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Raising Consciousness

Some seemingly unconscious patients have startlingly complex brain activity. What does that mean about their potential for recovery? And what can it tell us about the nature of consciousness?

By Emily Singer

In 2003, 39-year-old Terry Wallis uttered his first word ("mom") in the 19 years since a car accident had left him with severe brain damage. He had spent much of the previous two decades in what neurologists call a minimally conscious state, somewhere in the gray area between coma and consciousness. In the years before his awakening, however, Wallis's family had noticed that he was growing more alert and responsive, occasionally nodding, grunting, or even crying, until one day he spontaneously started to speak. Though Wallis still has serious impairments in memory and movement, he continues to make remarkable gains.

No one knows what spurred Wallis's return to the waking world. But neurologist Nicholas Schiff is determined to find out. A researcher at the Weill Cornell Medical College in New York City, Schiff is one of a handful of scientists studying people like Wallis, patients who spend months or years seemingly unaware of the outside world and unable to communicate. Using new brain-imaging techniques, Schiff is hoping to better understand the complex nature of consciousness--and find ways to help treat the thousands of patients who suffer from severe consciousness disorders.

Eight months after Wallis's first words, Schiff and his collaborators began taking snapshots of Wallis's brain using a new method that can create detailed maps of the brain's nerve fibers. What they found surprised them. Over the next year and a half, the researchers' images seemed to show that Wallis's brain had partially healed itself. But how? And what triggered the healing process?

In the last few decades, improved medical technologies have kept more people alive after brain injuries, but many of them have been left in apparently permanent states of impaired consciousness. Immediately after a severe brain injury, a patient often enters a coma--a period of unconsciousness that typically lasts days or, at most, weeks. Those who survive do not necessarily awaken; instead, they may enter a vegetative state or a

minimally conscious state (MCS), which can last for years. While it's difficult to determine how many minimally conscious patients there are in the United States (MCS was introduced as a diagnostic category only in 2002), some estimates put the number at 25,000 or more--about 10 times the number of vegetative patients. (The two conditions can be difficult even for neurologists to distinguish. Vegetative patients are defined as those totally unaware of their environment, while patients who are in a minimally conscious state may occasionally laugh or cry, reach for objects, or even respond to simple questions.)

Unlike Wallis, most patients who spend years in a minimally conscious state never wake up. Prospects for recovery diminish as time ticks by, so many doctors adopt a sort of therapeutic nihilism toward those who are persistently unconscious, assuming that their cases are hopeless, says Steven Laureys, a neurologist at the University of Liège in Belgium. MCS patients have few treatment options, and most don't get rigorous long-term follow-up or intensive rehabilitation. Wallis, for example, had no neurologist, and not much medical history was collected during his 19-year hiatus from consciousness.

However, recent studies from Schiff's lab and others have shown that at least some of these seemingly unaware patients have a startlingly high level of brain activity, mentally reacting to stories and commands much as a healthy person would. Schiff and others who study minimally conscious patients are careful to distinguish them from patients such as Terri Schiavo, who received nationwide media attention in 2005. Schiavo was in a vegetative state, which she entered after lack of oxygen led to widespread brain-cell death. When a brain injury is caused by trauma, on the other hand, the damage is often limited to the nerve fibers that connect different parts of the brain, and some neural circuits may remain intact. Among these patients, the new imaging studies are revealing a surprising potential for some restoration of normal brain activity.

The findings offer hope for a group of people largely given up for lost by the medical community. Schiff and others are working to piece together the structural or functional changes that enable some MCS patients to awaken; eventually, the researchers hope to design treatments that can spur those changes in others. At the same time, they are opening a window on a hidden world. "Consciousness is a subjective, first-person experience," says Laureys. "It is very tricky to conclude the absence of consciousness based on the absence of response at the bedside. There might be some inner world that we have no way to assess."

Mental Tennis

In 1998, Joy Hirsch, a neuroscientist at the Columbia University Medical Center in New York City, paved the way for studies that use functional MRI (fMRI) to assess impaired consciousness. By measuring blood flow in the brain, fMRI can pinpoint regions that are active when, for example, a person is feeling anger or working on an abstract problem. Hirsch wanted a way to locate--and thus protect--the language area in babies who needed brain surgery. While most previous fMRI studies had required volunteers to perform specific tasks, such as reading or speaking, to activate the relevant parts of the brain, Hirsch found that just reading a story to the babies could stimulate the region involved in speech. It became obvious, she says, that the same technique could be used to test cognitive function in minimally conscious patients.

Aided by further improvements in imaging technology, in 2005 Hirsch and Schiff used fMRI to examine how two minimally conscious patients responded to stories told by friends and family members. The results were similar to those seen in healthy volunteers. The stories triggered activity in the language centers and other areas of the brain, suggesting that certain clusters of neurons remained intact and functioning. When a patient listened to his sister tell stories about their childhood, for example, parts of his visual system lit up, suggesting that he might be imagining those scenes.

The findings sparked intense interest among neurologists, but without direct reports from the subjects themselves, it was difficult to judge exactly what the patients were experiencing. Were they trapped in a lonely mental prison, aware of the world outside but unable to respond to it? Did they experience only isolated moments of awareness? Or was the brain activity simply a sort of cognitive reflex, triggered by a familiar voice and a few evocative words or names?

In 2005, Adrian Owen, a neuroscientist at the Medical Research Council in Cambridge, England, began a series of experiments to address these questions. Owen and his coworkers created a brain-imaging test they hoped would indicate whether someone was actually aware of his or her environment. An MCS patient was instructed to imagine playing tennis when she heard the word "tennis," or to imagine walking through her house when she heard the word "house"; she was then positioned in the scanner and given auditory prompts. The test was designed to evaluate both short-term memory, because the instructions were given well before the prompts, and the capacity for sustained attention, because the patient was told to continue imagining a scene until asked to stop. Most important, it was designed to require intentional action.

If you're healthy, imagining that you're playing tennis or navigating your house activates specific parts of your brain--respectively, the supplementary motor areas, which control

motor responses, and the parahippocampal gyrus, which plays a role in memory of scenes. So the scientists knew exactly what to look for in patients with impaired consciousness. Their subject was a 23-year-old woman who'd been left in a vegetative state after a car accident in 2005. At the time of the study, five months had elapsed since her accident, meaning that statistically, she had a 20 percent chance of some recovery. She showed no outward signs of awareness.

The results of the test were shocking, even "spectacular," according to a commentary accompanying their publication in the journal *Science* last fall. "When we cued her with the word ‘tennis,' her brain would activate in a way that is indistinguishable from a healthy person," says Owen. The same was true for the word "house." "We think the fMRI demonstrated unequivocally that she is aware," he says.

While the patient met all the clinical requirements for being in a vegetative state, her fMRI clearly showed a brain capable of relatively complex stimulus-processing. Still, it's not yet certain what conclusions can be drawn from her case. "We have studied over 60 patients in Belgium and have never seen activation compatible with conscious perception," says Laureys. "I definitely think this is the exception, but I can't tell if it's a one-in-a-thousand or a one-in-a-million case." Owen now plans to run the same tests on more patients, using a variation of fMRI that shows brain responses in real time.

Perhaps the most perplexing question raised by the results concerns the patient's state of mind: is she truly conscious? That's a matter of some debate: Owen believes the patient was aware of herself and her surroundings, but other neurologists aren't so sure. "No one knows what she really was thinking during scanning," says Laureys.

The answer may come with Owen's next round of experiments, which are designed to perform what some consider the best test of consciousness--asking a person about his or her state of mind. Using real-time fMRI, scientists can ask patients questions and gauge their responses on the basis of their brain activity. For example, since scientists know the activity patterns associated with imagined games of tennis and walks through houses, they could tell their patients to think of tennis for yes and house tours for no, then ask binary questions while performing brain scans.

Like Schiff and Hirsch's findings, Owen's are both fascinating and disquieting, largely because neurologists don't yet know what to do with them. Does the brain activity of the woman Owen studied mean she will soon wake up? What about other patients with similar injuries? Schiff, for one, plans to see if some of his patients who show visible signs of awareness can replicate Owen's results. "My guess is that some of them will be

able to do it," he says.

Lesions of Consciousness

We'll probably never know whether Terry Wallis also had some awareness before his awakening. But a type of brain imaging known as diffusion tensor imaging (DTI) has given researchers hints about how his brain has changed since.

DTI is a variation of MRI that offers an unprecedented view of the brain's wiring system--the long, thin tails of neurons that carry electrical signals between different regions. Wallis's first DTI scan, recorded eight months after his first word, revealed that he had profound brain damage. But scientists also discovered possible signs that new neural connections had sprouted between brain structures. In particular, a large area in the back of his brain appeared to have more neural fibers than normal, all oriented in the same direction. The area encompassed by these new fibers included a part of the brain known as the precuneus, which is highly active during conscious wakefulness but less active during sleep or anesthesia.

Eighteen months after that scan, Wallis was doing even better. He could move his previously paralyzed legs, an improvement "as unexpected as him recovering speech," says Schiff. When the researchers imaged his brain a second time, they found that the unusual area in the back had normalized, while a region involved in regulating movement seemed to have grown more connected. The findings were published last year in the *Journal of Clinical Investigation*.

The researchers can't yet be sure that the changes they saw in the brain images really do indicate the growth of new neuronal connections, nor that those changes sparked Wallis's recovery. "Why did he emerge? None of us can answer this," says Hirsch. "But it suggests a biological underpinning to recovery."

Brain imaging might eventually be used as a diagnostic tool to help spot those who are most likely to recover. "We need to develop better ways to model and measure the emergence to consciousness and collect enough data so that we can make statistical predictions for recovery," says Schiff. However, identifying the telltale changes that predict awakening promises to be difficult. Schiff and Hirsch have scanned more than a dozen other patients in addition to Wallis, including several who have awakened, and they have yet to find specific patterns or changes in brain activity that might signal that a patient is improving. But they're still looking--at whether the network hubs of the brain are active, for example, or whether activity in different brain areas is in sync. "We think

of patients with traumatic brain injury as patients with lesions of consciousness," says Hirsch. She hypothesizes that consciousness arises from a network of connections rather than in a specific location in the brain.

The brain is constantly processing information: sights and sounds are recorded and synthesized in different parts of the brain, then fused together in other areas, creating a cohesive picture of the outside world. And early evidence indicates a link between consciousness and the ability to integrate information. In a study of 60 patients in the vegetative state, Laureys found that the seven patients who later awakened recovered brain metabolism in regions that connect the cortex with the thalamus, a relay center in the brain.

Injury to the brain may tear the nerve fibers that relay messages between different regions, impeding the integration process. Similarly, Schiff believes that the circuits left intact in minimally conscious and vegetative patients may communicate erratically, making it difficult for the brain to coördinate complex tasks involving multiple brain areas. Patients with impaired consciousness also exhibit low levels of neural activity, Schiff says; their brains may take a stab at a particular task, generating the brief appearance of responsiveness, but then peter out. A patient's occasional moments of clarity, then, might come from brief spurts of synchronized activity. "Some patients may harbor the capacity for functional recovery, but it depends on recruiting circuit-level neuronal responses to sustain a state like that of the brain working normally," Schiff says. Emotional events, such as a sister's description of childhood memories, may do a better job of activating those circuits, which could explain why emotional stories seem to trigger the strongest responses.

Understanding what causes impairments in consciousness could ultimately shed light on a larger puzzle: what allows a healthy person to be aware of self and surroundings? "I think that a detailed understanding of the necessary and sufficient conditions for the recovery of consciousness will provide immensely important insights into the fundamental nature of the human conscious state," says Schiff.

Abandoned

Schiff's ultimate goal, of course, is to spark awakenings like that of Terry Wallis in other minimally conscious patients. At a neuroscience meeting last October, he presented preliminary evidence that electrically stimulating the thalamus, which sends sensory information to the cerebral cortex, might help patients recover consciousness. Schiff and his team used deep brain stimulation--a therapy used to treat Parkinson's disease, where

an electrode is implanted in the brain--to stimulate thalamic neurons in a 38-year-old minimally conscious patient who had suffered a severe traumatic brain injury six years before. They found that when the neurons were stimulated, the patient was more responsive and coördinated, even able to eat a meal with some independence.

Though Schiff is reluctant to talk about his group's findings before they are published in a peer-reviewed paper, he and other neurologists are clearly excited about them. "This is a very interesting and important observation," says James Bernat, a neurologist at Dartmouth Medical School, who adds that Schiff's result is particularly noteworthy because the patient had been in a minimally conscious state for so long. Previous studies of deep brain stimulation, carried out mostly in Japan, have involved recently injured patients, who might have improved anyway.

To prove the efficacy of deep brain stimulation in treating consciousness disorders, and to determine just which patients it might help, other researchers will need to duplicate Schiff's success. But that's a tall order. Research on minimally conscious and vegetative patients presents enormous obstacles--the logistics of transporting patients from long-term-care facilities to imaging labs, the ethical and legal issues involved in testing people who cannot give informed consent, and the technical challenge of scanning patients who may move unpredictably and may not be able to comprehend instructions to stay still.

But the biggest barrier to larger studies is funding. Terry Wallis is one of the most remarkable recovery cases Schiff has ever seen. And yet he's examined him just twice: first when a British television station flew Wallis and his family from Arkansas to New York, where Schiff and collaborators could scan his brain; and then when the producers of an HBO documentary paid Wallis's fare to New York 18 months later, so that scientists could assess the changes that had taken place since the first scan.

One might expect that some of the exciting research with minimally conscious patients in the last two years would bring more money to the field, but that has yet to happen. In early November, Schiff received disappointing news: the National Institutes of Health, the primary biomedical funding agency in the United States, had declined to fund larger studies of the diagnostic methods he and others have been developing. He says that while some grant reviewers are excited by the recent findings, others are reluctant to spend money on a group of patients they see as beyond hope. "I think it shows a discriminatory bias against this patient pool," says Schiff.

Neurologists studying disorders of consciousness say fatalism about their patients'

prospects extends far beyond the walls of funding organizations. Wallis's family, for example, petitioned for a neurologist annually for 19 years without success. And Schiff says the families of patients enrolled in his studies often thank him for being interested at all. "Their uniform experience is that no one cares," he says. "They are completely abandoned by people who would otherwise have taken care of them."

If Schiff and others are right, this population of abandoned patients includes many people aware of their surroundings. And Wallis's recovery serves as an example of just how much some of these patients might be able to improve if they can be gently prodded back to the world of full consciousness. As Wallis works diligently on his rehab exercises, Schiff continues his dogged search for clues as to how to spark such a recovery in others, coming ever closer to understanding the mysteries of consciousness.

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