The Search for Consciousness

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In recent years, rapid technological developments in the field of neuroimaging have provided new methods for assessing residual cognition, detecting consciousness, and even communicating with patients who clinically appear to be in a vegetative state. Here, I highlight some of the major implications of these developments, discuss their scientific, clinical, legal, and ethical relevance, and make my own recommendations for future directions in this field.

The vegetative state is a clinical condition that is often described as "wakefulness without awareness." These patients open their eyes, frequently move spontaneously, and will often exhibit sleeping and waking cycles, although they remain entirely non-responsive to any form of external prompting or stimulation (beyond simple reflexes). On this basis, it is assumed that they lack any awareness, including who they are, where they are, and the predicament they are in. However, it is now well accepted that around 40% of these patients are misdiagnosed and will show reproducible behavioral signs of awareness when examined by specialized clinical teams. Nevertheless, many covertly aware patients escape detection altogether, even by experienced teams, and can remain erroneously diagnosed as being in a vegetative state for decades.

In 2006, we put a young woman who had been diagnosed as being in a vegetative state into a functional magnetic resonance imaging (fMRI) scanner and asked her to imagine she was playing a game of tennis (Owen et al., 2006). What we found has had repercussions for clinical care, diagnosis, prognosis, and medical-legal decision making after severe brain injury, but it also sheds light on more basic scientific questions about the nature of conscious behavior and the neural representation of our own thoughts and intentions. My goal in this NeuroView is to briefly review the most important of these issues and to make some suggestions about where I think the field should go from here.

When we asked our patient to imagine playing tennis, fMRI activity increased in the premotor cortex, an area of the brain known to be involved in initiating and imagining movements. When we asked her to relax, activity in this region diminished. We had seen this pattern many times in studies of healthy participants, who we had also asked to imagine playing tennis in the scanner. We then asked the patient to imagine moving from room to room in her house and a very different pattern of fMRI activity emerged. This included the parietal cortex and part of the parahippocampal gyrus, two brain regions that are known to be involved in spatial navigation. Again, this pattern of fMRI activity was indistinguishable from that seen in healthy participants. On the basis of these fMRI findings, we concluded that our patient was not vegetative at all, but conscious and aware, despite the fact that she had been entirely physically non-responsive for more than 5 months at that point.

Our reasoning was simple; following a severe brain injury, when the request to move a hand or finger is followed by an appropriate and reliable motor response, it is deemed sufficient to conclude that the patient is aware. By analogy, if the request to imagine playing tennis is followed by an equally reliable fMRI change in a predefined brain region (in this case, the premotor cortex), shouldn't we give that response the very same weight? Skeptics may argue that brain responses are somehow less physical, reliable, or immediate than motor responses but, as is the case with motor responses, all of these arguments can be dispelled with careful measurement, replication, and objective verification. Replication was integral to our initial study, because the distinct patterns of fMRI activity in response to the two imagery tasks were observed across repeated trials (Owen et al., 2006). Indeed, our patient's responses were consistent enough to allow us to draw far more elaborate conclusions than just the fact that she was "consciously aware." For example, at the very least, sustained attention (required to maintain focus throughout each task), language comprehension (required to understand the task instructions), response selection (required to switch between alternate tasks), and working memory (required to remember which task to perform when instructed) must have all been substantially intact for these fMRI responses to occur at all. These are all aspects of "top-down" cognitive control that are typically associated with normal levels of conscious awareness.

In a follow-up study, we reported that around 17% of a group of patients who behaviorally appeared to be entirely vegetative were, in fact, conscious and able to generate reliable responses of this sort in the fMRI scanner (Monti et al., 2010). However, the main focus of that study was a traumatically brain-injured patient who had been repeatedly diagnosed as vegetative over a 5-year period. By imagining playing tennis to convey a "yes" response and imagining walking around his house to convey a "no" response, this patient was able to communicate the answers to a series of biographical questions, such as whether he had brothers or sisters and the last place he'd visited before his accident 5 years earlier—all pieces of information that we did not know at the time but could verify as being correct with the family at a later date. Despite these astonishing results, it remained completely impossible to establish any form of traditional communication at the bedside (i.e., through speech, limb movement, eye blinks, etc.).

Many groups around the world have now gone on to use techniques based on similar principles to detect covert awareness in patients who appear to be clinically vegetative. A recent independent review of 37 published studies and 1,041 patients confirmed our initial estimate that around 20% are covertly aware despite being entirely behaviorally non-responsive (Kondziella et al., 2016). So, let me now consider what these findings mean for our understanding of conditions like the vegetative state and for how we think about consciousness more generally.

First, they immediately raise the possibility that many of the patients who have been diagnosed as vegetative worldwide—and there are hundreds of thousands—might not be vegetative at all, but simply physically non-responsive and trapped in their immobile bodies. Technically, these patients have not been *misdiagnosed*, in the sense that an error of judgment has been made, because the accepted diagnostic criteria are based on *behavior* and they really do exhibit no *behavioral* markers of awareness. Nevertheless, the existing criteria do not accurately capture their actual state of awareness, and in this sense, their vegetative state diagnosis is clearly incorrect. On this basis, I would argue that there is an urgent need for a re-evaluation of the existing diagnostic guidelines for all behaviorally non-responsive patients and for the formal inclusion of fMRI into those guidelines.

Some steps in this direction have been made; both the Royal College of Physicians in the UK (2015) and the American Academy of Neurology in the US (2018) have recently recognized that fMRI may be important for the management of vegetative-state patients. But this is not enough. This is already a mature field, with many validated methods available for assessing cognition, detecting awareness, and even communicating with covertly aware patients, based solely on their fMRI responses. In my view, functional neuroimaging should already be the standard of care for patients who appear to be non-responsive following a serious brain injury. That is not to say it is applicable, or even necessary, in every single case. For example, in addition to considerations of scanner availability, the physical stress incurred by patients as they are transferred to a suitably equipped fMRI facility can be significant. Some patients are unable to remain still in the scanner, while metal implants, including plates and pins, which are common following any serious injury, may rule out fMRI altogether. Nevertheless, if functional brain imaging was adopted more widely in this population, diagnostic accuracy would undoubtedly improve dramatically.

Second, these findings have important implications for the law—in particular, for the increasing number of legal cases that have raised the possibility of using fMRI to inform judicial decisions about the prolongation, or otherwise, of life after severe brain injury. In most of these cases, the key medical and legal decisions revolve around several inter-related factors: (1) whether the patient is conscious or "aware" of their condition, (2) whether there is any chance of significant recovery, and (3) what the patient would have said had they had been consulted about their current condition in advance. It is now absolutely unassailable that fMRI can detect covert awareness in some patients who appear to be entirely vegetative, and subject to the appropriate quality controls and scientific guidance, there is no *a priori* reason why such data could not be used to guide a court's opinion about "whether the patient is conscious or 'aware' of their condition." The case for using functional neuroimaging to predict whether a patient might experience some recovery is also compelling. For example, Di et al. (2008) reviewed 15 separate studies involving 48 published cases and concluded that functional neuroimaging can predict recovery from the vegetative state with 93% specificity and 69% sensitivity. Similarly, in a study of 41 patients, Coleman et al. (2009) showed that the results of fMRI testing correlated significantly with subsequent recovery while a specialist behavioral assessment did not. The third factor is perhaps more controversial but, in my opinion, equally compelling; using the technique introduced by Monti et al. (2010), it is entirely possible to ask a covertly aware patient whether they want to continue living in their current situation, obviating any need to determine what they "would have wanted" in advance. What is most tantalizing about this prospect is that it would allow a seriously brain-injured patient to express their *current* wishes, which may well have changed radically in the interval (sometimes decades) since they expressed any premorbid opinion. With that said, would a "yes" or a "no" response be sufficient to be sure that the patient retained the necessary cognitive and emotional capacity to make such an important decision? Clearly much more work needs to be done and many more questions would need to be asked of a patient before one could be sure that this was the case, and even then, new ethical and legal frameworks would need to be introduced to determine exactly how such situations are managed and by whom. But ultimately, the morally challenging question of whether theirs is a life that is "worth living" (Kahane and Savulescu, 2009) is one that could be answered directly by the patient using fMRI.

In the more immediate term, fMRI is already being used to involve some covertly aware patients in their own day-to-day therapeutic care and management. For example, we have described one patient who had been repeatedly diagnosed as vegetative for 12 years yet was able to provide correct answers to 12 different questions, including whether he was in any physical pain (twice he reported that he was not) and whether he still enjoyed watching hockey on TV (he did) (Fernández-Espejo and Owen, 2013), across several fMRI sessions.

Despite this promising start, communication with entirely physically non-responsive patients is still very much in its infancy. Yet, 20 years from now, so-called brain-computer interfaces, or BCIs, will likely be as commonplace as smartphones, flat-screen TVs, and mobile touchscreen devices. A BCI takes a brain response, analyzes it, and turns it into an action that reflects the user's intention. That action might be as simple as moving a cursor across a computer screen (e.g., to spell a word) or as complex as manipulating a robot arm to help someone drink a cup of coffee. fMRI is not well suited for such applications because of its size, lack of portability, and relatively high cost. BCIs based on electroencephalography (EEG) already exist but vary widely in terms of their accuracy and ease of use and typically require visual fixation (e.g., to an array of letters). This precludes their use by most physically non-responsive patients who, by definition, cannot purposely direct their gaze. Functional near-infrared spectroscopy (fNIRS) is another technology that is evolving rapidly with BCI applications in mind. fNIRS systems detect where cortical activity is occurring by measuring how much near-infrared light is absorbed by blood vessels at specific wavelengths, which varies depending on how much oxygen is in the blood running through them. Unlike fMRI, fNIRS is portable, silent, and relatively cheap. We have recently used this technique to communicate with a behaviorally non-responsive patients who was admitted to the intensive care unit (ICU) with Guillain-Barré syndrome (Abdalmalak et al., 2017). By imagining playing tennis for ''yes'' and relaxing for ''no,'' the patient was able to answer several clinically important questions about his wishes and well-being, including whether he felt safe and whether he was in any pain.

Which brings me to my final question: where do we go from here? We know that fMRI can be used to assess residual cognition, detect consciousness, and even communicate with patients who clinically appear to be in a vegetative state, but what is the next big frontier? In my opinion, this field now needs to apply what has been learned from two decades of functional neuroimaging studies in chronic vegetative-state patients to the *acute* phase of brain injury—that is, to the first few days after a serious injury when patients are at their most vulnerable and prognosis is most uncertain. Coma following a severe brain injury is a medical emergency and requires immediate admission to an ICU for life-sustaining therapies such as airway management and vascular support. A comatose patient will, at most, open their eyes to painful stimuli but will not track with their eyes or fixate. Accurate diagnosis and prognostication are extremely challenging and treatment decisions are typically based on unreliable behavioral responses, which are highly dependent on a multitude of clinical and environmental factors rather than on objective and quantifiable indicators. Mortality rates approximate 40% in this population, and most of these deaths (70%) are associated with withdrawal of life-sustaining therapy based on these outdated clinical indicators (Turgeon et al., 2011). Just as it has in chronic conditions like the vegetative state, fMRI has the potential to improve diagnosis and provide a point-of-care system that can accurately predict outcomes for unresponsive, brain-injured patients in the ICU. Of course, neuroimaging studies in this population are not only technically challenging, but also pose even more difficult ethical issues than the studies that we, and others, have conducted in chronic vegetative-state patients (Weijer et al., 2016)—for example, how and when should the results be used to inform clinical decision making and how best to balance the risks associated with scanning these patients against the potential clinical and scientific benefits of fMRI? Clearly more work needs to be done but, in my opinion, there remains little doubt that functional neuroimaging has the potential to significantly and directly impact the assessment and clinical care of critically-ill patients in the earliest stages of a brain injury. As a result, it will inform medical ethics and legal discussions (in terms of withdrawal of life-sustaining therapies) and drive efforts to develop interventions to facilitate recovery and quality of life in these patients.

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