When thoughts become actions: functional neuroimaging in the vegetative state

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'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.'

The vegetative state is one of the least understood and most ethically troublesome conditions in modern medicine. The term describes a unique disorder in which patients who emerge from coma appear to be awake, but show no signs of awareness. The diagnosis is not normally considered until between 1 and 3 months *post ictus*, at which point 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 is generally sufficiently preserved hypothalamic and brain stem autonomic functions to permit survival with medical care.

A number of recent studies have demonstrated that functional neuroimaging may have an important role 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. So-called 'activation studies' have the potential to demonstrate distinct and specific physiological responses (changes in regional cerebral blood flow or changes in regional cerebral hemodynamics) to controlled external stimulation without the need for any overt behavioral response by the patient. Indeed, in recent years 'normal' or 'near normal' patterns of brain activity have been reported in response to many types of stimuli, including faces, speech, semantically ambiguous sentences and pain in patients meeting all of the clinical criteria for a diagnosis of vegetative state.

A question that is often asked of such studies is whether the presence of 'normal' brain activation in patients who are diagnosed as vegetative 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 patient (e.g., you cannot choose to not recognize a face or to not understand speech that is presented clearly in your native language). By the same argument, 'normal' neural responses in patients who are diagnosed as vegetative do not necessarily indicate that these patients have any conscious experience associated with processing those same types of stimuli.

The logic described above exposes a central conundrum 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 if another being is consciously aware is to ask them. 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 or the movement of a hand, as documented cases of the locked-in syndrome have demonstrated), but it is this answer that allows us to infer conscious awareness. But what if the ability to blink an eye or move a hand is lost, yet conscious awareness remains? By definition, patients who are diagnosed as vegetative are not able to elicit any behavioral responses. Thus, even if such a patient were consciously aware, they would have no means for conveying that information to the outside world.

We recently used functional magnetic resonance imaging (fMRI) to detect conscious awareness in a young woman 5 months after a traumatic brain injury [1]. The patient was diagnosed as vegetative based on an independent and comprehensive 6-week assessment by an experienced neurorehabilitation team. Prior to the scan, the patient was instructed to perform two mental imagery tasks when cued by the words 'tennis' and 'house'. One task involved imagining playing a game of tennis and the other involved imagining moving from room-to-room in her house. During the scan, the word 'tennis' elicited significant activity in the supplementary

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motor area (SMA), a region known to be involved in imagining (as well as actually performing) coordinated movements. In contrast, the word 'house' elicited significant activity in the parahippocampal gyrus (PPA), the posterior parietal cortex and the lateral premotor cortex, all regions that have been demonstrated to contribute to imaginary, or real, spatial navigation. We 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. Moreover, her decision to cooperate with us by imagining particular tasks when asked to do so represented a clear act of intention which confirmed beyond any doubt that she was consciously aware of herself and her surroundings.

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Of course, sceptics will argue that, just as in the examples described above, wholly automatic neural responses to single words can occur in the absence of conscious awareness and may explain the pattern of findings observed. However, in our patient, the activity observed was not transient (e.g., <10 s), as would be expected for an automatic response to a single word, but persisted for the full 30 s of each mental imagery task (e.g., far longer than would be expected, even given the hemodynamics of the blood oxygen level-dependent [BOLD] response). In fact, the task-specific changes persisted until the patient was cued with the word 'relax' indicating that she should rest. In addition, these responses did not occur in regions that have been shown to be associated with word processing, but in the SMA for one word and in the PPA for another. Finally, the BOLD responses in the patient were statistically significant at the single-subject level and were indistinguishable from those of healthy volunteers performing identical imagery tasks in the scanner. Importantly, when healthy volunteers undergo exactly the same fMRI procedure as our patient, yet are not given any prior instructions to use the words 'tennis' and 'house' to guide imagery, no sustained activity is observed in the SMA, PPA or any of the other regions that were commonly activated in our patient and the healthy volunteers who were asked to do the mental imagery tasks. Therefore the most parsimonious explanation remains that this patient was consciously aware and willfully following the instructions given to her, despite her diagnosis of vegetative state.

'In some patients, standard clinical techniques, including structural MRI, may be sufficient to rule out any potential for normal activation, without the need for fMRI.'

This finding raises a number of 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 vegetative patients. For example, at five months *post ictus* (as was the case in the patient described above), 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 described above did not). International guidelines, including those of the Royal College of Physicians, UK, and the Multi-Society Task Force representing five major medical societies in the USA, suggest that a diagnosis of permanent vegetative state should not be made in cases of traumatic brain injury until 12 months *post ictus* and 6 months *post ictus* 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.

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That said, although it remains to be seen whether similar fMRI responses will be found in other patients who have been diagnosed as

vegetative, there is little *a priori* reason to suppose that this is the only patient for whom this will be the case. 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.

Second, it is important to emphasize that negative 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.

Future work should focus on the development, application and integration of emerging technologies, such as real-time fMRI and electroencephalogram-based brain–computer interfaces to permit a fuller assessment of the nature and limits of residual cognitive function in noncommunicative patients, including those who are diagnosed as vegetative. The presence of reproducible and robust task-dependent fMRI responses to command, without the need for any practice or training, suggests a novel method by which some of these patients may be able to use their residual cognitive capabilities to communicate their thoughts to those around them by simply modulating their own neural activity. The use of functional neuroimaging in this context will clearly continue to present innumerable logistical and theoretical problems. However, the detection and elucidation of conscious awareness in this group of patients has such major clinical and scientific implications that these efforts are clearly justified.

Executive summary

Introduction

- Recent studies have demonstrated that functional magnetic resonance imaging may reveal residual cognitive functions, and even conscious awareness, in some patients who are assumed to be vegetative, yet retain abilities that have evaded detection using standard clinical approaches.

Caution

- The technique will not be applicable to all vegetative patients and negative findings cannot be used as evidence for lack of awareness.

Conclusions

- This technique may provide a new means for detecting conscious awareness when existing clinical techniques have been unable to provide such information.

Future perspective

- Future work should focus on the development, application and integration of emerging technologies to provide a method by which some noncommunicative patients may be able to use their residual cognitive capabilities to communicate their thoughts by simply modulating their own neural activity.

Bibliography

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