Functional neuroimaging in patients with disorders of consciousness: What to care about?

Neuroethics Day
ETHICS OF NEUROSCIENCE, NEUROSCIENCE OF ETHICS

Friday 20 May 2016
Aix-Marseille University, France

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Institut du Cerveau et de la Moelle épinière – ICM
Paris, France
&
Coma Science Group
GIGA Research & Neurology Department
University & University Hospital of Liège, Belgium
A clinical definition of consciousness

Awareness = command following

Conscious Wakefulness

Locked-in syndrome

Minimally Conscious State
- MCS+ (command following)
- MCS- (non-reflex movements)

“Vegetative”/unresponsive wakefulness syndrome

Drowsiness

REM Sleep

Sleep St I-II

Deep sleep

General Anesthesia

Coma

Wakefulness = eyes opening

Demertzi et al, Encyclopedia of Consciousness 2009
Laureys, Trends in Cognitive Sciences 2005
Attitudes towards pain

Do you think patients in a …

**p<.001**

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Do you think VS patients feel pain?</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.01</td>
<td>1.00 - 1.02</td>
<td>.050</td>
</tr>
<tr>
<td>Women</td>
<td>1.25</td>
<td>0.99 - 1.58</td>
<td>.060</td>
</tr>
<tr>
<td>Northern Europe</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central Europe</td>
<td>0.81</td>
<td>0.58 - 1.14</td>
<td>.240</td>
</tr>
<tr>
<td>Southern Europe</td>
<td>1.10</td>
<td>0.76 - 1.60</td>
<td>.600</td>
</tr>
<tr>
<td>Paramedical professionals</td>
<td>1.56</td>
<td>1.20 - 2.00</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Religious respondents</td>
<td>1.37</td>
<td>1.10 - 1.70</td>
<td>.004</td>
</tr>
<tr>
<td><strong>Do you think MCS patients feel pain?</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>2.38</td>
<td>1.33 - 4.26</td>
<td>.003</td>
</tr>
<tr>
<td>Religious respondents</td>
<td>1.83</td>
<td>1.05 - 3.18</td>
<td>.031</td>
</tr>
</tbody>
</table>

Predicted response: “agreement”

Demertzi et al, Progress in Brain Research 2009
End-of-life issues

- VS worse than death for the patient: 55%
- VS worse than death for their families: 80%
- MCS worse than VS for the patient: 54%
- MCS worse than VS for their families: 42%

Demertzi et al, Journal of Neurology 2011
Attitudes towards pain & end-of-life

Treatment can be stopped in chronic...

- Feel pain
- Do not feel pain

Demertz & Racine et al, Neuroethics 2012
What is to diagnose as conscious?
Evaluating consciousness

- Motor Responsiveness
- Cognitive Capacity

**Coma**

- Arousal = eye opening

**Vegetative/Unresponsive**

- Minimally Responsive

**Communication?**

- Awareness? = response to command or non-reflex movements

**Good Recovery**

- Professional reinsertion

**Severe Disability**

**Moderate Disability**

**Live independently**

**Perspectives**

Laureys et al, Curr Opin Neurol 2005
Visual pursuit

Vanhaudenhuyse et al, JNNP 2008
Misdiagnosis of vegetative state

n=103 post-comatose patients

45 Clinical diagnosis of “vegetative state”
27 Coma Recovery Scale diagnosis

40% misdiagnosis

38% Schnakers et al Ann Neurol 2006; BMC Neurology 2009
37% Childs et al Neurology 1993
43% Andrews et al BMJ 1996
Complementary methodologies
Neuroimaging paradigms

Active paradigms

“Imagine playing tennis”

“Imagine visiting the rooms of your house”

Owen et al, Science 2006
Monti & Vanhaudenhuyse et al, NEJM 2010

Passive paradigms

median nerve

Heine, Di Perri, Soddu, Laureys, Demertzi
In: Clinical Neurophysiology in Disorders of Consciousness, Springer-Verlag 2015

Demertzi & Laureys, In: I know what you are thinking: brain imaging and mental privacy, Oxford University Press 2012
Yes-No communication with fMRI

Owen, Coleman, Boly, Davis, Laureys & Pickard, Science 2006
The problem of aphasia in the assessment of consciousness in brain-damaged patients

Steve Majerus¹,³, Marie-Aurélie Bruno²,³, Caroline Schnakers², Joseph T. Giacino⁴ and Steven Laureys²,³,*

Progress in Brain Research, Vol. 177
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Bruno et al, J Neurology 2012
Neuroimaging paradigms

Active paradigms
“Imagine playing tennis”
“Imagine visiting the rooms of your house”

Passive paradigms
median nerve

Heine, Di Perri, Soddu, Laureys, Demertzi
In: Clinical Neurophysiology in Disorders of Consciousness,
Springer-Verlag 2015

Demertzi & Laureys, In: I know what you are thinking: brain imaging and mental privacy, Oxford University Press 2012
Noxious stimulation

Boly et al, Lancet Neurol 2008
Two awareness networks

Internal awareness network

External awareness network

Demertzi, Soddu, Laureys Curr Opin Neurobiology 2013
Laureys, Scientific American 2007
Intrinsic brain activity & awareness

External awareness
or anticorrelated network

Internal awareness
or Default mode network

Demertzi & Whitfield-Gabrieli, in: *Neurology of Consciousness* 2nd ed. 2015
Demertzi, Soddu, Laureys, *Curr Opin Neurobiology* 2013
Demertzi et al, *Front Hum Neurosci* 2013
Laureys, *Scientific American* 2007
Cognitive-behavioral coupling at “resting” state

External-internal: $r = -0.44$, $p < .02$
Mean switch: 0.05Hz (range: 0.01-0.1)

Vanhaudenhuyse* & Demertzi* et al, Journal of Cognitive Neuroscience 2011
(*equal contribution)
Hypnotic modulation of resting state

- Normal wakefulness
- Autobiographical mental imagery
- Hypnosis

Demertz et al, Progress in Brain Research 2011
Awareness is modified in hypnosis

Demertzi, Vanhaudenhuyse, Noirhomme, Faymonville, Laureys, J Physiol Paris in press
Default connectivity in patients

Vanhaudenhuyse & Noirhomme et al, Brain 2010
Two awareness networks in DOC

Di Perri et al, Lancet Neurol in press
## Mutliple networks

### Resting state networks and consciousness
Alterations of multiple resting state network connectivity in physiological, pharmacological, and pathological consciousness states

<table>
<thead>
<tr>
<th>Default mode network</th>
<th>Executive control network left</th>
<th>Executive control network right</th>
<th>Salience network</th>
<th>Sensorimotor network</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="default_mode_network.png" alt="Image" /></td>
<td><img src="executive_control_network_left.png" alt="Image" /></td>
<td><img src="executive_control_network_right.png" alt="Image" /></td>
<td><img src="salience_network.png" alt="Image" /></td>
<td><img src="sensorimotor_network.png" alt="Image" /></td>
</tr>
<tr>
<td>(x=56, y=48, z=57)</td>
<td>(x=56, y=48, z=57)</td>
<td>(x=6, y=20, z=5)</td>
<td>(x=1, y=21, z=51)</td>
<td></td>
</tr>
</tbody>
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<tr>
<th>Auditory network</th>
<th>Visual medial network</th>
<th>Visual lateral network</th>
<th>Visual occipital network</th>
<th>Cerebellum</th>
</tr>
</thead>
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<td><img src="auditory_network.png" alt="Image" /></td>
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<td><img src="visual_occipital_network.png" alt="Image" /></td>
<td><img src="cerebellum.png" alt="Image" /></td>
</tr>
<tr>
<td>(x=13, y=17, z=1)</td>
<td>(x=11, y=48, z=5)</td>
<td>(x=17, y=23, z=5)</td>
<td>(x=13, y=50, z=1)</td>
<td>(x=1, y=50, z=14)</td>
</tr>
</tbody>
</table>

Heine … & Demertzì, Frontiers in Psychology 2012
Fewer “neuronal” networks in DOC

Demertzi & Gómez et al, Cortex 2014
Finding the discriminative features

Demertzi & Antonopoulos et al, Brain 2015
Classification of new patients

- 26 MCS, 19 VS/UWS
- 14 trauma, 28 non-trauma, 3 mixed
- 34 patients assessed >1m post-insult

Clinical diagnosis
- MCS
- VS/UWS

Demertzì & Antonopoulos et al, Brain 2015
Cross-modal interaction in conscious processing

Bekinschtein et al, PNAS 2009
Default connectivity in anesthesia

Boveroux et al, Anesthesiology 2010
Multimodal imaging

Bruno et al, Progress in Brain Research 2011
Tshibanda et al, Neuroradiology 2010
The ethical relevance of technology-based assessment

<table>
<thead>
<tr>
<th>Results of Tests</th>
<th>Beneficial Effects</th>
<th>Harmful Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>- brain activity than neurological examination</td>
<td>Relatives: decisions to limit life-sustaining treatment</td>
<td>Relatives: may lose hope, purpose, and meaning in life</td>
</tr>
<tr>
<td>+ brain activity than neurological examination</td>
<td>Clinical management: may be intensified by the chance of further recovery</td>
<td>Relatives: false hopes</td>
</tr>
<tr>
<td>Same as neurological examination</td>
<td>Clinicians &amp; relatives: may be affirmed in their decision about the level of treatment</td>
<td>Clinicians &amp; relatives: may be disappointed &amp; treatment cost/effectiveness may be poor</td>
</tr>
</tbody>
</table>
Communication in LIS
Third vs. first-person perspective

Disorders of consciousness | Medico-ethical imperative | Clinical evaluation | Active/Passive paradigms | Resting state | LIS | Perspectives

Nizzi & Demertzi et al, Consciousness and Cognition 2012
Demertzì et al, in press
‘Le scaphandre et le papillon’ (2007)
Direction: Julian Schnabel
New knowledge, new nosology

Gantner, Bodard, Laureys & Demertzi, Fut Neurol 2013
Bruno & Vanhaudenhuyse et al, J Neurology 2011
Translational research

Medico-ethical issues in DOC

Biomarkers (fMRI, PET, EEG)

Diagnostic & prognostic use (multimodal imaging)

Coma → Vegetative state
Eye-opening and reflex behavior only

EMG, ERP or fMRI might reveal subclinical command-following

AWARENESS

Minimally conscious state
Voluntary movements or command-following

Communication

EEG (brain-computer interfaces) or real-time fMRI might enable communication that is not dependent on motor pathways

Emergence
Interactive communication

www.nature.com/clinicalpractice/neuro

Laureys & Boly, Nature Clinical Practice 2008
Owen, Schiff & Laureys, Prog Brain Res 2009
Neuro-ethical issues to consider:

• The moral significance of Consciousness
  → ontological understanding: consciousness = personhood = moral agency
  → relational or contextual understanding: patients have value for others

• Legal challenges: responses to critical questions with NI

• Cognitive neuroscience is about brain/mind reading
  → to what degree do we neuroscientists have the right to interfere with a patient’s intimacy, such as cognitive contents, in the absence of their consent?
  → in essence, where do we draw the limits of deciphering another person’s cognitive content, like dreams, ongoing mentation etc? What is the additive value of it to a societal level?
Niko Schiff & Henning Voss, Weill Cornel Medical College

Julia Sophia Crone & the Salzburg team

The departments of Neurology and Radiology in Liege and Paris

...but mostly patients and their families!

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