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CHAPTER 16

A multimodal approach to the assessment of patients with disorders of consciousness

M.R. Coleman[1,3,*], T. Bekinschtein[1,2], M.M. Monti[1,2], A.M. Owen[1,2] and J.D. Pickard[1,3]

[1] *Impaired Consciousness Research Group, Wolfson Brain Imaging Centre, University of Cambridge, UK*
[2] *MRC Cognition and Brain Sciences Unit, Cambridge, UK*
[3] *Academic Neurosurgery Unit, University of Cambridge, UK*

Abstract: Unlike other neurological conditions, the heterogeneous pathology linked to disorders of consciousness currently excludes a distinction between the vegetative and minimally conscious states based upon pathological presentation. The clinical assessment is therefore made on the basis of the patient's clinical history and exhibited behaviour. This creates a particular challenge for the clinician who has to decide whether a certain behaviour, which might be inconsistent or incomplete, reflects a conscious or an unconscious process. In an alarmingly high number of cases, identified during clinical audit, this decision process has been shown to be particularly fallible. The behavioural assessment is not only highly subjective, but also dependent upon the ability of the patient to move or speak; it is the only way someone can demonstrate they are aware. To address this problem we propose a multimodal approach, which integrates objective tools, such as electrophysiology and functional brain imaging, with traditional behavioural scales. Together this approach informs the clinical decision process and resolves many of the dilemmas faced by clinicians interpreting solely behavioural indices. This approach not only provides objective information regarding the integrity of residual cognitive function, but also removes the dependency on the patient to move or speak by using specially designed paradigms that do not require a motor output in order to reveal awareness of self or environment. To demonstrate this approach we describe the case of BW, who sustained a traumatic brain injury seven months prior to investigation. BW was admitted to a five-day assessment programme, which implemented our multimodal approach. On behavioural assessment BW demonstrated evidence of orientation and visual pursuit. However, he showed no response to written or verbal command, despite holding command cards and scanning text. Electrophysiology confirmed that he retained a preserved neural axis supporting vision and hearing, and suggested some evidence that he was able to create a basic memory trace. A hierarchical fMRI auditory paradigm suggested he was able to perceive sound and speech, but revealed no evidence of speech comprehension or ability to respond to command. This was corroborated in the visual modality using a hierarchical paradigm demonstrating that he was able to perceive motion, objects and faces, but retained no evidence of being able to respond to command. We briefly review work by other teams advocating the use of brain imaging and electrophysiology and discuss the steps that are now

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[*] Corresponding author.
Tel.: +44 1223 348135; Fax: +44 1223 274393;
E-mail: mrc30@cam.ac.uk

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required in order to create an international standard for the assessment of persons with impaired consciousness after brain injury.

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Introduction

The assessment of persons with disorders of consciousness [vegetative state (VS), minimally conscious state (MCS)] is fraught with difficulties and challenges. Unlike other neurological conditions, disorders of consciousness are not distinguished by a particular pathology or quantifiable marker. Instead, the diagnostic decision-making process is informed by the clinical team's interpretation of the behaviours exhibited by a patient over a period of observation. Although specialist behavioural scales, such as the Sensory Modality Assessment and Rehabilitation Technique (SMART, Gill-Thwaites and Munday, 1999) and Coma Recovery Scale-Revised (CRS-R, Giacino et al., 2004), have been created to facilitate this process, the interpretation of exhibited behaviour remains highly subjective and heavily dependent upon the skills of the examiner. Whilst there is a growing consensus that the behavioural assessment should be conducted repeatedly over a number of weeks to quantify the incidence and context in which a response is made (Gill-Thwaites, 2006), the reliance upon the patient being able to move or speak, in order to demonstrate evidence of awareness, continues to be a central flaw. Indeed, the incidence of spasticity in long-term neurological conditions is widely recognised and occupies a large part of any neurorehabilitation programme (Elliott and Walker, 2005; Andrews, 2005). Hence, even if a patient were to retain some awareness of self and/or environment they may be unable to produce a motor output to signal that awareness to the examiner. The interpretation of exhibited behaviours is complicated further by the fact that we currently have an incomplete knowledge of consciousness and there remains considerable debate as to whether certain behaviours should be classified as conscious as opposed to unconscious processes. For instance, the American Multi-Society Task Force on PVS (1994), whom large parts of the world refer to for definition of the VS, assert that fixation and visual pursuit are conscious processes and mark the first signs of progression from the VS to an MCS (Giacino et al., 2002). In contrast, the Royal College of Physicians (2003), whom the United Kingdom and some parts of Europe refer to for a definition of VS, suggest these behavioural features are atypical for the VS, but not inconsistent. In the absence of a consensus, the clinical team's task is made no easier in those patients who do retain the ability to move or vocalise, since in the majority of such patients, behaviours are often inconsistent or incomplete and frequently constrained by factors, such as medication, nutrition, seating and posture.

The particular difficulties and challenges associated with the assessment of persons with disorders of consciousness have been further exposed in several clinical audits (Andrews et al., 1996; Childs et al., 1993). In a review of 40 patients referred to a specialist rehabilitation unit, Andrews and colleagues considered 17 (43%) of the patients as having been misdiagnosed. Notably most were found to have severe visual impairments and joint contractures, but when assessed by a specialist team, nearly all were able to communicate. Andrews postulated that a number of factors were likely to underlie this very high rate of misdiagnosis, including the rarity of the condition and the lack of experience and knowledge amongst non-specialist medical teams. The greatest potential for misdiagnosis thus occurs where patients are assessed in non-specialist units, by clinical teams who have not had the opportunity to accumulate knowledge or experience of these conditions. Moreover, due to the lack of a national/international protocol for the assessment of these patients, the level of assessment varies considerably from one centre to another. Thus, one patient might undergo properly administered SMART or CRS assessments by a multidisciplinary team over several weeks, whereas another patient might be assessed on a single occasion with an inappropriate behavioural scale such as the Glasgow Coma Scale (GCS), which is unable to distinguish VS from MCS (see Gelling et al., 2004). In 2005 the UK government published the National Service Framework (NSF) for long-term conditions, in which it set out generic standard requirements for the care and treatment of persons with wide ranging neurological conditions. Although the NSF does not address individual conditions, there is clearly support for efforts to establish a basic level of assessment and treatment for persons with impaired consciousness. Hence, in this chapter we describe the assessment approach taken by the Cambridge Impaired Consciousness Research Group, and use a case example to demonstrate how the approach combines information from many sources to inform the diagnostic decision-making process, whilst making efforts to avoid the possibility of misdiagnosis.

Existing criteria

At present the Royal College of Physicians (2003) provides guidelines documenting the requirements for a diagnosis of VS. The guidelines define the terms ‘wakefulness’ and ‘awareness’ and explain how they define the condition of VS by outlining a series of clinical features that have been documented in people who are in a VS. The guidelines specify a number of preconditions that must be satisfied before a diagnosis can be made, including: establishing the cause of the condition as far as possible; excluding the possibility of persisting effects of sedative, anaesthetic or neuromuscular blocking drugs, which might mask behaviours; ascertaining that there are no treatable structural causes; and excluding the possibility that continuing metabolic disturbances may be responsible for the patient’s behavioural presentation, but critically stop short of outlining a protocol for the subsequent assessment of patients or advocating any particular test. The guidelines do express an expectation that at least two doctors undertake the assessment and that they should take into account information from other staff including occupational therapists, but do not specify what training these people should have had. In hindsight the guidelines are a reflection of information available to the working party at that time — the SMART and CRS had not been validated, and empirical investigations using electrophysiology and functional brain imaging were in their infancy. However, in the six years that have passed, a large amount of research has been undertaken in this field and one might argue, particularly in light of the NSF, that there is good reason to reconvene a working party to address these shortfalls.

The need to establish tools to facilitate assessment

When Jennett and Plum first coined the term ‘vegetative state’, they based their terminology on the patient’s behavioural features, largely because they wanted to be able to assess patients at the bedside, but also because quantifiable measures, such as blood flow and electrical function, had not proved helpful in distinguishing patients. However, by choosing the term ‘vegetative state’, they did not assume a particular pathological lesion or physio-anatomical abnormality, and openly stated they expected others to clarify the underlying pathophysiological mechanisms and develop more appropriate assessment tools. Unfortunately, perhaps due to the rarity of the condition, or historical nihilism that has existed in many parts of the medical community towards this patient group (Andrews, 1993), empirical studies, with the aim of addressing these issues, have only really gathered pace in the last two decades.

Behavioural assessment tools

A number of behavioural assessment tools have been created and validated, and there is now a general consensus that the behavioural assessment should explore each sensory modality in turn through a series of stimuli which scale in complexity. In each case the examiner must determine whether, to the best of their experience, the patient retains purely reflexive responses or higher order, cortically mediated, purposeful responses to stimuli. Two behavioural assessment scales which embrace this hierarchical modular structure are SMART (Gill-Thwaites and Munday, 1999) and CRS-R (Giacino et al., 2004). In addition to the hierarchical structure embedded in both of these scales, the authors state that these assessments should be conducted repeatedly over a period of several weeks, where the Royal College of Physicians' preconditions have been met and where every effort has been made to optimise the environment and physiological factors, which Andrews (1996) and others have highlighted can seriously effect the assessment of a patient with impaired consciousness. There has also been evidence obtained, which encourages examiners to undertake the assessment of patients in different positions, including the standing position (Elliott et al., 2005) and numerous opinion papers encouraging a multidisciplinary approach, whereby the findings from formal behavioural assessments are combined with those of each allied health profession and those of family members (Gill-Thwaites, 2006). It is undoubtedly the view of some specialist centres that where longitudinal behavioural assessments have been conducted using SMART or CRS by experienced staff, the chances of misdiagnosis are likely to be greatly diminished (Giacino and Smart, 2007; Wilson et al., 2005). However, it is still apparent that the behavioural assessment of patients does fail to detect signs of awareness in a number of patients who retain islands of cerebral function (Eickoff et al., 2008; Coleman et al., 2007; Di et al., 2007; Owen et al., 2006, 2005, Staffen et al., 2006).

Electrophysiological assessment tools

Although early work using the electroencephalogram (EEG) proved unhelpful in informing the diagnostic decision-making process due to a lack of sensitivity (Young, 2000; Higashi et al., 1977), more recent work with sensory and cognitive evoked potentials has proved more beneficial (Neumann and Kotchoubey, 2004). Short-latency evoked potentials (several milliseconds to several tens of milliseconds after a stimulus) can tell the examiner whether a particular sensory pathway is functioning and whether there is any delay in propagation of sensory signals from receptors via ascending pathways to the cortex. Hence, where a conduction delay has been identified, the examiner can integrate this information into how they undertake the examination (i.e. leaving longer for the patient to respond in the case of a delay along the auditory pathway) and also in how they might interpret the patient's behavioural response to a particular stimulus. Nevertheless, despite the clear utility of short-latency sensory evoked potentials, and the widespread availability in most regional hospitals, these simple measures are rarely used. Another group of evoked potentials, referred to as event-related potentials (ERPs), are also rarely used clinically, but have growing empirical support. ERPs, which measure time-locked cortical function between 100 and 1000 ms after a stimulus, represent a non-invasive technique to obtain information about how the cortex processes signals and prepares actions. In short, ERPs are able to identify individual physiological components that contribute to a particular cognitive process, such as detecting an infrequent event in an auditory sequence. Empirical ERP studies with this patient group have expanded greatly since the Royal College of Physicians convened in 2003. Since that time ERP studies have identified aspects of preserved speech processing in patients considered to fulfil the clinical criteria defining VS and MCS (Schnakers et al., 2008; Kotchoubey et al., 2005). In a recent ERP study, Schnakers and colleagues presented patients with sequences of names containing the patients own name. In MCS patients, Schnakers found a larger P300 response to the patients own name in both a passive condition and an active condition in which she instructed the patient to count the number of times they heard their own name. Interestingly she found no P300 differences in the VS group in both the passive and active conditions. In a series of word meaning tasks, Kotchoubey has also identified cortical ERP responses to various semantic stimulus features, including related and unrelated word pairs and semantically incongruent word endings to sentences. ERP studies have also shown some useful prognostic utility — identifying those patients who might go on to recover consciousness or progress to a VS following severe brain injury (Wijnen et al., 2007; Fischer and Luaute, 2005). In terms of informing the diagnostic decision-making process, ERPs would appear to represent an objective screening tool, which is capable of identifying those patients who might harbour covert cognitive function and thus would benefit from further investigation using brain imaging techniques.

Brain imaging assessment tools

When the Royal College of Physicians working party convened in 2003, there were a number of published brain imaging studies assessing the residual metabolic function of patients with disorders of consciousness (Rudolf et al., 1999; Tommasino et al., 1995; De Volder et al., 1990; Levy et al., 1987), but only two published studies that had sought to reveal residual cognitive function in disorder of consciousness patients. De Jong et al. (1997) had used $H_2^{15}O$ positron emission tomography (PET) to measure regional cerebral blood flow changes in response to a story told by the patient's mother. In comparison to non-word sounds, de Jong and colleagues found increased blood flow in the anterior cingulate and temporal cortices, possibly reflecting emotional processing of the contents, or tone, of the mothers speech. In another study, Menon and colleagues had used PET to study covert visual processing in response to familiar faces. When their 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'. Although both studies gave some indication of the utility of brain imaging to explore residual cognitive function, both studies only described single cases and it was unclear whether the utility of these tests would extend to groups of patients. Furthermore, although both provided interesting glimpses of retained function, neither task provided sufficient information to change the patient's diagnosis, since both could have occurred automatically without the patient necessarily being aware of the stimuli. The use of PET as a viable assessment tool to aid the assessment of this patient group was also limited by issues of radiation burden, precluding repeated investigation and follow-up. PET studies were also known to require group studies in order to satisfy standard statistical criteria and were therefore less applicable to the clinical evaluation of heterogeneous disorders of consciousness patients. Given these limitations the Royal College of Physicians working party had insufficient evidence to advocate any particular test, and work in this area rapidly switched emphasis from PET 'activation studies' to functional magnetic resonance imaging (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 (Owen et al., 2001). fMRI has since been used to explore different aspects of cognitive function including speech comprehension and notably the ability of a patient to respond to command through mental imagery (Eickoff et al., 2008; Coleman et al., 2007; Di et al., 2007; Owen et al., 2006, 2005; Staffen et al., 2006; Bekinschtein et al., 2005). Ideally, fMRI studies should be designed to explore cognitive function in a hierarchal manner — starting with primary perceptual responses to sensory stimuli and following the chain of physiological events as information undergoes higher order levels of processing through to conscious interpretation and action. Although no single paradigm achieves all these goals, when combined they now, arguably, have the ability to provide clinically useful information which informs and may even change a patient's diagnosis. Indeed, when combined, the speech processing paradigm described by Coleman et al. (2007) and the volition task described by Owen et al. (2006) are capable of demonstrating aspects of speech comprehension and the ability to respond to command without requiring any form of motor output. Furthermore, when performed successfully, the volition paradigm described by Owen et al. (2006) provides unequivocal evidence that a patient retains awareness of themselves and/or their environment and thus has the potential to inform the diagnostic decision-making process.

Additional brain imaging tools

In addition to functional brain imaging, diffusion tensor imaging (DTI) is also slowly emerging as a possible tool, with which to explore the pathophysiological basis of disorders of consciousness and monitor change. DTI relies on modified MRI techniques that render a sensitivity to microscopic, three-dimensional water motion within tissue. In cerebro-spinal fluid, water motion is isotropic, that is, roughly equivalent in all directions. In white matter, however, water diffuses in a highly directional or anisotropic manner. Due to the structure and insulation characteristics of myelinated fibres, water in these white matter bundles is largely restricted to diffusion along the axis of the bundle. DTI can thus be used to calculate two basic properties: the overall amount of diffusion and the anisotropy (Douaud et al., 2007; Benson et al., 2007; Kraus et al., 2007). To date there has only been one study using DTI to evaluate white matter integrity in patients with disorders of consciousness (Voss et al., 2006). In that study, two patients with traumatic brain injury were described: one who had remained in MCS for 6 years and one who had recovered expressive language after 19 years in MCS. Voss and colleagues quantified the amount of diffusion and anisotropy to discover widespread changes in white matter integrity for both of these patients. However, of particular significance they found increased anisotropy and directionality in the bilateral medial parieto-occipital regions in the second patient that reduced to normal values in a scan performed 18 months later. This coincided with increased metabolic activity, and the authors interpreted these findings as evidence of axonal regrowth. This study not only demonstrated the potential of DTI to quantify the amount of white matter loss in patients with disorders of consciousness, it also demonstrated the potential of this technique to monitor change — possibly induced in the future by pharmacological or surgical intervention.

The creation of a multimodal approach to the assessment of patients with impaired consciousness

Despite the existence of the above methods and empirical evidence supporting their ability to inform the diagnostic decision-making process, the Royal College of Physicians working party has not yet reconvened, nor has there been any consensus statement regarding the use of objective assessment tools such as ERPs or fMRI from other groups such as the American Neurological Association. Therefore, in the remainder of this chapter we will describe the multimodal assessment approach we have developed that combines the above methods to inform the diagnostic decision-making process. At each stage we will highlight how the additional information provided by these techniques informs the decision-making process and how it may reduce the rate of misdiagnosis.

The Cambridge assessment approach

Patients are recruited to a one-week programme of assessment ideally within six months of injury, where all preconditions set out by the Royal College of Physicians have been satisfied and the patient is medically stable. Patients referred to the study must be over 16 years of age and must be able to tolerate lying supine for a period of 2 h. Prior to recruitment all patients are reviewed in their normal care setting to determine whether they have any contra-indications preventing exposure to a strong magnetic field and whether they are able to tolerate lying supine, whilst not showing excessive spontaneous head movement — these criteria are essential in order to obtain useful functional imaging data and ensure their safety. All patients referred to the programme of assessment are admitted to a research ward, where they are cared for in an individual room by the in-house neurosurgical team. Due to the fact this is a one-week assessment approach rather than a longer term treatment and rehabilitation referral, no change to the patient's medication is made during the one-week programme, although every effort is made to reduce medications, where possible, that might mask behaviours prior to referral. Patients are admitted on a Monday and discharged the same week on the Friday. Each patient undergoes daily behavioural assessments using the SMART and CRS-R (Gill-Thwaites and Munday, 1999; Giacino et al., 2004). These assessments are conducted alternately in the morning and afternoon each day, with the patient sitting in their wheel chair in a neutral environment free from distraction. During these assessments the examiner observes the patient at rest, without stimulation, for a minimum of 10 min during each session. The examiner then assesses the patient's response using stimuli of increasing complexity to systematically assess each sensory modality in turn. Hence, in the visual modality the examiner begins by assessing the patient's response to light and threat — proceeds to assess their response to pictures and objects — then assess whether they track a picture, object or mirror — followed by an assessment of whether they are able to discriminate colours or people and follow written commands. At each level the examiner is carefully documenting the response observed — even when a response is not seen at the lower level, they continue through each stage until they are satisfied there is no response. Indeed, particular caution is adopted over the first couple of sessions, since basic reflex responses are diminished in patients retaining higher order function. Hence, curtailing an examination because no response was observed to basic stimuli can miss important information unless the examiner is careful. This approach is also applied to the auditory, tactile, olfactory and gustatory modalities and the order of assessment is carefully rotated each day (i.e. commencing with the auditory modality during the second session) so as to avoid any order effect in the patient's response pattern. In addition to formal behavioural assessment sessions, the key to learning about patients is to also observe them spontaneously during physiotherapy and interaction with nursing staff and family members. A detailed family interview is also conducted to learn about the time course of change and behavioural pattern and responsiveness seen by members of the patient's family. During this interview great care is taken to determine the context in which behaviours were observed.

Electrophysiology

In addition to behavioural assessment, a battery of sensory evoked potentials and an EEG are undertaken on the second day of admission. Although published work regarding the use of the EEG with this patient group has been inconclusive with regard to its diagnostic and prognostic role (Young, 2000; Higashi et al., 1977), the Cambridge team feels the information obtained is useful to their overall assessment. The EEG provides a crude measure of consciousness; reveals evidence of sleep phenomena; and detects non-convulsive epileptiform activity, which may be influencing a patient's responsiveness. However, most importantly, it can give some early indications of residual cognitive function — for instance, if a patient is listening to a conversation in their environment, it is possible to detect a Mu rhythm (9–13 Hz) over the fronto-central regions of the cortex (Miner et al., 1998). Similarly through the use of standard activation procedures it is possible to assess whether the EEG is responsive to light, sound and noxious stimuli.

Following the EEG a series of sensory evoked potentials are undertaken, including a visual, auditory and somatosensory evoked potential (American Neurophysiology Society, 2006a, b, c). These measures provide crucial information about the integrity of the neural axis and inform the interpretation of behavioural assessments and the paradigms adopted for assessment with fMRI. Hence, an absent auditory evoked potential would instigate further clinical assessment, and the research team may decide to only pursue visual paradigms in the MRI scanner. In addition to a series of sensory evoked potentials, an upper limb motor evoked potential is also acquired from the biceps and abductor pollicis brevis muscle bilaterally in response to transcranial magnetic stimulation applied over the vertex using a circular coil (Ray et al., 2002). This test provides information about the integrity of descending motor pathways and again greatly informs the behavioural assessment.

In addition to the battery of sensory electrophysiology, two ERP paradigms are undertaken. The first ERP assessment consists of two classic Pavlovian conditioning tasks. The first, a delayed conditioning exercise, records the eye blink and conditioned response to a repeated puff of air to the eye following an auditory tone. In volunteers, the air puff initially produces an eye blink, which can be measured by surface electrodes adjacent to the eye. However, with repeated presentation of the tone and air puff, a learned or conditioned response is observed, such that the closure of the eye (conditioned response) starts to occur before the eye blink and therefore serves as an adaptive or defensive response to the air puff. This conditioned response is thought to reflect a primitive, hardwired, subconscious neural system involving the cerebellum, but with no cortical component (Clark et al., 2001; Clark and Squire, 1998). The second eye blink conditioning paradigm involves the presentation of two tones: a target tone which always precedes the air puff, and a non-target tone which occurs without the air puff. This is called a trace conditioning exercise, and its name comes from the fact that some kind of trace must be left in the nervous system for an association to be learned between the target tone and the air puff. This response is again thought to reflect a hardwired neural system. However, in contrast to the delayed conditioning exercise, the hippocampus is thought to be involved in order for a declarative memory trace to be stored and used to recognise the association between the target tone and the air puff, which additionally occurs at a 500–1000 ms interval following the target tone. Interestingly, in healthy volunteers a conditioned response in the trace exercise only occurs in those persons who are able to identify an association between the target tone and the air puff at post-test recall, and is severely impaired in amnesic patients with damage that includes the hippocampus (Clark et al., 2002). Hence, in disorders of consciousness patients, this test has the potential to indicate those patients who might harbour the potential to consciously process information.

The second ERP assessment combines a classic mismatch negativity paradigm (MMN, Ulanovsky et al., 2003) with a higher order P300 auditory odd-ball paradigm (Squires et al., 1975). In this paradigm a patient hears a sequence of auditory tones with two embedded levels of auditory regularity. At the first level, referred to as local, or within trial, the patient hears four identical tones, which are followed by a fifth sound that can be identical (local standard) or different (local deviant) to the preceding tones. In this within trial violation, an ERP response to the deviant produces an MMN response, consistent with building a subconscious memory trace to identify the within trial auditory violation. At the second level, referred to as global, or between trial, the patient's detection of violation between the series of tones forming the local standard and the series of tones producing the local deviant is assessed. This global, between trial, ERP reflects a P300 auditory odd-ball P3b response and is thought to provide an index of working memory and conscious access (Bekinschtein et al., 2009). Together these two ERP paradigms are able to provide an objective, early indication that a patient may retain residual cognitive function, which may or may not be apparent during traditional behavioural assessment.

Brain imaging

Once basic sensory evoked potentials have been performed, all patients undergo a series of anatomical MRI scans, including axial T2, proton density, inversion recovery and haemosiderin-sensitive sequences using a 3T MRI Magnetom Trio Tim Scanner (Siemens Medical Systems, Germany). In addition to the anatomical series of scans, all patients undergo DTI using an axial diffusion weighted dataset with an echo planar imaging sequence and diffusion sensitising gradients applied along 12 non-collinear directions using five b values ranging from 340 to 1590 s/mm^2 and five $b = 0$-images. Then, over two sessions the patient is assessed with a series of auditory and visual fMRI paradigms.

Auditory fMRI paradigm

In the first instance all patients are assessed using the hierarchal speech processing task described by Coleman et al. (2007). This task consists of four conditions: two speech conditions (high-ambiguity sentences and low-ambiguity sentences), an unintelligible noise and a silence condition. Using these stimuli it is possible to assess three levels of auditory processing: (1) whether the patient retains a primary auditory cortex response to sound by comparing hearing conditions (sentences and signal correlated noise) versus silence, (2) whether the patient retains local processing to distinguish speech from non-speech by comparing speech conditions versus signal correlated noise and (3) whether the patient retains distributed cortical activity consistent with retrieving semantic information to interpret sentences, by comparing high-ambiguity sentences versus low-ambiguity sentences. Where patients are found to show high level 3 responses, indicating they may retain aspects of speech comprehension, they are then investigated using the volition paradigm described by Owen et al. (2006) to determine whether they are able to respond to command by manipulating their neural activity. In this paradigm, patients are asked to perform two mental imagery tasks. In the first task a patient is asked to imagine playing tennis every time they hear the command 'tennis' and to relax when they hear the command 'relax'. The task is presented in a classic box design (on–off), whereby the patient is instructed to imaging playing tennis (on) and to maintain this activity, before being asked to relax (off) for 30 s. In total a patient is asked to perform the 'on' and 'off' task five times over a 5-min scan period. In the second task the patient is asked to imagine moving around the rooms of their home every time they hear the command 'house' and to relax every time they hear the command 'relax' throughout the same block design. In healthy volunteers the motor imagery (tennis task) produces robust supplementary motor cortex activation, which can be seen in real-time whilst the patient is in the scanner (Boly et al., 2007). In contrast, the spatial navigation — house task — produces bilateral parahippocampal gyrus, posterior parietal-lobe and lateral premotor cortex activation, which can also be seen in real-time, where scanner facilities exist (Boly et al., 2007). Indeed, recently the real-time capabilities of the scanner have been adapted in order to assess a patient's response to a series of questions, where they have successfully demonstrated appropriate neural responses in the motor and spatial navigation task. In this later task, patients are asked to imagine playing tennis to indicate 'yes' and to imagine moving around the rooms of their home to indicate 'no'. Using this series of auditory paradigms the team is able to comprehensively determine whether a patient responds to sound, demonstrates activation consistent with speech comprehension, and whether ultimately they are able to respond to command and moreover express their thoughts, intentions, emotions and memories.

Visual fMRI paradigm

Although many disorders of consciousness patients demonstrate fluctuating periods of wakefulness, often exhibiting long periods of eye closure, there are still many opportunities for exploring retained cognitive function through visual stimulation, where an intact neural axis has been indicated by sensory evoked potentials. As with all fMRI paradigms created by the Cambridge team, the visual paradigm routinely employed consists of a series of scans, which scale in stimulus complexity — moving from basic perceptual responses to conscious volitional performance. At the first level a patient is presented with a pattern-reversal checkerboard in order to determine whether they maintain a preserved neural axis to the primary visual cortex. At the second level the patient's response to a static pattern of squares is compared to their response to the same pattern of squares scrolling in either the horizontal or vertical plane, in order to determine whether the patient retains motion perception. At the third level the patient is shown a series of congruent objects which are contrasted against a scrambled version of the same object in order to determine whether they are able to discriminate objects. At the fourth level the patient is shown a series of faces and a series of houses in order to determine whether they retain aspects of face and object perception. If this is observed, a fifth and final level is undertaken, where a patient is shown a picture of a face superimposed on a picture of a house and asked, at 30-s intervals, to either attend to the picture of the face or to attend to the picture of house. If the patient is found to demonstrate the same pattern of activation he/she showed to individual pictures of faces and houses at level 4, in correspondence with the command to look and maintain fixation upon the face or house, there is every indication the patient is consciously following a command and is able to discriminate visual information. Hence, in both the visual and auditory modality a series of hierarchal paradigms are employed with each patient to explore the retention of cognitive function, which do not require the patient to move or speak in order to demonstrate that they retain an awareness of self or environment.

Diagnostic decision making and feedback to the referral team and family members

Once the above investigations have been performed, the findings of serial behavioural assessments, sensory and cognitive electrophysiology, together with anatomical and DTI, and not least functional brain imaging, are collated to form an impression of whether the investigated patient shows responses consistent with the VS or MCS or a conscious, severely disabled condition. The team's diagnostic impression is formed with full knowledge of the patient's medications, which might mask their ability to respond, and knowledge of whether they have any form of infection. This information is fed back to the referring team within one week of discharge, and it is expected that they will continue behavioural assessments together with necessary medical interventions, before making a diagnosis. In addition to feeding back to the referring medical team, great effort is made to provide comprehensive and prompt feedback to the patient's family, whom it should be noted have rarely received information about such conditions. Hence, within one week of discharge the family receives a detailed report of all the findings of the above tests, together with explanation and summary of what the findings mean and how that interpretation has been reached. In addition to receiving a report the family is also invited to a meeting where slides showing the results of each test are shown. Unless requested by the family, the patient's regular care team including therapists are invited to this meeting so that everyone has had chance to discuss the findings and discuss future courses of action. For the purposes of diagnosis, the more widely held opinion that fixation and visual pursuit are inconsistent with the VS, is adopted throughout the assessment process.

Application of the multimodal assessment approach to a single patient

To briefly illustrate the above assessment approach, the case of a 19-year-old male (BW) who sustained a traumatic brain injury following a road traffic accident in 2007 is described.

Clinical history

BW had sustained a depressed frontal skull fracture with underlying contusions and subarachnoid haemorrhage in August 2007 following a high-speed road traffic accident and had undergone a decompressive bifrontal craniotomy. Following a period of acute care, during which he had been weaned off sedation, but failed to recover consciousness, he was transferred to an interim brain injury assessment unit.

Behavioural assessment

Prior to referral seven months post ictus, BW had undergone repeated behavioural assessment using SMART. Over 10 sessions BW had demonstrated consistent evidence of orientation to visual and auditory stimuli, fixation and visual pursuit. BW focused on objects and people and tracked a mirror in the vertical and horizontal plane. BW also localised to upper limb tactile stimulation and intriguingly demonstrated accurate and quick pursuit of an object with his left and right hand — holding his hand open in an appropriate shape to hold a ball, whilst a ball was moved in different directions just out of reach of his hand. BW showed no response to verbal command and curiously held instruction cards and appeared to scan written instructions, but showed no response.

The referring team had reached the impression that BW demonstrated behaviours consistent with the minimally conscious spectrum, but were unclear why BW failed to respond to written or verbal command, despite the fact he demonstrated clear indications of scanning written text. Similarly, without a response to command or behaviour indicating that BW was able to discriminate stimuli, they were at a loss in terms of where they could go with his rehabilitation. On admission to Cambridge, BW demonstrated the same intriguing pattern of behaviour, scoring 11 out of 23 on the CRS-R assessment (subscale scores = auditory startle 1; pursuit eye movements 3; object manipulation 4; oral reflexive movement 1; communication 0; eye opening without stimulation 2).

Sensory electrophysiology

BW demonstrated a slowed EEG background consisting of intermixed theta and delta frequencies with a breach rhythm over the bifrontal craniotomy wound. The EEG showed no evidence of epileptiform abnormalities or sleep phenomena and was unresponsive to eye opening. A brainstem auditory evoked potential revealed a preserved response from the eighth cranial nerve, pons and midbrain, bilaterally, with onset latencies within the normal range. A somatosensory and visual evoked potential also showed preserved primary sensory cortex responses bilaterally, with no evidence of conduction deficits.

Cognitive electrophysiology

BW demonstrated a conditioned response in the trace conditioning exercise, implying he was able to create a basic memory trace. BW also demonstrated an MMN equivalent response in the within-trial, local deviant, auditory violation task, consistent with the trace conditioning task, but showed no evidence of detecting the between-trial, global deviant thought to reflect conscious access of working memory.

Brain imaging

Axial T2, proton density, inversion recovery and haemosiderin-sensitive sequences revealed multiple areas of low intensity on T2 and gradient echo sequences near the grey–white matter junction of both cerebral hemispheres with more focal resolving haemorrhagic areas in both frontal lobes. There were also areas of low intensity surrounding the brainstem in keeping with haemosiderin deposition related to previous subarachnoid haemorrhage. Small focal areas of haemorrhage were also seen in both thalami, but there were no intrinsic brainstem lesions. The lateral and third ventricles were moderately prominent, including the temporal horn.

Speech processing

BW demonstrated bilateral superior temporal lobe activation to hearing sound versus silence (Fig. 1), and greater left superior temporal lobe activation to hearing speech versus signal correlated noise (Fig. 2). However, no evidence of distributed cortical activation consistent with volunteers retrieving semantic information was observed at level 3 — ambiguous versus unambiguous sentence contrast. A second speech processing task adopting the same design and structure as that described by Coleman et al. (2007), but replacing ambiguous sentences with anomalous sentences created by replacing content words to make them incoherent, whilst preserving phonological, lexical and syntactic structure, also showed an identical pattern of response — BW showed bilateral superior temporal activation to sound, left superior temporal activation to speech, but no evidence of distributed activation consistent with semantic retrieval.

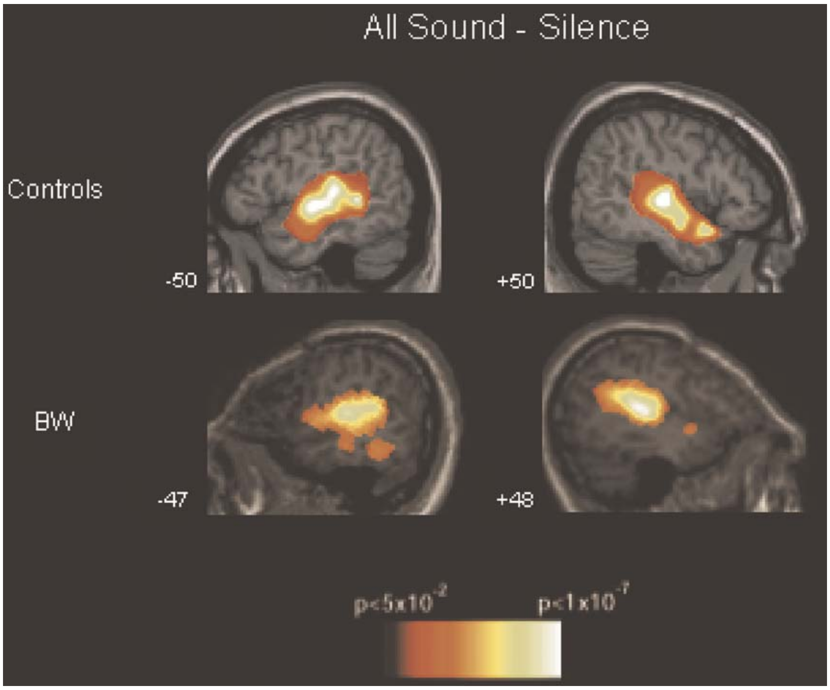

Fig. 1. fMRI speech processing paradigm — sound versus silence contrast results for BW. Bilateral superior temporal lobe activation can be seen consistent with healthy volunteers. Activations are thresholded at $p < 0.05$ false discovery rate corrected for multiple comparisons and shown on slices where the peak activation was observed.

Response to command

BW showed no appropriate areas of cortical activation in response to the commands ‘imagine playing tennis’ or ‘imagine moving around the rooms of your home’ over repeated trials.

Discrimination of visual information

BW demonstrated primary V1 activation to a reversing checkerboard, consistent with his visual evoked potential. BW also demonstrated V5/MT activation in response to a moving pattern, consistent with behavioural evidence of motion perception. BW also showed appropriate fusiform gyrus activation in response to pictures of faces and appropriate parahippocampal activation in response to pictures of houses. However, consistent with the auditory volition task, these same areas of activation were not seen time locked to the commands ‘look at the house’ or ‘look at the face’ during the visual volition task.

Diffusion tensor imaging

DTI revealed reduced (−38%) fractional anisotropy (FA; whole brain white matter 0.26) in comparison to healthy control subjects (mean 0.42), indicating widespread loss of white matter integrity (Fig. 3). Moreover, DTI revealed a significantly increased apparent diffusion coefficient (whole brain white matter 0.0008) in comparison to healthy volunteers (0.0006), suggesting loss of cortico-cortical connectivity. Indeed, a qualitative view of white matter paths using DTIquery (Sherbondy et al., 2005) revealed a loss of inferior temporal and inferior frontal pathways (Fig. 4), thought to mediate aspects of speech comprehension (Rodd et al., 2005; Davis and Johnsrude, 2003; Scott and Johnsrude, 2003; Scott et al., 2000).

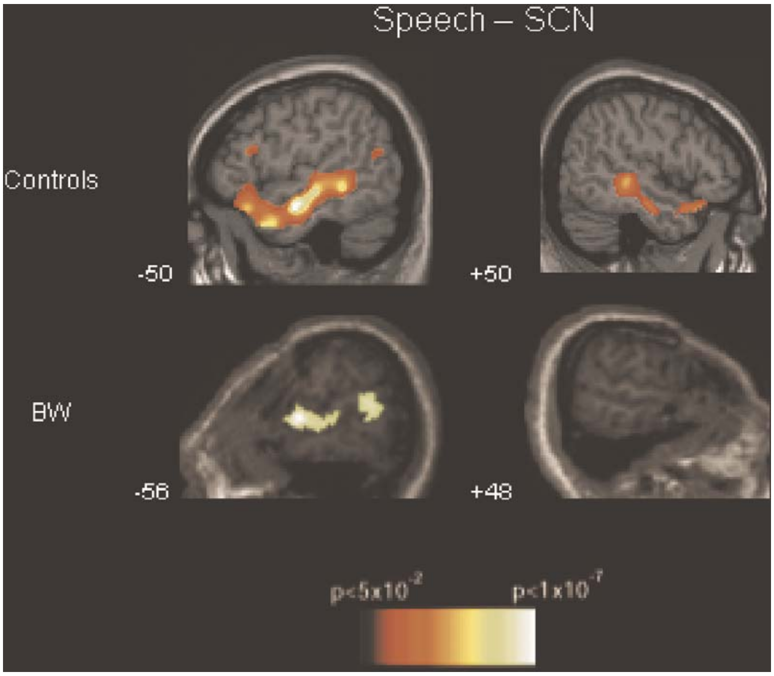

Fig. 2. fMRI speech processing paradigm — sentences (ambiguous and unambiguous) versus signal correlated noise (SCN) contrast results for BW. Left hemisphere superior temporal lobe activation can be seen consistent with healthy volunteers. Activations are thresholded at $p<0.05$ false discovery rate corrected for multiple comparisons and shown on slices where the peak activation was observed.

Implications for the diagnostic decision-making process

The multimodal assessment approach undertaken in Cambridge corroborated earlier behavioural assessments of BW, but through the use of electrophysiology and brain imaging helped to resolve much of the assessment team's worry that they might be missing something. Electrophysiology and brain imaging confirmed that BW retained basic perceptual responses to visual and auditory information, but found no evidence of speech comprehension or ability to discriminate. Indeed, DTI provided strong visual information to suggest that the level of cortical integration required to support the higher level tasks, investigated during the SMART assessment, was no longer sufficient and thus BW retained some basic perceptual function, but was unable to comprehend or discriminate commands. Whilst this case illustrates how a multimodal assessment approach can help to resolve some of the dilemmas faced by the clinical team interpreting complex behavioural patterns, the assessment approach can also reveal evidence of covert function, where behavioural markers are absent and thus reduce the rate of misdiagnosis (see Owen et al., 2006).

Adoption of a standard assessment protocol

Since the Royal College of Physicians working party convened in 2003, there has been a considerable amount of empirical investigation with disorder of consciousness patients. As a result a number of electrophysiological and brain imaging paradigms have emerged as beneficial sources of information from which to inform the diagnostic decision-making process and thus work towards reducing the apparent high rates of misdiagnosis that exist for this patient population,

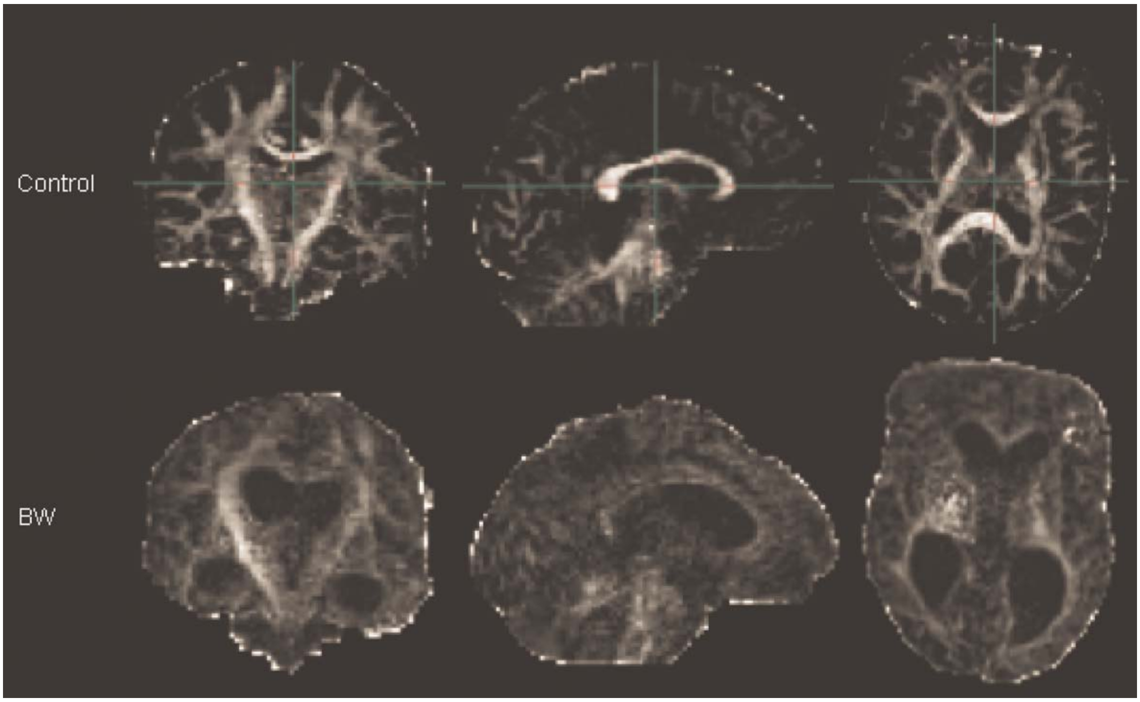

Fig. 3. Diffusion tensor imaging; fractional anisotropy maps showing widespread white matter loss for BW.

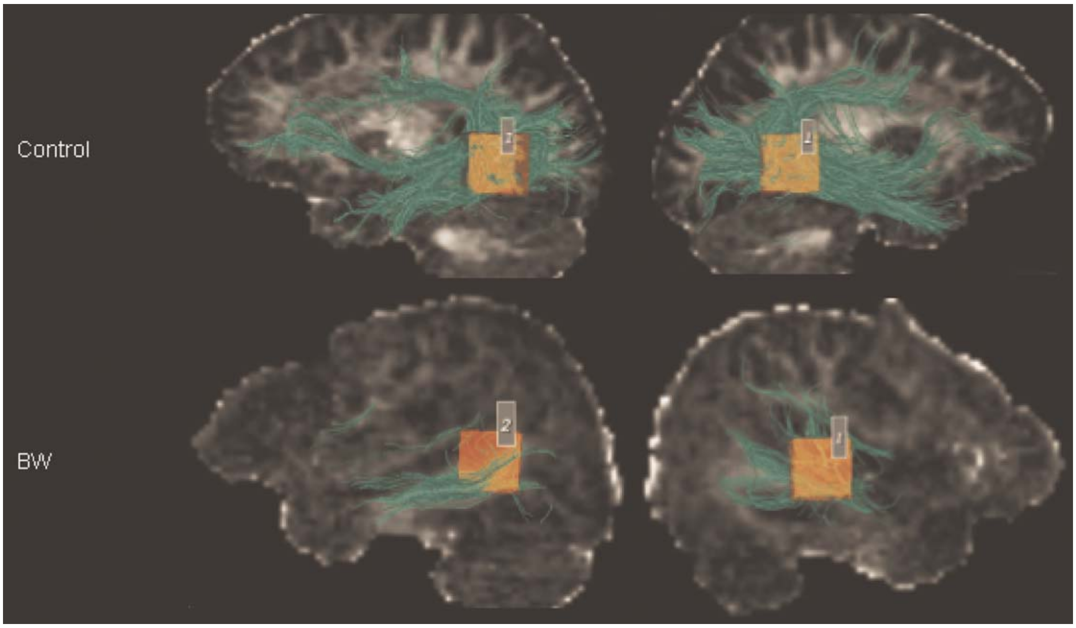

Fig. 4. Temporal lobe tractography maps showing loss of inferior temporal and inferior frontal pathways for BW.

where assessments rely solely on the exhibited behaviour of the patient. In the UK alone there are an estimated 12–15 persons per million thought to be in a VS, in any six-month period, with three times this figure thought to be in an MCS (Jennett, 2005). The vast majority of these patients are not assessed in specialist units, and primary care trusts are often reluctant to refer them to such units, where the period of stay may be many months at a cost in excess of 4000 pounds per week. Local resources are often limited, and due to the rarity of these conditions, clinicians rarely have opportunity to build up sufficient knowledge and experience (Andrews, 1993). One solution is to have a number of specialist units in the country offering a fixed-period, fixed-price referral service, who combine the technologies described above to provide a comprehensive screening process, which is repeated at least once within the first 12 months following a brain injury. Where this assessment process identifies patients who retain aspects of cognitive function, these patients are referred onto specialist rehabilitation centres for further rehabilitation, thus allocating additional funding to those who might benefit the most. Although this approach would significantly reduce the number of patients who are 'warehoused' in palliative care homes, without having been appropriately assessed in the first instance (see concerns raised by Fins et al., 2007, regarding current practice), the additional proviso that each patient is reviewed a second time within the first 12 months of injury would also safeguard against missing anyone who follows a slower course of recovery. Whilst some larger hospitals do have the appropriate knowledge and skills to assess patients with recognised behavioural scales, few have the resources to undertake electrophysiology or brain imaging. In these cases a referral could be made to acquire this data, which is then integrated into the referring unit's ongoing assessment programme — indeed, this is predominately the practice of those centres currently referring patients to Cambridge. In those centres, without the resources the former practice could be undertaken to reduce the rate of misdiagnosis. In all cases this approach would work to ensure the limited funds of primary care trusts are more efficiently managed and channelled to those who might benefit the most.

Information and support for families

It is often forgotten that the main victims of severe brain injury leading to impaired consciousness are the patient's family and friends. Although many hospitals offer general advice and counselling services, very little printed information exists specifically relating to disorders of consciousness. In a survey of patients' families attending the Cambridge assessment programme, none of the families had received any information about disorders of consciousness during their stay in acute or chronic care facilities. Similarly, none of the families had had anybody sit down with them and explain what the different conditions were and how they were diagnosed. Nearly every family had had some contact with the charity Headway (www.headway.org.uk), either accessing their website for general information or speaking to one of their advisors via their telephone helpline. However, all noted that they did not specifically offer an information booklet describing disorders of consciousness. Every family questioned said the Internet had been their main or only source of information, and most described searching endlessly for some sort of information about the condition. Indeed, many had subsequently contacted the authors of research publications to ask for advice. In all cases the families recounted stories of struggling to obtain clear answers about their relatives' condition, of a constant air of confusion, the regular occurrence of health care workers talking over their relative, and a common nihilism towards such conditions by medical personnel. One family, whose youngest son had suffered an intra-cerebral bleed, were asked if they had any other sons and were told to concentrate on them. Many had received blunt and negative comments, which had not helped them to adjust to the distressing situation they found themselves in. In each case, the family felt having the opportunity to see the damage underlying their relatives' condition via brain imaging, and to a lesser extent electrophysiology, had helped them to understand what had happened. The need to educate and inform families cannot therefore be understated, and any assessment process must ensure that central to its aims are the families and their care. In a large number of cases there is very little that can be done to help the patient, but there is a considerable amount that can be done for the family, whose lives change and who suffer enormous grief, depression, anxiety and often financial hardship as a result of the injury.

Conclusion

In this chapter we have called for the adoption of a standard protocol to assess patients with impaired consciousness after brain injury that not only addresses the limitations of the current behavioural assessment of patients, but also attempts to address the unacceptably high rate of misdiagnosis indicated by clinical audits. In this chapter we have reviewed some of the accumulated empirical evidence supporting the use of electrophysiology and brain imaging with this patient group and have outlined a multimodal assessment approach that informs the diagnostic decision-making process. In our opinion there is now sufficient evidence supporting the use of objective tests — and impetus — (see Department of Health, 2005)to warrant reconvening the Royal College of Physicians working party on VS and/or other governing bodies in order to establish a standard protocol.

Information for families

An information booklet written for families and carers, which describes disorders of consciousness, can be found at www.coma-science.com.

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