When consciousness persists and sends a sign

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The recent discovery of a neuronal signature of consciousness by researchers from ULg's and CHU Liège's Coma Science Group, has helped to better understand the emergence of conscious states in human beings. In addition, this has led to a new test which, once it has been validated, should help to reliably establish the existence or nonexistence of residual consciousness in patients whose brain has suffered extensive damage.
What is consciousness? Owing to its many definitions, the polysemic usage of the term has long since obscured all debates concerning it. Nowadays, however, there seems to be a consensus on an operational definition: consciousness resides in the ability to relate mental states to oneself.

According to the work of the Coma Science Group, which is part of ULg’s and CHU Liège’s Cyclotron Research Center (CRC), and studies carried out by the laboratories of Stanislas Dehaene and Lionel Naccache (Institut du Cerveau et de la Moelle Épinière, Paris), multiple unconscious mental representations are continuously competing with each other on the edge of the "global conscious workspace" (terminology inspired by the Global Workspace Theory,
Relying mainly on functional neuroimaging techniques, the neurosciences are endeavouring to systematically identify the neuronal correlates of consciousness. In 1999, the group of Professor Steven Laureys, currently an FNRS senior research fellow and head of the Coma Science group, was able to observe brain activity in certain brain-damaged patients using positron emission tomography (PET) in two successive situations: first of all, when they were in a vegetative state and then when they had regained consciousness. By comparing these two states, researchers were able to identify a crucial frontoparietal network giving access to consciousness. Published in Neuroimage and Journal of Neurology, Neurosurgery & Psychiatry(1), these discoveries helped to determine the Global Workspace neuronal correlate and its "connectivity hypothesis" of consciousness.

In patients in a vegetative state, part of the brain is logically still active, but only in the primary areas (visual, auditory, somatosensory, etc.) and not in the hierarchically superior regions of the associative cortices of the frontoparietal network from which they are disconnected. In 1999, Steven Laureys and his team already sensed that the vegetative state was, above all, a disconnection syndrome of thalamo-cortical "loops" and between the primary areas and those in the conscious workspace. They further demonstrated this in an article published in the The Lancet(2) in 2000.

To put it plainly, consciousness involves the activation of neuronal connectivity distributed in the frontoparietal network constituting the conscious workspace(3), as well as corticocortical and thalamocortical loops, i.e. circuits that respectively form a "resonance" between regions of the cortex and between the thalamus and regions of the cortex. Consciousness seems to be indissociable from these feedback loops, which constitute the brain's « theater spotlight » which allows an unconscious mental representation to enter into the conscious workspace.

The two dimensions of consciousness

ULg's and CHU Liège's Coma Science Group has continued to work and publish on this theme. In 2011, an article appeared in the Journal of Cognitive Neuroscience written by Dr. Audrey Vanhaudenhuyse, now FNRS post-doc, and her colleagues from the Coma Science Group. What was it about? Consciousness of the environment and self-consciousness. "The notion of self-consciousness has such philosophical connotations that it would perhaps be better to refer to internal consciousness", Steven Laureys immediately points out. "It encompasses all the thoughts we access when we are focused on our internal world. We are therefore in the universe of stimulus-independent mental imagery, the daydreams of the awake subject, etc."

Thanks to functional magnetic resonance imagining (fMRI), the researchers from Liège, just like Michael Greicius' team at the University of Stanford with whom they work, revealed areas, within the abovementioned frontoparietal network, that are preferentially linked to consciousness of the self and others, and consciousness of the outside world. The areas in the first case (self-consciousness) include medial associative areas (precuneus, posterior and anterior cingulate cortex, mesial frontal cortex). The areas in the second case (consciousness of the outside world) are the lateral frontoparietal areas.

The two dimensions of consciousness are anticorrelated, since a subject focusing on "his little voice inside" is less receptive to stimuli from the environment, and vice-versa. Furthermore, when the BOLD signal (Blood-Oxygen-Level Dependent) was examined using fMRI in a resting awake subject, whose brain becomes the stage for so-called default activity in the areas of consciousness, researchers observed that this activity was not constant but, on the contrary, continuously fluctuating. In addition, a negative correlation appeared between the activity in the areas involved in self-consciousness and those involved in the consciousness of the outside
“Apparently, there is a toing and froing between one dimension and the other approximately every 20 seconds”, Steven Laureys emphasises.

**Clearing the grey area**

13 May 2011. New article by the Coma Science Group researchers, in *Science* this time. Title: Preserved Feedforward But Impaired Top-Down Processes in the Vegetative State(5). Primary author: Dr. Mélanie Boly, currently FNRS post-doc. This article, which involved a collaboration between researchers from University College London and the University of Milan, takes us one step further in the identification of the neuronal signature of consciousness. A crucial issue since it affects the very essence of the human being. But it also has another, just as essential facet. The work described in Science aims to develop a high-performance "consciousness test" that would clear the "grey area" with which clinicians are often faced when they have to make a distinction between patients in a vegetative state and patients in a minimally conscious state. This test would not, under any circumstances, require the understanding of any form of language.

Several studies have shown that, based almost exclusively on the examination of the subject's motor responses (for instance, withdrawing a hand or not when the doctor asks the subject to make a movement), the clinical "bedside" diagnosis is wrong one in three times, and even in 40% of cases as demonstrated by Dr. Caroline Schnakers, FNRS post-doc, and Steven Laureys(6). And yet, even if his thoughts cannot be expressed, the patient in a minimally conscious state has a residual consciousness of his environment, which is fluctuating but real. He may follow his reflection in a mirror or hold someone's hand if asked, for instance. Moreover, a patient such as this has better chances of recovering than a patient in a vegetative state and has the ability to feel physical pain, as stated in an article by the Coma Science Group published in 2008 in *The Lancet Neurology*(7).

To reduce the error rate, it appears vital to use a standardised and sensitive behavioural scale such as the Coma Recovery Scale-Revised (CRS-R). Positron emission tomography and fMRI - techniques that allow you to indirectly "see" the brain in action - would allow more in-depth investigations. However, since they are too expensive and extensive, they cannot be systematically used to establish a detailed diagnosis. An important breakthrough has recently been made in understanding the "workings" behind the emergence of conscious states. This discovery has led to an original method of diagnosis of altered states of consciousness. Based on high-density electroencephalography (EEG) rather than PET or fMRI, this precise and reliable test, which is currently in the pipeline, could be used on a large scale. The essential difference between this test and its classic equivalent is the number of sensors applied to the subject’s scalp - 256 instead of 20.
Acoustic clicks

Let's go directly to the heart of the experiment carried out by the Coma Science Group, in collaboration with English and Italian researchers. As established by Steven Laureys' group in 1999, the emergence of conscious states, as we have said before, requires the activation of neurons located in the frontoparietal network, but also valid connections within this network and between the latter and hierarchically inferior levels.

But what is the exact nature of this connectivity? Owing to the lack of temporal resolution - several minutes - of PET or fMRI, this question could not be answered. Working in milliseconds, high-density EEG seemed to be the best solution to overcome this obstacle. However, it was also necessary to have a sophisticated mathematical model capable of determining the network of brain regions behind the EEG signal collected, based on all the data recorded, and the direction of the connections linking the said regions. As it happens, such a model had just been recently developed in London by Karl Friston: *Dynamic Causal Modeling*.

The research led by Mélanie Boly and Steven Laureys focused on consciousness of the outside world which, as we have seen, involves lateral frontoparietal areas. Forty-two people took part in the experiment: 22 healthy subjects, eight subjects in an unresponsive wakefulness syndrome (vegetative state) and 13 subjects in a
minimally responsive/conscious state. "We had to make a very strict selection among a great number of patients", Steven Laureys explains. "There could be no ambiguity and no grey area among those who were going to take part in our experiment. In short, the diagnosis could not leave any doubts: unconscious for some, minimally conscious for the others."

In order to successfully carry out their work, the researchers used the auditory cognitive evoked potential technique. Using EEG, this method aims to record brief changes in the brain's electrical signal in response to sound stimulation. The sounds chosen were "acoustic clicks" with different tones - bip, bip, bip..., bop, bop, bop..., bîîp, bîîp, bîîp..., etc.

Wearing a cap equipped with 256 electrodes, first healthy subjects then brain-damaged subjects were showered with "acoustic clicks" for 15 minutes. Why for such a long time? Because consciousness fluctuates in the minimally conscious subject, its signature does not appear continuously.

In healthy subjects, the brain's electrical response modifies with every sudden change in tone, but habituation occurs when the same sound is repeated. Moreover, the response recorded decreases during sleep or under anaesthetic. The researchers also considered that it could probably be an indicator of consciousness.

The brain responds to a change in tone in several hundredths of a millisecond in healthy subjects. In the second phase of its studies, the Coma Science Group team observed that the same was true in patients in a minimally conscious state. On the other hand, the response recorded in patients in a vegetative state turned out to be weaker and more transient (less than 100 milliseconds).

Why? Mélanie Boly, Steven Laureys and their colleagues endeavoured to carefully analyse the phenomenon and grasp the "intimate mechanism", by using Karl Friston's mathematical model.

**Top-down connections**

In all subjects, including those in a vegetative state, it appeared that a change to the tone of the "acoustic clicks" activated the primary auditory cortex in the temporal lobe. This cortex is responsible for analysing the frequency of the sounds, the location of the sound source, etc., while the secondary auditory cortex
reconstitutes the sounds. These two cortices were connected by bidirectional links generating a feedback effect.

As we have previously seen, access to consciousness requires information processed in the hierarchically inferior regions (here, the auditory cortices) to be sent back to the frontoparietal network constituting the conscious workspace and that a feedback loop be established between these different levels of structures. So what did the Coma Science Group researchers discover when they used Karl Friston's Dynamic Causal Modeling? In healthy subjects and patients in a minimally conscious state, the frontoparietal network sent signals back to the temporal lobe where the auditory cortices are located, thus ensuring the abovementioned reverberant feedback loop. On the other hand, in unconscious patients, while the ascending connections (from the temporal lobe to the frontoparietal network) were indeed present, the top-down connections were not. The feedback loop was therefore "broken". This explains the weakness and the brevity of the brain's automatic response in these patients when they "hear" a change in the tone of the "acoustic clicks" played to them.

"Our study suggests that access to consciousness is indissociable from this top-down communication", Steven Laureys says. This result concords with the model of consciousness elaborated by the Coma Science Group and with the data obtained from healthy subjects by Stanislas Dehaene and Lionel Naccache. "On a theoretical level, we have suggested that the first stages of perception depend on unconscious processes and that
conscious perception emerges from the dialogue between the specialised subconscious processors and the conscious workspace", Lionel Naccache explains - see above.

Besides its interest in terms of fundamental research, the discovery of the Coma Science Group neuroscientists also seems to mark the beginning of a diagnostic test (a "consciousness test" independent of language comprehension or any active participation of the patient) based on high-density EEG. Within a clinical framework, this test aims to offer a highly reliable solution to the issue of the presence of residual consciousness (minimally conscious state) in severely brain-damaged patients. An advance such as this would especially allow neurologists to better establish their diagnosis and prognosis and to modulate the quantity of analgesics administered - contrary to patients in a vegetative state, patients in a minimally conscious state feel physical pain. Furthermore, families could know whether their loved one was conscious or not when they visited. Finally, end-of-life decisions could be made based on a more solid foundation.

At first sight, the results of the ULg researchers' work seem to indicate that they have elaborated a new EEG consciousness test, based on top-down connections. The universities of New York, Cambridge and London Ontario will help to define its sensitivity and specificity by applying it to hundreds of patients in an altered state of consciousness. Does this mean the beginning of a new era of care for such patients?

(3) More precisely, the cardinal elements of this central network are the prefrontal cortex, the anterior cingulate cortex, certain regions of the parietal and temporal cortices, as well as the thalamic nuclei.