Imaging of CNS responses in patients with impaired levels of consciousness

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Terry Schiavo °1963, vegetative 1990, † 2005

« Beyond any doubt whatsoever, Terri is in a vegetative state »
- Ronald Cranford MD, Neurology, Minneapolis, MN

« There is a great likelihood that Terri is in a minimally conscious state »
- William Cheshire MD, Neurology, Mayo Clinic, Jacksonville, FL

« 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

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Problems

Clinical
  Diagnosis, prognosis & treatment

Scientific
  Neural correlates of consciousness

Ethical
  Right to die, right to live
Overview

Disorders of consciousness
Clinical evaluation
Electrophysiology
Neuroimaging
Ethics & quality of life
Mind brain beliefs

- The Mind and Brain are two separate things: 67% agree, 33% disagree.
- The Mind is fundamentally physical: 36% agree, 64% disagree.
- Some spiritual part of us survives death: 70% agree, 30% disagree.
- Each of us has a soul which is separate from the body: 65% agree, 35% disagree.

Zeman 2005 in The Boundaries of Consciousness (Ed) Laureys

www.comascience.org
consciousness ?
consciousness ?
consciousness ?
what is it like to be bat?

Thomas Nagel The Philosophical Review 1974
Consciousness

Laureys, Trends in Cognitive Sciences, 2005

www.comascience.org
Disorders of consciousness
Clinical entities

- Acute Brain Injury
- Coma
  - Fast Recovery
  - Vegetative State
    - Locked-In Syndrome
    - Brain Death
  - Permanent Vegetative State
  - Minimally Conscious State
    - Recovery of Consciousness
- Permanent Minimally Conscious State
Clinical evaluation
Brain death criteria

Wijdicks, NEJM 2001
Motor activity in brain death

residual spinal activity:
- finger jerks
- undulating toe flexion sign
- triple flexion response
- Lazarus sign
- pronation-extension reflex
- facial myokymia

Lazarus' sign in brain death
Bueri et al Mov Disord. 2000, 15:583-6
Reflex versus voluntary

“VOLUNTARY” / “WILLED”

“REFLEX” / “AUTOMATIC”
Blink and you live

Laureys et al., Progress in Brain Research, 2005
Glasgow Coma Scale

Teasdale & Jennett, Lancet, 1974

E - eye opening

C. Not assessable

4. Spontaneous

3. To speech

2. To pain

1. None

AROUSAL

Laureys et al., Yearbook of Intensive Care Medicine, 2002
Glasgow Coma Scale

V - verbal response

1. None
2. Incomprehensible sounds
3. Inappropriate words
4. Confused speech
5. Oriented conversation

T. Not assessable

Laureys et al., Yearbook of Intensive Care Medicine, 2002

Teasdale & Jennett, Lancet, 1974

Teasdale & Jennett, Yearbook of Intensive Care Medicine, 2002
Glasgow Coma Scale

M - motor response

6. Obeys simple commands
   - Smiling face
   - Commands given

5. Localizes pain
   - Pasting face
   - Pain given

4. Withdraws (normal flexion)
   - Smiling face
   - Flexion given

3. Stereotyped flexion
   - Smiling face
   - Flexion given

2. Stereotyped extension
   - Smiling face
   - Extension given

1. None
   - Smiling face
   - No response given
Glasgow Liège Scale

**R – brainstem reflexes**

5. Fronto-orbicular

4. Vertical oculovestibular

3. Pupillary light

2. Horizontal oculovestibular

1. Oculocardiac

0. None  BRAINDEAD

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Laureys et al., *Yearbook of Intensive Care Medicine*, 2002

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Born et al., *Neurosurgery*, 1985
# Coma Recovery Scale

## Échelle de Récupération du Coma

**Version Revue Française**

**Formulaire de rapport**

<table>
<thead>
<tr>
<th>Patient:</th>
<th>Date atteinte cérébrale:</th>
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<tbody>
<tr>
<td>Etiologie:</td>
<td>Date admission:</td>
</tr>
<tr>
<td>Diagnostic initial:</td>
<td>Date:</td>
</tr>
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<td>Examineur:</td>
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### Fonction Motrice

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<thead>
<tr>
<th>Score</th>
<th>Description</th>
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<tbody>
<tr>
<td>6</td>
<td>Utilisation fonctionnelle des objets*</td>
</tr>
<tr>
<td>5</td>
<td>Réaction motrice automatique*</td>
</tr>
<tr>
<td>4</td>
<td>Manipulation d’objets*</td>
</tr>
<tr>
<td>3</td>
<td>Localisation des stimulations nociceptives*</td>
</tr>
<tr>
<td>2</td>
<td>Flexion en retrait</td>
</tr>
<tr>
<td>1</td>
<td>Posture anormale stéréotypée</td>
</tr>
<tr>
<td>0</td>
<td>Néant / Flaccidité</td>
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### Fonction Oromotrice/Verbaire

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
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<tbody>
<tr>
<td>3</td>
<td>Production verbale intelligible*</td>
</tr>
<tr>
<td>2</td>
<td>Production vocale / Mouvements oraux</td>
</tr>
<tr>
<td>1</td>
<td>Réflexes oraux</td>
</tr>
<tr>
<td>0</td>
<td>Néant</td>
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</table>

### Communication

<table>
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<th>Score</th>
<th>Description</th>
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<tbody>
<tr>
<td>2</td>
<td>Fonctionnelle : exacte*</td>
</tr>
<tr>
<td>1</td>
<td>Non fonctionnelle : intentionnelle*</td>
</tr>
<tr>
<td>0</td>
<td>Néant</td>
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</table>

### Éveil

<table>
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<th>Score</th>
<th>Description</th>
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<tr>
<td>3</td>
<td>Attention</td>
</tr>
<tr>
<td>2</td>
<td>Ouverture des yeux sans stimulation</td>
</tr>
<tr>
<td>1</td>
<td>Ouverture des yeux avec stimulation</td>
</tr>
<tr>
<td>0</td>
<td>Aucun éveil</td>
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</table>

**Score Total**

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*Indique l'émergence de l'état de conscience minimale* 
*Indique un état de conscience minimale*
EEG & consciousness

Patient 1

Awake

Asleep

Patient 2

Nicolas Schiff, Cornell U, NY

www.comascience.org
• **frequency analysis**: 
  ratio of power in high and low beta ranges

• **bispectral analysis**: 
  ratio of bicoherence in fast & slow frequencies

• **time domain analysis**: 
  burst suppression ratio
EEG-BIS in sleep
EEG-BIS in coma

Schnakers, Majerus and Laureys, Neuropsychological Rehabilitation, 2005

www.comascience.org
Cognitive evoked potentials

minimally conscious state

Laureys, Perrin et al., Neurology, 2004

www.comascience.org
P300 to given name

Perrin et al, Archives in Neurology, 2006
Neuroimaging

① resting brain function
② brain activation studies
  • passive paradigms
  • active paradigms
Neuroimaging
Resting metabolism

Laureys, Owen & Schiff, Lancet Neurology, 2004
(sleep data from Pierre Maquet; anesthesia data from Mike Alkire)
Global metabolism

Laureys, Maquet, Moonen, Encyclopedia of Neuroscience, 2007

www.comascience.org
Global metabolism

POST-HERNIATION SEVERE BILATERAL PARAMEDIAN MESODIENCEPHALIC INJURIES

Schiff et al, Brain 2002
Regional changes

Laureys et al, New Encyclopedia of Neuroscience (Ed.) Larry Squire, in press

www.comascience.org
Functional connectivity

Laureys et al., Lancet, 2000
Sleep

Maquet et al. Nature 1996
Sleep

adapted from Maquet et al Progress in Brain Research 2005
General anesthesia: propofol

16 volunteers
corrected P < 0.05

Kaisti et al, Anesthesiology 96 (2002) 1358-70
General anesthesia
Absence seizures

Negative correlation with GSWD

Laufs et al, *Epilepsia* 2006
Absence seizures

paroxysmal loss of consciousness
bilateral synchronous spike-wave discharges
staring,
cessation of ongoing activities,
some automatic activity (e.g., turning and rotating movements, raising and lowering extremities)

Salek-Haddadi et al.,
Temporal lobe epilepsy

Complex partial seizure n=8

Blumenfeld et al, Cerebral Cortex, 2004
Sleepwalking

Patient compared to 24 controls

ECD-SPECT
Conscious “default” resting state

www.comascience.org
Consciousness area?

Conscious controls (n=110)  Vegetative state (n=33)

Locked in syndrome (n=5)  Minimally conscious state (n=7)

Laureys, Owen and Schiff, Lancet Neurology, 2005
Precuneus in vegetative state
“miracle” recovery

Patient 1

Voss, ... Schiff, Journal of Clinical Investigation, 2006
Precuneus in sleep

Data from Maquet, Laureys and Peigneux (n=22)
Precuneus in anesthesia

Data from Bonhomme and Fiset (n=8)
Precuneus in dementia

Salmon et al, Progress in Brain Research, 2005
Neuroimaging

① resting brain function
② brain activation studies
  • passive paradigms
  • active paradigms
Do they feel pain?
Do they feel pain?
Vegetative is not brain dead

Laureys, Nature Reviews Neuroscience, 2006
Cortical activation

Controls (n=15)

PVS (n=15)
Disconnected S1

A

B

Laureys et al., Neuroimage, 2002
"...a (wo)men’s brain is a mystery... and even more so in this state."
Do they hear anything?

Laureys et al., Brain, 2000
Boly et al, Archives of Neurology, 2004
Magnetoencephalography

PVS
somatosensory evoked magnetic field

CONTROL
time-locked gamma band activity

from Urs Ribary, Nico Schiff et al, NY
Auditory disconnection

Boly et al Archives of Neurology, 2004

www.comascience.org
Emotional processing

Laureys et al., Neurology, 2004

www.comascience.org
Speech processing in MCS

“Healthy” volunteer
29 year old male

Minimally conscious patient
33 year old male

Schiff et al., Neurology, 2005
Neuroimaging

① resting brain function
② brain activation studies
  • passive paradigms
  • active paradigms
When thoughts become action

Boly et al, NeuroImage, 2007
Passive paradigms

Owen, Coleman, Boly, Davis, Laureys and Pickard, Science, 2006
Active paradigms

Owen, Coleman, Boly, Davis, Laureys and Pickard, Science, 2006
fMRI precedes the clinic

vegetative | minimally conscious

Di et al, Neurology, 2007
Ethics & quality of life
Stopping the treatment

“therapeutic obstinacy must have its limits!!”
Locked-in syndrome (LIS)
Quality of life in LIS

Short Form-36
n=17
duration 6±4 y
Conclusions
Not all “coma”

NORMAL CONSCIOUSNESS  COMA  VEGETATIVE STATE  MINIMALLY CONSCIOUS STATE  LOCKED-IN SYNDROME

AROUSAL  AWARENESS  AROUSAL  AWARENESS  AROUSAL  AWARENESS  AROUSAL  AWARENESS

Laureys, Owen and Schiff, Lancet Neurology, 2005

www.comascience.org
Conclusions

• Diagnosis
  • misdiagnosis (40%)
  • need for objective markers: EEG and ERP?
  • behavioral evaluation (CRS-R) “gold standard”

• Prognosis
  • fMRI precedes the clinic

• Treatment
  • objectively measure effect of treatment
Conclusions

- **Physiopathology**
  - **Vegetative state**
    disconnection syndrome with impaired fronto-parietal “workspace”
  - **Minimally conscious state**
    preserved pain and emotional processing

- **Ethics**
  - **Locked-in syndrome**
    right to care, right to die