EDITORIAL REVIEW

What is it like to be vegetative or minimally conscious?

Steven Laureys and Melanie Boly

Purpose of review
Patients in a vegetative or minimally conscious state continue to pose problems in terms of diagnosis, prognosis and treatment. Despite recent waves of international media attention following Terri Schiavo's death and the 'miracle recovery' of Terry Wallis, research efforts aimed at increasing our knowledge about brain function in these conditions remain scarce and must address a series of difficulties, including financial and ethical barriers. Here we review current possibilities and limitations of clinical and para-clinical assessment of chronic disorders of consciousness.

Recent findings
During the past year the field has witnessed publication of significant, yet isolated, case reports in top-ranking journals, including *Science* and *Nature*. Such milestone reports and other impressive recent technological advances in the study of vegetative and minimally conscious patients reveal enthralling areas of science that must find their way to clinical medical reality.

Summary
Consciousness is a subjective experience whose study has remained within the purview of philosophy for millennia. That has finally changed, and empirical evidence from functional neuroimaging offers a genuine glimpse at a solution to the infamous mind–body conundrum. New technological and scientific advances offer the neurological community unique ways to improve our understanding and management of vegetative and minimally conscious patients.

Keywords
consciousness, ethics, functional magnetic resonance imaging, minimally conscious state, vegetative state

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Abbreviations

DBS deep brain stimulation
DOC disorder of consciousness
MRI magnetic resonance imaging
MCS minimally conscious state

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Introduction

About 50 years ago, before the era of neurocritical care, things were relatively simple. Following severe brain damage, comatose patients either died or, more rarely, recovered with cerebral deficit of varying severity. The invention of the positive pressure mechanical ventilator by Bjorn Ibsen in the 1950s in Copenhagen and the development of intensive care in the 1960s in the industrialized world have meant that heart function and systemic circulation can be sustained by artificial respiratory support in patients suffering traumatic and nontraumatic brain damage. The resulting profound unconscious states had never previously been encountered, because until that time all such patients had died instantly from apnoea. This change forced the medical community to redefine death, leading to its neurological definition: brain death (i.e. irreversible coma with absent brainstem reflexes) [1].

In the 1960s Fred Plum and Jerome Posner from New York first described the rare but terrifying situation of comatose patients recovering consciousness but remaining unable to move or speak, classically communicating only via eye movements. In their milestone book 'The diagnosis of stupor and coma' [2], they termed this condition the 'locked-in syndrome'. In 1972 Bryan Jennett from Glasgow and Fred Plum reported in the *Lancet* the clinical criteria for another artefact of modern intensive care: the vegetative state [3]. Patients in a vegetative state awaken from their coma (i.e. they open their eyes) but remain unaware (i.e. they exhibit solely reflex behaviour). Hence, until very recently patients surviving severe brain damage were considered to be comatose, vegetative or conscious. In 2002, the Aspen Neurobehavioral Conference Workgroup recognized that the clinical reality was even more complicated and that some patients showed signs of voluntary behaviour (and hence could not be considered vegetative) but remained unable to communicate functionally. The Workgroup reported diagnostic criteria for a new clinical entity: the minimally conscious state (MCS) [4].

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Treating patients with an acute or chronic disorder of consciousness (DOC) remains challenging. The debate on the need to continue or to stop 'futile' treatment in hopeless acute comatose states was begun in the 1970s, and the need to withhold/withdraw treatment in desperate cases is now widely accepted in intensive care [5]. Today, almost half of all deaths in critical care units follow a decision to withhold or withdraw therapy [6]. Since the 1994 meta-analysis conducted by the Multi-Society Task Force on Persistent Vegetative State was published [7], we have learned that the chances of recovery from a chronic vegetative state are close to zero 1 year after traumatic and 3 months after nontraumatic brain damage. In these cases of permanent vegetative state, treatment can be considered futile and its withdrawal can be ethically justified, based on the principles of patient autonomy, beneficence and nonmaleficence. Outcomes in MCS patients are considered to be better, and at present no time intervals for possible permanency of the condition have been established. No generally accepted standards of care have been proposed for patients in MCS.

How should we best care for these patients with a chronic DOC? Can withholding or withdrawal of treatment be justified in some cases? It is generally accepted that competent patients should consent to any treatment that they receive and have the right to make choices regarding their bodies and lives. The primary factor determining the level of treatment for an incompetent patient should reflect that patient's personally expressed wishes in their situation. By definition, however, patients in vegetative state or MCS cannot communicate their wishes.

What is it like to be unconscious or minimally conscious? Can patients with DOCs experience suffering or satisfaction? What is their quality of life? Is the level and content of consciousness in these patients with such severely damaged brains in any way comparable to our own? These questions are difficult to answer. The philosopher Thomas Nagel, author of the landmark paper 'What is it like to be a bat?' [8], might even argue that the subjective aspect of the mind will never be sufficiently accounted for by the objective methods of reductionistic science. We prefer a more pragmatic approach and believe that scientific and technological advances will ultimately improve our understanding and management of patients suffering from severe DOCs.

To be or not be . . . vegetative

Good medical management begins by making a correct diagnosis. There is an irreducible limitation in knowing for certain whether any other being is conscious [9]. Vegetative patients can move extensively, and clinical studies (for review, see Majerus *et al.* [10]) have shown how difficult it is to differentiate reflex or 'automatic' from voluntary or 'willed' movements [11]. This results in an underestimation of behavioural signs of consciousness and hence misdiagnosis, which is estimated to occur in about one-third to nearly half of chronically vegetative patients [12,13]. In this issue, Giacino and Smart (pp. 614–619), from the New Jersey Neuroscience Institute and JFK Johnson Rehabilitation Institute, discuss the crucial role played by adapted behavioural assessment tools in the diagnostic work-up of DOC. Differentiating vegetative from minimally conscious patients requires expertise, experience and effort. Clinical testing for the absence of consciousness in vegetative state is much more problematic and slippery than testing for absence of wakefulness in coma. Vegetative state is one end of a spectrum of awareness, and the subtle differential diagnosis with MCS necessitates repeated evaluations by skilled examiners employing standardized rating scales such as the Coma Recovery Scale-Revised, developed by Giacino *et al.* [14]. Diagnostic error may in part be accounted for by the fact that signs of consciousness in these patients often are subtle and fluctuating. Other causes could be related to limited examination skills and lack of knowledge of diagnostic criteria.

Giacino and Smart also point to international differences in diagnostic criteria for vegetative state. They argue that the vegetative state patient exhibiting brain activation indicative of mental imagery of 'tennis playing', reported last year in *Science* by the Cambridge and Liège coma groups [15], would have been diagnosed as MCS according to US guidelines, given that the reported patient showed visual fixation. Visual fixation is one of the more controversial clinical signs of consciousness. The 2003 UK Royal College of Physicians Guidelines [16] considered fixation as a 'compatible but atypical feature', whereas the 2002 US Aspen Workgroup [4] criteria regard sustained (but not brief) fixation as a purposeful movement and hence as a sufficient sign of MCS. There are no guidelines specifying what time interval differentiates a sustained from a brief visual fixation. Other controversial clinical signs are the definition and clinical assessment of visual tracking, blinking in response to visual threat, and orientated motor responses to noxious stimuli. It is clear that international consensus on nosological criteria is a prerequisite for establishing evidence-based medicine in our field.

Do they suffer?

Schnakers from the Coma Science Group of Liège and Zasler from the Concussion Care Centre of Virginia (pp. 620–626) examine current knowledge to inform decisions regarding the management of pain in DOCs. Like consciousness, pain is a subjective experience. By definition, patients in vegetative state and MCS cannot communicate their feelings and possible pain perception. The behavioural assessment of motor or autonomic signs

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(i.e. heart rate, respiratory frequency, blood pressure, pupillary diameter and skin conductance) have been demonstrated not to be reliable indicators of conscious perception of pain (e.g. see studies done in general anaesthesia [17]).

Only two positron emission tomography studies have studied brain processing linked to pain in vegetative state and the findings were contradictory. Laureys *et al.* [18] compared cerebral activation by high-intensity electrical stimulation of the median nerve at the wrist between 15 vegetative state patients (12 nontraumatic, mean post-insult time 1 month) and 15 healthy volunteers. The results demonstrated preserved and robust activation of the brainstem, thalamus and primary somatosensory cortex in every patient. However, this residual activation was like an island, disconnected from the rest of the 'pain matrix' (including the anterior cingulate cortex, which is considered critical in the affective and cognitive processing of pain) and the higher order cortical network that is considered necessary for conscious processing. Kassubek *et al.* [19] used similar methodology in seven vegetative state patients (all anoxic, mean post-insult time 1.5 years) and confirmed activation in primary somatosensory cortex but also – and surprisingly – in secondary somatosensory, insular and anterior cingulate cortices.

Schnakers and Zasler, considering the current levels of clinical and scientific uncertainty, propose that pain treatment be given to all patients in vegetative state or MCS. Current clinical guidelines do not share this view and do not propose the use of analgesics in vegetative state [7] (e.g. Terri Schiavo died without administration of therapeutic doses of opiates). The pros and cons of the use of analgesia in those who are severely brain damaged, and are unable to communicate possible perception of pain, are complex. Systematic use of narcotic analgesics in DOCs could lead to undesired sedation and subsequent underestimation of signs of consciousness. On the contrary, some patients might experience hyperalgesia, requiring more aggressive analgesic therapy. As concluded by Schnakers and Zasler, much more research is needed to develop scientifically based guidelines. Such research, however, faces major ethical challenges. For some scholars noxious stimuli cannot be applied to patients who are unable to provide written informed consent. In DOCs exploration of behavioural responses to nociceptive stimuli (e.g. applying pressure to the fingernail bed with a pencil, applying pressure to the supraorbital ridge or jaw angle, pinching the trapezium, or rubbing the sternum) is a routine clinical procedure that is used to evaluate the state of consciousness. Reactivity to pain is part of widely used 'consciousness scales', such as the Glasgow Coma Scale.

Caring for severely brain damaged patients represents such an immense humane, affective and social problem that it warrants further research to understand better the underlying cerebral dysfunction of vegetative state and MCS. Excluding the study of possible residual perception of pain from research protocols would in our view not be ethically justifiable. Fins (pp. 650–654) from Cornell University in New York discusses the need for an ethical framework based on prudential ethic with respect to dissemination of new scientific methodology and technology, distinguishing investigational from clinical efforts and complementing neuroimaging studies with longitudinal epidemiological inquiry into the natural history of DOCs. His eloquent essay addresses the ethical implications of recent technological developments for public policy, emerging therapeutics, and diagnostic and prognostic assessment in these challenging patient populations.

Hope from functional neuroimaging

At present, we still do not have validated prognostic markers that allow us to predict the chances of recovery in the individual patient in vegetative state or MCS. Galanaud, Naccache and Puybasset (pp. 627–631) from Pitié Salpêtrière Hospital in Paris discuss the predictive value of advanced magnetic resonance imaging (MRI) methods such as voxel-based volumetry or morphometry (i.e. objective quantification of changes in brain structure), magnetic resonance spectroscopy [i.e. measurement of metabolites such as *N*-acetyl-aspartate (a biomarker for neuronal integrity), choline (a marker for cell membrane turnover) and creatine (for cellular energetic function)] and MRI diffusion tensor imaging (i.e. assessment of the density, integrity and directionality of white matter tracts) in coma and related conditions. The reviewed evidence is still sparse and preliminary, and requires confirmation from ongoing large-scale multicentre studies. We hope that in the near future early para-clinical prognostic markers will allow us to identify irreversibility in vegetative patients, similar to current markers of irreversibility in coma such as electroencephalography (absent or burst-suppression electrical activity) and somatosensory evoked potentials (absence of N20 responses).

Positron emission tomography and functional MRI studies have not yet been shown to be reliable markers of recovery of consciousness. They have allowed us to reject the ancient view that vegetative patients are neocortically dead or apallic [20]. A succession of neuroimaging data has shown cerebral activation in isolated and disconnected islands of 'lower level' cortices or 'pallium' in response to auditory, visual, somatosensory and noxious stimuli [21]. Functional neuroimaging studies (e.g. see the reports by Boly and coworkers [22,23]) have also provided scientific evidence that residual brain function in vegetative state is very different from the brain's integrative capacity in MCS. These studies have confirmed that vegetative state and MCS are truly different physiological entities [24].

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Owen and Coleman (pp. 632–637) from Cambridge review their hierarchical functional MRI approach to assessing language perception in DOC, beginning with basic acoustic processing and progressively going on to more complex aspects of cognition. Although it is very powerful and informative, the limitation of this approach is that – in the absence of a full understanding of the neural correlates of consciousness – even a normal activation in response to passive sensory stimulation cannot be taken as incontestable proof of consciousness. In contrast, repeated and prolonged activation in response to an instruction to perform a mental imagery task would provide undeniable evidence of voluntary task-dependent brain activity, and hence of consciousness. This ground-breaking approach was validated by Boly *et al.* [25] in healthy control individuals, and it has been successfully applied to identify conscious perception in a (thus far unique) patient behaviourally diagnosed as being in a post-traumatic vegetative state, studied by Owen *et al.* [15].

Thought stimulation and thought translation devices

Therapeutic options in vegetative state and MCS are limited, and at present there is no pharmacological or nonpharmacological treatment proven to be efficient in DOCs. Moruzzi and Magoun's pioneering work in the 1940s demonstrated the critical role played by the brainstem and thalamic reticular system in higher brain activation [26]. Since the 1970s, multiple attempts have been made to use electrical stimulation of the tegmental midbrain, nonspecific thalamic nuclei and globus pallidus to improve arousal and awareness in patients in vegetative state. During the 1980s, a large multicentre study enrolled patients in France, Japan and the USA (its most famous patient being Terri Schiavo). However, none of these trials employing deep brain stimulation (DBS) in vegetative state yielded convincing results. In 2000, a report published in the *Lancet* [27] showed that restoration of functional disconnections between intralaminar thalamus and frontal cortices paralleled recovery of consciousness from vegetative state. This year, a well documented chronic post-traumatic MCS patient, carefully selected by means of functional neuroimaging, demonstrated unequivocal behavioural improvements related to intralaminar thalamic DBS [28]. Schiff and Fins (pp. 638–642 and 650–654) from Cornell University in New York consider their and other DBS cases within a historical context and examine the challenges for further clinical development of the technique.

Brain computer interfaces or thought translation devices permit communication via voluntary electroencephalography control, without any motor involvement. Technological improvements in such devices have now enabled locked-in patients to control their surroundings in ways that were not possible previously [29]. Andrea Kübler and Boris Kotchoubey (pp. 643–649) from the University of Tübingen discuss the role of brain computer interfaces not only as a communication instrument in locked-in syndrome but also as a diagnostic tool in DOCs. It is thrilling to witness the use of this powerful approach in the assessment of possible residual consciousness in patients clinically diagnosed as 'vegetative state' or 'MCS'.

Conclusion

The question of what it feels like to be minimally conscious has not yet been resolved, but the technology at least to attempt to address this issue now exists. Severe brain damage represents an immense social and economic problem that warrants further research. Unconscious, minimally conscious and locked-in patients are vulnerable and deserve special procedural protection, but they are also vulnerable to being denied proper care if the medical community does not increase its research efforts.

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