEE, pp. 1–7.

Wang F et al. (2015). A novel audiovisual brain–computer interface and its application in awareness detection. Sci Rep 5: 9962. https://doi.org/10.1038/srep09962. Nature Publishing Group.

Wang F et al. (2016). An auditory BCI system for assisting CRS-R behavioral assessment in patients with disorders of consciousness. Sci Rep 6: 1536–1539. https://doi.org/10.1038/srep32917.

Wannez S et al. (2017a). The repetition of behavioral assessments in diagnosis of disorders of consciousness. Ann Neurol 81: 883–889. https://doi.org/10.1002/ana.24962.

Wannez S et al. (2017b). Prevalence of coma-recovery scale-revised signs of consciousness in patients in a minimally conscious state. Neuropsychol Rehabil 28: 1350–1359. https://doi.org/10.1177/1352458506070750. in press.

Wilhelm B, Jordan M, Birbaumer N (2006). Communication in locked-in syndrome: effects of imagery on salivary pH. Neurology 67: 534–535. https://doi.org/10.1212/01.wnl.0000228226.86382.5f.

Xiao J et al. (2016). An auditory BCI system for assisting CRS-R behavioral assessment in patients with disorders of consciousness. Sci Rep 6: 32917. https://doi.org/10.1038/srep32917. Nature Publishing Group.

Xiao J, Xie Q et al. (2018a). Assessment of visual pursuit in patients with disorders of consciousness based on a brain–computer interface. IEEE Trans Neural Syst Rehabil Eng 4320 (Study 1): 1–12. https://doi.org/10.1109/TNSRE.2018.2835813.

Xiao J, Pan J et al. (2018b). Visual fixation assessment in patients with disorders of consciousness based on brain–computer interface. Neurosci Bull 26: 679–690. Springer Singapore. doi: 10.1007/s12264-018-0257-z.

Zhang Y et al. (2017). Transcranial direct current stimulation in patients with prolonged disorders of consciousness: combined behavioral and event-related potential evidence. Front Neurol 8: 620. https://doi.org/10.3389/fneur.2017.00620.