When Thoughts Become Actions: Imaging Disorders of Consciousness

Adrian M. Owen

Abstract How can we ever know, unequivocally, that another person is aware? Notwithstanding deeper philosophical considerations about the nature of consciousness itself, the only reliable method we have for detecting awareness in others is by eliciting a predicted response to an external prompt or command. Logically, therefore, our ability to detect awareness in others is determined not by whether they are aware or not but by their ability to communicate that fact through a recognised behavioural response. This problem exposes a central conundrum in the study of awareness in general and, in particular, how it relates to the vegetative state. From this perspective, I discuss various solutions to this problem using functional neuroimaging. In particular, I will contrast those circumstances in which fMRI data can be used to infer awareness in the absence of a reliable behavioural response with those circumstances in which it cannot.

1 Introduction

How can any of us be absolutely sure that another human is consciously aware? When I ask this question, I am not seeking to raise any deep philosophical notions about the nature of consciousness itself but rather to pose a much more pragmatic, down-to-earth question: How can I know that you (or any other person) is aware? By this I mean, how can I know that you are aware of who you are, aware of where you are (in time and space) and aware of what you are doing right now (reading this article)? The answer is that I can only really know if you tell me, via some form of recognised behavioural response. That response may be a spoken answer or a non-verbal signal (which may be a movement as simple as the blink of an eye), but it is that response, and only that response, that would allow me to infer awareness.

A.M. Owen (✉)
Centre for Brain and Mind, Room 224, Natural Sciences Building, The University of Western Ontario, London, Ontario, N6A 5B7, Canada
e-mail: adrian.owen@uwo.ca

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Thus, *awareness* is an internal state of being that can only be measured via some form of self-report. In this sense, it differs fundamentally from that other central pillar of consciousness, wakefulness, which can be measured and monitored accurately by simple observation (if your eyes are open, then it is very likely that you are 'awake') or by using techniques such as electroencephalography (EEG) to measure the electrical signals that characterise the normal waking state. Thus, our ability to know unequivocally that another being is consciously *aware* is determined not by whether they are aware or not but by their ability to communicate that fact through a recognised behavioural response. But what if the ability to speak, blink an eye or move a hand is lost, yet conscious awareness remains?

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.

Indeed, 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 in general and, in particular, how it relates to conditions such as the vegetative state. Following the logic above, in a case where every opportunity for self-report has been lost (in fact, this is a central requirement for a diagnosis of vegetative state), 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 identified 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.

Recent advances in neuroimaging technology may provide a solution to this problem. 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. In this chapter, 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 activity following acute brain injury and has implications for clinical care, diagnosis, prognosis and medical–legal decision-making after serious brain injury.

2 An Historical Perspective

Substantial evidence now exists to suggest that so-called 'activation' methods, such as $H_2{}^{15}O$ positron emission tomography (PET) and fMRI, can be used to link changes in regional cerebral blood flow to specific cognitive processes without the need for any overt response (e.g., a motor action or a verbal response; for review, see Owen et al. 2001). 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, 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. 2002, 2005a, b; 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 behaviorally 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 6 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.

3 On the Relationship Between Brain Activity and Awareness

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 to this question 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 cannot choose to not recognise 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 and the effects of priming (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 masked information can be primed to 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, b; 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, b; 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).

4 Brain Activity as a Form of Response

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. When healthy participants in the scanner are asked to imagine moving their arms, robust activity is observed in the premotor cortex (Owen et al. 2006; Boly et al. 2007; Owen and Coleman 2008b; Monti et al. 2010). This response is utterly reliable, even at the single-subject level, and can be observed when the motor imagery task is compared to periods of rest or to other types of imagery tasks, such as navigating one's way around a familiar environment (Owen et al. 2006; Boly et al. 2007). Indeed, the localised changes in fMRI signal associated with these mental activities are so reliable that they can be used in place of a more traditional behavioural (e.g., motor) response, that is, as a proxy for a motor action or what I shall henceforth call a 'brain act.' For example, when healthy participants are asked to answer simple "yes/no" questions in the scanner (e.g., "Have you ever been to Paris?") by imagining moving their arms (and thereby activating the premotor cortex) to convey the answer "yes" and to relax (and thereby not activating the premotor cortex) to convey the answer "no," the factually correct answer can be decoded from their brain activity with 100% accuracy (Owen and Coleman 2008b; see also Monti et al. 2010). Importantly, this approach differs from all of the passive tasks described above (e.g., speech or face perception) because the pattern of fMRI activity is entirely dependent on the participant making a conscious choice to exert a specific wilful, or voluntary, response, rather than the stimulus per se. For example, an entirely different pattern of fMRI activity (e.g., either an increase in premotor cortex indicating a "yes" response or a lack of increase indicating a "no" response) may be generated following an identical physical stimulus ("Have you ever been to Paris?"), depending on whether the factually correct answer is "yes" or "no."

Thus, like any other form of action that requires response selection, such brain acts require awareness of the various contingencies that govern the relationship between any given stimulus (in this case, a question that has a factual answer) and a response (in this case, one of two possibilities that will only be known when the factually correct answer has been accessed from long-term memory). Put simply, fMRI responses of this sort can be used to measure awareness because awareness is necessary for them to occur. Indeed, the fact that they occur at all allows an observer to conclude not only that the instigator of the response is aware but also that multiple cognitive processes that are typically associated with conscious awareness are also intact and working normally. For example, an intact long-term memory is required to access the factually correct answer, short-term (or 'working') memory is required to maintain attention between the stimulus and the response and to guide the search for the correct answer, attentional switching is required (as the instigator of the responses switches between the various mental states that code for "yes" and "no"), sustained attention is required to maintain the appropriate mental state (typically for 30 s at a time) and, of course, response selection is required to make the final decision about which brain act to initiate. In short, because brain acts represent a neural proxy for motor behaviour, they also confirm 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 2008a; Monti et al. 2009).

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 (the brain act) represents a conscious choice is absolutely central to the debate about the use of functional neuroimaging to measure covert awareness. A significant development in this field, therefore, has been application of such paradigms in patients who are entirely behaviourally non-responsive (Owen et al. 2006; Boly et al. 2007; Owen and Coleman 2008b; Monti et al. 2010). 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).

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, shouldn't we 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/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/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?

This same logic was used recently 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 (Owen et al. 2006, 2007). 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 the activity 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 et al. (2010) showed that four (17%) were able to generate reliable responses of this sort in the fMRI scanner.

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 is possible using the same approach. Thus, a healthy volunteer was able to reliably convey a "yes" response by imagining playing tennis and a "no" response by imagining moving around a house, thereby providing the answers to simple questions posed by the experimenters using only his brain activity. This technique was further refined by Monti 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 5-year period, similar questions were posed and successfully decoded using the same approach (Monti et al. 2010). However, 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.

Clearly, the patient described by Monti et al. (2010) was 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. Likewise, 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, her (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.

These types of approaches 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).

Of course, sceptics may still argue that brain acts do not 'prove' that a person is consciously aware, even in situations where behaviourally unresponsive patients have been able to use this method to provide factually correct answers to five biographical questions about themselves (Monti et al. 2010). However, such sceptics would likely remain unsatisfied even if 500 questions had been asked and 500 correct answers had been given. The important point is that, by using spatially and temporally reliable fMRI changes as willed responses, we are simply applying the very same criteria that any of us would have to use to determine that any other walking, talking human being was consciously aware, that is, we would pose a question (or a series of questions) and we would make our judgement based on the response(s). It is difficult to imagine a circumstance in which any of us would spontaneously ask another person a series of five questions (drawn from an almost limitless pool of possible questions that could be asked), receive five factually correct answers and then conclude that they were not consciously aware (NB: Philosophically of course, it is possible to imagine that such a person could exist, wholly unaware, yet able to answer an infinite number of questions with factually correct answers, yet in the absence of any data to suggest that such a person does or can exist, I will not consider this possibility any further). Of course, it is true that it is impossible to know much about a patient's internal mental world on the basis of the answers to five simple questions, but the important point is that, as long as an answer can be conveyed with a "yes" or a "no," the possibility now exists for them to be asked. Indeed, there is no reason why such a patient could not be asked (and could answer) the most difficult question of all: "Are you conscious?"

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