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A Focus on Subtle Signs and Motor Behavior to Unveil Awareness in Unresponsive Brain-Impaired Patients: The Importance of Being Clinical

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Abstract

Brain-injured patients in a state of cognitive motor dissociation exhibit a lack of command following using conventional neurobehavioral examination tools but a high level of awareness and language processing when assessed using advanced imaging and electrophysiology techniques. Because of their behavioral unresponsiveness, cognitive motor dissociation patients may seem clinically indistinguishable from those suffering from a “true” disorder of consciousness that affects awareness on a substantial level (coma, vegetative state/unresponsive wakefulness state, or minimally conscious state ‘minus’). Yet,

by expanding the range of motor testing across limb, facial and ocular motricity, we may detect subtle, purposeful movements even in the subset of patients classified as vegetative state/unresponsive wakefulness state. We propose the term of clinical cognitive motor dissociation to describe patients showing these slight but determined motor responses and exhibiting a characteristic akinetic motor behavior as opposed to a pyramidal motor system behavior. These patients may harbor hidden cognitive capabilities and significant potential for a good long-term outcome. Indeed, we envision cognitive motor dissociation as ranging from complete (no motor response) to partial (subtle clinical motor response) forms, falling within a spectrum of progressively better motor output in patients with considerable cognitive capabilities. In addition to providing a decisional flowchart, we present this novel approach to classification as a graphical model that illustrates the range of clinical manifestations and recovery trajectories fundamentally differentiating “true” disorders of consciousness from the spectrum of cognitive motor dissociation.

Advanced imaging and electrophysiology techniques (AIEs) can detect intact awareness and significant cognitive abilities in unresponsive brain-impaired patients, a condition called cognitive motor dissociation (CMD). However, the tools as well as experts competent in analyzing and interpreting the results are not widely available. We propose that inspection of overall motor behavior and detection of subtle clinical signs across limb, facial, and ocular motricity using extended testing by means of the Coma Recovery Scale-Revised (CRS-R)[1] in conjunction with the Motor Behavior Tool-Revised (MBT-r)[2,3] are clinical keys to revealing the presence of intentional movement and awareness. In addition, we describe an algorithm-based procedure for evaluating unresponsive brain-injured patients using clinical and basic paraclinical exams. Finally, we present a graphical representation modelling the range of clinical manifestations of patients with "true" disorders of consciousness and cognitive motor dissociation as well as potential recovery trajectories after major brain impairment.

Diagnosing cognitive motor dissociation: a clinical and technical challenge

The existence of covert awareness was first demonstrated in 2006[4] and the term CMD was introduced in 2015[5] to describe patients with command following discernible by specific AIE-derived neural signatures but without externally observable motor responses. In their recent article in this journal, Martin Monti and Caroline Schnakers[6] proposed an algorithmic flowchart to determine when AIEs should be used. We welcome their efforts to establish criteria for whether AIEs are suitable on an individual patient basis. As already pointed out by the authors, currently, AIEs are not warranted in routine clinical practice if evidence of a conscious motor response is observed during bedside neurobehavioral assessment.

Ideally, AIEs should be employed for patients with a higher probability of harboring covert awareness, although guidelines establishing such probabilities are only slowly emerging now. Performing AIEs and interpreting their results, especially in the acute setting, requires considerable technical and medical expertise. A possible solution to the logistics posed by these technologies might be a hub-and-spoke model, as proposed by Young et al.[7], whereby peripheral collaborating sites with less resources (i.e., spokes) collect AIE data locally, then send the data to a specialized medical center (i.e., hub) that provides the expertise for processing and analysis. This could help reduce geographical and financial gaps and

guarantee the detection of covert awareness in patients who might otherwise be misdiagnosed. Still, there are at least two major limitations. First, this approach is currently only viable in health systems with sizeable economical resources. Second, given that patients in the acute setting often suffer from considerable executive, attentional or language dysfunction from which they would eventually recover, there is an unquantifiable risk of misclassifying such patients as lacking conscious awareness when strict AIE assessment protocols are used. Proving that an unresponsive patient is aware is hard, but proving that the patient is lacking awareness is harder, if not impossible.

***Clinical* unmasking of "covert" awareness**

We argue that a practical and immediate advance in detecting patients with apparent covert awareness can be achieved by further expanding the current clinical assessment scales. Recent studies indicate that a significant fraction of patients with covert awareness defined by the combination of traditional standardized neurobehavioral assessments and AIEs can be identified *clinically*, circumventing the need for AIEs in these subjects.[2,3] Current clinical assessment scales, including the thorough CRS-R, often fail to diagnose awareness in patients who show subtle signs of interaction, even in those retaining some motor localization of the painful stimulus, visual fixation or visual tracking. In the acute care setting, the rate of patients with covert awareness misdiagnosed as lacking consciousness is at least as high as 15% when using the CRS-R as this is the percentage of unresponsive cases (as classified by the CRS-R) for which AIEs captured evidence of unequivocal brain activation in response to a command.[8] In our experience, we estimate the misclassification rate to be around 30% when comparing the CRS-R diagnosis (e.g. vegetative state) at admission to an acute neurorehabilitation unit to the diagnosis at discharge.[9]

Patients with "true" disorders of consciousness are not motionless but display an array of reflexive behaviors and, after recovering fragments of awareness, purposeful motor behavior. These patients often progress through a prolonged or permanent confusional state, associated with motor hyperactivity (agitation) stemming from an underlying lack of orientation and incoherent cognition. On the cognitive level, such residual fragments of consciousness may be detected using the CRS-R as limited but overt and reproducible motor responses, with patients failing to regain consistent and accurate communication systems

(via speech or gesture). In contrast to the motor patterns observed in patients suffering from "true" disorders of consciousness, relatively focal lesions that globally affect the motor output channels can cause a characteristic lack of motor or verbal interaction in CMD patients, hiding their considerable cognitive capability. As mentioned above, the residual signs in such motionless patients may be too subtle to be identified using the CRS-R alone. We have evaluated, and propose using, a complementary clinical tool, the MBT-r (see description in Table 1), designed to detect subtle motor behaviors that are overlooked by the CRS-R that establishes strict criteria for scoring a specific motor behavior as an expression of consciousness.[2] In a prospective validation study, the MBT-r was shown to identify a subset of patients whose cognitive abilities were underestimated by the CRS-R, and demonstrated excellent inter-rater agreement.[3] Subsequent data from a sample of 141 patients undergoing inpatient rehabilitative care suggested that the MBT-r used in conjunction with the CRS-R lead to greater sensitivity in detecting awareness than the CRS-R alone, and identified patients with a high probability of functional recovery at discharge.[9]

Scrutinize clues and pitfalls to maximize the clinical detection rate of awareness

During the assessment of unresponsive patients, it is essential to scrutinize the clues and pitfalls that may support the diagnosis of CMD.[10] Bringing all this together, we created a flowchart that considers clinical, pathophysiological, radiological and electrophysiological aspects in order to establish an early diagnosis of either a "true" disorder of consciousness or CMD (Figure 1).[11] We propose using the suggested flowchart as soon as possible, i.e. in the intensive care unit 24 hours after sedation withdrawal, always considering residual anesthesia as a potential confounder. A comprehensive clinical assessment should be carried out at least three times a week in conjunction with pathophysiological considerations and paraclinical investigations if necessary. As indicated in the flowchart, we use conventional structural magnetic resonance imaging as an adjunctive exam to dichotomize patients into "true" disorders of consciousness or clinical CMD.[12] It is not our intention to challenge the importance of AIEs. In its most complete form, i.e. in the complete absence of motor response, CMD is only uncovered if task-based AIEs demonstrate evidence of command following. Resting-state AIE examinations also play an important role, and the pursuit of covert awareness should include an investigation of the functional architecture dynamics using resting-state functional magnetic resonance imaging

and positron emission tomography, concentrating primarily on the brain's ability to shift between the internal (default mode) and external awareness (frontoparietal) networks. The brain's aptitude to switch between intrinsic and extrinsic network activation has been associated with recovery of consciousness,[13] and could potentially be used as a biomarker for covert awareness. Neurophysiological evaluations such as non-task evoked potentials, help to discriminate clinical CMD (especially with aphasia and attention deficit) from patients suffering from a "true" disorder of consciousness[14], thus contributing to a better understanding of the underlying network mechanisms.

A spectrum of clinical manifestations and recovery trajectories: neuroanatomical and physiological rationale for a new model

Given that brain function in CMD patients is likely to be closer to that of healthy and locked-in state subjects than to minimally conscious state 'plus' patients with reliable command following,[15,16] we suggest that there is a dividing line separating "true" disorders of consciousness from CMD and locked-in state patients. However, we propose this partition should be considered as a gradient rather than a sharp boundary. In other words, while we should avoid simplistic dichotomizations, this concept forms the basis of a new approach to classification in which unresponsive patients with CMD are in a distinct category from unresponsive patients without CMD. We envision a spectrum of different motor/cognitive states, ranging from complete CMD that cannot be detected even by extended clinical testing to partial CMD (clinical CMD) with subtle clinical signs and typical motor behavior to classical locked-in state (preservation of vertical eye movements/eye blinking) (Figure 2).

The cognitive abilities of CMD patients may range from the limited language comprehension functions of minimally conscious state 'plus' patients to the almost intact cognitive capabilities of complete locked-in state patients.[17] This raises the question of how to distinguish CMD patients at the lower end of the cognitive spectrum from those with "true" disorders of consciousness who have regained some command-following abilities (e.g., minimally conscious state patients). Based on pathophysiological considerations, a key feature clinically dichotomizing most CMD and "true" disorders of consciousness might be the presence of brainstem release signs in the absence of brainstem lesions. Such release signs imply widespread destruction of the cortico-cortical networks relevant for awareness.

However, it is essential to initially exclude additional brainstem or cerebellar lesions as these can complicate the clinical assessment for at least two reasons. First, these lesions can disrupt the ascending arousal system, affecting wakefulness despite the relative intactness of structures essential for awareness. Second, circumscribed lesions of the corticospinal tract and the tracts connecting the higher modulatory centers and the rubral and/or vestibular nuclei in the rostral part of the brainstem can cause tetraplegia with decorticate or decerebrate posturing, respectively, which may be falsely attributed to larger lesions located more cranially.

While the exact nature of awareness remains an unsolved complex problem of neuroscience, it is a plausible assumption that it requires the activation of large-scale decentralized cortico-cortical networks.[18] This decentralization increases the robustness of awareness against focal damage. It also means that large and widespread lesions will be necessary to significantly disrupt this fundamental function of the brain.[12] Classically, neurological practice has considered bilateral lesions of the cortex, or of the upper brainstem and central thalamus or lesions altering both as a requirement for producing coma.[19] Because of such widespread lesions, a functional cortical disconnection is detected clinically as decorticate or decerebrate posturing,[20] pathological roving eye movements (ping-pong gaze, i.e., short-cycle periodic alternating gaze)[21] and/or incessant paroxysmal sympathetic hyperactivity[22]. These clinical manifestations have long been associated with poor outcome; and, on a pathophysiological level, are likely caused by a disruption of modulatory (mainly inhibitory) corticorubral-spinal, cortico-vestibular, cortico-mesencephalic and/or cortico-diencephalic tracts (see negative MBT-r signs in Table 1).

Patients within the CMD spectrum as opposed to those with “true” disorders of consciousness are not only characterized by specific clinical, radiological and pathophysiological features but, most importantly, by their particular recovery trajectories.[9] An early diagnosis of CMD does not automatically imply a good outcome, as the individual prognosis depends heavily on the specific cerebral functions affected. Overall; however, CMD patients have far better long-term outcomes, as measured by multiple prognostic scales.[8,9,23]

Conclusion

In conclusion, we want to underscore the importance of a thorough clinical assessment targeted to observing the motor behavior, as well as the role of careful clinical and paraclinical screening (Figure 1), selecting conventional structural magnetic resonance imaging before proceeding to more sophisticated technical diagnostic tools. We present this approach as a model depicting the spectrum of clinical manifestations and recovery trajectories after significant brain impairment (Figure 2).

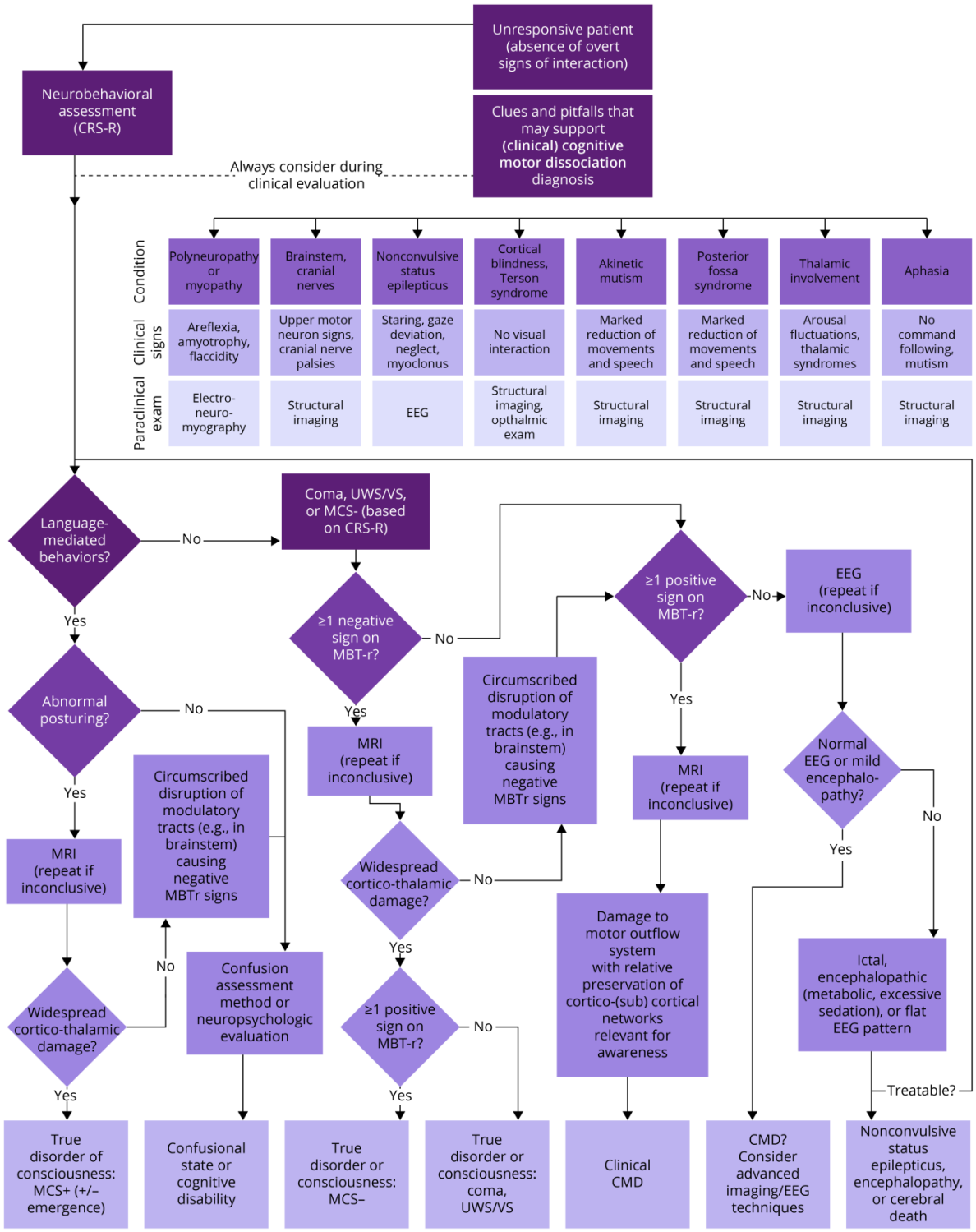
Table 1. The Motor Behavior Tool – revised (MBT-r)

Positive signs		
Sign	**Observations**	**Comments**
1. Spontaneous non-reflexive movement	Any non-stereotypical, non-contextualized and non-repetitive intentional motor behavior.	Observation of spontaneous behavior without stimulation at baseline or at any moment.
2. Response to a command	Any non-reflexive intentional response to a verbal command.	Use the CRS-R command-following protocol.[1]
3. Visual fixation or visual pursuit	Any visual fixation or visual pursuit in any direction.	Defined as eyes changing from an initial to a new fixation point, or eyes tracking a moving target.
4. Response in a motivational context	Any appearance or increase in frequency of non-reflexive motor response in a salient context.	E.g., on hearing a familiar voice, the patient's mother tongue or the patient's own or nickname.
5. Response to a noxious stimulation		
5a. Defensive response – *nipple sign*	Any attempt of defense when twisting the patient's nipple while holding the patient's arm.	Before scoring, exclude stereotypical posturing as a confounding factor.
5b. Defensive response – *nailbed sign*	Any defense gesture to deep pressure applied to a nailbed (test all four extremities).	The kinematics of an intentional defense differ from those of a nociceptive withdrawal reflex.[2]
5c. Grimace	Any non-reflexive grimace on administering a noxious stimulation.	Do not score the reflexive rictus-like grimace of stereotypical posturing or tetanus.
Negative signs (brainstem release signs)		
6. Decorticate posturing,	Spontaneous or stimulus-induced stereotypical posturing (decorticate	In the absence of brainstem lesions, these signs reflect large

decerebrate posturing or incessant paroxysmal sympathetic hyperactivity	or decerebrate posturing) or incessant neurovegetative responses (i.e., rapid-onset episodes of tachycardia, hypertension, tachypnea, fever, diaphoresis, dystonic posturing of up to 30 minutes duration).	and widespread forebrain lesions resulting in functional disconnection of the red nucleus (decorticate posturing), of vestibulo-/tecto- reticulospinal postural reflexes (decerebrate posturing) or of neurovegetative centers.
7. Pathological conjugate roving eye movements (ping-pong gaze)	Resembles slow eye movements of light sleep; can persist with open or closed eyes, lack total excursion, or move from an extreme gaze to the midline instead of to the opposite extreme; may present or lack pauses between excursions.	Also called short-cycle periodic alternating gaze. Caused by large and widespread lesions causing a disconnection between the cortical inhibitory control and brainstem gaze centers.

A positive sign is scored even if subtle if it stands out clearly from a reflexive or stereotypical background movement. Note that repeatability is not necessary for the MBT-r: the observation of a single subtle intentional movement, e.g., visual pursuit obviously discernible from the baseline eye movement, is scored as a positive sign. When in doubt, the sign is not recorded. To facilitate interpretation of subtle signs, whenever possible, patients are filmed with the consent of their relatives. An older version of the MBT-r included the absence of oculocephalic reflex as a negative sign (as an alternative to roving eye movements). While this clinical finding is associated with bad prognosis, it is not a brainstem release sign.

Figure 1. Flowchart for acute assessment of unresponsive patients with a suspected major cerebral impairment.



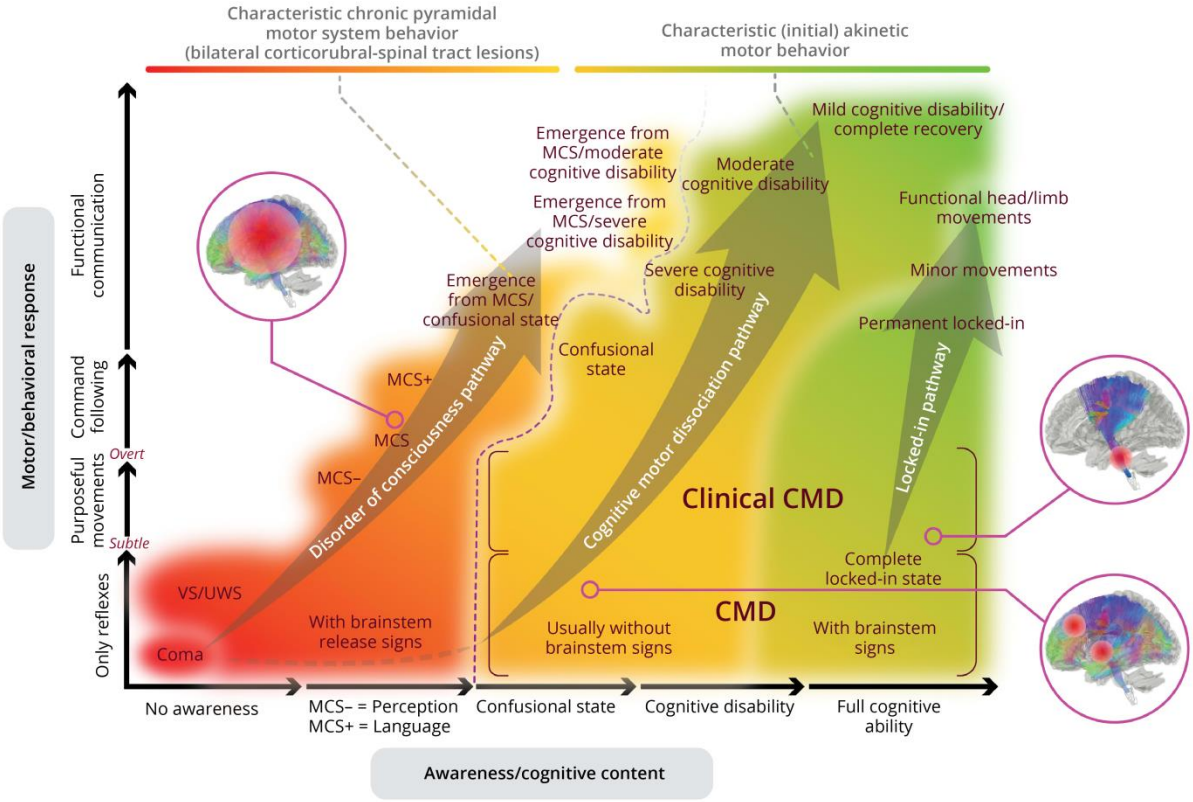
For an explanation of MBT-r signs, see Table 1. For a better understanding of the different nosological diagnoses (“true” disorders of consciousness versus cognitive motor dissociation spectrum), see the model in Figure 2. Language-mediated behavior includes command

following, intelligible verbalization and communication. Abnormal posturing refers to stereotypical decorticate and decerebrate posturing (one of the negative MBT-r signs). Note that the vertical eye movements/eye blinking of an incomplete locked-in state are considered as overt signs of interaction.

Figure 1 created using the web-based diagram application Lucidchart (Lucid Software Inc., South Jordan, Utah, United States). It is an updated version of a flowchart published under an open access Creative Common CC BY license.[10]

Abbreviations: CMD = cognitive motor dissociation; CRS-R = Coma Recovery Scale – Revised; EEG = electroencephalography; MBT-r = Motor Behavior Tool revised, MCS = Minimally Conscious State (+ = 'plus', - = 'minus'); MRI = (structural) magnetic resonance imaging; VS/UWS = vegetative state/unresponsive wakefulness syndrome.

Figure 2. Model of Behavioral and Cognitive Evolution after Severe Brain Impairment



The diagnostic spectrum and clinical evolution after severe brain impairment is represented on a two-dimensional graph comparing the degree of cognitive content (x-axis) against the degree of behavioral response (y-axis). The red-yellow-green color gradient represents an approximation of the degree of recovery, with red being the worst and green the best. Both cognitive content and behavioral response are determined using the CRS-R in conjunction with the MBT-r, which we developed to expand the range of motor testing to detect subtle, purposeful movements (so-called positive signs) and brainstem release signs (so-called negative signs). Concerning the motor/behavioral response of CMD patients, the functional ambulation category quantifies the degree of functional motor recovery. In cases of a total lack of motor response, AIEs may unveil CMD-defining covert cognition. For patients with a good behavioral response, confusion and neuropsychological assessment protocols distinguish between the different degrees of functional recovery. Patients with a severe brain impairment appear to fall mainly into two categories – “true” disorders of consciousness (spanning from VS/UWS to MCS+, red hues) and CMD/locked-in state (yellow-green hues) – with different underlying lesions (represented by the symbolic brain images), clinical manifestations (e.g., brainstem release signs) and prognosis (represented by the arrows along the recovery pathways). The circles/ellipses surrounding the different

diagnoses (VS/UWS, MCS-, etc.) account for the fact that many patients never recover after a specific point in the recovery pathway. Widespread lesions across heteromodal cortical association areas and cortico-thalamic tracts cause the impairment in patients suffering from “true” disorders of consciousness. Consequently, many of these patients may suffer chronically from a total (VS/UWS) or partial (MCS) lack of awareness. Posturing typically lasts after conscious emergence, causing characteristic clinical motor patterns usually not seen in CMD patients. CMD patients, on the other hand, are characterized by a total (complete CMD, with covert cognition only detectable by AIEs) or near-total (clinical CMD with subtle, purposeful movements) lack of determined movements. Most CMD patients do not develop brainstem release signs, except for complete locked-in state patients, who typically manifest decorticate/decerebrate posturing. We indicate the potential recovery pathways using symbolic arrows.

Figure 2 was created using the vector graphics editor Adobe Illustrator (Adobe Inc., San Jose, California, United States). Brain images were derived from the population-averaged tractography atlas by Yeh et al.[24]

Abbreviations: AIEs = Advanced imaging and electrophysiology techniques (AIEs); CMD = cognitive motor dissociation; CRS-R = Coma Recovery Scale – Revised; MBT-r = Motor Behavior Tool – revised; MCS = Minimally Conscious State (+ = ‘plus’, - = ‘minus’); VS/UWS = vegetative state/unresponsive wakefulness state.

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