Cognitive Motor Dissociation: Gap Analysis and Future Directions

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Abstract

Background/objective. Patients with disorders of consciousness who are behaviorally unresponsive may demonstrate volitional brain responses to motor imagery or motor commands detectable on functional MRI or EEG. This state of cognitive motor dissociation (CMD) may have prognostic significance.

Methods. The Neurocritical Care Society's Curing Coma Campaign identified an international group of experts who convened in a series of monthly online meetings between September 2021 and April 2023 to examine the science of CMD and identify key knowledge gaps and unmet needs.

Results. The group identified major knowledge gaps in CMD research including (1) lack of information about patient experiences and caregiver accounts of CMD, (2) limited epidemiological data on CMD, (3) uncertainty about underlying mechanisms of CMD, (4) methodological variability that limits testing of CMD as a biomarker for prognostication and treatment trials, (5) educational gaps for health care personnel about the incidence and potential prognostic relevance of CMD, and (6) challenges related to identification of patients with CMD who may be able to communicate using brain computer interfaces.

Conclusion. To improve the management of patients with disorders of consciousness, research efforts should address these mechanistic, epidemiological, bioengineering, and educational gaps to enable large-scale implementation of CMD assessment in clinical practice.

Introduction

It has become clear that some patients with a disorder of consciousness (DoC) who appear unresponsive on behavioral assessments (e.g., the Coma Recovery Scale Revised, CRS-R)[1] are, in fact, able to voluntarily engage in mental activities that can be detected with techniques such as electroencephalography (EEG) and functional magnetic resonance imaging (fMRI).[2–5] This state, whereby a patient's behavioral phenotype does not match their level of residual cognitive function and awareness, has been referred to with several labels (e.g., covert awareness, functional locked-in syndrome, non-behavioral minimally conscious state),[6] and cognitive motor dissociation (CMD);[7] in this manuscript we will use CMD. Detection of CMD has several implications for clinical care. Early detection has been associated with better long term functional outcomes.[3, 8] CMD challenges several key aspects of caring for DoC patients and creates new opportunities in the context of diagnosis, prognosis, interventions, and ethical decision-making. CMD can be considered a novel diagnostic group, differentiable in its characteristics (e.g., functional outcomes, responsiveness to interventions) from other diagnostic categories of DoC, or a confounding factor where impaired motor-output is preventing self-expression on behavioral assessments. CMD is discussed as a state in which cognitive function and behavioral responsiveness become dissociated after brain injury, and future mechanistic, epidemiological, and outcomes data will determine whether the nosology of DoC requires modification. The available data indicate that CMD and the concept of covert consciousness will not only stand the test of time, but will likely change how we perceive and treat DoC in the future.

The CMD state: Nomenclature and historical aspects

Writers and poets described the existence of some form of human cognition without physical (motor) functions (Figure 1), long before covert consciousness was formally reported in the medical literature. For instance, Alexandre Dumas in 1844 (The Count of Monte Cristo) and Emile Zola in 1868 (Thérèse Raquin) described characters with locked-in syndrome, more than 100 years before Fred Plum and Jerome Posner's seminal account in "stupor and coma" (Figure 2).[9] Similarly, the acclaimed children's book author Roald Dahl described covert consciousness in a short story ('William and Mary', 1959)[10] almost half a century before the term "cognitive motor dissociation" (CMD) was coined in 2015.[7] In that work the main character was a conscious man devoid of all motor output, including absence of eye movements, only connected to the external world by a brain-computer interface (BCI). [11]

The dissociation between cognition and motor expression is conceptualized within the broader context of motor cognition, which involves motor imagery, planning, and execution.[12–14] The existence of CMD was first reported in 2006 in regard to a young woman who was behaviorally unresponsive after traumatic brain injury (TBI).[2] Yet, when asked to engage in mental imagery tasks, she demonstrated a pattern of fMRI activation identical to that in awake healthy controls. The ability of the patient to reliably understand spoken commands and intentionally execute tasks via brain activation "confirmed beyond any doubt that she was consciously aware of herself and her surroundings".[2] Reports of similar findings in large patient cohorts[4] and use of EEG for detection and characterization of brain activation followed soon,[5, 15, 16] along with the observation that CMD may occur in the acute phase after brain injury in the intensive care setting.[3, 5]

While many labels have been used to describe this state of covert consciousness or closely related states, including non-behavioral minimally conscious state (MCS),[17] MCS*,[18, 19] functional locked-in syndrome,[20, 21] see [6] for review), CMD is most commonly used [6] and will be used in this manuscript. Importantly, CMD should be distinguished from phenomena such as covert cortical processing,[22] in which patients whose behavioral exam does not reveal language expression or comprehension (i.e., coma, vegetative state [VS; sometimes also referred to as unresponsive wakefulness syndrome], or MCS-) show engagement of associative cortex, as detected with EEG or fMRI, in response to language or music stimulation. Crucially, while response to active, task-based paradigms is sufficient to detect awareness, and thus CMD, a response within association cortices to a passive, stimulation-based paradigm does not allow for such inference.[23]

Additionally, it is important to distinguish CMD from the related, but distinct, concept of covert awareness (CA). As originally described,[2] the idea of CA refers to patients who appear behaviorally non-responsive in conventional neurobehavioral clinical assessments (e.g., CRS-R), but can demonstrate the presence of awareness via non-muscle dependent means (e.g., fMRI, EEG). While CA and CMD overlap, they apply to different subsets of patients. Specifically, by definition, CA can only occur in behaviorally unresponsive patients; that is, patients with a diagnosis of coma or VS and, potentially, patients with a complete locked-in syndrome. Conversely, CMD, understood as a dissociation between the residual cognitive abilities of a patient and their capacity for motor expression,[7] can occur in VS patients as well as MCS minus, partial and complete Locked-in Syndrome. In other words, CMD patients with the ability to demonstrate behaviorally some level of non-verbal responsiveness (e.g., MCS-; partial locked-in syndrome) would not qualify for CA. These patents cannot, by definition, have CA, since they can reveal in standard clinical tests to have some level of awareness, but can have CMD (e.g., if they could demonstrate response to command via fMRI or EEG).

There are several shortcomings related to the term 'CMD'. First, etymologically, CMD could also connote a state in which motor function is much better than cognition (in other words the opposite of what it is intended to indicate). Second, depending on the technology used, covert consciousness may be detected with different frequencies.[24] Third, ethical [25] and juridical[26] implications of the term are poorly understood.[27, 28] Finally, most biological phenomena exist on a continuum that categories such as CMD artificially lump. Thus, although CMD highlights the existence of a category of patients not captured by standard DoC nosology (e.g., coma, VS, MCS; Table 1 and Figure 3) and is likely to have practical clinical relevance, it may not sufficiently reflect the complex endo-phenotype continuum of states that are characterized by loss of motor activity but preserved consciousness.[29, 30] For example, it is possible for a patient to have some degree of self-awareness while being behaviorally unresponsive, and, due to sensory or other cognitive impairment, also unable (or unwilling) to demonstrate a positive response in neuroimaging, and thus not meeting the definition of CMD.[31]

Epidemiology of CMD

Determining the incidence and prevalence of CMD is challenging for several reasons, including evolving means of detection of the state, lack of consensus on nomenclature and classification, and that CMD is likely heterogeneous and transient. Most published studies are case reports or small case series;[24, 32] a handful were conducted in more substantial samples. Amongst 54 patients (52 with prolonged DoC) tested with a motor imagery fMRI paradigm (i.e., imagine playing tennis), 2 patients clinically diagnosed as being in VS and 3 in MCS were able to perform the fMRI task (9% of the sample).[4] One of these patients was also able to answer ‘yes’ or ‘no’ to autobiographical questions and was able to communicate by using either motor or spatial imagery (2% of the sample). Using the same fMRI paradigms in 122 patients (97 with prolonged DoC), 4% of patients diagnosed as VS and 27% as MCS[33] met criteria for CMD. Using an EEG based active paradigm, 16 out of 104 patients with acute DoC (15% of the sample) showed an electrical brain activity compatible with a willful response;[3] at 12 months responders had better outcome than non-responders. In a confirmatory cohort,[8] the same group reported a CMD rate of 12%. There is clearly an unmet need for larger, multi-center studies to improve statistical power and more precisely understand the epidemiology of CMD.

Additional perspective can be derived from systematic overviews. In two separate metanalyses, patients who had behaviorally been diagnosed with VS were less likely to be diagnosed with CMD (14-19%) than those with MCS minus (32-33%; of note some of the earlier studies did not distinguish between MCS minus and MCS plus).[24, 32] Importantly, in one analysis MCS- patients had a similar rate of CMD as VS patients.[32] In the acute post injury phase, CMD was reported in coma (8%), VS (7%), and most commonly in MCS- (20%).[3] No demographic or disease related variables such as time from injury were found to be reliably predictive of CMD, but TBI patients were more likely to have CMD. These observations highlight the importance of careful and precise behavioral assessments when studying CMD. Both meta-analyses also found that patients with TBI were more likely to have CMD than those with other brain injuries, suggesting that the etiology of brain injury might impact the probability of covert awareness.[24, 32]

Further efforts to identify the demographic and clinical characteristics of such patients are needed to help clinicians identify this challenging population. The technical complexity of identifying patients with CMD represents a major challenge to accurately estimating the prevalence, the incidence, and the profile of this state. We therefore call for harmonization of protocols in the detection of CMD and a consensus on defining criteria to allow reliable epidemiological studies.

Mechanisms of CMD

The presence of volitional mental activity in the absence of purposeful behavior suggests a dissociation between self-awareness and self-expression. Given that the majority of CMD studies have utilized motor imagery/command or spatial navigation tasks, a dissociation between motor planning and motor output is believed to underlie CMD. Evidence supporting this conceptual model is limited, as few prior studies have examined the structural and functional basis of CMD. The most direct evidence for a dissociation of motor planning and motor output was provided by a diffusion MRI tractography study in a patient with CMD, which revealed disconnection of the corticospinal tract in the setting of preserved connectivity between the thalamus and supplementary motor area.[34] This study, though limited to a single patient, offers proof-of-principle for current conceptual and pathophysiological models of CMD as a motor disconnection syndrome. A second diffusion MRI study of global brain connectivity found that the connectomes of patients with CMD had more complex patterns of connectivity than those of patients without CMD.[35] These two diffusion MRI studies indicate that CMD may be a focal motor disconnection syndrome superimposed upon a complex architecture of global brain connectivity.

Detection of the CMD state relies largely on motor imagery or motor command paradigms. Studies investigating motor movements have revealed that coordinated network function between cortical and subcortical structures are required to accomplish the cardinal neuronal steps of motor cognition involved in achieving a movement (the “motor goal”). These include the prerequisite of attention, state assessments (i.e., position of joints), computation of muscle forces needed to achieve the “motor goal”, activation of the respective muscles via the primary motor cortex and controlling steps (re-adjustments and fine tuning involving larger networks including the cerebellum).[36, 37] Studies investigating motor imagery support the notion of shared neural mechanisms with motor control within cortico-subcortical networks.[12–14] However, the required inhibition of motor movement in pure motor imagery studies needs to be considered when interpreting motor command studies.

Functional connectivity mapping studies have not yielded a consistent neural architecture, or pattern of connectivity, that underlies CMD. As with patients who show overt, behavioral signs of consciousness,[38–41] the default mode network (DMN) appears to be at least partially preserved in patients with CMD. However, even the association between DMN connectivity and CMD has been called into question.[42] Until studies are performed in larger cohorts of CMD patients with diverse etiologies of brain injury, examining a broad distribution of cortical and subcortical networks, the functional network connectivity patterns underlying CMD will remain unresolved. These studies should be designed to account for the possibility that multiple types of lesions and network disconnections may be implicated in the pathogenesis of CMD.

In the absence of robust brain network mapping data, most current insights into the neural dynamics underlying CMD have been generated from electrophysiological studies. Though they lack the spatial resolution and subcortical measurements provided by structural and functional MRI, electrophysiological techniques provide an opportunity for continuous or repeated measures of brain function in patients with CMD. Given emerging evidence for the prognostic relevance of the CMD state in the ICU,[3, 8] the identification of resting-state EEG signatures that correspond to CMD are of great interest. Indeed, resting-state EEG is the most widely accessible tool for measuring neuronal dynamics worldwide, and as such, there is great interest in leveraging resting-state EEG to identify signs of CMD.[43]

Yet whereas the spectral, coherence, and complexity properties of the resting EEG in patients with overt signs of consciousness are well-established,[44–46] the EEG correlates of CMD are less well understood. The degree of thalamocortical network dysfunction that may underlie behavioral states can be determined by analyzing the spectral power of the EEG, with higher frequency peaks indicating preservation of thalamocortical function.[16, 43, 47, 48] Yet in small cohorts of brain-injured patients with CMD, the temporal and spatial characteristics of EEG features that distinguish CMD from non-CMD appear to be variable.[16] The relationship of other EEG properties such as those indicating functional connectivity (i.e., weighted mutual information or coherence metrics) to CMD are largely unexplored. The presence of sleep spindles has also been associated with CMD, suggesting that this sleep-based indicator of thalamocortical integrity has potential as a surrogate biomarker, or a screening tool, to identify patients with CMD.[49] Similarly, brain complexity measured with transcranial magnetic stimulation (TMS) and EEG may detect patients with CMD.[50, 51] Consistent with these electrophysiological observations from EEG data, positron emission tomography (PET) studies have shown preserved metabolism in patients diagnosed with CMD.[18, 33]

To advance knowledge about the pathophysiologic and neuroanatomic correlates of CMD, the primary goal should be to acquire multimodal datasets, with complementary EEG, MRI, TMS-EEG and PET data, in patients who are diagnosed with CMD based on task-based fMRI or task-based EEG. Only with large, multimodal datasets and a precision-medicine approach to brain mapping[52] can we begin to identify the full repertoire of brain network connectivity patterns and neural dynamics that can support CMD. A fundamental unanswered question is whether there is a network connectivity pattern, or electrophysiological signature, that is shared by all patients with CMD, or whether multiple, heterogeneous brain network connectivity patterns and neuronal dynamics can lead to the same physiologic state. Though we encourage ongoing development of animal models to study DoC, we acknowledge the unique challenge of developing an animal model for CMD. Specifically, the lack of language comprehension and the cognitive demands associated with a motor imagery or spatial navigation task make task-based fMRI and EEG challenging in most animals.

Techniques to detect CMD

To be applied widely for prognostication, decision making, and treatment trials beyond highly specialized centers; the detection of CMD should be standardized with a focus on accessibility, reliability and reproducibility. Ideal properties of such a biomarker beyond reliability and reproducibility would include being low cost, non-invasive, hierarchically quantitative, widely available and applicable, and linked to short- and long-term outcomes, including patient-centered outcomes.

Paradigm structure to detect CMD. The fundamental principle for unmasking CMD relies on the detection of a biological signal (e.g., patterns of neuronal activity) that serves as a marker for the brain's mental effort to complete a cognitive task (Figure 4). An example of the experimental design is exposing subjects to two behavioral conditions (e.g., asking them to move in condition A and stay still in condition B), and the response is evaluated using fMRI or EEG. Stimuli are typically presented in a block design to identify the underlying cognitive efforts. For example, alternating repeatedly between the commands of "keep opening and closing your right/left hand" and "stop opening and closing your right/left hand". Many paradigms are built on motor imagery and have been used to successfully detect CMD; however, a methodological concern is the high level of cognitive demand associated with asking a brain-injured subject to imagine performing a task. In addition to hand movement, other paradigms use motor imagery (involving swimming, [16] playing tennis, [2, 16] navigating through a room[2]), deviant sounds,[53] odd-ball paradigms,[54] arbitrary words,[55] and attention to one's own name.[56]

Imaging techniques. Willful modulation of brain activity was first discovered using task-based fMRI with a motor imagery paradigm.[2] The investigators asked a patient that had clinically been diagnosed with VS and controls to imagine playing tennis or walking through their apartment while monitoring their brain activity with blood oxygenation level dependent (BOLD) fMRI. BOLD imaging does not measure neural activity directly but rather a correlate of the hemodynamic response to neural activity, specifically an increase in the level of oxygenated hemoglobin determined by regional blood flow changes coupled to neuronal activity. This technique is very sensitive to sources of noise, such as head motion, which can induce changes in the BOLD signal that are orders of magnitude larger than what is related to neural activity. In DoC patients, high rates of spontaneous motion can lead to excessive motion artifacts.[57] Additional potential confounders include carbon dioxide levels and brain metabolism.

Electrophysiological techniques. The first studies establishing electrophysiological approaches to diagnose CMD focused on patients with chronic DoC.[16, 58] More recently, EEG based paradigms were successfully applied early after brain injury in the critical care setting.[3, 5, 8] In EEG based studies, the principal comparison is in analyzing how EEG changes systematically between two different tasks, such as motor imagery versus rest. Conventionally, EEG is analyzed as power spectral density, or the power within prespecified frequency ranges at each electrode. Systematic differences in EEG activity between different tasks are determined using machine learning algorithms (i.e., Support Vector Machine learning).[3, 5, 8, 16, 58] EEG needs to undergo preprocessing to reduce artifacts (e.g., from electrical 50 or 60 Hz noise, muscle activation, eye movements). Sedatives and ictal activity (i.e., seizures) need to be considered.[3] Generalizability of CMD evaluations using EEG as an alternative to fMRI is limited at this point as multicenter studies are lacking.

<u>Other techniques</u>. There are several other techniques that may have potential to further phenotype patients beyond the clinical exam. Notably, many of these techniques do not detect covert consciousness, but may provide quantifiable signatures that associate with CMD. Clinically non-detectable muscle activation to commands using EMG has been reported to support the distinction between MCS and VS. Automated pupillometer assessments paired with mental arithmetic identified 17 of 43 patients with command following in patients with locked-in syndrome and may carry some relevance for CMD patients.[59] Olfactory sniffing of pleasant and unpleasant odors has also been studied in patients with DoC as a correlate for remnants of consciousness[60, 61] that correlated with long term survival.[62] BCI may allow patient interaction with the acquisition paradigm, possibly providing additional avenues to detect CMD.[63–65]

<u>Related assessments of brain physiology in CMD patients</u>. Approaches discussed here are not primarily conceptualized to detect CMD but provide contextual information in CMD patients that may allow screening for CMD testing, insights into underlying mechanisms, and may provide surrogate prognostic information. Correlation of the BOLD signal among brain regions at rest allows identification of functionally connected brain networks.[66] Changes in connectivity within and between these networks including the default mode network have been found to correlate with the level of consciousness and outcome of coma survivors.[67, 68] While this approach is more feasible to acquire in acute and chronic DoC patients than task-based fMRI, it does not directly confirm the CMD state like task-based fMRI. An important area of future research is to determine the correlates of CMD on resting-state networks and whether they consistently exist.[42] These techniques allow for rapid, non-invasive, sampling of brain activity, albeit indirectly and with relatively low signal-to-noise ratio. Metabolic background activity visualized using PET imaging is preserved in CMD patients with command following revealed by fMRI.[33] Spectral decomposition of the EEG signal correlates with the degree of thalamocortical network function underlying behavioral fluctuations and recovery in patients with DoC.[43] EEG correlates of network connectivity are incompletely investigated in CMD patients, but EEG based assessments of thalamocortical network function using the ABCD classification[16] and cortico-cortical connectivity[16, 46, 69, 70] are well-established to study DoC. Assessment of the complexity of the EEG response to single-pulse TMS, known as the

perturbational complexity index (PCI), has been shown to be sensitive to states of consciousness across multiple models in healthy volunteers (e.g., sleep, anesthesia) as well as in DoC patients.[50] Given this technique's high sensitivity (94.7%) to identify MCS detected with standard clinical assessments, it harbors the potential for uncovering instances of CMD.[50] Controversy exists as to whether or not some of these tools such as resting state MRI could detect CMD with reasonable certainty.[71]

Limited expertise in the community impedes the wide-spread application of all of the above techniques to detect CMD. Simplification and standardization of these approaches is required, paired with training of a larger community that will be able to apply these techniques in the clinic. Future studies will need to address these limitations to develop reliable biomarkers for CMD.

General challenges in detecting CMD

Until recently, the detection of consciousness in DoC patients has been based on behavioral assessments performed at the patients' bedside. Yet, misdiagnosis is frequent (up to 40% of cases) and signs of consciousness can be missed if such assessments are not performed with the right tools and/or in the right setting.[72] A quiet, well-lit environment with a comfortable temperature and upright positioning is required to ensure optimal patient comfort, alertness and responsiveness. Additionally, the recently published guidelines from the American and European Academies of Neurology (AAN and EAN) give several recommendations for ensuring an optimal diagnosis, such as administering serial assessments of well-validated and sensitive tools (e.g., the CRS-R in subacute and chronic settings) by healthcare professionals. [29, 30] These guidelines also recommend that such assessments be done in awake, medically stable patients who are not over-sedated or paralyzed and whose conditions that may confound accurate diagnosis are considered and treated beforehand when possible (e.g., hydrocephalus, seizures, encephalopathies, pneumonia, urinary tract infections). Some of these confounders (e.g., pain, cortical sensory deficits, aphasia, apraxia, spastic paresis) are challenging to detect and/or treat because of the current lack of assessment and therapeutic tools. In the subacute to chronic DoC context, spastic paresis is one of the most challenging confounders since it is very common in these patients (>90% in prolonged DoCs) and often poorly treated.[73, 74] Surprisingly little is known on how spastic paresis develops over time in DoC patients and what factors influence its progression.[75] A better understanding of the mechanisms of spastic paresis would lead to more efficient treatments, which are crucially needed not only for an accurate diagnosis but, more importantly, for the patient's functional recovery and comfort.

In clinical practice, evidence of subtle signs of consciousness are frequently missed. Careful neurological examination is the foundation to make an accurate behavioral diagnosis and detect CMD. The motor behavioral tool (MBT) and the MBT-revised are clinical assessments that were developed to identify subtle motor functions not identified using the CRS-R.[76, 77] Increasingly, behavioral signs of consciousness that are not captured by the CRS-R[78, 79] and even caregiver perceptions[80] have been reported that may serve as screening tools even if clinical significance is less certain. However, it is controversial if patients who do exhibit these clinical signs can be labeled as CMD as in the strictest sense no behavioral signs of consciousness should be detectable in CMD patients. On the background of this discussion, the AAN,[29] but particularly, the EAN [30] recommend adopting a multi-modal approach including neuroimaging and electrophysiology studies and a flowchart has recently been published to help clinicians determine when such techniques should be considered.[23] Compared to fMRI, EEG is the better candidate for successful implementation in a clinical setting when considering cost, practicality, availability, and level of expertise needed for recordings. Determining the types of paradigms to use and analyses to perform is one of the biggest challenges since protocols vary widely across the literature and often require advanced expertise.

A recent expert group endorsed by the International Federation of Clinical Neurophysiology recommended active qEEG combined with a motor paradigm to detect CMD at the bedside.[81] Using active paradigms has nevertheless challenges in terms of cognitive load for the patient and might lead to false negatives. Additionally, due to fluctuations in arousal and vigilance, future studies should investigate the need for serial assessments and the threshold to ensure diagnostic accuracy. Passive paradigms have been considered as an alternative but, besides potentially leading to false positives, experts have been debating if a response would reflect CMD or a distinct clinical phenomenon (such as higher-order cortex motor dissociation).[5] Finally, consensus on how analyses should be performed as well as on how to develop an offline, widely available computing workflow to analyze EEG (signal processing and statistical analysis) is critically needed. Consensus on all these items would lead clinicians to be more confident in the detection of this state and allow them to communicate more clearly and effectively with families.

Translation to the real world

Access to advanced imaging and electrophysiology based technologies required to detect CMD in most clinical settings remains limited. This is driven in part by inconsistent access to technology, but more importantly by the need for trained and highly specialized personnel to implement data acquisition, analysis, and interpretation. A recent algorithmic decision-making approach to aid in patient evaluation emphasized the need to ensure that, prior to resorting to advanced imaging and electrophysiology-based technologies , standardized assessment protocols have been applied following best practices (e.g., by trained personnel, with appropriate instruments, serially, in the absence of confounding factors).[23] Shortcomings associated with bedside assessment protocols (e.g., the characteristic variability in arousal of MCS patients, masking factors, level of assessor's experience, and instrument used for the assessment) can lead to false negatives. While adherence to best practices can help minimize false negatives,[23] advanced imaging and electrophysiology-based technologies will still be needed to detect CMD. Furthermore, at present there is no framework to assist clinicians in deciding, out of a large possible panel of relevant advanced imaging and electrophysiology-based technologies and protocols, which might be the most appropriate on a single-case basis. The implementation of telemedicine services can provide an opportunity to close some of these gaps, particularly in decision-making and analysis, by connecting specialized staff with hospitals and rehabilitation facilities in the community.[82, 83] Remote CMD diagnosis utilizing the advances of telemedicine has the potential to dramatically enhance the impact and scope of CMD detection.

Advances in artificial intelligence have revolutionized delivery of care in many areas of medicine [84]. Scientific developments to identify reproducible advanced imaging and electrophysiology-based technologies signals that can be detected by AI programs as well as dissemination of these programs are essential steps for future real world CMD detection. Sharing of advanced imaging and electrophysiology-based technologies analysis codes through open-source repositories would facilitate reaching these goals. However, these efforts cannot be realized without increasing awareness of CMD prevalence, diagnostics and therapeutic potentials. Community outreach to medical service providers and the public at large through educational events, newsletters and internet resources are essential to enhance referral patterns and to build the necessary infrastructures for detection and treatment of patients with CMD.

Outcomes, trajectories, and prognosis

Recovery is a broad umbrella term that covers a range of outcomes from re-emergence of overt consciousness to a complete recovery, including neurological and mental function. Shortly after brain injury, re-emergence of overt consciousness beyond a confusional state was found in 4 ICU patients with CMD[5]. Patients with CMD during their ICU stay were more often able to take care of themselves for at least 8 hours a day at one year post-insult.[3] More recently, CMD in an ICU setting was found to be an independent predictor to earlier time to recovery (trajectory of recovery) and was associated with better functional outcomes (as assessed by GOS-E scores) as early as 3 months after injury.[8] CMD and non-CMD patients discharged to rehabilitation level settings were clinically indistinguishable at discharge, but those with CMD showed a much earlier time to functional recovery (GOS-E of 4 or above). While the GOS-E is commonly used to evaluate the recovery after brain injury,[3, 5] the scale has limited ability to distinguish different levels of consciousness; for example, GOS-E 2 include VS and MCS- and GOS-E 3 include MCS+ and Emerged from MCS (EMCS) representing crucial outcome metrics in just these patients. Regardless, these results raise concerns regarding the practice of using behavioral responsiveness and ability to participate with rehabilitation interventions to screen patients for eligibility to receive neurorehabilitation. Theoretically, identifying patients with a specific recovery trajectory may help selecting the intensity and timing of rehabilitation interventions and may allow identification of some behaviorally unresponsive patients with CMD who could benefit from rehabilitation interventions.

Ideal outcome metrics do not currently exist but should include level of consciousness as defined by the CRS-R, basic functional (GOS-E and modified Rankin scales) as well as patient centered outcomes (such as activities of daily living, quality of life metrics, and cognition). We encourage researchers to utilize the NIH common data elements batteries of outcomes[85] and those currently under development to study DoC.[86]

Studies on trajectory of recovery and outcome in CMD patients are limited (Figure 5). The ideal time for the evaluation of outcomes has evolved with more studies demonstrating delayed recovery in patients after brain injury.[87–91] For example, one study demonstrated 59% recovery of consciousness by 1 year, and 74% by 5-year follow-up after TBI.[92] In another cohort study of 484 patients approximately half of those with severe TBI and three-quarters of those with moderate TBI recovered the ability to function independently at home for at least 8 hours per day. More importantly, in VS patients at 2-week, 77% recovered consciousness and 25% regained orientation by 12-month.[93] However, in another study including patients with prolonged VS due to anoxia, only 21% of them (9/43) recovered responsiveness after two years.[89] Functional recovery can continue over a 10-year period with more than two thirds of TBI patients who were unable to follow commands prior to rehabilitation achieving independence in mobility and self-care, and about one quarter achieving independent cognitive function.[94] Moreover, early diagnosis of MCS (within 90 days post-injury) is important as MCS patients have a higher rate of survival and consciousness recovery compared to VS patients.[90] Younger age, shorter time post-injury, higher CRS-R total score, presence of EEG reactivity to eye opening and relatively preserved metabolism of the frontoparietal network are also predictors of better outcome.[88, 95] Well-designed multicenter studies evaluating composite patient-centered outcomes with short and long-term endpoints (3, 6, 12 months, and up to 5-10 years) are needed to understand the prognostic significance of CMD and the potential benefits of therapeutic interventions in this population.

Therapeutic interventions to improve outcomes of unconscious patients

Significant advances have been made over the past decade in therapeutic approaches for patients with DoC.[96–98] Several pharmacological (e.g., amantadine, zolpidem, apomorphine) and non-pharmacological (e.g., electric, magnetic, and ultrasound-based) interventions have been tested in both open-label and randomized double-blind clinical trials. However, since treatment efficacy is typically assessed through behavioral responsiveness using standardized protocols (e.g., CRS-R), response detection is insensitive to CMD and may result in false negatives (i.e., patients who cognitively improve following an intervention but cannot demonstrate it through behavior). If indeed some patients first regain willful brain activity,[3, 95, 99] suggesting the presence of CMD, before being able to manifest it behaviorally, it is crucial to incorporate assessments of the underlying mechanisms and effects of interventions on brain function in DoC patients. Thus in designing future therapeutic trials, investigators will have to consider whether a transition from VS to CMD should be included as a favorable therapeutic response and whether behavioral assessments should be complemented with advanced neuroimaging and neurophysiological assessments (e.g., covert response to command, detection of intact DMN connectivity, residual brain metabolism in the fronto-parietal network). This is especially important if CMD is a transitional state that portents later recovery, a finding that could have an important impact on management decisions, access to therapy, or even end-of-life decisions.

Better understanding of CMD endotypes would also help in defining interventions specific for this group of patients. Indeed, a better characterization of this entity and its underlying mechanisms will allow tailoring interventions to promote the ability to behaviorally express signs of consciousness (e.g., overt response to command) rather than – or in addition to – interventions targeting the recovery of conscious processes themselves. So far, the most straightforward strategy would be to target the motor system when a patient is found to be in CMD. For instance, one could target the primary motor cortex with tDCS or rTMS rather or in addition to the prefrontal cortex. However, the lack of motor-related conscious behaviors in patients with CMD might not only be the consequence of impairment in motor pathways but could also be linked to motor dysexecution (e.g., impaired movement planning and organization), the latter being mainly dependent on the activity of the prefrontal cortex but also on that of wider brain networks that include subcortical as well as cerebellar structures. In line with the above, a case report of a patient that based on behavioral assessments had been in VS for 3 years but later was diagnosed with CMD (response to EEG and fMRI active paradigms) reported a response to command after a tDCS session applied over the dorsolateral prefrontal cortex,[100] suggesting that stimulation of this brain region may facilitate initiation and motor execution of a command in some patients with CMD. In this context, therapeutic options could also target specific pathways to stimulate both command integration and motor execution.

Due to several factors including immobilization, patients with DoC are prone to develop spastic paresis, as already stated, which can especially impact their ability to execute a motor command. More attention should be brought to interventions aiming to manage motor disorders such as spastic paresis.[101, 102] However, it must be recognized that the exact impact of motor disorders such as spastic paresis in the context of CMD remains to be determined.

Patient and caregiver perspectives

Although CMD may be present in 15-20% of patients who appear unresponsive after severe brain injury,[24] information about their state of mind and emotional wellbeing is essentially non-existent. One of the first CMD patients ever to be reported was able to answer yes-no questions in the fMRI scanner;[103] the degree to which these techniques can be used to assess a person's decision making capacity and are a representation of full cognitive function remains unknown.[104, 105] At this point it should not be used for this purpose.

In the absence of data, a first reference point may be studies on the quality of life in people with the locked-in syndrome. In a survey of 168 members of the French association for people in locked-in syndrome (‘ALIS – Association du Locked-In syndrome’) participants rated their global subjective well-being using the Anamnestic Comparative Self-Assessment scale. Strikingly, the majority reported good subjective well-being: almost 3 out of 4 respondents declared happiness; and only 1 out of 4 stated to be unhappy.[106] Of note, the happy and unhappy groups did not differ in terms of sociodemographic and physical/functional variables. Instead, an important determinant of well-being was time: The longer people had lived in a locked-in state, the more likely they were to feel well, indicating that it may take up to a year until a patient's subjective well-being reaches a steady state.[107] Additionally, patients indicated a higher degree of happiness dependent on social support. Although generalizations of these survey results have to be made with caution as they do not represent a cross sectional unbiased sample, subsequent surveys replicated the finding [108]. Regarding caregivers’ quality of life, it appears that accurate medical information and fulfillment of practical needs are the most important aspects for families of patients with DoC and locked-in syndrome.[109]

Inferences about the emotional well-being of CMD patients from data derived from people with locked-in syndrome must be made with caution given the inability to communicate in CMD,[110] which renders the development of BCI one of the most urgent areas of research to improve the lives of people in CMD. We need to better understand subjective experiences and memories of CMD, including aspects of isolation, pain, and loneliness.[25] Anecdotally, CMD patients do not remember being in a CMD state (after they have emerged from that state) and often do not even remember any of the acute care events,[111] but data investigating memory and other neuropsychological phenomena are limited. As to caregivers, the family can be relieved or devastated by detection of the CMD state.[112] Important unresolved problems include how to communicate the evaluation, techniques, results, and implications of CMD testing with families.

Ethical dimensions

Patients with acute and chronic disorders belong to vulnerable populations as an accurate diagnosis is challenging due to logistics (e.g., chronic patients treated in a resource limited context without access to adequate technology and expertise) and confounders (e.g., sedative medications and metabolic confounders frequently encountered early after injury). In the acute setting, the detection and communication of this diagnosis to relatives can have enormous impact on goals of care decisions. Considering that CMD patients might have some level of understanding, we are obligated to try integrating them in decision making. The exclusion of the patient from these discussions due to their inability to participate speaks to the urgency to develop BCIs to serve as communication aids.[65, 113]

However, as there are no means presently available to ascertain the level of cognitive function in CMD patients, the depth of understanding in these patients is open to question. Indeed, there can be a huge gap between the ability to willfully respond to simple commands and the cognitive ability to make decisions after weighing pros and cons. In the same way that MCS “plus” patients are (by definition) incapable to reliably communicate using a simple motor code, most CMD patients might not actually be able to use any BCI.

Making informed decisions requires the ability to understand risks, benefits and alternatives invoking what has been described as a “sliding scale of competence” where the significance of the choice is matched with a reciprocal ability to explain and justify that choice. [114] The reliability of the communication channel for these patients will largely depend on the consistency of their responses,[113] which is closely tied to the development of advanced BCI technologies. This channel will be a very important aspect largely dependent on technologies that are currently far from standard practices.[4, 115, 116]

Pain perception is another important consideration. A patient in a CMD state is highly likely to be able to perceive pain. This is one of the reasons why making the diagnosis of CMD is an ethical imperative so pain can be treated even if there are no overt behavioral manifestations of distress or independent of any prognostic or therapeutic consequences. To work towards this neuropalliative response should be viewed as a central professional obligation of all those who care for patients with severe brain injury.[117]

Probing CMD and, more generally, cognition through brain imaging like fMRI and EEG in clinically unresponsive patients also raises the question of "neural privacy" violation without the patient's consent. Neural privacy is a relatively recent concept relating to the access of our inner mental life through brain imaging.[118] Although logical, this concern is dramatically attenuated by the fact that the opportunity to establish a CMD diagnosis constitutes a greater benefit to advance care because of its prognostic value,[3, 8] possible therapeutic implications, and/or the potential for communication.[113] Once we can communicate with the patient we would be able to ascertain *their* consent. Until then an un-nuanced advance of neurorights that fails to balance negative rights (such as neural privacy) with positive rights (such as the right to have one’s consciousness identified) can have a detrimental effect on research efforts to identify CMD and therapeutically engage individuals with this condition.[118] Finally, as we seek to establish paradigms to identify CMD, it is important to respond to distributive justice concerns about the availability of advanced technologies like functional neuroimaging which may not be available in resource-poor contexts.

A critical appraisal of the CMD terminology

As we consider the refinement and the potential renaming of CMD, it is important to make explicit what is normatively at stake.[9] This is not just an academic exercise, but an effort that is meant to benefit patients who experience the discordance of mind and behavior and who are at risk of being misidentified as unconscious when in fact they remain very much “in the room”. Their hidden consciousness matters because without its identification they remain isolated and segregated from the human community.

It is important that clinicians and translational neuroscientists be as precise as possible given the state of available technology and our prevailing knowledge of the underlying neurobiology of this condition. Misconstruals matter, and if good facts make for good ethics, how we identify CMD or covert consciousness will have a normative bearing on all that follows. We need to think critically about type I errors when we identify consciousness when it is not present and type II errors where we falsely believe it does not exist, when in fact it is our detection methods that are flawed. Both these errors are consequential.

As importantly, as we name or think to rename CMD we must consider the moral valuation of these appellations as well as the consequences of a name change, should we choose to go in that direction. As we write, scholars interchangeably use CMD, covert consciousness, functional locked-in syndrome,[20, 21] and non-behavioral MCS amongst other names[6] to describe the discordance between observed behavior and cognitive processing discernable on functional imaging or on EEG.

Each of these can mislead and/or imply a moral valuation about a particular brain state and it is important to be careful not to bring value judgments to these descriptors or assume too much because of a name. Does "covert" consciousness imply full consciousness that is not detected while a "liminal" state of consciousness suggests one that is noted but diminished? And either way, how can we know what that state means to the person who is experiencing it? The only consciousness that we truly know is our own and thus it is a challenge to even imagine the experience of others when they are thought to have CMD. As critically if they have CMD, that designation does not make a claim about that brain state *by intent* which is not true of the alternatives.

We need to be careful neither to apply a label carrying content without evidentiary support nor to impose our views of that state as observers of people in CMD who actually experience the condition. Yes, it can be hard to bear witness but so too it is perilous to assume knowledge of the plight of the other. As the disability rights adage goes, "Nothing about us without us."[119] The point of these advocates is to let the people so affected by the disability give voice to the experiences and priorities of that population so they can inform choices made about them. This is the holy grail of coma science: to advance the rights of people with DoC by giving them the ability to give voice to their own thoughts as best they can through means of integrative functional communication.[112]

In the aggregate, these concerns suggest that we should be cautious in descriptors of this complex brain state which implies a valuation about the patient's experience and adopt more neutral language which simply describes the condition and does not make a judgment about it. In this vein, CMD is cleaner than adjectives like "covert" or "liminal."

We should consider the consequence of a name change from CMD to some other alternative. CMD first appeared in the literature in 2015 and although gradually adopted in the DoC academic community, it is already deeply entrenched in the literature. While it is not perfect it has become the *lingua franca* of this space and is being picked up by other clinical communities. Given the slow pace of the dissemination of medical knowledge and the need to accompany new knowledge with undergraduate, postgraduate, and continuing medical education, any name change would require a new effort to get the word out, slowing knowledge dissemination and ultimately undermining patient care. The perfect need not be the enemy of the good: There is no guarantee that any new proposal will not have its own set of conceptual flaws.

Conclusion

To summarize, CMD is well-established as a state in the acute, subacute, and chronic phase following brain injury; can be detected with different techniques; is not infrequent; and carries prognostic relevance. However, underlying mechanisms of CMD are uncertain; the role CMD may play in treatment algorithms needs to be defined; and more careful characterization of the epidemiology within different brain injuries and at different timepoints in relation to injury onset need to be pursued (Table 2). CMD has emerged as an important and promising state that is likely to change the way we see and treat DoC already in the near future.

Table 1. Glossary of states*

Term	**Definition**
Coma	Patients demonstrate complete absence of arousal (e.g., eye opening) and awareness (e.g., comprehension). No behavioral evidence of command following.[120]
Vegetative state (VS)	Presence of arousal (i.e., eye opening) without awareness. No command following. Patients may have preserved sleep wake cycles evidenced on EEG. This state has also been referred to as 'unresponsive wakefulness syndrome' (UWS).[120]
Minimally conscious state (MCS)	Patients do not show consistent command following but have some evidence of verbal or non-verbal awareness. MCS has been subclassified as MCS- and MCS+ (see below).[121]
MCS–	Patients in this MCS subcategory do not show behavioral evidence of command following but reproducibly track the examiner through the room with their eyes or demonstrate attending to a stimulus.[122]
MCS+	Patients in this MCS subcategory demonstrate command-following (e.g., intelligible verbalization and intentional communication) but this is inconsistent and only present intermittently.[122]
Cognitive motor dissociation (CMD)	Evidence of command following on fMRI and/or EEG without behavioral evidence of command following (coma, VS, MCS-).[7]
Emerged from MCS (EMCS)	Patients that 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).[121]
Locked-in syndrome	Patients are awake and conscious but have no means of producing speech, limb or facial movements. Typically, vertical eye-movements and blinking are preserved.[9]

* Please note that this is not intended as a comprehensive list of all terms and conditions that have been proposed to capture the varying states of DoC. The purpose of this glossary is to capture the most crucial states discussed in the manuscript and reflect the definition how the terms were used for this purpose.

Table 2. Major identified gaps by the CMD Coma Science Working Group of the Curing Coma Campaign

1.	Lack of an empiric agreement for a label with a definition that best captures the CMD concept. May involve the need for a Delphi approach.
2.	Access to patient accounts of being in CMD. These could be obtained via BCI during CMD or structured interviews after re-emergence from DoC.
3.	Limited insight into the caregiver perspectives of families and health care professionals caring for patients with CMD.
4.	Lack of large, multicenter assessments of CMD prevalence in patients with different brain injuries assessed at standardized timepoints in relation to the onset of brain injuries and careful characterization of confounders (e.g., metabolic issues, infection, sedation, seizures), both early and late after brain injury.
5.	Uncertainty about mechanisms underlying CMD with characterization on a network and cellular level necessitating large, multimodal assessments of brain structure and function.
6.	Lack of a standardized approach to detect CMD that takes patient (e.g., age, sex), contextual (e.g., injury mechanism, sedation), and logistic factors (e.g., ICU vs. nursing home environment) into account. The focus should be on reproducibility and reliability to develop CMD diagnosis as a biomarker.
7.	Lack of education of a larger workforce comfortable with applying currently available approaches to detect CMD.
8.	To translate CMD detection to the real world, both hardware and software issues have to be overcome, possibly utilizing telemedicine services. Generalizability of developed technology to be applicable in a low-resource setting should guide these efforts.
9.	Determining how detection of CMD relates to patient centered outcome metrics such as quality of life and long-term outcomes.
10.	To establish CMD as an early endpoint in clinical trials to support recovery of consciousness and long-term functional outcomes in patients with DoC
11.	To develop a BCI that reinstates a communication channel with DoC patients when diagnosed with CMD.
12.	To characterize residual cognitive functions in CMD not only to foster efficient communication, but also to understand if some patients could be involved in decision making and take decisions on their own care. Integrating CMD and BCI technology into shared decision making approaches is a long-term goal.

Figure legends.

Figure 1. CMD seen through the eyes of artificial intelligence artist (generated by Midjourney) and a case in point that AI in the near future may help not only identifying but also expressing covert consciousness in people with CMD

Figure 2. Timeline of key concepts and key publications. This figure depicts a timeline of key events, concepts, publications, and rating scales related to disorders of consciousness, including cognitive motor dissociation. Images reprinted with permission or in the public domain; courtesy of Wikicommons. AAN – American Academy of Neurology; CMD – cortical motor dissociation; CMS – cortically mediated states; DoC – disorders of consciousness; EEG – electroencephalography; HMD – higher-order cortex motor dissociation; ICU – intensive care unit; MCS – minimally conscious state; MCS* - minimally conscious state star; MRI – magnetic resonance imaging; VS – vegetative state

Figure 3. CMD within the spectrum of behavioral states of consciousness after brain injury.

Figure 4. Detecting CMD: the most used techniques. fMRI using motor imagery paradigm to detect CMD state in a patient in vegetative state (modified after Owen et al, Science 2006; Claassen et al, ICM 2019). **Behavioral assessment**. A. behavioral assessment demonstrates no evidence of command following. B. **Data acquisition during motor commands**. MRI or EEG recorded while patient hears motor imagery or motor commands. C. **Data analysis and CMD classification**. MRI. Averaged BOLD signal is generated from the active (e.g., "keep opening …") and contrast task (e.g., "stop opening …"), respectively, and the subtracted from each other. The BOLD signal change can then statistically be analyzed in predefined regions of interest (modified after Owen et al, Science 2006). EEG. Power spectral density (PSD) is generated from the electrical signal recorded from each electrode. Machine learning algorithms (e.g., support vector machine learning) are applied to the generated dataset (PSD within prespecified frequency bands; e.g., 8-13 Hz or alpha frequency range) to determine if there are systematic differences between the active (e.g., "keep opening …") and contrast task (e.g., "stop opening …"; modified after Claassen et al, NEJM 2019).

Figure 5. Two cases of patients with CMD. Patient 1 (Panel A) was a 30- year-old woman who was admitted with a sinus venous thrombosis causing a large frontal intracerebral hemorrhage with herniation and elevated intracranial pressure. She was in a prolonged coma, CMD was detected on day 3, followed by first eye opening on day 8, and initially inconsistent command following on day 10. She subsequently recovered, was discharged to acute rehabilitation services on day 20, and fully recovered 1 year after injury. Patient 2 (Panel B) was a 35-year-old woman who had suffered bilateral thalamic, occipital and cerebellar ischemic strokes from a top of the basilar and bilateral PCA thrombosis complicated by secondary hemorrhagic conversion. Clinically she was in a coma followed by a prolonged vegetative state without auditory

response and flexion withdrawal after noxious stimulation no command following, no visual pursuit, no localization to noxious stimulation, no object localization or automatic motor response, no vocalizations. Using fMRI CMD was detected at more than 6 years after the injury and preceded first signs of command following within the following year.

Details Page

I confirm that this manuscript complies with all instructions to authors. All authorship requirements have been met and the final manuscript was approved by all authors. I confirm that this manuscript has not been published elsewhere and is not under consideration by another journal. The use of a reporting checklist is not appropriate for this manuscript. I confirm compliance with Ethical approval and informed consent. This was not an animal study.

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Figure 1

Figure 2

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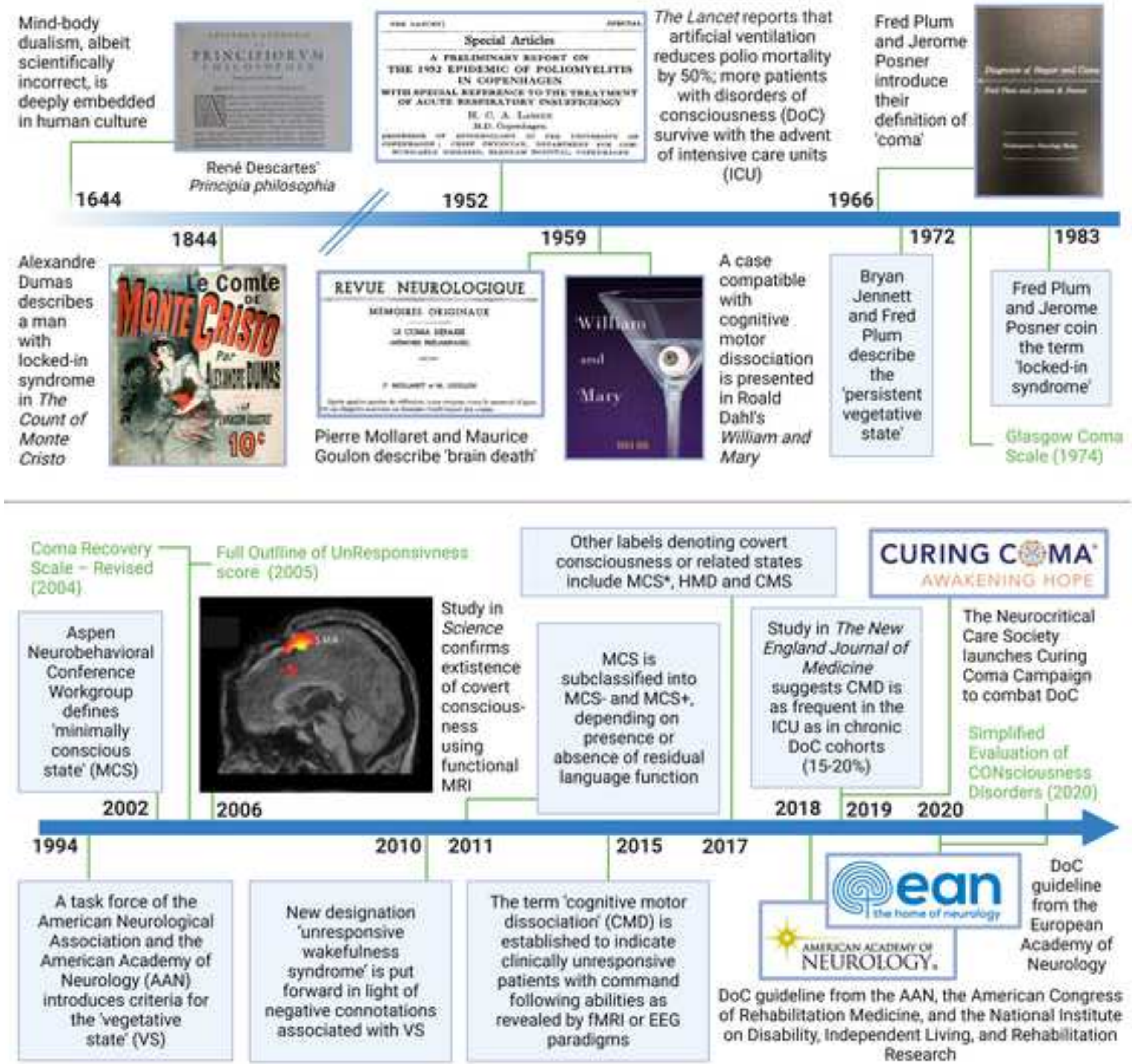

Figure 3

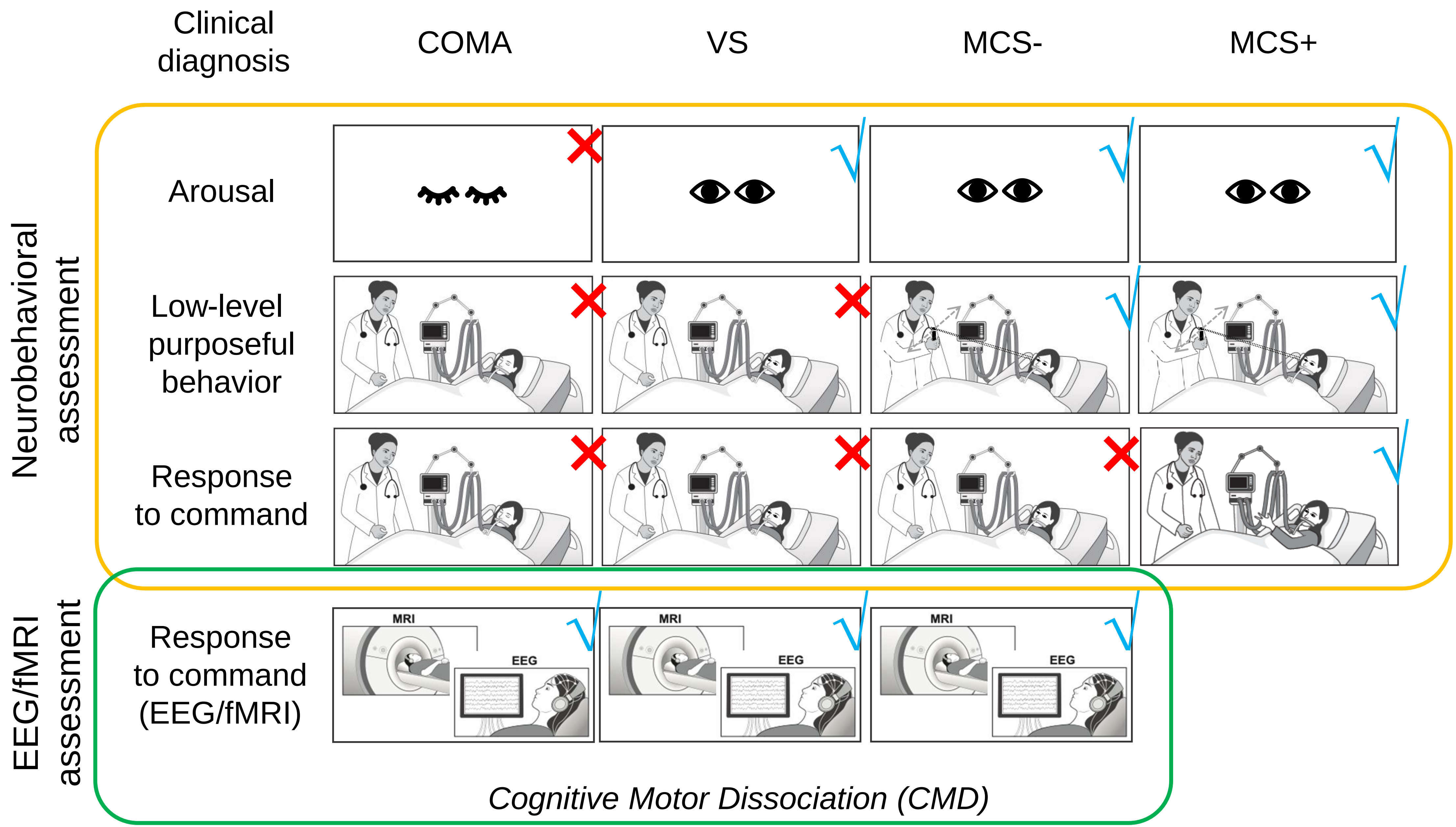
Clinical diagnosis
COMA
VS
MCS-
MCS+
Neurobehavioral assessment
Arousal
Low-level purposeful behavior
Response to command
EEG/fMRI assessment
Response to command (EEG/fMRI)
MRI
EEG
MRI
EEG
MRI
EEG
Cognitive Motor Dissociation (CMD)

Figure 4

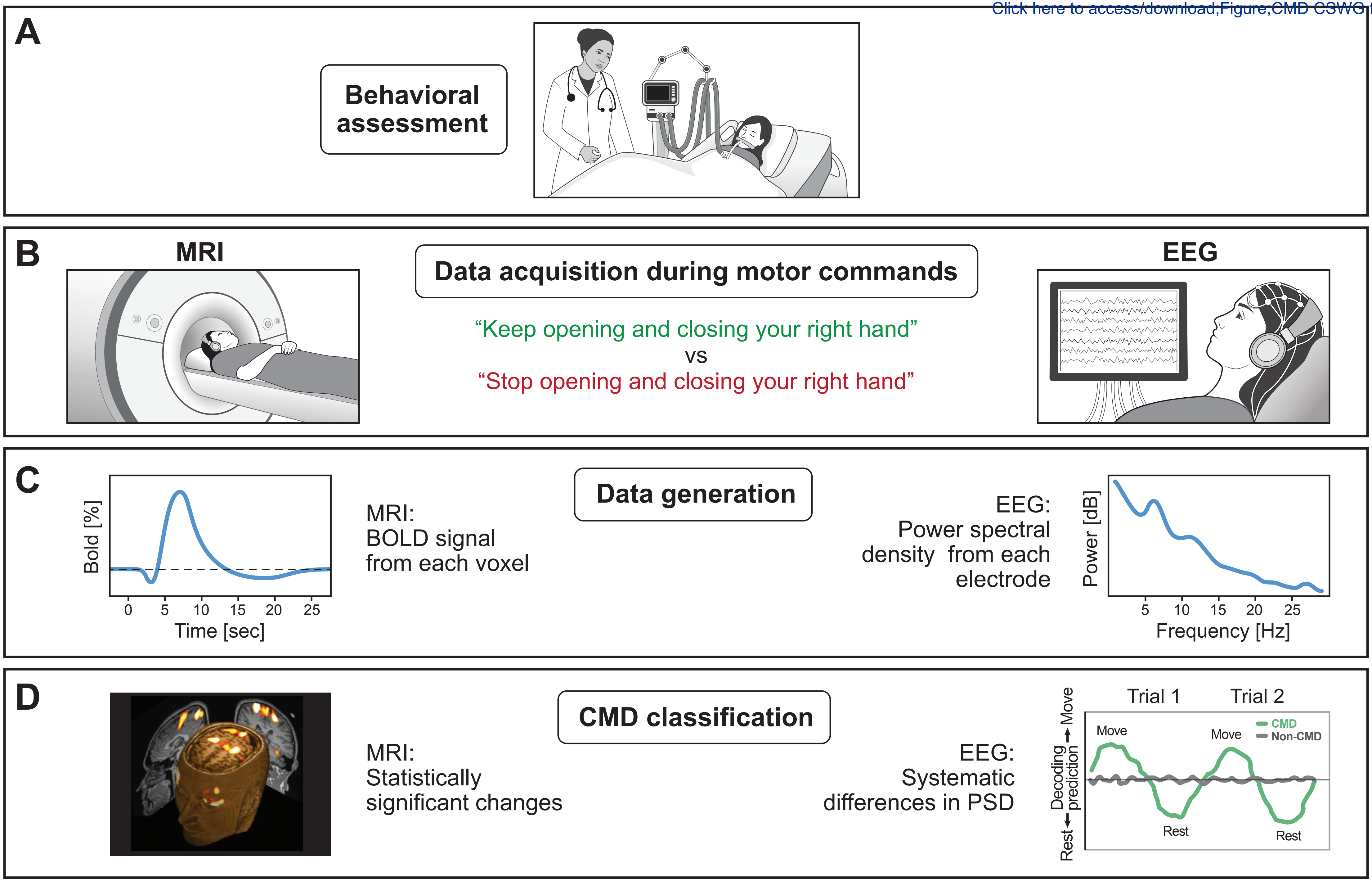
A
Behavioral assessment
B
MRI
Data acquisition during motor commands
EEG
“Keep opening and closing your right hand”
vs
“Stop opening and closing your right hand”
C
Data generation
Bold [%]
0 5 10 15 20 25
Time [sec]
MRI:
BOLD signal
from each voxel
EEG:
Power spectral
density from each
electrode
Power [dB]
5 10 15 20 25
Frequency [Hz]
D
CMD classification
MRI:
Statistically
significant changes
EEG:
Systematic
differences in PSD
Trial 1
Trial 2
CMD
Non-CMD
Move
Move
Rest
Rest
Rest ← Decoding prediction → Move

Figure 5

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