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Recent advances in disorders of consciousness: Focus on the diagnosis

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Abstract

Background: Over the last two decades, there has been a considerable increase in knowledge of brain function in patients with disorders of consciousness following a coma. Differentiating between patients in unresponsive wakefulness syndrome and in minimally conscious state still represents a major clinical, legal and ethical challenge.
Objectives: This review focuses on recent behavioural and neuroimaging studies in this specific population.
Results: The growing interest in the use of neuroimaging techniques as new diagnostic tools has stimulated research in this area and created further challenges to clinical categorization and management. This study proposes a diagnostic procedure combining the use of behavioural scales and neuroimaging techniques. In cases of dissociation between behavioural and ancillary test results, it is suggested that a diagnostic label of 'non-behavioural MCS' (MCS*) be used to provide a more clinically accurate diagnosis (and, in theory, prognosis) when the bedside exam shows no evidence of consciousness, yet the neurodiagnostic work-up does.
Conclusion: More neuroimaging research is needed before clinical implementation to reach the single-subject diagnosis level, as well as to address the sensitivity and specificity of each technique, whether single or combined.

Keywords

Clinical assessment, diagnosis, disorders of consciousness, minimally conscious state, neuroimaging techniques, unresponsive wakefulness syndrome, vegetative state

History

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Introduction

Patients with disorders of consciousness (DOC) after severe brain injury have been studied for a long time, but even more extensively in the past few decades, as illustrated by the increased number of publications in the scientific literature (Figure 1). Concurrently, the use of neuroimaging and electrophysiological technologies has also rapidly evolved. These changes are leading to profound modifications in DOC terminology (Figure 1), diagnostic and prognostic evaluation, as well as treatment options and ethical frameworks associated with this unique patient population.

Typically, if patients survive severe brain injury secondary to such events as trauma, stroke or hypoxia/anoxia (e.g. cardiac arrest), they fall into a coma, which is a condition of unwakefulness (no eyes opening) and unconsciousness [1]. Coma is a transient state, which usually evolves into a vegetative state (previously called apallic syndrome [2] or coma vigil [3]), characterized by the return to wakefulness (eye opening), but without awareness of self and environment [4]. In 2010, unresponsive wakefulness syndrome (UWS) was proposed as a replacement term for vegetative state [5], because it better describes the condition and it removes the impression that these patients are 'vegetable-like' [6–8].

When patients show inconsistent but reproducible signs of consciousness, such as command following, visual pursuit or appropriate emotional responses, they are diagnosed as being in a minimally conscious state (MCS) [9]. Because many patients fall into this category, it has been recently subcategorized as MCS+ and MCS−, depending on the presence or absence of command following, respectively [10]. It is, however, not yet clear if this population present temporal fluctuations in awareness (i.e. presence vs. absence of consciousness) and/or if they also have a different kind (e.g. a lower level) of consciousness as compared to 'fully' conscious subjects (or, alternatively, some combination of the aforementioned). Kotchoubey et al. [11] will address this latter controversy in this issue. Emergence from MCS occurs when patients regain functional communication or functional use of objects.

Another condition that can be easily misdiagnosed as a DOC is the locked-in syndrome (LIS) [12]. This rare clinical entity results from a ventral brainstem lesion, typically vascular, that damages cortico-spinal tracts, leading to complete paralysis of voluntary muscles except for eye movements, which allow communication [13, 14].

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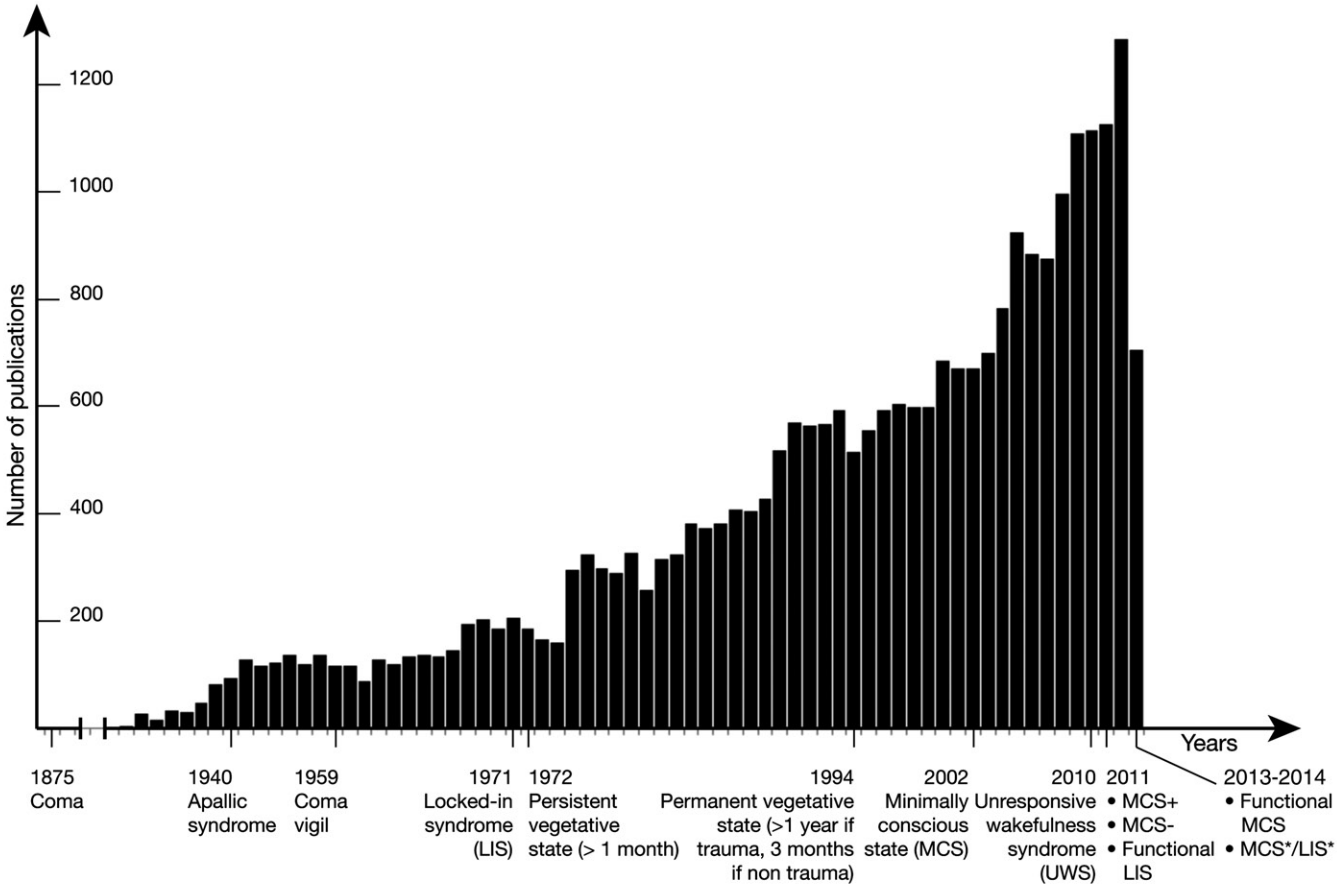

Figure 1. Number of published papers per year on patients with disorders of consciousness and evolution of the terminology. Medline search updated to June 2013. Keywords used were 'coma', 'vegetative state', 'unresponsive wakefulness syndrome', 'minimally conscious state' and 'locked-in syndrome'.

In most patients with DOC, the process of recovery is fast, within days or weeks, but, in some cases, recovery may be longer, lasting months or even years. Unfortunately, a few patients may not recover and remain in a UWS or MCS for decades. In this article, recent advances will be reviewed with an emphasis on the diagnosis of consciousness. The assessment of consciousness in patients with DOC, including neuroimaging findings, will be examined. Evaluation of communication and implications for diagnosis will then be discussed. A review of important issues related to the management of this challenging population will conclude the article. Each article in this special issue of *Brain Injury*, which is dedicated to DOC, will also be briefly introduced.

Assessment of consciousness

The differential diagnosis between UWS and MCS is often challenging, as these states occupy a border zone between unconsciousness and awareness. At present, the clinical standard for detecting signs of consciousness is based on bedside behavioural examination. The frequency of misdiagnoses by clinical consensus methods is, however, disturbingly high (up to 40%) [15, 16]. Motor deficits (paralysis, spasticity), impaired cognition (aphasia, apraxia), sensory impairment (blindness, deafness), pain and fatigability of patients with DOC are some of the factors that account for misdiagnosis [17]. The use of pharmacological agents with sedating properties can also impede assessment of conscious awareness in persons with DOC. Additionally, other medical conditions associated with acquired brain injury [18], such as sleep disturbance, communicating hydrocephalus and/or epilepsy, can interfere with the assessment of consciousness. See Boly and Maganti [19], in this issue, for more information on epilepsy.

Standardized and validated scales have been developed to help in optimizing the bedside assessment, such as the Coma Recovery Scale-Revised (CRS-R [20]) and the Full Outline of Unresponsiveness scale (FOUR [21]) (the latter designed for use in the intensive care setting). The use of specific assessment tools is also recommended to detect responsiveness. For instance, a mirror should be employed to evaluate visual pursuit [22], in both the horizontal and the vertical axes (see Thonnard et al. [23] in this issue). Similarly, the patient's own name should be used to assess auditory localization, as it is a self-referential stimulus, like their own face [24, 25]. The use of written commands are also advised in the case of absence of response to oral commands. One should also know that blinking in response to a threat is not necessarily a sign of consciousness [26] and as a blink reflex may be elicited due to corneal stimulation by air flow, one should approach with a finger and not an open palm on visual threat testing. Visual fixation cannot be definitively determined as a sign of consciousness, at least in patients with anoxia [27], whereas resistance to eye opening seems to be related to consciousness

[28]. Repeated assessments occurring over time with a pre-assessment arousal protocol are strongly encouraged as the level of consciousness fluctuates in most patients with DOC. Assessments should also be performed by trained professionals. Moreover, extended examinations are preferable as they allow one to detect higher level behaviours [29].

Even with the best possible clinical assessment, the level of consciousness can still be under-estimated. For example, when using electromyography in behaviourally unresponsive patients, it is possible to detect voluntary micro-movements that can be impossible to observe at the patient's bedside, as demonstrated by the study of Habbal et al. [30] in this issue. The increasing body of evidence from neuroimaging and electroencephalographic techniques has also served to highlight the problematic nature of behavioural assessment based on a patient's bedside level of responsiveness. Indeed, the absence of responsiveness does not necessarily imply the absence of awareness, as it will be discussed in the next sections.

Neuroimaging techniques and differential diagnosis

Attempts to objectively measure consciousness started with the use of fluorodeoxyglucose positron emission tomography (FDG-PET) to examine spontaneous brain metabolic activity at rest. Early PET studies showed a massive global decrease in brain metabolism in patients with UWS [31, 32]. Recovery of consciousness does not, however, always parallel an increase in global metabolism, but rather a restoration of functional connectivity in a widespread frontoparietal network encompassing the prefrontal and posteroparietal cortices including the precuneus and the thalami [33, 34]. More recently, studies have shown broad activity metabolic impairment in this bilateral frontoparietal network in patients in UWS, whereas patients in MCS have this network partially preserved [35, 36]. The internal network is more affected than the external network (related to the processing of environmental stimuli) in patients in MCS [35]. The internal network involves the precuneus and is thought to support spontaneous thinking, daydreaming and mind wandering. Moreover, patients in MCS+ showed preservation of language processing areas as compared to patients in MCS− [10]. ^{15}O-radiolabelled water-PET studies using passive auditory or noxious stimulations detected a disconnection between primary sensory areas and higher-order associative cortices in patients in UWS [37, 38], whereas patients in MCS showed relatively preserved functional connectivity between these brain areas [39, 40].

Functional magnetic resonance imaging (fMRI) may also examine spontaneous brain activity, measuring neuronal activation based on blood oxygen level dependent changes. Similar to the internal network observed in FDG-PET studies, the default mode network is a set of brain regions (encompassing the precuneus, the posterior parietal lobe and the medial prefrontal cortex), which is more active at rest than when individuals are involved in attention-demanding cognitive tasks [41]. Activity in this network is correlated with clinical levels of consciousness, likely reflecting some inner mental processes [42]. At the group level, patients in MCS present relatively preserved functional connectivity in the default mode network, whereas patients in UWS show little activity [43, 44]. Notably, the default mode network is absent in the case of brain death [44, 45], but seems surprisingly preserved in anaesthetized monkeys [46]. Beside this decreased connectivity seen in the default mode network, hyperconnectivity has also recently been detected in deep structures of the limbic system (orbitofrontal cortex, insula, hypothalamus and ventral tegmental area), with a greater hyperconnectivity in patients in UWS compared with patients in MCS [47]. Moreover, the brain's global functional connectivity seems greater in patients in MCS compared to UWS [48]. Another use of fMRI is through active paradigms, where patients are asked to perform mental tasks, such as motor or visuo-spatial imagery tasks. Interestingly, many fMRI studies have shown that some patients in UWS and MCS are able to perform mental tasks on request, as they elicit reproducible and specific brain activation patterns comparable to the responses of healthy, 'fully' conscious subjects [49–54].

Recent structural imaging developments have also provided new insight into patients with DOC. Diffusion tensor imaging (DTI) is an MRI technique measuring patterns of water molecule diffusion that reveals microscopic details about tissue architecture and, hence, the structural integrity of axon tracts in the brain. Interestingly, a potential axonal re-growth in the precuneus has been observed with this technique in a single case report of a patient who recovered verbal communication after 19 years in MCS [55]. Patients in MCS and UWS seem to differ significantly in sub-cortical white matter and in the thalamic regions, while no difference could be detected in the brainstem [56].

Electroencephalography (EEG) is also commonly used in patients with DOC to record their brain's electrical activity at the bedside. Like fMRI imagery tasks, EEG studies using active paradigms showed that some behaviourally unresponsive patients were, in fact, able to follow commands. More specifically, the amplitude of the electrical component was modulated when the patient's attention was focused on a task while undergoing a stimulus [57–60]. Studies using quantitative and connectivity EEG measures have also demonstrated the ability of this technique to differentiate between patients in MCS from those in UWS at the group level [61–66].

The aforementioned findings have increased our understanding of how brain lesions affect consciousness in patients with DOC. However, most of the studies have reported results at the group level in order to differentiate patients in UWS from MCS. The studies noted also often include only a small sample size or come from single case reports, which do not possess sufficient statistical significance to allow implementation at the individual patient level. Moreover, resting-state studies and studies using passive stimulation do not allow a strong claim to be made regarding residual brain activity as a sign of consciousness in the absence of any quantitative measurements. On the other hand, active paradigms using fMRI and EEG allow the detection of consciousness in some patients, but the absence of a positive result cannot be taken as proof of the absence of consciousness [51]. In this regard, it can be useful to combine different techniques in the evaluation of consciousness in a single patient. Indeed, if the result of multiple neuroimaging examinations converges on a positive or negative outcome, then greater confidence can be achieved in the assessment of the level of consciousness.

Combinations of different techniques to detect consciousness

To illustrate the utility of combining different techniques, but also to highlight the dissociation that can exist between behaviour and consciousness, this study presents two case reports of female patients from the multimodal diagnostic programme carried out at the University Hospital in Liège, Belgium. This programme for patients with DOC combines repeated behavioural assessments with an array of neuroimaging-based examinations, aiming at the detection of consciousness and possible means of communication. Both patients were admitted in 2010 with a clinical diagnosis of UWS. Lila, 41 years old, was status post an anoxic brain insult 4 years and 9 months prior to her admission to the centre. Mary, 35 years old, was status post an ischaemic stroke 6 years and 2 months prior to admission. Repeated behavioural assessments with the CRS-R confirmed the diagnosis of UWS in both patients. They showed no command following, no visual pursuit, no localization to noxious stimulation, no object localization or automatic motor response nor vocalizations. The only behavioural differences were the presence of auditory startle, abnormal posturing and sporadic fluctuation of arousal in Lila, whereas Mary showed no auditory response and flexion withdrawal after noxious stimulation. Clinical EEG in Lila showed a basic rhythm, with theta waves interspersed with long periods of slow waves. The EEG of Mary demonstrated moderate diffuse brain activity in the right hemisphere and severe diffuse brain activity in the left hemisphere, characterized by slow delta wave activity. The EEG of Mary also presented generalized angular rhythmic delta slow wave trains, predominant in the left hemisphere with an extension to the right hemisphere, corresponding to electrical sub-clinical seizures. The neuroimaging results showed striking differences between the two patients (Figure 2). The FDG-PET results demonstrated hypometabolic activity in the entire frontoparietal network and in the thalami of Lila; whereas, Mary had these same regions relatively preserved. Resting-state fMRI results showed no preservation of the default mode network in Lila, but a preserved one in Mary. Similarly, no brain activity compatible with the mental imagery tasks could be observed in Lila, while consistent brain activation was detected during the motor imagery task (‘imagine playing tennis’) and the spatial navigation imagery task (‘imagine walking into your house’) in Mary. Finally, diffusion tensor imaging results of Lila showed severe atrophy of the white matter tracts; whereas, in Mary these structures were relatively preserved (Figure 2). In conclusion, these examinations confirmed the diagnosis of UWS in Lila, but refuted Mary’s diagnosis of UWS. In Mary’s case, even if no conscious behaviour could be observed at the bedside, she seemed to have preserved awareness according to the neuroimaging assessments.

For this latter kind of patient, the term functional LIS has been proposed [67], as these patients are conscious (like the classically described patient with LIS) based on functional neuroimaging results (and, hence, the term functional). It may, however, be confusing as well as a misnomer to use this term, given the fact that LIS is not a DOC. Patients in LIS, by definition, are able to functionally communicate, which may not be the case in the aforementioned example. Similarly, the term functional MCS has been suggested to refer to UWS patients showing consistent brain activation during mental imagery fMRI [68], holding the same ambiguity and leading to unwarranted confusion. Patients in MCS are, by definition, unable to consistently communicate or use objects in a functional manner. The term non-behavioural MCS (abbreviated as MCS*) may be more convenient and clinically accurate, as it is not only more descriptive but also consistent with other MCS terminology (i.e. MCS+ and MCS−). In short, when the diagnosis is made with neuroimaging or EEG techniques, the use of an asterisk could be added to the diagnosis. If the neuroimaging data is more typical of a LIS pattern (i.e. preservation of the cerebral cortex with a lesion in the brainstem), one could refer to them as LIS*. If patients in MCS− show command following during ancillary testing, they could be diagnosed as in MCS+*. Another potential scenario can be a patient in MCS who shows atypically lower brain activity in neuroimaging. In this case, the patient is considered conscious at the bedside and the clinical assessment of consciousness is the one that should be taken into account. Neuroimaging results should, so far, only be considered in the case of absence of consciousness at the bedside and/or positive results (e.g. during active paradigms).

Other single case reports have also compared the results of different techniques to evaluate the level of consciousness of patients with DOC [69–71]. It is also possible to employ concurrent multimodal assessment of consciousness. For instance, transcranial magnetic stimulation (TMS, a non-invasive stimulation technique) combined simultaneously with electromyography has demonstrated impairment of cortical inhibitory circuits that are correlated with the level of consciousness in patients with DOC by stimulating the motor cortex and recording the subsequent activity in the controlateral hand muscle [72]. TMS can also be coupled with EEG to directly record the brain’s electrical activity after perturbation. By doing so, this technique has been shown to successfully differentiate between patients with UWS from MCS [73, 74]. For an extensive review about TMS-EEG, see Napolitani et al. [75] in this issue. The potential use of TMS in combination with fMRI to assess consciousness in patients with DOC is also reviewed by Guller and Giacino [76] in this issue of *Brain Injury*.

Before implementing these promising tools as part of a more regimented clinical routine for the diagnosis of consciousness, one needs to investigate the degree of diagnostic accuracy of these techniques at the individual level. Due to the nature of statistical procedures and the absence of a true measure of bedside consciousness, it is currently not possible to calculate the conventional measures of clinical utility (i.e. sensitivity and specificity). In this issue, Cruise et al. [77], nevertheless, propose some guidelines to follow to approximate these values and, hence, estimate the clinical utility of neuroimaging techniques in the detection of consciousness in patients with DOC.

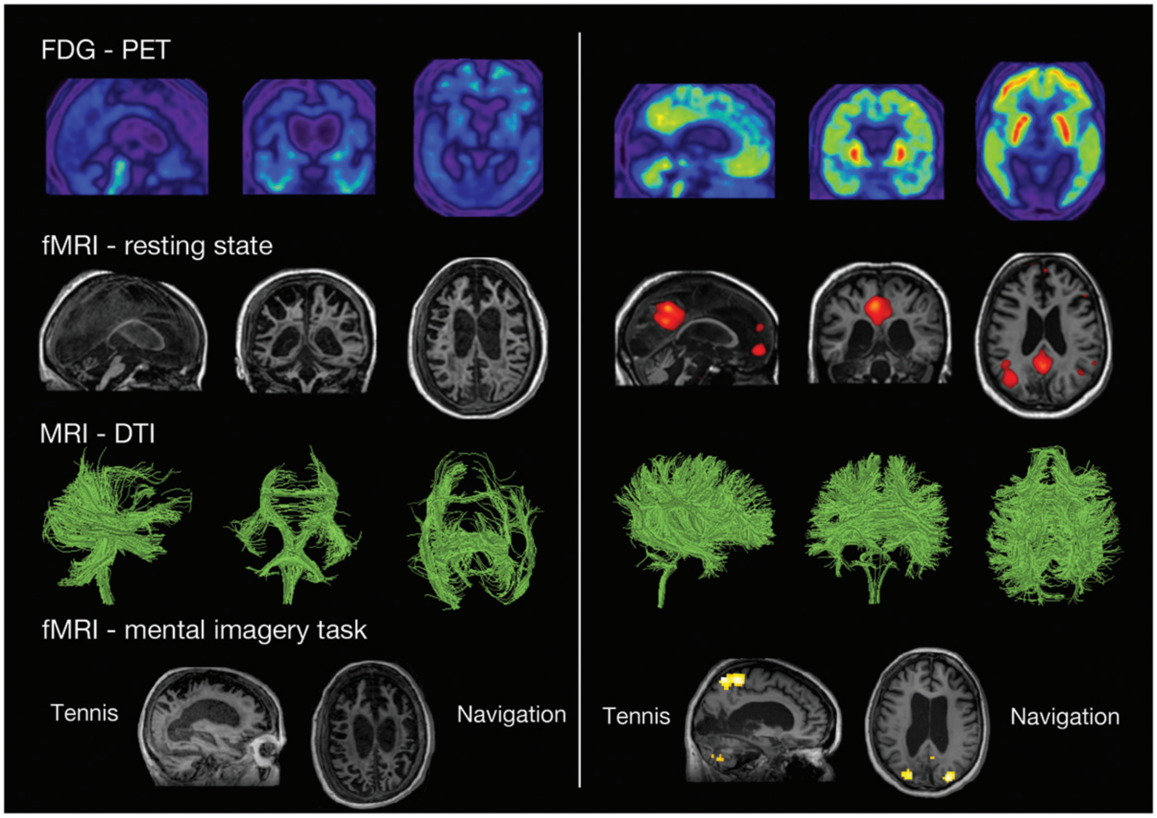

Figure 2. Combining neuroimaging techniques to assess residual consciousness. Two cases of patients diagnosed as unresponsive wakefulness syndrome (UWS) at the bedside. One patient, Lila, shows brain activity compatible with this diagnosis (on the left) while brain activity observed in the second case, Mary, is incompatible with the diagnosis of UWS (on the right). Combination of fluorodesoxyglucose-positron emission tomography (FDG-PET), resting-state functional magnetic resonance imaging (fMRI, here the default mode network), mental task fMRI (motor and spatial imagery tasks) and diffusion tensor imaging (DTI) techniques. From left to right, sagittal, coronal and axial view of the brain for each patient. Images based on analyses from [35, 43, 50] and unpublished work by F. Gomez.

Assessment of communication

Once consciousness has been detected in a patient, the next step is to investigate means of communication. Indeed, once it is known that patients retain some level of consciousness, the aim is to provide them a way to meaningfully interact with their environment. At the bedside, this can be done with standardized protocols searching for reliable responses to specific commands that could then be used for binary communication (e.g. to say 'yes' give a thumbs up, to say 'no' close your eyes) [78]. The method of facilitated communication has also been tried in several patients to help them communicate. This controversial procedure, the validity of which has been questioned, is based on a person, called the facilitator, who supports the hand or arm of the patient, while using a keyboard or other devices [79].

Communication can also be investigated with brain–computer interfaces (BCIs) using an active paradigm in fMRI and EEG [80]. As it has been seen previously, one can ask the patient to perform tasks on request and take advantage of the responses to facilitate functional communication. For instance, one patient in MCS has been able to accurately answer yes–no biographical questions using the original tennis-navigation paradigm [50]. This was repeated with another patient in MCS using, in this instance, the multiple-choice communication paradigms, but the information communicated was not correct [51]. Current paradigms use questions where the answers are known in order to verify the accuracy of the responses. BCIs are starting to be used more widely, especially with LIS patients, as well as becoming more diversified, as illustrated by the development of new real-time spelling device communication interfaces [81]. Advances in this field will undoubtedly help to improve the quality-of-life for some of these patients and their families.

Diagnostic implications

The differential diagnosis between patients in UWS and MCS has important implications regarding prognosis, treatment management and related ethical considerations. Concerning prognosis, patients in MCS have a better chance to recover than patients in UWS [82]. Late recovery of MCS patients is also more frequent, with up to 30% improving after more than a year following the loss of consciousness [83]. Interestingly, patients in MCS* (i.e. UWS patients who show consistent brain activation compatible with consciousness, see above) also have a higher chance of recovering than patients in UWS, as demonstrated in a recent study using mental imagery tasks [68]. In addition to the level of residual consciousness, other factors which determine the prognosis are the age (younger patients recover better than older patients [84]), the aetiology (traumatic brain injury has a better outcome than non-traumatic brain lesions [85]), the time since onset (the earlier, the better [86]) and the neuroimaging and electrophysiological testing findings [66, 87, 88]. The presence of pupillary light reflexes, auditory event-related potentials (N100, P300, N400, mismatch negativity component) and somatosensory evoked potentials hold prognostic value [89–96]. Conventional MRI [97, 98], DTI [99] and fMRI (using passive stimulation [87], resting-state default mode network connectivity [100] and mental imagery [68]) examinations have also predicted recovery of consciousness.

Accurate diagnosis of consciousness is also essential for the optimal medical care of patients with DOC. Indeed, depending on the diagnosis (and hence prognosis), the medical team may choose to use pharmacological treatments to potentially improve arousal and awareness, to use palliative medicines or, in some scenarios, withdraw therapeutic intervention. Amantadine (a dopaminergic agonist) and zolpidem (a non-benzodiazepine agonist of gamma-aminobutyric acid receptors) are among the most employed pharmacological treatments to promote recovery of consciousness in patients with DOC (for a review, see Gosseries et al. [101]). A recent multi-centre study reported a faster rate of recovery in patients with DOC after traumatic brain injury receiving amantadine daily for 4 weeks [102]. The paradoxical 'awakening' effect of zolpidem only affects a small proportion of the patients administered this agent ($\sim$7% [103, 104]) but, when it does, dramatic transient improvements have been observed after its administration (the effect lasting $\sim$4 hours) [105, 106]. Specialized early treatment including acute medical care and more than 90 minutes of daily rehabilitation are also likely to result in improved consciousness in patients with DOC [107].

Perception of pain is another problem related to the diagnosis, as discussed by Chatelle et al. [108] in this issue and elsewhere [109]. Indeed, patients in MCS are more likely to experience pain (notably due to the presence of spasticity [110]) and may benefit from analgesic treatment aimed at improving their quality-of-life, decreasing autonomic responses to pain and optimizing comfort in cases of palliative care [39, 111, 112]. As noted by several authorities, when the level of pain awareness is in doubt, it is always better to prophylax for pain accordingly [109, 113].

Similarly, the question about the appropriateness of withdrawing life-sustaining medical treatment depending on the presence or absence of consciousness remains a hotly debated topic. Legal precedence, in several countries, has established the right of the medical team to withdraw artificial nutrition and hydration from patients in UWS [114, 115], but not in MCS [116, 117]. One can, therefore, see through these examples the urgent need to precisely diagnose patients with DOC as the knowledge of patients otherwise perceived as unconscious fundamentally alters their ethical, legal and therapeutic standing.

Issues related to the management of patients with disorders of consciousness

Patients with DOC are functionally completely dependent on others for care and sustenance. Both family and healthcare professionals play a key role in patient care, because they are the ones making the decisions. The decisions should be based on the patients' best interest and in accordance with the patient's desires as those may have been conveyed, legally or otherwise. Caregivers are, however, often influenced by medical, religious and/or moral assumptions [118] and their attitude can differ according to the diagnosis and the point of view [119]. For example, in a European survey, 66% of healthcare professionals agreed to withdraw treatment in cases of chronic UWS (>1 year), but only 28% agreed in cases of chronic MCS. However, 82% and 67% of these responders wished not to be kept alive in UWS and in MCS, respectively. Demertzi et al. [120] report in this issue the attitudes towards patients in LIS.

Families of patients who are in DOC are perhaps the ones who endure the most difficult situation. Family members and significant others are highly subject to distress, anxiety and depression [121–123]. Beside the emotional aspects, they also need to deal with medical information, manage the cost of medical care and consider therapeutic and/or end-of-life options. Developing coping strategies such as active coping, instrumental support, planning and acceptance is crucial to improve the quality-of-life of caregivers [124]. Families who receive comprehensive education and hands on training with follow-up support may be more likely to provide better care to their loved ones [107]. Likewise, healthcare workers managing patients with DOC are also subject to burnout, especially in the nursing profession and to a large degree dependent on the number of direct care time spent with such patients [125, 126]. Preventing burnout among caregivers and enhancing the well-being of professionals who suffer such burnout should be an integral part of promoting more efficient medical care for patients with DOC and also benefit caretakers, whether family, significant others or direct care staff.

Conclusions

Recent advances regarding patients with DOC subsequent to coma have been reviewed in this article. New findings have led to the re-definition of clinical criteria for diagnosis and bring new knowledge about patient recovery, prognosis and therapeutic interventions. Differentiating between patients in UWS and MCS still represents a major clinical, ethical and medico-legal challenge. While bedside behavioural assessment remains the current clinical standard for detecting awareness, it cannot stand alone any longer as the sole differential diagnostic tool in patients with DOC for detecting the presence of the same. A diagnostic protocol combining behavioural scales and neuroimaging techniques was proposed. In cases of dissociation between behavioural and ancillary testing, especially in the case of patients who are diagnosed as being UWS by bedside testing but then diagnosed MCS with neuroimaging techniques, a proposed label of 'non-behavioural MCS' was suggested (MCS* or LIS* if brain activity is more compatible with a LIS) to give a more accurate diagnosis and, therefore, prognosis. More neuroimaging research is, however, needed to reach the single-subject level diagnosis and to address the sensitivity and specificity of each single or combined technique, which is of absolute necessity to be part of a diagnostic process in the standardized clinical work-up of these patients.

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Declaration of interest

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References

1. Plum F, Posner JB. The diagnosis of stupor and coma. In: Davis FA, editor. Zeitschrift für die gesamte Neurologie und Psychiatrie. Philadelphia, PA: Davis; 1983.
2. Kretschmer E. Das apallische syndrom. Z ges Neurol Psychiat 1940;169:576–579.
3. Calvet J, Coll J. Meningitis of sinusoid origin with the form of coma vigil. Review of Otoneuroophtalmology 1959;31:443–445.
4. The Multi-Society Task Force on PVS. Medical aspects of the persistent vegetative state (1). New England Journal of Medicine 1994;330:1499–1508.
5. Laureys S, Celesia GG, Cohadon F, Lavrijsen J, Leon-Carrion J, Sannita WG, Sazbon L, Schmutzhard E, von Wild KR, Zeman A, et al. Unresponsive wakefulness syndrome: A new name for the vegetative state or apallic syndrome. BMC Medicine 2010;8:68.
6. Gosseries O, Bruno MA, Chatelle C, Vanhaudenhuyse A, Schnakers C, Soddu A, Laureys S. Disorders of consciousness: What's in a name? Neurorehabilitation 2011;28:3–14.
7. von Wild K, Laureys ST, Gerstenbrand F, Dolce G, Onose G. The vegetative state-a syndrome in search of a name. Journal of Medicine & Life 2012;5:3–15.
8. Machado C, Estevez M, Carrick FR, Rodriguez R, Perez-Nellar J, Chinchilla M, Machado Y, Perez-Hoz G, Carballo M, Fleitas M, et al. Vegetative state is a pejorative term. Neurorehabilitation 2012;31:345–347.
9. Giacino JT, Ashwal S, Childs N, Cranford R, Jennett B, Katz DI, Kelly JP, Rosenberg JH, Whyte J, Zafonte RD, et al. The minimally conscious state: Definition and diagnostic criteria. Neurology 2002; 58:349–353.
10. Bruno MA, Majerus S, Boly M, Vanhaudenhuyse A, Schnakers C, Gosseries O, Boveroux P, Kirsch M, Demertzi A, Bernard C, et al. Functional neuroanatomy underlying the clinical subcategorization of minimally conscious state patients. Journal of Neurology 2012; 259:1087–1098.
11. Kotchoubey B, Vogel D, Lang S, Muller F. What kind of consciousness is minimal? Brain Inj 2014;28(9):1156–1163.
12. Gosseries O, Bruno MA, Vanhaudenhuyse A, Laureys S, Schnakers C. Consciousness in the locked-in syndrome. In: Laureys S, Tononi G, editors. The neurology of consciousness: Cognitive neuroscience and neuropathology. Oxford: Elsevier; 2009. p 191–203.
13. Feldman MH. Physiological observations in a chronic case of ''locked-in'' syndrome. Neurology 1971;21:459–478.
14. Bauer G, Gerstenbrand F, Rumpl E. Varieties of the locked-in syndrome. Journal of Neurology 1979;221:77–91.
15. Schnakers C, Vanhaudenhuyse A, Giacino JT, Ventura M, Boly M, Majerus S, Moonen G, Laureys S. Diagnostic accuracy of the vegetative and minimally conscious state: Clinical consensus versus standardized neurobehavioral assessment. BMC Neurology 2009;9:35.
16. Gill-Thwaites H. Lotteries, loopholes and luck: Misdiagnosis in the vegetative state patient. Brain Injury 2006;20:1321–1328.
17. Schnakers C. Clinical assessment of patients with disorders of consciousness. Archives Italiennes de Biologie 2012; 150:36–43.
18. Whyte J, Nordenbo AM, Kalmar K, Merges B, Bagiella E, Chang H, Yablon S, Cho S, Hammond F, Khademi A, et al. Medical complications during inpatient rehabilitation among patients with traumatic disorders of consciousness. Archives of Physical Medicine & Rehabilitation 2013;94(10):1877–83.
19. Boly M, Maganti R. Monitoring epilepsy in the intensive care unit: Current state of facts, and potential interest of high density EEG. Brain Inj 2014;28(9):1151–1155.
20. Giacino JT, Kalmar K, Whyte J. The JFK coma recovery scale-revised: Measurement characteristics and diagnostic utility. Archives of Physical Medicine & Rehabilitation 2004;85: 2020–2029.
21. Wijdicks EF, Bamlet WR, Maramattom BV, Manno EM, McClelland RL. Validation of a new coma scale: The FOUR score. Annals of Neurology 2005;58:585–593.
22. Vanhaudenhuyse A, Schnakers C, Bredart S, Laureys S. Assessment of visual pursuit in post-comatose states: Use a mirror. Journal of Neurology, Neurosurgery & Psychiatry 2008; 79:223.
23. Thonnard M, Wannez S, Keen S, Brédart S, Bruno M-A, Gosseries O, Demertzi A, Thibaut A, Chatelle C, Charland-Verville V, et al. Detection of visual pursuit in patients in minimally conscious state: A matter of stimuli and visual plane? Brain Inj 2014;28(9): 1164–1170.
24. Cheng L, Gosseries O, Ying L, Hu X, Yu D, Gao H, He M, Schnakers C, Laureys S, Di H. Assessment of localisation to auditory stimulation in post-comatose states: Use the patient's own name. BMC Neurology 2013;13:27.
25. Laureys S, Perrin F, Bredart S. Self-consciousness in non-communicative patients. Consciousness & Cognition 2007;16:722–741.
26. Vanhaudenhuyse A, Giacino J, Schnakers C, Kalmar K, Smart C, Bruno MA, Gosseries O, Moonen G, Laureys S. Blink to visual threat does not herald consciousness in the vegetative state. Neurology 2008;71:1374–1375.
27. Bruno MA, Vanhaudenhuyse A, Schnakers C, Boly M, Gosseries O, Demertzi A, Majerus S, Moonen G, Hustinx R, Laureys S. Visual fixation in the vegetative state: An observational case series PET study. BMC Neurology 2010;10:35.
28. van Ommen J, Gosseries O, Bruno MA, Vanhaudenhuyse A, Thibaut A, Charland-Verville V, Heine L, Laureys S. Resistance to eye opening in patients with disorders of consciousness: Reflex or voluntary? In: Neurology J, editor. European Neurological Society Annual Meeting. Volume 260. Barcelona. Spain; 2013.
29. Godbolt AK, Stenson S, Winberg M, Tengvar C. Disorders of consciousness: Preliminary data supports added value of extended behavioural assessment. Brain Injury 2012;26:188–193.
30. Habbal D, Gosseries O, Noirhomme Q, Renaux J, Lesenfants D, Bekinschtein T, Majerus S, Laureys S, Schnakers C. Volitional electromyographic responses in disorders of consciousness. Brain Inj, 2014; 28(9):1171–1179.
31. Tommasino C, Grana C, Lucignani G, Torri G, Fazio F. Regional cerebral metabolism of glucose in comatose and vegetative state patients. Journal of Neurosurgical Anesthesiology 1995;7:109–116.
32. Rudolf J, Ghaemi M, Haupt WF, Szelies B, Heiss WD. Cerebral glucose metabolism in acute and persistent vegetative state. Journal of Neurosurgical Anesthesiology 1999;11:17–24.
33. Laureys S, Owen AM, Schiff ND. Brain function in coma, vegetative state, and related disorders. Lancet Neurology 2004;3: 537–546.
34. Laureys S, Faymonville ME, Luxen A, Lamy M, Franck G, Maquet P. Restoration of thalamocortical connectivity after recovery from persistent vegetative state. Lancet 2000;355:1790–1791.
35. Thibaut A, Bruno MA, Chatelle C, Gosseries O, Vanhaudenhuyse A, Demertzi A, Schnakers C, Thonnard M, Charland-Verville V, Bernard C, et al. Metabolic activity in external and internal awareness networks in severely brain-damaged patients. Journal of Rehabilitation Medicine 2012;44:487–494.
36. Kim YW, Kim HS, An YS. Brain metabolism in patients with vegetative state after post-resuscitated hypoxic-ischemic brain injury: Statistical parametric mapping analysis of F-18

fluorodeoxyglucose positron emission tomography. Chinese Medical Journal (England) 2013;126:888–894.
37. Laureys S, Faymonville ME, Degueldre C, Fiore GD, Damas P, Lambermont B, Janssens N, Aerts J, Franck G, Luxen A, et al. Auditory processing in the vegetative state. Brain 2000;123: 1589–1601.
38. Laureys S, Faymonville ME, Peigneux P, Damas P, Lambermont B, Del Fiore G, Degueldre C, Aerts J, Luxen A, Franck G, et al. Cortical processing of noxious somatosensory stimuli in the persistent vegetative state. Neuroimage 2002;17:732–741.
39. Boly M, Faymonville ME, Schnakers C, Peigneux P, Lambermont B, Phillips C, Lancellotti P, Luxen A, Lamy M, Moonen G, et al. Perception of pain in the minimally conscious state with PET activation: An observational study. Lancet Neurology 2008;7:1013–1020.
40. Boly M, Faymonville ME, Peigneux P, Lambermont B, Damas P, Del Fiore G, Degueldre C, Franck G, Luxen A, Lamy M, et al. Auditory processing in severely brain injured patients: Differences between the minimally conscious state and the persistent vegetative state. Archives of Neurology 2004;61:233–238.
41. Vanhaudenhuyse A, Demertzi A, Schabus M, Noirhomme Q, Bredart S, Boly M, Phillips C, Soddu A, Luxen A, Moonen G, et al. Two distinct neuronal networks mediate the awareness of environment and of self. Journal of Cognitive Neuroscience 2011;23: 570–578.
42. Vanhaudenhuyse V, Noirhomme Q, Tshibanda LJ, Bruno MA, Boveroux P, Schnakers C, Soddu A, Perlbarg V, Ledoux D, Brichant JF, et al. Default network connectivity reflects the level of consciousness in non-communicative brain-damaged patients. Brain 2010;133:161–171.
43. Soddu A, Vanhaudenhuyse A, Bahri M, Bruno MA, Boly M, Demertzi A, Tshibanda J, Phillips C, Stanziano M, Ovadia-Caro S, et al. Identifying the default-mode component in spatial IC analyses of patients with disorders of consciousness. Human Brain Mapping 2011;33:778–796.
44. Soddu A, Vanhaudenhuyse A, Demertzi A, Bruno MA, Tshibanda L, Di H, Boly M, Papa M, Laureys S, Noirhomme Q. Resting state activity in patients with disorders of consciousness. Functional Neurology 2011;26:37–43.
45. Boly M, Tshibanda L, Vanhaudenhuyse A, Noirhomme Q, Schnakers C, Ledoux D, Boveroux P, Garweg C, Lambermont B, Phillips C, et al. Functional connectivity in the default network during resting state is preserved in a vegetative but not in a brain dead patient. Human Brain Mapping 2009;30:2393–2400.
46. Vincent J, Patel G, Fox M, Snyder A, Baker J, Van Essen D, Zempel J, Snyder L, Corbetta M, Raichle M. Intrinsic functional architecture in the anaesthetized monkey brain. Nature 2007;447: 83–86.
47. Di Perri C, Bastianello S, Bartsch A, Pistarini C, Maggioni G, Magrassi L, Imberti R, Pichiecchio A, Laureys S, Di Salle F. Limbic hyperconnectivity in the vegetative state. Neurology 2013; 81:1417–1424.
48. Kotchoubey B, Merz S, Lang S, Markl A, Muller F, Yu T, Schwarzbauer C. Global functional connectivity reveals highly significant differences between the vegetative and the minimally conscious state. Journal of Neurology 2013;260:975–983.
49. Owen AM, Coleman MR, Boly M, Davis MH, Laureys S, Pickard JD. Detecting awareness in the vegetative state. Science (New York, N.Y) 2006;313:1402.
50. Monti M, Vanhaudenhuyse A, Coleman MR, Boly M, Pickard JD, Tshibanda L, Owen AM, Laureys S. Willful modulation of brain activity in disorders of consciousness. New England Journal of Medicine 2010;362:579–589.
51. Bardin JC, Fins JJ, Katz DI, Hersh J, Heier LA, Tabelow K, Dyke JP, Ballon DJ, Schiff ND, Voss HU. Dissociations between behavioural and functional magnetic resonance imaging-based evaluations of cognitive function after brain injury. Brain 2011; 134:769–782.
52. Rodriguez Moreno D, Schiff ND, Giacino JT, Kalmar K, Hirsch J. A network approach to assessing cognition in disorders of consciousness. Neurology 2010;75:1871–1878.
53. Bekinschtein TA, Manes FF, Villarreal M, Owen AM, Della-Maggiore V. Functional imaging reveals movement preparatory activity in the vegetative state. Frontiers in Human Neuroscience 2011;5:5.
54. Monti MM, Pickard JD, Owen AM. Visual cognition in disorders of consciousness: From V1 to top-down attention. Human Brain Mapping 2013;34:1245–1253.
55. Voss HU, Uluc AM, Dyke JP, Watts R, Kobylarz EJ, McCandliss BD, Heier LA, Beattie BJ, Hamacher KA, Vallabhajosula S, et al. Possible axonal regrowth in late recovery from the minimally conscious state. Journal of Clinical Investigation 2006;116: 2005–2011.
56. Fernandez-Espejo D, Bekinschtein TA, Monti MM, Pickard JD, Junque C, Coleman MR, Owen AM. Diffusion weighted imaging distinguishes the vegetative state from the minimally conscious state. Neuroimage 2011;54:103–112.
57. Schnakers C, Perrin F, Schabus M, Majerus S, Ledoux D, Damas P, Boly M, Vanhaudenhuyse A, Bruno MA, Moonen G, et al. Voluntary brain processing in disorders of consciousness. Neurology 2008;71:1614–1620.
58. Schnakers C, Perrin F, Schabus M, Hustinx R, Majerus S, Moonen G, Boly M, Vanhaudenhuyse A, Bruno MA, Laureys S. Detecting consciousness in a total locked-in syndrome: An active event-related paradigm. Neurocase 2009;15:271–277.
59. Cruse D, Chennu S, Chatelle C, Bekinschtein TA, Fernandez-Espejo D, Pickard JD, Laureys S, Owen AM. Bedside detection of awareness in the vegetative state: A cohort study. Lancet 2011;378: 2088–2094.
60. Lule D, Noirhomme Q, Kleih SC, Chatelle C, Halder S, Demertzi A, Bruno MA, Gosseries O, Vanhaudenhuyse A, Schnakers C, et al. Probing command following in patients with disorders of consciousness using a brain-computer interface. Clinical Neurophysiology 2013;124:101–106.
61. Lehembre R, Bruno MA, Vanhaudenhuyse A, Chatelle C, Cologan V, Leclercq Y, Soddu A, Macq B, Laureys S, Noirhomme Q. Resting state EEG study of comatose patients: A connectivity and frequency analysis to find differences between vegetative and minimally conscious states. Functional Neurology 2012;27:41–47.
62. Gosseries O, Schnakers C, Ledoux D, Vanhaudenhuyse A, Bruno MA, Demertzi A, Noirhomme Q, Lehembre R, Damas P, Goldman S, et al. Automated EEG entropy measurements in coma, vegetative state/unresponsive wakefulness syndrome and minimally conscious state. Functional Neurology 2011;26:25–30.
63. Boly M, Garrido MI, Gosseries O, Bruno MA, Boveroux P, Schnakers C, Massimini M, Litvak V, Laureys S, Friston K. Preserved feedforward but impaired top-down processes in the vegetative state. Science (New York, N.Y) 2011;332:858–862.
64. Wu DY, Cai G, Zorowitz RD, Yuan Y, Wang J, Song WQ. Measuring interconnection of the residual cortical functional islands in persistent vegetative state and minimal conscious state with EEG nonlinear analysis. Clinical Neurophysiology 2011;122: 1956–1966.
65. Fingelkurts AA, Bagnato S, Boccagni C, Galardi G. Dissociation of vegetative and minimally conscious patients based on brain operational architectonics: Factor of etiology. Clinical EEG & Neuroscience 2013;44:209–220.
66. Schnakers C, Ledoux D, Majerus S, Damas P, Damas F, Lambermont B, Lamy M, Boly M, Vanhaudenhuyse A, Moonen G, et al. Diagnostic and prognostic use of bispectral index in coma, vegetative state and related disorders. Brain Injury 2008;22: 926–931.
67. Bruno MA, Vanhaudenhuyse A, Thibaut A, Moonen G, Laureys S. From unresponsive wakefulness to minimally conscious PLUS and functional locked-in syndromes: Recent advances in our understanding of disorders of consciousness. Journal of Neurology 2011; 258:1373–1384.
68. Vogel D, Markl A, Yu T, Kotchoubey B, Lang S, Muller F. Can mental imagery functional magnetic resonance imaging predict recovery in patients with disorders of consciousness? Archives of Physical Medicine & Rehabilitation 2013;94:1891–1898.
69. Bruno MA, Fernández-Espejo D, Lehembre R, Tshibanda L, Vanhaudenhuyse A, Gosseries O, Lommers E, Noirhomme Q, Boly M, Napolitani M, et al. Multi-modal neuroimaging in patients with disorders of consciousness showing ‘‘functional hemispherectomy’’. Progress in Brain Research 2011;193:323–333.
70. Fernandez-Espejo D, Junque C, Cruse D, Bernabeu M, Roig-Rovira T, Fábregas N, Rivas E, Mercader J. Combination of diffusion tensor and functional magnetic resonance imaging during recovery from the vegetative state. BMC Neurology 2010;10:77.

71. Coleman MR, Bekinschtein TA, Monti MM, Owen AM, Pickard JD. A multimodal approach to the assessment of patients with disorders of consciousness. Progress in Brain Research 2009;177: 231–248.
72. Lapitskaya N, Gosseries O, De Pasqua V, Pedersen AR, Nielsen JF, de Noordhout AM, Laureys S. Abnormal corticospinal excitability in patients with disorders of consciousness. Brain Stimulation 2013; 6:590–597.
73. Rosanova M, Gosseries O, Casarotto S, Boly M, Casali AG, Bruno MA, Mariotti M, Boveroux P, Tononi G, Laureys S, et al. Recovery of cortical effective connectivity and recovery of consciousness in vegetative patients. Brain 2012;135:1308–1320.
74. Ragazzoni A, Pirulli C, Veniero D, Feurra M, Cincotta M, Giovannelli F, Chiaramonti R, Lino M, Rossi S, C M. Vegetative versus minimally conscious states: A study using TMS-EEG, sensory and event-related potentials. PLoS One 2013;8:e57069.
75. Napolitani M, Bodart O, Canal P, Seregni F, Laureys S, Rosanova M, Massimini M, Gosseries O. Transcranial magnetic stimulation combined with high-density EEG in altered states of consciousness. Brain Inj 2014;28(9):1180–1189.
76. Guller Y, Giacino J. Concurrent TMS-fMRI: Potential applications to traumatic brain injury and disorders of consciousness. Brain Inj 2014;28(9):1190–1196.
77. Cruise D, Gantner I, Soddu A, Owen A. Lies, damned lies, and diagnoses: Estimating the clinical utility of assessments of covert awareness in the vegetative state. Brain Inj 2014;28(9):1197–1201.
78. Whyte J, DiPasquale M, Vaccaro M. Assessment of command-following in minimally conscious brain injured patients. Archives of Physical Medicine & Rehabilitation 1999;80:653–660.
79. Bruno M-A, Schnakers C, Vanhaudenhuyse A, Moonen G, Laureys S. Facilitated communication in severe traumatic brain injury. In: Journal of Neurology, editor. European Neurological Society Annual Meeting. Berlin, Germany; 2010.
80. Naci L, Monti MM, Cruse D, Kubler A, Sorger B, Goebel R, Kotchoubey B, Owen AM. Brain-computer interfaces for communication with nonresponsive patients. Annals of Neurology 2012; 72:312–323.
81. Sorger B, Reithler J, Dahmen B, Goebel R. A real-time fMRI-based spelling device immediately enabling robust motor-independent communication. Current Biology 2012;22:1333–1338.
82. Noe E, Olaya J, Navarro MD, Noguera P, Colomer C, Garcia-Panach J, Rivero S, Moliner B, Ferri J. Behavioral recovery in disorders of consciousness: A prospective study with the spanish version of the coma recovery scale-revised. Archives of Physical Medicine & Rehabilitation 2012;93:428–433.
83. Luauté J, Maucort-Boulch D, Tell L, Quelard F, Sarraf T, Iwaz J, Boisson D, Fischer C. Long-term outcomes of chronic minimally conscious and vegetative states. Neurology 2010;75: 246–252.
84. Howell K, Grill E, Klein AM, Straube A, Bender A. Rehabilitation outcome of anoxic-ischaemic encephalopathy survivors with prolonged disorders of consciousness. Resuscitation 2013;84: 1409–1415.
85. The Multi-Society Task Force on PVS. Medical aspects of the persistent vegetative state (2). New England Journal of Medicine 1994;330:1572–1579.
86. Whyte J, Gosseries O, Chervoneva I, DiPasquale MC, Giacino J, Kalmar K, Katz DI, Novak P, Long D, Childs N, et al. Predictors of short-term outcome in brain-injured patients with disorders of consciousness. Progress in Brain Research 2009;177:63–72.
87. Di H, Boly M, Weng X, Ledoux D, Laureys S. Neuroimaging activation studies in the vegetative state: Predictors of recovery? Clinical Medicine 2008;8:502–507.
88. Kotchoubey B. Event-related potentials predict the outcome of the vegetative state. Clinical Neurophysiology 2007;118:477–479.
89. Luaute J, Fischer C, Adeleine P, Morlet D, Tell L, Boisson D. Late auditory and event-related potentials can be useful to predict good functional outcome after coma. Archives of Physical Medicine & Rehabilitation 2005;86:917–923.
90. Daltrozzo J, Wioland N, Mutschler V, Kotchoubey B. Predicting coma and other low responsive patients outcome using event-related brain potentials: A meta-analysis. Clinical Neurophysiology 2007;118:606–614.
91. Fischer C, Luaute J, Nemoz C, Morlet D, Kirkorian G, Mauguiere F. Improved prediction of awakening or nonawakening from severe anoxic coma using tree-based classification analysis. Critical Care Medicine 2006;34:1520–1524.
92. Qin P, Di H, Yan X, Yu S, Yu D, Laureys S, Weng X. Mismatch negativity to the patient's own name in chronic disorders of consciousness. Neuroscience Letters 2008; 448:24–28.
93. Steppacher I, Eickhoff S, Jordanov T, Kaps M, Witzke W, Kissler J. N400 predicts recovery from disorders of consciousness. Annals of Neurology 2013;73:594–602.
94. Cavinato M, Freo U, Ori C, Zorzi M, Tonin P, Piccione F, Merico A. Post-acute P300 predicts recovery of consciousness from traumatic vegetative state. Brain Injury 2009;23:973–980.
95. Estraneo A, Moretta P, Loreto V, Lanzillo B, Cozzolino A, Saltalamacchia A, Lullo F, Santoro L, Trojano L. Predictors of recovery of responsiveness in prolonged anoxic vegetative state. Neurology 2013;80:464–470.
96. Xu W, Jiang G, Chen Y, Wang X, Jiang X. Prediction of minimally conscious state with somatosensory evoked potentials in long-term unconscious patients after traumatic brain injury. Journal of Trauma and Acute Care Surgery 2012;72:1024–1029.
97. Weiss N, Galanaud D, Carpentier A, Tezenas de Montcel S, Naccache L, Coriat P, Puybasset L. A combined clinical and MRI approach for outcome assessment of traumatic head injured comatose patients. Journal of Neurology 2008;255:217–223.
98. Paterakis K, Karantanas AH, Komnos A, Volikas Z. Outcome of patients with diffuse axonal injury: The significance and prognostic value of MRI in the acute phase. Journal of Trauma 2000; 49:1071–1075.
99. Perlbarg V, Puybasset L, Tollard E, Lehericy S, Benali H, Galanaud D. Relation between brain lesion location and clinical outcome in patients with severe traumatic brain injury: A diffusion tensor imaging study using voxel-based approaches. Human Brain Mapping 2009;30:3924–3933.
100. Norton L, Hutchison RM, Young GB, Lee DH, Sharpe MD, Mirsattari SM. Disruptions of functional connectivity in the default mode network of comatose patients. Neurology 2012;78: 175–181.
101. Gosseries O, Charland-Verville V, Thonnard M, Bodart O, Laureys S, Demertzi A. Amantadine, apomorphine and zolpidem in the treatment of disorders of consciousness. Curr Pharm Des. 2014;20(26):4167–4184.
102. Giacino JT, Whyte J, Bagiella E, Kalmar K, Childs N, Khademi A, Eifert B, Long D, Katz DI, Cho S, et al. Placebo-controlled trial of amantadine for severe traumatic brain injury. New England Journal of Medicine 2012;366:819–826.
103. Whyte J, Myers R. Incidence of clinically significant responses to zolpidem among patients with disorders of consciousness: A preliminary placebo controlled trial. American Journal of Physical Medicine & Rehabilitation 2009;88:410–418.
104. Thonnard M, Gosseries O, Demertzi A, Lugo Z, Vanhaudenhuyse A, Bruno MA, Chatelle C, Thibaut T, Charland-Verville V, Habbal D, et al. Effect of zolpidem in chronic disorders of consciousness: A prospective open label study. Funct Neurol. 2013 Oct-Dec;28(4):259–64.
105. Clauss RP, Guldenpfennig WM, Nel HW, Sathekge MM, Venkannagari RR. Extraordinary arousal from semi-comatose state on zolpidem. A case report. South African Medical Journal 2000;90:68–72.
106. Brefel-Courbon C, Payoux P, Ory F, Sommet A, Slaoui T, Raboyeau G, Lemesle B, Puel M, Montastruc JL, Demonet JF, et al. Clinical and imaging evidence of zolpidem effect in hypoxic encephalopathy. Annals of Neurology 2007;62:102–105.
107. Seel RT, Douglas J, Dennison AC, Heaner S, Farris K, Rogers C. Specialized early treatment for persons with disorders of consciousness: Program components and outcomes. Archives of Physical Medicine & Rehabilitation 2013;94:1908–1923.
108. Chatelle C, Thibaut A, Whyte J, De Val M, Laureys S, Schnakers C. Pain issue in disorders of consciousness. Brain Inj 2014;28(9):1202–1208.
109. Schnakers C, Zasler ND. Pain assessment and management in disorders of consciousness. Current Opinion in Neurology 2007; 20:620–626.
110. Thibaut A, Chatelle C, Ziegler E, Bruno MA, Laureys S, Gosseries O. Spasticity after stroke: Physiology, assessment and treatment. Brain Injury 2013;27:1093–1105.

111. Chatelle C, Majerus S, Whyte J, Laureys S, Schnakers C. A sensitive scale to assess nociceptive pain in patients with disorders of consciousness. Journal of Neurology, Neurosurgery & Psychiatry 2012;83:1233–1237.
112. Deschepper R, Laureys S, Hachimi-Idrissi S, Poelaert J, Distelmans W, Bilsen J. Palliative sedation: Why we should be more concerned about the risks that patients experience an uncomfortable death. Pain 2013;154:1505–1508.
113. Zasler ND, Martelli MF, Nicholson K. Post-traumatic pain disorders: Medical assessment and management. In: Zasler N, Katz D, Zafonte R, editors. Brain injury medicine: principles and practice. 2nd ed. New York: Demos publishers; 2013. p 954–973.
114. Gevers S. Withdrawing life support from patients in a persistent vegetative state: The law in the Netherlands. European Journal of Health Law 2005;12:347–355.
115. Ferreira N. Latest legal and social developments in the euthanasia debate: Bad moral consciences and political unrest. Medical Law 2007;26:387–407.
116. Chan TK, Tipoe GL. Should we continue treatment for M? The benefits of living. J Med Ethics 2014 Feb;40(2):131–3.
117. Manning J. Withdrawal of life-sustaining treatment from a patient in a minimally conscious state. Journal of Law & Medicine 2012; 19:430–435.
118. Kuehlmeyer K, Borasio GD, Jox RJ. How family caregivers' medical and moral assumptions influence decision making for patients in the vegetative state: A qualitative interview study. Journal of Medical Ethics 2012;38:332–337.
119. Demertzi A, Ledoux D, Bruno MA, Vanhaudenhuyse A, Gosseries O, Soddu A, Schnakers C, Moonen G, Laureys S. Attitudes towards end-of-life issues in disorders of consciousness: A European survey. Journal of Neurology 2011;258:1058–1065.
120. Demertzi A, Jox R, Racine E, Laureys S. Attitudes and neuroethics on locked-in syndrome. Brain Inj 2014;28(9):1209–1215.
121. Cruzado JA, Elvira de la Morena MJ. Coping and distress in caregivers of patients with disorders of consciousness. Brain Injury 2013;27:793–798.
122. Leonardi M, Giovannetti AM, Pagani M, Raggi A, Sattin D. Burden and needs of 487 caregivers of patients in vegetative state and in minimally conscious state: Results from a national study. Brain Injury 2012;26:1201–1210.
123. Pagani M, Giovannetti AM, Covelli V, Sattin D, Raggi A, Leonardi M. Physical and mental health, anxiety and depressive symptoms in caregivers of patients in vegetative state and minimally conscious state. Clin Psychol Psychother 2014; in press.
124. de la Morena MJ, Cruzado JA. Caregivers of patients with disorders of consciousness: Coping and prolonged grief. Acta Neurologica Scandinavica 2013;127:413–418.
125. Gosseries O, Demertzi A, Ledoux D, Bruno MA, Vanhaudenhuyse A, Thibaut A, Laureys S, Schnakers C. Burnout in healthcare workers managing chronic patients with disorders of consciousness. Brain Injury 2012;26:1493–1499.
126. Matilde L, Marco P, Mara GA, Alberto R. Burnout in healthcare professionals working with patients with disorders of consciousness. Work 2013;45:349–356.