Purpose of review
We discuss recent developments in the use of neuroimaging and, in particular, functional MRI, in the assessment of patients diagnosed as vegetative state or minimally conscious state.

Recent findings
In the last year, there has been a substantial increase in the number of research studies published which have used state-of-the-art neuroimaging methods to assess residual cognitive functioning in patients diagnosed with disorders of consciousness. Work using functional MRI has demonstrated aspects of retained speech processing, emotional processing, comprehension and even conscious awareness in a small number of patients behaviourally meeting the criteria defining the vegetative and minimally conscious states.

Summary
The assessment of patients with disorders of consciousness relies heavily upon the subjective and consequently fallible interpretation of observed behaviour. Recent studies have demonstrated an important role for functional MRI in the identification of residual cognitive function in these patients. Such studies may be particularly useful when there is concern about the accuracy of the diagnosis and the possibility that residual cognitive function has remained undetected. In our opinion, the future use of functional MRI will substantially increase our understanding of disorders of consciousness following severe brain injury.

Keywords
awareness, consciousness, functional MRI, minimally conscious state, vegetative state

Introduction
An accurate and reliable evaluation of the level and content of cognitive processing is of paramount importance for the appropriate management of severely brain-damaged patients in altered states of consciousness [1]. Objective behavioural assessment of residual cognitive function can be extremely challenging in these patients, as motor responses may be minimal, inconsistent, and difficult to document, or may be undetectable because no cognitive output is possible. This difficulty leads to errors and a potentially high-level of misdiagnosis in the vegetative state [2–4], minimally conscious state (MCS) [5] and locked-in syndrome [6]. Recent advances in functional neuroimaging suggest a novel solution to this problem; so-called ‘activation’ studies can be used to assess cognitive functions in altered states of consciousness without the need for any overt response on the part of the patient. In several recent cases, this approach has been used to identify residual cognitive function and even conscious awareness in patients who behaviourally meet the criteria defining the vegetative state, yet retain cognitive abilities that have evaded detection using standard clinical methods. Similarly, in other studies, the cognitive capabilities of patients diagnosed as MCS have been explored using functional neuroimaging. Such studies suggest that the future integration of emerging functional neuroimaging techniques [7,8] with existing clinical and behavioural methods of assessment will be essential for improving our ability to reduce diagnostic errors between these related conditions. Moreover, such efforts may provide important new prognostic indicators, helping to disentangle differences in outcome on the basis of a greater understanding of the underlying mechanisms responsible and thus improve therapeutic choices in these challenging populations [8].

Functional MRI
Until recently, the majority of neuroimaging studies in vegetative state and related disorders of consciousness (DOCs) used either fluorodeoxyglucose PET or single photon emission computed tomography (SPECT) to measure resting cerebral blood flow and glucose metabolism [9–20]. Typically, widespread reductions in metabolic activity of up to 50% were reported, although in a few cases normal cerebral metabolism [17] and blood flow [21] were found in patients thought to be in a vegetative state. In some cases isolated ‘islands’ of metabolism were identified in circumscribed regions of cortex, suggesting...
the potential for cognitive processing in a subset of patients [17]. In one recent and remarkable case of late recovery from minimally conscious state, longitudinal PET examinations revealed increases in resting metabolism coincident with marked clinical improvements in motor function [22**]. While metabolic studies are useful in this regard, they can only identify functionality at the most general level; that is, mapping cortical and subcortical regions that are potentially recruitable, rather than relating neural activity within such regions to specific cognitive processes. Methods such as H$_2^{15}$O PET and functional MRI (fMRI), however, can be used to link distinct and specific physiological responses (changes in regional cerebral blood flow or changes in regional cerebral haemodynamics) to specific cognitive processes in the absence of any overt response (e.g. a motor action or a verbal response) on the part of the patient [23].

Early activation studies in patients with DOCs used H$_2^{15}$O PET, in part because the technique was more widely available and in part because the multiple logistic difficulties of scanning critically ill patients in the strong magnetic field that is integral to fMRI studies had yet to be resolved. In the first of such studies, H$_2^{15}$O PET was used to measure regional cerebral blood flow in a posttraumatic vegetative patient during an auditorily presented story told by his mother [24]. Compared with 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 et al. [25] 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 state patients, high-intensity noxious electrical stimulation activated midbrain, contralateral thalamus and primary somatosensory cortex in every patient [26]. Unlike controls, however, the patients did not activate secondary somatosensory, insular, posterior parietal or anterior cingulate cortices.

H$_2^{15}$O PET studies are limited by issues of radiation burden, which may preclude essential longitudinal or follow-up studies in many patients or even a comprehensive examination of multiple cognitive processes within any one session. The power of PET studies to detect statistically significant responses is also low and group studies are often needed to satisfy standard statistical criteria [23]. Given the heterogeneous nature of DOC and the clinical need to define each individual in terms of their diagnosis, residual functions and potential for recovery, such limitations are of paramount importance in the evaluation of these patients.

A significant development in this rapidly evolving field has been the relative shift of emphasis from PET ‘activation studies’ using H$_2^{15}$O methodology, to fMRI. Not only is MRI more widely available than PET, it offers increased statistical power, improved spatial and temporal resolution and has no associated radiation burden [23]. Recently, Di et al. [27*] used event-related fMRI to measure brain activation in seven vegetative patients and four MCS 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 vegetative patients and four MCS patients exhibited activity in ‘higher-order’ associative temporal-lobe areas. Whilst this result is encouraging (particularly because the two vegetative patients who showed the most widespread activation subsequently improved to MCS 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 with 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 [28]) 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 [29**,30].

Staffen et al. [31*] 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 which 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 patients’ own names (compared with others’ names) in locked in, MCS and some vegetative state patients [32*]. 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. As the authors point out [31], however, 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.

Recently, it has been argued that fMRI studies in patients with vegetative state and other DOCs should be conducted hierarchically [33] (see also [34, 35]); beginning with the simplest form of processing within a particular domain (e.g. auditory) and then progressing sequentially through more complex cognitive functions. 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 ‘‘ceak/creek’’ came from a ‘‘beam’’ in the ‘‘ceiling/sealing’’ ) are compared with 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 [36]. A recent study [37] has explored the utility of this approach in the assessment of DOCs; residual language function in a group of seven vegetative state and five MCS patients was graded according to their brain activation on this hierarchical series of paradigms. Three of the vegetative state patients and two of the MCS patients demonstrated some evidence of preserved speech processing (when all sentences were compared with signal-correlated white noise), whilst four patients showed no significant activation at all, even when responses to sound were compared with silence. Most strikingly, two of the vegetative state patients showed a significant response in the semantic ambiguity contrast, consistent with high-level comprehension of the semantic aspects of speech. The authors suggested that such a hierarchy of cognitive tasks provides the most valid mechanism for defining the depth and breadth of preserved cognitive function in severely brain-damaged patients in altered states of consciousness.

A question that is often asked of such studies, however, is whether the presence of ‘normal’ brain activation in patients diagnosed with DOC 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 [38]; that is to say, they will occur without the need for willful intervention on the part of the participant (e.g. you can not choose to not recognise 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 with DOCs 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 DOCs. There is, as yet, no universally agreed definition of consciousness and even less so self-consciousness or sense of self/being [39**]. Deeper philosophical considerations notwithstanding, the only reliable method that we have for determining if 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, and only this answer, that allows us to infer conscious awareness.

Owen et al. [40**] have recently adapted this logic using fMRI to demonstrate preserved conscious awareness in a patient fulfilling the criteria for a diagnosis of vegetative state. 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’. Importantly, these particular tasks were chosen, not because they invoke a set of fundamental cognitive processes that are known to reflect conscious awareness, but because imagining playing tennis and imagining moving around the house elicits extremely reliable, robust and statistically distinguishable patterns of activation in specific regions of the brain [38]. Indeed, a recent analysis of these paradigms in a large group of healthy volunteers [42] has shown that they permit the identification of volitional brain activity (and thus of consciousness) at the single-patient level, without the need for any motor response.

Given the reliability of these responses across individuals, activation in these regions in patients with DOCs can be used as a ‘neural marker’, confirming that the patient retains the ability to understand instructions, to carry out different mental tasks in response to those instructions and, therefore, is able to exhibit willed, voluntary behaviour in the absence of any overt action. During the periods that the vegetative patient was asked to imagine playing tennis, significant activity was observed in the supplementary motor area [40**]. In contrast, when she was asked to imagine walking through her home, significant activity was observed in the parahippocampal gyrus, the posterior parietal cortex and the lateral premotor cortex. Her neural responses were indistinguishable from those observed in healthy volunteers performing the same imagery tasks in the scanner [40**, 42] (Fig. 1). In a supplementary study [41**], noninstructive sentences containing the same key words as those used with the patient (e.g. ‘The man enjoyed playing tennis’) were shown to produce no sustained activity in any of these brain regions 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.

**Limitations**

The findings of Owen et al. [40**,41**] raise a number of important issues regarding the use of fMRI in the assessment of patients with DOCs. 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 5 months post ictus (as was the case in the patient described in [40**]), 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 (a decision process not started until 12 months post-traumatic and 6 months nontraumatic). 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.

More generally, the acquisition, analysis, and interpretation of fMRI data from patients with severe brain damage are also complex [43**]. For example, in patients with brain damage, the coupling of neuronal activity and local haemodynamics, essential for fMRI activation measurements, is likely to be different from that in...
fMRI appears to offer a complementary approach to the
care of these patients is difficult because voluntary movements
may be very small, inconsistent and easily exhausted. The
investigation should also be complex enough that the cognitive processes of
interest will be studied (i.e., preferably beyond stimulus perception), yet not so complex that the tasks could easily
overload the cognitive capacities of a tired or inattentive
patient. Many studies also suffer from the reverse inference problem described above [29**, 30]. In order that the imaging data obtained from patients with DOC can be interpreted, control studies are essential which must
produce well documented, anatomically specific, robust,
and reproducible activation patterns in healthy volunteers.
In vegetative state, MCS, and locked-in syndrome, epis-
sodes of low arousal and sleep are common and close
patient monitoring – preferably through electroence-
phalograph recording – during activation scans is essen-
tial so that these periods can be avoided. Spontaneous
movements during the scan itself may also compromise
the interpretation of functional neuroimaging data, par-
cularly with fMRI scans. Processing of functional neuro-
imaging data may also present challenging problems
in patients with acute brain damage. For example, the
presence of gross hydrocephalus or focal pathology may
complicate the fitting of functional imaging data to struc-
tural imaging data, and the normalization of these images
through reference to a healthy brain. Under these circum-
stances, statistical assessment of activation patterns is
complex and interpretation of activation foci with standard
cortical coordinates may be impossible.

Finally and most importantly, negative fMRI findings in
patients with DOC should never be used as evidence for
impaired cognitive function or lack of awareness [38]. For
example, a patient may fall asleep during the scan or may
not have properly heard or understood the task instruc-
tions, leading to so-called ‘false negative’ results. False
negative findings in functional neuroimaging studies are
common, even in healthy volunteers. 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.

Conclusion
DOCs present unique problems for diagnosis, prognosis,
treatment and everyday management. At the patient’s
bedside, the evaluation of possible cognitive function in
these patients is difficult because voluntary movements
may be very small, inconsistent and easily exhausted. fMRI appears to offer a complementary approach to the
clinical assessment of patients with vegetative state and
other altered states of consciousness and can objectively
describe (using population norms) the regional distri-
bution of cerebral activity under various conditions of
stimulation. Indeed, in some rare cases, fMRI has demon-
strated preserved 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. In our opinion, the
future use of fMRI will substantially increase our under-
standing of severely brain-injured patients.

References and recommended reading
Papers of particular interest, published within the annual period of review, have
been highlighted as:
• of special interest
•• of outstanding interest
Additional references related to this topic can also be found in the Current
World Literature section in this issue (p. 740).

1 Bernat JL. Chronic disorders of consciousness. Lancet 2006; 367:1181–
1192. Excellent review covering diagnosis, brain function, therapy and prognosis in vegetative state and MCS.


7 Schiff ND. Multimodal neuroimaging approaches to disorders of conscious-

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13 Momose T, Matsu T, Kosaka N. Effect of cervical spinal cord stimulation
(cSCS) on cerebral glucose metabolism and blood flow in a vegetative patient
assessed by positron emission tomography (PET) and single photon emission

14 Rudolf J, Sobesky J, Ghaemi M, et al. The correlation between cerebral
glucose metabolism and benzodiazepine receptor density in the acute vege-


Bekinschtein T, Leiguarda R, Armony J, et al. Selective brain activity in deaf patients who behaviourally met the criteria defining the vegetative state, yet retain cognitive abilities that have evaded detection using standard clinical methods.


This single case study demonstrated, for the first time, that fMRI can be used to detect conscious awareness in patients who behaviourally meet the criteria defining the vegetative state, yet retain cognitive abilities that have evaded detection using standard clinical methods.


This excellent review describes the theoretical framework, design and potential clinical applications of functional neuroimaging protocols in patients with DOCs.


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