Chapter 3
Brain-Computer Interfaces and its Place in the Management of Disorders of Consciousness

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Abstract
Brain-computer interfaces (BCI) constitute a growing and constantly evolving field of study showing promising applications that span a multitude of potential disciplines. In this chapter, we will introduce BCIs and the roles that different technologies and paradigms play specifically for the management of patients with a disorder of consciousness (DoC). We will provide an overview of the state of the art concerning BCI research in the field of DoC by highlighting some of the most paramount works in the current literature. Contrasting the advances in research with current recommendations and applications in clinical practice exposes the severe lack of recognition that BCI usage receives in routine care for patients with a DoC. To conclude, we mention some potentially interesting future perspectives to further develop this domain.

Keywords: Disorders of consciousness, Brain injury, Brain-computer interface, Electroencephalography, Functional neuroimaging, Evoked potentials, Resting state, Passive paradigm, Active paradigm

What are BCIs and why can patients with a disorder of consciousness benefit from them?

A brain-computer interface (BCI) is defined as a system allowing for communication between the brain and the external environment, independent from any peripheral neural or muscular pathways [1]. The basic principle is straightforward; volatile modulation of brain activity in response to a specific task (e.g., imagination of a movement) is measured by one of many possible data acquisition techniques, processed accordingly with extraction of relevant features, and finally translated to a desired artificial output (Fig. 3.1). This direct link between the central nervous system and the user's immediate surroundings creates the opportunity to get insight into their cognition or to uncover intent, enabling users to communicate or use assistive technologies. Biomedical BCI applications often use this principle to bypass damaged motor pathways and to subsequently circumvent the associated impaired functionalities. Although the principle is simple, the patient populations that BCIs are designed for are rather heterogeneous in terms of brain damage and subsequent needs. There is no one-size-fits-all solution, leading to a plentitude of BCI acquisition, preprocessing, and analysis techniques, ideally tailored to the single patient.

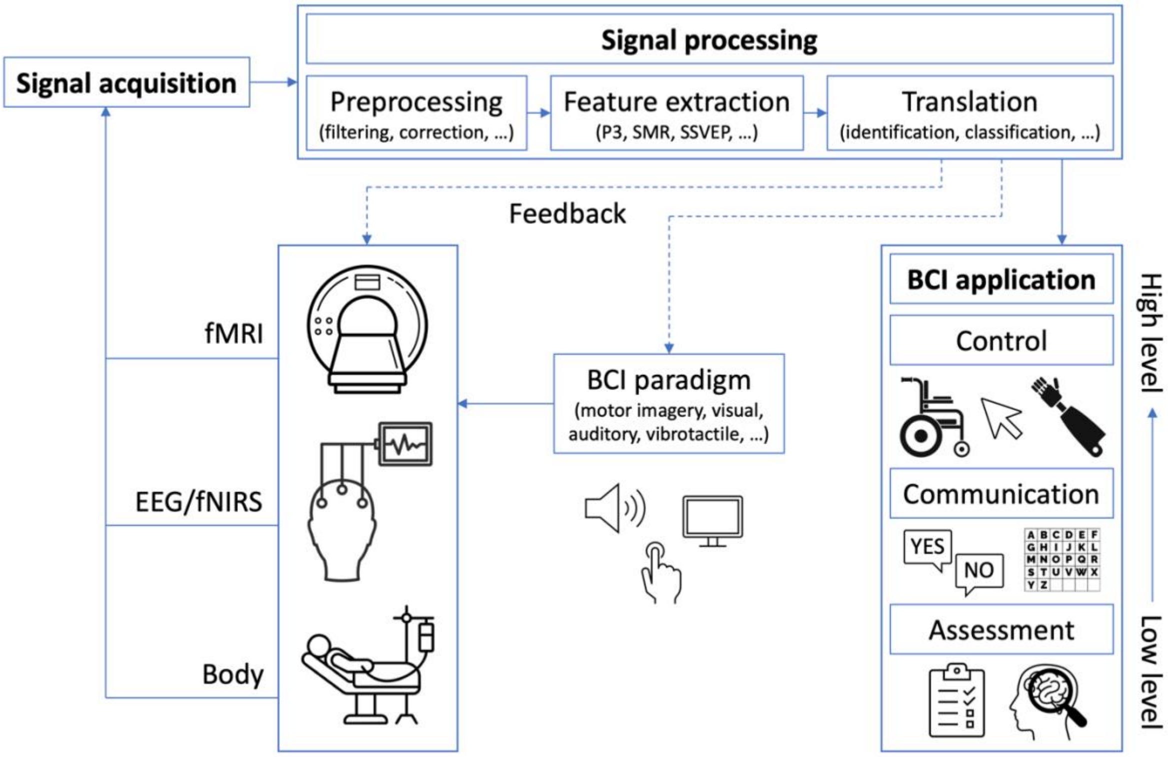

Fig. 3.1 Schematic overview of a typical BCI setup. A certain paradigm is presented to the patient, from which the response can be measured as brain activity (through direct electrophysiological recordings (e.g., EEG) or as a metabolic proxy (e.g., hemodynamic response; fMRI, fNIRS)) or using other physiological signals (e.g., EMG, EOG, breathing). The resulting signal is processed accordingly; usually consisting of preprocessing to clean the data of artifacts, extraction of relevant stimulus-related features, and translation to a useful output. This control signal depends on the specific intended BCI use, which can range from low-level applications that inform about the user's health to high-level applications of communication or control using assistive technologies. The output can additionally be reused as feedback directly to the patient or to dynamically adapt the paradigm, which then results in a closed-loop BCI.

BCI = brain-computer interface, EEG = electroencephalography, fMRI = functional magnetic resonance imaging, fNIRS = functional near-infrared spectroscopy, EMG = electromyography, EOG = electrooculography

The eventual applicability of a BCI system is heavily dependent on the choice of an appropriate data acquisition technique. Numerous possible sensory modalities exist foremost with varying degrees of invasiveness [2]. The most direct way to measure brain signals is by implanting intracortical microelectrodes that pick up extracellular potentials in the immediate vicinity of neural populations of interest [3]. This technique allows to capture neural activity at virtually any desired location within the brain with a very high precision. Partially invasive BCIs on the other hand rely on electrocorticography (ECoG), during which electrodes are placed on the brain surface to detect electrical activity originating from the cerebral cortex. Both techniques measure closely to the generators for their respective perceptible activity which minimizes attenuations and distortion caused by propagation of the signals throughout multiple tissues. The resulting data consequently requires limited additional preprocessing due to the relative lack of noise (i.e., no eyeblink or muscle artifacts to remove, no need to correct for head movements). These recordings are of high quality, benefitting from a good spatial resolution (high precision - albeit never whole-brain) alongside an excellent temporal resolution in the order of milliseconds. The main downside of invasive techniques is undoubtedly the need for surgery, as craniotomy is required even for partially invasive interventions. The risk of complications such as infection or tissue damage, deteriorating effects such as rejection or encapsulation of the electrodes, and limited flexibility in terms of finetuning options following implantation, dictates that invasive BCIs should only be considered when deemed overwhelmingly beneficiary without (further) compromising the user's health [4]. The aforementioned considerations alongside more general ethical issues associated with implantation of medical devices explain why the vast majority of BCI applications are strictly noninvasive.

In this chapter, we specifically focus on BCIs for severely brain-injured patients with disorders of consciousness (DoC). These patients form a heterogenous group who, following a period of coma, experience no or limited awareness of themselves or the environment. Broadly, the unresponsive wakefulness syndrome (UWS; sometimes also referred to as vegetative state (VS)) [5] and minimally conscious state (MCS) [6] can be distinguished. The former group is fully unaware despite periods of arousal, while the latter shows fluctuating awareness levels over time. MCS patients can be subcategorized in MCS- or MCS+, based on the absence or presence of preserved language processing [7] and more specifically command following, intelligible vocalization, and intentional communication [8]. Patients who recover functional communication or object use are considered emergent from MCS (EMCS) [6]. Although no longer considered as DoC by definition, they can greatly benefit from BCI applications to facilitate communication or in the form of assistive technology as they are often still severely disabled. Nevertheless, patients with a DoC are vulnerable as a result of their compromised health conditions, which is why most (if not all) BCI applications in this population exclusively rely on noninvasive data acquisition techniques.

One of the earliest and undoubtedly the most famous application of a BCI paradigm in patients with DoC stems from 2006 and concerns the work of Owen and colleagues [9]. They were able to probe awareness in a patient diagnosed as unresponsive at the bedside through detection of reproducible responses to mental imagination of playing tennis and a spatial navigation task using functional magnetic resonance imaging (fMRI). fMRI scanners are however large, stationary, and very expensive, limiting their availability to hospital settings. One can also argue whether examples like these can truly be considered a BCI, since it lacks the often-associated real-time aspect due to long acquisition times and the eventual analysis that occurs offline after the fact (even if online applications are possible, e.g., [10]). Another technique which relies on brain activity measured as the associated hemodynamic response is functional near-infrared spectroscopy (fNIRS). fNIRS and fMRI both estimate blood flow properties; the former based on changes in light absorption of (de)oxygenated blood (with a high temporal resolution) rather than the magnetic properties leveraged by the latter. Certain fNIRS-based BCI systems allow for direct visualization of the hemodynamic response which shows whether users are correctly performing the presented task in real time [11]. fNIRS offers a lower spatial resolution compared to fMRI, and the number of applications in practice remains limited since these acquisition systems are not commonly available. Current BCI research focusses predominantly on electroencephalography (EEG), which captures electrical fields at the scalp level originating from the summated postsynaptic potentials of synchronously firing pyramidal neurons in the cortex. EEG provides a direct measure of brain activity equivalent to both discussed invasive techniques and shares their high temporal resolution, with the added value of being more easily applicable and having few contraindications, making it a valuable option for patients with a DoC. A tradeoff is again the significantly worse spatial resolution due to the presence of volume conduction and the overall noisier signal, resulting in the need for extensive preprocessing. fNIRS is an ideal candidate for multimodal use with EEG because of their complementary nature [12]. Another important aspect to consider is the fact that both these methods are restrained to the cortex, while fMRI can reveal subcortical neural activity as well, such as in the parahippocampal gyrus for spatial navigation [9, 13].

Importantly, in this clinical population of patients with a DoC, BCIs have the capacity of being used as a method of assessment of (covert) consciousness, which once detected can be exploited to assess higher-level functions like communication. The following section will delve deeper into this aspect and the subsequent implications it has on diagnostic taxonomy.

BCIs help to refine the taxonomy of disorders of consciousness

Behavioral assessment is currently still the gold standard for diagnosis of patients with a DoC in clinical practice, by evaluating auditory, visual, (oro-)motor, and communication abilities. Without the use of standardized scales such as the Coma Recovery Scale-Revised (CRS-R) [14], misdiagnosis percentages have been observed as high as 41% [15]. Regardless of sensitive behavioral scales, factors such as deafness, blindness, motor deficits, and fluctuations in arousal may hamper the patient's ability to physically respond and thus mask signs of consciousness. It has recently become strikingly apparent that the underlying conscious state of patients with a DoC is not always unambiguously reflected by their behavioral profile at the bedside. This can go beyond inconsistencies caused by fluctuations in awareness, which should be accounted for through repetition of behavioral assessments [16]. Overt awareness, as quantified using methods such as the CRS-R or its faster alternative SECONDs [17], is in certain cases an underestimation of a patient's residual cognitive capabilities. Neurophysiological or neuroradiological evaluation can bypass the behavioral impairments that often lie at the root of this problem and can therefore provide a more accurate diagnosis. The emergence of BCI usage in DoC research has led to the conceptualization of covert awareness [18, 19]; the presence of non-behavioral signs of consciousness as revealed by neuroimaging or electrophysiological paradigms.

Notably, covert awareness as a concept is descriptive rather than diagnostic. Actual diagnostic terms have been used almost interchangeably throughout the literature. A recent systematic review showed that a consensus for an unambiguous nomenclature to define these clinical entities has yet to be reached [20]. The authors pointed out that prior use of the proposed taxonomies could be considered contradictory between certain studies. Moreover, one specific instance of covert awareness can often not be univocally represented by a single term since there is a considerable degree of overlap between definitions, and there does not seem to be a clear hierarchical structure either. Amongst the different terms proposed for covert awareness are MCS star or non-behavioral MCS (MCS*), cognitive motor dissociation (CMD), higher-order cortex motor dissociation (HMD), functional locked-in syndrome (LIS) and certain subcategories of the cortically mediated state (CMS) (Fig. 3.2). MCS* was introduced for patients who would be behaviorally diagnosed as UWS, while their residual underlying brain activity is more in line with MCS [21]. It reflects a broad categorization also including those with preserved brain activity during the resting state [19]. CMD usually describes the subsample of patients that exhibits covert awareness in the form of covert command following in response to active paradigms specifically [22]. HMD on the other hand describes patients who show no behavioral signs of language comprehension while nevertheless exhibiting brain responses to certain passive paradigms (i.e., sound or language) [23]. MCS* similarly encompasses CMD and HMD when considering unresponsive patients according to the aforementioned definitions. Yet another related categorization has been introduced based on behavior and neuroimaging. It considers MCS patients showing relative preservation of non-communicating behavior or brain activity in resting state, passive, or active paradigms to be in a cortically mediated state or CMS and patients showing communication at the bedside or using neuroimaging to be in the conscious state (CS) [24]. Finally, functional locked-in syndrome denoted the dissociation between patients' motor dysfunction and their preserved higher cognitive functions as shown by the ability to communicate using functional imaging techniques only [7]. Its use has been criticized over the years due to the apparent association with LIS, which is by definition not a DoC and concerns only patients with a very distinct neuropathology [21]. As highlighted in a recent gap analysis paper on CMD conducted by the Coma Science Working Group, there is an urgent need to refine the terminology of these different states [25].

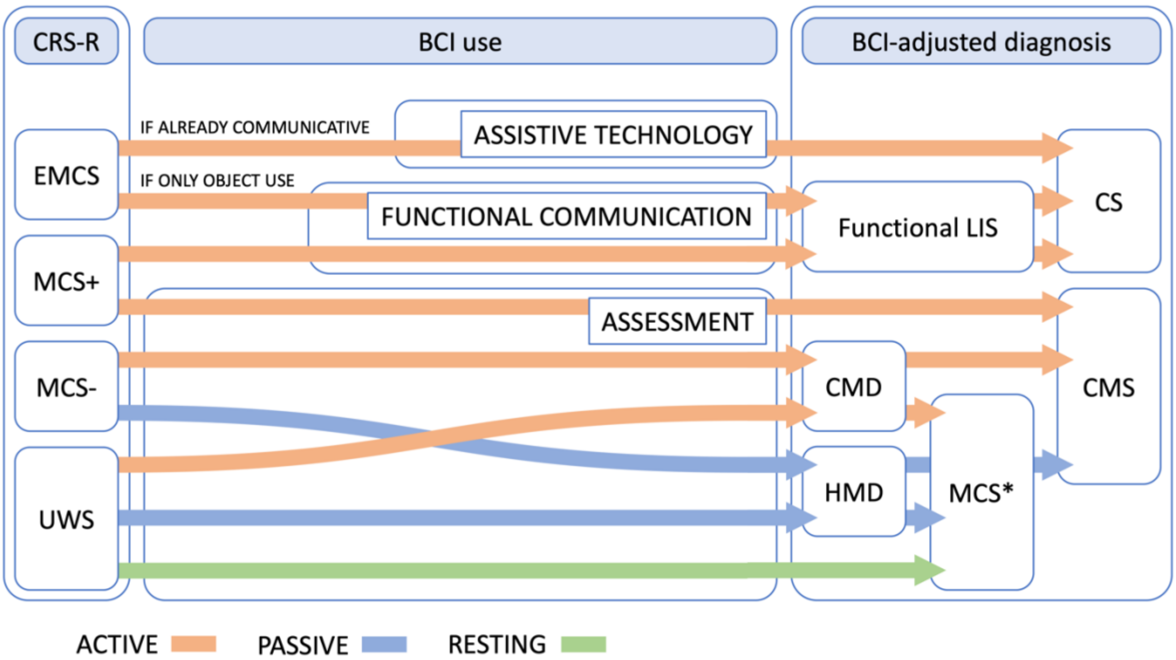

Fig. 3.2 Overview of the classical DoC diagnoses as determined through behavioral evaluation, their respective potential BCI uses, and the resulting refined diagnoses. Behavioral diagnoses with the CRS-R range from states closest to coma without awareness despite arousal (UWS), over minimal consciousness characterized by either preserved intentional behaviors (MCS-) or additional language-related capabilities (MCS+), to emergence from a DoC diagnosed through functional object use or functional communication (EMCS). UWS and MCS- patients can be categorized as either CMD or HMD depending on whether they show responses to active (i.e., command following) or passive (i.e., sound or language perception) paradigms, respectively. UWS patients who show preserved brain activity in line with MCS using any assessment or BCI technique, including resting-state electrophysiological or neuroimaging-based evaluations, are considered MCS*. Both MCS subcategorizations furthermore fall under CMS in case non-communicating behavior is determined by functional neuroimaging. For MCS+ patients, as well as EMCS patients for whom only object use is present, it might be possible to establish functional communication by means of active BCI paradigms. Such patients are subsequently considered as functional LIS. The most high-level BCI uses are reserved for EMCS patients as they are able to benefit from assistive technologies (e.g., wheelchair control, internet access) in case communication was already restored. All instances in which functional communication is present (including MCS+ and EMCS patients) comprise the CS.

UWS = unresponsive wakefulness syndrome, MCS = minimally conscious state, EMCS = emergence from MCS, CMD = cognitive motor dissociation, HMD = higher-order cortex motor dissociation, MCS = non-behavioral MCS, LIS = locked-in syndrome, CMS = cortically mediated state, CS = conscious state*

The last decade's increase in BCI and neuroimaging-supported research has allowed us to get an idea of the overall occurrence of covert awareness in DoC, as several synthesizing works have since then shed light on the significant prevalence of this phenomenon. Using resting-state positron emission tomography (PET), Thibaut et al. recently demonstrated that a large percentage of UWS patients had residual brain metabolism compatible with the diagnosis of MCS, as much as 67% of the sample [19]. Perhaps more importantly, this study highlighted the prognostic implications of covert awareness, as MCS* patients presented a better outcome after one year. These results are in line with other studies [26]. BCI paradigms beyond resting-state examinations can be categorized into passive and active paradigms. Passive paradigms differ from resting-state alternatives in the sense that external stimuli are applied in order to elicit brain responses. These do not necessarily require active engagement but rather decode cognitive states from the subject's cerebral signals in a reactive manner. Responses are often indicative of neural processing related to sensory information which, according to several definitions of the phenomenon, is not always sufficient to infer the presence of consciousness. Nevertheless, they do provide interesting insights that could still be used to differentiate between clinical entities of DoC. Active paradigms encompass techniques that match closest to those observed in a typical BCI setup. These can often stem from a passive equivalent by instructing the subject to perform a specific task related to the stimulus (e.g., asking to count the occurrence of the subject's own name (SON) rather than simply presenting it). Active paradigms are based on willful modulation of neural activity in response to a command and involve activation of higher-order cognitive processes, which is indicative of consciousness. A review of the literature showed that 15% of patients with a clinical diagnosis of UWS could willfully modulate their brain activity to follow commands as measured with EEG and fMRI [27]. More recent studies detected CMD in as high as a quarter of unresponsive patients, which was also correlated with better outcome [28]. These findings are undoubtedly most striking for completely unresponsive patients, however an even higher proportion of responders to both active and passive paradigms was found in behavioral MCS, as was later reinforced by a subsequent meta-analysis [29].

Hence it seems that a considerable proportion of patients could benefit from both passive and active BCI technologies. In the next section we will review several BCI approaches developed and used in the field of DoC specifically.

The applications of BCIs in research for patients with a disorder of consciousness

Following the very first use of a BCI paradigm in the field of DoC, research over the subsequent years has been continuously investigating different techniques for their link to consciousness in addition to potential diagnostic and prognostic capabilities. Resulting is a substantial body of evidence comprising various study setups and findings which has helped shape our current understanding of impaired consciousness. This section provides an overview of some of the most famous and important works in this regard. BCI applications in practice can come in many forms regardless of whether they are to be presented in an active or passive manner. Each of these main paradigms will be illustrated, roughly ordered according to their prevalence within BCI research for patients with DoC.

P3

Most of the research involving BCIs in the field of DoC is based on the P3, an event-related potential (ERP) component which can be observed in response to an oddball paradigm. It manifests as a positive infliction following an unexpected deviant stimulus in a sequence of regular counterparts with a higher probability of occurrence. The P3 consists of an early and late subcomponent, referred to as P3a and P3b respectively [30]. The frontal P3a is thought to reflect exogenous attention and is elicited by stimuli processed in a bottom-up fashion, which can be task independent. The parietal P3b on the other hand suggests top-down cognitive processing of task-relevant features through endogenous attention. The BCI paradigms discussed next mostly rely on this latter component due to its relation to conscious processing [31] and will therefore be implied when referencing P3 unless explicitly stated otherwise.

P3 responses in DoC patients differ from healthy subjects both in terms of increased latency and reduced amplitude [32, 33]. This same observation can be made when comparing UWS and MCS, however this is not always sufficient to discriminate between the two [34]. Although all manifestations of the P3 can be ascribed to one and the same principle, the elicitation of this ERP component can be achieved by stimuli targeting different senses. Each of these have their respective advantages and disadvantages and are therefore fit to be employed in different types of applications.

One of the major applications of the visual P3 is that of the spelling device. By presenting the subject with a grid of letters and symbols from which selections are alternatingly illuminated, it is possible to determine the character being focused on through detection of a P3 response. The efficacy of such visual speller design was shown in healthy subjects as well as LIS patients, reaching accuracies up to 90% and 70% respectively [35]. This specific application is however already quite a high-level example, as it requires visual fixation and its goal to reach communication is therefore primarily reserved for those in more advanced stages of recovery.

The auditory P3 on the other hand is less prone to physical limitations beyond deafness. Most auditory oddball paradigms consist of only two stimuli (i.e., a standard and deviant one), although extension to more classes is certainly feasible. However, in a study implementing a four-choice paradigm, only one MCS patient out of 13 showed command following without functional communication, highlighting the need for sufficiently simplified tests [36].

The P3 component can furthermore be studied by means of the ‘local-global’ protocol, which embeds two levels of auditory regularity, both within as across trials [37]. The presence of a global effect has been proposed as a signature of consciousness; however, this was found to be foremost true on an individual patient basis [38, 39]. The auditory P3 fails to reach the discriminatory power of other EEG-derived measures such as power or functional connectivity on the group level [40, 41].

Another commonly applied auditory oddball paradigm is that of the SON. Aside from the SON being deviant among unrelated names, the use of such salient stimulus should elicit a larger response. This paradigm can be presented as either an active or passive task by asking the subject to count their own name or by giving no further instructions instead. Multiple studies showed that the SON under active conditions evoked stronger responses in DoC patients [42, 43], although passive implementations can still lead to significant results by adopting an appropriate experimental design [44].

It should be noted that such paradigms are attention mediated and thus require cooperation from the subject. It is therefore crucial that patients are actively aroused when awareness seems lost. P3 responses can furthermore be elicited through (vibro)tactile stimulation. Instructing patients who showed no behavioral command following (8 UWS, 4 MCS-) to count the occurrence of vibrations administered at either the left or right hand established covert command following in one MCS- patient, as was confirmed by preserved glucose uptake in the language network using PET [45]. Repetition of BCI assessments using this paradigm is important to detect command following in unresponsive patients, which can even result in the establishment of binary communication in certain cases [46]. When both vibrotactile and auditory P3 paradigms are applied to patients with a DoC, performances were found to be independent of one another, exemplifying the usefulness of multimodal BCI assessments [47]. The combination of stimuli targeting different senses leads to the notion of hybrid BCIs, as will be discussed further.

Motor imagery

The seminal work of Owen and colleagues involving imagination of playing tennis and spatial navigation is a prime example of motor imagery using fMRI [9]. Imagination of certain tasks will activate associated brain regions, which can subsequently be visualized by functional neuroimaging. This exact paradigm was later used in a large cohort of 54 patients with a DoC, five of which could willfully modulate their brain activity to follow commands (3 MCS, 2 UWS) [13]. One MCS patient could even achieve binary communication as a result by associating playing tennis with “yes” and imagining navigating one’s house with “no”.

The same concept is used in EEG as well and can be characterized by sensorimotor rhythms (SMR); oscillatory electrophysiological brain activity in the beta frequency range (13-35 Hz) that is associated with movement. Reduced SMRs, or event-related desynchronizations, are observed when a person prepares for or executes a motion, and more importantly, also when imagining doing so. The inverse effect occurs after the movement during relaxation as event-related synchronization [48]. When applied as a task involving the imagination of squeezing their hand or moving their toes to a sample of exclusively UWS patients, 19% responded and thus seemingly exhibited covert awareness [49]. It became apparent afterwards that such results should be interpreted carefully, since their conclusions were later refuted following reanalysis [50]. A slightly larger percentage of covert command following could be observed in MCS patients, namely 22% [51]. This study did not specify whether these patients were diagnosed as MCS- or MCS+, which would have revealed the prevalence of type II errors in this paradigm based on the number of negative responders in the latter cohort. When applied to an acute cohort of 16 severely brain-injured patients in an intensive care setting, this exact paradigm using both EEG and fMRI showed that the former had a lower sensitivity (33.3% vs. 42.9%) but a higher specificity (100% vs. 50%) compared to the latter for detecting behavioral signs of language [23]. CMD was identified in four patients (3 UWS, 1 MCS-), while passive listening paradigms additionally revealed two instances of HMD (both MCS-). The following year, a study investigating patients with a prolonged DoC used a motor imagery task with four commands, consisting of ‘tennis’, ‘opening/closing hand’, ‘spatial navigation’, and ‘swimming’ [52]. Evidence of the capacity to follow commands was found in 21 out of 28 patients based on EEG (3 UWS, 11 MCS, 7 EMCS); nine of whom also demonstrated similar evidence using fMRI (1 UWS, 5 MCS, 3 EMCS).

SSVEP

Steady-state visually evoked potentials (SSVEP) are neural responses to periodic visual stimuli. Presenting a flickering stimulus will induce measurable rhythmic EEG patterns in the occipital

brain region at that same frequency [53]. An SSVEP-based speller and P3-based alternative were used in a cohort of seven LIS patients to assess and compare performance [54]. The SSVEP variant resulted in more instances of high accuracy (at least 70%), that being all seven users rather than just three with P3, along with a lower mental workload and higher overall satisfaction. Such BCIs are characterized by fast response times and having a low susceptibility to noise. They furthermore require no training and can subsequently be used by many subjects. One potential drawback however is the paradigm's usual reliance on shifts in gaze to express attention, thus requiring voluntary eye control. As a solution, Lesenfants and colleagues implemented a gaze-independent approach by presenting both stimulation frequencies in an overlapping grid pattern [55]. Two out of six LIS patients showed response to command by achieving offline accuracies above chance level; one out of four even being able to communicate online. Extension to more than two target classes is straightforward and leads to overall improved results, as illustrated in another cohort of five LIS patients [56].
Evoked responses can similarly be elicited using auditory and somatosensory stimuli (resulting in SSAEPs and SSSEPs, respectively), but less commonly employed in practice [57]. One study investigated a combined SSSEP and P3 EEG paradigm with vibrotactile stimulation in a sample of 14 patients with a DoC; all of whom responded to the former but none to the latter [58]. Interestingly, a subsample of eight patients did show evidence of bottom-up attention (i.e., P3a response), who were the only ones to exhibit command following either behaviorally or through alternative fMRI paradigms. These findings suggest the relevance of P3a beyond unconscious processing, while highlighting the non-specificity of SSSEPs and the problem of false negatives for the classical P3 paradigm. Auditory steady-state responses were more recently investigated for their diagnostic capacity. Passive listening to modulated tones in the low gamma frequency range (±40 Hz) correlated with behavioral scores and could consistently differentiate between UWS and MCS [59, 60].

<u>Hybrid BCIs</u>

Rather than relying on one single signal, it is also possible to integrate multiple physiological measures into a hybrid BCI. Such a multimodal signal can consist of brain activity provoked by different paradigms (e.g., motor imagery and oddball task) or combined with a non-brain signal (e.g., ocular activity or heart rate). The different components of a hybrid BCI can be structured simultaneously to reinforce one another or sequentially to facilitate complementary actions (e.g., focusing on an item and the subsequent selection thereof) [61].
One of the most widely employed hybrid paradigms is that of a combined visual P3 and SSVEP, which can be realized by presenting images of target and non-target stimuli flickering at different frequencies. Command following could be revealed in approximately one third of patients with a DoC in response to familiar and unfamiliar faces [62], and similarly by assessing arithmetic abilities through number processing and mental calculation tasks [63]. The same principle was used more recently in a large cohort with the intention of detecting covert awareness [64]. CMD was determined for patients with BCI accuracies above chance level, which was apparent in 40% of UWS and 48% of MCS cases. The use of an asynchronous hybrid BCI, which gives the user more control by dynamically readjusting the window of opportunity to respond, enabled three out of seven MCS patients to achieve online binary communication while also improving behavioral scores [65]. What should be noted is that the hybrid BCIs in every single one of the aforementioned studies outperformed the separate paradigms, highlighting the added value of this seemingly more complex multimodal approach.

Alongside the observation that even healthy people can outright fail to achieve proficiency with a certain paradigm (BCI illiteracy, in 15-30% of users [66]), some techniques might also not be applicable in patients with a DoC as a result of specific impairments (i.e., blindness or deafness). The use of hybrid BCIs can combat both issues by targeting multiple senses. Wang and colleagues first illustrated the improved discriminatory power of an audiovisual P3 BCI during detection of awareness, resulting in command following and number recognition for five out of seven patients with a DoC (1 UWS, 4 MCS+) [67]. The latest years have seen a substantial increase in audiovisual hybrid BCI implementations, including but not limited to: tools to supplement the CRS-R for assessment of communication abilities [68], gaze-independent auxiliary detection of awareness at the bedside [69], improved object recognition [70], and evaluation of sound localization [71]. Moreover, many studies seem to consider multiple control signals by default, which is expedited by the constant evolution of the field and the more advanced technologies that become available as a result.

Body-computer interfaces (biofeedback machines)

As an alternative to BCIs using brain activity, it is furthermore possible to infer communication or command following from other types of physiological activity, presented here as body-computer interfaces. With electromyography (EMG, recording of muscle activity), it is possible to detect subliminal muscular responses as part of an active BCI paradigm. Bekinschtein and colleagues used EMG to reveal command following in one out of eight UWS and in both MCS patients enrolled in their study (MCS- and MCS+), suggesting its use in awareness detection [72]. A later study on a bigger cohort showed similar results for UWS, with only one out of ten being able to respond [73]. However, the issue of false negatives associated with EMG was made apparent as well, since none of the eight MCS- and merely three out of 20 MCS+ patients had significant discernible responses to target commands. Finally, Lesenfants et al. proposed a novel methodology that evaluated responses on a single-trial basis to overcome the undesired influence of fluctuations in arousal and awareness in a total of 45 brain-injured patients [74]. This implementation illustrated command following in all LIS (n=2), EMCS (n=3), and MCS+ (n=14) patients, with two out of eight MCS- patients showing an EMG response as well.

One downside of EMG in this context is that the sensor is usually applied to a specific muscle which is not necessarily a muscle that a patient still has some degree of control over. Muscular responses detected with EMG might furthermore be unreliable due to spastic paresis, a motor disorder extremely frequent in patients with a DoC [75]. As an alternative, it has been shown that LIS patients for instance could control a speller to write text through voluntary control of breath and sniffing [76]. This paradigm later proved unsuccessful when applied to UWS patients, however it did enable one out of 14 MCS patients to follow commands without any further motor control [77]. Interestingly, this specific patient was one out of three included MCS- cases while none of the MCS+ patients could perform the paradigm, illustrating a 100% false negative rate in this group. A more recent study investigated the potential of olfactory function as a biomarker for consciousness and concluded that the sniff response could reliably discriminate between UWS and MCS at the group level [78]. As for clinical implications, the presence of this sniff response was found to be indicative of full recovery of consciousness at the single-patient level and associated with survival rates in the long term.

The body-computer interface techniques mentioned up to this point for the most part still require residual voluntary control of the sensory modality in question up to a certain extent. Also, they might be influenced by spontaneous movements or eyeblinks. Recently, it has been shown that volatile and non-intentional actions can be distinguished based on brain activity preceding the action [79]. By gaining a deeper understanding of these biomarkers of volition, false positives and false negatives might be avoided. Besides, further encouragement of the use of paradigms that are not only motor-independent, but that rely on completely involuntary processes is warranted. Pupillometry for instance can probe awareness by measuring subtle changes in pupil diameter associated with cognitively demanding mental tasks. The effectiveness of this paradigm has been proven by establishing binary communication in LIS patients, going as far as revealing command following in an MCS patient [80]. Salivary pH has been successfully used for this same purpose as well, during which an LIS patient had to either imagine the taste of a lemon or milk [81].

Aside from the handful of non-brain activity based BCI instances mentioned here, there is an apparent lack of further application beyond one-time implementations for research purposes. The nature of these techniques gives room to substantially more degrees of freedom and the subsequent increased need for standardization. As they are currently nowhere near being part of routine clinical practice, they are rarely mentioned by international guidelines, if at all. The following section will therefore go over clinical recommendations regarding the more usual BCI realizations instead, as these become increasingly common in the management of patients with a DoC.

Recommendations for BCI use according to current guidelines for clinical management of patients with a disorder of consciousness

Despite the limited but steadily increasing amount of BCI research involving patients with a DoC, its role as part of routine clinical practice is still not nearly as established as behavioral or resting-state evaluations. In an effort to further promote the integration of BCIs in this field while also illustrating the present state of the art, we provide an overview of current recommendations as published in several recent clinical guidelines. Most of these concern neurophysiological techniques in the broader sense, which relate to BCI paradigms either directly or indirectly and can therefore be extrapolated to fit the narrative of this chapter, seeing as they might facilitate the detection of covert awareness. The guidelines in question consist of synthesizing works drafted by the European Academy of Neurology [82], the American Academy of Neurology [83], and the UK Royal College of Physicians [84] regarding the use of resting state, passive, and active paradigms to diagnose patients with a DoC.

Regarding neurophysiological examination in general, the consensus is predominantly positive towards the insights it provides into DoC as well as the management of patients affected by it. EU guidelines advocate for multimodal evaluations that integrate the current standardized clinical methods with EEG-based techniques and functional neuroimaging, where all approaches hold an equal weight in categorizing states of consciousness. The importance of avoiding misdiagnosis and uncovering covert awareness is hereby especially highlighted. They suggest resting-state fMRI and PET to complement behavioral evaluation and strongly recommend standard clinical EEG to rule out confounding factors that could affect consciousness (e.g., non-convulsive status epilepticus), albeit primarily through qualitative visual inspection.
US guidelines recommend incorporation of functional imaging or electrophysiological studies in case of confounders for behavioral evaluation (e.g., brain injury-related sequalae such as

severe hypertonus) or persistent ambiguity despite serial behavioral evaluations, in which auxiliary assessment may lead to an alternate diagnosis. They do however asterisk this by stating that there is insufficient evidence to conclusively support or refute such techniques as clinically useful adjuncts to current established methods of awareness detection (i.e., behavioral evaluation). Functional neuroimaging is furthermore not widely available and may not be clinically feasible in a significant proportion of patients.
UK guidelines go one step further and explicitly state that advanced neuroimaging techniques and electrophysiology, as opposed to visual analysis of EEG or structural imaging by means of computed tomography or MRI, might not be considered as part of routine clinical evaluation for patients with prolonged DoC. Alongside the arguments made by the US guidelines, this conclusion is based on the current lack of interpretability as well as ethical considerations due to the lack of access and uncertainty of their prognostic implications. Despite this reluctance to acknowledge the clinical significance of any functional imaging technique, the UK guidelines do recognize the potentially greater clinical applicability of task-free examinations in non-research settings. The use of PET is specifically mentioned since prior research investigating metabolic brain activity has resulted in accurate outcome prediction [85].

EU guidelines limit their recommendation of passive fMRI paradigms to research protocols because of limited effects and considerable heterogeneity. They do however encourage the use of salient stimuli and/or familiar activities to increase sensitivity in both active and passive paradigms when examining patients with a DoC. Passive EEG paradigms, including cognitive evoked potentials (i.e., P3), might be considered as part of multimodal assessment. The value that they exhibit for differentiating UWS from MCS patients is however accompanied by low sensitivity even in healthy controls due to the need for attention, calling for the use of advanced statistical and analysis techniques.
US guidelines do not recommend nor refute passive fMRI paradigms for diagnostic purposes based on a single study matching their inclusion criteria which indicated limited effectiveness [86]. They do recognize the probable prognostic utility of both passive fMRI (activation of auditory association cortex) and EEG (presence of P3) paradigms using the SON presented by a familiar voice, since these were associated with increased chances of recovering consciousness and favorable outcomes [87, 88].
Passive fMRI paradigms fall under advanced neurophysiological examinations according to UK guidelines and are therefore inherently not considered as part of routine clinical evaluation of patients with a DoC. EEG sensory evoked potentials are only deemed useful when investigating the integrity of associated pathways in case no visual or auditory startle is discernible, rather than for the purpose of detecting signs of awareness. Cognitive evoked potentials (including P3) on the other hand should be able to distinguish between levels of DoC [89] but are held back by their poor predictive value compared to standard EEG visual inspection and reactivity [90].

EU guidelines suggest that active fMRI paradigms should be considered as part of multimodal assessment in patients without command following at the bedside. A similar recommendation is given for active paradigms based on either standard or high-density EEG since these equally allow for identification of patients who present CMD. It follows that both active fMRI and EEG paradigms have a high specificity but very low sensitivity for detection of covert awareness. The absence of command following should therefore not necessarily imply the absence of

consciousness. Consequently, they call for further refinement of the framework in which these techniques will be used for future research and clinical implementations.
US guidelines do not recommend active fMRI paradigms when executed in the form of a word-counting task based on a study suggesting its inability to distinguish UWS from MCS [91], while no conclusive advice is given for motor imagery due to a lack of evidence [92]. Active EEG paradigms were not considered. They are however cautiously optimistic about the diagnostic value of EMG to detect command following as it could differentiate between UWS and MCS in multiple instances, evidently after adjusting for involuntary movements [73, 74].
UK guidelines for the most part disregard sophisticated neurophysiological techniques which by default includes active BCI paradigms. They reinforce this judgment by referring to the false negative findings of fMRI motor imaging tasks that arise even in healthy controls, of which the clinical significance has not been sufficiently established.

To conclude, it seems there are important differences between the guidelines and attitudes towards neuroimaging-based assessment (and therefore towards BCIs as well) of patients with a DoC. EU and US guidelines are generally positive towards the possibility of supplementing behavioral evaluations with resting-state neuroimaging assessments, especially in case of physical limitations. Passive paradigms are not recommended nor refuted by either EU or US guidelines. According to the EU guidelines, active paradigms could be a helpful tool in patients without behavioral command following, while the US guidelines are positive towards EMG to assess covert command following. UK guidelines are rather skeptical towards any application of neuroimaging in patients with a DoC. It is apparent that important steps in the direction of improving clinical care of DoC patients have already been made, however there exist several important avenues for future research.

Future research and clinical directions to encourage development and implementation of BCIs for patients with a disorder of consciousness

Although individual studies have shown impressive results and hold great promise for clinical implementation, there is a large heterogeneity in experimental setup and subsequent success rates which cannot be overlooked. The lack of standardization in the field is likely the main reason for the conservative attitude towards clinical integration of BCI-based assessment. This leads to a substantial gap between scientific advancements and clinical availability and applicability. Standardization of data acquisition and analysis should be invested in to compile convincing evidence for the day-to-day usage of these technologies (e.g., by ensuring that single studies are not overfitting the data). Only then can the clinical usage of state-of-the-art techniques be promoted. Recent efforts to define common data elements (i.e., through the use of dedicated case report forms describing all information that needs to be collected and reported) for neuroimaging in patients with a DoC are a good step in that direction [93]. On the data analysis side, standardized and ready-to-apply pipelines should be made widely available to facilitate clinical implementation in non-expert centers [94].

Despite the little everyday use of these technologies, it is of utmost importance to be prepared for the ethical considerations that assessment using BCI technologies will undoubtedly raise. In other populations, several concerns regarding personhood, stigma, autonomy, privacy, research ethics, safety, responsibility, and justice have been identified [95]; once more exemplifying the need for proper recommendations and regulations. BCI-based assessment in patients with a DoC specifically introduces an additional major concern, namely the question of the presence of awareness or the lack thereof, especially in cases where overt awareness is lacking [96]. This in turn leads to another important issue: can we trust the machine? While BCIs can certainly contribute to the clinical care and acceptance of the patient's current cognitive state by family members, several potential negative effects become apparent as well. Underestimating the level of consciousness as determined by a BCI (i.e., false negative results) would induce false despair, while overestimation (i.e., false positive results) would evoke false hope and unrealistic expectations for patients' caregivers and loved ones [97].

Several approaches to reduce these false positive and negative results as well as overfitting exist. First, it is important to define and use proper benchmark populations to test assessment and BCI systems initially [98]. The choice of healthy volunteers as control group could be suboptimal, as they did not suffer severe brain injury and are therefore not immediately comparable. The inclusion of LIS patients might be the better solution but is more challenging to implement in practice. In reality, not all studies include a control group at all, which is problematic as the false positive and negative rates in a conscious population then remain unknown. Second, the use of proper statistics is very important as well. This was illustrated by Goldfine and colleagues who showed that using an appropriate methodological approach produced results that could no longer be deemed significant, effectively refuting the apparent observed responses [50]. The choice of a well-suited statistical test can lead to unbiased estimations of significance and provide a robust interpretation of results, irrespective of the applied validation schemes [99]. However, statistical procedures that are too strict might also be harmful by increasing the type II error rates and potentially underestimating the patient's level of consciousness, which is the foremost reason to perform assessments and BCI sessions in patients with DoC in the first place.

Aside from these technical validations and approaches to avoid false results, clinical safeguards can be put into place to obtain the most accurate findings. Resonating with other literature reviewed above, it is important to note that some patients perform well at one BCI assessment while failing to do so with another (e.g., [47]). Ideally, multiple BCIs are tested for the same patient to identify a technology that aligns with their cognitive and physical ability to avoid false negatives. Likewise, the arousal fluctuations frequently observed in DoC (e.g., with EEG [100]) lead to a behavioral underestimation of consciousness if patients are not assessed at least five times within ten days [16]. Following this literature, it would be best if BCIs were tested multiple times before accepting negative results. However, because of the longer preparation times among other reasons, BCI systems are usually tested only once. The use of closed-loop BCI systems that can track patients' arousal levels and solely assess at suitable moments could help to overcome this current limitation, similar to closed-loop systems that trigger a treatment based on the patient's level of vigilance [101]. To minimize chances of obtaining false positive BCI results, one option would be to cross-check these with other neuroimaging modalities to establish whether the neural substrates required for the specific BCI are indeed still intact [45].

The importance of BCIs in leading to the discovery of covert awareness cannot be understated. How this should be implemented in clinical practice however is currently still unsure. As active assessments might be more prone to false negative results, they could underestimate the degree to which a patient is conscious. Hence, active paradigms might be best preserved for communication or control applications. Passive paradigms on the other hand would be better suited for assessment. In patients performing well at passive paradigms, active tasks could be tried next to evaluate potential further diagnostic improvements. One open question in the field remains how the clinical management of patients with an improved diagnosis based on neuroimaging should change. One could argue that treatment should be made readily available for these patients, however it is unsure if and how these expensive options would translate to increased welfare and quality of life [102]. In comatose patients, the added value of BCI tools for the clinical treatment is more straightforward. BCI applications are becoming more frequently tested in acute settings, showing that up to 30% of the patients are covertly aware already in the intensive care unit, that is including patients in a coma [103]. Although a negative test result is not a vote in favor of ceasing life sustaining treatment in these patients, it should influence pain management and medical decision making for those who are found to be covertly aware.

Despite the current state of the art not yet being translated to the clinic, some future perspectives can already be discussed. Over the past years, new treatment options have been identified for patients with a DoC [104]. These can potentially improve the behavioral diagnosis and underlying physiology of a selection of patients, such as an UWS patient who regained command following after transcranial direct current stimulation (tDCS) and showed activation with fMRI mental imagery [105], or strictly lead to physiological improvements [106]. In the latter group, it remains to be investigated whether the lack of behavioral improvement is a result of the physiological changes being unrelated to consciousness, or due to physical limitations of the patient. The use of additional techniques to prime the brain to a better attentional state and to ensure that patients are optimally arousable can in turn reveal more signs of consciousness. For example, tDCS has shown its potential to effectively modulate cortical excitability in patients with a DoC and could therefore allow for easier detection of changes in brain states as leveraged by the BCI [107]. Presenting preferred music on the other hand showed its beneficial effect by increasing responses to the SON paradigm [108]. The plentitude of potential extensions, improvements, and more advanced or elegant assessment and BCI tools hold promise for bringing these techniques to the patient’s bedside in the near future.

Conclusion

BCIs to detect covert awareness have been developed and tested in research settings with varying success. They should be simple and easy to use, something that is sometimes overlooked during the development of demanding BCI systems with more complicated interactions. Besides the technical advancements, repeated BCI assessments are indicated to reduce false negative results. Appropriate statical approaches, not too strict nor too liberal, should be adopted to minimize false negative and false positive findings. Standardization and replication of approaches is needed to increase confidence in these techniques and to better assess their clinical usability. Once these conditions are met, the application of assessment and BCI tools might evolve to be widespread recommended by clinical guidelines worldwide. Such advancement would facilitate clinical translation and BCI use might become more standard practice. However, it is important that the ethical aspects of BCI implementation in the clinics (e.g., how clinical management should change after assessment) are mapped and addressed.

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