

Detecting Consciousness: A Unique Role for Neuroimaging

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Abstract

How can we ever know, unequivocally, that another person is conscious and aware? Putting aside deeper philosophical considerations about the nature of consciousness itself, historically, the only reliable method for detecting awareness in others has been through a predicted behavioral response to an external prompt or command. The answer may take the form of spoken words or a nonverbal signal such as a hand movement or the blink of an eye, but it is this answer, and only this answer, that allows us to infer awareness. In recent years, rapid technological developments in the field of neuroimaging have provided new methods for revealing thoughts, actions, and intentions based solely on the pattern of activity that is observed in the brain. In specialized centers, these methods are now being employed routinely to detect consciousness in behaviorally nonresponsive patients when all existing clinical techniques have failed to provide that information. In this review, I compare those circumstances in which neuroimaging data can be used to infer consciousness in the absence of a behavioral response 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 profound implications for clinical care, diagnosis, prognosis, and medical-legal decision-making (relating to the prolongation, or otherwise, of life after severe brain injury). It also sheds light on more basic scientific questions about the nature of consciousness and the neural representation of our own thoughts and intentions.

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INTRODUCTION

For most of us, consciousness comes in two flavors, wakefulness and awareness. For example, think about what happens when you undergo a general anesthetic in the context of major surgery—you close your eyes and start to fall asleep (i.e., you lose wakefulness), and you stop having any sense of where you are, who you are, and the predicament that you are in (i.e., you lose awareness). Wakefulness and awareness are

two separate components of consciousness that are, at least partially, dissociable. The wakefulness component of consciousness is relatively easy to assess using purely behavioral methods: If a person’s eyes are open, then they are awake. For those who would like to be more empirical about it, then techniques such as electroencephalography (EEG) can be used to identify the pattern of electrical signals that characterize the normal waking state in an entirely objective manner. Assessing the awareness component of consciousness is much more difficult. Thus, we cannot just look at a person and know, unequivocally, that they are aware (in this context, I use “awareness” in the commonly understood lay sense; that is, awareness of who we are, where we are in time and space, what we did yesterday, and what our plans may be for tomorrow). In this instance, EEG is also rather limited because there is no standard pattern of resting state EEG signals that will reliably differentiate a state of awareness from a state of unawareness.

So how might we assess awareness in another person? The answer is, we can’t, unless the subject of our enquiry is both willing and able to tell us that (s)he is aware. The response may involve verbal affirmation (e.g., “Yes, I am aware”), or an agreed physical signal that is matched to a given stimulus (e.g., the squeezing of a hand in response to the request, “Please squeeze my hand if you are aware”), but some sort of response is always required in order for us to reliably infer that awareness is present. Thus, although the wakefulness component of consciousness can be measured and monitored behaviorally or by using techniques such as EEG, the awareness component of consciousness is an internal state of being that can only be “measured” via some form of self-report.

In a clinical context, this self-report is often referred to as command following. Thus, if a patient is reliably able to squeeze the doctor’s hand when requested to do so, (s)he is said to have followed the command and is therefore known to be aware. This is not a new idea: In their seminal text *Diagnosis of Stupor and Coma*, Plum & Posner (1983, p. 3) stated, “The limits of consciousness are hard to define

satisfactorily and quantitatively and we can only infer the self-awareness of others by their appearance and by their acts.” Again, the inference here is that a distinct action is required in response to a specific command in order for us to unequivocally determine that another person is aware. Although this link between command following and awareness may appear to be rather obvious, it is understandable that some—philosophers, in particular—may find fault in the logic. They might argue, for example, that we can manufacture machines that can “follow commands” by squeezing an arm in response to a request to do so (indeed, we can manufacture machines that can do a whole lot more than that), but such arguments dodge my original question. I did not ask whether we can make a machine that can give the impression that it is aware (we certainly can), but rather, whether a human being who can respond to command by, say, raising an arm or squeezing a hand when asked to do so, is necessarily aware? In this review, I argue that this is most certainly the case and, further, that it is the key to unlocking signs of covert consciousness in situations where all forms of physical response have been rendered unavailable.

WAKEFULNESS WITH (AND WITHOUT) AWARENESS

Following the logic above, our ability to detect awareness in others is limited not by whether they are aware or not, but rather by their ability to communicate that fact through a recognized behavioral response. In recent years, improvements in intensive care have led 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 & Plum 1972) (see sidebar On the Nature of Consciousness).

ON THE NATURE OF CONSCIOUSNESS

Any discussion about disorders of consciousness such as the vegetative state is problematic because it suggests disruption of an underlying well-understood and clearly defined system known as consciousness. This, of course, is not the case; there is, as yet, no universally agreed definition of consciousness (Laureys et al. 2007). Widely accepted definitions often refer to awareness of the self and the environment (Plum & Posner 1983), and accordingly, patients with disorders of consciousness (e.g., the vegetative state) are often described as lacking “awareness of self or environment.” Such descriptions inevitably provoke further questions, including what constitutes awareness and what level of awareness is sufficient for a patient to be described as consciously aware. On the other hand, Koch (2007) has recently stated that the distinction between consciousness and awareness is largely one of social convention, with no clear difference between them. I suggest that the central problem in the assessment of the vegetative state and other disorders of consciousness is not in understanding the nature of consciousness itself, but rather in defining where the transition point lies between what most people would agree is an unconscious or unaware state and what most would agree is a conscious or aware state. This transition point is not always easily recognized in people with severe brain damage, particularly in patients whose neurological course (improvement or deterioration) is evolving slowly.

Thus, such patients often exhibit sleeping and waking cycles, will spontaneously open their eyes (hence, they are “awake”), and may even appear to “look” around a room, although they never fixate on anything, or anyone, and never follow (or track) an object or a person, whether asked to do so or not. The assessment of these patients is extremely difficult and relies heavily on subjective interpretation of observed behavior at rest and in response to stimulation (see sidebar Assessing Awareness Behaviorally). A diagnosis is made after repeated examinations have yielded no evidence of sustained, reproducible, purposeful, or voluntary behavioral response to visual, auditory, tactile, or noxious stimuli. Unfortunately, this means that a positive diagnosis (of vegetative state) is ultimately dependent on a negative finding (no signs of awareness) and is, therefore, inherently

ASSESSING AWARENESS BEHAVIORALLY

Any assessment of awareness that is based on exhibited behavior 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 behavioral assessment is highly subjective: Behaviors 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 willful, 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 the vegetative state (Andrews et al. 1996; Childs et al. 1993; Schnakers et al. 2006, 2009).

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 is widely accepted as adequate evidence of absence.

But imagine a clinical condition in which a brain-injured patient was left entirely conscious (awake and aware), but was nevertheless completely incapable of generating any sort of physical response, be it the blink of an eye, the movement of a hand, or a spoken word—indeed, imagine that the ability to make any behavioral response whatsoever was lost completely, yet conscious awareness remains. Following the arguments above, in such a case (where absolutely every opportunity for command following has been lost), it would be logically impossible to determine whether any level of awareness remains. Irrespective of how aware the patient was, or how skilled the observer was, awareness could not (and typically would not) be inferred because of the complete lack of any responses to external stimulation. 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. In the absence of such a response, how could awareness ever be detected? Against this background, it is an unfortunate, but inevitable, fact that a population of patients must exist who retain at least some level of residual conscious awareness yet remain entirely unable to convey that fact to those around them.

ASSESSING COGNITION IN THE ABSENCE OF BEHAVIOR

Recent advances in neuroscience may provide a solution to this problem. If measurable brain responses could be marshaled and used as a proxy for a behavioral response (a thought response, perhaps), then we might find such patients by asking them to signal awareness by generating a pattern of brain activity that is indicative of a specific thought or intention. In the past few years, positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and electroencephalography (EEG) have all been brought to bear on this problem, with varying degrees of success (Cruse and Owen 2010). Such approaches are fraught with problems, not least because in the absence of any corroborative behavior, they often depend, by definition, on a reverse inference (Poldrack 2006, Christoff & Owen 2006); that is to say, the engagement of a given cognitive process has to be inferred solely on the basis of the observed activation in a particular brain region.

PET and fMRI Studies in Nonresponsive Patients

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 nonword 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 behavioral responses to the external sensory stimulation.

Normal brain activity in response to complex external stimulation, however, has generally been the exception rather than the rule in studies of vegetative patients. For example, in one study of 15 patients, high-intensity noxious electrical stimulation activated midbrain, contralateral thalamus, and primary somatosensory cortex in every patient (Laureys et al. 2002). However, unlike control participants, the patients did not show the activation in secondary somatosensory, insular, posterior parietal, or anterior cingulate cortices that would be consistent with higher-level cognitive processing.

Di et al. (2007) used event-related fMRI to measure brain activity in seven vegetative patients and four minimally conscious patients (see sidebar Disorders of Consciousness) in response to the patient's own name spoken by a familiar voice. Two of the vegetative patients exhibited no significant activity at all, three patients exhibited activation in primary auditory areas, and two vegetative patients and four minimally conscious patients exhibited activity in higher-order associative temporal lobe areas. Although this result was encouraging (particularly because the two vegetative patients who showed the most widespread activation subsequently improved to minimally conscious state in the following months), like many of these early studies, it lacked cognitive specificity; that is to say, responses to the patient's own name spoken by a familiar voice were compared only to responses to the attenuated noise of the MRI scanner. Therefore, the activation observed may have reflected a specific response to each patient's own name, but it is equally possible that it reflected a low-level orienting response to speech in general, an emotional response to the speaker (see Bekinschtein et al. 2004), or any one of a number of possible cognitive processes relating to the imperfectly matched auditory stimuli.

DISORDERS OF CONSCIOUSNESS

The term "disorders of consciousness" is typically used to refer to three conditions: (a) coma, (b) vegetative state, and (c) minimally conscious state (Giacino et al. 2002, Plum & Posner 1983, Roy. Coll. Phys. 1996/2003). These conditions arise as a result of either a traumatic (e.g., a blow to the head) or a nontraumatic (e.g., a stroke) brain injury and may include damage to areas of the brainstem that mediate wakefulness and/or to cortico-cortical axonal connections that mediate cognitive function and awareness. Although particular patterns of pathology are commonly linked to each of these conditions, they are exclusively defined according to the behaviors exhibited by the patient rather than pathology. The key criteria are: (a) Coma describes an acute condition, typically lasting two to four weeks after brain injury. Comatose patients do not open their eyes and exhibit only reflex responses to stimulation. Unlike vegetative state, therefore, the wakefulness component of consciousness is typically lost. (b) In contrast, the vegetative state describes a condition in which patients open their eyes and demonstrate sleep-wake cycles. Like comatose patients, they do not exhibit purposeful behavior, retaining reflex responses only. (c) The minimally conscious state differs from these conditions through the presence of inconsistent but reproducible evidence of awareness. In contrast to the comatose and vegetative states, minimally conscious patients demonstrate inconsistent but purposeful responses to command and/or sensory stimulation.

Two related conditions that are often confused with coma, the vegetative state, or the minimally conscious state are the locked-in syndrome and brain death. The locked-in syndrome is not a disorder of consciousness but is critically important in the differential diagnosis. Locked-in syndrome patients are awake and fully conscious but have no means of producing speech, limb, or facial movements (Plum & Posner 1983). Brain death, or more accurately brainstem death, is a clinical term that refers to a complete and irreversible loss of brainstem function (Roy. Coll. Phys. 1998), resulting in the inevitable cessation of life. The diagnostic criteria for brain death require the loss of all brainstem reflexes. Vegetative patients typically retain such reflexes and rarely require a life-support system to regulate cardiac and respiratory functions. For an excellent review of death and the brain, see Laureys (2005).

Staffen et al. (2006) used event-related fMRI to compare sentences containing the patient's own name (e.g., "James, hello James"), spoken by a variety of unfamiliar voices, with sentences containing another first name, in a patient who

had been vegetative for ten months at the time of the scan. In this case, because identical speech stimuli were used that differed only with respect to the name itself, activations can be confidently attributed to cognitive processing that is specifically related to the patient's own name. Differential cortical processing was observed to the patient's own name in a region of the medial prefrontal cortex, similar to that observed in three healthy volunteers. Selective cortical processing of one's own name (when it is compared directly with another name) requires the ability to perceive and access the meaning of words and may imply some level of comprehension on the part of this patient. However, as the authors point out (Staffen et al. 2006), a response to one's own name is one of the most basic forms of language, is elicited automatically (you can not choose to not attend to your own name), and may not depend on the higher-level linguistic processes that are assumed to underpin comprehension.

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 nonspecific 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*") were 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 (Coleman et al. 2007, 2009; Owen et al. 2005a,b; Rodd et al. 2005). Nineteen of the patients (approximately 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). These results provide compelling evidence for intact high-level residual linguistic processing in some patients who behaviorally meet the clinical criteria for vegetative and minimally conscious states.

EEG Studies in Nonresponsive Patients

Performing fMRI in severely brain-injured patients is enormously challenging; in addition to considerations of cost and scanner availability, the physical stress incurred by patients as they are transferred to a suitably equipped fMRI facility is significant. Movement artefacts often occur in imaging datasets from patients who are unable to remain still; metal implants, including the plates and pins that are common in many traumatically injured populations, may rule out fMRI altogether. EEG measures the activity of groups of cortical neurons from scalp electrodes and is far less expensive than fMRI, both in terms of initial cost and maintenance. EEG recordings are unaffected by any resident metallic implants and, perhaps most importantly, can be used at the bedside (Vaughan et al. 2006). In brain-injured patients, EEG recordings are typically made in the acute period and allow for broad assessments of cortical damage including the occurrence of brain death (see sidebar Disorders of Consciousness). However, uncertainty about the causes of abnormal raw EEG patterns (i.e., damage to the cortex itself or to subcortical structures that influence cortical activity) provides challenges for its use as a more precise tool for the assessment of awareness (Kulkarni et al. 2007). As well as concentrating on aspects of the resting EEG, a number of studies have investigated whether cognitive event-related potentials (ERPs)—averages of segments of EEG locked to the presentation of a stimulus—can be used to assess residual

cognitive function in patients with disorders of consciousness. For example, recently it was shown that violations of prosody in nonlinguistic emotional exclamations elicited a reliable N300 component in 6 out of 27 vegetative or minimally conscious patients, suggesting a level of processing of auditory stimuli in these patients beyond their most basic features (Kotchoubey et al. 2009; also see Kotchoubey et al. 2003a, 2005). As is the case for fMRI, one popular stimulus, employed in these cognitive tasks due to its high level of saliency, is the patient's own name. When presented infrequently among tones and other names, a reliable mismatch negativity has been observed in some coma, vegetative state, and minimally conscious state patients, demonstrating some selectivity of those patients' neural responses to hearing their own name (Qin et al. 2008).

BRAIN ACTIVITY AND AWARENESS

But does the presence of normal brain activation, whether acquired through PET, fMRI, or EEG, in behaviorally nonresponsive 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; for review, see Schacter 1994) to studies of learning and speech perception during anesthesia (e.g., Bonebakker et al. 1996, Davis et al. 2007), 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 behavior 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 or minimally conscious do not necessarily indicate that these patients have any conscious experience associated with processing those same types of stimuli.

Anesthetic Studies

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 (Rodd et al. 2005) that have been shown to elicit normal patterns of brain activity in some vegetative and minimally conscious patients (Coleman et al. 2007, 2009; Owen et al. 2005a,b). During three scanning sessions, the participants were nonsedated (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 described above. However, when Davis et al. (2007) examined the effects of anesthesia 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 state patients who show this specific pattern of neural activity during the presentation of ambiguous semantic material may be consciously aware (e.g., Coleman et al. 2007, 2009; Owen et al. 2005a,b). 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 CONSCIOUS 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.

fMRI Studies in Healthy Participants

Many such experiments have been conducted in healthy participants in recent years, for example, to decode mental decisions or thoughts (e.g., Cerf et al. 2010, Haynes et al. 2007), to demonstrate that fMRI can be deployed as a brain-computer interface (Weiskopf et al. 2004), or simply to examine the neural correlates of various types of mental imagery (Aguirre et al. 1996, Jeannerod & Frak 1999). In one study, healthy volunteers were asked to freely decide which of two tasks to perform

(add or subtract two numbers) and to covertly hold onto that decision during a delay (Haynes et al. 2007). A classifier was trained to recognize the characteristic fMRI signatures associated with the two mental states and in 80% of trials was able to decode which of the two tasks the volunteers were intending to perform before they actually performed it. The principle employed was that certain types of thought are associated with a unique brain activation pattern that can be used as a signature for that specific thought. If a classifier is trained to recognize these characteristic signatures, a volunteer's thoughts can be ascertained (within the constraints of the experimental design) using her/his brain activity alone. More recently, pattern classification of fMRI signals was also used to decode movement intentions moments before their initiation (Gallivan et al. 2011).

Genuine thought-translation devices or brain-computer interfaces as they are widely known, have been developed for fMRI, although to achieve acceptable levels of accuracy they typically rely on mental imagery as a proxy for the physical response being decoded. For example, in one early study, four non-naïve participants learned, with the aid of feedback, to willfully regulate their fMRI signal using self-chosen visual imagery strategies (e.g., pictures of buildings, spatial navigation, clenching, dancing) (Weiskopf et al. 2004). In a more sophisticated design, information derived from both the timing (onset and offset) and the source location of the hemodynamic response was used to decode which of four possible answers was being given to questions (Sorger et al. 2009). To indicate their choice (or thought), participants imagined one of two tasks, beginning at one of four times and continuing for different prespecified durations. An automated decoding procedure deciphered the answer by analyzing the single-trial blood-oxygen-level-dependent responses in real time with a mean accuracy of 94.9%.

Crucially, these paradigms differ from all of the passive fMRI tasks described above (e.g., speech or face perception) that have been used

in nonresponsive patients because the fMRI activity observed depends on the participant making a conscious choice to exert a specific willful, or voluntary, response.

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 any nonresponsive population, including those with 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 behavioral (e.g., motor or speech) response in patients who are entirely behaviorally nonresponsive (Boly et al. 2007, Owen et al. 2006). 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 & 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 study (Boly et al. 2007), 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 (**Figure 1**). 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 of these regions 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 behavior, confirming that the participant retains the ability to understand instructions and to carry out different mental tasks in response to those instructions, and therefore is able to exhibit willed, voluntary behavior in the absence of any overt action. Thus, like any other form of action that requires response selection, these brain responses require awareness of the various contingencies that govern the relationship between any given stimulus (in this case, the cue word for one of two possible imagery tasks) and a response (in this case, imagining the task). Put simply, fMRI responses of this sort can be used to measure awareness because awareness is necessary for them to occur.

fMRI Studies in Nonresponsive 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. The patient, who was involved in a complex road traffic accident and had sustained very severe traumatic brain injuries, had remained entirely unresponsive for a period of six months prior to the fMRI scan. During the scanning session, the patient was instructed to perform the two mental imagery tasks described above. When she was asked to imagine playing tennis (**Figure 1**, patient 5), significant activity was observed repeatedly 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 that 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 behaviorally diagnosed as vegetative, Monti et al. (2010) showed that 4 (17%) were able to generate reliable responses of this sort in the fMRI scanner (**Figure 1**, patients 1–4).

After a 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 is followed by an appropriate brain response, 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. For example, if a patient who was assumed to be unaware raised his/her hand in response 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 10 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 playing tennis), and was able to do this on every one of 10 trials, would we not

have to accept that this patient was consciously aware? Like most neuroimaging investigations, replication of this sort was inherent in both of the studies described above (Monti et al. 2010, Owen et al. 2006) because the statistically significant results depended on multiple, similar responses being exhibited across repeated trials.

It has also been suggested that fMRI responses of this sort could reflect an "implicit preconscious neural response" to the key words that were used in those studies (Greenberg 2007, Nachev & Husain 2007). Although no empirical evidence exists to support this possibility, it is nevertheless important to consider its theoretical plausibility. In the volunteers studied by Boly et al. (2007) and in the patients reported by Owen et al. (2006) and Monti et al. (2010), the observed activity was not transient, but rather persisted for the full 30 seconds of each imagery task, i.e., far longer than would be expected, even given the hemodynamics of the fMRI response. In fact, these task-specific changes persisted until the volunteers and the patients were cued with another stimulus indicating that they should switch tasks. No evidence exists to show that single-word stimuli (such as "tennis," "house," or "rest") can unconsciously elicit sustained (i.e., 30 seconds) hemodynamic responses in the supplementary motor area, the parahippocampal gyrus, the posterior parietal cortex, or the lateral premotor cortex, yet considerable data exist to suggest that they cannot. For example, although it is well documented that some words can, under certain circumstances, elicit wholly automatic neural responses, such responses are typically transient and last for just a few seconds. In addition, the activation patterns observed in the studies by Boly et al. (2007), Owen et al. (2006), and Monti et al. (2010) were entirely predicted and were not in brain regions that are known to be involved in word processing, but rather in regions that are known to be involved in the two imagery tasks (also see Weiskopf et al. 2004). In short, temporally sustained fMRI responses in these regions of the brain are impossible to explain in terms of automatic responses to either single key words or to short

sentences containing those words. In fact, non-instructive sentences containing the same key words (e.g., “The man enjoyed playing tennis”) have been shown to produce no sustained activity in any of these brain regions in healthy volunteers, nor is activity seen when the words tennis and house are presented to naïve participants who have not been previously instructed to perform the imagery tasks (Owen et al. 2007). Finally, the recent evidence of Davis and associates (2007), which shows that even mildly sedated healthy volunteers cannot perform the basic semantic processes that are necessary for speech comprehension, provides additional evidence that words such as tennis and house cannot produce sustained automatic responses in distinct neural regions; producing word-specific neural responses requires, at the very least, comprehension of those words, be it conscious or unconscious.

Another approach to detecting covert awareness after brain injury is to target processes that require the willful 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 severely brain-injured patient produced a very similar pattern of activity, confirming that he could willfully adopt differential mind-sets as a function of the task conditions and could actively maintain these mind-sets across time; covert abilities that were entirely absent from his documented behavioral repertoire. As in the tennis/spatial navigation examples described above, because the external stimuli (a series of words) were identical in the two conditions, 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.

Following similar logic, Monti et al. (2012) used an entirely different type of approach to demonstrate that a patient who was unable to exhibit any signs of command following during standard behavioral testing could nevertheless demonstrate reliable and robust responses in predefined brain regions by willfully modulating his brain activity. The stimuli used were superimposed pictures of faces and houses. When healthy volunteers are requested, following a cue tone, to shift their attentional focus from a face to a house (or vice versa), a distinct shift in fMRI activity from the fusiform gyrus (the FFA) to the parahippocampal gyrus (the parahippocampal place area) is observed (or vice versa) (Monti et al. 2012). With continuous, repeated cues, this effect manifests as a time-locked alternation of activity between these two functionally distinct brain regions, despite the fact that the stimulus remains unchanged throughout. Thus, this change is driven not by the external stimulus per se but rather by the will or the intention of the participant to focus on one or the other aspect of the stimulus and is therefore a reliable indicator of conscious intent (consider, for example, that the participant is not obliged to shift attention—although it would not be in keeping with the experimental instructions, the participant is entirely free to choose not to follow those instructions). When asked to perform the same task, the activity observed in the patient closely resembled the activity observed in the healthy volunteers and, as such, provided the only conclusive evidence that he could indeed follow commands (Monti et al. 2012).

These types of approach all illustrate a paradigmatic shift away from passive (e.g., perceptual) fMRI tasks to more active (e.g., willful) 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 participants themselves. Such behavior (albeit neural behavior) provides a proxy for a motor action and is, therefore, an appropriate vehicle for reportable awareness (Zeman 2009).

EEG Studies in Nonresponsive Patients

Schnakers and associates (2008b) very elegantly extended the passive “own name” paradigm described above to include a volitional aspect whereby in half of the blocks, patients were instructed to count the number of instances of their own name, in contrast to passively listening to identical stimuli in the remaining blocks. Like healthy controls, a group of minimally conscious patients demonstrated reliably larger P3 components, linked to target detection, during the active counting task. Because the only aspect of the task that differed between the two conditions was the patient’s intention (to count or to listen), as guided by the prior instruction, it was possible to unequivocally infer that these patients could follow commands and, therefore, that they were aware. In contrast, overt (motor) forms of command following were, at best, inconsistent when the patients were tested behaviorally.

Motor imagery also produces clearly distinguishable modulation of EEG sensorimotor rhythms (Cincotti et al. 2003, Wolpaw et al. 1991) similar to those seen during motor execution, and this has been the basis of several recent attempts to detect conscious awareness after severe brain injury. For example, in one early study, Kotchoubey and colleagues (2003b) described a completely locked-in patient whose slow EEG activity differed significantly between trials when he was asked to “try” to move the left, as compared to the right, hand. In the EEG record, imagined movements (motor imagery) are evident in the form of reductions of power—or event-related desynchronizations (ERDs)—of the mu (~ 7 – 13 Hz) and/or beta (~ 13 – 30 Hz) bands over the topographically

appropriate regions of the motor cortex, for example, over the lateral premotor cortex for hand movements and over more medial premotor cortex for toe movements (Pfurtscheller & Neuper 1997). In some individuals, these ERDs may also be accompanied by event-related synchronizations (relative increases in power) over motor areas contralateral to, or surrounding, the ERD (Pfurtscheller et al. 2006, 2008). Using classification techniques, it is now possible, on the basis of these EEG responses alone, to determine with a high degree of accuracy the form of motor imagery being performed by a conscious individual (Guger et al. 2003). For example, Cruse et al. (2011) recently reported a new EEG-based classification technique in which two mental imagery responses (squeezing the right hand or squeezing the toes) were successfully decoded offline in 9 out of 12 healthy individuals, with accuracy rates varying between 60% and 91%. The same approach was then used to attempt to detect evidence of command following in the absence of any overt behavior, in a group of 16 patients who met the internationally agreed criteria for a diagnosis of vegetative state. Three of these patients (19%) were repeatedly and reliably able to generate appropriate EEG responses to the two distinct commands (“squeeze your right hand” or “squeeze your toes”), despite being behaviorally entirely unresponsive, indicating that they were aware and following the task instructions (**Figure 2**). In two cases, this was also verified with fMRI. Indeed, on the basis of such data, far broader conclusions about residual cognition can be drawn. For example, performance of this complex task makes multiple demands on many cognitive functions, including sustained attention (over 90-second blocks), response selection (between the two imagery tasks), language comprehension (of the task instructions), and working memory (to remember which task to perform across multiple trials within each block)—all aspects of top-down cognitive control that are usually associated with, and indeed could be said to characterize, normal conscious awareness (Naccache 2006).

Is it possible that appropriate patterns of activity could be elicited in these patients in the absence of awareness? Could they somehow reflect an automatic response to aspects of the task instructions, such as the words right-hand and toes, and not a conscious and overt action on the part of the patient? This is extremely unlikely for a number of reasons. First, the task instructions were delivered once at the beginning of each block of 15 tones that signaled the time to begin each imagery trial. Any automatic response to the previously presented verbal instruction would then have to abate and recur in synchrony with these tones; cues that carried no information in and of themselves about the task to be performed. Indeed, 75% of the healthy control participants tested in that study returned positive EEG outcomes when completing this motor imagery task. However, when these same individuals were instructed *not* to follow the commands—i.e., not to engage in motor imagery—not one participant returned a positive EEG outcome. Evidently, any automatic brain responses generated by listening to the instructions are not sufficient for significant task performance; rather, an act of consistently timed, volitional command following is required. In this context then, it is clear that successful performance of these EEG tasks represents a significant cognitive feat, not only for those patients who were presumed to be vegetative but also for healthy control participants. That is to say, to be deemed successful, each respondent must have consistently generated the requested mental states to command for a prolonged period of time within each trial and must have consistently done so across numerous trials. Indeed, one behaviorally vegetative patient was able to produce EEG responses that were classified with a success rate of 78%. In other words, consistently appropriate EEG responses were generated across approximately 100 trials. Conversely, when assessed behaviorally using accepted, standard clinical measures that were administered by experienced, specialist teams, none of these patients exhibited any signs of awareness, including visual fixation, visual pursuit, or localization to pain.

These results demonstrate that consistent responses to command—a reliable and universally accepted indicator that a patient is not vegetative—need not be expressed behaviorally at all but rather can be determined accurately on the basis of EEG responses.

In a follow-up study (Cruse et al. 2012), 23 minimally conscious state patients (15 with traumatic brain injury and eight with nontraumatic brain injury) completed the same motor imagery EEG task (**Figure 2**). Consistent and robust responses to command were observed in the EEG of 22% of the minimally conscious state patients (5/23). Etiology had a significant impact on the ability to successfully complete this task, with 33% of traumatic patients (5/15) returning positive EEG outcomes compared with none of the nontraumatic patients (0/8). The results suggest that the overt behavioral signs of awareness exhibited by nontraumatic minimally conscious patients appear to be an accurate reflection of their covert cognitive abilities measured using this novel EEG technique. In stark contrast, they demonstrated that one-third of a group of traumatically injured patients in the minimally conscious state possess a range of high-level cognitive faculties that are not evident from their overt behavior.

As a result of the strains of rapid acceleration and deceleration on the brain, the most common neuropathological changes following traumatic brain injury are diffuse axonal injury (Adams et al. 1982, Gennarelli et al. 1982) that predominantly affects both hemispheres, the corpus callosum, brainstem, and cerebellum in the vegetative state and minimally conscious state (Adams et al. 1999, Kinney et al. 1994, Jennett et al. 2001). On the other hand, when these conditions are caused by a nontraumatic injury, such as hypoxic-ischemic encephalopathy, a selective and widespread damage to the neocortex and thalamus is observed, possibly due to the differences in the oxygen requirements of these structures (Adams et al. 2000, Adams & Duchon 1992, Kinney et al. 1994). In the broadest sense then, what is known about the neuropathological mechanisms underlying traumatic brain injury and nontraumatic brain

injury, particularly in relation to the relative preservation of the cortex following traumatic brain injury, is reflected here in the differential degree of functional deficit observed across the two groups.

These data also reemphasize the disparity between behavioral signs of awareness and those that may be detected with functional neuroimaging. Thirty-eight percent of those eight minimally conscious state patients who were incapable of following commands with their behavior—i.e., those producing only low-level, nonreflexive behaviors such as visual pursuit—were nevertheless capable of following commands with this EEG paradigm. Indeed, 75% (3/4) of traumatically brain-injured minimally conscious state patients who could not follow commands behaviorally were capable of returning a positive EEG outcome compared with none of the nontraumatically injured minimally conscious state patients. This result adds to the significant body of evidence that an apparent inability to follow commands with external responses does not necessarily reflect the true absence of the cognitive capability to do so (Cruse et al. 2011, Monti et al. 2010, Owen et al. 2006, Schnakers et al. 2008b). Rather, a significant proportion of behaviorally nonresponsive patients retains a range of high-level cognitive capacities beyond those indicated by their behavior.

Anesthetic Studies

In a recent study (Adapa et al. 2011), fMRI was used in healthy volunteers who were asked to imagine playing a game of tennis while sedated using the same task design that has been used to detect covert consciousness in some vegetative and minimally conscious patients (Monti et al. 2010, Owen et al. 2006). During three scanning sessions, the participants were nonsedated (awake), lightly sedated, and deeply sedated and were asked to imagine playing tennis following a prompt. Task-related activity in the premotor cortex was markedly attenuated even at light levels of sedation and was completely absent when the participants were deeply sedated. Following the cessation of propofol and recovery of

awareness, robust activity was again observed in the premotor cortex following the instruction to resume the imagery tasks. This result confirms that healthy volunteers who are measurably nonaware (i.e., unconscious) are not able to generate the characteristic pattern of brain activity that is associated with imagining playing tennis, suggesting that awareness is likely to be necessary for this response to occur in patients.

COMMUNICATION BASED ON BRAIN ACTIVITY

fMRI Studies in Nonresponsive Patients

Owen & Coleman (2008b) extended the general principles discussed 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 imagining playing tennis and a “no” response by imaging moving around a house, thereby using only their brain activity to provide the answers to simple questions posed by the experimenters. This technique was further refined by Monti et al. (2010), who successfully decoded three “yes” and “no” responses from each 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 et al. 2010) (**Figure 3**). Thus, this patient was able to convey biographical information that was not known to the experimenters at the time (but was verified as factually correct), such as his father’s name and the last place that he had visited on vacation before his accident five years earlier. In contrast, and despite a reclassification to minimally conscious state following the fMRI scan, it

remained impossible to establish any form of communication with this patient at the bedside.

Of course, skeptics may argue that fMRI activity alone cannot prove that a person is consciously aware, nor able to communicate, even when a behaviorally nonresponsive patient has been able to provide factually correct answers to five biographical questions about himself using only his brain activity to do so (Monti et al. 2010). However, such skeptics would likely remain unsatisfied after 500 questions, even if 500 correct answers had been decoded. The important point is that by using spatially and temporally reliable fMRI changes as willed responses, we are simply adopting exactly the same behavioral criteria that any of us would accept as reasonable evidence that another person was conscious and aware. For example, it is difficult to imagine a situation in which someone asked another person five questions (drawn from an almost limitless pool of possible questions), received five factually correct answers, and then concluded that the subject of the interrogation was not consciously aware. Returning to a point made in the introduction, this is not to say that we can't make machines that can achieve this same feat, nor that such machines are in any sense "aware," but my argument is that for humans to accomplish this, they must necessarily be aware. (Philosophically, of course, it is possible to imagine that a person could exist who is wholly unaware yet able to respond to an infinite number of questions with factually correct answers, but in the absence of any data to suggest that such a person does or can exist, I do not consider this possibility any further.)

EEG Studies

As discussed above, Kotchoubey and colleagues (2003b) described a completely locked-in patient whose slow EEG activity differed significantly between trials in which he was asked to "try" to move the left or right hands, which in the most basic sense reflects a form of communication. Similarly, Kübler and colleagues (2005) showed that locked-in patients with ALS could learn to modulate their sensorimotor

rhythms with more than 70% accuracy, but they did not test any patients diagnosed with a disorder of consciousness (e.g., vegetative state) with this paradigm.

A method for using the P300 modulation paradigm, originally proposed by Farwell & Donchin (1988), also holds promise as an EEG-based communication device. Participants are presented with a screen displaying a matrix of letters, A to Z, and are asked to fixate on the letter that they are trying to communicate (e.g., in order to spell a word). Columns and rows in the matrix flash in a pseudorandomized order, and it is possible to deduce which letter is being attended to by identifying which column and row flashes immediately prior to an evoked P300 component. This technique has proved to be very effective for severely paralyzed and locked-in patients (Kleih et al. 2011, Nijboer et al. 2008), although because it requires visual fixation, it is likely to be of limited use in the vegetative and minimally conscious states. A possible solution to this problem was provided by Sellers & Donchin (2006), who introduced a simpler version of this general paradigm that comprised both visual and auditory versions. The participants were presented with only four visual or auditory stimuli, namely, yes, no, pass, and end. Locked-in patients with ALS could use this system to communicate (Kübler et al. 2009), although classification accuracies were lower in the auditory than in the visual domain.

Building on much of this earlier work, the success of recent EEG techniques for detecting awareness in nonresponsive patients (Cruse et al. 2011, 2012) paves the way for the development of a true brain-computer interface (Birbaumer 2006)—or simple, reliable communication devices—in this patient group. It seems likely that such devices will provide a form of external control and communication based on mappings of distinct mental states—for example, imagining right-hand movements to communicate yes and toe movements to communicate no. Indeed, the degrees of freedom provided by EEG have the potential to take this beyond the sorts of binary responses that have worked well using fMRI (Monti et al.

2010) to allow methods of communication that are far more functionally expressive, based on multiple forms of mental state classification (Farwell & Donchin 1988, Sellers & Donchin 2006, Wolpaw et al. 2002). The development of techniques for the real-time classification of these forms of mental imagery (e.g., Cruse et al. 2011, 2012) will open the door for routine two-way communication with some of these patients, ultimately allowing them to share information about their inner worlds, experiences, and needs.

IMPLICATIONS

Diagnosis

An obvious clinical consequence of the emergence of novel neuroimaging techniques that permit the identification of covert awareness and communication in the absence of any behavioral response is the possibility of improved diagnosis after severe brain injury. Unfortunately, at present, although several of the neuroimaging approaches discussed in this review hold great promise for improving diagnostic accuracy in behaviorally nonresponsive patients, the accepted assessment procedure continues to be a careful neurological exam by a trained examiner that focuses on a set of standard behavioral tests (see sidebar *Assessing Awareness Behaviorally*). 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) behavior 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 behavioral 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, because the accepted diagnostic standard is based on behavior, and no behavioral marker of awareness was missed. Likewise, the patient described by Monti et al. (2010) was clearly not vegetative because he could generate "yes" and "no" responses in real time by willfully 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. Finally, in the recent study by Cruse et al. (2011), three patients who were clinically defined as vegetative state were able to produce up to 100 responses to command that were detectable only with EEG. Similarly, in the follow-up study (Cruse et al. 2012), a significant minority of minimally conscious patients was able to generate EEG responses that were entirely inconsistent with their formal diagnoses (no evidence of consistent command following). These findings suggest an urgent need for a re-evaluation of the existing diagnostic guidelines for behaviorally nonresponsive patients (including the vegetative state and related disorders of consciousness) and for the development and formal inclusion of validated, standardized neuroimaging procedures into those guidelines.

Prognosis

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 behavioral markers before the prognostically important (for a diagnosis of permanent vegetative state) 12-month threshold was reached, 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. In an excellent review of the available literature, Di et al. (2008) considered 15 separate $H_2^{15}O$ PET and fMRI studies involving 48 published cases that were classified as absent cortical activity, typical activity (activity in low-level primary sensory cortices only), and atypical activity (activity in higher-level associative cortices). The results suggest that atypical activity patterns appear to predict recovery from vegetative state with 93% specificity and 69% sensitivity. That is to say, 9 out of 11 patients exhibiting atypical activity patterns recovered consciousness, whereas 21 out of 25 patients with typical primary cortical activity patterns and 4 out of 4 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 by Coleman et al. (2009), direct evidence of prognostically important information from the neuroimaging data was reported that was at odds with the behavioral assessment at the time of scanning. Thus, contrary to the clinical impression of a specialist team using behavioral 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 behavioral presentation at the time of the investigation, but correlated significantly with subsequent behavioral recovery, six months after the scan. In this case, the fMRI data predicted subsequent recovery in a way that a specialist behavioral assessment could not.

Recently, an effort has also been made to quantify those particular aspects of the raw EEG signal that may be associated with subsequent outcome in patients after serious brain

injury. For example, it has been observed (Babiloni et al. 2009) that occipital source power in the alpha band (8–13 Hz) of resting EEG, as calculated with low-resolution electromagnetic tomography, is correlated with recovery outcome at three-month follow-up in a group of vegetative state patients; those who made a behavioral recovery had higher resting alpha band power than those who did not make a significant recovery. The prognostic value of resting EEG has also been demonstrated by Schnakers and colleagues (2008a), who calculated the bispectral indices, a composite measure of the frequency content of the EEG, in a mixed group of vegetative state and minimally conscious state patients. The bispectral indices were positively correlated with behavioral scores of awareness at the time of testing and associated with outcome at one-year post trauma.

End-of-Life Decision-Making

The possibility of using fMRI or EEG for the detection of awareness in behaviorally non-responsive patients (Cruse et al. 2011, Owen et al. 2006) 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. At present, in most civilized jurisdictions, 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 discusses this with those closest to the patient. In England and Wales, for example, the courts require that a decision to withdraw nutrition and hydration should be referred to them before any action is taken (Roy. Coll. Phys. 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” (Roy. Coll. Phys. 1996). With the emergence of novel neuroimaging techniques that permit the identification of covert awareness in the absence of any behavioral response (Cruse et al. 2011, Owen et al. 2006), the wording of this statement acquires renewed resonance. 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 & Coleman 2008a), 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 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 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 to be 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. Given the portability, relatively low cost, and apparent reliability of new EEG-based techniques, which may allow such questions to be asked very quickly and efficiently at the bedside (e.g., Cruse et al. 2011, 2012), such procedures could soon be used by some patients to express their thoughts, control their environment, and increase their quality of life.

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 et al. (2010), no willful 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) cannot be determined. Accordingly, negative fMRI and EEG findings in patients should never be used as evidence for impaired cognitive function or lack of awareness.

CONCLUSIONS AND FUTURE DIRECTIONS

In the past few years, neuroimaging methods—most notably fMRI and EEG—have been brought to bear on one of the most complex and challenging questions in clinical medicine, that of detecting conscious awareness in patients who are entirely incapable of any physical behavior. The results have exposed an important limitation in our understanding of consciousness and how it is measured—that is, our absolute dependence on a behavioral response for determining whether another human being is conscious or not—and, as such, they have changed the way that many of us think about behavior itself. Thus, an “act” in the sense that Plum and Posner meant it in *Diagnosis of Stupor and Coma* (1983) need no longer be a physical act in the traditional sense (e.g., the blink of an eye or the squeezing of a hand) but, with the aid of modern neuroimaging methods, can now be an act that occurs entirely within the brain itself—a “brain act,” perhaps. The recent use of reproducible and robust task-dependent fMRI responses as a form of communication in patients who are assumed to be vegetative (e.g., Monti et al. 2010) represents an important milestone in this process. Thus, information was communicated using only a brain act—information that could not have been known by the experimenters at the time yet could be independently verified later (using more traditional methods of communication with the family) as being factually correct and true. More recently, the use of EEG—a more portable and cost-effective method that can be used at the bedside—to detect consciousness in patients who appeared to be entirely vegetative (Cruse et al. 2011) again reveals our overdependence on traditional forms of behavior for inferring consciousness. Thus, in one of those cases, the

patient was able to perform approximately 100 measurable responses to command that were detected and correctly classified in his EEG record, yet he remained entirely incapable of generating a single physical response despite intense and prolonged clinical examination.

Indeed, the fact that responses like this occur at all allows us to infer 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 appropriate imagery response (squeeze the hand or squeeze the toes), short-term (or working) memory is required to maintain attention following the stimulus (a simple beep) and to guide the search for the appropriate response at any given point in the task, attentional switching is required (to switch between the various mental states that code for the two imagery tasks), sustained attention is required to maintain the appropriate mental state, 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 behavior, they also confirm that the participant retains the ability to understand instructions and to carry out different mental tasks in response to those instructions, and therefore is able to exhibit willed, voluntary behavior in the absence of any overt action. On this basis, brain acts permit the identification of awareness at the single-subject level, without the need for a motor response.

Although these studies suggest that in the near future, some patients who are entirely behaviorally unresponsive may be able to routinely communicate their thoughts to those around them by simply modulating their neural activity, the use of both fMRI and EEG in this context will continue to present innumerable logistic, computational, and theoretical problems (Owen & Coleman 2007). In some ways, so-called functional near-infrared spectroscopy (fNIRS) combines the advantages of both fMRI and EEG. fNIRS exploits the penetrability of

biological tissue by light in the near-infrared spectrum (700–1,000 nm) to infer neural activity. The amount of near-infrared light that is absorbed by blood vessels depends on the concentration of oxygenated and deoxygenated hemoglobin (Villringer & Chanceb 1997). fNIRS is portable, virtually noiseless, considerably cheaper, and less susceptible to movement artefacts than fMRI and has better spatial resolution than EEG. Although the technique allows reliable measurement of hemodynamic responses only in cortical tissue close to the head surface (up to ≈ 3 cm depth), this would be perfectly acceptable (and likely to be considerably better than EEG) for monitoring the sorts of imagery-related responses that have been detected over premotor regions in recent studies (Cruse et al. 2011, 2012; Monti et al. 2010; Owen et al. 2006). Although in its infancy, some early applications have demonstrated the potential of fNIRS as an efficient brain-computer interface in nonresponsive patients. For example, Haida et al. (2000) were able to detect appropriate brain activation within the motor cortex during a motor imagery task and within language regions during a speech-related task in a completely locked-in ALS patient. Similarly, Naito et al. (2007) mapped two mental imagery tasks, calculation and singing, to “yes” and “no” responses, and were able to detect responses

with fNIRS in 40% of 17 completely locked-in patients with 74% accuracy. It remains to be seen whether this technique will prove to be effective in identifying and/or communicating with any patients who have been clinically diagnosed as being in a vegetative state.

In summary, imaging the brain’s responses using fMRI, EEG, or less mature techniques such as fNIRS has provided a truly unique role for neuroimaging in the detection of consciousness and has, to some extent, redefined the limits of what we mean by “behavior.” In several cases, conscious patients have been “found” by fMRI or EEG, and their behavior (albeit brain behavior) has allowed them to communicate with the outside world in the absence of any physical responses. Of course, just because some of these patients can answer “yes” and “no” questions by modulating their brain activity does not yet mean that we understand everything about their internal mental world. Are they depressed? Are they in pain? Do they want to live or die? We cannot presume to know the answers to these questions. But as long as a question can be answered with a “yes” or a “no” response, then recent developments in brain imaging have provided a means for them to be asked. Indeed, there is no reason why such patients could not be asked the most difficult question of all—“Are you conscious?”

SUMMARY POINTS

1. The only reliable method for detecting awareness in others is through a predicted behavioral response to an external prompt or command—in clinical contexts, this kind of response is often referred to as command following.
2. Following serious brain injury, some patients who are assumed to be entirely unaware, and therefore vegetative, may actually be aware yet simply unable to signal that fact through any recognized behavioral response.
3. Normal brain responses to various forms of passive external stimulation (e.g., faces, speech) have been widely reported in patients with disorders of consciousness, including the vegetative state. However, similar activity has been reported in anesthetized (i.e., unconscious) healthy individuals, suggesting that such responses in patients may be automatic and not indicative of covert awareness.

4. A significant recent addition to this field has been the development of fMRI and EEG paradigms that render awareness reportable in the absence of any overt behavioral response (e.g., motor or speech). These paradigms involve command following in the sense that participants must activate specific brain regions in response to commands—the tasks can be used to measure awareness because awareness is necessary for them to occur.
5. Using fMRI, 17% of patients who had been diagnosed as entirely vegetative on the basis of repeated clinical (behavioral) assessment were able to reliably modulate their brain activity to command, indicating that they were, in fact, conscious and aware.
6. Using EEG at the bedside, a similar approach has been used with comparable levels of success. Of patients diagnosed as entirely vegetative, 19% were able to indicate covert awareness by modulating their EEG responses to command. (EEG is portable and more cost-effective than fMRI.)
7. These techniques have recently been extended to demonstrate that two-way communication (“yes” and “no” questions) with entirely nonresponsive patients is achievable in a limited number of cases, paving the way for true brain-computer interfaces—or simple, reliable communication devices—in this group.
8. These findings have profound implications for clinical care, diagnosis, prognosis, and end-of-life decision-making, but they also shed light on more basic scientific questions about the nature of conscious behavior and the neural representation of our own thoughts and intentions.

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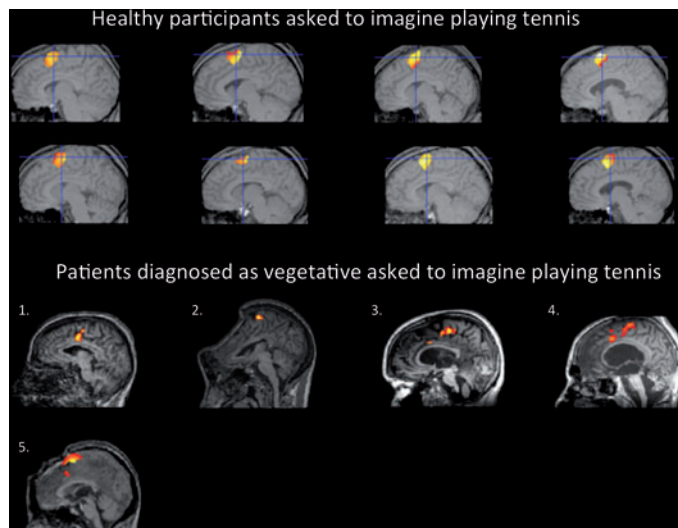


Figure 1

When eight healthy participants were asked to imagine playing tennis, significant activity was observed in the premotor cortex (*top*) in every single case, indicating that they had understood the instruction and were responding by carrying out the appropriate type of mental imagery; that is, following a command. When patients who were behaviorally entirely nonresponsive and were diagnosed as being vegetative were asked to carry out the same mental imagery task, a formally identical pattern of activity was observed in approximately 17% of cases studied. This result confirms that, in spite of an inability to respond physically, these patients can still demonstrate command following by modulating their cortical fMRI activity. Adapted from Boly et al. 2007 (healthy participants), Owen et al. 2006 (Patient 5) and Monti et al. 2010 (Patients 1–4).

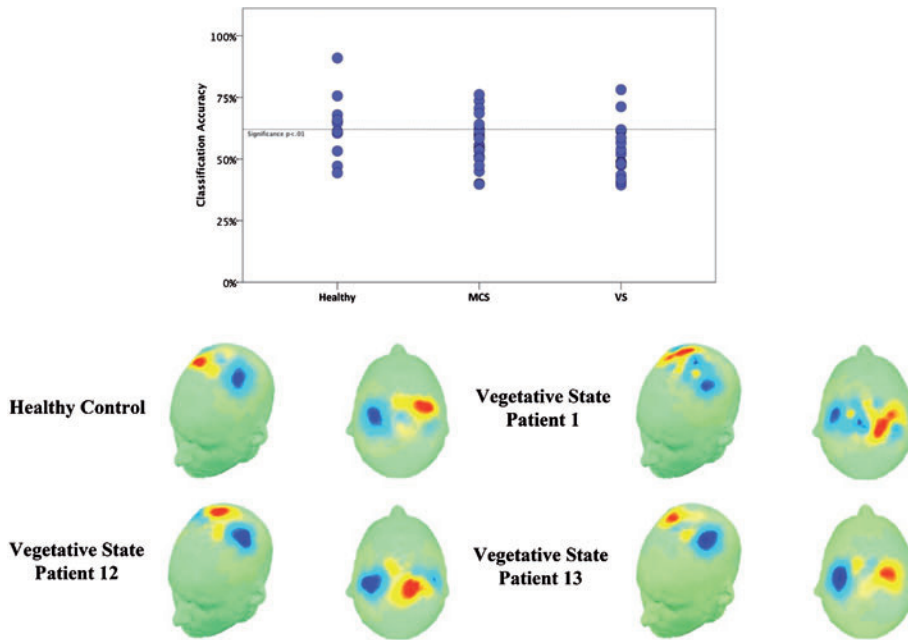


Figure 2

Three of 16 (19%) patients who had been diagnosed as vegetative were repeatedly and reliably able to generate appropriate electroencephalography (EEG) responses to two distinct commands (“squeeze your right hand” or “squeeze your toes”) despite being behaviorally entirely unresponsive. Thus, when the scalp distributions of data from a classification procedure are plotted (*bottom*), it is evident that the neurophysiological basis of the positive EEG outcome—with clear foci over the hand and toe motor areas—are formally identical when compared between a healthy control participant and the three patients (maps show the scalp distribution of the single feature—time-point x frequency-band—with the highest absolute coefficient value from one training run of the cross-validation procedure. Red colors indicate coefficient values greater than zero; blues indicate values less than zero). These data confirmed that these patients were, in fact, aware and able to follow task instructions, which, in two cases, was independently verified using fMRI. A similar procedure in a group of minimally conscious patients revealed that 22% were able to reliably and repeatedly follow commands by modulating their EEG responses (*top*). Adapted from Cruse et al. (2011, 2012).

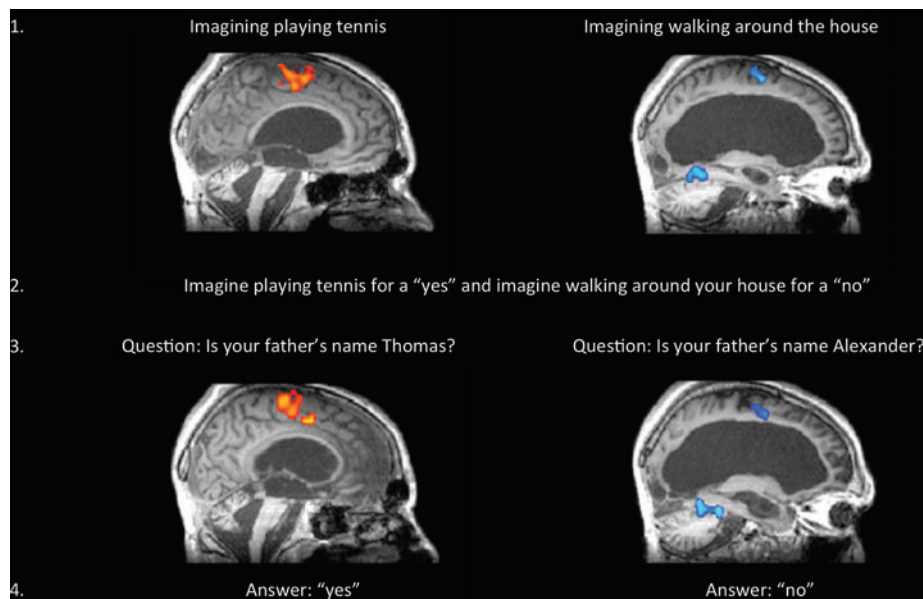


Figure 3

When 16 healthy participants were asked to imagine playing tennis to convey one response (“yes” or “no”) and to imagine moving around the rooms of their home to convey the alternative response (“yes” or “no”), their answers to three questions each were decoded with 100% accuracy (Monti et al. 2010). The same procedure was then used with a patient who had been repeatedly diagnosed as vegetative over a five-year period following a road traffic accident. The patient was first asked to imagine playing tennis and then to imagine moving around the rooms of his home in order to generate anatomical localizers in the premotor cortex and parahippocampal gyrus, respectively (1). In a subsequent series of scans (2), he was asked to imagine playing tennis to convey one response (“yes” or “no”) and to imagine moving around the rooms of his home to convey the alternative response (“yes” or “no”). When asked, “Is your father’s name Thomas?” the pattern of activity observed was almost identical to the pattern that had previously been associated with him imagining playing tennis—a “yes” response (3). When asked, “Is your father’s name Alexander?” the pattern of activity observed was almost identical to the pattern that had previously been associated with him imagining moving from room to room in his house—a “no” response (3). The patient answered five “yes” or “no” questions in a row correctly (4), confirming that he was conscious and able to recall biographical detail about his life. Adapted from Monti et al. 2010.



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