What awareness in coma?

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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
Reducing consciousness to 2D

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

Consciousness = command following

- Lucid Dreaming
- REM Sleep
- St I-II Sleep
- St III-IV Sleep
- General Anesthesia
- Coma
- Minimally Conscious State
  - more than reflex movements
  - no communication
- Conscious Wakefulness
- Locked-in syndrome
- Drowsiness
- Vegetative state

Wakefulness = eyes opening

Laureys, *Trends in Cognitive Sciences* 2005

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Locked-in syndrome (LIS)

- Presence of sustained eye opening
- Aphonia or severe hypophonia
- Ocular mode of communication
- Quadriplegia or quadriparesis-Types:
  - Classical
  - Incomplete
  - Total
- Preserved cognitive abilities
Questionnaire

Age category
Gender
Nationality (NL, BE..)
Profession Other (...)

Would you like to keep alive if you were in:
1. Vegetative state (> 1year)?
2. Minimally conscious state (> 1year)?
3. Locked-in syndrome (> 1year)?
Scientific perspective
Consciousness ≠ whole brain

Laureys et al, Lancet Neurology 2004
Consciousness ≈ frontoparietal

areas systematically dysfunctional in the vegetative state

areas resuming metabolism after recovery from the vegetative state

Laureys et al, Neuroimage 1999

Laureys et al, J Neurol Neurosurg Psychiatry, 1999
Two awareness networks

GLOBAL NEURONAL WORKSPACE

INTERNAL AWARENESS NETWORK

EXTERNAL AWARENESS NETWORK

Boly et al., Human Brain Mapping 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)

Boly et al, PNAS 2007
(also Dehaene et al, Nat Rev Neuroci 2001; Rees et al, Nat Rev Neuroci 2001)

NEURAL CORRELATE OF INTERNAL (SELF) AWARENESS

Self-referential stimuli

Laureys et al, Consciousness & Cognition 2007
(also Mason et al, Science, 2007; Golland et al, Neuropsychologia 2008)

OWN NAME
- 15 controls: Perrin et al. 2005
- 16 controls: Kampe et al. 2003
- 3 controls: Staffen et al. 2006
- 1 MCS patient: Laureys et al. 2004
- 1 VS patient: Staffen et al. 2006

OWN FACE
- 12 controls: Platek et al. 2006
- 6 controls: Kircher et al. 2001
“Resting state” default brain activity

Anti-correlation of internal and external awareness networks

Spontaneous brain fluctuations predict conscious perception of external stimuli

Switching 1/20s (0.05 Hz)

Boly et al, Ann NY Acad Sci 2009

Boly et al, PNAS 2007
External vs internal awareness

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

Vanhaudenhuyse & Demertzi, *J Cogn Neurosci* in press  
www.comascience.org
“Resting state” default brain activity

Vanhaudenhuyse et al, *Brain*, 2010
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
Outcome

- Acute Brain Injury
- Coma
- Locked-In Syndrome
- Vegetative State
  - Fast Recovery
  - Minimally Conscious State
    - Recovery of Consciousness
- Permanent Vegetative State
- Brain Death
- Permanent Minimally Conscious State?

Laureys, *Scientific American* 2007
n=103 post-comatose patients

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

40% potential misdiagnoses

Schnakers et al., *BMC Neurology* 2009
Eye tracking: use a mirror!

Vanhaudenhuyse et al., *J Neurol Neurosurg Psychiatry* 2008

www.comascience.org
‘Self’ processing in MCS

Meaningless Noise

Acoustically Matched Cries

Patient’s Own Name

Laureys et al., *Neurology* 2004
fMRI: predictor of outcome?

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

Di et al., *Neurology* 2007
Coleman et al., *Brain* 2008

ATYPICAL ‘HIGH LEVEL’ CORTICAL ACTIVATION
P300 to the own name

Perrin et al., Archives in Neurology 2006

www.comascience.org
“Mindreading”

Signs of consciousness on fMRI

≠ “automatic” brain response
Yes-No communication with fMRI

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

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## Communication via fMRI

### Definitions

### Scientific perspective

### Clinical interest

### Ethical issues

### Conclusions

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<table>
<thead>
<tr>
<th>response option</th>
<th>encoding parameters</th>
<th>single-trial time courses and RTCs</th>
<th>ranking (correlation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>brain location 'motor imagery' ROI</td>
<td><img src="image" alt="fMRI response" /></td>
<td>1st (0.89)</td>
</tr>
<tr>
<td></td>
<td>onset 0s</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>offset 10s</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>brain location 'mental calculation' ROI</td>
<td><img src="image" alt="fMRI response" /></td>
<td>2nd (0.52)</td>
</tr>
<tr>
<td></td>
<td>onset 5s</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>offset 10s</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>brain location 'motor imagery' ROI</td>
<td><img src="image" alt="fMRI response" /></td>
<td>3rd (0.06)</td>
</tr>
<tr>
<td></td>
<td>onset 5s</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>offset 15s</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>brain location 'mental calculation' ROI</td>
<td><img src="image" alt="fMRI response" /></td>
<td>4th (-0.20)</td>
</tr>
<tr>
<td></td>
<td>onset 10s</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>offset 20s</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Sorger et al, *Prog Brain Res* 2009

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Coma or total locked-in syndrome?

21-y old woman
basilar artery thrombosis - day 49

Other names PASSIVE
Count TARGET (other name)
Own name PASSIVE
Count TARGET (own name)

Schnakers et al, *Neurology*, 2008
Schnakers et al, *Neurocase*, 2009

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Questionnaire

**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

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Nociception and pain

Nociception Coma Scale

<table>
<thead>
<tr>
<th>Score</th>
<th>Item</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MOTOR RESPONSE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Localization to Noxious Stimulation</td>
<td>The non-stimulated limb must locate and make contact with the stimulated limb part at the point of stimulation.</td>
</tr>
<tr>
<td>2</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>1</td>
<td>Abnormal Posturing</td>
<td>Movements, stereotyped or extension of the upper and/or lower extremities, occurs immediately after the stimulus is applied.</td>
</tr>
<tr>
<td>0</td>
<td>None/Placid</td>
<td>There is no discernible movement following application of noxious stimulation, secondary to hypnosis or disinhibition.</td>
</tr>
<tr>
<td><strong>VERBAL RESPONSE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Intelligible Verbalisation</td>
<td>Production of words in response to noxious stimulation. Each verbalisation must consist of at least 1 consonant-vowel-consonant (CVC) triad.</td>
</tr>
<tr>
<td>2</td>
<td>Vocalisation / Oral Movement</td>
<td>Occasional vocalisation or repetitive facial grimace with obvious physical movement</td>
</tr>
<tr>
<td>1</td>
<td>Groans</td>
<td>Groaning or gasping</td>
</tr>
<tr>
<td>0</td>
<td>None</td>
<td>Arousal</td>
</tr>
<tr>
<td><strong>VISUAL RESPONSE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Eyeball Movements</td>
<td>Eye movements include slight deviation or fixation point</td>
</tr>
<tr>
<td>2</td>
<td>Eye movement</td>
<td>Eyelid opening</td>
</tr>
<tr>
<td>1</td>
<td>Sustained</td>
<td>Sustained fixation</td>
</tr>
<tr>
<td>0</td>
<td>None</td>
<td>No change</td>
</tr>
<tr>
<td><strong>FACIAL EXPRESSION</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Cry</td>
<td>Cries are observed spontaneously or due to noxious stimulation</td>
</tr>
<tr>
<td>2</td>
<td>Grimace</td>
<td>Gyrate or observe spontaneous facial grimace</td>
</tr>
<tr>
<td>1</td>
<td>Oral reflexive movements / Sustained response</td>
<td>Chomping, jaw clenching, tongue protrusion, vocalisation, chewing movement</td>
</tr>
<tr>
<td>0</td>
<td>None</td>
<td>No change</td>
</tr>
</tbody>
</table>

Schnakers et al, *Pain*, in press

www.comascience.org
Do they feel pain?

Noxious electrical stimulation

Laureys et al., *Neuroimage* 2002

Low level disconnected cortical activation

www.comascience.org
Pain in minimally conscious state

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

Boly et al., Lancet Neurology 2008

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

www.comascience.org
Curative treatment: Deep brain stimulation?

Object Naming During Titration

Schiff et al., Nature 2007
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
Quality of life

Short Form-36 in brainstem stroke LIS patients (n=17; duration 6±4 y)

Laureys et al., Prog Brain Res, 2005

Reintegration to Normal Living Index in ALS patients (n=30; duration 6±5 y)

Lulé et al., Prog Brain Res, 2009

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Quality of Life

**Case 1**
24-year-old girl
LIS for 6 years
Good social interactions
Occasionally depressed
No suicidal thoughts
Never considered euthanasia
No Reanimation in case of cardiac arrest

- **Control subjects n=820**
- **X Locked-in patients n=65**

Bruno et al., *in preparation*
Bruno et al., *Pediatric Neurology* 2009
Quality of Life

**Case 2**

17-year-old girl
LIS for 1 year
Good social interactions
Occasionally depressed
No suicidal thoughts
Never considered euthanasia
Reanimation in case of cardiac arrest

Better than ever before
+ 5  As good as best period in my life
+ 4  Almost as good as best period in my life
+ 3  Very good
+ 2  Good
+ 1  Rather a bit on the good side
0   Neither good nor bad
- 1  Rather a bit on the bad side
- 2  Bad
- 3  Very bad
- 4  Almost as bad as worst period in my life
- 5  As bad as worst period in my life

Worse than ever before

- Control subjects \( n = 820 \)
- X Locked-in patients \( n = 65 \)

Bruno et al., *in preparation*
Bruno et al., *Pediatric Neurology* 2009

www.comascience.org
March 20, 2016

The Coma Science Society

Locked-in: Gefangen im eigenen Körper
Karl-Heinz Pantke

If you want to talk to me, I look up for yes
Julia Tavalaro and Richard Tayson

Putain de silence
Philippe Vigand, Stéphane Vigand

A Love Story
Anne Cherrier

Laetitia Bohn-Derrien

Temoignage
Fervane

March 20, 2016
Conclusions
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
Laureys & Boly, Nature Clinical Practice 2008
Owen, Schiff & Laureys, Prog Brain Res 2009
THANK YOU

Slides can be downloaded from www.comascience.org

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Athena Demertzi, Marie-Curie
Olivia Gosseries FNRS
Camille Chatelle FNRS
Marie Thonnard non-FRIA
Victor Cologan FRIA
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Muriel Kirsch MD
Audrey Maudoux MD FNRS
Isabelle Lutte MD ULB

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Andrea Soddu Physics
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