

Coma, Persistent Vegetative States, and Diminished Consciousness

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Glossary

Apnea testing – A test needed to confirm brain death by checking whether the patient has a breathing reflex when disconnected from the positive pressure ventilator.

Brain-computer interfaces (BCIs) – Real-time muscular-independent systems that permit the translation of the electrical activity of the brain into commands, to control devices.

Deep brain stimulation (DBS) – An invasive surgical treatment involving the implantation of a medical device (brain pacemaker), which sends electrical impulses to specific parts of the brain.

Default mode network – A set of brain areas, encompassing the posterior cingulate cortex/precuneus, the medial prefrontal cortex, and bilateral temporoparietal junctions, which seem to be activated in the absence of any external stimulation, and show decreased activity during cognitive processing.

Event-related potentials (ERPs) – Averaged EEG signals that detect time-locked responses to sensory, motor, or cognitive activities. Short-latency or exogenous ERPs, ranging from 0 to 100 ms after the presentation of a stimulus, correspond to the activation of the ascending pathways to the primary cortex. Cognitive or endogenous ERPs are obtained after 100 ms of the presentation of a stimulus, and reflect both subcortical and cortical structures, including associative areas.

Functional connectivity – The temporal correlation of a neurophysiological index (i.e., cerebral metabolic rates of glucose, regional cerebral blood flow) measured in different remote brain areas.

Neuron-specific enolase – The neuronal form of the glycolytic enzyme enolase, which is found almost exclusively in neurons and cells of neuroendocrine origin and is used as a marker of ischemic brain damage.

Introduction

The management of coma and related disorders of consciousness (DOC) is a major clinical challenge. Patients in a vegetative state and minimally conscious state continue to pose problems in terms of their diagnosis, prognosis, and treatment. Bedside assessment remains the gold standard. Neuroimaging and electrophysiological measures can now identify signs of awareness inaccessible to clinical examination, which permit a better understanding of the mechanisms of human consciousness and improve our care of DOC patients.

Defining Consciousness

Consciousness is a first-person experience, which consists of two major components, wakefulness and awareness. Wakefulness refers to the level of consciousness and it is supported by the function of the subcortical arousal systems in the brainstem, the midbrain, and the thalamus. Clinically, it is indicated by opening of the eyes. Awareness refers to the contents 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 the environment and of self. Clinically, awareness of the environment is assessed by evaluating command following and observing nonreflex motor behavior, such as eye tracking and oriented

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 and ourselves (see [Figure 1](#)).

A Short History of Disorders of Consciousness

About 50 years ago, before the era of neurocritical care, things were relatively simple. After a severe brain damage, comatose patients either died or, more rarely, recovered with more or less cognitive deficits. The invention of the positive pressure mechanical ventilator by Bjorn Ibsen in the 1950s, and the widespread use of intensive care in the 1960s, in the industrialized world, changed the picture. They stated that severely brain damaged patients could now have their heartbeat and systemic circulation sustained by artificial respiratory support. Such profound unconscious states had never been encountered before as, until that time, all these patients had died instantly from apnea.

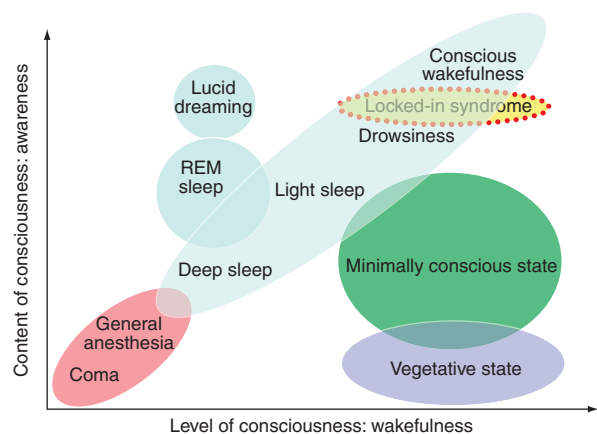


Figure 1 Simplified illustration of the two major components of consciousness and the way they correlate within the different physiological, pharmacological and pathological modulations of consciousness. Reproduced from [Laureys S \(2005\)](#) The neural correlate of (un)awareness: Lessons from the vegetative state. *Trends in Cognitive Sciences* 9: 556–559.

As a consequence, medicine was forced to redefine death, using a neurological definition, that of brain death.

In the 1960s, Fred Plum and Jerome Posner described for the first time the locked-in syndrome (LIS), to refer to fully conscious coma survivors who are unable to communicate due to physical paralysis. In 1972, Bryan Jennet and Fred Plum published the clinical criteria of another artifact of modern intensive care, the vegetative state (VS), a state of 'wakefulness without awareness.' In 2002, the Aspen Neurobehavioral Conference Workgroup realized that clinical reality was yet more complicated. Some patients showed signs of voluntary behavior, and therefore they were no longer vegetative, but still remained unable to functionally communicate. Based on these observations, they published the diagnostic criteria of a new clinical entity, the minimally conscious state (MCS).

Defining the Clinical Entities of Consciousness

Brain Death

Brain death means human death determined by neurological criteria. The current definition of death is the permanent cessation of the critical functions of the organism as a whole, such as, neuroendocrine and homeostatic regulation, circulation, respiration, and consciousness. Most countries, including the United States, require death of the whole brain including the brainstem. Some other countries, like the United Kingdom and India, rely on the death of the brainstem only, arguing that the brainstem is at once the through-station for nearly all hemispheric input and output, the center generating wakefulness (an essential condition for conscious awareness), and the center of respiration. Classically, brain death is caused by a massive brain lesion, such as trauma, intracranial hemorrhage, or anoxia. Using the brainstem formulation of death, however, unusual but existing cases of catastrophic brainstem lesions, usually of hemorrhagic origin, sparing the thalami and cerebral cortex, can be declared brain dead in the absence of clinical brainstem function, despite intact intracranial circulation. Hence, a patient with a primary brainstem lesion who did not

develop raised intracranial pressure might theoretically be declared dead by the UK doctrine, but not by the US doctrine.

In 1995, the American Academy of Neurology published the criteria for brain death, which have been used to model many institutional policies. The criteria are (1) demonstration of coma; (2) evidence for the cause of coma; (3) absence of confounding factors, including hypothermia, drugs, electrolyte, and endocrine disturbances; (4) absence of brainstem reflexes; (5) absent motor responses; (6) positive apnea testing (see 'Glossary'); (7) a repeat evaluation in 6 h is advised, but the time period is considered arbitrary; and (8) confirmatory laboratory tests are only required when specific components of the clinical testing cannot be reliably evaluated. At present, no recovery from brain death has been reported.

Coma

Patients that sustain severe brain damage may spend some time in coma, which lasts for a couple of days or weeks. Patients in coma cannot be awakened even when intensively stimulated and, hence, are not aware of the environment and of themselves (see [Figure 1](#)). Coma is distinguished from syncope or concussion in terms of its duration, which is at least 1 h. Coma 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 complementary examinations influence the management and prognosis of coma. Traumatic etiology is known to have a better outcome than nontraumatic anoxic cases. In terms of clinical signs, after 3 days of observation, a 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) (see 'Glossary'), and (for anoxic coma) biochemical markers, such as high levels of serum neuron-specific enolase (see 'Glossary').

Vegetative State

In the VS there is dissociation between wakefulness, which is preserved, and awareness, which is absent

(see [Figure 1](#)). These patients regain sleep–wake cycles. However, their motor, auditory, and visual functions are restricted to mere reflexes and show no adapted emotional responses. The VS is usually caused by diffuse lesions on the gray and white matter. According to the 1994 Multi-Society Task Force on persistent vegetative state (PVS), the criteria for the diagnosis of VS are the following: (1) no evidence of awareness of self or environment and an inability to interact with others; (2) no evidence of sustained, reproducible, purposeful, or voluntary behavioral responses to visual, auditory, tactile, or noxious stimuli; (3) no evidence of language comprehension or expression; (4) intermittent wakefulness manifested by the presence of sleep–wake cycles; (5) sufficiently preserved hypothalamic and brainstem autonomic functions to permit survival with medical and nursing care; (6) bowel and bladder incontinence; and (7) variably preserved cranial nerve and spinal reflexes.

The VS may be a transition to further recovery, or 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, or 3 months after nontraumatic (anoxic) injury. The VS is characterized as 'persistent,' when a patient is in this state for more than 1 month. As both terms are abbreviated as 'PVS,' it has been suggested to avoid these terms and, instead, mention the etiology and the time spent in VS. At present, there are no validated prognostic markers for individual patients except that the chances for recovery depend on patient's age, etiology, and time spent in the VS.

Minimally Conscious State

The MCS has been defined in 2002 by the Aspen Workgroup as a DOC in order to describe non-communicating patients that show inconsistent, but discernible signs of behavioral activity that is more than reflexive in at least one of the following behavioral signs: (1) purposeful behavior, including movements or affective behavior that occurs in contingent relation to relevant environment stimuli and is not due to reflexive activity, such as pursuit eye movement 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, (2) following simple commands; (3) gestural or verbal yes/no response, regardless of accuracy; and (4) intelligible verbalization.

Like the VS, the MCS may be chronic and sometimes permanent. Emergence from the MCS is defined by the ability to exhibit functional interactive communication or functional use of objects. Given that the criteria for the MCS have only recently been introduced, there are few clinical studies of patients in this condition. Similar to the VS, traumatic etiology has a better prognosis than nontraumatic anoxic brain injuries. Preliminary data show that the overall outcome in the MCS is more favorable than in the VS.

The Locked-In Syndrome

The LIS describes patients who are awake and conscious, but have no means of producing speech, limb, or facial movements, resembling patients in a VS. LIS most commonly results from lesions to the brainstem. According to the 1995 American Congress of Rehabilitation Medicine criteria, LIS patients demonstrate: (1) sustained eye-opening (bilateral ptosis should be ruled out as a complicating factor), (2) quadriplegia or quadriparesis, (3) aphonia or hypophonia, (4) a primary mode of communication that uses vertical or lateral eye movement or blinking of the upper eyelid to signal yes/no responses, and (5) preserved cognitive abilities. Since there is only motor output problem, LIS is not a DOC, but it is included here as it can be misdiagnosed as one. Based on motor capacities, LIS can be divided into three categories: (1) classic LIS, which is characterized by quadriplegia and anarthria with eye-coded communication; (2) incomplete LIS, which is characterized by remnants of voluntary responsiveness other than eye movement; and (3) total LIS, which is characterized by complete immobility including all eye movements, combined with preserved consciousness.

Once an LIS patient becomes medically stable, and given appropriate medical care, life expectancy now is for several decades. Even if the chances of good motor recovery are very limited, existing eye-controlled, computer-based communication technology (i.e., BCI, see 'Glossary') currently allows these patient to control their environment. Neuropsychological testing batteries adapted and validated for eye-response communication, have shown preserved intellectual capacities in LIS patients, whose lesions are restricted to brainstem pathology. Recent surveys show that chronic LIS patients self-report a meaningful quality of life and the demand for euthanasia, albeit existing, is infrequent.

Evaluation of the Disorders of Consciousness

Good medical management starts with good diagnosis. However, as awareness is a first-person perspective, its objective assessment is difficult. For that reason, at the bedside, clinicians need to infer it via the evaluation of motor activity and command following. Diagnosing DOC correctly is extremely challenging. This is mainly because these patients are usually deprived of the capacity to make normal physical movements and may show limited attentional capacities. Aphasia, apraxia, and cortical deafness or blindness are other possible confounders in the assessment of DOC. This, in combination with the difficulty to define uncertain behavioral signs as voluntary or reflexive, can partially explain the high rate of incorrect diagnosis of DOC, which has been estimated to be around 40% of the cases. Besides these difficulties, one should also consider that some of the diagnostic criteria for VS and MCS do not share international consensus, such as, visual fixation, eye tracking, blinking to visual threat, and oriented motor responses to noxious stimuli.

Behavioral Evaluation

In 1974, Teasdale and Jennett's Glasgow coma scale (GCS) was published in *'The Lancet.'* This standardized bedside tool to quantify consciousness

became a medical classic, thanks mainly to its short and simple administration. The GCS measures eye, verbal, and motor responsiveness. There may be some concern as to what extent eye-opening is sufficient evidence for assessing brainstem function. Additionally, the verbal responses are impossible to be measured in cases of intubation and tracheotomy. Most importantly, the GCS is not sensitive enough to detect transition from the VS toward the MCS.

To differentiate VS patients from MCS patients, the most appropriate scale is the coma recovery scale-revised (CRS-R). The CRS-R has a similar structure to the GCS, containing, in addition to motor, eye, and verbal subscales, also auditory, arousal, and communication subscales. Despite its longer administration (i.e., *c.* 20 min) as compared to the GCS and the full outline of unresponsiveness (FOUR), it is the most sensitive in differentiating VS patients from MCS patients. This is because it assesses every behavior according to the diagnostic criteria of the VS and the MCS, such as, the presence of visual pursuit and visual fixation. Importantly, the way we assess these behavioral signs need to be standardized and uniform, permitting between-centers comparisons. For example, for the assessment of visual pursuit, some scales use an object or finger (FOUR), some use a mirror, a person, an object, and a picture (Western Neuro-Sensory Stimulation Profile), some use an object and a person (Wessex Head Injury Matrix; Sensory Modalities Assessment and Rehabilitation Technique), and some a moving person (Coma/Near Coma Scale). We have shown that the use of a mirror is more sensitive in detecting eye tracking and, hence, identify MCS patients. These findings stress that self-referential stimuli have attention-grabbing properties and are important in the assessment of DOC.

Despite their pros and cons, each scale contributes differently in establishing the diagnosis and prognosis of DOC. The administration and interpretation of findings 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 administration (e.g., clinical routine vs. research purposes).

In Search for Objective Markers of Consciousness

Electrophysiology

The EEG allows recording of the spontaneous electrical brain activity, permitting the identification of the level of vigilance and the detection of functional cerebral anomalies, such as seizures or encephalopathy. In brain death, the EEG shows absent electrocortical activity with a sensitivity and specificity of around 90%. In coma, a burst suppression in the EEG heralds a bad outcome. In the VS, the EEG often shows a diffuse slowing and it is only sporadically isoelectric. Similarly, in MCS there is a general slowing on the EEG. In LIS, the EEG does not reliably distinguish these patients from VS patients. However, a close-to-normal EEG should have the physician consider the possibility of LIS.

The use of ERPs (see ‘Glossary’) is useful to predict the outcome in DOC. Bilateral absence of cortical potentials (i.e., N20) or SEPs heralds a bad outcome in coma. The presence of ‘mismatch negativity’ (MMN), a late cognitive ERP component that is elicited in auditory ‘oddball’ paradigms, is predictive of recovery of consciousness. In VS, SEPs may show preserved primary somatosensory cortical potentials (SEPs), and brainstem auditory-evoked potentials (BAEPs) often show preserved brainstem potentials. Endogenous-evoked potentials, measuring the brain’s response to complex auditory stimuli, such as the patient’s own name (as compared to other names) permits to record a P300 response, which delayed in DOC patients when compared to controls. However, a P300 is not a reliable marker of consciousness as it can also be detected during deep sleep and anesthesia.

Resting cerebral metabolism

Cortical metabolism in coma survivors is reduced on an average to 50%–70% of the normal values. A global depression of cerebral metabolism is not unique to coma. When anesthetic drugs are titrated to the point of unresponsiveness, the resulting reduction in brain metabolism is similar to that observed in pathological coma. Another example of transient metabolic depression can be observed during slow-wave sleep. In this daily physiological condition, the cortical cerebral

metabolism can drop to nearly 40% of the normal values – while in REM-sleep, the metabolism returns to normal waking values (see [Figure 2](#)).

In brain death the so-called ‘empty-skull sign’ is observed, denoting functional decapitation. VS patients show substantially reduced, but not absent, overall cortical metabolism, up to 40%–50% of the normal values. In some VS patients who subsequently recovered, global metabolic rates for glucose metabolism did not show substantial changes. Hence, the relationship between the global levels of brain function and the presence or absence of awareness is not absolute. It rather seems that some areas in the brain are more important than others for its emergence. Statistical analyses of metabolic positron emission tomography (PET) data have

identified a dysfunction in a wide frontoparietal network encompassing the polymodal associative cortices: bilateral lateral frontal regions, parieto-temporal and posterior parietal areas, mesiofrontal, posterior cingulate, and precuneal cortices (see [Figure 3](#)). However, awareness seems not to be exclusively related to the activity in this ‘global workspace’ cortical network, but, as importantly, to the functional connectivity within this system and with the thalami. Long-range, frontoparietal, and thalamocortical ‘functional disconnections,’ with nonspecific intralaminar thalamic nuclei, have been identified in the VS. Moreover, recovery is paralleled by a functional restoration of this frontoparietal network and part of its thalamocortical connections.

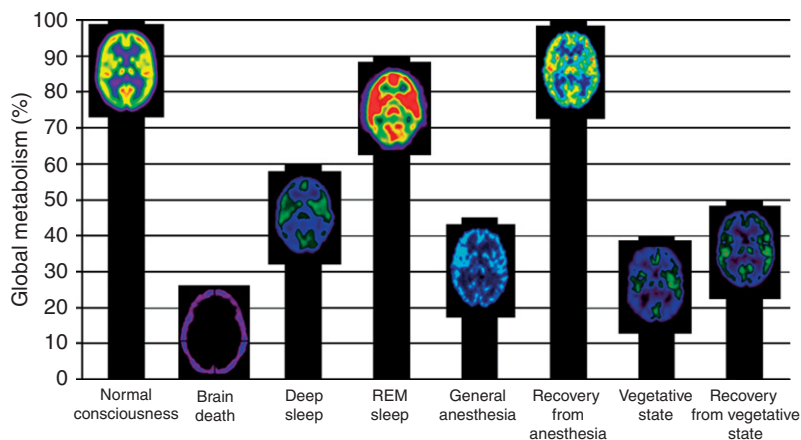


Figure 2 Global cerebral metabolism in healthy, pharmacological and disorders of consciousness. Adapted from [Laureys S, Owen AM, and Schiff ND \(2004\) Brain function in coma, vegetative state, and related disorders. *Lancet Neurology* 3: 537–546.](#)

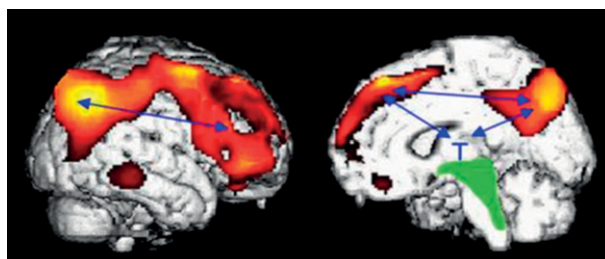


Figure 3 The frontoparietal “awareness network” (orange) is systematically the most impaired region in the vegetative state. The blue arrows represent the functional disconnections within this “awareness network” and with the thalami. The green area represents the relatively spared activity in the brainstem and hypothalamus. Adapted from [Laureys, et al. \(1999\), *NeuroImage*.](#)

Cortical activation to passive external stimulation

In brain death, external stimulation does not lead to any neural activation. In coma and VS patients, noxious stimulation was shown to activate only low-level primary cortices. Hierarchically higher-order areas of the pain matrix, encompassing the anterior cingulate cortex, failed to activate. Importantly, the activated cortex was shown to be isolated and functionally disconnected from the frontoparietal network, considered critical for conscious perception.

Similarly, auditory stimulation in VS was found to activate primary auditory cortices, but not higher-order, multimodal areas, from which they were disconnected (see [Figure 4](#)). In MCS, the activation was more widespread and there was an integrate functional connectivity between primary auditory cortices and the posterior temporal/temporoparietal and prefrontal associative areas.

Emotionally complex auditory stimuli, such as stories told by a familiar voice, lead to more widespread brain activation as compared to meaningless noise. Such context-dependent, higher-order auditory processing in MCS, often not assessable at the patient's bedside, indicate that content does matter when talking to these patients.

However, given the absence of a thorough understanding of the neural correlates of consciousness,

functional neuroimaging results must be used with caution as proof or disproof of awareness in severely brain-damaged patients. Recently, Adrian Owen from Cambridge University in collaboration with our laboratory proposed a more powerful approach to identify 'volition without action' in noncommunicative brain-damaged patients. Rather than using passive external stimulation paradigms, patients were being scanned while asked to perform a mental imagery task. In one exceptional VS patient, task-specific activation was observed, unequivocally demonstrating consciousness in the absence of behavioral signs of consciousness. Interestingly, the patient subsequently recovered. Other studies also showed that VS patients with atypical brain activation patterns, after functional neuroimaging, showed clinical signs of recovery of consciousness – albeit sometimes many months later.

Treatment

To date, there are no 'standards of care' for therapeutic management in DOC. Many studies have been conducted under suboptimal or uncontrolled settings, and for that reason, no evidence-based recommendations can be made. MCS patients, however, were shown to benefit more than VS

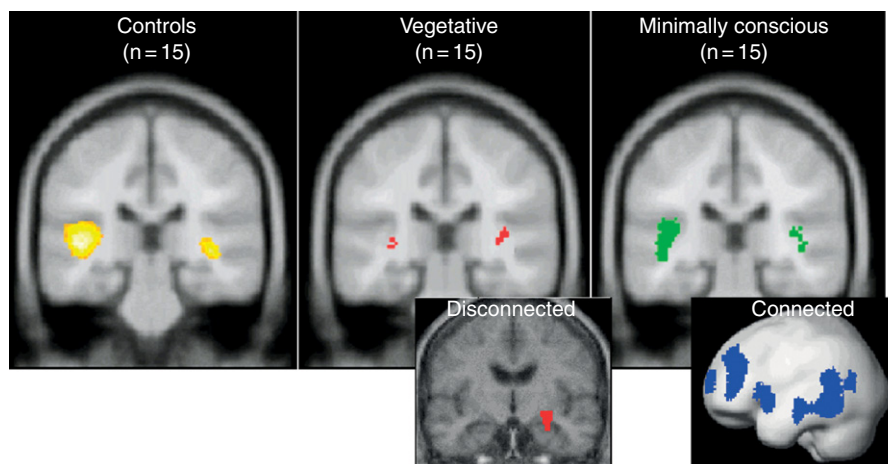


Figure 4 External stimuli still induce robust activation in primary sensory areas in vegetative patients. In the minimally conscious state, the activation is more widespread extending to multimodal associative areas. Functional connectivity studies (see 'Glossary') show that the activity of the primary cortex is isolated and disconnected from the rest of the brain, like the parahippocampal gyrus (red areas in the left inset). In the minimally conscious state, we observe a more integrated processing with preserved functional connectivity between low-level sensory areas and frontalparietal regions, which are thought to be involved in the emergence of conscious perception (blue areas in the right inset). Adapted from Boly, *et al.* (2004), *Archives of Neurology*.

after invasive treatment with DBS (see ‘Glossary’). More particularly, bilateral thalamic stimulation, implanted over 6 years after acute trauma, has just been shown to cognitively improve an MCS patient, resulting in stimulation-related recovery of functional object use and intelligible verbalization. In the VS, despite some sparse evidence that DBS may benefit these patients, its effectiveness to this population is limited, mainly due to uncontrolled experimental settings. In any case, the technique awaits confirmation from studies on larger cohorts of patients, but illustrates that DBS in well-chosen patients, selected on the basis of functional neuroimaging results, can offer a real therapeutic option, at least in chronic MCS patients.

Pharmaceutical interventions with amantadine, mainly a dopaminergic agent, was shown to increase metabolic activity in a chronic MCS patient. Similarly, zolpidem, a nonbenzodiazepine sedative drug, may improve arousal and cognition in some brain-injured patients. However, placebo controlled randomized trials are needed before we making assertive conclusions about the effectiveness of the drug in DOC patients.

Conclusion

Currently, it is an exciting time for the study of DOC. The gray zone transitions between them, in the clinical spectrum following coma, are beginning to be better defined by adding powerful imaging methodology to bedside behavioral assessment. However, it should be stressed that these exciting developments are not yet a reality. The first obstacle to be overcome relates to the engendered ethical problems. An ethical framework that emphasizes balancing clear protections for patients with DOC along with access to research and medical progress is preferred. Moreover, most of the discussed areas of advances in coma science regard single case studies. Only large scale multicentric clinical trials will enable these research tools to find their way to a better evidence-based care for coma survivors.

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See also: Ethical Implications: Pain, Coma, and Related Disorders; General Anesthesia.

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Biographical Sketch



Athena Demertzi, MSc, PhD student, graduated from the Faculty of Psychology at the Aristotle University of Thessaloniki, Greece in 2005. Soon after, she pursued her research master's in cognitive neuroscience, neuropsychology, and psychopathology, at Maastricht University, The Netherlands, where she specialized in the field of neuropsychology. During her master's, she conducted her research internship at the Blixembosch Rehabilitation Centre, Eindhoven, The Netherlands, where she studied self-awareness deficits in everyday life following brain injury. She graduated in August 2007, and next joined the Coma Science Group as an early stage researcher appointed by the Marie Curie Research Training Network 'DISCOS' – Disorders and Coherence of the Embodied Self. Under the supervision of Steven Laureys, she investigates the neural basis of the elementary personal identity in patients with altered states of consciousness, such as vegetative and minimally conscious patients.



Steven Laureys, MD, PhD, is a senior research associate at the Belgian National Fund of Scientific Research (FNRS) and Clinical Professor at the Department of Neurology, Sart Tilman Liège University Hospital. He graduated as a medical doctor from the Vrije Universiteit Brussel, Belgium. While specializing in neurology he entered his research career and obtained his MSc in pharmaceutical medicine working on pain and stroke, using *in vivo* microdialysis and diffusion magnetic resonance imaging (MRI) in the rat (1997). Drawn by functional neuroimaging, he moved to the Cyclotron Research Center at the University of Liège, Belgium, where he obtained his PhD (2000) and his 'thèse d'agrégation de l'enseignement supérieur' (2007), studying residual brain function in coma, vegetative, minimally conscious, and locked-in states. He is board-certified in neurology (1998), and in palliative and end-of-life medicine (2004). A recipient of the William James Prize (2004) from the Association for the Scientific Study of Consciousness (ASSC) and the Cognitive Neuroscience Society (CNS) young investigator award (2007), he recently published *The Boundaries of Consciousness* (Elsevier 2005) and *The Neurology of Consciousness* (Academic Press 2009). He nowadays leads the Coma Science Group at the Cyclotron Research Centre at the University of Liège, Belgium.



Melanie Boly, MD, PhD student, is currently a research fellow at the Belgian National Funds for Scientific Research (FNRS) and Neurologist in training at the University Hospital CHU Sart Tilman. Under Steven Laureys' supervision, she performed several studies comparing auditory and noxious stimuli cerebral processing in minimally conscious and vegetative state patients. In collaboration with the team of Adrian Owen in Cambridge, she also elaborated a method to assess the presence of voluntary brain activity, and thus of consciousness, in noncommunicative, brain-injured patients. This method has already proven to be of potential interest in the early detection of signs of awareness in patients previously diagnosed as being in a vegetative state. Her interests include the study of recovery of neurological disability and of neuronal plasticity by means of multimodal functional neuroimaging (EEG-fMRI, PET, and MEG), and behavioral assessment in severely brain-damaged patients with altered states of consciousness.