

# A new era of coma and consciousness science

Adrian M. Owen<sup>1,\*</sup>, Nicholas D. Schiff<sup>2</sup> and Steven Laureys<sup>3</sup>

<sup>1</sup>*MRC Cognition and Brain Sciences Unit; Impaired Consciousness Research Group,  
Wolfson Brain Imaging Center, University of Cambridge, UK*

<sup>2</sup>*Department of Neurology and Neuroscience, Weill Medical College of Cornell University, New York, NY, USA*

<sup>3</sup>*Coma Science Group, Cyclotron Research Center and Department of Neurology,  
University of Liège, Liège, Belgium*

**Abstract:** In the past ten years, rapid technological developments in the field of neuroimaging have produced a cornucopia of new techniques for examining both the structure and function of the human brain *in vivo*. In specialized centers, many of these methods are now being employed routinely in the assessment of patients diagnosed with disorders of consciousness, mapping patterns of residual function and dysfunction and helping to reduce diagnostic errors between related conditions such as the vegetative and minimally conscious states. Moreover, such efforts are beginning to provide important new prognostic indicators, helping to disentangle differences in outcome on the basis of a greater understanding of the underlying mechanisms responsible and providing information that will undoubtedly contribute to improved therapeutic choices in these challenging populations. Of course, these emerging technologies and the new information that they provide will bring new ethical challenges to this area and will have profound implications for clinical care and medical–legal decision-making in this population of patients. We review the most recent work in this area and suggest that the future integration of emerging neuroimaging techniques with existing clinical and behavioral methods of assessment will pave the way for new and innovative applications, both in basic neuroscience and in clinical practice.

**Keywords:** coma; vegetative state; minimally conscious state; locked-in syndrome; functional MRI; consciousness; ethics

## Introduction

It has been a tremendously exciting decade for research into disorders of consciousness. Rapid technological advances have produced a variety of novel neuroimaging approaches that allow a comprehensive assessment of brain function (e.g. cognitive performance) to be combined with

detailed information about brain *structure* (e.g. anatomy) and *connectivity*. Thus, in less than ten years, low-resolution metabolic group studies and block design ‘activation studies’ using H<sub>2</sub><sup>15</sup>O positron emission tomography (PET) have largely given way to event-related functional magnetic resonance imaging (fMRI) investigations that combine high-resolution anatomical imaging with sophisticated psychological paradigms. Until recently, such methods were used primarily as a correlational tool to ‘map’ the cerebral changes that are associated with a particular cognitive process or function, be it an action, a reaction

---

\*Corresponding author.  
Tel.: +44 1223 355294; Fax: +44 1223 359062;  
E-mail: adrian.owen@mrc-cbu.cam.ac.uk

(e.g. to some kind of external stimulation) or a thought. But recent advances in imaging technology, and in particular the ability of fMRI to detect reliable neural responses in individual participants in real time, are beginning to reveal patient's thoughts, actions or intentions based solely on the pattern of activity that is observed in their brain. New techniques such as diffusion tensor imaging (DTI) are also being used to probe the structural integrity of white matter tracts between key brain regions and emerging methods such as resting state fMRI are beginning to reveal how the intrinsic functional connectivity of the brain is altered by serious brain injury. Throughout this new volume of *Progress in Brain Research – Coma Science: Clinical and Ethical Implications*, the influence of this 'technical revolution' is palpable; from methodologically themed chapters on multimodal approaches to assessment, advances in fMRI, DTI and MRI spectroscopy through to more philosophical chapters on the problem of unreported awareness and the moral significance of phenomenal consciousness. In the following sections, we review some of the key findings in this area and discuss how novel neuroimaging methods and approaches are beginning to make a significant impact on the assessment and management of patients with disorders of consciousness. The results have profound implications for clinical care, diagnosis, prognosis and ethical and medical–legal decision-making, but are also beginning to address more basic scientific questions concerning the nature of consciousness and the neural representation of our own thoughts and intentions.

### **fMRI: from passive paradigms to the assessment of awareness**

An accurate and reliable evaluation of the level and content of cognitive processing is of paramount importance for the appropriate management of patients diagnosed with disorders of consciousness. Objective behavioral assessment of residual cognitive function can be extremely difficult as motor responses may be minimal, inconsistent, and difficult to document, or may be

undetectable because no cognitive output is possible (for a comprehensive discussion of this issue — including the limitations of behavioral assessment — see Giacino et al., 2009). This situation may be further complicated when patients with disorders of consciousness have underlying deficits in the domain of communication functions, such as aphasia (the consequences of receptive and/or productive aphasia on the already limited behavioral repertoire presented in these patients are reviewed in Majerus et al., 2009). 'Activation' methods, such as H<sub>2</sub><sup>15</sup>O PET and fMRI can be used to link residual neural activity to the presence of covert cognitive function. A significant development over the past ten years has been the relative shift of emphasis from PET activation studies using H<sub>2</sub><sup>15</sup>O methodology, to functional magnetic resonance imaging (fMRI; see Chapters by Coleman et al., 2009; Soddu et al., 2009; Sorger et al., 2009; Monti et al., 2009). Not only is MRI more widely available than PET, it offers increased statistical power, improved spatial and temporal resolution and does not involve radiation. Given the heterogeneous nature of this patient group and the clinical need to define each individual in terms of their diagnosis, residual functions and potential for recovery, these technical benefits are of paramount importance in the evaluation of disorders of consciousness.

Recent notable examples include Di et al. (2007) who used event-related fMRI to measure brain activation in seven vegetative patients and four minimally conscious patients in response to the patient's own name spoken by a familiar voice. Two of the vegetative patients exhibited no significant activity at all, three patients exhibited activation in primary auditory areas and two vegetative patients and four minimally conscious patients exhibited activity in 'higher-order' associative temporal-lobe areas. This result is encouraging, particularly because the two vegetative patients who showed the most widespread activation subsequently improved to a minimally conscious state in the following months. Staffen et al. (2006) also used event-related fMRI to compare sentences containing the patient's own name (e.g. 'Martin, hello Martin'), with sentences using

another first name, in a patient who had been vegetative for ten months at the time of the scan. Differential cortical processing was observed to the patient's own name in a region of the medial prefrontal cortex, similar to that observed in three healthy volunteers. These findings concur closely with a recent electrophysiological study, which has shown differential P3 responses to patient's own names (compared to other's names) in some vegetative patients (Perrin et al., 2006). Selective cortical processing of one's own name (when it is compared directly with another name) requires the ability to perceive and access the meaning of words and may imply some level of comprehension on the part of these patients. However, as several authors have pointed out, a response to one's own name is one of the most basic forms of language and may not depend on the higher-level linguistic processes that are assumed to underpin comprehension (Perrin et al., 2006; Owen and Coleman, 2008; Laureys et al., 2007).

Several recent studies have sought to address this problem of interpretation by adopting an 'hierarchical' approach to fMRI assessment of language processing in disorders of consciousness (Owen et al., 2005a, b; Coleman et al., 2007, in press). At the highest level, responses to sentences containing semantically ambiguous words (e.g. 'the *creak/creek* came from a *beam* in the *ceiling/sealing*') are compared to sentences containing no ambiguous words (e.g. 'her secrets were written in her diary'), in order to reveal brain activity associated with spoken language *comprehension* (Rodd et al., 2005). In one large study of 41 patients, 2 who had been diagnosed as behaviorally vegetative were shown to exhibit 'normal' fMRI activity during the speech comprehension task (Coleman et al., in press). Moreover, these fMRI findings were found to have no association with the patients' behavioral presentation at the time of investigation and thus provide additional diagnostic information beyond the traditional clinical assessment. These results illustrate how technically complex event-related fMRI designs are now being combined with well-characterized psycholinguistic paradigms to demonstrate that some of the processes involved in activating, selecting and integrating

contextually appropriate word meanings may be intact in some vegetative patients, despite their clinical diagnoses.

Does the presence of 'normal' brain activation in patients with disorders of consciousness indicate a level of awareness, perhaps even similar to that which exists in healthy volunteers when exposed to the same type of information? 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 willful 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). In addition, there is a wealth of data in healthy volunteers, from studies of implicit learning and the effects of priming (Schacter, 1994) to studies of learning and speech perception during anesthesia (Davis et al., 2007) that have demonstrated that many aspects of human cognition can go on in the absence of awareness. Even the semantic content of masked information can be primed to affect subsequent behavior without the explicit knowledge of the participant, suggesting that some aspects of semantic processing may occur without conscious awareness (Dehaene et al., 1998). By the same argument, 'normal' neural responses in patients who are diagnosed with disorders of consciousness do not *necessarily* indicate that these patients have any conscious experience associated with processing those same types of stimuli. This logic exposes a central conundrum in the study of conscious awareness and in particular, how it relates to the vegetative and minimally conscious states; our ability to know unequivocally that another being is consciously aware is determined, not by whether they are aware or not, but by their ability to communicate that fact through a recognized behavioral response (for a fuller discussion of this 'problem of unreportable awareness' see Adam Zeman's chapter, 2009).

A significant recent development in this field, therefore, has been the development of fMRI paradigms that render awareness *reportable* in the absence of an overt behavioral (e.g. motor or speech) response (Owen et al., 2006; Boly et al.,

2007). Crucially, these paradigms differ from the passive tasks described above (e.g. speech perception) because ‘normal’ patterns of fMRI activity are only observed when the patient exerts a willful, or voluntary, response that is not elicited automatically by the stimulus (for a fuller discussion of this issue, see Monti et al., 2009). Some of these techniques make use of the general observation that imagining performing a particular task generates a robust and reliable pattern of brain activity in the fMRI scanner that is similar to actually performing the activity itself. For example, imagining moving or squeezing the hands will generate activity in the motor and premotor cortices (Boly et al., 2007) while imagining navigating from one location to another will activate the same regions of the parahippocampal gyrus and the posterior parietal cortex that have been widely implicated in map-reading and other so-called spatial navigation tasks (Jeannerod and Frak, 1999; Aguirre et al., 1996). The robustness and reliability of these fMRI responses across individuals means that activity in these regions can be used as a neural proxy for behavior, 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 behavior in the absence of any overt action. On this basis, they permit the identification of awareness at the single-subject level, without the need for a motor response (for discussion, see Owen and Coleman, 2008; Monti et al., 2009).

This approach was used recently to demonstrate that a young woman who fulfilled all internationally agreed criteria for the vegetative state was, in fact, consciously aware and able to make responses of this sort using her brain activity (Owen et al., 2006, 2007). Thus, when the patient was asked to imagine playing tennis or navigate her way around her house, significant activity was observed that was indistinguishable from that exhibited by healthy volunteers performing the same tasks (Boly et al., 2007).

An alternative approach that has been explored recently is to target processes that require the willful adoption of ‘mind-sets’ in carefully matched (perceptually identical) experimental

and control conditions. Monti et al. (2009) describe a study in which healthy volunteers were presented with a series of neutral words, and alternatively instructed to just listen, or to count, the number of times a given target was repeated. The counting task revealed the frontoparietal network that has been previously associated with target detection and working memory. When tested on this same procedure, a minimally conscious patient produced a very similar pattern of activity, confirming that he could willfully adopt differential mind-sets as a function of the task condition and could actively maintain these mind-sets across time. A similar approach has been adopted recently by Schnakers et al. (2008b) who used, as targets, the patient’s own name and other ‘non-salient’ names (e.g. similarly frequent names that had no relation to the patient or his/her family). All of the minimally conscious patients that were tested exhibited a significant response when passively listening to their own name. In addition, however, 9 of 14 patients exhibited more activity when instructed to count the number of times their own name (or another target name) occurred than when they passively heard it. This approach also allowed awareness to be identified in a case of complete locked-in syndrome (Schnakers et al., 2009).

These types of approach all illustrate a paradigmatic shift away from passive (e.g. perceptual) tasks to more active (e.g. willful) tasks in the fMRI and electroencephalography (EEG) assessment of residual cognitive function in patients with disorders of consciousness. What sets such tasks apart is that the neural responses required are not produced automatically by the eliciting stimulus, but rather, depend on time-dependent and sustained responses generated by the participant. Such behavior (albeit neural ‘behavior’) provides a proxy for an (e.g. motor) action and is, therefore, an appropriate vehicle for *reportable awareness* (also see Zeman, 2009; Overgaard, 2009).

### **fMRI as a form of communication?**

One major aim of clinical assessment in disorders of consciousness is to harness and nurture any

available response, through intervention, into a form of reproducible communication, however rudimentary. The acquisition of any interactive and functional verbal or nonverbal method of communication represents an important milestone. Clinically, it demarcates the upper boundary of minimally conscious state (MCS) (see Giacino et al., 2009). More importantly, from a quality of life perspective, it allows such patients to communicate their wishes (e.g. concerning treatment options), and, therefore, to exert their right to autonomy. Thus, a key future question for functional neuroimaging is whether fMRI data could ever be used in this way; that is as a form of *communication*, replacing speech or a motor act in patients for whom such forms of behavioral expression are unavailable?

Several recent studies using fMRI suggest that this may be possible. For example, Haynes et al. (2007) asked healthy volunteers to freely decide which of two tasks to perform (to add or subtract two numbers) and to covertly hold onto that decision during a delay. After the delay they performed the chosen task, the result indicating which task they had intended to do (and eventually executed). A classifier was trained to recognize the characteristic fMRI signatures associated with the two mental states and in 80% of trials was able to decode from activity in medial and lateral regions of prefrontal cortex which of the two tasks the volunteers were intending to perform. Another previous study has shown that fMRI can be used as a ‘brain–computer interface’ (BCI) that allows real-time communication of thoughts (Weiskopf et al., 2004); healthy volunteers learned to regulate the fMRI signal in a particular brain area using their own fMRI signal as feedback. In general terms, a brain–computer interface is any system that translates an individual’s thoughts and intentions into signals to control a computer or communicate via external hardware, thereby establishing a ‘direct’ connection between the brain and the external world without any need for motor output (Kubler and Neumann, 2005; for further discussion, see Sorger et al., 2009). In recent years, significant progress has been made in developing sophisticated noninvasive BCI methods for

‘decoding thoughts’ using both fMRI and EEG (e.g. Birbaumer and Cohen, 2007; deCharms, 2007). However, all of these methods require extensive training of participants, the decoding algorithm, or both. Moreover, accuracy rates are typically in the 60–80% range rendering them of limited use in clinical decision-making. In an exciting new development, Sorger et al. (2009) have developed a novel information encoding technique that exploits the fact that the signal-to-noise ratio in fMRI time courses is sufficiently high to reliably detect BOLD signal onsets and offsets on a single-trial level with a high degree of accuracy. Eight healthy participants ‘answered’ multiple-choice questions with 95% accuracy by intentionally generating single-trial BOLD responses in three tasks that were then ‘decoded’ in real time with respect to three influenceable signal aspects (source location, onset and offset). Although this ‘proof of concept’ was in healthy participants, such feats of rudimentary ‘mind-reading’ increase the likelihood that in the near future, some patients with disorders of consciousness may also be able to communicate their thoughts to those around them by simply modulating their own neural activity.

### **Resting state fMRI**

Another important new direction in the use of fMRI data in the assessment of patients with disorders of consciousness is in the examination of so-called ‘resting-state’ data (for a comprehensive discussion of this area see Soddu et al., 2009). Recently, increasing attention has been paid to the ‘intrinsic’ functional connectivity of the brain, and this can be revealed by examination of fMRI data collected while the participant is not performing any active task (e.g. they are ‘at rest’). Resting state data is very easy to obtain in vegetative and minimally conscious patients, as it does not require the participant to perform any task. Boly et al. (2009a, b) have recently investigated spontaneous activation in patients with disorders of consciousness and showed that resting state connectivity in the ‘default network’ is decreased in proportion to the degree of

consciousness impairment. Specifically, they demonstrated that cortico-thalamic BOLD functional connectivity (i.e. between posterior cingulate/precuneal cortex and medial thalamus) was notably absent, but cortico-cortical connectivity was preserved within the default network in one vegetative state patient studied 2.5 years following cardio-respiratory arrest (Boly et al., 2009a). In a second study, resting state connectivity was investigated using probabilistic independent component analysis in 14 noncommunicative brain damaged patients and 14 healthy controls (Boly et al., 2009b). Connectivity in all default network areas was found to be linearly correlated with the degree of ‘clinical consciousnesses’ (from healthy controls, to locked-in syndrome, to minimally conscious state, vegetative state and coma). Moreover, precuneus connectivity was found to be significantly stronger in minimally conscious patients than vegetative state patients. As might be expected given their preserved level of awareness, in locked-in syndrome patients, default network connectivity was not significantly different from controls (for further discussion see Soddu et al., 2009). In this volume, Boly et al. (2009) suggest a theoretical framework for understanding the properties that grant a system a state of consciousness, and highlight the notion of ‘integration’ as a necessary (but not sufficient) component of consciousness. While measures of integration have been proposed previously, the fact that these may be computationally out of reach for a system such as the brain, makes studies of intrinsic connectivity (e.g. using resting state data) a relatively crude, but informative, approximation of the levels of functional integration available at different levels of consciousness.

Using a somewhat different, but related, approach to understanding consciousness and its breakdown, Massimini et al. (2009) propose a theoretically grounded methodology for assessing a system’s capability for producing consciousness. Adopting a ‘perturbational approach’ they suggest that the combination of transcranial magnetic stimulation (TMS) and high density EEG may make it possible to evaluate the amount of functional integration of a system – a theoretical requisite for conscious experience.

### Diffusion tensor imaging

Another significant development in the last decade has been the development of various methods for assessing the structural connectivity of the brain (for a comprehensive discussion of some of these techniques, see Tshibanda et al., 2009). DTI is a noninvasive magnetic resonance technique that allows examination of white matter fiber tracts in vivo. In white matter, water diffusion is higher along the direction of fiber bundles (due to axonal organization and the myelin sheath). This *anisotropy* is measured with MRI to determine anatomical connectivity. To date, detailed histopathological studies have shown no pathological distinctions between vegetative state and some minimally conscious state patients (Jennett et al., 2001). This approach has been used to great effect recently by Voss et al. (2006) who used DTI to longitudinally characterize brain structural connectivity in a minimally conscious patient who regained expressive and receptive language 19 years after sustaining a traumatic brain injury. DTI not only revealed severe diffuse axonal injury, as indicated by volume loss in the medial corpus callosum, but also large regions of increased connectivity (relative to healthy controls) in posterior parts of the brain (i.e. precuneal areas). In a second DTI study 18 months later, these posterior regions of white matter anisotropy were reduced in directionality. At the same time point, significant increases in anisotropy within the midline cerebellar white matter were shown to correlate with the observed clinical improvement in motor control during the previous 18 months. These findings strongly suggest that the observed structural changes within the patient’s white matter played a role in his functional recovery.

Coleman et al. (2009) have also used this technique as part of a multimodal approach to the assessment of patients with disorders of consciousness. In one minimally conscious patient described in detail, DTI revealed reduced (–38%) fractional anisotropy in comparison to healthy control subjects, indicating widespread loss of white matter integrity. Moreover DTI revealed a significantly increased apparent

diffusion coefficient in comparison to healthy volunteers, suggesting loss of cortico-cortical connectivity. Indeed, a qualitative view of white matter paths revealed a loss of the inferior temporal and inferior frontal pathways that have been shown to mediate aspects of speech comprehension in some of the psycholinguistic fMRI tasks described above (e.g. Rodd et al., 2005). Of note, a prospective cohort study of serial DTI imaging following severe traumatic brain injury and coma found that cognitive and behavioral improvement correlated with recovery of normal to supranormal fractional anisotropy in preselected white matter regions (Sidaros et al., 2008). These findings showed a directional specificity with improvements in fractional anisotropy seen only in the eigenvectors of the diffusion tensor associated with diffusion parallel to the axonal fibers; these results are consistent with the Voss et al. (2006) study and supportive of possible axonal regrowth.

In the coming years, we expect that the increasing use of routinely acquired DTI data in disorders of consciousness will yield larger prospective studies in this patient group which will ultimately determine whether the sorts of slow structural changes reported by Voss et al. (2006) occur frequently in severe traumatic brain injury and whether they have any influence on functional outcomes (e.g. see Perlberg et al., 2009; Tollard et al., 2009; Tshibanda, 2009).

### **The impact on diagnosis and prognosis**

As the use of multimodal imaging methods in the assessment of disorders of consciousness is translated to clinical routine, the likely effects on diagnosis and prognosis are beginning to become more apparent. The main goal of the clinical assessment in the vegetative and minimally conscious states is to determine whether the patient retains any purposeful response to stimulation, albeit inconsistent, suggesting they are at least partially aware of their environment and/or themselves. Crucially, this decision separates vegetative state from minimally conscious state patients and has, therefore, profound implications

for the subsequent care of the patient and rehabilitation, as well as legal and ethical decision-making. Unfortunately, the behavior elicited by these patients is often ambiguous, inconsistent and typically constrained by varying degrees of paresis making it very challenging to disentangle purely reflexive from voluntary behaviors (for further discussion, see Giacino et al., 2009), a fact that undoubtedly contributes to the high rate of diagnostic error (37–43%) in this patient group (Andrews et al., 1996; Childs et al., 1993; Schnakers et al., 2006). In several recent cases, neuroimaging data has been entirely inconsistent with the formal clinical diagnosis which remains based on standard behavioral criteria. For example, the patient described by Owen et al. (2006), was clearly able to produce voluntary responses (albeit neural responses) to command, yet was unable to match this with any form of motor response at the bedside. Paradoxically therefore, this patient's (motor) behavior was consistent with a diagnosis of vegetative state which effectively depends on *an absence of evidence of awareness or purposeful response*, yet her brain imaging data were equally consistent with the alternative hypothesis, that she was entirely aware during the scanning procedure. Clearly the clinical diagnosis of vegetative state based on behavioral assessment was inaccurate in the sense that it did not accurately reflect her internal state of awareness. On the other hand, she was not *misdiagnosed* in the sense that no behavioral marker of awareness was missed. Similarly, the minimally conscious patient described by Monti et al. (2009) was able to 'perform' a complex working memory task in the scanner, in the sense that his brain activity revealed consistent and repeatable command following. While this 'behavior' does not necessarily alter the patient's formal diagnosis (from 'low' MCS) it certainly demonstrated a level of responsiveness that was not revealed by the behavioral examination.

A second question concerns the implications that emerging neuroimaging approaches may have for prognosis in this patient group. At present, predicting survival, outcome and long-term cognitive deficits in individual patients with severe brain injury based on clinical assessment is

very difficult (see extensive reviews by Whyte et al., 2009; Katz et al., 2009; Azouvi et al., 2009; Zasler, 2009). It is of interest that in the case described by Owen et al. (2006), the patient began to emerge from her vegetative state to demonstrate diagnostically relevant behavioral markers before the prognostically important 12-month threshold was reached (for a diagnosis of *permanent* vegetative state), suggesting that early evidence of awareness acquired with functional neuroimaging may have important prognostic value. Indeed, with a marked increase in the number of studies using neuroimaging techniques in patients with disorders of consciousness a consistent pattern is starting to emerge. Di et al. (2008), reviewed 15 separate  $H_2^{15}O$  PET and fMRI studies involving 48 published cases which were classified as 'absent cortical activation', 'typical activation', (involving low level primary sensory cortices) and 'atypical activation' (corresponding to higher-level associative cortices). The results show that atypical activity patterns appear to predict recovery from vegetative state with 93% specificity and 69% sensitivity. That is to say, 9 of 11 patients exhibiting atypical activity patterns recovered consciousness, whereas 21 of 25 patients with typical primary cortical activity patterns and 4 out of 4 patients with absent activity failed to recover. This important review strongly suggests that functional neuroimaging data can provide important prognostic information beyond that available from bedside examination alone.

In another recent study of 41 patients with disorders of consciousness, Coleman et al. (in press; also see Coleman et al., 2009) found direct evidence of prognostically important information within neuroimaging data that was at odds with the behavioral assessment at the time of scanning. Thus, contrary to the clinical impression of a specialist team using behavioral assessment tools, two patients who had been referred to the study with a diagnosis of vegetative state, did in fact demonstrate clear signs of speech comprehension when assessed using fMRI. More importantly however, across the whole group of patients, the fMRI data were found to have *no association* with the behavioral presentation at the time of the

investigation, but correlated significantly with subsequent behavioral recovery, six months after the scan. In this case, the fMRI data predicted subsequent recovery in a way that a specialist behavioral assessment could not. In future, the full utility of neuroimaging in this context will become clearer when even larger studies are conducted, preferably involving multiple centers using standardized techniques and paradigms.

### Therapeutic advances

At present, there is no empirically proven intervention to facilitate recovery in the vegetative state and related disorders of consciousness (e.g. Schnakers et al., 2008a; also see extensive review by Zafonte et al. (2009) on pharmacotherapy of arousal and Taira (2009), on intrathecal administration of GABA agonists). The favored approach is to create a stable clinical environment for natural recovery to take place. The greatest difficulty preventing the development of treatment options is the extent and heterogeneity of pathology underlying these conditions. It is increasingly accepted; therefore, that novel treatments designed for the individual or a small group of very similar patients will be necessary. One such approach is deep brain stimulation (DBS), which uses stereotactically placed electrodes to deliver electrical stimulation to the thalamus (also see Moll et al., 2009, on subpallidal DBS-induced wakeful unawareness during anesthesia). DBS has recently been employed by Schiff et al. (2007) with startling results in a patient in post traumatic MCS. Electrical stimulation, delivered via electrodes implanted bilaterally into the central thalamus, was found to produce increased periods of arousal and responsiveness to command in a 38-year-old male who had remained in a minimally conscious state for six and a half years following the injury. The changes correlated closely with the commencement of DBS and could not be attributed to gradual recovery over time. Importantly however, the patient was at the upper boundary of the minimally conscious state before DBS was commenced. He had also produced inconsistent, but reproducible evidence of communication and

fMRI had shown preservation of cortical language networks. Yamamoto and Katayama (2005) used a similar technique on more severely impaired patients and reported positive effects in 8 out of 21 vegetative patients, who subsequently emerged from vegetative state and obeyed commands. However, in that study, DBS was commenced within 3–6 months of brain injury and it is not clear whether the behavioral improvement simply reflected natural recovery. There are now widespread calls for the methodology of Schiff et al. (2007) to be extended to a larger number of more severely impaired patients in order to evaluate the potential of this technique to facilitate recovery.

### Neuroimaging and ethics

Neuroimaging of severely brain-injured, noncommunicative populations of patients raises several important 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. In an excellent discussion of these issues (Fins, 2009), Joseph Fins notes that ‘the utter *and fixed* futility of the vegetative state became the ethical and legal justification for the genesis of the right-to-die movement in the United States’ (Fins, 2003, 2006; Fins et al., 2008). At present, although several of the neuroimaging approaches discussed in this chapter hold great promise to improve both diagnostic and prognostic accuracy, the standard approach remains the careful and repeated neurological exam by a trained examiner.

That said, in future, the routine use of techniques such as fMRI and quantitative EEG in the diagnostic process (e.g. for the detection of awareness), will raise additional issues relating to legal decision-making and the prolongation, or otherwise, of life after severe brain injury (see Levy and Savulescu, 2009; Lutte, 2009). At present, decisions concerning life support (nutrition and hydration) are generally taken once a diagnosis of *permanent* vegetative state has been made. To date, fMRI has not demonstrated unequivocal signs of awareness in any patient that has survived beyond the time point required

for such a diagnosis (Owen and Coleman, 2008; Laureys and Boly, 2008). Thus, whether fMRI will ever be used in this context will only become apparent when more patients have been scanned, although if evidence for awareness were to be found in a patient who had progressed beyond the threshold for a diagnosis of permanent vegetative state, this fact would certainly have profound implications for this decision-making process. On the other hand, it is important to point out that neuroimaging is unlikely to influence legal proceedings where negative findings have been acquired. False-negative findings in functional neuroimaging studies are common, even in healthy volunteers, and they present particular difficulties in this patient population. For example, a patient may have low levels of arousal or even fall asleep during the study (e.g. see review by Bekinschtein et al. (2009) on the influence of arousal fluctuations on patients’ responsiveness) or the patient may not have properly heard or understood the task instructions, leading to an erroneous negative result. Accordingly, single negative fMRI or EEG findings in patients should not be used as evidence for impaired cognitive function or *lack* of awareness.

Ethical concerns are also sometimes raised concerning the participation of severely brain-injured patients in functional neuroimaging studies (e.g. to assess pain perception; see Demertzi et al., 2009), studies that require invasive procedures (e.g. intra-arterial or jugular lines required for quantification of PET data or modeling), 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. We side with a proposed ethical framework that emphasizes balancing access to research and medical advances alongside protection for vulnerable patient populations. 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 (also see

Lulé et al., 2009, on quality of life in the locked-in syndrome). However, it is important to stress that these severely brain-injured patients are also vulnerable to being denied potentially life-saving therapy if clinical research cannot be performed adequately (for further discussion, see Fins, 2009).

## Conclusions

Disorders of consciousness present unique problems for diagnosis, prognosis, treatment and everyday management. In this chapter, we have reviewed a number of areas where novel neuroimaging methods and approaches are beginning to make a significant impact on the assessment and management of these patients. For example, cognitive activation studies using event-related fMRI are now being used to objectively describe (using population norms) the regional distribution of cerebral activity at rest and under various conditions of stimulation. Indeed, in several rare cases, functional neuroimaging has demonstrated *conscious awareness* in patients who are assumed to be vegetative, yet retain cognitive abilities that have evaded detection using standard clinical methods. Similarly, in some patients diagnosed as minimally conscious, functional neuroimaging has revealed residual cognitive capabilities that extend well beyond that evident from even the most comprehensive behavioral assessment. Moreover, these detailed functional images are now being combined with high-resolution information about anatomy and images of structural connectivity, acquired using techniques such as DTI, to produce an increasingly cohesive picture of normal and abnormal brain function following serious brain injury.

Although insufficient population data currently exists, evidence to include the use of such techniques in the formal diagnostic and prognostic procedure in this patient group is accumulating rapidly. The emerging view is not that brain imaging should replace behavioral assessment, but rather that it should be used, wherever possible, to acquire further information about the patient and their condition. In doing so, the current alarmingly high rate of misdiagnosis in

this patient group will undoubtedly fall. Likewise, clinical teams will have the best possible information for planning and monitoring interventions to facilitate recovery.

## Acknowledgments

The authors acknowledge the generous support of the James S. McDonnell Foundation. AMO is supported by the Medical Research Council (UK). NS is supported by NS02172, NS43451 and the Charles A. Dana Foundation. SL is a Research Associate at the Fonds National de la Recherche Scientifique de Belgique (FNRS).

## References

- Aguirre, G. K., Detre, J. A., Alsup, D. C., & D'Esposito, M. (1996). The parahippocampus subserves topographical learning in man. *Cerebral Cortex*, *6*, 823–829.
- Andrews, K., Murphy, L., Munday, R., & Littlewood, C. (1996). Misdiagnosis of the vegetative state: Retrospective study in a rehabilitation unit. *British Medical Journal*, *313*, 13–16.
- Azouvi, P., Vallat-Azouvi, C., Belmont, A., & Azouvi, P. (2009). Cognitive deficits and long-term outcome after traumatic coma. In S. Laureys, N. D. Schiff, & A. M. Owen (Eds.), *Coma science: Clinical and ethical implications – Progress in Brain Research* (this volume). Oxford: Elsevier.
- Bekinschtein, T., Cologan, V., Dahmen, B., & Golombek, D. (2009). You are only coming through in waves: Wakefulness variability and assessment in patients with impaired consciousness. In S. Laureys, N. D. Schiff, & A. M. Owen (Eds.), *Coma science: Clinical and ethical implications – Progress in Brain Research* (this volume). Oxford: Elsevier.
- Birbaumer, N., & Cohen, L. G. (2007). Brain-computer interfaces: Communication and restoration of movement in paralysis. *Journal of Physiology*, *579*, 621–636.
- Boly, M., Coleman, M. R., Davis, M. H., Hampshire, A., Bor, D., Moonen, G., 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.
- Boly, M., Massimini, M., & Tononi, T. (2009). How could information integration theory be applied to the differential diagnosis of patients in altered states of consciousness? In S. Laureys, N. D. Schiff, & A. M. Owen (Eds.), *Coma science: Clinical and ethical implications – Progress in Brain Research* (this volume). Oxford: Elsevier.
- Boly, M., Tshibanda, L., Vanhaudenhuyse, A., Noirhomme, Q., Schnakers, C., Ledoux, D., et al. (2009a). Functional connectivity in the default network during resting state is

- preserved in a vegetative but not in a brain dead patient. *Human Brain Mapping*, 30(8), 2393–2400.
- Boly, M., Vanhaudenhuyse, A., Tshibanda, L., Bruno, M.-A., Boveroux, P., Noirhomme, Q., et al. (2009b). Default network connectivity reflects the level of consciousness in non-communicative brain damaged patients. Submitted.
- Childs, N. L., Mercer, W. N., & Childs, H. W. (1993). Accuracy of diagnosis of persistent vegetative state. *Neurology*, 43, 1465–1467.
- Coleman, M. R., Davis, M. H., Rodd, J. M., Robson, T., Ali, A., Pickard, J. D., et al. (in press). Towards the routine use of brain imaging to aid the clinical diagnosis of disorders of consciousness. *Brain*.
- Coleman, M. R., Monti, M. M., Bekinschtein, T., Pickard, J., & Owen, A. M. (2009). A multimodal approach to the assessment of patients with disorders of consciousness. In S. Laureys, N. D. Schiff, & A. M. Owen (Eds.), *Coma science: Clinical and ethical implications – Progress in Brain Research* (this volume). Oxford: Elsevier.
- Coleman, M. R., Rodd, J. M., Davis, M. H., Johnsrude, I. S., Menon, D. K., Pickard, J. D., et al. (2007). Do vegetative patients retain aspects of language comprehension? Evidence from fMRI. *Brain*, 130, 2494–2507.
- Davis, M. H., Coleman, M. R., Absalom, A. R., Rodd, J. M., Johnsrude, I. S., Matta, B. F., et al. (2007). Dissociating speech perception and comprehension at reduced levels of awareness. *Proceedings of the National Academy of Sciences*, 104(41), 16032–16037.
- deCharms, R. C. (2007). Reading and controlling human brain activation using real-time functional magnetic resonance imaging. *Trends in Cognitive Sciences*, 11, 473–481.
- Dehaene, S., Naccache, L., Le Clec, H. G., Koechlin, E., Mueller, M., Dehaene-Lambertz, G., et al. (1998). Imaging unconscious semantic priming. *Nature*, 395, 597–600.
- Demertzi, A., Schnakers, C., Ledoux, D., Chatelle, C., Bruno, M.-A., Vanhaudenhuyse, A., et al. (2009). Different beliefs about pain perception in the vegetative and minimally conscious states: A European survey of medical and paramedical professionals. In S. Laureys, N. D. Schiff, & A. M. Owen (Eds.), *Coma science: Clinical and ethical implications – Progress in Brain Research* (this volume). Oxford: Elsevier.
- Di, H., Boly, M., Weng, X., Ledoux, D., & Laureys, S. (2008). Neuroimaging activation studies in the vegetative state: Predictors of recovery? *Clinical Medicine*, 8, 502–507.
- Di, H. B., Yu, S. M., Weng, X. C., Laureys, S., Yu, D., Li, J. Q., et al. (2007). Cerebral response to patient's own name in the vegetative and minimally conscious states. *Neurology*, 68, 895–899.
- Fins, F. (2009). The ethics of measuring and modulating consciousness: The imperative of minding time. In S. Laureys, N. D. Schiff, & A. M. Owen (Eds.), *Coma science: Clinical and ethical implications – Progress in Brain Research* (this volume). Oxford: Elsevier.
- Fins, J. J. (2003). Constructing an ethical stereotaxy for severe brain injury: Balancing risks, benefits and access. *Nature Reviews Neuroscience*, 4(4), 323–327.
- Fins, J. J. (2006). *A palliative ethic of care: Clinical wisdom at life's end*. Sudbury, MA: Jones and Bartlett.
- Fins, J. J., Illes, J., Bernat, J. L., Hirsch, J., Laureys, S., & Murphy, E. (2008). Neuroimaging and disorders of consciousness: Envisioning an ethical research agenda. *American Journal of Bioethics Neuroscience*, 8, 3–12.
- Giacino, J. T., Schnakers, C., Rodriguez-Moreno, D., Schiff, N. D., & Kalmar, K., (2009). Behavioral assessment in patients with disorders of consciousness: Gold standard or fool's gold? In S. Laureys, N. D. Schiff, & A. M. Owen (Eds.), *Coma science: Clinical and ethical implications – Progress in Brain Research* (this volume). Oxford: Elsevier.
- Haynes, J.-D., Sakai, K., Rees, G., Gilbert, S., Frith, C., & Passingham, R. E. (2007). Hidden intentions in the human brain. *Current Biology*, 10, 1016.
- Jennett, B., Adams, J. H., Murray, L. S., & Graham, D. I. (2001). Neuropathology in vegetative and severely disabled patients after head injury. *Neurology*, 56, 486–490.
- Jeannerod, M., & Frak, V. G. (1999). Mental simulation of action in human subjects. *Current Opinions in Neurobiology*, 9, 735–739.
- Katz, D., Polyak, M., Coughlin, D., Nichols, M., & Roche, A. (2009). Natural history of recovery from brain injury after prolonged impairment of consciousness: Patients admitted to inpatient rehabilitation. In S. Laureys, N. D. Schiff, & A. M. Owen (Eds.), *Coma science: Clinical and ethical implications – Progress in Brain Research* (this volume). Oxford: Elsevier.
- Kubler, A., & Neumann, N. (2005). Brain-computer interfaces – The key for the conscious brain locked into a paralyzed body. *Progress in Brain Research*, 150, 513–525.
- Laureys, S., & Boly, M. (2008). The changing spectrum of coma. *Nature Clinical Practice Neurology*, 4, 544–546.
- Levy, N., & Savulescu, J. (2009). The moral significance of phenomenal consciousness. In S. Laureys, N. D. Schiff, & A. M. Owen (Eds.), *Coma science: Clinical and ethical implications – Progress in Brain Research* (this volume). Oxford: Elsevier.
- Laureys, S., Perrin, F., & Brédart, S. (2007). Self-consciousness in non-communicative patients. *Consciousness and Cognition*, 16, 722–741.
- Lulé, D., Zickler, C., Häcker, S., Bruno, M. A., Pellas, F., Demertzi, A., et al. (2009). Life may be worth living in locked-in syndrome. In S. Laureys, N. D. Schiff, & A. M. Owen (Eds.), *Coma science: Clinical and ethical implications – Progress in Brain Research* (this volume). Oxford: Elsevier.
- Lutte, I. (2009). Defining personal loss after severe brain damage. In S. Laureys, N. D. Schiff, & A. M. Owen (Eds.), *Coma science: Clinical and ethical implications – Progress in Brain Research* (this volume). Oxford: Elsevier.
- Majerus, S., Bruno, M. A., Schnakers, C., Giacino, J. T., & Laureys, S. (2009). The problem of aphasia in the assessment of consciousness in brain damaged patients. In S. Laureys, N. D. Schiff, & A. M. Owen (Eds.), *Coma science: Clinical and ethical implications – Progress in Brain Research* (this volume). Oxford: Elsevier.
- Massimini, M., Boly, M., Casali, A., & Tononi, G. A. (2009). A perturbational approach to implement theoretical measures

- of consciousness at the patient's bedside. In S. Laureys, N. D. Schiff, & A. M. Owen (Eds.), *Coma science: Clinical and ethical implications – Progress in Brain Research* (this volume). Oxford: Elsevier.
- Moll, C. K. E., Sharott, A., Hamel, W., Münchau, A., Buhmann, C., Hidding, U., et al. (2009). Waking up the brain. A case study of stimulation-induced wakeful unawareness during anesthesia. In S. Laureys, N. D. Schiff, & A. M. Owen (Eds.), *Coma science: Clinical and ethical implications – Progress in Brain Research* (this volume). Oxford: Elsevier.
- Monti, M. M., Coleman, M. R., & Owen, A. M. (2009). From V1 to volition: Hierarchical assessment of visual cognition and attention with fMRI. In S. Laureys, N. D. Schiff, & A. M. Owen (Eds.), *Coma science: Clinical and ethical implications – Progress in Brain Research* (this volume). Oxford: Elsevier.
- Overgaard, M. (2009). How can we know if patients in coma, vegetative state or minimally conscious state are conscious? In S. Laureys, N. D. Schiff, & A. M. Owen (Eds.), *Coma science: Clinical and ethical implications – Progress in Brain Research* (this volume). Oxford: Elsevier.
- Owen, A. M., & Coleman, M. (2008). Functional imaging in the vegetative state. *Nature Reviews Neuroscience*, 9, 235–243.
- Owen, A. M., Coleman, M. R., Davis, M. H., Boly, M., Laureys, S., & Pickard, J. D. (2006). Detecting awareness in the vegetative state. *Science*, 313, 1402.
- Owen, A. M., Coleman, M. R., Davis, M. H., Boly, M., Laureys, S., & Pickard, J. D. (2007). Response to comments on “Detecting awareness in the vegetative state”. *Science*, 315, 1221c.
- Owen, A. M., Coleman, M. R., Menon, D. K., Berry, E. L., Johnsrude, I. S., Rodd, J. M., et al. (2005a). Using a hierarchical approach to investigate residual auditory cognition in persistent vegetative state. In S. Laureys (Ed.), *The boundaries of consciousness: Neurobiology and neuropathology. Progress in Brain Research* (Vol. 150, pp. 461–476). London: Elsevier.
- Owen, A. M., Coleman, M. R., Menon, D. K., Johnsrude, I. S., Rodd, J. M., Davis, M. H., et al. (2005b). Residual auditory function in persistent vegetative state: A combined PET and fMRI study. *Neuropsychological Rehabilitation*, 15(3–4), 290–306.
- Perlbarg, V., Puybasset, L., Tollard, E., Lehericy, S., Benali, H., & Galanaud, D. (2009). Relation between brain lesion location and clinical outcome in patients with severe traumatic brain injury: A diffusion tensor imaging study using voxel-based approaches. *Human Brain Mapping*, in press. Available at <http://www3.interscience.wiley.com/journal/122440012/abstract?CRETRY=1&SRETRY=0>
- Perrin, F., Schnakers, C., Schabus, M., Degueldre, C., Goldman, S., Bredart, S., et al. (2006). Brain response to one's own name in vegetative state, minimally conscious state, and locked-in syndrome. *Archives of Neurology*, 63, 562–569.
- Rodd, J. M., Davis, M. H., & Johnsrude, I. S. (2005). The neural mechanisms of speech comprehension: fMRI studies of semantic ambiguity. *Cerebral Cortex*, 15, 1261.
- Schacter, D. L. (1994). Priming and multiple memory systems: Perceptual mechanisms of implicit memory. In D. L. Schacter & E. Tulving (Eds.), *Memory systems* (pp. 233–268). Cambridge, MA: MIT Press.
- Schiff, N. D., Giacino, J. T., Kalmar, K., Victor, J. D., Baker, K., Gerber, M., et al. (2007). Behavioural improvements with thalamic stimulation after severe traumatic brain injury. *Nature*, 448, 600–603.
- Schnakers, C., Giacino, J., Kalmar, K., Piret, S., Lopez, E., Boly, M., et al. (2006). Does the FOUR score correctly diagnose the vegetative and minimally conscious states? *Annals of Neurology*, 60, 744–745.
- Schnakers, C., Perrin, F., Schabus, M., Hustinx, R., Majerus, S., Moonen, G., et al. (2009). Detecting consciousness in a total locked-in syndrome: An active event related paradigm. *Neurocase*, 25, 1–7.
- Schnakers, C., Hustinx, R., Vandewalle, G., Majerus, S., Moonen, G., Vanhauzenhuysse, A., et al. (2008a). Measuring the effect of amantadine in chronic anoxic minimally conscious state. *Journal of Neurology Neurosurgery and Psychiatry*, 79, 225–227.
- Schnakers, C., Perrin, F., Schabus, M., Majerus, S., Ledoux, D., Damas, P., et al. (2008b). Voluntary brain processing in disorders of consciousness. *Neurology*, 71, 1614–1620.
- Sidaros, A., Engberg, A. W., Sidaros, K., Liptrot, M. G., Herning, M., Petersen, P., et al. (2008). Diffusion tensor imaging during recovery from severe traumatic brain injury and relation to clinical outcome: A longitudinal study. *Brain*, 131, 559–572.
- Soddu, A., Boly, M., Papa, M., Laureys, S., & Malach, R. (2009). Reaching across the abyss: Recent advances in functional magnetic resonance imaging (fMRI) and their potential relevance to deficits of consciousness. In S. Laureys, N. D. Schiff, & A. M. Owen (Eds.), *Coma science: Clinical and ethical implications – Progress in Brain Research* (this volume). Oxford: Elsevier.
- Sorger, B., Dahmen, B., Reithler, J., Gosseries, O., Maudoux, A., Laureys, S., et al. (2009). Another kind of ‘BOLD response’: Answering multiple choice questions by differential single-trial fMRI responses. In S. Laureys, N. D. Schiff, & A. M. Owen (Eds.), *Coma science: Clinical and ethical implications – Progress in Brain Research* (this volume). Oxford: Elsevier.
- Staffen, W., Kronbichler, M., Aichhorn, M., Mair, A., & Ladurner, G. (2006). Selective brain activity in response to one's own name in the persistent vegetative state. *Journal of Neurology, Neurosurgery & Psychiatry*, 77, 1383–1384.
- Taira, T. (2009). Intrathecal administration of GABA agonists in the vegetative state. In S. Laureys, N. D. Schiff, & A. M. Owen (Eds.), *Coma science: Clinical and ethical implications – Progress in Brain Research* (this volume). Oxford: Elsevier.
- Tollard, E., Galanaud, D., Perlbarg, V., Sanchez-Pena, P., Le Fur, Y., Abdennour, L., et al. (2009). Experience of diffusion tensor imaging and 1H spectroscopy for outcome prediction in severe traumatic brain injury: Preliminary results. *Critical Care Medicine*, 37(4), 1448–1455.

- Tshibanda, J. F., Galanaud, D., Vanhaudenhuyse, A., Boly, M., Laureys, S., & Puybasset, L. (2009). MRI spectroscopy and diffusion tensor imaging in coma survivors: Promises and pitfalls. In S. Laureys, N. D. Schiff, & A. M. Owen (Eds.), *Coma science: Clinical and ethical implications – Progress in Brain Research* (this volume). Oxford: Elsevier.
- Voss, H. U., Uluç, A. M., Dyke, J. P., Watts, R., Kobylarz, E. J., McCandliss, B. D., et al. (2006). Possible axonal regrowth in late recovery from the minimally conscious state. *The Journal of Clinical Investigation*, *116*, 2005–2011.
- Weiskopf, N., Mathiak, K., Bock, S. W., Scharnowski, F., Veit, R., Grodd, W., et al. (2004). Principles of a brain-computer interface (BCI) based on real-time functional magnetic resonance imaging (fMRI). *IEEE Transactions on Biomedical Engineering*, *51*, 966–970.
- Whyte, J., Gosseries, O., Chervoneva, I., DiPasquale, M. C., Giacino, J., Kalmar, K., et al. (2009). Predictors of short-term outcome in brain injured patients with disorders of consciousness. In S. Laureys, N. D. Schiff, & A. M. Owen (Eds.), *Coma science: Clinical and ethical implications – Progress in Brain Research* (this volume). Oxford: Elsevier.
- Yamamoto, T., & Katayama, Y. (2005). Deep brain stimulation therapy for the vegetative state. *Neuropsychological Rehabilitation*, *15*(3/4), 406–413.
- Zafonte, R., Hammond, F., Dennison, A., & Chew, E. (2009). Pharmacotherapy of arousal: Balancing the risks and benefits. In S. Laureys, N. D. Schiff, & A. M. Owen (Eds.), *Coma science: Clinical and ethical implications – Progress in Brain Research* (this volume). Oxford: Elsevier.
- Zasler, N. (2009). Life expectancy and disorders of consciousness after traumatic brain injury. In S. Laureys, N. D. Schiff, & A. M. Owen (Eds.), *Coma science: Clinical and ethical implications – Progress in Brain Research* (this volume). Oxford: Elsevier.
- Zeman, A. (2009). The problem of unreportable awareness. In S. Laureys, N. D. Schiff, & A. M. Owen (Eds.), *Coma science: Clinical and ethical implications – Progress in Brain Research* (this volume). Oxford: Elsevier.