Tutorial
Resting state fMRI as a means to assess the consciousness after severe brain injury

1st Summer School
Interdisciplinary Research on Brain Network Dynamics

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The problem

Patients cannot express themselves

How can we evidence C in the absence of communication?
What is the minimum information we need?
How can we be conscious? (1)

We need a brain (all of it?)

Typical brain

Primary cerebellar agenesis

Frontal air-filled cavity
How can we be conscious? (2)

We need a functional brain

Laureys et al., Lancet Neurology, 2004
(sleep data from Pierre Maquet; anesthesia data from Mike Alkire)
Is she conscious?
Behavioural signs of C

Laureys et al, Curr Opin Neurol 2005
We cannot always trust behavior

**Standardized assessment**

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

**Neuroimaging**

- Table 2: Diagnostic results by modality

<table>
<thead>
<tr>
<th>Clinical consensus diagnosis</th>
<th>18F-FDG PET</th>
</tr>
</thead>
<tbody>
<tr>
<td>UWS</td>
<td>MCS</td>
</tr>
<tr>
<td>24 (21%)</td>
<td>5 (4%)</td>
</tr>
<tr>
<td>12 (11%)</td>
<td>71 (63%)</td>
</tr>
<tr>
<td>36 (32%)</td>
<td>76 (68%)</td>
</tr>
</tbody>
</table>

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

40% misdiagnosed

Schnakers et al, Ann Neurol 2006; BMC Neurol 2009

Stender & Gossieres et al, Lancet 2014
Neuroimaging paradigms

Owen et al, Science 2006
Monti & Vanhaudenhuyse et al, NEJM 2010
Boly et al, Lancet Neurol 2008

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
Neuroimaging to find “hidden minds”

Imagine Tennis to answer 'YES'
Imagine Navigating to answer 'NO'

Is your father’s name Alexander?

Is your father’s name Thomas?

The stream of thought (Chapter IX)
The principles of psychology 1890
Some numbers…

- The human brain is approximately 2% of body’s weight
- 80% of this energy for neuronal signalling → most of consumed energy used for function
- Stimulus & performance-evoked changes in brain energy consumption are surprisingly small (typically <5%)

While conscious awareness is a low bandwidth phenomenon and therefore energetically inexpensive, it is dependent upon a very complex, dynamically organized, non-conscious state of the brain that is achieved at great expense

A control state?

Cognitive psychology: Mental chronometry (measures the time required to complete specific mental operations isolated by the careful selection of task and control states)

fMRI: Subtracting functional images acquired in a task state from ones acquired in a control state

Task deactivations

Task performance - Rest (fixation/eyes closed) $\rightarrow$ Deactivations

The brain’s default mode at rest

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
Default mode network in DOC

Vanhaudenhuyse & Noirhomme et al, Brain 2010
Intrinsic Connectivity Networks


Task            Rest

Smith et al, PNAS 2009
Independent component analysis (ICA)
A challenge…

Heine et al, Frontiers in Psychology 2012
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

- **Number of subjects (%) with neuronal networks**
  - **HEALTHY**
  - **MCS**
  - **VS/UWS**

- **Single-patient classification**
  - **Performance measures**
    - Accuracy
    - TPR healthy
    - TPR patients
    - Selected RSNs
  - **Healthy vs. all patients**
    - Neuronal: 85.3% accuracy, TPR healthy: .82, TPR patients: .87
    - Selected RSNs: Auditory, DMN

Demertzi & Gómez et al, Cortex 2014
Effect of pathology

Seed-based functional connectivity

seeds

Default mode network
Seed-based functional connectivity

Demertzi & Antonopoulos et al, Brain 2015
Connectivity reflects C state

Demertzi & Antonopoulos et al, Brain 2015
Which network discriminates best?

<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)

Demertzi & Antonopoulos et al, Brain 2015
Crossmodal connectivity classifies DOC

- 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_{age}: 43y, 15 non-trauma; all chronic), from 2 different centers

Demertzi & Antonopoulos et al, Brain 2015
Classifier generalizes to healthy
Why does it matter?
Neuroimaging and Disorders of Consciousness: Envisioning an Ethical Research Agenda

Joseph J. Fins, Weill Medical College of Cornell University*
Judy Illes, University of British Columbia*
James L. Bernat, Dartmouth Medical School**
Joy Hirsch, Columbia University**
Steven Laureys, University of Liege**
Emily Murphy, Stanford Law School**

*Co-lead authors.
**Equal authors in alphabetical order.
## Balancing costs-benefits

<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 exam</td>
<td>Relatives: decisions to limit life-sustaining treatment</td>
<td>Relatives: may lose hope, purpose, and meaning in life</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ brain activity than neurological exam</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>
Benefit for science

Gantner, et al, Fut Neurol 2013
Continuity of self-image

LIS patients (n=44)   Healthy controls (n=20)

Interpersonal attitudes impact experienced personhood

Nizzi, Blandin, Demertzis *NeuroEthics* 2018

Benefit for patients?
Benefit for caregivers?

Table III. Percentage of healthcare workers presenting a burnout.

<table>
<thead>
<tr>
<th>Profession</th>
<th>Burnout</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician</td>
<td>8%</td>
</tr>
<tr>
<td>Nurse</td>
<td>24%</td>
</tr>
<tr>
<td>Nursing assistant</td>
<td>23%</td>
</tr>
<tr>
<td>Physio-/speech-/ergo-therapist</td>
<td>8%</td>
</tr>
<tr>
<td>Psychologist/social worker</td>
<td>10%</td>
</tr>
</tbody>
</table>

n=523

Gosseries, Demertzi et al, Brain Injury 2012
Consciousness has a moral significance

Demertz et al, *J Neurol* 2011

Demertz & Racine et al, *Neuroethics* 2012
Neuro-ethical considerations

• 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

- fMRI rs fc connectivity carries information about cognition
- fMRI rs fc connectivity can be used in the clinical setting
- fMRI rs fc connectivity needs to generalize to unconscious conditions
- NI studies have ethical consequences
Thank you

Coma Science Group & PICNIC Lab

The departments of Neurology and Radiology in Liège & Paris

…and mostly patients and their families!

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