CHAPTER

13

The Assessment of Conscious Awareness in the Vegetative State

Adrian M. Owen, Nicholas D. Schiff and Steven Laureys

OUTLINE

ABSTRACT

The assessment of patients in the vegetative state is extremely complex and depends frequently on subjective interpretations of the observed spontaneous and volitional behaviour. In recent years, a number of studies have demonstrated an important role for functional neuroimaging in the identification of residual cognitive function, and even conscious awareness, in some patients fulfilling the clinical criteria for vegetative state. Such studies, when successful, may be particularly useful where there is concern about the accuracy of the diagnosis and the possibility that residual cognitive function has remained undetected. However, use of these techniques in severely brain-injured persons is methodologically complex and requires careful quantitative analysis and interpretation. In addition, ethical frameworks to guide research in these patients urgently need to be developed to accommodate these emerging technologies.

INTRODUCTION

In recent years, improvements in intensive care have increased the number of patients who survive severe acute brain injuries. Although the majority of these patients recover from coma within the first days of the insult, others evolve to a state of 'wakeful unawareness' or vegetative state. Clinically, recognizing unambiguous signs of conscious perception of the environment and of the self in such patients can be extremely challenging. This difficulty is reflected in frequent misdiagnoses of the condition and confusion between the vegetative state and related conditions such as minimally conscious state and locked-in syndrome [1, 2]. Like all severely brain-injured patients, bedside evaluation of residual brain function in vegetative state is difficult because motor responses may be very limited or inconsistent. In addition, the clinical assessment of cognitive function relies on inferences drawn from present or absent responses to external stimuli at the time of the examination [3]. Recent advances in functional neuroimaging suggest a novel solution to this problem; in several cases, so-called activation studies have been used to identify residual 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 this chapter, we first describe the major clinical characteristics of vegetative state following severe brain injury. We then discuss the contribution of neuroimaging studies to the assessment of conscious awareness in the vegetative state. Finally, we review the major methodological and ethical impediments to conducting such studies in disorders of consciousness.

CLINICAL DESCRIPTION

Patients in the vegetative state are awake, but are assumed to be entirely unaware of self and environment [4, 5]. Jennett and Plum cited the Oxford English Dictionary to clarify their choice of the term 'vegetative': to be vegetate is to 'live a merely physical life devoid of intellectual activity or social intercourse' and vegetative describes 'an organic body capable of growth and development but devoid of sensation and thought'. '*Persistent* vegetative state' is a term that was chosen arbitrarily to describe a vegetative state present 1 month after acute traumatic or non-traumatic brain injury but does not imply irreversibility [6]. '*Permanent* vegetative state' denotes irreversibility. The Multi-Society Task Force on vegetative state concluded that 3 months following a non-traumatic brain injury and 12 months after traumatic injury, the condition of vegetative patients may be regarded as 'permanent'. These guidelines are best applied to patients who have suffered diffuse traumatic brain injuries and post-anoxic events; other non-traumatic aetiologies may be less well predicted (see for example [7, 8]) and require further considerations of aetiology and mechanism in evaluating prognosis. Even after long and arbitrary delays, some exceptional patients may show limited recovery. This is more likely in patients with non-traumatic coma without cardiac arrest who survive in the vegetative state for more than 3 months. The diagnosis of vegetative state should be questioned when there is any degree of sustained visual pursuit, consistent and reproducible visual fixation, or response to threatening gestures [6]. It is essential to establish the formal absence of any sign of conscious perception or deliberate action before making the diagnosis (Box 13.1).

RESTING BRAIN FUNCTION

In the vegetative state, the brainstem is relatively spared whereas the grey or white matter of both cerebral hemispheres is widely and severely injured. Overall cortical metabolism of vegetative patients is 40–50% of normal values [9–20]. Some studies however, have found normal cerebral metabolism [17] or blood flow [21] in patients in a persistent vegetative state. In *permanent* vegetative state (i.e., 12 months after a trauma or 3 months following a non-traumatic brain injury), brain metabolism values drop to 30–40% of normal values (Figure 13.1) [9]. This progressive loss of metabolic functioning over time is the result of progressive Wallerian and transsynaptic neuronal degeneration. Characteristic of vegetative patients is a relative sparing of metabolism in the brainstem (encompassing the pedunculopontine reticular formation, the hypothalamus and the basal forebrain) [22]. The functional preservation of these structures allows for the preserved arousal and autonomic functions in these patients. Another hallmark of the vegetative state is a systematic impairment of metabolism in the polymodal associative cortices (bilateral prefrontal regions, Broca's area, parieto-temporal and posterior parietal areas and precuneus) [18]. These regions are known to be important in various functions that are necessary for consciousness, such as attention, memory and language

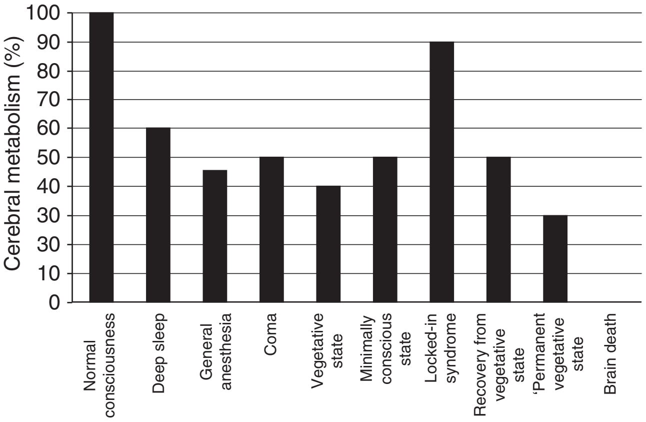

FIGURE 13.1 Cerebral metabolism in the different diagnostic groups. *Source*: Adapted from Laureys *et al*. (2004) *Lancet Neurol* 9:537–546.

BOX 13.1

VEGETATIVE PATIENTS WITH ATYPICAL BEHAVIOURAL FRAGMENTS

Stereotyped responses such as grimacing, crying or occasional vocalization are frequently observed on examination of vegetative state patients. These behaviours are assumed to arise primarily from brainstem circuits and limbic cortical regions that are preserved in the vegetative state. Rarely, however, patients meeting the diagnostic criteria for the vegetative state exhibit behavioural features that prima facie appear to contravene the diagnosis. A series of studies of chronic vegetative patients examined with multimodal imaging techniques identified three such patients with unusual behavioural fragments. Using FDG-PET (fluorodeoxyglucose-positron emission tomography), structural magnetic resonance imaging (MRI) and magnetoencephalography (MEG) preserved islands of higher resting brain metabolism measured by PET imaging and incompletely preserved evoked MEG gamma-band responses were correlated with structural imaging and behavioural fragments [17]. Among those studied was a patient who had been in a vegetative state for 20 years who infrequently expressed single words (typically epithets) in isolation of environmental stimulation [23]. MRI images demonstrated severe subcortical injuries. Resting FDG-PET measurements of the patient's brain revealed a global cerebral metabolic rate of <50% of normal across most brain regions with small regions in the left hemisphere expressing higher levels of metabolism (see Figure 13.2). MEG responses to bilateral auditory stimulation were confined to the left hemisphere and localized to primary auditory areas. Taken together, the imaging and neurophysiological data appeared to identify isolated sparing of left sided thalamo-cortical-basal ganglia loops that normally support language function in Heschl's gyrus, Broca's area and Wernicke's area. Similar observations in two other vegetative state patients provide novel evidence that isolated cerebral networks may remain active in rare vegetative state patients. Importantly, the preservation of these isolated behaviours does not herald further recovery in patients in chronic vegetative states who have been repeatedly examined and carefully studied with imaging tools. Reliable observations of such unusual features should prompt further investigation in an individual patient.

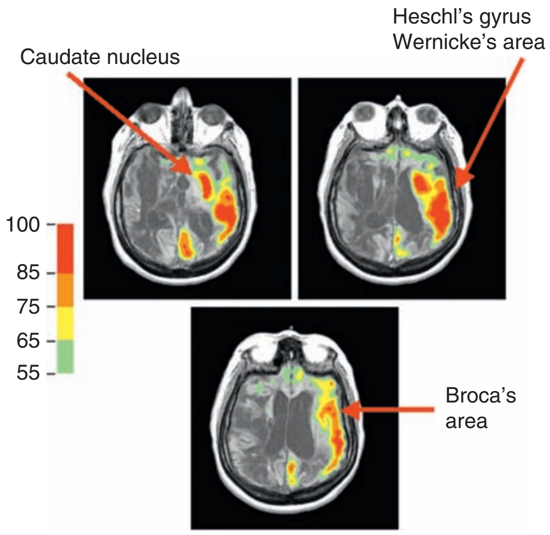

FIGURE 13.2 Preservation of regional cerebral metabolic activity in a vegetative state patient. FDG-PET data for vegetative state patient with occasional expression of isolated words is displayed co-registered with structural MRI (from Schiff *et al*. [23]). PET voxels are normalized by region and expressed on a colour scale ranging from 55% to 100% of normal.

[24]. It is still unknown whether the observed metabolic impairment in this large cortical network reflects an irreversible structural neuronal loss [25] or functional and potentially reversible damage. However, in those rare and fortunate cases where vegetative patients recover awareness of self and environment, positron emission tomography (PET) shows a functional recovery of metabolism in these same cortical regions [19]. Moreover, the resumption of long-range functional connectivity between these associative cortices and the intralaminar thalamic nuclei parallels the restoration of their functional integrity [26]. The cellular mechanisms which underlie this functional normalization remain unclear: axonal sprouting, neurite outgrowth, cell division (known to occur predominantly in associative cortices in normal primates) [27] have been proposed as candidate processes.

BRAIN ACTIVATION STUDIES

While metabolic studies are useful, 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 [13]. On the other hand, methods such as $H_2{}^{15}O$ PET and functional magnetic resonance imaging (fMRI) can be used to link residual neural activity to the presence of covert cognitive *function*. In short, functional neuroimaging, or so-called activation studies, have the potential to demonstrate distinct and specific physiological responses (changes in regional cerebral blood flow (rCBF) or changes in regional cerebral haemodynamics) to controlled external stimulation in the absence of any overt response (e.g., a motor action) on the part of the patient (Box 13.2). In the first of such studies, $H_2{}^{15}O$ PET was used to measure rCBF in a post-traumatic vegetative patient during an auditorily presented story told by his mother [28]. Compared to non-word 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*. [7] also used PET, but to study covert *visual* processing in response to familiar faces. During 'experimental' scans, the patient was presented with pictures of the faces of family and close friends, while during 'control' scans scrambled versions of the same images were presented which contained no meaningful visual information whatsoever. Previous imaging studies in healthy volunteers have shown that such tasks produce robust activity in the right fusiform gyrus, the so-called human 'face area' (e.g., [29, 30]). The same visual association region was activated in the vegetative patient when the familiar face stimuli were compared to the meaningless visual images [7, 31] (Figure 13.3).

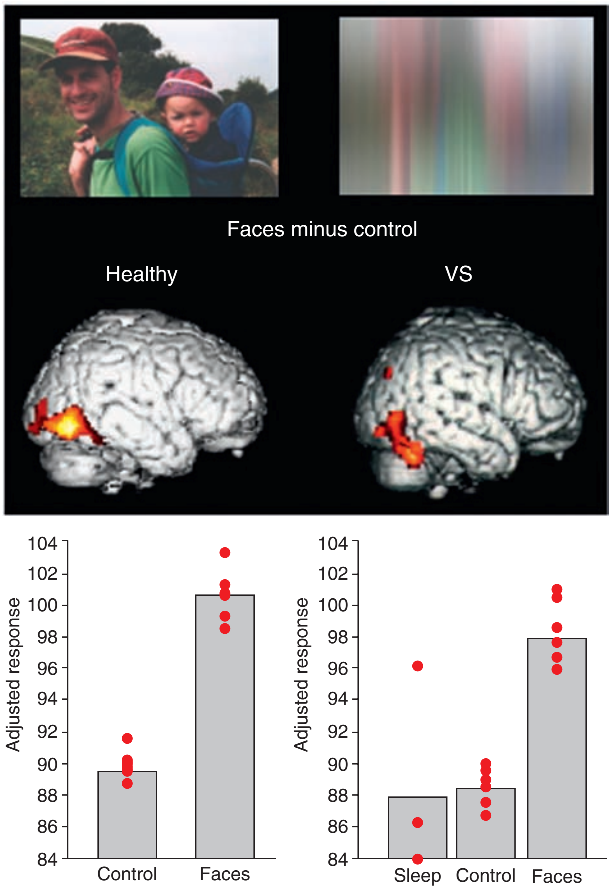

FIGURE 13.3 Example stimuli (top) from the face perception task used by Menon *et al*. [7]. Surface rendered normalized PET data from the familiar face perception task superimposed on standard 3D magnetic resonance template (middle) for a healthy control subject (left) and a patient diagnosed as vegetative state (right). Subtraction shown is faces minus control stimuli. In both cases, strong right hemisphere activation in the fusiform gyrus is clearly visible. Graphs below represent individual adjusted blood flow response for each scan (red dots) within each condition at peak co-ordinates within this region. The vegetative state patient fell asleep during three scans (labelled 'sleep'). *Source*: Figure adapted from Menon *et al*. [7].

In cohort studies of patients unequivocally meeting the clinical diagnosis of the vegetative state, simple noxious somatosensory [32] and auditory [20, 33] stimuli have shown systematic activation of primary sensory cortices and lack of activation in higher-order associative cortices from which they were functionally disconnected. High intensity noxious electrical stimulation activated midbrain, contralateral thalamus and primary somatosensory cortex in each and every one of the 15 vegetative patients studied, even in the absence of detectable cortical evoked potentials [32]. However, secondary somatosensory, insular, posterior parietal and anterior cingulate cortices, which were activated in all control subjects, failed to show significant activation in a single vegetative patient (Figure 13.4).

Moreover, in the vegetative state patients, the activated primary somatosensory cortex was shown to exist as an island, functionally disconnected from higher-order associative cortices of the pain matrix. Similarly, although simple auditory click stimuli activated bilateral primary auditory cortices in vegetative patients, hierarchically higher-order multimodal association cortices were not activated. Moreover, a cascade of functional disconnections were observed along the auditory cortical pathways, from primary auditory areas to multimodal and limbic areas [33] suggesting that the observed residual cortical processing in the vegetative state does not lead to integrative processes which are thought to be necessary for awareness.

In a recent review of the relevant literature it was argued that functional neuroimaging studies in

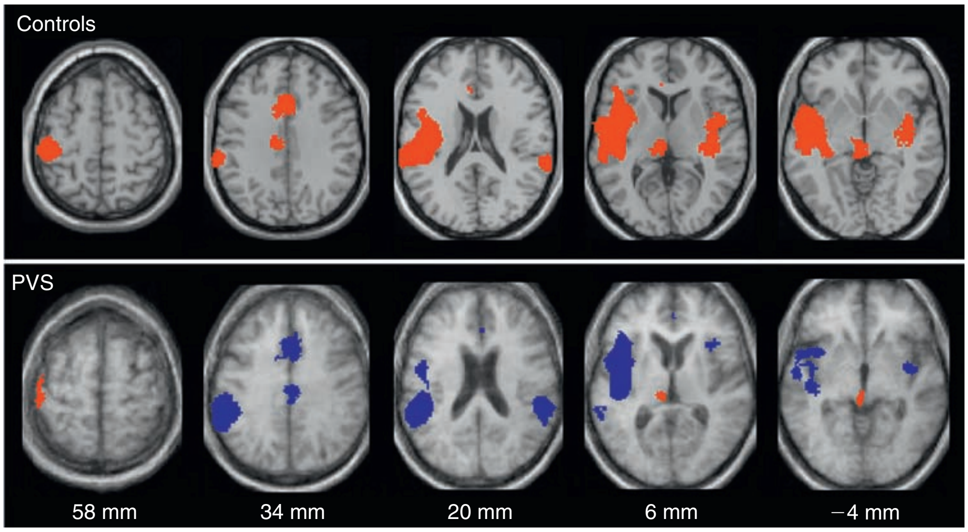

FIGURE 13.4 (Upper) Brain regions, shown in red, that activated during noxious stimulation in controls (subtraction stimulation–rest). (Lower) Brain regions that activated during stimulation in vegetative state patients, shown in red (subtraction stimulation–rest) and regions that activated less in patients than in controls (interaction (stimulation vs. rest) × (patient vs. control)), shown in blue. Projected on transverse sections of a normalized brain MRI template in controls and on the mean MRI of the patients (distances are relative to the bicommissural plane). *Source*: Adapted from Laureys *et al*. [32].

patients meeting the clinical criteria for vegetative state should be conducted hierarchically [34, see also 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 had all been successfully employed in functional neuroimaging studies of vegetative patients. These paradigms increased in complexity systematically from basic acoustic processing to more complex aspects of language comprehension and semantics. Indeed, in a recent study exploring the utility of this approach residual language function in a group of seven vegetative and five minimally conscious patients has been graded according to their brain activation on this hierarchical series of paradigms [36]. Three patients, diagnosed as vegetative, demonstrated some evidence of preserved speech processing, whilst the remaining four patients showed no significant activation at all, even in response to sound when compared to silence. 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 patients meeting the clinical criteria for persistent vegetative state and discuss how such an approach might be extended to allow clear inferences about the level of ‘awareness’ or consciousness to be made.

A question that is often asked of such studies, however, 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 wilful intervention on the part of the participant (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. Thus, such patients *may* retain discreet islands of subconscious cognitive function, which exist in the absence of awareness.

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 him/her. The answer may take the form of a spoken response or a non-verbal 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 that allows us to infer conscious awareness. In short, our ability to know unequivocally that another being is consciously aware is ultimately determined, not by

BOX 13.2

METHODOLOGICAL ISSUES

The acquisition, analysis and interpretation of neuroimaging data in severe brain injury are methodologically extremely complex. In quantitative PET studies, the absolute value of cerebral metabolic rates depends on many assumptions for which a consensus has not been established in cases of cerebral pathology. For example, the estimation of the cerebral metabolic rate of glucose using FDG-PET requires a correction factor, known as the lumped constant. It is generally accepted that this lumped constant is stable in normal brains. However, in traumatic brain injury, a significant global *decrease* in lumped constant has recently been reported [37] and in severe ischaemia, regional lumped constant values are known to *increase* significantly as a result of glucose transport limitation [38]. Second, cerebral glucose use as measured by FDG may not always be tightly coupled with oxygen use in patients because altered metabolic states, including anaerobic glycolysis, may occur acutely after brain injury [39–41]. Third, because PET provides measurements per unit volume of intracranial contents, they may be affected by the inclusion of metabolically inactive spaces such as cerebrospinal fluid or by brain atrophy which may artificially lower the calculated cerebral metabolism [42, 43].

As described in the main text, so-called activation studies using $H_2^{15}O$ PET or fMRI together with established sensory paradigms provide a direct method for assessing cognitive processing and even conscious awareness in severely brain-injured patients. However, like metabolic studies, these investigations are methodologically complex and the results are rarely equivocal. For example, in brain-injured patients, the coupling between neuronal activity and local haemodynamics, essential for all $H_2^{15}O$ PET and fMRI activation measurements, is likely to be different from healthy control [44–47], making interpretation of such datasets extremely difficult. Notwithstanding this basic methodological concern, the choice of experimental paradigm is also critical. For example, abnormal brainstem auditory evoked responses may make the use of auditory stimuli inappropriate and alternative stimuli (i.e., visual) should be considered. The paradigm should also be sufficiently complex to exercise the cognitive processes of interest, preferably beyond those that are simply involved in stimulus perception, yet not so complex that they might easily overload residual cognitive capacities in a tired or inattentive patient. In addition, it is essential that the experimental paradigm chosen produces well-documented, anatomically specific, robust and reproducible activation patterns in healthy volunteers in order to facilitate interpretation of imaging data in patients. In vegetative state, episodes of low arousal and sleep are also frequently observed and close patient monitoring (preferably by means of simultaneous electroencephalographic (EEG) recording) during activation scans is essential to avoid such periods. Spontaneous movements during the scan itself may also compromise the interpretation of functional neuroimaging data, particularly scans acquired using fMRI. Data processing of functional neuroimaging data may also present challenging problems in patients with acute brain injury. For example, the presence of gross hydrocephalus or focal pathology may complicate co-registration of functional data (e.g., acquired with PET or fMRI) to anatomical data (e.g., acquired using structural MRI), and the normalization of images to a healthy reference brain. Under these circumstances statistical assessment of activation patterns is complex and interpretation of activation foci in terms of standard stereotaxic co-ordinates may be impossible. Finally, where PET methodology is employed, issues of radiation burden must also be considered and may preclude longitudinal or follow-up studies in many patients.

whether they are aware or not, but by their ability to communicate that fact through a recognized behavioural response. 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 such behavioural responses. Following the logic of this argument then, even if such a patient *were* consciously aware, he/she would, by definition, have no means for conveying that information to the outside world.

A novel approach to this conundrum has recently been described, using fMRI, to demonstrate preserved conscious awareness in a patient fulfilling the criteria for a diagnosis of vegetative state [48, 49]. In mid-2005, the patient was involved in a road traffic accident. On admission to hospital she had a Glasgow

Coma Scale score of 4. A computed tomography scan revealed diffuse brain swelling, intraventricular blood in the left lateral ventricle, low attenuation in the left frontal lobe close to the corpus callosum and attenuation change in the right frontal and left posterior temporal regions. The following day she underwent a bifrontal decompressive craniectomy and a month later a ventriculoperitoneal shunt was inserted into the right lateral ventricle. Between the time of the accident and the fMRI scan in early January 2006, the patient was assessed by a multidisciplinary team employing repeated standardized assessments consistent with the procedure described by Bates [50]. Throughout this period the patient's behaviour was consistent with accepted guidelines defining the vegetative state [51]. She would open her eyes spontaneously, exhibited sleep/wake cycles and had preserved, but inconsistent, reflexive behaviour (startle, noxious, threat, tactile, olfactory). No elaborated motor behaviours (regarded as 'voluntary' or 'willed' responses), were observed from the upper or lower limbs. There was no evidence of orientation, fixation or tracking to visual or auditory stimuli. No overt motor responses to command were observed.

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'. These instructions were elaborated outside of the scanner in an attempt to induce a rich and detailed mental picture during the scan itself. Thus, one task involved imagining playing a vigorous game of tennis, swinging for the ball with both forehand and backhand, for the entire duration of each scanning block. The other task involved imagining moving slowly from room to room in her house, visualizing the location and appearance of each item of furniture as she did so. In a third condition, the patient was asked to 'just relax'.

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. For example, in a series of studies in healthy volunteers [48, 52] imagining playing tennis has been shown to elicit activity in the supplementary motor area, a region known to be involved in imagining (as well as actually performing) co-ordinated movements, in each and every one of 34 participants scanned. In contrast, imagining moving from room to room in a house commonly activates the parahippocampal cortices, the posterior parietal lobe and the lateral premotor cortices, all regions that have been shown to contribute to imaginary, or real, spatial navigation.

Given the reliability of these responses across individuals, activation in these regions can be used as a 'neural marker', confirming that the participant 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.

When the patient who was clinically diagnosed as vegetative was asked to imagine playing tennis, significant activity was observed in the supplementary motor area that was statistically indistinguishable from that observed in healthy awake volunteers (see Figure 13.5). In contrast, the instruction to imagine

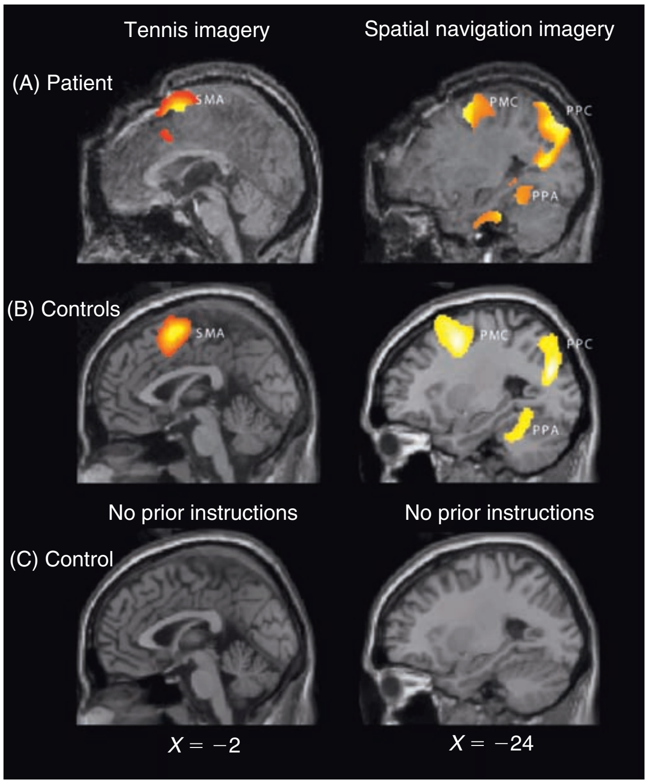

FIGURE 13.5 (A) Supplementary motor area (SMA) activity during tennis imagery and parahippocampal gyrus (PPA), posterior parietal lobe (PPC) and lateral premotor cortex (PMC) activity while imagining moving around a house in the patient described by Owen *et al*. [49]. (B) Statistically indistinguishable activity in all four brain regions in a group of 12 healthy volunteers asked to perform the same imagery tasks. (C) The result when a healthy volunteer underwent exactly the same fMRI procedure as the patient described by Owen *et al*. [50], with the exception that non-instructive sentences (e.g., 'The man played tennis', 'The man walked around his house') were used. Using an identical statistical model to that used with the patient, *no* significant sustained activity was observed in the SMA, the PPA, the PPC, the PMC, nor any other brain region. All results are similarly thresholded at a False Discovery Rate (FDR) $p < .05$, corrected for multiple comparisons.

walking through the rooms of her house elicited significant activity in the parahippocampal gyrus, the posterior parietal cortex and the lateral premotor cortex, which was again indistinguishable from that observed in healthy volunteers (Figure 13.5). 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.

Of course, sceptics may argue that the words 'tennis' and 'house' could have automatically triggered the patterns of activation observed in the supplementary motor area, the parahippocampal gyrus, the posterior parietal lobe and the lateral premotor cortex in this patient in the absence of conscious awareness. However, no data exists supporting the inference that such stimuli can unconsciously elicit sustained haemodynamic responses in these regions of the brain. Indeed, considerable data exists to suggest such words do not elicit the responses that were observed. For example, although it is well documented that some words can, under certain circumstances, elicit wholly automatic neural responses in the absence of conscious awareness, such responses are typically transient (i.e., lasting for a few seconds) and, unsurprisingly, occur in regions of the brain that are associated with word processing. In the patient described by Owen *et al*. [48, 49], the observed activity was not transient, but persisted for the full 30 seconds of each imagery task, that is far longer than would be expected, even given the haemodynamics of the fMRI response. In fact, these task-specific changes persisted until the patient was cued with another stimulus indicating that she should rest. Such responses are impossible to explain in terms of automatic brain processes. In addition, the activation observed in the patient was not in brain regions that are known to be involved in word processing, but rather, in regions that are known to be involved in the two imagery tasks that she was asked to carry out. Again, sustained activity in these regions of the brain is impossible to explain in terms of unconscious responses to either single 'key' words or to short sentences containing those words. In fact, in a supplementary study [49], non-instructive 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 (see Figure 13.5, lower panel).

The most parsimonious explanation is, therefore, that this patient was consciously aware and wilfully

BOX 13.3

ETHICAL ISSUES

Severely brain-injured, non-communicative patients raise several ethical concerns. Foremost is the concern that diagnostic and prognostic accuracy is assured, as treatment decisions typically include the possibility of withdrawal of life support. At present, although the approaches discussed above hold great promise to improve both diagnostic and prognostic accuracy, the standard approach remains the careful and repeated neurological examination by a trained examiner.

Ethical concerns are often raised concerning the participation of severely brain-injured patients in neuroimaging activation studies (especially to assess pain perception), studies that require invasive procedures (e.g., intra-arterial or jugular lines required for quantification of PET data or modelling) or the use of neuromuscular paralytics. By definition, unconscious or minimally conscious patients cannot give informed consent to participate in clinical research and written approval is typically obtained from family or legal representatives depending on governmental and hospital guidelines in each country. Nonetheless, it is not without precedent for studies in these patient populations to be refused for grants, ethics committee approval or data publication based on a view that no research study is ethical in patients who cannot provide consent. We side with a proposed ethical framework that emphasizes balancing access to research and medical advances alongside protection for vulnerable patient populations [53]. Severe brain injury represents an immense social and economic problem that warrants further research. Unconscious, minimally conscious and locked-in patients are very vulnerable and deserve special procedural protections. However, it is important to stress that they are also vulnerable to being denied potentially life-saving therapy if clinical research cannot be performed adequately.

following the instructions given to her, despite her diagnosis of vegetative state.

CONCLUSIONS

Vegetative state presents unique problems for diagnosis, prognosis, treatment and everyday management (Box 13.3). 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. Functional neuroimaging appears to offer a complimentary 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 at rest and under various conditions of stimulation. Indeed, in some rare cases, functional neuroimaging has demonstrated preserved cognitive function and even (in two cases so far) *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 PET, MEG/EEG and especially fMRI will substantially increase our understanding of severely brain-injured patients.

ACKNOWLEDGEMENTS

Steven Laureys is Senior Research Associate at the Fonds National de la Recherche Scientifique de Belgique (FNRS) and is supported by grants from the European Commission. Nicholas Schiff is supported by NS02172, NS43451 and the Charles A. Dana Foundation. Adrian M. Owen is supported by the Medical Research Council, UK and thanks Dr. Martin Coleman and the Cambridge Impaired Consciousness Research Group and the staff of the Welcome Trust Research Facility for their major contribution to some of the work described in this chapter [48, 49]. The authors thank the James S. McDonnell Foundation for funding the present work.

References

1. Andrews, K., Murphy, L., Munday, R. and Littlewood, C. (1996) Misdiagnosis of the vegetative state: Retrospective study in a rehabilitation unit. *BMJ* 313 (7048):13–16.
2. Childs, N.L., Mercer, W.N. and Childs, H.W. (1993) Accuracy of diagnosis of persistent vegetative state. *Neurology* 43 (8):1465–1467.
3. Wade, D.T. and Johnston, C. (1999) The permanent vegetative state: Practical guidance on diagnosis and management. *BMJ* 319 (7213):841–844.
4. Jennett, B. and Plum, F. (1972) Persistent vegetative state after brain damage. A syndrome in search of a name. *Lancet* 1 (7753):734–737.
5. Jennett, B. (2002) *The Vegetative State: Medical Facts, Ethical and Legal Dilemmas*, Cambridge: Cambridge University Press.
6. The Multi-Society Task Force on PVS (1994) Medical aspects of the persistent vegetative state (1). *New Engl J Med* 330 (21):1499–1508.
7. Menon, D.K., Owen, A.M., Williams, E.J., *et al.* (1998) Cortical processing in persistent vegetative state. *Lancet* 352 (9123):200.
8. Wilson, B.A., Gracey, F. and Bainbridge, K. (2001) Cognitive recovery from 'persistent vegetative state': Psychological and Personal Perspectives. *Brain Injury* 15 (12):1083–1092.
9. Tommasino, C., Grana, C., Lucignani, G., Torri, G. and Fazio, F. (1995) Regional cerebral metabolism of glucose in comatose and vegetative state patients. *J Neurosurg Anesthesiol* 7 (2):109–116.
10. De Volder, A.G., Goffinet, A.M., Bol, A., Michel, C., de, B.T. and Laterre, C. (1990) Brain glucose metabolism in postanoxic syndrome. Positron emission tomographic study. *Arch Neurol* 47 (2):197–204.
11. Levy, D.E., Sidtis, J.J., Rottenberg, D.A., *et al.* (1987) Differences in cerebral blood flow and glucose utilization in vegetative versus locked-in patients. *Ann Neurol* 22 (6):673–682.
12. Rudolf, J., Ghaemi, M., Haupt, W.F., Szelies, B. and Heiss, W.D. (1999) Cerebral glucose metabolism in acute and persistent vegetative state. *J Neurosurg Anesthesiol* 11 (1):17–24.
13. Momose, T., Matsui, T. and Kosaka, N. (1989) 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* 7 (7):243–246.
14. Rudolf, J., Sobesky, J., Ghaemi, M. and Heiss, W.D. (2002) The correlation between cerebral glucose metabolism and benzodiazepine receptor density in the acute vegetative state. *Eur J Neurol* 9 (6):671–677.
15. Edgren, E., Enblad, P., Grenvik, A., *et al.* (2003) Cerebral blood flow and metabolism after cardiopulmonary resuscitation. A pathophysiologic and prognostic positron emission tomography pilot study. *Resuscitation* 57 (2):161–170.
16. Beuthien-Baumann, B., Handrick, W., Schmidt, T., *et al.* (2003) Persistent vegetative state: Evaluation of brain metabolism and brain perfusion with PET and SPECT. *Nucl Med Comm* 24 (6):643–649.
17. Schiff, N.D., Ribary, U., Moreno, D.R., *et al.* (2002) Residual cerebral activity and behavioural fragments can remain in the persistently vegetative brain. *Brain* 125 (Pt 6):1210–1234.
18. Laureys, S., Goldman, S., Phillips, C., *et al.* (1999) Impaired effective cortical connectivity in vegetative state: Preliminary investigation using PET. *Neuroimage* 9 (4):377–382.
19. Laureys, S., Lemaire, C., Maquet, P., Phillips, C. and Franck, G. (1999) Cerebral metabolism during vegetative state and after recovery to consciousness. *J Neurol Neurosurg Psychiatr* 67:121.
20. Boly, M., Faymonville, M.E., Peigneux, P., *et al.* (2004) Auditory processing in severely brain injured patients: Differences between the minimally conscious state and the persistent vegetative state. *Arch Neurol* 61 (2):233–238.
21. Agardh, C.D., Rosen, I. and Ryding, E. (1983) Persistent vegetative state with high cerebral blood flow following profound hypoglycemia. *Ann Neurol* 14 (4):482–486.
22. Laureys, S., Faymonville, M.E., Goldman, S., *et al.* (2000) Impaired cerebral connectivity in vegetative state. In *Physiological Imaging of the Brain with PET* A. Gjedde, S.B. Hansen, G.M. Knudsen, and O.B. Paulson, (eds.) San Diego, CA: Academic Press. pp. 329–334.

23. Schiff, N., Ribary, U., Plum, F. and Llinás, R. (1999) Words without mind. *J Cogn Neursci* 11 (6):650–656.
24. Baars, B., Ramsoy, T. and Laureys, S. (2003) Brain, conscious experience the observing self. *Trends Neurosci* 26:671–675.
25. Rudolf, J., Sobesky, J., Grond, M. and Heiss, W.D. (2000) Identification by positron emission tomography of neuronal loss in acute vegetative state. *Lancet* 355:155.
26. Laureys, S., Faymonville, M.E., Luxen, A., Lamy, M., Franck, G. and Maquet, P. (2000) Restoration of thalamocortical connectivity after recovery from persistent vegetative state. *Lancet* 355 (9217):1790–1791.
27. Gould, E., Reeves, A.J., Graziano, M.S. and Gross, C.G. (1999) Neurogenesis in the neocortex of adult primates. *Science* 286 (5439):548–552.
28. de Jong, B., Willemsen, A.T. and Paans, A.M. (1997) Regional cerebral blood flow changes related to affective speech presentation in persistent vegetative state. *Clin Neurol Neurosurg* 99 (3):213–216.
29. Haxby, J.V., Grady, C.L., Horwitz, B., Ungerleider, L.G., Mishkin, M., Carson, R.E., Herscovitch, P., Schapiro, M.B. and Rapoport, S.I. (1991). Dissociation of object and spatial visual processing pathways in human extrastriate cortex. *Proc Natl Acad Sci USA* 88:1621–1625.
30. Haxby, J.V., Horwitz, B., Ungerlieder, L.G., Maisog, J.M., Pietrini, P. and Grady, C.L. (1994) The functional organization of human extrastriate cortex: A PET-rCBF study of selective attention to faces and locations. *J Neurosci* 14:6336–6353.
31. Owen, A.M., Menon, D.K., Johnsrude, I.S., *et al.* (2002) Detecting residual cognitive function in persistent vegetative state. *Neurocase* 8 (5):394–403.
32. Laureys, S., Faymonville, M.E., Peigneux, P., *et al.* (2002) Cortical processing of noxious somatosensory stimuli in the persistent vegetative state. *Neuroimage* 17 (2):732–741.
33. Laureys, S., Faymonville, M.E., Degueldre, C., *et al.* (2000) Auditory processing in the vegetative state. *Brain* 123 (Pt 8):1589–1601.
34. Owen, A.M., Coleman, M.R., Menon, D.K., Berry, E.L., Johnsrude, I.S., Rodd, J.M., Davis, M.H., and Pickard, J.D. (2005) Using a hierarchical approach to investigate residual auditory cognition in persistent vegetative state. In Laureys, S. (eds.). *The Boundaries of Consciousness: Neurobiology and Neuropathology. Progress in Brain Research*, Vol. 150, pp. 461–476. London: Elsevier.
37. Owen, A.M., Coleman, M.R., Menon, D.K., Johnsrude, I.S., Rodd, J.M., Davis, M.H., Taylor, K. and Pickard, J.D. (2005) Residual auditory function in persistent vegetative state: A combined PET and fMRI study. *Neuropsychol Rehabil* 15 (3–4):290–306.
38. Coleman, M.R., Rodd, J.M., Davis, M.H., Johnsrude, I.S., Menon, D.K., Pickard, J.D. and Owen, A.M. (2007) Do vegetative patients retain aspects of language? Evidence from fMRI. *Brain* 130:2494–2507.
39. Wu, H.M., Huang, S.C., Hattori, N., *et al.* (2004) Selective metabolic reduction in gray matter acutely following human traumatic brain injury. *J Neurotrauma* 21 (2):149–161.
40. Hamlin, G.P., Cernak, I., Wixey, J.A. and Vink, R. (2001) Increased expression of neuronal glucose transporter 3 but not glial glucose transporter 1 following severe diffuse traumatic brain injury in rats. *J Neurotrauma* 18 (10):1011–1018.
41. Bergsneider, M., Hovda, D.A., McArthur, D.L., *et al.* (2001) Metabolic recovery following human traumatic brain injury based on FDG-PET: Time course and relationship to neurological disability. *J Head Trauma Rehabil* 16 (2):135–148.
40. Goodman, J.C., Valadka, A.B., Gopinath, S.P., Uzura, M. and Robertson, C.S. (1999) Extracellular lactate and glucose alterations in the brain after head injury measured by microdialysis. *Crit Care Med* 27 (9):1965–1973.
41. Hovda, D.A., Becker, D.P. and Katayama, Y. (1992) Secondary injury and acidosis. *J Neurotrauma* 9 (Suppl 1):S47–S60.
42. Herscovitch, P., Auchus, A.P., Gado, M., Chi, D. and Raichle, M. E. (1986) Correction of positron emission tomography data for cerebral atrophy. *J Cereb Blood Flow Metab* 6 (1):120–124.
43. Videen, T.O., Perlmutter, J.S., Mintun, M.A. and Raichle, M. E. (1988) Regional correction of positron emission tomography data for the effects of cerebral atrophy. *J Cereb Blood Flow Metab* 8 (5):662–670.
44. Sakatani, K., Murata, Y., Fukaya, C., Yamamoto, T. and Katayama, Y. (2003) BOLD functional MRI may overlook activation areas in the damaged brain. *Acta Neurochir Suppl* 87:59–62.
45. Gsell, W., De Sadeleer, C., Marchalant, Y., MacKenzie, E.T., Schumann, P. and Dauphin, F. (2000) The use of cerebral blood flow as an index of neuronal activity in functional neuroimaging: Experimental and pathophysiological considerations. *J Chem Neuroanat* 20 (3–4):215–224.
46. Hamzei, F., Knab, R., Weiller, C. and Rother, J. (2003) The influence of extra- and intracranial artery disease on the BOLD signal in FMRI. *Neuroimage* 20 (2):1393–1399.
47. Rossini, P.M., Altamura, C., Ferretti, A., *et al.* (2004) Does cerebrovascular disease affect the coupling between neuronal activity and local haemodynamics? *Brain* 127 (Pt 1):99–110.
48. Owen, A.M., Coleman, M.R., Davis, M.H., Boly, M., Laureys, S. and Pickard, J.D. (2006) Detecting awareness in the vegetative state. *Science* 313:1402.
49. Owen, A.M., Coleman, M.R., Davis, M.H., Boly, M., Laureys, S. and Pickard, J.D. (2007) Response to Comments on 'Detecting awareness in the vegetative state'. *Science* 315:1221c.
50. Bates, D. (2005) Incidence and prevalence of the vegetative and minimally conscious states. *Neuropsychol Rehabil* 15:175.
51. Royal College of Physicians (2003) *The Vegetative State: Guidance on Diagnosis and Management [Report of a Working Party]*, London: Royal College of Physicians.
52. Boly, M., Coleman, M.R., Davis, M.H., *et al*. (2007) When thoughts become actions: An fMRI paradigm to study volitional brain activity in non-communicative brain injured patients. *Neuroimage* 36(3):979–992.
53. Fins, J.J. (2003) Constructing an ethical stereotaxy for severe brain injury: Balancing risks, benefits and access. *Nat Rev Neurosci* 4 (4):323–327.
54. Turkstra, L.S. (1995) Electrodermal response and outcome from severe brain injury. *Brain Injury* 9 (1):61–80.