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Perspective

Confronting the grey zone after severe brain injury

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In recent years, rapid technological developments in the field of neuroimaging have provided several new methods for revealing thoughts, actions and intentions based solely on the pattern of activity that is observed in the brain. In specialized centres, these methods are now being employed routinely to assess residual cognition, detect consciousness and even communicate with some behaviorally non-responsive patients who clinically appear to be comatose or in a vegetative state. In this article, we consider some of the ethical issues raised by these developments and the profound implications they have for clinical care, diagnosis, prognosis and medical-legal decision-making after severe brain injury.

On February 25, 1990, Theresa 'Terri' Schiavo lost consciousness after suffering a cardiac arrest in her Florida apartment. When paramedics arrived, she was not breathing and she had no pulse. She was intubated and ventilated, but the prolonged period of oxygen deprivation caused severe brain damage. Ms. Schiavo's prognosis was uncertain. It was unclear if she would recover and, if she did, whether that recovery would be meaningful.

Within a year of her injury, two physicians independently diagnosed Ms. Schiavo as being in a vegetative state. Ms. Schiavo would awaken and fall asleep, but she displayed no awareness of herself or her environment. She did not follow the clinical team's verbal commands, such as 'raise your right arm.' She did not look at objects in her environment with purpose. There was no evidence that she recognized simple objects, like a cup or a ball. And she was unable to communicate. Ms. Schiavo received aggressive rehabilitation for several years, but to no avail.

In 1998, eight years after her injury, Ms. Schiavo's husband, Michael Schiavo, petitioned the Florida courts to remove her feeding tube so that she would be allowed to die. Mr. Schiavo's petition triggered a cascade of highly publicized legal proceedings. Ms. Schiavo's parents, Robert and Mary Schindler, objected to her husband's petition. They argued that their daughter was conscious and that the removal of food and fluids was inconsistent with her Roman Catholic values.

Ms. Schiavo lacked an advance directive, but extensive testimony provided to the Florida court indicated that she had previously expressed that she did not want to live in such a condition. Her parents, however, refused to give up on their daughter. The Schindlers began an aggressive publicity campaign and lobbied to keep their daughter alive. They selected a notable pro-life activist, Randall Terry, as their spokesperson. From the media to the kitchen table, everyone had something to say about the case. Determining what choice should be made, and who ought to make it, became a matter of fierce debate.

Finally, in 2005, the court allowed Ms. Schiavo's husband to withdraw treatment for good. In all, the case involved numerous legal proceedings; multiple suits in the Florida Second District Court of Appeals; and extensive political lobbying in Florida and Washington D.C. The final decision to remove Ms. Schiavo's feeding tube followed the U.S. Supreme Court holding in *Cruzan v. Director, Missouri Department of Health* (1990). This case, which involved a similar petition to withdraw treatment from a patient in a vegetative state, affirmed the 'right to die' for incapacitated persons when authorized by a legally appointed surrogate and supported by 'clear and convincing' evidence of the

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patient's previously expressed wishes. In Ms. Schiavo's case, and under Florida law, this precedent supported her husband's decision. As legal expert David Garrow put it in The Baltimore Sun: 'The most-reviewed and the most-litigated death in American history' was over.

Ms. Schiavo's autopsy revealed widespread brain damage, with profound shrinkage of key cortical regions. After a prolonged period without oxygen, brain cells begin to die off through a process called, apoptosis (for review, see [1]). Brain cells are never replaced, and the volume of the brain slowly decreases over time. Apoptosis is common in the vegetative state, particularly in patients who have sustained a cardiac arrest or some other form of hypoxia, such as near drowning or suffocation.

Dr. Jon Thogmartin, the Pinellas and Pasco County medical examiner, reported total and irreversible damage of Ms. Schiavo's visual centres, confirming that she was unable to process visual information at the time of her death. This was an important observation because, in the fight to keep Ms. Schiavo alive, a critical piece of evidence presented by her parents was a videotape in which she was described as 'seeing' and 'responding' to her mother. Damage to key parts of Ms. Schiavo's cortex made it quite clear that she retained no semblance of awareness at all. She lacked the basic building blocks of cognition. The physical scaffolds upon which consciousness is supported had been demolished.

As Ms. Schiavo's saga unfolded in the U.S., another story about brain injury was being quietly written on the other side of the Atlantic. Anthony Bland, a 22-year-old Liverpool soccer fan, suffered a severe brain injury in the 1989 Hillsborough stadium disaster. Mr. Bland's case preoccupied the British press for months and the English courts for years. Like Ms. Schiavo, Mr. Bland was diagnosed as being in a vegetative state. But unlike Ms. Schiavo, Mr. Bland's family and clinical team were in agreement that it was best to allow him to 'die with dignity.' [2]

The judge in Mr. Bland's case, Sir Stephen Brown, ruled, for the first time in English courts, that artificial feeding constitutes 'medical treatment' and that discontinuing this treatment would be consistent with good medical practice [2]. The lawyer appointed to act on behalf of Mr. Bland appealed the decision, arguing that the withdrawal of treatment would be tantamount to murder. This appeal was rejected by the House of Lords.

In 1993, four years after his injury, Bland became the first vegetative state patient in England to die through the legal withdrawal of artificial nutrition and hydration. Unlike Ms. Schiavo's case, there was relatively little opposition, and a rather sober, British treatment by the media who noted that times had now changed and in cases where there 'was no hope' patients should be allowed to exercise their 'right to die.' [3]

Ms. Schaivo's and Mr. Bland's cases, as well as those of other brain-injured patients, have crystalized public and clinical perceptions of what we have termed the 'grey zone' [4]. Patients in the vegetative state are both 'there' and 'not there' at the same time, lingering in the indeterminate space between life and death. This liminal neurological status is difficult to process. Physicians and patients' families often have preconceived notions about what it means to be 'conscious,' to be 'alive,' to 'suffer,' or to have a 'life that is worth living.' When the clinical data are unclear or contested, these preconceived notions can quickly fill gaps in reasoning. This can lead to a breakdown in trust and communication between clinical staff and families. Processing the ambiguity of these patients' conditions and determining what is best for them can devolve into ideological arguments, rather than a rigorous, fact-finding exercise. As we learned in the case of Ms. Schiavo, social, political, and media backdrops only serve to amplify these divisions.

Clinical research on brain injury has advanced rapidly over the past 25 years. Innovations in brain-injury rehabilitation and assessment reveal ways to improve both the speed and quality of recovery [5,6]. Likewise, new developments in functional neuroimaging and electrophysiological (EEG) methods allow physicians to more accurately diagnose brain-injured patients and improve prognostic accuracy [7–9]. Indeed, these methods reveal that a significant proportion of brain-injured patients — estimated to be ~15–20% — who satisfy all clinical criteria for the vegetative state diagnosis are, instead, 'covertly conscious' [10]. Their consciousness is manifest in their brain activity, not behavior, and neuroimaging or EEG methods are the only way to discover that they are conscious ([11], see Figure 1).

To some extent, neurological practices and policies have also kept pace with this neuroscientific revolution. The Royal College of Physicians National Clinical Guidelines on Prolonged Disorders of Consciousness recognizes that neuroimaging and other emerging scientific techniques may be important for the management of brain-injured patients. Likewise, the U.S. Practice Guideline Update on Disorders of Consciousness contains recommendations that are reflective of current scientific knowledge about brain-injury management [12]. Notably, both guidelines contain explicit commentary about the use of advanced neuroimaging and EEG

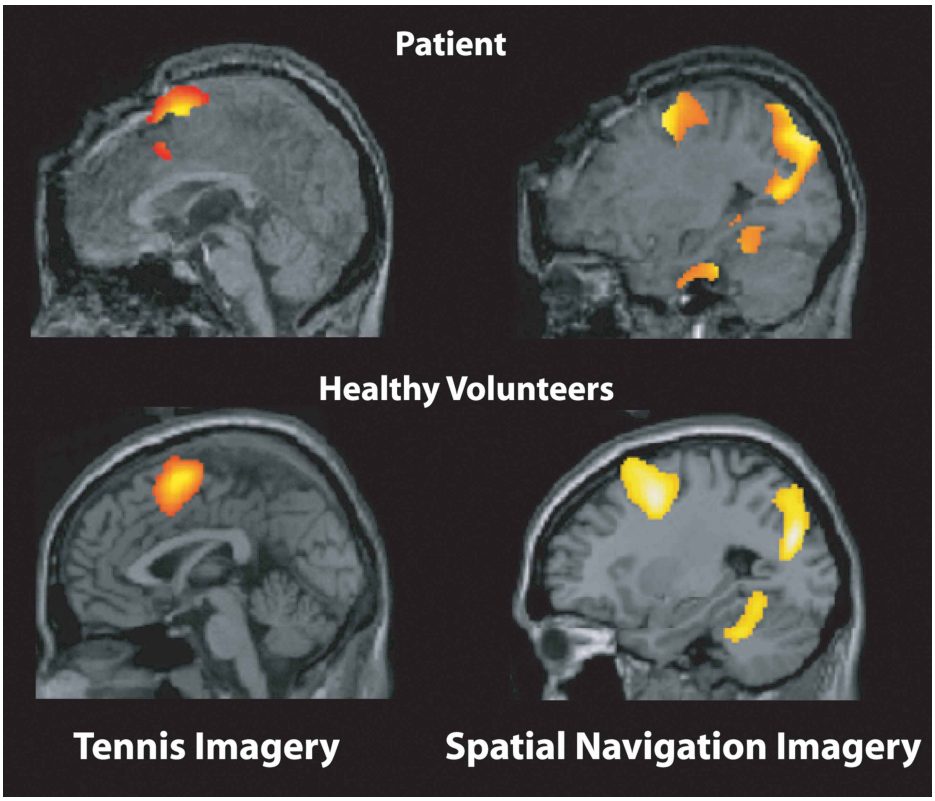

Figure 1. Functional Neuroimaging Mental Imagery Task.

In 2006, functional neuroimaging was used to demonstrate for the first time that a patient who fulfilled all the clinical criteria for a vegetative state diagnosis was, in fact, conscious and aware. When asked to 'imagine playing tennis' (top left) the pattern of activity in her brain was indistinguishable from that of healthy participants (bottom left). When asked to 'imagine moving around your house', (top right) her pattern of brain activity was, again, like that of healthy participants (bottom right).

methods. The U.S. Practice Guideline Update even goes so far as to recommend the use of these methods for diagnosis and prognosis, *but only* if they are feasible, cost-effective, and do not result in harm.

We agree with these clinical guideline updates. But we also think they could be stronger. Neuroimaging and EEG research in brain-injured patients is already a mature field. Many validated methods are available for assessing cognition, detecting awareness, predicting spontaneous recovery, and even communicating with patients, based solely on their neuroimaging or EEG responses [13]. Moreover, the speed at which these techniques are being developed far outpaces that of the consensus process for revising clinical guidelines. A compelling case could be made that advanced neuroimaging and EEG assessment should already be the *standard of care* for patients following severe brain injury.

This is not to say that neuroimaging and EEG are feasible in every single case. Scanners used to detect covert consciousness are expensive and require cost-intensive infrastructures to operate. Meanwhile, EEG methods require specialized personnel for accurate data acquisition and processing. Additionally, the physical stress incurred by patients as they are transferred to a suitably equipped scanning facility can be significant. Some patients are unable to remain still in the scanner, while metal implants, including plates and pins, might rule out neuroimaging altogether. Nevertheless, if functional neuroimaging and EEG were adopted more widely in this population, diagnostic and prognostic accuracy would undoubtedly improve. Clinical recommendations that more precisely track the rapid advances in this research might help this process.

The prospect of using these methods in routine clinical assessment raises complex methodological and ethical questions [14–19]. Above all, there are unanswered questions about how neuroimaging or EEG data would (or would not) inform clinical decisions. If, for example, the neuroimaging and EEG methods designed over the past 10 years to detect covert consciousness had been available to examine Ms. Schiavo, and the data

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confirmed what we now know from her autopsy report, would this have changed her parents' intentions regarding the withdrawal of treatment? Court documents suggest that Ms. Schiavo's parents were committed to keeping her alive, even if she remained permanently unconscious. Yet this question highlights important considerations regarding the significance of neuroimaging or EEG findings in light of the values that guide a family's decisions [20].

Consider, further, how this information might be used in jurisdictions where clinical staff are given more decisional authority, such as those in the U.K.. Would evidence of covert consciousness guide a physician's decisions about what treatments to offer? And how might this enhance — or deter from — deliberations amongst clinical staff and families regarding the discontinuation of treatment?

Whether or not this information would influence cases of prolonged disorders of consciousness, it will surely impact treatment decisions in the *acute* phase of brain injury. At the time of her death, Ms. Schiavo had been unresponsive for 15 years. Yet most decisions to withdraw treatment are made within the first few days after injury, when patients are most vulnerable and the prognosis is uncertain [21]. An uncertain or guarded prognosis can influence the decision to withdraw ventilator support or the decision to transition to a permanent tracheostomy, just days after injury.

Little work has been done to examine the use of functional neuroimaging in the intensive care unit (ICU), yet some early results are encouraging. In a pilot study by our lab, two groups of comatose patients were scanned with functional neuroimaging at two ICUs in London, Ontario, Canada. Several of these patients exhibited signs of intact cognitive function, including language comprehension. One patient also showed clear signs of covert consciousness and went on to make a good recovery, leaving the ICU just months after neuroimaging evaluation.

These findings are consistent with those from a recent EEG study at the Columbia University ICU [7]. In this study, EEG evidence of motor cortex activation to spoken command was observed in 16 seemingly unconscious brain-injured patients just days after injury. Compared with others who showed no motor cortex activation, these patients recovered faster and with greater odds of a positive outcome.

More work needs to be done, yet there is little doubt that, if applied successfully in the ICU, functional neuroimaging and EEG assessment of covert consciousness could have a significant impact on the treatment of critically ill, brain-injured patients. These data would not only improve diagnostic accuracy, but they could also assist physicians in predicting spontaneous recovery and positive or poor outcomes. This information could be important for making consequential decisions. Increased access to these methods, and awareness of their prognostic implications, could assist families and physicians in avoiding premature decisions to discontinue treatment [22].

Neuroscience is beginning to unravel the mysterious grey zone between life and death. It is at the nexus of trying to figure out the difference between body and person, between brain and mind. As Francis Crick wrote in his seminal 1995 book *The Astonishing Hypothesis*: 'you, your joys and your sorrows, your memories and your ambitions, your sense of personal identity and free will, are in fact no more than the behavior of a vast assembly of nerve cells and their associated molecules.' Only a few years after Crick wrote these words, neuroscientists began to uncover how that three-pound lump of grey and white matter inside our heads generates every thought, feeling, plan, intention and experience we ever have.

We are at a critical juncture in which these big scientific questions may come to directly inform — and improve — clinical care. Will neuroimaging and EEG data help stakeholders better understand a brain-injured patient's condition and positively inform clinical decisions? More research is needed to definitively answer this question, but we remain confident that they will.

Abbreviations

EEG, electrophysiological; ICU, intensive care unit.

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Competing Interests

The Authors declare that there are no competing interests associated with the manuscript.

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