Declaring the state of consciousness of severely brain-damaged patients who are incapable of communication remains a challenge for physicians. Clinical evaluation of these people is traditionally based on examination of their motor responses with the help of behavioural scales. Interestingly, these patients can be paralysed, deaf, blind, suffering from aphasia or attention deficit disorders, which may lead to an underestimation of their level of consciousness. According to a study published in 2009 in *BMC Neurology* (1), the risk of misdiagnosis has been estimated at 40%. Nevertheless, the systematic use of the "Coma Recovery Scale-Revised" (CRS-R), a standardised and sensitive behavioural scale developed in the US by Joseph Giacino at the *New Jersey Neuroscience Institute* and validated in French and Dutch by Caroline Schnakers and Steven Laureys of the *Coma Science Group*, reduced the percentage of misdiagnosis rate to 31%.

This figure is obviously far from satisfactory. Also, researchers have continuously been working on the development of objective, motor-independent control tools for detecting possible signs of consciousness which may be missed during clinical examination. For any given patient, distinguishing between the two conditions known as the vegetative state/unresponsive wakefulness syndrome (VS/UWS) and the *minimally conscious state* (MCS) is at the heart of the problem. At the same time, diagnostic errors may also concern patients in a *locked-in syndrome* (LIS). Indeed, LIS patients are trapped in a motionless body, which sometimes can lead to be mistakenly considered as unconscious or minimally conscious even though their level of consciousness is actually intact.
"This is a grey area, the boundaries between the two conditions VS/UWS and MCS are difficult to diagnose by merely examining the patient's motor response. Hence, the obligation is to develop irrefutable objective consciousness markers. And this is especially true because a patient's future prognosis, namely her/his chances of recovery, is more favourable in the case of the MCS". In addition, treatments differ, because, while patients in a VS/UWS are oblivious to physical pain, patients in a MCS can still feel pain (2). Therefore, the administration of painkillers in cases where medical cares could be painful is highly recommended for patients in MCS.

**Wandering mind**

The minimally conscious state was demonstrated in 2002 by Joseph Giacino. It describes patients who are capable of following simple instructions in a "reproducible" way but still have fluctuating consciousness with regard to their environment. For example, they may execute voluntary movements from time to time, smile at family members or follow a moving object with their eyes; nevertheless, they will never succeed in communicating their thoughts. Patients in a vegetative/non-responsive state, on the other hand, have no consciousness of the external world and can only make involuntary reflex movements. As such, the results of clinical examination of the VS/UWS patients often remain clouded in uncertainty as discussed above.

Complementary use of Functional Magnetic Resonance Imaging (fMRI and/or Positron Emission Tomography) has made it possible to reduce the number of misdiagnoses around twenty per cent. In this type of examination, patients are usually asked to follow simple instructions during which their brain activity is recorded. But these tools are costly, relatively inaccessible and non-portable, very sensitive to patients' movements while in the scanner and are hindered by the time-scale required to acquire data.

In the meantime, many projects have focussed on the use of brain-computer interfaces based on electroencephalography (EEG) and event related potentials.

Some of these systems allow for motor control which in turn permits to overcome the pitfalls of a possible motor paralysis that the patient might be experiencing. Importantly, brain-computer interfaces assume that the patient in question still understands language. Hence, the principle of these systems, like that of the neuroimaging exams mentioned above, is to measure brain activity while the patient is requested to perform a mental task. An example of such tasks would, for example, require the patient to concentrate on a visual or auditory stimulus. But, as we have already seen, patients may suffer from sensory deficiencies (blindness, deafness...), language problems (aphasia) or attention deficit disorders. Such diagnostic approach is therefore obsolete.

How can this difficulty be resolved? In an article which was published in *Brain* (3) in September 2015, researchers from the Coma Science Group and the Massachusetts Institute of Technology (MIT), in Boston, demonstrated that it was possible to solve the problem by using functional MRI "in the resting state", that is to say in awake subjects who are not performing any tasks. However, even when the mind is at leisure to do nothing, wandering consciousness always spontaneously leads to thoughts and feelings. Therefore, in every individual, there is some default brain activity. In fact, the word "resting" is misleading when speaking about the brain because it is never completely inactive except where brain death has occurred. This intrinsic inactivity which is characteristic of a so-called "resting" brain is quantifiable by means of fMRI and has provided the basis for the development of a method for distinguishing patients in a minimally conscious state from those in a vegetative/non-responsive state.
In the exploration phase, the crossmodal connectivity between auditory and visual cortices was higher in patients in minimally conscious state (MCS) than those in vegetative state/unresponsive wakefulness syndrome (VS/UWS).

In the generalization phase, this connectivity pattern discriminated single patients with high accuracy. The panel summarizes the classifier’s decision on the validation data set including patients independently assessed in Salzburg (SAL) and New York (NY). Based on the crossmodal interaction, 20 out of the 22 independently assessed patients were classified congruently, namely the behavioural diagnosis matched the classification outcome. The three-dimensional space indicating connectivity between left auditory, right auditory and occipital cortex has been compressed into two dimensions to represent the distance of each patient from the decision plane (arbitrary values).

What traffic is on the motorway?

Recordings by means of fMRI in resting subjects makes it possible to identify six networks. The first of these, which is made up of medial associative regions (the precuneus, the anterior and posterior cingulate cortex, the medial frontal and lateral cortices and the posterior temporal cortex), is linked to self-awareness which is understood as the fact of being focussed on one's inner world - What am I going to do this evening? Will I manage to finish my work on time? "This is the realm of the little inner voice that speaks to us and is also the realm of mental imagery", explains Steven Laureys. The second network which activates lateral frontoparietal regions, is focussed on knowledge of the external world which is built by our perceptions - It's warm in this room. I'm getting a pain in my back... The third network: that of salience, including the insula. Its function is to identify, among others, certain emotionally marked stimuli which are seen to be important for the organism such as pain or anxiety.

The other three networks are sensory in nature, auditory, visual and somatosensory. "With the help of statistical analyses, it is easy to specify these six networks", says Steven Laureys. "But on the other hand, it is much more difficult to analyse them". This is exactly what the researchers of the Coma Science Group and the Massachusetts Institute of Technology, tasked themselves with.
Brain activity in the different networks fluctuates. Therefore we observe a negative correlation between the activity of the regions involved in self-awareness and that of regions involved in awareness of the external world. The connections of our brain (the wiring) are fixed, in such a way that, in a healthy individual, the regions that are interconnected communicate with each other on a permanent basis with a greater or lesser level of intensity, even when an individual is experimentally anaesthetised by means of propofol, for example, as evidenced by the work of the CRC (4). Steven Laureys uses the analogy of the brain as a motorway with vehicles that can be seen passing along it by means of fMRI technology and these vehicles are more numerous when the subject is in the waking state than when asleep.

Athena Demertzi and Georgios Antonopoulos, both of whom are researchers at the CRC, are the two first authors of the article published in Brain. With their colleagues, they studied 73 individuals suffering from consciousness problems, 51 of whom were patients cared for in Liege. By means of 10-minute recordings by fMRI in the resting state, they were able to quantify, in the six above-mentioned networks, brain activity in these brain-damaged individuals.

Can they hear? Can they see? Have they retained their sense of touch? Do they feel any emotions? Are they self-aware? Are they conscious of the external world? The answers to these questions are an ideal to be achieved. For the moment, the method is not finely-tuned enough to be able to address the nature of the abovementioned issues. Indeed, what the study measured was to determine whether a given patient was totally unconscious or whether she/he had the residual consciousness characteristic of a minimally conscious state.

In more than 90% of cases

By comparing the activity measurements for each network, the use of algorithms for statistical classification (classifiers) revealed that the auditory network was the most effective for establishing the separation between patients in a vegetative / unresponsive state and patients in a minimally conscious state. Additionally, the higher the score of the individuals on the Coma Recovery Scale-Revised, the more this this network appeared to be clearly active. "However, it is not merely made up of auditory regions but it also recruits visual and sensorimotor regions, for example. This is logical: when we hear somebody, we can easily picture their face, think of their job, etc.", comments the head of the Coma Science Group.

This raised the question as to whether, within the auditory system, some elements were more informative than others. The classifiers demonstrated that this was indeed the case, that the activity in the connection between the auditory and visual regions of the network, therefore in the crossmodal auditory and visual interaction zone, was the best predictor of the presence or absence of consciousness in the examined patients.

Initially, fMRI data were collected and analysed for 51 patients that made up the "Liege sample". These individuals were selected based on their state of consciousness (VS/UWS or MCS) as repeatedly diagnosed with a high degree of certainty using the "Coma Recovery Scale-Revised". In order to establish the validity of their classification method by means of fMRI in resting state, the researchers tested patients recruited in two other hospitals: Weill Cornell Medical College in New York, and Salzburg University Hospital. The results confirmed those that had initially been obtained in Liege: the automatic classification method worked in more than 90% of cases.

According to Dr Susan Whitfield-Gabrieli from the Massachusetts Institute of Technology, co-author of the article published in Brain, "we are faced with an important advance in the area of diagnosis by neuroimaging. The interest of progress in matters relating to fMRI technology applied to the resting state, is that we can gather the data in a systematic and highly reliable way in many centres around the world". She adds: "In this way,
the new paradigm goes beyond the imbroglios caused by behavioural performance in task-based activation studies".

Test under anaesthetic?

The method does, however, have its limitations. On one hand, certain patients find themselves in an area very close to the boundary which statistical algorithms have established as the dividing line between the vegetative/non-responsive state and the minimally conscious state. The answer provided by the computer with regards to the binary "yes-no" method must be treated with caution. Also, it seems that the technique is only applicable, on average, in half of the scanned patients. Why is this so? Because the data collected from fMRI cannot be used when the patient has moved in the scanner, and this applies to 50% of cases. "We are studying the possibility of changing the paradigm for patients by conducting the test while the patients are under anaesthetic", indicates Steven Laureys. "This approach has been the subject of much criticism because it is claimed that consciousness is absent when patients are in this state. Nonetheless, using fMRI technology, we have demonstrated that it is possible to demonstrate the wiring of the different networks. Lizette Heine, a research fellow at the FNRS, is currently studying the question in brain-damaged patients".

Another question that begs for an answer is the predictive power of classifiers. Can they really make it possible to make a prediction with regards to the development of the state of consciousness of each patient? In other words, what can we expect for each patient when we base clinical outcome on the statistical values representing the distinction between the vegetative/non-responsive state and the minimally conscious state? According to Athena Demertzi, studies currently under way are not satisfactory when merely identifying signs of consciousness. It should also make it possible to predict the chances of a good recovery after a coma. However, this conclusion has yet to be confirmed for large groups which has not been the case up to the present.

FMRI during the resting state has become one of the tools for establishing possible signs of residual consciousness in patients suffering from severe brain-damage. It must be seen as a complementary tool for clinical examination, next to computer-
brain interface and all the techniques relating to functional neuroimaging. One of the next challenges will be to combine this new approach with others in order to reduce the level of uncertainty with regards to the diagnosis and prognosis of these challenging patients.


