



tDCS in patients with DOC

What have been done so far?

What should be done next?

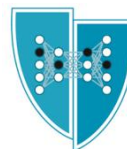
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www.giga.ulg.ac.be
www.comascience.org
neuromodulationcenter.org



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I have no interest to disclose.

PESG and IBIA staff have no interest to disclose.

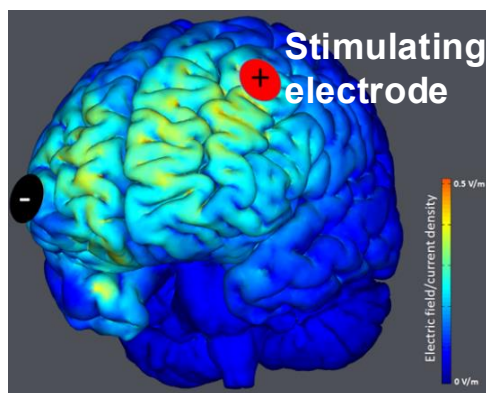
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What's tDCS?

transcranial Direct Current Stimulation - tDCS

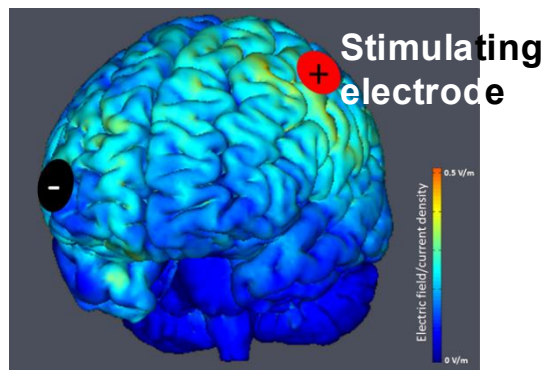
Prefrontal stimulation



2 electrodes (or more)
Weak electrical current (1-2mA)

→ *Membrane polarization*
Anode: ↗ excitability
Cathode: ↘ excitability

Motor stimulation



→ *Long term effects*
Neural excitability & plasticity (LTP-LTD)
Ion channels (Na^+ , Ca^{2+})
NMDA receptors



Why tDCS?

- Modulates spontaneous neuronal activity
- Non-expensive
- Reliable sham condition (for research)
- Easy to administer (→ clinical translation)
- No severe adverse effects



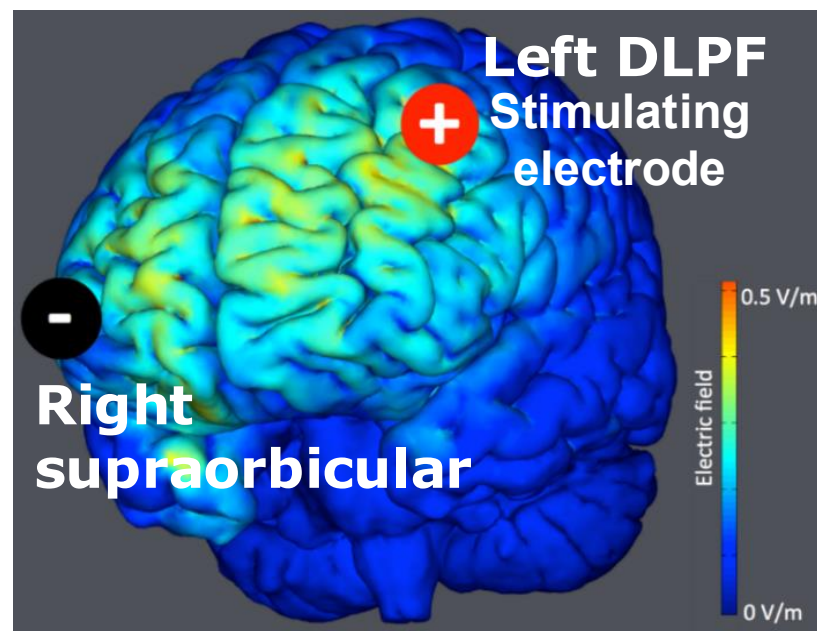
tDCS single session

ARTICLES

tDCS in patients with disorders of consciousness

Sham-controlled randomized double-blind study

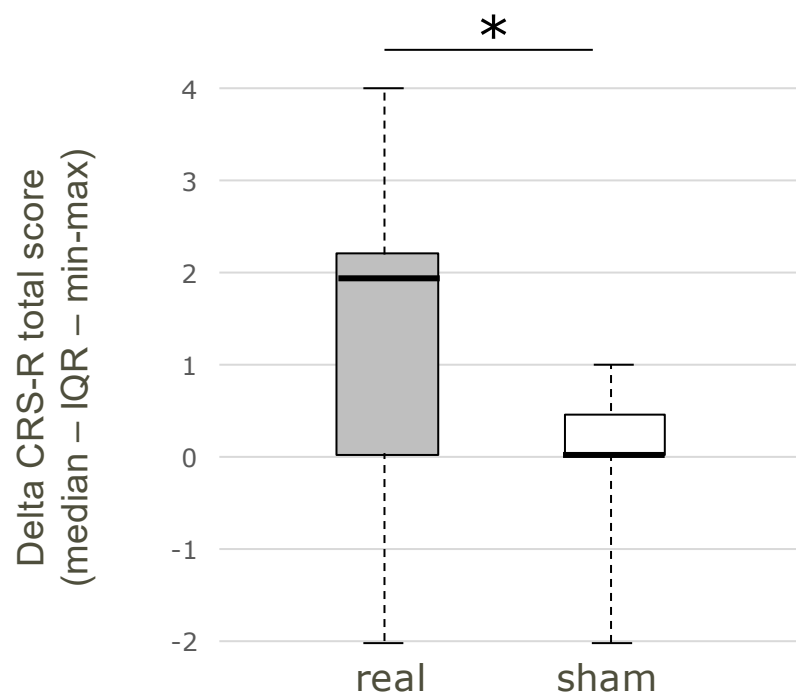
- Randomized, double blind, sham controlled, cross-over study
- Single stimulation – 2 mA; 20 min
- Prefrontal stimulation
- Coma Recovery Scale-R (CRS-R)
- 55 patients included (43 ± 18 y)
 - 25 VS/UWS & 30 MCS
 - 35 chronic (>3m) & 20 acute
 - 25 TBI & 30 nTBI





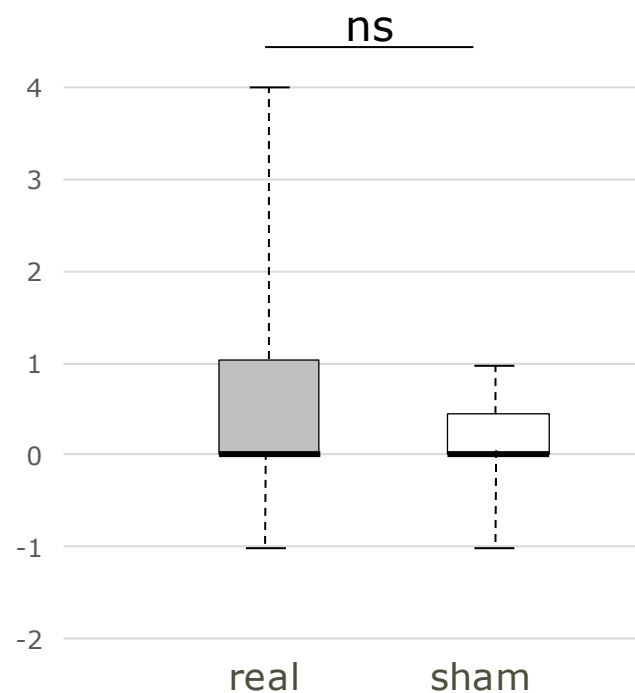
tDCS single session

Treatment effect in MCS – no improvement in UWS/VS



MCS (n=30)

Effect size: 0.38



UWS (n=25)

* $p < 0.05$



tDCS single session

- No side effects
- Change of diagnosis
 - 3 MCS → EMCS – acute
 - 2 UWS → MCS – acute
- 15/55 responders
 - 13/30 MCS – 5 patients >1y post injury
 - 2/25 UWS – 2 acute
- VS/UWS – limited effects but 1 session only!



How to improve tDCS effects?



<50% showed clinical improvement & effect did not last

→ Responders versus non-responders

Comparing brain metabolism and gray matter atrophy in responders versus non-responders

→ Duration of the effects

Increasing the number of sessions

→ Targeting other brain regions critical for consciousness

Precuneus

Fronto-parietal network

→ Can tDCS be used in clinical setting?

Translational study



Difference between tDCS
responders versus
non-responders?



Neural correlates

Brain Stimulation 8 (2015) 1116–1123



ELSEVIER

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: www.brainstimjrnل.com

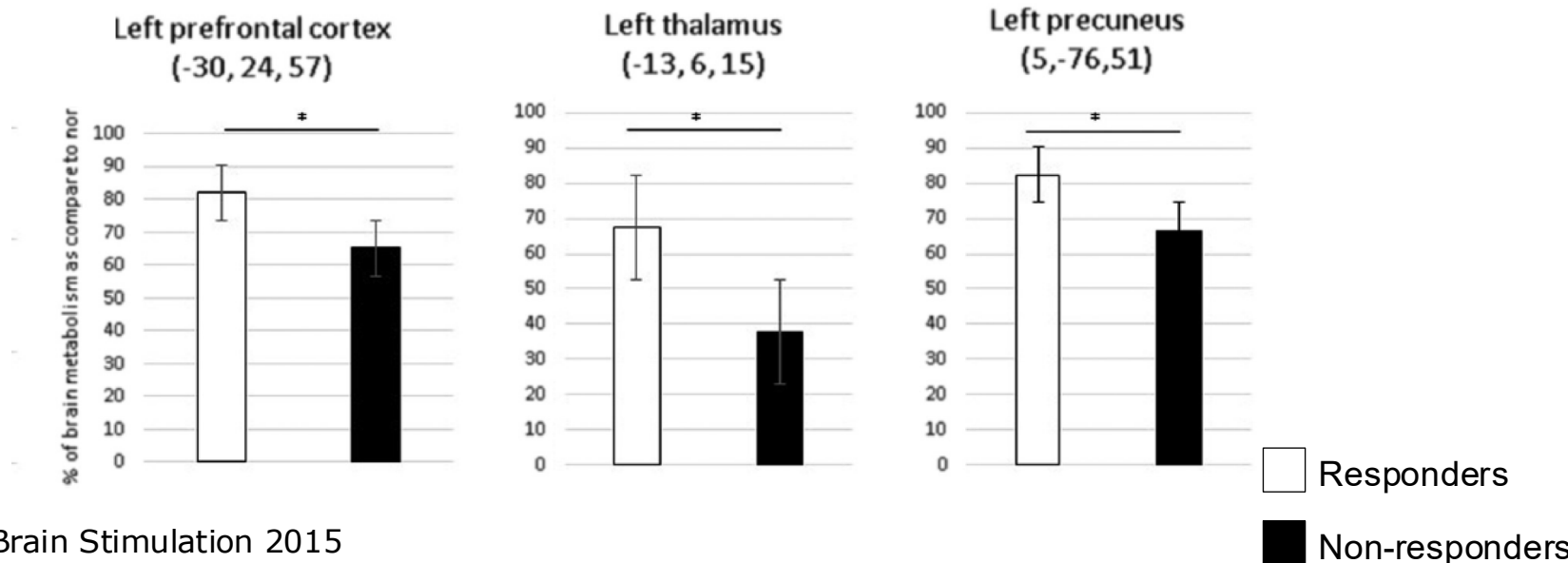


Clinical Response to tDCS Depends on Residual Brain Metabolism and Grey Matter Integrity in Patients With Minimally Conscious State

Aurore Thibaut^{a,*,1}, Carol Di Perri^{a,1}, Camille Chatelle^{b,c}, Marie-Aur lie Bruno^a, Mohamed Ali Bahri^d, Sarah Wannez^a, Andrea Piarulli^{a,e}, Claire Bernard^f, Charlotte Martial^a, Lizette Heine^a, Roland Hustinx^f, Steven Laureys^a

8 tDCS responders versus
13 tDCS non-responders

Regional brain metabolism





Neural correlates

Brain Stimulation 8 (2015) 1116–1123



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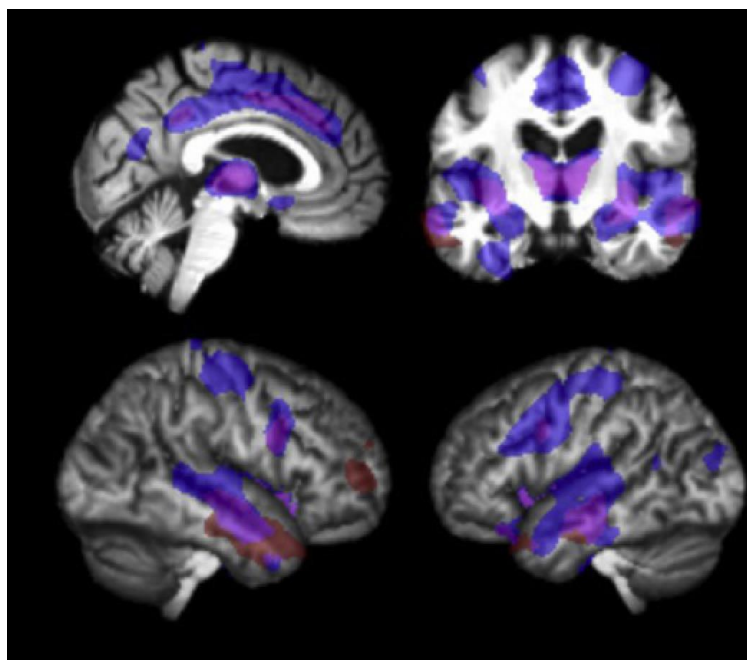


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8 tDCS responders versus
13 tDCS non-responders

Grey matter atrophy – VBM

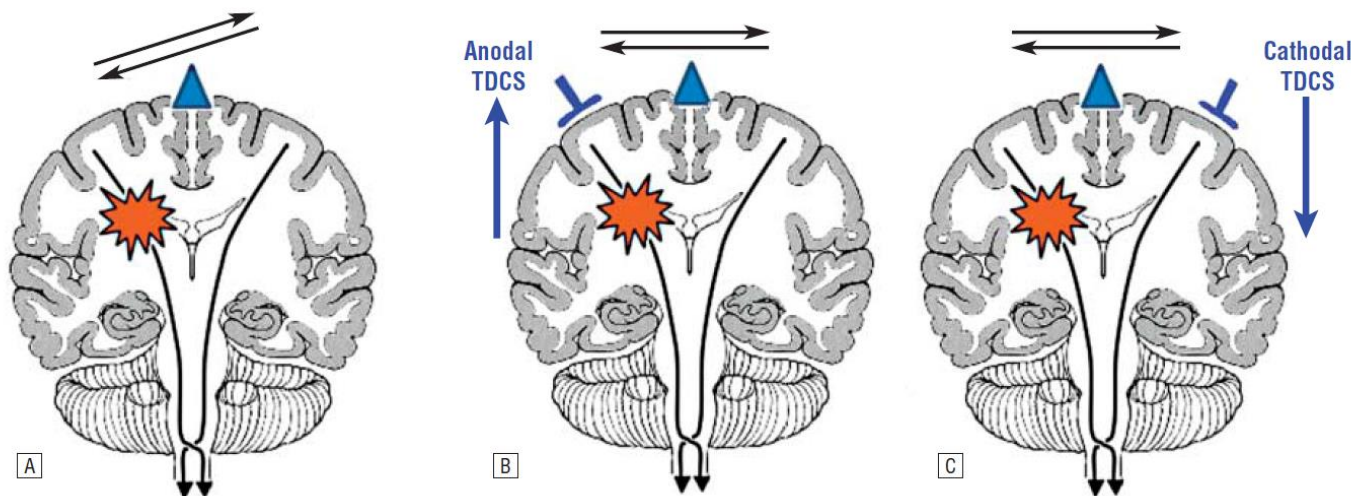


- More atrophic in responders
- More atrophic in non-responders
- Overlapping



Neural correlates

Severe brain injured patients $\neq$ stroke or moderate TBI



Schaulg, Renga, Nair 2008, JAMA Neurology

Stroke: stimulate affected hemisphere / inhibit unaffected

TBI: stimulate affected brain region

DOC: extensive brain lesion → tDCS (partially) **preserved area**



How to increase the duration
of the effects?



Repeated tDCS

BRAIN INJURY
<http://dx.doi.org/10.1080/02699052.2016.1274776>



ORIGINAL ARTICLE

Controlled clinical trial of repeated prefrontal tDCS in patients with chronic minimally conscious state

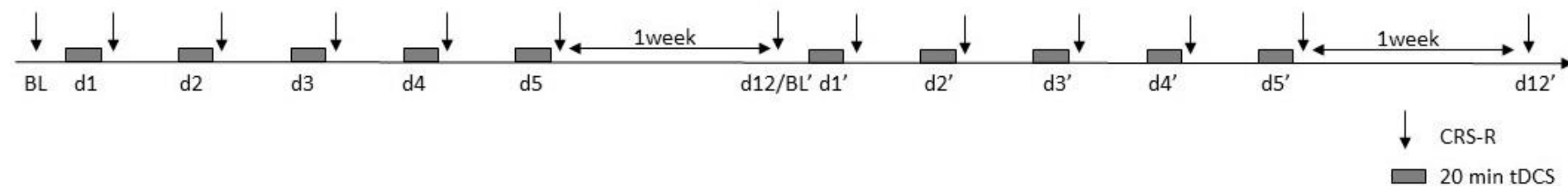
Aurore Thibaut^{a,b}, Sarah Wannez^a, Anne-Francoise Donneau^c, Camille Chatelle^{a,d}, Olivia Gosseries^a, Marie-Aur lie Bruno^a, and Steven Laureys^a

^aComa Science Group, GIGA-research, University of Li ge, Li ge, Belgium; ^bSpaulding Neuromodulation Center, Spaulding Rehabilitation Hospital, Harvard Medical School, Boston, MA, USA; ^cBiostatistics, Department of Public Health, University of Li ge, Li ge, Belgium; ^dLaboratory for NeuroImaging of Coma and Consciousness, Massachusetts General Hospital, Boston, MA, USA

- ➔ *Increase the duration of the effects*
- ➔ *Improve the benefits & the number of responders*

session 1: real or sham

session 1: sham or real

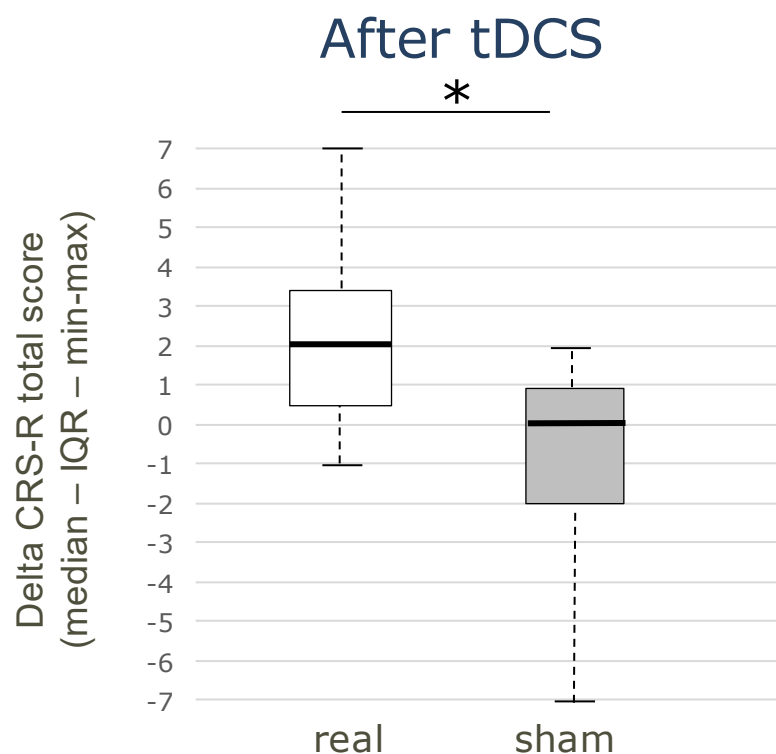




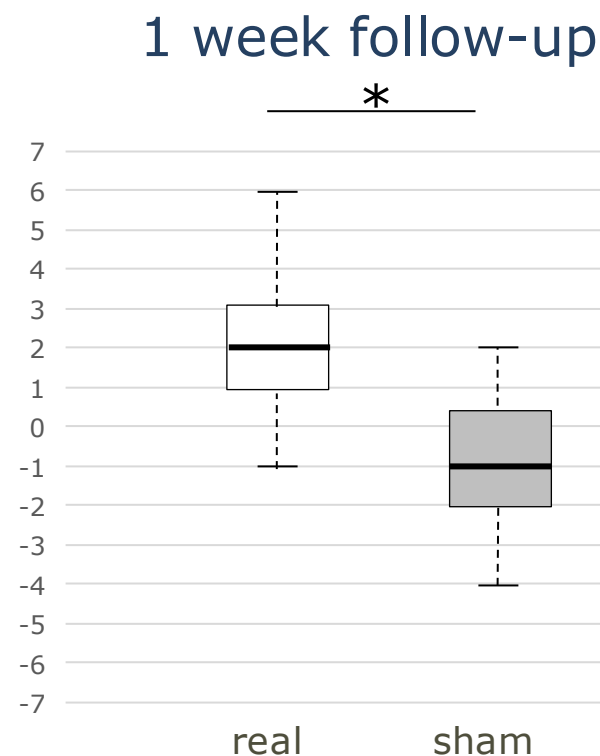
Repeated tDCS

16 patients in MCS (> 3months; 12 TBI; 47 ± 16 y)

Treatment effect: delta CRS-R day 5 & day 12 (follow-up)



Effect size: 0.43



Effect size: 0.57

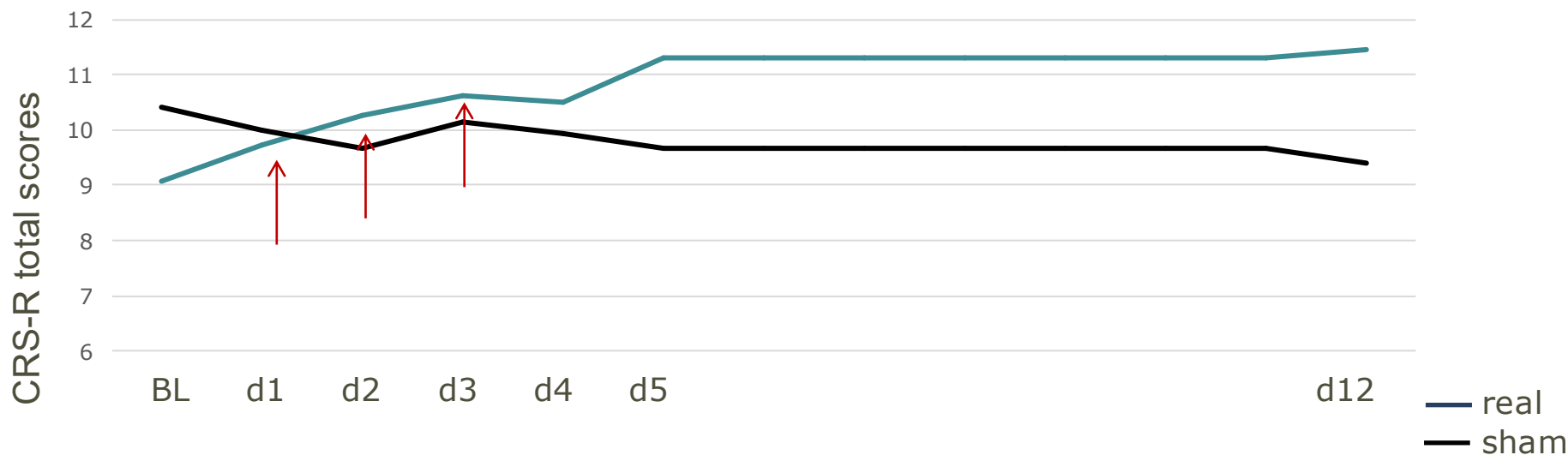
* $p < 0.05$



Repeated tDCS

Longitudinal analysis:

- Real session: significant + time evolution ($p < 0.001$)
- Sham session: no evolution across time ($p = 0.64$)



Some patients responded after 1, 2 or 3 days of tDCS

↑ responders (9/16 – 56%)

Single stim: 43% responders – effect size : 0.38 (versus 0.57)



Repeated tDCS



Archives of Physical Medicine and Rehabilitation

journal homepage: www.archives-pmr.org

Archives of Physical Medicine and Rehabilitation 2014;95:283-9



ORIGINAL ARTICLE

Transcranial Direct Current Stimulation Effects in Disorders of Consciousness



Efthymios Angelakis, PhD,^{a,b} Evangelia Liouta, MSc,^{a,b} Nikos Andreadis, PhD,^a Stephanos Korfiatis, MD,^{a,b} Periklis Ktonas, PhD,^a George Stranjalis, MD, PhD,^{a,b} Damianos E. Sakas, MD, PhD^{a,b}

From the ^aHellenic Center for Neurosurgical Research "Prof. Petros Kokkalis," Athens; and ^bEvangelismos Hospital, Department of Neurosurgery, Medical School, National and Kapodistrian University of Athens, Athens, Greece.

5 sessions over DFPLC
7 UWS and 6 MCS - chronic
→ Moderate clinical effects
→ Changes of EEG background
in patients who improved
clinically

5 sessions over M1 or DFPLC
7 UWS and 3 MCS - chronic
→ All MCS showed clinical
improvement immediately after
treatment

Journal of the Neurological Sciences 375 (2017) 464–470



Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns



Repeated transcranial direct current stimulation in prolonged disorders of consciousness: A double-blind cross-over study



Anna Estraneo^{a,*}, Angelo Pascarella^a, Pasquale Moretta^a, Orsola Masotta^a, Salvatore Fiorenza^a, Grazia Chirico^a, Emanuela Crispino^a, Vincenzo Loreto^a, Luigi Trojano^{a,b}

^a Neurorehabilitation Unit and Research Lab. for Disorder of Consciousness, Mauderi ICS, Telese Terme, Italy

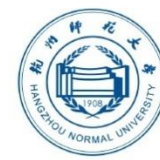
^b Neuropsychology Lab., Dept. of Psychology, Second University of Naples, Caserta, Italy



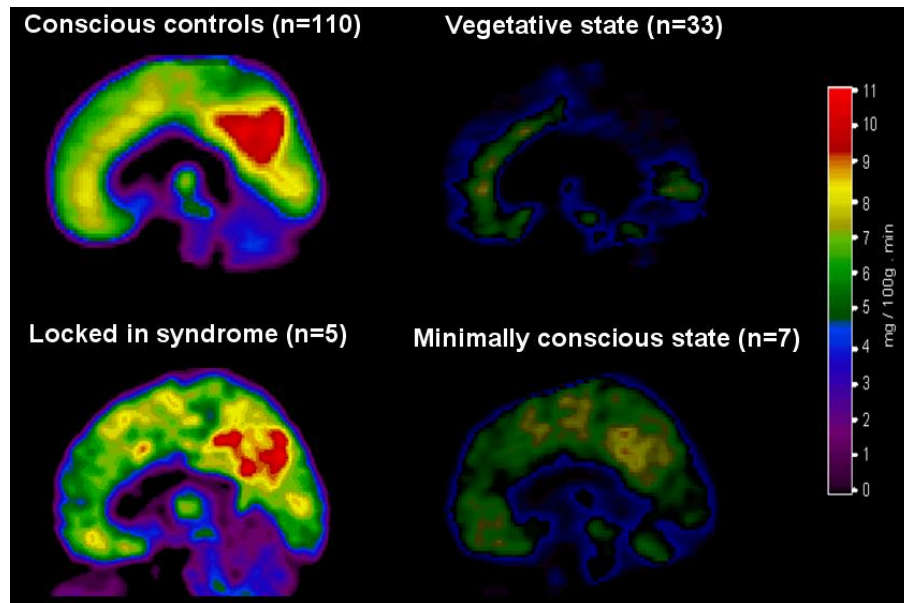
Targeting other brain regions
critical for consciousness
recovery?



Targeting other areas?



Precuneus: critical hub for consciousness



Anode: posterior parietal cortex
Cathode: right SOR

2mA; 20min

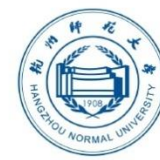
5 tDCS sessions

Active and sham – 1w washout

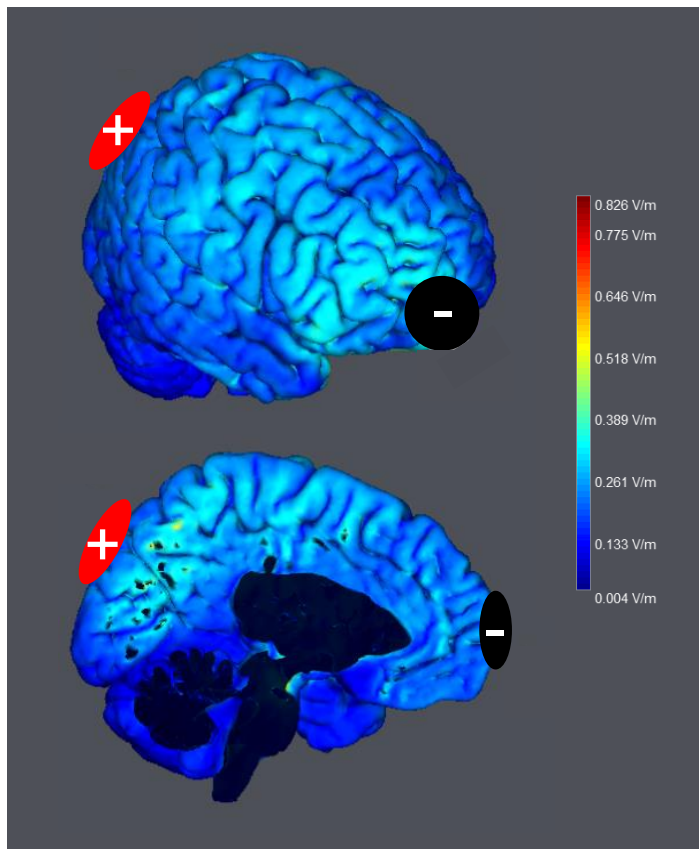
Laureys et al, Lancet Neurology, 2004



Targeting other areas?



Precuneus: critical hub for consciousness



Anode: posterior parietal cortex
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5 tDCS sessions

Active and sham – 5d washout



tDCS – Precuneus



Contents lists available at [ScienceDirect](http://www.sciencedirect.com)

Brain Stimulation

journal homepage: <http://www.journals.elsevier.com/brain-stimulation>



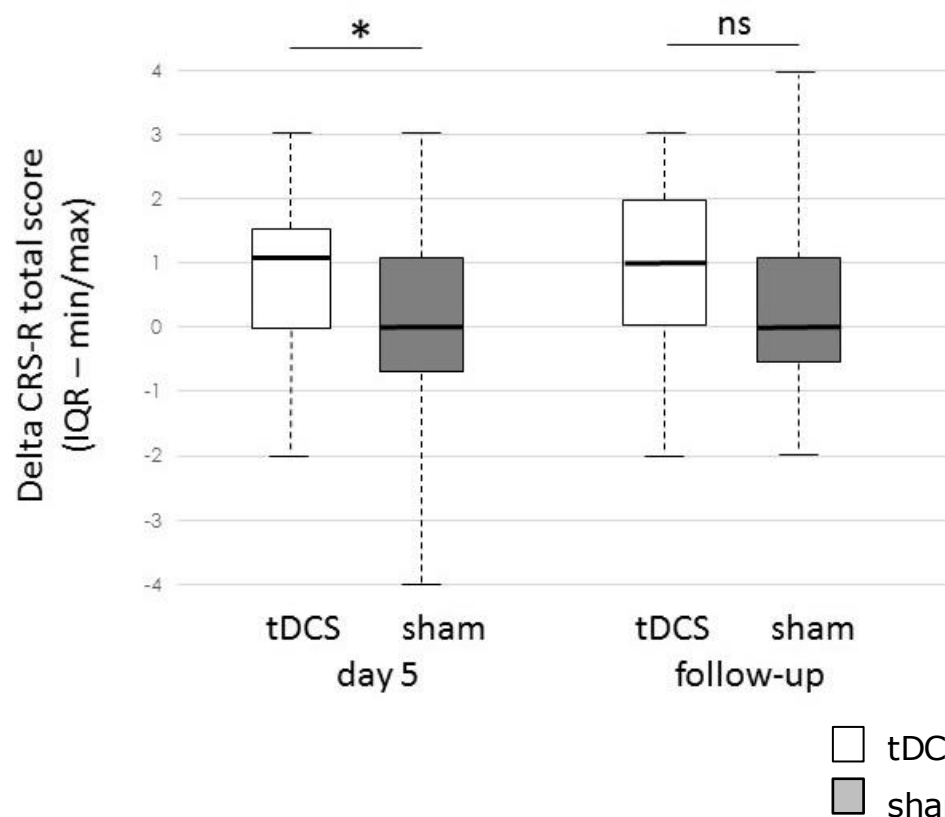
Repeated stimulation of the posterior parietal cortex in patients in minimally conscious state: A sham-controlled randomized clinical trial

33 MCS >3 months post-insult
(57 ± 11 y; 20 TBI)

9 responders (27%)
Sub-acute > chronic

No effect at 5d follow-up

Effect size : 0.31

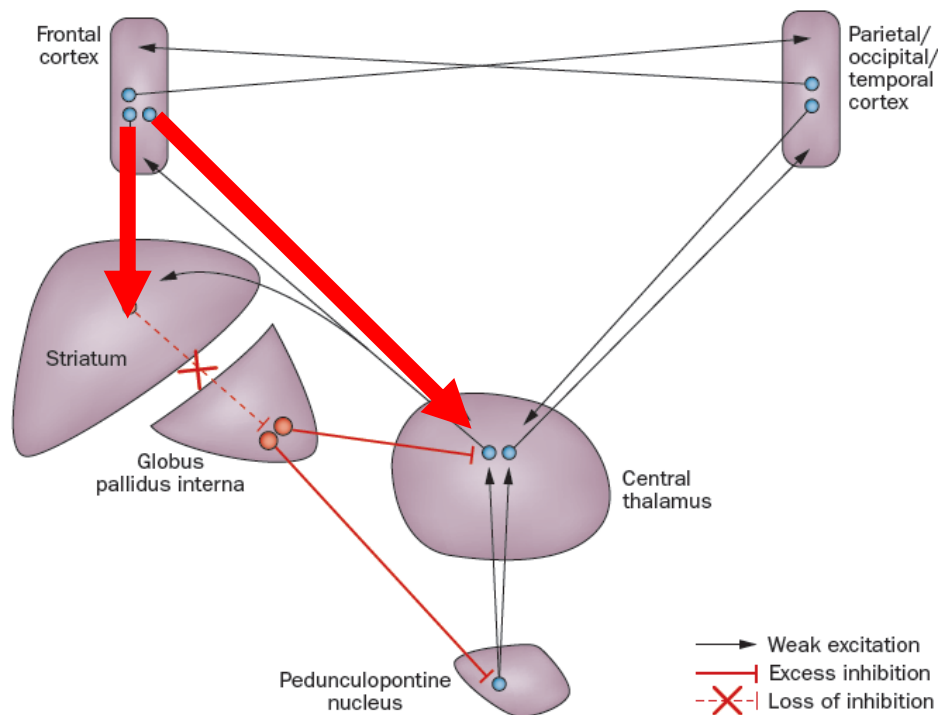
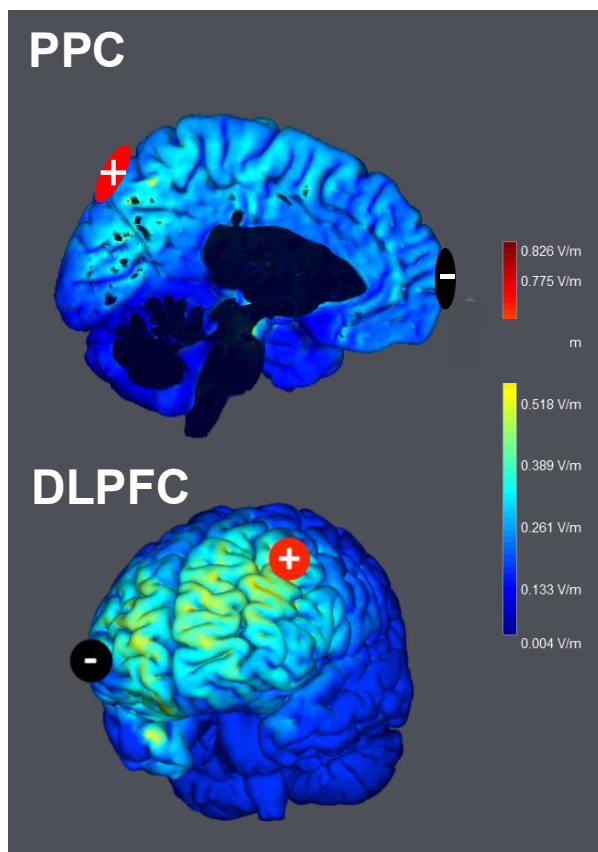




tDCS – Precuneus



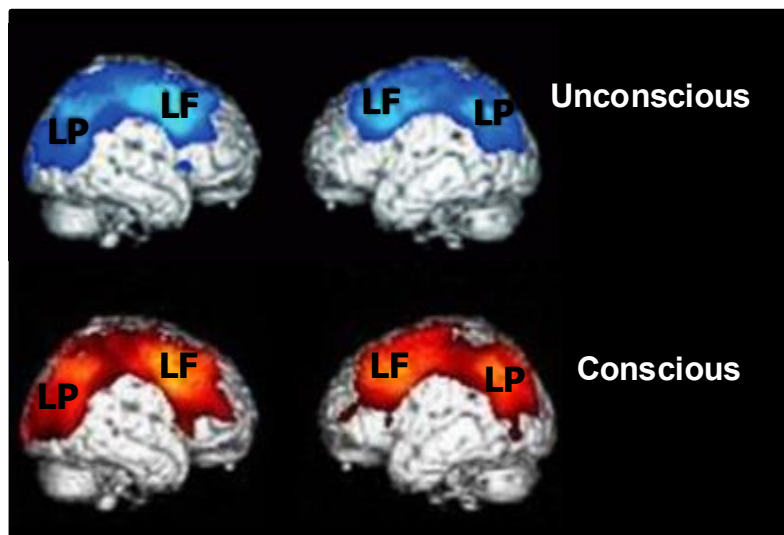
Prefrontal tDCS better than posterior parietal tDCS?





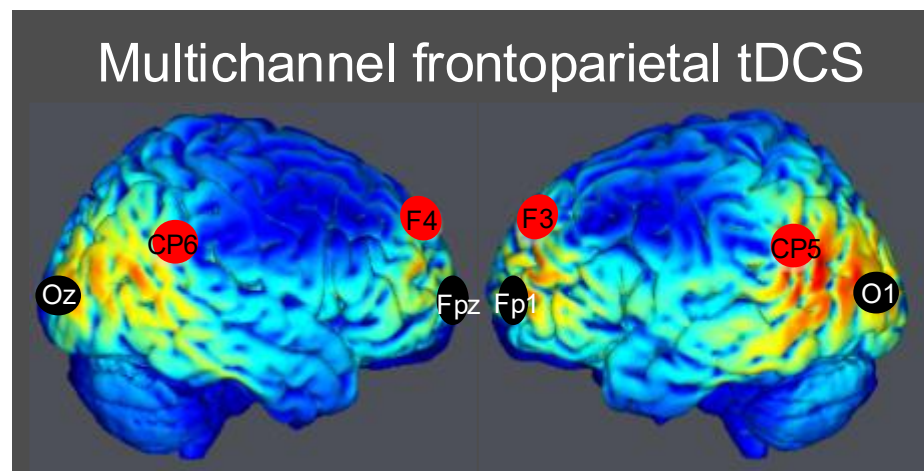
Frontoparietal network
External consciousness network
Critical for consciousness recovery

➔ Stimulation of the external consciousness network bilaterally



● Hypometabolic areas

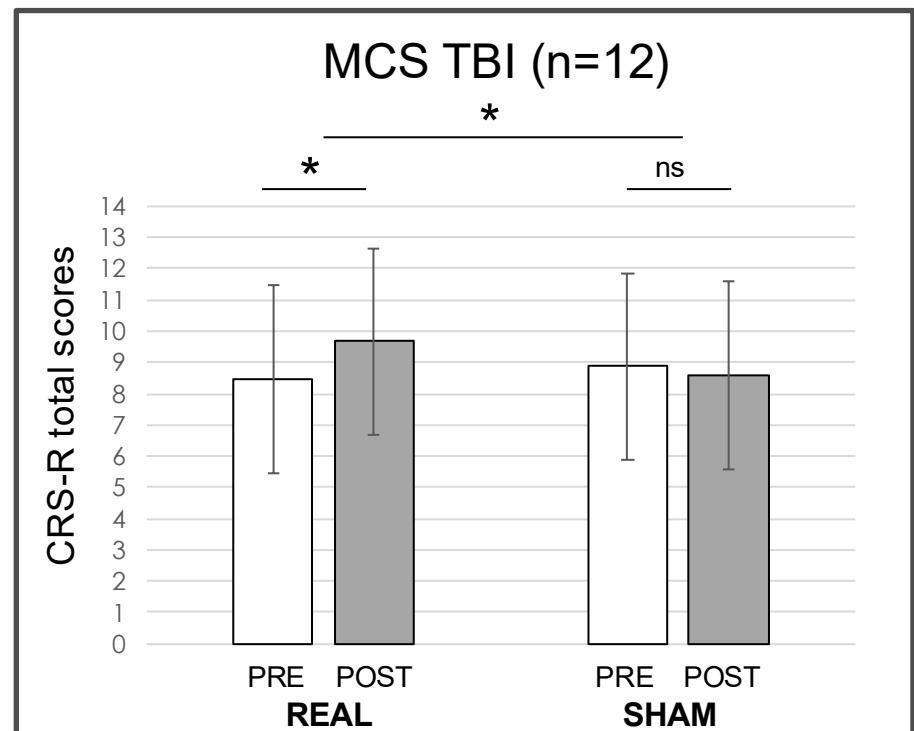
● Preserved areas



Fronto-parietal multichannel tDCS

20 MCS & 11 VS/UWS; 13 TBI & 18 NTBI; > 1m post injury
 4 anodes and 4 cathodes – 1mA; 20min
 Single stimulation – real & sham
 CRS-R & EEG

- Treatment effect : **TBI MCS**
- No effect in VS/UWS
- No effect in MCS nTBI
- 5 responders all MCS TBI
- No side-effects





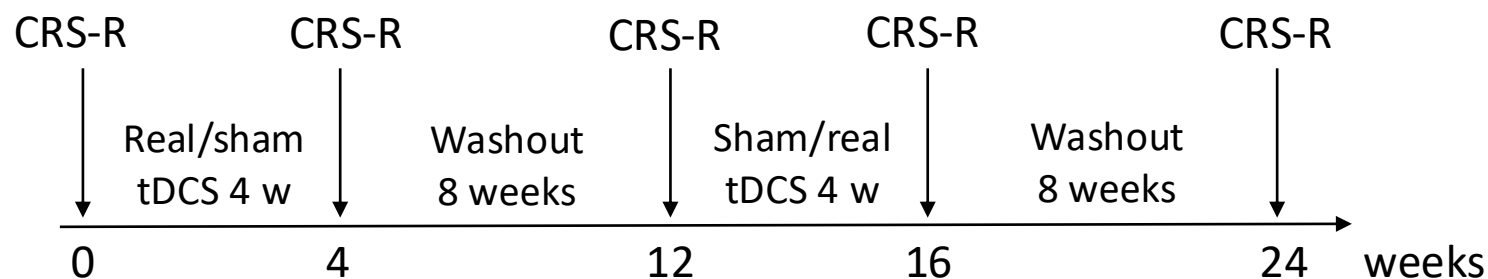
Can tDCS be used in daily
clinical practice?



Clinical translation



- Feasibility of tDCS for daily use
 - By relatives/caregivers
 - Repeated tDCS – 20 sessions





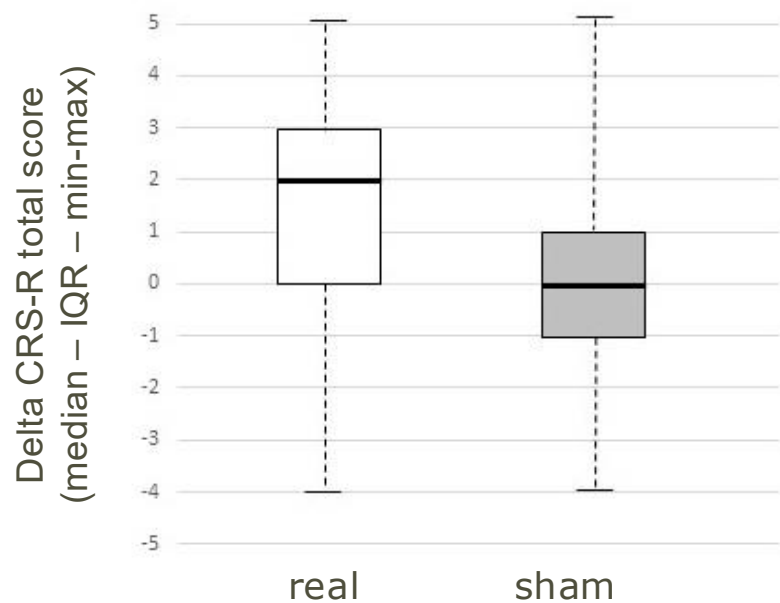
Clinical translation

27 MCS patients completed the study (43 ± 13 y, 9TBI, TSO 9 ± 7 y)

Compliance: $93 \pm 14\%$

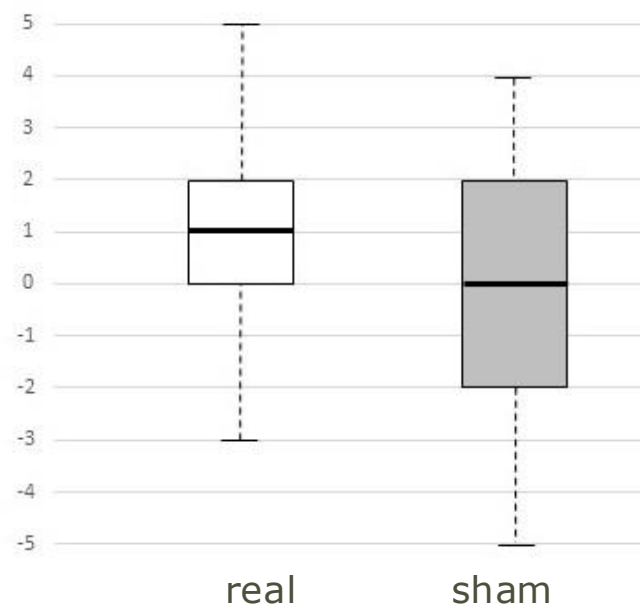
Post tDCS

$p=0.052$ – $d=0.46$



8 weeks follow-up

ns



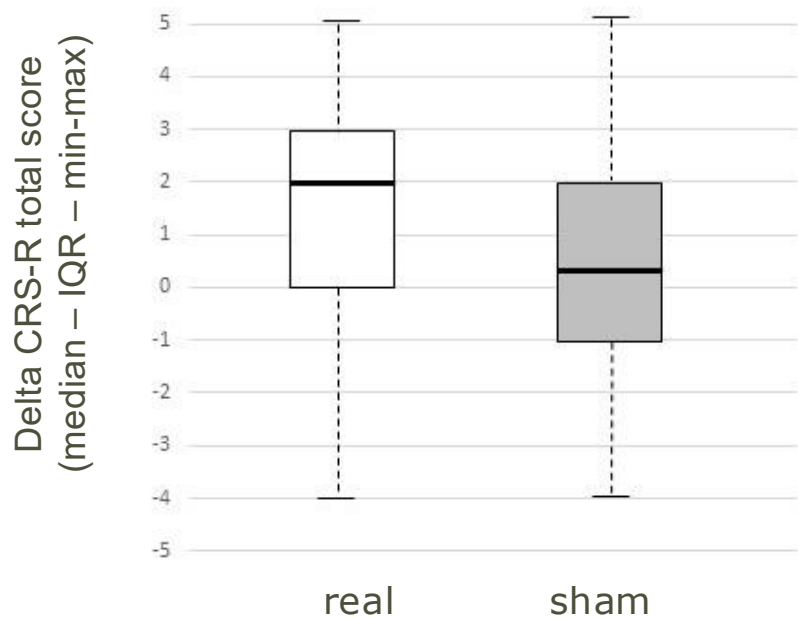


Clinical translation

22 patients received at least 80% of tDCS sessions

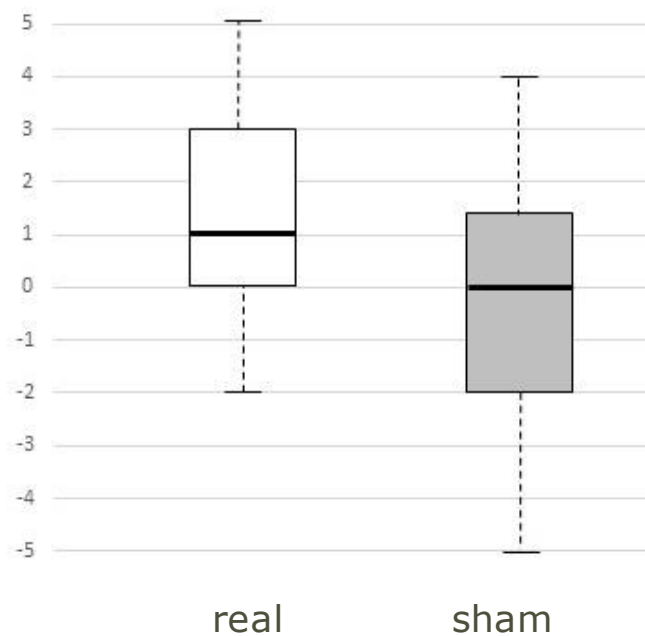
Post tDCS

$p=0.042$ – $d=0.56$



8 weeks follow-up

$p=0.059$



➔ Relevant clinical improvement: >80% tDCS sessions



Conclusions

- **Prefrontal** tDCS → consistent clinical improvement
- Repeated tDCS → increase duration of the effects
→ increase number of responders
- tDCS is safe and can be used in clinical practice

Next?

- Neurophysiological correlates of tDCS
- Patients' tailored montage – based on patients' brain lesion
- Deeper brain structures – multichannel tDCS / tPCS
- Large sample – multicentric study (DOC-SIG study)

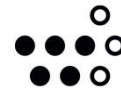
THANK YOU



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