SCIENCE AND SOCIETY

Detecting awareness after severe brain injury

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Abstract | Recent developments in functional neuroimaging have provided a number of new tools for assessing patients who clinically appear to be in a vegetative state. These techniques have been able to reveal awareness and even allow rudimentary communication in some patients who remain entirely behaviourally non-responsive. The implications of these results extend well beyond the immediate clinical and scientific findings to influencing legal proceedings, raising new ethical questions about the withdrawal of nutrition and hydration and providing new options for patients and families in that decision-making process. The findings have also motivated significant public discourse about the role of neuroscience research in society.

The definition and assessment of consciousness is still one of the most challenging areas of contemporary neuroscience. Empirically, consciousness is often separated into two components: wakefulness (also known as 'arousal', referring to the level of consciousness) and awareness (the contents of consciousness)[1]. Wakefulness is a state in which the eyes are open and in which, typically, there is a degree of motor arousal, whereas awareness is accompanied by the ability to have (and the act of having) an experience of some kind[2]. Wakefulness is relatively easy to measure by confirming that the eyes are open and/or that the resting state electroencephalography (EEG) recording exhibits a pattern that is typical for the normal waking state. Measuring awareness is much more difficult. Indeed, objective functional biomarkers of awareness are lacking (Supplementary information S1 (box)) and, clinically, the ability to follow commands — either verbally or behaviourally — has to be used as a proxy measure for awareness. However, consistent command-following is not always possible in severely brain-injured patients and residual awareness has to be inferred on the basis of any behaviour that is observed. The subjective nature of this inference undoubtedly contributes to the well-documented rate of misdiagnosis in this population[3–5].

The vegetative state is a clinical condition that is often described as 'wakefulness without awareness' (REF. 6) (BOX 1). These patients open their eyes, frequently move spontaneously and will often exhibit sleeping and waking cycles. Hence, the waking component of consciousness is demonstrably preserved. However, careful and repeated examination of the patient's spontaneous and elicited behaviour will yield no evidence of a sustained, reproducible, purposeful or voluntary behavioural response to visual, auditory, tactile or noxious stimulation. In short, such patients exhibit no spontaneous purposeful behaviour and are entirely non-responsive to any form of prompting or stimulation (beyond simple reflexes), and it is on this basis that it is assumed that the awareness component of consciousness is absent. It is now well accepted[3–5] that when specialized clinical teams examine these patients, up to 43% will show inconsistent, but reproducible, behavioural signs of awareness and will be reclassified as being in a minimally conscious state[7]. Nevertheless, it remains likely that some covertly aware patients will escape detection, even by experienced teams, and will remain erroneously diagnosed as being in a vegetative state[8].

Recently, the results of some functional MRI (fMRI) and EEG studies have called into question the extent to which we can reliably consider a patient unaware simply because they exhibit no overt behavioural response to external stimulation[8–11]. Indeed, these studies have revealed a subset of patients who are aware but entirely physically unresponsive; thus, although they fulfil all internationally agreed criteria for the vegetative state, which are based on behavioural signs, clear signs of command-following can be demonstrated using fMRI or EEG. In some cases, these developments in functional neuroimaging technology have even allowed such patients to communicate with the outside world for the first time since their brain injury[10].

In this Perspective article, we begin by reviewing the 'state-of-the-art' of the two methods — fMRI and EEG — that have been successfully used to detect covert awareness in the vegetative state, with a focus on the major developments that have emerged within the past 5 years. We then describe the paradigmatic case of a recent patient who, despite fulfilling all of the accepted diagnostic criteria for the vegetative state 12 years after a serious brain injury, was shown — using both fMRI and EEG — to be fully aware and able to communicate cognitively and therapeutically relevant information about his condition. Last, we use this case and the broader issues that it raises to guide a discussion about how these new methods are affecting diagnosis, prognosis and legal decision making, with reference to their specific challenges and limitations.

State-of-the-art

fMRI responses as evidence of awareness. In 2006, we introduced a method for eliciting covert command-following (and therefore detecting the awareness component of consciousness) with fMRI[9]. Using this technique, a patient who fulfilled all of the internationally agreed clinical criteria for the vegetative state was shown to be covertly aware and able to wilfully respond to commands by simply modulating her fMRI activity. Specifically, while in the scanner, the patient was asked to imagine hitting a tennis ball back and forth to an imaginary

Box 1 | **Vegetative state: a syndrome in search of a name**

Before 1972, there was no universally accepted term to refer to patients who did not exhibit normal levels of consciousness after a brain injury. Until then, the only reports available in the literature were single-case studies in which various terms were used to refer to these patients. Some of the most common were 'apallic syndrome', 'akinetic mutism', 'post-traumatic dementia' or the still widely used 'coma vigil'. In 1972, Jennett and Plum[6] coined the term 'vegetative state' in an article entitled 'Persistent vegetative state after brain damage. A syndrome in search of a name'. They chose this term to stress the (relative) preservation of the 'vegetative' (that is, non-conscious) functions of the brain in these patients, such as sleep–wake cycles, respiration, digestion and thermoregulation. At that time, 'persistent' was used to indicate that the condition had lasted for at least a month post-injury. Forty years on, 'vegetative state' is still the most widely used term for this condition in the medical and scientific communities. However, given the pejorative connotations, a European Task Force on Disorders of Consciousness has recently proposed the neutral descriptive term 'unresponsive wakefulness syndrome' (REF. 64). The authors acknowledged the problems inherent in making strong claims about awareness in patients with severe brain damage, as highlighted by recent functional neuroimaging studies, and shifted the terminological focus from the lack of awareness to the lack of response. Since it was introduced in 2010, the new term has received modest support from the medical and scientific communities.

coach when she heard the word 'tennis' and to imagine walking from room to room in her house when she heard the word 'house'. When a group of control volunteers were asked to perform the same two mental imagery tasks[12], imagining playing tennis was associated with robust activity in the supplementary motor area (SMA) in each and every one of the participants. By contrast, imagining moving around their houses activated the parahippocampal cortices (PPA), the posterior parietal lobe and the lateral premotor cortices — all regions that have been shown to contribute to imaginary, or real, spatial navigation[13–17]. The robustness and reliability of these fMRI responses across individuals was sufficient to allow activity in these brain regions (when observed in response to the appropriate command) to be used as a neural proxy for physical behaviour[8–10,12,18]. Critically, the fMRI responses in the patient were indistinguishable from those observed in the control volunteers in both tasks[9,12]. On this basis, it was concluded that, contrary to her formal diagnosis, she had retained the ability to understand spoken commands and to respond to them through her brain activity, confirming beyond doubt that she was consciously aware. A follow-up study[10] demonstrated that, out of a group of 23 patients in a vegetative state, 4 were able to generate similarly reliable fMRI responses to commands and were therefore also covertly aware.

Subsequently, similar logic has been used to validate several other approaches to the assessment of covert awareness in physically non-responsive patients. For example, in one study[19], a group of patients who were diagnosed as vegetative were instructed to attempt to move either their left or right hand in order to establish whether motor preparation could be used as proxy for extant command-following. Although no overt muscular activity was detected in any of the patients, two out of five patients exhibited fMRI activity in the dorsal premotor cortex contralateral to the side of the hand that they were instructed to move, suggesting that they were at least attempting to follow the command. In another example[20], a patient was asked to either just listen to a series of common words or to count the number of times a given word was repeated in a continuous sequence. During the counting condition, the patient's fMRI response was similar to that observed in a group of control participants, confirming that he was able to wilfully adopt different mindsets in the presence of an unchanging external stimulus; in short, he was able to follow commands by modulating his brain activity according to the task instructions. In a third study[21], the authors presented participants with pictures containing a superimposed face and house and instructed them to shift their attentional focus from one to the other, and back again. This task typically elicits a cycling pattern of increases and decreases in fMRI activity in the fusiform and parahippocampal gyri when attention is switched between faces and houses, respectively. One patient who showed no physical signs of command-following ability was nevertheless able to generate this characteristic pattern of cycling fMRI activity when asked to repeatedly shift attention between the two components of the unchanging compound stimulus.

Importantly, the neural responses that characterize all of these tasks are not automatically produced by the eliciting stimulus but rather depend on the will or the intention of the participant to generate and sustain a response to the given instruction. Such (neural) behaviour provides a proxy for a motor action and is therefore an appropriate vehicle for reportable awareness[22]. Indeed, given the complexity of the tasks used and the specificity of the responses measured, one can draw far more elaborate conclusions about the mental state of these patients than the fact that they are merely 'conscious'. For example, at the very least, sustained attention (required to maintain focus through each task), language comprehension (required to understand the task instructions), response selection (required to switch between alternative tasks or conditions) and working memory (required to remember which task to perform when instructed) must all be substantially preserved. These are all aspects of 'top-down' cognitive control that are typically associated with normal levels of conscious awareness.

EEG responses as evidence of awareness. In spite of its demonstrable success in detecting covert awareness, performing fMRI in patients who are in a vegetative state is exceptionally challenging. Considerations of cost, scanner availability and physical stress incurred by the patients as they are transferred to the fMRI facility limit its use in some cases. In addition, movement artefacts, which commonly occur in patients who are unable to remain still, and metal implants, which are commonly used in many traumatically injured patient populations, may rule out fMRI altogether. For these reasons, several groups have sought to explore whether cheaper and more portable techniques such as EEG can be used to detect covert awareness at the bedside.

EEG was first successfully used in this context in a study[23] in which a group of patients were instructed to count the number of times they heard their own name (in a mixed sequence of names) and were then asked to just passively listen to identical stimuli (the control condition). A group of patients who were formally diagnosed as minimally conscious but who, at best, showed intermittent overt command-following, exhibited reliably larger P3 components in the EEG recording when counting the number of times their own name was presented.

Later attempts to fashion EEG into a technique capable of detecting covert awareness in entirely non-responsive patients focused on adaptations of the motor imagery tasks that had previously proved successful in the fMRI context. When an individual plans or imagines a movement, sensorimotor cortical activity is reflected in the EEG recording as reductions of power — that is, an event-related desynchronization (ERD) — of the mu and/or beta (~7 Hz–30 Hz) bands over 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[24]. In some individuals, these ERDs may also be accompanied by an event-related synchronization (ERS; relative increases in power) over motor areas contralateral to, or surrounding, the ERD[25,26]. One study[11] exploited these known EEG responses to develop a novel technique for classifying imaginary command-following in non-responsive patients. Specifically, two mental imagery responses (squeezing the right hand or wiggling the toes) were successfully decoded in 3 out of 16 patients who met the internationally agreed criteria for a diagnosis of vegetative state. As is the case for the fMRI responses described above, these spatially specific and time-locked EEG responses are only elicited when a participant wilfully performs the tasks as instructed, and it is on this basis that conscious awareness can be inferred. Another group[27] also analysed the data from this study[11] using a more conservative statistical model that pushed two out of the three 'positive' patients to just beyond the widely accepted $P < 0.05$ threshold for significance (to $P < 0.06$ and $P < 0.09$, respectively). Their results suggest that in these two cases, the EEG response became less consistent over time and provide an argument for future iterations of the task structure to be altered to accommodate this. Nevertheless, it is reassuring to note that corroborative data, including the fMRI test of command-following described above[9,10], was acquired in these patients during the same week as the EEG testing and confirmed that they were indeed aware[28].

EEG systems are portable, relatively inexpensive and available in many hospitals, and thus are a good candidate for becoming the gold-standard for the assessment of awareness in non-responsive patients. However, from the discussion above, it is clear that, to date, they have failed to achieve the levels of sensitivity that have been obtained using fMRI. For example, in the study described above[11], 25% of the control individuals tested were not able to produce reliably classifiable EEG responses. Moreover, if the more conservative criteria[27] are applied, 60% of the control participants would be classified as being 'non-conscious'. By contrast, all of the control individuals tested in two separate studies using the fMRI motor imagery tasks described above were able to produce reliable activity in the appropriate areas of the brain[10,12]. A more recent study[29] refined the EEG approach by using a simpler and more clinically viable paradigm that also satisfied all of the more conservative statistical criteria suggested earlier[27]. The task required participants to actually try to move their hands and, unlike the two previous studies[11,27], 100% of the control volunteers showed reliable ERD and ERS responses[29]. Moreover, in a patient who had been repeatedly diagnosed as vegetative for 12 years (described in detail below), reliable modulations of sensorimotor beta rhythms were observed after commands to try to move, and these were classified significantly at a single-trial level (FIG. 1). However, a large-scale group study will be necessary before it will be clear whether the sensitivity and specificity of EEG methods in this context matches that of fMRI.

fMRI for communication. The reliability of fMRI for detecting when participants are imagining playing tennis or moving around their house suggests that the same general technique could be used as a robust communication tool when associated with 'yes' and 'no' responses. A study from 2008 (REF. 30) first demonstrated that this was possible in a control participant, who was able to provide accurate answers to simple 'yes' and 'no' questions by imagining one of the two tasks. The approach was refined[10] to the point that it was able to successfully decode 'yes' or 'no' responses from every one of the 16 control participants with 100% accuracy, based solely on their real-time changes in the SMA (during tennis imagery) and the PPA (during spatial navigation). Moreover, a patient who had been repeatedly diagnosed as vegetative for 5 years was able to use the same approach to accurately communicate biographical information — such as his father's name — in response to specific 'yes' and 'no' questions posed by the experimenters[10].

To date, this is the only approach that has been successfully used to establish accurate functional communication with any patient who was diagnosed as vegetative at the time of the scan, although recently even more elaborate methods have been developed in control participants that move beyond simple 'yes' and 'no' responses. For example, a

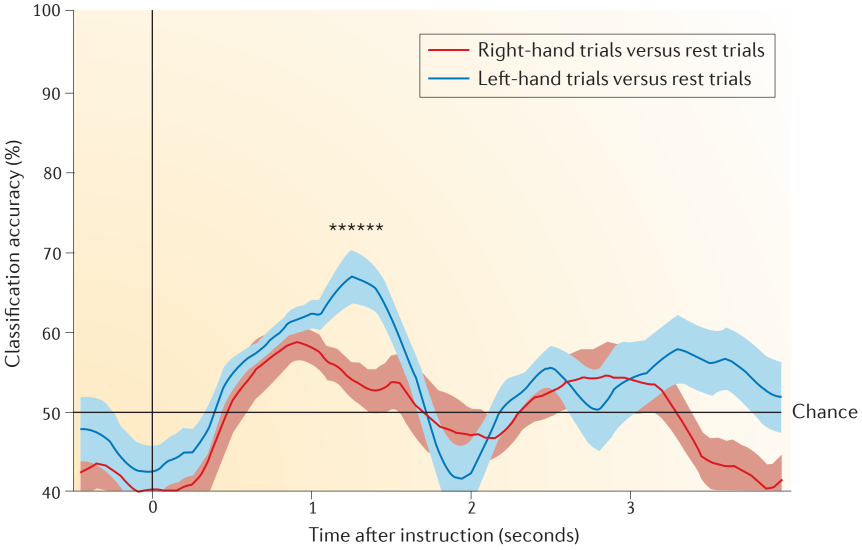


Figure 1 | **Electroencephalography activity demonstrating command-following and awareness in a patient diagnosed as being in a vegetative state for 12 years.** The plot shows the time courses of classification accuracies (versus rest) for the trials when the patient, described in detail in this article and diagnosed as vegetative for 12 years, was ask to move his right hand and left hand. Red and blue lines show means of the tenfold smoothed classification accuracies. Shaded areas show ±1 standard errors. The asterisks denote the time points with significantly above chance classification for left-hand trials versus rest trials ($P < 0.025$). When the frequency band used in the single-trial classification procedure was narrowed to only that which produced a significant event-related synchronization for left-hand trials (high-beta band, 25 Hz–30 Hz), significantly above chance classifiability was established for right-hand trials as well as left-hand trials. These data confirmed that this patient was in fact aware and able to follow task instructions to (attempt to) move his left and right hands despite there being no detectable physical response to command. For detailed methods, see REF. 29. Figure is reproduced from REF. 29.

recently developed[31] fMRI-based technique allowed real words to be spelt by participants as they lay in the scanner. In order to select a letter, the participants had to generate activity in specific cortical locations (by engaging in different pre-learned mental tasks), at a particular time point (by delaying the start of the mental task) and for a specific duration (also see REF. 32). The various permutations of task, onset and duration resulted in 27 unique brain responses that were assigned to 27 characters (A–Z plus SPACE) and an automated decoding procedure deciphered the answer by analysing the single-trial fMRI responses in real time with a mean accuracy of 82%.

The potential of such approaches for establishing dynamic brain-based 'conversations' between control participants and experimenters is beyond doubt. However, their applicability in patients who are actually physically non-responsive is less clear. For example, many brain-injured patients who are found to be covertly aware using fMRI or EEG will nevertheless not retain the cognitive resources required to understand and execute complex multidimensional tasks such as those developed in the recent study[31]. Fatigue is also likely to be a limiting factor given that control participants required 60 minutes to spell the answers to two questions, and slowed responses after brain injury may also interfere with the onsets and durations of the mental imagery tasks. Notwithstanding these limitations, the rapid rate of technological progress in this field suggests the real possibility of functional and versatile brain-activity-based communication in physically non-responsive patients in the near future.

A paradigmatic example

It is notable that the key patient in the original fMRI study described above[9] showed some inconsistent signs of awareness in the months following the scanning session. In this sense, the apparent dissociation between her external motor behaviour and preserved cognitive functioning may have reflected an early stage of recovery in which changes that were not yet clinically evident could nevertheless be detected by direct interrogation of her brain function. Recovery of this sort, however, rarely occurs once a patient has received a diagnosis of permanent vegetative state. After a traumatic brain injury, the vegetative state is considered permanent, and thus irreversible, when it lasts longer than 1 year. For non-traumatic cases, for which the prognosis is generally worse, the duration is 6 months[2] (or 3 months according to US guidelines[33]). According to the Multi-Society Task Force on Persistent Vegetative State, recovery after those intervals is exceedingly rare and almost always involves a severe disability[34]. It is among these cases that ethical and legal decisions pertaining to the withdrawal of life-sustaining treatment (that is, artificial hydration and nutrition) usually take place[35,36].

To motivate further discussion of the key issues and how they might be addressed by advances in neuroimaging, we will briefly describe the case of a patient who had been repeatedly diagnosed as vegetative for 12 years after a traumatic brain injury but was able to demonstrate that he was aware using both fMRI and EEG, and convey the answers to clinically relevant questions about his condition[37].

The patient was a male who, in December 1999 and at the age of 26 years, had suffered a severe closed head injury in a motor-vehicle accident. On admission to hospital, he had a Glasgow Coma Scale[38] score of 4, meaning that he was unable to open his eyes or produce any sound, and his only response was extension to painful stimulation (a decerebrate response). A computed tomography scan on the day of the injury revealed severe contralateral midline-shift, herniation, haemorrhaging and contusion in his left parietal and temporal lobes. Over the next 12 years, the patient was assessed regularly by experienced neurologists and multidisciplinary teams, and throughout this period, his behaviour remained consistent with the internationally accepted criteria for the vegetative state (Supplementary information S2 (box)). Indeed, over one 14-month period in 2012–2013, a total of 20 standardized behavioural assessments were performed (Supplementary information S2 (box)) by a multidisciplinary team, at different times of the day and in different postural positions, using the Coma Recovery Scale-Revised[39]. The highest scored achieved was 7, meaning that the patient had some auditory and visual startle, flexion withdrawal, oral reflexive movement and eye-opening without stimulation — all symptoms that are characteristic of the 'classic' vegetative state. That said, this extended profile was only observed in 4 out of the 20 assessment sessions (Supplementary information S2 (box)); on 15 of these occasions, he failed to show any sign of visual startle, and in 5 sessions, eye-opening was only observed after external stimulation. In short, the patient never once showed any behaviour to contradict the fact that he was in a permanent vegetative state that had remained unchanged for the past 12 years. At the time of submission of this article, the clinical profile of the patient remained unchanged.

In February 2012, 12 years and 2 months after his accident, the patient was first scanned using fMRI (for methodological details, see Supplementary information S2 (box)). He was first asked to imagine playing tennis; this yielded consistent activity in the SMA, which was formally identical to that which has been repeatedly observed in control participants[12]. This response was observed on a number of occasions and across multiple scan runs. He was then asked to imagine moving from room to room in his house and a less typical pattern involving the occipitoparietal junction was observed. Although the patient did not engage the PPA — the region most commonly activated by control participants when performing this task — the more posterior cortical area that he did engage has been reported to show activity during mental navigation in a number of previous studies[12,13,17,40]. Moreover, activity in this same region was observed on a number of occasions and across multiple scan runs. This activity was therefore adopted as an indicator of command-following in this patient and, together with his activity in the SMA during imaginary tennis, it was used to motivate questioning using the 'yes' and 'no' approach described above[10]. Using this method, the patient was able to provide correct answers to multiple externally verifiable questions, including his own name, the name of his personal support worker (who he had only encountered in the years following his accident) and the current date. Several non-verifiable questions were then posed, including some pertaining to his care preferences (for example, whether he liked watching ice hockey games on TV) and others pertaining to details about his current clinical condition (for example, whether he was in any physical pain)[37]. To date, answers to 12 different questions have been obtained across several sessions (TABLE 1). Importantly, the patient did not respond on every occasion that he was scanned; sometimes no significant activity was observed, which was possibly indicative of a lack of attention, motivation or will on that particular day.

EEG was also used at the bedside to confirm that the patient was aware[29], making him the first case in which awareness has been demonstrated using two independent

Table 1 | **Communication in a patient presumed to be in a vegetative state for 12 years**

Question	Correct or incorrect information	Number of times question asked	What the question assesses
Is a banana yellow?	Correct	Once	Basic semantic knowledge
Is your name John?	Correct name	Twice	Self-identity
Is your name Mike?	Incorrect name	Twice	
Is the year 1999?	Incorrect year	Once	Orientation in time
Is the year 2012?	Correct year	Once	
Are you in a supermarket?	Incorrect	Once	Orientation in space
Are you in a hospital?	Correct	Once	
Is your support worker's name Bob?	Incorrect name	Once	New knowledge (familiar people)
Is your support worker's name Sarah?	Correct name	Twice	
Is your support worker's name Julia?	Incorrect name	Once	
Do you like watching (ice) hockey on TV?	NA	Once	Personal preference and quality of life
Are you in pain?	NA	Once	Clinical condition and quality of life

NA, not applicable. Note that the names of the patient and support worker have been changed in the interests of privacy; all other information is factually correct. Some of these data are from REF. 42.

imaging methods (fMRI and EEG) in the absence of any supportive evidence from clinical (behavioural) examination. In that study, the patient was asked to try to move his left or right hand, and reliable modulations of sensorimotor beta rhythms were observed that could be classified significantly (as responses to command) at a single-trial level (FIG. 1). Finally, in a more recent fMRI study, the same patient has been able to provide the correct answers to a series of questions using an entirely unrelated technique based on decoding selective attention to the words 'yes' and 'no' (REFS 41,42).

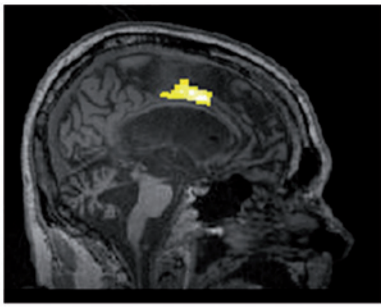
In summary, when considering the fMRI and EEG[29] (imagery) tasks that this patient had to perform repeatedly in order to signal a response, together with the answers that he gave to the questions that were posed using fMRI, it is possible to draw strong conclusions about his cognitive status and likely level of competency. At the very least, he could switch, sustain and select his focus of attention, he could comprehend language and select appropriate responses, he could maintain and manipulate information in working memory, he could recall events from before his accident and lay down new memories for events that have occurred since (see FIG. 2 and REF. 42), he could express opinions about personal preferences and he could access information about his bodily state (TABLE 1). By contrast, none of the data that has been collected has suggested that any cognitive function is impaired or that this patient lacks competency in any measurable domain.

Implications

Diagnosis. It is notable that the patient described above was repeatedly and rigorously assessed by experienced teams and showed no behavioural sign of awareness on any of these occasions; indeed, this continued to be the case even after awareness had been established unequivocally with fMRI and EEG. Technically, however, he was not misdiagnosed (as vegetative) in the sense that any error of judgement was made, because the accepted diagnostic criteria are based on behaviour and no behavioural marker of awareness was missed. Nevertheless, the existing criteria did not accurately capture his actual state of awareness, and in this sense, his vegetative state diagnosis was clearly incorrect. What then is the appropriate diagnostic label for such patients who can follow commands with a measurable brain response but physically remain entirely non-responsive? The term 'non-behavioural minimally conscious state' has been suggested[43]. However, because attention, language comprehension and working memory are demonstrably preserved in these patients, we have argued that 'minimally conscious' does not adequately describe their residual cognitive abilities[8]. Indeed, the patient described above was consistently and reliably able to communicate (using fMRI), which places him well beyond the diagnostic criteria describing the minimally conscious state. The term 'functional locked-in syndrome' has also been proposed for patients who demonstrate consistent and reliable communication using adjunctive technologies[44,45]. In its classical clinical presentation, 'locked-in syndrome' refers to patients who are left with only vertical eye movements and/or blinking, which often permit rudimentary communication. Cognitive function, however, is generally fully preserved, at least in those cases in which the lesion is limited to the ventral pons[46]. Patients like the one described here are clearly 'locked in' in the general sense of the term but do not have many of the neuropathological and clinical features of the classic locked-in syndrome. Moreover, at present, there is still considerable uncertainty about the full extent of residual cognitive function in such patients and thus about the suitability of the term 'functional locked-in syndrome'. That said, this is precisely the sort of question that can be explored with fMRI. Indeed, the patient described above has already been able to report that he remembers his own name and that he knows the current date and where he is[42], confirming that he is well orientated in time and space. He has also provided information about events that have occurred in the years since his accident, confirming that he is still able to encode new memories. There is a recently developed[46] standardized neuropsychological assessment for locked-in syndrome that uses simple eye movements as responses (in most cases to provide 'yes' or 'no' answers to questions), and there is no technical or theoretical reason why a similar approach could not be used with fMRI data in entirely non-responsive patients, although the data would take considerably longer to acquire. To this end, fMRI has recently been used[47] to assess complex logical reasoning ability in a patient who was assumed to be in a vegetative state.

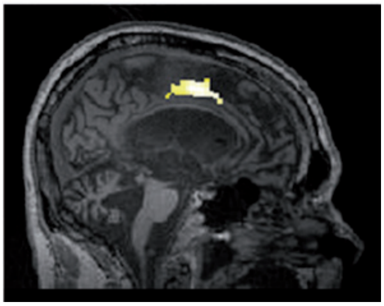
a

Imagining playing tennis



b

Imagine playing tennis for a 'yes' and walking around your house for a 'no'



'Is your personal support worker's name Sarah?'

Figure 2 | **Functional MRI-based communication in a patient diagnosed as being in a vegetative state for 12 years.** The communication protocol described in REF. 10 was used in a patient who had been repeatedly diagnosed as vegetative over a 12-year period following a traffic accident. **a** | The patient was first asked to imagine playing tennis and then to imagine moving around the rooms of his house in order to generate anatomical localizers in the premotor cortex and the occipitoparietal junction, respectively. **b** | In a subsequent series of scans, he was asked to imagine playing tennis to convey one response ('yes' or 'no') and to imagine moving around the rooms of his house to convey the alternative response. When asked whether his personal support worker's name was Sarah, the pattern of activity observed was almost identical to the pattern that had previously been associated with him imagining playing tennis — a 'yes' response — confirming he was capable of encoding new memories years after his accident.

Prevalence. We have used a single patient above to illustrate our main arguments, but it is important to emphasize that this is not a unique case. In the largest study to date[10], 4 out of 23 patients in a vegetative state (that is, 17%) were shown to be covertly aware using fMRI. A similar percentage (that is, 19%) of an independent group of patients diagnosed as vegetative has also been shown to be covertly aware using EEG[11]. Importantly, however, although false-positive results are statistically unlikely in these studies, the occurrence of false-negative results is impossible to quantify (see BOX 2 for a detailed discussion of this topic). At best, we can conclude that 'at least' 17–19% of patients in a vegetative state in the general population may harbour covert command-following abilities.

It is also important to consider the relationship between prevalence and other clinical factors, such as aetiology and time post-injury. The most common acute causes of the vegetative state are traumatic brain injury (TBI) and hypoxic ischaemic encephalopathy[33]. Although formal conclusions cannot yet be drawn on the basis of the small number of cases available, it is notable that all but one of the patients who have been shown to be covertly aware to date — across two separate group studies[10,11] and several single-case studies[9,29] — are in a vegetative state as a result of a TBI. To our knowledge, no study has specifically assessed the relationship between the prevalence of covert awareness and the amount of time that has elapsed since brain injury. However, recent evidence suggests that the (widely held) notion (for example, see REF. 48) that preserved consciousness does not occur in patients who have survived for many years after TBI is incorrect. The patient described above is an unequivocal example of this, as his covert awareness was discovered as late as 12 years after his injury: that is, well beyond the point that his condition would be diagnostically labelled 'permanent'. Similar cases of covert awareness in patients in a chronic (long-term) vegetative state have also been reported elsewhere in the literature[10,11].

As far as the prevalence of communication in patients who are assumed to be vegetative is concerned, it is still very early days. To our knowledge, this has only been attempted in two published studies[10,42], in addition to the patient described above, providing insufficient data from which strong conclusions can be drawn. Nevertheless, there is no logical reason to assume that this will be rare within the (17–19%) population of clinically vegetative patients that is found to be covertly aware, as the cognitive demands of imagining playing tennis to indicate a 'yes' response are not substantially different from those that are required to simply imagine playing tennis at a specific time and for a specific duration[41]. Moreover, a less cognitively demanding technique for fMRI communication using changes in selective attention has recently been shown to be more sensitive than motor imagery in control participants[41] and an effective communication tool for patients[42].

Judicial implications. At present, in most jurisdictions, decisions concerning life support (nutrition and hydration) are generally only taken once a diagnosis of 'permanent vegetative state' has been made: that is, once one of the critical time thresholds described above has been reached. Until recently, fMRI or EEG had not demonstrated unequivocal signs of awareness in any patient who had survived beyond the time point required for such a diagnosis, but the case described in detail above is a vivid exception to that rule[29,42]. That is to say, the patient has persisted in a condition of physical non-responsiveness for more than 12 years and has therefore long since met all of the internationally agreed criteria for a diagnosis of permanent vegetative state and could, consequently, be the subject of a legal petition to withdraw nutrition and hydration. In his particular case, this has not been discussed because his family feels, like many in this situation, that there is sufficient reason to continue to maintain the patient in his current state. Public opinion as well as scientific opinion on this issue is divided over questions of economics, quality of life and the moral significance of consciousness itself. Kahane and Savulescu[49] have pointed out that, although it is often assumed that we have strong moral reasons to sustain the life of conscious patients, that assumption may be questionable in some circumstances. For example, if a patient was experiencing great agony that could not be relieved, being kept alive may be a source of harm rather than benefit. Even if conscious brain-damaged patients do not feel physical pain, some may still experience great mental suffering if they have retained the cognitive and neural machinery to do so. In short, is every life worth living? On this basis, Kahane and Savulescu argue that "enjoyment of consciousness might actually give stronger moral reasons not to preserve a patient's life and, indeed, that these might be stronger when patients retain significant cognitive function" (REF. 49).

Although withdrawal of nutrition and hydration has not been considered in the patient described in detail here, we are aware of a number of cases that are currently being considered in various different legal jurisdictions involving patients with similar clinical profiles. Typically, these cases involve one of two scenarios. The first involves a dispute among family members; for example, the next of kin wishes to proceed with withdrawing nutrition and hydration, but other family members contest this decision on the grounds that it is not what the patient would have wanted (or what they want). The second involves a dispute between medical staff and family members; for example, medical staff recommend withdrawing nutrition and hydration on the grounds of futility (the patient will never recover), but family members contest this opinion. In most of these cases, the key medical and legal decisions revolve around several inter-related factors. These factors are, first, whether there is any chance of significant recovery; second, whether the patient is conscious or 'aware' of his or her condition; and third, what the patient would have wanted if they could have been consulted about his or her current condition. In the latter case, an advanced directive or a 'living will' is often used to guide the court's decision or, in the absence of such a document, the closest relatives are consulted and asked to evaluate what they think the patient would have wanted.

Regarding the first of these factors, at present, there is no unequivocal evidence that the discovery of positive fMRI responses is predictive of recovery, although there are certainly some suggestions that this might be the case. For example, in the original case described in REF. 9, the patient began to emerge from her vegetative state in the months following her scan, suggesting that early fMRI evidence of awareness may have some prognostic value. Similarly, in the large group study (of 41 patients)[50], the fMRI data were shown to significantly correlate with subsequent behavioural recovery 6 months after the scan. Finally, a comprehensive review of the available literature[51] considered 15 separate neuroimaging studies involving 48 published cases that were classified as 'absent cortical activity', 'typical activity' (that is, activity in low level primary sensory cortices only) and 'atypical activity' (that is, activity in higher-level associative cortices); its results suggest that atypical activity patterns appear to predict recovery from a vegetative state with a 93% specificity and 69% sensitivity. Specifically, 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 in whom activity was absent failed to recover. This suggests that functional neuroimaging data can provide important prognostic information beyond that available from bedside examination alone.

Regarding the remaining two points of legal discussion, the case for the use of fMRI is even more compelling. It is now clear that fMRI can be used to detect covert awareness in some cases in which no clinical evidence exists to confirm that is the case[9,10,42], and, subject to the appropriate quality controls and scientific guidance, there is no reason why such data could not be used to guide a court's opinion about whether the patient is conscious or 'aware' of his or her condition. Again, the patient described in detail above is a case in point; although multiple clinical assessments over 12 years suggested that he was 'awake but unaware', the fact that he was able to report his own name, where he was, what year it was and whether or not he was in any pain demonstrates beyond any doubt that he was 'conscious' and 'aware of his condition'. More compellingly still, the fact that he could communicate, albeit in a rather rudimentary way (using fMRI), obviates any need for the court to consult the relatives about what the patient would have wanted and the need to locate, or rely upon, an advanced directive in reaching a decision. Ultimately, the morally challenging question of whether this is a life that is 'worth living' (REF. 49) is one that could be answered directly by the patient himself. Regarding this question, a recent survey of 91 locked-in patients established that the majority were 'happy' with their quality of life and showed that ratings of 'happiness' improved with the amount of time spent in a locked-in state[52,53]. Although surprising, these data underline the importance of any technique that may allow a seriously brain-injured patient to express their current opinion — especially as this opinion may have changed radically over the (sometimes) many years since an advanced directive was written.

Box 2 | **Negative findings**

As in most neuroimaging studies, all of the approaches discussed in this article were designed, for the most part, to minimize the possibility of false positives (that is, detecting awareness when the patient is not, in fact, aware). Various methods are used to ensure that this is the case: for example, testing control participants who are asked to follow, and then to ignore, the task instructions in order to ensure that the signature patterns of activity only occur when they wilfully (that is, intentionally) follow the commands[11,29,65]. By contrast, negative results are much more difficult to interpret and do not necessarily confirm that a patient is unaware. For example, a patient may fail to hear or understand the instructions, have low levels of arousal or even fall asleep during the scan or simply choose not to participate (as unlikely as this may seem). In addition, the neuroimaging methods used may simply be insensitive to small changes in brain activity in some patients[11]. In one recent study[66], negative neuroimaging results were returned in two patients who were demonstrably minimally aware and could follow commands behaviourally (in one of those cases, the patient could even communicate behaviourally). Of course, in some of these cases, the alternative hypothesis — that the patient is indeed unconscious and unaware at the time of the scan — is also possible, but in this unique situation in which no independent verification is possible, it is impossible to distinguish between true negatives and false negatives. In other words, no conclusions or claims about the preservation or loss of residual awareness in patients can be drawn on the basis of a negative finding.

Ethical implications: disclosure. Unlike in many areas of neuroscientific research, the results of individual fMRI or EEG tests for covert awareness have profound implications for the patients and for their relatives and caregivers. However, although there is general agreement among the scientific community that summary data should be disclosed to individual participants after the completion of any research trial[54–56], not all authors agree that individual research results should ever be disclosed[57–59]. Indeed, in most areas of neuroscientific research, ethical, legal and sometimes scientific considerations may preclude the disclosure of individual results to the participants and their families. However, the US National Bioethics Advisory Commission, the UK Medical Research Council and the Canadian Institutes of Health Research all agree that individual results should be disclosed if they are scientifically valid and confirmed, and have clinical relevance or significant implications for the participant's health[55,60,61]. We argue that the discovery of covert consciousness in patients presumed to be vegetative is just such a case, because all of these requirements are fulfilled. Consider, as an example, the patient described above. The methods have been shown to be sufficient to detect consciousness and allow communication in a number of patients and are therefore scientifically valid and confirmed[9–12,29,42]. In addition, the information that has been obtained by deploying those methods (for example, he is conscious, he is well orientated in time and space, he can encode new memories, and so on) has clear clinical relevance. Last, the fact that he could answer questions specifically related to his clinical condition (for example, whether he was in any pain) demonstrates that the research has important implications for the participants' health. As such, we argue that the moral and practical imperative in these cases far outweighs any legal, ethical or scientific concerns.

An exception may occur in those cases in which fMRI or EEG testing has returned negative results. As we have discussed above, a negative result in this context (for example, no evidence that the patient is conscious) is not easy to interpret because false negatives are impossible to avoid and detect (BOX 2). Therefore, negative results do not provide any information to support the conclusion that the patient is unaware and, on the basis of the arguments above, the imperative to disclose them is reduced. However, in reality, the lack of disclosure may lead some to assume that a lack of awareness has been confirmed. For this reason, we suggest that negative results should also be disclosed to the patient's family and special care should be taken to explain what conclusions can and cannot be drawn in their presence.

Box 3 | The future: brain–computer interfaces

After the development of electroencephalography (EEG)-based methods for detecting awareness in patients diagnosed as being in the vegetative state, a logical step is to develop tools for controlling aspects of the environment — so called 'brain–computer interfaces' (BCIs). BCIs typically involve real-time analysis and classification of brain responses to infer and execute a desired command that reflects the user's intention[67,68]. The physical changes produced in the system are communicated to the BCI user in real time to achieve bidirectional feedback. As a paradigmatic example of the extraordinary possibilities that BCI systems can offer, a patient suffering from long-term tetraplegia was recently taught to control a robotic arm as an assistive device and use it to drink coffee from a bottle[69]. However, research using BCIs in entirely non-responsive patients is in its infancy, and there are many challenges beyond those that exist for the development of BCIs in control participants and other clinical groups. For example, the level of arousal, awareness and cognition varies dramatically between non-responsive patients (as well as at different times within the same patient)[7], and thus to maximize the chances of success, a BCI system will need to be as robust (to deal with this variation) and as straightforward to use as possible[67]. In addition, the majority of BCI techniques that have been developed for conscious participants rely on visual stimulation and feedback. By definition, patients in a vegetative state lack the ability to fixate on, or pursue, objects in their visual field[33], which precludes the use of visually based BCI systems and suggests that other modalities should be used[67,68]. In a recent proof-of-principle study, implanted electrodes in a locked-in patient were used to decode his intention to produce one of four vowels and to translate the output into the intended vowel sound using a synthesizer[70]. Absence of consent may preclude the use of such invasive procedures in patients in a vegetative state, at least until such time that consent itself may be obtained using some of the methods described in this article.

Conclusions and future directions

The notion that we might one day be able to convey our thoughts, without recourse to speech or action, has pre-occupied scientists — and science fiction writers — for decades. In this Perspective, we have focused on recent technological developments in the field of neuroimaging that 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 centres in Canada, the United States, the United Kingdom and Belgium, these methods are now being routinely used to detect consciousness and even to communicate with some behaviourally non-responsive patients who clinically appear to be comatose or in a vegetative state. On the basis of the data available, we suggest that there is an urgent need for a re-evaluation of the existing diagnostic categories and guidelines for behaviourally non-responsive patients and for the development and formal inclusion of validated, standardized neuroimaging procedures in those guidelines.

One question that remains, for both neuroscience and clinical practice, is: where will this research lead us? There is no doubt that there currently exists a broad fascination, among both the general public and the media, about whether the methods described in this article could, and should, be used to ask patients whether or not they want to go on living. Although this is already a practical possibility, it is important to consider whether a simple 'yes' or 'no' response to such a question would be sufficient to establish that a patient has retained the necessary cognitive and emotional capacity to make such a complex decision. Clearly, it would not. Indeed, given the potential implications, if a robust and reliable response was obtained to such a question, one would want to be absolutely sure that the patient retained a level of decision-making capacity commensurate with the importance of any decision that might be made based on that response. In this context, decision-making capacity may be better considered as a continuum with different thresholds depending on the importance of the potential consequences of the decision, rather than an 'all or nothing' problem[62]. Clearly, decisions about the withdrawal of life support are of utmost importance, and as they are radical and irreversible, an appropriate level of decision-making capacity should be demonstrated before such a question could be even considered. A recent publication[63] has laid out the conceptual foundations for a mechanistic explanation of capacity that would allow the necessary steps for incorporating neuroimaging data into the standard capacity assessment used in clinical practice. We are entering an era in which high-level assessments of residual cognitive function may soon be made based solely on fMRI or EEG data[47], although a full assessment of the capacity for complex decision making using any of the tools described in this article would still be extremely lengthy, logistically complex and practically unfeasible in most contexts. Nevertheless, with the rapid emergence and deployment of so-called 'brain–computer interfaces' for applications as diverse as gaming and the military (see BOX 3 for further discussion), we would venture that it is only a matter of time before all of these obstacles are overcome.

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Competing interests statement

The authors declare no competing financial interests.

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