Clinical approaches in disorders of consciousness

Differentiating unresponsiveness from unconsciousness

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Reducing awareness to 2D

Consciousness | Neural correlates | Diagnosis | Prognosis | Treatment | Ethics | Conclusion

Demertzi, Soddu, Laureys, *Curr Opin Neurobiology*, 2013

www.comascience.org
Consciousness ≈ top-down

Clinical interest

Consciousness | Neural correlates | Diagnosis | Prognosis | Treatment | Ethics | Conclusion

Laureys et al., Current Opinion in Neurology, 2005

Motor responsiveness

Consciousness

Vegetative/unresponsive

Minimally responsive

Aroused

= eye opening - only reflex movements

Awareness?

= non-reflex movements or response to command

Communication?

Severe disability

Moderate disability

Live independently

Good recovery

Professional reinsertion

Disorders of consciousness | behavioural evaluation | electrophysiology | neuroimaging | methods, ethics & quality of life | perspectives
Signs of consciousness on fMRI

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

Owen, Coleman, Boly, Davis, Laureys & Pickard, Science, 2006
Yes-No communication with fMRI


3/16 VS/UWS (19%)
- 2/5 traumatic (40%)
- 1/11 non-traumatic (9%)

Cruse et al, *Neurology* 2012

7/23 MCS (30%)
- 7/15 traumatic (49%)
- 0/8 non-traumatic (0%)
A new era for BCIs

Unresponsiveness ≠ Unconsciousness


Copyright © 2012, the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins. Anaesthesia 2012; 116:946–9

Brain injury, 2012, 1–13, Early Online

REVIEW

Brain–computer interfacing in disorders of consciousness

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Clinical Neurophysiology

Contents lists available at ScienceDirect

Clinical Neurophysiology

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Voluntary brain processing in disorders of consciousness

**Table 2**
Demographic and evoked-related potentials data in patients in a minimally conscious state (MCS)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y</th>
<th>Gender</th>
<th>Etiology</th>
<th>Time since onset</th>
<th>SON (P3)</th>
<th>Active SON (P3)</th>
<th>Active TUN (P3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCS1</td>
<td>35</td>
<td>M</td>
<td>Trauma</td>
<td>23.7 y</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>MCS2</td>
<td>47</td>
<td>F</td>
<td>Hemorrhage</td>
<td>7.2 mo</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MCS3</td>
<td>26</td>
<td>M</td>
<td>Trauma</td>
<td>4.3 y</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>MCS4</td>
<td>63</td>
<td>F</td>
<td>Trauma</td>
<td>3.6 mo</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MCS5</td>
<td>56</td>
<td>M</td>
<td>Anoxia</td>
<td>1.1 mo</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MCS6</td>
<td>56</td>
<td>M</td>
<td>Anoxia</td>
<td>3.1 y</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>MCS7</td>
<td>59</td>
<td>M</td>
<td>Trauma</td>
<td>8.8 mo</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MCS8</td>
<td>50</td>
<td>F</td>
<td>Anoxia</td>
<td>1.9 mo</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MCS9</td>
<td>36</td>
<td>F</td>
<td>Trauma</td>
<td>22.3 y</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MCS10</td>
<td>55</td>
<td>M</td>
<td>Anoxia</td>
<td>22 d</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>MCS11</td>
<td>64</td>
<td>M</td>
<td>Trauma</td>
<td>22 d</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>MCS12</td>
<td>60</td>
<td>F</td>
<td>Anoxia</td>
<td>6.9 y</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>MCS13</td>
<td>64</td>
<td>M</td>
<td>Metabolic</td>
<td>16 d</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MCS14</td>
<td>74</td>
<td>M</td>
<td>Trauma</td>
<td>11.1 mo</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**SON** = subject’s own name; **active SON** = counting own name; **active TUN** = counting target unfamiliar name.

**ABSTRACT**

**Background.** Disentangling the vegetative state from the minimally conscious state is often difficult when relying only on behavioral observation. In this study, we explored a new active evoked-related potentials paradigm as an alternative method for the detection of voluntary brain activity.

**Methods.** The participants were 22 right-handed patients (9 traumatic) diagnosed as being in a vegetative state (VS) (n = 8) or in a minimally conscious state (MCS) (n = 14). They were presented sequences of names containing the patient’s own name or other names, in both passive and active conditions. In the active condition, the patients were instructed to count her or his own name or to count another target name.

**Results.** Like controls, MCS patients presented a larger P3 to the patient’s own name, in the passive and in the active condition. Moreover, the P3 to target stimuli was higher in the active than in the passive condition, suggesting voluntary compliance to task instructions like controls. These responses were even observed in patients with low behavioral responses (e.g., visual fixation and pursuit). In contrast, no P3 differences between passive and active conditions were observed for VS patients.

**Conclusions.** The present results suggest that active evoked-related potentials paradigms may permit detection of voluntary brain function in patients with severe brain damage who present with a disorder of consciousness, even when the patient may present with very limited to questionably any signs of awareness. *Neurology* 2008;71:1614-1620.

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**Schnakers et al, Neurology, 2008**

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**BCI in DOC**
BCI in DOC

Coma or total locked-in syndrome?
21-y old woman
basilar artery thrombosis - day 49

Other names PASSIVE
Count TARGET (other name)
Own name PASSIVE
Count TARGET (own name)

Fellinger et al *Clin Neurophysiol*, 2011

Schnakers et al, *Neurocase*, 2009
Pupil-based Brain Computer Interfaces

Einhauser et al, *Current Biology*, in press
Language-dependent responsiveness

“Resting” default mode connectivity

Vanhaudenhuyse et al, Brain 2010
Should we trust the test?

Jox, Bernat, Laureys, Racine, *Lancet Neurology* 2012
Consciousness ≈ connectivity

**EEG-TMS**

Rosanova and Gosseries et al, *Brain* 2012

www.comascience.org
Consciousness \approx PCI


www.comascience.org
EEG-TMS perturbational complexity index
in sleep, anesthesia & coma

Casali and Gosseries et al,
*Science Transl Med*, in press
Outcome in anoxic coma

Anesthesiology 2012; 117:1311-21
Diffusion Tensor Imaging to Predict Long-term Outcome after Cardiac Arrest
A Bicentric Pilot Study

Charles-Edouard Luyt, M.D., Ph.D.,* Damien Galanaud, M.D., Ph.D.,† Vincent Perlbarg, Ph.D., ‡ Audrey Vanhaudenhuyse, Ph.D., † Robert D. Stevens, M.D., † Rajee Gupta, M.D., # Horstense Beasant, M.D., † Alexandre Knekt, M.D., †‡ Gerard Audibert, M.D., †‡ Alain Combines, M.D., Ph.D., †‡ Jean Chaute, M.D., †‡ Hubert Bonnini, Ph.D., †‡ Steven Laureys, M.D., Ph.D., †‡ Louis Poupart, M.D., # for the Neuro Imaging for Coma Emergence and Recovery Consortium

<table>
<thead>
<tr>
<th></th>
<th>Good outcome</th>
<th>Bad outcome</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>90%</td>
<td>83%</td>
<td>94%</td>
</tr>
<tr>
<td>Specificity</td>
<td>63%</td>
<td>88%</td>
<td>100%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fractional anisotropy</th>
</tr>
</thead>
<tbody>
<tr>
<td>gCC</td>
</tr>
<tr>
<td>bCC</td>
</tr>
<tr>
<td>sCC</td>
</tr>
</tbody>
</table>

Consciousness | Neural correlates | Diagnosis | Prognosis | Treatment | Ethics | Conclusion

http://www.comascience.org
Nociception and pain

Nociception Coma Scale –R

<table>
<thead>
<tr>
<th>Score</th>
<th>Item</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Localization to Noxious Stimulation</td>
<td>The non-stimulated limb must locate and make contact with the stimulated body part at the point of stimulation.</td>
</tr>
<tr>
<td>2</td>
<td>Flexion Withdrawal</td>
<td>There is isolated flexion withdrawal of at least one limb. The limb must move away from the point of stimulation.</td>
</tr>
<tr>
<td>1</td>
<td>Abnormal Posturing</td>
<td>Movements occur in response to the upper and/or lower extremities, seen immediately after the stimulus is applied.</td>
</tr>
<tr>
<td>0</td>
<td>None/Motor</td>
<td>There is no measurable movement following application of nociceptive stimulation, secondary to movement of facial muscles.</td>
</tr>
</tbody>
</table>

**VERBAL RESPONSE**

<table>
<thead>
<tr>
<th>Score</th>
<th>Item</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Involuntary Verbalization</td>
<td>Production of words in response to noxious stimulation. Each verbalization must consist of at least 3 component-connector-component (C-C) trials. For each trial, the patient is asked a series of personal questions. If the patient responds with a single word, the examiner asks, &quot;What's wrong?&quot; If the patient responds with a single word, the examiner asks, &quot;What's wrong?&quot; If the patient responds with a single word, the examiner asks, &quot;What's wrong?&quot; If the patient responds with a single word, the examiner asks, &quot;What's wrong?&quot;</td>
</tr>
<tr>
<td>2</td>
<td>Vocalization/Oral Movement</td>
<td>Positive response to stimulus, no change to conscious state.</td>
</tr>
<tr>
<td>1</td>
<td>Groan</td>
<td>Positive response to stimulus, no change to conscious state.</td>
</tr>
<tr>
<td>0</td>
<td>None</td>
<td>No change</td>
</tr>
</tbody>
</table>

**VISUAL RESPONSE**

<table>
<thead>
<tr>
<th>Score</th>
<th>Item</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Fixation</td>
<td>Positive response to stimulus, no change to conscious state.</td>
</tr>
<tr>
<td>2</td>
<td>Eye movements</td>
<td>Positive response to stimulus, no change to conscious state.</td>
</tr>
<tr>
<td>1</td>
<td>Squeal</td>
<td>Positive response to stimulus, no change to conscious state.</td>
</tr>
<tr>
<td>0</td>
<td>No change</td>
<td>No change</td>
</tr>
</tbody>
</table>

Total score > 3 / 9 = analgesic treatment

Chatelle et al, JNNP 2012

Chatelle et al, under review

www.comascience.org
Ethical framework

**Target Article** *The American Journal of Bioethics, 8(9): 3–12, 2008*

**Neuroimaging and Disorders of Consciousness: Envisioning an Ethical Research Agenda**

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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.


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Results of additional diagnostic testing and their possible ethically relevant effects

<table>
<thead>
<tr>
<th>Results of Tests</th>
<th>Beneficial Effects</th>
<th>Harmful Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tests show <em>less brain activity than</em></td>
<td>Relatives may better cope with the decision to withdraw life-sustaining treatment</td>
<td>Relatives may lose hope, purpose, and meaning in life</td>
</tr>
<tr>
<td>neurological examination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tests show <em>more brain activity than</em></td>
<td>Clinical management may be intensified by the chance of further recovery</td>
<td>False hopes may be nurtured, leading to long-term harm, disappointment &amp; suffering</td>
</tr>
<tr>
<td>neurological examination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tests show <em>the same level of brain activity</em></td>
<td>Clinicians and relatives may be affirmed in their decision about the level of treatment</td>
<td>Clinicians and relatives may be disappointed &amp; treatment cost/effectiveness may be poor</td>
</tr>
</tbody>
</table>
Conclusion

Human conscious awareness
≈ emergent property of collective
critical neural network dynamics,
involving a frontoparietal global workspace

Diagnostic use
≈ 40% clinical misdiagnosis

Prognostic use
multimodal imaging

Therapeutic use
pain treatment

Ethical challenges

Laureys & Schiff, NeuroImage, 2012
Sanders et al, Anesthesiology, 2012
Laureys & Boly, Nature Clinical Practice, 2008