

Consciousness revealed: new insights into the vegetative and minimally conscious states

Damian Cruse and Adrian M. Owen

Medical Research Council Cognition and Brain Sciences Unit, Chaucer Road, Cambridge, UK

Correspondence to Damian Cruse, Medical Research Council Cognition and Brain Sciences Unit, 15 Chaucer Road, Cambridge CB2 7EF, UK
E-mail: damian.cruse@mrc-cbu.cam.ac.uk

Current Opinion in Neurology 2010, 23:656–660

Purpose of review

In recent years, the results of neuroimaging studies have fundamentally changed the way we think about the vegetative and minimally conscious states.

Recent findings

Functional MRI studies have demonstrated that some high-level cognitive functions, such as language comprehension and target detection, are preserved in a subset of patients with disorders of consciousness. Similar methods have even allowed a patient who was assumed to be in a vegetative state to communicate. PET has provided insights into similarities and differences in the ways in which pain is processed by this patient group, whereas electrophysiological methods have revealed further evidence of awareness as well as learning.

Summary

The prognostic and diagnostic information provided by these new approaches clearly argues for their future use alongside conventional assessment techniques. By demonstrating that a behaviourally unresponsive patient could communicate by means of his/her thoughts using functional MRI, these new techniques open up a new direction of research into the development of more sophisticated communication devices that may be used more generally by these patients. In our opinion, such devices, employing electroencephalograph among other techniques, may soon allow for patients who retain sufficient cognitive abilities to communicate, to do so outside of an MRI scanner.

Keywords

consciousness, electroencephalograph, functional MRI, minimally conscious state, vegetative state

Curr Opin Neurol 23:656–660
© 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins
1350-7540

Introduction

Conventional assessments of the level of cognitive functioning that is preserved following severe brain injury, such as the Glasgow Coma Score [1] and the Coma Recovery Scale [2], rely on a patient demonstrating their awareness and cognitive capabilities by means of overt motor actions. It is a challenge, however, to objectively perform these assessments, as motor responses may be difficult to discern or inconsistently present in this patient group.

It is becoming increasingly clear that relying on an overt behavioural response in this way may result in a misdiagnosis of a patient's level of awareness. In 2006, Owen *et al.* [3] endeavoured to recharacterize the way in which an individual can be said to respond to command, by including the haemodynamic response of the brain detected with functional MRI (fMRI). In that study, a patient who appeared to be vegetative was asked to perform two mental imagery tasks – imagining playing

tennis and imagining walking through the rooms of her house – tasks that are associated with differential activation of a number of distinct brain regions. The resulting patterns of brain responses that were comparable with those observed in healthy, awake, controls when performing these imaginations to command, allowed Owen *et al.* to conclude that the patient was responding to command and therefore retained a level of awareness that was not apparent from her (lack of) behaviour.

The outcome of that study served to highlight the issue of misdiagnosis in this patient group, along with the potential for functional neuroimaging methods to provide an objective measure of awareness in other patients with disorders of consciousness (DOCs). As shall be discussed below, this potential has continued to be realized in recent years, with evidence emerging for both the diagnostic and prognostic utility of these methods. Neuroimaging studies in this patient group are also providing more fundamental insights into those neural structures and mechanisms that support awareness. The current

article provides a review of recent advances in the use of functional neuroimaging that continue to contribute to our understanding of the vegetative and minimally conscious states (VS; MCS).

The anatomy of awareness

High-resolution MRI techniques have allowed for the investigation of those brain structures that are most important for determining the level of awareness that is demonstrated behaviourally by patients with disorders of consciousness. One focus has been the so-called 'default mode network' (DMN) of brain regions [4], including the precuneus, temporo-parietal junction, and medial prefrontal cortex, which show idling activity when an individual is at rest, and relative deactivations when engaged in a task. Reductions in the functional connectivity of these brain regions have been observed in nonpathological states of altered consciousness, such as anaesthesia ([5] cf. [6], for a review).

In the case of patients in the vegetative state (VS), significantly reduced functional connectivity within regions of the DMN has also been observed [7]. The level of functional connectivity within these regions has also been shown to be negatively correlated with behavioural signs of awareness, with VS patients showing reduced connectivity relative to MCS patients, both of which are reduced relative to healthy controls [8^{*}]. Boly *et al.* [9], however, described a VS patient with preserved cortico-cortical connectivity within the DMN, but absent cortico-thalamic connectivity, highlighting the importance of the thalami in behavioural demonstrations of awareness.

This theme has been expanded by Fernández-Espejo *et al.* [10^{*}], who showed significant reductions in the thalamic volume of patients in a VS or MCS. Interestingly, their analysis technique allowed the authors to investigate the particular regions of the thalami that were most affected, and observed atrophy predominantly in the dorsal body of the thalamus for MCS patients, with much more widespread bilateral atrophy in the group of VS patients. Not only do these findings highlight the importance of particular structures, such as the thalamus and its connectivity with the cortex, in underpinning awareness, they also provide a potential diagnostic tool for determining objectively whether a patient is in a VS or MCS based upon the particular structural features that remain preserved. This information could then be used to guide the most effective means of treatment in these patients.

Electrophysiological insights

In brain-injured patients, recordings of the electroencephalograph (EEG) are typically made in the acute

period and allow for broad assessments of cortical damage including the occurrence of brain death. However, uncertainty about the causes of abnormal raw EEG patterns (i.e., damage to the cortex itself, or to subcortical structures that influence cortical activity) provides challenges for its use as a more precise diagnostic tool in assessments of the patient's state of awareness (cf. [11]).

Recently, an effort has been made to quantify those particular aspects of the raw EEG signal that may be associated with particular behaviours or subsequent outcomes in patients with disorders of consciousness. For example, it has been observed [12] that occipital source power in the alpha band (8–13 Hz) of resting EEG, as calculated with low-resolution electromagnetic tomography (LORETA), is correlated with recovery outcome at 3-month follow-up in a group of VS patients; those who made a behavioural recovery had higher resting alpha band power than those who did not make a significant recovery. The prognostic value of resting EEG has also been demonstrated by Schnakers *et al.* [13], who calculated the bispectral indices (BIS), a composite measure of the frequency content of the EEG, in mixed group of VS and MCS patients. The BIS was shown to be positively correlated with behavioural scores of awareness at the time of testing and associated with outcome at 1-year post-trauma.

Apart from concentrating on aspects of the resting EEG, a number of studies have investigated whether cognitive event-related potentials (ERPs) – averages of segments of EEG locked to the presentation of a stimulus – can be used to determine the level of awareness in patients with disorders of consciousness. For example, recently it was shown that violations of prosody in nonlinguistic emotional exclamations elicited a reliable N300 component in six out of 27 patients in the VS or MCS, suggesting a level of processing of auditory stimuli beyond their most basic features in these patients [14].

One popular stimulus, employed in these cognitive tasks due to its high level of saliency, is the patients' own names. When presented infrequently among tones and other names, a reliable mismatch negativity (MMN) has been observed in some coma, VS, and MCS patients, demonstrating some selectivity of those patients' neural responses to hearing their own name [15]. This response was also associated with subsequent recovery at 3-month follow-up, with four out of five of those coma and VS patients who had demonstrated reliable MMNs recovering to MCS, whereas none of the patients who did not elicit an MMN made a similar recovery.

Schnakers *et al.* [16] very elegantly extended this type of paradigm to include a volitional aspect whereby, in half of the blocks, patients were instructed to count the number

of instances of their own name, in contrast to passive listening in the remaining blocks. Like healthy controls, a group of MCS patients demonstrated reliably larger P3 components, linked to target detection, during the active counting task. As the only aspect of the task that differed between the two conditions was the patient's intention (to count or to listen), as guided by the prior instruction, it was possible to unequivocally infer that these patients could follow commands and, therefore, that they were aware. In contrast, overt (motor) forms of command following were, at best, inconsistent when the patients were tested behaviourally. This also highlights the possibility that EEG/ERP may be able to identify some cognitive abilities, such as target detection, that may be retained by these patients in spite of the lack of any behavioural evidence.

Bekinschtein *et al.* [17**] demonstrated that objective measures of retained brain function need not involve direct assessment of neural activity, by employing electromyography (EMG) to infer a level of awareness in a group of patients in the VS or MCS. Using a trace-conditioning paradigm, in which one of two tones was associated with the presentation of an aversive air-puff to the eye, Bekinschtein *et al.* observed anticipatory eye movements (recorded by EMG) in a number of VS and MCS patients that were specific to the conditioned stimulus and not to the unpaired tone. Because such anticipatory learning in trace-conditioning paradigms requires an awareness of the contingencies involved when compared with learning in more simple classical conditioning paradigms, the authors were able to infer that these behaviourally VS and MCS patients retained some level of awareness. Importantly, evidence of such learning was also related to the likelihood of some subsequent behavioural recovery.

It has also been shown recently that a differential autonomic response to neutral and emotional auditory stimuli, as measured by electrodermal activity (EDA) at the fingers, is retained in some patients who are in a coma [18*]. The magnitude of this response was also correlated with behavioural measures of awareness in these patients.

Evidence is emerging, therefore, that nonhaemodynamic measures of neural activity, or indeed, indirect measures such as EMG or EDA, can provide important diagnostic and prognostic information following serious brain injury. The further development of paradigms to this end is of particular importance in this patient group due to the considerably reduced cost and portability of such method when compared with MRI. With electrophysiological techniques, a greater proportion of patients can be assessed, including those who may not have access to an MRI due to geographic, financial, or physical (i.e.,

metal plates or pins) reasons. Broadening the availability of objective measures in this way will have clear implications for patients and caregivers alike.

Contributions from functional MRI and PET

Although the fMRI results of Owen *et al.* [3] demonstrated that some DOC patients are able to perform complex mental imagery tasks, the extent to which specific high-order cognitive functions remain intact in these patients is still underspecified. One recent insight has come from an fMRI study, conducted by Monti *et al.* [19], who contrasted the haemodynamic response during a task in which patients were instructed to listen passively to a stream of speech, with a task in which they were instructed to count the number of times a target word was heard. An MCS patient produced activations in a frontoparietal network of regions that were comparable with those observed in healthy controls, suggesting that he retained some high-level cognitive functions, including target detection and working memory.

Adding to the evidence for preferential processing of 'own-name' stimuli, greater activation of the anterior cingulate cortex has been observed in a group of DOC patients when hearing their own name relative to unfamiliar names [20]. The degree to which this preferential response was evident was also shown to correlate with the patients' behavioural level of awareness at the time. Differential haemodynamic responses to speech and its meaning, relative to nonlinguistic stimuli, have also been observed in a number of fMRI studies of VS and MCS patients [21,22], indicating that some aspects of language comprehension are preserved in these patients. Recently, Coleman *et al.* [23**] reported that the extent to which the BOLD responses of DOC patients demonstrated a preserved ability to process speech-related stimuli – from simple processing of nonlinguistic sounds through to complex sentences containing ambiguous words – was highly correlated with the patients' behavioural recovery 6 months later. This finding is one of the clearest demonstrations yet of the utility of functional neuroimaging in the prognostic assessment of these patients.

One new area of research that is beginning to receive attention is the question of what 'it is like' to be in a VS or MCS. It has been reported that the opinions of medical professionals are divided as to whether patients in a VS can feel pain or not (56% responded in the affirmative [24]). The outcomes of those interviews also demonstrated a strong predictive value of religiosity in judgments about whether VS patients are able to feel pain (the more religiously inclined the professional, the more likely they were to believe that such patients can feel pain). Such findings reveal just how little is known empirically about what 'it is like' to be in this state.

Boly *et al.* [25] sought to provide some insight into this issue by investigating the extent to which MCS and VS patients respond to pain, a question with clear ethical and therapeutic implications. By investigating activations, measured with PET, to noxious electrical stimulation of the median nerve, they observed that the neural responses to pain in a group of MCS patients were equivalent to those seen in healthy controls. In contrast, as a whole, a group of VS patients did not show comparable patterns of activation. However, given the enormous heterogeneity in this patient group and the relatively low statistical power afforded by PET techniques, fMRI studies of pain processing in these patients are required before the true significance of this finding can be established. Recent efforts to characterize the ways in which other emotional stimuli, such as images of close family members [26], are processed by these patients have been largely inconclusive; in particular, they have not established how such stimuli are processed, over-and-above other (e.g., nonemotional) visual stimuli. This is, however, an interesting potential future direction and will surely increase our understanding of what 'it is like' to be in a VS or MCS.

Conclusion

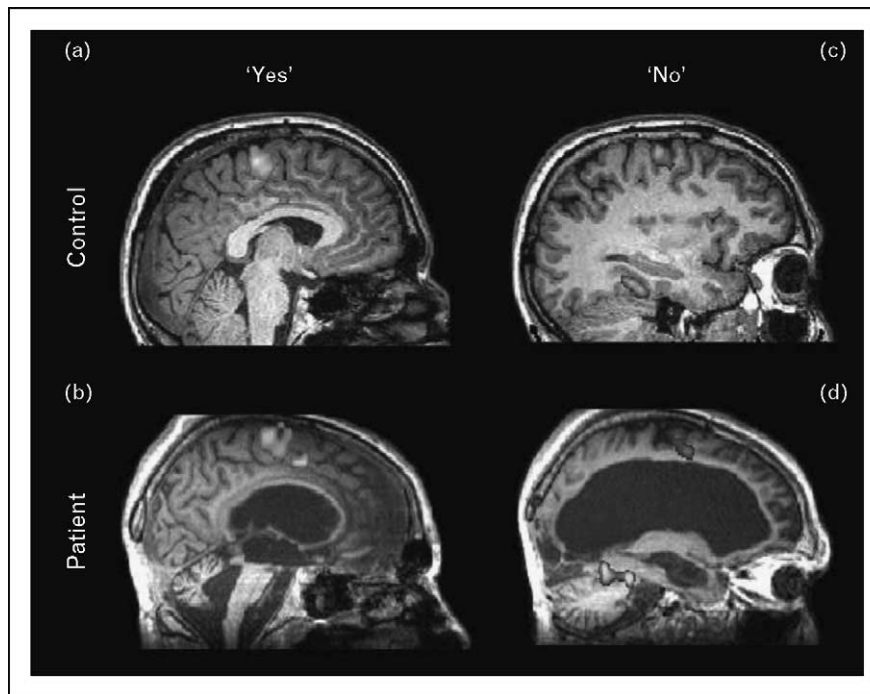
It is clear from this review that direct and indirect functional neuroimaging techniques have prognostic and

diagnostic value for patients with DOCs. Their development and use alongside behavioural measures is important, therefore, as they continue to contribute to a more accurate understanding of each patient individually, as well as the group as a whole.

The potential for functional neuroimaging techniques to benefit patients in a more direct way was recently demonstrated by Monti *et al.* [27**], who mapped the two mental imagery tasks employed previously by Owen *et al.* [3] – playing tennis and navigating around a house – onto the responses 'yes' and 'no'. Patients were instructed to perform one imagery task to respond 'yes' and the other to respond 'no'. Remarkably, a patient who had been repeatedly diagnosed as VS over a 5-year period was able to respond correctly to a series of autobiographical yes/no questions using this method. This is the first time that two-way communication has been demonstrated in such a patient and demonstrated, not only that he was aware, but that many of his higher cognitive functions were largely intact (Fig. 1).

This finding has opened a door into a world of possibilities for the development of ways with which to provide some communicative abilities to those (apparently) VS or MCS patients who may retain sufficient cognitive abilities to do so. It is clear, however, that an fMRI-based task is not going to be able to provide such a solution for the

Figure 1 Communicating with a patient who was assumed to be in a vegetative state for 5 years



Imaging results from two sample questions scans for the patient and a healthy volunteer. Panels (a) and (b) depict two question scans, indicating a 'yes' response. Panels (c) and (d) depict two question scans indicating a 'no' response. Reproduced with permission from [27**].

majority of patients due to the expense of MRI scanner and the frequency with which these patients will have access to it. There is already an extensive body of research that has shown that sophisticated EEG-based brain–computer interfaces (BCIs) can allow physically impaired individuals a degree of control over computerized and mechanical devices [28]. The relatively lower cost of the EEG method, and its indifference towards metal implants (such as pins and plates) that would preclude an individual from ever entering an MRI scanner, coupled with the existing EEG-BCI literature, clearly point to the future potential of the EEG method in this patient group.

Acknowledgements

This research was supported by generous funding from the Medical Research Council (U.1055.01.002.00001.01) and the James S. McDonnell Foundation. Both authors acknowledge no conflicts of interest.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 709).

- 1 Teasdale G, Jennett B. Assessment of coma and impaired consciousness: a practical scale. *Lancet* 1974; 2:81–84.
 - 2 Giacino JT, Kalmar K, Whyte J. The JFK Coma Recovery Scale-Revised: measurement characteristics and diagnostic utility. *Arch Phys Med Rehabil* 2004; 85:2020–2029.
 - 3 Owen AM, Coleman MR, Davis MH, *et al.* Detecting awareness in the vegetative state. *Science* 2006; 313:1402.
 - 4 Gusnard DA, Raichle ME. Searching for a baseline: functional imaging and the resting human brain. *Nat Rev Neurosci* 2001; 2:685–694.
 - 5 Peltier SJ, Keressens C, Hamann ST, *et al.* Functional connectivity changes with concentration of sevoflurane anesthesia. *Neuroreport* 2005; 16:285–288.
 - 6 Boly M, Phillips C, Tshibanda L, *et al.* Intrinsic brain activity in altered states of consciousness: how conscious is the default mode of brain function? *Ann NY Acad Sci* 2008; 1129:119–129.
 - 7 Cauda F, Micon BM, Sacco K, *et al.* Disrupted intrinsic functional connectivity in the vegetative state. *J Neurol Neurosurg Psychiatry* 2009; 80:429–431.
 - 8 Vanhaudenhuyse A, Noirhomme Q, Tshibanda L, *et al.* Default network connectivity reflects the level of consciousness in noncommunicative brain damaged patients. *Brain* 2010; 133:161–171.
- This study provides a strong link between connectivity and consciousness that speaks not only to our understanding of DOC patients, but also to our understanding of how consciousness is supported by the brain.
- 9 Boly M, Tshibanda L, Vanhaudenhuyse A, *et al.* Functional connectivity in the default network during resting state is preserved in a vegetative but not in a brain dead patient. *Hum Brain Mapping* 2009; 30:2393–2400.
 - 10 Fernández-Espejo D, Junque C, Bernabeu M, *et al.* Reductions of thalamic volume and regional shape changes in the vegetative and the minimally conscious states. *J Neurotrauma* 2010; 27:1187–1193.
- By employing a new analysis technique, the study shows results that offer insights not only into the role of the thalami as a whole in supporting awareness in patients with DOCs but also into the ways in which its subregions may contribute differentially.
- 11 Kulkarni VP, Lin K, Bendabis SR. EEG findings in the persistent vegetative state. *J Clin Neurophysiol* 2007; 24:433–437.
 - 12 Babiloni C, Sarà M, Vecchio F, *et al.* Cortical sources of resting-state alpha rhythms are abnormal in persistent vegetative state patients. *Clin Neurophysiol* 2009; 120:719–729.
 - 13 Schnakers C, Ledoux D, Majerus S, *et al.* Diagnostic and prognostic use of bispectral index in coma, vegetative state and related disorders. *Brain Inj* 2008; 22:926–931.
 - 14 Kotchoubey B, Kaiser J, Bostanov V, *et al.* Recognition of affective prosody in brain-damaged patients and healthy controls: a neurophysiological study using EEG and whole-head MEG. *Cogn Affect Behav Neurosci* 2009; 9:153–167.
 - 15 Qin P, Di H, Yan X, *et al.* Mismatch negativity to the patient's own name in chronic disorders of consciousness. *Neurosci Lett* 2008; 448:24–28.
 - 16 Schnakers C, Perrin F, Schabus M, *et al.* Voluntary brain processing in disorders of consciousness. *Neurology* 2008; 71:1614–1620.
 - 17 Bekinschtein TA, Shalom DE, Forcato C, *et al.* Classical conditioning in the vegetative and minimally conscious state. *Nat Neurosci* 2009; 12:1343–1349.
- This study demonstrated for the first time that patients with DOCs are able to learn associations and also highlighted the utility of nonhaemodynamic indirect measures of neural activity such as electromyography.
- 18 Daltrozzo J, Wioland N, Mutschler V, *et al.* Emotional electrodermal response in coma and other low-responsive patients. *Neurosci Lett* 2010; 475:44–47.
- Following demonstrations of the utility of indirect measures of neural activity, this study also highlights a new branch of research into the ways in which emotional stimuli are processed by DOC patients.
- 19 Monti MM, Coleman MR, Owen AM. Executive functions in the absence of behavior: functional imaging of the minimally conscious state. *Prog Brain Res* 2009; 177:249–260.
 - 20 Qin P, Di H, Liu Y, *et al.* Anterior cingulate activity and the self in disorders of consciousness. *Human Brain Mapping* 2010.
 - 21 Fernández-Espejo D, Junque C, Vendrell P, *et al.* Cerebral response to speech in vegetative and minimally conscious states after traumatic brain injury. *Brain Inj* 2008; 22:882–890.
 - 22 Coleman MR, Rodd JM, Davis MH, *et al.* Do vegetative patients retain aspects of language comprehension? Evidence from fMRI. *Brain* 2007; 130:2494–2507.
 - 23 Coleman MR, Davis MH, Rodd JM, *et al.* Towards the routine use of brain imaging to aid the clinical diagnosis of disorders of consciousness. *Brain* 2009; 132:2541–2552.
- This study, involving a large number of DOC patients, provides one of the most robust demonstrations for the prognostic utility of functional neuroimaging assessments yet reported.
- 24 Demertzi A, Schnakers C, Ledoux D, *et al.* Different beliefs about pain perception in the vegetative and minimally conscious states: a European survey of medical and paramedical professionals. *Prog Brain Res* 2009; 177:329–338.
 - 25 Boly M, Faymonville ME, Schnakers C, *et al.* Perception of pain in the minimally conscious state with PET activation: an observational study. *Lancet Neurol* 2008; 7:1013–1020.
 - 26 Zhu J, Wu X, Gao L, *et al.* Cortical activity after emotional visual stimulation in minimally conscious state patients. *J Neurotrauma* 2009; 26:677–688.
 - 27 Monti MM, Vanhaudenhuyse A, Coleman MR, *et al.* Willful modulation of brain activity in disorders of consciousness. *N Engl J Med* 2010; 362:579–589.
- The remarkable finding here of two-way communication with a behaviourally nonresponsive patient highlights how much more there is to learn about the vegetative and minimally conscious states and opens the possibility for more sophisticated communicative devices in the future.
- 28 Kubler A, Neumann N. Brain–computer interfaces: the key for the conscious brain locked into a paralysed body. *Prog Brain Res* 2005; 150:513–525.