In Search of Hidden Minds

Finding signs of consciousness among severely brain-injured patients is medically challenging—and morally imperative

By Joseph J. Fins and Nicholas D. Schiff

We both stood anxiously at Maggie Worthen's bedside, trying to determine if this 23-year-old patient might be able to communicate with us. Nearly two years had passed since the cataclysmic stroke that left her almost entirely paralyzed. We asked her if the woman at the foot of her bed was her mom and instructed her to look down if the answer was yes. We waited, watching Maggie carefully. After several seconds, she replied, gazing slowly downward with her left eye. The movement was subtle but deliberate—a clear response, full of meaning and emotion.

A stroke left Maggie Worthen in a minimally conscious state, but she regained a limited ability to communicate and even paint—with hand-over-hand help from her mother, Nancy.

It was a stunning breakthrough. Most of the doctors who treated Maggie after her stroke thought she was in the vegetative state, a condition in which people's eyes are open, but they have no awareness of themselves, others or their surroundings. Such patients are normally viewed as lost to their families and unable to recover. One doctor, though, had diagnosed Maggie as being in the minimally conscious state (MCS), in which people show inconsistent signs of awareness, such as responding to their name one day but not the next. This observant doctor had noticed that sometimes—but only sometimes—Maggie tracked moving objects with her left eye.

So Maggie and her mother, Nancy, traveled to see us at Weill Cornell Medicine in New York City, where we have been investigating how the brain recovers from what are known as disorders of consciousness. This label encompasses a range of states, including coma, the vegetative state, MCS and so-called locked-in syndrome [*see box on next page*].

Nancy agreed to let Maggie participate in our research and also to let us tell their story here. Over the course of Maggie's evaluation, Nancy learned that her daughter was indeed conscious and that she knew who Nancy was. Armed with that information, Nancy was able to get Maggie greater rehabilitative care. Mother and daughter pursued speech and art therapy. And before Maggie's death in August 2015 from complications related to pneumonia, she was regaining some ability to interact and had even spoken a few words—something that would have never been possible had Nancy accepted the initial verdict that her daughter was in the vegetative state.

Maggie's case frames many of the ethical and scientific challenges we in the medical community and society at large face when it comes to patients who

FAST FACTS
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1. Patients with disorders of consciousness, including those in the so-called minimally conscious state, are often presumed to be in a permanent vegetative state—an error that limits their access to rehabilitation and any chance at recovery.
2. These patients can be difficult to identify because their awareness of themselves, others and their surroundings breaks through only episodically and inconsistently.
3. Interventions that stimulate the brain networks involved in consciousness, though, are helping some severely brain-injured people regain the ability to communicate.

PAGE 44: STEPHEN SMITH *Getty Images* (*composite*); THIS PAGE: COURTESY OF NANCY WORTHEN

appear unconscious or barely responsive but might still harbor high-level cognitive function. Historically, these individuals have been relegated to nothing more than "custodial care," but we now have better options: improved imaging technology, interventions using deep-brain stimulation and certain medications are providing new ways to identify and reach out to conscious patients among the severely brain-injured. As our capabilities increase, so does our obligation to help these people reestablish relationships severed by injury.

Too Little, Too Soon

Maggie sustained her injury in 2006, just a week before her graduation from Smith College. Fighting for her life in a nearby hospital, she received her degree in Spanish in absentia while her classmates marched, all wearing little blue ribbons in her honor. Against the odds, Maggie survived those first few weeks, and her mother ignored repeated pleas to withhold or withdraw care. Maggie moved from acute care to rehabilitation to a nursing home, and there she lingered—among patients who were mostly decades older—until she came to New York.

Sadly, Maggie's journey is typical. After receiving brilliant, lifesaving emergency care, people with disorders of consciousness are routinely tracked into less aggressive treatment before their prognosis is clear. In *Rights Come to Mind: Brain Injury, Ethics, and the Struggle for Consciousness* (Cambridge University Press, 2015), one of us (Fins) chronicled Maggie's story and how our health care system tends to marginalize patients with severe brain injury, presuming that nothing can or perhaps should be done. More than 50 families interviewed for the book shared how brain-injured relatives were often subjected to premature palliative care recommendations. If they did manage to qualify for rehabilitation, it was too little, too soon; many were not completely stable when they were discharged from the hospital and struggled with ongoing medical issues.

Eventually many people with disorders of consciousness wind up, as Maggie did, in a nursing home, which can put their lives at risk. Chronic care settings are often poorly equipped to provide the kind of sophisticated medical surveillance these patients need. And because they receive no further rehabilitation, nursing home care limits their potential recovery. Spontaneous improvement from the vegetative state becomes rare after three months to a year, depending on the type of initial injury. Before that, though, some patients do begin to recover from the vegetative state, shifting into a minimally conscious state.

Unfortunately, that transition can go unnoticed. One notable study in 2009, by Caroline Schnakers of the University of Liège in Belgium and her colleagues, found that 41 percent of 44 patients thought to be in a vegetative state were in

Disorders of Consciousness

Coma
Many serious conditions—from poisoning to heart attack to brain injury—can lead to coma, which may have evolved as a way to protect neurons from death. Comatose patients do not open their eyes or respond to stimuli—even painful ones. Nor do they have a sleep-wake cycle. They show no cognitive or motor function.

Vegetative State
Coma patients can progress to a vegetative state, in which they intermittently open their eyes but still have no cognitive or motor function. Although many patients do emerge from the vegetative state, it is considered more likely to be permanent after anywhere from three months to a year, depending on the underlying cause.

Minimally Conscious State
Patients who surface to the minimally conscious state begin to show fleeting signs of awareness. They can sometimes follow commands, make gestures or show other nonreflexive behaviors. For instance, they may smile or laugh at an appropriate time or respond to their name.

Cognitive Motor Dissociation
This proposed category would apply to a subset of patients who appear to be in a coma or a vegetative or minimally conscious state but display clear cognitive activity when examined via brain imaging or similar technologies. Without a two-way communication channel allowing such patients to respond and initiate dialogue, it is impossible to gauge their level of consciousness.

Confusional State
As people recover consciousness, they may pass through a confusional state, in which they appear disoriented. These patients have a limited range of cognitive function but cannot yet be formally tested using standard neuropsychometric measures.

Locked-in Syndrome
In this condition, people have normal conscious awareness but severe motor impairment, limiting their ability to communicate. As made famous by the memoir and film *The Diving Bell and the Butterfly,* some locked-in syndrome patients can use coded eye movements to communicate, but new brain-interface technologies may offer them improved options. These patients rarely recover any motor control.

New techniques make it easier to find conscious patients among the severely brain-injured—upping our obligation to help them.

fact minimally conscious. This alarming error rate can be attributed to several factors. Diagnostic criteria for MCS have existed only since 2002, and it is difficult for busy care staff to observe consciousness that breaks through only episodically. Part of it may also stem from the right-to-die movement in the U.S. In 1976 Chief Justice Richard Hughes of the New Jersey Supreme Court justified the removal of Karen Ann Quinlan's ventilator because she had "no realistic possibility of returning to any semblance of cognitive or sapient life."

That view holds true only for people who, like Quinlan, are permanently in the vegetative state. But it is often extended to many more patients with different disorders of consciousness, who can improve—sometimes dramatically, even decades after their original brain damage.

THE AUTHORS

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Perhaps the most famous example is Terry Wallis, who was minimally conscious for 19 years after a car accident before recovering speech and near-normal cognition. We made substantial efforts over the course of several years to establish reliable communication with Maggie, and she made significant, if inconsistent, progress. A detailed look at her injuries—and the unique challenges they posed to her recovery—shows why the routine neglect of minimally conscious patients is both scientifically confounding and ethically problematic.

Regaining Awareness

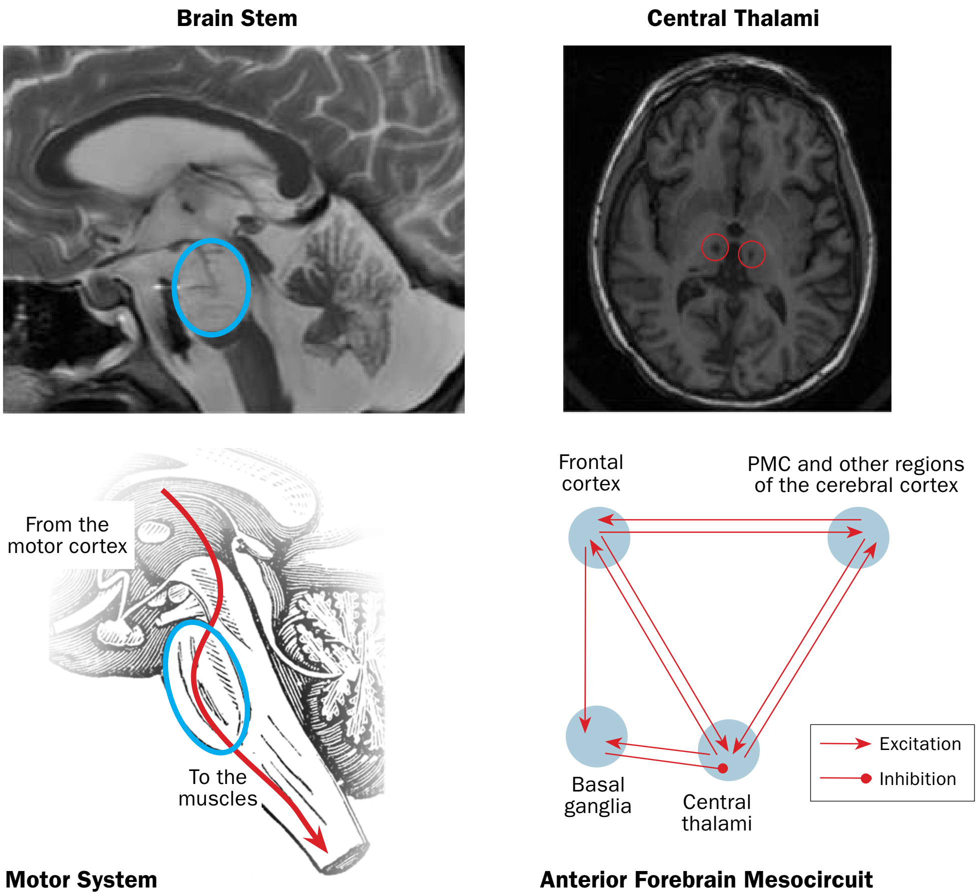
Maggie was an otherwise healthy college senior when she suffered a rare event of unknown origin. A large clot blocked off the single artery supplying blood to most of her brain stem, causing widespread damage there. Because nearly all the descending motor fibers to her spinal cord passed through this damaged area, she was left with almost no ability to move any part of her body. Maggie's massive brain stem injury also harmed nearby structures that normally send arousal inputs from the brain stem to the corticothalamic system, supporting overall levels of activity during wakefulness.

In addition, Maggie had two small but crucially placed injuries in the central regions of both thalami, egg-shaped masses at the base of the brain that serve as a kind of information hub. The central thalamic neurons in particular have extensive connections to the frontal cortex, which carries out many tasks, including planning. In any multifocal brain injury, the central thalamic neurons receive less input and, as a result, become structurally and functionally impaired, but in Maggie's case, they were directly compromised, too. In essence, she presented with a more serious version of a core problem within the central thalami that many severely brain-injured patients face.

These neurons form the key node in what is called the anterior forebrain mesocircuit—linking the thalami, frontal cortex and basal ganglia [*see illustration on next page*]. The network as a whole helps to regulate levels of arousal and, during wakeful periods, allocate attention. In this way, it supports a wide range of cognitive functions. Research suggests that getting the anterior forebrain mesocircuit back online is crucial for regaining consciousness, and the level of its function tracks with a patient's level of behavioral recovery. But reactivating the central thalamic neurons after severe brain injury is challenging for two reasons: not only are they physically less connected and receiving less stimulation than usual, but abnormal overactivity of parts of the basal ganglia also inhibits their output.

Also, the anterior forebrain mesocircuit is not the only network in play. Neurologist Steven Laureys of the University of Liège and his colleagues have found an even stronger graded correlation between recovering consciousness and metabolic activity in the posterior medial parietal complex (PMC), the main component in the brain's frontoparietal network. This region exhibits the highest resting metabolic rate in the human brain. Neurologist Marcus Raichle of Washington University in St. Louis and his colleagues have hypothesized that it supports a default-mode network, responsible for maintaining and updating consciousness with relevant contextual information, and helps us to interpret sensations and predict actions. The default-mode network is also associated with self-monitoring and access to personal memories.

Maggie had no specific damage to the PMC, but we have found evidence that it works in tandem with the anterior forebrain mesocircuit to support the recovery of consciousness. Other researchers have found that altered structural connections between the thalami and the PMC are statistically linked to behavioral outcomes: the more wiring between the two, the greater a patient's awareness. Scientists have also found a functional



Two scans reveal the extent of Maggie's stroke. A large clot blocked the single artery supplying blood to her brain stem, causing widespread damage (*circled, top left*). Because nearly all the nerve fibers from her motor cortex to her muscles passed through this area, she was almost completely paralyzed (*bottom left*). She also suffered two injuries to the central thalami (*circled, top right*), a key component in the anterior forebrain mesocircuit (*bottom right*). This network, along with the posterior medial parietal complex (PMC), is critical to maintaining consciousness. Maggie's injury, plus abnormally strong inhibitory signals from the basal ganglia, muted communication within this network.

COURTESY OF NICHOLAS D. SCHIFF (*brain scans*); © ISTOCK.COM (*motor system*); SOURCE: "DISORDERS OF CONSCIOUSNESS AFTER ACQUIRED BRAIN INJURY: THE STATE OF THE SCIENCE," BY JOSEPH T. GIACINO ET AL., IN *NATURE REVIEWS NEUROLOGY*, VOL. 10; FEBRUARY 2014 (*anterior forebrain mesocircuit diagram*)

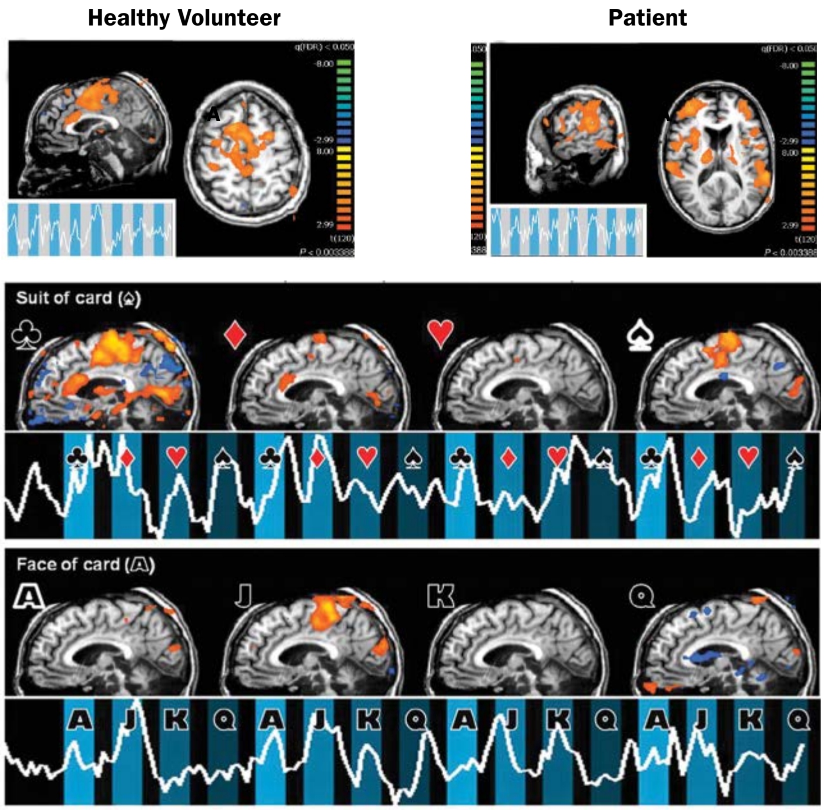
tie. In experimental studies, researchers at McGill University anesthetized healthy volunteers and then gave them drugs to induce a moment of consciousness. The subjects could respond to commands even though the level of anesthesia was held constant, and this brief awakening was linked to greater activation in both the central thalami and the PMC.

Reading Minds

Maggie's injury to the central thalami, in combination with her extensive brain stem injury, created a very challenging path to making or recognizing recovery. Recently, though, we have made significant advances in our ability to assess patients with severe brain injuries. Now we can ask them to carry out specific mental actions and view their response, if any, via functional MRI, electroencephalography (EEG) and related techniques. Even among patients who show limited or no overt signs of consciousness, these methods can offer proof of volition and awareness.

The first such example came in 2006. Neuroscientist Adrian M. Owen, now at the University of Western Ontario, and his colleagues at the University of Cambridge and the University of Liège worked with a 23-year-old woman who was considered vegetative after a car accident. Based on behavioral criteria, she showed no awareness or response to commands. But when they placed her in an fMRI scanner and asked her repeatedly to imagine playing tennis, the resulting images showed strong, consistent patterns of brain activation within the supplementary motor area of the frontal lobe. They noted that the same locations lit up in healthy volunteers who were asked to imagine the same activity.

Our group has used versions of this approach in a few brain-injured people—including Maggie. To evaluate her capacity to register information and respond, we initially asked her to imagine different motor tasks. Her results showed that she produced very strong patterns of brain activation when we asked her to imagine swimming, which had been one of her favorite sports. These patterns were comparable to those of normal subjects. We also found that Maggie could activate the same regions to answer ques-



A Card Trick to Detect Cognition

When we examined Maggie using functional MRI, we found clear evidence of her hidden cognitive abilities. First, we asked her to imagine swimming, which had been one of her favorite sports. Her brain showed increased blood flow primarily in the supplementary motor area (*top row, right*). A healthy volunteer who also imagined swimming generated a similar pattern of brain activation (*top row, left*).

Next we tested whether Maggie could use this same mental activity to answer a multiple-choice question about playing cards. We asked her to imagine swimming when the suit or face we showed her matched the ace of spades. Initially she seemed to answer affirmatively to both the club and spade, but an analysis revealed that only her response to the club was statistically significant. So, too, she appeared to respond to the jack, not the ace. But we later found evidence suggesting that she had answered correctly and that her injuries had caused a one-card delay.

FROM "DISSOCIATIONS BETWEEN BEHAVIOURAL AND FUNCTIONAL MAGNETIC RESONANCE IMAGING-BASED EVALUATIONS OF COGNITIVE FUNCTION AFTER BRAIN INJURY," BY JONATHAN C. BARDIN ET AL., IN *BRAIN*, VOL. 134, NO. 3; MARCH 1, 2011

tions, such as picking the suit or face of a playing card from four choices.

At first, though, her responses were confounding. A statistical analysis showed that her answers were not just the product of chance, but they did not appear to be accurate either [*see box above*]. We speculated that perhaps her replies were somehow delayed. So we reanalyzed the data and discovered evidence that her intended responses had been coming in one question late. When we shifted Maggie's responses back a question, they were correct. We knew that isolated central thalamic injuries such as hers could slow down cognitive processing, but the finding still came as a surprise—and served to underscore once more the complexity of assessing patients like Maggie.

Hope for Recovery

Outcomes following severe brain injuries fall on a continuum, but researchers have identified two types of patients who are more likely to regain at least some level of communication. One subset includes minimally conscious patients with a certain base amount of reserve in their remaining corticothalamic systems, as assessed by brain imaging. In 2007, in collaboration with colleagues at various institutions, we helped one such patient who had been minimally conscious for six years.

Over the course of six months we used deep-brain stimulation (DBS) to repeatedly apply a small electric current directly to his central thalami. After the treatment, this individual regained spoken language, the ability to direct his attention, motor control, and the ability to chew and swallow. The DBS regimen had activated the central thalamic neurons enough to rouse the patient from MCS into a behavioral range best described as a confusional state. With continued stimulation—the device was left on during the day—his gains were sustained for six years until he died from pneumonia.

Researchers have also studied medications such as amantadine, an antiviral drug also used to treat Parkinson's disease, and the sedative zolpidem, among others. These pharmacological interventions have helped several other MCS patients regain communication, either intermittently or as part of a more enduring recovery. Similar to the DBS approach, the compounds are known to activate neurons across the anterior forebrain mesocircuit.

In contrast, Maggie exemplifies a second class of patients—with very severe injuries to the motor output systems of the brain but less severe injury within the corticothalamic system—

We now segregate disabled conscious people in our health care system, denying them the chance to rejoin their communities.

who may stand an even better chance of regaining reliable communication because they retain more covert cognitive function. One of us (Schiff) has proposed the term "cognitive motor dissociation" (CMD) to describe them. These patients fulfill the behavioral criteria for coma, vegetative state or minimally conscious state, but when they are evaluated using fMRI or EEG, they show that they can follow commands by imagining actions and producing specific patterns of brain activity.

More important, the tests cannot fully reveal cognitive capacity. These patients cannot initiate communication, ask questions or engage in a dialogue in the same way that locked-in syndrome patients can. But recent studies looking at EEG activity during sleep and wake states, as well as cerebral metabolic activity, strongly support the idea that brain function in CMD patients more closely resembles that of healthy control subjects and locked-in patients than minimally conscious patients who can only communicate or follow motor commands intermittently.

CMD patients such as Maggie whose cognitive capacity is dissociated from their motor function present the most profound ethical challenge. Damage to the anterior forebrain mesocircuit, particularly injuries to the central thalami, leads to a fluctuating ability to stay alert and sustain attention, which can put dormant cognitive resources out of reach. It is difficult to assess what these patients are aware of and to figure out how to reestablish two-way communication.

The Right to Reintegration

Patients like Maggie need more than physiological reintegration to recover. They need societal reintegration as well. Currently we segregate disabled conscious individuals in the health care system, treat them as if they are not aware and deny them the opportunity to participate in civil society. But that opportunity is a basic human right they hold under our prevailing laws. Both the Americans with Disabilities Act and the United Nations Convention on the Rights of Persons with Disabilities assert that individuals with disability have the right to be maximally integrated.

Segregation is a strong word, and we use it advisedly. For physical disabilities, it can mean the inability to access public accommodations for want of a ramp. For disorders of consciousness, it is the denial of a voice, which is nothing short of a proxy for consciousness. Patients with disorders of consciousness cannot be reintegrated into their communities unless we restore to them some form of functional communication. Note the cognates—communication and community. One enables the other and helps patients with disorders of consciousness return to the nexus of their homes and families.

Physicist and novelist C. P. Snow once said that "scientists have the future in their bones." We must be forward-looking when considering therapeutic interventions for CMD patients. Their variable levels of arousal and attention mean that it may be difficult for them to use standard augmentative communication technologies. But before her death, Maggie was well on her way to using a system with a high-resolution, fast closed-circuit camera, which improved her learning using rapid auditory feedback and enabled some communication, with her generating downward eye movements. It was real progress from where she had been but just a small step toward reliable engagement with the outside world.

We anticipate that faster and more reliable feedback technologies, now in use with locked-in patients, will be able to help some CMD patients communicate reliably. Once even one of these patients crosses that threshold, it will be hugely significant—even historic. In that moment, isolation, segregation and silence will no longer be their plight; rights will then come to mind for patients who have for too long had them abridged. M

MORE TO EXPLORE

- **Disorders of Consciousness after Acquired Brain Injury: The State of the Science.** Joseph T. Giacino et al. in *Nature Reviews Neurology,* Vol. 10, No. 2, pages 99–114; February 2014.
- **Preservation of Electroencephalographic Organization in Patients with Impaired Consciousness and Imaging-Based Evidence of Command-Following.** Peter B. Forgacs et al. in *Annals of Neurology,* Vol. 76, No. 6, pages 869–879; December 2014.
- **Cognitive Motor Dissociation Following Severe Brain Injuries.** Nicholas D. Schiff in *JAMA Neurology,* Vol. 72, No. 12, pages 1413–1415; December 2015.
- **Frequency-Selective Control of Cortical and Subcortical Networks by Central Thalamus.** Jia Liu et al. in eLife, Vol. 4, Article No. e09215; December 10, 2015.
- **Rights Come to Mind: Brain Injury, Ethics, and the Struggle for Consciousness.** Joseph J. Fins. Cambridge University Press, 2015.

From Our Archives

- **Is Anybody in There?** Adrian M. Owen; *Scientific American,* May 2014.