Assessment of consciousness with electrophysiological and neurological imaging techniques

Marie-Aurélie Bruno[a,*], Olivia Gosseries[a,*], Didier Ledoux[a], Roland Hustinx[b] and Steven Laureys[a]

[a]Coma Science Group, Cyclotron Research Centre, University of Liège and [b]Department of Nuclear Medicine, University Hospital of Liège, Liège, Belgium

Correspondence to Dr Steven Laureys, Coma Science Group, Cyclotron Research Center, University of Liège, Sart-Tilman B30, 4000 Liège, Belgium
Tel: +32 4 366 23 16; fax: +32 4 366 29 46;
e-mail: steven.laureys@ulg.ac.be

[*] Marie-Aurélie. Bruno and Olivia Gosseries contributed equally to the writing of this article.

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Purpose of review
Brain MRI (diffusion tensor imaging and spectroscopy) and functional neuroimaging (PET, functional MRI, EEG and evoked potential studies) are changing our understanding of patients with disorders of consciousness encountered after coma such as the 'vegetative' or minimally conscious states.

Recent findings
Increasing evidence from functional neuroimaging and electrophysiology demonstrates some residual cognitive processing in a subgroup of patients who clinically fail to show any response to commands, leading to the recent proposal of 'unresponsive wakefulness syndrome' as an alternative name for patients previously coined 'vegetative' or 'apallic'.

Summary
Consciousness can be viewed as the emergent property of the collective behavior of widespread thalamocortical frontoparietal network connectivity. Data from physiological, pharmacological and pathological alterations of consciousness provide evidence in favor of this hypothesis. Increasing our understanding of the neural correlates of consciousness is helping clinicians to do a better job in terms of diagnosis, prognosis and finally treatment and drug development for these severely brain-damaged patients. The current challenge remains to continue translating this research from the bench to the bedside. Only well controlled large multicentric neuroimaging and electrophysiology studies will enable to identify which paraclinical diagnostic or prognostic test is necessary for our routine evidence-based assessment of individuals with disorders of consciousness.

Keywords
consciousness, electroencephalography, functional MRI, minimally conscious state, PET, vegetative state/unresponsive wakefulness syndrome

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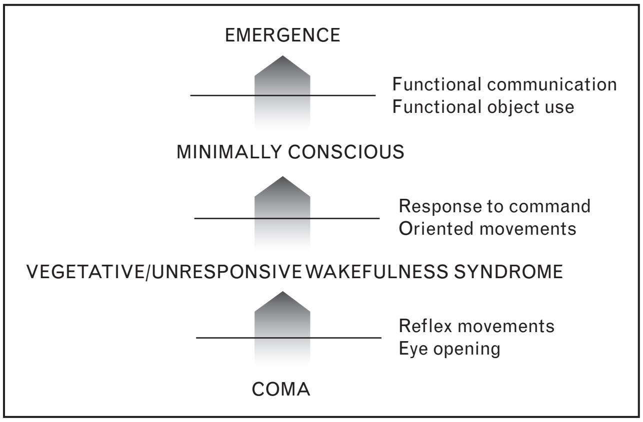
Introduction

We will here review the medical (i.e. diagnostic, prognostic, and therapeutic) and scientific interest of neuroimaging and electrophysiological studies in disorders of consciousness (DOC) [1•]. Following severe brain damage and coma, some patients may awaken (i.e. open the eyes) but remain unresponsive (i.e. only showing reflex movements). In Europe, this clinical syndrome was initially termed apallic syndrome or coma vigil, but it was later redefined as vegetative state [2]. Since its description more than 35 years ago, an increasing number of functional neuroimaging and event related potential studies (e.g. for recent studies see [3,4]) have shown that it sometimes may be difficult to make strong claims about 'vegetative' patients' awareness [5]. This situation is further complicated when patients have underlying deficits in verbal or nonverbal communication functions, such as aphasia, agnosia or apraxia [6•,7•]. It appears that part of the healthcare, media and lay public continues to feel some unease regarding the unintended denigrating 'vegetable-like' connotation seemingly intrinsic to the term vegetative state. The European Task Force on Disorders of Consciousness therefore recently proposed an alternative name: 'unresponsive wakefulness syndrome' (UWS) [8•]. Hence, physicians are recently offered to refer to these patients as UWS, a more neutral and descriptive term, pertaining to patients showing a number of clinical signs (hence syndrome) of unresponsiveness (i.e. without response to commands or oriented voluntary movements) in the presence of wakefulness. In contrast to coma, which is an acute condition lasting no more than some days or weeks, vegetative state/UWS can be a chronic condition lasting years or

Figure 1 Clinical criteria of disorders of consciousness



Key points

- Consciousness can be viewed as the emergent property of the collective behavior of widespread thalamocortical frontoparietal network connectivity.
- Electrophysiological and neuroimaging assessments are increasing our understanding of the neural correlates of consciousness and hence permitting to improve diagnosis, prognosis and management of coma and related disorders.
- Recent studies have demonstrated some residual cognitive processing in a subgroup of patients who clinically fail to show any response to commands, leading to the recent proposal of 'unresponsive wakefulness syndrome' as an alternative name for patients previously coined 'vegetative' or 'apallic'.
- The current challenge remains to continue translating this research from the bench to the bedside offering large controlled multicentric studies to enable identification of evidence-based paraclinical diagnostic and prognostic tests in patients with disorders of consciousness.

remain permanent. Patients who do recover, classically evolve to a minimally conscious state (MCS), defined by the presence of nonreflex voluntary movements such as orientation to pain, eye tracking or reproducible albeit inconsistent command following. By definition, MCS patients cannot communicate their thoughts or wishes [9]. Finally, in pseudocoma or locked-in syndrome, patients may awaken from coma fully conscious but paralyzed, only able to communicate by eye movements. The medical and ethical management of these vulnerable patients is very complex and a recent article reviewed the even more challenging (but fortunately very rare) situation of locked-in syndrome in children [10•]. Locked-in patients illustrate how difficult it can be to make inferences about subjective conscious awareness in severely motor impaired brain lesioned patients. How can we measure consciousness at the bedside (Fig. 1)?

Quantifying consciousness

The clinical assessment of consciousness relies on disentangling automatic responses from nonreflex-oriented movements or command following. This can be very challenging in coma and related disorders. Motor responses may be very small, inconsistent and easily exhausted, potentially leading to diagnostic errors [11]. A recent prospective study on 103 coma survivors showed that the clinical consensus diagnosis of 'vegetative state/UWS', attributed to 44 patients, was incorrect in 18 cases when properly assessed using a standardized consciousness scale, the Coma Recovery Scale-Revised [12••]. Such a high rate of diagnostic error (i.e. 41%) should prompt clinicians to use validated behavioral scales of consciousness before making the diagnosis of vegetative state/UWS.

Similar to the problem of quantifying consciousness, it remains a clinical and ethical challenge to measure conscious perception of pain in these patients with DOC. A European survey showed that 56% of 1166 medical and 68% of 538 paramedical professionals thought that 'vegetative' patients could feel pain [13•]. Healthcare givers with religious affiliation reported more often that vegetative state/UWS patients might experience pain. Different beliefs on possible pain perception may have consequences in terms of analgesic treatment. When the decision to treat for pain is taken, it remains difficult to monitor the therapeutic effect in these noncommunicative patients. Schnakers *et al.* [14•] therefore proposed a new scale to standardize and evaluate nociception in DOC, the Nociception Coma Scale. When patients score more than 7 on a total score of 12, the authors propose to start analgesia. Objective paraclinical neuroimaging studies are needed to increase our understanding of residual sensation in DOC patients and to propose evidence-based medical guidelines for their care [15•].

Paraclinical diagnostic markers

Structural MRI studies such as diffusion tensor imaging permit to quantify lesions to the brain's white matter tracts, often invisible to conventional radiological approaches [16]. Fernandez-Espejo *et al.* [17•] used this technique in 25 DOC patients of traumatic and nontraumatic cause and showed that vegetative state/UWS could be differentiated from MCS with a 95% accuracy.

Functional imaging such as PET permits to quantify the brain's glucose metabolism in 'resting' (i.e. unstimulated) conditions. Phillips *et al.* [18••] recently developed a 'relevance vector machine' automated consciousness classifier using metabolic PET scans to categorize, with a 100% accuracy, eight conscious locked-in from 13 unconscious vegetative state/UWS patients. Cerebral PET imaging can also be employed to disentangle reflex from nonreflex movements. Bruno *et al.* [19•] showed that anoxic vegetative state/UWS patients with ($n=5$) or without ($n=5$) visual fixation presented an identical brain metabolism and corticocortical functional connectivity, concluding that visual fixation does not necessarily reflect consciousness.

Resting state functional MRI similarly can measure the brain's 'default' activity looking at spontaneous hemodynamic fluctuations in blood-oxygen-level-dependent (BOLD) signal. It has long remained controversial whether these spontaneous fluctuations reflect consciously directed mental activity. However, recent evidence shows that this technique can be used to correlate subjective 'internal' self-related thoughts with activity in midline cortical structures and 'external' sensory perceptions with lateral frontoparietal activity [20]. If this is true, it would be useful to assess fMRI 'resting state' brain fluctuations, considered to reflect spontaneous thoughts, in coma and 'vegetative' patients – who are not supposed to have any thoughts or feelings. Boly *et al.* [21] were the first to use this approach in brain death and vegetative state/UWS, showing a complete absence of 'default mode network' connectivity in the former and a partially preserved activity in the latter condition. Building on these results, Vanhaudenhuyse *et al.* [22••] studied resting-state fMRI connectivity in 14 severely brain-damaged patients of mixed cause, reporting a nonlinear disintegration when conscious locked-in syndrome patients were compared to MCS, vegetative state/UWS and comatose states. Similarly, dysfunctional 'default mode network' connectivity was reported by others in small case series of vegetative state/UWS [23,24], but its diagnostic value at the individual patient level remains to be shown.

fMRI activation studies classically measure the brain's response to external sensory stimuli. Qin *et al.* [25] has studied auditory processing in 11 DOC patients using an autoreferential attention-grabbing stimulus, that is the patient's own name. They reported a linear correlation between activation of the limbic system (anterior cingulate cortex) and the level of consciousness as quantified by the Coma Recovery Scale-Revised. However, such 'passive' stimulation-induced brain activation does permit to make strong claims about the patient's consciousness.

Monti *et al.* [26••] used a so called 'active' paradigm in which patients were instructed to follow simple commands. Their study enrolled 54 DOC cases of different cause in imaging centers in Cambridge and Liège, asking patients to perform two mental imagery tasks: 'imagine playing tennis' (activating motor areas) and 'imagine to walk around in your house' (activating parahippocampal brain regions). Of the 31 patients previously diagnosed as MCS based on standardized behavioral assessments, only one was able to show reliable fMRI activation in the expected brain areas, illustrating that the employed technique only has a sensitivity of 3% in minimally conscious DOC patients (i.e. has a 97% false negative rate). It is more difficult to calculate the technique sensitivity and specificity in vegetative state/UWS patients, as there is no gold standard for assessing consciousness. Indeed, in the published case series, four out of 23 clinically 'unconscious' patients showed fMRI signs of command following and hence of consciousness (i.e. 17%). Nevertheless, given the known low sensitivity, it could be that other patients might have been (minimally) conscious, yet were unable to do the task or show statistically significant brain activation. However, in those individual patients in whom reliable and long-lasting (>30 s) command-related fMRI activation was observed, there seems no other logical alternative explanation other than that they repeatedly understood and replied to the commands and hence truly showed conscious awareness [27,28]. Similarly, a recent study by Rodrigez-Moreno *et al.* [29] used a silent picture-naming task as an 'active' fMRI paradigm searching for proof of consciousness in 10 DOC patients of mixed cause.

In addition to demonstrate proof of consciousness, fMRI can now be used to communicate with some (very exceptional) DOC patients. Indeed, one clinically noncommunicative patient studied in the Liège University Hospital was shown to correctly answer five out of six simple questions regarding his family members' names [26••]. Here, it was set that to communicate 'yes' one should imagine playing tennis (and hence motor area activation was identified using an automated user-independent relative-similarity classifier) and to communicate 'no' the spatial navigation task should be performed (activating parahippocampal areas). fMRI muscle-independent communication currently even goes beyond such yes–no answers to opened questions and is offering the possibility to answer multiple choice questions [30•]. Evidently, these data should be seen as proofs of concept rather than as a practical means to truly assure long-term communication. EEG-based communication devices, called brain–computer interfaces, are therefore being developed as a more practical, transportable and cheaper alternative.

Similarly to the described fMRI 'active' paradigms, EEG-based technology will aim to answer two questions: 'Is the patient conscious?' and, if the answer is affirmative; 'What is that consciousness like?', needing functional communication [31]. The practical utility of demonstrating voluntary brain activity using nonclinical means was recently illustrated in the case of a 21-year-old comatose woman who failed to show any motor sign of conscious awareness up to 49 days after an extensive brainstem and thalamic stroke [32]. Only EEG evoked potential based on command following (i.e. counting a target name in a list of names) permitted to make the diagnosis of complete locked-in syndrome shown at the ICU. Similarly, EEG-based evidence of conscious processing (i.e. count a deviant sound sequence in a series of beeps) was demonstrated in three out of four MCS patients while no 'willful' modulation of evoked potentials was recorded in four vegetative state/UWS patients [33]. Ongoing multicentric trials are validating the possible prognostic value of these tests.

Paraclinical tests predicting outcome

Structural MRI diffusion tensor imaging combined with MRI spectroscopy holds promising potential as an objective quantitative outcome-prediction tool [34,35•]. This method provides useful metabolic information on brain damage that may not be visible on classical morphologic imaging. In a cohort of 43 DOC patients studied 2–5 weeks after a traumatic brain injury, the combination of both MRI measurements permitted to predict 1-year unfavorable outcome with up to 86% sensitivity and 97% specificity [36•]. This approach is also being employed in vegetative state/UWS [37] and MCS patients [38]. The prognostic value of MRI spectroscopy was also shown in 90 children with nonaccidental trauma [39•].

The prognostic value of functional MRI 'passive' activation studies was proposed by Di *et al.* [40] concluding that vegetative state/UWS patients with absent or 'low-level' sensory cortex activation showed 100 and 84% of bad outcome, respectively, whereas those showing 'higher-level' associative cortex activation showed a 82% recovery rate (i.e. resulting in a 93% specificity and 69% sensitivity of the included 14 studies encompassing 48 patients). A prospective study using auditory stimulation in 22 vegetative state/UWS and 19 MCS patients recently confirmed the predictive value of fMRI activation studies by demonstrating that the level of cerebral processing correlated with patients' recovery at 6 months follow-up [41•].

Similarly, electrophysiological studies have aimed to predict outcome from DOC. A standardized classification method of routine 'resting-state' EEG showed a correlation at the group level with 3-month outcome measures in 46 DOC patients of varying cause [42]. In a retrospective study of 'resting-state' routine EEG from 50 vegetative state/UWS patients, Babiloni *et al.* [43] showed that increased alpha wave power correlated with 3-month recovery. Cologan *et al.* [44•] recently reviewed the literature on sleep–wake EEG recordings in DOC, discussing the positive predictive value of sleep 'spindle' waves for recovery of consciousness. Using evoked potentials and 'passive' auditory oddball stimuli, the presence of a 'P300' wave to rare stimuli correlated with recovery of consciousness in 34 patients with posttraumatic vegetative state/UWS [45]. Finally, the presence of Pavlovian eye-puff trace conditioning was proposed as a marker of learning in 20 DOC patients, correlating with recovery [46••]. In addition to their clinical diagnostic and prognostic usefulness, these studies have evident neuroscientific importance, helping in our understanding of the neural correlates of human consciousness.

Conclusion

Consciousness can be viewed as the emergent property of the collective behavior of widespread thalamocortical frontoparietal network connectivity [47]. Many of the above-presented studies, and increasing evidence from neuroscientific studies not discussed here on physiological (e.g. sleep [48•,49] and hypnosis [50,51]), pharmacological (e.g. in general anesthesia [52•]) and pathological alterations of consciousness (e.g. [53,54,55•,56•]) provide evidence in favor of this hypothesis. For most neuroscientists, you are your brain. However, such a scientific perspective of human consciousness, awareness or mind is not universally accepted. A recent survey of 782 medical and 290 paramedical professionals showed that more than one-third regarded mind and brain as separate entities. Such dualistic perceptions were predicted most strongly by personal religious and philosophical convictions [57]. The study of consciousness has indeed been the subject of philosophy for centuries. Functional neuroimaging and electrophysiology has now changed this, permitting to make measurements of the brain's activity and correlate this with conscious perception in health and disease. This short review on last year's articles in the field illustrates the increase in our understanding of the neural correlates of consciousness. This knowledge helps clinicians to do a better job in terms of diagnosis [58], prognosis [59] and finally, we hope, treatment [60] and may improve industry drug development (e.g. the use of functional imaging in demonstrating the effect of amantadine [61] and methylphenidate [62] on 'consciousness' networks in DOC patients). Increasing evidence from functional neuroimaging and electrophysiology demonstrates some residual cognitive processing in a subgroup of patients who clinically fail to show any response to commands. This led to the recent proposal of 'unresponsive wakefulness syndrome' as an alternative name for patients previously coined 'vegetative' or 'apallic'. The current challenge remains to continue translating this research from the bench to the bedside – within a well defined ethical framework (e.g. see [63–65]). Only well controlled large multicentric neuroimaging and electrophysiology studies will enable to identify which paraclinical diagnostic or prognostic test is necessary, at any given time, for our routine evidence-based assessment of individuals with DOC.

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