Coma and Disorders of Consciousness: Scientific Advances and Practical Considerations for Clinicians

Olivier Bodart, Steven Laureys, Olivia Gossseries
Department of Neurology, Coma Science Group, Cyclotron Research Center, University of Liège, University Hospital of Liège, Liège, Belgium

Abstract

Recently, neuroscientists and clinicians have seen the rapid evolution of diagnoses in disorders of consciousness. The unresponsive wakefulness syndrome-vegetative state, the minimally conscious state plus minus, and the functional locked-in syndrome have been defined using new neuroimaging techniques. Diffusion tensor imaging, positron emission tomography, functional magnetic resonance imaging, electroencephalography, and transcranial magnetic stimulation techniques have all promoted important discoveries in the field of disorders of consciousness. This has led to a better understanding of these patients' condition and to the development of new prognosis, therapeutic, and communication tools. However, low sensitivity and artifacts problems need to be solved to bring these new technologies to the single-patient level; they also need to be studied in larger scale and randomized control trials. In addition, new ethics questions have arisen and need to be investigated.

Keywords: Unresponsive wakefulness syndrome-vegetative state; Minimally conscious state; Consciousness; Functional magnetic resonance imaging (fMRI); Neuroimaging

Rapid evolution of neuroimaging technologies and paradigms has led to profound modifications in the nosology, prognosis, and treatment of patients with disorders of consciousness. We will first review the evolution of the revised diagnoses, then the neuroimaging techniques and paradigms that promoted these changes will be discussed. Finally, we investigate the potential impact this new knowledge may have on clinical practice.

Evolution of Nosology in Disorders of Consciousness

More than 10 years ago, Giacino et al. defined the diagnosis criteria for a new state of altered consciousness, the minimally conscious state. Until then, patients with disorders of consciousness were considered either in coma, in a persistent or permanent vegetative state, or in a severely disabled state. Patients in a vegetative state recover arousal (i.e., eyes opening), but not awareness of themselves and their environment.

This condition has been given a widely accepted name in 1972, and diagnosis criteria, etiology, and prognosis were summarized in 1994. However, recently this state has been widely studied, leading to changes in terminology. First, a new name has been proposed, the unresponsive wakefulness syndrome (UWS), as it better describes the condition (the patients are indeed awake—showing eye opening, but unresponsive—in the absence of command following, and can have several etiologies to their clinical signs—which are thus included in a syndrome); it also removes the impression given to the public that these patients are “vegetable-like”. Second, this population of unresponsive wakefulness syndrome patients has been shown to be in fact composed of different states of altered consciousness. With the application of the diagnosis criteria for the minimally conscious state, many patients have been rediagnosed. Patients in the minimally conscious state can show signs of consciousness such as command following (even if inconsistent), visual pursuit, localization to noxious stimulation, and appropriate responses to emotional stimuli without being able to functionally communicate.

Recently, it has been proposed to distinguish in this patient population those who show higher-order signs of consciousness (e.g., command following, intelligible verbalization, and nonfunctional communication) from those who show only low-level signs of consciousness (e.g., visual pursuit of a salient stimulus, noxious stimulation localization, appropriate emotional response). Advances in the field of neuroimaging, as we will discuss below, have also led to the proposition of the diagnosis of functional locked-in syndrome. Classical locked-in patients usually have most of their cognitive functions preserved, but because of the brainstem injury their motor output is near null (except for eye movements). Functional locked-in syndrome
represents patients who are behaviorally in an unresponsive wakefulness syndrome or minimally conscious state, but on neuroimaging show better consciousness than expected, with command following and even sometimes functional communication. Figure 1 summarizes the different diagnostic entities that can be encountered after a severe brain injury.

So far, the gold standard for consciousness assessment remains the behavioral evaluation. With the development of dedicated and validated scales such as the Coma Recovery Scale-Revised (CRS-R), trained clinicians and neuroscientists can make diagnosis of coma, unresponsive wakefulness syndrome, and the minimally conscious state and emergence from this state. The CRS-R is the best scale to distinguish the minimally conscious state from unresponsive wakefulness syndrome as it is composed of six subscales (auditory, visual, motor, oromotor, communication, and arousal) in which signs of consciousness are sought and is now widely used, as assessed by the number of validated translation in various languages that exist. At the acute stage, the Glasgow Coma Scale (GCS) is the most commonly used validated scale to predict the probability of recovery. The more recent Full Outline of Unresponsiveness (FOUR) Scale has proved to share good predictive value of functional outcome with the GCS, with the advantages of being appropriate for intubated patients and for the detection of minor signs of consciousness such as visual pursuit.

Even with the availability of validated scales, the rate of misdiagnosis remains high (~40%). There are many reasons for this. On the patient side, there might be limitations from motor dysfunction (paralysis, spasticity, hypotonic status), impaired cognitive processing (language processing, apraxia), a sensory deficit (such as deafness/blindness), fluctuation of vigilance (from the disorder of consciousness itself or from drugs), pain, etc. A lack of repeated evaluation, or evaluation over too short a time span can also lead to misdiagnosis. With the consequences that such errors can have on the management of these patients, neuroimaging and electroencephalography techniques were sought.

**Fig. 1** Proposed nosology of the diagnostic entities after a coma based on clinical behavioral assessment and on recent functional neuroimaging studies. UWS, unresponsive wakefulness syndrome; MCS, minimally conscious state; LIS, locked-in syndrome; fUS, functional locked-in syndrome. (Adapted from Bruno et al. Unresponsive wakefulness to minimally conscious PLUS and functional locked-in syndromes: recent advances in our understanding of disorders of consciousness. J Neurol 2011;258(7):1373-1384)

**Evolution in Neuroimaging Techniques**

A simple way to study the patients' injured brain is through magnetic resonance imaging (MRI). Magnetic resonance imaging provides valuable information on the number, nature, severity, and localization of brain
lesions. Given the high variety of lesions, researchers tried to establish a correlation between the localization, the nature and the number of lesions, and the patient's state of consciousness. The number of lesions correlates with the Glasgow Outcome Scale \(^1\) \((\text{GOS})\).\(^{17,18}\) Lesions in the thalamus, brainstem, and basal ganglia were found to be of poor prognosis, especially when they are bilateral.\(^{19-24}\) However, patients with unresponsive wakefulness syndrome and minimally conscious state patients cannot be differentiated on MRI. Indeed, some patients share the same kind of structural lesions with different states of disorders of consciousness.

The development of diffusion-weighted imaging (DWI) and its derived diffusion-tensor imaging (DTI) brought new tools for the structural evaluation of these patients.\(^{25}\) These imaging sequences are based on the principle that water-molecule movement (diffusion) is dependent on its molecular environment, with axon membranes acting as barriers. DTI can give information on the structural integrity of axon tracts, resulting in the ability to evaluate the anatomic connectivity between different parts of the brain. This technique reflects the level of consciousness and distinguishes between the group of unresponsive wakefulness syndrome patients and the group of minimally conscious state patients.\(^{26}\) Figure 2 illustrates structural damage highlighted by DTI in one disorder of consciousness patient as compared with a healthy subject. Diffusion-tensor imaging can also be used as a prognostic tool: specific brain areas (i.e., the internal capsule, the corpus callosum, the cerebral peduncle, and other white matter tracts) correlate with outcome.\(^{27,28}\) Moreover, DTI may have demonstrated axonal regrowth paralleling clinical improvement in one patient in a chronic minimally conscious state.\(^{29}\) Still, DTI only gives information on structural connectivity and not on its functionality.

**Fig. 2** Structural brain images from diffusion tensor imaging technique showing white matter tracts in a healthy control and in a patient with chronic disorders of consciousness.
This resting state was also studied with functional MRI (fMRI), with the identification of a somewhat similar widespread thalamocortical network named the default mode network. Functional connectivity in this network correlates with the level of consciousness, being null in brain-dead patients. Its preserved connectivity at the acute stage could hold good prognostic value.

Electrophysiological studies of this brain state using electroencephalography (EEG) have also shown prognostic value, as occipital alpha band power could be a predictor of recovery in unresponsive wakefulness syndrome patients. Using entropy measurements of the EEG signal, it is also possible to distinguish in the early stages unconscious (coma and unresponsive wakefulness syndrome) from minimally conscious patients.

Instead of measuring structural or functional connectivity (each can be present without the other one), transcranial magnetic stimulation combined with high-density EEG (TMS/hd-EEG) has been used recently to determine effective connectivity by stimulating a brain area and recording the subsequent electrical activity. Effective connectivity can be defined as the capacity of one element of a network to causally influence another. Effective connectivity assessed by this technique correlates with the level of consciousness, being high in healthy awake subjects, in locked-in patients and in patients who emerged from the minimally conscious state, intermediate in rapid eye movement sleep and in the minimally conscious state, and low in deep slow-wave sleep, under general anesthesia, and in unresponsive wakefulness syndrome patients (Fig. 3). Besides being able to distinguish between unresponsive wakefulness syndrome and minimally conscious state patients, effective connectivity parallels recovery of consciousness, and is thus a potentially valuable prognostic tool. However, more studies need to be performed to assess the prognosis utility of this new technology.

Fig. 3 Effective connectivity assessed by transcranial magnetic stimulation combined with high-density electroencephalography in a healthy control during wakefulness, rapid eye movement (REM), and non-REM sleep (NREM), and in patients in emergence from the minimally conscious state (EMCS), a minimally conscious state (MCS), and an unresponsive wakefulness syndrome (UWS). The crosses indicate the site of stimulation and effective connectivity is represented in white (i.e., brain activation following the initial stimulation, in the order of several hundred milliseconds). (Adapted from Massimini et al. Cortical reactivity and effective connectivity during REM sleep in humans. Cogn Neurosci 2010;1(3):176-183 and Rosanova et al. Recovery of cortical effective connectivity and recovery of consciousness in vegetative patients. Brain 2012;135(Pt 4):1308-1320)
In addition to having been considered at rest, brain activity has also been studied with different kinds of sensory stimulation using $^{15}$O-radiolabeled water-PET. In passive tasks using auditory, visual, and somatosensory stimuli, unresponsive wakefulness syndrome patients experienced respective activation of primary auditory, primary visual, and primary somatosensory cortices. In minimally conscious state patients, however, these stimuli activated a wider network of associative areas, similar to those observed in healthy controls. Studies confirmed these findings. Event-related potentials (ERP; averages stimulus-induced EEG responses) in EEG studies showed that late components can be used to evaluate the conscious processing of information. A selective disruption of top-down processes from high levels of a cortical hierarchy (e.g., from frontal to temporal cortex in an auditory paradigm) can lead to loss of consciousness in brain-damaged patients, and can differentiate unresponsive wakefulness syndrome from minimally conscious state patients at the group level. The problem with these paradigms resides in their passive design. Even if brain activation similar to controls is found, it is hard to definitely affirm this is a sign of consciousness in total absence of a volitional component from the patient.

To better deal with this problem, active protocols were designed. In the most widely known fMRI paradigm, one unresponsive wakefulness syndrome patient was asked to imagine playing tennis and to imagine walking through a house, resulting in the activation of the supplementary motor area and the parahippocampal cortex, respectively, as observed in healthy controls. This command-following protocol has been derived in several other studies using motor, language, and visual tasks, which showed similar results. In an attempt to duplicate these findings at the bedside, EEG-active protocols were designed. In the case of a total locked-in syndrome patient (i.e., complete immobility, including all eye movement), consciousness was detected only through the use of this method. Other EEG-based studies were conducted in patients with altered consciousness. The original paradigm was later used to try to establish communication with noncommunicative patients with disorders of consciousness. Interestingly, one patient with unresponsive wakefulness syndrome (diagnosis on admission; subsequent CRS-R testing showed fluctuating behavioral signs of awareness, albeit no capacity to communicate) was able to answer a yes or no questionnaire via brain activity modulation. This was repeated in the Bardin et al study. Some practitioners are beginning to use this kind of protocol to create real-time communication interfaces for these patients with disorders of consciousness using fMRI or ERPs.

Caution should, however, be taken with negative results. The absence of command using brain-activity modulation does not mean the patient is unconscious. Indeed, there are many causes for a false-negative. Technically, the number of potential sources of artifact is great. Fluctuation of arousal and cognitive dysfunction in language, auditory, visual, or memory processing can all lead to inadequate or absence of a patient response. Nevertheless, willful modulation of brain activity following command is an indisputable sign of consciousness. This leads to the question: What is the real state of consciousness for behaviorally diagnosed unresponsive wakefulness syndrome patients who can follow command using neuroimaging and electroencephalography techniques? The same question is valuable for unresponsive wakefulness syndrome and minimally conscious state patients who can communicate only through these cutting-edge tools. That is why the diagnosis of functional locked-in syndrome was proposed to better describe the condition of these patients. This also suggests the need to include ancillary examinations in the evaluation of patients with altered consciousness. Before this can be done, several problems need to be solved, including low sensibility and high amount of artifacts, especially in fMRI. This will render single-subject-level evaluation possible, which is of absolute necessity to be part of a diagnostic process in the clinical routine.

Clinical Implications

The variety of diagnoses and their determination has drastically changed in the last decade, as discussed above. Making an accurate diagnosis is all important regarding a patient's prognosis, treatment management, and related ethical considerations, as we will see below. To accurately detect signs of consciousness, one should know the most subtle ones, and those that are not in fact signs of awareness. In the CRS-R, visual pursuit and visual fixation are labeled as signs of the minimally conscious state. However, recently our team has shown that visual fixation, at least in anoxic patients, is not a sign of consciousness. Visual pursuit is still regarded as a sign of consciousness, and it should be assessed by using salient stimuli (a mirror is the best tool to detect visual pursuit). Finally, blinking to threat is probably reflexive, and is not a sign of awareness recovery.

Patients' relatives are understandably highly concerned about prognosis and possible outcome. Etiology is determinant for prognosis. Indeed, unresponsive wakefulness syndrome patients with traumatic brain injury have better outcome at 12 months than nontraumatic ones. With the latter definition of a minimally conscious state, studies have demonstrated a better prognosis for this population than for the unresponsive one. The rate of
recovery at the acute stage is another predictor of better recovery and better outcome. Less data are available on the long-term prognosis of these patients. Recovery later than 3 months post-injury for non traumatic unresponsive wakefulness syndrome is unlikely; it has been reported as associated with poor functional outcome. Late recovery of minimally conscious state patients is more frequent, with up to 30% improvement more than one year after the loss of consciousness, once again with a poor functional outcome.

Along with the etiology, the time from injury, and the level of residual consciousness, many paraclinical markers have been tested as potential predictors of recovery or of poor recovery. Auditory ERPs are the most studied, and some components such as the N100 (negative component at 100 ms indication of the sensory cortex processing of the stimulus) hold prognostic value.

In a meta-analysis, the P300 (positive component occurring 300 ms after the stimulus) and the mismatch negativity (MMN; obtained with a deviant tone in an otherwise repetitive auditory stimulus, reflecting sound discrimination) predict recovery of some degree of consciousness in patients recovering from coma. A tree-based classification uses the MMN, pupillary light reflexes, and somatosensory evoked potentials to predict awakening or non recovery with good accuracy. As discussed above, conventional MRI, DTI, and resting-state connectivity all carry prognostic value.

Accurate diagnosis is also important to evaluate probable residual brain process, and more importantly pain processing. Like somatosensory stimulations in the passive paradigms, pain processing is different in unresponsive wakefulness syndrome from the minimally conscious state. This has led clinicians to think that unresponsive wakefulness syndrome patients were not "feeling" pain in the sense healthy individuals do, thus affecting decisions concerning pain management and even end-of-life decisions. Better management of pain could be obtained if its evaluation in non communicative patients was easier. Hence, a dedicated scale, the Nociception Coma Scale (NCS) was designed. This allows for the fine-tuning of pain treatment—avoiding inefficient treatment leaving the patient in pain while avoiding excessive painkiller doses, possibly leading to a sedative side effect.

A more accurate diagnosis is necessary to better evaluate the efficacy of therapeutic options for the promotion of arousal and awareness in patients with disorders of consciousness. Recently, the first large-scale randomized control trial studying the effect of amantadine (a N-methyl-D-aspartate and dopaminergic agonist) on traumatic unresponsive wakefulness syndrome and minimally conscious state patients has shown interesting positive results in both subpopulations. Zolpidem (a non benzodiazepine agonist of GABA receptors) is another medication being tested in unconscious patients. Although there is no large-scale randomized control trial available, preliminary results have shown impressive results, but only in a small proportion of the patients and only transiently (the effect lasts ~4 h, then the patient falls into his or her previous state). Large-scale randomized control trials are awaited to better objective the potential effect of this therapeutic option. Other pharmacological treatments have been tested on smaller scales with poor results. As a non pharmacological intervention, deep brain stimulation (DBS) has shown the best effect. In one traumatic and chronic minimally conscious state patient, behavioral improvement was noticed after the activation of the electrodes implanted in the thalamus. The theory behind this invasive technique is related to the findings in the resting-state studies, showing functional disconnection in the thalamocortical network. Meanwhile, physical and cognitive rehabilitation, as well as sensory stimulation programs, are essential in the therapy planning for patients with disorders of consciousness.

Finally, accurate diagnosis is necessary when one considers the seriousness of the ethics questions in relation to non-communicative patients. Pain management is one issue. Given the high rate of misdiagnosis and the indirect measures of pain perception, painkillers should be given to all patients likely to be in pain as assessed with the NCS. A hard-to-make choice is an end-of-life decision, usually through artificial nutrition and hydration (ANH) withdrawal. According to a European study, ANH is acceptable if the patient is in an unresponsive wakefulness syndrome, less if in a minimally conscious state. U.S. laws also reflect this. It would be best to communicate with the concerned patient. With the recent development of ancillary tools and the continued development of brain-computer interfaces, this communication could become a reality. Clinicians would be able to address these issues with the patient, who would then make the final decision. But can we really rely on such indirect measures?

**Conclusion**

Recent scientific advances in the field of disorders of consciousness have changed clinicians and neuroscientists' view of severely brain-injured patients. With a better understanding of their conditions, one can expect better management possibilities, such as therapeutics options and communication tools. Information given to patients' relatives should also become more precise, with prognosis and outcome more easily understood. But there is still
a lot of work to be done. There cannot be any therapeutic guideline without more large-scale randomized control trials. There cannot be correct information on prognosis without long-term studies of the newly defined diagnosis. The neuroimaging and electrophysiological tools that permit much of the recent discoveries cannot be included in the clinical setting until they can be used at the single-subject level. In addition, all of these studies should be accompanied by ethical debate to frame further decisions.

Acknowledgments

This work was supported by the Belgian National Funds for Scientific Research (FNRS), Fonds Léon Frédéricq, Belgian interuniversity attraction pole, James S. McDonnell Foundation, Mind Science Foundation, European Commission (Mindbridge, DISCOS, DECODER & COST), Concerted Research Action (ARC 06/11-340), Public Utility Foundation "Université Européenne du Travail," "Fondazione Europea di Ricerca Biomedica," and the University of Liège. We also thank Erik Ziegler and Francisco Gomez for their help with the illustrations.

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