Article

Functional Neuroimaging Approaches to the Changing Borders of Consciousness

Quentin Noirhomme, Andrea Soddu, Audrey Vanhaudenhuyse, Rémy Lehembre, Marie-Aurélie Bruno, Olivia Gosseries, Athena Demertzi, Audrey Maudoux, Caroline Schnakers, Pierre Boveroux, Mélanie Boly, and Steven Laureys

Coma Science Group, Cyclotron Research Centre and Neurology Department, University and University Hospital of Liège, Belgium

Abstract. The bedside diagnosis of vegetative and minimally conscious patients is extremely challenging, and prediction of individual long-term outcome remains difficult. State-of the art neuroimaging methods could help disentangle complex cases and offer new prognostic criteria. These methods can be divided into to three categories: First, new anatomical MRI neuroimaging methods, like diffusion tensor imaging (DTI) or spectroscopy, and passive functional imaging methods (looking at the brain's activation induced by external stimuli), could provide new diagnostic and prognostic markers. Second, neuroimaging methods based on active collaboration from the patient could help to detect clinically unnoticed signs of consciousness. Third, developments in brain-computer interfaces based on EEG, functional MRI, or EMG offer communication possibilities in brain-damaged patients who can neither verbally nor nonverbally express their thoughts or wishes. These new approaches raise important issues not only from a clinical and ethical perspective (i.e., patients' diagnosis, prognosis and management) but also from a neuroscientific standpoint, as they enrich our current understanding of the emergence and function of the conscious human mind.

Keywords: disorder of consciousness, coma, vegetative state, minimally conscious state, functional imaging, EEG, PET, fMRI

Introduction

Acute brain injury, whether traumatic or anoxic, can cause coma. Until 50 years ago, most comatose patients died (e.g., from apnea) or seldomly recovered but with cerebral deficits of varying severity. Coma outcome improved following the invention of the artificial ventilator by Bjorn Ibsen in the 1950s, which in turn lead to the development of intensive care and to the dissociation of cardiac, respiratory, and brain function. Nowadays, although most patients recover from coma within the first days after the injury, some permanently lose all brainstem functions (brain death, i.e., irreversible coma with absent brainstem reflexes; Laureys, 2005b), whereas others progress to "wakeful unawareness," i.e., "awaken" from coma, open their eyes spontaneously or on stimulation, but remain unaware of self or environment (show only reflex motor response) – the vegetative state (VS) (Jennett & Plum, 1972). The latter will either not evolve anymore or will progress through different stages before fully or partly recovering consciousness (minimally conscious state, MCS). MCS patients show inconsistent but reproducible, limited but clearly discernible, evidence of awareness of self or environment (Giacino et al., 2002). There is yet another condition, the locked-in syndrome (LIS) (Plum, 1966), in which the patient emerges from coma fully aware but unable to move or communicate, except by small eye movement.

Consciousness has two main components: wakefulness and awareness (Figure 1). In normal physiological conditions, wakefulness and awareness are positively correlated (with the exception of rapid eye movement sleep). Patients in coma or anesthetized subjects are unconscious because they cannot be awakened. VS is a unique dissociated state of wakefulness without awareness (i.e., only motor reflexes can be observed). Wakefulness is supported by the function of the subcortical arousal systems in the brainstem and thalamus. Awareness is thought to be supported by the functional integrity of the cerebral cortex and its subcortical connections (Laureys, 2005a).

Nowadays, the clinical diagnosis of patients with disorders of consciousness (DOC) such as VS and MCS is based on the evaluation of motor activity and command following. This is extremely challenging because these patients are usually deprived of the capacity to make normal phys-

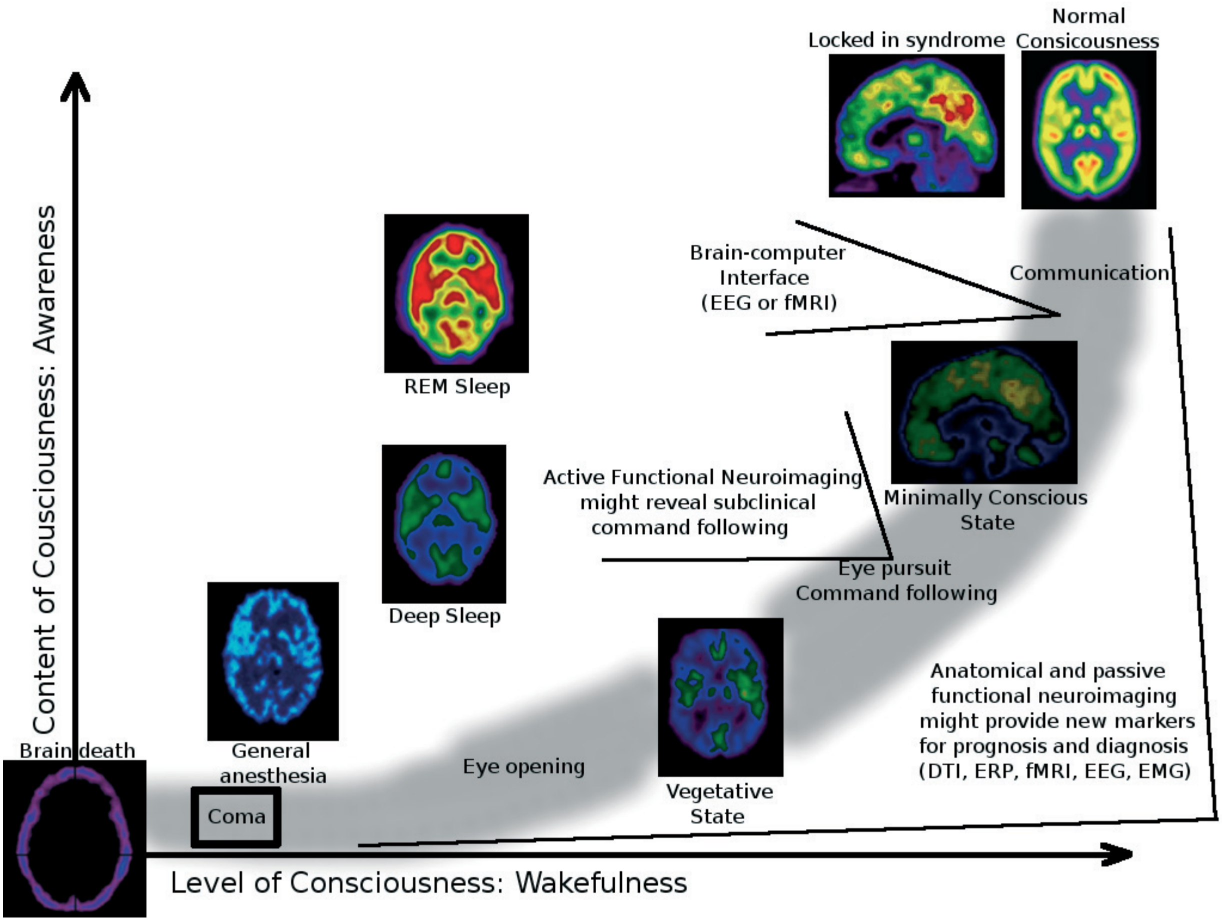

Figure 1. Illustration of the two major components of consciousness: the level of consciousness (i.e., arousal or wakefulness) and the content of consciousness (i.e., awareness) (adapted from Laureys, 2005). Physiological (sleep) and pharmacological (general anesthesia) modulation of arousal correlates with massive global decreases in cortical metabolism (in REM sleep metabolic activity is paradoxically prominent). Behaviorally, the transition from coma to vegetative state is characterized by recovery of arousal (but the lack of awareness). The transition from vegetative to minimally conscious state is characterized by nonreflexive movements or command following, and emergence from the minimally conscious state is characterized by the ability to communicate. New neuroimaging tools are offering better diagnostic and prognostic markers and EEG and fMRI paradigms are challenging the clinical borders of disorders of consciousness.

ical movements and may show only limited attentional capacities. Furthermore, clinical studies have shown how difficult it is to differentiate reflex from voluntary movements (see (Majerus, Gill-Thwaites, Andrews, & Laureys, 2005) for review). Finally, aphasia, apraxia, and cortical deafness or blindness are other possible confounders. Therefore, recognizing the subtle difference between MCS and VS requires repeated evaluations even by skilled examiners. Not surprisingly, the misdiagnosis rate between the two states is around 40% (Schnakers et al., 2009).

The prognosis for survival and recovery from coma, VS, MCS, or LIS is still difficult to establish at the individual level. Certain factors, however, increase the chances of recovery. The young age of the patient, a traumatic etiology, and the short duration of the state are linked to a better outcome ("Medical Aspects of the Persistent Vegetative State (1). The Multi-Society Task Force on PVS," 1994). Additionally, patients who are MCS for 1 month after brain injury have a better chance of recovery than patients who are VS 1 month postinjury. Patients who are vegetative 1 year (3 months) following a traumatic (anoxic) injury have very few chances of recovery. The life expectancy of most vegetative patients varies between 2 and 5 years, with very few patients staying more than 10 years in this state, whereas the average survival time for LIS patients is about 6 years (± 4 years). However, cases of recovery after many years have been reported (Laureys, Boly, & Maquet, 2006; Wijdicks, 2006).

Advanced magnetic resonance imaging (MRI) methods and functional neuroimaging now offers the possibility to improve the measurement of the spread of a brain lesion and to directly measure the brain's activity, not only at rest or during passive stimulation, but also in response to commands. These methods could enhance new important steps in the continuum from coma to recovery of consciousness and offer new markers for improving prognosis. We give here a brief overview of the clinical assessment of DOC through behavioral testing. Then, we report on the current developments in anatomical and functional neuroimaging methods that should help to define new diagnostic and prognostic markers. Active functional neuroimaging paradigms, where the patient must respond or pay attention to the stimuli, and which better define the boundary between VS and MCS, are presented next. We also show how these methods could pertain to the neuroimaging of emergence. Finally, we discuss some important ethical considerations and future directions.

Behavioral Assessment

While wakefulness is assessed by eye-opening (spontaneously or in response to stimulation), bedside assessment of awareness is more challenging. Awareness is a first-person perspective, and its clinical evaluation is limited to evaluating patients' motor responsiveness. To help clinicians, standardized bedside tools have been developed. The Glasgow Coma Scale (GCS) (Teasdale & Jennett, 1974) remains the gold standard in coma. The GCS assesses eye-opening and motor and verbal responsiveness. Some authors disagree whether evaluation of spontaneous or stimulation-induced opening of the eyes is sufficiently indicative of brain stem arousal system activity and have proposed coma scales that include brain stem reflexes like the Glasgow-Liège scale (Born, Albert, Hans, & Bonnal, 1985). However, only the GCS has experienced widespread use because of its short and simple administration. More sensitive scales are the Full Outline of Unresponsiveness (FOUR) (Wijdicks, Bamlet, Maramattom, Manno, & McClelland, 2005), the Coma Recovery Scale-Revised (CRS-R) (Giacino, Kalmar, & Whyte, 2004), and the Wessex Head Injury Matrix (WHIM) (Shiel, Horn, Wilson, Watson, Campbell, & McLellan, 2000). The CRS-R (Giacino et al., 2004) is a recent scale specifically developed to differentiate VS from MCS which explicitly incorporates current diagnostic criteria. The basic structure of the CRS-R is similar to the GCS, though its subscales are much more detailed and also contain auditory, arousal, and communication subscales.

A consensus on how to practically assess some of the behavioral responses used in these scales is often missing. For example, there is no agreement on what stimulus to employ in the assessment of visual pursuit movements – often one of the first clinical signs heralding the transition from the vegetative to the minimally conscious state. Vanhaudenhuyse and colleagues (Vanhaudenhuyse, Schnakers, Bredart, & Laureys, 2008) studied visual pursuit in 51 post-comatose patients comparing eye-tracking of a moving object, person, or mirror. They showed that more than a fifth of the minimally conscious patients with visual pursuit only showed eye-tracking when studied by means of a moving mirror and not by means of a moving object (i.e., the stimulus most frequently used in a routine neurological examination) or by means of a moving person. Other controversial clinical signs are the definition and clinical assessment of visual fixation, oriented motor responses to noxious stimuli, and blinking responses to visual threat. The latter was recently demonstrated as being present in about half of the patients who showed all the features typical of the VS (Vanhaudenhuyse, Giacino et al., 2008). The authors concluded it was not a reliable indicator of consciousness neither of recovery of consciousness.

Neuroimaging Diagnosis and Prognosis Markers

Classical and newly developed neuroimaging methods have been proposed to probe the spread of changes in brain anatomy and residual brain function in DOC. These studies track new diagnosis and prognosis markers employing four different methodological approaches: First, advanced anatomical imaging can assess changes not only in the brain's anatomy, but also in the brain's chemical properties or functional connectivity. Second, PET studies detect global and regional changes in brain metabolism. Nowadays, global changes are also tracked with EEG. Third, event-related studies are probing different brain systems by means of auditory or somatosensory stimulation paradigms. These studies employ a hierarchical approach, starting with simple stimuli (leading to low-level local brain activation) to progressively more complex ones (leading to activation of a progressively wider network of cerebral areas reflecting higher cognitive processing). Fourth, the brain can be probed by a recently introduced approach known as "default mode" or "resting state" network assessments (not based on the brain's response to external stimulation, but tracks functional connectivity in the "thinking" resting brain) (Boly, Phillips et al., 2008; Boly et al., 2009; Vanhaudenhuyse et al., 2010).

Anatomy and Anatomical Connectivity

Canonical MRI studies are limited to the study of the anatomical location of the lesion, while more advanced MRI methods, such as voxel-based volumetry or morphometry and spectroscopy enables, respectively, the objective quantification of changes in brain structure, and the 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) (see Galanaud, Naccache, & Puybasset, 2007 and Tshibanda, Vanhaudenhuyse, Galanaud, Boly, Laureys, & Puybasset, 2009, for review). Changes in anatomical connectivity can also be tracked through diffusion tensor imaging (DTI) (Galanaud et al., 2007) – a technique that has already shed light on the mechanisms of recovery from the minimally conscious state, identifying axonal regrowth in the brain of a patient who emerged from a minimally conscious state after 19 years of silence (Voss et al., 2006).

Global Activity

PET and EEG can track global changes in brain function. PET imaging studies showed a reduction of global metabolic activity of up to 50% of normal values in VS patients (Figure 1) (Laureys, Goldman et al., 1999; Laureys, Lemaire, Maquet, Phillips, & Franck, 1999). Similar global decreases in metabolic activity are observed in deep sleep and in anesthesia (Maquet, 1997). However, some well-documented VS patients have shown close to normal global metabolic activity (Schiff et al., 2002). The EEG bispectral index scale (BIS) and EEG entropy measurements, two global EEG measures, measure the depth of sedation in anesthesia (Struys et al., 1998; Viertio-Oja et al., 2004) and were tested on DOC patients. BIS values also gradually decrease during sleep (Noirhomme et al., 2009) and when patients evolve to a coma or VS (Schnakers, Ledoux et al., 2008). It was also shown to have prognostic value in DOC (Schnakers, Ledoux et al., 2008). However, BIS is a nonspecific measure of consciousness and does not systematically differentiate MCS from VS patients at the individual level (Schnakers, Majerus, & Laureys, 2005). The EEG entropy seems to offer similar results in DOC as does EEG-BIS monitoring (Gosseries, unpublished data).

Functional Neuroimaging

Preserved cortical information processing capabilities in a given area or network can be assessed by employing hemodynamic measurements (such as blood flow PET or fMRI) or magneto-electrical measurements of the brain (such as EEG or magnetoencephalography, MEG). In fMRI and PET studies, primary cortices still seem to activate in vegetative patients during external stimulation, whereas hierarchically higher-order multimodal association areas do not (reviewed in (Giacino, Hirsch, Schiff, & Laureys, 2006)). Similar results have been obtained with EEG evoked potential studies (Vanhaudenhuyse, Laureys, & Perrin, 2008, for a review). Early components of event-related potentials arising within 100 ms are related to activity in primary cortices. Later components (e.g., P3b, P600, contingent negative variation, readiness potential), seem related to the higher-order cognitive processing of the external stimuli.

The auditory system is the best probed one in DOC – due to the ability to present an auditory stimuli and the possibility to have graded complexity of stimuli (ranging from simple sounds, to words, and complete sentences). Probing the visual system requires sustained eye-opening and visual fixation, which is often difficult to obtain in DOC patients. Somatosensory stimulation is easier but does not permit administration of stimuli with graded complexity. Therefore, presentation of simple sounds, words, the patient's own name, or sentences have been most often used in mismatch negativity, oddball paradigm, or block-design paradigms (Coleman et al., 2007; Kotchoubey et al., 2005). In patients in a MCS, auditory stimuli triggers higher-order cortical activity normally not observed in VS (Boly et al., 2005). Along the same line, auditory stimuli with emotional valence (such as infant cries or the patient's own name, see Laureys et al., 2004; or a narrative told by the patient's mother, see Schiff et al., 2005) induce a much more widespread activation in patients in a minimally conscious state than meaningless stimuli do. However, the activation of higher-order cortical processing or the appearance of a P300 is not enough to distinguish an individual VS patient from a MCS patient. EEG studies have reported that some VS patients might be capable of processing semantic stimuli, indicating some comprehension of meaning (Kotchoubey, 2005) or reported a P300 response to salient stimuli (Perrin et al., 2006). In other experiments with fMRI, VS patients exhibited activity in higher-order areas similar to the activity observed in MCS patients and controls, either while listening to their own name spoken by a familiar voice (Di et al., 2007) or in a semantic ambiguity test (Coleman et al., 2007). These experiments indicate that content *does* matter when talking to a DOC patient.

Similarly, during noxious stimulation, only the brainstem, the thalamus, and the primary somatosensory cortex are activated in VS, and the latter is isolated and disconnected from the other brain areas (Boly et al., 2005; Laureys et al., 2002). These findings support the idea that patients in a vegetative state do not perceive pain in the same manner as healthy people. In contrast to VS patients, MCS patients showed an activation pattern of the complete pain matrix very similar to that observed in healthy controls encompassing thalamus, primary and secondary somatosensory, frontoparietal, and anterior cingulate cortices and with a preserved functional connectivity between these areas (Boly, Faymonville et al., 2008). These findings might be objective evidence of a potential pain perception capacity in MCS patients, which supports the idea that these patients need analgesic treatment.

All these studies support the idea of probing sensory brain areas but also higher cognitive networks with a hierarchical approach. Owen and Coleman (Owen & Coleman, 2008) suggested probing the auditory system with fMRI for its understanding of speech from basic to complex sentences (e.g., semantic ambiguity testing). Correspondingly, Kubler and Kotchoubey (Kubler & Kotchoubey, 2007) proposed a five-stage assessment involving resting EEG, passive stimulation (e.g., a standard oddball paradigm), stimulation following simple instructions, volitional tasks, and decision-making with a brain-computer interface (BCI). The last two levels are based on active responses and BCI and are discussed in the next sections.

Nowadays, we do not know whether these early signs of higher cortical activity could be seen as prognosis or diagnosis markers. In the former case, not enough patients have been probed yet to infer the higher activation as a good prognosis of a further evolution from VS to MCS (Di, Boly, Weng, Ledoux, & Laureys, 2008), or from MCS to emergence. In the latter case, it is too early to see these early neurological signs as new diagnostic marker.

Resting State

The study of the brain's activity in a *resting state* has emerged as a new way to probe brain functional connectivity. Over the last years, increasing attention has been paid to the study of spontaneous brain activity and its significance for cognition and behavior (Raichle, 2006). In particular, the concept of a *default mode of brain function* was introduced by Raichle et al. (Raichle, MacLeod, Snyder, Powers, Gusnard, & Shulman, 2001), after observing that a number of areas, including the precuneus, bilateral temporoparietal junctions, and medial prefrontal cortex, were more active at rest than when healthy subjects were involved in an attention-demanding cognitive task. This network of areas is now commonly referred to as the *default network*. Though its functional significance remains a matter of debate, it has been suggested as a candidate for the network subserving basic functions related to consciousness (Boly, Phillips et al., 2008; Greicius et al., 2008). Other networks are reliably found in healthy controls and are related to known brain systems, e.g., the extrinsic, salience, executive, auditory, or visual networks. Of potential major interest from a clinical perspective is that resting state fMRI acquisitions do not require patients' collaboration and are easier to perform compared to the classical task-based fMRI paradigms described above. Boly and colleagues recently studied such spontaneous activation in patients with DOCs, showing that default network connectivity decreased in severely brain-damaged patients in proportion to their degree of consciousness impairment, ranging from healthy controls and locked-in syndrome, to minimally conscious, vegetative and comatose patients (Boly et al., 2009; Audrey Vanhaudenhuyse et al., 2010). Furthermore, precuneus connectivity was found to be significantly stronger in minimally conscious patients compared to vegetative state patients.

Active Neuroimaging

The border between VS and MCS is defined by the presence of "voluntary" movements (e.g., eye-tracking; Vanhaudenhuyse, Giacino et al., 2008) and the ability to respond to commands in an inconsistent but reproducible way. In some patients, the recovery of consciousness could precede motor recovery. For this reason, paradigms demanding active collaboration of the subject have been proposed. In ERP studies, selective attention could be translated in the appearance of a P3 wave or in an increase of amplitude of a P3 response. In a study in which DOC patients were instructed to recite their own name (Schnakers, Perrin et al., 2008), the 14 studied MCS patients presented a larger P3 to the patient's own name while reciting than while just listening to the target, similar to results obtained in controls. In contrast, no differences in P3 waves between passive and active conditions were observed for VS patients. In another experiment (Bekinschtein, Dehaene, Rohaut, Tadel, Cohen, & Naccache, 2009), an auditory paradigm evaluated cerebral responses to violations of temporal regularities that were either local in time or global across several seconds. In controls, local violations led to an early response in auditory cortex, independent of attention, while global violations led to a late and spatially distributed response that was present only when subjects were attentive and aware of the violations. When applied to 8 DOCs patients, only conscious individuals presented a measurable global effect.

Similarly, in a fMRI paradigm based on mental imagery tasks, patients were instructed to imagine playing tennis or walking through their house (Boly et al., 2007). Despite the clinical diagnosis of VS, a patient who had suffered a traumatic brain injury 5 months earlier showed brain activation similar to that of the control subjects for both tasks (Owen, Coleman, Boly, Davis, Laureys, & Pickard, 2006). A few months after the study, the patient was also behaviorally recognized as MCS. With a comparable methodology based on EMG, Bekinschtein and colleagues (Bekinschtein, Coleman, Niklison, Pickard, & Manes, 2008) investigated command following (i.e., "move your hand") while recording EMG activity in 8 VS patients. In one such patient, significant command related subbehavioral threshold EMG changes could be demonstrated.

The results of these studies should not be misinterpreted as evidence that *all* patients in a VS may actually be conscious. We have not observed any similar signs of awareness in fMRI scans in a large cohort of VS patients studied at the University of Liège (Belgium). The most likely explanation for these results is that the patients were already beginning the transition to MCS at the time of the experiment. These paradigms might be a useful method to preclinically recognize MCS – like cognitive processing in patients behaviorally classified as VS.

Neuroimaging Emergence of Communication

Emergence from MCS is characterized by the ability to exhibit functional interactive communication. Functional neuroimaging could help us to distinguish LIS from VS, but also to disentangle more complex cases of DOC. Brain-computer interface (BCI), based either on EEG (Kubler & Kotchoubey, 2007) or on fMRI (Sorger et al., 2009), have been proposed as the ultimate way of probing consciousness. A BCI is a device that allows the brain to communicate to the external world without using the traditional pathways (e.g., muscle or voice) (Wolpaw, Birbaumer, McFarland, Pfurtscheller, & Vaughan, 2002). The neural activity of the brain is acquired, processed, and transformed into a simple command (e.g., yes/no). BCI is a growing field of research based on EEG or fMRI, but also intracranial electrodes. Nowadays BCIs work on detecting brain activity generated either by concentrating on a task (e.g., imagination/intention of movements, word task, etc.) or in response to external stimuli (e.g., event-related potential, steady-state visually evoked potential). BCIs have been tested on patients with amyotrophic lateral sclerosis (ALS) and LIS with some success (Kubler & Birbaumer, 2008). A BCI developed to work with DOCs should take into account the possibly highly fluctuating state of these patients and their tiredness. Demanding tasks, either too long or requiring too much concentration should be avoided. One way to address this problem is the continuation of the work initiated by Bekinschtein and colleagues based on detecting subthreshold EMG activity (Bekinschtein et al., 2008).

Conclusion

In clinical practice, the misdiagnosis of DOC patients is still frequent, despite the introduction of diagnostic criteria and the development of appropriate scales (e.g., the Coma Recovery Scale-Revised) to assess the patient's level and content of consciousness. Conscious patients can indeed be misdiagnosed as vegetative if they have severe, near-complete motor impairment or when voluntary movements are erroneously interpreted as reflexes. Standardized behavioral scales and quantitative individual assessments should therefore be employed repetitively in the clinical routine by trained medical staff, in order to minimize the risk of erroneous diagnosis.

Technological advances in neuroimaging allow us to increase our understanding of the human brain, and this knowledge can be exploited in order to develop new diagnostic and prognostic approaches. Studies have shown that a typical VS is characterized by a functional cortical disconnection syndrome. Only primary cortices seem to be activated but are disconnected from the frontoparietal "higher-order" cortical network. In the MCS, however, the latter areas can be activated and engaged at the lowest level of consciousness. Yet some vegetative patients have shown activation patterns similar to the ones observed in MCS. Is this enough to change their clinical diagnosis? This question needs more investigation before evidence-based answers can be provided to the medical community. Advanced diagnostic techniques based on mental imagery and on cognitive event-related potentials using active paradigms are currently being investigated. Techniques such as BCI are expected to be clinically used as a diagnostic tool in order to differentiate between conscious and unconscious patients.

DOC patients, especially patients in VS, present important ethical and moral issues.

For now, only clinical examinations can be taken into account when therapeutic decisions have to be made, even if fMRI, cognitive ERPs, or PET data sometimes precede the results of clinical recovery. Those neuroimaging studies remain in the research field, and the clinical application of these techniques still awaits validation from ongoing multicenter cohort studies. However, when those paraclinical examinations do become available, they can provide additional information that can be used to better understand the patient's situation and outcome. We think that, in the near future, multimodal approaches including bedside examination, electrophysiology, and functional imaging techniques will be employed to assess and treat disorders of consciousness.

Acknowledgments

This research was funded by the Belgian National Funds for Scientific Research (FNRS), the European Commission (DISCOS, COST, Mindbridge, DECODER), the James McDonnell Foundation, the Mind Science Foundation, the French Speaking Community Concerted Research Action, the Foundation Médicale Reine Elisabeth, and the University of Liège.

References

Bekinschtein, T. A., Coleman, M. R., Niklison, J., 3rd, Pickard, J. D., & Manes, F. F. (2008). Can electromyography objectively detect voluntary movement in disorders of consciousness? *Journal of Neurology, Neurosurgery, and Psychiatry, 79*, 826–828.

Bekinschtein, T. A., Dehaene, S., Rohaut, B., Tadel, F., Cohen, L., & Naccache, L. (2009). Neural signature of the conscious processing of auditory regularities. *Proceedings of the National Academy of Sciences USA, 106*, 1672–1677.

Boly, M., Coleman, M. R., Davis, M. H., Hampshire, A., Bor, D., Moonen, G. et al. (2007). When thoughts become action: An fMRI paradigm to study volitional brain activity in noncommunicative brain injured patients. *Neuroimage, 36*, 979–992.

Boly, M., Faymonville, M. E., Peigneux, P., Lambermont, B., Damas, F., Luxen, A. et al. (2005). Cerebral processing of auditory and noxious stimuli in severely brain injured patients: Differences between VS and MCS. *Neuropsychological Rehabilitation, 15*, 283–289.

Boly, M., Faymonville, M. E., Schnakers, C., Peigneux, P., Lambermont, B., Phillips, C. et al. (2008). Perception of pain in the minimally conscious state with PET activation: An observational study. *Lancet Neurology, 7*, 1013–1020.

Boly, M., Phillips, C., Tshibanda, L., Vanhaudenhuyse, A., Schabus, M., Dang-Vu, T. T. et al. (2008). Intrinsic brain activity in altered states of consciousness: How conscious is the default mode of brain function? *Annals of the New York Academy of Sciences, 1129*, 119–129.

Boly, M., Tshibanda, L., Vanhaudenhuyse, A., Noirhomme, Q., Schnakers, C., Ledoux, D. et al. (2009). Functional connectivity in the default network during resting state is preserved in a vegetative but not in a brain dead patient. *Human Brain Mapping, 30*, 2393–2400.

Born, J. D., Albert, A., Hans, P., & Bonnal, J. (1985). Relative prognostic value of best motor response and brain stem reflexes in patients with severe head injury. *Neurosurgery, 16*, 595–601.

Coleman, M. R., Rodd, J. M., Davis, M. H., Johnsrude, I. S., Menon, D. K., Pickard, J. D. et al. (2007). Do vegetative patients retain aspects of language comprehension? Evidence from fMRI. *Brain, 130*, 2494–2507.

Di, H., Boly, M., Weng, X., Ledoux, D., & Laureys, S. (2008). Neuroimaging activation studies in the vegetative state: Predictors of recovery? *Clinical Medicine, 8*, 502–507.

Di, H. B., Yu, S. M., Weng, X. C., Laureys, S., Yu, D., Li, J. Q. et al. (2007). Cerebral response to patient's own name in the vegetative and minimally conscious states. *Neurology, 68*, 895–899.

Galanaud, D., Naccache, L., & Puybasset, L. (2007). Exploring impaired consciousness: The MRI approach. *Current Opinion in Neurology, 20*, 627–631.

Giacino, J. T., Ashwal, S., Childs, N., Cranford, R., Jennett, B., Katz, D. I. et al. (2002). The minimally conscious state: Definition and diagnostic criteria. *Neurology, 58*, 349–353.

Giacino, J. T., Hirsch, J., Schiff, N., & Laureys, S. (2006). Functional neuroimaging applications for assessment and rehabilitation planning in patients with disorders of consciousness. *Archives of Physical Medicine and Rehabilitation, 87*(12 Suppl. 2), S67–S76.

Giacino, J. T., Kalmar, K., & Whyte, J. (2004). The JFK coma recovery scale-revised: Measurement characteristics and diagnostic utility. *Archives of Physical Medicine and Rehabilitation, 85*, 2020–2029.

Greicius, M. D., Kiviniemi, V., Tervonen, O., Vainionpaa, V., Alahuhta, S., Reiss, A. L. et al. (2008). Persistent default-mode network connectivity during light sedation. *Human Brain Mapping, 29*, 839–847.

Jennett, B., & Plum, F. (1972). Persistent vegetative state after brain damage: A syndrome in search of a name. *Lancet, 1,* 734–737.

Kotchoubey, B. (2005). Event-related potential measures of consciousness: Two equations with three unknowns. *Progress in Brain Research, 150*, 427–444.

Kotchoubey, B., Lang, S., Mezger, G., Schmalohr, D., Schneck, M., Semmler, A. et al. (2005). Information processing in severe disorders of consciousness: Vegetative state and minimally conscious state. *Clinical Neurophysiology, 116*, 2441–2453.

Kubler, A., & Birbaumer, N. (2008). Brain-computer interfaces and communication in paralysis: Extinction of goal directed thinking in completely paralysed patients? *Clinical Neurophysiology, 119*, 2658–2666.

Kubler, A., & Kotchoubey, B. (2007). Brain-computer interfaces in the continuum of consciousness. *Current Opinion in Neurology, 20*, 643–649.

Laureys, S. (2005a). The neural correlate of (un)awareness: Lessons from the vegetative state. *Trends in Cognitive Sciences, 9*, 556–559.

Laureys, S. (2005b). Science and society: Death, unconsciousness and the brain. *Nature Reviews Neuroscience, 6*, 899–909.

Laureys, S., Boly, M., & Maquet, P. (2006). Tracking the recovery of consciousness from coma. *Journal of Clinical Investigation, 116*, 1823–1825.

Laureys, S., Faymonville, M. E., Peigneux, P., Damas, P., Lambermont, B., Del Fiore, G. et al. (2002). Cortical processing of noxious somatosensory stimuli in the persistent vegetative state. *Neuroimage, 17*, 732–741.

Laureys, S., Goldman, S., Phillips, C., Van Bogaert, P., Aerts, J., Luxen, A. et al. (1999). Impaired effective cortical connectivity in vegetative state: Preliminary investigation using PET. *Neuroimage, 9*, 377–382.

Laureys, S., Lemaire, C., Maquet, P., Phillips, C., & Franck, G. (1999). Cerebral metabolism during vegetative state and after recovery to consciousness. *Journal of Neurology, Neurosurgery, and Psychiatry, 67*(1), 121.

Laureys, S., Perrin, F., Faymonville, M. E., Schnakers, C., Boly, M., Bartsch, V. et al. (2004). Cerebral processing in the minimally conscious state. *Neurology, 63*, 916–918.

Majerus, S., Gill-Thwaites, H., Andrews, K., & Laureys, S. (2005). Behavioral evaluation of consciousness in severe brain damage. *Progress in Brain Research, 150*, 397–413.

Maquet, P. (1997). Positron emission tomography studies of sleep and sleep disorders. *Journal of Neurology, 244*(4 Suppl. 1), S23–S28.

Noirhomme, Q., Boly, M., Bonhomme, V., Boveroux, P., Philipps, C., Peigneux, P. et al. (2009). Bispectral Index correlates with regional cerebral blood flow during sleep in distinct cortical and subcortical structures in humans. *Archives Italiennes de Biologie, 147*, 51–57.

Owen, A. M., & Coleman, M. R. (2008). Functional neuroimaging of the vegetative state. *Nature Reviews Neuroscience, 9*, 235–243.

Owen, A. M., Coleman, M. R., Boly, M., Davis, M. H., Laureys, S., & Pickard, J. D. (2006). Detecting awareness in the vegetative state. *Science, 313*(5792), 1402.

Perrin, F., Schnakers, C., Schabus, M., Degueldre, C., Goldman, S., Bredart, S. et al. (2006). Brain response to one's own name in vegetative state, minimally conscious state, and locked-in syndrome. *Archives of Neurology, 63*, 562–569.

Plum, F., & Posner, J. B. (1966). *The diagnosis of stupor and coma* (1st ed.). Philadelphia: Davis FA.

Raichle, M. E. (2006). Neuroscience. The brain's dark energy. *Science, 314*(5803), 1249–1250.

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences USA, 98*, 676–682.

Schiff, N. D., Ribary, U., Moreno, D. R., Beattie, B., Kronberg, E., Blasberg, R. et al. (2002). Residual cerebral activity and behavioral fragments can remain in the persistently vegetative brain. *Brain, 125*(Pt 6), 1210–1234.

Schiff, N. D., Rodriguez-Moreno, D., Kamal, A., Kim, K. H., Giacino, J. T., Plum, F. et al. (2005). fMRI reveals large-scale network activation in minimally conscious patients. *Neurology, 64*, 514–523.

Schnakers, C., Ledoux, D., Majerus, S., Damas, P., Damas, F., Lambermont, B. et al. (2008). Diagnostic and prognostic use of bispectral index in coma, vegetative state and related disorders. *Brain Injury, 22*, 926–931.

Schnakers, C., Majerus, S., & Laureys, S. (2005). Bispectral analysis of electroencephalogram signals during recovery from coma: Preliminary findings. *Neuropsychological Rehabilitation, 15*(3–4), 381–388.

Schnakers, C., Perrin, F., Schabus, M., Majerus, S., Ledoux, D., Damas, P., . . . Laureys, S. (2008). Voluntary brain processing in disorders of consciousness. *Neurology, 71*, 1614–1620.

Schnakers, C., Vanhaudenhuyse, A., Giacino, J., Ventura, M., Boly, M., Majerus, S., . . . Laureys, S. (2009). Diagnostic accuracy of the vegetative and minimally conscious state: Clinical consensus versus standardized neurobehavioral assessment. *BMC Neurology, 9,* 35.

Shiel, A., Horn, S. A., Wilson, B. A., Watson, M. J., Campbell, M. J., & McLellan, D. L. (2000). The Wessex Head Injury Matrix (WHIM) main scale: A preliminary report on a scale to assess and monitor patient recovery after severe head injury. *Clinical Rehabilitation, 14*, 408–416.

Sorger, B., Dahmen, B., Reithler, J., Gosseries, O., Maudoux, A., Laureys, S., & Goekel, R. (2009). Another kind of "BOLD response": Answering multiple-choice questions via online decoded single-trial brain signals. *Progress in Brain Research*.

Struys, M., Versichelen, L., Mortier, E., Ryckaert, D., De Mey, J. C., De Deyne, C. et al. (1998). Comparison of spontaneous frontal EMG, EEG power spectrum and bispectral index to monitor propofol drug effect and emergence. *Acta Anaesthesiologica Scandinavica, 42*, 628–636.

Teasdale, G., & Jennett, B. (1974). Assessment of coma and impaired consciousness. A practical scale. *Lancet, 2*(7872), 81–84.

The Multi-Society Task Force on PVS. (1994). Medical aspects of the persistent vegetative state. *New England Journal of Medicine, 330*, 1499–1508.

Tshibanda, L., Vanhaudenhuyse, A., Galanaud, D., Boly, M., Laureys, S., & Puybasset, L. (2009). Magnetic Resonance Spectroscopy and Diffusion Tensor Imaging in coma survivors: Promises and pitfalls. *Progress in Brain Research, 177,* 215–229.

Vanhaudenhuyse, A., Giacino, J., Schnakers, C., Kalmar, K., Smart, C., Bruno, M. A. et al. (2008). Blink to visual threat does not herald consciousness in the vegetative state. *Neurology, 71*, 1374–1375.

Vanhaudenhuyse, A., Laureys, S., & Perrin, F. (2008). Cognitive event-related potentials in comatose and postcomatose states. *Neurocritical Care, 8*, 262–270.

Vanhaudenhuyse, A., Noirhomme, Q., Tshibanda, L., Bruno, M.-A., Boveroux, P., Schnakers, C. et al. (2010). Default network connectivity reflects the level of consciousness in noncommunicative brain damaged patients. *Brain, 133,* 161–171.

Vanhaudenhuyse, A., Schnakers, C., Bredart, S., & Laureys, S. (2008). Assessment of visual pursuit in postcomatose states: Use a mirror. *Journal of Neurology, Neurosurgery, and Psychiatry, 79*, 223.

Viertio-Oja, H., Maja, V., Sarkela, M., Talja, P., Tenkanen, N., Tolvanen-Laakso, H. et al. (2004). Description of the Entropy algorithm as applied in the Datex-Ohmeda S/5 Entropy Module. *Acta Anaesthesiologica Scandinavica, 48*, 154–161.

Voss, H. U., Uluc, A. M., Dyke, J. P., Watts, R., Kobylarz, E. J., McCandliss, B. D., . . . Schiff, N. D. (2006). Possible axonal regrowth in late recovery from the minimally conscious state. *Journal of Clinical Investigation, 116*, 2005–2011.

Wijdicks, E. F. (2006). Minimally conscious state vs. persistent vegetative state: The case of Terry (Wallis) vs. the case of Terri (Schiavo). *Mayo Clinic Proceedings, 81*, 1155–1158.

Wijdicks, E. F., Bamlet, W. R., Maramattom, B. V., Manno, E. M., & McClelland, R. L. (2005). Validation of a new coma scale: The FOUR score. *Annals of Neurology, 58*, 585–593.

Wolpaw, J. R., Birbaumer, N., McFarland, D. J., Pfurtscheller, G., & Vaughan, T. M. (2002). Brain-computer interfaces for communication and control. *Clinical Neurophysiology, 113*, 767–791.

Quentin Noirhomme

Coma Science Group, Cyclotron Research Centre
University of Liège
Bât. B30 Allée du 6 août n° 8
4000 Liège
Belgium
Tel. +32 4 366-2335
Fax +32 4 366-2946
E-mail quentin.noirhomme@ulg.ac.be