Neurophysiology of “vegetative” unresponsive wakefulness & minimally responsive patients

Steven Laureys
Coma Science Group
Cyclotron Research Centre & Neurology Dept
University & University Hospital of Liège
Belgium

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Reducing consciousness to 2D

Laureys, Trends in Cognitive Sciences, 2005
Consciousness ≠ whole brain

Laureys et al, Lancet Neurology, 2004

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Consciousness \approx \text{frontoparietal}

Areas systematically dysfunctional in "vegetative" state

Laureys et al, *Neuroimage* 1999

Areas recovering metabolism after recovery from "vegetative" state

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

Conscious controls (n=110)  Vegetative state (n=33)
Locked in syndrome (n=5)  Minimally conscious state (n=7)

Axonal re-growth in Terry Wallis

Laureys et al, Lancet Neurology, 2004

Voss et al, J Clin Invest, 2006
Frontoparietal "global workspace"

- **Persistent vegetative state**: preserved arousal, no awareness
- **Coma**: no arousal, no awareness
- **Sleep**: no arousal, no awareness
- **General anesthesia**: no arousal, no awareness

(sleep data: Maquet et al 2000; anesthesia: Kaisti et al 2002)
Consciousness ≠ primary cortex

"VEGETATIVE" UNRESPONSIVE

MINIMALLY RESPONSIVE

Laureys et al, *Brain*, 2000
Boly et al, *Archives of Neurology*, 2004
Consciousness ≈ top-down

Consciousness \approx \text{thalamo-cortical}

Intralaminar nuclei "reconnections" in spontaneous recovery from "vegetative" unresponsive state

Intralaminar nuclei stimulation induces "recovery" from minimally responsive state

Laureys et al, Lancet 2000

Schiff et al, Nature 2007
Two awareness networks

Laureys, *Scientific American* 2007

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External and internal awareness

EXTERNAL (SENSORY) AWARENESS (laser stimulation)

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

Boly et al, PNAS 2007

INTERNAL (SELF) AWARENESS (own name)

Perrin et al, Neuropsychologia 2005
Qin et al, Human Brain Mapping, 2010
“Resting” default mode connectivity

Vanhaudenhuyse et al, Brain 2010
Boly et al, Human Brain Mapping 2009

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Clinical interest

- Coma
- Arousal = eye opening
- Vegetative/Unresponsive
- Minimally responsive
- Communication?
- Awareness? = response to command or non-reflex movements
- Moderate disability
- Severe disability
- Live independently
- Professional reinsertion
- Good recovery

Laureys et al., Current Opinion in Neurology, 2005
A new name for « vegetative »

Unresponsive wakefulness syndrome: a new name for the vegetative state or apallic syndrome

Steven Laureys, Gastone G Celesia, François Cohadon, Jan Lavedrisse, José León-Carrion, Walter G Sanmiguel, Leon Szaboni, Erich Schmutzhard, Klaus R von Wild, Adam Zeman, and Giuliano Dolce for the European Task Force on Disorders of Consciousness.

http://www.biomedcentral.com/1741-7015/8/68

"There's nothing we can do... he'll always be a vegetable."

Laureys et al, BMC Medicine 2011
Diagnostic error

n=103 post-comatose patients
- 45 clinical consensus diagnosis 'vegetative state'
- 18 signs of awareness (Coma Recovery Scale)

40% potential misdiagnosis

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

Vanhaudenhuyse et al
*Neurol Neurosurg Psychiatry 2008*
Signs of consciousness on fMRI

Owen, Coleman, Boly, Davis, Laureys & Pickard, Science, 2006

“He's not in coma... he's playing tennis!”
Yes-No communication with fMRI

Healthy Subject

Answers « YES »

« Vegetative State »

Answers « NO »

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

www.comascience.org
EEG-based Brain Computer Interfaces

www.decoderproject.eu

Coma or total locked-in syndrome?
21-y old woman
basilar artery thrombosis - day 49

Pz (µV)
-25
-20
-15
-10
-5
0
5
10
15
20
25

-200
50
100
150
200
250
300
350
400
450
500
550
600
650
700
750
800
850
900
950
1000

Ms

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

controls

frequencies (Hz)

time (ms)

theta
synchronization

MCS

frequencies (Hz)

time (ms)

theta
synchronization

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

Fellinger et al Clin Neurophysiol, 2011
Predicting outcome in chronic DOC

ACTIVATION TO THE OWN NAME

ATYPICAL 'HIGH LEVEL' CORTICAL ACTIVATION

Perrin et al, *Arch Neurol* 2006


Understanding plasticity

Landness and Bruno et al, *Brain*, in press

www.comascience.org
Multimodal imaging

Bruno et al, Prog Brain Res, 2011
Tshibanda et al, Neuroradiology, 2010
Nociception and pain

Do you think that patients in a vegetative state can feel pain?

- Medical doctors: 56% Yes, 44% No
- Paramedical professionals: 66% Yes, 32% No

Do you think that patients in a vegetative state can feel pain?

- Religious caregivers: 64% Yes, 36% No
- Non-religious caregivers: 52% Yes, 42% No

Nociception Coma Scale

**Motor Response**
1. Localization to auditory stimulation
2. Pupillary Light Reflex
3. Pain Withdrawal
4. Abnormal Posturing
5. None

**Verbal Response**
1. Inaudible Verbalization
2. Vocalization: Oral Movement
3. Gagging
4. None

**Visual Response**
1. Fixation
2. Eye movement: Stare
3. No change

**Facial Expression**
1. Cry
2. Grimace
3. Oral effector movements: Stare response
4. None

Total score >7/12 = analgesic treatment

Demertzi et al, Prog Brain Res, 2009

Schnakers et al, Pain, 2010
Do they feel pain?

Noxious electrical stimulation

a Healthy control
b Brain death
c Vegetative state

Low level disconnected cortical activation

Pain in minimally conscious state

http://neurology.thelancet.com

Curative treatment: Drugs? no evidence based therapy

Demertzi et al Expert Rev Neurotherapeutics 2008
Schnakers et al J Neurol Neurosurg Psychiatry 2008
Ethical issues

Attitudes towards end-of-life issues in disorders of consciousness: a European survey

A. Demertzi · D. Ledoux · M.-A. Bruno · A. Vanhaudenhuyse · O. Gosselies · A. Soddu · C. Schnakers · G. Moonen · S. Laureys

2,475 medical professionals

I would like to be kept alive if I were in a chronic...

![Bar chart showing attitudes towards end-of-life issues in VS and MCS]

Fig. 2 End-of-life attitudes towards the vegetative state (VS) and minimally conscious states (MCS) depending on geographic region. Bars represent % agreement (white: Northern, grey: Central, black: Southern Europe; *P < 0.05, **P < 0.001)

Demertzi et al, J Neurology 2011
Quality of life

A survey on self-assessed well-being in a cohort of chronic locked-in syndrome patients: happy majority, miserable minority

Marie-Aurélie Bruno, Jan L Bernheim, Didier Ledoux, Frédéric Pellias, Atheria Demertzis, Steven Laureys

Bruno et al, BMJ Open, 2011
**Translational research**

Neural correlates of conscious awareness
- ≈ emergent property of widespread fronto-parietal connectivity

Diagnostic use
- ≈ 40% misdiagnosis

Prognostic use
- multimodal MRI

Therapeutic use
- pain treatment / deep brain stimulation thalamus

**Ethical issues**

- EMG, ERP or fMRI might reveal subclinical command-following
- EEG (brain–computer interfaces) or real-time fMRI might enable communication that is not dependent on motor pathways

Coma → Vegetative state → Minimally conscious state → Emergence
- Eye-opening and reflex behavior only
- Voluntary movements or command-following
- Interactive communication

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

www.comascience.org
New knowledge, new nosology

- Coma
  - ClinicalTesting
    - BrainDeath
    - Vegetative/Unresponsive
    - ClassicalLocked-In
      - MinimallyConsciousState
        - MCS- (non-reflex movements)
        - MCS+ (command following)
          - Emergence from MCS (communication)
            - SevereDisability
              - GoodRecovery
  - Para-ClinicalTesting
    - FunctionalLocked-In

THANK YOU

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