

Eyes Open, Brain

By Steven Laureys

Recent progress in medical care has greatly increased the number of people who survive acute brain damage. Doctors can save the lives of many patients who suffer trauma to the brain (often after a road accident) or a lack of oxygen (for example, after a cardiac arrest or drowning), but if the damage is severe, the victim will slip into a coma. Individuals in this condition do not open their eyes; at best, they will show some reflex movements of the limbs. Coma rarely lasts longer than two to five weeks. Those who regain consciousness typically do so within days. Others will die, and still others will awaken from their coma but remain unconscious, entering what is called the vegetative state.

Even for experts, the vegetative state is a very disturbing condition. It illustrates how the two main components of consciousness can become completely dissociated: wakefulness remains intact, but awareness—encompassing all thoughts and feelings—is abolished. By wakefulness, I mean that patients in a vegetative state have sleep/wake cycles. At the times when they seem to be awake, their eyes open and sometimes wander. At other times they keep their eyes shut and appear to be asleep, although they may open them and stir when touched or spoken to. These patients usually can breathe without technical assistance and can make a variety of spontaneous movements—such as grinding teeth, swallowing, crying, smiling, grasping another's hand, grunting or groaning—but these motions are always reflexive and not the result of purposeful behavior. Typically patients will not fix their eyes on anything for a sustained period, but in rare instances they may briefly follow a moving object or turn fleetingly toward a loud sound.

Shut

New brain-imaging techniques are giving researchers a better understanding of patients in the vegetative state



HALFWAY WORLD: People in the vegetative state are awake without being aware. They can open their eyes and breathe without assistance, but they cannot obey commands or make purposeful movements.

Many people in a vegetative state regain consciousness in the first month after a brain injury. After a month, however, the patient is said to be in a persistent vegetative state (PVS) and the probability of recovery diminishes as more time passes. Every year in the U.S. at least 14,000 new victims of acute brain damage remain vegetative one month after their injury. In 1994 the Multi-Society Task Force on PVS (a team of 11 researchers from various institutions) concluded that the chances of recovery are close to zero if the patient shows no signs of awareness one year after a traumatic brain injury or three months (later revised to six) after brain damage from lack of oxygen or other causes. For these very long-standing cases, the task force proposed the name “permanent vegetative state.”

The study of PVS was thrust into the public spotlight in 2005 as politicians debated the case of Terri Schiavo, a Florida woman who had been in a vegetative state since 1990. (Her parents and husband disagreed over whether she could ever recover; the courts ultimately allowed doctors to remove Schiavo’s feeding tube, and she died of dehydration 13 days later.) The controversy highlighted the importance of developing more effective ways to determine whether a patient is permanently vegetative or in a more hopeful condition. Scientists have recently studied the use of brain-imaging techniques to identify signs of awareness that could be hidden in an unresponsive patient. If physicians had access to reliable methods of detecting conscious awareness, they might be able to better distinguish between brain-

damaged patients who have a chance of recovery and those who face bleaker prospects. At the same time, this research may shine a new light on the nature of consciousness itself.

A Difficult Diagnosis

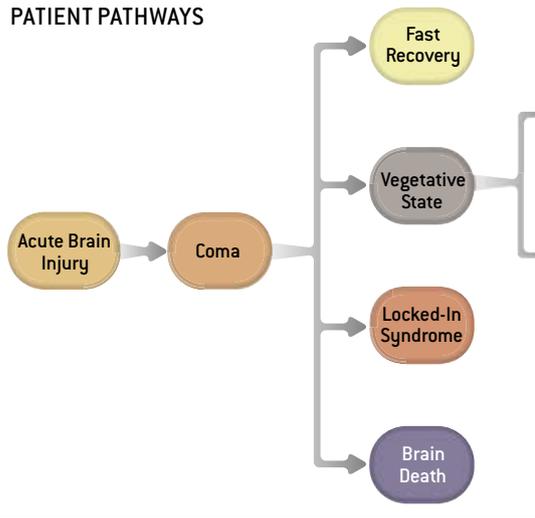
IN PATIENTS WHO RECOVER from the vegetative state, the first signs of consciousness are often minimal and appear gradually. The patient may start making deliberate, nonreflexive movements but remain unable to express and communicate thoughts and feelings. To classify these cases, doctors have created a clinical category called the minimally conscious state. Like the vegetative state, the minimally conscious state may be a transient condition on the way to further recovery of consciousness, or it may be chronic and sometimes permanent. An important difference, though, is that patients who have remained in the minimally conscious state for years still have a chance of recovery. In a much publicized case, Terry Wallis, an Arkansas man who had been in a minimally conscious state since a road accident in 1984, started talking in 2003. Wallis also regained some ability to move his limbs, although he cannot walk and still needs around-the-clock care.

Making the distinction between the vegetative and minimally conscious states is challenging and requires repeated examinations by well-trained physicians who have experience with such patients. Clinicians making the diagnosis of a vegetative state will base their judgment on the absence of behavioral signs of consciousness. Put simply, if a patient looks awake (meaning he or

AWAKE BUT NOT AWARE

After brain injury that leads to coma, a patient’s progress may follow one of several paths (left). If the patient does not die or quickly recover, he or she will most likely transition to the vegetative state. (In rare cases, a person may develop locked-

PATIENT PATHWAYS



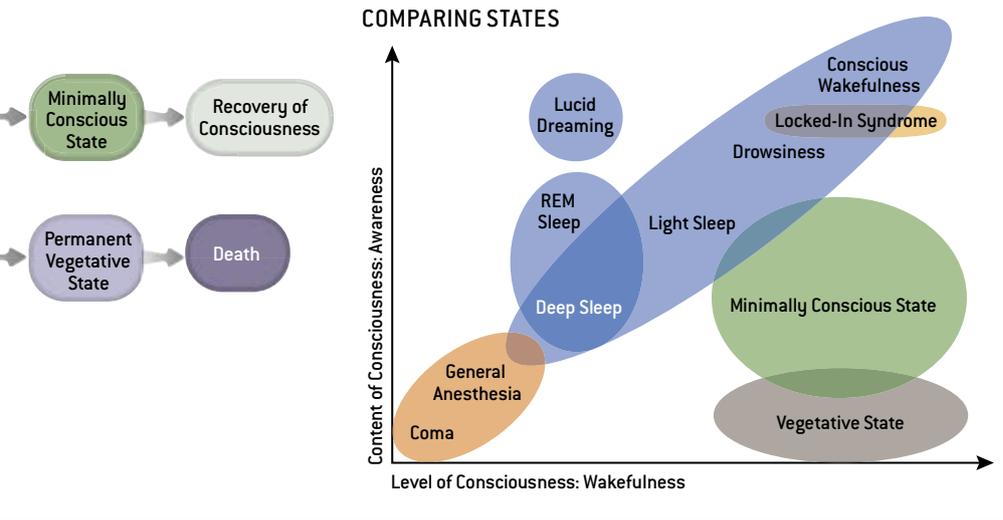
she has his or her eyes open), repeatedly fails to obey commands (such as “pinch my hand” or “look downward”) and makes only reflexive movements, the doctor will conclude that the patient is in a vegetative state.

In the early 1990s, however, studies led by Nancy Childs of the Healthcare Rehabilitation Center in Austin, Tex., and Keith Andrews of the Royal Hospital for Neurodisability in London showed that more than one third of the patients initially diagnosed as being in a vegetative state in fact showed some signs of awareness when carefully examined. To obtain a more reliable diagnosis, doctors need to employ standardized clinical tests that gauge a patient’s responses to a wide variety of auditory, visual and tactile stimuli. Examples of such tests include the Coma Recovery Scale, developed by Joseph Giacino of the JFK Johnson Rehabilitation Institute in Edison, N.J., and the Sensory Modality Assessment Rehabilitation Technique, created by Helen Gill-Thwaites, also at the Royal Hospital for Neurodisability. The diagnostic superiority of these specialized consciousness scales is beyond doubt, but they are much more time-consuming than a routine neurological examination

Overview/*The Vegetative State*

- Every year thousands of Americans who have suffered brain injuries transition from coma to a vegetative state. If patients remain in this state for more than a year, their chances of regaining consciousness are close to zero.
- Researchers are trying to develop brain-imaging techniques for diagnosing the vegetative state, which would allow doctors to better determine which brain-damaged patients have a chance of recovery.
- Functional neuroimaging of vegetative patients has revealed new clues to the mechanisms of consciousness, but more research is needed before physicians can use this tool for diagnosis and prognosis.

in syndrome, a complete paralysis of the body's voluntary muscles.) The patient may then evolve to the minimally conscious state and often to further recovery of consciousness or remain in the vegetative state permanently. Compared with people in other mental states (right), vegetative patients have a high level of wakefulness—unlike comatose individuals, they have sleep/wake cycles—but none of the awareness that characterizes normal conscious wakefulness.



or a simpler test such as the Glasgow Coma Scale.

But conscious awareness is a subjective experience that is inherently difficult to measure in another being. Might even the most careful assessment miss signs of awareness in acutely brain-damaged, noncommunicative patients? Over the past decade investigators have struggled to find an objective test that could confirm or dispute a clinical diagnosis of the vegetative state. Structural imaging of the brain—employing either magnetic resonance imaging (MRI) or x-ray computed tomographic (CT) scanning—can help doctors visualize the extent of brain damage, but such techniques cannot detect signs of consciousness. Recent studies, though, indicate that examining MRI images of traumatic brain injuries may help physicians predict whether a patient will emerge from the vegetative state. For example, patients with damage to certain regions, such as the brain stem and the corpus callosum (the band of tissue connecting the cerebral hemispheres), appear to have a poorer chance of recovery.

Furthermore, investigations using a new technique called MRI diffusion tensor imaging—which gauges the integrity of the brain's white matter, the

neuronal axons that carry nerve impulses—have increased understanding of the mechanisms underlying recovery from the vegetative state. A team led by Nicholas Schiff of Cornell University, for instance, recently used diffusion tensor imaging to show the regrowth of axons in the brain of Wallis, the patient who emerged from a minimally conscious state after 19 years of silence.

Another widely used tool is the electroencephalogram (EEG), which measures the brain's electrical activity. EEG results can reveal a patient's state of wakefulness because electrical activity slows during nondreaming sleep. For patients in a coma, the instrument can confirm the clinical diagnosis of brain death (when the EEG becomes isoelectric—that is, a flat line). The EEG is not as reliable, though, for measuring changes in awareness. For patients in the vegetative state, the device can nei-

ther confirm their diagnoses nor predict their chances of recovery. My colleagues and I at the University of Liège in Belgium have demonstrated that minimally conscious patients show an electrical brain response called the P300 potential when hearing their own names, but not when hearing other first names. Some patients in a chronic vegetative state, however, demonstrated similar P300 responses, so the technique appears to have no diagnostic use.

A Consciousness Region?

PERHAPS THE MOST promising method for investigating the vegetative state is functional neuroimaging. Studies employing positron-emission tomography (PET) have shown that the metabolic activity of the brain—as measured by its consumption of glucose—decreases in the vegetative state to less than half of normal values. These experiments were first performed in the late 1980s by a group led by Fred Plum of Cornell and later repeatedly confirmed by several European groups, including ours. But some patients who recover from the vegetative state do so without substantial changes in overall brain metabolism, as reported by our laboratory in the late 1990s.

Moreover, we observed that some fully conscious and healthy volunteers have global brain metabolism values comparable to those seen in some patients in a vegetative state. And Schiff has reported that a few vegetative patients had a close to normal cortical metabolism. Hence, measuring overall levels of energy consumption in the brain cannot indicate the presence of awareness.

Our group could, however, identify areas in the brain that appear to be particularly important for the emergence of awareness. Comparing patients in a vegetative state with a large cohort of healthy

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volunteers, we found a significant lack of metabolic activity in the widespread network of polymodal associative cortices (located in the frontal and parietal lobes of the brain) that are involved in the cognitive processing of sensory information [see box below]. We showed that awareness is also related to the so-called cross talk, or functional connectivity, within this frontoparietal network and with centers deeper in the brain, notably the thalamus. In our vegetative patients, the long-distance connections between one cortex and another, as well as the links between the cortices and the thalamus, appeared to be disrupted. Moreover, recovery from the vegetative state is paralleled by a functional restoration of the frontoparietal network and its connections.

Unfortunately, patients in a minimally conscious state seem to show a rather similar cerebral dysfunction. As a result, PET measurements of brain metabolism cannot distinguish between the vegetative and minimally conscious states when the patient is at rest. The technique did reveal differences, though, when analyzing changes in brain function induced by external stimuli such as pain and spoken words.

We studied pain perception by electrically stimulating the hand (which was experienced as painful by healthy control subjects) and using PET to gauge cerebral blood flow, which is another marker for neural activity. In both the vegetative patients and the controls, the results indicated activity in the brain stem, the thalamus and the primary somatosensory cortex, which receives sensory information from the peripheral nerves. In the vegetative patients, however, the rest of the brain failed to respond. The small cortical region that did show activity (the primary somatosensory cortex) was isolated and disconnected from the rest of the brain, in particular from the networks believed to be critical for conscious pain perception. (These results can reassure family members and caregivers that patients in a vegetative state do not perceive pain in the same way that healthy people do.)

The PET studies found a similar pattern when we talked to vegetative pa-

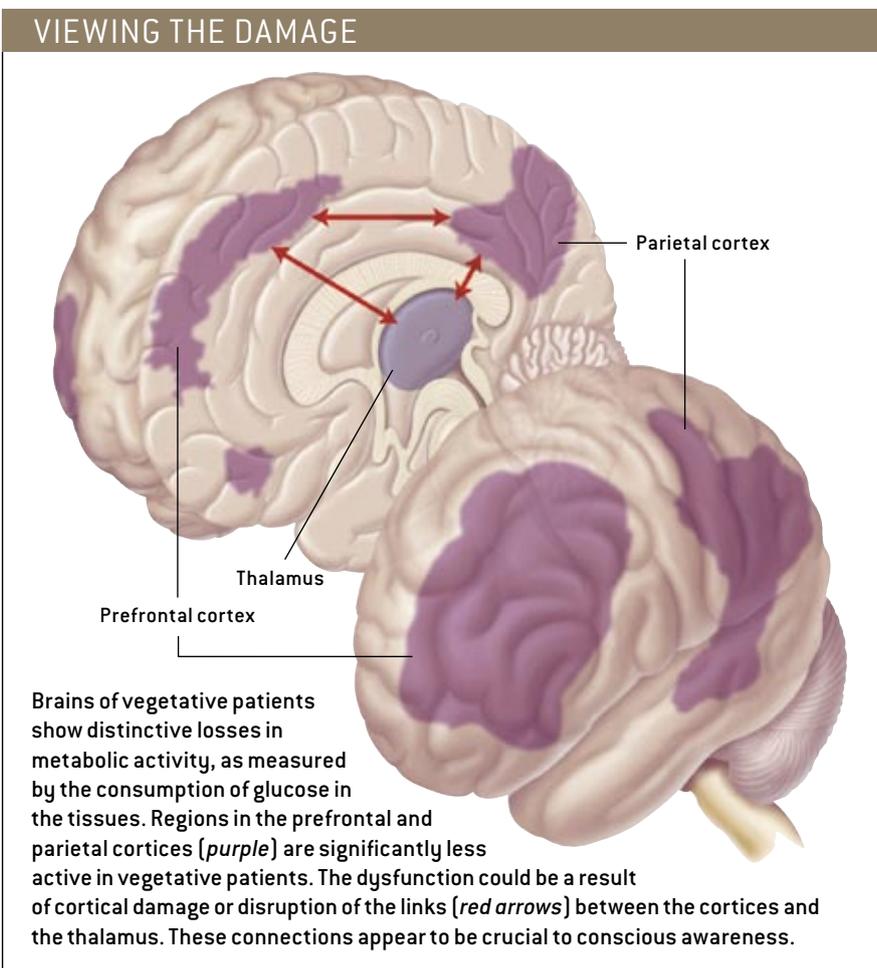
tients. Just as for somatosensory stimulation, the activity was limited to the lowest cortical centers (in this case, the primary auditory cortices) while higher-order polymodal areas failed to respond and remained functionally disconnected. This level of cerebral processing is considered insufficient for auditory awareness. In minimally conscious patients, however, auditory stimuli can trigger large-scale, higher-order cortical activity normally not observed in the vegetative state. Schiff was the first to use functional MRI (fMRI) on patients in the minimally conscious state and showed that their language networks were activated during the presentation of a personally meaningful story read by a familiar voice. When played backward, the story did not provoke such a response, whereas it did so in healthy control subjects.

Similarly, in 2004 our group reported that auditory stimuli with emotional

power (such as infant cries and the patient's own name) induce a much more widespread activation in minimally conscious patients than meaningless noise does. These results indicate that content does matter when talking to a minimally conscious patient. But to develop this technique into a diagnostic tool, we knew we had to show that complex auditory stimuli never activate large-scale networks in vegetative patients.

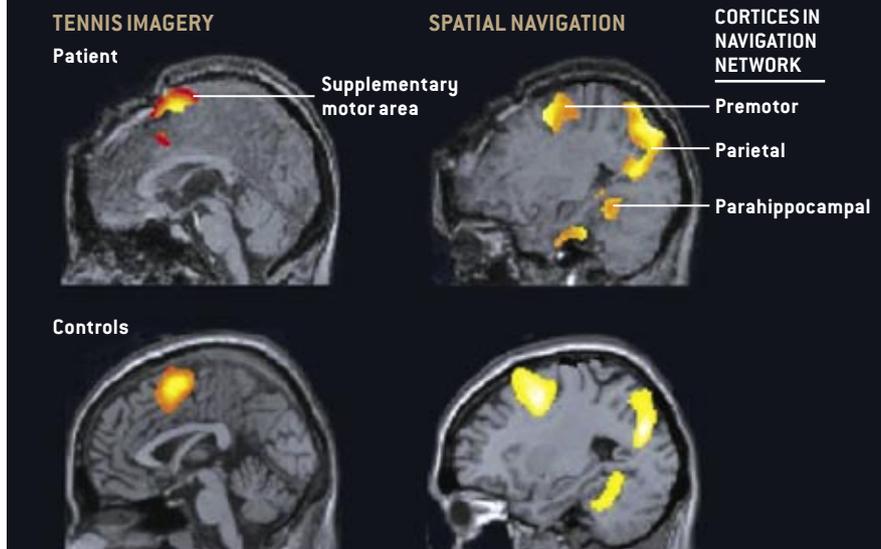
Tennis in the Brain

THIS HYPOTHESIS FACED its toughest test last year when a team led by Adrian Owen of the University of Cambridge, in collaboration with Melanie Boly from our group, studied a 23-year-old woman who had suffered a traumatic injury to the front of her brain in a traffic accident. She remained comatose for more than a week and then evolved to a vegetative state. She spontaneously opened her eyes but never responded



SIGNS OF RECOVERY

Functional neuroimaging of a 23-year-old brain-damaged woman (*top images*) showed activity in a motor area when she was asked to imagine playing tennis and activation of a spatial navigation network when she was asked to envision walking through her house. Similar responses were seen in healthy control subjects (*bottom images*), indicating that the woman was beginning the transition from the vegetative to the minimally conscious state.



to any verbal or nonverbal commands.

Five months after the accident Owen and his colleagues studied the woman's brain using fMRI. During the scanning, the researchers played recordings of spoken sentences—for example, “There was milk and sugar in his coffee”—along with noise sequences that acoustically matched those sentences. The spoken sentences triggered activity in her superior and middle temporal gyri, brain regions involved in understanding speech and the meaning of words; the same pattern was observed in healthy control subjects. These results possibly indicated conscious linguistic processing in the vegetative woman, but not necessarily. Studies of healthy patients have shown that such processing may also occur during sleep and even under general anesthesia.

To clarify whether the patient was consciously responding to language, the investigators conducted a second study in which they asked her to perform mental imagery tasks. When she was asked to imagine playing a game of tennis, the fMRI scans showed activity in the supplementary motor area of her brain, just as it did in the control subjects. When she

was asked to imagine walking through the rooms of her house, the scans showed activation of the network involved in spatial navigation—the premotor, parietal and parahippocampal cortices. Again, the response was indistinguishable from that seen in the healthy subjects. Despite the clinical diagnosis that the patient was in a vegetative state, she understood the tasks and repeatedly performed them and hence must have been conscious.

The first question raised by these spectacular results was whether the patient was misdiagnosed. Although repeated expert assessments had confirmed that she was in the vegetative state at the time of the study, the examinations revealed that her eyes briefly fixed on objects. This finding is sometimes observed in the vegetative state, but it is atypical and should prompt

physicians to search for other signs of awareness. During another examination about six months after the study, the patient was able to fix her eyes on an object for a sustained period (more than five seconds) and could track her own mirror image; both these signs herald a transition to the minimally conscious state. Currently the patient is still minimally conscious, sometimes obeying commands but not communicating.

Given her young age and the cause and duration of the vegetative state, we knew from the start that the patient's chances of recovery were not zero but about one in five. Thus, the results of the study should not be misinterpreted as evidence that all patients in a chronic vegetative state may actually be conscious. In fact, we have not observed any similar signs of awareness in functional scans of more than 60 other vegetative patients studied at the University of Liège. The most likely explanation of the results is that our 23-year-old patient was already beginning the transition to the minimally conscious state at the time of the experiment. Indeed, a recent study by Di Haibo of Zhejiang University in China and his colleagues confirmed that the activation of higher-level brain regions during fMRI tests can predict recovery to the minimally conscious state.

These findings underline the point that ascertaining consciousness is a tricky business. We have learned much from new imaging techniques that measure neural activity in brain-damaged patients, but more research is needed before scientists can use functional neuroimaging to confirm a diagnosis of the vegetative state and to help in the prognosis and treatment of this devastating medical condition. For the time being, doctors must continue to rely on thorough clinical examinations when making their difficult therapeutic decisions. SA

MORE TO EXPLORE

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