EXPERT REVIEWS

Is there anybody in there? Detecting awareness in disorders of consciousness

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The bedside detection of awareness in disorders of consciousness (DOC) caused by acquired brain injury is not an easy task. For this reason, differential diagnosis using neuroimaging and electrophysiological tools in search for objective markers of consciousness is being employed. However, such tools cannot be considered as diagnostic *per se*, but as assistants to the clinical evaluation, which, at present, remains the gold standard. Regarding therapeutic management in DOC, no evidence-based recommendations can be made in favor of a specific treatment. The present review summarizes clinical and paraclinical studies that have been conducted with neuroimaging and electrophysiological techniques in search of residual awareness in DOC. We discuss the medical, scientific and ethical implications that derive from these studies and we argue that, in the future, the role of neuroimaging and electrophysiology will be important not only for the diagnosis and prognosis of DOC but also in establishing communication with these challenging patients.

Keywords: assessment • brain–computer interface • brain death • coma • communication • deep brain stimulation • default mode network • disorder of consciousness • electrophysiology • functional neuroimaging • minimally conscious state • neurorehabilitation • vegetative state

Defining consciousness & picturing its clinical states

Consciousness is here defined as a first-person experience that consists of two major components: arousal and awareness (Figure 1) [1]. Arousal refers to the level of alertness and is supported by the function of the subcortical arousal systems in the brainstem, midbrain and thalamus [2]. Clinically, it is indicated by opening of the eyes. Awareness refers to the content of consciousness, and it is thought to be supported by the functional integrity of the cerebral cortex and its subcortical connections. Awareness can be further reduced to awareness of environment and of self [3]. Clinically, awareness of environment is assessed by evaluating command following and observing nonreflex motor behavior, such as eye tracking and localized responses to pain. Awareness of self, clinically a more ill-defined concept, can be assessed by the patients' response to autoreferential stimuli, such as the patients' own face in the mirror. An illustrative example of the relationship between the two components of consciousness is the transition from full wakefulness to deep sleep: the less aroused we get, the less aware we become of our surroundings.

This review focuses on clinical methods and research techniques that are currently employed for assessing residual consciousness in coma survivors. The disorders of consciousness (DOC) are described below.

Brain death

The concept of brain death, as death based on neurological criteria, has been widely accepted worldwide [4]. Irreversible coma and absence of brain stem reflexes are the major clinical criteria that are followed by most US hospitals, but these criteria are apparently not practised in the same way by all institutions [5]. This implies that brain death may be determined in various ways, a fact that may have consequences in after death practices, such as organ transplantation [6]. In 1995, the American Academy of Neurology published the diagnostic guidelines for brain death [7], which are:

- Demonstration of coma;
- Evidence for the cause of coma;
- Absence of confounding factors, including hypothermia, drugs, electrolyte and endocrine disturbances;

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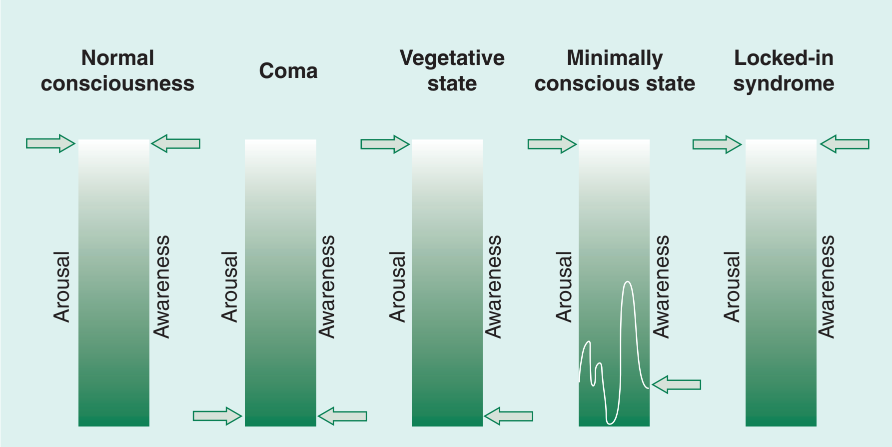

Figure 1. Spectrum of disorders of consciousness as defined by the relationship between arousal and awareness. Comatose patients cannot be aroused and, hence, are not aware of the environment or of themselves [3]. In the vegetative state, there is a dissociation between arousal, which recovers, and awareness, which remains absent [12]. The minimally conscious state characterizes patients who demonstrate inconsistent but reproducible behavioral evidence of awareness of self or environment, but are unable to communicate their thoughts and feelings [15]. The locked-in syndrome describes patients who are awake and conscious, but can only communicate by using small eye movements [18]. The locked-in syndrome is not a disorder of consciousness but it is included here as it can be misdiagnosed as one.
Adapted from [58].

- Absence of brainstem reflexes;
- Absent motor responses;
- Positive apnea testing;
- A repeat evaluation in 6 h is advised, but the time period is considered arbitrary;
- Confirmatory laboratory tests are only required when specific components of the clinical testing cannot be reliably evaluated.

Classically, brain death is caused by a massive brain lesion, such as trauma, intracranial hemorrhage or anoxia. No recovery from brain death has ever been reported over the last 50 years in a patient fulfilling the above mentioned clinical criteria [8].

Coma

After severe brain damage, patients may spend a couple of days or weeks in coma. Coma is a time-limited condition leading either to death, to recovery of consciousness or to transition to vegetative state (VS) [9]. It can result from bihemispheric diffuse cortical or white matter damage or brainstem lesions bilaterally, affecting the subcortical reticular arousing systems. Many factors, such as etiology, the patient's general medical condition, age, clinical signs and complimentary examinations influence the management and prognosis of coma. In terms of clinical signs, after 3 days of observation, bad outcome is heralded by the absence of pupillary or corneal reflexes, stereotyped or absent motor response to noxious stimulation, bilateral absent cortical responses of somatosensory evoked potentials (SEPs) and, for anoxic coma, biochemical markers (i.e., high levels of serum neuron-specific enolase) [10].

Vegetative state

The VS is a 'state of arousal without awareness' (Figure 1). These patients regain sleep–wake cycles. However, their motor, auditory and visual functions are restricted to mere reflexes and they show no adapted emotional responses [11]. According to the 1994 Multi-Society Task Force, the criteria for the diagnosis of VS are the following [12]:

- No evidence of awareness of self or environment and an inability to interact with others;
- No evidence of sustained, reproducible, purposeful, or voluntary behavioral responses to visual, auditory, tactile or noxious stimuli;
- No evidence of language comprehension or expression;
- Intermittent wakefulness manifested by the presence of sleep–wake cycles;
- Sufficiently preserved hypothalamic and brainstem autonomic functions to permit survival with medical and nursing care;
- Bowel and bladder incontinence;
- Variably preserved cranial nerve and spinal reflexes.

The VS is usually caused by diffuse lesions on gray and white matter. It can be a transition to further recovery, or it may be permanent. 'Permanent' VS refers to patients whose chances for recovery are close to zero. This is the case for VS that lasts more than 1 year after traumatic injury or 3 months after nontraumatic injury. The VS is characterized as 'persistent' when the patient is in this state for more than 1 month [12]. As both terms are abbreviated as 'PVS' (persistent vegetative state), it has been suggested to avoid this abbreviation and, instead, mention the etiology and the time spent in VS [201]. At present, there are no validated paraclinical prognostic markers for individual patients except that the chances of recovery depend on the patient's age, etiology and length of time spent in the VS [13].

Minimally conscious state

The minimally conscious state (MCS) was defined as a DOC in 2002 by the Aspen Workgroup. Patients in MCS manifest at least one of the following:

- Purposeful behavior, including movements or affective behavior contingent to relevant environment stimuli which are not due to reflexive activity, such as: visual pursuit or sustained fixation occurring in direct response to moving or salient stimuli, smiling or crying in response to verbal or visual emotional but not neutral stimuli, reaching for objects demonstrating a relationship between object location and direction of reach, touching or holding objects in a manner that accommodates the size and shape of the object, and vocalizations or gestures occurring in direct response to the linguistic content of questions;

- Following simple commands:
  - Gestural or verbal yes/no response, regardless of accuracy;
  - Intelligible verbalization [14].

Like the VS, MCS may be chronic and sometimes permanent. Emergence from MCS is defined by the ability to exhibit functional interactive communication or functional use of objects. It should be kept in mind that the boundary between MCS and higher states of consciousness is arbitrary and merely set for convention (i.e., allowing clear communication and enrollment in research studies) as opposed to the boundary between VS and MCS which is, at least in principle, absolute (i.e., any evidence of awareness suffices to define MCS). Similarly to the VS, traumatic etiology has a better prognosis than nontraumatic anoxic brain injuries [15]. Additional data from the Belgian Federal Project on PVS suggest that overall outcome in MCS is better than for VS [16].

Locked-in syndrome

In the locked-in syndrome (LIS) there is no dissociation between arousal and awareness. According to the 1995 American Congress of Rehabilitation Medicine criteria, LIS patients demonstrate [17]:

- Sustained eye opening (bilateral ptosis should be ruled out as a complicating factor);
- Quadriplegia or quadriparesis;
- Aphonia or hypophonia;
- A primary mode of communication via vertical or lateral eye movements, or blinking of the upper eyelid to signal yes/no responses;
- Preserved cognitive abilities.

Based on motor capacities, LIS can be divided into three categories:

- Classic LIS, which is characterized by quadriplegia and anarthria with eye-coded communication;
- Incomplete LIS, which is characterized by remnants of voluntary responsiveness other than eye movements;
- Total LIS, which is characterized by complete immobility including all eye movements, combined with preserved consciousness [18].

The LIS can result from a bilateral ventral pontine lesion [3] but mesencephalic lesions have also been reported [19]. Once a LIS patient becomes medically stable and is given appropriate medical care, life expectancy is estimated up to several decades [19]. Even if the chances of good motor recovery are very limited, existing eye-controlled computer-based communication technology currently allows these patients to control their environment [20]. Neuropsychological testing batteries adapted and validated for eye-response communication have shown preserved intellectual capacities, at least in LIS patients whose lesions are restricted to brainstem pathology [21]. Recent surveys seem to show that chronic LIS patients self-report meaningful quality of life and the demand for euthanasia, albeit existing, is infrequent [19,22].

Clinical assessment

The objective assessment of consciousness is difficult due to its first-person nature. For that reason, clinicians need to infer awareness via the evaluation of motor activity and command following. This is extremely challenging for DOC and LIS, as these patients are usually deprived of the capacity to make normal physical movements and they often show limited attentional capacities. Aphasia, apraxia and cortical deafness or blindness are other possible confounders in the assessment of DOC. We will next discuss the clinical consciousness scales that are mostly used in clinical settings [23].

Consciousness scales

The most common and most widely used tool, mainly thanks to its short and simple administration, is the Glasgow Coma Scale (GCS) [24]. The GCS measures eye, verbal and motor responsiveness. However, there may be some concern as to what extent eye opening is sufficient evidence for assessing brainstem function [25]. Additionally, the verbal responses are impossible to measure in cases of intubation and tracheostomy. The scale requires the clinician to arrive at a certain judgment (e.g., 'the patient follows commands') without any formal guidance on how to arrive at that judgment (i.e., what and how many commands to use and how to assess confounds such as motor or sensory or spontaneous movements). Finally, the GCS is not sensitive to detect transition from VS to MCS [26].

A recently proposed alternative to the GCS is the Full Outline of Unresponsiveness (FOUR) [27]. The scale is named after the number of subscales it contains (eye, motor, brainstem and respiratory functioning) as well as after the maximum score that each subscale can take (four). The advantage of the FOUR is that it does not need a verbal response and, hence, can be employed in intubated patients. The FOUR can discriminate between VS and MCS patients as it assesses visual pursuit, one of the first signs that announces emergence from VS, but it does not test all the behavioral criteria of MCS [14]. It is also more sensitive in detecting LIS patients because, in contrast to the GCS, it explicitly asks patients to move their eyes to command [27].

To differentiate VS from MCS patients, the most appropriate scale is the Coma Recovery Scale-Revised (CRS-R) [28]. The CRS-R has a similar structure to the GCS, testing, in addition to motor, eye and verbal responsiveness, audition, arousal and communication abilities. Despite its longer administration compared with the GCS and the FOUR (i.e., approximately 15 min), it is the most sensitive at differentiating VS from MCS patients [26]. This is because it assesses every behavior according to the diagnostic criteria of VS and MCS, such as the presence of visual pursuit and visual fixation [14]. Importantly, the way we assess these behavioral signs needs to be standardized and uniform, permitting between-center comparisons. For example, for the assessment of visual pursuit, the CRS-R [28] and the Western Neuro-Sensory Stimulation Profile (WNSSP) [29] employ a moving mirror; the Coma/Near Coma Scale [30], the Wessex Head Injury Matrix (WHIM) [31] and the Sensory Modalities Assessment and Rehabilitation Technique (SMART) [32] use a moving person; and the WNSSP, the SMART, the WHIM and the FOUR [27] use a moving object or finger. We recently demonstrated that the use of a mirror is the most sensitive in detecting eye tracking. These findings stress that self-referential stimuli have attention grabbing properties and are preferred in the assessment of DOC [33].

The clinical assessment via behavioral scales can be biased by several limitations: first, by intrinsic limitations in the measures' precision and validity, which can be overcome by selecting the 'best' measure each time; and second, by intrinsic behavioral fluctuations of the patients which can be corrected by repeated sessions of evaluation. Despite their pros and cons, each scale contributes differently in establishing the diagnosis and prognosis of DOC. The administration and interpretation of the results should be decided and discussed in terms of the person who uses the scale, the place where it is administered (e.g., intensive care vs chronic rehabilitation settings) and the reasons for their administration (e.g., clinical routine vs research purposes) [34].

Misdiagnosis

Incorrect diagnosis of DOC is not a rare phenomenon and it has been estimated that approximately 40% of VS patients are misdiagnosed [35,36]. It was recently found that of 29 patients that were initially diagnosed as VS using the GCS, four of them were in a MCS according to the FOUR scale and seven more patients were identified as MCS using the CRS-R scale [26]. These results imply that even though the diagnostic criteria for VS and MCS have been clearly established, the rate of misdiagnosis has not changed since the 1990s [35,36]. This may be attributed partially to the fact that, although the criteria may have been defined, they still remain not operationalized in the sense that there is not an exact procedure as to how to identify evidence of conscious behavior [37,38].

In LIS, diagnostic error is also frequent. Unless the physicians are familiar with the syndrome, it may be up to a couple of years before LIS it is diagnosed and, in many cases, it is a family member who realizes that the patient is conscious [39].

The high diagnostic error rate can be explained by the fact that physical function in these patients, which is the main way to exhibit their awareness, is limited. Additionally, it is difficult to differentiate between voluntary and reflexive behavior, as there is inconsistency in responses and lack of sensitivity of the personnel to accurately observe signs of consciousness [23]. An objective way that has been proposed to overcome such obstacles is to follow single-case experimental designs, adapting the assessment procedure on the patient's particular case, in the form of an individualized quantitative behavioral assessment [40]. This method identifies a particular behavior that is tested for consistency in response to command and it further checks whether this behavior changes over time, either in response to treatment or spontaneously. It has been proposed that the rate for the incorrect diagnostic evaluation of the VS will be minimized by combining behavioral, electrophysiological and functional neuroimaging procedures [41,42].

Paraclinical assessment

Electrophysiological and functional neuroimaging methods permit the identification of objective markers of consciousness and quantify residual brain function in DOC. The EEG is informative of the general vigilance level of patients and can detect functional abnormalities, such as seizures. However, evoked responses to environmental stimuli, such as evoked potentials (EPs), may be more informative about the cognitive state of a patient. EPs derive statistically from the EEG and they are comprised of different components which can be classified into two main categories: short latency or exogenous, and cognitive or endogenous [43]. Exogenous components are elicited within a time range between 0 and 100 ms after the presentation of a stimulus; they correspond to the activation of the ascending pathways to the primary cortex and are thought to reflect the physical properties of the stimulus. Examples of exogenous components are the SEPs, the brainstem auditory EPs (BAEPs) and middle-latency auditory EPs (MLAEPs). Endogenous components are obtained after 100 ms of the presentation of a stimulus, reflecting the activity of both cortical and subcortical structures including associative areas, and are thought to depend on the psychological significance of the stimulus. Examples of endogenous components are the mismatch negativity (MMN; a response to an oddball situation in an inattentive subject) and the P300 (a response to an unpredictable target stimulus) [44]. Evoked electrophysiological responses, as is mentioned later, are signatures of neural activity that may differentiate conscious from unconscious processing and are easy to employ at the patient's bedside.

Functional neuroimaging permits objective measurement of the brain's activity at rest and during various states of external stimulation [45]. The main principle behind this methodology is that performance on a sensorimotor or a cognitive task increases the brain's need for extra energy. One form of energy is glucose, the metabolic levels of which are measured by the fluoro-deoxy-D-glucose PET (FDG-PET) technique. Another form of energy is oxygen, the excessive levels of which in certain brain areas are measured by the functional MRI (fMRI) technique.

Diagnostic value

The EEG is the most employed test to confirm the diagnosis of brain death. This is done by showing absence of electrocortical activity (i.e., isoelectric EEG), which diagnoses brain death with a sensitivity and specificity of approximately 90% [46]. In the VS, the EEG most often shows continuous diffuse slowed electrical activity in the theta (4–7.5 Hz) and/or delta (1–3.5 Hz) frequency ranges. In the MCS, bilateral, but predominantly ipsilesional polymorphic theta activity may be the most prominent abnormality [47]. In LIS, the EEG pattern differs across patients and, thus, cannot be used as a reliable measure for detecting consciousness and to discriminate LIS from DOC [48]. However, when a close-to-normal EEG pattern is observed, the possibility of LIS should be taken into consideration [19]. The patients' underlying background EEG was also shown to influence the evoked electrophysiological responses to stimuli of different complexity [49].

Certain types of P300, such as the P3a and P3b, are a function of attention and memory, respectively [50]. It was shown that VS and MCS patients elicit a P300 response more frequently when ecological stimuli were used as compared with meaningless tones [51]. The patient's own name, a salient attention-grabbing stimulus, was found to elicit a P300 response in VS and MCS [52]. However, as P300 can also be elicited during subliminal perception [53] and during sleep [54], it can be considered as a purely conditioned response to one's own name, and therefore may not imply consciousness [55]. Recently, the P300 as a response to a patient's own name and to other target names was employed to document command following in DOC. Schnakers and colleagues studied 22 severely brain damaged patients employing an 'active' auditory paradigm [56]. Subjects were instructed to count the number of times they heard either their own name or an unfamiliar target name. In controls, this increase of attention to a target leads to an increase of the P300 response. Similar results were obtained in low-level MCS patients (i.e., those only showing visual fixation tracking but no behavioral command following). None of the studied VS patients demonstrated such responses.

In terms of neuroimaging methodology, PET scans in brain death show absence of neuronal metabolism in the whole brain, that is, an 'empty-skull sign' [8]. Cortical metabolism in coma and in VS is reduced by up to 40–50% of normal values. Recovery from the VS, however, is not always associated with a return to near normal global cerebral metabolic levels; rather, metabolic changes are observed regionally [57]. PET studies on pain perception in the VS have demonstrated restricted brain activation to primary somatosensory cortices, isolated and disconnected from the rest of the brain [58]. However, in absence of a full understanding of the neural correlates of conscious perception, it remains difficult to interpret functional imaging data in brain damaged patients as proof or disproof of their conscious experience [59]. LIS patients demonstrate higher global brain metabolic levels compared with the VS [60]. The absence of metabolic signs of reduced function in any area of the gray matter highlights the fact that these patients suffer from a pure motor de-efferentation and recover an entirely intact intellectual capacity [19].

Functional MRI data collected by Owen and colleagues from Cambridge University in collaboration with our group suggested that a patient, behaviorally diagnosed as vegetative, showed indistinguishable brain activity from that observed in healthy people when asked to imagine playing tennis and mentally visit rooms of her house [61]. This implies that this patient, despite the clinical diagnosis of VS, understood the tasks and, hence, must have been conscious. Of note is the fact that, a few months later, the patient evolved into a MCS. The most likely explanation of these results is that the patient was no longer in a VS at the time of the experiment.

Prognostic value

Some clinical studies have suggested that ventricular dilatation, the motor score on the GCS, spontaneous eye movements [62] and blinking to threat herald favorable outcome in the VS [63]. Recent evidence, however, have suggested that presence of blinking to threat does not reliably predict recovery in the VS as its positive predictive value (i.e., patients showing preserved blinking to treat response who subsequently recovered) was estimated at 30% [64].

Electrophysiological data in coma support the suggestion that a burst suppression EEG heralds bad outcome [3]. The presence or absence of exogenous and endogenous EPs plays an important role in the prognosis of DOC. Although the absence of cortical SEPs herald poor outcome, their presence does not necessarily imply recovery [65]. Given the low positive predictive values of exogenous EPs, it has been suggested that clinical routine tests should also include the assessment of higher order cortical activity via endogenous EPs. The presence of MMN, for example, has been found to be of high positive prognostic value notably in anoxic coma [66]. In summary, it can be concluded that absent exogenous EPs are well established prognosticators of poor outcome, whereas the presence of endogenous components, notably the MMN and P300, appear to predict favorable outcome [67].

In the postacute phase, structural MRI findings have demonstrated that lesions of the corpus callosum, corona radiata and dorsolateral brainstem are predictors of bad outcome in VS patients [68]. A recent review of fMRI activation studies has shown that activation of higher-level brain regions also seem to predict recovery [69]. Compared with seven VS patients who exhibited a more frequently encountered low-level primary cortical activation when the patient's own name paradigm was employed, Di and colleagues identified two VS patients who demonstrated a more widespread activation, beyond the primary auditory cortices. Only these two VS patients showing close-to-normal brain activation functionally improved to MCS at 3 months follow-up. In that sense, the fMRI precedes the results of the clinical recovery.

Treatment

To date, there are no 'standards of care' for therapeutic management in DOC. Studies were conducted under suboptimal or uncontrolled settings and, for that reason, no evidence-based recommendations can be made. However, pilot data demonstrate that DOC patients and, more particularly, MCS patients, can benefit from some rehabilitative interventions [70]. These interventions can be separated between pharmacologic and nonpharmacologic.

Pharmacologic treatment

Generally speaking, the response of DOC patients to pharmacologic treatment remains unsatisfactory [71]. However, pharmacologic studies have shown that amantadine, mainly a dopaminergic agent, was linked to better outcome in traumatic DOC [72,73]. In addition to behavioral amelioration, a recent PET study with a chronic anoxic MCS patient showed a drug-related increase in frontoparietal metabolism after the administration of amantadine (Figure 2) [74]. Nevertheless, cohort placebo-controlled randomized trials or blinded within-subject crossover designs are needed before making any assertive conclusions for the effectiveness of the drug.

Other pharmacologic agents that have been reported to lead to favorable functional outcome are levodopa and bromocriptine (also dopaminergic agents) [75], baclofen [76] (GABA agonist administered mainly against spasticity) and zolpidem (nonbenzodiazepine sedative drug that is used against insomnia in healthy people). Table 1 summarizes recent pharmacologic studies in DOC (after the year 2000), estimating their quality of evidence based on the criteria proposed by the Oxford Centre of Evidence-Based Medicine [202]. As can be shown from Table 1, no level-1a studies have been conducted yet.

Nonpharmacologic treatment

Despite some sparse evidence that deep brain stimulation (DBS) may have some ameliorating effects on arousal in VS [77], generally speaking, its effectiveness to this population is limited. This can be attributed to the uncontrolled settings of these studies in combination with the underlying neuropathology of VS patients. More particularly, VS patients exhibit widespread thalamic and cortical neuronal damage [78], whose stimulation is difficult to lead to functional reintegration [79]. Schiff and colleagues recently proposed a protocol for the application of DBS, which mainly focuses on patients' selection based on the neuropathological and behavioral profile. According to this protocol, patients eligible for DBS application will be those who manifest preserved states of arousal, fluctuating behavioral performance and for whom there is specific information about the connections between the central thalamus (coming from functional neuroimaging evidence), cerebral cortex, basal ganglia and other subcortical structures [79]. The first application of their protocol took place in a recent study of a 38-year-old, severe traumatic brain-injured patient, who was in a MCS for 6 years [80]. The patient's condition did not ameliorate despite a 2-year rehabilitation program and 4 years in a nursing home. However, after applying DBS in the central thalamus, the patient exhibited improved levels of arousal, motor control and interactive behavior. It should be noted that the fMRI of this patient demonstrated a preserved large-scale bihemispheric language network, which implied that there was at least a preserved substrate for a neural recovery to take place [81].

Other nonpharmacologic interventions for DOC are sensory stimulation techniques, physical and occupational therapy. These techniques are mainly conducted for two purposes: to prevent complications and/or to enhance recovery. It should be noted that, in terms of efficacy, preventing complications in a patient (e.g., contracture or pressure sore prevention) does not necessarily imply effects on recovery. Sensory stimulation refers to two types of approaches: the multisensory stimulation approach and the sensory regulation approach [82]. The former embraces the principles of behaviorism and states that enhanced environmental stimulation of the sensory systems is hoped to enhance synaptic reinnervations and eventually improve outcome. Sensory regulation is based on the principles of information processing and focuses on the enhancement of selective attention by regulating the environment. At present, the beneficial effects of all approaches described above remain debated and not evidence-based [83].

Physical therapy aims to improve motor and physical disturbances via techniques that include protocols of postural changes, management and prevention of joint contractures as well as hygienic management. There is evidence that early [84] and increased intervention [85] leads to better

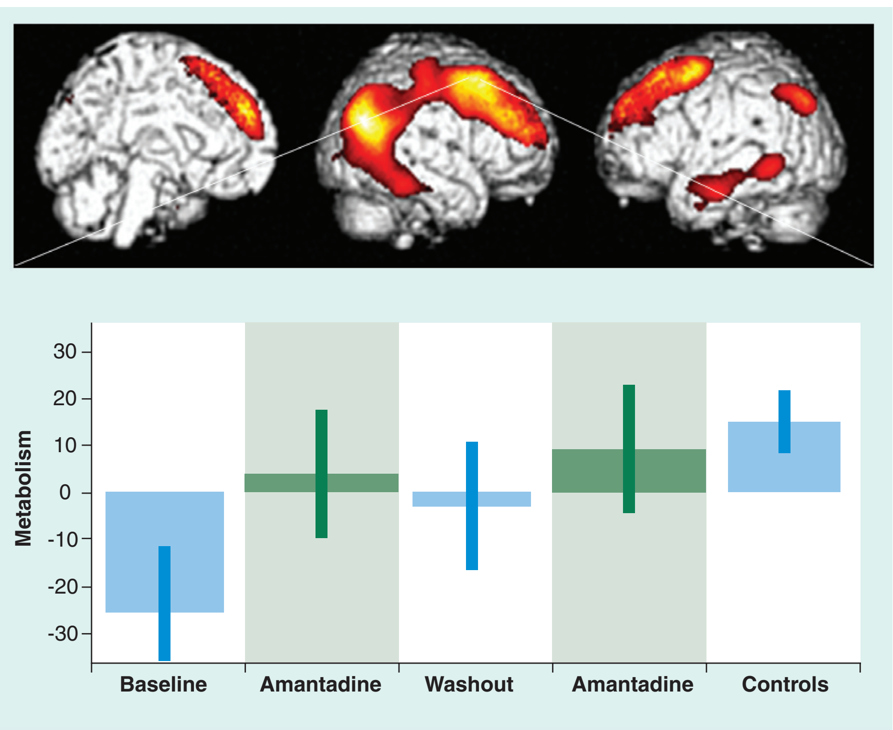

Figure 2. Amantadine-related changes in cerebral metabolism in an anoxic minimally conscious patient. The metabolic activity of bilateral fronto–temporo–parietal associative and right sensory–motor cortices is decreased at baseline, increases after 5 weeks of amantadine treatment, decreases during washout and returns to near-normal levels after re-administration.
Adapted from [75].

outcomes. VS patients, however, are often denied the opportunity of early intervention either because, due to their slow progress, physicians estimate that they have already achieved the final level of responsiveness or because they need to be on the waiting list for a specialized rehabilitation center [86].

Occupational therapy supports the view that being engaged in a creative and productive activity will enhance the physical and emotional rehabilitation of patients [87]. Occupations differ between patients based on their needs, roles and interests, and concern three different areas of function: self-maintenance (e.g., personal care), productivity (e.g., work) and leisure [88]. Nevertheless, occupational therapy interventions in DOC are not frequent and, when employed, the aim is to enhance motor function, sensory/cognitive skills and interpersonal/intrapersonal performance components [88]. The effectiveness of this treatment is also limited [89].

Expert commentary

The diagnosis of DOC is difficult due to its subjective character. Clinicians need to infer the presence of awareness in these patients based on motor responses to external stimulation. Distinguishing between voluntary and reflexive behavior will eventually disentangle VS from MCS patients. To date, however, there is no consensus as to what 'reflexive' and 'voluntary' means [90], similar to the debate about what consciousness means. Additionally, DOC patients can manifest muscular spasticity or paralysis. In that perspective, high diagnostic error in DOC is common. Therefore, the need for standardized, validated behavioral scales is emphasized.

From the previous discussion it is clear that there is a need for an alternative nonmotor-dependent means for the assessment of DOC. Such opportunity is offered by functional neuroimaging and electrophysiological tools. The fMRI study of mental imagery to command by Owen and colleagues [61] challenge the present status of clinical bedside diagnosis and encourage the application of sophisticated neuroimaging techniques in clinical practice. Similarly, subclinical electromyography (EMG) was shown to detect preserved awareness (i.e., command following) in one of ten VS and in both tested MCS patients [91]. In that perspective, the gray zone that lies between these two distinct clinical entities of consciousness is expected to be more clearly defined. However, the evidence of such studies should be interpreted carefully as it concerns case reports or small cohort groups, and it is characterized by physiological and behavioral variability. This means that the employed paraclinical methods to study DOC do not solve the problem of confounding impairments in sensory processing. Additionally, if the paraclinical examination of the patient measures a 'trait' (i.e., an enduring

Table 1. The efficacy of pharmacologic treatment in disorders of consciousness.

Drugs	Study (first author, year)	Number of patients and etiology	Diagnosis	Placebo control	Reported functional outcome	Level of evidence	Ref.
Dopaminergic agents							
Amantadine	Schnakers (2008)	1 anoxic	MCS	No	Positive	3b	[74]
	Patrick (2006)	10 TBI	Low responsive level	No	No effect	1b	[99]
	Hughes (2005)	123 TBI	Coma	NA	No effect	2b	[100]
	Saniova (2004)	41 TBI	'Persistent unconsciousness'	NA	Positive	2b	[101]
	Meythaler (2002)	35 TBI	MCS	Yes	Positive	1b	[102]
Bromocriptine	Brahmi (2004)	4 intoxication	Coma	No	Positive	4	[103]
Levodopa	Matsuda (2003)	3 TBI	VS	No	Positive	4	[104]
Nonbenzodiazepine sedative							
Zolpidem	Cohen (2008)	1 anoxic	Lethargic	No	Positive	4	[105]
	Shames (2008)	1 anoxic	MCS	No	Positive	4	[106]
	Singh (2008)	1 TBI	MCS	No	No effect	4	[107]
	Brefel-Courbon (2007)	1 hypoxic	Akinetic mutism	Yes	Positive	3b	[94]
	Clauss (2006)	2 TBI, 1 anoxic	VS	No	Positive	4	[108]
	Clauss (2000)	1 TBI	Semi-comatose	No	Positive	4	[109]
GABA agonist							
Baclofen	Sarà (2007)	1 non-TBI	VS	No	Positive	4	[110]

Medline search included studies conducted between January 2000 and June 2008.
MCS: Minimally conscious state; NA: Not applicable; TBI: Traumatic brain injury; VS: Vegetative state.
Level of evidence data from [202].

pattern characteristic of the patient), a single examination may prove useful, but if it targets at a patient's 'state' (i.e., a psychological or physiological pattern that may fluctuate), then multiple measures are needed.

Another critical point to the study of awareness in DOC is the subsequent ethical considerations. According to some authors, it is ethically controversial whether noncommunicative patients can be included in clinical trials since they are unable to provide informed consent and, thus, cannot protect themselves from potential dangers. However, excluding such patients from research studies under the argument of nonmaleficence, they are also excluded from the opportunity to potentially benefit from these studies. For that reason, an ethical framework that balances between clear protections for patients with DOC and access to research and medical progress is preferred [92,93]. Based on this framework, better end-of-life decisions can be made by allowing severely brain-injured patients, who have been misdiagnosed based on bedside evaluation but who have relatively preserved cognitive capacity, decide on the course of their own lives.

Five-year view

The clinical and subclinical detection of awareness in DOC, with the aid of functional neuroimaging and electrophysiological tools, is expected to flourish in the next 5 years. Clinical diagnosis will be facilitated by moving from isolated case reports toward large-scale multicenter cohort studies. The derivates of such studies are expected to become more widely applicable in clinical routine. In this way, prognosis and outcome prediction will be further validated. In terms of treatment, nowadays no evidence-based recommendations can be made in favor of this or the other therapeutic option. Preliminary evidence of the efficacy of some pharmacologic (e.g., amantadine [74] and zolpidem [94]) and nonpharmacologic interventions (e.g., DBS [80]) in DOC patients will be further supported by functional neuroimaging studies, which are expected to reveal the physiological modifications of these interventions. Advances in communication technology are also expected in the coming years [42]. To date, facilitation in communication is beginning to be achieved for LIS patients. Salivary pH changes, for example, have been reported as an alternative paradigm to communicate with a LIS patient who was providing 'yes' answers by imagining lemon and 'no' answers by imagining milk [95,96]. A recent impressive breakthrough, however, is the use of brain–computer interfaces (BCIs) [20], a technique which allows electrical brain signals to control external devices that do not require muscular activity. In the future, BCI devices are expected to be applicable also in DOC, by providing these patients with a 'voice' of their own [97,98]. It would be thrilling to view the use of these powerful technologies in the assessment and possible treatment of DOC.

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Information resources

- Coma Science Website
  www.comascience.org
- American Academy of Neurology (AAN) clinical practice guidelines
  www.aan.com/go/practice/guidelines

Key issues

- Incorrect diagnosis of disorders of consciousness (DOC) is still very common in clinical practice, despite the introduction of clear-cut diagnostic criteria.
- Standardized validated behavioral tools should be employed in the assessment of DOC.
- The Glasgow Coma Scale remains the gold standard in the behavioral assessment of comatose patients, but the Coma Recovery Scale–Revised is probably the most validated scale to disentangle vegetative from minimally conscious state patients.
- The bedside diagnosis of the vegetative state is difficult, and requires repeated examination by trained experts. The interest of paraclinical markers is currently being studied.
- The vegetative state is not brain death.
- The therapeutic management of DOC currently lacks large-scale randomized controlled trials permitting conclusive answers to propose or reject specific pharmacologic or nonpharmacologic interventions.
- Pharmacologic treatment with amantadine and zolpidem show behavioral amelioration in some DOC patients but still no conclusive recommendations for the efficacy of these drugs can be made.
- Functional neuroimaging is expected to show the putative therapeutic efficacy in smaller cohort studies and be quicker and cheaper.
- Functional neuroimaging and electrophysiological tools offer an objective way to measure the brain's activity in DOC. Despite their great promise, at present no evidence-based recommendations for their diagnostic and prognostic use in clinical routine can be proposed.

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