

CORRESPONDENCE



Willful Modulation of Brain Activity in Disorders of Consciousness

TO THE EDITOR: The report by Monti et al. (Feb. 18 issue)¹ has raised concern worldwide among relatives of patients in a persistent vegetative state. Could their loved ones be conscious after all?

However, in addressing such concerns, perhaps the mechanism of brain injury should be considered. It is worthwhile noting that all five patients who were in a vegetative or minimally conscious state and were found to be responsive on functional magnetic resonance imaging (MRI) were comatose as a result of traumatic brain injury rather than anoxic brain injury. The mechanism of injury differs between these two conditions. Multifocal damage with diffuse axonal injury occurs in traumatic injury, whereas in anoxic injury a diffuse anoxic cascade results in toxic metabolite formation, cell death, and loss of vasogenic regulation. Cerebral metabolic activity has been shown to occur to a greater extent in patients with traumatic brain injury than in those with anoxic injury.² Moreover, the global inability to modulate blood flow in anoxic brain injury makes functional MRI unsuitable as a

marker of consciousness. On the basis of our existing knowledge, the evidence remains against the presence of willful consciousness in patients who are in a persistent vegetative state from anoxic brain injury.

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No potential conflict of interest relevant to this letter was reported.

1. Monti MM, Vanhauzenhuyse A, Coleman MR, et al. Willful modulation of brain activity in disorders of consciousness. *N Engl J Med* 2010;362:579-89.

2. Schiff ND, Ribary U, Moreno DR, et al. Residual cerebral activity and behavioural fragments can remain in the persistently vegetative brain. *Brain* 2002;125:1210-34.

TO THE EDITOR: Monti and colleagues report that a patient in a persistent vegetative state was able to use a technique to answer yes or no to questions during functional MRI. However, we believe that a concern should be addressed to avoid weakening the strength of this message. The functional MRI studies in patients in a vegetative state should be conducted hierarchically.¹ As we know, it is not possible to comprehend speech unless it can be perceived. Until the investigators confirm that all lower levels of cognition are preserved using functional MRI, they could assess the patient's ability to generate willful, neuroanatomically specific responses during two established mental-imagery tasks. Such tasks would increase in complexity systematically from basic acoustic processing of nonspeech to more complex aspects of responses during two established mental-imagery tasks.² Such a hierarchy of cognitive tasks could provide a more reliable conclusion

THIS WEEK'S LETTERS

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and the most valid mechanism for evaluating preserved awareness in patients in a vegetative state.

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No potential conflict of interest relevant to this letter was reported.

1. Owen AM, Coleman MR. Functional neuroimaging of the vegetative state. *Nat Rev Neurosci* 2008;9:235-43.
2. Owen AM, Coleman MR, Boly M, Davis MH, Laureys S, Pickard JD. Detecting awareness in the vegetative state. *Science* 2006; 313:1402.

TO THE EDITOR: According to Monti et al., the rediagnosis of two patients with positive brain response led the authors to underscore the importance of careful clinical examination. We only partially agree. The retest process that is described in the article cannot exclude the effect of psychological suggestion, which might make the clinicians misclassify originally involuntary signs as voluntary.

In addition, the limited brain regions examined in this study might contribute to the negative results among the remaining 30 patients who were in a minimally conscious state. During the mental-imagery tasks, other brain regions, such as the premotor cortex and the posterior parietal cortex, may be activated.¹ Furthermore, other unexpected brain regions may be recruited because of post-injury brain reorganization and plasticity.

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1. Boly M, Coleman MR, Hampshire A, et al. When thoughts become action: an fMRI paradigm to study volatile brain activity in non-communicative brain injured patients. *Neuroimage* 2007; 36:979-92.

TO THE EDITOR: The work by Monti et al. showing that functional MRI may reveal willful brain activation in a small proportion of patients in a vegetative or minimally conscious state confirms the potential role of neuroimaging technology to elucidate mechanisms of brain recovery and to refine the diagnostic boundaries among disorders of consciousness.¹ This distinction is of paramount importance for prognosis, treatment

decisions, and medicolegal judgments. However, in the accompanying editorial, Ropper² cautions that this work is still preliminary. Moreover, troubling ethical concerns are hidden behind the issue of clinical research. The emotionally moving tragedy of Terri Schiavo has taught us that erroneous or misleading statements can be disseminated by print and broadcast media in the absence of adequate critical examination and background information.³ The premature dissemination of reports regarding these emerging technologies before validation in multicenter studies could cause confusion and misunderstanding and raise questions from the public. The accurate clinical prediction of the long-term outcome in patients with disorders of consciousness remains the main guide for making treatment-limitation decisions, as well as for disentangling the knot between bioethics and human mercy.

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1. Owen AM, Coleman MR, Boly M, Davis MH, Laureys S, Pickard JD. Detecting awareness in the vegetative state. *Science* 2006; 313:1402-3.
2. Ropper AH. Cogito ergo sum by MRI. *N Engl J Med* 2010; 362:648-9.
3. Quill TE. Terri Schiavo — a tragedy compounded. *N Engl J Med* 2005;352:1630-3.

THE AUTHORS REPLY: As Byrne and Hardiman point out, there is considerable evidence that the mechanisms of traumatic and nontraumatic brain injuries differ substantially. We therefore appreciate their drawing attention to our statement that “no [functional MRI] responses were observed in any of the patients with nontraumatic brain injuries.” We also appreciate their echoing our report that only “a small proportion of patients . . . have brain activation reflecting some awareness and cognition.”

We agree with Ma and colleagues that hierarchical approaches to testing patients in a vegetative state are very powerful.¹ This power, however, is mostly expressed in the context of negative findings. Indeed, the ability to willfully modulate brain activity in response to verbal commands must imply integrity of lower-level processes, including audition and language comprehension. Where no activity was observed, a hierarchical

approach could have provided information about whether the patients were aphasic or deaf.

Sun and Zhou raise two important issues relating to the interpretation of behavioral and neuroimaging data. The first point relates to the inescapable subjective element intrinsic in bedside evaluation. In this respect, neuroimaging, being quantitative and based on a uniform analysis with well-defined statistical criteria, is much less susceptible to bias. With respect to the neuroimaging analysis, it is possible that our region-of-interest approach, which was based on well-established data from healthy volunteers, excluded other regions that also might have covaried with the imagery tasks. However, even though differences in functional neuroanatomy are to be expected after severe brain injury, it is not clear how to interpret activations in entirely unexpected neuroanatomical locations. Hence, benchmarking the findings in our patients against those in healthy volunteers, while conservative, gives us greater confidence when positive results are observed.

Finally, we agree with the opinion of Striano and colleagues regarding the potential of neuroimaging in this group of patients and with Ropper's statement concerning the limits of what we know about the inner life of these patients.² We stress, however, that there is no ambiguity or

confusion surrounding the results of our multicenter study: functional neuroimaging can uncover signs of awareness in patients who, because of motor impairment, appear on clinical assessment to be in a vegetative state. Furthermore, our report is based on a large functional neuroimaging study, which matches previous behavioral reports.³ What is unclear and deserves careful discussion is how this research can be effectively translated into clinical practice to address the misdiagnosis rate of 40% that has pervaded behavioral assessments.⁴

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Since publication of their article, the authors report no further potential conflict of interest.

1. Owen AM, Coleman MR. Functional neuroimaging of the vegetative state. *Nat Rev Neurosci* 2008;9:235-43.
2. Ropper AH. Cogito ergo sum by MRI. *N Engl J Med* 2010; 362:648-9.
3. Schnakers C, Vanhaudenhuyse A, Giacino J, et al. Diagnostic accuracy of the vegetative and minimally conscious state: clinical consensus versus standardized neurobehavioral assessment. *BMC Neurol* 2009;9:35.
4. Owen AM, Schiff ND, Laureys S. A new era of coma and consciousness science. *Prog Brain Res* 2009;177:399-411.

Stent Graft or Balloon Angioplasty Alone for Dialysis-Access Grafts

TO THE EDITOR: Haskal et al. (Feb. 11 issue)¹ report prolonged vascular access with the use of a stent graft among patients undergoing balloon angioplasty for failing dialysis-access grafts. Despite the impressive results, some aspects of the work need additional discussion.

Balloon angioplasty induces vessel-wall injury, a process that is responsible for late restenosis. The mean access age at inclusion in this study was more than 2 years, and one wonders whether angioplasties were performed in some of those grafts before inclusion in the study. For example, how many percutaneous interventions had been done in the venous anastomosis before inclusion in the study? Was there any difference in prestudy interventions between the two groups? Moreover, the rate of procedural success was 73% among

patients who underwent balloon angioplasty alone and 94% among those who received a stent graft. This discrepancy could be an alternative explanation of the stent graft's success.

Some authors argue that stenosis is clinically important only if it is associated with a decline in access flow.² Only 18 to 25% of stenoses had a documented flow decrease in this study. In another 16% of stenoses, there was "abnormal flow on Doppler ultrasonography." Might such patients have been treated too early, when they had only borderline stenosis?³

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