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MEDICAL DISPATCH

SILENT MINDS

What scanning techniques are revealing about vegetative patients.

by Jerome Groopman

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Ten years ago, Adrian Owen, a young British neuroscientist, was working at a brain-imaging center at Addenbrooke's Hospital, at the University of Cambridge. He had recently returned from the Montreal Neurological Institute, where he used advanced scanning technology to map areas of the brain, including those involved in recognizing human faces, and he was eager to continue his research. The imaging center was next to the hospital's neurological intensive-care unit, and Owen heard about a patient there named Kate Bainbridge, a twenty-six-year-old schoolteacher who had become comatose after a flulike illness, and was eventually diagnosed as being in what neurologists call a vegetative state. Owen decided to scan Bainbridge's brain. "We were looking for interesting patients to study," he told me. "She was the first vegetative patient I came across."

For four months, Bainbridge had not spoken or responded to her family or her doctors, although her eyes were often open and roving. (A person in a coma appears to be asleep and is unaware of even painful stimulation; a person in a vegetative state has periods of wakefulness but shows no awareness of her environment and does not make purposeful movements.) Owen placed Bainbridge in a PET scanner, a machine that records changes in metabolism and blood flow in the brain, and, on a screen in front of her, projected photographs of faces belonging to members of her family, as well as digitally distorted images, in which the faces were unrecognizable. Whenever pictures of Bainbridge's family flashed on the screen, an area of her brain called the fusiform gyrus, which neuroscientists had identified as playing a central role in face recognition, lit up on the scan. "We were stunned," Owen told me. "The fusiform-gyrus activation in her brain was not simply similar to normal; it was exactly the same as normal volunteers'."

Excited by this result, Owen resolved to try to conduct brain scans of other vegetative patients in the Cambridge area. Since 1997, he has studied several dozen people, though he decided to use speech sounds rather than photographs to stimulate their brains. (Owen was concerned that showing images of faces might not be a reliable way to test recognition, since the eyes of vegetative patients often wander. "We shifted to auditory responses because you can always put a pair of headphones on the person and know that you are transmitting sound," he said.) Three years ago, he began using a functional MRI (fMRI) scanner, which is faster than a PET scanner, capturing changes in blood flow in the brain almost as they occur. The patients' brains were scanned while they listened to a recording of simple sentences interspersed with meaningless "noise sounds." The scans of some of the patients showed the same response to the sentences as scans of healthy volunteers, but Owen wasn't sure that the patients had understood the words. "So we went the next step up the cognitive ladder, to look at comprehension," he said.

Psycholinguists have shown that when we hear a noun at the beginning of a sentence we tend to associate the word with its most common meaning. For example, Owen said, most people hearing a sentence that begins, "The shell was . . ." think of an object typically found at the beach. But if the sentence is completed by the phrase "fired at the tank," the listener quickly corrects himself, a process that is evident on a brain scan. "You can actually see it happening and



image it on the scanner,” Owen said. “The beautiful thing about the psychological task is that we just do it automatically. When you play ambiguous sentences, areas in the inferior frontal lobe and in the posterior temporal lobe become activated, and these areas are very important for speech comprehension. They show that you understand the meaning of the word: it’s not just about perceiving speech; it’s about decoding. Your brain somehow appreciates that there are two meanings to a word like ‘shell.’ ”

Owen eventually identified two vegetative patients whose brains showed the same activity in response to ambiguous sentences as the brains of healthy volunteers. He also took brain scans of healthy physicians, who were presented with the ambiguous sentences while under general anesthesia. Owen found that, as the effects of the anesthesia increased, the physicians showed less activity in the brain regions associated with comprehension. “That, of course, is in keeping with our personal experience of consciousness, which is that as you sort of drift into sleep you understand less and less of what is around you,” he said. (An article about this experiment appears this week in *PNAS*, the journal of the National Academy of Sciences.)

Owen’s final experiment was the most ambitious: a test to determine whether vegetative patients who seemed able to comprehend speech could also perform a complex mental task on command. He decided to ask them to imagine playing tennis. (“We chose sports, and tried to find one that involved a lot of upper-body movements and not too much running around,” he said.) First, he took brain scans of thirty-four healthy volunteers who were instructed to picture themselves playing the game for at least thirty seconds. Their brains showed activity in a region of the cerebrum that would be stimulated in an actual match. “This was an extremely robust activation, and it wasn’t difficult to tell whether somebody was imagining tennis or not,” Owen said. He then repeated the experiment using one of the vegetative patients, a woman who had been severely injured in a car accident. The woman had to be able to hear and understand Owen’s instructions, retrieve a memory of tennis—including a conception of forehand and backhand and how the ball and the racquet meet—and focus her attention for at least thirty seconds. To Owen’s astonishment, she passed the test. “Lo and behold, she produced a beautiful activation, indistinguishable from those of the group of normal volunteers,” he said. (Another vegetative patient, a man in his twenties, also passed the test, though Owen, having learned that the man was a soccer fan, asked him to imagine playing that sport instead of tennis.)

In September, 2006, Owen, along with Martin Coleman, a neuroscientist at Addenbrooke’s, and four other researchers, published an article about the tennis experiment in *Science* and ignited a vigorous debate. In letters to the journal, some neurologists argued that the woman must have been misdiagnosed—a claim that Owen disputed. “She fulfilled all of the internationally agreed-upon criteria, and there wasn’t anything that she did that would lead anybody to say she wasn’t vegetative,” he told me. “Now, naturally, in hindsight she wasn’t vegetative; she was actually conscious. It’s a very interesting issue, because it means that she was in fact misdiagnosed, but not misdiagnosed in the sense that somebody made an error. Clearly, she is consciously aware of things around her. So something is missing in the diagnostic criteria.”

For decades, doctors assumed that patients who have been diagnosed as vegetative lack any capacity for conscious thought. Most are previously healthy people who suffered a traumatic brain injury, or oxygen deprivation after a heart attack or stroke, and have been regarded more or less as zombies: patients whose bodies continue to function—sometimes for decades—but whose minds are incapable of willed activity. (The term “vegetative” was proposed in 1972, by Bryan Jennett, a neurosurgeon, and Fred Plum, a neurologist, who chose it based on a definition in the O.E.D: “an organic body capable of growth and development but devoid of sensation and thought.”) In the occasional newspaper stories about someone who suddenly recovered consciousness after spending years in a vegetative state, the event was invariably described as a medically inexplicable “miracle.” The Mohonk Report, a paper prepared by a group of experts in brain injury and presented to Congress last year, cited estimates suggesting that there are approximately thirty-five thousand Americans in a vegetative state and another two hundred and eighty thousand in a minimally conscious state—a less severe condition, in which patients show erratic evidence of deliberate behavior, such as responding to a simple command or focussing on a person or an object for a sustained period. Because insurers typically won’t pay for rehabilitation, on the assumption that such patients are unlikely to improve, most are given little in the way of therapy. “These people with brain trauma are out of our view,” Joseph Fins, an internist and medical ethicist at Weill Cornell Medical College, in Manhattan, and a member of the Mohonk group, told me. “We ignore them, and we sequester them in places where we can’t see them, usually in nursing homes.”

According to several American and British studies completed in the late nineties, patients suffering from what is

known as “disorders of consciousness” are misdiagnosed between fifteen and forty-three per cent of the time. Physicians, who have traditionally relied on bedside evaluations to make diagnoses, sometimes misinterpret patients’ behavior, mistaking smiling, grunting, grimacing, crying, or moaning as evidence of consciousness. A neuroscientist showed me a video on the Internet of Terri Schiavo, the Florida woman who spent fifteen years in what most doctors agree was a vegetative state—tests revealed almost no activity in her cortex—and whose death, in 2005, provoked fierce debate over the rights of severely brain-damaged patients. (Schiavo died after the Supreme Court rejected her parents’ appeal of a judge’s decision approving her husband’s request that her feeding tube be removed. An autopsy showed extensive brain damage.) In the video, a man’s voice can be heard praising Schiavo for opening her eyes in response to his instructions, and the neuroscientist told me that he was impressed until he muted the sound. “With the sound off, it is clear that her movements are random,” the neuroscientist said. “But, with the voice-over, it is easy to make a misdiagnosis.” (The prognosis for patients such as Schiavo, who suffered brain damage owing to oxygen deprivation following cardiac arrest, is much worse than for those who suffer brain damage as the result of a head injury.)

Doctors can also miss signs of consciousness in vegetative patients, according to the British and American studies. Ten months after Owen and his colleagues completed the tennis experiment with the vegetative woman, she was brought back to the imaging center and placed in an MRI machine. “We were absolutely dismayed, because we scanned her and there was nothing,” Owen recalled. The team tested the woman again the next day. This time, in response to a command to play tennis, her brain showed normal activity in the regions that mediate arm movements. Owen now repeats scans for each patient, conducting them twice a day for three days. Patients with brain injuries have “seriously impaired attention capabilities and their levels of general arousal are likely to be shot,” he said. Recent research by Owen and other neuroscientists may eventually help make diagnoses more accurate, but it is not yet clear how the new brain-scan data will affect the medical understanding of consciousness. As Owen put it, “The thought of coma, vegetative state, and other disorders of consciousness troubles us all, because it awakens the old terror of being buried alive. Can any of these patients think, feel, or understand those around them? And, if so, what does this tell us about the nature of consciousness itself?”

Owen’s article in *Science* was accompanied by an editorial by Lionel Naccache, a neurologist at the Hôpital Pitié-Salpêtrière, in Paris, who called the results of the tennis experiment “spectacular.” “Despite the patient’s very poor behavioral status, the fMRI findings indicate the existence of a rich mental life, including auditory language processing and the ability to perform mental imagery tasks,” Naccache wrote. Yet he cautioned against drawing general conclusions about vegetative patients from a single case, and asked, “If this patient is actually conscious, why wouldn’t she be able to engage in intentional motor acts, given that she had not suffered functional or structural lesion of the motor pathways?” Prompted by questions like this, Naccache and several of his colleagues are conducting brain-imaging experiments with the goal of identifying objective indicators of consciousness, and thus enabling doctors to better evaluate patients who are unable to communicate their awareness of themselves or their environment.

We assimilate information unconsciously all the time; at any given moment, we process thousands of stimuli, of which we pay attention to only a few. As you read this sentence, you may not be aware of the birds singing in the back yard, but your brain has analyzed the sound and concluded that it poses no threat to you. In the past several decades, scientists have uncovered particularly dramatic examples of unconscious processing. In the early seventies, researchers at M.I.T. studied four patients who had experienced trauma to an area of the brain involved in vision and had been found to have a condition that was later called “blindsight.” These patients’ eyes functioned normally, but they did not perceive much of what was in their field of vision. When the researchers flashed a light at the patients and asked them to describe what they saw, the patients reported that they had seen nothing. Yet the researchers noticed that their eyes often located the source of the light. In a second experiment, a blindsight patient was shown pictures of faces displaying happiness, sadness, anger, and fear. The patient said that he could not see the faces, yet he was frequently able to correctly identify the emotions. The researchers concluded that, despite the patient’s injuries, pathways in his brain had been preserved which allowed him to process at least some visual data, even though he wasn’t consciously aware of doing so.

In the early nineteen-hundreds, the Austrian neurologist Hermann Zingerle described patients who, because of tumors or other abnormalities of the parietal lobe on the right side of the brain, ignored the left side of the body and objects in the left field of vision. (The right side of the brain controls awareness of the left side of the body.) For

example, some of these patients would shave only the right side of their faces, since they were unaware of their left cheeks. In the nineteen-eighties, researchers determined that patients who had the syndrome—now called “neglect”—could process some objects in the left field of vision. In one experiment, a patient was shown two pictures of a house. The images were identical except that, in one, flames were emerging from a window on the left side of the façade. The patient said that she couldn’t see any difference between the images, but, when she was asked which house she would want to occupy, she almost always chose the one that was not on fire. “This is more complex than blindsight, because it means that the patient was unconsciously able to interpret and understand the symbolic meaning of the pictures,” Naccache said. “It is a powerful experiment to demonstrate that unconscious perception and unconscious cognition can reach upper levels of the brain.”

From these and other recent experiments, including his own, Naccache and his research team are developing a working medical definition of consciousness. “When we are conscious, the key property is our ability to report to ourselves or to others the content of the representation—as when I say, for example, ‘I am perceiving a flower,’ or the fact that I am conscious of speaking with you now on the telephone,” Naccache told me. “You have patients who are conscious, or who are able to make reports, but you can prove that some stimuli escaped their conscious reports, as in the case of blindsight or neglect. You can study the neural fate of these representations by showing that, even if the stimuli were not reported by the subject, they were still processed in the brain.” He added that, in the case of Owen’s vegetative patient who imagined playing tennis, it’s impossible to know whether she reported the event to herself—which would suggest that she is capable of conscious thought—or whether, as in the case of the blindsight and neglect patients, she had no subjective awareness of the experience. However, Naccache believes that consciousness also requires an ability to sustain a representation over time, which Owen’s patient clearly was able to do. “In assessing apparently vegetative patients who are unable to speak, and thus report, the direction of research should be to look for sustained representation,” he said. “If we can prove by neuroimaging techniques that this person is able to actively maintain a given representation during tens of seconds, it provides strong evidence of conscious processing.”

Naccache has recently incorporated a third neurological feature into his definition of consciousness: broadcasting. In a person who is conscious, he explained, information entering the brain is processed in a few areas and then distributed—or broadcast—to many others. “It’s as though there is a kind of ignition in the brain, and then information is made available to a very rich number of regions,” Naccache told me. “And that makes sense, that the information is initially represented locally and then made available to a vast network, because the person has this ability to maintain the representation within the network for a long time.”

In 2005, Naccache conducted an experiment whose outcome suggested the importance of broadcasting as a marker of consciousness. First, he and his research team presented a series of words to three epileptic patients, who had had electrodes implanted temporarily in various brain regions, in an effort to locate the source of their seizures. The electrodes enabled doctors to record the activity in a given region. Some of the words, such as “blood” and “rape,” were chosen for their negative emotional connotations. The rest of the words, which included “chair” and “house,” were considered neutral. Each word was shown to the patients for twenty-nine milliseconds and then replaced with an image of a geometric figure, such as a rectangle. The patients reported seeing only the geometric figures. However, Naccache’s team discovered that in each patient the amygdala, a brain structure that is associated with strong negative emotions, such as fear, displayed much more activity in response to the negative words than to the neutral words.

“The picture we have now is that, unconsciously, many areas of the brain can process information, and that unconscious representation can be very abstract and very rich—much more than neuroscientists thought some decades ago,” Naccache said. “But now we can begin to identify some limits of unconscious cognition. The activation picked up by the electrodes is not only evanescent but restricted to the amygdala and a few other regions, without broadcasting and amplification through the brain.” Owen’s tennis-playing patient may have been broadcasting information during the experiment, Naccache said, though he added that he is uncertain whether her diagnosis should be upgraded from vegetative to minimally conscious. Moreover, he said, brain-scan research cannot yet tell us much about such a patient’s prospects for improvement.

The J.F.K. Johnson Rehabilitation Institute, in Edison, New Jersey, is among the world’s largest centers for the treatment of brain injuries and one of the few places where patients suffering from disorders of consciousness participate in research studies and receive innovative therapy. In 2002, Joseph Giacino, a neuropsychologist at the institute, was the co-chair of the Aspen Work Group—which was made up of experts in brain injury—and helped

formulate the criteria for diagnosing a minimally conscious state. “I think the rehabilitation field was ahead of the curve in understanding that there were subpopulations of patients who were not in a coma, were not in a vegetative state, but really were not conscious, at least in the way we think about normal consciousness,” Giacino told me. “In the medical literature, these patients were lumped together with everybody else.”

The techniques that Giacino uses to diagnose patients require no sophisticated technology. He recalled making rounds at the institute with two eminent neurologists and stopping at the bedside of a woman who had had a brain hemorrhage. The neurologists examined the woman, who lay with her eyes half closed and did not respond to the doctors’ commands. The neurologists concluded that she was in a vegetative state. “So I sort of sheepishly said, ‘Let me show you what happens when we stimulate her,’ ” Giacino recalled. He had been using a technique called “deep-pressure stimulation,” which involves squeezing a patient’s muscles with force and precision. Giacino started with the woman’s face and worked his way down to her toes, pinching her muscles between his fingers. As he explained, the nerve endings of the muscles send impulses to the brain stem, which relays them to other brain structures and rouses the patient to consciousness. “I did a cycle of deep-pressure stimulation, and within a minute or so she was talking to us,” Giacino said. “The neurologists were flabbergasted.” The woman was able to say her name and her husband’s name, and answer simple questions, such as “Is there a cup at your bedside?” After a few minutes, however, she became unresponsive again.

The woman had what Giacino calls a “drive disorder,” in which a patient is unable to speak, move, or, possibly, think unless physically stimulated—by touch. Doctors believe that such disorders are caused by damage to the limbic lobes or to other parts of the brain that trigger and sustain behavioral responses. Some patients with drive disorders respond to drugs that increase brain levels of dopamine, a neurotransmitter that is associated with arousal. “Imagine if the woman were in a nursing home,” Giacino said. “Somebody would stop by for three minutes, check her bedpan, and present simple commands like ‘Squeeze my hand,’ ‘Close your eyes,’ and ‘Open your mouth.’ She is not going to do any of those things, but she clearly had a significant amount of preserved function. It had to be harnessed externally.” At J.F.K. Johnson, patients with drive disorders receive behavioral and drug therapy. (Some patients improve, but prospects for recovery are largely determined by the extent and nature of the damage to the drive system.)

Since 2002, the institute has been experimenting with using brain scans to assist with diagnoses. Giacino cited the case of a male patient whose condition had been diagnosed as vegetative but who appeared to have strong emotional responses to people around him. “If a nurse came in to do his care, it looked like he was screaming silently,” Giacino recalled. “His mouth would be wide open, and he had an agonized, contorted face, like the one in Edvard Munch’s painting ‘The Scream.’ The expression would occur if there was a lot of noise around him, or if he was being physically handled, but then his mother would come into the room, lower the lights, talk with him in a soothing voice, and it would just go away.” When doctors scanned the man’s brain, they discovered that portions of the right hemisphere involved in emotional processing were intact. (Other parts of the right hemisphere were damaged.) “This shows you how treacherous diagnostic assessment can be,” Giacino said. “One can retain one piece of a network but be disconnected from other structures and other networks, so that there is almost no subjective awareness associated with this complex behavior. I’ve seen other patients with other behaviors that seem to be outside the scope of a vegetative state. Then you image them and you find out some circuits are still relatively preserved, while most of the rest of the brain is not.”

However, brain-scan technology has also helped doctors identify one patient at J.F.K. Johnson as a candidate for an experimental therapy. The patient, a thirty-eight-year-old man who suffered a head injury and had been living in a nursing home for six years, arrived at the institute in 2004. He appeared to be minimally conscious; he occasionally mouthed single words when prompted, but he was unable to respond reliably to simple questions, or to chew and swallow. (He had a feeding tube.) In 2001, PET and fMRI scans had been taken of the man’s brain, and, according to Giacino, one of many researchers involved in the case, “the findings were totally unexpected. The PET scan showed little metabolic activity, but the fMRI scan showed that the region of the cortex involved in processing language functioned in a fairly normal way.” The researchers speculated that, because of damage to the man’s frontal lobe, thalamus, and brain stem—areas involved in regulating arousal—the nerve signals in his brain were muted. As Nicholas Schiff, a neurologist at Weill Cornell Medical College who led the study of the man’s brain, put it, “It’s as if a radio were turned to such a low volume that you couldn’t hear the music distinctly.” He added, “The scans confirmed our expectation that this patient had a greater capacity for language than he demonstrated.”

In August, Schiff, Giacino, Joseph Fins, and Ali Rezai, a neurosurgeon at the Cleveland Clinic, along with twelve other researchers, published an article about the case in *Nature*. The researchers described implanting electrodes in the man's thalamus, which, by stimulating the brain tissue, had enabled him to regain considerable physical and mental function. "Deep brain stimulation can promote significant late functional recovery from severe traumatic brain injury," they wrote. When the electrodes were turned on in the man's thalamus, his speech improved, his movements became more fluid, and he was able to chew and swallow. When the researchers turned off the electrical stimulation, the man soon relapsed. He is now being given regular doses of electrical stimulation and is able to speak in short sentences and to chew and swallow. The researchers concluded that the case "challenges the existing practice of early treatment discontinuation" for minimally conscious patients who show some "interactive behaviors."

Few vegetative or minimally conscious patients ever recover fully, and many are unlikely to improve. (Some neurologists estimate that an adult who has been vegetative for six months following a traumatic brain injury has only a twenty-per-cent chance of regaining consciousness.) For the past three years, Schiff and Fins have been studying the brain of Terry Wallis, a forty-three-year-old man in rural Arkansas who had been the subject of national news stories in 2003, when it was reported that he had begun to speak after spending nineteen years in a nursing home, in a minimally conscious state. Schiff and Fins contacted Wallis's family and offered to help him obtain medical care during his recovery, and to use brain scans to document his progress. In 1984, Wallis, a nineteen-year-old truck mechanic, had been in a car accident and sustained a severe brain injury; he was also paralyzed. Wallis's father had asked the nursing home to arrange an evaluation of his son by a neurologist, but was told that such an assessment was too expensive and, in any case, would not be useful. In 2003, when Wallis began to speak, he received twelve weeks of physical therapy, which was covered by Medicaid, but the Arkansas Department of Health and Human Services rejected his request for further treatment, concluding that he had not made sufficient progress. One day, in 2005, Fins, who had contacted Wallis's congressman to solicit his help in obtaining additional medical care for Wallis, asked Mrs. Wallis for her son's Social Security number. "I was on the phone, and Mrs. Wallis said to Terry, 'What's your Social Security number?'" Fins recalled. "He gives his number, and I write it down. And I said, 'Mrs. Wallis, was that Terry?' And she said, 'Yup. The first time he told us his Social Security, we thought he was wrong. But we looked it up, and he was right.'"

Fins was astonished. Not only has Wallis recovered memories from his life before the accident but, Fins said, "he is picking up American culture. He now knows the song 'Bad boys, bad boys, what are you gonna do.' Why is that important? It's important because that song didn't exist in 1984, so Terry is laying down new memories. It shows sustained improvement." In 2006, Schiff arranged for Wallis to be taken to Weill Cornell Medical College, where he examined his brain using a sophisticated technique called diffusion tensor imaging, which assesses the number and health of axons, long fibres that transmit nerve impulses from one brain cell to another. The scans suggested that the axons in Wallis's brain were growing and forming new connections—a finding that contradicts the long-standing assumption that a damaged brain is incapable of healing after such a lengthy period. "We need to do longitudinal studies, to see if these kinds of changes are accruing over time, whether they happen frequently or infrequently, and what their association with the patient's level of function is," Schiff told me. In some cases, he speculated, the brain may sometimes be able to bypass an injured area and devise novel ways of connecting axons. Still, he went on, much about Wallis's recovery—and the neurological developments that are driving it—remains a mystery. "After nineteen years, Terry spoke a few words, but within seventy-two hours he recovered fluent, expressive, and receptive language," Schiff said.

Kate Bainbridge, the first vegetative patient that Adrian Owen studied in Cambridge, has also made considerable progress, recovering the use of her arms, and much of her mental function, although she is unable to walk. She still has difficulty talking, and uses a letter board to communicate with people who are not used to her speech. "Most scans show what is wrong with your brain, which doctors need to know," Bainbridge wrote to me in an e-mail. "But Adrian Owen's scans show what is working. I say they found parts of my brain were working. It really scares me to think what might have happened to me if I had not had the scans. They show people it was worth carrying on even though my body was unresponsive." ♦

PHOTOGRAPH: BILL ARMSTRONG, "APPARITION #906" (2005)/CLAMP ART