Effects of sham-controlled double blind transcranial direct current stimulation in patients with disorders of consciousness

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AIM of the study

Assessing the effect of transcranial direct current stimulation (tDCS) on cognition in patients with disorder of consciousness

In a double blind sham controlled randomized study
## Why direct current stimulation?

<table>
<thead>
<tr>
<th>Stimulation</th>
<th>Population</th>
<th>Effects</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prefrontal cortex</td>
<td>Healthy subjects</td>
<td>Memory</td>
<td>Marshall et al, J Neurosci 2004</td>
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<tr>
<td></td>
<td>Alzheimer’s patients</td>
<td>Memory</td>
<td>Ferrucci et al, Neurology 2008</td>
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<td></td>
<td>Aphasic patients</td>
<td>Language</td>
<td>Baker et al, Stroke 2010</td>
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</tbody>
</table>

- Non-invasive
- Easy to apply
- Cheap equipment
Methods

- Anode
- Cathode

- Direct current
- 2 mA
- 20 minutes

Randomised double blind sham controlled
Methods

Responders: CRS-R post tDCS > pre-tDCS > sham > pre-sham

Statistics: Stata 10.0
- ANOVA
- Wilcoxon signed-rank test

Giacino, Arch Phys Med Rehabil 2004
Stata 10.0 (StataCorp. 2007. Stata Statistical Software: Release 10. College Station, TX: StataCorp LP)

www.comascience.org
Population

- 55 patients (16 women)
- 25 VS/UWS, 30 MCS
- aged 43 ± 18 y
- 25 traumatic / 30 non-traumatic
- 20 acute / 35 chronic (>3 months post insult)
Group data (n=55)

N=55
17 responders
• 2 UWS; acute
• 15 MCS;
  7 acute/8 chronic
Group data (n=55)

17 responders
- 2 UWS; acute
- 15 MCS;
  7 acute/8 chronic
UWS/UV vs MCS

MCS (n=30) | VS/UWS (n=25)

<table>
<thead>
<tr>
<th>CRS-R mean scores</th>
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<tr>
<td>PRE</td>
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<tr>
<td>tDCS</td>
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* indicates statistical significance.
Responders: audition subscale

- Consistent movement to command
- Reproducible movement to command
- Localisation of sounds
- Auditory sartle
- None

<table>
<thead>
<tr>
<th></th>
<th>PRE tDCS</th>
<th>POST tDCS</th>
<th>PRE sham</th>
<th>POST sham</th>
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</thead>
<tbody>
<tr>
<td>Consistent movment to command</td>
<td>*</td>
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<tr>
<td>Auditory sartle</td>
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<tr>
<td>None</td>
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</table>
Responders: motor subscale

- Functional use of objects
- Automatic motor reaction
- Object manipulation
- Localization of noxious stimulation
- Flexion withdrawal
- Abnormal posturing
- None

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<thead>
<tr>
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<tr>
<td><strong>tDCS</strong></td>
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<tr>
<td><strong>sham</strong></td>
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* *
Responders: communication

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None

* *
tDSCS presumed mode of action

Short term effects
Modification of neuronal excitability (action potential)

Long term effects
Action on opening of ion channels \( (\text{Na}^+, \text{Ca}^{2+}) \)
Increase NMDA receptors excitability
improve neuron excitability

Nitsche et al., J Physiol 2000
Nitsche et al., Neuroscientist 2010

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Prefrontal stimulation
- Improvement of DMN connectivity (MRI)
- Increase of regional electrical activity in the PF and AC cortexes (EEG) (% and δ/θ)

Motor stimulation
- rCBF increase in the left M1, right prefrontal cortex, right S1 (PET-scan)
- Functional connectivity increased within premotor, motor and sensorimotor areas (EEG)
**tDCS – advantages**

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

But invasive and pharmacological

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

Schiff et al., Nature 2008
Thibaut et al., in prep
tDCS criticisms

Limitations:

- Short term effect
- Moderate clinical changes
- Superficial effect
- Improve electrode position
tDCA – long term

Effects last ± 90 minutes
- Short improvement
- Back to initial state

Daily stimulations (5days)
improvement and extension of benefits

Hummel et al., Lancet 2006
Antal et al., J Pain Symptom Manage 2010
tDCS – long term

Prospective, randomized, controlled and double-blind study

* tDCS = 20 minutes
tDCES - M1

Cognitive effects + Motor effects?

Parameters:
2 mA – 20 min
Anode: M1
Cathode: supraorbicular controlateral cortex

- 1. Behavioral assessments: CRS-R & Ashworth
- 2. TMS: MEP & motor threshold

Lang et al., 2004
Bohannon and Smith, 1987
tDCS – M1

Real session

CRS-R Ashworth TMS
motor subscale Ashworth TMS
motor subscale Ashworth TMS

tDCS

20 min

45 min

24h

Placebo session

CRS-R Ashworth TMS
motor subscale Ashworth TMS
motor subscale Ashworth TMS

20 min

45 min

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1. Comparison of the results with:
   - cortical lesions (MRI)
   - cerebral metabolism (PET-scan)
   Stimulation of preserved or damaged cortex?

2. EEG before and after tDCS
   Better understanding of neurophysiological effect of tDCS
Conclusion

tDCS improves cognition in minimally conscious state patients both acute and chronic; traumatic and non traumatic

Future studies:
1. long term tDCS
2. tDCS on M1
3. neurophysiological effects