Ain’t no rest for the brain

Neuroimaging and neuroethics in dialogue for non-communicating brain-injured patients

NUEVOS DESAFÍOS EN NEUROCIENCIAS COGNITIVAS
New Challenges in the field of Cognitive Neuroscience

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A clinical definition of consciousness

Laureys et al, Trends Cogn Sci 2005

Awareness = command following

Conscious Wakefulness

Drowsiness

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

"Vegetative"/unresponsive wakefulness syndrome

General Anesthesia

Coma

Deep sleep

Sleep St I-II

Deep sleep

Wakefulness

= eyes opening

Laureys et al, Trends Cogn Sci 2005
Attitudes towards pain

Do you think patients in a ... can feel pain?

<table>
<thead>
<tr>
<th>Question</th>
<th>Predictors</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you think VS patients feel pain?</td>
<td>Age</td>
<td>1.01</td>
<td>1.00 - 1.02</td>
<td>.050</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>1.25</td>
<td>.99 - 1.58</td>
<td>.060</td>
</tr>
<tr>
<td></td>
<td>Northern Europe</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Central Europe</td>
<td>.81</td>
<td>.58 - 1.14</td>
<td>.240</td>
</tr>
<tr>
<td></td>
<td>Southern Europe</td>
<td>1.10</td>
<td>.76 - 1.60</td>
<td>.600</td>
</tr>
<tr>
<td></td>
<td>Paramedical professionals</td>
<td>1.56</td>
<td>1.20 - 2.00</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Religious respondents</td>
<td>1.37</td>
<td>1.10 - 1.70</td>
<td>.004</td>
</tr>
<tr>
<td>Do you think MCS patients feel pain?</td>
<td>Women</td>
<td>2.38</td>
<td>1.33 - 4.26</td>
<td>.003</td>
</tr>
<tr>
<td></td>
<td>Religious respondents</td>
<td>1.83</td>
<td>1.05 - 3.18</td>
<td>.031</td>
</tr>
</tbody>
</table>

Predicted response: "agreement"
Attitudes towards end-of-life

- 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%

Demertzis et al, J Neurol 2011
Attitudes towards pain and end-of-life

Treatment can be stopped in chronic...

- Feel pain
- Do not feel pain

<table>
<thead>
<tr>
<th>Agreement</th>
<th>VS/UWS</th>
<th>MCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>**</td>
<td>59</td>
<td>29</td>
</tr>
<tr>
<td>NS</td>
<td>77</td>
<td>38</td>
</tr>
</tbody>
</table>

**p < .001

Demertz & Racine et al, Neuroethics 2012
Behavioral evaluation of patients

COGNITIVE CAPACITY

VEGETATIVE/UNRESPONSIVE

MOTOR RESPONSIVENESS

coma

minimally responsive

Communication ?

severity of disability

professional reinsertion

moderate disability

live independently

severe disability

good recovery

awareness ? = response to command or non-reflex movements

Communication ?

arousal = eye opening

Laureys et al, Curr Opin Neurol 2005
Behavioral diagnosis: gold standard?

Standardized assessment

- n=103 post-comatose patients
- 45 Clinical diagnosis of VS
- 27 Coma Recovery Scale VS

40% misdiagnosed

Schnakers et al, Ann Neurol 2006; BMC Neurol 2009

PET Neuroimaging

<table>
<thead>
<tr>
<th>Clinical consensus diagnosis</th>
<th>UWS</th>
<th>MCS</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>VS/UWS</td>
<td>24 (21%)</td>
<td>5 (4%)</td>
<td>29 (26%)</td>
</tr>
<tr>
<td>MCS</td>
<td>12 (11%)</td>
<td>71 (63%)</td>
<td>83 (74%)</td>
</tr>
<tr>
<td>Total</td>
<td>36 (32%)</td>
<td>76 (68%)</td>
<td>112 (100%)</td>
</tr>
</tbody>
</table>

UWS=unresponsive wakefulness syndrome. MCS=minimally conscious state.

Table 2: Diagnostic results by modality

Stender et al, Lancet 2014
Detecting awareness with fMRI

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

Boly et al, Lancet Neurol 2006

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
The brain’s default mode of function

Demertzi & Whitfield-Gabrieli, in: Neurology of Consciousness 2nd ed. 2015
Demertzi, Soddu, Laureys, Curr Opin Neurobiology 2013
Demertzi et al, Front Hum Neurosci 2013
Raichle et al, PNAS 2001
The brain’s default mode of function

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
The cognitive counterpart of resting state

Anticorrelated activity is modified in hypnosis

Demertzi, Soddu, Faymonville et al, Progress in Brain Research 2011
Awareness is modified in hypnosis

Internal awareness
External awareness

External-internal: $r=-0.41$,
Mean switch: 0.05Hz (0.04-0.05)

External-internal: $r=-0.24$,
Mean switch: 0.03Hz (0.02-0.05)

Demertzi, Vanhaudenhuyse, Noirhomme, Faymonville, Laureys, J Physiol Paris in press
Anticorrelated activity is absent in DOC.
Systems-level intrinsic connectivity

Demertzi & Gómez et al, Cortex 2014
Heine et al, Front Psychol 2012; Smith et al, PNAS 2009; Beckmann et al, Phil. Trans. R. Soc. B 2005
Fewer “neuronal” networks in DOC

Demertzi & Gómez et al, Cortex 2014
Intrinsic connectivity networks

Default mode network

Demertzis & Antonopoulos et al, Brain 2015
Intrinsic connectivity reflects the level of C
Which network discriminates best?

**MCS > VS/UWS**

<table>
<thead>
<tr>
<th>Network</th>
<th>t value</th>
<th>Rank</th>
<th>p value</th>
<th>TP</th>
<th>TN</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auditory</td>
<td>8.32</td>
<td>1</td>
<td>&lt;.001</td>
<td>25</td>
<td>18</td>
<td>43/45</td>
</tr>
<tr>
<td>Visual</td>
<td>7.79</td>
<td>2</td>
<td>&lt;.001</td>
<td>23</td>
<td>15</td>
<td>38/45</td>
</tr>
<tr>
<td>Default mode</td>
<td>6.95</td>
<td>3</td>
<td>&lt;.001</td>
<td>23</td>
<td>15</td>
<td>38/45</td>
</tr>
<tr>
<td>Frontoparietal</td>
<td>6.82</td>
<td>4</td>
<td>&lt;.001</td>
<td>23</td>
<td>15</td>
<td>38/45</td>
</tr>
<tr>
<td>Salience</td>
<td>6.21</td>
<td>5</td>
<td>&lt;.001</td>
<td>24</td>
<td>15</td>
<td>39/45</td>
</tr>
<tr>
<td>Sensorimotor</td>
<td>5.87</td>
<td>6</td>
<td>&lt;.001</td>
<td>24</td>
<td>13</td>
<td>37/45</td>
</tr>
</tbody>
</table>

*FWE p < 0.05 (cluster-level)*
Crossmodal connectivity classifies independently assessed patients

- **Training set:** 45 DOC (26 MCS, 19 VS/UWS)
  - 14 trauma, 28 non-trauma, 3 mixed
  - 34 patients assessed >1m post-insult
- **Test set:**
  - **16 MCS, 6 VS/UWS** \(M_{\text{age}}: 43\text{y}, 15\) non-trauma; all chronic
  - From 2 different centers

Demertzi & Antonopoulos et al, Brain 2015
Classifier generalizes to healthy
# 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>
New knowledge, new nosology

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?
Conclusions

Medico-ethical issues in DOC

Biomarkers (fMRI, PET, EEG)

Diagnostic & prognostic use (multimodal imaging)
Thank you!

Coma Science Group & PICNIC Lab
The departments of Neurology and Radiology in Liège and Paris

...and mostly patients and their families!

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