SCIENCE AND SOCIETY

Functional neuroimaging of the vegetative state

Adrian M. Owen and Martin R. Coleman

Abstract | A number of recent studies have demonstrated a role for state-of-the-art neuroimaging methods in the assessment of patients in the vegetative state and other so-called 'disorders of consciousness'. In several cases, functional MRI has been used to show that aspects of speech perception, emotional processing, language comprehension and even conscious awareness might be retained in some patients who behaviourally meet all of the criteria that define the vegetative state. This work 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), as well as for more basic scientific questions about the nature of consciousness and the neural representation of our own thoughts and intentions.

> *The limits of consciousness are hard to define satisfactorily and we can only infer the self-awareness of others by their appearance and their acts.* Plum and Posner[1]

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 progress to a condition that is 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[2]. However, the assessment of these patients is extremely difficult and relies heavily on the 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 responses to visual, auditory, tactile or noxious stimuli[3,4]. Thus, a positive diagnosis of a vegetative state is ultimately dependent on a negative finding (no signs of awareness), and is therefore inherently vulnerable to a Type II error or 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 considered adequate evidence of absence.

This logic exposes a central conundrum in the study of awareness in general and, in particular, in how awareness relates to the vegetative state. There is as yet no universally agreed definition of consciousness and, to an even geater extent, no definition of 'self-consciousness' or 'sense of self/being' (REF. 5) (BOX 1). Leaving deeper philosophical considerations aside, the only reliable method that we have for determining whether another being is conscious is by eliciting a predicted response to an external prompt or command. The response can take the form of spoken words or a non-verbal signal (which can be a movement as simple as the blink of an eye), but it is this response and only this response that allows us to infer awareness. In short, our ability to know unequivocally that another being is consciously aware is ultimately determined not by whether they are aware, but by their ability to communicate that awareness through a recognized behavioural response.

So what if the ability to speak or blink an eye or move a hand is lost, yet conscious awareness remains? In this Perspective, we explore this possibility in the context of recent studies that have suggested that functional neuroimaging might have an important part to play in the assessment of patients who are assumed to be vegetative but might retain cognitive abilities that have escaped detection using standard clinical methods.

Diagnosis and misdiagnosis

A diagnosis of vegetative state is currently made on the basis of the patient's detailed clinical history, supported by behavioural observations (BOX 2). The clinical criteria for the diagnosis are that there must be no evidence of awareness of self or environment, no response to external stimuli of a kind suggesting volition or purpose, and no evidence of language comprehension or expression. These clinical criteria are typically addressed using one of several behavioural assessment scales that were specifically developed for this patient group[6,7]. Using these techniques, the patient's spontaneous and elicited behavioural responses to sensory and cognitive stimuli are recorded over multiple sessions. The assessor must carefully determine on the basis of the patient's behaviour whether the patient is aware, and in so doing must exclude the possibility that the patient is in a minimally conscious state or is suffering from locked-in syndrome (BOX 2).

Any assessment that is based on exhibited behaviour will be prone to error for a number of reasons, however. 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, in the absence of stimulation, typically reflexive and automatic, but in certain contexts they might be the only means of communication available to a patient and might therefore reflect a volitional act. These difficulties, coupled with inadequate experience and knowledge on the part of the assessor engendered through the relative rarity of these complex conditions, contribute to an alarmingly high rate of misdiagnosis (up to 43%)[8,9].

Box 1 | **On the relationship between consciousness and awareness**

Although the vegetative state is often referred to as a 'disorder of consciousness', this term is problematic because it suggests that there is disruption of an underlying, well-understood and clearly defined system known as 'consciousness'. Consciousness, however, is not well understood and remains one of the most challenging areas of neuroscience[5]. When referring to patients such as those who are in the vegetative state, consciousness is often separated into two basic components: arousal (or 'wakefulness') and awareness[1]. Accordingly, vegetative patients are thought to lack awareness (of self and environment) but have maintained arousal (such as eye opening and sleep–wake cycles). Separating consciousness in this way is helpful, but it inevitably provokes further questions, such as what constitutes awareness (if indeed it is a subcomponent of consciousness) and what level of awareness is necessary for a patient to be described as conscious? We 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 (be it improvement or deterioration) is evolving slowly. In this Perspective, we adopt the view of Koch[49], who suggests that the distinction between awareness and consciousness is largely one of social convention, and that in fact there is no clear difference between them. Thus, we use 'consciousness', 'awareness' and the commonly used term 'conscious awareness' interchangeably.

A role for functional neuroimaging

Functional neuroimaging studies of patients in the vegetative state evolved from earlier work that used resting cerebral blood flow and glucose metabolism to report reductions in metabolic activity of up to 50% in this patient group[10–12]. In some of these cases, isolated 'islands' of metabolism were identified in circumscribed regions of the cortex, suggesting the potential for cognitive processing in a subset of patients[12]. Unlike resting-state metabolic measures, so-called 'activation studies' using $H_2{}^{15}O$ positron emission tomography (PET) can be used to link changes in regional cerebral blood flow to specific cognitive processes, without the need for any overt response (such as a motor action or a verbal answer) on the part of the patient[13]. In the first of such studies, regional cerebral blood flow in a post-traumatic patient who had been diagnosed as being in the vegetative state was measured while the patient's mother read him a story[14]. Compared with the effects of 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. In another patient who had been diagnosed as being in the vegetative state[15], PET was used to study covert visual processing in response to familiar faces. When the patient was presented with pictures of the faces of their family and close friends, robust activity was observed in the right fusiform gyrus — the so-called human 'face area' (or FFA). In both cases, the brain activation was observed in the absence of any behavioural responses to the external sensory stimulation.

'Normal' brain activity in response to external stimulation, however, has generally been the exception rather than the rule in studies of vegetative patients. For example, in one study of fifteen patients, high-intensity noxious electrical stimulation activated the midbrain, the contralateral thalamus and the primary somatosensory cortex in every patient[16]. However, unlike control subjects, the patients did not show the activation in the secondary somatosensory, insular, posterior parietal or anterior cingulate cortices that would be consistent with higher-level cognitive processing.

$H_2{}^{15}O$ PET studies involve radiation, which might preclude essential longitudinal or follow-up studies in many patients or even a comprehensive examination of multiple cognitive processes in any one session. The power of PET studies to detect statistically significant responses is also low, and group studies are often needed to satisfy standard statistical criteria[13]. Given the heterogeneous nature of the vegetative state and the clinical need to define each individual in terms of their diagnosis, their residual functions and their potential for recovery, such limitations are of paramount importance in the evaluation of these patients.

A significant development in this rapidly evolving field has been the relative shift of emphasis from PET activation studies using $H_2{}^{15}O$ methodology to functional MRI (fMRI) studies. Not only is MRI more widely available than PET, it also offers increased statistical power and improved spatial and

Box 2 | **The vegetative state: differential diagnosis**

The term 'disorders of consciousness' is typically used to refer to three conditions: coma, vegetative state and minimally conscious state[1,3,4,50]. These conditions arise as a result of either traumatic (for example, a blow to the head) or non-traumatic (for example, stroke) brain injury and can include damage to areas of the brainstem that mediate wakefulness and/or to corticocortical axonal connections that mediate cognitive function and awareness. Although general patterns of pathology have been linked to these conditions[51], they are exclusively defined according to the behaviours that are exhibited by the patient, as the pathology is extremely heterogeneous (see table). Coma describes an acute condition that typically lasts 2–4 weeks after brain injury. Using the terminology described in BOX 1, comatose patients show no evidence of arousal or awareness. By contrast, patients in the vegetative state exhibit evidence of arousal (such as eye opening) but no evidence of awareness. Finally, patients in the minimally conscious state retain both dimensions of consciousness. However, by definition, evidence of awareness is inconsistent. The locked-in syndrome is not a disorder of consciousness, but it is critically important in the differential diagnosis. Patients with locked-in syndrome are awake and fully conscious but have no means of producing speech or limb or facial movements[1]. 'Brain death' or, more accurately, 'brainstem death' is a clinical term that refers to a complete and irreversible loss of brainstem function[52] (leading to death). 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 REF. 53).

Diagnosis	Arousal/wakefulness	Awareness	Communication
Coma	Do not open eyes No sleep–wake pattern	No evidence	None
Vegetative state	Open eyes Sleep–wake pattern	No evidence	None
Minimally conscious state	Open eyes Sleep–wake pattern	Inconsistent but reproducible evidence	Ranges from none to inconsistent, but reproducible
Locked-in syndrome	Open eyes Sleep–wake pattern	Fully aware	Consistent, using vertical eye movement

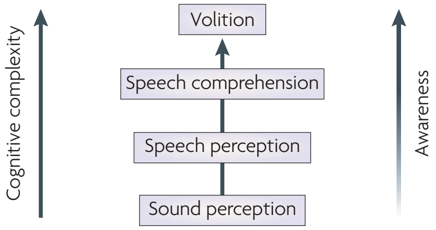

Figure 1 | **A proposed hierarchical approach to the use of fMRI to assess residual cognitive function in patients in the vegetative state.** 'Normal' activation at each level confirms that all lower levels of cognition must also be intact (that is, it is not possible to comprehend speech unless it can be perceived). The point at which awareness emerges on this hierarchical structure remains unclear, although recent work in anaesthetized volunteers suggests that the neural correlates of high-level speech comprehension do not occur in the absence of awareness[35] (see BOX 3).

temporal resolution and does not involve radiation[13]. However, the use of fMRI in this context is not without its difficulties — in particular, the design of paradigms that allow the unambiguous interpretation of positive results (when they occur) in behaviourally unresponsive patients is extremely complex. Recently, Di *et al.*[17] used event-related fMRI to measure brain activation in seven patients who had been diagnosed as being in the vegetative state and four who had been diagnosed as being in a minimally conscious state, while the patients heard their own name being spoken by a familiar voice. Two of the patients who were diagnosed as being in the vegetative state exhibited no significant activity at all, three exhibited activation in primary auditory areas, and the remaining two, as well as the four minimally conscious patients, exhibited activity in 'higher-order' associative temporal lobe areas. Although this result is encouraging (particularly because the two vegetative patients who showed the most widespread activation subsequently improved to the minimally conscious state in the following months), it lacks cognitive specificity; that is, responses to the patient's own name being spoken by a familiar voice were compared only with responses to the attenuated noise of the MRI scanner. Therefore, the activation that was observed might have reflected a specific response to each patient's own name, but equally it might have reflected a low-level orienting response to speech in general, an emotional response to the speaker (see REF. 18) or any one of a number of possible cognitive processes relating to the imperfectly matched auditory stimuli. As a result, the interpretation hinges on a reverse inference — a common practice in neuroimaging by which the engagement of a given cognitive process is inferred solely on the basis of the observed activation in a particular brain region[19,20].

We have recently argued that fMRI studies in vegetative patients should be conducted hierarchically[21–23], beginning with the simplest form of processing in a particular domain and then progressing sequentially through more complex cognitive functions. In the auditory domain, such tasks would increase in complexity systematically from basic acoustic processing of non-speech sounds to more complex aspects of language comprehension and semantics (FIG. 1). At the highest level, responses to sentences containing semantically ambiguous words (for example, "The creak/creek came from a beam in the ceiling/sealing.") might be compared with responses to sentences containing no ambiguous words (for example, "Her secrets were written in her diary."), in order to reveal brain activity associated with spoken-language comprehension[24].

A recent study explored the utility of this approach in the assessment of the vegetative and minimally conscious states[25]. In this study, residual language function in a group of seven patients who had been diagnosed as being in the vegetative state and five patients who had been diagnosed as minimally conscious was graded according to the patients' brain activation on this hierarchical series of paradigms. Three of the vegetative patients and two of the minimally conscious patients demonstrated some evidence of preserved speech processing (when activity in response to all sentences was compared with activity in response to signal-correlated white noise) (FIG. 2), whereas four patients showed no significant activation at all, even when responses to sound were compared with responses to silence. Most strikingly, two of the vegetative patients showed a significant response in the semantic ambiguity test, consistent with high-level comprehension of the semantic aspects of speech. On this basis, we suggest that such a hierarchy of cognitive tasks provides the most valid mechanism for defining the depth and breadth of preserved cognitive function in severely brain-damaged patients in altered states of consciousness.

fMRI as a behavioural response

Given that the internationally agreed diagnostic criteria for the vegetative state revolve around the concept of (a lack of) evidence of awareness, a key question regarding the results of the functional neuroimaging studies described above is whether the presence of 'normal' brain activation in patients who meet the behavioural criteria for the vegetative state indicates a level of consciousness, perhaps even a level similar to that which exists in healthy volunteers when they perform the same tasks. If so, can functional neuroimaging data ever be used as a form of 'behavioural response' — that is, to replace speech or a motor act in patients for whom such forms of behavioural expression are unavailable?

Several recent studies using fMRI suggest that this is already the case. For example, Haynes *et al.*[26] asked healthy volunteers to freely decide which of two tasks to perform (to add or subtract two numbers), and to covertly hold onto that decision during a delay. After the delay, the volunteers performed the chosen task and the result indicated which task they had intended to do (and eventually executed). A classifier was trained that could recognize the characteristic fMRI signatures that were associated with the two mental states,

Glossary

Classifier
A mathematical algorithm used to categorize data into one of a number of groups or classes. Where imaging data is concerned, a classifier is often used to identify activation patterns and assign these to particular 'mental states'.

Coma
An acute state of unconsciousness immediately after a brain injury, during which the patient exhibits no evidence of arousal or awareness.

Event-related fMRI
A technique that measures the brain's haemodynamic response to events (for example, stimuli) occurring at specific moments in time.

Locked-in syndrome
A condition in which an individual is fully conscious but unable to move or speak due to quadriplegia and anarthria.

Masked information
Stimuli that are presented in such a way that they are not consciously perceived.

Minimally conscious state
A condition in which an individual demonstrates wakefulness and inconsistent but reproducible evidence of awareness of self or environment.

PET activation studies
Studies that use radioactive tracers to measure blood flow or metabolism in the brain in response to a particular stimulus or task.

Vegetative state
A condition of wakefulness without awareness. An individual in the vegetative state might open their eyes and show sleep–wake cycles, but shows no purposeful response to stimulation.

and in 80% of trials it was able to decode from activity in the medial and lateral regions of the prefrontal cortex which of the two tasks the volunteers were intending to perform. The principle used was that certain types of thought are associated with a unique brain-activation pattern that can be used as a signature for that specific type of thought. If a classifier can recognize these characteristic signatures, a volunteer's thoughts can be ascertained (within the constraints of the experimental design) using their brain activity alone. Another recent study showed that fMRI can even be used as a 'brain–computer interface' (BCI) that allows real-time communication of thoughts[27]: healthy volunteers learned to regulate the fMRI signal in a particular brain area using their own fMRI signal as feedback.

Such feats of rudimentary 'mind-reading', involving reproducible and robust task-dependent fMRI responses to command without the need for any practise or training, suggest a novel method by which both healthy participants and patients might be able to communicate their thoughts to those around them simply by modulating their own neural activity.

Detecting awareness using fMRI

We recently adopted a similar principle to develop a method for detecting awareness in patients for whom no overt behavioural response is possible[28,29]. The technique makes use of the general observation that imagining performing a particular task generates a pattern of brain activity that is similar, although often less pronounced, to that which is generated when the activity is actually performed[30]. For example, imagining moving or squeezing one's hands will generate activity in the motor and premotor cortices[29], whereas imagining navigating from one location to another will activate the same regions of the parahippocampal gyrus and posterior parietal cortex that have been widely implicated in map reading and other so-called spatial-navigation tasks[31,32]. In one recent study[29], we asked 34 volunteers 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 (SMA) in every one of the participants that was scanned. By contrast, imagining moving from room to room in a house activated the parahippocampal place area (PPA), the posterior parietal lobe and the lateral premotor cortices — all regions that have been shown to contribute to imaginary or real spatial navigation[29] (FIG. 3).

The robustness and reliability of these fMRI responses across individuals demonstrates that activity in these regions can be used as a neural proxy for behaviour, confirming that the volunteer retains the ability to understand instructions and carry out different mental tasks in response to those instructions and, therefore, that they can exhibit willed, voluntary behaviour in the absence of any overt action. On this basis, we argued, they permit the identification of volitional brain activity at the single-subject level, without the need for a motor response[28,33].

We recently used this approach to demonstrate that a young woman who fulfilled all of the internationally agreed criteria for the vegetative state was, in fact, consciously aware and able to make responses using her brain activity[28,33]. Before 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 SMA[28], and this activity was indistinguishable from that which was observed in the healthy volunteers scanned by Boly *et al.*[29] (FIG. 4). 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[28]. Again, this activity was indistinguishable from that which was observed in healthy volunteers[29] (FIG. 4). We concluded that, despite the fact that she fulfilled all of the clinical criteria for a diagnosis of vegetative state, the patient retained the ability to understand spoken commands and respond to them through her brain activity, confirming beyond any doubt that she was consciously aware of herself and her surroundings.

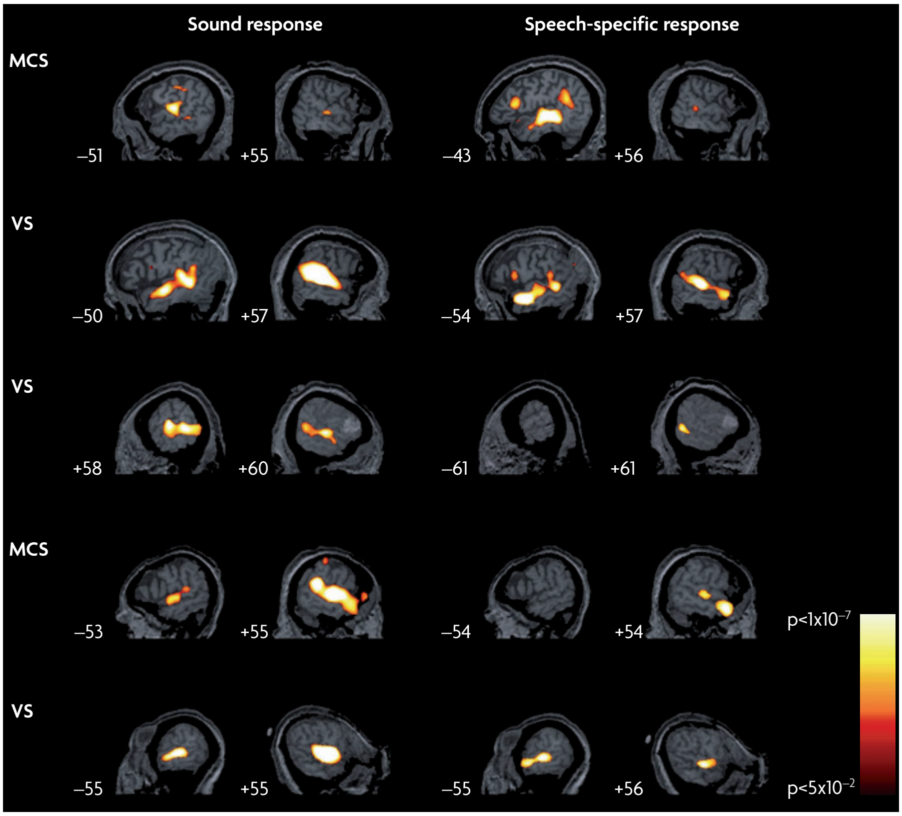

Figure 2 | **Residual language function in patients diagnosed as either vegetative or minimally conscious.** Three of seven patients who had been diagnosed as being in the vegetative state (VS) and two of five patients who had been diagnosed as being in the minimally conscious state (MCS) showed normal responses to both sounds and speech (compared with responses to non-speech sound). Importantly, although these two sub-groups clearly differed behaviourally (as evidenced by their different clinical diagnoses), neuroimaging findings were indistinguishable. Numbers represent the x-value of MNI co-ordinates. Figure reproduced, with permission, from REF. 25 © (2007) Oxford University Press.

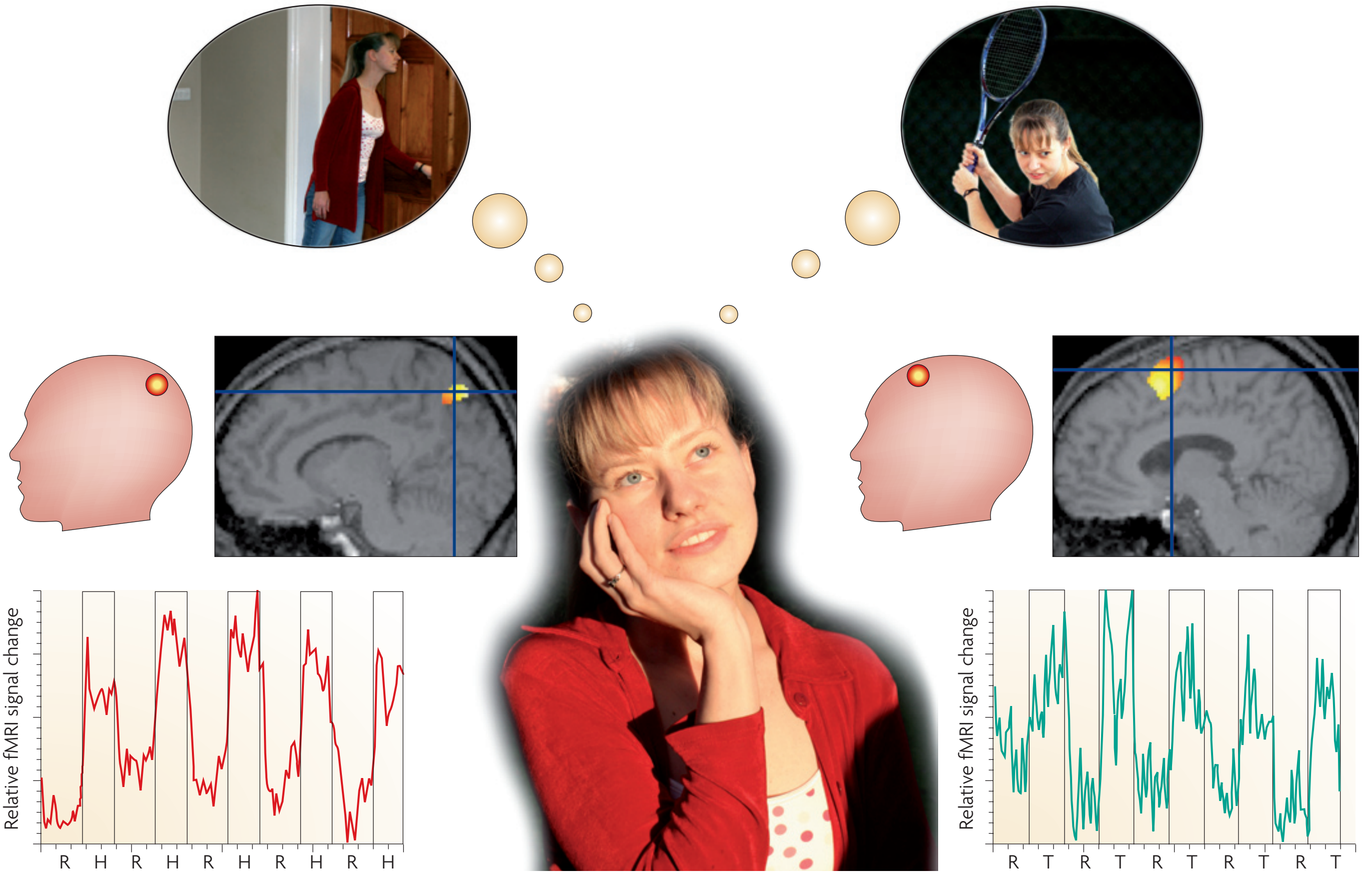

Figure 3 | **Changes in brain activity when one imagines performing a task.** Imagining performing a task produces changes in brain activity that are similar, although often less pronounced, to changes that occur when one actually performs that task. The left-hand side of the figure shows how imagining moving from room to room in a house activates the posterior parietal cortex: this activity appears as a bright blob towards the back of the brain in a functional MRI (fMRI) scan. (The parahippocampal gyrus and lateral premotor cortex are also activated, but this activation is not shown.) The right-hand side of the figure shows how imagining playing tennis activates the supplementary motor area (SMA). When volunteers are instructed to alternate between imagining moving around their house (H) and resting (R) every 30 seconds (left-hand graph), a clearly sustained and alternating time-course of brain activity is observed (in this case in the parietal lobe). A similar effect is observed in the SMA when volunteers are instructed to alternate between imagining playing tennis (T) and resting (R) every 30 seconds (right-hand graph).

Relating brain responses to awareness

Does being able to imagine playing tennis really mean that you are consciously aware? Put another way, could the same activation pattern have been produced automatically, in the absence of awareness? Many types of stimuli, including faces, speech and pain, elicit relatively 'automatic' responses from the brain; that is, the response occurs without the need for active intervention on the part of the participant (for example, you cannot 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 and the effects of priming[34] to studies of learning and speech perception during anaesthesia[35,36], 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 might occur without conscious awareness[37]. By the same argument, 'normal' neural responses in patients who have been diagnosed as vegetative do not necessarily indicate that the patients have any conscious experience associated with processing these same types of stimuli. As an illustration of this concept, Davis *et al.*[35] recently used fMRI in sedated healthy volunteers who were exposed to the same speech stimuli that have elicited normal patterns of brain activity in vegetative patients[25]. The blood-oxygen-level-dependent (BOLD) response to short sentences (compared with the response to signal-correlated noise) when these volunteers were heavily sedated was indistinguishable from the response when they were fully awake (BOX 3). Similarly, it is possible that vegetative patients might retain discreet islands of subconscious cognitive function that exist in the absence of awareness.

On the other hand, the fact that automatic brain responses can occur to a variety of external stimuli does not necessarily mean that all brain responses that are observed in any given situation have occurred automatically. Indeed, in the study by Weiskopf *et al.*[27] described above, it is possible that the fMRI signal change observed was automatic (that is, was not under conscious control). However, this seems highly unlikely because the volunteers presumably reported that they were attempting to guide the signal, and the end result (the signal change) matched their own expectations as well as those of the experimenters. But what if the volunteers had not been asked about their own experiences

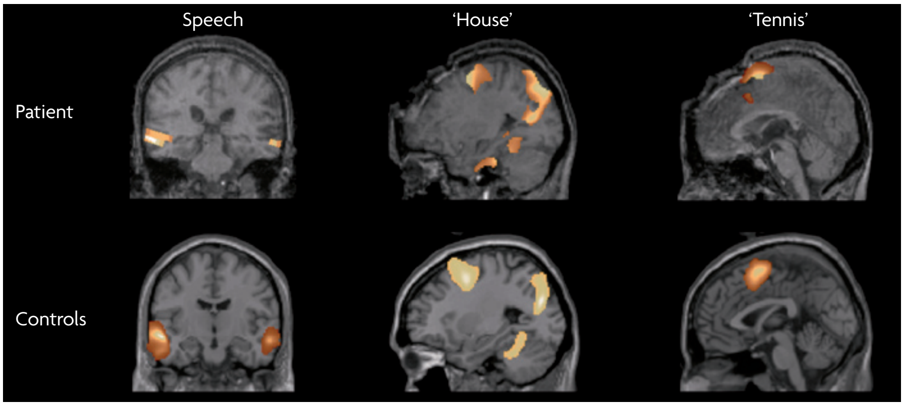

Figure 4 | **Conscious responses to stimuli in a patient who fulfilled all the clinical criteria defining the vegetative state.** The left-hand images show the response of the superior and middle temporal gyri to hearing sentences versus hearing signal-correlated noise in a patient who fulfilled all of the internationally agreed criteria for the vegetative state and in a group of healthy volunteers. The images in the middle column show how similar sustained activity was observed in the parahippocampal gyrus, the posterior parietal lobe and the lateral premotor cortex of the patient and the controls when they were instructed to imagine moving around a house. Activity in the supplementary motor area was observed when the patient and the volunteers were instructed to imagine playing tennis (right-hand images). Images reproduced, with permission, from REF. 28 © (2006) American Association for the Advancement of Science.

after the event? Would we be less convinced that it was their conscious selves that were voluntarily and wilfully modulating their own brain activity to generate the expected response in the SMA and PPA? When an actual neural outcome matches the expected outcome so perfectly, do we really need the volunteer to provide a verbal report to verify what we think we have seen?

It has been suggested that the activation that we observed in our patient when we asked her to perform mental imagery tasks in the fMRI scanner could have reflected an "implicit preconscious neural response" (REFS 38,39). Such an explanation would require empirical evidence, first, that the word 'tennis' can produce a statistically significant change in activity in the SMA of a single individual who is not consciously aware; second, that the word 'house' can produce a statistically significant change in activity in anatomically different regions of the brain, including the parietal lobe and the parahippocampal cortices, in the same unconscious individual; and, third, that in both cases these responses are sustained for up to 30 seconds and then stop when the (unconscious) participant is presented with another word (such as 'rest'). We know of no data that support the inference that such stimuli elicit unconscious, sustained haemodynamic responses in these anatomically specific regions of the brain, yet there is a considerable amount of data that suggest that they would not. 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 the volunteers studied by Boly *et al.*[29] and in the patient reported by Owen *et al.*[28], the observed activity was not transient, but persisted for the full 30 seconds of each imagery task — far longer than would be expected if the response was automatic, even given the haemodynamics of the fMRI response. In fact, these task-specific changes persisted until the volunteers and the patient were cued with another stimulus indicating that they should switch tasks. In addition, the activation patterns that were observed in the volunteers and in the patient were entirely predicted and were located 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 that the participants were asked to carry out before the scanning session (see also REF. 27). 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 short sentences containing these words. In fact, non-instructive sentences containing the same key words (for example, "The man enjoyed playing tennis.") produce no sustained activity in any of these brain regions in healthy volunteers[33]. Similarly, when the words 'tennis' and 'house' are presented to uninstructed participants, no sustained activity is observed in either the SMA or the PPA.

Finally, the recent evidence of Davis and colleagues[35] showing 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' are unlikely to produce 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 (BOX 3).

Clinical implications

The results of our study[28] were widely discussed in both the academic literature and the popular press[40–43]. In particular, the implications for diagnosis, prevalence and prognosis were discussed, sparking further debate in the emerging field of neuroethics. Some commentators suggested that this case might be unique and discussed the possibility of misdiagnosis[40,44]. Here we consider these complex issues in the context of the available data.

Diagnosis. The first question is whether the patient really did fulfil the behavioural criteria for the vegetative state at the time of the scan. A widely reported audit of vegetative patients admitted for review to the Royal Hospital for Neurodisability in London found that 43% of those admitted with a diagnosis of vegetative state were in fact misdiagnosed[8]. At the time of her scan, the patient we described[28] showed behavioural signs that were entirely consistent with the accepted guidelines defining the vegetative state and that were observed on multiple assessments over a prolonged period by an experienced multidisciplinary team.

Although the diagnosis at the time of scanning[28] was entirely uncontroversial, it was suggested subsequently that if the patient had been evaluated in the United States rather than in the UK then her diagnosis would have been minimally conscious state rather than vegetative state[44]. Although there are some differences between the US and UK criteria, our patient would have been diagnosed as being in the vegetative state according to either countries' guidelines. Visual fixation is of particular importance in this regard: in the United States, evidence of reproducible and sustained (typically for more than 2 seconds) visual fixation is considered to be one of the crucial early markers of emergence to a minimally conscious state. At the time of scanning, our patient did not demonstrate any reproducible fixation or any evidence of visual pursuit.

Box 3 | **Using anaesthesia to study brain responses at different levels of awareness**

An alternative approach to examining whether 'normal' patterns of brain activity that arise in response to external stimulation require awareness is to use an anaesthetic agent combined with functional MRI (fMRI) in healthy volunteers. Davis and colleagues[35] recently used such an approach to study the effects of propofol on the brain activity of healthy volunteers, using a number of language tasks that were identical to some of those that revealed 'normal' patterns of activity in patients in the vegetative state[25]. Volunteers were scanned while they listened to sentences that contained ambiguous words, matched sentences without ambiguous words, and signal-correlated noise. During three scanning sessions, the participants were sequentially not sedated (awake), lightly sedated (they exhibited a slowed response to conversation) and deeply sedated (they exhibited no conversational response, but were rousable by loud command). Equivalent temporal lobe responses to sentences (compared with responses to signal-correlated noise) were observed, bilaterally, at all three levels of sedation, implying that a 'normal' brain response to speech sounds is not a reliable correlate of awareness. This result suggests that caution needs to be exercised when interpreting normal responses to speech in patients who have been 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.*[35] examined the effects of anaesthesia on ambiguous sentences, the frontal lobe and posterior temporal lobe activity that occurs in the awake individual (and that 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[22] of neural activity might be consciously aware. However, such conclusions unfortunately remain 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.

Paradoxically, therefore, this patient's behaviour was consistent with a diagnosis of vegetative state, which effectively depends on an absence of evidence of awareness or purposeful response, yet her brain-imaging data were equally consistent with the alternative hypothesis — that she was entirely aware during the scanning procedure. What, then, was she? Clearly the clinical diagnosis of vegetative state based on behavioural assessment was inaccurate in the sense that it did not accurately reflect her internal state of awareness. On the other hand, she was not misdiagnosed in the sense that no behavioural marker of awareness was missed. It has been suggested that the term 'non-behavioural minimally conscious state' should be adopted to describe such cases[45,46]. However, a 'non-behavioural fully conscious state' is equally plausible.

Prevalence. A second major question is whether the patient we described[28] is a unique case or whether it is likely that there are other apparently vegetative patients with non-behavioural signs of awareness. The early evidence suggests that this patient is not unique, but that the prevalence of awareness in patients with no behavioural markers is likely to be rare. Within 6 months of our publication[28], we found comparable signs of awareness in a 46-year old man who had sustained a traumatic brain injury following an assault. When this man was assessed within 6 months of sustaining his injury using recognized behavioural assessments over repeated sessions, he showed no behavioural signs of sustained, reproducible or purposeful response to sensory or cognitive stimulation. Nevertheless, when he was asked to imagine playing football he demonstrated clear SMA activation that was consistent with that of healthy volunteers performing the same task. However, this second case is the only other example of awareness that we have encountered among the 17 vegetative patients that have now been scanned using this paradigm.

Prognosis. The third question concerns the implications that these findings might have for prognosis. Both of the patients described above were assessed within 6 months of sustaining their injury and, therefore, before critical time thresholds relating to the probability of further recovery had been reached. This early period after a traumatic brain injury is widely recognized as the time during which the greatest change occurs in this patient group, with up to 20% of patients subsequently recovering consciousness and 5% recovering some level of social independence[3]. For this reason, international guidelines suggest that a diagnosis of permanent vegetative state should not be made in cases of traumatic brain injury until 12 months post-injury[3,4]. Although neither of the two patients met the criteria for permanent vegetative state at the time of scanning, the discovery of signs of awareness at any stage is likely to have important implications for prognosis in this patient group. Non-traumatic brain injuries can be declared permanent earlier — at 6 months post-injury in the UK and three months post-injury in the United States — reflecting the poorer prognosis in this group[3,4]. For these reasons, comparisons between these patients and other notable cases of vegetative state in the UK (for example, Tony Bland) and the United States (for example, Terry Schiavo) are inappropriate. Both Tony Bland and Terri Schiavo were the victims of non-traumatic brain damage and fulfilled the criteria for permanent vegetative state when legal proceedings concerning the withdrawal of nutrition and hydration were finally enacted (Supplementary information S1 (Box)).

The question remains as to whether our two patients were beginning to emerge from a vegetative state to a minimally conscious state at the time of the scan and at a stage where their awareness was detectable through functional imaging but not through any behavioural observation. In fact, both of these patients subsequently progressed to demonstrate diagnostically relevant behavioural markers before the prognostic 12-month threshold was reached, suggesting again that early evidence of awareness acquired with functional neuroimaging might have important prognostic value.

Judicial implications

The possibility of using fMRI for the detection of awareness in the vegetative state raises a number of issues for legal decision-making relating to the prolongation, or otherwise, of life after severe brain injury. According to the Royal College of Physicians[4], "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". At present, decisions concerning life-sustaining intervention (nutrition and hydration) are made only once a diagnosis of permanent vegetative state has been made. Thus, in both of the cases described above, the scans that revealed awareness were acquired before the time at which this decision-making process is legally permitted to begin. In cases in which the critical threshold for a diagnosis of permanent vegetative state has passed, the medical team formally review the evidence and discuss the patient's premorbid wishes with those closest to the patient. In England and Wales, the courts require that a decision to withdraw nutrition and hydration should be referred to them before any action

Box 4 | Treatment options for disorders of consciousness

At present there is no empirically proven intervention to facilitate recovery in the vegetative state and related disorders of consciousness. The favoured approach is to create a stable clinical environment for natural recovery to take place. The greatest difficulty preventing the development of treatment options is the extent and heterogeneity of the pathology that underlies these conditions. It is increasingly accepted, therefore, that novel treatments designed for the individual or for a small group of carefully screened patients will be necessary. One such approach is deep brain stimulation (DBS), which uses stereotactically placed electrodes to deliver electrical stimulation to the thalamus. Developed initially in Japan[54] and France[55], the technique has recently been used by Schiff and colleagues[45] with startling results. Electrical stimulation, delivered through electrodes implanted bilaterally into the central thalamus, was found to produce increased periods of arousal and responsiveness to command in a 38-year old male who had remained in a minimally conscious state for six and a half years following injury. The changes correlated closely with the commencement of DBS and could not be attributed to gradual recovery over time.

What distinguished the efforts of Schiff and colleagues from those of earlier investigators[56] was that they limited their inclusion criteria to patients who were in a minimally conscious state and beyond the period during which spontaneous recovery is recognized to occur (typically the first 12 months post ictus). For DBS to have utility, it is thought that there must be intact but under-activated integrated cortical networks. Indeed, those patients who responded in the earlier studies[56] were probably in the course of natural recovery (DBS was commenced within 3–6 months of brain injury) or in a minimally conscious state when DBS was commenced. It is now widely anticipated that brain imaging will facilitate patient selection and the assessment of such novel interventions, whether they are mechanical, surgical or pharmacological. Indeed, Schiff and colleagues[45] used fMRI before DBS to identify preserved language networks in their patient.

is taken[4]; this is not the case in the United States or in many other countries, where such decisions are often made between doctors and the patient's family.

Whether fMRI will ever be used in this context remains to be seen. Certainly, if evidence for awareness were to be found in a patient who had progressed beyond the threshold for a diagnosis of permanent vegetative state, this fact would surely have profound implications for this decision-making process. On the other hand, neuroimaging data would need to be treated cautiously where negative findings were found. 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 might fall asleep during the scan or might not have properly heard or understood the task instructions. Accordingly, negative fMRI results in vegetative patients do not necessarily imply impaired cognitive function or lack of awareness, and such findings should be interpreted with caution.

Conclusions

In the past two decades, functional neuroimaging has become the technique of choice for neuropsychologists, cognitive neuroscientists and many others in the wider neuroscientific community with an interest in the relationship between the brain and behaviour. Until recently, these new methods of investigation have primarily been used as a correlational tool to 'map' the cerebral changes that are associated with a particular cognitive process or function, be it an action, a reaction (for example, to some kind of external stimulation) or a thought. Recent advances in imaging technology, however, and in particular in the ability of fMRI to detect reliable neural responses in individual participants in real-time, allow the identification of covert, but willed, actions or intentions based solely on the pattern of activity that is observed in the brain. The recent case of a patient who was diagnosed as being in the vegetative state provides a clear example of such an application[28]. The fact that she was consciously aware was evident only by examination of her time-locked and sustained fMRI responses following instructions to perform specific mental tasks in the absence of any overt action. On this basis it was possible to infer that not only was she thinking, she was in fact thinking about a particular activity (within the constraints of the tasks that were given to her) at a given point in time.

Although there are currently insufficient population data to warrant fMRI investigation being introduced as standard, evidence to support its use in diagnosis and prognostic assessment is being published every year[47]. The prevailing view is not that brain imaging should replace behavioural assessments, but rather that it should be used, wherever possible, to acquire further information about the patient. In doing so, one can reasonably expect that the current rate of misdiagnosis will fall. Patients will be examined with all available tools and will thus be given the greatest opportunity to respond. Likewise, care teams will have the best possible information for planning and monitoring interventions to facilitate recovery (BOX 4). Although behavioural markers and brain imaging will undoubtedly reveal inconsistencies, it is these inconsistencies that will ultimately improve the accuracy of diagnosis in this patient group.

Using fMRI in this manner paves the way for new and innovative applications of functional neuroimaging, both in basic neuroscience and in clinical practice. For example, the presence of reproducible and robust task-dependent fMRI responses to command without the need for any practise or training[29,48] suggests a novel method by which both healthy participants and patients might be able to communicate their thoughts to those around them simply by modulating their own neural activity. The use of functional neuroimaging in this context will undoubtedly continue to present innumerable logistic and theoretical problems. However, its clinical and scientific implications are so major that such efforts are clearly justified.

Adrian M. Owen is at the Medical Research Council Cognition and Brain Sciences Unit, 15 Chaucer Road, Cambridge, CB2 7EF, UK.

Martin R. Coleman is at the Cambridge Impaired Consciousness Research Group, Wolfson Brain Imaging Centre, BOX 65, Addenbrooke's Hospital, Cambridge, CB2 0QQ, UK.

e-mails: adrian.owen@mrc-cbu.cam.ac.uk; mrc30@cam.ac.uk

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FURTHER INFORMATION

Adrian M. Owen's homepage: http://www.mrc-cbu.cam.ac.uk/~adrian

Cambridge Impaired Consciousness Research Group homepage: http://www.coma-science.com

SUPPLEMENTARY INFORMATION

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