Diagnosis and treatment in patients with disorders of consciousness

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Coma Science Group – GIGA Consciousness, University of Liège, Belgium
Neurorehabilitation Lab, Harvard Medical School, USA
Overview

- Disorders of Consciousness
  - Clinical entities
  - Consciousness and the brain
  - Brain processing in DOC

- Diagnosis
  - Consciousness
  - Nociception and pain

Break
Overview

- Paraclinical diagnosis
  - Active paradigms
  - Passive paradigms
  - Case reports
- Treatments
  - Pharmacological
  - Brain stimulation
- Locked-in Syndrome
- Near-death experiences
Disorders of consciousness

Clinical entities
Clinical entities

Acute Brain Injury → Coma

- Vegetative State
  - 1972: Jennett (Glasgow) & Plum (NY)
  - 1966: Plum & Posner (NY)
  - Locked-In Syndrome

- Fast Recovery

- Minimally Conscious State
  - 2002, Aspen Workgroup

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

- Recovery of Consciousness

- Permanent Minimally Conscious State

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

Laureys, Scientific American, 2007
Clinical entities

- COMA
- VEGETATIVE STATE
- MINIMALLY CONSCIOUS STATE
- NORMAL CONSCIOUSNESS

Coma

- No eyes opening
- No sign of consciousness
- Lasting min 1 hour

Posner et al, 2007
Vegetative/unresponsive wakefulness syndrome

- No sign of consciousness
- No environment interaction
- No voluntary behavior in response to visual, auditory, tactile and painful stimuli
- No language comprehension – no language expression
- Wake-sleep cycle

Multi-Society Task Force on Persistent Vegetative State guidelines, 1994
Laureys et al., 2010
There's nothing we can do... he'll always be a vegetable.

Laureys et al, *BMC Medicine* 2011
Minimally conscious state

- Limited but clearly discernible evidence of self or environmental awareness - one or more of the following behaviors:
  - Following simple commands
  - Gestural or verbal yes/no responses (regardless of accuracy)
  - Intelligible verbalization
  - Purposeful behavior, including movements or affective behaviors that occur in contingent relation to relevant environmental stimuli:
    - appropriate smiling/vocalizations or gestures
    - reaching for objects
    - touching or holding objects
    - visual pursuit or fixation

Aspen Workgroup, 2002; Bruno & Vanhaudenhuyse et al., 2011
MCS: new terminology

Minimally Conscious state

MCS +
Following simple command

MCS+ > MCS-

MCS -
Pain localisation
Visual pursuit
Accurate smiling or crying

Bruno & Vanhaudenhuyse et al., 2011; Bruno et al., 2011
Minimally conscious state

- **MCS plus**
  - reproducible command following
  - intelligible verbalizations
  - intentional communication

- **MCS minus**
  - Purposeful behavior, including movements or affective behaviors that occur in contingent relation to relevant environmental stimuli:
    - appropriate smiling/vocalizations or gestures
    - reaching for objects
    - touching or holding objects
    - visual pursuit or fixation

Aspen Workgroup, 2002; Bruno & Vanhaudenhuyse et al., 2011
Minimally conscious state

Emergence from MCS:

- Functional interactive communication
- Functional use of two different objects

Aspen Workgroup, 2002; Bruno & Vanhaudenhuyse et al., 2011
Consciousness # whole brain

Laureys et al, Lancet Neurology, 2004
Consciousness $\approx$ 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

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

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

Laureys et al, Lancet Neurology, 2004

Axonal re-growth in Terry Wallis

Voss et al, J Clin Invest, 2006
Two awareness networks

GLOBAL NEURONAL WORKSPACE

INTERNAL AWARENESS NETWORK

EXTERNAL AWARENESS NETWORK

Boly... Laureys, *Human Brain Mapping* 2008
External vs internal awareness

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

Vanhaudenhuyse et al, J Cogn Neurosci, 2010
Disorders of consciousness

Brain processing in DOC
Can they feel pain?

Schnakers, Chatelle, Majerus, Gossseries, Deval and Laureys, Experts Rev in Neurother, 2010
Can they hear us?

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

Meaningless Noise

Acoustically Matched Cries

Patient’s Own Name

Laureys et al., Neurology, 2004
Conclusion

- DOC: different clinical entities associated with various levels of consciousness: coma, VS/UWS, MCS (plus and minus)
- Neural correlates of conscious awareness
  - ≈ emergent property of widespread fronto-parietal connectivity
- Non communicative patients with DOC may be able to perceive the external world
  - Audition
  - Pain/emotion
Diagnosis

Consciousness
Clinical entities

Laureys et al, Lancet Neurol, 2004
“Reflex” versus “Voluntary”

“VOLUNTARY” / “WILLED”

“REFLEX” / “AUTOMATIC”
Bruno et al, Coma and disorders of consciousness, Eds Schnakers and Laureys, 2012
Glasgow Coma Scale

E - eye opening

1. None
   - PAIN
2. To pain
   - PAIN
3. To speech
   - HELLO
4. Spontaneous
   - Not assessable

AROUSAL

Teasdale et al., 1974
V - verbal response

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

T. Not assessable

AWARENESS

A.C. Cidon
ICU Liège,
March 2002

WHERE AM I?

STUPID!!!

GROAN

...
Glasgow Coma Scale

M - motor response

6. Obeys simple commands
   ![M6](image)

5. Localizes pain
   ![M5](image)

4. Withdraws (normal flexion)
   ![M4](image)

3. Stereotyped flexion
   ![M3](image)

2. Stereotyped extension
   ![M2](image)

1. None
   ![M1](image)
Grade the best possible response after at least 3 trials in an attempt to elicit the best level of alertness. A score of E4 indicates at least 3 voluntary excursions. If eyes are closed, the examiner should open them and examine tracking of a finger or object. Tracking with the opening of 1 eyelid will suffice in cases of eyelid edema or facial trauma. If tracking is absent horizontally, examine vertical tracking. Alternatively, 2 blinks on command should be documented. This will recognize a locked-in syndrome (patient is fully aware). A score of E3 indicates the absence of voluntary tracking with open eyes. A score of E2 indicates eyelids opening to loud voice. A score of E1 indicates eyelids open to pain stimulus. A score of E0 indicates no eyelids opening to pain.

4 Eyelids open or opened, tracking or blinking to command
3 Eyelids open but not tracking
2 Eyelids closed but opens to loud voice
1 Eyelids closed but opens to pain
0 Eyelids remain closed with pain

Wijdicks et al., 2005
Grade the best possible response of the arms. A score of **M4** indicates that the patient demonstrated at least 1 of 3 hand positions (thumbs-up, fist, or peace sign) with either hand. A score of **M3** indicates that the patient touched the examiner’s hand after a painful stimulus compressing the temporomandibular joint or supraorbital nerve (localization). A score of **M2** indicates any flexion movement of the upper limbs. A score of **M1** indicates extensor posturing. A score of **M0** indicates no motor response or myoclonus status epilepticus.

- **4** Thumbs up, fist, or peace sign to command
- **3** Localizing to pain
- **2** Flexion response to pain
- **1** Extensor posturing
- **0** No response to pain or generalized myoclonus status epilepticus

Wijdicks et al., 2005
Grade the best possible response. Examine pupillary and corneal reflexes. Preferably, corneal reflexes are tested by instilling 2-3 drops of sterile saline on the cornea from a distance of 4-6 inches (this minimizes corneal trauma from repeated examinations). Cotton swabs can also be used. The cough reflex to tracheal suctioning is tested only when both of these reflexes are absent. A score of **B4** indicates pupil and cornea reflexes are present. A score of **B3** indicates one pupil wide and fixed. A score of **B2** indicates either pupil or cornea reflexes are absent, **B1** indicates both pupil and cornea reflexes are absent and a score of **B0** indicates pupil, cornea and cough reflex (using tracheal suctioning) are absent.

4 Pupil and corneal reflexes present  
3 One pupil wide and fixed  
2 Pupil or corneal reflexes absent  
1 Pupil and corneal reflexes absent  
0 Absent pupil, corneal, and cough reflex
Determine spontaneous breathing pattern in a nonintubated patient, and grade simply as regular R4, irregular R2, or Cheyne-Stokes R3 breathing. In mechanically ventilated patients, assess the pressure waveform of spontaneous respiratory pattern or the patient triggering of the ventilator R1. The ventilator monitor displaying respiratory patterns is used to identify the patient generated breaths on the ventilator. No adjustments are made to the ventilator while the patient is graded, but grading is done preferably with PaCO2 within normal limits. A standard apnea (oxygen-diffusion) test may be needed when patient breathes at ventilator rate R0.

4 Not intubated, regular breathing pattern
3 Not intubated, Cheyne-Stokes breathing pattern
2 Not intubated, irregular breathing pattern
1 Breathes above ventilator rate
0 Breathes at ventilator rate or apnea
## GCS or FOUR?

<table>
<thead>
<tr>
<th></th>
<th>GCS</th>
<th>FOUR</th>
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<tbody>
<tr>
<td>VS/UWS</td>
<td>71</td>
<td>63</td>
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<tr>
<td>MCS</td>
<td>75</td>
<td>83</td>
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</table>

\[ n = 146 \]

Bruno et al., 2011
Coma Recovery Scale-Revised (CRS-R)

AUDITORY FUNCTION SCALE
4 - Consistent Movement to Command *
3 - Reproducible Movement to Command *
2 - Localization to Sound
1 - Auditory Startle
0 - None

VISUAL FUNCTION SCALE
5 - Object Recognition *
4 - Object Localization: Reaching *
3 - Visual Pursuit *
2 - Fixation *
1 - Visual Startle
0 - None

MOTOR FUNCTION SCALE
6 - Functional Object Use *
5 - Automatic Motor Response *
4 - Object Manipulation *
3 - Localization to Noxious Stimulation *
2 - Flexion Withdrawal
1 - Abnormal Posturing
0 - None/Fiaclid

OROMOTOR/VERBAL FUNCTION SCALE
3 - Intelligible Verbalization *
2 - Vocalization/Oral Movement
1 - Oral Reflexive Movement
0 - None

COMMUNICATION SCALE
2 - Functional: Accurate†
1 - Non-Functional: Intentional *
0 - None

AROUSAL SCALE
3 - Attention
2 - Eye Opening w/o Stimulation
1 - Eye Opening with Stimulation
0 - Unarousable

n=103 post-comatose patients

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

- 41% potential misdiagnosis

- 41 clinical consensus diagnosis ‘minimally conscious state’
  - 4 (10%) had emerged from the MCS

Schnakers, Vanhaudenhuyse, Giacino, Ventura, Boly, Majerus et al., BMC Neurol, 2009
Diagnosis

Nociception and pain
Pain

“Unpleasant sensory and emotional experience associated with real or potential tissue damage”

“The inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment.”

International association for the study of pain (IASP) Pain 1994 and 2012
Pain

“Unpleasant sensory and emotional experience associated with real or potential tissue damage”

“The inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment.”

Nociception

“The neural process of encoding noxious stimuli”
(transduced and encoded by nociceptors).

“Pain sensation is not necessarily implied”.

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“Pain sensation is not necessarily implied”.

➔ « Pain is always subjective »

International association for the study of pain (IASP) Pain 1994 and 2012
Pain and nociception

Behavioral diagnosis

VS/UWS

MCS -

MCS +

EMCS

Functional communication

Signs of consciousness (non reflex behaviors)

Signs of language preservation

Cognitive function

Coma

Pain and nociception

Pain and nociception

Behavioral diagnosis

VS/UWS

MCS -

MCS +

EMCS

Functional communication

Cognitive function

Coma

## Behavioral scales

### Pain scales

<table>
<thead>
<tr>
<th>Population</th>
<th>Pain scales</th>
<th>Facial expression</th>
<th>Vocalization/Verbalization</th>
<th>Body movements</th>
<th>Consolability</th>
<th>Arousal</th>
<th>Physiological parameters</th>
<th>Activity pattern</th>
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<td>Demented elderly</td>
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<td>PACSLAC (Pain Assessment Checklist for Seniors with Limited Ability to Communicate) (78)</td>
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<td>ECPA (L’Echelle Comportementale pour Personne Agées) (79)</td>
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<td>PAINAD (Pain Assessment in Advanced Dementia) (80)</td>
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<td></td>
<td>NOPPAIN The Non-Communicative Patient’s Pain Assessment Instrument (81)</td>
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<td>CNPI (Checklist of Nonverbal Pain Indicators) (82)</td>
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<td>Abbey Pain Scale (83)</td>
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<td>Newborns/preverbal children</td>
<td>PIPP (Premature Infant Pain Profile) (84)</td>
<td>✓</td>
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<td>NIPS (Neonatal Infant Pain Scale) (85)</td>
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<td>CHEOPS (Children’s Hospital of Eastern Ontario Pain Scale) (86)</td>
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<td>FLACC (Face, Legs, Arms, Cry, Consolability) (87)</td>
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<td>Sedated/intubated patients</td>
<td>PPPM (Parents’ Postoperative Pain Measure) (88)</td>
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<td>BPS (Behavioral Pain Scale) (89)</td>
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<td>COMFORT Scale (90)</td>
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<td>✓</td>
<td>✓</td>
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</table>

Schnakers, Chatelle et al. AAPS 2012
### Nociception Coma Scale

**Total score: 12**

<table>
<thead>
<tr>
<th>VERBAL RESPONSE</th>
<th>VISUAL RESPONSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 – Verbalisation intelligible</td>
<td>3 – Fixation</td>
</tr>
<tr>
<td>2 – Vocalisation</td>
<td>2 – Eyes movements</td>
</tr>
<tr>
<td>1 – Groaning</td>
<td>1 – Startle</td>
</tr>
<tr>
<td>0 – None</td>
<td>0 – None</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MOTOR RESPONSE</th>
<th>FACIAL EXPRESSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 – Localization to noxious</td>
<td>3 – Cry</td>
</tr>
<tr>
<td>2 – Flexion withdrawal</td>
<td>2 – Grimace</td>
</tr>
<tr>
<td>1 – Abnormal posturing</td>
<td>1 – Oral reflexive movement/</td>
</tr>
<tr>
<td>0 – None/Flaccid</td>
<td>Startle response</td>
</tr>
<tr>
<td></td>
<td>0 – None</td>
</tr>
</tbody>
</table>
Nociception Coma Scale

- Concurrent validity: good
- Interrater reliability: good to excellent
- Effect of clinical diagnosis: yes

Schnakers, Chatelle et al. *Pain* 2010
Nociception Coma Scale revised

Chatelle, Majerus, Whyte, Laureys and Schnakers. JNNP 2012
NCS-R and brain metabolism

NCS-R total scores correlate with posterior part of the anterior cingulate cortex ➔ cognitive-affective dimension of pain (Rainville, 1997)

Chatelle et al. Neurorehabilitation and Neural Repair 2014
21 yo, MCS, Polytrauma 8 days post injury
Treatment: 1mg perfuzalgan before cares (mobilisation)
Revised

1mg/h morphine (continuous)
Prevalence: 88% (n=59) suffered from spasticity (MAS≥1) and 60% (n=39) suffered from severe spasticity (MAS≥3)

Conclusion: guidelines on clinical management

- High rate of misdiagnosis if non sensitive scales are used
  - Acute stage/ICU: FOUR
  - Chronic stage: CRS-R
- Useful for monitoring recovery/medical complications
- Caveats
  - Language dependent
  - Relying strongly on motor abilities
Conclusion: guidelines on clinical management

- Need to improve management of potential pain: 76% documented potential pain, 59% not treated with analgesics

- NCS-R: useful tool for clinical management of nociception/pain:
  - Sudden increase in NCS-R scores can alert clinicians of a potential pain/medical complications, further investigation is needed

- Caveats
  - Motor/verbal dependent
BREAK (~15 min)
Paraclinical diagnosis

Active paradigms
Active paradigm – fMRI

“He’s not in coma... he’s playing tennis!”

Owen, Coleman, Boly, Davis, Laureys & Pickard, Science, 2006
Active paradigm – fMRI

Healthy Subject

Answers « YES »

Answers « NO »

« VEGETATIVE STATE »

Active paradigm – fMRI

Atypical cortical activity

VS/UWS

MCS

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)

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)

Active paradigm – EEG

Schnakers, Boly, Majerus and Laureys, Neurol, 2008
Coma or total locked-in syndrome?

21-y old woman
basilar artery thrombosis - day 49

Schnakers et al, Neurocase, 2009
Active paradigm – EEG

“MOVE YOUR FOOT”

HEATHY CONTROL SUBJECT

“MOVE YOUR HAND”

“VEGETATIVE” UNRESPONSIVE PATIENT

Cruse, Chennu, Chatelle et al., Lancet 2011; Neurology 2012

3/16 UWS patients successfully completed task

www.thelancet.com
Active paradigm – EMG

« Move your right hand » - 1/8 UWS & 2/2 MCS increased EMG

Bekinschtein et al JNNP 2008
Paraclinical diagnosis

Passive paradigms
Default mode network

Connectivity in DMN correlated with LOC

Vanhaudenhuyse et al, Brain, 2010
126 patients (81 MCS, 41 VS/UWS, 4 locked-in syndrome)

- Traumatic (n=48) and non-traumatic (n=78) etiology
- Chronic (>1 month, n=110) and subacute (n=16) setting
- Coma Recovery Scale – Revised
- Fluorodeoxyglucose positron emission tomography (FDG-PET)
- Functional magnetic resonance imaging during mental activation tasks (fMRI)

PET scan

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<tr>
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<th>Clinical consensus diagnosis</th>
<th>FDG-PET</th>
<th>Mental imagery fMRI</th>
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<tbody>
<tr>
<td>Completed examinations (out of 122)</td>
<td>122 (100%)</td>
<td>112 (91%)</td>
<td>72 (59%)</td>
</tr>
<tr>
<td>Number of interpretable examinations (out of all completed)</td>
<td>89 (73%)</td>
<td>112 (100%)</td>
<td>70 (97%)</td>
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<tr>
<td>Overall congruence with CRS-R (95% CI)</td>
<td>78%</td>
<td>85%</td>
<td>63%</td>
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<td>95%</td>
<td>67%</td>
<td>89%</td>
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<tr>
<td>Sensitivity to MCS</td>
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<td>93%</td>
<td>45%</td>
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<tr>
<td>Overall outcome prediction</td>
<td>-</td>
<td>74%</td>
<td>56%</td>
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<tr>
<td>Positive outcome prediction</td>
<td>-</td>
<td>67%</td>
<td>63%</td>
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<tr>
<td>Negative outcome prediction</td>
<td>-</td>
<td>92%</td>
<td>52%</td>
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Stender and Gossersy and al, The Lancet 2014
### PET Scan

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<td>112 (100%)</td>
<td>70 (97%)</td>
</tr>
<tr>
<td>Overall congruence with CRS-R (95% CI)</td>
<td>78%</td>
<td>85%</td>
<td>63%</td>
</tr>
<tr>
<td>Congruence with CRS-R diagnoses of VS/UWS</td>
<td>95%</td>
<td>67%</td>
<td>89%</td>
</tr>
<tr>
<td>Sensitivity to MCS</td>
<td>67%</td>
<td>93%</td>
<td>45%</td>
</tr>
<tr>
<td>Overall outcome prediction</td>
<td>-</td>
<td>74%</td>
<td>56%</td>
</tr>
<tr>
<td>Positive outcome prediction</td>
<td>-</td>
<td>67%</td>
<td>63%</td>
</tr>
<tr>
<td>Negative outcome prediction</td>
<td>-</td>
<td>92%</td>
<td>52%</td>
</tr>
</tbody>
</table>

Stender and Gossieres and al, The Lancet 2014
PET scan

<table>
<thead>
<tr>
<th></th>
<th>Clinical consensus diagnosis</th>
<th>FDG-PET</th>
<th>Mental imagery fMRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed examinations (out of 122)</td>
<td>122 (100%)</td>
<td>112 (91%)</td>
<td>72 (59%)</td>
</tr>
<tr>
<td>Number of interpretable examinations (out of all completed)</td>
<td>89 (73%)</td>
<td>112 (100%)</td>
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</tr>
<tr>
<td>Negative outcome prediction</td>
<td>-</td>
<td>92%</td>
<td>52%</td>
</tr>
</tbody>
</table>

Stender and Gosseries and al, The Lancet 2014
Transcranial Magnetic Stimulation/Electroencephalography (TMS/EEG)

Napolitani and Bodart et al, Brain Inj, 2017
Wakefulness

Deep sleep

Massimini et al, Science, 2005
Passive paradigm – TMS/EEG

Rosanova and Gosseries et al, Brain, 2012
Passive paradigm – TMS/EEG

Rosanova and Gosseries et al, Brain, 2012
Passive paradigm – TMS/EEG

Rosanova and Gosseries et al, Brain, 2012
Passive paradigm – TMS/EEG

Rosanova and Gosseries et al, Brain, 2012
Perturbational complexity index (PCI)

Perturbational complexity index in comatose patients

Paraclinical diagnosis

Case reports
Case reports

Behavioral assessment

TMS-EEG

MRI

PET scan

BCI

EEG
Case reports

- 41 years old
- 4 years et 9 months post anoxia
- Diagnosis: vegetative/unresponsive state

- 35 years old
- 6 years and 10 months post ischemic stroke
- Diagnosis: vegetative/unresponsive state

Gosseries, Zasler and Laureys, Brain Inj, 2014
## CRS-R

### Fonction Auditive
- 4 - Mouvement systématique sur demande*
- 3 - Mouvement reproductible sur demande*
- 2 - Localisation de sons
- 1 - Réflexe de sursaut au bruit
- 0 - Néant

### Fonction Visuelle
- 5 - Reconnaissance des objets*
- 4 - Localisation des objets : atteinte*
- 3 - Poursuite visuelle*
- 2 - Fixation*
- 1 - Réflexe de clignement à la menace
- 0 - Néant

### Fonction Motrice
- 6 - Utilisation fonctionnelle des objets*
- 5 - Réaction motrice automatique*
- 4 - Manipulation d’objets*
- 3 - Localisation des stimulations nociceptives*
- 2 - Flexion en retrait
- 1 - Posture anormale stéréotypée
- 0 - Néant / Flaccidité

### Fonction Oromotrice/Verbeal
- 3 - Production verbale intelligible*
- 2 - Production vocale / Mouvements oraux
- 1 - Réflexes oraux
- 0 - Néant

### Communication
- 2 - Fonctionnelle : exacte*
- 1 - Non fonctionnelle : intentionnelle*
- 0 - Néant

### Éveil
- 3 - Attention
- 2 - Ouverture des yeux sans stimulation
- 1 - Ouverture des yeux avec stimulation
- 0 - Aucun éveil

### Score total
<table>
<thead>
<tr>
<th>CRS-R</th>
<th>CRS-R</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 4 5 5 4 3</td>
<td>4 4 5 5 4 3</td>
</tr>
<tr>
<td>X X X X X</td>
<td>X X X X X</td>
</tr>
<tr>
<td>X X X X X</td>
<td>X X X X X</td>
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<td>X X X X X</td>
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<td>X X X X X</td>
<td>X X X X X</td>
</tr>
<tr>
<td>X X X X X</td>
<td>X X X X X</td>
</tr>
</tbody>
</table>

* Symptômes observés dans le bilan initial
X Symptômes observés dans le bilan de suivi
Case reports

Gosseries, Zasler and Laureys, Brain Inj, 2014
Conclusion

- Behavioral assessment ≈ 40% misdiagnosis
- FDG-PET complement beside examinations and can predict long-term recovery of patients in chronic VS/UWS
- Active fMRI/EEG/EMG paradigms are less suited for differential diagnosis, but may provide a strong complementary tool
- TMS-EEG may provide for the first time a passive measure of consciousness at the single subject level
- Encourage to use **multimodal assessment** of the level of consciousness!
Treatment

Pharmacological
Amantadine

Dopaminergic agent (Parkinson)

Amantadine

Dopaminergic agent (Parkinson)

Schnakers et al, J Neurol Neurosurg Psychiatry 2008
Zolpidem

short-acting nonbenzodiazepine GABA-A agonist hypnotic

1/15 responders  = 6.7%

4/84 responders  = 5%

4/60 responders
= 6.7%
Without change of diagnosis
Thonnard and Gosseries et al, Funct Neurol 2014
Zolpidem

short-acting nonbenzodiazepine GABA-A agonist hypnotic


n=3 MCS responders
Zolpidem inhibits Gpi

Chatelle et al, *Front Hum Neurosci*, 2014
Treatment

Brain stimulation
## Recent RCTs on NIBS in DOC

### Past 5 years:

<table>
<thead>
<tr>
<th>Procedure</th>
<th>NIBS</th>
<th>N</th>
<th>Time since injury</th>
<th>Procedure</th>
<th>Results</th>
<th>Effect sizes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>tDCS</strong></td>
<td>Thibaut et al, 2014</td>
<td>55</td>
<td>1 week to 19 years</td>
<td>Single session (20 minutes) of active and sham stimulation over the left DLPFC with CRS-R before and after tDCS</td>
<td>13/30 patients in MCS and 2/25 patients in UWS clinically improved (recovery of visual pursuit or command following). At the group level, clinical improvement (2 points on the CRS-R) for MCS patients. No side-effects observed.</td>
<td>For MCS (n=30); d=0.38</td>
</tr>
<tr>
<td></td>
<td>Striano et al, 2017</td>
<td>16</td>
<td>&gt; 3 months</td>
<td>5 sessions of active and sham tDCS (20 minutes a day) over the DLPFC. CRS-R performed before, after 5 days of tDCS and at 1-week follow-up</td>
<td>9/16 responders. Clinical improvement maintained up to one week after the end of the stimulation. No side-effects observed.</td>
<td>After tDCS; d=0.43; at 1 week follow-up; d=0.57</td>
</tr>
<tr>
<td><strong>tRNS</strong></td>
<td>Thibaut et al, 2017</td>
<td>13</td>
<td>&gt; 3 months</td>
<td>5 days of active and sham tDCS over the DLPFC (20 min/day). EEG and CRS-R at baseline, after 5 days and 3-month follow-up</td>
<td>Behavioral (CRS-R total score) and EEG changes in 5/13 patients (3 in MCS and 2 in UWS). At the group level, no statistical difference between the two groups.</td>
<td>/</td>
</tr>
<tr>
<td><strong>rTMS</strong></td>
<td>Zang et al, 2017</td>
<td>26</td>
<td>1 to 18 months</td>
<td>20 sessions of rTMS for 20 days</td>
<td>No behavioral or EEG improvements. No side-effects observed.</td>
<td>/</td>
</tr>
<tr>
<td></td>
<td>Marle et al, 2017</td>
<td>27</td>
<td>10 months to 14 years</td>
<td>20 sessions of rTMS per week</td>
<td>No behavioral or EEG improvements. No side-effects observed.</td>
<td>/</td>
</tr>
<tr>
<td></td>
<td>Huang et al, 2017</td>
<td>33</td>
<td>&gt; 3 months</td>
<td>5 sessions of rTMS after 5 days up</td>
<td>One session of active or sham 20-Hz rTMS over M1 for 10 minutes (1000 pulses in 20 trains). CRS-R and CBF velocity of the MCA before and after rTMS</td>
<td>No behavioral (CRS-R) changes. Temporary increase in peak systolic velocity and mean flow velocity of the left MCA for MCS. No effects in UWS or in sham group. No side-effects observed.</td>
</tr>
<tr>
<td><strong>rNRS</strong></td>
<td>Moncusa et al, 2017</td>
<td>9</td>
<td>30 days to 4 months</td>
<td>5 sessions of for 20 minutes at baseline, at 3-day follow-up</td>
<td>No treatment effect on the CRS-R nor on the EEG. Clinical improvement in 1 patient (up to 1-week follow-up - UWS became MCS - paralleled by EEG power spectra improvement. No information on side-effects.</td>
<td>/</td>
</tr>
</tbody>
</table>

### Relevant Literature:

- Thibaut et al, *Lancet Neurol*
Transcranial direct current stimulation

- Transcranial direct current stimulation = tDCS
- Constant, weak direct current through electrodes
- The current induces intracerebral current flow that either increases or decreases the neuronal excitability in the specific area being stimulated
tDCS mechanisms

Short term effects

Long term
## Transcranial direct current stimulation

<table>
<thead>
<tr>
<th>Stimulation</th>
<th>Population</th>
<th>Effects</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hemiplegic patients</td>
<td>Dexterity and strength</td>
<td>Hummel et al. Lancet, 2006</td>
</tr>
<tr>
<td></td>
<td>Spastic patients</td>
<td>Spasticity &amp; ADL (activity of daily life)</td>
<td>Wu et al., Arch Phys Med Rehabil 2012</td>
</tr>
<tr>
<td></td>
<td>Alzheimer’s patients</td>
<td>Memory</td>
<td>Ferrucci et al. Neurology, 2008</td>
</tr>
<tr>
<td></td>
<td>Aphasic patients</td>
<td>Language</td>
<td>Baker et al. Stroke, 2010</td>
</tr>
</tbody>
</table>

Thibaut et al, Rev Neurol, 2013
tDSCS – single session

- Randomized, double blind, sham controlled, cross-over study
- Direct current: 2 mA; 20 min
- 55 patients included (25 VS/UWS; 30 MCS; 35 chronic; 25 TBI; 43±18y)

Thibaut et al., Neurology, 2014
Transcranial direct current stimulation

Treatment effect: delta CRS-R total scores

MCS (n=30)

VS/UWS (n=25)

Thibaut et al., Neurology, 2014
15/55 responders

Patient who showed new signs of consciousness after tDCS and not before tDCS or before and after sham

- 2 VS/UWS; subacute (<3m)
- 13 MCS (6 >1y post insult)

Diagnostic change

- 2 VS/UWS $\rightarrow$ MCS
- 2 MCS $\rightarrow$ EXIT (subacute)
# tDCS – single session

<table>
<thead>
<tr>
<th>SUBSCALES</th>
<th>RECOVERY</th>
<th>NUMBER OF PATIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUDITORY</td>
<td>Consistent command following</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Reproducible command following</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Localization to sounds</td>
<td>1</td>
</tr>
<tr>
<td>VISUAL</td>
<td>Object recognition</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Object localization</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Visual pursuit</td>
<td>5</td>
</tr>
<tr>
<td>MOTOR</td>
<td>Functional use of object</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Automatic motor reaction</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Object manipulation</td>
<td>3</td>
</tr>
<tr>
<td>OROMOTOR</td>
<td>Vocalisation</td>
<td>3</td>
</tr>
<tr>
<td>COMMUNICATION</td>
<td>Functional communication</td>
<td>2</td>
</tr>
<tr>
<td>AROUSAL</td>
<td>Without stimulation</td>
<td>2</td>
</tr>
</tbody>
</table>

Thibaut et al., Neurology, 2014
tDCS to unveil covert consciousness

• 67yo woman in UWS for 4y after subarachnoid hemorrhage
• Out of 7 CRS-R, 1 localization to pain
• Consistent response to command only after tDCS
• Neuroimaging consistent with MCS*

➔ tDCS may facilitate motor execution of command when cognitive functions are preserved
Single stimulation: effects ± 60 min\(^1\)

⇒ short-lasting improvements, back to initial state

1. Increase the duration of the effects
2. Increase the number of responders

Randomized sham controlled double blind cross-over

\(^1\)Nitsche et al., 2001; Thibaut et al., 2017
tDCS – repeated sessions

16 patients in MCS (> 3 months; 12 TBI; 47 ± 16 y)

Treatment effect: delta CRS-R day 5 & day 12 (follow-up)

After tDCS

Effect size: 0.43

1 week follow-up

Effect size: 0.57

* p<0.05

Thibaut et al., 2016
tDCS – repeated sessions

Longitudinal analysis:
- Real session: significant + time evolution ($p<0.001$)
- Sham session: no evolution across time ($p=0.64$)

Some patients responded after 1, 2 or 3 days of tDCS

 responders (9/16 – 56%)

Single stim: 43% responders – effect size : 0.38 (versus 0.57)

Thibaut et al., 2016
Predicting clinical response

tDCS responders ≠ non-responders

Brain metabolism (PET-scan)
≠ responders & non-responders

Grey matter atrophy (MRI)
Grey matter atrophy
in responders
in non-responders

Brain connectivity (hd-EEG)
theta centrality

responders
non-responders
tDCS – Precuneus

RCT crossover – 5 sessions

33 MCS >3 months post-insult (57±11y; 20 TBI)

9 responders (27%)
Sub-acute > chronic

No effect at follow-up

Effect size : 0.31
Motor cortex: common & efficient
tDCS target
For patients with DOC?
→ Immobilization, paresis...
→ Improve behavioral responsiveness
→ Covert consciousness

Group level (n=10): no significant improvement (p=0.55; ES=0.10)

Single-subject level: 2 responders

Single stimulation & small sample size

Martens et al., *Brain Injury* 2019
Stimulating different brain areas

Group level: Prefrontal tDCS best area to target

Single-subject level: Patient’s tailored montage
Clinical translation

- **Feasibility of tDCS for daily use**
  - By relatives/caregivers (20 sessions)
  - 27 MCS patients – compliance: 93±14%
  - No clinical effects
  - 22 MCS patients received ≥80% tDCS sessions
  - Significant effects & trend at 8-week follow-up – no AE

Post tDCS 8 weeks follow-up

Martens et al, *Brain Stimulation* 2018
Deep Brain Stimulation

Intralaminar nuclei stimulation induces “recovery” from minimally responsive state

Deep Brain Stimulation

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

Laureys et al, Lancet 2000

Schiff et al, Nature 2007

MCS ➔ emerged – prolonged effects

sustained attention, intelligible words, functional objects use

No RCT & side-effects
Combined treatment: potential solution?

Giacino, Fins, Laureys, Schiff, Nature Rev Neurol 2014
Conclusion

- Potential interest of pharmacological...
  - Zolpidem
  - Amantadine

- and non pharmacological treatments
  - tDCS
  - DBS

- More validation studies are needed
- Assessment of the daily use in clinical setting
Locked-In Syndrome
LIS - Definition

Bauer et al. (1989):

- **Classical LIS**
  - Complete immobility except for vertical eye movements and blinks.

- **Incomplete LIS**
  - Some preserved voluntary motricity (head, superior or inferior limbs).

- **Complete LIS**
  - Total immobility including ocular motricity

Laureys, Pellas, Van Eeckhout, Ghorbel, Schnakers, Perrin et al., Prog Brain Res, 2005
LIS - Diagnosis

<table>
<thead>
<tr>
<th>Person who gave the LIS diagnosis</th>
<th>Number of patients (n=84) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical doctor</td>
<td>52 (62%)</td>
</tr>
<tr>
<td>Family member</td>
<td>28 (33%)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (5%)</td>
</tr>
</tbody>
</table>

Questionnaire ALIS 2007; Bruno, et al., 2010
LIS – Cognitive functions

Schnakers, Majerus, Goldman, Boly, Van Eeckhout, Gay et al, J Neurol, 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. Gossery · A. Soddu · C. Schnakers · G. Moonen · S. Laureys

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

**  **  **

**  **  *

**  *  **

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

2,475 medical professionals
Ethical issues: what about LIS?

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 Pellas, Athena Demertzi, Steven Laureys

Bruno et al, BMJ Open, 2011
Ethical issues

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

Marie-Aurélie Bruno,1 Jan L Bernheim,2 Didier Ledoux,1 Frédéric Pellás,3 Athena Demartzi,4 Steven Laureys4

Bruno et al, BMJ Open, 2011
Conclusion

- LIS # DOC in terms of brain lesions and level of consciousness
- Preserved cognitive abilities
- Happy majority?
  - Pain
  - Communication
  - Don’t forget the minority!
Near-death experiences
Near-death experiences: definition

- Near-Death Experience (NDE): “Profound psychological events with transcendental & mystical elements typically occurring to individuals close to death or in situations of intense physical or emotional danger”.

- a set of mental events with highly emotional, self-related, mystical & spiritual aspects
- recurrent “features” (e.g., feeling of peacefulness, out-of-body experiences, …)
- classically occurring in an altered state of consciousness

Greyson, 2000
Near-death experiences: historical background

Platon's Republic
315 B.C.

Jerome Hieronymus Bosch
1516

Pierre Jean du Monchaux
1740

Amiral Beaufort
1795

Albert Heim
1892
Near-death experiences

Main explanatory models

- Spiritual theories ★ “dualistic” approach toward the mind–brain relationship
- Neurobiological theories ★ brain mechanisms might underlie NDEs
- Psychological theories ★ psychological reaction to impending death
Near-death experiences: Identification

Greyson NDE scale: Scores ≥7 = NDE experiencer

Cognitive

(1) Did time seem to speed up or slow down?
   0 = No
   1 = Time seemed to go faster or slower than usual
   2 = Everything seemed to be happening at once; or time stopped or lost all meaning

(2) Were your thoughts speeded up?
   0 = No
   1 = Faster than usual
   2 = Incredibly fast

(3) Did scenes from your past come back to you?
   0 = No
   1 = I remembered many past events
   2 = My past flashed before me, out of my control

(4) Did you suddenly seem to understand everything?
   0 = No
   1 = Everything about myself or others
   2 = Everything about the universe

Affective

(5) Did you have a feeling of peace or pleasantness?
   0 = No
   1 = Relief or calmness
   2 = Incredible peace or pleasantness

(6) Did you have a feeling of joy?
   0 = No
   1 = Happiness
   2 = Incredible joy

(7) Did you feel a sense of harmony or unity with the universe?
   0 = No
   1 = I felt no longer in conflict with nature
   2 = I felt united or one with the world

(8) Did you see, or feel surrounded by, a brilliant light?
   0 = No
   1 = An unusually bright light
   2 = A light clearly of mystical or other-worldly origin

Greyson, 1983
Near-death experiences: Identification

Greyson NDE scale: Scores ≥7 = NDE experiencer

Paranormal

(9) Were your senses more vivid than usual?
   0 = No
   1 = More vivid than usual
   2 = Incredibly more vivid

(10) Did you seem to be aware of things going on elsewhere, as if by ESP?
     0 = No
     1 = Yes, but the facts have not been checked out
     2 = Yes, and the facts have been checked out

(11) Did scenes from the future come to you?
     0 = No
     1 = Scenes from my personal future
     2 = Scenes from the world's future

(12) Did you feel separated from your body?
     0 = No
     1 = I lost awareness of my body
     2 = I clearly left my body and existed outside it

(13) Did you seem to enter some other, unearthly world?
     0 = No
     1 = Some unfamiliar and strange place
     2 = A clearly mystical or unearthly realm

(14) Did you seem to encounter a mystical being or presence, or hear an unidentifiable voice?
     0 = No
     1 = I heard a voice I could not identify
     2 = I encountered a definite being, or a voice clearly of mystical or unearthly origin

(15) Did you see deceased or religious spirits?
     0 = No
     1 = I sensed their presence
     2 = I actually saw them

(16) Did you come to a border or point of no return?
     0 = No
     1 = I came to a definite conscious decision to return to life
     2 = I came to a barrier that I was not permitted to cross; or was sent back against my will

Greyson, 1983
Near-death experiences: features

<table>
<thead>
<tr>
<th>Feature</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peacefulness</td>
<td>90</td>
</tr>
<tr>
<td>Out-of-Body experience</td>
<td>80</td>
</tr>
<tr>
<td>Bright light</td>
<td>70</td>
</tr>
<tr>
<td>Altered time perception</td>
<td>60</td>
</tr>
<tr>
<td>Unearthly environment</td>
<td>50</td>
</tr>
<tr>
<td>Happiness/joy</td>
<td>40</td>
</tr>
<tr>
<td>Harmony/unity</td>
<td>30</td>
</tr>
<tr>
<td>Border</td>
<td>20</td>
</tr>
<tr>
<td>Heightened senses</td>
<td>10</td>
</tr>
<tr>
<td>Understanding</td>
<td>30</td>
</tr>
<tr>
<td>Presence</td>
<td>20</td>
</tr>
<tr>
<td>Speeded thoughts</td>
<td>10</td>
</tr>
<tr>
<td>Encounters</td>
<td>30</td>
</tr>
<tr>
<td>Extrasensory perception</td>
<td>20</td>
</tr>
<tr>
<td>Precognitive visions</td>
<td>10</td>
</tr>
<tr>
<td>Life review</td>
<td>0</td>
</tr>
</tbody>
</table>

Life-threatening “Real NDEs” n=140
Total score 16 ± 6
(7-30/32)
Near-death experiences: features

Greyson NDE scale features frequencies (%)

- Peacefulness
- Out-of-Body experience
- Bright light
- Altered time perception
- Unearthly environment
- Happiness/joy
- Harmony/unity
- Border
- Heightened senses
- Understanding
- Presence
- Speeded thoughts
- Encounters
- Extrasensory perception
- Precognitive visions
- Life review

Life-threatening “Real NDEs” n=140
Total score 16 ± 6 (7-30/32)
- Anoxia 15 ± 6 (7-29)
- Trauma 16 ± 6 (7-26)
- Other 16 ± 6 (7-30)

Non-life-threatening “NDE-like” n=50
Total score 17 ± 7 (7-30/32)

Charland-Verville et al., 2015
Near-death experiences: neural correlates

Right temporo-parietal stimulation

Hypercarbia (Meduna, 1950)
- Bright light
- Recollection of memories
- OBEs
- Mystical insights

Induction of an illusory shadow person.

Presence ~ left temporoparietal

Induction of an illusory shadow person.
Aim: Reproduce NDEs in controlled laboratory setting

Hypothesis: Induced hypoxic loss of consciousness produces NDE like memories (Lempert, 1994)

Charland-Verville et al., (in prep)
Near-death experiences: laboratory setting

33 healthy volunteers aged 25 ± 5 y (range 20-46); 19 women (58%)

Induction of vasovagal syncope:
45 s hyperventilation while squatting, fast rising, 10 s Valsalva maneuver

Simultaneous high-density video-EEG recordings
Greyson NDE scale & semi-structured recorded audio interviews

Induced loss of consciousness: 26/33 (79%)
Duration of loss of consciousness: 24 ± 7 s (range 14-45)

NDE total scores: 6 ± 4 (range 0-17)

Identified NDErs: 9/26 (35%)

1 subject excluded because of bad quality EEG recording

Charland-Verville et al., (in prep)
Near-death experiences: laboratory setting

Greyson NDE scale features frequencies (%)

- Peacefulness
- Out-of-Body experience
- Bright light
- Altered time perception
- Unearthly environment
- Happiness/joy
- Harmony/unity
- Border
- Heightened senses
- Understanding
- Presence
- Speeded thoughts
- Encounters
- Extrasensory perception
- Precognitive visions
- Life review

Life-threatening “Real NDEs” n=140
Total score 16 ± 6 (7-30/32)
Anoxia 15 ± 6 (7-29)

Syncope “NDE-like” n=26
Total score 6 ± 5 (0-17/32)

Charland-Verville et al., (in prep)
Near-death experiences: laboratory setting

Charland-Verville et al., (in prep)
That’s it folks!
THANK YOU!

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