DISORDERS OF CONSCIOUSNESS

Diagnostic accuracy of brain imaging in the vegetative state

Adrian M. Owen

Differential diagnosis in the vegetative and minimally conscious states is notoriously difficult. A new report compares the diagnostic accuracy of two neuroimaging methods, using bedside behavioural assessment as a reference. The results highlight the many theoretical and methodological challenges in studying this patient group.

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Accurate diagnosis in disorders of consciousness is critical for appropriate care, but the vegetative state and the minimally conscious state can be difficult to distinguish. In an article published recently in *The Lancet*, Stender and colleagues[1] compared the diagnostic and prognostic usefulness of ^{18}F-fluorodeoxyglucose PET (^{18}F-FDG PET) and functional MRI (fMRI). The authors conclude that ^{18}F-FDG PET has clinical value in diagnosis and outcome prediction in disorders of consciousness, and is more accurate than fMRI for differential diagnosis.

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The vegetative state is a clinical condition that has been described as 'wakefulness without awareness'.[2] Patients in the vegetative state can open their eyes, frequently move spontaneously, and will often exhibit sleeping and waking cycles; however, careful and repeated examination of the patient's spontaneous and elicited behaviour will yield no evidence of sustained, reproducible, purposeful, or voluntary behavioural response to visual, auditory, tactile or noxious stimulation. In short, the patients are entirely nonresponsive to any form of prompting or stimulation beyond simple reflexes and, on this basis, they are assumed to lack any awareness of self or surroundings.

It is now well accepted that when these patients are examined by specialized clinical teams, up to 43% will show inconsistent but reproducible behavioural signs of awareness, and will be reclassified as being in a minimally conscious state.[3] Nevertheless, some covertly aware patients will escape detection altogether, even by experienced teams, and will remain erroneously diagnosed as being in a vegetative state.[4,5]

In the present study, Stender and colleagues[1] assessed the diagnostic utility of ^{18}F-FDG PET in 81 minimally conscious patients and 41 patients in the vegetative state. The ^{18}F-FDG PET technique was shown to have high sensitivity to the minimally conscious state and high congruence with clinical behavioural scores, and accurately predicted outcome approximately 1 year later. In addition, of the 41 patients diagnosed as vegetative, 13 (32%) were shown to have metabolism consistent with minimal consciousness. By contrast, fMRI mental imagery tasks that have been shown previously to detect covert consciousness in patients clinically diagnosed as vegetative[4,5] seemed to have lower sensitivity, congruence and prediction outcomes than the PET technique. Stender and co-authors concluded that functional MRI is less reliable for differential diagnostic purposes than is ^{18}F-FDG PET.[1]

While any large-scale assessment of the diagnostic efficacy of new tools for clinical evaluation of patients in vegetative or minimally conscious states is most welcome, this study also highlights some of the methodological perils and theoretical pitfalls of research in these challenging patient groups. Most importantly, the ^{18}F-FDG PET and fMRI techniques employed by Stender *et al.*[1] have fundamental differences that render any direct comparison, in terms of diagnostic utility, inappropriate. ^{18}F-FDG PET directly measures the metabolic integrity of cortical networks believed to underpin consciousness, while fMRI mental imagery indirectly demonstrates consciousness by defining awareness as intentional neural modulation (or neural 'command following'). Crucially, metabolic integrity of cortical networks is necessary for consciousness, but does not guarantee it. By contrast, intentional neural modulation only occurs in conscious patients and is, therefore, sufficient to confirm consciousness in the absence of overt behavioural command following. Thus, any conclusion about the diagnostic utility of ^{18}F-FDG PET (either in absolute terms or in contrast with another technique) is inevitably spurious because there is no accurate way to confirm the findings.

> How do you evaluate a new neuroimaging technique when your point of reference ... is ... unreliable... ?

The importance of this distinction between the methodologies is illustrated by considering the 'requirements' of ^{18}F-FDG PET versus fMRI mental imagery. In ^{18}F-FDG PET, all that is required is that the patient, while resting, shows metabolic signs that suggest some level of residual cortical function that might be indicative of covert consciousness. Indeed, in the Stender *et al.*[1] study, even incomplete or partial preservation of activity in the frontoparietal cortex at an extremely lenient threshold for statistical significance ($P<0.05$, uncorrected for multiple comparisons) was considered sufficient for patients to be (re)classified as minimally conscious.

For a positive fMRI response, the patient had to reliably and repeatedly respond to commands by turning on and off an anatomically specific area of the brain, demonstrating that they could perceive and comprehend spoken language (the task instructions), commit them to working memory, selectively attend to perceptual cues, associate stimuli with responses, and switch attention between different mental representations.[4,5] In summary, the bar is much higher for fMRI mental imagery than for ^{18}F-FDG PET and, by extension, the confidence with which one can conclude that a nonresponsive patient is actually conscious is much higher for fMRI than for ^{18}F-FDG PET. The fact that only 59% of the participants completed the fMRI testing, whereas 91% completed the PET study, further muddies the waters for any direct comparison.

To level the playing field, a more appropriate approach would be to compare the diagnostic utility of ^{18}F-FDG PET with that of resting-state fMRI (where the patient is asked to do nothing but relax in the absence of any direct stimulation). In both cases, some proportion of patients would show activity, suggesting that covert awareness was possible, although neither technique would provide definitive confirmation.

The fundamental issue here concerns the lack of access to any 'ground truth' where ^{18}F-FDG PET is concerned. How do you evaluate a new neuroimaging technique when your point of reference (behavioural examination) is woefully unreliable, even in the hands of experienced teams?[3] Again, a positive fMRI result sidesteps this problem by removing the need for corroborative behavioural evidence: if a patient is able to modulate their fMRI activity to report their own name, their support worker's name and the current year,[6] the physician can be confident that they are not in a vegetative state, regardless of their behavioural score on the Coma Recovery Scale-Revised.[7–9]

Unfortunately, when such unequivocal signs of consciousness are lacking (as is the case with the ^{18}F-FDG PET data discussed here), it is almost impossible to avoid circular reasoning. For example, Stender and colleagues[1] cite the lack of behavioural gold standards as a primary motivation for the development of neuroimaging paradigms for detecting consciousness; however, these same behavioural tests are relied on to validate the neuroimaging paradigms within that study. Similarly, the authors rightly point to the unreliability of clinical assessment by non-specialized teams, yet the primary outcome measure was obtained by reference to hospital medical reports, the referring physician or the legal guardian.

In conclusion, bedside assessment, ^{18}F-FDG PET and active fMRI paradigms all have roles in the assessment of patients in vegetative or minimally conscious states. One should keep in mind, however, that the information they provide is quite different, rendering any direct comparison of their diagnostic accuracy misguided.

The Brain and Mind Institute, Department of Psychology, Natural Sciences Building, The University of Western Ontario, London, ON N6A 5B7, Canada.
adrian.owen@uwo.ca

Competing interests
The author declares no competing interests.

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