Consciousness research: Relevance to neurocritical care

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Why study consciousness

• An integral part of clinical assessment

• Unanswered/incompletely answered questions

• Broader scientific relevance

• Societal value
LoC: canonical clinical variable

• Reduced conscious level a key feature of neurological illness
• Conscious level also a key prognostic factor (TBI, SAH)
• Also a prognostic feature in non-neurological critical illness
  – Probably a marker of disease severity
  – Also because coma results in important systemic consequences
    (airway protection, immobility, nutrition...plus others)
• Detailed and accurate descriptors are critical for
  – Defining management decisions
  – Prognostication
  – Assessment of interventions
  – Treatment stratification
• Characterisation now requires more than clinical evaluation
ASSESSMENT OF COMA AND IMPAIRED CONSCIOUSNESS

A Practical Scale

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Summary A clinical scale has been evolved for assessing the depth and duration of impaired consciousness and coma. Three aspects of behaviour are independently measured—motor responsiveness, verbal performance, and eye opening.

Eye Opening

Spontaneous eye opening, with sleep/wake rhythms, is most highly scored on this part of the scale and it indicates that the arousal mechanisms in the brainstem are active. But arousal does not imply awareness, and we believe it is unwise to try to decide whether a patient is attentive on the basis of eye movements. Patients in the persistent vegetative state, who are subsequently shown to be structurally decorticate, have often been

consciousness are described and recorded. Systems for describing patients with impaired consciousness are not consistent. Indeed, many clinicians retreat from any formal scheme in favour of a general description of the patient's state, without clear guidelines as to what to describe and how to describe it.

In practice, such unstructured observations commonly result in ambiguities and misunderstandings when information about patients is exchanged and when groups of patients treated by alternative methods are compared, or reported from different centres. There is no general agreement about what terms to use, nor are those in common use interpreted similarly by different workers. Almost every report of patients in coma offers yet another classification. Most divide the spectrum of altered conscious-

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Chart for recording assessment of consciousness.
### JFK Coma Recovery Scale—Revised

**Kathleen Kalmar and Joseph T. Giacino**

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**NEUROPSYCHOLOGICAL REHABILITATION**


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**JFK COMA RECOVERY SCALE - REVISED**

**Record Form**

<table>
<thead>
<tr>
<th>Patient:</th>
<th>Date:</th>
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**AUDITORY FUNCTION SCALE**

- **4.** Consistent Movement to Command *
- **3.** Reproducible Movement to Command *
- **2.** Localization to Sound
- **1.** Auditory Startle
- **0.** None

**VISUAL FUNCTION SCALE**

- **5.** Object Recognition *
- **4.** Object Localization: Reaching *
- **3.** Visual Pursuit *
- **2.** Fixation *
- **1.** Visual Startle
- **0.** None

**MOTOR FUNCTION SCALE**

- **6.** Functional Object Use †
- **5.** Automatic Motor Response *
- **4.** Object Manipulation *
- **3.** Localization to Noxious Stimulation *
- **2.** Flexion Withdrawal
- **1.** Abnormal Posturing
- **0.** None/Falciid

**OMOTOR/VERBAL FUNCTION SCALE**

- **3.** Intelligible Verbalization *
- **2.** Vocalization/Oral Movement
- **1.** Oral Reflexive Movement
- **0.** None

**COMMUNICATION SCALE**

- **2.** Functional: Accurate †
- **1.** Non-Functional: Intentional *
- **0.** None

**AROUSAL SCALE**

- **3.** Attention
- **2.** Eye Opening w/o Stimulation
- **1.** Eye Opening with Stimulation
- **0.** Unarousable

**TOTAL SCORE**

Denotes emergence from MCS †
Denotes MCS *
A Practice Parameter of the American Congress of Rehabilitation Medicine

Assessment Scales for Disorders of Consciousness: Evidence-Based Recommendations for Clinical Practice and Research

Report of the American Congress of Rehabilitation Medicine, Brain Injury-Interdisciplinary Special Interest Group, Disorders of Consciousness Task Force: Ronald T. Seel, PhD, Task Force Chair, Mark Sherer, PhD, John Whyte, MD, PhD, Douglas I. Katz, MD, Joseph T. Giacino, PhD, Amy M. Rosenbaum, PhD, Flora M. Hammond, MD, Kathleen Kalmar, PhD, Theresa Louise-Bender Pape, DrPH, MA, Ross Zafonte, DO, Rosette C. Biester, PhD, Darryl Kaelin, MD, Jacob Kean, PhD, Nathan Zasler, MD
The vegetative state

Martin M Monti, Steven Laureys, Adrian M Owen

The vegetative state may develop suddenly (as a consequence of traumatic or non-traumatic brain injury, such as hypoxia or anoxia; infection; or haemorrhage) or gradually (in the course of a neurodegenerative disorder, such as Alzheimer’s disease). Although uncommon, the condition is perplexing because there is an apparent dissociation between the two cardinal elements of consciousness: awareness and wakefulness. Patients in a vegetative state appear to be awake but lack any sign of awareness of themselves or their environment. Large retrospective clinical

SOURCES AND SELECTION CRITERIA
This paper is largely based on a personal database of articles from all three authors, including the most recent published work in primary research journals as well as recent and influential reviews and chapters on the subject. We also searched PubMed using the keyword “vegetative state” and the limits “classical article, review and meta-analysis”
Unanswered (or incompletely answered) questions

• How should we assess patients with DoC?
• How and when can we predict prognosis?
• Can we impact on their natural history?
• How should we stratify patients for therapy?
  – Aetiology?
  – Neuroanatomical substrate?
  – Extent and variability of conscious level?
  – Neurochemical substrate?
• How do we account for heterogeniety?
Towards the routine use of brain imaging to aid the clinical diagnosis of disorders of consciousness

M. R. Coleman,1 M. H. Davis,2 J. M. Rodd,3 T. Robson,4 A. Ali,4 A. M. Owen1,2 and J. D. Pickard1,5
Divided functional imaging responses into “typical” (perceptual activation) and “atypical” (cognitive association processes) 

Presence of "atypical" high level associative activation predicts recovery of consciousness with a 93% specificity and 69% sensitivity 

(Chi-square test: p<0.001).
Robust prediction of non-recovery is a critical clinical/ethical issue:
- What AUC would be clinically acceptable to make decisions?
- What AUC would be ethically acceptable to make decisions?
- What AUC would be societally acceptable to make decisions?
- What confidence intervals of prediction would be acceptable?
- How long should we wait to assess prognosis in these studies?
- Should assessment include potential therapies?
Placebo-Controlled Trial of Amantadine for Severe Traumatic Brain Injury

Joseph T. Giacino, Ph.D., John Whyte, M.D., Ph.D., Emilia Bagiella, Ph.D.,

Behavioural improvements with thalamic stimulation after severe traumatic brain injury

Covert cognition almost exclusively seen in traumatic brain injury – not in cardiac arrest
Aetiological differences in neuroanatomy of the vegetative state: insights from diffusion tensor imaging and functional implications

Virginia F J Newcombe,1,2 Guy B Williams,2 Daniel Scoffings,3 Justin Cross,3 T Adrian Carpenter,2 John D Pickard,2,4 David K Menon1,2
Figure 2. Arousal and awareness, the two components of consciousness in coma, vegetative state, minimally conscious state, and locked-in syndrome.
Arousal pathways

Orexinergic  Noradrenergic  Dopaminergic  Cholinergic  Histaminergic
Three patients with PVS after TBI

They recovered after levodopa.

These patients all had Parkinsonian features.

MRI suggested TAI plus lesions of either:
   - ventral tegmental area
   - substantia niagra

Where DA dysfunction likely, consider L-DOPA
Incidence of Clinically Significant Responses to Zolpidem Among Patients with Disorders of Consciousness
A Preliminary Placebo Controlled Trial

ABSTRACT

• One of 15 patients (6.7%) demonstrated a clinically significant, replicable, response (vegetative state to the minimally conscious state).

• The remaining 14 participants showed no evidence of a subclinical response.

• This response pattern is bimodal, not normally distributed

• VS, diagnosed clinically, is neurochemically and therapeutically heterogenous
Clinical and Imaging Evidence of Zolpidem Effect in Hypoxic Encephalopathy

Christine Brefel-Courbon, MD,1–3 Pierre Payoux, MD,3
Fabierine Ory, MD,2 Agnes Sommet, MD,1
Tarik Slaoui, MD,2 Gaelle Raboyeu, PhD,3
Beatrice Lemesle, MA,2 Michele Puel, MD,2,3
Jean-Louis Montastruc, MD,1
Jean-Francois Demonet, PhD,3
and Dominique Cardebat, PhD3†

- Randomized, double-blind, placebo-controlled, N=1 trial of zolpidem in akinetic mutism.

- Zolpidem improved motor & neuropsych status

- 18F-FDG PET: increased frontal metabolism

- H215O PET: ant cingulate/orbitofrontal activation.

- Transient motor and cognitive improvement

- Paradoxical effect due to activation of limbic loops?

• 21 patients with VS Rx with DBS; up to 10 yr follow up

• DBS target: mesencephalic reticular nucleus (2), thalamic centromedian-parafascicular complex (19).

• 8 emerged from VS, followed commands; 7 remained bedridden
The effect of posture

Figure 1: The median highest ranked behaviour and total number of behaviours observed in the lying and standing position.

Matching patients to “arousal” therapies is not trivial:
- Neuroanatomical substrates that predict neurochemistry?
- Imaging of resting state activity and connectivity?
- Pharmacological challenge with functional imaging?
- PET ligand studies for each neurochemical system?
- Serial trial of therapies (not practical for clinical trials)?
- Does neurochemical augmentation need to be spatially targeted?
Broader clinical/scientific relevance

• Broader insights into cognitive neuroscience

• Relevance to anaesthesia and to sedation in critically ill patients

• Interactions of consciousness with immunity and host response
Subsequent studies have shown that semantic processing can be preserved in the absence of LIFG activation during sedation – may need to consider new models of language processing.
Unresponsiveness ≠ Unconsciousness


These concepts emphasize the need for developing anesthetic regimens and depth of anesthesia monitors that specifically target mechanisms of consciousness, connectedness, and responsiveness.
Electrophysiological correlates of behavioural changes in vigilance in vegetative state and minimally conscious state

Eric Landsness,¹,²,* Marie-Aurélie Bruno,¹,* Quentin Noirhomme,¹ Brady Riedner,² Olivia Gossieres,¹ Caroline Schnakers,¹ Marcello Massimini,³ Steven Laureys,¹ Giulio Tononi² and Mélanie Boly¹

- Behavioural “sleep” in both VS and MCS
- Classical neurophysiology of sleep common in MCS, rare in VS
Clock genes and sleep

Dominic Landgraf • Anton Shostak • Henrik Oster

Mammals
- PERs
- CRYs
- CLOCK/NPAS2
- BMAL1
- REV-ERBα
- RORα

Drosophila
- PER
- TIM
- CYC
- CLC
- VRI
- PDP1

Plasticity

Clock genes & sleep
- Melatonin
- Corticoids
- Prolactin
- ANS
- Melatonin
- Corticoids
- Food uptake
- Cytokines
- Adipokines
- Ghrelin

Immunity

Metabolism
Retinoid-related orphan receptors (RORs): critical roles in development, immunity, circadian rhythm, and cellular metabolism

Anton M. Jetten
Societal/patient engagement

• Area of immense interest – opportunity to engage with the public

• Recognition of family burdens – bereavement without the solace of death

• Making the case for the individual patient
Filmed over six months in the country's leading brain injury unit (Addenbrooke's Hospital, Cambridge), it follows the journey of a man who, by only moving his eyes, is eventually asked if he wants to live or die. Two other families are also plunged into the most ethically difficult decision in modern medicine.
The Mind Reader: Unlocking My Voice

DURATION: 1 HOUR

In a world exclusive, Panorama follows a group of severely brain injured patients and reveals the revolutionary efforts made to help them communicate with their families and the outside world.

SHOW MORE
This talk is dedicated to Kate Bainbridge, who didn’t just recover from being in a vegetative state, but still thinks of herself as a rock chick!
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