Transcranial Direct Current Stimulation (tDCS) in patients with disorders of consciousness

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Annual IUAP meeting, May 22, 2014
Disorders of consciousness

NORMAL CONSCIOUSNESS

AROUSAL

AWARENESS

Laureys, Owen and Schiff, Lancet Neurology, 2005
Disorders of consciousness

Laureys, Owen and Schiff, Lancet Neurology, 2005
Disorders of consciousness

NORMAL CONSCIOUSNESS

COMA

Introduction | tDCS | Studies | Conclusion

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VEGETATIVE STATE/UNRESPONSIVE WAKEFULNESS SYNDROME

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MINIMALLY CONSCIOUS STATE

AROUSAL

AWARENESS

Laureys, Owen and Schiff, Lancet Neurology, 2005
Clinical entities
Clinical entities

Laureys, Scientific American, 2007
Clinical entities

- Acute Brain Injury
  - Coma
    - Fast Recovery
    - Vegetative State
    - Locked-In Syndrome
    - Brain Death
Clinical entities

- Acute Brain Injury
- Coma
  - Fast Recovery
  - Vegetative State
    - Minimally Conscious State
    - Permanent vegetative State
  - Locked-In Syndrome
  - Brain Death

Clinical entities

- Acute Brain Injury
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    - Fast Recovery
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      - Locked-In Syndrome
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      - Permanent Vegetative State
    - Minimally Conscious State
      - Recovery of Consciousness
    - Permanent Minimally Conscious State

Laureys, Scientific American, 2007

www.comascience.org
Clinical entities

- Acute Brain Injury → Coma
  - Locked-In Syndrome
  - Brain Death
  - Fast Recovery
  - Vegetative State
    - Minimally Conscious State
      - Recovery of Consciousness
      - Permanent Minimally Conscious State

How to improve recovery?
### Pharmacological treatments

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Study (first author, year)</th>
<th>Number of patients and etiology</th>
<th>Diagnosis</th>
<th>Placebo control</th>
<th>Reported functional outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dopaminergic agents</strong></td>
<td></td>
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</tr>
<tr>
<td>Amantadine</td>
<td>Giacino (2012)</td>
<td>184 TBI</td>
<td>MCS/VS</td>
<td>Yes</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td>Schnakers (2008)</td>
<td>1 anoxic</td>
<td>MCS</td>
<td>No</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td>Patrick (2006)</td>
<td>10 TBI</td>
<td>Low responsive level</td>
<td>No</td>
<td>No effect</td>
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<tr>
<td></td>
<td>Hughes (2005)</td>
<td>123 TBI</td>
<td>Coma</td>
<td>NA</td>
<td>No effect</td>
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<tr>
<td></td>
<td>Sainiova (2004)</td>
<td>41 TBI</td>
<td>‘Persistent unconsciousness’</td>
<td>NA</td>
<td>Positive</td>
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<tr>
<td>Meythaler (2002)</td>
<td></td>
<td>35 TBI</td>
<td>MCS</td>
<td>Yes</td>
<td>Positive</td>
</tr>
<tr>
<td><strong>Bromocriptine</strong></td>
<td>Brahmi (2004)</td>
<td>4 Intoxication</td>
<td>Coma</td>
<td>No</td>
<td>Positive</td>
</tr>
<tr>
<td><strong>Levodopa</strong></td>
<td>Matsuda (2003)</td>
<td>3 TBI</td>
<td>VS</td>
<td>No</td>
<td>Positive</td>
</tr>
<tr>
<td><strong>Nonbenzodiazepine sedative</strong></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Zolpidem</td>
<td>Cohen (2008)</td>
<td>1 anoxic</td>
<td>Lethargic</td>
<td>No</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td>Shames (2008)</td>
<td>1 anoxic</td>
<td>MCS</td>
<td>No</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td>Singh (2008)</td>
<td>1 TBI</td>
<td>MCS</td>
<td>No</td>
<td>No effect</td>
</tr>
<tr>
<td></td>
<td>Brefel-Courbon (2007)</td>
<td>1 hypoxic</td>
<td>Akinetic mutism</td>
<td>Yes</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td>Clauss (2006)</td>
<td>2 TBI, 1 anoxic</td>
<td>VS</td>
<td>No</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td>Clauss (2000)</td>
<td>1 TBI</td>
<td>Semi-comatose</td>
<td>No</td>
<td>Positive</td>
</tr>
<tr>
<td><strong>GABA agonist</strong></td>
<td>Sara (2007)</td>
<td>1 non-TBI</td>
<td>VS</td>
<td>No</td>
<td>Positive</td>
</tr>
</tbody>
</table>

Pharmacological treatment

Introduction | tDCS | Studies | Conclusion

Schnakers et al
J Neurol Neurosurg Psychiatry 2008

www.comascience.org
Consciousness ≈ thalamo-cortical

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

Laureys et al, Lancet 2000

Giacino, Fins, Laureys, Schiff, Nature Rev Neurol 2014
Consciousness \approx \text{thalamo-cortical}

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

Intralaminar nuclei stimulation induces “recovery” from minimally responsive state


MCS \rightarrow \text{emerged}

# Why direct current?

<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>

Cheap & easy to use

Thibaut et al, Rev Neurol, 2013
tDSCS presumed mode of action

**Short term effects** (Nitsche et al., J Physiol 2000)
Modification of neuronal excitability (action potential)

Thibaut et al., Rev Neurol, 2013
tDCS presumed mode of action

**Short term effects**  (Nitsche et al., J Physiol 2000)
Modification of neuronal excitability (action potential)

**Long term effects**  (Nitsche et al., Neuroscientist 2010)
Action on opening of ion channels ($Na^+$, $Ca^{2+}$)
Increase NMDA receptors excitability
→ improve neuron excitability

Thibaut et al., Rev Neurol, 2013
Methods

- Direct current
- 2 mA; 20 minutes
- Anode: PFDL (F3)
- Randomised, double blind, sham controlled

Thibaut et al, *Neurology, 2014*
Methods

- Direct current
- 2 mA; 20 minutes
- Anode: PFDL (F3)
- Randomised, double blind, sham controlled

Session 1
- CRS-R
- tDSCS
- 20’

Session 2
- CRS-R
- tDSCS
- 24h
- CRS-R
- 20’

Thibaut et al, Neurology, 2014
Results

- 55 patients (43±18y)
- 25 VS/UWS, 30 MCS
- 25 TBI, 30 NTBI
- 35 chronic (>3 months)

Thibaut et al, Neurology, 2014
Results

- 55 patients (43±18y)
- 25 VS/UWS, 30 MCS
- 25 TBI, 30 NTBI
- 35 chronic (>3 months)

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

- 2 UWS; acute
- 13 MCS (5>1y post insult)

Thibaut et al, Neurology, 2014
Neurophysiology

Prefrontal stimulation
- Increase of DMN connectivity (rsfMRI)
- Increase of α rhythm (EEG)

Motor stimulation
- rCBF Increase in the left M1, right prefrontal cortex, right S1 (PET-scan)
- Functional connectivity Increase within premotor, motor and sensorimotor areas (EEG)

Keeser et al., J Neurosci, 2011
Lang et al., Eur J Neurosci, 2005
Polania, Nitsche and Paulus, HBM, 2010
Responders vs Non-responders: PET

Responders (n=8) vs non-responders (n=17)

Left prefrontal cortex (stimulated area) and thalamus were more preserved in responders as compared to non-responders.
Responders vs Non-responders: PET

**Behavioral improvement**

<table>
<thead>
<tr>
<th>CRS-R improvement</th>
<th>Responders n=8</th>
<th>Non-responders n=17</th>
</tr>
</thead>
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<td></td>
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**Left DLPF/MPFC metabolism (% of normal)**

<table>
<thead>
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<th>% of brain metabolism</th>
<th>Responders n=8</th>
<th>Non-responders n=17</th>
</tr>
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Thibaut et al, *in prep*
Repeated tDCS

Effects last ± 90 minutes (Hummel et al., Lancet, 2006)
➔ Short improvement, back to initial state
Repeated tDCS

**Effects last ± 90 minutes** (Hummel et al., *Lancet*, 2006)

→ Short improvement, back to initial state

**Daily stimulations** (5days) (Fregni et al., *Pain*, 2006)

Improvement and extension of benefits
Randomised sham controlled double blind study
Repeated tDCS

Effects last ± 90 minutes (Hummel et al., *Lancet*, 2006)
⇒ Short improvement, back to initial state

Daily stimulations (5 days) (Fregni et al., *Pain*, 2006)
Improvement and extension of benefits
Randomised sham controlled double blind study

*tdCS = 20 minutes
Repeated tDCCS

Chronic MCS – N=13

real tDCCS

sham tDCCS

- 7 responders (out of 13 patients)

* <0.025
rtDCS in chronic patients

Repeated tDCS in chronic patients at home or nursing home

**Protocol:**

- tDCS over the prefrontal dorsolateral cortex
- 5 days per week during 4 weeks (2 tDCS sessions – real & sham)
- Stimulations made by the family (video)
- Assessment: CRS-R before – after 4 weeks – one month later
- Double blind randomized study (2 months of washout)
- Chronic patients (> 1 year post insult) in MCS at home or nursing home
rtDSCS in chronic – EEG

tDSCS coupled with 8 electrodes EEG

Record cortical activity before, during and after the stimulation

Electrodes: record and stimulate

➤ Understand the underlying neurophysiological effect of tDSCS on a damage or preserved area
Consciousness ≈ connectivity

mesocircuit fronto-parietal model

Giacino, Fins, Laureys, Schiff, Nature Rev Neurol 2014
Consciousness $\approx$ connectivity

mesocircuit fronto-parietal model

Consciousness \approx \text{connectivity}

mesocircuit fronto-parietal model

Frontal cortex - Striatum - Globus pallidus interna - Central thalamus - Parietal/occipital/temporal cortex

amantadine

zolpidem

Giacino, Fins, Laureys, Schiff, Nature Rev Neurol 2014
Consciousness $\approx$ connectivity

mesocircuit fronto-parietal model

Deep brain stimulation

Consciousness $\approx$ connectivity

THANK YOU
Criticism:

**Limitations:**

- Short term effect (after 1-2h patients return to their initial state)
- Moderate clinical change
- Unknown neurophysiological effects on DOC
Clinical improvement

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

- 2 UWS; acute
- 13 MCS (5>1y post insult)

2 VS/UWS $\Rightarrow$ MCS
Visual pursuit
Response to command

2 MCS $\Rightarrow$ EXIT
Functional communication
Functional use of objects

Thibaut et al, Neurology, 2014
Conclusion

• A single stimulation transiently improves CRS-R scores
• Preserved metabolism in the stimulated area is requested
• 5 days of tDCS increase the lasting of the effects

➢ Could daily stimulations be helpful for patient’s recovery?
➢ Could tDCS be implemented in daily clinical practice?

Future: tDCS could help patients with disorders of consciousness (acute or chronic) to increase their interaction with their environment
tDCS – advantages

**DBS** and **Amantadine** improve cognitive functions of patients with disorder of consciousness.

But side effects

**tDCS** → improve cognition of patients in minimally conscious state without risk of brain damage or seizure.

Schiff et al., Nature 2008
Thibaut et al., Neurology 2014
Reducing consciousness to 2D

Laureys, Trends in Cognitive Sciences, 2005
tDCS - Motor

Cognitive effects $\rightarrow$ Motor effects $\rightarrow$

Parameters:
- 2 mA – 20 min
- Cathode: M1 (C3&C4) (↓ spasticity)
- Anode: DLPF (F3&F4) (↑ signs of consciousness)

1. Behavioral assessments: CRS-R & Ashworth
2. EEG

Hummel et al., Lancet, 2006
Vandermeeren Y et al., Acta Neurol Bel, 2013