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Chapter 18

Using functional magnetic resonance imaging and electroencephalography to detect consciousness after severe brain injury

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INTRODUCTION

In recent years, improvements in intensive care have led to an increase in the number of patients who survive severe brain injury. Although some of these patients go on to make a good recovery, many do not, and some of these individuals progress to a condition known as the vegetative state. Central to the description of this complex condition is the concept of "wakefulness without awareness," according to which vegetative patients are assumed to be entirely unaware, despite showing clear signs of wakefulness (Jennett and Plum, 1972). Thus, such patients often exhibit sleeping and waking cycles, will spontaneously open their eyes (hence, they are "awake"), and may even appear to "look" around a room, although they never fixate on anything, or anyone, and never follow (or "track") an object or a person, whether asked to do so or not. However, the assessment of these patients is extremely difficult and relies heavily on subjective interpretation of observed behavior at rest and in response to stimulation. A diagnosis is made after repeated examinations have yielded no evidence of sustained, reproducible, purposeful, or voluntary behavioral response to visual, auditory, tactile, or noxious stimuli. Thus, a positive diagnosis (of vegetative state) is ultimately dependent on a negative finding (no signs of awareness) and is therefore inherently vulnerable to a type II error or a *false negative* result. Indeed, internationally agreed diagnostic criteria for the vegetative state repeatedly emphasize the notion of "*no evidence of awareness of environment or self*" – in this instance, absence of evidence does appear to be considered adequate evidence of absence. Indeed, any assessment that is based on exhibited behavior after brain injury will be prone to error for a number of reasons. First, an inability to move and speak is a frequent outcome of chronic brain injury and does not necessarily imply a lack of awareness. Second, the behavioral assessment is highly subjective: behaviors such as smiling and crying are typically reflexive and automatic, but in certain contexts they may be the only means of communication available to a patient and therefore reflect a willful, volitional act of intention. These difficulties, coupled with inadequate experience and knowledge engendered through the relative rarity of these complex conditions, contribute to an alarmingly high rate of misdiagnosis (up to 43%) in this patient group (Childs et al., 1993; Andrews et al., 1996; Schnakers et al., 2009).

Recent advances in neuroimaging technology suggest a possible solution to this problem. If measurable brain responses could be marshaled and used as a proxy for a motor response then it may be possible to assess residual cognition, and even awareness, in severely brain injured patients without relying on (unreliable) behavioral signs. In this chapter, recent studies that have used both functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) in this context will be reviewed. The results suggest an urgent need for a re-evaluation of the existing diagnostic guidelines for behaviorally nonresponsive patients (including the vegetative state and related disorders of consciousness) and for the development and formal inclusion of validated, standardized neuroimaging procedures into those guidelines.

DIFFERENTIAL DIAGNOSIS IN DISORDERS OF CONSCIOUSNESS

The term "disorders of consciousness" is typically used to refer to three conditions: (1) coma, (2) vegetative state,

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and (3) minimally conscious state (Plum and Posner, 1983; Giacino et al., 2002; Royal College of Physicians, 2003). These conditions arise as a result of either traumatic (e.g., a blow to the head) or a nontraumatic (e.g., stroke) brain injury and may include damage to areas of the brainstem that mediate wakefulness and/or to cortico-cortical axonal connections that mediate cognitive function and awareness. Although particular patterns of pathology are commonly linked to each of these conditions, they are exclusively defined according to the *behaviors* exhibited by the patient rather than pathology. The key criteria are: (1) coma describes an acute condition, typically lasting 2–4 weeks after brain injury. A comatose patient does not open their eyes and only exhibits reflex responses to stimulation. Unlike vegetative state, therefore, the wakefulness component of consciousness is typically lost. (2) In contrast, the vegetative state describes a condition in which a patient opens their eyes and demonstrates sleep–wake cycles. Like comatose patients, they do not exhibit purposeful behavior, retaining reflex responses only. (3) The minimally conscious state differs from these conditions through the presence of inconsistent but reproducible evidence of awareness. In contrast to the comatose and vegetative states, minimally conscious patients demonstrate inconsistent but purposeful responses to command and/or sensory stimulation (see also Ch. 29).

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

FUNCTIONAL MAGNETIC RESONANCE IMAGING STUDIES

Decoding thoughts in healthy participants

In recent years, many attempt have been made to "decode" mental decisions or thoughts in healthy participants (e.g., Haynes et al., 2007; Cerf et al., 2010), in order to demonstrate that fMRI can be deployed as a brain–computer interface (Weiskopf et al., 2004) or simply to examine the neural correlates of various types of mental imagery (Aguirre et al., 1996; Jeannerod and Frak 1999). In one study, healthy volunteers were asked to freely decide which of two tasks to perform (add or subtract two numbers) and to covertly hold onto that decision during a delay (Haynes et al., 2007). A classifier was trained to recognize the characteristic fMRI signatures associated with the two mental states and in 80% of trials was able to decode which of the two tasks the volunteers were intending to perform, *before they actually performed it*. The principle employed was that certain types of thought are associated with a unique brain activation pattern that can be used as a signature for that specific thought. If a classifier is trained to recognize these characteristic signatures, a volunteer's thoughts can be ascertained (within the constraints of the experimental design) using their brain activity alone. More recently, pattern classification of fMRI signals was also used to decode movement intentions, moments before their initiation (Gallivan et al., 2011).

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

Using mental imagery to detect consciousness in nonresponsive patients

A significant recent addition to this field has been the development of fMRI paradigms that render awareness reportable in patients who are either entirely behaviorally nonresponsive and therefore diagnosed as vegetative (Owen et al., 2006; Boly et al., 2007), or partially responsive and diagnosed as minimally conscious state (Bardin et al., 2011, 2012). The most successful of these techniques make use of the general principle observed in studies of healthy participants that imagining performing a particular task generates a robust and reliable pattern of brain activity in the fMRI scanner that is similar to actually performing the activity itself. For example, imagining moving or squeezing the hands will generate activity in the motor and premotor cortices (Jeannerod and Frak, 1999), while imagining navigating from one location to another will activate the same regions of the parahippocampal gyrus and the posterior parietal cortex that have been widely implicated in map reading and other so-called spatial navigation tasks (Aguirre et al., 1996).

In one study (Boly et al., 2007), 34 healthy volunteers were asked to imagine hitting a tennis ball back and forth to an imaginary coach when they heard the word "tennis" (thereby eliciting vigorous imaginary arm movements) and to imagine walking from room to room in their house when they heard the word "house" (thereby eliciting imaginary spatial navigation). Imagining playing tennis was associated with robust activity in the supplementary motor area in each and every one (100%) of the participants scanned (Fig. 18.1). In contrast, imagining moving from room to room in a house activated the parahippocampal cortices, the posterior parietal lobe and the lateral premotor cortices; all regions that have been shown to contribute to imaginary, or real, spatial navigation (Aguirre et al., 1996; Boly et al., 2007). A recent follow-up study has demonstrated that such responses can be reliably produced in single participants (classified correctly in at least 80% of cases) using a hospital-grade 1.5 T scanner, lending the technique to widespread clinical use (Fernández-Espejo et al., 2014).

The robustness and reliability of these fMRI responses across individuals means that activity in these regions can be used as a neural proxy for behavior, confirming that the participant retains the ability to understand instructions, to carry out different mental tasks in response to those instructions and, therefore, is able to exhibit willed, voluntary behavior in the absence of any overt action. Thus, like any other form of action that requires *response selection,* these brain responses require awareness of the various contingencies that govern the relationship between any given stimulus (in this case, the cue word for one of two possible imagery tasks) and a response (in this case, imagining the task). Put simply, fMRI responses of this sort can be used to measure awareness because awareness is necessary for them to occur.

Owen et al. (2006, 2007) used this same logic to demonstrate that a young woman who fulfilled all internationally agreed criteria for the vegetative state was, in fact, consciously aware and able to make responses of this sort using her brain activity. The patient, who had been involved in a complex road traffic accident and had sustained very severe traumatic brain injuries, had remained entirely unresponsive for a period of 6 months prior to the fMRI scan. During the scanning session, the patient was instructed to perform the two mental imagery tasks described above. When she was asked to imagine playing tennis (Fig. 18.1, patient 5), statistically significant activity was observed repeatedly in the supplementary motor area (Owen et al., 2006) that was indistinguishable from that observed in the healthy volunteers scanned by Boly et al. (2007). Moreover, when

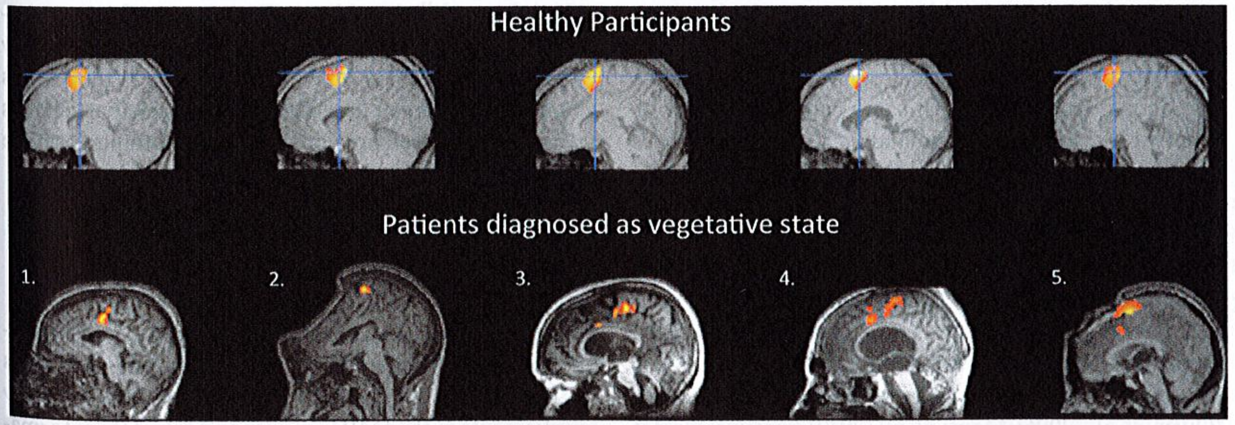

Fig. 18.1. Top row: Five healthy participants asked to imagine playing tennis in the fMRI scanner (adapted from Boly et al., 2007). In all five cases, significant activity was observed in the premotor cortex, indicating that they had understood the instruction and were responding by carrying out the appropriate type of mental imagery; that is, *following a command.* Bottom row: Formally identical responses in five patients who behaviorally meet the clinical criteria for a diagnosis of vegetative state (adapted from Owen et al., 2006 (patient 5) and Monti et al., 2010 (patients 1–4)), confirming that, in spite of an inability to respond physically, these patients can still demonstrate *command following* by modulating their cortical fMRI activity. Such responses are observed in approximately 17% of vegetative patients.

she was asked to imagine walking through her home, significant activity was observed in the parahippocampal gyrus, the posterior parietal cortex and the lateral premotor cortex which was again indistinguishable from those observed in healthy volunteers (Owen et al., 2006, 2007). On this basis, it was concluded that, despite fulfilling all of the clinical criteria for a diagnosis of vegetative state, this patient retained the ability to understand spoken commands and to respond to them through her brain activity, rather than through speech or movement, confirming beyond any doubt that she was consciously aware of herself and her surroundings. In a follow-up study of 23 patients who were behaviorally diagnosed as vegetative, Monti et al. (2010) showed that four (17%) were able to generate reliable responses of this sort in the fMRI scanner (Fig. 18.1, patients 1–4).

After a severe brain injury, when the request to move a hand or a finger is followed by an appropriate motor response, the diagnosis can change from vegetative state (no evidence of awareness) to minimally conscious state (some evidence of awareness). By analogy then, if the request to activate the supplementary motor area of the brain by imagining moving the hand is followed by an appropriate brain response, shouldn't we give that response the very same weight? Skeptics may argue that brain responses are somehow less physical, reliable, or immediate than motor responses but, as is the case with motor responses, all of these arguments can be dispelled with careful measurement, replication, and objective verification (Owen et al., 2006, 2007; Boly et al., 2007; Monti et al., 2010; Fernández-Espejo and Owen, 2013; Hampshire et al., 2013; Naci et al., 2013; Naci and Owen, 2013). For example, if a patient who was assumed to be unaware raised his/her hand to command on just one occasion, there would remain some doubt about the presence of awareness given the possibility that this movement was a chance occurrence, coincident with the instruction. However, if that same patient were able to repeat this response to command on 10 occasions, there would remain little doubt that the patient was aware. By the same token, if that patient was able to activate his/her supplementary motor area in response to command (e.g., by being told to imagine hand movements), and was able to do this on every one of 10 trials, would we not have to accept that this patient was consciously aware? Like most neuroimaging investigations, replication of this sort was inherent in both the studies described above (Owen et al., 2006; Monti et al., 2010) because correct classification of the characteristic neural signatures required statistically similar significant results across repeated trials.

It has also been suggested that fMRI responses of this sort could reflect an "implicit preconscious neural response" to the key words that were used in those studies (Greenberg 2007; Nachev and Husain 2007). While no empirical evidence exists to support this possibility, it is nevertheless important to consider its theoretical plausibility. In the volunteers studied by Boly et al. (2007), and in the patients reported by Owen et al. (2006) and Monti et al. (2010), the observed activity was not transient but persisted for the full 30 seconds of each imagery task, i.e., far longer than would be expected, even given the hemodynamics of the fMRI response. In fact, these task-specific changes persisted until the volunteers and the patients were cued with another stimulus indicating that they should switch tasks. No evidence exists to show that single-word stimuli (such as "tennis," "house," or "rest") can unconsciously elicit sustained (i.e., 30 seconds) hemodynamic responses in the supplementary motor area, the parahippocampal gyrus, the posterior parietal cortex or the lateral premotor cortex premotor cortex, yet considerable data exist to suggest that they cannot. For example, although it is well documented that some words can, under certain circumstances, elicit wholly automatic neural responses, such responses are typically transient and last for just a few seconds. In addition, the activation patterns observed in the studies by Boly et al. (2007), Owen et al. (2006), and Monti et al. (2010) were entirely predicted and were not in brain regions that are known to be involved in word processing, but rather, in regions that are known to be involved in the two imagery tasks (also see Weiskopf et al., 2004). In short, temporally sustained fMRI responses in these regions of the brain are impossible to explain in terms of automatic responses to either single "key" words or to short sentences containing those words. In fact, noninstructive sentences containing the same key words (e.g., "The man enjoyed playing tennis") have been shown to produce no sustained activity in any of these brain regions in healthy volunteers, nor is activity seen when the words "tennis" and "house" are presented to naïve participants who have not been previously instructed to perform the imagery tasks (Owen et al., 2007).

Using anesthesia to induce behavioral nonresponsiveness in healthy participants

The relationship between mental imagery and consciousness was investigated further by Adapa and colleagues (Adapa, 2011; Adapa et al., 2011), who sedated healthy participants in the fMRI scanner and asked them to imagine playing a game of tennis using exactly the same task design that has been used to detect covert consciousness in some vegetative and minimally conscious patients (Owen et al., 2006; Monti et al., 2010). During three scanning sessions, the participants were nonsedated (awake), lightly sedated (a slowed response to conversation), and

deeply sedated (no conversational response, rousable by loud command), and were asked to imagine playing tennis following a prompt. When fully awake, task-related activity was observed in the premotor cortex replicating the earlier results of Boly et al. (2007) and Owen et al. (2006). However, task-related activity in the premotor cortex was markedly attenuated even at light levels of sedation and was completely absent when the participants were deeply sedated. Following the cessation of propofol and recovery of awareness, robust activity was again observed in the premotor cortex following the instruction to resume the imagery tasks. This result confirms that healthy volunteers who are measurably nonaware (i.e., "unconscious") are *not able* to generate the characteristic pattern of brain activity that is associated with imagining playing tennis, suggesting that awareness is likely to be necessary for this response to occur in patients.

Other functional magnetic resonance imaging approaches to detecting consciousness in nonresponsive patients

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

Following similar logic, Monti et al. (2013) used an entirely different type of approach to demonstrate that a patient who was entirely unable to exhibit any signs of command following during standard behavioral testing could nevertheless demonstrate reliable and robust responses in predefined brain regions by willfully modulating his brain activity. The stimuli used were superimposed pictures of faces and houses. When healthy volunteers are requested, following a cue tone, to shift their attentional focus from a face to a house (or vice versa), a distinct shift in fMRI activity from the fusiform gyrus (the FFA), to the parahippocampal gyrus (the "parahippocampal place area") is observed (or vice versa) (Monti et al., 2013). With continuous repeated cues this effect manifests as a time-locked alternation of activity between these two functionally distinct brain regions, despite the fact that the stimulus remains unchanged throughout. Thus, this change is driven not by the external stimulus *per se* but by the will or the intention of the participant to focus on one or the other aspect of the stimulus and is therefore a reliable indicator of conscious intent. When asked to perform the same task, the activity observed in the patient closely resembled the activity observed in the healthy volunteers and, as such, provided the only conclusive evidence that he could indeed follow commands (Monti et al., 2013).

These types of approach all illustrate a paradigmatic shift towards the use of active (e.g., willful) tasks in the assessment of covert awareness after serious brain injury. What sets such tasks apart is that the neural responses required are not produced *automatically* by the eliciting stimulus, but rather, depend on time-dependent and sustained responses generated by the participants themselves. Such behavior (albeit neural "behavior") provides a proxy for a motor action and is, therefore, an appropriate vehicle for reportable awareness (Zeman, 2009).

Using functional magnetic resonance imaging to communicate with behaviorally nonresponsive patients

Owen and Coleman (2008b) extended the general principles discussed above, by which active mental rehearsal is used to signify awareness, to show that communication of "yes" and "no" responses was possible using the same approach. Thus, a healthy volunteer was able to reliably convey a "yes" response by imagining playing tennis and a "no" response by imaging moving around a house, thereby providing the answers to simple questions posed by the experimenters using only their brain activity. This technique was further refined by Monti et al. (2010), who successfully decoded three "yes" and "no" responses from each of 16 healthy participants with 100% classification accuracy using only their real time changes in the supplementary motor area (during tennis imagery) and the parahippocampal place area (during spatial navigation). Moreover, in one traumatic brain injury patient who had been repeatedly diagnosed as vegetative over a 5 year period, similar questions were posed and successfully decoded using the same approach (Monti et al., 2010). Thus, this patient was able to convey biographical information that was not known to the experimenters at the time (but was verified as factually correct) such as his father's name and the last place that he had visited on vacation before his accident 5 years earlier. In contrast, and despite a reclassification to minimally conscious state following the fMRI scan, it remained impossible to establish any form of communication with this patient at the bedside.

An obvious application for approaches of this sort is to begin to involve some of these patients in the decision making processes involved in their own therapeutic care and management. To date, this has only been achieved successfully in one patient, who had been repeatedly diagnosed as vegetative for 12 years following a traumatic brain injury (Fernández-Espejo and Owen, 2013). The patient was a male who, in December 1999 and at the age of 26, had suffered a severe closed head injury in a motor vehicle accident. On admission to hospital he had a Glasgow Coma Scale (Teasdale and Jennett, 1974) 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. Over the next 12 years, the patient was assessed regularly by experienced neurologists and multidisciplinary teams and throughout this period his behavior remained consistent with the internationally accepted criteria for the vegetative state. Indeed, over one 14 month period in 2011–2013, a total of 20 standardized behavioral assessments were performed by a multidisciplinary team, at different times of the day and in different postural positions, using the Coma Recovery Scale – Revised (Giacino et al., 2004), and his diagnosis was unchanged throughout. In February 2012, 12 years and2 months after his accident, the patient was first scanned using the fMRI mental imagery approach described above (Owen et al., 2006; Monti et al., 2010). The patient was able to provide correct answers to multiple externally verifiable questions, including his own name, his whereabouts, the name of his personal support worker (who he had only encountered in the years following his accident), the current date, and other basic factual information (e.g., whether a banana is yellow). Two nonverifiable questions were then posed, including one pertaining to his care preferences (e.g., whether he liked watching (ice) hockey games on TV), and another to details about his current clinical condition (e.g., whether he was in any physical pain). Within the time constrains of the scanning visits, the majority of responses to these questions were verified in independent sessions that posed the reverse questions (e.g., "Is your name Mike?" versus "Is your name Scott?"). At the time of the patient's death in 2013, answers to 12 different questions had been obtained across several sessions, despite the fact that the patient remained entirely physically nonresponsive at the bedside (Fernández-Espejo and Owen, 2013).

Although techniques like the ones described above require that the patient engages in rather specific types of mental imagery (playing tennis or moving from room to room through a house), that is not really the main point that allows consciousness to be detected and communication to occur. All that is required to detect consciousness is a reliable indicator that a patient can turn his or her attention to a specific scenario, because this then serves as a "neural proxy" for a physical "response to command". By extension, if it can be shown that the patient can turn his or her attention to two separate scenarios, then communication is possible because those two separate scenarios can be linked to "yes" responses and "no" responses, respectively. Thus mental imagery is not necessary at all but serves as a simple vehicle for guiding a patient's attention one way or another.

Naci and colleagues (Naci and Owen, 2013; Naci et al., 2013) used this general principle to develop a novel tool for communicating with nonresponsive patients based on how they selectively directed their attention to sounds while in the fMRI scanner. It is well established that selective attention can significantly enhance the neural representation of attended sounds (Bidet-Caulet et al., 2007), although most previous studies have focused on group level changes rather than individual responses that are crucial for work with (individual) brain injured patients. In their first study (Naci et al., 2013), 15 healthy volunteers answered questions (e.g., "Do you have brothers or sisters?") in the fMRI scanner, by selectively attending to the appropriate word ("yes" or "no"), which was played to them auditorily, interspersed with "distractor" stimuli (digits 1–9). Ninety percent of the answers were decoded correctly based on activity changes within the attention network of the brain (i.e., 90% classification accuracy). Moreover, the majority of volunteers conveyed their answers with less than 3 minutes of scanning, which represents a significant time saving over the mental imagery methods described above (Owen et al., 2006, 2007; Boly et al., 2007). Indeed, a formal comparison between the two approaches revealed improved individual success rates and an overall reduction in the scanning times required to correctly detect responses; 100% of volunteers showed significant task-appropriate activity to the selective attention task compared to 87% to the motor imagery. This result is consistent with previous studies showing that a proportion of healthy volunteers do not produce reliably classifiable brain activation during mental imagery tasks (Boly et al., 2007).

In a follow-up study, Naci and Owen (2013) used the same approach to test for residual conscious awareness and communication abilities in three behaviorally nonresponsive brain injured patients. As in the previous study of healthy participants, the patients had to either "count" or "relax" as they heard a sequence of sounds. The word *count* at the beginning of the sequence instructed the patient to count the occurrences of a target word (*yes* or *no*), while the word *relax* instructed them to relax and ignore the sequence of words. Reliable activity increases in the attention network of the brain after the word *count* relative to the word *relax* was taken as evidence of command following. All three patients (two of whom were diagnosed as being in a minimally conscious state and one as being in a vegetative state) were able to convey their ability to follow commands inside the fMRI scanner by following the instructions in this way. In stark contrast, extremely limited or a complete lack of behavioral responsivity was observed in repeated bedside assessments of all three patients. These results confirm that selective attention is an appropriate vehicle for detecting covert awareness in some behaviorally nonresponsive patients who are presumed to mostly or entirely lack any cognitive abilities whatsoever.

In a following series of scans, communication was attempted in two of the patients. The communication scans were similar to those in the command-following scan, with one exception. Instead of an instruction (count or relax), a binary question (e.g. "Is your name Steven?") preceded each sound sequence. Thus, each patient then had to willfully choose which word to attend to (count) and which to ignore, depending on which answer he wished to convey to the specific question that had been asked. Using this method, the two patients (one diagnosed as minimally conscious state and one diagnosed as vegetative state) were able to use selective attention to repeatedly communicate correct answers to questions that were posed to them by the experimenters (Naci and Owen, 2013). In the absence of external cues as to which word the patient was attending to, the functional brain activation served as the only indicator of the patient's intentions – and in both cases, led to the correct answers being decoded. For example, when asked "Are you in a supermarket?" one patient showed significantly more activation for "no" than "yes" sequences in a network of brain areas that had been previously activated when that patient was focusing attention on external cues. Conversely, when asked "Are you in a hospital?" the patient showed significantly more activation for "yes" than "no" sequences in the same regions. Despite his diagnosis (vegetative state for 12 years), the fMRI approach allowed this patient to establish interactive communication with the research team in four different fMRI sessions. The patient's brain responses within specific regions were remarkably consistent and reliable across two different scanning visits, 5 months apart, during which the patient maintained the long-standing vegetative state diagnosis. For all four questions, the patient produced a robust neural response and was able to provide the correct answer with 100% classification accuracy. The patient's brain activity in the communication scans not only further corroborated that he was, indeed, consciously aware but also revealed that he had far richer cognitive reserves than could be assumed based on his clinical diagnosis. In particular, beyond the ability to pay attention, these included autobiographical knowledge and awareness of his location in time and space.

ELECTROENCEPHALOGRAPHIC STUDIES

Performing fMRI in severely brain injured patients is enormously challenging; in addition to considerations of cost and scanner availability, the physical stress incurred by patients as they are transferred to a suitably equipped fMRI facility is significant. Movement artifacts often occur in imaging datasets from patients who are unable to remain still, while metal implants, including plates and pins which are common in many traumatically injured populations, may rule out fMRI altogether. EEG measures the activity of groups of cortical neurons from scalp electrodes and is far less expensive than fMRI, both in terms of initial cost and maintenance. EEG recordings are unaffected by any resident metallic implants and, perhaps most importantly, can be used at the bedside (Vaughan et al., 2006). In brain injured patients, EEG recordings are typically made in the acute period and allow for broad assessments of cortical damage including the occurrence of brain death. However, uncertainty about the causes of abnormal raw EEG patterns (i.e., damage to the cortex itself, or to subcortical structures which influence cortical activity) provides challenges for its use as a more precise tool for the assessment of awareness (Kulkarni et al., 2007).

Using electroencephalography to detect consciousness in nonresponsive patients

Schnakers and associates (2009) used an elegant volitional "own name" paradigm in which, in half of the blocks, patients were instructed to count the number of times they heard their own name, while in the other half they were instructed to passively listen to identical stimuli without counting. Like healthy controls, a group of minimally conscious patients demonstrated reliably larger P3 components, linked to target detection, during the active counting task. As the only aspect of the task that differed between the two conditions was the patient's intention (to count or to listen), as guided by the prior instruction, it was possible to unequivocally infer that these patients could follow commands and therefore that they were aware. In contrast, overt (motor) forms of command following were at best inconsistent when the patients were tested behaviorally.

Motor imagery also produces clearly distinguishable modulation of EEG sensorimotor rhythms (SMR) (Wolpaw et al., 1991; Cincotti et al., 2003) similar to those seen during motor execution, and has been the basis of several recent attempts to detect conscious awareness after severe brain injury. For example, in one early study, Kotchoubey and colleagues (2003) described a completely locked-in patient whose slow EEG activity differed significantly between trials when he was asked to "try" to move the left hand, as compared to the right. In the EEG record, imagined movements (motor imagery) are evident in the form of reductions of power – or event-related desynchronizations (ERD) – of the μ (~7–13 Hz) and/or β (~13–30 Hz) bands over the topographically appropriate regions of the motor cortex – for example, over the lateral premotor cortex for hand movements and over more medial premotor cortex for toe movements (Pfurtscheller and Neuper, 1997). In some individuals, these ERDs may also be accompanied by event-related synchronizations (ERS; relative increases in power) over motor areas contralateral to, or surrounding, the ERD (Pfurtscheller et al., 2006; 2008). Using classification techniques it is now possible, on the basis of these EEG responses alone, to determine the form of motor imagery being performed by a conscious individual with a high degree of accuracy (Guger et al., 2003). For example, Cruse et al. (2011) recently reported a new EEG-based classification technique in which two mental imagery responses (squeezing the right hand or squeezing the toes) were successfully decoded offline in nine out of 12 healthy individuals with accuracy rates varying between 60% and 91%. The same approach was then used to attempt to detect evidence of command following in the absence of any overt behavior, in a group of 16 patients who met the internationally agreed criteria for a diagnosis of vegetative state. Three of these patients (19%) were repeatedly and reliably able to generate appropriate EEG responses to the two distinct commands ("squeeze your right hand" or "squeeze your toes"), despite being behaviorally entirely unresponsive, indicating that they were aware and following the task instructions (Fig. 18.2). Indeed, on the basis of such data, far broader conclusions about residual cognition can be drawn. For example, performance of this complex task makes multiple demands on many cognitive functions, including sustained attention (over 90 second blocks), response selection (between the two imagery tasks), language comprehension (of the task instructions) and working memory (to remember which task to perform across multiple trials within each block) – all aspects of "top-down" cognitive control that are usually associated with, indeed, could be said to characterize, normal conscious awareness (Naccache, 2006).

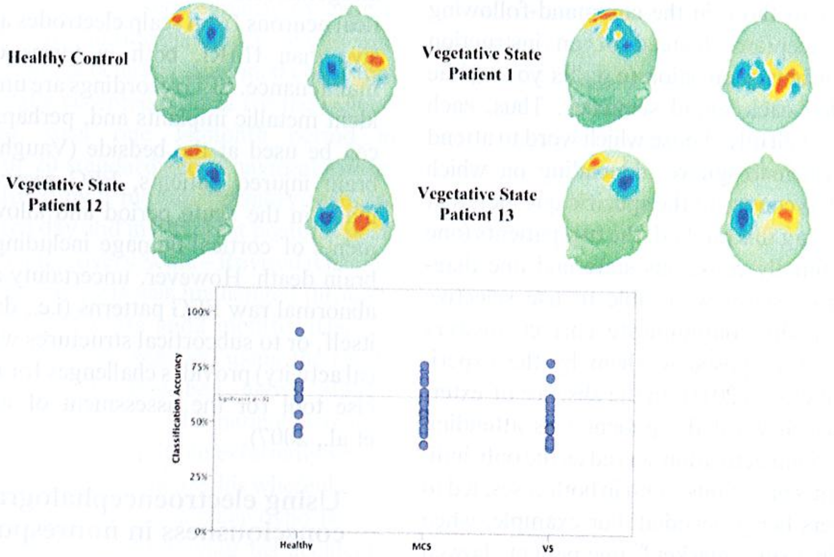

Fig. 18.2. Top: Three of 16 (19%) patients who had been diagnosed as vegetative were repeatedly and reliably able to generate appropriate EEG responses to two distinct commands ("squeeze your right hand" or "squeeze your toes"), despite being behaviorally entirely unresponsive. Thus, when the scalp distributions of data from a classification procedure are plotted, it is evident that the neurophysiologic basis of the positive EEG outcome – with clear foci over the hand and toe motor areas – are formally identical when compared between a healthy control participant and the three patients. (Maps show the scalp distribution of the single feature – time-point × frequency-band – with the highest absolute coefficient value from one training run of the cross-validation procedure. Red colors indicate coefficient values greater than zero, blue indicate values less than zero.) These data confirmed that these patients were, in fact, aware and able to follow task instructions. Bottom: A similar procedure in a group of minimally conscious patients revealed that 22% were able to reliably and repeatedly follow commands by modulating their EEG responses. (Adapted from Cruse et al., 2011, 2012a.)

In a more recent study, Cruse et al. (2012b) refined their EEG approach using a simpler and more clinically viable paradigm that required participants to actually try to move their hands and, unlike the previous study (Cruse et al., 2011), 100% of the healthy volunteers showed reliable ERD and ERS responses (Cruse et al., 2012b). Moreover, in one of the patients studied by Naci and Owen (2013), who had been repeatedly diagnosed as vegetative for 12 years, reliable modulations of sensorimotor β rhythms were observed following commands to try to move and these could be classified significantly at a single-trial level. This patient is the first published case of a clinically vegetative patient in whom awareness has been demonstrated using two independent imaging methods (fMRI and EEG) in the absence of any supportive evidence from clinical (behavioral) examination (for a complete description of this case, see Fernández-Espejo and Owen, 2013).

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

These results demonstrate that consistent responses to command – a reliable and universally accepted indicator that a patient is not vegetative – need not be expressed behaviorally at all but rather, can be determined accurately on the basis of EEG responses (Cruse et al., 2012b).

In a follow-up study (Cruse et al., 2012a), 23 minimally conscious state patients (15 traumatic brain injury and eight nontraumatic brain injury) completed the same motor imagery EEG task (Fig. 18.2). Consistent and robust responses to command were observed in the EEG of 22% of the minimally conscious state patients (5/23). Etiology had a significant impact on the ability to successfully complete this task, with 33% of traumatic patients (5/15) returning positive EEG outcomes, compared with none of the nontraumatic patients (0/8). The results suggest that the overt behavioral signs of awareness exhibited by nontraumatic minimally conscious patients appear to be an accurate reflection of their covert cognitive abilities measured using this novel EEG technique. In stark contrast, they demonstrated that one-third of a group of traumatically injured patients in the minimally conscious state possess a range of high-level cognitive faculties that are not evident from their overt behavior.

As a result of the strains of rapid acceleration and deceleration on the brain, the most common neuropathologic change following traumatic brain injury is diffuse axonal injury (Adams et al., 1982; Gennarelli et al., 1982) which predominantly affects both hemispheres, the corpus callosum, the brainstem and the cerebellum in the vegetative state and minimally conscious state (Kinney et al., 1994; Adams et al., 1999; Jennett et al., 2001) (see also Chs 29 and 35). On the other hand, when these conditions are caused by a nontraumatic injury, such as hypoxic-ischemic encephalopathy, a selective and widespread damage to the neocortex and thalamus is observed, possibly due to the differences in the oxygen requirements of these structures (Adams and Duchen, 1992; Kinney et al., 1994; Adams et al., 2000). In the broadest sense then, what is known about the neuropathologic mechanisms underlying traumatic brain injury and nontraumatic brain injury, particularly in relation to the relative preservation of the cortex following traumatic brain injury, is reflected here in the differential degree of functional deficit observed across the two groups.

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

Using electroencephalography to communicate with behaviorally nonresponsive patients

As described above, Kotchoubey and colleagues (2003) described a completely locked-in patient with amyotropic lateral sclerosis (ALS) whose slow EEG activity differed significantly between trials in which he was asked to "try" to move the left or right hands, which in the most basic sense reflects a form of communication. Similarly, Kübler and colleagues (2005) showed that locked-in patients with ALS could learn to modulate their sensorimotor rhythms with more than 70% accuracy, but did not test any patients diagnosed with a disorder of consciousness (e.g., vegetative state) with this paradigm.

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

Building on much of this earlier work, the success of recent EEG techniques for detecting awareness in nonresponsive patients (Cruse et al., 2011, 2012a, b) paves the way for the development of a true "brain–computer interface" (Birbaumer 2006) – or simple, reliable communication devices – in this patient group. It seems likely that such devices will provide a form of external control and communication based on mappings of distinct mental states, for example, imagining right hand movements to communicate "yes" and toe movements to communicate "no." Indeed, the degrees of freedom provided by EEG have the potential to take this beyond the sorts of binary responses that have worked well using fMRI (Monti et al., 2010; Fernández-Espejo and Owen, 2013; Naci and Owen, 2013; Naci et al., 2013), to allow methods of communication that are far more functionally expressive, based on multiple forms of mental state classification (Farwell and Donchin, 1988; Sellers and Donchin, 2006; Wolpaw et al., 2002). The development of techniques for the real-time classification of these forms of mental imagery (e.g., Cruse et al., 2011, 2012a, b) will open the door for routine two-way communication with some of these patients, ultimately allowing them to share information about their inner worlds, experiences, and needs.

IMPLICATIONS

Diagnosis

An obvious clinical consequence of the emergence of novel neuroimaging techniques that permit the identification of covert awareness and communication in the absence of any behavioral response is the possibility of improved diagnosis after severe brain injury. It is notable that in one of the cases described above (Cruse et al., 2012b; Fernández-Espejo and Owen, 2013; Naci and Owen, 2013) the patient was repeatedly and rigorously assessed by experienced teams and showed no behavioral sign of awareness on any of these occasions; indeed, this continued to be the case even after awareness had been established unequivocally with both fMRI and EEG. Technically however, he was not *misdiagnosed* (as vegetative) in the sense that any error of judgment was made, because the accepted diagnostic criteria are based on behavior, and no behavioral 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 nonresponsive? The term "nonbehavioral minimally conscious state" has been suggested (Fins and Schiff, 2006), although 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 (Fernández-Espejo and Owen, 2013; Naci and Owen, 2013). 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 solely adjunctive technologies (Giacino et al., 2009; Laureys and Schiff, 2012). In its classic clinical presentation, locked-in syndrome refers to patients who are left with only vertical eye movements and/or blinking, which often permits rudimentary communication. Cognitive function, however, is generally fully preserved, at least in those cases where the lesion is limited to the ventral pons (Schnakers et al., 2008c). Patients like the one described here are clearly "locked in" in the general sense of the term, but do not have many of the same neuropathologic 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 has already been able to report that he remembers his own name and that he knows the current date and where he is (Naci and Owen, 2013), confirming that he is well oriented 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. Schnakers et al. (2008c) have recently developed a standardized neuropsychological assessment for locked-in syndrome that uses simple eye movements as responses (in most cases to provide "yes"/"no" answers to questions). There is no technical or theoretical reason why a similar approach could not be used with fMRI data in entirely nonresponsive patients, although the data would take considerably longer to acquire. To this end, Hampshire et al. (2013) have recently used fMRI to assess complex logical reasoning ability in a patient who was assumed to be in a vegetative state. Adapting a verbal reasoning paradigm from Baddeley (1968), Hampshire et al. (2013) presented participants with statements describing the ordering of two objects, a face, and a house. Participants were instructed to deduce which of the objects was in front, and to visualize the object in their mind. For example, if they heard the statement "the face is not followed by a house," the correct answer would be "house." Conversely, if they heard "the face precedes the house," the correct answer would be "face". One patient, who, based on the behavioral diagnosis, was assumed to be in the vegetative state, engaged the same brain regions as healthy individuals in response to the reasoning task demands. This result was consistent with the patient's positive outcome in the fMRI command following task (Owen et al., 2006; Boly et al., 2007) and suggested that, despite the long-standing clinical diagnosis of vegetative state, the patient was not only consciously aware, but, critically, retained capacity for higher order cognition, in particular, for solving logically complex verbal problems.

Prognosis

A related issue concerns the implications that emerging neuroimaging approaches may have for prognosis in this patient group. It is of interest that in the case described by Owen et al. (2006), the patient began to emerge from her vegetative state to demonstrate diagnostically relevant behavioral markers before the prognostically important (for a diagnosis of permanent vegetative state) 12 month threshold was reached, suggesting that early evidence of awareness acquired with functional neuroimaging may have important prognostic value. Long-term follow-up in that case confirmed that the patient emerged to be minimally conscious with some (limited) behavioral communication abilities until her death some years later. Indeed, with a marked increase in the number of studies using neuroimaging techniques in patients with disorders of consciousness, a consistent pattern is beginning to emerge. In an excellent review of the available literature, Di et al. (2008) considered 15 separate $H_2{}^{15}O$ PET and fMRI studies involving 48 published cases which were classified as "absent cortical activity," "typical activity" (activity in low level primary sensory cortices only), and "atypical activity" (activity in higher level associative cortices). The results suggest that atypical activity patterns appear to predict recovery from vegetative state with a 93% specificity and 69% sensitivity. That is to say, nine of 11 patients exhibiting atypical activity patterns recovered consciousness, whereas 21 of 25 patients with typical primary cortical activity patterns and four out of four patients with absent activity failed to recover. This important review strongly suggests that functional neuroimaging data can provide important prognostic information beyond that available from bedside examination alone. Similarly, in the large recent study of 41 patients by Coleman et al. (2009), direct evidence of prognostically important information from the neuroimaging data was reported that was at odds with the behavioral assessment at the time of scanning. Thus, contrary to the clinical impression of a specialist team using behavioral assessment tools, two patients who had been referred to the study with a diagnosis of vegetative state did in fact demonstrate clear signs of speech comprehension when assessed using fMRI. More importantly, however, across the whole group of patients, the fMRI data were found to have no association with the behavioral presentation at the time of the investigation but correlated significantly with subsequent behavioral recovery, 6 months after the scan. In this case, the fMRI data predicted subsequent recovery in a way that a specialist behavioral assessment could not.

Recently, an effort has also been made to quantify those particular aspects of the raw EEG signal that may be associated with subsequent outcome in patients after serious brain injury. For example, it has been observed (Babiloni et al., 2009) that occipital source power in the α band (8–13 Hz) of resting EEG, as calculated with low-resolution electromagnetic tomography (LORETA), is correlated with recovery outcome at 3 month follow-up in a group of vegetative state patients; those who made a behavioral recovery had higher resting α band power than those who did not make a significant recovery. The prognostic value of resting EEG has also been demonstrated by Schnakers and colleagues (2008a), who calculated the bispectral indices (BIS), a composite measure of the frequency content of the EEG, in a mixed group of vegetative state and minimally conscious state patients. The BIS was shown to be positively correlated with behavioral scores of awareness at the time of testing and associated with outcome at 1 year post-trauma.

Finally, Stender et al. (2014) investigated the prognostic value of neuroimaging with both fluorodeoxyglucose (FDG) positron emission tomography (PET) at rest and fMRI during the mental tasks described above (Owen et al., 2006; Boly et al., 2007; Monti et al., 2010) in 41 vegetative state patients and 81 minimally conscious state patients. Thirteen (32%) of the patients diagnosed as unresponsive using standard clinical methods showed brain activity suggestive of minimal consciousness on at least one of these two neuroimaging tests and nine of these patients (69%) subsequently recovered consciousness. However, PET correctly predicted outcome in 75 of 102 patients, and fMRI in 36 of 65 patients.

Legal issues

The possibility of using fMRI or EEG for the detection of awareness in behaviorally nonresponsive patients (Owen et al., 2006; Cruse et al., 2011; Fernández-Espejo and Owen, 2013; Naci and Owen, 2013) raises a number of issues for legal decision making relating to the prolongation, or otherwise, of life after severe brain injury. Foremost is the concern that diagnostic and prognostic accuracy is assured, as treatment decisions often include the possibility of withdrawal of life support. At present, in most civilized jurisdictions, decisions concerning life support (nutrition and hydration) are only made once a diagnosis of *permanent* vegetative state has been made. In cases in which the critical threshold for a diagnosis of permanent vegetative state has passed, the medical team formally review the evidence and discuss this with those closest to the patient. In England and Wales, for example, the courts require that a decision to withdraw nutrition and hydration should be referred to them before any action is taken (Royal College of Physicians, 2003). On the other hand, decisions not to use resuscitation in the case of cardiac arrest, or not to use antibiotics or dialysis, can be taken by the doctor in the best interests of the patient after full discussion with all those concerned. Interestingly, according to the same working party, "one cannot ever be certain that a patient in the vegetative state is wholly unaware . . . in view of this small but undeniable element of uncertainty, it is reasonable to administer sedation when hydration and nutrition are withdrawn to eliminate the possibility of suffering, however remote" (Royal College of Physicians, 2003). With the emergence of novel neuroimaging techniques that permit the identification of covert awareness in the absence of any behavioral response (Owen et al., 2006; Cruse et al., 2011; Fernández-Espejo and Owen, 2013; Naci and Owen, 2013), the wording of this statement acquires renewed resonance. In the case described by Owen et al. (2006), and in most of the similar cases that have appeared in the subsequent literature (e.g., Owen and Coleman, 2008a), the scans that revealed awareness were acquired before the time at which the decision making process governing withdrawal of life support is legally permitted to begin (i.e., the patients had not yet reached the point where a diagnosis of *permanent* vegetative state could be made). Therefore, even if the neuroimaging evidence had been admissible as part of the formal diagnostic and prognostic evaluation, in those particular cases it was too early for the process governing end-of-life decisions to begin and therefore the situation did not arise. The same is not true of the patient described in detail above (Cruse et al., 2012b; Fernández-Espejo and Owen, 2013; Naci and Owen, 2013); that is to say, the patient had persisted in a condition of physical nonresponsiveness for more than 12 years and had therefore long since met all of the internationally agreed criteria for a diagnosis of *permanent* vegetative state; the patient could therefore be the subject of a legal petition to withdraw nutrition and hydration. Although this did not occur in this particular case, 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: (1) 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); (2) 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: (1) whether there is any chance of significant recovery; (2) whether the patient is conscious or "aware" of her/his condition; and (3) what the patient would have wanted if they could have been consulted about their 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 or EEG responses is predictive of recovery, although there are certainly some suggestions that this might be the case (Di et al., 2008; Coleman et al., 2009). Regarding the remaining two points of legal discussion, the case for the use of fMRI is becoming increasingly compelling. It is now clear that fMRI can be used to detect covert awareness in some cases where no clinical evidence exists to confirm that is the case (Owen et al., 2006, 2007; Monti et al., 2010; Cruse et al., 2011, 2012b; Fernández-Espejo and Owen, 2013; Naci and Owen, 2013), and, subject to the appropriate quality controls and scientific guidance, there is no *a priori* reason why such data could not be used to guide a court's opinion about "whether the patient is conscious or 'aware' of her/his condition." Again, the patient described in detail by Fernández-Espejo and Owen (2013) is a case in point; although multiple clinical assessments across 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 (fMRI) way, 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" (Kahane and Savulescu, 2009) is one that could be answered directly by the patient himself.

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

CONCLUSIONS

In the last few years, neuroimaging methods – most notably fMRI and EEG – have been brought to bear on one of the most complex and challenging questions in clinical medicine, that of detecting residual cognitive function, and even covert awareness, in patients who have sustained severe brain injuries. The results demonstrate that responses need no longer be *physical* responses in the traditional sense (e.g., the blink of an eye or the squeezing of a hand), but can now include responses that occur entirely within the brain itself. The recent use of reproducible and robust task-dependent fMRI responses as a form of "communication" in patients who are assumed to be vegetative (e.g., Monti et al., 2010; Fernández-Espejo and Owen, 2013; Naci and Owen, 2013) represents an important milestone in this process. In some of these cases, these patients have been able to communicate information that could not have been known by the experimenters at the time, yet could be independently verified later (using more traditional methods of communication with the family), as being factually correct and true. More importantly perhaps, in one case, a patient has used these methods to answer clinically and therapeutically relevant questions (including "Are you in any pain?") that could not be answered in any other way, including via a third party. More recently, the use of EEG – a more portable and cost-effective method that can be used at the bedside – to detect consciousness in patients who appeared to be entirely vegetative or minimally conscious (Cruse et al, 2011, 2012a, b) opens the door to the development and routine use of true BCIs in some of these patients (Owen, 2013). Thus, in one case reported by Cruse et al. (2011), the patient was able to perform approximately 100 measurable responses to command that were detected and correctly classified in his EEG record, within a relatively short time period. As an example of the extraordinary possibilities that BCIs may offer in the future, 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 (Hochberg et al., 2012). Whether such methods could ever be developed to the point that they might allow rudimentary motor control, communication, and even contribute to rehabilitative efforts in patients who are entirely nonresponsive is not clear, although the major barriers are likely to be logistic and clinical, rather than purely technical. For example, the level of arousal, awareness, and cognition varies dramatically between nonresponsive patients (as well as at different times within the same patient); thus, in order to maximize the chances of success, any effective BCI system will need to be as robust to this variation, and as straightforward to use, as possible (Naci et al., 2012). In addition, the majority of BCI techniques that have been developed for conscious participants rely on visual stimulation and feedback (often called "biofeedback"). By definition, vegetative state patients lack the ability to fixate on or pursue objects in their visual field, which precludes the use of visually based BCI systems and suggests that other modalities should be used (Chatelle et al., 2012; Naci et al., 2012). In a recent proof of principle study, implanted electrodes in a locked-in patient were used to decode his intention to orally produce one of four vowels and to translate the output using a synthesizer (Guenther et al., 2009). Again, while truly impressive, multiple hurdles will need to be overcome before such methods might be applied to "covertly conscious" patients who have previously been thought to be vegetative.

One question that remains, both for neuroscience and for clinical practice, is where this research will lead us. There is no doubt that there currently exists a broad fascination, both among the general public and the media, about whether the methods described in this review 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 ensure that a patient 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, rather than an "all or nothing" problem (Buchanan and Brock, 1989), with different thresholds required depending on the importance of the potential consequences of the decision. Clearly, decisions about the withdrawal of life support are of utmost importance, as they are radical and irreversible, and therefore, an appropriate level of decision making capacity should be demonstrated before such a question could be even considered. Peterson and colleagues (2013) have recently 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. Clearly, we are entering an era where high-level assessments of residual cognitive function may soon be made based solely on fMRI (Hampshire et al., 2013) or EEG data, although a full assessment of the capacity for complex decision making using any of the tools described in this review 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, the military, and coma, within the next decade all of these obstacles will almost certainly be overcome.

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