Eyes Wide Open, Brain Wide Shut?

(un)consciousness in the vegetative state

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Neurology Dept
University & University Hospital of Liège
Belgium

David Kopf lecture
on Neuroethics
Oct 20, 2009, Chicago

www.comascience.org
Disorders of consciousness

Terry Schiavo °1963, vegetative 1990, † 2005

« Irreversible loss of the capacity for consciousness and social interaction equals death »
- Robert Veatch, 1975

« Should organs from patients in permanent vegetative state be used for transplantation? »
- Hoffenberg, Lancet 1997
Reducing consciousness to 2D

Laureys, *Trends in Cognitive Sciences*, 2005
Reducing awareness to 2D

Scientific interest
Consciousness ≠ whole brain

Laureys, Owen & Schiff, *Lancet Neurology*, 2004
Consciousness ≈ frontoparietal

areas that are systematically dysfunctional in the vegetative state

areas that recover metabolism after recovery from the vegetative state

Laureys et al, Neuroimage 1999

Laureys et al, J Neurol Neurosurg Psychiatry, 1999
Precuneus ≈ hub in the network

Laureys et al, Lancet Neurology, 2004

Axonal re-growth in Terry Wallis

Voss et al, J Clin Invest, 2006
Precuneus ≈ hub in the network
Frontoparietal “global workspace”

- Preserved arousal
  - No awareness

- No arousal
  - No awareness

(sleep data: Maquet et al 2000; anesthesia: Kaisti et al 2002)
Frontoparietal “global workspace”

Laureys, *Trends in Cognitive Sciences* 2005
Consciousness ≠ primary cortex

Laureys et al, *Brain*, 2000
Boly et al, *Archives of Neurology*, 2004
Consciousness ≈ thalamo-cortical

Intralaminar nuclei “reconnections” in spontaneous recovery from the vegetative state

Intralaminar nuclei stimulation induces “recovery” from the minimally conscious state

Laureys et al, Lancet 2000
Schiff et al., Nature 2007
Two awareness networks

GLOBAL NEURONAL WORKSPACE

INTERNAL AWARENESS NETWORK

EXTERNAL AWARENESS NETWORK

External and internal awareness

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

Peri-luminal laser stimulation on the hand (24 subjects)

perceived (433±23 mJ) > unperceived (438±21 mJ)

(also Dehaene et al, *Nat Rev Neurosci* 2001; Rees et al, *Nat Rev Neurosci* 2001)

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

Auto-referential stimuli

“Resting state” default brain activity

Anti-correlation of internal and external awareness networks

Boly et al, Ann NY Acad Sci 2009

Spontaneous brain fluctuations predict conscious perception of external stimuli

Boly et al, PNAS 2007

Switching 1/20s (0.05 Hz)
“Resting state” default brain activity

Boly et al, Human Brain Mapping 2009
Clinical interest
Disorders of consciousness

Laureys, *Scientific American* 2007

**Consciousness | Neural correlates | Diagnosis | Prognosis | Treatment | Ethics | Conclusion**

**Permanent Minimally Conscious State?**

**1952, artificial respirator (Ibsen, Copenhagen)**
Redefinition of death based on neurological criteria

**1966**
Plum & Posner (NY)

**1972**
Jennett (Glasgow) & Plum (NY)

**1994, Multi-Society Task Force on PVS**
>1 year (traumatic)
>3 months (non-traumatic; anoxic)

**2002, Aspen Workgroup**

**Permanent Minimally Conscious State**
QUESTIONS

do not write your name / answer by YES or NO

<table>
<thead>
<tr>
<th>Age category:</th>
<th>&lt; 18 years</th>
<th>18-30 years</th>
<th>31-50 years</th>
<th>&gt; 50 years</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nationality:</td>
<td>USA</td>
<td>European</td>
<td>Other</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Profession:</td>
<td>Medical doctor</td>
<td>Healthcare</td>
<td>Other</td>
<td></td>
<td></td>
<td></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)?

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 on functional neuroimaging would this change your diagnosis?
Diagnosis
Misdiagnosis of vegetative state

n=103 post-comatose patients

45 clinical consensus diagnosis of “vegetative state”

27 Coma Recovery Scale diagnosis

40% misdiagnosis of VS

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

Vanhaudenhuyse et al
*J Neurol Neurosurg Psychiatry 2008*
Command following on fMRI

Owen, Coleman, Boly, Davis, Laureys & Pickard, Science, 2006
BOLD increase in mental imagery ≠ “automatic” brain response

Soddu et al, Prog Brain Res 2009
### Communication via fMRI

<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="image1" alt="fMRI response" /></td>
<td>1st (0.89)</td>
</tr>
<tr>
<td></td>
<td>onset 0s</td>
<td><img src="image2" alt="fMRI response" /></td>
<td></td>
</tr>
<tr>
<td></td>
<td>offset 10s</td>
<td><img src="image3" alt="fMRI response" /></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>brain location 'mental calculation' ROI</td>
<td><img src="image4" alt="fMRI response" /></td>
<td>2nd (0.52)</td>
</tr>
<tr>
<td></td>
<td>onset 5s</td>
<td><img src="image5" alt="fMRI response" /></td>
<td></td>
</tr>
<tr>
<td></td>
<td>offset 10s</td>
<td><img src="image6" alt="fMRI response" /></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>brain location 'motor imagery' ROI</td>
<td><img src="image7" alt="fMRI response" /></td>
<td>3rd (0.06)</td>
</tr>
<tr>
<td></td>
<td>onset 5s</td>
<td><img src="image8" alt="fMRI response" /></td>
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</tr>
<tr>
<td></td>
<td>offset 15s</td>
<td><img src="image9" alt="fMRI response" /></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>brain location 'mental calculation' ROI</td>
<td><img src="image10" alt="fMRI response" /></td>
<td>4th (-0.20)</td>
</tr>
<tr>
<td></td>
<td>onset 10s</td>
<td><img src="image11" alt="fMRI response" /></td>
<td></td>
</tr>
<tr>
<td></td>
<td>offset 20s</td>
<td><img src="image12" alt="fMRI response" /></td>
<td></td>
</tr>
</tbody>
</table>
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
The problem of aphasia in the assessment of consciousness in brain-damaged patients

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

\textit{Progress in Brain Research}, Vol. 177
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Metabolism in language network
Prognosis

Laureys & Boly
What is it like to be vegetative or minimally conscious?
Figure 5. Linear discriminant analysis. Plotting the two discriminant functions (or canonical roots) against each other separated the GOS 1–3 group (unfavorable outcome, closed circles), the GOS 4–5 group (favorable outcome, open circles), and the control group (open squares). NAA, N-acetyl aspartate; Cr, creatine; GOS, Glasgow Coma Scale; DTI, diffusion tensor imaging.
fMRI predictor of outcome?

Vegetative vs. minimally conscious states

ATYPICAL
‘HIGH LEVEL’ CORTICAL ACTIVATION

Activation studies predict outcome

n=48 patients

6 fMRI studies (n=17) and 8 PET (n=32)
32 non-traumatic

38% “high level” activation (n=18)
- 7 traumatic
- 82% (9/11) recovered consciousness (6 traumatic)
- 93% specificity
- 69% sensitivity

62% absent or primary “low level” cortical activation (n=30)
- typical activation pattern (n=25; 52%; 8 traumatic)
- 84% (21/25) failed to recover (7 traumatic)
- no cortical activation (n=5; 10%; 1 traumatic)
- 100% (4/4) failed to recover (1 traumatic)

Di et al, Clinical Medicine, 2008
EEG : bi-spectral index

Consciousness | Neural correlates | Diagnosis | Prognosis | Treatment | Ethics | Conclusion


Also see
Tue 8:00
541.1
*Victor et al*
on coherence

Treatment

- symptomatic
- curative

"...a (woman’s) brain is a mystery... and even more so in this state”

Pedro Almodovar - Hable con ella
Do you think that...

5A patients in a vegetative state can feel pain?
5B patients in a vegetative state should receive pain medication?

6A patients in a minimally conscious state can feel pain?
6B patients in a minimally conscious state should receive pain medication?

7A patients in a locked-in syndrome can feel pain?
7B patients in a locked-in syndrome should receive pain medication?

Assuming surrogate informed consent, is it acceptable to do functional neuroimaging studies on:
8A. pain perception in the vegetative state?
8B. perception of thirst and hunger in the vegetative state?

9A. pain perception in the minimally conscious state?
9B. perception of thirst and hunger in the minimally conscious state?
Nociception and pain

Nociception Coma Scale

<table>
<thead>
<tr>
<th>Score</th>
<th>Item</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Motor Response</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Localization to Nerve Stimulation</td>
<td>The non-stimulated limb must locate and make contact with the stimulated body 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>Slow, stereotyped deviation or extension of the upper and/or lower extremities across immediately after the stimulus is applied.</td>
</tr>
<tr>
<td>0</td>
<td>None/Trivial</td>
<td>There is no discernible movement following application of noxious stimulation, secondary to hyperesthesia or flaccid muscle tone.</td>
</tr>
<tr>
<td></td>
<td>Verbal Response</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Intelligible Verbalization</td>
<td>Production of words in response to noxious stimulation. Each verbalization must consist of at least 1 complex-vocal consonant (C-V-C) triad. For that triad,</td>
</tr>
<tr>
<td>2</td>
<td>Vocalization/Oval Movement</td>
<td>As above.</td>
</tr>
<tr>
<td>1</td>
<td>Groans</td>
<td>Vocalization is analogous to groans.</td>
</tr>
<tr>
<td>0</td>
<td>None</td>
<td>No vocalization.</td>
</tr>
<tr>
<td></td>
<td>Visual Response</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Fixation</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Eye movements</td>
<td>Fixation point</td>
</tr>
<tr>
<td>1</td>
<td>Startle</td>
<td>NO RESPONSE, AWAKENING, PERRIGEY</td>
</tr>
<tr>
<td>0</td>
<td>None</td>
<td>NO RESPONSE</td>
</tr>
<tr>
<td></td>
<td>Facial Expression</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Cry</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Grimace</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Oral reflexive movements/Startle response</td>
<td>Chomping of jaws, tongue pumping, twisting, chewing movement.</td>
</tr>
<tr>
<td>0</td>
<td>None</td>
<td>There is no discernible facial expression following application of noxious stimulation.</td>
</tr>
</tbody>
</table>

Demertzi et al, Prog Brain Res, 2009

Schnakers et al, Pain, in press

Consciousness | Neural correlates | Diagnosis | Prognosis | Treatment | Ethics | Conclusion
Do they feel pain?

Noxious electrical stimulation

Low level disconnected cortical activation

Pain in minimally conscious state


http://neurology.thelancet.com

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

Schnakers et al. *J Neurol Neurosurg Psychiatry* 2008

Also see
Tue 9:00
541.6
*Williams et al* on zolpidem
Curative treatment: Deep brain stimulation?


Object Naming During Titration

<table>
<thead>
<tr>
<th>Intelligible</th>
<th>Non-intelligible</th>
<th>No response</th>
</tr>
</thead>
<tbody>
<tr>
<td>ON</td>
<td>P&lt;0.001</td>
<td>OFF</td>
</tr>
</tbody>
</table>
Ethical challenges
Do you think that...

10A. Invasive interventions are justified to 
**diagnose** and study disorders of 
consciousness or to provide 
**prognostic** information?

10B. Invasive interventions are justified to develop 
**treatments** for 
disorders of consciousness

Do you think that it is acceptable to withhold or withdraw treatment in patients:
11. in the vegetative state (> 1 year)?
12. in the minimally conscious state (> 1 year)?
13. in the locked-in syndrome (> 1 year)?

14. Are you religious?
   If yes: Christian Muslim Jewish Hindu Other
Ethical framework

Neuroimaging and Disorders of Consciousness: Envisioning an Ethical Research Agenda

Joseph J. Fins, Weill Medical College of Cornell University*
Judy Illes, University of British Columbia* 
James L. Bernat, Dartmouth Medical School** 
Joy Hirsch, Columbia University** 
Steven Laureys, University of Liege** 
Emily Murphy, Stanford Law School**

*Co-lead authors. 
**Equal authors in alphabetical order.

End-of-life decisions

LETTER TO THE EDITOR

Organ donation after physician-assisted death

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Organ Procurement After Euthanasia: Belgian Experience

D. Ysebaert, G. Van Beumen, K. De Greef, J.P. Squifflet, O. Detry, A. De Roover, M.-H. Delbouille,
W. Van Donink, G. Roeyen, T. Chapelle, J.-L. Bosmans, D. Van Raemdonck, M.E. Faymonville,
S. Laureys, M. Lamy, and P. Cras
Quality of life in LIS

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

Reintegration to Normal Living Index in Amyotrophic Lateral Sclerosis (n=30; duration 6±5 y)

Laureys et al, Prog Brain Res 2005
Lulé et al, Prog Brain Res 2009
Conclusion
Conclusions

Neural correlates of awareness
≈ fronto-parietal global neuronal workspace
≈ thalamo-cortical functional connectivity

Diagnostic uncertainty
≈ 40% error rate for the vegetative state

Prognostic uncertainty
await (f)MRI prospective multicenter studies

Therapeutic challenges
symptom & pain control / curative

Ethical issues

Owen, Schiff & Laureys, *Prog Brain Res*, 2009

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THANK YOU
slides can be downloaded on website
EU funded positions open

PhD candidates:
Audrey Vanhaudenhuyse
Marie-Aurélie Bruno
Olivia Gosseries
Athena Demertzi
Camille Chatelle
Marie Thonnard
Victor Cologan
Jean-Floris Tshibanda MD
Pierre Boveroux MD
Muriel Kirsch MD
Audrey Maudoux MD
Isabelle Maudoux MD

Collaborations:
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Milano M Massimini et al
Wisconsin G Tononi et al
Tubingen & Wurzburg A Kübler
Paris L Puybasset et al
Hangzhou China H Di
Salzburg M Schabus
Lyon F Perrin
Weizmann R Malach et al
Naples M Papa

PhDs:
Melanie Boly MD
Didier Ledoux MD
Caroline Schnakers
Quentin Noirhomme Engineering
Andrea Soddu Physics
Betina Sorger Maastricht
Dorothee Lule Tubingen

Visiting fellows: Natalia Lapitskaia, Remy Lehembre, Jonathan Orban, Francisco Gomez...

SfN-sponsored Neuroethics Social Hour
Tuesday 6:30-8:30, N139 convention center
www.comascience.org