Chapter 6
Decoding Thoughts in Disorders of Consciousness

Adrian M. Owen and Lorina Naci

Abstract Recent developments in functional neuroimaging have provided a number of new tools for assessing patients who clinically appear to be in a vegetative or minimally conscious state. These techniques have been able to reveal awareness and even allow rudimentary communication, in some patients who remain entirely behaviorally nonresponsive. In some centers, these methods are now being employed routinely in the assessment of severely brain-injured patients, mapping patterns of residual function and dysfunction and helping to reduce diagnostic errors in these conditions. The implications of these results extend well beyond the immediate clinical and scientific findings to suggest an urgent need for a reevaluation of the existing diagnostic guidelines for behaviorally nonresponsive patients to include information derived from functional neuroimaging.

Keywords Disorders of consciousness • fMRI • Mental states • Decoding

6.1 Introduction

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 where, typically, there is a degree of motor arousal, while awareness is accompanied by the ability to have (and the act of having) an experience of some kind [2]. Wakefulness is relatively easily measured by confirming that the eyes are open and/or that the resting state electroencephalography (EEG) 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 (see Supplementary Online Information), and, clinically, the

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ability to follow commands – either verbally or behaviorally – 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 behavior that is observed. The subjective nature of this inference undoubtedly contributes to the well-documented rate of misdiagnosis in this population [3–5].

Recent advances in neuroimaging technology have suggested a number of possible solutions to this problem. In this chapter, recent studies that have used functional magnetic resonance imaging (fMRI) in this context will be reviewed.

6.2 Decoding Mental States Using fMRI

In recent years, many attempts have been made to "decode" mental decisions or thoughts in healthy participants using neuroimaging [6–10]. The principle often employed capitalizes on the fact 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 statistical classifier is trained to recognize these characteristic signatures, a volunteer's thoughts can be decoded (within the constraints of the experimental design) using their brain activity alone.

To achieve acceptable levels of accuracy, these methods often 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) [10]. 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 [11]. To indicate their choice (or "thought"), participants imagined one of two tasks, beginning at one of four times and continuing for different pre-specified 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 %.

In one large study [6], 34 healthy volunteers were asked to imagine hitting a tennis ball back and forth to an imaginary coach when they heard the word "tennis" (thereby eliciting vigorous imaginary arm movements) and to imagine walking from room to room in their house when they heard the word "house" (thereby eliciting imaginary spatial navigation). Imagining playing tennis was associated with robust activity in the supplementary motor area in each and every one of the participants scanned. In contrast, imagining moving from room to room in a house activated the parahippocampal cortices, the posterior parietal lobe, and the lateral premotor cortices, all regions that have been shown to contribute to imaginary or real spatial navigation [12]. By simply examining the responses elicited during the imagery tasks, Boly and colleagues [6] were able to "decode" which task was being mentally "performed." Moreover, the robustness and reliability of fMRI responses across individuals meant that activity in these regions could be used to confirm that the participants retained the ability to understand instructions to carry out different mental tasks in response to those instructions and, therefore, were able to exhibit willed, voluntary brain behavior in the absence of any overt action. On this basis, Boly and colleagues [6] argued that, like any other form of action that requires a choice between one of several possible responses, these brain responses require *awareness*, that is to say, awareness of the various contingencies that govern the relationship between a given stimulus (in this case, the cue word for one of two possible imagery tasks) and a response (in this case, imagining a type of action). Put simply, fMRI responses of this sort can be used to measure awareness because awareness is necessary for them to occur.

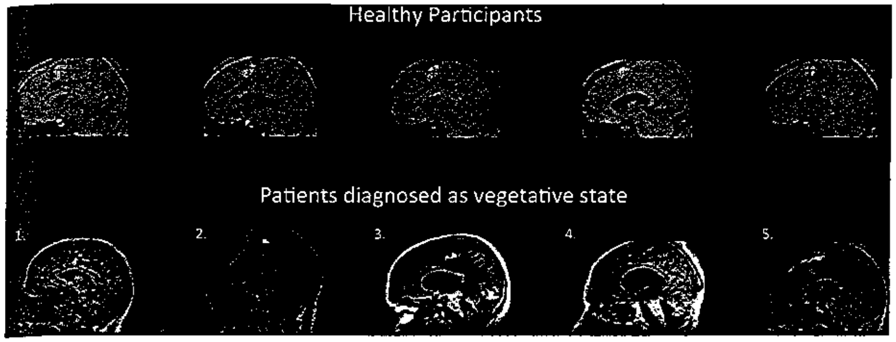

Fig. 6.1 *Top row*: Five healthy participants asked to imagine playing tennis in the fMRI scanner (Adapted from [6]). In all five cases, significant activity was observed in the premotor cortex, indicating that they had understood the instruction and were responding by carrying out the appropriate type 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. [14] (patient 5) and [15] (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

Owen et al. [13, 14] used this same logic to demonstrate that a young woman who fulfilled all internationally agreed criteria for the vegetative state was, in fact, consciously aware and able to make responses of this sort using her brain activity. The patient, who was involved in a complex road traffic accident and had sustained very severe traumatic brain injuries, had remained entirely unresponsive for a period of 6 months prior to the fMRI scan. During two different scanning sessions, the patient was instructed to perform the two mental imagery tasks described above. In each case she was asked to imagine playing tennis/moving around the rooms of her home (for 30 s) when she heard the word *tennis/house* and to relax (for 30 s) when she heard the word *relax*. When she was asked to imagine playing tennis (Fig. 6.1, patient 5), significant activity was observed repeatedly in the supplementary motor area [14] that was indistinguishable from that observed in the healthy volunteers scanned by Boly et al. [6]. Moreover, when she was asked to imagine walking hrough her home, significant activity was observed in the parahippocampal gyrus, he posterior parietal cortex, and the lateral premotor cortex which was again indisinguishable from those observed in healthy volunteers [13, 14]. The patient's brain ctivity was statistically robust, reproducible, task appropriate (enhanced following he "tennis"/"house" cue and returning to baseline following the "relax" cue), susained over long time intervals (30 s), and repeated over each 5-min session. On this asis, it was concluded that, despite fulfilling all of the clinical criteria for a diagnois of vegetative state, this patient retained the ability to understand spoken comnands and to respond to them through her brain activity, rather than through speech r movement, confirming that she was consciously aware of herself and her suroundings. In a follow-up study of 23 patients who were behaviorally diagnosed as egetative, Monti et al. [15] showed that 4 (17 %) were able to generate reliable esponses of this sort in the fMRI scanner (Fig. 6.1, patients 1–4).

After a severe brain injury, when the request to move a hand or a finger is folowed by an appropriate motor response, the diagnosis can change from vegetative tate (no evidence of awareness) to minimally conscious state (some evidence of wareness). By analogy then, if the request to activate, say, the supplementary motor rea of the brain by imagining moving the hand is followed by an appropriate brain esponse, we should give that response the very same weight [16–18]. Skeptics may rgue that brain responses are somehow less physical, reliable, or immediate than otor responses but, as is the case with motor responses, all of these arguments can e dispelled with careful measurement, replication, and objective verification [6, 14, 5, 16, 19, 20, 21]. For example, if a patient who was assumed to be unaware raised is or her hand to command on just one occasion, there would remain some doubt bout the presence of awareness given the possibility that this movement was a hance occurrence, coincident with the instruction. However, if that same patient ere able to repeat this response to command on ten occasions, there would remain ittle doubt that the patient was aware. By the same token, if that patient was able to ctivate his or her supplementary motor area in response to command (e.g., by being old to imagine hand movements) and was able to do this on every one of ten trials, e would have to accept that this patient was consciously aware. Like most neuromaging investigations, replication of this sort was inherent in both of the studies escribed above [14, 15], because the statistically significant results depended on ultiple, similar responses being exhibited across repeated trials.

Monti et al. [15] employed the same general principle – that is, using the neural ignature of active mental rehearsal to signify awareness – to show that commuication of "yes" and "no" responses was possible with fMRI. Thus, three "yes" nd "no" responses were decoded from each of 16 healthy participants with 100 % ccuracy using only their real-time changes in the supplementary motor area (durng tennis imagery) and the parahippocampal place area (during spatial navigaion). Moreover, in one traumatic brain injury patient, who had been repeatedly iagnosed as vegetative over a 5-year period, similar questions were posed and uccessfully decoded using the same approach [15]. Indeed, this patient was able o convey biographical information that was not known to the experimenters at e 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 [16]. 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 [22] 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 [23], and his diagnosis was unchanged throughout. In February 2012, 12 years and 2 months after his accident, the patient was first scanned using the fMRI mental imagery approach described above [14, 15]. 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 non-verifiable 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 constraints 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?" vs. "Is your name Scott?"). In total, answers to 12 different questions were obtained across several sessions, despite the fact that the patient remained entirely physically nonresponsive at the bedside [16].

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.

A related and possibly simpler approach to detecting covert awareness after brain injury, therefore, is to target processes that require the willful adoption of "mind-sets" in carefully matched (perceptually identical) experimental and control conditions. For example, Monti et al. [24] presented healthy volunteers with a series of neutral words and alternatively instructed them to just listen, or to count, the number of times a given word was repeated. As predicted, the counting task revealed the frontoparietal network that has been previously associated with target detection and working memory. When tested on this same procedure, a severely brain-injured patient produced a very similar pattern of activity, confirming that he could willfully adopt differential mind-sets as a function of the task conditions and could actively maintain these mind-sets across time. These covert abilities 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.

Naci and colleagues [20, 21] took this general principle even further and developed 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 [25], 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 [20], 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. Moreover, the majority of volunteers conveyed their answers with less than 3 min of scanning, which represents a significant time saving over the mental imagery methods described above [6, 14]. 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 reliable brain activation during mental imagery tasks [6].

In a follow-up study, Naci and Owen [21] 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 [21]. 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 (Fig. 6.2). 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 4 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 % 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.

These types of approaches all illustrate a paradigmatic shift toward 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

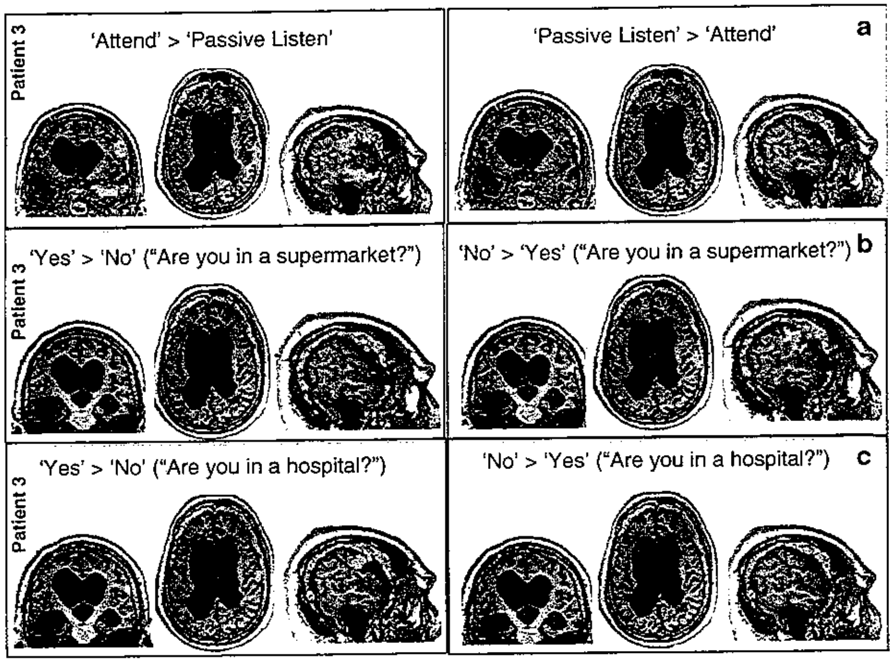

Fig. 6.2 Command-following (**a**) and communication (**b**, **c**) scans in patient 3, clinically diagnosed as being in a vegetative state. Brain activity is overlaid on the patient's native anatomic volume. The opposite directions of each contrast (i.e., $a>b$ or $b>a$) are shown on the left and right sides of each panel. (**a**) The command-following scan also served to localize the brain foci of attention unique to the patient. (**b**, **c**) Selective attention to the answer word (either yes or no) during each communication scan was investigated within these regions. Attention to the answer in each question (**b**, no; **c**, yes) significantly activated the precentral or motor region

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 [26].

Nevertheless, while "active" paradigms have proven themselves to be an effective means for assessing residual awareness in some nonresponsive patients, it remains likely that many patients will lack the necessary cognitive resources for carrying out these tasks in the scanner and will therefore fail to exhibit signs of awareness even when it may exist. To address this issue, recent efforts have focused on developing new methods for detecting awareness in the absence of an explicitly willed task. Naci and colleagues [27] used a richly evocative stimulus – a highly suspenseful movie – to capture attention naturally in the absence of structured instruction. They asked whether a common neural basis can account for how different individuals form similar conscious experiences and, if so, whether it could be used to interpret those experiences without recourse to self-report in behaviorally nonresponsive patients. They reasoned that executive function, in particular, might provide an empirical window by which the cognitive aspect of human conscious

experience can be quantified. By their very nature, engaging movies are designed to give viewers a shared conscious experience driven, in part, by the recruitment of similar executive processes, as each viewer continuously integrates their observations, analyses, and predictions while filtering out any distractions, leading to an ongoing involvement in the movie's plot.

When healthy participants viewed a highly engaging short movie by Alfred Hitchcock – the so-called Master of Suspense – in the fMRI scanner, they displayed highly synchronized brain activity in supramodal frontal and parietal regions, which support executive function [28, 29]. The movie's executive demands, assessed quantitatively with a dual-task procedure [30] by an independent group, predicted activity in frontal and parietal regions of the healthy participants, who had watched the movie without a secondary task in the scanner. Importantly, the movie's suspense ratings, provided by a third independent healthy group, demonstrated that individual participants had a similar qualitative experience of the movie, which also predicted activity in the frontal and parietal regions. Together, these results suggested that the movie's executive demands drove brain activity in frontal and parietal regions and, further, that the synchronization of this activity across individuals underpinned their similar experience. By extension, the degree to which each individual's frontoparietal brain activity could be predicted from the rest of the group's represented a reliable neural index of how similar his or her cognitive experience was to the others'.

Naci et al. [27] then used this approach in two entirely behaviorally nonresponsive patients with unknown levels of consciousness, in order to examine and quantify their experience of the world. fMRI data was acquired from the two patients, as they freely viewed the same Hitchcock movie. One patient, who had remained behaviorally nonresponsive for a 16-year period prior to scanning, demonstrated a highly similar brain response to that of the three independent control groups. The patient's brain activity in frontal and parietal regions was tightly synchronized with the healthy participants' over time, and crucially, it reflected the executive demands of specific events in the movie, as measured both quantitatively and qualitatively in healthy individuals (Fig. 6.3). This suggested that the patient could continuously engage in complex thoughts about real-world events unfolding over time and, thus, that he was consciously aware. Further, the patient's brain response suggested that his conscious experience was highly similar to that of each and every healthy participant, including his moment-to-moment perception of the movie content, as well as his executive engagement with its plot. These processes are likely to include updating the contents of working memory (e.g., to follow the plot), relating events in the movie to past experiences (e.g., to appreciate that a gun is a dangerous weapon), and coding the foreshadowing cues (i.e., events that might have future relevance to the plot) characteristic of movies of this type.

In summary, this approach can determine not only whether any given patient is conscious but also infer what the contents of that conscious experience might actually be, thus, revealing important practical and ethical implications for the patient's standard of care and quality of life [31].

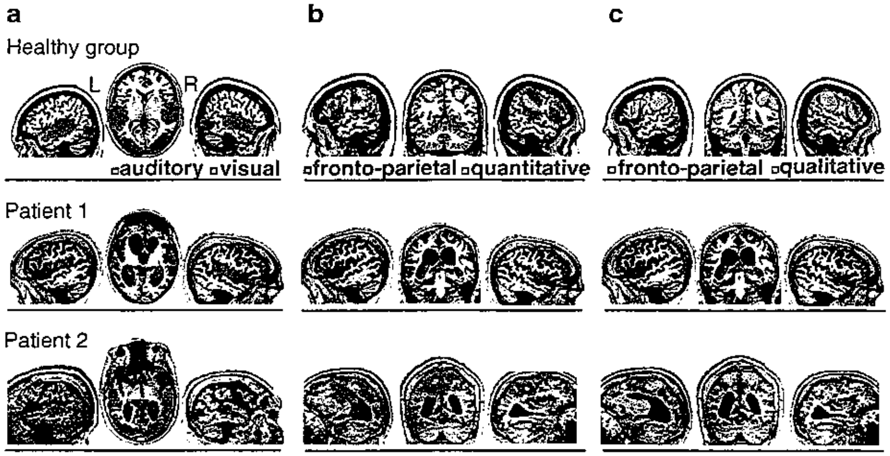

Fig. 6.3 Decoding executive function in one behaviorally nonresponsive patient. *Healthy group*: (a) group-level auditory (*purple*) and visual (*blue*) independent components. (b, c) The healthy group's activity predicted by the quantitative (b)/qualitative (c) executive measure (*green*) is overaid on the group frontoparietal independent component (*red*); overlap areas are displayed in yelow. *Patient 1*: (a) The healthy group's auditory independent component predicted significant activity in patient 1's auditory cortex (*purple*). (b, c) No evidence of visual responses or executive processing similar to the healthy participants' was observed. *Patient 2*: (a) The healthy group's auditory and visual independent components predicted significant activity in patient 2's auditory (*purple*) and visual (*blue*) cortex, respectively. (b, c) The quantitative (b) and qualitative (c) executive measures predicted activity (*green*) in the patient's frontal and parietal regions. Overlap with activity predicted by the healthy group's frontoparietal independent component (*red*) is displayed n *yellow* (Adapted from [27])

6.3 Diagnostic Implications

An obvious clinical consequence of the emergence of novel neuroimaging techniques hat permit the identification of covert awareness and communication in the absence of any behavioral response is the possibility of improved diagnosis after severe brain njury. It is notable that in one of the cases described above [16, 21, 32], the patient was repeatedly and rigorously assessed by experienced teams and showed no behavoral 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, and who can follow commands with a measurable brain response, but physically remain entirely nonresponsive? The term "non-behavoral minimally conscious state" has been suggested [33], although because attention, anguage comprehension, and working memory are demonstrably preserved in these patients, we have argued that "minimally conscious" does not adequately describe their residual cognitive abilities [16, 17, 21]. 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 [34, 35]. In its classical 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 [36]. 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 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 has already been able to report that he remembers his own name and that he knows the current date and where he is [21], 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. [36] 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. [19] 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 [37], Hampshire et al. [19] 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 [6, 14] 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.

6.4 False-Negative Results

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 eard or understood the task instructions, leading to an erroneous negative result. ndeed, in the recent study by Monti et al. [15], no willful fMRI responses were bserved in 19 of 23 patients – whether these are *true*-negative findings (i.e., those 9 patients were indeed vegetative) or *false-negative* findings (i.e., some of those atients were conscious, but this was not detected on the day of the scan) cannot be etermined. Accordingly, negative fMRI and EEG findings in patients should never e used as evidence for impaired cognitive function or lack of awareness.

.5 Conclusions

n the last few years, neuroimaging methods have been brought to bear on one of the ost complex and challenging questions in clinical medicine, that of detecting esidual cognitive function, and even covert awareness, in patients who have sus-ained severe brain injuries. The results demonstrate that responses need no longer e *physical* responses in the traditional sense (e.g., the blink of an eye or the squeez-ng of a hand), but can now include responses that occur entirely within the brain tself. The recent use of reproducible and robust task-dependent fMRI responses as form of "communication" in patients who are assumed to be vegetative [15, 16, 1] represents an important milestone in this process. In some cases, these patients ave been able to communicate information that was not known by the experiment-rs at the time, yet could be independently verified later (using more traditional ethods of communication with the family), as being factually correct and true [15, 1]. More importantly perhaps, in one case, a patient has used these methods to nswer clinically and therapeutically relevant questions (including "Are you in any ain?") that could not be answered in any other way, including via third party. indings such as these have profound implications for clinical care, diagnosis, prog-osis, and end-of-life decision-making but also shed light on more basic scientific uestions about the nature of conscious behavior and the neural representation of ur own thoughts and intentions.

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