Detecting Awareness in the Vegetative State

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The assessment of residual brain function in the vegetative state, is extremely difficult and depends frequently on subjective interpretations of observed spontaneous and volitional behaviors. For those patients who retain peripheral motor function, rigorous behavioral assessment supported by structural imaging and electrophysiology is usually sufficient to establish a patient's level of wakefulness and awareness. However, it is becoming increasingly apparent that, in some patients, damage to the peripheral motor system may prevent overt responses to command, even though the cognitive ability to perceive and understand such commands may remain intact. Advances in functional neuroimaging suggest a novel solution to this problem; in several recent cases, so-called "activation" studies have been used to identify residual cognitive function and even *conscious awareness* in patients who are assumed to be vegetative, yet retain cognitive abilities that have evaded detection using standard clinical methods.

Key words: **activation; cognitive function; fMRI scan; vegetative state**

The clinical features of the vegetative state were formally introduced into the literature by Jennett and Plum[1] and later clarified and refined by the Multi-Society Task Force on Persistent Vegetative State[2,3] and the Royal College of Physician.[4] Etiology is variable, although the condition may arise as a result of road traffic accident, ischemic attack, anoxia, encephalitis, or viral infection. A diagnosis is only made after repeated examinations that have yielded *no evidence whatsoever* of sustained, reproducible, purposeful, or voluntary behavioral response to visual, auditory, tactile, or noxious stimuli. There must also be no evidence of language comprehension or expression, although there is generally sufficiently preserved hypothalamic and brain-stem autonomic functions to permit survival with medical care. Unlike patients in coma, the vegetative state is characterized by an irregular but cyclic state of circadian sleeping and waking. It is this waking pattern, combined with the wide range of reflexive responses, that are often observed in vegetative patients that can result in this activity being misinterpreted as evidence of volitional (willful) behavior and even the return of conscious awareness. However, although these patients will often appear to be awake and will make nonpurposeful movements, rigorous observation reveals no consistent activities that are voluntary or learned, and no responses to command or mimicry.[5] In short, these patients show no signs of being aware of themselves or of their environment.

An accurate and reliable evaluation of the level and content of cognitive processing is of paramount importance for the appropriate management of patients diagnosed with vegetative state. Objective behavioral assessment of residual cognitive function can be extremely difficult, as motor responses may be minimal, inconsistent, and difficult to document, or may be undetectable because no cognitive output is possible. A number of recent studies have shown that functional neuroimaging may have an important role to play in the identification of residual cognitive function in some patients who are assumed to be vegetative, yet retain cognitive abilities that have evaded detection using standard clinical approaches. Unlike resting blood flow and glucose metabolism, which provide markers of neural capacity and potential, so-called "activation" methods such as $H_2{}^{15}O$ positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) can be used to link residual neural activity to the presence of covert cognitive *function*. In short, activation studies have the potential to demonstrate distinct and specific physiological responses (changes in regional cerebral blood flow (rCBF), or changes in regional cerebral haemodynamics) to controlled external stimulation without the need for any overt behavior (e.g., a motor *action*) by the patient.

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In the first of such studies, $H_2{}^{15}O$ PET was used to measure rCBF in a post traumatic vegetative patient during an auditorily presented story told by his mother.[6] Compared to nonword sounds, activation was observed in the anterior cingulate and temporal cortices, possibly reflecting emotional processing of the contents, or tone, of the mother's speech. In another patient diagnosed as vegetative, Menon and colleagues[7] used PET to study covert *visual* processing in response to familiar faces. When the patient was presented with pictures of the faces of family and close friends, robust activity was observed in the right fusiform gyrus, the so-called human "face area." Importantly, both of these studies involved single, well-documented cases; in cohort PET studies of patients unequivocally meeting the clinical diagnosis of the vegetative state, normal brain activity in response to external stimulation has generally been the exception rather than the rule. For example, in one study of 15 vegetative patients, high-intensity noxious electrical stimulation activated midbrain, contralateral thalamus, and primary somatosensory cortex in every patient.[8] However, unlike control subjects, the patients did not activate secondary somatosensory, insular, posterior parietal, or anterior cingulate cortices.

Recently, Di and colleagues[9] used event-related fMRI to measure brain activation in seven vegetative patients in response to the patient's own name spoken by a familiar voice. Two of the vegetative patients exhibited no significant activity at all, three patients exhibited activation in primary auditory areas, and two patients exhibited activity in "higher-order" associative temporal-lobe areas. While this result is encouraging (particularly because the two vegetative patients who showed the most widespread activation subsequently improved to minimally conscious state in the following months), it lacks *cognitive specificity*; that is to say, responses to the patient's own name spoken by a familiar voice were compared only to responses to the attenuated noise of the MRI scanner. Therefore, the activation observed *may* have reflected a specific response to one's own name, but it is equally possible that it reflected a low-level orienting response to speech in general, an emotional response to the speaker (see Ref. 10), or any one of a number of possible cognitive processes relating to the unmatched auditory stimuli. As a result, the interpretation hinges on a *reverse inference,* a common practice in neuroimaging by which the engagement of a given cognitive process is inferred solely on the basis of the observed activation in a particular brain region.[11,12]

Staffen and colleagues[13] used event-related fMRI to compare sentences containing the patient's own name (e.g., "Martin, hello Martin") with sentences using another first name, in a patient who had been vegetative for 10 months at the time of the scan. In this case, because identical speech-stimuli were used that differed only with respect to the name itself, activations can be confidently attributed to cognitive processing that is specifically related to the patient's own name. Differential cortical processing was observed to the patient's own name in a region of the medial prefrontal cortex, similar to that observed in three healthy volunteers. These findings concur closely with a recent electrophysiological study, which has shown differential P3 responses to a patient's own name (compared to other's names) in some vegetative patients.[14] Selective cortical processing of one's own name (when it is compared directly with another name) requires the ability to perceive and access the meaning of words and may imply some level of comprehension on the part of this patient. However, as the authors point out,[13] a response to one's own name is one of the most basic forms of language and may not depend on the higher-level linguistic processes that are assumed to underpin comprehension.

It has recently been argued that fMRI studies in vegetative patients should be conducted hierarchically[15–17] beginning with the simplest form of processing within a particular domain (e.g., auditory) and then progressing sequentially through more complex cognitive functions (see FIG. 1).

By way of example, a series of auditory paradigms was described that have all been successfully employed in functional neuroimaging studies of vegetative patients. These paradigms increase in complexity systematically from basic acoustic processing to more complex aspects of language comprehension and semantics. At the highest level, responses to sentences containing semantically ambiguous words (e.g., "the *creak/creek* came from a *beam* in the *ceiling/sealing*") are compared to sentences containing no ambiguous words (e.g., "her secrets were written in her diary"), in order to reveal brain activity associated with spoken language *comprehension.*[18] A recent study has explored the utility of this approach in the assessment of vegetative state;[19] residual language function in a group of seven vegetative patients was graded according to their brain activation on this hierarchical series of paradigms. Three of the vegetative patients demonstrated some evidence of preserved speech processing when all sentences were compared to signal-correlated white noise (see FIG. 2), while four patients showed no significant activation at

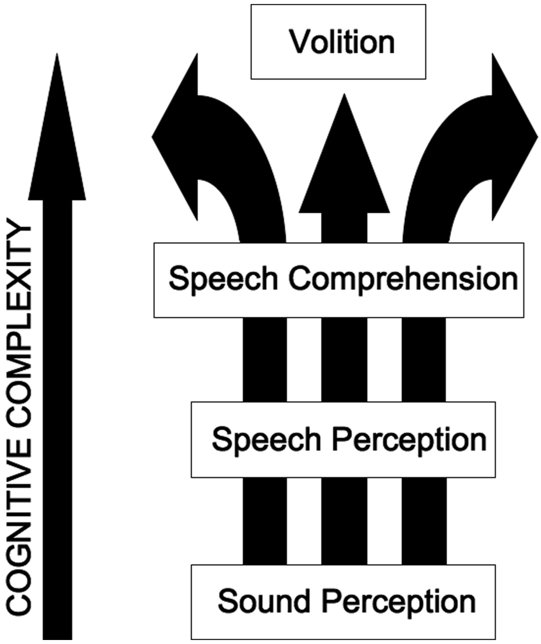

FIGURE 1. A hierarchical approach to the assessment of cognitive function in the vegetative state. At the most basic level, sound perception is assessed by comparing all auditory stimuli (speech + white noise) to silence. Once a response to sound has been established, a speech-specific response is assessed by comparing all speech sounds to signal-correlated noise. Once a speech response has been identified, the comparison between ambiguous and unambiguous sentences provides a measure of comprehension. Finally, volition is assessed by testing for sustained, word-specific imagery responses.

all, even when responses to sound were compared to silence. Most strikingly, two of the vegetative patients showed a significant response in the semantic ambiguity contrast, consistent with high-level comprehension of the semantic aspects of speech. These results provide compelling evidence for high level residual linguistic processing in some patients meeting the clinical criteria for vegetative state and suggest that some of the processes involved in activating, selecting, and integrating contextually appropriate word meanings may be intact, despite their clinical diagnoses.

The question that remains, however, is whether the presence of "normal" brain activation in patients who are diagnosed as vegetative [6–8,15,16,19–21] indicates a level of conscious awareness, perhaps even similar to that which exists in healthy volunteers when performing the same tasks. Many types of stimuli, including faces, speech, and pain will elicit relatively "automatic" responses from the brain; that is to say, they will occur without the need for willful intervention on the part of the participant (e.g., you cannot choose to *not* recognize a face, or to *not* understand speech that is presented clearly in your native language). In addition, there is a wealth of data in healthy volunteers, from studies of implicit learning and the effects of priming[22] to studies of learning and speech perception during anaesthesia,[23] that have demonstrated that many aspects of human cognition can go on in the absence of awareness. Even the semantic content of masked information can be primed to affect subsequent behavior without the explicit knowledge of the participant, suggesting that some aspects of semantic processing may occur without conscious awareness.[24] By the same argument, "normal" neural responses in patients who are diagnosed with disorders of consciousness do not *necessarily* indicate that these patients have any conscious experience associated with processing those same types of stimuli. Thus, such patients *may* retain discreet islands of subconscious cognitive function, which exist in the absence of awareness.

To investigate this issue, Davis and colleagues[23] used the anesthetic agent propofol to study the effects of sedation on the brain activity of healthy volunteers using some of the same tasks that have been employed previously to assess residual cognitive function in the vegetative state. Volunteers (all anesthesiologists) were scanned while listening to the sentences containing the ambiguous words just described, matched sentences without ambiguous words, and signal-correlated noise. During three scanning sessions, participants were nonsedated (awake), lightly sedated (a slowed response to conversation), and deeply sedated (no conversational response, rousable by loud command). Equivalent temporal-lobe responses for sentences compared to signal-correlated noise were observed bilaterally at all three levels of sedation, suggesting that speech perception was relatively impervious to the effects of sedation. However, the additional inferior frontal and posterior temporal responses to ambiguous sentences that are known to provide a neural marker for semantic processing [and have been shown to exist in a minority of patients diagnosed as vegetative (see Ref. 19)] were absent, even during light sedation, suggesting a marked impairment of sentence comprehension. These findings suggest a graded degradation of cognitive function in response to sedation such that "higher-level" semantic processes can be impaired at relatively low levels of sedation, while perceptual processing of speech remains resilient even during deep sedation.[23]

These results suggest that extreme caution needs to be exercised when interpreting "normal" patterns of brain activity in patients who are diagnosed as vegetative.[6–8,15–16,19–21] For example, because "normal"

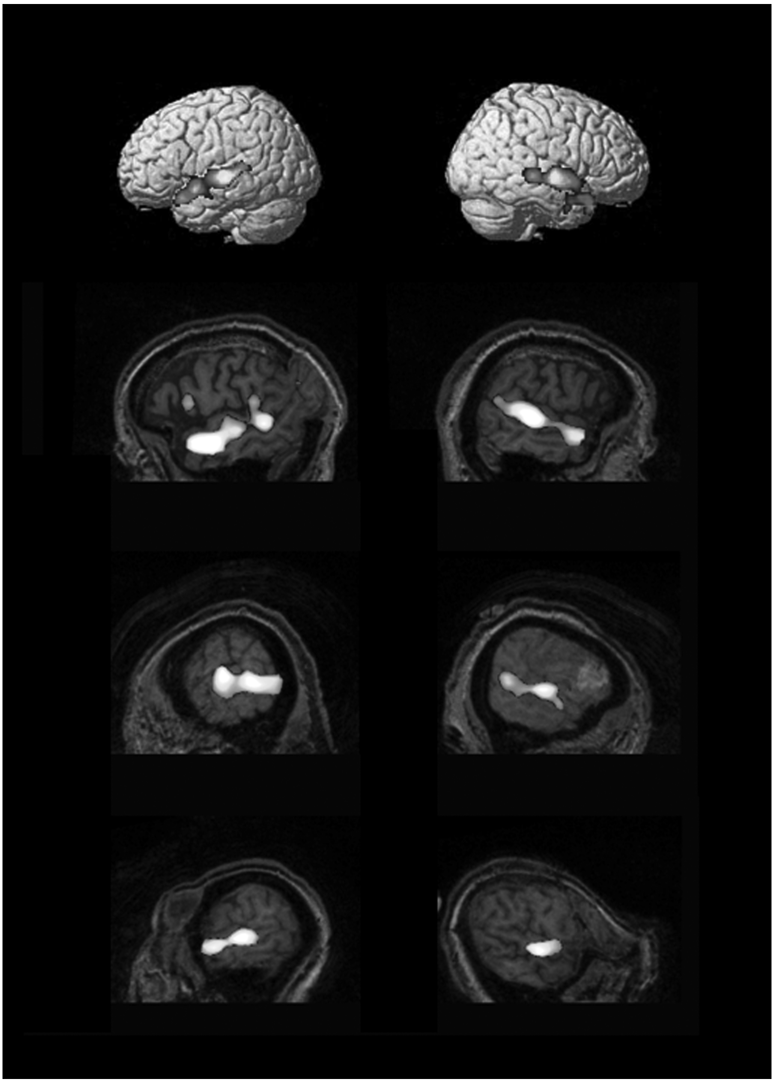

FIGURE 2. Speech-specific responses in healthy volunteers (**top**) and in three vegetative patients (adapted from Coleman *et al.*[19]). The fMRI responses of the three patients when speech sounds were compared with signal-correlated noise are very similar to those observed in healthy, awake volunteers.

brain activity (that is to say, activity that was indistinguishable from awake individuals) was observed in the deeply sedated volunteers studied by Davis and colleagues[23] when these participants were clearly not "aware," similar response in the vegetative state cannot be taken as signs of awareness. It could be argued that this problem of interpretation applies to the majority of activation studies that have been conducted in vegetative patients to date. On the other hand, the fact that the characteristic pattern of frontal and posterior temporal-lobe activity associated with sentence comprehension is only observed in fully awake, healthy volunteers[23] suggests that vegetative patients who show this same pattern[16–19] *may* be consciously aware. Unfortunately, such conclusions remain entirely speculative; the fact that awareness is *associated* with the activity changes that are thought to reflect sentence comprehension does not mean that it is *necessary* for them to occur.

This conundrum exposes a central difficulty in the study of conscious awareness and in particular, how it relates to the vegetative state. Deeper philosophical considerations notwithstanding, the only reliable method that we have for determining whether another being is consciously aware is to ask him/her. The answer may take the form of a spoken response or a nonverbal signal (which may be as simple as the blink of an eye, as documented cases of the locked-in syndrome have demonstrated), but it is this answer that allows us to infer conscious awareness. In short, our ability to know unequivocally that another being is consciously aware is ultimately determined, not by whether they are aware or not, but by their ability to communicate that fact through a recognized behavioral response. But what if the ability to blink an eye is lost, yet conscious awareness remains? By definition, patients who are diagnosed as vegetative are not able to elicit such behavioral responses. Following the logic of this argument, then, even if such a patient *were* consciously aware, he/she would, by definition, have no means for conveying that information to the outside world.

A novel approach to this problem has recently been described,[25,26] using fMRI, to demonstrate preserved conscious awareness in a patient fulfilling the criteria for a diagnosis of vegetative state. In mid-2005, the patient concerned was involved in a traffic accident. On admission to hospital she had a Glasgow Coma Scale score of 4. A computed tomography scan revealed diffuse brain swelling, intraventricular blood in the left lateral ventricle, low attenuation in the left frontal lobe close to the corpus callosum, and attenuation change in the right frontal and left posterior temporal regions. The following day she underwent a bifrontal decompressive craniectomy, and a month later a ventriculoperitoneal shunt was inserted into the right lateral ventricle. Between the time of the accident and the fMRI scan in early January 2006, the patient was assessed by a multidisciplinary team employing repeated standardized assessments consistent with the procedure described by Bates.[27] Throughout this period the patient's behavior was consistent with accepted guidelines defining the vegetative state.[2–4] She would open her eyes spontaneously, exhibited sleep/wake cycles, and had preserved, but inconsistent, reflexive behavior (startle, noxious, threat, tactile, olfactory). No elaborated motor behaviors (regarded as "voluntary" or "willed" responses) were observed from the upper or lower limbs. There was no evidence of orientation, fixation greater than 5 s, or tracking to visual or auditory stimuli. No overt motor responses to command were observed.

Prior to the fMRI scan, the patient was instructed to perform two mental imagery tasks when cued by the instructions "imagine playing tennis" or "imagine visiting the rooms in your home." These instructions were elaborated outside of the scanner in an attempt to induce a rich and detailed mental picture during the scan itself. Thus, one task involved imagining playing a vigorous game of tennis, swinging for the ball with both forehand and backhand, for the entire duration of each scanning block. The other task involved imagining moving slowly from room to room in her house, visualizing the location and appearance of each item of furniture as she did so. In a third condition, the patient was asked to "just relax." Importantly, these particular tasks were chosen, not because they involve a set of fundamental cognitive processes that are known to reflect conscious awareness, but because imagining playing tennis and imagining moving around the house elicit extremely reliable, robust, and statistically distinguishable patterns of activation in specific regions of the brain. For example, in a series of studies in healthy volunteers,[28] imagining playing tennis has been shown to elicit activity in the supplementary motor area, a region known to be involved in imagining (as well as actually performing) coordinated movements, in each and every one of 34 participants scanned. In contrast, imagining moving from room to room in a house commonly activates 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. In sharp contrast, when healthy volunteers are simply prompted with words such as "tennis" or "house" (with no prior instructions) or even with action sentences containing the same key words such as "The man enjoyed playing tennis" or "The woman looked around her house," no sustained activity is observed in these brain regions[26] (see FIG. 3).

These "wilful" responses in specific brain regions are sufficiently robust to allow rudimentary communication in healthy volunteers using real-time fMRI (FIG. 4). For example, in one recent study a volunteer provided blinded experimenters with a list of names (e.g., Terry, Chris, Steve) and a list of relations (e.g., father, brother, brother-in-law) and was asked to imagine playing tennis in order to convey a "yes" response to specific questions such as "Is you father called Terry?" (Owen *et al.*, unpublished findings). Over short 30-second repeating blocks of questions and rest, activity in the supplementary motor area was sufficient to establish when the volunteer was conveying "yes" and when he was not responding (indicating "no").

In short, these brain responses can be used as a "neural marker," confirming that the participant retains the ability to understand instructions, to remember those instructions (from the prescan instruction period), and to carry out specific and highly constrained mental tasks in response to those instructions. In this sense, the participant has been shown to exhibit a willed or

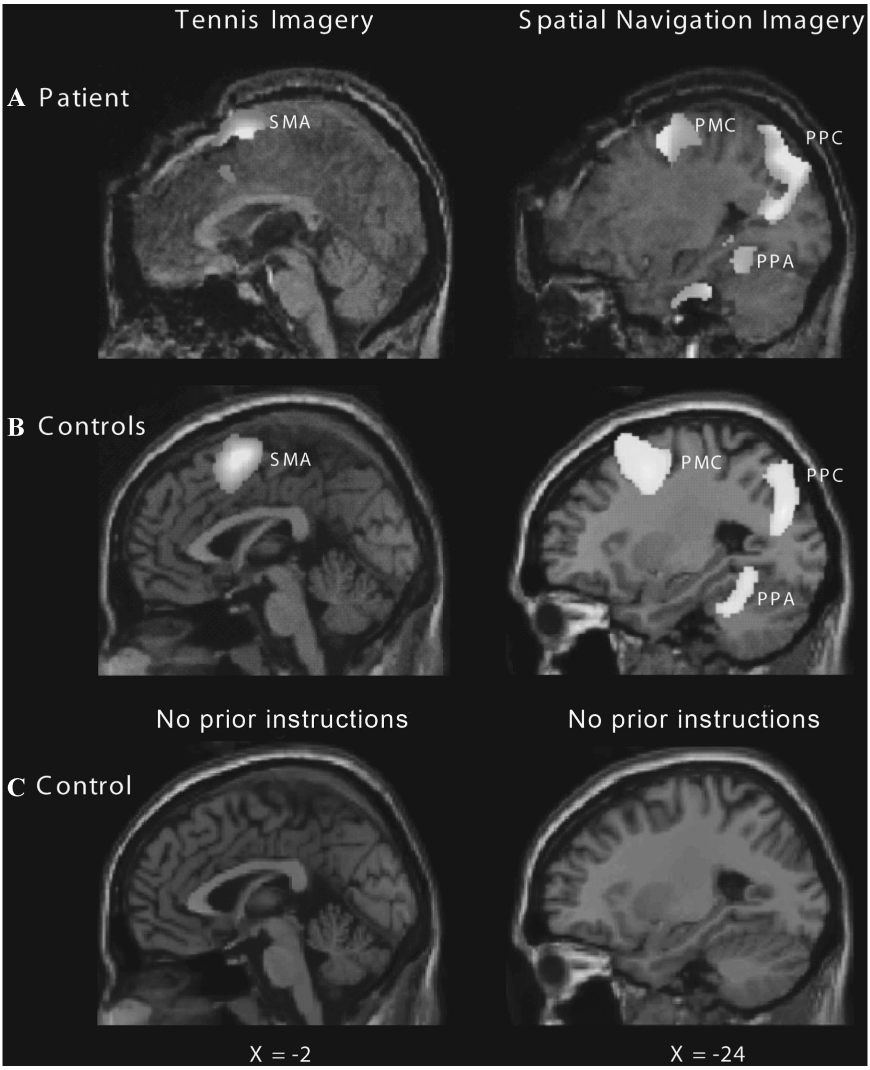

FIGURE 3. Indistinguishable fMRI activity in a patient in a vegetative-state (**A**) and healthy controls; (**B**) while imagining playing tennis (*left column*) or moving around a house (*right column*) (adapted from Owen *et al.*[25]); (**C**) the results from healthy volunteers when noninstructive sentences involving the same key words (e.g., "The man enjoyed playing tennis") were used (Owen *et al.*[26]). An identical negative result is generated when the words "tennis" and "house" are used in volunteers who are instructed to passively listen to the words without instruction to engage in mental imagery.

voluntary *response* that is the neural equivalent of lifting an arm or blinking an eye.

When the patient who was clinically diagnosed as vegetative was asked to imagine playing tennis, significant activity was observed in the supplementary motor area that was statistically indistinguishable from that observed in healthy awake volunteers.[25] In contrast, the instruction to imagine walking through the rooms of her house elicited significant activity in the parahippocampal gyrus, the posterior parietal cortex, and the lateral premotor cortex, which was again indistinguishable from that observed in healthy volunteers. 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.

It has been suggested that the words "tennis" and "house" could have automatically triggered the patterns of activation observed in the supplementary mo-

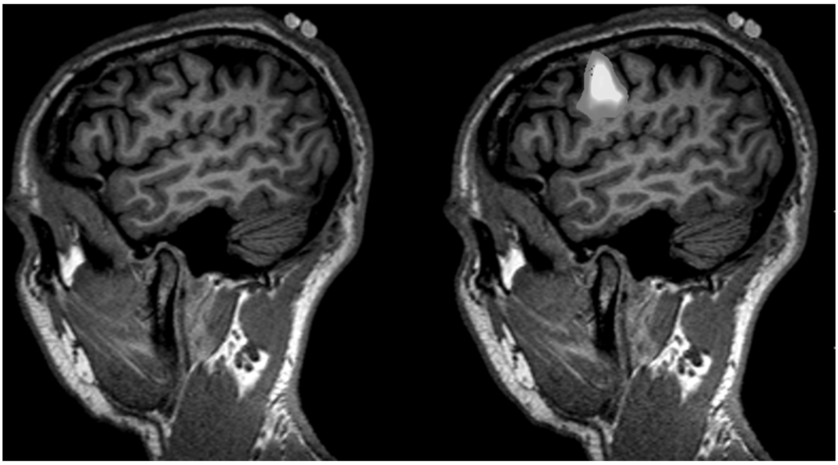

FIGURE 4. Real-time communication in a healthy volunteer using fMRI. The volunteer was instructed to imagine playing tennis when he wanted to convey the word "yes." On the **left**, the response to the question "Is your father called Chris?" yields no significant activity in the supplementary motor area. In contrast, on the **right**, the response to the question "Is your father called Terry?" yields significant activity in this region. The volunteer's father was called Terry (his brother was called Chris).

tor area, the parahippocampal gyrus, the posterior parietal lobe, and the lateral premotor cortex in this patient in the absence of conscious awareness.[29] For this to be a plausible alternative explanation the following four points would all need to be true: (1) the word "tennis" can produce a statistically significant change in activity in the supplementary motor cortex of a single individual who is not consciously aware; (2) the word "house" can produce a statistically significant change in activity in different regions of the brain, including the parietal lobe and the parahippocampal cortices in the same unconscious individual; (3) in both cases, these responses are sustained for up to 30 s and then stop when the (unconscious) participant is presented with another word (e.g., "rest"); (4) in both cases, the anatomically specific and sustained responses are repeatable up to 10 times each.

Of course, all of these scenarios are theoretically *possible*, although we know of no data to support the fact that they are even likely and considerable data to support the fact that they are not (similarly, we have argued, it is theoretically possible that none of us is aware—our behavioral responses through life merely reflecting the "automatically" triggered activity in our brains—but we feel that this is unlikely). For example, although it is well documented that some words can, under certain circumstances, elicit wholly automatic neural responses in the absence of conscious awareness, such responses are typically transient (i.e., lasting for a few seconds) and, unsurprisingly, occur in regions of the brain that are associated with word processing (rather than, say, motor imagery). In the patient described here, the observed activity was not transient, but persisted for the full 30 s of each imagery task, that is, far longer than would be expected, even given the hemodynamics of the fMRI response. In fact, these task-specific changes persisted until the patient was cued with another stimulus indicating that she should rest. Such responses are impossible to explain in terms of automatic brain processes. In addition, the activation observed in the patient was not in brain regions that are known to be involved in word processing, but rather, in regions that are known to be involved in the two imagery tasks that she was asked to carry out. Again, sustained activity in these regions of the brain is impossible to explain in terms of unconscious responses to either single "key" words or to short sentences containing those words. In fact, noninstructive sentences containing the same key words as those used with the patient (e.g., "The man enjoyed playing tennis") produce *no* sustained activity in any of these brain regions in healthy volunteers.[26] Finally, of course, the recent evidence of Davis and colleagues[23] showing that even mildly sedated healthy volunteers cannot perform the basic semantic processes that are necessary for speech comprehension, provides the strongest argument for why points (1)–(3) cannot hold true; producing word-*specific* neural responses requires, at the very least, comprehension of those words, be it conscious or unconscious.

The most parsimonious explanation is, therefore, that this patient was consciously aware and willfully following the instructions given to her, despite her diagnosis of vegetative state.

The finding described earlier raises a number of important issues regarding the use of functional neuroimaging in the assessment of patients who are diagnosed as vegetative. First, although this technique provides a new means for detecting conscious awareness when standard clinical approaches are unable to provide that information, the method will not be applicable to all vegetative patients. For example, within six months of traumatic brain injury (as was the case in the patient previously described), the incidence of recovery of consciousness following a traumatic brain injury remains at nearly 20%, with a quarter of those recovering, moving on to an independent level of function. Nontraumatic injuries are considered to have a much poorer prognosis. Similarly, the likelihood of recovery is much lower in patients who meet the diagnostic criteria for the *permanent* vegetative state (the patient previously described did not). International guidelines, including those of the Royal College of Physicians in the United Kingdom and the Multi-Society Task Force representing five major medical societies in the United States suggest that a diagnosis of *permanent* vegetative state should not be made in cases of traumatic brain injury until 12 months post injury and 6 months post injury for cases of anoxic brain injury. In many of these cases, standard clinical techniques, including structural MRI, may be sufficient to rule out any *potential* for normal activation, without the need for fMRI.

That said, although it is almost certainly the case that similar fMRI responses will not be found in most patients who meet the clinical criteria for vegetative state, there is little a priori reason to suppose that this is the only patient for whom this will be the case. In fact, we have recently assessed a second traumatic brain injury patient who showed evidence of eye opening, sleep–wake cycles, and preserved reflexes, but no sustained, reproducible, or purposeful overt behavioral response to sensory or cognitive stimulation. However, he exhibited consistent patterns of brain activity when asked to imagine playing a game of football. This activity was observed in medial and lateral regions of the supplementary motor cortex, consistent with actual, or imagined, movement of the legs and lower body.

It is, however, extremely important to emphasize that negative functional neuroimaging findings in patients who are diagnosed as vegetative cannot be used as evidence for *lack* of awareness. For example, a patient may fall asleep during the scan or may not have properly heard or understood the task instructions, leading to so-called "false negative" results. Nevertheless, positive findings, when they occur and can be verified by careful statistical comparison with data from healthy volunteers, can be used to detect conscious awareness in patients, without the need for conventional methods of communication such as movement or speech.

Competing Interest

The authors declare no competing interest.

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