Chronic disorders of consciousness: medical practice and neuroscientific revolution

Interdisziplinäres Symposium über chronische Bewusstseinsstörungen

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Athena Demertzi, MSc
Neuropsychologist
PhD candidate

Coma Science Group
Cyclotron Research Center
Department of Neurology, CHU
University of Liège, Belgium

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Overview

- Definitions
- Scientific perspective
  - Neural correlate of consciousness
- Clinical interest
  - Diagnosis, prognosis, treatment
- Ethical issues
  - End-of-life
  - Quality of life
- Conclusions

‘Le scaphandre et le papillon’ (2007)
Direction: Julian Schnabel
Definitions
Lesion paradigm

Definitions | Scientific perspective | Clinical interest | Ethical issues | Conclusions

Conscious

Locked-in syndrome

Conscious Wakefulness

Drowsiness

 Lucid Dreaming

REM Sleep

St I-II Sleep

St III-IV Sleep

Minimally Conscious State
- more than reflex movements
- no communication

General Anesthesia

Coma

Vegetative state

Awareness = command following

Wakefulness = eyes opening

Demertzi, Laureys & Boly, *Encyclopaedia of Consciousness* 2009
Laureys, *Trends in Cognitive Sciences* 2005

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<table>
<thead>
<tr>
<th>Questionnaire</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age category</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Nationality (NL, BE..)</td>
</tr>
<tr>
<td>Profession</td>
</tr>
<tr>
<td>Other (…)</td>
</tr>
</tbody>
</table>

**Would you like to be kept alive if you were in:**

1. Vegetative state (> 1 year)?
2. Minimally conscious state (> 1 year)?
3. Locked-in syndrome (> 1 year)?
Scientific perspective
Consciousness in the brain?

Dualism persists in 1/3 of clinicians

Demertzi et al., *Ann NY Acad Sci* 2009

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Consciousness ≠ whole brain

Laureys et al, Lancet Neurology 2004
Two awareness networks

GLOBAL NEURONAL WORKSPACE

INTERNAL AWARENESS NETWORK

EXTERNAL AWARENESS NETWORK

Baars, Ramsøy & Laureys, *TINS* 2003
Boly et al., *HBM* 2008

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External and internal awareness

**NEURAL CORRELATE OF EXTERNAL (SENSORY) AWARENESS**

Peri-luminal laser stimulation on hand (N=24)

- Perceived (433±23 mJ) > Unperceived (438±21 mJ)

Soddu et al., *Prog Brain Res* 2009
(also Dehaene et al, *Nat Rev Neuroci* 2001; Rees et al, *Nat Rev Neuroci* 2001)

**NEURAL CORRELATE OF INTERNAL (SELF) AWARENESS**

Self-referential stimuli

- Own Name
  - 15 controls: Perrin et al. 2005
  - 16 controls: Kampe et al. 2003
  - 3 controls: Stassen et al. 2006
  - 1 MCS patient: Laureys et al. 2004
  - 1 VS patient: Stassen et al. 2006

- Own Face
  - 12 controls: Platek et al. 2006
  - 6 controls: Kircher et al. 2001

“Resting state” default brain activity

Functional role to behavior

Anti-correlated
Switching 0.05 Hz (range 0.01-0.1Hz)
1/20 s (range 10-100 s)

Vanhaudenhuyse & Demertzi, *J Cogn Neurosci* 2010
Flexibility of resting networks

Definitions | Scientific perspective | Clinical interest | Ethical issues | Conclusions

Demertzi et al., in preparation

\[ r = -0.41 \]

Switching of 0.05Hz (range 0.04-0.05Hz)

1/20 s

[Diagram a. NORMAL WAKEFULNESS]

\[ r = -0.24 \]

Switching 0.03Hz (range 0.02 0.05Hz)

1/33 s

[Diagram b. HYPNOTIC STATE]

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4A. Do you think functional neuroimaging can differentiate between the vegetative and minimally conscious states?

4B. If a behaviorally vegetative patient would show normal activation of functional neuroimaging would this change your diagnosis?
Clinical interest
Reflex versus voluntary
Assessing consciousness

Definitions | Scientific perspective | Clinical interest | Ethical issues | Conclusions

Laureys et al., Curr Opinion Neurol 2005

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Misdiagnosis of vegetative state

n=103 post-comatose patients

45 clinical diagnosis of “vegetative state”

27 Coma Recovery Scale diagnosis

40% misdiagnosis

38% Schnakers et al Ann Neurol 2006; BMC Neurology 2009
37% Childs et al Neurology 1993
43% Andrews et al BMJ 1996
“Resting state” default brain activity

Boly et al., HBM 2009
Vanhaudenhuyse & Noirhomme et al, Brain 2010

www.comascience.org
“Mindreading”

Signs of consciousness on fMRI

Owen, Coleman, Boly, Davis, Laureys & Pickard, Science 2006
≠ “automatic” brain response
Yes-No communication with fMRI

Imagine Tennis to answer 'YES'
Imagine Navigating to answer 'NO'

Is your father's name Alexander?
Is your father's name Thomas?

Monti & Vanhaudenhuyse, Coleman, Boly, Pickard, Tshibanda, Owen, Laureys
New England J Med 2010

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Do you think that:

5A. Patients in a VS can feel pain?
5B. Patients in a VS should receive pain medication?

6A. Patients in a MCS can feel pain?
6B. Patients in a MCS should receive pain medication?

7A. Patients in a LIS can feel pain?
7B. Patients in a LIS should receive pain medication?

Assuming surrogate informed consent, is it acceptable to do functional neuroimaging studies on:

8A. Pain perception in the VS?
8B. Perception of thirst and hunger in the VS?

9A. Pain perception in the MCS?
9B. Perception of thirst and hunger in the MCS?

Do you think invasive interventions are justified to...

10A. Diagnose and study disorders of consciousness or to provide prognostic information?
10B. Develop treatments for disorders of consciousness?
Treatment

- symptomatic
- curative

"...a (woman’s) brain is a mystery... and even more so in this state”
Pedro Almodovar - Hable con ella
Nociception and pain

Definitions | Scientific perspective | Clinical interest | Ethical issues | Conclusions

Nociception Coma Scale

<table>
<thead>
<tr>
<th>Score</th>
<th>Item</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>MOTOR RESPONSE</td>
</tr>
<tr>
<td>5</td>
<td>Location to Noxious Stimulation</td>
<td>The non-stimulated limb must locate and make contact with the stimulated limb at the point of stimulation.</td>
</tr>
<tr>
<td>3</td>
<td>Flexion Withdrawal</td>
<td>There is isolated flexion withdrawal of at least one limb. The limb must move away from the point of stimulation.</td>
</tr>
<tr>
<td>2</td>
<td>Abnormal Posturing</td>
<td>Movements that are not the natural response to pain, e.g., primitive defense reactions.</td>
</tr>
<tr>
<td>1</td>
<td>None/Placid</td>
<td>There is no discernible movement following application of noxious stimulation, secondary to hypotension or focal artifact.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VERBAL RESPONSE</td>
</tr>
<tr>
<td>2</td>
<td>Intelligible Verbalizations</td>
<td>Production of words in response to noxious stimulation. Each verbalization must consist of at least 3 consonant-vowel-consonant (C-V-C) trisyllables that have a meaning.</td>
</tr>
<tr>
<td>1</td>
<td>Vocalization/Ocular Movement</td>
<td>Movement of eyes or head, to the side of pain, or towards the side of pain.</td>
</tr>
<tr>
<td>0</td>
<td>None</td>
<td>No movement.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VISUAL RESPONSE</td>
</tr>
<tr>
<td>2</td>
<td>Eye movements</td>
<td>Palpebral movements elicited by noxious stimulation.</td>
</tr>
<tr>
<td>1</td>
<td>No response</td>
<td>No movement elicited by noxious stimulation.</td>
</tr>
<tr>
<td>0</td>
<td>None</td>
<td>No movement.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FACIAL EXPRESSION</td>
</tr>
<tr>
<td>2</td>
<td>Oral reflexive movements</td>
<td>Mouth opening and closing, chewing.</td>
</tr>
<tr>
<td>1</td>
<td>No response</td>
<td>No movement elicited by noxious stimulation.</td>
</tr>
</tbody>
</table>

Demertzi et al, Prog Brain Res 2009

Schnakers et al, Pain 2010

www.comascience.org
Do they feel pain?

Definition | Scientific perspective | Clinical interest | Ethical issues | Conclusions

Noxious electrical stimulation

Laureys et al., *Neuroimage* 2002

www.comascience.org
Curative treatment: Drugs?
no evidence based therapy

Demertzi et al., Expert Rev Neurotherapeutics 2008
Schnakers et al., J Neurol Neurosurg Psychiatry 2008
Curative treatment: Deep brain stimulation?

Definitions | Scientific perspective | Clinical interest | Ethical issues | Conclusions

Object Naming During Titration

Schiff et al., *Nature* 2007

www.comascience.org
Do you think it is acceptable to withhold or withdraw treatment in patients:

11. In the vegetative state?
12. In the minimally conscious state?
13. In the locked-in syndrome?

Are you religious?
If yes, please state your affiliation
Ethical challenges
When the diagnosis of a permanent VS is considered definite, it should be discussed with the relatives, [...] who should then be given the time to consider the implications, including the possibility of withdrawing artificial means of administering nutrition and hydration. 
(The Royal College of Physicians, 2003)
Attitudes’ survey

Aim:
1. Debrief and update attitudes towards VS
2. Determine attitudes for MCS

A 16-item questionnaire (Yes-No responses)
Attendees at conferences and meetings
32 European countries
September 2007 - October 2009

Statistical Analysis (SPSS v.16)
• Chi-square tests ($p=.05$)
• Multiple Logistic Regression models (method: Enter)
  • Predicted outcome: Agreement
  • Predictors: age, gender, region, profession and religiosity
### Attitudes’ survey (n=2475)

**Definitions | Scientific perspective | Clinical interest | Ethical issues | Conclusions**

### Demographic data

<table>
<thead>
<tr>
<th>Demographic data</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ±SD (range)</td>
<td>39±14 (18-88)</td>
</tr>
<tr>
<td>Gender, no. (%)</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>1314 (53%)</td>
</tr>
<tr>
<td>Men</td>
<td>1098 (44%)</td>
</tr>
<tr>
<td>Missing</td>
<td>63 (3%)</td>
</tr>
<tr>
<td>Respondents by European Region, no (%)</td>
<td></td>
</tr>
<tr>
<td>Northern</td>
<td>402 (16%)</td>
</tr>
<tr>
<td>Central</td>
<td>1213 (49%)</td>
</tr>
<tr>
<td>South</td>
<td>855 (35%)</td>
</tr>
<tr>
<td>Missing</td>
<td>5 (0%)</td>
</tr>
<tr>
<td>Profession, no. (%)</td>
<td></td>
</tr>
<tr>
<td>Medical professionals</td>
<td>1608 (65%)</td>
</tr>
<tr>
<td>Paramedical professionals</td>
<td>651 (26%)</td>
</tr>
<tr>
<td>Missing</td>
<td>216 (9%)</td>
</tr>
<tr>
<td>Religiosity, no. (%)</td>
<td></td>
</tr>
<tr>
<td>Religious respondents</td>
<td>1407 (57%)</td>
</tr>
<tr>
<td>Non-religious respondents</td>
<td>1004 (40%)</td>
</tr>
<tr>
<td>Missing</td>
<td>64 (3%)</td>
</tr>
</tbody>
</table>

### Graphs

- VS is worse than death for the family: 80%
- VS is worse than death for the patient: 55%
- MCS is worse than VS for the family: 42%
- MCS is worse than VS for the patient: 54%

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End-of-life attitudes (n=2475)

- **It is acceptable to stop treatment in...**
  - Chronic VS: 66%
  - Chronic MCS: 28%

- **I would like to be kept alive if I were in...**
  - Chronic VS: 18%
  - Chronic MCS: 33%

* *p < .001

Definitions | Scientific perspective | Clinical interest | Ethical issues | Conclusions

Demertzi et al., submitted

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End-of-life attitudes: predictors

<table>
<thead>
<tr>
<th>Predictor variable</th>
<th>It is acceptable to stop ANH in a chronic VS</th>
<th>It is acceptable to stop ANH in a chronic MCS</th>
<th>I would like to be kept alive in a chronic VS</th>
<th>I would like to be kept alive in a chronic MCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age†</td>
<td>0.98 (0.97-0.99)**</td>
<td>0.98 (0.98-0.99)**</td>
<td>1.01 (1.01-1.02)*</td>
<td>1.00 (0.99-1.01)</td>
</tr>
<tr>
<td>Women</td>
<td>0.79 (0.64-0.97)*</td>
<td>0.91 (0.73-1.13)</td>
<td>0.87 (0.67-1.12)</td>
<td>0.92 (0.75-1.13)</td>
</tr>
<tr>
<td>Southern Europe</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Northern Europe</td>
<td>3.36 (2.38-4.74)**</td>
<td>3.82 (2.79-5.23)**</td>
<td>0.34 (0.21-0.55)**</td>
<td>0.47 (0.34-0.66)**</td>
</tr>
<tr>
<td>Central Europe</td>
<td>1.84 (1.49-2.26)**</td>
<td>2.24 (1.77-2.83)**</td>
<td>0.72 (0.56-0.92)*</td>
<td>0.69 (0.56-0.85)**</td>
</tr>
<tr>
<td>Medical professionals</td>
<td>1.18 (0.94-1.49)</td>
<td>0.91 (0.73-1.15)</td>
<td>1.18 (0.88-1.59)</td>
<td>1.28 (1.02-1.62)*</td>
</tr>
<tr>
<td>Religious respondents</td>
<td>0.45 (0.37-0.55)**</td>
<td>0.46 (0.37-0.55)**</td>
<td>2.20 (1.70-2.85)**</td>
<td>2.24 (1.84-2.73)**</td>
</tr>
</tbody>
</table>

** p< 0.001, * p< 0.05;

Note: Predicted response: ‘agreement’. An odds ratio higher than 1 signifies more agreement with the statement, whereas an odds ratio less than 1 notifies less agreement.

†For continuous variables, the odds ratio equals the relative change in the odds ratio when the variable is increased by one unit.
Conclusions
Translational research

Neural correlates of conscious awareness
≈ fronto-parietal neuronal ‘global workspace’
≈ cortico-thalamo-cortical functional connectivity

Diagnostic use
≈ 40% signs of consciousness in vegetative state

Prognostic use
(f)MRI prospective multicenter studies

Therapeutic use
 symptom & pain treatment / curative thalamic DBS

Ethical issues

Tononi & Laureys, *The Neurology of Consciousness* 2009
Owen, Schiff & Laureys, *Prog Brain Res* 2009

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THANK YOU

Slides can be downloaded from www.comascience.org

PhD candidates:
Marie-Aurélie Bruno
Olivia Gosseries
Pierre Boveroux MD
Muriel Kirsch MD
Audrey Maudoux
Camille Chatelle
Marie Thonnard
Victor Cologan

Collaborations:
NY J Giacino, N Schiff, J Fins
Cambridge A Owen
Milano M Massimini
Wisconsin G Tononi
Tubingen & Wurzburg A Kübler
Paris L Puybasset
Hangzou China H Di
Salzburg M Schabus
Lyon F Perrin

PhDs:
Melanie Boly MD
Andrea Soddu
Quentin Noirhomme, Ing
Didier Ledoux MD
Audrey Vanhaudenhuyse
Caroline Schnakers

Also:
Christophe Phillips, PhD Ing
Pierre Maquet, MD PhD

the patients & families