In following the scale of consciousness…

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After a coma, knowing whether a patient has been plunged into a vegetative or minimally conscious state is essential: prognosis and treatment depend on it. Nevertheless a study carried out in Belgium on 103 patients has confirmed that doctors get their diagnosis wrong in numerous cases.

In fairy tales a Prince’s kiss is enough to wake up a Beauty condemned to long years of deep sleep. Reality is clearly less romantic for those who, following a physiological problem or a traumatism, find themselves in an altered state of consciousness. ‘Can he hear us? Does he understand us? Is he trying to communicate? Is he still thinking? Is he suffering? Will he one day rejoin reality and, if that is the case, in how long a time?’ ask those close to the patient. Replying to their questions - in as far as knowledge permits - depends on an evaluation of the sufferer’s state of consciousness. But at the moment too many poor diagnoses are given: they exceed 40% in certain categories of sufferer, which is not without determining repercussions on their prognoses and treatment. This realisation has just been revealed in a study published on the 21st of July in *BMC Neurology* (1). It has been signed by, amongst others, the neuropsychologist and FNRS candidate Caroline Schnakers (of the Coma Science Group) and by Professor Steven Laureys (Coma Science Group, Cyclotron Research Centre and the Liège University Hospital Centre Department of Neurology, and FNRS Maître de Recherches).
How can this situation be changed and the rate of errors diminished? ‘It would suffice to add, systematically, to the results of medical imaging and to clinical examinations, which remain essential, an established and standardised behavioural assessment scale, such as for example the Coma Recovery Scale-Revised (CRS-R). Developed by Joseph Giacino, of the New Jersey Neurosciences Institute (USA), it has been used in this study in order to be able to establish adequate diagnoses,’ comments Professor Laureys.

The coma, a point of departure

These painful stories of patients deprived of their consciousness to various degrees generally start with a coma. Contrary to what is often believed, this state rarely persists beyond four weeks. The comatose patient experiences no arousal, he keeps his eyes shut, and he shows no interaction with his environment, even if he can sometimes respond to painful stimuli. The coma can conclude with a total recovery, or by brain death, and thus the raising of discussions concerning organ donation (Read Organ transplants like no other and the article Organ donation after physician-assisted death). In addition, beyond certain intermediary situations such as locked-in syndrome (communication is possible for the sufferer, but only through eye movements) (Read: Walled up consciousness), certain patients do not regain consciousness on coming out of a coma: they move towards a neuro-vegetative state.
In this vegetative state, opening of the eyes is now possible, either spontaneously or in response to stimulation. Eye movements can also occur but without the gaze really tracking. In fact the reactions of the patient remain reflexes: he has no language or interaction with others. This vegetative state sometimes becomes permanent: any possibility of improvement is thus reduced to a minimum. 'According to American studies, when the initial coma has been caused by cranial trauma, it is estimated that there is no longer any hope of the sufferer returning to himself after a year spent in a vegetative state. If the initial coma is caused by an anoxia, as for example after a cardiac arrest, this delay falls to three months. As far as I am concerned I have never seen an exception to this observation,' stresses Professor Laureys, who knows how much this chronic altered state of consciousness can give rise to painful ethical dilemmas for the family and the medical team. At the moment one man has been living in such a condition for over 32 years.

As the chronic vegetative state is the bearer of a very sombre prognosis, what is it that affects these men and women whom the press sometimes announce, with much fanfare, have just emerged from a coma (sic!) after years and years of unconsciousness? Well, these sufferers find themselves in a higher state of consciousness: they are in what has been called, since 2002, a 'minimally conscious state'.

A pale reflection of consciousness

The work by Professor Laureys on the behaviour of patients and on the functioning of their brain (through PET-scan) has contributed significantly to understanding and having this essential new classification accepted. The patients concerned, even if they do not communicate, do not only carry out reflex movements: sporadically they demonstrate a pale reflection of consciousness. Clearly, since this discovery, doctors who had wrongly judged that this new category of the state of consciousness had little interest or that it was all in all quite artificial have been compelled to think it through again. 'In the eyes of the medical body, it is the whole image of 'poor patients with no possible communication' which has been turned upside down,' admits Professor Laureys. Furthermore, invited to the Vatican a few years ago in order to present his work, Professor Laureys had to insist and clarify that the discovery of intentional reactions in people in minimally conscious states did not for all that justify 'pro-life' considerations in terms of all the other patients in a vegetative state, as his hosts would have wished...

'In fact, these patients have minimal but precise behavioural reactions and significant interaction with their environment. They will for example shake hands on request, follow an object with their eyes, follow the mirror in which they see themselves, laugh or cry in an appropriate manner,' specifies the neurologist. 'Their brains react, as well, to the use of their first names: this element, which is it seems one of the markers of the consciousness of self, is now being studied in our centre in order to confirm its interest in the examination of patients. Even more fundamentally, the latter feel emotions - we have demonstrated so in a 2004 study - and they feel pain - Doctor Mélanie Boly has also proved it, at Liège in 2008 (see the images). And, above all, they are amongst those people who, one day, have a chance of waking up.' Like Terry Wallis.

When this American, the victim of an accident close to twenty years previously, recently 'returned to himself', he pronounced - you couldn't make it up! - the words 'Mother' and 'Pepsi'! But contrary to what could be read in certain newspapers, Terry Wallis obviously did not come out of a coma. Joseph Giacino, who had the opportunity of examining him, confirmed that he had been well and truly plunged into a minimally conscious state. This man, whom certain images of American cars made groan when he was in an 'unconscious' state,
had the rare luck to cross the stages which brought him back to consciousness. And which allowed him to discover that his daughter was now 20 years old…

**Persistent errors…**

To return to the Liège study, since a number of years it has been demonstrated that a behavioural assessment scale allows one to determine as closely as possible the real state of consciousness of each patient and that it thus leads to differences in terms of diagnosis. 'Around 15 years ago, an American and an English study drew attention to the fact that in from 3 to 4 cases out of 10 (from 37% to 43%) doctors spoke of a vegetative state whilst they should have been evaluating a minimally conscious state,' continues the neurologist. 'The study by Caroline Schnakers confirms that we in this country are still at that stage.'

The Liège University Hospital Centre is responsible in Belgium for the registering and follow-up of patients which have entered the federal project (see [http://www.health.fgov.be/coma](http://www.health.fgov.be/coma)) in accordance with which every sufferer in an altered state of consciousness passes through an appraisal centre (there are 17 of them, spread across the country) at which they are subjected to analysis. Dr Schnakers carried out her study on 103 (71 men) out of these 500 patients, aged between 19 and 55 and placed in intensive care, in neurology units or rehabilitation centres. The doctors responsible entrusted their diagnosis concerning each patient to her. For her part she carried out a behavioural assessment of the patients on leaning on the criteria of the CRS-R. This assessment scale turns out to be more precise and more capable of taking into account complex situations than, for example, the Glasgow Coma Scale, which however already enables different centres to carry out standardised assessments. Over the past fifteen years several specialised behavioural assessment scales have been developed. 'SMART, developed by Professor Keith Andrews’ team is without doubt currently the main competitor to CRS-R,' states Professor Laureys. 'An evaluation comparing the two models is under way.' The difference between SMART is that the use of CRS-R is free. Convinced of its great effectiveness and its reliability the Liège team offers a 15 page booklet and a video aimed at spreading the learning of its use to every motivated doctor, nurse, physiotherapist, neuropsychologist or ergotherapist. 'Using such a scale in every centre finally allows us to speak a common language,' notes the neurologist.
In the Liège study the results obtained by Caroline Schnakers are incontestable: 41% of the patients in altered states of consciousness had been wrongly diagnosed as being in a vegetative state. To put it in other terms, whilst 44 people had been judged to be in a vegetative state on the basis of the medical team’s clinical consensus, 18 were in a minimally conscious state. The errors were more frequent for people considered to be chronic patients (14/29). For the 18 sufferers whose diagnosis was judged to be uncertain by the medical team, 16 have also showed signs of consciousness. In most cases it was a question of eye movements. ‘The systematic use of a sensitive and standardised behavioural scale allows us to diminish diagnostic errors or to limit their uncertainties,’ concludes Caroline Schnakers. A small revealing ‘detail’: amongst the 41 patients considered to be in a minimally conscious state, 4 (10%) had already emerged from this state.

‘In teams it is not always so easy to change habits and to introduce tools which are added to the examinations already made and which we are used to,’ admits Professor Laureys. ‘Nevertheless, those who take these patients into their care know to what extent this task can be difficult and frustrating. The improvements in our knowledge concerning them can only be considered a plus. Moreover, establishing a good diagnosis is essential for the prognosis, a possible decision to halt therapeutics or to put treatments in place...’ At present, for the lack of always determining accurately the patients’ states, we risk stopping the re-education for people we have wrongly labelled as being in a vegetative state. Or we don’t prescribe pain killers when it is necessary. Or we don’t offer them all the therapies that are being developed.
New treatment pathways

'By chance, a South African team has discovered that a medicine aimed at sleep allows certain patients in a minimally conscious state to recover consciousness and to communicate...during the period the molecule is active,' states Professor Laureys. This activity, 'miraculous' when it occurs, is currently the object of a study being led at Liège in collaboration with a Chinese team led by Dr Haibo Di. Furthermore, another medicine, but this time an antiviral, also activates the brain of certain sufferers: the latter do not communicate whilst they are taking it, apart from possibly pronouncing a few words, but their condition improves. They manage to eat through the mouth, for example. Admittedly this effect is less spectacular than that produced by the first substance used, but it works in a larger number of cases. Here again a study is underway but the Liège team has already demonstrated its effects, using PET scan, on the brain of patients in a state of altered consciousness (2).
Furthermore, in 2000 The Lancet published the work of Professor Laureys concerning the regaining of the connectivity between the cortex and the thalamus in these patients. 'When a patient recovers in passing from a vegetative state to a minimally conscious one, what changes in the brain is the connection between the thalamus and a section of the grey matter,' pinpoints Professor Laureys. 'After these observations, Nicolas Schiff's New York team, with which we collaborate, developed the idea of placing a stimulator in this area of the thalamus, which is what we do for other pathologies, such as Parkinson's disease for example.' This invasive technique, for which the patient's agreement cannot be obtained, because of the very nature of things,
is only considered with the informed consent of his family. It is anticipated that patients in altered states of consciousness will have such brain stimulators implanted at the Liège University Hospital Centre.

**An attack on unconsciousness**

The routine use of CRS-R is finally inscribed in the global advances concerning progress carried out as much at the patient's bedside as in our overall understanding of how the brain works. In recent years genuine leaps forward have been accomplished, in a large part due to medical imaging. A battery of more and more sophisticated tests benefits each patient. At Liège the close collaboration between Professor Laurey’s team and the University Hospital Centre’s doctors contributes to these tests being optimized. And the hospital regularly receives patients from abroad for a complete evaluation and to participate in research protocols.


‘Our philosophy consists of using all the weapons at our disposal to understand what is happening in the brain,’ the neurologist assures us. ‘Thus, for example, PET-Scan allows us to study the activity of the brain metabolism, plus the quantity of cerebral activity, induced by stimulation or otherwise. Functional magnetic resonance imaging, now practiced with non-radioactive products, completes the examination. In addition an electroencephalogram - now carried out with 256 electrodes - gives us an indication of the brain's electrical activity. Plus, thanks to Transcranial Magnetic Stimulation (TMS) we can monitor the functional integrity of the motor pathways and quantify possible motor damage. With TMS (linked to electroencephalography) we can also study the communication or the connectivity between the different parts of the brain. This state of the art technology was introduced to the University Hospital Centre thanks to a collaboration with the Italian neurologist Marcello Massimini, currently a guest professor at the University of Liège. Magnetoencephalography (MEG), of which the only available machine in Belgium is found in Brussels, indicates the brain's electrical activity by showing if it is still generating small electromagnetic signals and the potentials called forth also provides with precious indications.'
Nonetheless the technological progress in imaging is not sufficient. 'All the results obtained are linked to great clinical expertise, which is the very basis of the work,' Professor Laureys reminds us. Convinced that it is necessary to go beyond a situation in which traditionally colleagues are also competitors, he has forged solid links with other research teams, including some located in the United States. As for his Liège Centre, it resembles the Tower of Babel a little bit, with the various nationalities of those who work there or come to carry out research (3).

An attack on the neurological code of consciousness

'The work which we are carrying out is particularly difficult, all the more so given that a comatose patient is not the most collaborative there is,' smiles Professor Laureys. But the challenge is worth the trouble. 'We are looking to discover the neuronal correlate of consciousness, in other words to understand exactly what is happening in the brain, in order to be able to define the subjective perception of consciousness as described by Descartes.' (Read: Is Cartesian dualism dead?) The stakes bring to mind those of the geneticists who penetrated our genetic code. But here it is the neurological code of consciousness that the researchers are tracking down. Next February Professor Steven Laureys will broach the subject before the Medicine and Physiology Commission of the Nobel Laureates meeting. Fine recognition of the high level work he and his team are carrying out. But all of that does not stop him from pleading that on the ground all the services concerned finally use the behavioural scale that leads to the patients' consciousness. And it does so without waiting for Prince Charming...

(3) The team of Professor Laureys' collaborators, from those who belong to the Coma Science Group or those who, at the University Hospital Centre, collaborate closely with the latter, is made up of the following:

Neurology: Pr Moonen, Dr M. Boly, B Dahmen (from Germany); nuclear medicine: Pr Hustinx; neuroradiology: Dr Tshibanda (Ongoing doctorate); anaesthetics: Pr Brichant, Dr P. Boveroux (Ongoing doctorate), Dr M. Kirsch (Ongoing doctorate); intensive care: Pr Darnas, Dr D Ledoux. Neurosurgery: Pr Martin, Dr Kachten; ORL: Pr Lefebvre, A. Maudoux (Ongoing doctorate). Collaborators at the CRC: A. Lumen (director), P. Maquet, E. Salmon, G. Garraux, C. Phillips (engineer), E. Balteau (Physicist), D. Ledoux, Q. Noirhomme (engineer), A. Soddu (physicist, from Rome), D. Lule (biologist, from Ulm), F. Mezj (engineer, from Bogota), S. Kleih (biologist, from Tubingen), Dr C. Schnakers, Dr I. Lutte (lawyer and neurologist), A. Vanhaudenhuyse (Neuropsychologist), M-A. Bruno (Neuropsychologist), V. Cologan (biologist, from Paris); O. Gossieres (Neuropsychologist), A. Demerts (Neuropsychologist, from Athens), C. Chatelle (Neuropsychologist), M. Thonnard (Neuropsychologist) and Pr Marcello Massimini (neurologist, from Milan, guest professor).