

# Residual cognitive function in comatose, vegetative and minimally conscious states

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## Purpose of review

The clinical evaluation of cognition in non-communicative severely brain-damaged patients is inherently difficult. In addition to novel behavioural 'consciousness-scales', the role of para-clinical markers of consciousness, such as event related potentials and functional neuroimaging is reviewed.

## Recent findings

New behavioural scales for vegetative and minimally conscious patients have been shown to reduce diagnostic error but regrettably remain underused in clinical routine. Electrophysiological studies have confirmed their role in estimating outcome and possibly cognition. Several recent functional neuroimaging studies have shown residual cortical function in undeniably vegetative patients. This cortical activation, however, seems limited to primary 'low-level' areas and does not imply 'higher-order' integration, considered necessary for conscious perception. Minimally conscious patients show large-scale high-order cerebral activation, apparently dependent upon the emotional relevance of the stimulation.

## Summary

Careful clinical assessment of putative 'conscious behaviour' in vegetative and minimally conscious patients is the first requirement for their proper diagnosis and management. Complementary functional neuroimaging and electrophysiological studies will have a major impact on future clinical decision making and may guide selective therapeutic options. At present, more experimental evidence and the elucidation of methodological and ethical controversies are awaited prior to their routine clinical use.

## Keywords

brain injury, coma, functional imaging, minimally conscious state, vegetative state

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## Abbreviations

<b>EEG</b>	electroencephalogram
<b>ERP</b>	event related potential
<b>FDG</b>	fluorine-18-labelled deoxyglucose
<b>fMRI</b>	functional magnetic resonance imaging
<b>GCS</b>	Glasgow Coma Scale
<b>MCS</b>	minimally conscious state
<b>MMN</b>	mismatch negativity
<b>PET</b>	positron emission tomography
<b>SEP</b>	somatosensory evoked potentials

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## Introduction

Survivors of severe traumatic or hypoxic-ischemic brain damage classically go through different clinical entities before partially or fully recovering consciousness. Coma is defined as 'unrousable unresponsiveness'. After some days to weeks comatose patients will eventually open their eyes. When this return of 'wakefulness' is accompanied by reflexive motor activity only, devoid of any voluntary interaction with the environment, the condition is called a vegetative state. The vegetative state may be a transition to further recovery, or not (for a succinct review of ethical and legal problems in permanent vegetative state see Jennett [1]). Signs of voluntary motor activity should be actively searched for in vegetative state patients, as they herald the minimally conscious state (MCS) [2,3,4]. Functional communication indicates the next boundary – emergence from MCS – in the course of recovery (see Fig. 1) [5,6].

At present, consciousness cannot be measured objectively by any machine. Its estimation requires expert clinical interpretation of 'motor responsiveness'. The present paper will first summarize some new behavioural assessment tools, especially developed to untangle the vegetative state from MCS. Next, neurophysiological markers of consciousness and cognition, encompassing event related potentials (ERPs) and functional neuroimaging, will be reviewed, as will their putative diagnostic and prognostic value.

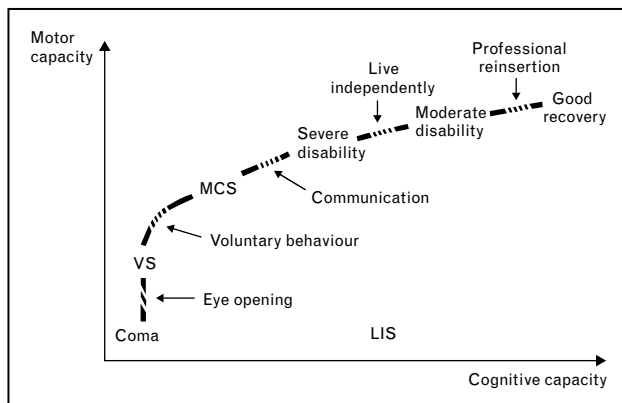
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**Figure 1. Different clinical entities encountered on the gradual recovery from coma, illustrated as a function of cognitive and motor capacity**



Restoration of spontaneous or elicited eye-opening, in the absence of voluntary motor activity, marks the transition from coma to vegetative state (VS) [1\*]. The passage from the VS to the minimally conscious state (MCS) is marked by reproducible evidence of 'voluntary behaviour' defined as (1) simple command following, (2) gestural or verbal yes/no responses (regardless of accuracy), (3) intelligible verbalization, or (4) motor activity occurring in contingent relation to relevant, often emotional, stimuli (also including pursuit eye movement or sustained fixation) [2\*]. Emergence from MCS is signalled by the return of functional communication or object use. The Glasgow Outcome Scale then terms patients as severely disabled until return of autonomy (coined moderate disability). Return to work or school determines the transition to 'good recovery'. Note that our clinical evaluation of cognition depends upon motor responsiveness. The locked-in syndrome (LIS) [5\*] is the extreme example of intact cognition with nearly complete motor deficit (only permitting eye-coded communication). It remains controversial from what stage neurological recovery is 'meaningful' and when a palliative care approach is warranted [6\*].

### Behavioural assessment tools

When examining brain-damaged patients with altered states of consciousness, it remains challenging to reliably document the presence or the absence of any motor behaviour that reflects conscious cognitive activity. Recent reviews have restated the shortcomings of the Glasgow Coma Scale (GCS), the currently most widely used assessment tool, for detecting subtle behavioural signs of consciousness once patients are in a vegetative state or MCS [2\*,7\*]. For these clinical entities, more sensitive and reliable tools are the Coma Recovery Scale [8], Wessex Head Injury Matrix [9] and the Western NeuroSensory Stimulation Profile [10]. Unfortunately, these are not yet extensively used. In the past two years, four new behavioural assessment tools have been developed (summarized in Table 1).

Giacino *et al.* [11\*\*] revised their Coma Recovery Scale. This 25-item scale specifically aims to differentiate the vegetative state and MCS by characterizing each of its items as being compatible with either state. Contrary to previous scales, it includes all items necessary to differentiate the vegetative state and MCS, based on their most

recent defining criteria, which is very helpful in avoiding misdiagnosis. The Coma Recovery Scale-Revised also contains items that explicitly mark the emergence from MCS.

Another interesting tool is the Sensory Modality Assessment and Rehabilitation Technique (SMART) developed by Gill-Thwaites and Munday [12\*\*]. It is intended to serve both as an assessment and as a treatment technique for patients in low awareness states. It includes eight subscales and also differentiates between vegetative state and MCS (for each item, the responses are rated following five levels, the last level being incompatible with the vegetative state and signalling MCS).

Third, the Disorders of Consciousness Scale (DOCS) [13\*,14] is somewhat similar to the SMART but its distinctive feature is that it directly relates the different items to specific brain structures. Although this initiative might appear promising, it should be interpreted cautiously as brain-behaviour relationships are complex and a given behaviour can be executed in different ways, hence recruiting different cerebral networks.

All scales have been shown to have good inter-rater reliability and sensitivity for monitoring recovery of residual conscious cognitive activity. They do not, however, provide a formal assessment of neuropsychological functioning and do not permit measuring the level of impairment of memory, attention, language or executive functions in patients that have begun to recover consciousness. In this respect, Neumann and Kotchouby [15\*\*] recently proposed a neuropsychological test-battery that has been adapted for use in conscious but low functioning patients, using simple dichotomous yes/no answers. This tool seems promising for use in MCS patients with severe physical disability. Although measuring many cognitive functions, however, it currently does not provide assessment for attention and working memories, although these are frequently impaired in these patients.

A final set of empirical studies and reviews has continued to explore the prognostic validity of behavioural assessment scales for predicting outcome or response to treatment [2\*,3\*,4\*\*,16\*\*,17]. Some of these studies show that the initial rate of change in scores (during the first 2 weeks of admission) is a good statistical predictor of outcome several months later, at least at the group level [13\*,16\*\*]. Other studies, however, have stressed the heterogeneity of individual outcome profiles, as well as the necessity to control for confounding variables such as excessive centrally-acting medication or patient posture (i.e., lying in bed versus upright position) which might hinder accurate measurement of subtle signs of awareness [18–21].

**Table 1. Comparison of defining and psychometric characteristics of the new assessment tools proposed during 2004–2005**

	CRS-R [11**]	SMART [12**]	DOCS [13*,14]	Neumann and Kotchoubey [15**]
Primary goal	Sensitive behavioural assessment of patients in low awareness states Reliably differentiate VS and MCS Differentiate MCS from emergence of MCS	Sensitive behavioural assessment of patients in low awareness states Reliably differentiate VS and MCS Treatment of patients in VS or MCS	Sensitive behavioural assessment of patients in low awareness states	Neuropsychological assessment in low-functioning, physically disabled but conscious patients
Structure	25 items divided in 6 subscales (visual, motor, auditory, oro-motor, communication, arousal) and ranging from reflex movements to cognitively mediated behaviour Precise operational definitions for all items and scoring procedures	8 formal assessment techniques (visual, auditory, tactile, olfactory, gustatory, motor, functional communication, wakefulness/arousal) 5-level rating scale for responses (no response, reflexive, withdrawal, localizing, discriminating)	34 items divided in 8 subscales (auditory, visual, tactile, olfactory, proprioceptive/ vestibular, taste/swallowing, testing readiness) 3-level rating scale for responses (no response, general response, localized response)	Standard neuropsychological tests adapted for dichotomous responses and measuring non-verbal intelligence, memory, executive functioning and language comprehension Event-related potential protocols for habituation, auditory differentiation, memory updating, emotional prosody, semantic analysis and movement intention paradigms
Baseline assessment	Yes	Informal interview collecting information from family and carers	Precise operational definitions for most items	NA
Inter-rater reliability	Excellent	Yes	Yes	Not reported
Test-retest reliability	Excellent (except for visual and oro-motor subscales)	Excellent	Better than predicted by chance Not reported	Not reported
Concurrent validity (relative to other assessment scales)	Good	Good	Not tested, but good construct validity, based on principal component analysis of residuals	NA
Prognostic validity	Not reported	Not reported	Probabilistic prediction of recovery of consciousness 1 year later	NA
Sensitivity	10 patients (13%) considered as being in VS diagnosed as being in MCS	17 patients (28%) considered as being in VS by referring physician diagnosed as MCS	Reported sensitivity to pharmacological treatment effects	Able to detect neuropsychological deficits in severely paralysed patients; however, the non-observation of characteristic ERP components might be difficult to interpret

CRS-R, Coma Recovery Scale-Revised; SMART, Sensory Modality Assessment and Rehabilitation Technique; DOCS, Disorders of Consciousness Scale; VS, vegetative state; MCS, minimally conscious state; NA, not applicable.

In the acute setting of post-cardiac arrest coma, Booth *et al.* [22<sup>•</sup>] reviewed 11 relevant studies involving 1914 patients and concluded that early simple physical examination (that is, absent withdrawal response to pain, absent corneal or pupil reflexes at 24 h or absent motor response at 72 h after admission) permits the strong prediction of death or poor outcome. No clinical findings strongly predicted good outcome. In contrast to previous meta-analyses [23], the authors defined poor outcome as death, vegetative state or severe neurological disability (the latter included conscious patients with functional communication but remaining dependent on others). There is no uniform definition of what constitutes a good versus a poor outcome but it must be emphasized that some patients and families may have very different perceptions of what comprises an acceptable and 'meaningful' neurological outcome. The authors' results should not be directly extended to the decision to withdraw from medical care.

### Event-related potentials

ERPs have been used for a long time to evaluate both sensory and cognitive functions of patients with severe disorders of consciousness [24<sup>•</sup>]. A lot of ERP meta-analyses have confirmed that the absence of cortical somatosensory evoked potentials (SEPs) are good predictors of unfavourable outcome (for a review of 2891 patients see Robinson and Mickleson [25]), the outcome being worse (vegetative state or death) for patients with hypoxia–ischemia than for a traumatic cause. SEPs may also provide moderately useful prognostic data for predicting good outcomes. For example, traumatic brain-injured patients with normal SEPs (at least in one hemisphere) showed a high chance of regaining consciousness (93%) [26<sup>•</sup>]. Similar results were reported for comatose children [27,28<sup>•</sup>]. Recent systematic reviews [26<sup>•</sup>,28<sup>•</sup>,29<sup>•</sup>,30] have again highlighted the superior predictive value of SEPs compared with other tests. For example, a meta-analysis of 25 studies [29<sup>•</sup>] confirmed that SEPs are superior, with few exceptions, to pupillary responses, motor responses, GCS, electroencephalogram (EEG) and computed tomography for the prediction of outcome after acute severe brain damage (for a prospective study on comatose children see Carter and Butt [28<sup>•</sup>]).

A very promising candidate for predicting (good) outcome is the mismatch negativity (MMN), a component which appears in auditory oddball paradigms. In a prospective cohort study of 346 comatose patients, Fischer and colleagues [31<sup>••</sup>,32] confirmed the high specificity of the MMN (91% of patients not regaining consciousness had no MMN) but also its low sensitivity (that is, only 33% of patients regaining consciousness had a MMN). The interesting finding is that a very high proportion of patients (89%) evoking this component later regained consciousness.

To estimate the integrity of language comprehension in brain damaged non-communicative patients, long-latency ERPs to words were used. Schoenle and Witzke [33<sup>•</sup>] recorded ERPs in response to sentences ending with semantically congruent and incongruent words. In normal volunteers, an N400 component can be identified for incongruous words. Interestingly, an N400 response to incongruous words was reported in some vegetative state patients (12%), in a majority (77%) of 'near-vegetative state' patients (the authors used this term for patients with signs of habituation, orienting reactions, or visual fixation or pursuit), and in nearly all (90%) of the patients who are not in a vegetative state (showing 'some meaningful behaviour'). A differential cognitive ERP (P300 wave) was observed to the patient's first name in the MCS [34<sup>•</sup>]. Unpublished data from Perrin *et al.*, however, show that P300 responses to patients' own names can also be observed in a well-documented chronic vegetative state, showing no subsequent recovery. Long-latency ERPs (P300 and N400 responses) was also observed by the group of Kotchoubey [35<sup>•</sup>,36<sup>•</sup>] in some vegetative state patients with EEG-background activity above 4 Hz (the functional significance of this finding in terms of patients' possible awareness will be discussed in the next section). These studies suggest that P300 or N400 responses do not necessarily reflect conscious perception and cannot be used to differentiate vegetative state from MCS patients.

### Functional neuroimaging

Fluorine-18-labelled deoxyglucose (FDG) positron emission tomography (PET) has shown global cortical metabolism to be 50–70% of normal values in hypoxic or traumatic coma [37<sup>••</sup>]. In traumatic cases, whole brain metabolism correlates poorly with the level of consciousness, as measured by the GCS [38,39<sup>•</sup>]. Bergschneider and colleagues recently showed a lower regional metabolism in thalamus, brainstem and cerebellar cortex of comatose compared to non-comatose survivors studied within 5 days of their brain injury [40]. Previous studies failed to show a correlation between cerebral metabolism and outcome but a preliminary report on 14 patients showed that a higher grey to white matter metabolic ratio measured within 2 weeks after moderate traumatic brain injury predicted a good recovery at 1-year follow-up [39<sup>•</sup>].

In the vegetative state cerebral metabolism is known to be even lower than in coma (40–50% of normal values). The most impaired is the frontoparietal network of polymodal associative cortices [37<sup>••</sup>,41]. This network encompasses lateral posterior parietal, prefrontal and parieto-temporal regions and midline precuneal, posterior cingulate and mesiofrontal areas [42] and is known to be the most active 'by default' in resting non-stimulated conditions in conscious controls [43]. A combined voxel-based three dimensional magnetic resonance imaging

and FDG-PET study [44<sup>\*</sup>] in five chronic non-traumatic vegetative state patients showed that the regional distribution of the cortical metabolic dysfunction is unrelated to the regional distribution of the structural damage (i.e. grey matter atrophy). These results are in line with the ERP (see above), H<sub>2</sub><sup>15</sup>O-PET and fMRI evidence demonstrating that vegetative state patients are not 'appalic' (i.e. have some preserved neocortical function).

In addition to FDG-PET [37<sup>\*\*</sup>] or single photon emission computed tomography [45] studies on 'resting' brain function which are useful to identify brain regions that are potentially recruitable, fMRI or H<sub>2</sub><sup>15</sup>O-PET 'activation studies' offer the possibility to link residual neural activation to controlled external stimulation in the absence of any overt motor response of the patient. Owen *et al.* [46<sup>\*</sup>,47<sup>\*</sup>] have proposed an elegant hierarchical approach to the study of residual cognitive function in severely brain damaged patients. Their strategy focuses on the auditory modality (the easiest to assess in non-collaborative patients) and aims to disentangle acoustic, perceptual, phonological and semantic levels of processing (Table 2). Using this approach, a patient in a vegetative state 9 months following a basilar artery thrombosis (a notably uncommon cause of vegetative state) was reported to show partially intact responses to semantically ambiguous stimuli, 'thought to tap higher aspects of speech comprehension' [47<sup>\*</sup>]. These results do not necessarily imply, however, that the patient was aware. As pointed out by the authors, some aspects of semantic processing may occur without conscious awareness. Imaging studies in healthy controls have shown that the semantic content of masked (unconscious) information can be primed to affect subsequent behaviour without explicit knowledge of the participant [48]. In the same line, in a debatable study, noxious stimulation in vegetative state patients was reported to activate not only primary somatosensory cortex (as previously reported in well-documented vegetative state patients [49]) but also bilateral insular cortex. The insula is thought to be important for pain perception and is found to be reliably activated in pain neuroimaging studies [50]. A recent

PET study [51], however, showed activation of insular cortex during general anaesthesia in volunteers, reflecting cerebral autonomic responses (not conscious perception of pain) evoked by the stimulation.

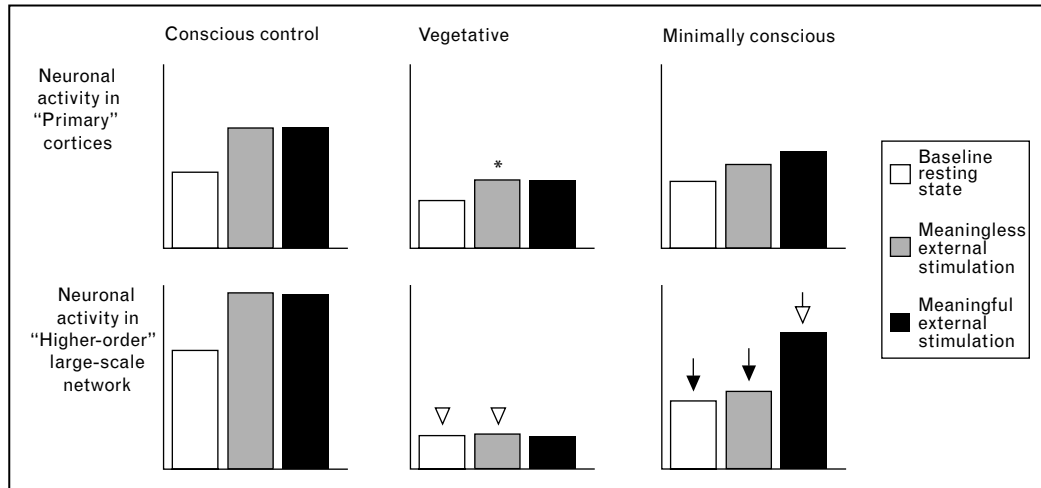
Preliminary data on the MCS show that overall cerebral metabolism is decreased to values slightly higher but comparable to those observed in vegetative state [34<sup>\*</sup>,52<sup>\*</sup>]. Several functional 'activation' studies using auditory stimuli have demonstrated large-scale 'higher-order' cortical activation in MCS, normally not observed in vegetative state patients [34<sup>\*</sup>,53<sup>\*\*</sup>,54<sup>\*</sup>,55<sup>\*\*</sup>]. In two well-documented MCS patients, Schiff *et al.* [53<sup>\*\*</sup>] showed selective activation in components of the cortical language networks during presentation of narratives read in a familiar voice and containing personally meaningful content (compared to baseline). Presentation of the narratives played backward activated the same networks as forward narratives in the healthy controls, but not the MCS patients. In the same line, Laureys *et al.* [34<sup>\*</sup>] reported a MCS patient in whom auditory stimuli with emotional valence (infant cries and the patient's own name) induced a much more widespread activation than did meaningless signal-correlated noise. Bekinschtein *et al.* [54<sup>\*</sup>] showed amygdala activation induced by stimuli with emotional valence (the voice of the patient's mother compared with an unfamiliar voice) in a MCS patient 5 months after trauma.

Boly *et al.* [55<sup>\*\*</sup>] studied 30 brain-damaged patients and reported activation spreading to 'higher-order' cortices in MCS while remaining limited to 'primary' auditory areas in vegetative state patients who were presented simple auditory clicks. Similarly, a fMRI follow-up case study by Bekinschtein *et al.* [56<sup>\*</sup>] used a word presentation paradigm and observed more widespread activation when a posttraumatic vegetative state patient evolved to a MCS. Vegetative state and MCS patients seem not only to show differences in functional segregation but also, and more importantly, in functional integration. Indeed, cortico-cortical functional connectivity between auditory cortex and a large network of temporal and prefrontal

**Table 2. Hierarchical strategy to evaluate cognition in non-communicative severely brain-damaged patients**

Level of processing	Question posed	Contrast used	Regions involved
Acoustic	Basic response to any sound?	Noise bursts, silence	Auditory superior and middle temporal gyri
Perceptual	Discrimination between different categories of sound (i.e. recognise speech as more than a sound?)	Speech sounds, signal correlated noise	Superior temporal gyri, extending ventrolaterally into superior temporal sulcus
Phonological	Recognise words in absence of overall meaning (i.e. content of words)?	3 increasing levels of intelligibility (depending on signal-to-noise ratios)	Left anterior and superior temporal lobe
Semantic	Understand meaning of sentence?	Ambiguous sentences (containing words with more than one meaning), unambiguous sentences	Left posterior inferior temporal cortex and bilateral inferior frontal gyri

Strategy proposed by Owen *et al.* [46<sup>\*</sup>] for neuroimaging, but also applicable to event related potentials studies [15<sup>\*\*</sup>,33<sup>\*</sup>].

**Figure 2. Oversimplified scheme summarizing functional neuroimaging data in the vegetative state and minimally conscious state**

Neuronal activity in 'low-level' compared to large-scale 'higher-level' cortices distinguishes 'vegetative' from 'minimally conscious' processing. Note that compared with controls, baseline resting metabolism (white bars) is massively reduced in vegetative state (VS) [42] but also minimally conscious state (MCS) [34\*,52\*] patients and is lowest in 'higher-level' cortices (reflecting a deficient 'default resting state'; i.e. vitiated inner speech and mental imagery). In the VS, external stimulation still activates 'low-level' (\*) cortices but these are isolated and disconnected from 'higher-level' processing (open triangles) [49,55\*\*,56\*,63,64] (for exceptions see Owen *et al.* [47\*]). In MCS patients, meaningful stimuli (often with emotional valence; grey bars) result in widespread cortical activation (open arrow) while meaningless stimuli (black bars) frequently fail to do so (filled arrows) [34\*,53\*\*,54\*].

cortices was more efficient in 15 MCS patients than in 15 vegetative state patients [55\*\*]. Finally, Coleman *et al.* [57\*], using simultaneous FDG-PET and EEG recording, reported preserved neurometabolic coupling between neuronal electrical function and cerebral metabolism in four MCS patients but not in the six studied vegetative state patients [57\*]. Such findings encourage ongoing developments of neuromodulatory therapeutic interventions [16\*\*] and deep-brain stimulation strategies in MCS patients [52\*,58].

## Conclusion

The bedside evaluation of consciousness in non-communicative brain-damaged patients is inherently difficult. New standardized behavioural scales are offering better means to disentangle vegetative from minimally conscious patients but our clinical assessment of cognitive capacity directly depends upon the residual motor capacity. Complementary examinations such as electrophysiological [59\*,60\*] and functional neuroimaging [37\*\*,61\*] studies can objectively measure brain function at rest and during increasingly complex levels of external stimulation. These studies are permitting modelling of the residual neural processing pathognomonic of vegetative and minimally conscious states [52\*]. It is hoped that this information will not only refine our diagnosis [62] but also yield predictive value and form the basis of future therapeutic strategies [52\*,58]. Fig. 2 [63,64] schematically summarizes the reviewed functional imaging data.

It can, however, be argued that all the discussed ERP and neuroimaging 'activation' paradigms merely identify

neural activation reflecting passive 'automatic' processing (that is occurring without the need for wilful intervention on the part of the subject) rather than demonstrating preserved awareness. In this respect, Owen *et al.* [46\*] have proposed that future studies explicitly instruct subjects to remember or imagine well-defined sensory-motor or cognitive mental actions. This strategy, if identifying robust and anatomically specific changes at the single-subject level, could better reflect volitional or 'consciously willed' neural activation and hence be clear evidence for awareness of the self and environment in this clinically challenging patient population. Negative findings, of course, could again not be interpreted as evidence for lack of awareness.

## 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 (pp. 767–768).

- 1 Jennett B. 30 years of the vegetative state: clinical, ethical and legal problems. In: Laureys S, editor. *Progress in brain research. Volume 150. The boundaries of consciousness: neurobiology and neuropathology.* Amsterdam: Elsevier; 2005. pp. 541–548.

This state-of-the-art review was written by an unrivalled expert in the field who, 30 years ago, collaborated in coining the term 'vegetative state'.

- 2 Giacino J. The minimally conscious state: defining the borders of consciousness. In: Laureys S, editor. *Progress in brain research. Volume 150. The boundaries of consciousness: neurobiology and neuropathology.* Amsterdam: Elsevier; 2005. pp. 385–400.

This paper is an exhaustive review of defining criteria, epidemiology, neuropathology and assessment issues for the MCS.

- 3 Giacino JT. The vegetative and minimally conscious states: consensus-based criteria for establishing diagnosis and prognosis. *NeuroRehabilitation* 2004; 19:293–298.

This paper elegantly summarizes practice recommendations proposed by the Multi Society Task Force on the vegetative state and the Aspen workgroup on the MCS.

- 4** Giacino J, Whyte J. The vegetative and minimally conscious states: current knowledge and remaining questions. *J Head Trauma Rehabil* 2005; 20: 30–50.

This is an excellent review of defining criteria, neuropathology, prognosis, assessment and treatment issues for vegetative state and MCS.

- 5** Laureys S, Pellas F, van Eeckhout P, *et al.* The locked-in syndrome: what is it like to be conscious but paralyzed and voiceless? In: Laurey S, editor. *Progress in brain research*. Volume 150. The boundaries of consciousness: neurobiology and neuropathology. Amsterdam: Elsevier; 2005. pp. 495–511.

This is a timely review on the quality of life in the locked-in syndrome based on data collected by the French association ALIS.

- 6** Fins JJ. Clinical pragmatism and the care of brain damaged patients: Towards a palliative neuroethics for disorders of consciousness. In: Laurey S, editor. *Progress in brain research*. Volume 150. The boundaries of consciousness: neurobiology and neuropathology. Amsterdam: Elsevier; 2005. pp. 569–586.

This review proposes an ethical framework for consciousness research in non-communicative brain-damaged patients and discusses the regulatory complexity when studying patients who are unable to provide consent.

- 7** Majerus S, Gill-Thwaites H, Andrews K, *et al.* Behavioral evaluation of consciousness in severe brain damage. In: Laurey S, editor. *Progress in brain research*. Volume 150. The boundaries of consciousness: neurobiology and neuropathology. Amsterdam: Elsevier; 2005. pp. 401–418.

This review provides a comprehensive discussion of behavioural assessment techniques and clinical issues for bedside assessment of patients in coma, vegetative state and MCS.

- 8** Giacino JT, Kezmarzky MA, DeLuca J, *et al.* Monitoring rate of recovery to predict outcome in minimally responsive patients. *Arch Phys Med Rehabil* 1991; 72:897–901.

- 9** Shiel A, Horn SA, Wilson BA, *et al.* The Wessex Head Injury Matrix (WHIM) main scale: a preliminary report on a scale to assess and monitor patient recovery after severe head injury. *Clin Rehabil* 2000; 14:408–416.

- 10** Ansell BJ, Keenan JE. The Western Neuro Sensory Stimulation Profile: a tool for assessing slow-to-recover head-injured patients. *Arch Phys Med Rehabil* 1989; 70:104–108.

- 11** 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.

This paper presents validation data for the new JFK Coma Recovery Scale. This scale might prove to be highly valuable in making reliable diagnoses for patients in a vegetative state.

- 12** Gill-Thwaites H, Munday R. The sensory modality assessment and rehabilitation technique (SMART): a valid and reliable assessment for vegetative state and minimally conscious state patients. *Brain Inj* 2004; 18:1255–1269.

This paper presents a new behavioural assessment technique that covers more sensory input modalities than most previous scales. This tool might also be very useful in helping to establish reliable diagnoses in patients in altered states of consciousness.

- 13** Pape TL, Senno RG, Guernon A, *et al.* A measure of neurobehavioral functioning after coma. Part II: Clinical and scientific implementation. *J Rehabil Res Dev* 2005; 42:19–28.

This extensive two-part paper reports on a new behavioural assessment scale for patients in altered states of consciousness.

- 14** Pape TL, Heinemann AW, Kelly JP, *et al.* A measure of neurobehavioral functioning after coma. Part I: Theory, reliability, and validity of disorders of consciousness scale. *J Rehabil Res Dev* 2005; 42:1–18.

- 15** Neumann N, Kotchoubey B. Assessment of cognitive functions in severely paralyzed and severely brain-damaged patients: neuropsychological and electrophysiological methods. *Brain Res Brain Res Protoc* 2004; 14: 25–36.

This paper presents a very interesting neuropsychological test battery for evaluating higher cognitive functions in severely motor-disabled patients.

- 16** Whyte J, Katz D, Long D, *et al.* Predictors of outcome in prolonged post-traumatic disorders of consciousness and assessment of medication effects: A multicenter study. *Arch Phys Med Rehabil* 2005; 86:453–462.

This longitudinal observational cohort study from seven acute rehabilitation facilities in the US and Germany showed a positive effect of amantadine and a negative effect of dantrolene on traumatic brain injury outcome. Neuro-rehabilitation needs such well-designed studies in order to propose long awaited evidence-based therapeutic guidelines.

- 17** Giacino JT, Trott CT. Rehabilitative management of patients with disorders of consciousness: grand rounds. *J Head Trauma Rehabil* 2004; 19:254–265.

- 18** Lammi MH, Smith VH, Tate RL, *et al.* The minimally conscious state and recovery potential: a follow-up study 2 to 5 years after traumatic brain injury. *Arch Phys Med Rehabil* 2005; 86:746–754.

- 19** McMillan TM, Herbert CM. Further recovery in a potential treatment withdrawal case 10 years after brain injury. *Brain Inj* 2004; 18:935–940.

- 20** Strens LH, Mazibrada G, Duncan JS, *et al.* Misdiagnosing the vegetative state after severe brain injury: the influence of medication. *Brain Inj* 2004; 18:213–218.

- 21** Elliott L, Coleman M, Shiel A, *et al.* Effect of posture on levels of arousal and awareness in vegetative and minimally conscious state patients: a preliminary investigation. *J Neurol Neurosurg Psychiatry* 2005; 76:298–299.

- 22** Booth CM, Boone RH, Tomlinson G, *et al.* Is this patient dead, vegetative, or severely neurologically impaired? Assessing outcome for comatose survivors of cardiac arrest. *JAMA* 2004; 291:870–879.

This systematic review and meta-analysis encompassed 1914 patients from 11 studies on the prognosis of post-cardiac arrest coma.

- 23** Zandbergen EG, de Haan RJ, Stoutenbeek CP, *et al.* Systematic review of early prediction of poor outcome in anoxic-ischaemic coma. *Lancet* 1998; 352:1808–1812.

- 24** Giaquinto S. Evoked potentials in rehabilitation. A review. *Funct Neurol* 2004; 19:219–225.

This comprehensive review discusses the role of ERP as prognostic, longitudinal monitoring and cortical remodelling tools in clinical and research rehabilitation settings.

- 25** Robinson LR, Micklesen PJ. Somatosensory evoked potentials in coma prognosis. *Phys Med Rehabil Clin N Am* 2004; 15:43–61.

- 26** Amantini A, Grippo A, Fossi S, *et al.* Prediction of 'awakening' and outcome in prolonged acute coma from severe traumatic brain injury: evidence for validity of short latency SEPs. *Clin Neurophysiol* 2005; 116:229–235.

This study, encompassing 60 patients with coma of 7 days or longer, confirmed the high predictive value of SEPs and stresses that in TBI, differently from post-anoxic coma, the presence of normal N20 responses has a favourable prognostic value.

- 27** Schalamon J, Singer G, Kurschel S, *et al.* Somatosensory evoked potentials in children with severe head trauma. *Eur J Pediatr* 2005; 164:417–420.

- 28** Carter BG, Butt W. A prospective study of outcome predictors after severe brain injury in children. *Intensive Care Med* 2005; 31:840–845.

This prospective clinical study in a paediatric intensive care unit confirmed the predictive role of SEPs in 102 severely brain-injured children.

- 29** Carter BG, Butt W. Are somatosensory evoked potentials the best predictor of outcome after severe brain injury? A systematic review. *Intensive Care Med* 2005; 31:765–775.

This meta-analysis of 25 articles shows the superior predictive power of SEPs compared with clinical examination (pupillary and motor responses and GCS), EEG and computed tomography.

- 30** Zingler VC, Pohlmann-Eden B. Diagnostic pitfalls in patients with hypoxic brain damage: three case reports. *Resuscitation* 2005; 65:107–110.

- 31** Fischer C, Luaute J, Adeleine P, *et al.* Predictive value of sensory and cognitive evoked potentials for awakening from coma. *Neurology* 2004; 63:669–673.

This milestone article corroborates the high specificity of MMN in a prospective cohort study of 346 comatose patients.

- 32** Luaute J, Fischer C, Adeleine P, *et al.* Late auditory and event-related potentials can be useful to predict good functional outcome after coma. *Arch Phys Med Rehabil* 2005; 86:917–923.

- 33** Schoenle PW, Witzke W. How vegetative is the vegetative state? Preserved semantic processing in vegetative state patients: evidence from N400 event-related potentials. *NeuroRehabilitation* 2004; 19:329–334.

This was the first study to suggest that N400 responses can be evoked in patients with severe disorders of consciousness, notably some vegetative state patients.

- 34** Laureys S, Perrin F, Faymonville ME, *et al.* Cerebral processing in the minimally conscious state. *Neurology* 2004; 63:916–918.

This PET activation study illustrated that stimuli with emotional valence induce more widespread cerebral activation in MCS than does neutral stimulation.

- 35** Kotchoubey B, Lang S, Mezger G, *et al.* Information processing in severe disorders of consciousness: Vegetative state and minimally conscious state. *Clin Neurophysiol* 2005; 116:2441–2453.

This is a thought-provoking paper on the presence of electrophysiological indicators of remaining cortical functions in vegetative state and MCS patients.

- 36** Hinterberger T, Wilhelm B, Mellinger J, *et al.* A device for the detection of cognitive brain functions in completely paralyzed or unresponsive patients. *IEEE Trans Biomed Eng* 2005; 52:211–220.

This paper presents original data and reviews the possibilities of brain-computer interfaces in unresponsive patients with remaining cognitive abilities.

- 37** Laureys S, Owen AM, Schiff ND. Brain function in coma, vegetative state, and related disorders. *Lancet Neurol* 2004; 3:537–546.  
 This review summarizes the functional neuroanatomy of brain death, coma, vegetative state, MCS, and the locked-in syndrome.
- 38** Bergsneider M, Hovda DA, Lee SM, *et al.* Dissociation of cerebral glucose metabolism and level of consciousness during the period of metabolic depression following human traumatic brain injury. *J Neurotrauma* 2000; 17:389–401.
- 39** Wu HM, Huang SC, Hattori N, *et al.* Selective metabolic reduction in gray matter acutely following human traumatic brain injury. *J Neurotrauma* 2004; 21:149–161.  
 This PET study on 14 TBI patients shows a higher grey to white matter metabolism ratio in cases with good recovery 1 year after trauma.
- 40** Hattori N, Huang SC, Wu HM, *et al.* Correlation of regional metabolic rates of glucose with Glasgow Coma Scale after traumatic brain injury. *J Nucl Med* 2003; 44:1709–1716.
- 41** Laureys S. Functional neuroimaging in the vegetative state. *NeuroRehabilitation* 2004; 19:335–341.
- 42** Laureys S, Goldman S, Phillips C, *et al.* Impaired effective cortical connectivity in vegetative state: preliminary investigation using PET. *Neuroimage* 1999; 9:377–382.
- 43** Greicius MD, Menon V. Default-mode activity during a passive sensory task: uncoupled from deactivation but impacting activation. *J Cogn Neurosci* 2004; 16:1484–1492.
- 44** Juengling FD, Kassubek J, Huppertz HJ, *et al.* Separating functional and structural damage in persistent vegetative state using combined voxel-based analysis of 3-D MRI and FDG-PET. *J Neurol Sci* 2005; 228:179–184.  
 This was the first study employing a voxel-based approach to the analysis of structural lesions in the vegetative state.
- 45** Beuthien-Baumann B, Holthoff VA, Rudolf J. Functional imaging of vegetative state applying single photon emission tomography and positron emission tomography. *Neuropsychol Rehabil* 2005; 15:276–282.
- 46** Owen AM, Coleman MR, Menon DK, *et al.* Using a hierarchical approach to investigate residual auditory cognition in persistent vegetative state. In: Laureys S, editor. *Progress in brain research. Volume 150. The boundaries of consciousness: neurobiology and neuropathology.* Amsterdam: Elsevier; 2005. pp. 457–471.  
 This review proposes an elegant systematic methodology for functional neuroimaging paradigms in the vegetative state and presents some preliminary results.
- 47** Owen AM, Coleman MR, Menon DK, *et al.* Residual auditory function in persistent vegetative state: a combined pet and fmri study. *Neuropsychol Rehabil* 2005; 15:290–306.  
 This well-detailed case report illustrates the hierarchical approach as proposed by the Cambridge Coma Group to investigate residual auditory cognition in vegetative state.
- 48** Dehaene S, Naccache L, Le Clec HG, *et al.* Imaging unconscious semantic priming. *Nature* 1998; 395:597–600.
- 49** Laureys S, Faymonville ME, Peigneux P, *et al.* Cortical processing of noxious somatosensory stimuli in the persistent vegetative state. *Neuroimage* 2002; 17:732–741.
- 50** Treede RD, Kenshalo DR, Gracely RH, *et al.* The cortical representation of pain. *Pain* 1999; 79:105–111.
- 51** Hofbauer RK, Fiset P, Plourde G, *et al.* Dose-dependent effects of propofol on the central processing of thermal pain. *Anesthesiology* 2004; 100:386–394.
- 52** Schiff N. Modelling the minimally conscious state: measurements of brain function and therapeutic possibilities. In: Laureys S, editor. *Progress in brain research. Volume 150. The boundaries of consciousness: neurobiology and neuropathology.* Amsterdam: Elsevier; 2005. pp. 473–493.  
 This is an authoritative well-written review proposing models of brain function in MCS and the vegetative state.
- 53** Schiff ND, Rodriguez-Moreno D, Kamal A, *et al.* fMRI reveals large-scale network activation in minimally conscious patients. *Neurology* 2005; 64:514–523.  
 This describes a milestone study on language processing in MCS patients using fMRI illustrating that these patients retain widely distributed cortical systems with potential for cognitive and sensory function.
- 54** Bekinschtein T, Niklison J, Sigman L, *et al.* Emotion processing in the minimally conscious state. *J Neurol Neurosurg Psychiatry* 2004; 75:788.  
 This was a groundbreaking PET activation study on emotional processing in MCS.
- 55** Boly M, Faymonville ME, Peigneux P, *et al.* Auditory processing in severely brain injured patients: differences between the minimally conscious state and the persistent vegetative state. *Arch Neurol* 2004; 61:233–238.  
 This PET activation study was the first to compare residual auditory processing in the vegetative state as compared with MCS patients.
- 56** Bekinschtein T, Tiberti C, Niklison J, *et al.* Assessing level of consciousness and cognitive changes from vegetative state to full recovery. *Neuropsychol Rehabil* 2005; 15:307–322.  
 This well-documented fMRI and behavioural investigation studied a patient while in the vegetative state and after recovery of consciousness.
- 57** Coleman MR, Menon DK, Fryer TD, *et al.* Neurometabolic coupling in the vegetative and minimally conscious states: preliminary findings. *J Neurol Neurosurg Psychiatry* 2005; 76:432–434.  
 This combined PET-EEG study was the first to illustrate the importance of the homeostatic coupling between neuronal electrical and metabolic function, differentiating the vegetative state from MCS.
- 58** Schiff ND, Plum F, Rezaei AR. Developing prosthetics to treat cognitive disabilities resulting from acquired brain injuries. *Neurol Res* 2002; 24:116–124.
- 59** Kotchoubey B. Event-related potential measures of consciousness: two equations with three unknown. In: Laureys S, editor. *Progress in brain research. Volume 150. The boundaries of consciousness: neurobiology and neuropathology.* Amsterdam: Elsevier; 2005. pp. 427–444.  
 This stimulating review discusses what ERP can and cannot tell about cognition and consciousness.
- 60** Kobylarz EJ, Schiff N. Neuropsychological correlates of persistent vegetative and minimally conscious states. *Neuropsychol Rehabil* 2005; 15:323–332.  
 This is a recommended review discussing EEG power spectra and coherence analyses in vegetative state and MCS.
- 61** Kobylarz EJ, Schiff ND. Functional imaging of severely brain-injured patients: progress, challenges, and limitations. *Arch Neurol* 2004; 61:1357–1360.  
 This is a nice overview of the challenges encountered in functional neuroimaging studies of severe brain damage.
- 62** Fins JJ, Plum F. Neurological diagnosis is more than a state of mind: diagnostic clarity and impaired consciousness. *Arch Neurol* 2004; 61:1354–1355.
- 63** Schiff ND, Ribary U, Moreno DR, *et al.* Residual cerebral activity and behavioural fragments can remain in the persistently vegetative brain. *Brain* 2002; 125:1210–1234.
- 64** Laureys S, Faymonville ME, Degueldre C, *et al.* Auditory processing in the vegetative state. *Brain* 2000; 123:1589–1601.