Functional MRI in disorders of consciousness: advantages and limitations

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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

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Abbreviations

DOC	disorder of consciousness
fMRI	functional MRI
MCS	minimally conscious state

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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 "creak/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.

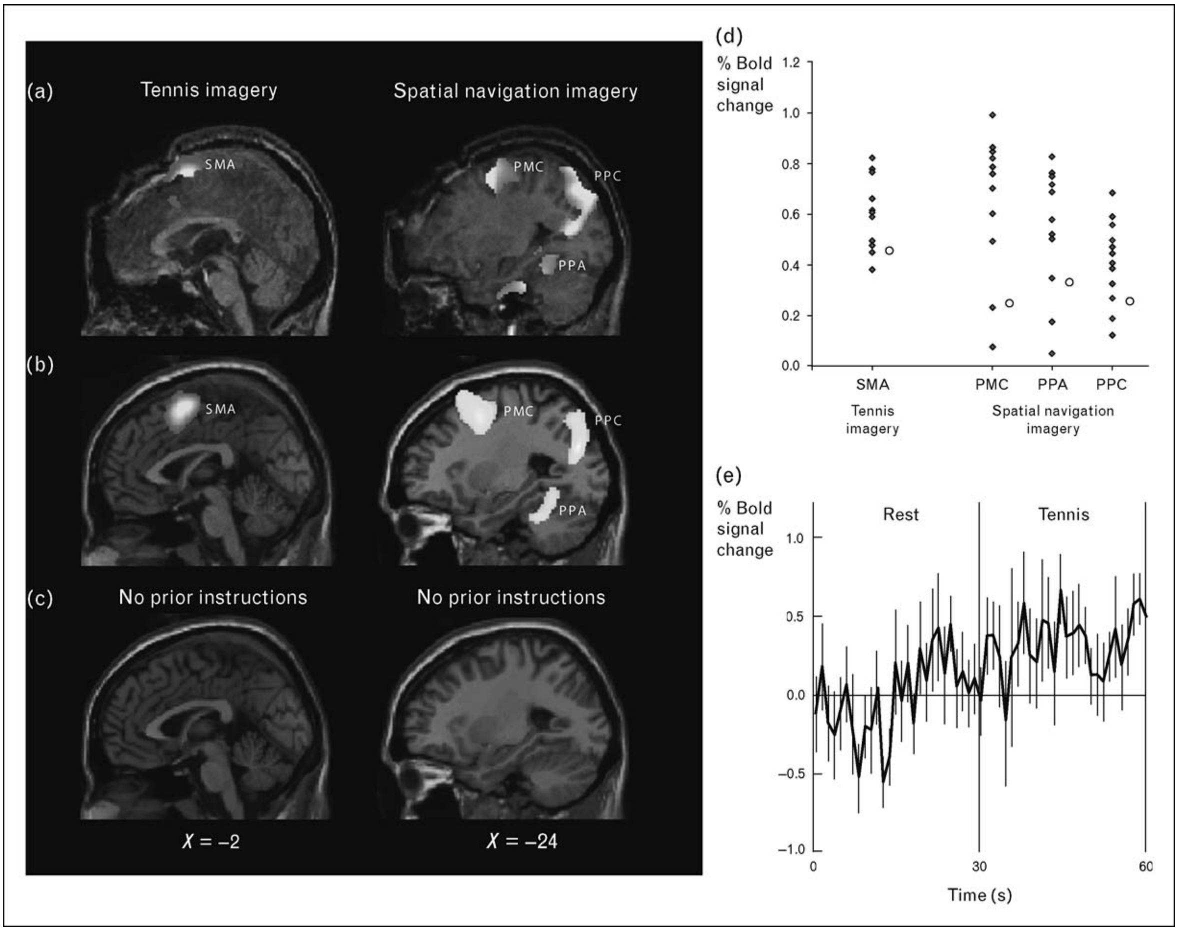
A question that is often asked of such studies, however, is whether the presence of 'normal' brain activation in patients diagnosed with DOC indicates a level of conscious awareness, perhaps even similar to that which exists in healthy volunteers when performing the same tasks. Many types of stimuli, 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 wilful 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••,41••] 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 involve a set of fundamental cognitive processes that are known to reflect conscious awareness, but because imagining playing tennis and imagining moving around the house elicit 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

Figure 1 Searching for a neural correlate of consciousness in a vegetative patient



Indistinguishable functional MRI (fMRI) activity in a vegetative state patient (a) and healthy controls (b) while imagining playing tennis (left column) or moving around a house (right column) [40••]. (c) The results from healthy volunteers when noninstructive sentences involving the same key words were used [41••]. (d) Signal intensity changes in the vegetative state patient plotted against 12 healthy volunteers performing the same two tasks. Signal intensity changes for the patient are all within the normal range. (e) A sustained 30 s fMRI response in the supplementary motor cortex was observed when the vegetative state patient was asked to imagine playing tennis (right), relative to rest (left). PMC, premotor cortex; PPA, parahippocampal gyrus; PPC, posterior parietal cortex; SMA, supplementary motor area.

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 healthy controls [44–47], making interpretation of such data sets extremely difficult. Notwithstanding this basic methodological concern, the choice of the experiment is also crucial [33,34]. For example, if brainstem auditory evoked responses are abnormal, auditory stimuli may be inappropriate and alternative stimuli – such as visual stimuli – should be considered. 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, episodes of low arousal and sleep are common and close patient monitoring – preferably through electroencephalograph recording – during activation scans is essential so that these periods can be avoided. Spontaneous movements during the scan itself may also compromise the interpretation of functional neuroimaging data, particularly with fMRI scans. Processing of functional neuroimaging 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 structural imaging data, and the normalization of these images through reference to a healthy brain. Under these circumstances, statistical assessment of activation patterns is complex and interpretation of activation foci with standard stereotaxic 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 instructions, 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 distribution of cerebral activity under various conditions of stimulation. Indeed, in some rare cases, fMRI has demonstrated 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 understanding 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.

2 Andrews K, Murphy L, Munday R, *et al.* Misdiagnosis of the vegetative state: retrospective study in a rehabilitation unit. BMJ 1996; 313:13–16.

3 Childs NL, Mercer WN, Childs HW. Accuracy of diagnosis of persistent vegetative state. Neurology 1993; 43:1465–1467.

4 Tresch DD, Sims FH, Duthie EH, *et al.* Clinical characteristics of patients in the persistent vegetative state. Arch Intern Med 1991; 151:930–1012.

5 • Schnakers C, Giacino J, Kaknar K, *et al.* Does the FOUR score correctly diagnose the vegetative and minimally conscious states? Ann Neurol 2006; 60:744–745.
This paper describes a study in which the new Full Outline of UnResponsiveness (FOUR) scale was compared with the Glasgow Coma Scale (GCS) and the Coma Recovery Scale-Revised (CRS-R) in 60 severely brain-injured, postcomatose patients.

6 Leon-Carrion J, van Eeckhout P, Dominguez-Morales Mdel R, *et al.* The locked-in syndrome: a syndrome looking for a therapy. Brain Inj 2002; 16:571–582.

7 •• Schiff ND. Multimodal neuroimaging approaches to disorders of consciousness. J Head Trauma Rehabil 2006; 21:388–397.
An excellent review of recent neuroimaging studies in vegetative state and MCS that argues persuasively for a multimodal approach to the assessment of DOCs. Recommendations are made for frameworks guiding the introduction of neuroimaging into the clinical evaluation process.

8 •• Laureys S, Giacino JT, Schiff ND, *et al.* How should functional imaging of patients with disorders of consciousness contribute to their clinical rehabilitation needs? Curr Opin Neurol 2006; 19:520–527.
This paper discusses the problems of evidence-based neurorehabilitation in DOCs and provides a thorough review of recent functional neuroimaging studies in vegetative state and MCS. The authors argue that controlled studies and careful patient selection are required to fully evaluate the potential of therapeutic interventions in DOCs.

9 Tommasino C, Grana C, Lucignani G, *et al.* Regional cerebral metabolism of glucose in comatose and vegetative state patients. J Neurosurg Anesthesiol 1995; 7:109–116.

10 De Volder AG, Goffinet AM, Bol A, *et al.* Brain glucose metabolism in postanoxic syndrome: positron emission tomographic study. Arch Neurol 1990; 47:197–204.

11 Levy DE, Sidtis JJ, Rottenberg DA, *et al.* Differences in cerebral blood flow and glucose utilization in vegetative versus locked-in patients. Ann Neurol 1987; 22:673–682.

12 Rudolf J, Ghaemi M, Haupt WF, *et al.* Cerebral glucose metabolism in acute and persistent vegetative state. J Neurosurg Anesthesiol 1999; 11:17–24.

13 Momose T, Matsui 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 computed tomography (SPECT). Radiat Med 1989; 7:243–246.

14 Rudolf J, Sobesky J, Ghaemi M, *et al.* The correlation between cerebral glucose metabolism and benzodiazepine receptor density in the acute vegetative state. Eur J Neurol 2002; 9:671–677.

15 Edgren E, Enblad P, Grenvik A, *et al.* Cerebral blood flow and metabolism after cardiopulmonary resuscitation: a pathophysiologic and prognostic positron emission tomography pilot study. Resuscitation 2003; 57:161–170.

16 Beuthien-Baumann B, Handrick W, Schmidt T, *et al.* Persistent vegetative state: evaluation of brain metabolism and brain perfusion with PET and SPECT. Nucl Med Commun 2003; 24:643–649.

17 Schiff ND, Ribary U, Moreno DR, *et al.* Residual cerebral activity and behavioural fragments can remain in the persistently vegetative brain. Brain 2002; 125 (Pt 6):1210–1234.

18 Laureys S, Goldman S, Phillips C, *et al.* Impaired effective cortical connectivity in vegetative state: preliminary investigation using PET. Neuroimage 1999; 9:377–382.

19 Laureys S, Lemaire C, Maquet P, *et al.* Cerebral metabolism during vegetative state and after recovery to consciousness. J Neurol Neurosurg Psychiatry 1999; 67:121.

20 Boly M, Faymonville ME, Peigneux P, *et al.* Auditory processing in severely brain injured patients: differences between the minimally conscious state and the persistent vegetative state. Arch Neurol 2004; 61:233–238.

21 Agardh CD, Rosen I, Ryding E. Persistent vegetative state with high cerebral blood flow following profound hypoglycemia. Ann Neurol 1983; 14:482–486.

22 •• Voss HU, Uluc AM, Dyke JP, *et al.* Possible axonal regrowth in late recovery from the minimally conscious state. J Clin Invest 2006; 116:2005–2011.

An extraordinary case of late recovery from MCS 19 years following trauma is described. The authors used state-of-the-art diffusion tensor MRI combined with PET to identify possible axonal regrowth.

23 Owen AM, Epstein R, Johnsrude IS. fMRI: applications to cognitive neuroscience. In: Jezzard P, Mathews PM, Smith SM, editors. Functional magnetic resonance imaging: an introduction to methods. Oxford: Oxford University Press; 2001. pp. 311–327.

24 de Jong B, Willemsen AT, Paans AM. Regional cerebral blood flow changes related to affective speech presentation in persistent vegetative state. Clin Neurol Neurosurg 1997; 99:213–216.

25 Menon DK, Owen AM, Williams EJ, *et al.* Cortical processing in persistent vegetative state. Lancet 1998; 352:200.

26 Laureys S, Faymonville ME, Peigneux P, *et al.* Cortical processing of noxious somatosensory stimuli in the persistent vegetative state. Neuroimage 2002; 17:732–741.

27 • Di HB, Yu SM, Weng XC, *et al.* Cerebral response to patient's own name in the vegetative and minimally conscious states. Neurology 2007; 68:895–899.

An fMRI study of seven vegetative state patients and four MCS patients listening to own name stimuli spoken by a familiar voice compared with attenuated machine noise baseline. Activation in two vegetative state patients and four MCS patients extended beyond primary auditory cortex.

28 Bekinschtein T, Leiguarda R, Armony J, *et al.* Emotional processing in the minimally conscious state. J Neurosurg Neurol and Psychiatry 2004; 75:788.

29 •• Poldrack RA. Can cognitive processes be inferred from neuroimaging data? Trends Cogn Sci 2006; 10:59–63.

An excellent critique on the use and misuse of 'reverse inference' in functional neuroimaging. The author argues that neuroscientists should be circumspect in the use of reverse inference, particularly when cognitive selectivity of the brain region in question cannot be established.

30 Christoff K, Owen AM. Improving reverse neuroimaging inference: cognitive domain versus cognitive complexity. Trends Cogn Sci 2006; 10:352–353.

31 • Staffen W, Kronbichler M, Aichhorn M, *et al.* Selective brain activity in response to one's own name in the persistent vegetative state. J Neurol Neurosurg Psychiatry 2006; 77:1383–1384.

This well controlled study examined fMRI activity in a single vegetative state patient during sentences that included his own name compared with sentences that included another name. The results were remarkably similar to those observed in healthy controls.

32 • Perrin F, Schnakers C, Schabus M, *et al.* Brain response to one's own name in vegetative state, minimally conscious state, and locked-in syndrome. Arch Neurol 2006; 63:562–569.

This well controlled study describes a differential P3 response in locked-in, MCS and some vegetative state patients when presented with their own names compared with other common first names, possibly suggesting partially preserved semantic processing in DOCs.

33 Owen AM, Coleman MR, Menon DK, *et al.* Using a heirarchical approach to investigate residual auditory cognition in persistent vegetative state. In: Laureys S, editor. The boundaries of consciousness: neurobiology and neuropathology. Progress in Brain Research, vol. 150. London: Elsevier; 2005. pp. 461–476.

34 Owen AM, Coleman MR, Menon DK, *et al.* Residual auditory function in persistent vegetative state: a combined PET and fMRI study. Neuropsychol Rehabil 2005; 15:290–306.

35 Laureys S, Owen AM, Schiff N. Brain function in coma, vegetative state, and related disorders. Lancet Neurol 2004; 3:537–546.

36 Rodd JM, Davis MH, Johnsrude IS. The neural mechanisms of speech comprehension: fMRI studies of semantic ambiguity. Cereb Cortex 2005; 15:1261–1269.

37 Coleman MR, Rodd JM, Davis MH, *et al.* Do vegetative patients retain aspects of language: evidence from fMRI. Brain 2007; 130:2492–2507.

38 Owen AM, Coleman MR, Boly M, *et al.* Using fMRI to detect awareness in the vegetative state. Arch Neurol 2007; 64:1098–1102.

39 •• Laureys S, Perrin F, Brédart S. Self-consciousness in noncommunicative patients. Conscious Cogn 2007; 31 May [Epub ahead of print].

A very thorough review of neuropsychological, neuropathological, electrophysiological and neuroimaging studies using own name and own face paradigms in conscious waking, sleep, pharmacolocial coma, pathological coma and related DOCs.

40 •• Owen AM, Coleman MR, Davis MH, *et al.* Detecting awareness in the vegetative state. Science 2006; 313:1402.

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.

41 •• Owen AM, Coleman MR, Davis MH, *et al.* Response to comments on 'Detecting awareness in the vegetative state'. Science 2007; 315:1221c.

Follow-up data demonstrated that the fMRI responses observed in [40••] from a patient who behaviourally met the criteria defining the vegetative state could not have occurred 'automatically', but rather, required a conscious or 'willed' response to the instructions given by the authors.

42 • Boly M, Coleman MR, Davis MH, *et al.* When thoughts become action: an fMRI paradigm to study volitional brain activity in noncommunicative brain injured patients. Neuroimage 2007; 36:979–992.

In this large multicentre study of healthy volunteers, the utility of volitional fMRI paradigms for the assessment of DOCs was demonstrated. Two novel tasks were introduced which permit the identification of volitional brain activity (and thus of consciousness) at the single-patient level, without the need for any motor response.

43 •• Giacino J, Hirsch J, Schiff N, *et al.* Functional neuroimaging applications for assessment and rehabilitation planning in patients with disorders of consciousness. Arch Phys Med Rehabil 2006; 87:67–76.

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

44 Sakatani K, Murata Y, Fukaya C, *et al.* BOLD functional MRI may overlook activation areas in the damaged brain. Acta Neurochir Suppl 2003; 87:59–62.

45 Gsell W, De Sadeleer C, Marchalant Y, *et al.* The use of cerebral blood flow as an index of neuronal activity in functional neuroimaging: experimental and pathophysiological considerations. J Chem Neuroanat 2000; 20:215–224.

46 Hamzei F, Knab R, Weiller C, *et al.* The influence of extra- and intracranial artery disease on the BOLD signal in FMRI. Neuroimage 2003; 20:1393–1399.

47 Rossini PM, Altamura C, Ferretti A, *et al.* Does cerebrovascular disease affect the coupling between neuronal activity and local haemodynamics? Brain 2004; 127 (Pt 1):99–110.