Using Functional Magnetic Resonance Imaging to Detect Covert Awareness in the Vegetative State

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The assessment of patients with disorders of consciousness, including the vegetative state, is difficult and depends frequently on subjective interpretations of the observed spontaneous and volitional behavior. For those patients who retain peripheral motor function, rigorous behavioral assessment supported by structural imaging and electrophysiological findings 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 although the cognitive ability to perceive and understand such commands may remain intact. Recent advances in functional neuroimaging suggest a novel solution to this problem; in several cases, so-called activation studies have been used to identify residual cognitive function and conscious awareness in patients who are assumed to be in a vegetative state yet retain cognitive abilities that have evaded detection using standard clinical methods.

The vegetative state is one of the least understood and most ethically troublesome conditions in modern medicine. Vegetative state describes a unique disorder in which patients who emerge from coma appear to be awake but show no signs of awareness of self or of environment. At the point that the diagnosis is made there must be no evidence 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 are generally sufficiently preserved hypothalamic and brainstem autonomic functions to permit survival with medical care.

An accurate and reliable evaluation of the level and content of cognitive processing is of paramount importance for the appropriate management of patients diagnosed as being in a vegetative state. Objective behavioral assessment of residual cognitive function can be difficult in these patients due to the fact that motor responses (the only means of communicating awareness in the absence of speech) may be minimal, inconsistent, and difficult to document or may be undetectable because no cognitive output is possible. Several recent studies reviewed by Laureys et al have shown that functional neuroimaging may have an important role in the identification of residual cognitive function in some patients who are assumed to be in a vegetative state 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 radioactive water positron emission tomography and functional magnetic resonance (fMR) imaging 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 or regional ce-
conscious awareness is ultimately de-
Unequivocally that another being is
sciousness. In short, our ability to know
allows us to infer conscious aware-
locked-in syndrome have demon-
bal signal (which may be as simple
of a spoken response or a nonver-
tional. The answer may take the form
consciously aware is to ask him or
liable method that we have for de-
it relates to the vegetative state.
scious cognitive function that exist
retain discreet islands of subcon-
stimuli. Therefore, such patients may
processing those same types of
scious awareness, perhaps even
in the absence of awareness.
This logic exposes a central co-
procedure described by Bates.3 Throughout
this period, the patient's behavior was
consistent with accepted guidelines de-
ining the vegetative state.4 She opened
her eyes spontaneously, exhibited sleep-
ent change in the right frontal
lobe close to the corpus callosum, and
attenuation change in the right frontal
and left posterior temporal regions. The
following day she underwent bifrontal
decompressive craniectomy, and 1
month later a ventriculoperitoneal shunt
was inserted into the right lateral ven-
ticle. Between the time of the crash and the
fMRI imaging in early January 2006, the
patient was assessed by a multidisci-
plinary team using repeated standard-
ized assessments consistent with the
the patient's behavior was
No elaborated motor behaviors (re-
garded as voluntary or willed re-
sponses) were observed from the up-
ner or lower limbs. There was no
evidence of orientation, fixation greater
than 5 seconds, or tracking to visual or
auditory stimuli. No overt motor re-
sponses to command were observed.
Before the fMR imaging, the patient
was instructed to perform 2 mental im-
agery tasks when cued by the instruc-
tions “imagine playing tennis” or “imag-
ine visiting the rooms in your house.”
These instructions were elaborated out-
side of the scanner in an attempt to in-
duce a rich and detailed mental picture
during the imaging. Therefore, one task
involved imagining playing a vigorous
game of tennis, swinging for the ball with
forehand and backhand, for the entire
duration of each imaging block. The
other task involved imagining moving
slowly from room to room in her house,
visualizing the location and appear-
ance of each item of furniture as she did
so. In a third condition, the patient was
asked to “just relax.”
Most important, 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 play-
tennis and imagining moving around
the house elicit reliable, robust, and sta-
tistically distinguishable patterns of ac-
tivation in specific regions of the brain.
For example, in a series of studies2,5 in
healthy volunteers, imagining playing
Tennis has been shown to elicit activity
in the supplementary motor area, a re-
region involved in imagining (as well as
actually performing) coordinated move-
ments in 34 participants imaged
(Figure 1). In contrast, imagining mov-
ing from room to room in a house com-
monly activates the parahippocampal
cortices, the posterior parietal lobe, and
the lateral premotor cortices, regions that
contribute to imaginary or real spatial
navigation. Given the reliability of these
responses across individuals, activa-
tion in these regions can be used as a
neural marker, confirming that the par-
ticipant retains the ability to under-
stand instructions, carry out different
mental tasks in response to those in-
structions, and exhibit willed volun-
tary behavior in the absence of any overt
action.
When the patient who was clini-
cally diagnosed as being in a vegetative
state was asked to imagine playing ten-
nis, significant activity was observed in
the supplementary motor area that was
statistically indistinguishable from that
observed in healthy awake volunteers
(Figure 2).2,3 In contrast, the instruc-
tion to imagine walking through the
rooms of her house elicited significant
activity in the parahippocampal gyrus,
posterior parietal cortex, and lateral pre-
motor cortex, which was again indistin-
guishable from that observed in healthy
volunteers. Despite her fulfilling all of
the clinical criteria for a diagnosis of
being in a vegetative state, we con-
cluded that this patient retained the abil-
ity to understand spoken commands and
to respond to them through her brain ac-
tivity rather than through speech or
movement. Moreover, her decision to co-
operate with us by imagining particu-
lar tasks when asked to do so repre-
sented a clear act of intention that confirmed beyond any doubt that she was consciously aware of herself and her surroundings.

Skeptics may argue that the words tennis and house could have automatically triggered the patterns of activation observed in the supplementary motor area, parahippocampal gyrus, posterior parietal lobe, and lateral premotor cortex activity while imagining moving around a house in the patient and in a healthy volunteer. However, we know of no data supporting the inference that such stimuli can unconsciously elicit sustained hemodynamic responses in these regions of the brain. Indeed, considerable data exist to suggest that such words do not elicit the responses that were observed. 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 (ie, lasting for a few seconds) and, not surprisingly, occur in regions of the brain that are associated with word processing.6 In our patient, the observed activity was not transient but persisted for the full 30 seconds of each imagery task (ie, far longer than would be expected given the hemodynamics of the fMR imaging 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 2 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 single keywords or to short sentences containing those words. In fact, we recently demonstrated that noninstructive sentences containing the same keywords as those used with our patient (eg, “the man enjoyed playing tennis”) produce no sustained activity in any of these brain regions in healthy volunteers.7 Therefore, the most parsimonious explanation is that this patient was consciously aware and was willfully following the instructions given to her, despite her diagnosis of being in a vegetative state.

Figure 1. Three healthy volunteers imagine playing tennis during real-time functional magnetic resonance (MR) imaging at the Medical Research Council Cognition and Brain Sciences Unit, Cambridge, England. Functional MR imaging data are superimposed on 3-dimensional anatomical reconstructions of structural MR data for online examination of brain activity during the imaging period. Similar significant activation is observed in the supplementary motor area in all 3 volunteers.

Figure 2. Supplementary motor area activity during tennis imagery in a patient diagnosed as being in a vegetative state and in a healthy volunteer (left). Parahippocampal gyrus, posterior parietal lobe, and lateral premotor cortex activity while imagining moving around a house in the patient and in a healthy volunteer (right).
This finding raises several important issues regarding the use of functional neuroimaging in the assessment of patients with disorders of consciousness. 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 patients in a vegetative state. For example, within 6 months of traumatic brain injury (as was the case for the patient described herein), the incidence of recovery of consciousness following traumatic brain injury remains at almost 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 being in a permanent vegetative state (the patient described herein did not). International guidelines, including those of the Royal College of Physicians in England and the Multi-Society Task Force representing 5 major medical societies in the United States, suggest that a diagnosis of being in a permanent vegetative state should not be made until 12 months after injury in cases of traumatic brain injury or until 6 months after injury in cases of anoxic brain injury. In many of these cases, standard clinical techniques, including structural MR imaging, may be sufficient to rule out any potential for normal activation, without the need for fMR imaging. That said, although it is almost certainly the case that similar fMR imaging responses will not be found in most patients who meet the clinical criteria for being in a 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 recently assessed a second patient with traumatic brain injury 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 soccer. 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 important to emphasize that negative functional neuroimaging findings in patients who are diagnosed as being in a vegetative state cannot be used as evidence for lack of awareness. For example, a patient may fall asleep during the imaging 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. On this basis, we suggest that functional neuroimaging should be more widely used in the assessment of patients with disorders of consciousness and particularly in those for whom existing clinical approaches have left some ambiguity about the diagnosis.

RELEVANCE TO THE STUDY OF NEUROSCIENCE

In the past 2 decades, rapid technological developments in the field of neuroimaging have produced a cornucopia of new techniques for examining the structure and function of the human brain in vivo. Detailed anatomical images, acquired through computed tomography and MR imaging, can now be combined with positron emission tomography, fMR imaging, quantitative electroencephalography, and magnetoencephalography to produce a cohesive picture of normal and abnormal brain function. As a result, functional neuroimaging has become the technique of choice for neuropsychologists, cognitive neuroscientists, and many others in the wider neuroscientific community with an interest in the relationship between brain and behavior. Until recently, these new methods of investigation have been used primarily as a correlational tool to map the cerebral changes that are associated with a particular cognitive process or function, be it an action, a thought, or a reaction (eg, to some kind of external stimulation). However, recent advances in imaging technology and particularly in the ability of fMR imaging to detect reliable neural responses in individual participants in real time are beginning to allow reverse inferences to be made (ie, to correctly identify a participant's thoughts, actions, or intentions based solely on the pattern of activity that is observed in his or her brain). The case of the patient described herein provides an example of such an application. The fact that she was consciously aware was evident only by examination of her time-locked and sustained fMR imaging responses following instructions to perform specific mental tasks in the absence of any overt action. On this basis, it was possible to infer not only that she was thinking but also what she was thinking at any given point in time (within the constraints of the tasks given to her). Similarly, in another study, healthy volunteers were instructed to choose to imagine playing tennis or navigating around their homes without informing the investigators of their choice. It was possible to determine with 100% accuracy which task was being performed by each participant during the imaging session based solely on his or her brain activity. Finally, in another recent fMR imaging study, participants were asked to freely decide which of 2 different tasks to perform and to covertly maintain that intention during a variable delay. During the delay, it was possible to decode from activity in the prefrontal cortex which of the 2 tasks the participants were covertly intending to perform. Such feats of rudimentary mind reading using fMR imaging pave the way for new and innovative applications of functional neuroimaging in basic neuroscience and in clinical practice. For example, the presence of reproducible and robust task-dependent fMR imaging responses to command without the need for any practice or training suggests a
novel method by which healthy participants and patients may be able to communicate their thoughts to those around them by simply modulating their neural activity. The use of functional neuroimaging in this context will continue to present innumerable logistic and theoretical problems. However, its clinical and scientific implications are so great that such efforts are clearly justified.

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