

Consciousness is missing—and so is research

After the Schiavo controversy in the USA, obstacles still hinder the study of people with little or no awareness

Earlier this year, the plight of Terri Schiavo, a brain-damaged Florida woman who had survived for 15 years in a vegetative state, focused worldwide attention on disorders of consciousness. As her husband and parents fought a bitter legal battle over whether to let her die, the case exposed a political chasm between those whose foremost concern is quality of life and those who want to preserve life whenever possible. Yet the Schiavo affair also exposed a scientific chasm—between what little is known about consciousness disorders and what needs to be known for caregivers to make informed life-or-death decisions.

Medical advances, in conjunction with better rescue procedures and safety devices, are saving an increasing number of brain-injured people from immediate death. Many survivors fall into a minimally conscious state (MCS) or persistent vegetative state (PVS), and most who do not emerge relatively quickly remain unconscious until they die, often years later. The number of such patients is huge, although it is camouflaged by their invisibility in nursing homes and long-term care facilities. Five years ago, the MCS caseload in the USA was estimated at 112,000–280,000 (Strauss *et al*, 2000), and studies from the 1970s to 1990s indicated a PVS caseload of 10,000–25,000 adults and 4,000–10,000 children (Multi-Society Task Force on PVS, 1994). Many of these cases resulted from traumatic brain injury.

Under pressure from survivors, the US Congress passed the Traumatic Brain Injury Act in 1996 to address various aspects of this huge problem, recalled George Zitnay, a drafter of the legislation and founder of the rehabilitation organization Virginia

NeuroCare, Inc. (Charlottesville, VA, USA). However, “very little has been done since then,” he added, because of insufficient funding and a lack of leadership at the national level. While noting that more brain-injured people survive now than a decade ago, he stressed that recovery had not improved significantly.

“We simply don’t understand the mechanisms of recovery from disorders of consciousness,” observed Joy Hirsch, a professor of functional neuroradiology at Columbia University Medical Center (New York, NY, USA), whose team studies brain activity in MCS patients (Schiff *et al*, 2005). The Schiavo case, she asserted, “has caught us in an embarrassing situation” in which the ignorance of the medical and scientific communities is being confronted by a “huge demand for understanding and for hypothesis-based approaches”. One approach is to monitor the brain with technologies such as positron-emission tomography (PET) and functional magnetic-resonance imaging (fMRI). Yet only a handful of groups worldwide conduct such studies. Financial and ethical obstacles largely account for why so little of this work is being done (Hirsch, 2005).

Brain scanning is especially costly because MCS and PVS patients must be transported to a research centre, and must remain motionless while they are probed with various stimuli. Because of their infirmities, however, subjects often cannot understand and follow instructions to stay still. Consequently, “we have a failure rate of around two in three” when imaging MCS patients with fMRI, said Steven Laureys, an assistant professor of neurology and neurosciences at the University of Liège, Belgium.

“But you have to pay the ambulance because we’re outside of the hospital. And intensive-care doctors need to be present. So it’s very, very expensive.”

Despite the increased need for money, key public donors in the USA, such as the National Institutes of Health (NIH; Bethesda, MD, USA) and the National Science Foundation (Arlington, VA, USA), devote few resources to consciousness disorders, according to researchers. “There aren’t a whole lot of funded applications in that area,” acknowledged Michael Weinrich, director of the NIH National Center for Medical Rehabilitation Research (Rockville, MD, USA), although he pointed out that the lack of funding might stem from a paucity of applications. Joseph Giacino, associate director of neuropsychology at the JFK Johnson Rehabilitation Institute (Edison, NJ, USA), said that he did not even apply to the NIH to support an ongoing study to test whether functional brain imaging can predict recovery from MCS. Instead, he relied on a longstanding programme at the US Department of Education National Institute on Disability and Rehabilitation Research (NIDRR; Washington, DC, USA). “NIDRR has separate funding for traumatic brain injury, and that kind of mechanism doesn’t really exist at NIH,” he said. In Belgium, Laureys reported difficulty in finding

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In addition to inadequate funding, ethical objections also hinder research on consciousness disorders, investigators said. Surprisingly, these objections do not seem to come from the same political or religious groups that vehemently protest against abortion and stem-cell research. Laureys recounted being invited to the Vatican because officials there liked his PET study showing brain activation in PVS patients who received electric shocks (Laureys *et al*, 2002). "These religious leaders are very concerned about these patients and, I think, would also like there to be more research done," he said. A similar stance is taken by Not Dead Yet (Forest Park, IL, USA), a disability-rights group that opposes the removal of feeding tubes from PVS and MCS patients. Stephen Drake, its research analyst, stated that the group favours more brain imaging of such patients, "who clearly have significant cognitive activity going on, but who are being written off in one way or another".

Ethical objections to consciousness research typically emerge from institutional review boards (IRBs) and from journals considering whether to publish a paper. Their arguments have three main elements: that unconscious subjects cannot consent to participation in a study; that a study will not benefit such subjects directly; and that a study involves more than a minimal risk of injury. PET scans, for instance, require the injection of a slightly radioactive tracer. As Owen observed, "life has gotten much easier ethically since we moved from PET to fMRI," which does not involve radioactivity.

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Whether or not these arguments are raised depends on the institution, locality and country in which a particular study is being evaluated. Some investigators reported few, if any, objections to their work. However, Hirsch said that an IRB had twice shut down one of her protocols. The first time, she recalled, "I was told that patients who cannot consent themselves cannot participate in research projects. So there's no such thing as proxy consent for participation in research." In response, she

money to support his work. Adrian Owen, a senior scientist at the MRC Cognition and Brain Sciences Unit in Cambridge, UK, said that his fMRI studies of consciousness disorders were "chronically under-funded" compared with his imaging research on Parkinson's disease, for which it was "generally possible to get money".

One reason why studies of MCS and PVS patients receive inadequate funding, said Giacino, is therapeutic nihilism, which is the "idea that these are people who are beyond help". Laureys blamed the word 'vegetative', noting that comparing patients to a vegetable implied that they "will never get out of this [condition]".

Another problematic word is 'consciousness' itself, with its "New Age connotations that can be off-putting to scientists", said Joseph Dial, executive director of the Mind Science Foundation (San Antonio, TX, USA), which awards small grants for consciousness research. Some researchers in this field, he added, have studied questionable phenomena, such as 'remote viewing', in which a person can supposedly describe something without ever having seen it. Nevertheless, even reputable explorations of consciousness must deal with its subjective component, and that emphasis, Dial said, is still "somewhat suspect in the scientific community".

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argued successfully that all her patients were from states that, unlike New York, permit proxy consent. Laureys said that ethical concerns had slowed publication of his study that exposed PVS patients to 60 seconds of electrical stimulation (Laureys *et al*, 2002).

In a 1998 report, the now-defunct US National Bioethics Advisory Commission recommended conditions under which an IRB might approve a research protocol that presented a greater-than-minimal risk to a subject with a mental disorder, but that did not directly benefit that subject (NBAC, 1998). However, the recommendations were problematic (Fins & Miller, 2000); for instance, their focus on mental disorders ignored traumatic brain injury. Furthermore, they have not yet been enacted into law, according to Joseph Fins, director of medical ethics at the New York-Presbyterian Weill Cornell Medical Center (New York, NY, USA).

By contrast, the European Parliament passed a Directive in 2001 that applies to persons who are incapable of legally consenting to clinical trials of medicinal products (European Commission, 2001). By mid-2005, several national legislatures had expanded the scope of the Directive to apply to all types of research on humans, said Francois Lemaire, a professor of medical intensive care at the University of Paris, France. Article 5 of the Directive states that an incapacitated adult who is unable to give informed legal consent may be included in clinical trials only if "there are grounds for expecting that administering the medicinal product to be tested will produce a benefit to the patient outweighing the risks or produce no risk at all."

The Directive requires that a complex clinical trial be placed in a single risk category and judged accordingly (Silverman *et al*, 2004). If applied strictly, this requirement could, for example, completely forbid a study of minimally conscious patients in which a subset would receive both a placebo—presumptively non-beneficial—and a PET scan, which would entail some risk. However,

Lemaire reported that the Directive has not led to bans on placebo-containing clinical trials, and Laureys said there has been a shift towards interpreting it as condoning studies that might benefit patient populations as a whole, not just individual patients. In fact, Article 3 refers to weighing risks and benefits "for the individual trial subject and other present and future patients".

Fins argues that two classes of incapacitated individuals must be recognized and treated separately. One class comprises "those who have historically been objects of exploitation", such as mentally impaired children who were drafted into studies "that were quite nefarious". The other class comprises "people whose very reason [why] they can't give consent is the object of study", such as PVS and MCS patients. "There should be mechanisms for surrogate consent" to study only the latter class, Fins contended, adding that "we have an obligation, if these people have a life of the mind," which he defined as thoughts, feelings and an inner life, "to really try to address their needs."

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Therefore, some observers see a moral imperative, not just an ethical trap, in the study of consciousness disorders. Given that families often make life-or-death decisions about PVS and MCS patients, Laureys described the barriers to research as "absurd" and "unbelievable". Yet investigators said it was too early to tell whether those barriers would persist in the wake of the Schiavo case.

The field, meanwhile, is hardly at a standstill. Zitnay organized an international symposium held in October 2005 in Johnstown (PA, USA) that explored the outcomes of traumatic and anoxic brain injury; he expects to provide the US Congress in 2006 with a consensus document arising from the meeting. Another significant conference on traumatic brain injury is due to take place next year in Bethesda (MD, USA), according to Giacino. At the Mind Science Foundation, which has supported several recent consciousness meetings, Dial spoke of his ambition to promote successful pilot

projects incubated by US\$15,000 grants from his organization. He plans to contact private and public entities that might increase funding per project to the US\$50,000 level and perhaps eventually to the US\$1 million level.

Even if studies of consciousness disorders proliferate, however, they might never bridge the attitudinal rift exposed by the Schiavo controversy. Drake supports the research because it indicates some brain activity and, hence, helps to justify keeping disabled patients alive. Yet, conversely, he asserted that physicians should not rely on findings of limited brain activity to justify denying food and water to patients, because such a denial requires "the kind of surety [that is] years, decades, away at the very least". For Fins, the results of these studies should elicit a more flexible response. "Values should follow from what it means to be in these states [of consciousness]," he said. Research, he added, might change opinions as to what is the right thing to do with unconscious patients.

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