Chapter 6

When thoughts become actions: Neuroimaging in non-responsive patients

Adrian M. Owen

Introduction

Until recently, clinical applications of imaging methods focused primarily on correlational approaches, mapping the cerebral changes associated with a particular cognitive process in a given disorder or disease and comparing those changes to the 'normal' pattern of activity observed in healthy participants. But advances in imaging technology, and in particular, the ability of functional magnetic resonance imaging (fMRI) to detect reliable neural responses in individual participants in real time, have opened up an entirely new area of clinical investigation based on the possibility that we might decode thoughts and intentions based solely on the pattern of activity observed in the brain. One field where significant use has been made of these advances is in the assessment of covert awareness, or consciousness, following acute brain injury. In recent years, improvements in intensive care have lead to an increase in the number of patients who survive severe brain injury. Although some of these patients go on to make a good recovery, many do not, and some of these individuals progress to a condition known as the vegetative state. Central to the description of this complex condition is the concept of 'wakefulness without awareness', according to which vegetative patients are assumed to be entirely unaware, despite showing clear signs of wakefulness (Jennett and Plum 1972). However, the assessment of these patients is extremely difficult and relies heavily on subjective interpretation of observed behaviour at rest and in response to stimulation. A diagnosis is made after repeated examinations have yielded no evidence of sustained, reproducible, purposeful, or voluntary behavioural response to visual, auditory, tactile, or noxious stimuli. Thus, a positive diagnosis (of vegetative state) is ultimately dependent on a negative finding (no signs of awareness) and is therefore inherently vulnerable to a Type II error or a *false negative* result. Indeed, internationally agreed diagnostic criteria for the vegetative state repeatedly emphasize the notion of '*no evidence of awareness of environment or self*'—in this instance, absence of evidence does appear to be considered adequate 'evidence of absence'. Any assessment that is based on exhibited behaviour after brain injury will be prone to error for a number of reasons. First, an inability to move and speak is a frequent outcome of chronic brain injury and does not necessarily imply a lack of awareness. Second, the behavioural assessment is highly subjective: behaviours such as smiling and crying are typically reflexive and automatic, but in certain contexts they may be the only means of communication available to a patient and therefore reflect a wilful, volitional act of intention. These difficulties, coupled with inadequate experience and knowledge engendered through the relative rarity of these complex conditions, contribute to an alarmingly high rate of misdiagnosis (up to 43%) in this patient group (Andrews et al. 1996; Childs et al. 1993; Schnakers et al. 2006).

These issues expose a central conundrum in the study of covert awareness—that is, awareness that is hard to detect—in general, and how it relates to conditions such as the vegetative state in particular.[1]

Historically, the only reliable method that we have had for determining if another being is consciously aware is to ask him or her. The answer may take the form of a spoken response or a non-verbal signal (which may be a movement as simple as the blink of an eye), but it is this answer, and only this answer, that allows us to infer awareness. Thus, while *wakefulness* can be measured and monitored accurately using techniques such as electroencephalography (EEG), *awareness* is an internal state of being that can only be 'measured' via some form of self-report. Put simply, our ability to establish that another being is consciously aware is ultimately determined, not by whether they are aware or not, but by their ability to communicate that fact through a recognized behavioural response. But what if the ability to speak, or blink an eye, or move a hand is lost, yet conscious awareness remains? Following the logic above, in a case where every opportunity for self-report has been lost, it would be impossible to determine whether any level of awareness remains. Of course, cases of 'locked-in syndrome' following acute brain injury or disease have been reported for many years, but where such cases are unexpectedly 'discovered' it is always through the (sometimes chance) detection of a minor residual motor response. Against this background it is an unfortunate, but inevitable, fact that a population of patients will exist who retain at least some level of residual conscious awareness, yet remain entirely unable to convey that fact to those around them. 'Discovering' such patients is, in my view, enormously important, for moral, scientific, clinical, and legal reasons. For example, if such cases do exist—that some patients are aware, but remain trapped within an entirely unresponsive body, is there not a moral imperative—however disturbing that may be—to recognize and document this fact? If nothing else, acknowledging the truth will ensure that all subsequent interactions and interventions with such patients are made in the knowledge that awareness *may* remain and may lead to a wider acceptance of this highly unusual condition. Moreover, wider acceptance will undoubtedly lead to an increase in scientific interest that will, in turn, accelerate progress towards possible interventions and therapies. Historically, the vegetative state and other so-called 'disorders of consciousness' have received very little attention in the scientific literature, in part because the assumed lack of any residual cognitive function, or potential for

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[1] We adopt the view of Koch (2007) who suggests that the distinction between awareness and consciousness is largely one of social convention, with no clear difference between them. Thus, 'consciousness', 'awareness', and the commonly used term 'conscious awareness' will be used interchangeably.

cognitive function, have deemed such efforts pointless. There is, as yet, no recognized treatment or intervention for this patient group that has been empirically tested and shown to be beneficial. However, as in all fields, wider acceptance and increased scientific attention are necessary precursors for such therapies to be found. But it is also clinically and legally important to correctly identify residual awareness in patients who are assumed to be vegetative and unaware, because treatment decisions often involve the possibility of withdrawal of life support (nutrition and hydration). In most countries, such decisions are only made once a diagnosis of *permanent* vegetative state has been made and if a patient was shown to have some level of awareness, then this information would be entirely incompatible with such a diagnosis. Thus, the identification of awareness would render any decision concerning the withdrawal of life support unlawful and, therefore, unlikely.

In this chapter, recent advances in neuroimaging technology will be discussed which may provide a mechanism for 'discovering' this lost population of patients. The central tenet is, that if measurable brain 'responses' could be marshalled and used as a proxy for a motor response, then a patient who is entirely unable to move may be able to signal awareness by generating a pattern of brain activity that is indicative of a specific thought or intention. Of course, this possibility raises as many questions as it does answers. In what circumstances should imaging be used to look for evidence of covert awareness? What sorts of 'brain responses' should be admissible as evidence of covert awareness and, in the absence of any possibility for behavioural verification, how much weight should be given to such evidence? I will explore these questions in the context of recent studies in both healthy populations and brain-injured patients that have sought to investigate covert awareness through the use of functional neuroimaging. Those circumstances in which fMRI data can be used to infer awareness in the absence of a behavioural response will be contrasted with those circumstances in which it cannot. This distinction is fundamental for understanding and interpreting patterns of brain 'activation' following acute brain injury and has implications for clinical care, diagnosis, prognosis, and medical–legal decision making after serious brain injury.

Functional neuroimaging as an assessment tool in disorders of consciousness

In the first study of its kind, de Jong et al. (1997) measured regional cerebral blood flow in a post-traumatic vegetative patient during an auditorily-presented story told by his mother. Compared to non-word sounds, activation was observed in the anterior cingulate and temporal cortices, possibly reflecting emotional processing of the contents, or tone, of the mother's speech. A year later, positron emission tomography (PET) was used in another patient diagnosed as vegetative to study visual processing in response to familiar faces (Menon et al. 1998). Robust activity was observed in the right fusiform gyrus, the so-called human 'face area' (or FFA). In both of these early cases, 'normal' brain activation was observed in the absence of any behavioural responses to the external sensory stimulation.

More recently, in the largest study to date, 41 patients with disorders of consciousness were graded according to their brain activation on a hierarchical series of language paradigms (Coleman et al. 2009). The tasks increased in complexity systematically from basic acoustic processing (a non-specific response to sound) to more complex aspects of language comprehension and semantics. At the highest level, responses to sentences containing semantically ambiguous words (e.g. 'the *creak/creek* came from a *beam* in the ceiling/sealing') are compared to sentences containing no ambiguous words (e.g. 'her secrets were written in her diary'), in order to reveal brain activity associated with spoken language *comprehension* (Rodd et al. 2005; Owen et al. 2005a, 2005b; Coleman et al. 2007, 2009). Nineteen of the patients (almost 50%), who had been diagnosed as either vegetative or minimally conscious, showed 'normal' or 'near normal' temporal-lobe responses in the low-level auditory contrast (sound responses) and in the mid-level speech perception contrast (a specific response to speech over and above the more general response to sounds). Four patients, including two who had been diagnosed as behaviourally vegetative, were also shown to exhibit 'normal' fMRI activity during the highest-level speech comprehension task, suggesting that the neural processes involved in *understanding* speech were also intact (Coleman et al. 2009). What is most remarkable about these fMRI findings is that the imaging results were found to have no association with the patients' behavioural presentation at the time of investigation and thus provide additional diagnostic information beyond the traditional clinical assessment. Moreover, the level of auditory processing revealed by the fMRI results *did* correlate strongly with the patients' subsequent behavioural recovery (assessed six months after the scan), suggesting that brain imaging may also provide valuable prognostic information not evident through bedside testing. These results provide compelling evidence for intact high level residual linguistic processing in some patients who behaviourally meet the clinical criteria for vegetative and minimally conscious states.

Brain activity and awareness

But does the presence of 'normal' brain activation in behaviourally non-responsive patients indicate awareness? In most of the cases discussed above and elsewhere in the literature, the answer is probably 'no'. Many types of stimuli, including faces, speech, and pain, will elicit relatively 'automatic' responses from the brain; that is to say, they will occur without the need for active (i.e. conscious) intervention on the part of the participant (e.g. you can not choose to not recognize a face, or to not understand speech that is presented clearly in your native language). In addition, a wealth of data in healthy volunteers, from studies of implicit learning (learning of information in an incidental manner, without awareness of what has been learned) and the effects of priming (where unconscious exposure to a stimulus influences a response to a later stimulus—see Schacter 1994 for review) to studies of learning and speech perception during anaesthesia (e.g. Davis et al. 2007; Bonebakker et al. 1996) have demonstrated that many aspects of human cognition can go on in the absence of awareness. Even the semantic content of information that is masked from conscious perception (e.g. by being presented very rapidly) can affect subsequent behaviour without the explicit knowledge of the participant, suggesting that some aspects of semantic processing may occur without conscious awareness (Dehaene et al. 1998). By the same argument, 'normal' neural responses in patients who are diagnosed as vegetative do not necessarily indicate that these patients have any conscious experience associated with processing those same types of stimuli. To investigate this issue directly, Davis et al. (2007) recently used fMRI in sedated healthy volunteers and exposed them to exactly the same speech stimuli that have been shown to elicit normal patterns of brain activity in some vegetative and minimally conscious patients (Owen et al. 2005a, 2005b; Coleman et al. 2007, 2009). During three scanning sessions, the participants were non-sedated (awake), lightly sedated (a slowed response to conversation), and deeply sedated (no conversational response, rousable by loud command). In each session, they were exposed to sentences containing ambiguous words, matched sentences without ambiguous words, and signal-correlated noise. Equivalent temporal-lobe responses for normal speech sentences compared to signal-correlated noise were observed, bilaterally, at all three levels of sedation, suggesting that a 'normal' brain response to speech sounds is not a reliable correlate of awareness. This result suggests that extreme caution needs to be exercised when interpreting normal responses to speech in patients who are diagnosed as vegetative, a problem of interpretation that applies to many of the activation studies that have been conducted in vegetative patients to date. However, when Davis et al. (2007) examined the effects of anaesthesia on ambiguous sentences, the frontal-lobe and posterior temporal-lobe activity that occurs in the awake individual (and is assumed to be a neural marker for semantic processing) was markedly absent, even during light sedation. This finding suggests that vegetative patients who show this specific pattern of neural activity during the presentation of ambiguous semantic material *may* be consciously aware (e.g. Owen et al. 2005a, 2005b; Coleman et al. 2007, 2009). However, as tantalizing as such conclusions might be, they are entirely speculative; the fact that awareness is *associated* with the activity changes that are thought to reflect sentence comprehension does not mean that it is *necessary* for them to occur (by simple analogy, the fact that amygdala activity is often observed during fMRI studies of fear does not mean that in all studies that have reported amygdala activity the participants were fearful).

Decoding responses based on brain activity

The studies described above confirm that many of the brain responses that have been observed to date using fMRI in brain damaged patients *could* have occurred automatically; that is, they could have occurred in the absence of any awareness of self (or others) on the part of the patient. But let us now consider an entirely different type of brain imaging experiment in which the responses observed *cannot* occur in the absence of awareness, because they are necessarily guided by a conscious choice, or *decision*, on the part of the participant. Many such experiments have been conducted in recent years, for example, to 'decode' mental decisions or thoughts in healthy volunteers (e.g. Haynes et al. 2007; Cerf et al. 2010), to demonstrate that fMRI can be deployed as a brain–computer interface (BCI; Weiskopf et al. 2004) or simply to examine the neural correlates of various types of mental imagery (Jeannerod and Frak 1999; Aguirre et al. 1996). Crucially, these paradigms differ from all of the passive tasks described above (e.g. speech or face perception) because the fMRI activity observed depends on the participant making a *conscious choice* to exert a specific wilful, or voluntary, response. In this sense, awareness is confirmed by such responses, simply because awareness is necessary for them to occur.

This contrast, between the responses observed in passive fMRI tasks that are (or at least *could be*) elicited automatically by an external stimulus and active tasks in which the response itself represents a conscious choice (and is therefore, by definition, a measure of conscious awareness), is absolutely central to the debate about the use of functional neuroimaging in disorders of consciousness. A significant recent addition to this field, therefore, has been the development of fMRI paradigms that render awareness reportable in the absence of an overt behavioural (e.g. motor or speech) response in patients who are entirely behaviourally non-responsive (Owen et al. 2006; Boly et al. 2007). The most successful of these techniques make use of the general principle observed in studies of healthy participants that imagining performing a particular task generates a robust and reliable pattern of brain activity in the fMRI scanner that is similar to actually performing the activity itself. For example, imagining moving or squeezing the hands will generate activity in the motor and premotor cortices (Jeannerod and Frak 1999), while imagining navigating from one location to another will activate the same regions of the parahippocampal gyrus and the posterior parietal cortex that have been widely implicated in map-reading and other so-called spatial navigation tasks (Aguirre et al. 1996).

In one recent study (Boly et al. 2007), 34 healthy volunteers were asked to imagine hitting a tennis ball back and forth to an imaginary coach when they heard the word 'tennis' (thereby eliciting vigorous imaginary arm movements) and to imagine walking from room to room in their house when they heard the word 'house' (thereby eliciting imaginary spatial navigation). Imagining playing tennis was associated with robust activity in the supplementary motor area in each and every one of the participants scanned. In contrast, imagining moving from room to room in a house activated the parahippocampal cortices, the posterior parietal lobe, and the lateral premotor cortices—all regions that have been shown to contribute to imaginary, or real, spatial navigation (Aguirre et al. 1996; Boly et al. 2007).

The robustness and reliability of these fMRI responses across individuals means that activity in these regions can be used as a neural proxy for behaviour, confirming that the participant retains the ability to understand instructions, to carry out different mental tasks in response to those instructions, and, therefore, is able to exhibit willed, voluntary behaviour in the absence of any overt action. On this basis, they permit the identification of awareness at the single-subject level, without the need for a motor response (for discussion, see Owen and Coleman 2008; Monti et al. 2009). In severe brain injury, when the request to move a hand or a finger is followed by an appropriate motor response, the diagnosis can change from vegetative state (no evidence of awareness) to minimally conscious state (some evidence of awareness). By analogy then, if the request to activate, say, the supplementary motor area of the brain by imagining moving the hand was followed by an appropriate brain response, I suggest that we should give that response the very same weight. Sceptics 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. For example, if a patient who was assumed to be unaware raised his or her hand to command on just one occasion, there would remain some doubt about the presence of awareness given the possibility that this movement was a chance occurrence, coincident with the instruction. However, if that same patient were able to repeat this response to command on ten occasions, there would remain little doubt that the patient was aware. By the same token, if that patient was able to activate his or her supplementary motor area in response to command (e.g. by being told to imagine hand movements), and was able to do this on every one of ten trials, would we not have to accept that this patient was consciously aware?

Detecting awareness in non-responsive patients

Owen et al. (2006, 2007) used this same logic to demonstrate that a young woman who fulfilled all internationally agreed criteria for the vegetative state was, in fact, consciously aware and able to make responses of this sort using her brain activity Prior to the fMRI scan, the patient was instructed to perform the two mental imagery tasks described above. When she was asked to imagine playing tennis, significant activity was observed in the supplementary motor area (Owen et al. 2006) that was indistinguishable from that observed in the healthy volunteers scanned by Boly et al. (2007). Moreover, when she was asked to imagine walking through her home, significant activity was observed in the parahippocampal gyrus, the posterior parietal cortex, and the lateral premotor cortex which was again, indistinguishable from those observed in healthy volunteers (Owen et al. 2006, 2007). On this basis, it was concluded that, despite fulfilling all of the clinical criteria for a diagnosis of vegetative state, this patient retained the ability to understand spoken commands and to respond to them through her brain activity, rather than through speech or movement, confirming beyond any doubt that she was consciously aware of herself and her surroundings. In a follow-up study of 23 patients who were behaviourally diagnosed as vegetative, Monti/Vanhaudenhuyse et al. (2010) showed that four (17%) were able to generate reliable responses of this sort in the fMRI scanner.

Another approach to detecting covert awareness after brain injury is to target processes that require the wilful adoption of 'mind-sets' in carefully matched (perceptually identical) experimental and control conditions. For example, Monti et al. (2009) presented healthy volunteers with a series of neutral words, and alternatively instructed them to just listen, or to count, the number of times a given word was repeated. As predicted, the counting task revealed the frontoparietal network that has been previously associated with target detection and working memory. When tested on this same procedure, a minimally conscious patient produced a very similar pattern of activity, confirming that he could wilfully adopt differential mind-sets as a function of the task condition and could actively maintain these mind-sets across time. As in the tennis/spatial navigation example described in detail above, because the external stimuli were identical in the two conditions (count words and listen to words), any difference in brain activity observed cannot reflect an 'automatic' brain response (i.e. one that can occur in the absence of consciousness). Rather, the activity must reflect the fact that the patient has performed a particular action (albeit a 'brain action') in response to the stimuli on one (but not the other) presentation; in this sense, the brain response is entirely analogous to a (motor) response to command and should carry the same weight as evidence of awareness.

These types of approach all illustrate a paradigmatic shift away from passive (e.g. perceptual) tasks to more active (e.g. wilful) tasks in the assessment of covert awareness after serious brain injury. What sets such tasks apart is that the neural responses required are not produced *automatically* by the eliciting stimulus, but rather, depend on time-dependent and sustained responses generated by the participant. Such behaviour (albeit neural 'behaviour') provides a proxy for a motor action and is, therefore, an appropriate vehicle for reportable awareness (Zeman 2009).

Using fMRI as a tool for communication in non-responsive patients

Owen and Coleman (2008b) extended the general principle described above, by which active mental rehearsal is used to signify awareness, to show that communication of 'yes' and 'no' responses was possible using the same approach. Thus, a healthy volunteer was able to reliably convey a 'yes' response by imaging playing tennis and a 'no' response by imaging moving around a house, thereby providing the answers to simple questions posed by the experimenters using only their brain activity. This technique was further refined by Monti/Vanhaudenhuyse et al. (2010) who successfully decoded the 'yes' and 'no' responses of 16 healthy participants with 100% accuracy using only their real time changes in the supplementary motor area (during tennis imagery) and the parahippocampal place area (during spatial navigation). Moreover, in one traumatic brain injury patient, who had been repeatedly diagnosed as vegetative over a five-year period, similar questions were posed and successfully decoded using the same approach (Monti/Vanhaudenhuyse et al. 2010). In contrast, and despite a re-classification to minimally conscious state following the fMRI scan, it remained impossible to establish any form of communication with this patient at the bedside.

fMRI in diagnosis and prognosis

The possibility of using fMRI for the detection of awareness in the vegetative state raises a number of issues for legal decision making relating to the prolongation, or otherwise, of life after severe brain injury. Foremost is the concern that diagnostic and prognostic accuracy is assured, as treatment decisions often include the possibility of withdrawal of life support. In an excellent discussion of these issues, Joseph Fins notes 'the utter and fixed futility of the vegetative state became the ethical and legal justification for the genesis of the right-to-die movement in the United States' (Fins 2003, 2006). At present, decisions concerning life support (nutrition and hydration) are only made once a diagnosis of *permanent* vegetative state has been made. In cases in which the critical threshold for a diagnosis of permanent vegetative state has passed, the medical team formally reviews the evidence and discuss this with those closest to the patient. In England and Wales the courts require that a decision to withdraw nutrition and hydration should be referred to them before any action is taken (Royal College of Physicians 1996). On the other hand, decisions not to use resuscitation in the case of cardiac arrest, or not to use antibiotics or dialysis, can be taken by the doctor in the best interests of the patient after full discussion with all those concerned. Interestingly, according to the same working party, 'one cannot ever be certain that a patient in the vegetative state is wholly unaware ... in view of this small but undeniable element of uncertainty, it is reasonable to administer sedation when hydration and nutrition are withdrawn to eliminate the possibility of suffering, however remote' (Royal College of Physicians 1996).

With the emergence of novel neuroimaging techniques that permit the identification of covert awareness in the absence of any behavioural response (Owen et al. 2006), the wording of the Royal College of Physicians 1996 statement ('*one cannot ever be certain that a patient in the vegetative state is wholly unaware*') acquires renewed resonance. Unfortunately, at present, although several of the neuroimaging approaches discussed in this chapter hold great promise for improving both diagnostic and prognostic accuracy in behaviourally non-responsive patients, the accepted assessment procedure continues to be a careful neurological exam by a trained examiner which focuses on a set of standard *behavioural* tests. However, in an increasing number of cases, neuroimaging findings have been reported that are entirely inconsistent with the formal clinical diagnosis. For example, the patient described by Owen et al. (2006), was clearly able to produce voluntary responses to command (albeit neural responses), yet was unable to match this with any form of motor response at the bedside. Paradoxically, therefore, this patient's (motor) behaviour was consistent with a diagnosis of vegetative state (an absence of evidence of awareness or purposeful response), yet her brain imaging data confirmed that the alternative hypothesis was correct, i.e. that she was entirely aware during the scanning procedure. Clearly the clinical diagnosis of vegetative state based on behavioural assessment was inaccurate in the sense that it did not accurately reflect her internal state of awareness. On the other hand, she was not *misdiagnosed* in the sense that no behavioural marker of awareness was missed. Likewise, the patient described recently by Monti/Vanhaudenhuyse et al. (2010) was clearly not vegetative because he could generate 'yes' and 'no' responses in real time by wilfully modulating his brain activity. In fact, these consistent 'responses to command' which allowed him to *functionally communicate* suggest a level of residual cognitive function that would actually place this patient beyond the minimally conscious state and (at least) into the severely disabled category. Similarly, the minimally conscious patient described by Monti et al. (2009) was able to 'perform' a complex working memory task in the scanner, in the sense that his brain activity revealed consistent and repeatable command following. While this 'behaviour' does not necessarily alter the patient's formal diagnosis (from 'low' minimally conscious state) it certainly demonstrated a level of responsively that was not evident from the behavioural examination. These findings suggest an urgent need for a re-evaluation of the existing diagnostic guidelines for the vegetative state and related disorders of consciousness and for the development and formal inclusion of validated, standardized, neuroimaging procedures into those guidelines.

A related issue concerns the implications that emerging neuroimaging approaches may have for prognosis in this patient group. It is of interest that in the case described by Owen et al. (2006), the patient began to emerge from her vegetative state to demonstrate diagnostically relevant behavioural markers before the prognostically important 12-month threshold was reached (for a diagnosis of permanent vegetative state), suggesting that early evidence of awareness acquired with functional neuroimaging may have important prognostic value. Indeed, with a marked increase in the number of studies using neuroimaging techniques in patients with disorders of consciousness, a consistent pattern is beginning to emerge. Di et al. (2008) reviewed 15 separate $H_2{}^{15}O$ PET and fMRI studies involving 48 published cases which were classified as 'absent cortical activity', 'typical activity' (a short-hand term used in that paper to denote activity in low level primary sensory cortices only), and 'atypical activity' (a short-hand term used in the paper to denote that activity was observed in higher level associative cortices). The results suggest that atypical activity patterns appear to predict recovery from vegetative state with a 93% specificity and 69% sensitivity. That is to say, nine of 11 patients exhibiting atypical activity patterns recovered consciousness, whereas 21 of 25 patients with typical primary cortical activity patterns and four out of four patients with absent activity failed to recover. This important review strongly suggests that functional neuroimaging data can provide important prognostic information beyond that available from bedside examination alone. Similarly, in the large recent study of 41 patients with disorders of consciousness described in detail above, Coleman et al. (2009) also found direct evidence of prognostically important information from the neuroimaging data that was at odds with the behavioural assessment at the time of scanning. Thus, contrary to the clinical impression of a specialist team using behavioural assessment tools, two patients who had been referred to the study with a diagnosis of vegetative state, did in fact demonstrate clear signs of speech comprehension when assessed using fMRI. More importantly, however, across the whole group of patients, the fMRI data were found to have no association with the behavioural presentation at the time of the investigation, but correlated significantly with subsequent behavioural recovery, six months after the scan. In this case, the fMRI data predicted subsequent recovery in a way that a specialist behavioural assessment could not.

In summary, although it is not yet the case that fMRI data forms part of the diagnostic and prognostic assessment of behaviourally non-responsive patients, more evidence to support its formal inclusion is being published each year (Owen and Coleman 2007) The prevailing view, endorsed by this author, is not that brain imaging should replace behavioural assessments, but rather that it should be used, wherever possible, to acquire further information about the patient. In doing so, and on the basis of the evidence reviewed above, one can reasonably expect that the current rate of misdiagnosis will fall because new methods of assessment, including neuroimaging, will identify instances in which the existing and accepted (behavioural) methods have resulted in some patients being classed as unaware when, in fact, awareness remains. Patients will be examined with all available tools and thus given the greatest opportunity to respond. Likewise, care teams will have the best possible information for planning and monitoring interventions to facilitate recovery. Although behavioural markers and brain imaging will undoubtedly reveal inconsistencies, it is these inconsistencies that will ultimately improve the accuracy of diagnosis and prognosis in this patient group.

fMRI and end-of-life decision making

Returning to the issue of the continuation, or otherwise, of life support in behaviourally non-responsive patients, in the case described by Owen et al. (2006), and in most of the similar cases that have appeared in the subsequent literature (e.g. Owen and Coleman 2008a), as noted above, the scans that revealed awareness were acquired before the time at which the decision making process governing withdrawal of life support is legally permitted to begin (i.e. the patients had not yet reached the point where a diagnosis of *permanent* vegetative state could be made). Therefore, even if the neuroimaging evidence had been admissible as part of the formal diagnostic and prognostic evaluation, in those particular cases, it was too early for the process governing end-of-life decisions to be made and therefore the situation did not arise. The same is not true of the patient described recently by Monti/Vanhaudenhuyse et al. (2010) who was able to communicate using his fMRI responses despite being repeatedly diagnosed as vegetative over a five-year period. In that case, the scan that revealed awareness was acquired and, indeed, the ability to functionally communicate was demonstrated, several years after the critical point for a diagnosis of permanent vegetative state had been reached. Even so, it is likely to be a number of years before such evidence could ever be used in the context of end-of-life decision making and significant legal, ethical, and technical hurdles will need to be overcome beforehand. For example, in principle it would be possible to ask the patient described by Monti/Vanhaudenhuyse et al. (2010) whether he wanted to continue living in his current situation (subject to an appropriate ethical framework being put into place), but 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 a complex decision? Clearly much more work would need to be done and many more questions asked of the patient (involving considerable time in the scanner), before one could be sure that this was the case and, even then, new ethical and legal frameworks will need to be introduced to determine exactly how such situations are managed and by whom. In the short term, it is more likely that this approach will be used to address less ethically challenging issues such as whether or not any patients who are in this situation are experiencing any pain. For example, using this technique, patients who are aware, but cannot move or speak, could be asked if they are feeling any pain, guiding the administration of analgesics where appropriate.

On the other hand, it is important to point out that neuroimaging of covert awareness is unlikely to influence legal proceedings where negative findings have been acquired. False-negative findings in functional neuroimaging studies are common, even in healthy volunteers, and they present particular difficulties in this patient population. For example, a patient may fall asleep during the scan or may not have properly heard or understood the task instructions, leading to an erroneous negative result. Indeed, in the recent study by Monti/Vanhaudenhuyse et al. (2010) no wilful fMRI responses were observed in 19 of 23 patients—whether these are *true* negative findings (i.e. those 19 patients were indeed vegetative) or *false negative* findings (i.e. some of those patients were conscious, but this was not detected on the day of the scan) can not be determined. Accordingly, negative fMRI findings in patients should never be used as evidence for impaired cognitive function or lack of awareness.

Consent and ethics

Finally, it is worth making a number of points about how the wider use of techniques such as fMRI could change the manner in which consent is sought in behaviourally unresponsive patients and the possible implications of such changes. If a patient cannot generate a behavioural response then they cannot consent to any procedure, be it a scientific investigation or a potential therapeutic intervention. In the case of fMRI, this does not present any especially difficult issues, since the technique is widely considered to be 'non-invasive'—hundreds of thousands of healthy volunteers take part in fMRI studies around the world every year—and so, most ethical committees who govern research in vulnerable populations will accept signed assent by the patient's next of kin for fMRI studies that are considered to be of sufficient clinical and scientific importance. Nevertheless, some do take the view that any scientific investigation, however benign, should be accompanied by informed consent by the individual taking part and some of the advances discussed above could make that possible, albeit retrospectively. Thus, a behaviourally non-responsive individual who was shown to be aware using fMRI could be asked to generate a 'yes' or 'no' response (e.g. by imagining playing tennis, etc) in order to retrospectively consent to the scanning procedure. More importantly, however, the same procedure could then be used to acquire consent *in advance* of further questioning which may involve more ethically challenging issues relating to the continuation, or otherwise, of life support. Such an approach may have major implications for trials involving new therapies, particularly where uncertainty about the outcome and/or side effects may make it unlikely that permission to try the procedure would be granted in the absence of patient consent. Finally, some may take the view that using fMRI in the manner described in this chapter is, in of itself, invasive in the sense that scientists are accessing the thoughts and intentions of those in the scanner by 'reading their brains'. To answer this question it is important to realize that, like the raising of an arm in response to the instruction to do so, activating the brain by, say, imagining playing tennis, is a voluntary response, which can be supressed at will. Thus, in the opinion of this author, using fMRI to scan a participant while we measure whether they are able to activate their premotor cortex in response to command, poses no more of an ethical issue than observing that same participant outside of the scanner and asking them to raise their left arm when told to do so.

Conclusions

The recent use of reproducible and robust task-dependent fMRI responses as a form of 'communication' in a behaviourally non-responsive patient (Monti/Vanhaudenhuyse et al. 2010) represents an important milestone in the use of neuroimaging methods in disorders of consciousness. It suggests that, in the near future, some patients with disorders of consciousness may be able to communicate their thoughts to those around them routinely, by simply modulating their own neural activity. However, given issues of cost, portability, and access, it seems unlikely that a long-term, routine solution to this problem will come from fMRI. Indeed, in spite of the major advances described in this chapter, performing fMRI in this patient group remains enormously challenging; the physical stress incurred by patients as they are transferred to a suitably equipped fMRI facility is significant. Movement artefacts in patients who are unable to remain still are also common, while metal implants, including plates and pins which are common in many traumatically injured populations, may rule out fMRI altogether. However, new techniques that use EEG, which is cheaper, portable, and more widely available than fMRI, may soon provide a more practical, everyday solution. Indeed, recent findings in disorders of consciousness suggest that EEG may be capable of decoding specific types of mental imagery even more reliably than fMRI (Cruse et al. 2011), which may pave the way for fully-fledged communication devices in this patient group, allowing them to share information about their inner worlds, experiences, and needs. The use of both EEG and fMRI in this context will continue to present innumerable ethical, logistic, and theoretical problems. However, its clinical and scientific implications are so major that the work to resolve these problems must continue.

Acknowledgements

I would like to thank the James S. McDonnell Foundation, the Medical Research Council, UK, and the Canada Excellence Research Chair (CERC) programme for their generous funding of my research programme.

References

Aguirre, G.K., Detre, J.A., Alsop, D.C., and D'Esposito, M. (1996) The parahippocampus subserves topographical learning in man. *Cerebral Cortex* 6: 823–9.

Andrews, K., Murphy, L., Munday, R., and Littlewood, C. (1996) Misdiagnosis of the vegetative state: retrospective study in a rehabilitation unit. *BMJ* 313: 13–16.

Boly, M., Coleman, M.R., Davis, M.H., Hampshire, A., Bor, D., Moonen, G., Maquet, P.A., Pickard, J.D., Laureys, S., and Owen, A.M. (2007) When thoughts become action: an fMRI paradigm to study volitional brain activity in non-communicative brain injured patients. *Neuroimage* 36: 979–92.

Bonebakker, A., Bonke, B., Klein, J., Wolters, G., Stijnen, T., Passchier, J., and Merikle, P.M. (1996) Information processing during general anaesthesia: Evidence for unconscious memory. In *Memory* *and Awareness in Anaesthesia*, eds B. Bonke, J.G.W. Bovill, and N. Moerman, 101–9. Lisse, Amsterdam: Swets and Zeitlinger.

Cerf, M., Thiruvengadam, N., Mormann, F., Kraskov, A., Quiroga, R.Q., Koch, C., and Fried, I. (2010) Online, voluntary control of human temporal lobe neurons. *Nature* 467: 1104–8.

Childs, N.L., Mercer, W.N., and Childs, H.W. (1993) Accuracy of diagnosis of persistent vegetative state. *Neurology* 43: 1465–7.

Coleman, M.R., Rodd, J.M., Davis, M.H., Johnsrude, I.S., Menon, D.K., Pickard, J.D., and Owen, A.M. (2007) Do vegetative patients retain aspects of language: Evidence from fMRI. *Brain* 130: 2494–507.

Coleman, M.R., Davis, M.H., Rodd, J.M., Robson, T., Ali, A., Pickard, J.D., and Owen, A.M. (2009) Towards the routine use of brain imaging to aid the clinical diagnosis of disorders of consciousness. *Brain* 132: 2541–52.

Cruse, D., Chennu, S., Chatelle, C., Bekinschtein, T.A., Fernandez-Espejo, D., Pickard, D.J., Laureys, S., and Owen, A.M. (2011) Bedside detection of awareness in the vegetative state. *The Lancet*. DOI:10.1016/S0140-6736 (11)61224-5.

Davis, M.H., Coleman, M.R., Absalom, A.R., Rodd, J.M., Johnsrude, I.S., Matta, B.F., Owen, A.M., and Menon, D.K. (2007) Dissociating speech perception and comprehension at reduced levels of awareness. *Proceedings of the National Academy of Sciences* 104(41): 16032–7.

de Jong, B., Willemsen, A.T., and Paans, A.M. (1997) Regional cerebral blood flow changes related to affective speech presentation in persistent vegetative state. *Clinical Neurology and Neurosurgery* 99(3): 213–16.

Dehaene, S., Naccache, L., Le Clec'H, G., Koechlin, E., Mueller, M., Dehaene-Lambertz, G., Van De Moortele, P.F., and Le Bihan, D. (1998) Imaging Unconscious Semantic Priming. *Nature* 395: 597–600.

Di, H., Boly, M., Weng, X., Ledoux, D., and Laureys, S. (2008) Neuroimaging activation studies in the vegetative state: predictors of recovery? *Clinical Medicine* 8: 502–7.

Fins, J.,* Illes, J.,* Bernat, J.L., Hirsch, J., Laureys, S., and Murphy, E.R. (*lead authors) (2008) Neuroimaging and disorders of consciousness: Envisioning an ethical research agenda. *American Journal of Bioethics—Neuroscience* 8(9): 3–12.

Fins, J.J. (2003) Constructing an ethical stereotaxy for severe brain injury: balancing risks, benefits and access. *Nature Reviews Neuroscience* 4(4): 323–7.

Fins, J.J. (2006) *A Palliative Ethic of Care: Clinical Wisdom at Life's End.* Sudbury (MA): Jones and Bartlett.

Fins, J.J. (2009) The ethics of measuring and modulating consciousness: the imperative of minding time. In *Coma science: Clinical and ethical implications—Progress in Brain Research*, eds S. Laureys, N.D. Schiff, and A.M. Owen, 371–82. Oxford: Elsevier.

Giacino, J.T., Schnakers, C., Rodriguez-Moreno, D., Schiff, N.D., and Kalmar, K. (2009) Behavioral assessment in patients with disorders of consciousness: Gold standard or fool's gold? In *Coma science: Clinical and ethical implications—Progress in Brain Research*, eds S. Laureys, N.D. Schiff, and A.M. Owen, 33–48. Oxford: Elsevier.

Haynes, J.D., Sakai, K., Rees, G., Gilbert, Frith, C., and Passingham, R.E. (2007) Reading Hidden Intentions in the Human Brain. *Current Biology* 17(4): 323–8.

Jeannerod, M. and Frak, V. (1999) Mental imaging of motor activity in humans. *Current Opinion in Neurobiology* 9: 735–9.

Jennett, B. and Plum, F. (1972) Persistent vegetative state after brain damage. *Lancet* 1: 734–7.

Koch, C. (2007) *The Quest for Consciousness: A Neurobiological Approach.* Colorado: Roberts and Company.

Menon, D.K., Owen, A.M., Williams, E.J., Minhas, P.S., Allen, C.M.C., Boniface, S., and Pickard, J.D. (1998) Cortical processing in persistent vegetative state. *Lancet* 352(9123): 200.

Monti, M.M., Coleman, M.R., and Owen, A.M. (2009) Executive Functions in the Absence of Behavior: Functional Imaging of the Minimally Conscious State. In *Coma science: Clinical and ethical implications—Progress in Brain Research*, eds S. Laureys, N.D. Schiff, and A.M. Owen, 249–60. Oxford: Elsevier.

Monti, M.M., Vanhaudenhuyse, A., Coleman, M.R., Boly, M., Pickard, J.D., Tshibanda, J-F.L., Owen, A.M., and Laureys, S. (2010) Willful modulation of brain activity and communication in disorders of consciousness. *New England Journal of Medicine* 362: 579–89.

Owen, A.M., Menon, D.K., Johnsrude, I.S., Bor, D., Scott, S.K., Manly, T., Williams, E.J., Mummery, C., and Pickard, J.D. (2002) Detecting residual cognitive function in persistent vegetative state. *Neurocase* 8: 394–403.

Owen, A.M., Coleman, M.R., Menon, D.K., Berry, E.L., Johnsrude, I.S., Rodd, J.M., Davis, M.H., and Pickard, J.D. (2005a) Using A Heirarchical Approach To Investigate Residual Auditory Cognition In Persistent Vegetative State. In *The boundaries of consciousness: neurobiology and neuropathology. Progress in Brain Research, vol. 150*, ed. S. Laureys, 461–76. London: Elsevier.

Owen, A.M., Coleman, M.R., Menon, D.K., Johnsrude, I.S., Rodd, J.M., Davis, M.H., Taylor, K., and Pickard, J.D. (2005b) Residual auditory function in persistent vegetative state: A combined PET and fMRI study. *Neuropsychological Rehabilitation* 15(3–4): 290–306.

Owen, A.M., Coleman, M.R., Davis, M.H., Boly, M., Laureys, S., and Pickard, J.D. (2006) Detecting awareness in the vegetative state. *Science* 313: 1402.

Owen, A.M. and Coleman M.R. (2007) Functional MRI in Disorders of Consciousness: Advantages and Limitations. *Current Opinion in Neurology* 20(6): 632–7.

Owen, A.M., Coleman, M.R., Davis, M.H., Boly, M., Laureys, S., Jolles, D., and Pickard, J.D. (2007) Response to Comments on 'Detecting awareness in the vegetative state'. *Science* 315: 1221c.

Owen, A.M. and Coleman, M. (2008a) Functional Imaging in The Vegetative State. *Nature Reviews Neuroscience* 9: 235–43.

Owen, A.M. and Coleman M.R. (2008b) Detecting awareness in the vegetative state. In *Molecular and Biophysical Mechanisms of Arousal, Alertness and Attention. Annals of the New York Academy of Sciences*, ed. D. Pfaff, 130–40. New York: Wiley-Blackwell.

Rodd, J.M., Davis, M.H., and Johnsrude, I.S. (2005) The Neural Mechanisms of Speech Comprehension: fMRI studies of Semantic Ambiguity. *Cerebral Cortex* 15: 1261–9.

Royal College of Physicians Working Group (1996) The permanent vegetative state. *Journal of the Royal College of Physicians of London* 30: 119–21.

Schacter, D.L. (1994) Priming and multiple memory systems: Perceptual mechanisms of implicit memory. In *Memory Systems*, eds D.L. Schacter and E. Tulving, 233–68. Cambridge (MA): MIT Press.

Schnakers, C., Giacino, J., Kalmar, K., Piret, S., Lopez, E., Boly, M., Malone, R., and Laureys, S. (2006) Does the FOUR score correctly diagnose the vegetative and minimally conscious states? *Annals of Neurology* 60: 744–5.

Weiskopf, N., Mathiak, K., Bock, S.W., Scharnowski, F., Veit, R., Grodd, W., Goebel, R., and Birbaumer, N. (2004) Principles of a brain-computer interface (BCI) based on real-time functional magnetic resonance imaging (fMRI). *IEEE Transactions on Biomedical Engineering* 51: 966–70.

Zeman, A. (2009) The problem of unreportable awareness. In *Coma science: Clinical and ethical implications—Progress in Brain Research*, eds S. Laureys, N.D. Schiff, and A.M. Owen, 1–10. Oxford: Elsevier.