Recent advances in paraclinical assessment of patients with disorders of consciousness
Who are we?

Prof. Steven Laureys, MD, PhD

Speech therapists
Physicians
Speech therapists
Neuropsychologists
Physiotherapists
Biologists
Engineers
Nurses
Computer scientists

www.comascience.org
Overview

- Consciousness and Disorders of Consciousness
- Diagnosis
- Paraclinical diagnosis
Reducing consciousness to 2D

Reducing consciousness to 2D

Boly et al, Ann NY Acad Sci, 2009
Vanhaudenhuyse & Demertzi et al, J Cogn Neurosci, 2011
Clinical entities

<table>
<thead>
<tr>
<th>Coma</th>
<th>UWS/VS</th>
<th>MCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>No eye opening</td>
<td>Eye opening</td>
<td>Eye opening</td>
</tr>
<tr>
<td>Reflex behaviour</td>
<td>Reflex behaviour</td>
<td>Non reflex behaviour</td>
</tr>
</tbody>
</table>

MCS +
higher level
(e.g. command following)

Emergence from MCS
Functional communication
Functional use of objects

LIS
No motor output
Preserved cognition

MCS−
lower level
(e.g. visual pursuit)

UWS=unresponsive wakefulness syndrome
VS=vegetative state
MCS=minimally conscious state

Bodart, Gosseries & Laureys, *Semin Neurol*, 2013
Clinical entities

Consciousness | Diagnosis | Paraclinical diagnosis

CMD (active); MCS* or HMD (Passive)

Dissociation between clinical diagnosis and neuroimaging results suggesting preserved higher cognitive abilities

Bodart, Gosseries & Laureys, Semin Neurol, 2013; Edlow & Chatelle et al., Brain 2017
Why is it important to assess consciousness?

Consciousness | Diagnosis | Paraclinical diagnosis

Prognosis
(non traumatic)

Treatment

Ethics


Thibaut et al, J Neurology 2014

Bruno et al, unpublished

Deceased
Unresponsive
Recovery
MCS
VS/UWS

It is acceptable to stop treatment in a chronic...
I would like to be kept alive if I were in a chronic...

Demertzi et al, J Neurology 2011

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
0 10 20 30 40 50 60 70 80 90 100

VS MCS

MCS

MCS

MCS

MCS
Pain?

Schnakers, Chatelle, Majerus, Gossseries, Deval and Laureys, Experts Rev in Neurother, 2010
Audition?

Laureys et al., Brain, 2000; Boly et al, Archives of Neurology, 2004
Consciousness ≈ 2 components

DOC: different clinical entities associated with various levels of consciousness: coma, VS/UWS, MCS (plus and minus)

New terminologies with paraclinical diagnosis: CMD, MCS*, HMD

Impact on care

Non communicative patients with DOC may be able to perceive external world
- Audition
- Pain/emotion

Summary

<table>
<thead>
<tr>
<th>Consciousness</th>
<th>Diagnosis</th>
<th>Paraclinical diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>≈ 2 components</td>
<td>DOC: coma, VS/UWS, MCS</td>
<td>CMD, MCS*, HMD</td>
</tr>
</tbody>
</table>
“Reflex” versus “Voluntary”
n=103 post-comatose patients

- 45 clinical consensus diagnosis ‘vegetative state’
- 18 signs of awareness (Coma Recovery Scale-Revised)

41% potential misdiagnosis

Schnakers, Vanhaudenhuyse, Giacino, Ventura, Boly, Majerus et al., BMC Neurol, 2009
**Coma Recovery Scale-Revised**

**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/Flaccid

**OROMOTOR/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

**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

---

How many assessments?

- Misdiagnosis
- Chronic
- 6 assessments
- Short time window (3 - 10 d)

Wannez et al., *Annals of Neurology*, 2017; Chatelle et al., EAN 2018
# Nociception Coma Scale - revised

**Total score : 9**

<table>
<thead>
<tr>
<th>Consciousness</th>
<th>Diagnosis</th>
<th>Paraclinical diagnosis</th>
</tr>
</thead>
</table>

## Verbal Response

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Verbalisation intelligible</td>
</tr>
<tr>
<td>2</td>
<td>Vocalisation</td>
</tr>
<tr>
<td>1</td>
<td>Groaning</td>
</tr>
<tr>
<td>0</td>
<td>None</td>
</tr>
</tbody>
</table>

## Motor Response

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Localization to noxious stimulation</td>
</tr>
<tr>
<td>2</td>
<td>Flexion withdrawal</td>
</tr>
<tr>
<td>1</td>
<td>Abnormal posturing</td>
</tr>
<tr>
<td>0</td>
<td>None/Flaccid</td>
</tr>
</tbody>
</table>

## Facial Expression

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Cry</td>
</tr>
<tr>
<td>2</td>
<td>Grimace</td>
</tr>
<tr>
<td>1</td>
<td>Oral reflexive movement/Startle response</td>
</tr>
<tr>
<td>0</td>
<td>None</td>
</tr>
</tbody>
</table>

Schnakers, Chatelle et al. Pain 2010
NCS-R total scores correlate with posterior part of the anterior cingulate cortex →cognitive-affective dimension of pain (Rainville, 1997)
NCS-R in acute setting

GCS mean scores

VS/UWS  |  MCS
Pre treatment  |  Post treatment

Level of consciousness

NCS-R mean scores

VS/UWS  |  MCS
Pre treatment  |  Post treatment

Level of consciousness

* p < 0.05

Summary

- High rate of misdiagnosis if non sensitive scales are used (up to 40%)
  - CRS-R
- 76% documented potential pain, 59% not treated with analgesics
  - NCS-R for assessing pain
- Useful for monitoring recovery/medical complications
- Caveats
  - Language dependent
  - Relying strongly on motor abilities
Active paradigm – EMG

« Move your right hand »

Bekinschtein et al JNNP 2008
Active paradigm – fMRI

"He's not in coma... he's playing tennis!"

Owen, Coleman, Boly, Davis, Laureys & Pickard, Science, 2006
Active paradigm – fMRI

HEALTHY SUBJECT

Answers « YES »  Answers « NO »

« VEGETATIVE STATE »

Active paradigm – EEG

Schnakers, Boly, Majerus and Laureys, Neurol, 2005
Active paradigm – EEG

Schnakers et al, Neurology, 2008; Schnakers et al, Neurocase, 2009
Active paradigm – EEG

Coma or total locked-in syndrome?

21-y old woman
basilar artery thrombosis - day 49

Perrin, Schnakers et al, Arch Neurol, 2005
Active paradigm – EEG

“MOVE YOUR FOOT”  “MOVE YOUR HAND”

HEATHY CONTROL SUBJECT

“VEGETATIVE” UNRESPONSIVE PATIENT

Cruse, Chennu, Chatelle et al., Lancet 2011; Neurology 2012
Command-following and aphasia

The problem of aphasia in the assessment of consciousness in brain-damaged patients

Steve Majerus\textsuperscript{1,2}, Marie-Aurélie Bruno\textsuperscript{2,3}, Caroline Schnakers\textsuperscript{2}, Joseph T. Giacino\textsuperscript{4} and Steven Laureys\textsuperscript{2,3,*}

*Progress in Brain Research, Vol. 177
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Metabolism in language network

![Graph showing metabolism in different conditions](image)
Brain metabolism

Stender et al, Current Biology, 2016
Brain metabolism

Consciousness ≠ whole brain

PET

Laureys et al, Lancet Neurology, 2004
**Brain metabolism**

- **PET**

Consciousness ≠ whole brain

**UNRESPONSIVE WAKEFULNESS / VEGETATIVE STATE**

- Consciousness
  - ≈ fronto-parietal network

**MINIMALLY CONSCIOUS STATE**

Magnetic resonance imaging

- Structural

White matter

- HC
- MCS
- UWS

A/P

H/B

L/R
Consciousness | Diagnosis | Paraclinical diagnosis

TMS/EEG

Napolitani and Bodart et al, Brain Inj, 2017
Consciousness = integration and differentiation

Tononi, BMC Neurosc., 2004
Wakefulness

Deep sleep

Massimini et al, Science, 2005
Passive paradigm – TMS/EEG

Rosanova and Gosseries et al, Brain, 2012
Passive paradigm – TMS/EEG

Rosanova and Gosseries et al, Brain, 2012
Passive paradigm – TMS/EEG

Rosanova and Gosseries et al, Brain, 2012
Passive paradigm – TMS/EEG

Rosanova and Gossseries et al, Brain, 2012
Perturbational complexity index

Perturbational complexity index

Unconsciousness

Perturbational complexity index

Summary

- Behavioral assessment ≈ 40% misdiagnosis
- FDG-PET as a good complement beside examinations
- Active fMRI/EEG/EMG paradigms are less suited for differential diagnosis, but may provide a strong complementary tool
- TMS-EEG may provide for the first time a passive measure of consciousness at the single subject level
- Encourage to use **multimodal assessment** of the level of consciousness!
Multimodality

Annen et al., Front. Hum. Neurosci. 2018
Multimodality

BCI accuracy UWS, PET UWS

<table>
<thead>
<tr>
<th>Patient UWS 6</th>
<th>C3</th>
<th>C4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amplitude (μV)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Time (s)</td>
<td>0</td>
<td>0</td>
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</tbody>
</table>

BCI VT2 accuracy: 0%

BCI accuracy UWS, PET MCS

<table>
<thead>
<tr>
<th>Patient MCS-2</th>
<th>C3</th>
<th>C4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amplitude (μV)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Time (s)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

BCI VT2 accuracy: 20%

BCI accuracy MCS, PET MCS

<table>
<thead>
<tr>
<th>Patient MCS-1</th>
<th>Left trial</th>
<th>Right trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>C3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>C4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Amplitude (μV)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Time (s)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

BCI VT3 accuracy: 70%

Annen et al., Front. Hum. Neurosci. 2018
Case reports

Behavioral assessment

TMS-EEG

MRI

PET scan

BCI

EEG
Case reports

- 41 years old
- 4 years et 9 months post anoxia
- Diagnosis: vegetative/unresponsive state

- 35 years old
- 6 years and 10 months post ischemic stroke
- Diagnosis: vegetative/unresponsive state

Gosseries, Zasler and Laureys, Brain Inj, 2014
## Case reports

### CRS-R

**Fonction auditive**
- 4 – Mouvement systématique sur demande*
- 3 – Mouvement reproductible sur demande*
- 2 – Localisation de sons
  - 1 – Réflexe de sursaut au bruit
  - 0 – Néant
- 1 – Réflexe de clignement à la menace
- 0 – Néant

**Fonction visuelle**
- 5 – Reconnaissance des objets*
- 4 – Localisation des objets : atteinte*
- 3 – Poursuite visuelle*
- 2 – Fixation*
- 1 – Réflexe de clignement à la menace
- 0 – Néant

**Fonction motrice**
- 6 – Utilisation fonctionnelle des objets
- 5 – Réaction motrice automatique*
- 4 – Manipulation d’objets*
- 3 – Localisation des stimulations nociceptives*
- 2 – Flexion en retrait
- 1 – Posture anormale stéréotypée
- 0 – Néant / Flaccidité

**Fonction oromotrice/verbalement**
- 3 – Production verbale intelligible*
- 2 – Production vocale / Mouvements oraux
- 1 – Réflexes oraux
- 0 – Néant

**Communication**
- 2 – Fonctionnelle : exacte*
- 1 – Non fonctionnelle : intentionnelle*
- 0 – Néant

**Éveil**
- 3 – Attention
- 2 – Ouverture des yeux sans stimulation
- 1 – Ouverture des yeux avec stimulation
- 0 – Aucun éveil

<table>
<thead>
<tr>
<th>Étapes</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRS-R</td>
<td>4</td>
<td>4</td>
<td>5</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>
Case reports

FDG - PET

Gosseries, Zasler and Laureys, Brain Inj, 2014
Case reports

FDG - PET

fMRI - resting state

Gossseries, Zasler and Laureys, Brain Inj, 2014
Case reports

FDG - PET

fMRI - resting state

MRI - DTI

Gossseries, Zasler and Laureys, Brain Inj, 2014
Case reports

FDG - PET

fMRI - resting state

MRI - DTI

fMRI - mental imagery task

Tennis

Navigation

Tennis

Navigation

Gossseries, Zasler and Laureys, Brain Inj, 2014

Consciousness | Diagnosis | Paraclinical diagnosis
Consciousness under the eye of science

- 2 components: arousal + awareness of ourselves and environment
- 2 awareness networks
- Consciousness ≈ frontoparietal / thalamo-cortical network
- Use standardized scales: CRS-R, NCS-R
- Motor and language caveats => misdiagnosis!
- Paraclinical assessments
  - High heterogeneity in sensitivity and specificity!!
  - Multimodality when available
- Ethical challenge: quality of life, care and end of life decisions
THANK YOU!

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D. Habbal, PhD
S. Wannez, PhD
O. Bodard, PhD
C. Martial, PhD
H. Cassol, PhD student
M. Carrière, PhD student
C. Aubinet, PhD student
A. Barra, PhD student
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L. Sanz, PhD student
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Patients & families

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