Coma and Disorders of Consciousness

Second Edition

Caroline Schnakers
Steven Laureys
Editors

Springer

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ISBN 978-3-319-55963-6 ISBN 978-3-319-55964-3 (eBook)
DOI 10.1007/978-3-319-55964-3

Library of Congress Control Number: 2017946341

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The registered company is Springer International Publishing AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

To medical teams and families we see every day and who inspire us.

Foreword I

Consciousness is synonymous with human existence. Rene Descartes' bold proclamation, "Cogito ergo sum" (I think therefore I am), elegantly captures this premise. The clear inference here is that self-doubt about one's own existence establishes proof of one's existence. We exist because we know we exist. But how does one come to know that someone else is aware of his existence? Without direct access to knowledge of the self, it is impossible to prove (or disprove) the awareness of another. In normal consciousness, this problem is obviated by the multitude of behavioral expressions of conscious awareness manifested by living beings nearly every waking moment. Words, gestures, and actions, the "stuff" of consciousness, provide compelling evidence of the inner life of another. A small but significant percentage (5–10%) of those who sustain severe acquired brain injury experience prolonged disturbance in consciousness. Most will eventually recover at least basic capacity for self and environmental awareness, but this may not occur for many months and, in some cases, years. During this period of severely altered consciousness, one's existence may be stripped of the usual harbingers of an active inner life. Sensory, motor, language, perceptual, and drive systems may all be compromised in the aftermath of severe brain injury. Consequently, the repertoire of behaviors available to signal retention of conscious awareness may be dramatically narrowed or lost altogether. This predicament presents one of humankind's greatest existential dilemmas—is consciousness lost, or simply no longer apparent? This question is at the heart of *Coma and Disorders of Consciousness* edited by Caroline Schnakers and Steven Laureys. Both researchers are responsible for many seminal papers in this rapidly advancing field. Together, they have assembled an outstanding list of authors and have compiled a comprehensive volume that aptly depicts the state of the science in assessment and treatment of patients with disorders of consciousness (DOC). The book opens with a discussion of the complexities involved in behavioral approaches to assessment. Despite the challenges outlined, behavioral methods remain the "gold standard" in diagnostic assessment. The second chapter on prognosis reviews recently published long-term outcome studies, which have shed new light on the potential for meaningful late recovery potential in a substantial minority of persons with DOC. The next three chapters review novel functional

neuroimaging and electrophysiologic approaches to assessment designed primarily to identify neurophysiologic signatures of consciousness in persons who lack behavioral expressions of self or environmental awareness. The issue of caregiver burden is explored in chapter six from a multidimensional perspective that considers the interpersonal and subjective impact of long-term caretaking. There are three chapters dedicated to the ubiquitous secondary sequelae of severe brain injury: spasticity, swallowing disorders, and sleep disturbance. The authors describe the neural systems underpinning these disorders and thoughtfully discuss their relation to impaired consciousness. Chapters 10–12 provide a review of treatments that aim to promote recovery by stimulating preserved brain circuitry. Interventions range from relatively low-cost, readily accessible procedures such as sensory stimulation and off-label drugs to highly specialized noninvasive and invasive electrical stimulation techniques. The book concludes with a provocative look at ethical dilemmas, states of consciousness associated with near-death experiences, and, finally, the future of coma science. Readers of *Coma and Disorders of Consciousness* will come away with a wealth of new knowledge about the science of consciousness and a profound sense of wonder in its majesty.

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Foreword II

During the last 30 years, I have had the opportunity to observe the evolution of knowledge as related to assessment and management of persons with disorders of consciousness (DOC). There has been much written, much debated, and much learned during that period of time. The neuroscientific understanding of DOC has matured significantly from basing opinions predominantly on neurological dogma to having evidence-based data in many areas to guide recommendations germane to assessment, prognosis, and treatment of this challenging population of patients.

As someone who had the pleasure of working with both Drs. Laureys and Schnakers, I was honored to be asked to write a foreword for *Coma and Disorders of Consciousness*, a timely and important contribution to the medical literature in this challenging area of medicine. The neurological spectrum that is subsumed under DOC is diverse, complex, and mystifying—this has served as a nidus for many researchers to attempt to define, explore, and better understand the nature of this condition, the essence of which is rooted in the concept of consciousness. But what truly defines consciousness in terms of the degree or breadth of conscious awareness in a given individual? Must conscious awareness include both awareness of self and environment? Should we assume someone is unaware because either we cannot show that they are aware or because they cannot tell us they are aware? How should our ability to prognosticate outcomes impact on clinical service provision including withdrawal or withholding of care if such is being considered? How should pain be assessed and treated in such individuals and what mechanisms are responsible for and differentially delineate the perception of pain versus the more complex phenomenon of suffering? Should the idea of treating someone to allow them to potentially become somewhat more aware be a worthwhile outcome if they were to remain severely disabled and dependent on others for care? This volume will help those engaged with this patient population, such as the treating clinician, family member, or advocate, to explore and stimulate improved practice and to further research in this area of neuroscience.

The text is unique and timely on many fronts, but most importantly it provides hope where often none may have existed and awareness of advances where many would have dismissed the potential for same. The clear message of this text is that

although the controversies associated with DOC remain partially shrouded in mystery, we are emerging into an era of better understanding that ultimately will positively impact clinical care and decision making.

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Preface

Consciousness is a word worn smooth by a million tongues. Depending upon the figure of speech chosen it is a state of being, a substance, a process, a place, an epiphenomenon, an emergent aspect of matter, or the only true reality.

George Armitage Miller

Fifty years ago, the field of disorders of consciousness was a very limited field of research. Severely brain-injured patients, who are most likely to present impaired consciousness during recovery, often died. In the 1950s, the introduction of artificial breathing changed everything. The life of these patients could be extended even in cases of severe lesions to brain areas supporting the control of vital functions. The clinician started to face patients who were alive but not reactive to their surroundings. In this context, a new field was called to emerge, the disorders of consciousness. In the 1960s, Plum and Posner defined for the first time a clinical entity called the coma. Slightly later, Jennett and Teasdale developed the well-known Glasgow Coma Scale for assessing the progress of comatose patients in intensive care units. The 1980s was characterized by the development of a new kind of treatment, the sensory stimulation programs. Finally, in the late 1990s, the emergence of neuroimaging techniques opened new opportunities to study brain reactivity in patients with severe brain injuries.

However, in spite of the medical advances and the increasing number of severely brain-injured patients, the assessment and treatment of patients recovering from coma represents a very difficult and delicate task even today. The detection of signs of consciousness is complicated by the frequent motor and cognitive limitations of these patients. Treatment options are nearly absent, leaving the clinician often with a situation of palliative rather than restorative care. Even in an experimental setting, the study of patients in a coma or related disorders of consciousness is a real challenge. These patients are easily exhausted, limiting the assessment window, and spontaneous motor reactions have to be controlled for. The development of a research environment adapted to the scientific investigation of these patients is time consuming and requests important clinical and scientific expertise. For over two decades, international research teams have been working on the scientific exploration

of disorders of consciousness, with both scientific and clinical research agendas. These research teams, bridging various medical (neurology, neurosurgery, intensive care, anesthesia, physical medicine, otorhinolaryngology) and paramedical disciplines (psychology, speech therapy, physical therapy) as well as engineering and biological disciplines, have been a major player in the development of new assessment, communication, and treatment techniques for disorders of consciousness at both behavioral and neuroimaging levels. Gathering an international crowd of experts, this version should offer readers an overview of the most recent advancements in this domain.

By focusing on both clinicians and researchers as potential readers of this book, we decided to include well-established findings about diagnostic/prognostic criteria, ethical issues, assessment techniques (i.e., behavioral scales, electrophysiological explorations, and structural/functional neuroimaging), and treatment procedures, but also techniques under development (i.e., neuromodulation) which, we hope, will stimulate ideas for future research.

In conclusion, we hope to have reached our aim by offering a comprehensive and reader-friendly book to readers both familiar or not with the difficult but intriguing field of disorders of consciousness.

We hope you enjoy reading this book.

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Chapter 1
Behavioral Assessment and Diagnosis of Disorders of Consciousness

Caroline Schnakers and Steve Majerus

Abstract Behavioral assessment is a critical step for the detection of signs of consciousness and, hence, for diagnosis of states of altered consciousness. However, because of the presence of compromising factors such as severe functional and cognitive impairment, accurate diagnosis is a challenging enterprise, leading to serious consequences on the patient's ongoing care but also on the patient's end of care. In this review, we will describe the behavioral characteristics of the main clinical entities through which severely brain-injured patients transit before fully recovering from coma, we will describe methods for assessing consciousness at the bedside, and we will discuss the existing tools that help clinicians formulating an accurate diagnosis.

Introduction

During these last years, there has been increasing fascination for the field of disorders of consciousness. Due to progress in intensive care, more and more severely brain-injured patients survive their initial brain insult, but many of these will go through various states of impaired consciousness. The prevalence of these patients is estimated at 46 per million in the United States, 14 per million in Great Britain [1], and 36 per million in Belgium [2]. Many patients will remain in a vegetative state for a more or less extended period of time before regaining some level of consciousness (minimally conscious state). Some of these cases have received important coverage

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C. Schnakers, S. Laureys (eds.), *Coma and Disorders of Consciousness*, DOI 10.1007/978-3-319-55964-3_1

by the media, such as the case of Terri Schiavo (1963–2005) who stayed in a vegetative state for 15 years after a cardiac arrest or the case of Terry Wallis who emerged from a minimally conscious state 19 years (1984–2003) after a severe traumatic brain injury [3]. At the same time, prolonged hospitalization is expensive. In the United States, the costs are estimated at 600,000–1,875,000 dollars per year per patient with severe traumatic injury [4]. Questions regarding end-of-life decisions are critical here, particularly in chronic vegetative patients. In a recent European survey ($n = 2475$), the majority of medical and paramedical professionals (66%) agreed to withdraw life support for chronic vegetative patients, while only 28% agreed for patients in a chronic minimally conscious state. Many clinicians reported that they would not want to be life-supported if they happened themselves to be in a chronic vegetative state (82%) or if they were in a chronic minimally conscious state (67%) [5]. The social, economic, and ethical consequences associated with disorders of consciousness, and particularly the vegetative state, are huge.

The term *vegetative* indicates preserved physiological functions (cardiac, respiratory, sleep/wake cycles) without clear signs of consciousness of either the self or the environment. In a sense, the body works without the mind. One of the few ways we have to differentiate patients in a vegetative state from conscious patients is to observe their spontaneous behaviors and their reactions to stimuli occurring in their environment. This behavioral assessment requests thorough expertise on behalf of the clinician. It also depends on the physical and mental capacities (particularly, the vigilance level) of the patient at the time of assessment. Missing signs of consciousness is not a rare fact, and diagnostic errors are frequent (i.e., around 40%) [6–8]. The diagnosis is, however, crucial. It influences the way the patient's care will be oriented and the way end-of-life decisions will be considered with the patient's family. Developing valid and sensitive behavioral scales to detect the presence of signs of consciousness, even subtle, therefore, represents a real challenge.

Disorders of Consciousness

Coma

Patients who survive a severe brain injury can remain unconscious for several weeks, being neither awake nor conscious. They are in a state called coma, defined as "a pathological state marked by severe and prolonged dysfunction of vigilance and consciousness" [9] (Fig. 1.1 and Table 1.1). This state usually results either from a lesion limited to the brainstem (involving the reticular activating system) or from a global brain dysfunction (most often caused by diffuse axonal injury after traumatic brain injury). The distinguishing features of coma are the continuous absence of eye opening (spontaneously or after stimulation) and the absence of oriented or voluntary motor or verbal (including vocalization) responses. There is no evidence of visual fixation or pursuit, even after manual eye opening. This state must last at least 1 h to be differentiated from a transient state such as syncope, acute

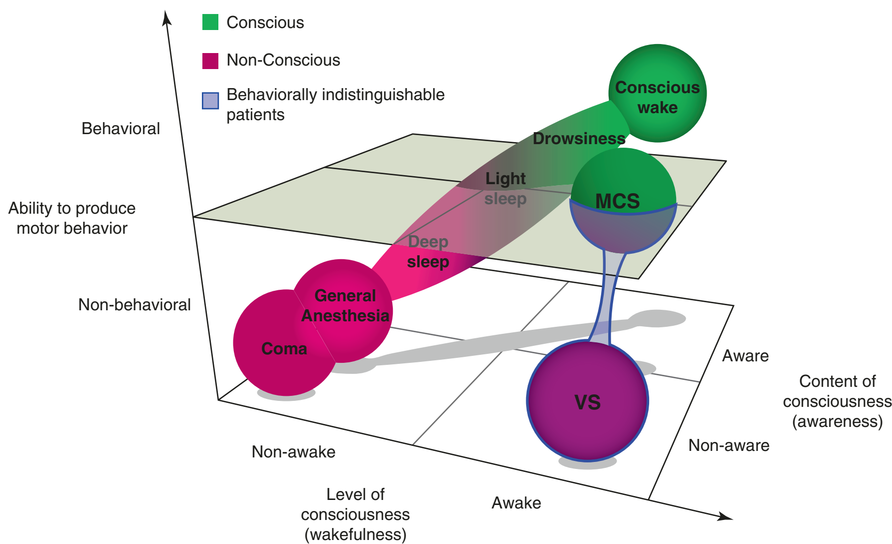

Fig. 1.1 The conundrum of consciousness. Disorders of consciousness are defined by two main components: the level of consciousness and the content of consciousness. This figure illustrates where different states (i.e., coma; vegetative state, VS; minimally conscious state, MCS, but also states related to sleep and anesthesia) are placed on both continuum. It also represents where patients with covert cognition would be placed (adapted from Monti et al., 2012)

confusion, or delirium. Prolonged coma is rare as this condition usually resolves within 2–4 weeks, most often evolving into a vegetative state or a minimally conscious state [10].

The prognosis is influenced by factors such as etiology (patients with traumatic brain injury have a better outcome than patients suffering from a cerebrovascular accident), general medical condition, and age. A negative outcome is expected if, after 3 days of observation, there are no pupillary or corneal reflexes, only stereotyped or absent motor responses to noxious stimulation, and an isoelectric electroencephalogram (EEG). A bilateral absence in parietal regions of the N20 evoked potential to somatosensory stimuli is also a strong predictor of death in comatose patients [11].

Being in a coma is different from being brain dead. In patients with brain death, critical functions such as respiration and circulation, neuroendocrine and homeostatic regulation, and consciousness are absent. The patient is apneic and unreactive to environmental stimulation. The term brain death requires a bedside demonstration of irreversible cessation of all functions of the brain, including brainstem functions. After controlling for a possible impact of pharmacological treatment, toxins, and hypothermia, the diagnosis of brain death can be made within 6–24 h, usually using a thorough assessment of brainstem reflexes, an apnea test (to demonstrate the absence of a breathing drive), and a cerebral angiography, an X-ray scan, or transcranial Doppler imaging (to demonstrate the absence of brain functions) [12].

Table 1.1 Comparison of the behavioral features of coma, VS, MCS−, MCS+, emergence from MCS (EMCS), and LIS

	Coma	VS	MCS−	MCS+	EMCS	LIS (classic)
Eye opening	None	Spontaneous	Spontaneous	Spontaneous	Spontaneous	Spontaneous
Movement	None	Reflexive/ patterned	Automatic/ object manipulation	Automatic/ object manipulation	Functional object use	Reflexive/ patterned
Response to pain	Posturing/ none	Flexion withdrawal/ posturing	Localization	Localization	N/A	Flexion withdrawal/ posturing
Visual response	None	Startle	Object localization/ pursuit/ fixation	Object recognition	Object recognition	Object recognition
Affective response	None	Random	Contingent	Contingent	Contingent	Random (presence of pathological laughs/tears)
Response to command	None	None	None	Reproducible	Consistent/ reproducible	Consistent (using eye-related commands)
Verbalization	None	None	Random vocalization/ none	Intelligible words	Intelligible words	None
Communication	None	None	Unreliable	Unreliable	Reliable	Reliable (using alphabetical board)

Vegetative State

In 1972, the term vegetative state (VS) was first introduced by Jennet and Plum to describe "an organic body capable of growth and development but devoid of sensation and thought" [13] (Fig. 1.1 and Table 1.1). This new clinical entity was identified following the implementation of artificial breathing techniques in intensive care units. Since then, the number of scientific studies performed on VS patients has continuously increased. More precisely, less than ten articles were published from 1975 to 1985, compared with more than five hundreds of articles from 2010 to 2015 (Fig. 1.2).

Behaviorally, patients in VS open their eyes spontaneously or in response to stimulation and present preserved autonomic functions (e.g., breathing, cardiovascular regulation, thermoregulation), but they are not conscious and show only reflexive behaviors [10]. The VS often results from an injury involving the white matter or bilateral lesions of the thalamus (i.e., intralaminar nuclei) [14, 15]. How can doctors explain to the family such a state? These patients breathe normally and have their eyes open. They even have prolonged periods with eyes closed, leading to the impression that the patient is sleeping. We now know that this impression may

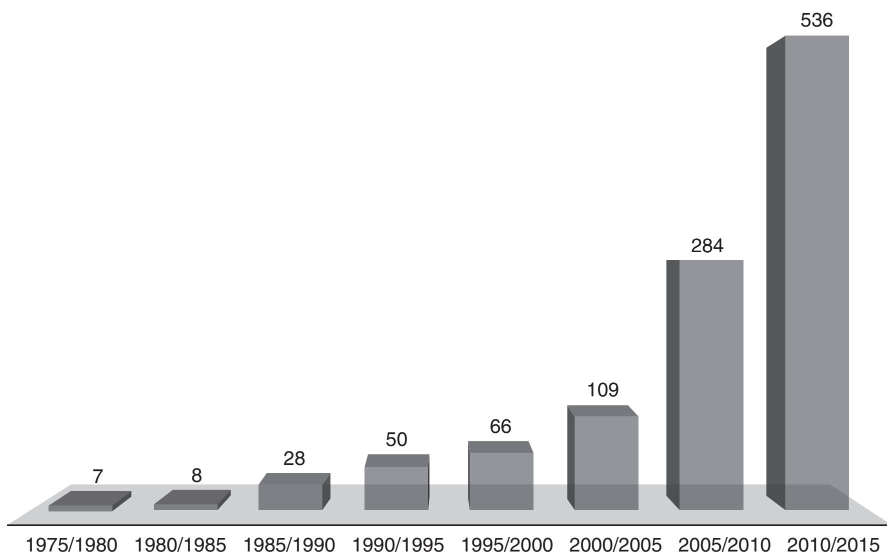

Fig. 1.2 Annual number of publications on vegetative state between 1975 and 2015. Results of a PubMed search using the terms vegetative state, consciousness, and awareness

be wrong. When the eyes are closed, no specific electroencephalographic changes are noticed, and EEG characteristics of the different sleep stages (e.g., slow wave sleep, rapid eye movement) are often absent [16]. The patients may also moan and show smiling, crying, or grimacing, but these behaviors are inappropriate and appear out of context. Even randomly produced single words have been reported in patients diagnosed with VS [17]. All of these features will puzzle the patient's family and complicate the work of the medical staff, who may be inclined to experience burnout (i.e., a recent study showed that one out of five healthcare workers caring for patients in a disorder of consciousness are in burnout, while 33% present an emotional exhaustion) [18]. Accurate information and psychological assistance are essential for helping the family (and also the medical staff) to cope with this dramatic situation [19].

The VS state may last for days, months, or even years. After 1 year, for traumatic etiologies, or 3 months, for non-traumatic etiologies, the VS can be considered as permanent. In such cases, the patient's chance of recovery is less than 5%. Only after that point can the ethical and legal issues concerning withdrawal of treatment be discussed [20]. Given the negative connotation of the term "vegetative state," the European Task Force on Disorders of Consciousness has proposed the use of a more neutral and descriptive term, such as "unresponsive wakefulness syndrome" [21]. During end-of-life decision-making, the presence of any sign of consciousness must be investigated and excluded using behavioral and neuroscientific approaches (such as neuroimaging and electrophysiology). The challenges that clinicians face when differentiating unconscious from conscious states are illustrated by cases that received lots of attention by the media such as Tony Bland in the United Kingdom

(1993), Terri Schiavo in the United States (2005), and Eluana Englaro in Italy (2009) [22–24]. Thorough examinations had been conducted for each of these patients; the extreme decision of end of life was considered. The distinction between conscious and unconscious states is very difficult to make given that patients can present subtle behavioral signs which can easily be missed and which differentiate the vegetative state from the minimally conscious state.

Minimally Conscious State

The minimally conscious state (MCS) was identified more recently than the VS and the coma. It was defined in 2002 by the Aspen Workgroup as being characterized by the presence of inconsistent but clearly discernible behavioral signs of consciousness (Fig. 1.1 and Table 1.1) [25]. Patients evolving from a VS to an MCS are still awake but begin to show oriented behaviors such as visual pursuit. The earlier this behavior appears, the better the outcome will be. The presence of oriented eye movements is therefore crucial, but it is also one of the most difficult signs of consciousness to detect and requires the use of sensitive diagnostic tools [8, 26, 27]. More globally, signs of consciousness in MCS patients may be hard to observe because they are inconsistent in time, due to high vigilance fluctuations. They must be replicated within a given examination to meet the diagnostic criteria for MCS. It is generally necessary to conduct serial examinations before an accurate diagnosis can be made. Complicating further the diagnosis is the fact that patients may fluctuate between VS and MCS before the level of consciousness stabilizes [28].

MCS is diagnosed when there is clear evidence of one or more of the following behaviors: simple command-following (e.g., “shake my hand”), gestural or verbal yes/no responses (regardless of accuracy), intelligible verbalization, and movements or affective behaviors that occur in contingent relation to relevant environmental stimuli and are not attributable to reflexive activity. Examples of contingent motor and affective responses include (1) episodes of crying, smiling, or laughter produced by the linguistic or visual content of emotional but not neutral stimuli, (2) vocalizations or gestures that occur in direct response to verbal prompts, (3) reaching for objects with a clear relationship between object location and direction of reach, (4) touching or holding objects in a manner that accommodates the size and shape of the object, and (5) visual pursuit or sustained fixation in response to moving or salient stimuli. As different functional neuroanatomical features have been observed, the MCS has recently been subdivided in two clinical entities, MCS+ and MCS−, based on the presence or absence of receptive and expressive language (i.e., response to command and intelligible verbalization) [29]. The specific behaviors required to fulfill the criteria for MCS+ and MCS− remain a matter of debate and require further empirical investigation before they can be incorporated into clinical practice.

Emergence from MCS is defined by the reemergence of reliable and consistent interactive communication (which may occur through speech, writing, yes/no signals, or augmentative communication devices) or a functional object use (i.e., discrimination and appropriate use of two or more objects) [25].

Patients in MCS may progress quickly or slowly, whereas others remain in this condition permanently. Formal prognostic guidelines do not exist for MCS. However, patients in MCS improve faster and have better prospects for functional recovery than those in VS, and outcomes are generally more favorable for those with traumatic versus non-traumatic injuries [30–32]. The original report describing this condition states that most of those who remain in MCS for 12 months will remain permanently severely disabled [33]. However, recent studies suggest that signs of recovery after severe brain injury may be observable over longer time periods and approximately one in five MCS patients will eventually continue his life at home or in the community. The duration of MCS nevertheless seems to be a strong predictor of the length of confusional state/posttraumatic amnesia [30]. The early recovery (within 8 weeks) of target conscious behaviors such as visual pursuit and response to command have been linked to good functional outcome several years after the injury [27, 31].

Don't Judge a Book by Its Cover: The Difficult Diagnoses of Locked-In Syndrome and Covert Cognition

Locked-In Syndrome

The locked-in syndrome (LIS) is marked by tetraplegia and anarthria in the context of preserved consciousness and a near-normal to normal cognitive functioning [34, 35] (Table 1.1). This state is caused by a lesion involving the ventral pons and, in 60% of cases, is due to basilar thrombosis. Functional neuroimaging typically shows preserved supratentorial areas (with hypometabolism in the cerebellum). Interestingly, significant hyperactivity has been observed bilaterally in the amygdala of acute LIS patients, likely reflecting anxiety generated by the inability to move or speak (stressing the importance of appropriate anxiety treatment soon after diagnosis) [36]. Because patients with LIS have spontaneous eyes opening, but are unable to speak or move the extremities, this state can be confused with VS. On average, the diagnosis of LIS is not established until 2.5 months post-onset. There is evidence that family members tend to detect signs of consciousness (55% of cases) prior to medical staff (23% of cases) [36]. Classic LIS consists of complete paralysis of the orobuccal musculature and all four extremities; however, vertical eye movements are spared, allowing nonverbal communication through directional gaze. Perceptual functions are also usually spared given that ascending corticospinal axons remain intact [34]. Bauer has described multiple varieties of LIS, including the incomplete form in which

there is residual motor activity (frequently, finger or head movements), and total LIS, in which there is complete immobility including both horizontal and vertical eye movements [37]. Total LIS cases have previously been reported but are rare and request the use of neuroimaging or electrophysiological methods to establish the diagnosis [38]. Data on life expectancy suggest that some patients with LIS can live for more than 12 years while remaining in LIS. Surprisingly, chronic LIS patients rate their quality of life similarly to the healthy population [39]. In the absence of other structural or functional brain abnormalities, patients with LIS are generally able to make independent decisions and communicate their preferences through augmentative communication devices [36].

Patients with Covert Cognition

A different group of patients who are unable to show any behavioral sign of consciousness but are able to respond mentally to active neuroimaging or electrophysiological paradigms has been identified more recently (Fig. 1.1). In 2006, Owen and colleagues reported the case of a non-communicative young woman with severe brain injury. When performing a mental imagery task, her brain activity was similar to the one observed in healthy controls [40]. Following this study, Monti and colleagues have tested 54 patients using the same paradigm. Only two patients diagnosed as being in a VS and three patients diagnosed as being in an MCS were able to perform the task (9% of the group). One of these patients was able to answer “yes” or “no” to autobiographical questions by using either motor or spatial imagery [41]. Since then, a series of studies has been published about the detection of willful brain activity in patients diagnosed as being in a VS, confirming the existence of patients with covert cognition [42].

It is tempting to think that these patients are with a severe form of LIS. However, unlike LIS patients, patients with covert cognition present impaired connectivity between subcortical and cortical, such as connections between the thalamus and the primary motor cortex which will prevent the execution of willful motor actions [43]. According to a recent meta-analysis, covert cognition seems rare in VS (14% of cases) but is more frequent in patients with traumatic brain injury than non-traumatic brain injury (32% vs. 19%) [42]. Future studies will nevertheless have to be multicentric in order to gather a sufficient amount of data to establish the profile of this possibly new clinical entity.

As previous findings have shown the presence of communication in some patients with covert cognition, recent studies have been trying to investigate the interest of brain-computer interfaces (BCIs) in severely brain-injured patients which may help those patients to communicate using neuroimaging or electrophysiology [41, 44–47]. BCI paradigms should not be used for diagnostic purpose. The tasks used to communicate are complex and could lead some patients

to be unable to respond even though they are conscious. Future studies will most likely have to better understand residual cognitive functioning in those patients before implementing successfully those augmentative communication techniques [48].

Bedside Assessment

Diagnostic Accuracy

Differentiating MCS from VS can be challenging as voluntary and reflexive behaviors may be difficult to distinguish and subtle signs of consciousness may be missed. The development of diagnostic criteria for MCS [25] should reduce the incidence of misdiagnosis relative to the rates reported before these criteria were established [6, 7]. However, a study comparing clinical non-standardized observation to examination with a standardized behavioral scale found that 41% of patients believed to be in VS were misdiagnosed [8]. This study also found that the majority of cases with an uncertain diagnosis were in MCS (89%), not in VS. Another 10% diagnosed with MCS based on non-standardized examination had actually emerged from this condition.

This high rate of misdiagnosis likely reflects several sources of variance. Variance in diagnostic accuracy may result from biases contributed by the examiner, patient, and environment. Examiner error may arise when the range of behaviors sampled is too narrow, response time windows are over- or under-inclusive, criteria for judging purposeful responses are poorly defined, and examinations are conducted too infrequently to capture the full range of behavioral fluctuation. The use of standardized rating scales offers some protection against these errors [32], although failure to adhere to specific administration and scoring guidelines may jeopardize diagnostic accuracy. The second source of variance concerns the patient. Fluctuations in arousal level, fatigue, subclinical seizure activity, occult illness (e.g., metabolic and infectious encephalopathies), pain, cortical sensory deficits (e.g., cortical blindness/deafness), motor impairment (e.g., generalized hypotonus, spasticity, or paralysis), or cognitive disturbance (e.g., aphasia, apraxia, agnosia) also decrease the probability of observing signs of consciousness [49]. Finally, the environment in which the patient is evaluated may bias the assessment. Paralytic and sedating medications, restricted range of movement stemming from restraints and immobilization techniques, poor positioning, and excessive ambient noise/heat/light can all decrease or distort voluntary behavioral responses.

Examiner bias can be greatly minimized by using standardized tools, but diagnostic accuracy is not always within the examiner's control. This is particularly troubling as clinical management, from rehabilitation to end-of-life decision-making, often depends on the behavioral observations of the examiner.

Behavioral Scales

In light of the behavioral fluctuations that commonly occur in this population, evaluations should be repeated over time, and measures should be sensitive enough to detect subtle but clinically meaningful changes in neurobehavioral responsiveness. Conventional bedside assessment procedures and neurosurgical rating scales such as the Glasgow Coma Scale [50] (GCS) have limited utility when used to monitor progress in patients with prolonged disturbance in consciousness. These procedures detect relatively gross changes in behavior and are not designed to distinguish random or reflexive behaviors from those that are volitional. The Full Outline of UnResponsiveness score (FOUR score) has greater sensitivity than the GCS for detecting different levels of brainstem function in the acute stage of severe brain injury [51], but because the FOUR score does not include a systematic assessment of signs of consciousness [25], it may not capture the transition from VS to MCS [52, 53]. Standardized rating scales have been devised for chronic disorders of consciousness (DOC) to address these shortcomings, to assess a broad range of neurobehavioral functions, and to rely on fixed administration and scoring procedures.

Standardized neurobehavioral assessment measures tailored for DOC patients include the Coma Recovery Scale – Revised (CRS-R) [54], the Coma-Near Coma Scale (CNC) [55], the Western Neurosensory Stimulation Profile (WNSSP) [56], the Western Head Injury Matrix (WHIM) [57], and the Sensory Modality Assessment and Rehabilitation Technique (SMART) [58]. Although item content varies across measures, all evaluate behavioral responses to a variety of auditory, visual, motor, and communication prompts. All of these instruments have been shown to have adequate reliability and validity; however, there is considerable variability in their psychometric integrity and clinical utility. Of these measures, the CRS-R is the only one that directly incorporates the existing diagnostic criteria for coma, VS, and MCS into the administration and scoring scheme (Table 1.2). Giacino and colleagues (2004) compared the CRS-R to the DRS in 80 patients with DOC and found that although the two scales produced the same diagnosis in 87% of cases, the CRS-R identified ten patients in MCS who were classified as VS on the DRS [28]. There were no cases in which the DRS detected features of MCS missed by the CRS-R. Schnakers and colleagues (2006) administered the GCS, CRS-R, and FOUR score to 60 patients with acute (i.e., trauma center) and subacute (i.e., rehabilitation center) brain injury resulting in disturbance in consciousness [52]. Among the 29 patients diagnosed with VS on the GCS, four were found to have at least one sign of consciousness on the FOUR. However, the CRS-R detected evidence of MCS in seven additional patients diagnosed with VS on the FOUR. All seven of these patients showed sustained oriented eye movements, a clinical sign heralding recovery from VS.

In 2010, the American Congress of Rehabilitation Medicine published the results of the first evidence-based review of neurobehavioral rating scales designed specifically for patients with DOC [59]. Six of the 13 scales that qualified for the review were recommended for use in clinical practice. The CRS-R received the strongest

Table 1.2 Coma Recovery Scale – Revised record sheet

Auditory function scale
4—Consistent movement to command[a]
3—Reproducible movement to command[a]
2—Localization to sound
1—Auditory startle
0—None
Visual function scale
5—Object recognition[a]
4—Object localization: reaching[a]
3—Pursuit eye movements[a]
2—Fixation[a]
1—Visual startle
0—None
Motor function scale
6—Functional object use[b]
5—Automatic motor response[a]
4—Object manipulation[a]
3—Localization to noxious stimulation[a]
2—Flexion withdrawal
1—Abnormal posturing
0—None/flaccid
Oromotor/verbal function scale
3—Intelligible verbalization[a]
2—Vocalization/oral movement
1—Oral reflexive movement
0—None
Communication scale
2—Functional: accurate[b]
1—Nonfunctional: intentional[a]
0—None
Arousal scale
3—Attention[a]
2—Eye opening without stimulation
1—Eye opening with stimulation
0—Unarousable

[a]Denotes MCS
[b]Denotes emergence from MCS

recommendation ("minor reservations"), based on its performance across a panel of psychometric quality indicators. The CRS-R is also one of the Traumatic Brain Injury (TBI) Common Data Elements (CDE) suggested by the US National Institute of Neurological Disorders and Stroke (NINDS) and the method of choice for monitoring recovery of consciousness in TBI research [60, 61].

More Specialized Behavioral Assessments

Individualized Quantitative Behavioral Assessment

Clinicians involved in the care of MCS patients often encounter situations in which the patients' behavioral responses are ambiguous or occur too infrequently to clearly discern their significance. These problems are often due to injury-related sensory, motor, and arousal deficits. For this reason, a technique referred to as Individualized Quantitative Behavioral Assessment (IQBA) was developed by Whyte and colleagues [62, 63]. IQBA is intended to address case-specific questions using individually tailored assessment procedures, operationally defined target responses, and controls for examiner and response bias. Once the target behavior (e.g., command-following, visual tracking) has been operationalized, the frequency of the behavior is recorded following administration of an appropriate command, following an incompatible command and during a rest interval. Data are analyzed statistically to determine whether the target behavior occurs significantly more often in one condition relative to other conditions. For example, when the frequency of observed behaviors is greater during the "rest" condition relative to the "command" condition, it is likely that the behaviors represent random movement rather than a purposeful response to command.

IQBA can be applied across a broad range of behaviors and can address many different types of clinical question. McMillan (1996) employed an IQBA protocol to determine whether a minimally responsive, TBI patient could reliably communicate a preference concerning withdrawal of life-sustaining treatment [64]. Responses to questions were executed using a button press. Results indicated that the number of affirmative responses to "wish to live" questions was significantly greater than chance suggesting that the patient could participate in end-of-life decision-making. McMillan's findings were subsequently replicated in a second IQBA assessment conducted by a different group of examiners [65].

Pain Assessment and the Nociception Coma Scale – Revised

Providing information as to whether a patient with DOC is in pain is important to both clinicians and families. However, self-report is not an option in patients with DOC because of the inability to communicate. The Nociception Coma Scale (NCS) is the first standardized tool developed to assess nociceptive pain in patients with severe brain injury. The first version of the NCS consisted of four subscales assessing motor, verbal, visual responses as well as facial expression [66]. The NCS has been validated in patients in intensive care and inpatient neurology/neurosurgery units, rehabilitation centers, and nursing homes. In comparison to other pain scales developed for non-communicative patients, the NCS has broader coverage and better diagnostic sensitivity, suggesting that it is an appropriate assessment tool for this

population. The visual subscale was subsequently deleted since further analysis showed that, following the application of noxious versus non-noxious stimuli, significantly higher scores were obtained on the motor, verbal, and facial expression subscales but not on the visual subscale. Using this revised version (NCS-R), a cutoff score of 4 (sensitivity of 73% and specificity of 97%) has been defined as a potential clinical threshold for detecting pain in patients with DOC [67]. Recent findings have also shown a correlation between NCS-R total scores and the activity in the anterior cingulate cortex (related to pain unpleasantness), reflecting further the relevance of this scale when monitoring pain in patients with DOC [68]. The scale has demonstrated good reliability and validity and currently exists in various languages (i.e., French, English, Italian, Dutch, and Thai) [66, 67, 69–72]. Finally, the interest of the NCS-R in assessing pain in a clinical setting has been investigated recently [73]. Thirty-nine patients with potential painful conditions (e.g., due to fractures, decubitus ulcers, or spasticity) were assessed with the NCS-R and the GCS during nursing cares before and after the administration of an analgesic treatment tailored to each patient's clinical status. The NCS-R scores, but not the GCS scores, were statistically lower during treatment when compared to the scores obtained before treatment, providing further evidence that the NCS-R is an interesting clinical tool specifically tailored for pain management.

Conclusion

Behavioral responses as well as brain activity differ among disorders of consciousness. The detection of signs of consciousness can be challenging at the bedside and the use of sensitive standardized scales is crucial. As misdiagnosis can lead to serious consequences especially in terms of pain treatment and end-of-life decision-making, neuroimaging could constitute a complementary tool when disentangling VS from MCS patients. In the future, the development of consciousness classifier based on residual brain activity or residual brain connectivity could also substantially help clinicians and constitute an automated diagnostic tool. This could particularly help for the detection of patients who are functionally locked-in.

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