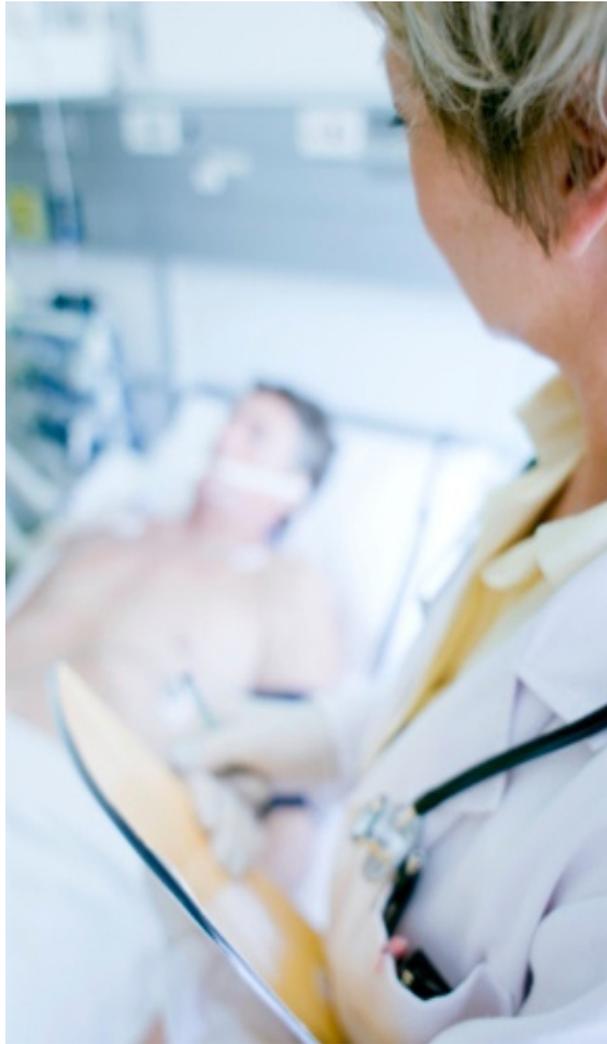


Uncovering Awareness: Medical and Ethical Challenges in Diagnosing and Treating the Minimally Conscious State

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Editor's note: Eight years ago an interdisciplinary group of scientists representing several institutions worked together to codify criteria for the minimally conscious state. Unlike vegetative patients, who have no conscious awareness, minimally conscious patients show signs of voluntary motor action and response. Technology, such as functional neuroimaging, is beginning to change the way medical professionals diagnose, treat, and communicate with patients once considered to have no or very little conscious awareness.

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Introduction

PV, a 12-year-old boy, was hit by a car while cycling to school. He was unconscious when bystanders found him; when the paramedics arrived, PV's condition was very bad. The Glasgow Coma Scale,¹ a standardized way to assess consciousness, recorded no eye opening ("eyes" response 1), no motor response to command or to noxious stimulation ("motor" response 1), and no production of speech sounds ("verbal" response 1) (see table 1). PV obtained the lowest Glasgow Coma Scale score possible (3/15), which indicates a deep coma. He needed tracheal intubation and mechanical ventilation to breathe. A CAT scan showed ventricle and meningeal hemorrhage with diffuse brain edema, indicating a severe brain injury. His electroencephalography showed diffuse slowing of the electrical activity of the brain, reflecting widespread brain dysfunction. The physicians informed PV's parents that the situation was critical and that if the swelling increased he might sustain brain death.

In the subsequent days the situation seemed to improve; after a week, PV opened his eyes and started to breathe without artificial help. He started to move his right arm, but later it turned out that these movements were reflexes, as he never responded to simple commands like "squeeze my hand." He was admitted to the neurology ward but remained in a vegetative state when transferred to a rehabilitation center three weeks later. For three months PV looked awake during the day and closed his eyes at night but never seemed to perceive anything said or shown to him. Finally, the medical doctor determined that PV was in a persistent vegetative state. The doctor had no treatment to propose, and PV's parents decided to take their son home.

At home, PV looked more awake. His mother was convinced that his eyes "looked different" when she spoke to him. PV's parents did not accept the doctor's diagnosis and sought help elsewhere. After they had visited a number of nontraditional medical practitioners, a speech therapist proposed a way to communicate with PV: the controversial "facilitated communication": a person (facilitator) held PV's hand to communicate on a special keyboard connected to a computer. It seemed that PV was given a voice by this "facilitated communication" method. Was he conscious after all? It is here that we first met PV at our consultation, 24 years after his acute brain insult.

Diagnosing the Minimally Conscious State

The vegetative state is defined by spontaneous or stimulation-induced eye opening without any sign of conscious awareness (all observed movements are reflexes).² It has been the subject of medical, public, and legal discussions since its formal definition in the 1970s. Since the 1990s, a subgroup of patients with severe alteration in consciousness who do not meet diagnostic criteria for the vegetative state have been reported in the scientific literature. These patients demonstrate some discernible minimal behavioral evidence of consciousness (voluntary or non-reflex motor action) but remain unable to reproduce these behaviors consistently. In 2002, Joseph Giacino at the JFK Johnson Rehabilitation Institute and an international group of allied experts were the first to introduce diagnostic criteria differentiating the vegetative state from the minimally conscious state.³

A six-year-old standardized and validated consciousness scale—the Coma Recovery Scale–Revised—is

Table 1

Glasgow Coma Scale (GCS)	
Eye Response (1–4)	
1.	No eye opening
2.	Eye opening to pain
3.	Eye opening to verbal command
4.	Eyes open spontaneously
Verbal Response (1–5)	
1.	No verbal response
2.	Incomprehensible sounds
3.	Inappropriate words
4.	Confused
5.	Orientated
Motor Response (1–6)	
1.	No motor response
2.	Stereotyped extension to pain
3.	Stereotyped flexion to pain
4.	Withdrawal from pain
5.	Localizing pain
6.	Obeys commands

Table 1: The Glasgow Coma Scale (GCS)¹ was published in 1974 as an aid in the clinical assessment of post-traumatic unconsciousness. The GCS has three components: eye (E), verbal (V), and motor (M) response to external stimuli.

now needed to differentiate between the vegetative state and the minimally conscious state when looking for small signs of consciousness (see table 2).⁴ In fact, our group, in collaboration with Dr. Giacino, showed that up to 41 percent of patients considered to be in a vegetative state (on the basis of routine bedside assessment and clinical consensus diagnosis) were in fact, as measured by the new scale, in a minimally conscious state.⁵ It is important to distinguish between the minimally conscious state and the vegetative state; in the former condition, patients should receive more-aggressive rehabilitation and treatment and are expected to have better chances of recovery. Previous studies by Keith Andrews in London and Nancy Childs in Texas had already shown high diagnostic error rates. We showed that by using a standardized bedside evaluation of consciousness (the Coma Recovery Scale–Revised), such diagnostic errors can be avoided.⁵ When PV was carefully examined by a trained and experienced clinician using the new scale, the results indicated that he was indeed conscious because he showed eye tracking.

How do we conclude that a patient is conscious? Clinically we look for signs of “command following.” Physicians will, for example, ask patients to squeeze their hand or to look up or look down. A patient’s ability to respond to such simple commands is regarded as proof of consciousness. Sometimes the movement is very small and is observed only during some examinations, seemingly disappearing when searched for later. There can be a series of reasons for missing fluctuating signs of consciousness. When patients are tired, for example, or experiencing side effects of drugs (for treatment of epileptic fits or spasticity, for example), or when they are suffering from an infection or increased intracranial pressure, their ability to respond might be diminished. On the other hand, sometimes when it seems as if the patient is responding to a command, he or she may in fact be making an unrelated reflex or spontaneous movement. When physicians do not see any evidence of command following, it may nevertheless be difficult to determine whether that apparent non-response truly means there is no conscious awareness. Maybe the patient is deaf and can’t hear the command; if inability to hear is suspected, physicians can also write down the command and invite an answer from the patient by showing him or her the written command. Maybe the patient has understood the command and tried to make the movement, but a lesion in the nerves, spinal cord, or brain stem connecting the muscle with the brain’s motor cortex has prevented a physical response. In this case, physicians will need to measure the brain’s activity directly, searching for signs of consciousness, as we will discuss below.

Another way to investigate whether a patient is conscious is by looking for movements that are not thought to be simple automatic reflexes: when patients follow moving persons or objects with their eyes, often one of the first signs of consciousness, or when they orient a potentially painful stimulus (after the doctor presses on a finger or toe, the patient locates and tries to touch that part of the body) or scratch their nose or pull their feeding tube, for example. Another common first sign of consciousness is a response to

Table 2

Coma Recovery Scale–Revised	
Auditory function	
4	Consistent Movement to Command*
3	Reproducible Movement to Command*
2	Localization to Sound
1	Auditory Startle
0	None
Visual function	
5	Object Recognition*
4	Object Localization: Reaching*
3	Visual Pursuit *
2	Fixation *
1	Visual Startle
0	None
Motor function	
6	Functional Object Use+
5	Automatic Motor Response*
4	Object Manipulation*
3	Localization to Noxious Stimulation*
2	Flexion Withdrawal
1	Abnormal Posturing
0	None/Flaccid
Oromotor/Verbal function	
3	Intelligible Verbalization*
2	Vocalization/Oral Movement
1	Oral Reflexive Movement
0	None
Communication	
2	Functional: Accurate+
1	Non-Functional: Intentional*
0	None
Arousal	
3	Attention
2	Eye Opening without Stimulation
1	Eye Opening with Stimulation
0	Unarousable
+Denotes emergence from minimally conscious state.	
*Denotes minimally conscious state.	

Table 2: The Coma Recovery Scale–Revised⁴ was specifically developed to differentiate vegetative states and minimally conscious states. The basic structure of the CRS-R is similar to that of the Glasgow Coma Scale, but its subscales are much more detailed, targeting more-subtle signs of recovery of consciousness. It includes auditory, visual, motor, oromotor/verbal, communication, and arousal subscales and ranges from 0 to 23.

emotional stimuli, like smiling at a girlfriend and not at another person or reacting to a joke or a funny story. In short, to reject the diagnosis of a vegetative state, physicians will look for signs that the patient is following a command or that he or she is making some other non-reflex or voluntary movement.

The Coma Recovery Scale- Revised offers the major advantage of looking for signs of consciousness in a systematic way using standardized stimuli. For example, visual pursuit is assessed by using a moving mirror at a defined distance and angle of movement, for the established number of trials considered necessary to distinguish spontaneous eye movements from conscious tracking of the eyes.⁶ But even the best standardized bedside assessment still has the potential flaw of needing motor responsiveness to prove the presence of consciousness. Here, novel brain-scanning technologies now offer a way to demonstrate signs of command following independent of muscle function.

With Adrian Owen from the Cambridge Cognition and Brain Sciences Unit, we proposed a way to do this by means of functional MRI (fMRI). We asked the patient to use mental imagery tasks, such as “imagine playing tennis” or “imagine walking around at home,” while we directly measured brain activity. In 2006 a much-reported case study published in *Science* indicated great interest in this technique.⁷ But the technique is not easy to employ in clinical routine: it is costly and is often invalidated by a patient’s uncontrolled movements in the scanner. Because of this, we came up with a more practical alternative called active evoked potentials,⁸ and we employed this technique in working with patient PV.

At the patient’s home, a trained experimenter placed electrodes on PV’s scalp to measure his brain’s electrical activity. Then PV was presented with a series of words, and the brain’s electrical activity was recorded. Next, he was asked to count the occurrences of a specific word among the presented series; a specific brain response could be repeatedly measured. This response is called a P3 wave and is known to depend on attention. If a P3 wave occurs in response to a specific word if and only if the command “concentrate on one of the words” is given, it proves command following and therefore consciousness, even in the absence of any motor sign of command following (see figure 1).⁸ PV passed these tests, showing not only eye tracking (a minimal motor sign of consciousness) but also command response. But what was he feeling and thinking?

How Conscious Is a Minimally Conscious Person?

PV is one of many patients for whom small but existing behavioral signs of consciousness were missed. He was considered to be in a persistent vegetative state, but he was in fact conscious, albeit minimally conscious. But how conscious? And conscious of what? To answer those questions we needed communication.

In PV’s case the family had found, independent of his treating physicians, alternative paths leading to the controversial facilitated communication technique. Facilitated communication is a technique by which a disabled person is physically assisted by another person (i.e., “a facilitator”) to communicate using a communication board or computer. We have tested this method and have shown it to be invalid in all patients tested, including PV.⁹ Put simply, when we presented words and objects to the patient in the absence of the “facilitator” and then asked him to communicate what had just been presented, we failed to get correct answers.

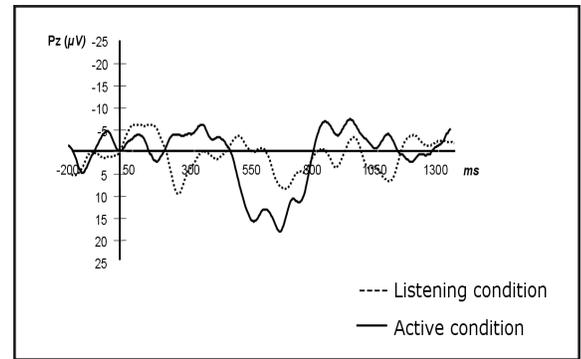


Figure 1. Illustration of the active event-related potential paradigm. A series of words was presented to a patient and the brain’s electrical activity was recorded. First the patient was asked to listen to words (listening condition). The patient was then asked to count the occurrences of a specific word among the presented series and a specific brain response was measured (active condition). This response is called a P3 wave and is known to depend on attention. The X-axis shows the latency of the active event-related potential in milliseconds and the Y-axis depicts voltage (microvolts, μV).⁸

Despite its use in rehabilitation centers and nursing homes throughout Europe and the United States, the method has never been scientifically explored in traumatic brain injury. Older studies showed its invalidity in most if not all cases when it was used in children with severe mental retardation or autism. Facilitated communication was not the solution to breaking down communication barriers with patients like PV.

But recent advances in brain scanning techniques have proven to be useful communication tools. With the Cambridge team, we used fMRI to turn the command-following mental imagery study into a communication device. With the patient inside the scanner, we aimed to record yes/no answers to questions. At present, we cannot reliably read a “yes” or “no” answer in the brain using fMRI. Hence we used this little trick: before putting the patient in the scanner, we explained that he needed to think about playing tennis to communicate “yes.” For “no,” he needed to imagine walking around the house.¹⁰ This novel technique was published in the *New England Journal of Medicine* in March 2010, where it was shown to be the only means to communicate with a 29-year-old post-traumatic brain injury survivor whose condition was comparable to PV’s.

When we read activation in the patient’s motor cortex, we knew he was imagining playing tennis and hence wanted to convey “yes.” When at other times we saw activation in another brain region (the hippocampus), we knew he must be imagining walking around in his house and hence read this as a “no.” However, in PV’s case the technique failed; he moved too much inside the scanner. We turned to evoked potential technology, measuring the brain’s electrical response to a series of external stimuli, and tried what is called “brain-computer interface” to show valid yes/no communication in PV. In this case, we present the patients a series of words (including “yes” and “no”). Using the EEG-based communication has some advantages over fMRI-based communication, but many technical problems, like those caused by muscle and eye movements, need to be resolved before this research will be ready for widespread clinical use. Because of the muscle and eye movement in the EEG, no communication could be established with PV. At present, the European Commission-funded DECODER grant aims to employ this technology in coma survivors who lack any form of motor-based communication. DECODER is a European collaborative project with eight partners, including the Université de Liège, which aims to develop brain-computer interfaces for non-responsive patients, which will provide them access to modern information and communication technologies such as the Internet, a personal computer, or home appliances.

Treating Minimally Conscious Patients

At present we can only guess at PV’s quality of life. Should we continue his treatment at all costs? Should we treat cardiac arrest or kidney failure or pneumonia in minimally conscious patients? In patients with a confirmed diagnosis of a vegetative state, we have medical, ethical, and legal guidelines permitting medical professionals to stop treatment when treatment has become futile or nonbeneficial. In vegetative states of traumatic origin, the chances of recovery are statistically close to zero 12 months after the acute injury (or three months in cases of cardiac arrest—we then call the condition a “permanent vegetative state”) and hence further treatment (artificial hydration and nutrition) can be withheld.¹¹ But what about patients in minimally conscious states?

We do not yet know whether something like a permanent minimally conscious state exists. Given that the criteria for minimally conscious states were formally defined only eight years ago, we lack reliable studies on long-term outcomes for patients like PV. It does seem, however, that chances of recovery are better for patients in minimally conscious states as compared to those in vegetative states. In contrast to patients in vegetative states—a state of wakeful unresponsiveness (i.e., unawareness)—patients in minimally conscious states show signs of conscious awareness and cognition but, by definition, lack the ability to communicate conscious thoughts. Do they feel emotion? Do they feel pain? Current brain scanning technology has helped to answer these challenging questions and to identify their ethical consequences.

The Weill Cornell Medical Center team led by Nicholas Schiff was the first to show brain-scanning evi-

dence of residual emotional processing. Schiff used fMRI to show activation in patients presented with personally meaningful stories read by the patient's mother, comparable to (albeit not identical to) that observed in healthy control subjects.¹² Our group confirmed these results using positron emission tomography (PET), which showed increased brain activation when comparing the presentation of meaningless noise, emotional stimuli (like baby cries), or autoreferential stimuli (like the patient's own name) in patients in minimally conscious states¹³ (figure 2). Such context-dependent, higher-order auditory processing shows that content does matter when talking to minimally conscious patients. Clinically (at the bedside), we had no reason to believe that emotional processing was taking place; patients in minimally conscious states did not react with measurably different bodily responses to stimuli with or without meaning.

The issue of pain perception and suffering is even more clinically and ethically relevant. Patients in a vegetative state lack higher-order cortical activation to noxious stimulation (low-level electrical shocks applied to the wrists)¹⁴ and very probably lack normal pain perception. But our group showed that the brain of a patient in a minimally conscious state activated very differently. The PET results of minimally conscious patients showed very similar brain activation to what we measured in healthy volunteers when shocks were applied, including in a brain area called the anterior cingulate cortex. This area is known to be involved in the emotional, affective, and cognitive processing of pain. Its high activation in minimally conscious patients indicated that such patients are consciously aware of pain. The results of these brain scan studies have direct consequences; we now know that if pain can be identified, even if patients have no ways of expressing or communicating their pain, painkillers are ethically required.¹⁵ Recently, a new scale, the Nociception Coma Scale, was specifically developed for assessing nociception—or pain response—in severely brain-injured patients.¹⁶ Developing and validating this scale constitutes the first step to better pain management for patients recovering from coma.

Conclusion

Finding small and fluctuating signs of consciousness in patients considered to be in vegetative states can sometimes be very challenging, especially when their condition has become chronic and access to neurological expertise is limited, as in intensive care or (sub)acute medical settings. But as we have seen, functional neuroimaging studies are revolutionizing our understanding of these chronic disorders of consciousness, and scientific studies have shown their usefulness to identify signs of consciousness unavailable to bedside clinical assessment. Some exceptional cases even use this technology as a communication device. It is important to stress that the reported studies at present remain research tools, performed in a strict ethical framework.¹⁷ Further study is needed to prove their usefulness in clinical reality.

This is exactly the aim of a McDonnell Foundation–funded Coma and Conscious Consortium, which will study the large-scale use of these technologies. We hope the efforts will lead to a better understanding of human consciousness and improve our clinical care in terms of diagnosis, prognosis, and treatment of patients like PV.¹⁸ At present, 26 years later, PV is at home, fully dependent on others for activities of daily living. He has recovered limited oral feeding abilities, but his dysphagia, or difficulty swallowing, still requires the use of a feeding tube. Efforts are now being made to find a way to communicate with PV and to increase his autonomy. In the next five years, with a step-by-step approach combining multimodal assessment techniques (i.e., func-

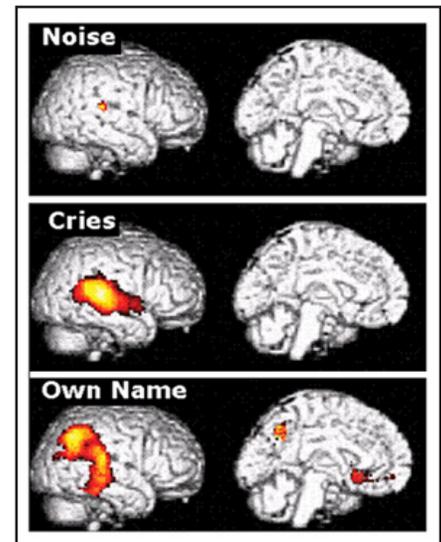


Figure 2. Brain activations during presentation of noise, infant cries, and the patient's own name. Stimuli with emotional valence (baby's cries and names) induce a much more widespread activation than does meaningless noise.¹³

tional neuroimaging and electrophysiology), we expect a decrease in the misdiagnosis of severely brain-injured patients and a better understanding of the mechanisms underlying consciousness. No evidence-based recommendations can be proposed regarding therapeutic management, even though preliminary results already show the efficacy of some pharmacologic (amantadine¹⁹ and zolpidem²⁰) and non-pharmacologic (deep brain stimulation¹⁸) interventions. Functional neuroimaging will guide us to a better understanding of the physiological modifications of the therapy. At the same time, efforts are being made to develop communication technologies that can offer patients any feasible way of communicating. Experts in rehabilitation engineering and speech-language pathology are continually improving brain-computer interface techniques, which are expected to be an important step in improving the quality of life of these patients. There are no existing guidelines regarding the care and revalidation of patients with disorders of consciousness. However, occupational therapy supports the view that engagement in a creative and productive activity will improve physical and emotional rehabilitation as well as the quality of life of patients.²¹

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Steven Laureys is a clinical professor of neurology at the University Hospital of Liège and a senior research associate at the Belgian National Funds for Scientific Research. He earned his M.D. and M.Sc. in pharmaceutical research from the University of Brussels, working on pain and stroke in rat models. He moved to the University of Liège in 1997, where he obtained his Ph.D. in medical sciences, studying perception in disorders of consciousness. He is board-certified in neurology and in palliative and end-of-life medicine. He now heads the Coma Science Group (www.comascience.org) and has published several books, the latest being *The Neurology of Consciousness* (Academic Press).

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