NEUROSCIENCE

Is Anybody in There?

Communicating with patients who appear to lack consciousness is becoming a reality

By Adrian M. Owen

Photograph by Gerald Slota

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I CAN TRACE MY SEARCH FOR CONSCIOUSNESS IN NONRESPONSIVE PATIENTS TO THE MOMENT IN 1997 when I met Kate, a young teacher from Cambridge, England, who had lapsed into a coma after a flulike illness. Within a few weeks Kate's doctors had declared her to be vegetative—meaning that although she had sleep-wake cycles, she lacked conscious awareness. Her eyes would open and close, and she would appear to look fleetingly around the hospital room, but she showed no signs of inner life and no responses to prompting by her family or doctors.

I was developing new brain-scanning methods at the University of Cambridge, and David Menon, my colleague there, who is an expert on acute brain injury, suggested that we put Kate into our positron-emission tomography (PET) scanner to see whether we could detect any signs of cognitive activity in her brain. It was a long shot, but we suspected that some of our new brain-imaging approaches just might work. While Kate was inside the machine, we showed her pictures of her friends and family by flashing them on a computer screen, and we looked for any signs of a response from her brain. The results were extraordinary. Not only did her brain respond to the faces, but the pattern of brain activity was strikingly similar to what we and others had seen when showing the faces of loved ones to healthy, aware individuals.

What did it this mean? Was Kate actually conscious despite her outward appearance, or was this some sort of reflexive response? It would take more than 10 years of research and improved methodology before we would know how to answer such questions.

Finding answers had become increasingly urgent. In recent years improvements in trauma care, roadside medicine and intensive care had led to more people surviving serious brain damage and ending up as Kate had—alive but with no evidence of preserved awareness. Such patients can be found in virtually every city and town with a skilled nursing facility. Determining their care and treatment—how much life support to give, how to weigh family wishes and the patient's advance directives (if they exist)—is a thorny ethical thicket, involving anguish and sometimes lawsuits. Some of these patients go on to recover to an extent, although it is difficult to predict which ones will and how much. Others enter a state of minimal consciousness, demonstrating inconsistent but reproducible signs of awareness [*see box on opposite page*]. And still others remain vegetative, sometimes for the rest of their days—which can last decades. Being able to distinguish among these states can make all the difference in determining what decisions are in a patient's best interests.

IMAGINE PLAYING TENNIS

IN THE YEARS FOLLOWING KATE'S SCAN, our team at Cambridge tried many ways to detect hidden awareness—what we call covert consciousness—in patients who had been declared vegetative. We played speech for them—long streams of spoken prose—and compared the response in their brain to what happened when we played speechlike noises that contained no real language. In a number of cases, we observed brain activity in putatively vegetative patients that looked like that of healthy participants—speech-perception regions of the brain would often respond when we played them speech but did not respond when we played them the speechlike noises. As before, however, we were unsure if the seemingly normal brain responses reflected an undetected consciousness or if they were more basic, automatic neural signals, largely independent of any higher-level conscious processing.

IN BRIEF

Improved trauma care has led to more people surviving brain injury but ending up in vegetative or minimally conscious states. Researchers are devising imaging techniques to determine which patients retain some awareness or might regain consciousness.

Functional magnetic resonance imaging has revealed, surprisingly, that a portion of patients who are labeled "vegetative" are conscious. Some can answer questions by imagining one activity for "yes" and another for "no."

Investigators are now turning to electrocardiographic technology to try to devise an easier, bedside approach to detecting consciousness. On the more distant horizon are brain-computer interfaces that would enable patients with hidden consciousness to communicate.

DISORDERS OF CONSCIOUSNESS

Lost in the Gray Zone

Consciousness seems like an all-or-nothing affair—either the lights are on, or they are off. But in fact, it can be present in degrees. Conditions in which it is compromised are known as disorders of consciousness (*below*). Most often they stem from trauma to the head or events, such as stroke or cardiac arrest, that result in a loss of oxygen to the brain: outcomes tend to be worse for loss of oxygen than for trauma. Patients may progress or regress from one category to another, except in the case of brain death, from which there is no recovery.

Brain death: All functions of the brain and brain stem have permanently ceased.

Coma: Loss of consciousness is complete; cycles of waking and sleeping disappear, and the eyes remain closed. Coma, which rarely lasts more than two to four weeks, is usually temporary; afterward, patients emerge into consciousness or one of the states below.

Vegetative state: Sleep-wake cycles occur, and the eyes may open spontaneously or in response to stimulation, but the only behaviors displayed tend to be reflexive. *Famous cases:* Terri Schiavo, Karen Ann Quinlan.

Minimally conscious state: Patients may seem vegetative but sometimes show signs of awareness, such as reaching for an object, following a command or responding to their environment. *Famous case:* Terry Wallis, who regained consciousness after 19 years.

Locked-in syndrome: Technically, this state is not a disorder of consciousness, because patients are fully conscious; however, they cannot move and may mistakenly be deemed vegetative or minimally conscious. Many patients do retain the ability to blink and move their eyes. *Famous case:* Jean-Dominique Bauby, who dictated a memoir by blinking his left eye.

I carried out a critical follow-up experiment with Menon, neuroscientist Matt Davis and others at Cambridge. We decided to sedate a group of healthy participants—in this case, a group of anesthesiologists—and expose them to the same combination of speech and nonspeech sounds that we had shown could elicit normal patterns of brain activity in some vegetative patients. Surprisingly, when these healthy subjects were rendered unconscious with the short-acting anesthetic propofol, the speech-perception areas of the brain were activated just as strongly as when the participants were wide awake. This crucial piece of evidence showed us that "normal" brain responses to speech in vegetative patients are not a reliable indicator of covert awareness. It seems that the brain processes speech automatically, even when we are not conscious and aware that we are doing it.

It was time to go back to the drawing board. We had to look at the issue of covert consciousness in a different way. The real question was not how we could activate these patients' brains but rather what kind of activity we would have to observe to be convinced that a patient was conscious. We drew our answer from the classic, clinical assessment of consciousness: response to command. This is the familiar squeeze-my-hand-if-you-can-hear-me test so often depicted in medical dramas on television. Of course, our patients were too injured to produce physical responses to commands, but could they produce a measurable brain response by just thinking about it?

Working with Mélanie Boly, a neurologist in Steven Laureys's laboratory at the University of Liège in Belgium, we set about measuring brain activity while healthy participants imagined doing various tasks, ranging from singing Christmas carols to walking from room to room in their home to playing a vigorous game of tennis. For many such scenarios, mentally performing the task generates a robust and reliable pattern of brain activity that is similar to actually performing the task.

Using functional magnetic resonance imaging (fMRI), which, unlike PET, requires no injection of tracer chemicals, we found that two of the best tasks were playing the imaginary game of tennis and mentally walking from room to room in one's home. Indeed, in every healthy participant we scanned, the tennis task elicited strong fMRI activity in the premotor cortex, a brain region that plays a role in planning movement. On the other hand, mentally touring one's home activated the parietal lobe and a deep-brain region called the parahippocampal gyrus, both of which are involved in representing and navigating spatial locations. Just like the TV doctor who tells the patient to "Squeeze my hand if you can hear me," we found we could elicit a reliable response to a command, visible by fMRI, by asking the volunteers to "Imagine playing tennis if you can hear me."

To our amazement, the technique worked the very first time we tried it with a seemingly vegetative patient. The young woman in question was involved as a pedestrian in a complex traffic accident and had sustained quite severe traumatic brain injuries. She had remained entirely unresponsive for five months before her fMRI scan, and she fulfilled all internationally agreed criteria for a vegetative-state diagnosis. During the scanning session, we instructed her to perform the two mental-imagery tasks repeatedly and in a given sequence. Remarkably, whenever she was asked to imagine playing tennis, significant brain activity showed up in the premotor cortex, just as in the healthy volunteers we had scanned earlier. And when she was asked to imagine walking through her home, we observed significant activity in the parietal lobe and parahippocampal gyrus, again, like the healthy volunteers. On this basis, we concluded that despite her inability to respond physically to external inputs, the patient was conscious. This finding changed how others treated her, including doctors, nurses and her family. While I cannot give details about specific patients, I can say that, in my experience, discovering that a patient is conscious spurs others to communicate, visit, reminisce, joke and otherwise improve the quality of that patient's life.

PUTTING OUR METHOD TO THE TEST

Over the next few years we tried this technique with as many patients as we could to test its reliability and to seek ways to improve it. By 2010, in another collaboration with Laureys and his group in Liège, we reported in the *New England Journal of Medicine* that of 23 patients who had been diagnosed as vegetative, four (17 percent) were able to generate convincing responses in the fMRI scanner. As part of the study, we explored the possibility of using the imaging tasks to have patients answer yes or no questions. One such patient had suffered a traumatic brain injury five years earlier and been repeatedly diagnosed as vegetative. While in the fMRI machine, he was told he would be asked a series of simple questions and should reply by imagining playing tennis (for "yes") or imagining moving from room to room in his house (for "no"). Incredibly, using this technique, he was able to successfully convey the answers to five questions about his life. He was able to indicate, for example, that "yes," he had brothers, "no," he did not have sisters, and "yes," his father's name was Alexander. (The name is changed here to protect confidentiality.) He also confirmed the last place he had visited on vacation before his injury. Researchers who interpreted the scans as yes or no did not know the answers to these questions, which were constructed based on input from the family [*see box at right*].

Given the complexity of the tasks used, it was evident that the patient had more going on cognitively than mere awareness of his surroundings. He retained a number of higher-level functions: he could switch, sustain and select his focus of attention, comprehend language and choose appropriate responses, maintain and manipulate information in working memory—for example, keeping the instructions for answering yes or no in mind while processing each new question—and recall events from before his accident. Although this patient could reliably and effectively "communicate" with us from within the scanner, no one was able to establish any form of communication at the bedside. Nevertheless, after the fMRI analysis was done, a thorough retesting using standard techniques led doctors to change his assessment to "minimally conscious"—a reminder that diagnosis can be uncertain and changeable for these patients.

In January 2011 I moved my entire research group to Western University in Ontario to pursue this problem with better resources, a bigger team and generous funding from the Canada Excellence Research Chair (CERC) program. This move allowed us to expand and refine our investigations to tackle a number of crucial questions, including whether we could use our technique to improve patient care. In the case of one young man who had been diagnosed as vegetative for 12 years, we were able to ask a question that could potentially change his life: "Are you in any pain?" In a dramatic moment that was captured for television by a BBC documentary team, he answered, "No," much to our relief.

Another question was more technical. Could we find a test that did not require an fMRI scanner? Performing fMRI in severely brain-injured patients is enormously challenging. In addition to considerations of cost and scanner availability, the physical stress on patients can be high as they are transferred, usually by ambulance, to a suitably equipped fMRI facility. Some patients are unable to remain still in the scanner, whereas metal implants, including plates and pins, which are common following a serious injury, may rule out fMRI altogether.

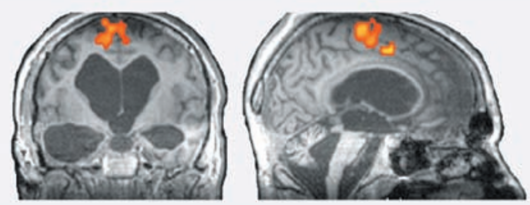
Our recent efforts have focused on building a less costly, more portable way of assessing brain activity using electroencephalography (EEG). EEG relies on noninvasive electrodes attached to the scalp and measures the activity of groups of neurons in the cortex, the deeply folded outer layers of the brain. It is unaffected by metallic implants and, perhaps most important, can be done at the bedside. Unfortunately, EEG does not easily detect changes

FINDINGS

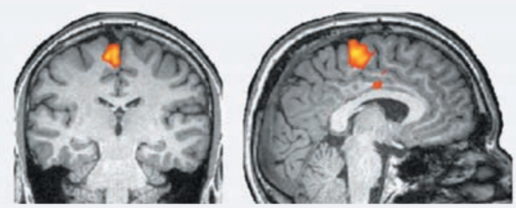
Reading Minds

To test a way of detecting consciousness and communicating with unresponsive patients, the author and his colleagues scanned the brain of a man who for five years was thought to be vegetative. They asked him various questions and told him to reply "yes" by imagining playing tennis and "no" by imagining touring his home. FMRI scanning of healthy people has shown that the tennis task increases blood flow to motor-planning regions of the brain and that the house tour increases it to spatial regions, making responses easy to distinguish. Remarkably, the man answered five questions correctly, including the two below.

The patient was asked, "Is your father's name Alexander?" He answered "yes" by visualizing himself playing tennis, which lit up a premotor region (*orange* and *yellow*). (The father's name is altered here for confidentiality.) The patient's scan pattern closely matched that of a healthy control subject imagining playing tennis.

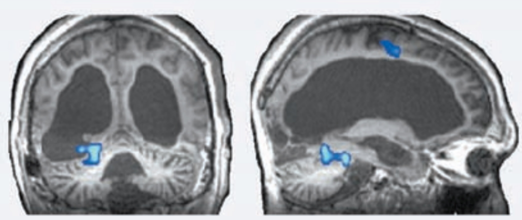


Patient

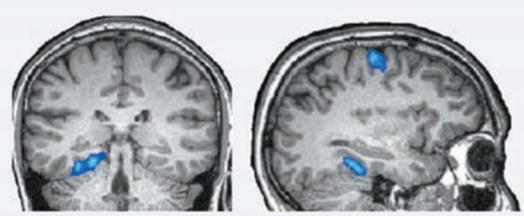


Control subject

The patient was asked, "Is your father's name Thomas?" He replied "no" by visualizing going from room to room in his home, which lit up spatial regions (*blue*). His scan was strikingly similar to that of the healthy control subject doing the same task.



Patient



Control subject

SOURCE: "WILLFUL MODULATION OF BRAIN ACTIVITY IN DISORDERS OF CONSCIOUSNESS," BY MARTIN M. MONTI ET AL., IN *NEW ENGLAND JOURNAL OF MEDICINE*, VOL. 362, NO. 7; FEBRUARY 2010

SCIENTIFIC AMERICAN ONLINE See a video about Kate, the formerly vegetative patient, at ScientificAmerican.com/may2014/consciousness in very deep brain structures, and its spatial resolution—its ability to detect a clear response in a particular brain region—is much lower than is the case with fMRI. To deal with these limitations, we adapted our mental-imagery tasks to produce activity on the surface of the cortex, in areas that control simple movements of the arms and legs. Damian Cruse, a postdoctoral fellow in my lab, found that if he asked healthy participants to imagine clenching their right hand or their toes, he could detect the difference, based on the EEG pattern that was generated. It did not work for everyone, but by 2011 it was reliable enough for us to start testing patients at their bedside.

We bought a Jeep (the "EEJeep"), fitted it with electrodes, amplifiers and the most powerful laptops we could find, and we hit the road, taking our equipment to patients. In November 2011 we reported our findings in the *Lancet*. They were similar to our results with fMRI: three out of 16 (19 percent) of the "vegetative" patients we tested using bedside EEG appeared to be conscious, based on their responses to commands to imagine squeezing their toes or hands. Not everyone was convinced by the study. EEG analysis is notoriously complicated, and the statistical algorithms we used were sufficiently novel and complex that they were challenged by another research group. Fortunately, we were able to confirm awareness in most of the patients who had responded well in the EEG study by using our more established fMRI technique. We subsequently tested and published a revised version of our EEG methodology that addressed the questions raised. With funding from the James S. McDonnell Foundation, we are collaborating with our counterparts in Liège and research teams in two other countries—including the team that initially challenged us—to develop standard protocols for using fMRI and EEG to detect covert consciousness in vegetative patients.

In principle, it is already possible to directly ask a patient if he or she wants to continue living in his or her current situation using our fMRI or EEG techniques.

WHAT NOW?

WHERE DO WE GO FROM HERE? The notion that we might one day be able to communicate by thought alone has preoccupied scientists and science-fiction writers for decades. The use of fMRI and EEG to detect awareness and begin to communicate with some otherwise nonresponsive patients paves the way for the development of true brain-computer interfaces that would relay a patient's thoughts to the outside world. It seems increasingly likely that such devices, when they become available, will work by translating specific thoughts into yes, no and perhaps other concepts. Creating systems that work for individuals who have sustained major brain injuries will be no easy task, however. Such patients rarely have control over their eye movements, ruling out interfaces that depend on blinking or directing one's gaze, and their depleted cognitive resources—a common result of brain injury—may preclude any system that requires extensive training, as the current ones do.

These obstacles notwithstanding, it seems likely, if not inevitable, that fMRI, EEG and perhaps newer technologies will increasingly be used to detect covert awareness in nonresponsive patients, raising a number of moral and legal questions. In cases where decisions have been made to withdraw nutrition and hydration, it is possible that evidence for covert consciousness could be used to overturn this decision. In principle, it is already possible to directly ask a patient if he or she wants to continue living in his or her current situation using our fMRI or EEG techniques. But would a yes or a no response be enough to signify that the patient has retained the cognitive and emotional capacity to make such an important decision? How many times would the question need to be asked and over how long a period? A 2011 survey of 65 patients with locked-in syndrome—a condition in which consciousness is intact, but the body is paralyzed—suggests that people have a surprising capacity to adapt to extreme disability: most expressed satisfaction with the quality of their lives. Clearly, new ethical and legal frameworks will be needed to guide exactly how such situations are managed and by whom.

As for Kate, a remarkable thing happened. Unlike most of the hundreds of vegetative patients I have seen over the years, she began to recover several months after her scan. She now lives at home with her family. She uses a wheelchair to get around and speaks with difficulty, but her cognitive faculties have returned, including her sense of humor and ability to appreciate the profound role that she—and her brain—has played in the process of scientific discovery. Although she did not remember her own brain scan when she first became fully conscious, Kate has since become passionate about the importance of such scans. "It scares me to think of what might have happened if I had not had mine," she wrote in a recent e-mail. "So please use my case to show people how good they are. I want more people to know about them. It was like magic—it found me." SA

MORE TO EXPLORE

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More information on the author's work: **www.owenlab.uwo.ca**

FROM OUR ARCHIVES

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