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ORIGINAL WORK

Brain–Computer Interfaces for Communication in Patients with Disorders of Consciousness: A Gap Analysis and Scientific Roadmap

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Abstract

Background: We developed a gap analysis that examines the role of brain–computer interfaces (BCI) in patients with disorders of consciousness (DoC), focusing on their assessment, establishment of communication, and engagement with their environment.

Methods: The Curing Coma Campaign convened a Coma Science work group that included 16 clinicians and neuroscientists with expertise in DoC. The work group met online biweekly and performed a gap analysis of the primary question.

Results: We outline a roadmap for assessing BCI readiness in patients with DoC and for advancing the use of BCI devices in patients with DoC. Additionally, we discuss preliminary studies that inform development of BCI solutions for communication and assessment of readiness for use of BCIs in DoC study participants. Special emphasis is placed on the challenges posed by the complex pathophysiologies caused by heterogeneous brain injuries and their impact on neuronal signaling. The differences between one-way and two-way communication are specifically considered. Possible implanted and noninvasive BCI solutions for acute and chronic DoC in adult and pediatric populations are also addressed.

Conclusions: We identify clinical and technical gaps hindering the use of BCI in patients with DoC in each of these contexts and provide a roadmap for research aimed at improving communication for adults and children with DoC, spanning the clinical spectrum from intensive care unit to chronic care.

Keywords: Coma, Communication, Head injury, Cognitive motor dissociation, Electroencephalography, Functional magnetic resonance imaging, Neural repair

Introduction

Recently, a subgroup of patients with disorders of consciousness (DoC) who demonstrate unequivocal brain responses to commands that are undetectable by bedside examination has been identified in both intensive care units and chronic care settings [1–4]. This condition is

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referred to as cognitive motor dissociation (CMD) [5, 6]. Use of neuronal signals to accurately assess level of consciousness and ability to communicate is a critical early step in linking patients with DoC with their environment via brain–computer interface (BCI).

However, the requirements of underlying neuronal substrate integrity that might support BCI use in DoC are unknown. Among essential practical concerns are the establishment of comprehensive approaches to survey sensory input channels, the choice of reporting brain signals, and the design of BCI interfaces capable of operating in patients with DoC. Additionally, setting thresholds to test patients' BCI readiness—suitability to test for use of BCI—and to consider acceptable BCI performance criteria in patients with DoC is situationally dependent on clinical contexts, as developed subsequently.

At present, because of the lack of clinical BCI applications, DoC represents a major ethical challenge for care of these persons. Recent studies suggest that a large fraction of patients with DoC harbor the capacity for covert cognition and may be capable of using some forms of BCIs [7]. Individual cases of such persons (e.g., Monti et al. [8], Thengone et al. [9]) are reported. These demonstrations, however, are limited to examples in which the patients are only able to respond to structured communications. The lack of an ability to initiate and form basic human connections underwrites an ethical imperative to develop solutions [10]. Moreover, it is possible that significant numbers of "unconscious" patients retain the basic human need for connection and would enthusiastically adopt BCI (even if invasive procedures were needed). Furthermore, the ethical imperative of autonomy also implies that these patients have a right to participate in decisions affecting their care, and BCI may facilitate the needed communications.

Although the focus of this article is on patients with DoC, we also implicitly refer to patients who have identifiable preserved higher levels of consciousness, despite wider structural brain injury, but who remain motorically severely impaired with only intermittent capacity to communicate (sometimes referred to as "locked-in plus"). Some of these patients are also clinically indistinguishable from patients with DoC based on standardized neurobehavioral scales and are among the most suitable candidates for BCI.

Table 1 serves as a reference for understanding definitions and abbreviations of key terms used throughout this article.

Table 1 Relevant glossary table (adapted from Claassen et al. [6])

Brain-computer interface (BCI)	System recording neural activity and translating it into artificial output; used for replacement, restoration, enhancement, supplementation and/or improvement of natural Central Nervous System (CNS) outputs; modification is obtained by changing interactions of the CNS with the rest of the body or the external world [11]
BCI communication modality	"One-way" BCI: allows communication via patient response to structured prompts only; i.e., one-way initiated communications "Two-way" BCI: supports fluent, bidirectional communication allowing the patient to initiate and independently craft communications; two-way initiation of communication (i.e., either by the patient or the examiner). Two-way BCIs can in principle allow for the patient's control of the environment
Coma	Patients demonstrate complete absence of arousal (e.g., eye opening) and awareness (e.g., comprehension), with no behavioral evidence of command following [118]
Vegetative state (VS)	Patients demonstrate presence of arousal (i.e., eye opening) without awareness, but no command following. Patients may have preserved sleep–wake cycles evidenced on EEG. This state has also been referred to as unresponsive wakefulness syndrome [118]
Minimally conscious state (MCS)	Patients do not show consistent command following, but have some evidence of verbal or nonverbal awareness. MCS has been subclassified as MCS − and MCS + (see below) [119]
MCS −	Patients in this MCS subcategory do not exhibit behavioral evidence of command following but reproducibly track the examiner around the room with their eyes or demonstrate attending to a stimulus [120]
MCS +	Patients in this MCS subcategory demonstrate command following (e.g., intelligible verbalization and intentional communication), but it is inconsistent and present only intermittently [120]
Cognitive motor dissociation (CMD)	Patients demonstrating evidence of command following on fMRI and/or EEG without behavioral evidence of command following (coma, VS, MCS −) [5]
Emerged from MCS	Patients who regain functional communication (which may occur through speech, writing, yes/no signals, or augmentative communication devices) or functional use of objects (i.e., discrimination and appropriate use of two or more objects) [119]
Locked-in syndrome (LIS)	Patients awake and conscious, but having no means of producing speech or limb or facial movements. Typically, but not necessarily, vertical eye movements and blinking are preserved [121]. Classical, complete, and incomplete locked-in syndromes vary based on the extent of paralysis and affected brainstem regions, while locked-in plus syndrome combines these features with disturbances of consciousness [122]

Work Group Meetings and Literature Review

The Curing Coma Campaign convened a Coma Science work group that included 16 clinicians and neuroscientists with expertise in DoC. The work group represented 16 international academic medical centers and the fields of neurology, neurosurgery, physical medicine and rehabilitation, neuropsychology, and neuroscience. The work group met online biweekly and performed a gap analysis of the primary question. No new studies were performed as part of this work, and no aspects of the activities required institutional review board approvals.

Uses of BCI in DoC

A BCI has been defined by Wolpaw et al. [11] as "a system that records neural activity and translates it into artificial output that replaces, restores, enhances, supplements, or improves natural central nervous system (CNS) outputs; it thereby modifies the interactions of the CNS with the rest of the body or with the external world." Although Wolpaw's definition excludes devices that only monitor and report on brain activity, here we include these devices, given the specific context of BCI for DoC and the purpose of establishing patients' readiness for receiving it. For such measurements to be called "BCI," the device must provide meaningful feedback based on the signal detected to the individual being monitored.

We make an important distinction throughout between "one-way" and "two-way" BCIs achieved via either noninvasive or implanted methods (as reviewed subsequently). This distinction of directionality is aimed at labeling an equality in being able to formulate questions and answers (two-way) versus an inequality (one-way); in this sense, although communications always are, in principle, bidirectional for patients, some BCIs are colloquially a "one-way street." A one-way BCI allows communication in response to structured questions; such demonstrations provide both information on covert cognitive processing and evidence of command following. However, one-way communication does not allow for patient initiation of communication, but only allows for the patient to respond to a structured message. Conversely, two-way BCIs support a fluent and bidirectional communication and allow the patient to freely construct the content of their communications. One-way BCI methods can provide real-time feedback, thus allowing answers with negligible delays for data processing; however, the real-time requirement does not have to be necessarily satisfied. One-way BCI depends on demonstration of covert cognition via command following, however, covert command following may be present without evidence of a communication channel.

For example, frequent implementation of one-way BCIs is obtained through functional magnetic resonance imaging (fMRI) or functional near-infrared spectroscopy (fNIRS), yet the slow dynamics of blood flow measurements, as used by fMRI or fNIRS [12] do not meet the speed requirements of fast spelling interfaces obtained with high performance BCI systems [13] that demonstrate fluent two-way communication systems suitable for use in patients with DoC.

Operational Definition of "BCI Readiness" for Communication in Patients with DoC

"BCI readiness" is defined here as the satisfaction of evidence that an individual warrants that pursuit of testing and training potential specific BCI solutions. Few data exist to inform criteria for BCI readiness in patients with DoC. Unless specifically addressing DoC, most BCI research focuses on humans with intact brain structures or only very limited regional loss of neurons (typically brainstem strokes or primary degenerative loss of the motor cortex) [14] and aims to identify standardized brain states (such as motor preparatory states) and signals (e.g., beta rhythm dynamics) that allow for reliable bit generation and decoding, as identified in intact nonhuman primates [15].

Our working definition, based on Shannon's 1948 theory of communication [16], considers BCI readiness in DoC as the demonstration that a "device" is able to take a signal from an injured brain to achieve one bit signaling (foundation of a formal communication channel), at a sufficient rate (bits/unit time) to practically establish communication via a control interface. BCI in DoC is thus a hybrid concept, compared with standard BCI applications, that must include methods to locate signals capable of reliably signaling a bit and must be personalized to the specific anatomical and functional characteristics associated with the patients with DoC's brain injuries. In the context of severe brain injury and DoC, effective BCI solutions necessitate careful analysis of many factors pertaining to brain signal localization, signal type, signal acquisition, processing and analysis algorithms, and appropriate CNS output.

In patients with reliable one bit communication, as is typical of the classic locked-in-syndrome (LIS) (e.g., as seen with isolated lesions in basis pons), methods exist to vet individual interfaces for their usefulness to improve an existing motor communication channel [17]. BCIs are quite effective in patients in whom a modest extension of the classical LIS lesion may produce complex sensorimotor integration deficits (e.g., central deafness [18]). However, in patients with DoC with only signal processing evidence of command following, it remains an open question whether such an individual patient with CMD in principle could harness these interfaces as patients with LIS are able to do.

Prerequisites for Effective BCI Solutions for Communication in Patients with DoC

Covert consciousness is a foundational prerequisite for BCI-enabled communication in DoC, although it is acknowledged that such an identification does not guarantee sufficient capacity to control a BCI. The uncertainty for communication recovery in patients with DoC is magnified by severe brain injury, variability or instability of brain signals, potentially compromised sensory pathways, and activity-dependent structural and functional neuroplasticity. Therefore, brain monitoring to identify neural correlates of communication recovery is crucial toward successful BCI-enabled communication solutions [9, 19]. Additionally, BCI applications in DoC may extend to those patients who demonstrate command following but suffer alterations of motor control systems [20] that might be bypassed by direct BCI interfaces. In such patients with DoC, overt behavioral evidence of command following could be present. A recent multinational study demonstrates that substantial fractions of patients likely exist in both categories [7].

BCI for communication purposes requires decoding of the patient's neural signals to control a device. Successful interaction between the patient's neuronal signals and the device enables the detection and decoding of patient-initiated messaging, and the control of fluent dialogue [21]. We recognize here that one-way systems and command following detection are a prerequisite for two-way communication. In this article, we focus on the challenges ahead of establishing such two-way communication systems in patients with DoC, in which the patient initiates communication and interacts unprompted using BCI.

BCI communication can be binary (i.e., yes or no encoding of the response, on semantic decoding of a request or question), or through spelling (i.e., spelling of a category such as "T-H-I-R-S-T," which can be initiated unprompted by the environment). Major prerequisites for BCI systems for communication (binary or spelling) include good quality (i.e., high signal-to-noise ratio), reliable (i.e., systematically present in certain conditions), reproducible (i.e., manifesting with stable characteristics), and robust (i.e., accessible despite interfering factors such as artifacts) brain signals. Furthermore, there are requirements of preserved functional sensory inputs (vision, hearing or touch), and cognitive abilities (varieties of attention, executive function, language interpretation and typically visuomotor skills) that allow patients to understand instructions and independently control BCI systems. Sufficient experience-dependent learning, if required by the interface, is also essential for BCI.

Biological Signals Capable of Identifying BCI Readiness

Over the past two decades a variety of techniques have been employed to assess brain response to external stimuli as a guide to identify the level of awareness in patients with DoC. Early methods generally focused on measuring brain responses during the passive presentation of sensory stimuli [22]. Although these passive responses can distinguish between the presence and absence of cortical processing, they provide little evidence for comprehension of sensory information, nor do they detect volitional brain activity. To address this limitation, Owen et al. [23] demonstrated in a landmark fMRI study that an active motor imagery paradigm can detect comprehension and volitional brain activity. They revealed that a patient whose clinical examination suggested a vegetative state (VS) could generate patterns of brain activity during motor imagery and spatial navigation tasks that were similar to those of healthy controls [23].

Following this first demonstration of covert awareness, a wide range of methods to assess active command following have emerged utilizing task-based fMRI and electroencephalography (EEG) [24–28]. Such active paradigms allow cognitive processing to be more sharply distinguished. Passive assessments that provide graded response profiles include somatosensory [29–31], visual [32, 33], auditory [31, 34], olfactory (fMRI [35], odor-dependent sniff responses, i.e., nasal flow patterns [36]) primary sensory evoked responses, as well as endogenous evoked responses that are not strictly time-locked to sensory stimulation such as mismatch negativity [37, 38], P300 (a signal generated in response to 'oddball' stimuli) [39], N400 (a signal generated in response to semantically unexpected linguistic stimuli) [40], and natural language stimuli such as study participant's own name [41, 42]. However, using a subset of these latter passive stimuli, paradigms for BCI have been developed [43–48].

I. Biological prerequisites

Clinical prerequisites critical to the establishment of effective BCI for communication in patients with DoC are detailed in Table 2.

II. Technical prerequisites

Noninvasive BCI systems either use electrical activity recorded from the scalp or, less commonly, the cortical hemodynamic activation detected through noninvasive methods. Invasive BCI systems detect the activity of ensembles of cortical neurons recorded from implanted electrodes [49]. Scalp EEG signals are most commonly used due to their high temporal resolution and they are noninvasive.

BCI systems are typically augmented using analytic metrics derived from the brain signals. Several novel methods of time series analysis have been applied to the

Table 2 Considerations for establishing effective BCI for communication in patients with DoC

Steps of evaluation	Description
1. Determine the patient's arousal state	Optimize the patient's arousal state to support communication (e.g., absence of coma, deep sedation or sedative medications) Assess absence of any cause of primary arousal disturbance, such as hypothalamic dysfunction causing thalamic storming and/or deep somnolence [123] Identify lesions associated with arousal deficits [124] Assess physiological stability, by inferring from vital signs and psychophysiological variables (galvanic skin response, heart rate, pupil reactivity)
2. Select the optimum sensory input	Select most viable pathways for sensory input: visual, auditory, or tactile Consider confounding factors that influence sensory input, such as (cortical) blindness, deafness, or sensory polyneuropathies [74] Preassess the integrity of relevant neural pathways via structural MRI [91], and determination of visual and auditory abilities through fMRI (Laureys and Schiff [22]) Consider the sensorimotor modality as the first choice [125]
3. Assess the motor channel	Consider confounding factors that can influence motor output, such as cranial nerve deficits, myelopathies, radiculopathies, polyneuropathies, myopathies [74] Consider electromyography (EMG) as the signal of first choice, if present [86] In case of absent motor responses, alternatively consider motor-related brain-based neural signals [19]
4. Assess the presence of a reliable brain signal, determine the best signal to use, and the best way to use the chosen signal	Establish a reliable statistical criterion for response to the test paradigm (i.e., distinction between 'presence' and 'absence') Establish if there is a need for real-time response for two-way communication Optimize parameters for EEG or NIRS signal acquisition. For NIRS: photon injection intensity and path calibration (interoptode distance). For EEG: identification of best channel or montage through set-up sessions Optimize sensitivity/specificity Use large and variegated training datasets, if/when conducting data-driven classifications, and if such datasets are available Ability to reach sufficient performance criterion level to move from command following to communication between patients and controls [126]
5. Determine the cognitive capacity (e.g., language development in children) and associated deficits (amnesia, agnosia, akinetic mutism)	Consider confounding factors that influence cognitive capacity, such as akinetic mutism. Lesions have to be characterized through MRI for detection of structural damage relevant to planning, initiation and regulation of motor output, including in frontal, subcortical, and cerebellar regions [91] Assess integrity of language processing (e.g., responses to semantic stimuli) [39] and receptive and/or expressive aphasia For two-way communication, additionally assess working memory buffer, situational orientation, and ability to establish a yes/no communication through visual protocols [8] Assess the ability to give feedback to clarify or correct output, as this is important for two-way communication
6. Determine one-way versus two-way communication possibility	One-way communication: brain signals are directed to the device, while there is absence of direct feedback to the patient Two-way communication: brain signals are directed to the device, and feedback is provided to the patient through visual or auditory cues. The patient can adjust brain signals in consequence, creating an interactive loop
7. Pediatric considerations	Consider developmental maturation of brain signals and cognitive/language functions Downsize EEG and NIRS montages and downscale cable and probe weights Use of appropriate and salient requests (including the substitution of training tools with toys when appropriate)

EEG signal in patients with DoC, such as perturbational complexity index and measurements of manifold/attractor structure for nonlinear analysis of EEG and event-related potentials (e.g., P300) [50–53]. However, they are not yet tested for the purposes of establishing communication in this patient population. Most methods that show promise for conversion into BCI for DoC rely upon imagined or intended motor actions [24].

Although this gap analysis is primarily focused on BCI for communication in patients with DoC, it should be noted that other BCI applications show clinical promise for other purposes including motor effector BCIs which allow patients to control external devices, multilevel spinal cord stimulation in patients with spinal cord injuries [54–56], closed-loop deep brain stimulation applications in treatment of depression [57], pain [58, 59], and movement disorders [60]. These successful applications in patients without DoC may pave the way for individualized applications in managing the range of neurological deficits in patients with DoC. A closed-loop stimulation system in patients with DoC to improve the level of consciousness and as a framework for BCI was recently proposed [61].

BCI System Architecture

All BCI system architectures satisfy a few core requirements (Fig. 1): (1) capturing either the electrical (through EEG) or hemodynamic (through optical probing with NIRS or varying magnetic field with fMRI) component of neural activity; (2) amplification and/or digitization of the neural signal and filtering for noise removal [62]; (3) real-time signal processing for extraction of features discriminative to the detection of communication intent; (4) real-time or quasi real-time classification of the features either in binary classes (e.g., yes or no) or in a very restricted pool of classes (e.g., right, left, front, rear), representing “menu” options for the user. Optionally, a fifth core element is introduced, which translates, through actuators, the classifications into device commands or events (e.g., moving a wheelchair toward the chosen direction, or opening a door).

Signal Processing

Electrophysiological activity in the brain is the result of complex interactions between spiking neurons and postsynaptic responses to the spiking activity. While the bulk of the brain’s electrophysiological activity is said to be “resting,” that is, not stimulus-evoked, the brain is able to modulate spiking activity in specific regions in response to demands. The goal of BCI is to identify and extract signals relevant to communication. Brain activity is a composition of cognitive signals and background activity generated and propagated by the neural networks. Thus, the first step in data processing for BCI is decomposition. In this context, decomposition is of features, also called modes, discriminative of communication intent from the overall brain signal. Mode decomposition can assist in isolating motor or cognitive responses to specific environmental cues, spontaneous motor and cognitive activation, resting brain activity, as well as artifactual contributions (e.g., eye-blink artifacts, MRI magnetic field interference) and drug-induced effects to be removed. Kamble et al. [63] provide an excellent review of adaptive signal decomposition approaches in EEG.

Several mathematical approaches exist to perform mode decomposition, including relatively simple frequency-based techniques, as well as more complex approaches such as principal component analysis (PCA) and independent component analysis (ICA). As above, the deliverable from these approaches is the identification and amplification of signals needed for communication. A first group uses consolidated mathematical approaches such as the Fourier transform, which decomposes the signal into a weighted sum of sine waves under the assumption of signal stationarity, and Bayesian filters, which estimate signal properties and their uncertainty conditional to the signal past history [62]. Among common geometrical approaches, the most used formulation is PCA, which decorrelates the data from different channels (i.e., electrodes), by separating geometrically orthogonal modes [64]. Another group applied multivariate statistical methods to uncover hidden sources from multiple channels. ICA is the most common: it assumes a generative model where observations are regarded as linear mixtures of non-Gaussian statistically independent sources, which are then separated so that they are maximally independent. Compared to PCA, ICA includes higher-order statistics to achieve independence. Two

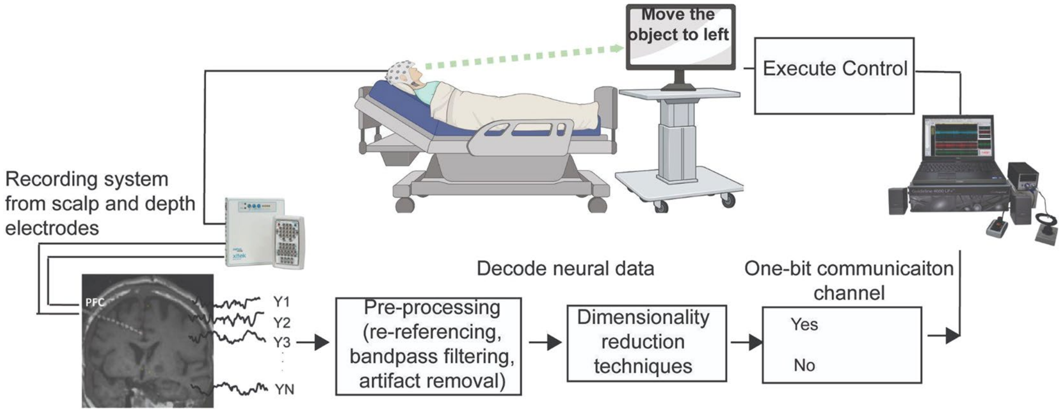

Fig. 1 Set-up for BCI systems for communication in a patient with DoC. DoC, disorders of consciousness

ICA-based algorithms commonly used for EEG source separation are Infomax [65] with its extensions [66], and FastICA [67]. In the fMRI field, MELODIC (http://www.fmrib.ox.ac.uk/fsl/) and GIFT (http://icatb.sourceforge.net/) allow for temporal concatenation of data and are the most widely used. JointICA was used when concurrent EEG and fMRI data were available from the same study participant, but the method needs further validation [68, 69]. Matrix factorization methods have also been introduced, which jointly factorize a matrix coupled with a tensor. This strategy is particularly convenient when EEG and functional MRI data have to be conjointly analyzed for unsupervised data fusion, to obtain one or more modes common to the two physiological data types. Objective functions are minimized to jointly factorize a matrix (commonly fMRI data) coupled with a tensor (commonly, the EEG data) in single study participants [70]. Matrix factorization has been successfully employed in the detection of epileptic foci in cases of refractory epilepsy, and some implementations can be adapted to study the default mode network [71].

Classification

Of all the BCI architectural stages, classification is frequently regarded as the most challenging. Many classification algorithms have been devised on the decomposed signals, using both classical signal processing and artificial intelligence strategies. Among these, support vector machine and linear discriminant analysis are the most commonly used. In recent studies, researchers are using deep neural networks for the classification of motor imagery tasks [72]. Importantly, a trade-off needs to be found between accuracy, speed, and degrees of freedom for the request (i.e., user's selection), which determines overall accuracy.

Technical Challenges When Using BCI for Patients with DoC

Successful employment of BCI systems to restore communication with patients affected by a DoC brings about additional challenges inherent to this population. First, necrosis, brain atrophy, hydrocephalus, skull replacements, and neurosurgical resections make accurate localization of brain activity a nontrivial task. Second, the neuroelectrical activity, as well as the hemodynamic response function, are often heavily disrupted, resulting in presentation of features deviant from the expected physiology, both in time and frequency domains. Hence, standard feature extraction needs to accommodate disease-specific and patient-specific abnormalities and might need on-purpose adaptations. Third, patients with DoC in both the acute and chronic settings are often subject to fast-evolving changes in their awareness and responsiveness, linked to general variations in health or medication scheduling, which hampers the repetition of assessments and the collection of confirmatory data [73]. Last, in children it is important to consider age-dependent neurophysiological differences, compared to adulthood. Establishment of the age-related tolerability and baseline levels of performance across BCI systems and paradigms is an emerging field in pediatrics. This research is essential, as it directly impacts our ability to understand and quantify how BCI user's performance is affected. Also, measures of BCI tolerability are not standardized.

Roadmap for Assessment of BCI Readiness for Communication in an Individual Study Participant with DoC

We developed this primer aimed at modeling the approach to establishing BCI in DoC based on current knowledge.

Assessment of a patients with DoC for BCI readiness requires the use of specialized quantitative behavioral assessment tools (Fig. 2); patients with DoC requiring BCI dissociate motor efference and motor control from the preservation of a widely integrated cognitively enabled brain.

Initial patient assessment should include structural brain imaging and measurement of the wakeful EEG at rest to gauge likelihood for useful progression into more specialized electrophysiological assessments. For study participants with DoC who qualify to be suitable for further evaluation and are unable to communicate via speech or gesture, a comprehensive stimulation response assessment should be undertaken (second line, see figure legend for Fig. 2). If either a motor or physiological signal providing a single bit information channel is identified (Fig. 2), patients should be comprehensively evaluated for establishing one-way or two-way communication systems via BCI. In some study participants with DoC, this stage required considerable iteration (e.g., Thengone et al. 2016 [9], see Supplementary Video of closed-circuit video capture of single direction eye-movement providing one-way BCI).

Initial Patient Assessment

Behavioral Assessment

Clinical confounders may impact production of explicit motor and behavioral responses to external stimuli contributing to pitfalls in bedside assessment. These confounders can be caused by interference with sensory input (neuropathy, myelopathy, sensory aphasia, vision and hearing impairment, sensory processing), motor output (neuropathy, myopathy, myelopathy, motor aphasia, frontal akinetic syndrome), intrinsic brain activity (thalamocortical dysfunction, uncontrolled seizures),

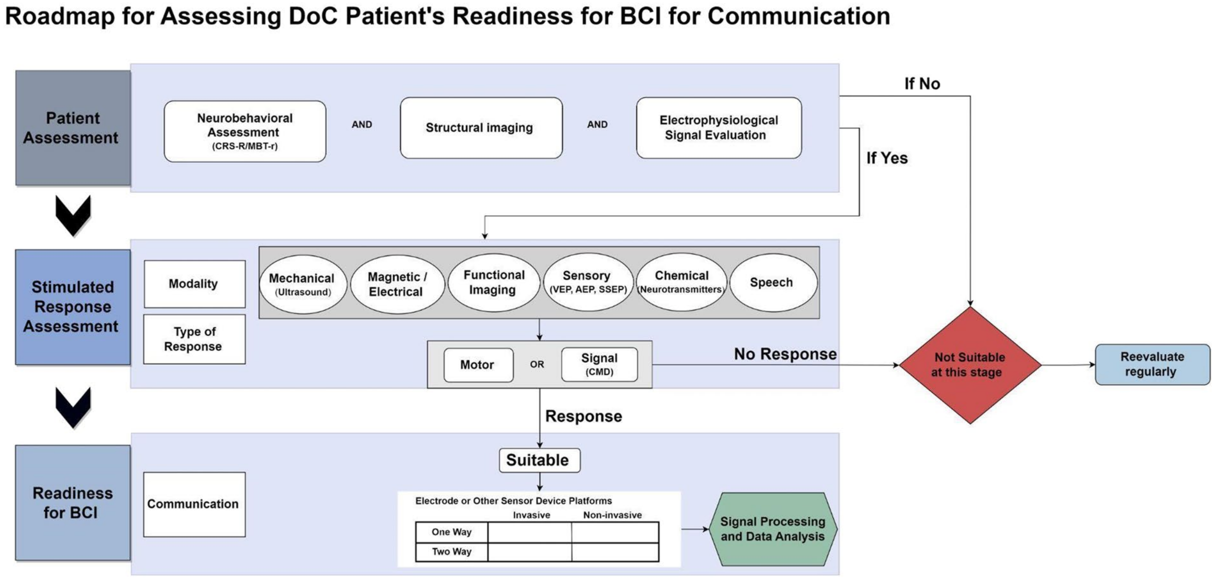

Fig. 2 Patients with a DoC need to be clinically assessed for their BCI readiness, as success of this approach can only be expected when certain minimal clinical prerequisites are met. Typically, a patient's clinical assessment would comprise three elements: (1) a neurobehavioral examination through a standardized or well validated scale for consciousness, such as CRS-R, complemented by MBT-r or a similar tool, (2) a neurological examination, possibly including a radiological investigation through structural imaging, such as brain CT or MRI, and (3) a neurophysiological assessment with standard electroencephalography and, possibly, evoked potentials. It is important for the initial clinical assessment to be comprehensive, so that sufficient elements can be gathered by the clinical team to recommend (or not) specific sensory response assessment for BCI candidacy. AEP, auditory evoked potentials, BCI, brain-computer interface, CMD, cognitive motor dissociation, CRS-R, Coma Recovery Scale-revised, CT, computed tomography, MBT-r, motor behavior tool-revised, MRI, magnetic resonance imaging, VEP, visual evoked potentials, SSEP, somatosensory evoked potentials

fluctuations and disorders of arousal [74]. In children, the problem may be worsened by brain immaturity, as the stage of brain development might be insufficient to satisfy the requirements for detectable behavioral and motor responses. In terms of quantitative neurobehavioral assessments, we suggest that at a minimum the Coma Recovery Scale-Revised (CRS-R) should be administered [75]. The CRS-R is a recommended measure with well-established psychometric properties for capturing DoC level behaviors. Additionally, the motor behavioral tool-revised [76] can be considered, as this measure provides an assessment of BCI readiness by identifying potential motor channels for evidence of command following and potential control pathways for signal measurement in individual study participants with DoC.

Structural Imaging

Structural imaging in study participants with DoC may reveal patterns consistent with the likelihood of producing significant motor impairment while preserving cognitive capacity for BCI use. In traumatic brain injuries, bilateral damage to the primary motor regions, internal capsule, or brainstem (as might be observed in radial diffuse axonal injury) may suggest greater likelihood for this pattern of impairment when forebrain structures are otherwise preserved [25]. Similarly, ventral brainstem ischemic lesions with tegmental extension may produce a mix of cognitive and complex sensory impairments along with paralysis [9, 18, 77]. Hypoxic-ischemic injuries combining bilateral motor cortex and primary visual cortex may be associated with a high-risk of 'isolation syndrome' with loss of visual processing and corticospinal movement control [78]. More specific anatomical information from specialized evaluation of connectivity utilizing diffusion tensor MRI (DT-MRI) methods may also reveal preservation of motor planning centers with loss of connection to primary motor cortical outflow [20], suggesting likelihood of the dissociation of cognitive capacity and motor outputs. If sufficient elements are found suggestive of structural brain integrity (e.g., through analysis of white matter tract integrity using DT-MRI) in the absence of command following capacity, sensory response assessment should focus on pathway integrity toward naturally perceived stimuli. In the first instance, this includes testing the (residual) ability to perceive and propagate the environmental sensorimotor, auditory and visual information to the brain through the ascending nervous system by means of neuroelectrical signal. Examination for somatosensory, auditory, and evoked potentials serve this purpose.

Electrophysiological Signal Evaluation

Several studies have linked the preservation of resting EEG to level of consciousness [79–81]. Other studies specifically suggest that an initial clinical assessment of the integrity of the wakeful EEG architecture can help identify CMD as the preservation of wakeful background features has been specifically linked to successful performance of command following paradigms [82, 83].

Stimulation Response Assessment to Identify a One-Way Communication Channel

A variety of tools are currently available to search stimulation types that are effective in assessment of covert command following in study participants with DoC. Most studies have concentrated on the use of fMRI and EEG methods [4, 24, 84]. Typically, methods utilize motor imagery or direct attempts at motor action [23, 85]. Similarly effective outputs have been established using electromyographic responses [86–88]. Although several neurophysiological studies have been published on pain perception in patients with DoC, to our knowledge, no study so far proposed using nociceptive stimuli for BCI applications in this patient population [89]. In addition, a wide range of alternative stimulation responses have proven successful in the population of patients with DoC; for example, a sharp difference in response to stimuli presented within peripersonal space has been observed even in some study participants with aphasia and attention deficits [90]. Most of these methods utilize auditory commands and broad read-outs from fMRI or EEG sensor space. In addition, many useful and effective paradigms also exist that can successfully detect perceptual activation but perhaps not be advanced to BCI systems (e.g., odor-dependent sniff responses [36]), passive visual stimulation, e.g., passive eye tracking or read out from visual cortices [33].

When no neuronal signal is observed in association with environmentally generated stimuli, functional network integrity can be probed through artificially induced brain stimulation. Among these methods are low intensity focused ultrasound, transcranial magnetic stimulation, transcranial direct current stimulation, transcranial alternating current stimulation and use of pharmacological agents such as N-methyl-D-aspartate (NMDA) receptor antagonists (e.g., amantadine) and paradoxical application of gamma-aminobutyric acid (GABA) agonist (e.g., zolpidem, lorazepam).

Although the general steps outlined in Fig. 2 will likely guide most evaluations, all BCI in DoC will require personalization to the study participant and the clinical setting. In all cases and at all levels, a binary response code should be proposed and trained, to obtain either a motor yes or no feedback from the patient, or purely neuronal feedback. This last option should be specifically pursued in study participants with CMD detected with advanced imaging or electrophysiology, clinical CMD (combined CRS-R/MBT-r evaluation or similar) [91], or inconsistent motor control. This last group encompasses patients with minimally conscious state plus (MCS+) or emerging from the MCS (EMCS) who have preserved cognition at a level closer to "locked-in plus" definition.

Importantly, in our framework, absolute absence of any evidence of response is the only condition for exclusion, whereas responses compatible with different levels of neurofunctional integrity and with variable consistency all encompass the spectrum of BCI readiness.

For nonexcluded patients, BCI readiness then needs to be individually characterized, by making a number of personalized technical choices, among which whether to pursue and train one-way or two-way communication, and whether to position electrodes invasively (i.e., intracranially) or noninvasively (i.e., at the scalp).

Gap Analysis

Clinical Assessment

A current practical concern is how and which thresholds should be set to test patients for BCI readiness. Detailed assessments are required to check for impairments in (1) motor output, (2) sensory input, (3) sensory processing or motor production, (4) arousal, or (5) desire to communicate [21]. However, a compact assessment strategy is not yet available, nor is there a specific BCI readiness tool. A major challenge is that the substrate requirements associated with preserved cognition sufficient to harness BCI tools are not known. Of note, for patients with DoC with the ability to demonstrate command following at the bedside (MCS+) or even having emerged from MCS with functional communication (accurate situational awareness on six questions), a 61% failure rate has been reported on active paradigm performance [7].

The wide heterogeneity in the pathology of patients with DoC calls for assessments that focus on domain-specific analyses of brain function rather than behavioral checklists. Domain-specific analyses will likely enable the identification of subsets of covertly conscious patients, capable of willful modulation of brain activity, although incapable of expression through explicit motor behavior. However, literature on how to specialize covert cognition assessment for the specific domains is still incomplete.

Assessors should consider that in patients with DoC, arousal and attention fluctuate over time, within and between days. In addition, fatigability often develops quickly even with low effort tasks. Repeating assessments increases the chance to observe the real capabilities of each patient, and to refine the selection of the most appropriate BCI. More data on how the entity of arousal fluctuations changes with the levels of consciousness over assessment repetitions are needed.

Sample Enrichment via Deep Phenotyping of DoC

Across the spectrum of patients with DoC, certain subsets of injury patterns can be anticipated to be more likely to result in sharp dissociation of preserved cognitive function and severely impaired motor output [20, 25, 48, 82, 92–96]. In DoC due to brain trauma, patterns of diffuse axonal injury that disrupt brainstem descending pathways (e.g., increased radial diffusivity at DT-MRI) are frequently encountered [25, 97]. Less common but often overlooked are cerebellar outflow lesions [91], which may specifically arise in pediatric patients with DoC [98]. Following cardiac arrest, an "isolation syndrome" has been observed involving the joint loss of primary motor cortices and primary visual cortices. This common injury pattern reflects the vulnerability of these neurons to hypoxic/anoxic injury [78]. In the acute setting, intensive care unit polyneuropathy and/or myopathy may often mask preserved cognitive function and require further assessments of patients [74]. Collectively, such regularities within particular etiological groups provide an opportunity for sample enrichment of studies of DoC, which could also specifically aim to identify subgroups with greater likelihood of BCI readiness.

Acute Versus Chronic Phase

In the acute setting, covert consciousness demonstrated by motor imagery is important for prognostication. However, pharmacological sedation might interfere with the employment of BCI. BCI should require short training when applied in the intensive care units, due to the high level of care required and the patients' rapid evolution. Hence, in the acute setting there is a need for flexibility in changing BCI approach and level of communication complexity. This should always be compliant with the estimated developmental level in children. Antiepileptic and antiseizure drugs might also interfere with the brain activity and connectivity, and thus with the employment of BCI [99]. The application of BCI when the brain injury is still in evolution, especially invasive BCI, can be ethically challenging. Issues related to vigilance fluctuation and language deficits might interfere with acquisition of task related potentials, may lead to less robust signals, and may be inappropriately conflated with an assessment of consciousness per se.

The chronic phase allows for personalization of BCI, as the therapists can access the home environment, consider the daily routines and the patients' attitudes and preferences manifest before injury, and then set goals. BCI accuracy depends on motivation and perseverance in this phase, as the tool is intended for long-term use.

Technology-Related Gaps

Type of Neural Signal

Both the electrical and neural metabolic activity can be used to establish BCI communication. The neuroelectrical signal, captured through EEG, is very dynamic and modulates in the order of milliseconds making EEG the most used BCI technique. Research on faster signals, e.g., based on neurotransmitter release, could be an avenue. Still, the metabolic signal is intrinsically slow, with modulation in the order of seconds; and hemodynamic responses are rarely fully preserved in patients with DoC, especially in the acute setting. For these reasons, functional techniques based on metabolic signals, such as fNIRS, are infrequently used. However, these methods can be complementary to those recording the fast-evolving electrical signal when there is a need to improve either detection, sensitivity, or the range of user's choices.

Noninvasive Versus Invasive Signal Acquisition

Noninvasive electroencephalography (EEG) has several shortcomings when applied to BCI: (1) poor spatial resolution, (2) unclear relationship to spiking activity, and (3) propensity to volume conduction, meaning the generators of activity can be quite distant from scalp contacts. Of note, high-density montages with 64 or more channels combined with source component analysis, can improve the spatial resolution.

Invasive electrical recordings enable higher spatial resolution, better signal-to-noise ratio, and offer the opportunity for single neuron recordings and acquisition of signals from deep brain structures. This is obtained at the cost of surgical implantation of electrodes, with associated risk of bleeding and infection. Importantly, most surgically implanted electrodes are only capable of recording local field potentials, though several types of electrodes (Utah arrays, Neurogrid, and Neuropixels) are capable of recording single neuron activity in small areas.

Given these shortcomings, there is a critical need for new techniques for neural signal acquisition. The ideal technique would be noninvasive, have high spatial and temporal resolution, and provide access to neuronal spiking information. Even if the requirements of BCI necessitate surgically implanted electrodes, wireless technology would represent a major advance, because current techniques require externally tunneled wires, which are inconvenient and can be a nidus for infection.

Biological Signal Reliability

Patients with severe brain injury may exhibit weak, intermittent, or severely distorted neural signals that are difficult to detect reliably. Optimal placement of sensors/electrodes that is customized to the patient's injury profile is necessary. Using neuronavigation techniques based on the patient's own MRI may improve localization. Mathematical methods for conjoint or symmetrical processing of data from multiple techniques can help increase localization precision, leveraging on information from each data source.

Signal Processing

When designing machine learning models for classification, a choice has to be made between supervised (i.e., relying on manual labeling) and unsupervised (i.e., fully automatic) algorithm training. Selecting the best category and algorithm can be resource-consuming and depends on the nature of the signal and the application. Factors to consider include ability to detect weak signals in recordings with high levels of noise, artifact detection and cancelation, and dimensionality reduction techniques (high dimensional continuous data and low computational capacity). There is thus a gap in identification of optimal signal processing approaches.

Assessing Failure

All approaches (invasive BCI, noninvasive BCI, and non-BCI) may fail to deliver information, especially on a single-trial basis. For a given study participant on a given day, it is possible that neither markers nor communication signals can be obtained, or that markers can be obtained (whether by BCI or its nonbrain-signal equivalent such as an individualized quantitative behavioral assessment), but not communication signals. Although positive predictive value may be high, negative predictive value is low due to high false negative rates. Any failure has explanations at many potential levels and there is a gap in codifying failure types. The particular confounds endemic to DoC, and to pediatrics (let alone pediatric DoC), are the fluctuations of arousal, attention, and willingness to comply. This highlights the particular importance of BCI in DoC applications.

Special Considerations in Pediatric Patients

The assessment and application of BCIs in pediatric patients with DoC poses additional challenges. One of the "hard problems" in pediatric DoC is conceptualizing a developmental age-specific model of consciousness that accounts for brain development as an integral variable in expression of conscious behavior. Additionally, from a practical perspective, the challenge is determining what is the minimal threshold (i.e., capacity) of consciousness that is developmentally appropriate and has to be "preserved" to successfully interact with the environment, and thereby access and train on BCI [100].

From a biological standpoint, arousal is consistently present in children of all age groups. However, the stability and reproducibility of behavioral responses are variable due to the immaturity of cognitive, communication and behavioral skills, especially in very young patients. In certain cases of pediatric DoC, the neurobiological substrates for consciousness may be different from those observed in adults. For example, children born with congenitally absent cortices can still show conscious behaviors, such as preferential responses to music, recognition of familiar and unfamiliar sounds and engaging in associative learning [101]. These observations carry important biological implications for potentially repurposing the brainstem to process certain neural correlates of consciousness in pediatric patients.

When assessing children with DoC, the manifestation of specific responses and behaviors is conditioned by the acquisition of specific cognitive abilities that support their emergence and stability. These cognitive abilities emerge as a function of brain maturation and interaction with the environment. Therefore, the developmental age is a more appropriate indication of expected levels of cognitive function than the chronological age. The younger the child developmentally, the more impacting the following factors may be: (1) increased variance in attention, comprehension and compliance; (2) altered characteristics of neural signatures which may differ from adults; and (3) alterations in event-related potentials and resting state networks that occur over the course of recovery (i.e., VS vs. MCS vs. conscious state) and need to be disentangled from changes that occur during the course of development and maturation [102–104].

Similarly, the reliability of specific neurophysiological biomarkers of consciousness identified in adults cannot be assumed in children. Each biomarker should be regarded conditionally to its reliability on the developmental trajectory, after evaluation of validity and reproducibility and fit for purpose or suitability. Establishing an age-referenced baseline performance and paradigms for different commercially available BCI systems in healthy children is necessary for designing developmentally appropriate BCI training programs for children with DoC.

Distinct subpopulations can be identified, based on the brain maturation and cognitive development and skills achievements that can identify BCI suitability. Compared to older children, infants and preverbal children likely have different requirements for successful BCI communication, especially for using BCI for real-time verbal and nonverbal communication. During the preverbal age, there is a need to find alternative modes of communication that are developmentally congruent, align with expected developmental cognitive skills, are reliable and consistent (e.g., affective responses to pain or simple commands).

Pediatric BCI paradigms should be customized, accessible, and age tiered. All BCI approaches in children must consider the dynamic nature of brain plasticity, preinjury baseline developmental skills and the impact of injury profile on development, maturation, and acquisition of new skills as well as remodeling and compensation. After severe brain injury, brain development can be stunted or plateaued, and regaining baseline skills or acquiring new ones is difficult to predict.

Studies of BCI use in children are scarce and yield varying results: some report lower performance [105, 106], whereas others suggest comparable results to adults [107]. However, BCI research has only marginally addressed children, and pediatric BCI applications have been recently identified to be an unmet need [108]. BCI paradigms for pediatrics should avoid dry, repetitive tasks, as children naturally have shorter attention spans. Engaging paradigms and "gamification" are key for successful implementation. Such captivating approaches may be highly beneficial for adults as well. Thus, there is a need to develop BCI software that seamlessly incorporates elements of play. Additionally, children are also likely to be more sensitive to fatigue and discomfort from prolonged BCI hardware use, highlighting the need for prioritizing ease-of-use, portability, and minimal invasiveness.

In the acute setting, the primary objective is to restore some form of communication, commonly in a binary (i.e., yes or no) format. Specifically, the communication of pain is of paramount importance. If some residual motor abilities are observed, somatic controls can be devised, including options like a smile switch, noncontact tongue switch, mechanomyographic switch, and dysarthric speech decoding. Similar to adults, factors that need to be considered in acute settings are patient's positioning, tolerability of the headsets, timing of interaction and training, and the interplay of sedative agents or antiepileptic drugs.

In the chronic setting, the focus shifts from primary binary communication addressing basic needs to more advanced communication accompanied by play, leisure, and better environmental control. Pediatric–oriented training protocols can be implemented to enable and/or accelerate the acquisition and mastery of BCI system control, such as mental speech BCI. While there is some promising evidence [109], success hinges on the patient's developmental stage. For example, the ability to comprehend spoken or written language, the ability to follow commands both simple and complex, and the ability to perform simple cognitive and spatial skills such as distinguishing "left" from "right," are needed to successfully execute certain tasks that directly depend on developmental stages.

Recent research highlights the usefulness of biomarkers such as auditory oddball paradigms (P300/auditory-evoked potential) in the pediatric population [110]. From a signal processing perspective, there is a need to distill the output of EEG markers into a statistical test of which EEG signals correlate with motor command following [109].

If invasive BCI is a preferred option in some pediatric cases [111–114], invasive implantation strategies must account for miniaturization and component downsizing, similarly to noninvasive approaches. In addition, a durable device should account for and adapt to the child's physical growth. In general, the pediatric age is often associated with an overall more optimistic prognosis, as brain injury survivors have higher probability to recover, compared with adults and the elderly. However, reports of chronic cases of DoC in pediatric patients are few and of shorter duration compared to adults.

Although BCI is promising and much needed in pediatric patients, its use could have a compounded impact on cognitive functions as it could cause perturbation of the already disturbed developmental processes. These factors may lower the risk/benefit ratios for BCI use in this age group. However, longitudinal studies are needed to assess developmental outcomes of BCI in children with DoC.

Importance of Personalized BCI

The above review exposes a need to balance general standards of demonstration for BCI readiness and criteria for establishing one- or two-way BCIs with the need to customize solutions for individual patients (finding the most reliable and robust response channel). Such individualization should first identify the optimal neuronal substrate for read out. For example, emerging methods that allow speech synthesis [115] and tools that identify the ability to activate Broca's area with silent speech [116] may become alternative or complementary substrates in individual patients. In children, a variety of cognitive and physiological changes need to be anticipated based on age and residual cognitive abilities. The perseverance of families or caregivers is fundamental in establishing communication to facilitate the child's engagement with protocols. A BCI activity library that includes requests or tasks that are appropriate for different developmental ages is needed. Such tasks should be engaging, motivating and fun, for children who slowly emerge from VS to higher levels of consciousness. Adaptive BCI interfaces may be able to learn and adjust to the patient's specific neural signatures over time.

Ethical and Legal Considerations

Despite advancements that have been made in several countries toward the legal protection of rights of patients with a DoC, appropriate regulation on the use of BCI is still widely missing. The extent to which device provision and training should be secured for patients with a DoC condition, which cognitive functions should be considered essential to training, the role of insurance and of state health care systems in the cost coverage, the maximum period of training after injury or with no clinically or socially meaningful improvement, and the professional roles in charge of both assessment and provision are unaddressed matters. Additionally, technical considerations, such as device lifetime, reuse on multiple patients, and dismissal must be addressed. Moreover, in the context of DoC, while BCI per se can be unrelated to communication (e.g., robotic arm control, exoskeleton), the use of BCI to promote communication is a primary intervention and, if possible, creates a potential for future consent [10]. However, the assessment strategy requires the identification of the patient's readiness or possibility to communicate, before considering ethical and/or practical engagement of BCI for other purposes. At present, international guidelines are mixed in their recognition of these considerations. As an example, UK guidelines for prolonged DoC (2020) contain no indications on communication enabling/restoration for covert consciousness. No guideline exists for BCI adoption, beyond general The National Institute for Health and Care Excellence recommendations on new technologies [117].

Recommendations to Improve BCI for Communication in DoC

Clinical Recommendations

I. It is of paramount importance to clearly define BCI readiness. This can be achieved through deep phenotyping of the DoC subpopulations. Phenotyping will help in identifying patients who are most likely to benefit from BCI, and will enable a more individualized approach to treatment and efficient use of resources for health.

II. All assessments for using BCI should be coupled with systematic procedures for arousal optimization.

III. There needs to be customization of study participant assessments for BCI in DoC. It is crucial to avoid the pitfalls of standardized scales and instead focus on individualized approaches to assessment and treatment.

IV. Once BCI readiness is established, study participants with DoC should be evaluated for capacity to utilize a BCI to further evaluate diagnosis.

Research Recommendations

I. Development and validation of hierarchical protocol to assess BCI readiness that can be used across clinically available and affordable platforms. We believe that an EEG-based approach is most likely to achieve these criteria at present.

II. Characterization of natural history of patients with CMD over time (restoration of communication using augmentative technologies or spontaneously recovering speech or gestural communication).

III. Set up pilot studies for identifying BCI readiness and successfully implementing BCI one-way and two-way communication. We deem this step is critical for the iterative refinement of techniques.

IV. Establishment of developmentally appropriate assessment tools for pediatric study participants with DoC. This will help with deep phenotyping across neuroimaging, electrophysiological, and behavioral levels.

V. Standardization of signal processing algorithms for evaluation of biological signals suitable for use in BCI for DoC. There is a need for a consensus on clinical evaluation and EEG analysis methodology. Relaxing statistical testing approaches or accepting as positive cerebral activation occurring in peripheral channels may lead to overoptimistic results, which should be avoided.

VI. Set up multicentric studies to enable larger sample sizes and more robust conclusions.

VII. Further investigation of the effects of simultaneous multisensory stimulation for BCI. As Stein, Stanford, and Rowland point out, the brain integrates inputs from two or more senses to form a distinct biological signal that enhances perception. The number of impulses evoked increases, and possibly shortens the time between sensory encoding and motor command. These studies may lead to new strategies for improving BCI communication in patients with DoC.

The present article could form an effective basis for development of collaborations among multinational Scientific Grant Organizations to issue requests for applications to systematically explore these topics.

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Author Contributions

All authors contributed to the planning and structuring of the report. Authors contributed to the process through writing and regular biweekly meetings beginning January 2021 and continuously attended by subsets of the authors until the present time. The initial development of the group was directed by NS, RS, and MD; NS directed the project development and biweekly meetings. The manuscript has been approved by all authors.

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Declarations

Conflicts of interest

No authors report conflicts of interest with respect to this work product.

Ethical Approval/Informed Consent

The study did not involve new research involving human study participants or animal subjects and did not require any institutional review board or Institutional Animal Care and Use Committee oversight.

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