Disclosure

Presenter has no relevant financial or non-financial interest to disclose.

What are the treatment options in patients with disorders of consciousness?

Géraldine Martens, PT, PhD candidate

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Specificities of therapeutic interventions for DOC patients

- **Absence of communication**
- Lack of interaction with their environment
- Severe motor disability (e.g., spasticity)
- Constantly bedridden
- Fatigability
- Aphasia, blindness, deaf, etc.

« Hable con Ella »
Pedro Almodóvar

➔ No active rehabilitative interventions

Pharmacological interventions

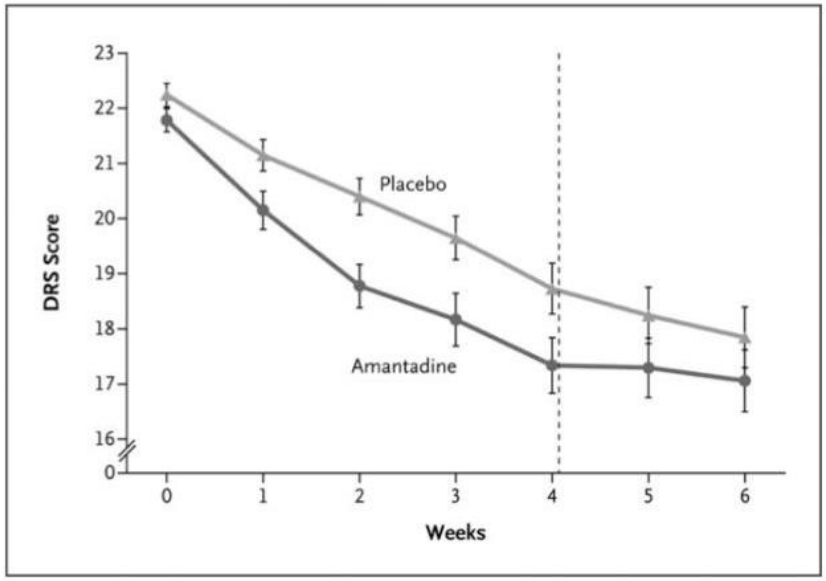
Pharmacological interventions

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

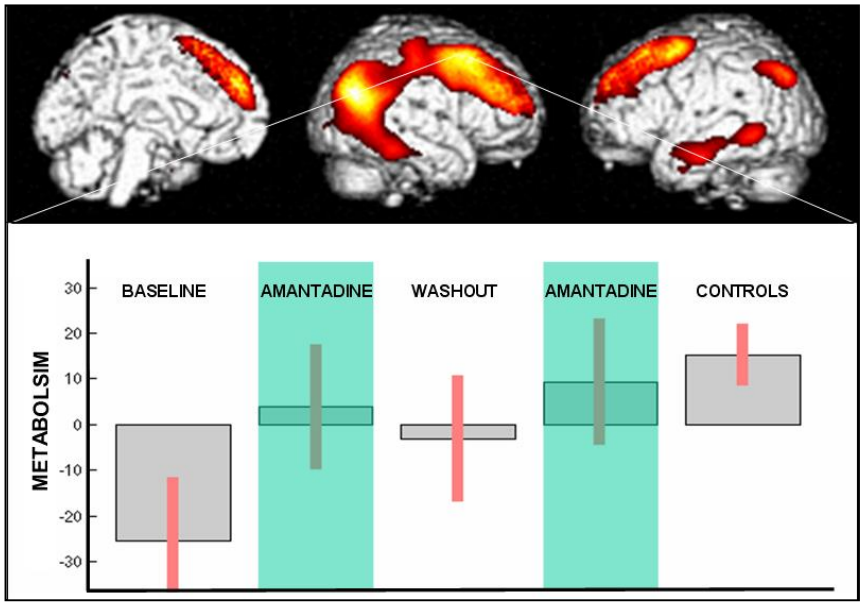
Adapted from Demertzi et al, *Expert Rev Neurotherapeutics*, 2008

Amantadine

- Dopaminergic agent (Parkinson)
- Enteral administration, 6 weeks treatment (200mg/2*day)
- Side effects (seizure)



Giacino & Whyte et al, *N Engl J Med*, 2012



Schnakers et al, J Neurol Neurosurg Psychiatry 2008

Zolpidem

- GABAergic agent
- Enteral/oral administration (10mg)
- No side effects (sleep)

- 5% responders dramatic effects!
- 20% (12/60) improved behaviors after zolpidem but in only 1 patient changed of diagnosis (regained functional communication)

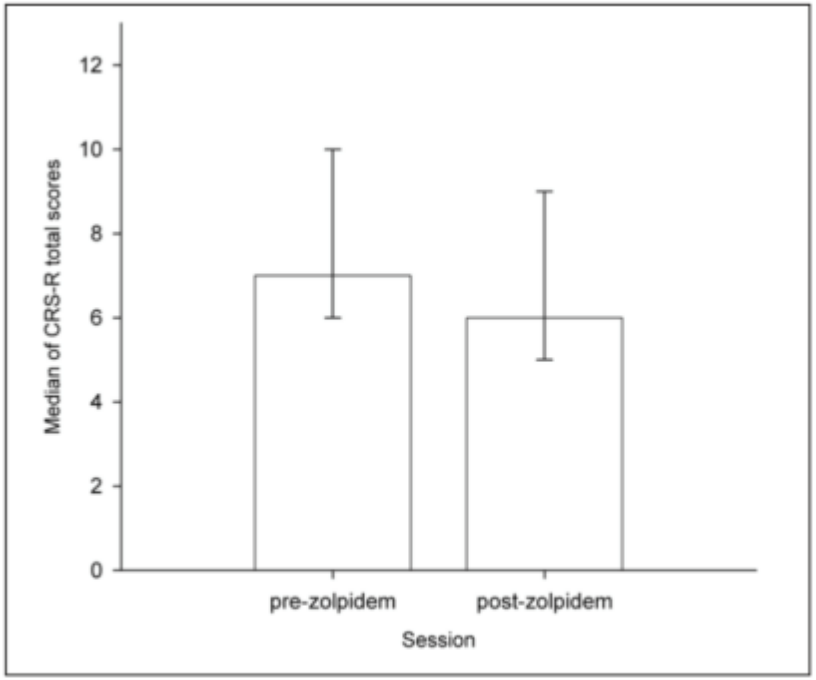


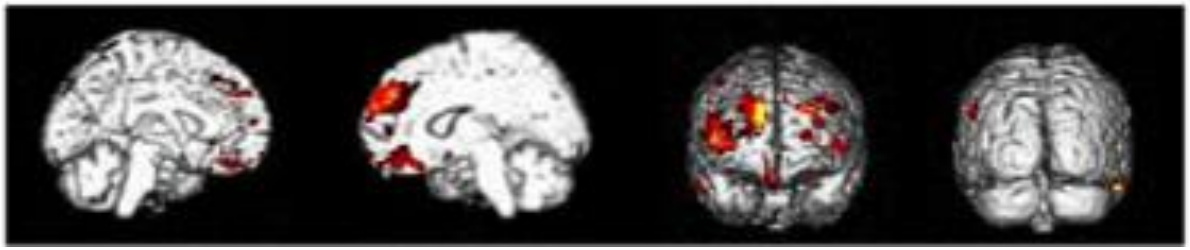
Figure 1 - Significant decrease of CRS-R total scores (ranging from 0 to 23) after zolpidem intake (interquartile range represented by errors bars) in the entire sample (n=60).

Whyte et al, Am J Phys Med Rehabil, 2009 & 2014
Thonnard & Gosseries et al, *Funct Neurol*, 2013

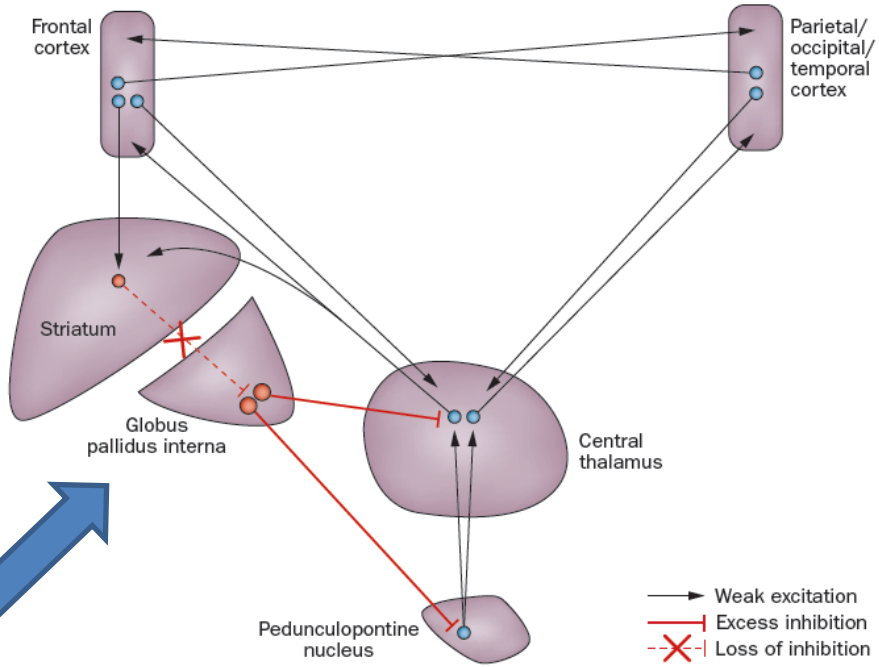
Zolpidem

A. Brain metabolism in zolpidem responders

Zolpidem
> Placebo



N=3

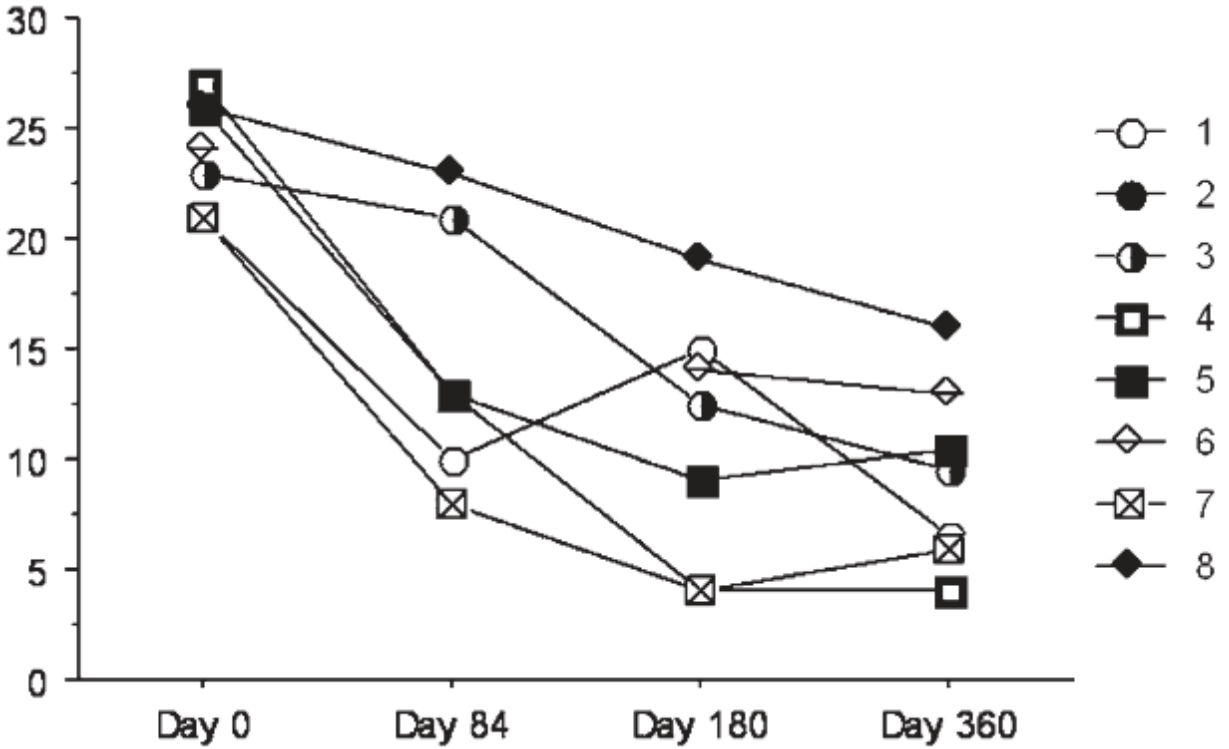


Zolpidem inhibits GPi

Chatelle et al, *Front Hum Neurosci,* 2014
Williams et al, *Elife*, 2013

Apomorphine

- Dopaminergic agent
- Subcutaneous administration (12h/day)
- Only case studies
- Side effects



Disability Rating Scale

Fridman et al, *Brain Injury,* 2009 & 2010

Pharmacological treatments conclusion

- Only a few pharmacological treatments
- Side effects / habituation
- Next:
  - Apomorphine multimodal trial
  - Zolpidem responders phenotype

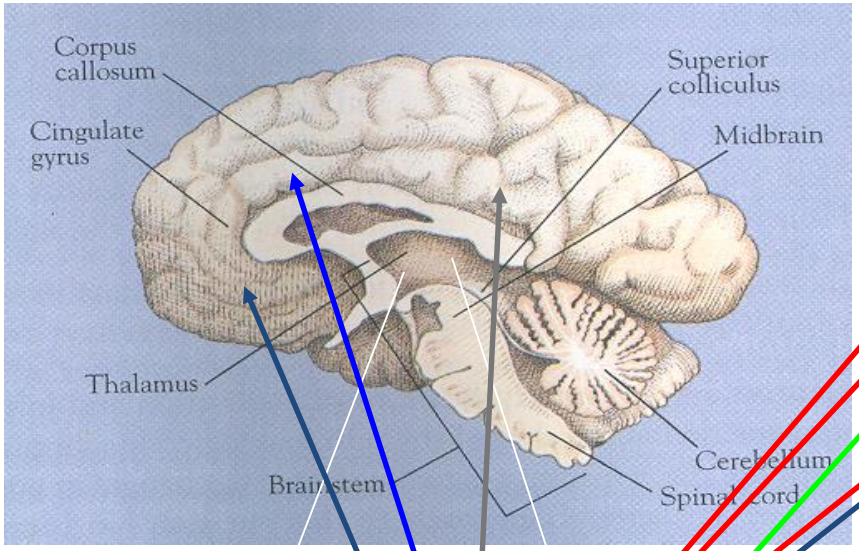
CLINICAL STUDY PROTOCOL
published: 19 March 2019
doi: 10.3389/fneur.2019.00248

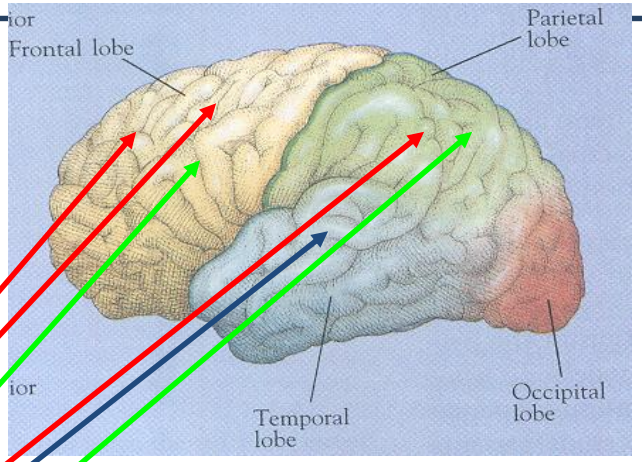
Treating Disorders of Consciousness With Apomorphine: Protocol for a Double-Blind Randomized Controlled Trial Using Multimodal Assessments

Leandro R. D. Sanz[1,2], Nicolas Lejeune[1,2,3,4], Séverine Blandiaux[1,2], Estelle Bonin[1,2], Aurore Thibaut[1,2,5,6], Johan Stender[7], Neal M. Farber[8], Ross D. Zafonte[5,6], Nicholas D. Schiff[9], Steven Laureys[1,2] and Olivia Gosseries[1,2]

Central Thalamic Deep Brain Stimulation

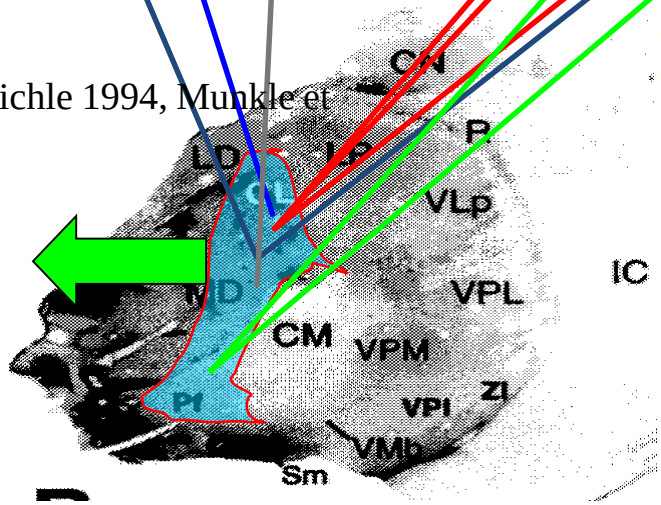
Projections from intralaminar nuclei



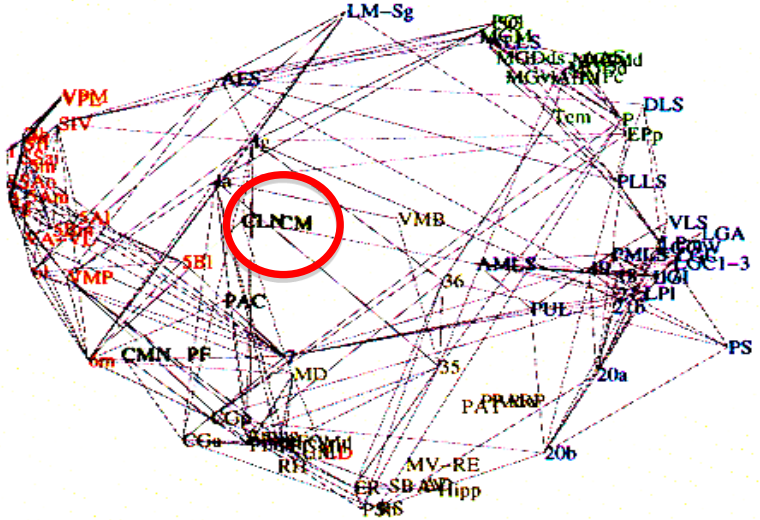


Adapted from:
Posner and Raichle 1994, Munkle et al. 2000.

Striatum



Multidimensional scaling of thalamocortical connectivities

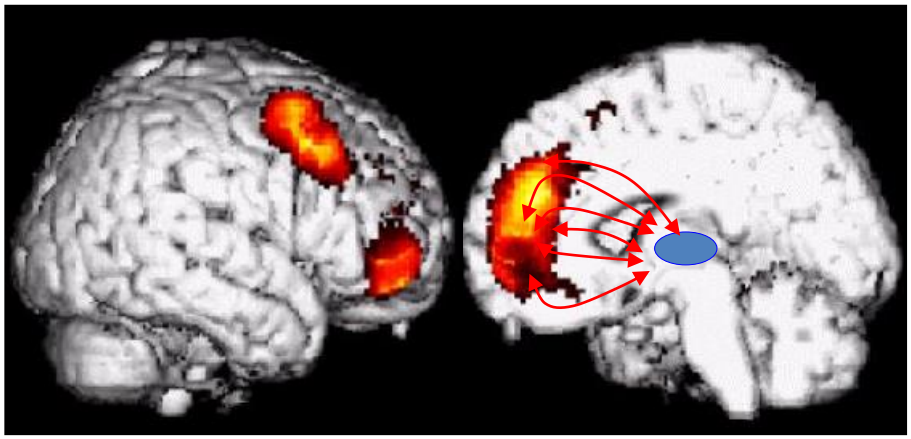


Scannell et al. 1999

Consciousness ≈ thalamo-cortical

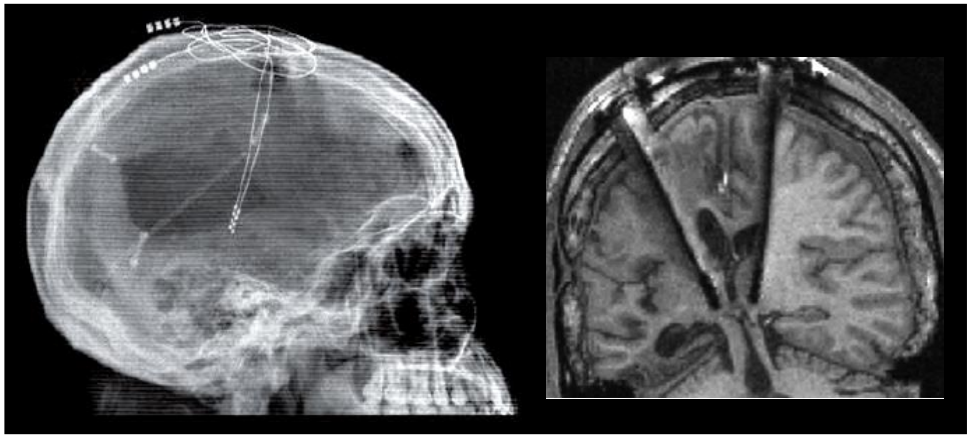
COMA SCIENCE GROUP

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



Laureys et al, *Lancet* 2000

Intralaminar nuclei stimulation induces “recovery” from minimally responsive state



Schiff et al, *Nature* 2007

MCS ➔ emerged – prolonged effects

- *sustained attention*
- *intelligible words*
- *functional objects use*

Deep Brain Stimulation conclusion

- DBS modulates specific cognitive and behavioral functions (arousal, functional limb movement, swallowing).
- Evidence of DBS carryover effects

- Limitations:
  - Strict inclusion criteria (e.g., no thalamic lesion)
  - Invasive
  - No randomized controlled study

Non-invasive brain stimulations
tDCS

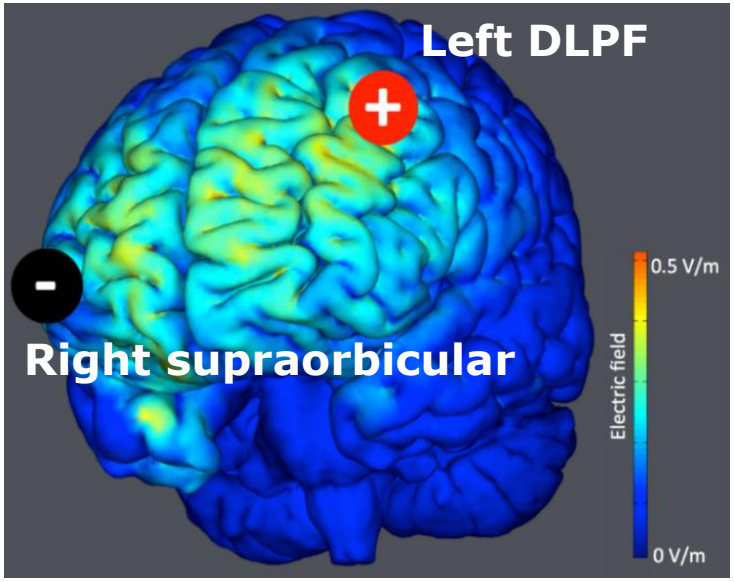
tDCS single session

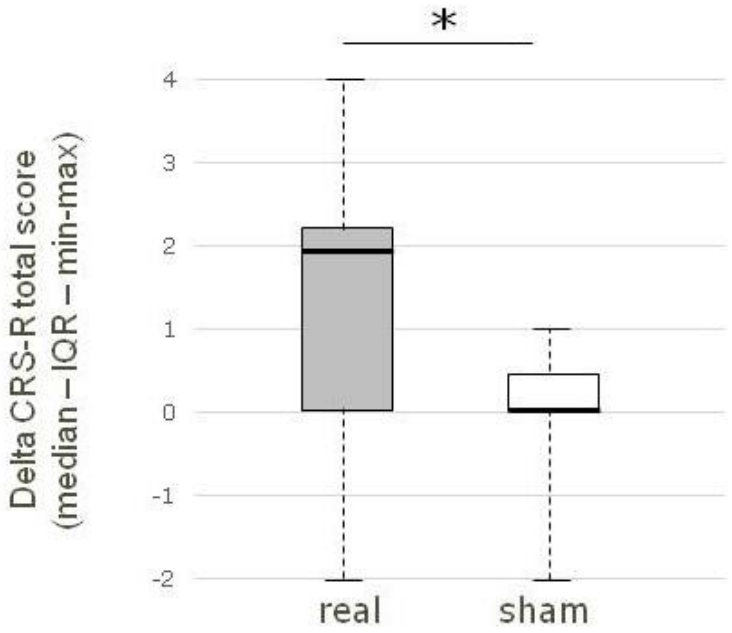
ARTICLES

tDCS in patients with disorders of consciousness

Sham-controlled randomized double-blind study

Crossover RCT (n=55)





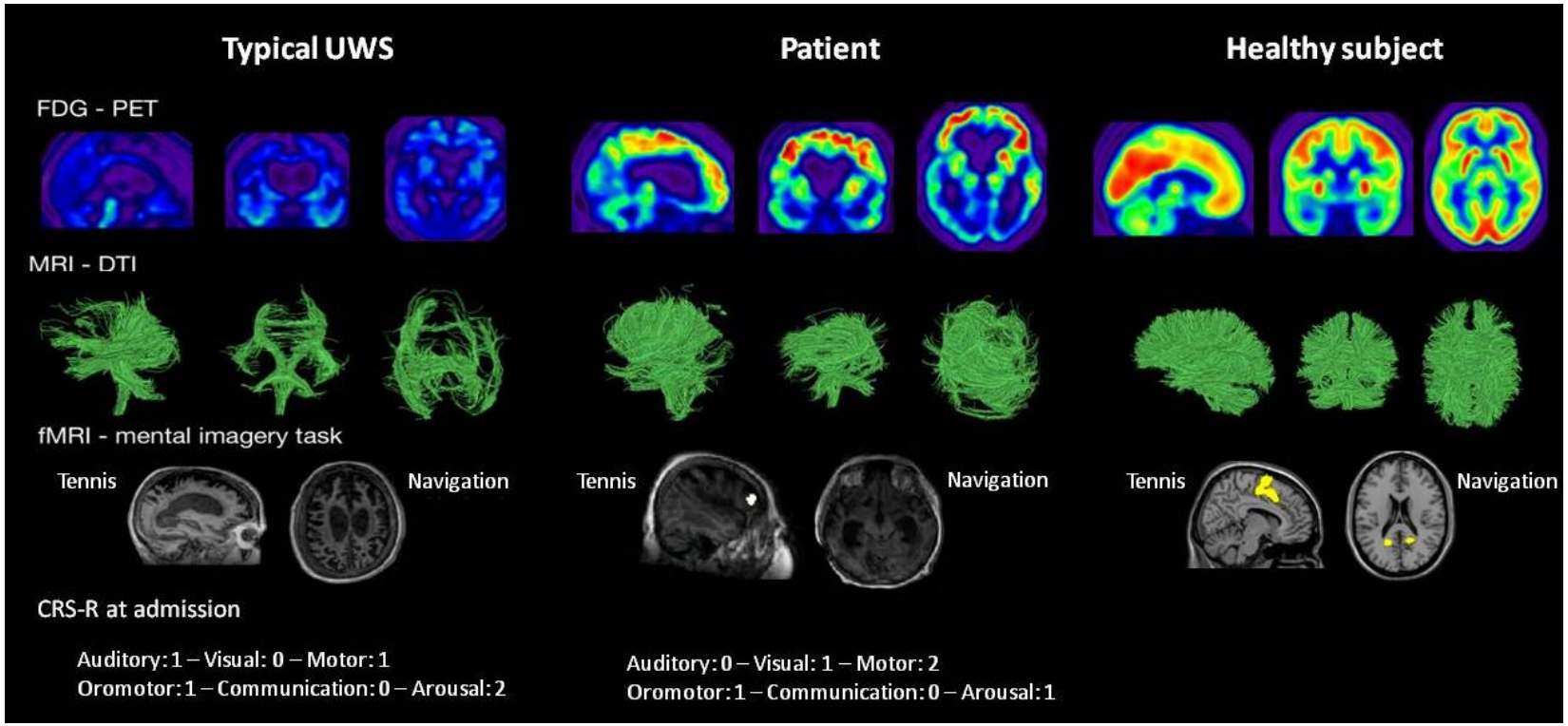
MCS
n=30

➔ No adverse events
➔ Clinical improvement in MCS only
➔ 13/30 responders (5 >1y post-insult)

Thibaut et al., Neurology, 2014

tDCS to unveil covert consciousness

- 67yo woman in UWS for 4 years after a subarachnoid hemorrhage
- Out of 7 standardized CRS-R she showed 1 localization to pain
- She demonstrated consistent response to command only after tDCS
- Neuroimaging exams were consistent with the diagnosis of MCS*



➔ tDCS may facilitate motor execution of the command when cognitive functions are preserved

Thibaut et al., Brain Stimulation, 2018

Neural correlates of responsiveness

Brain Stimulation 8 (2015) 1116–1123

Contents lists available at ScienceDirect

Brain Stimulation

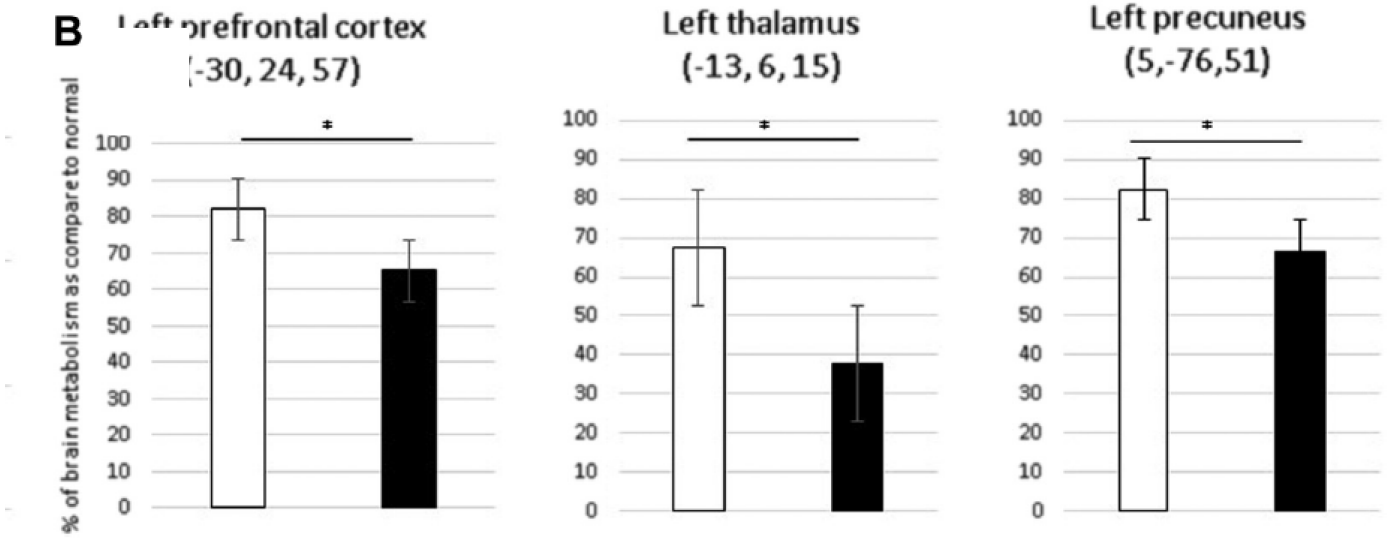
journal homepage: www.brainstimjrnl.com

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-Aurélie 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

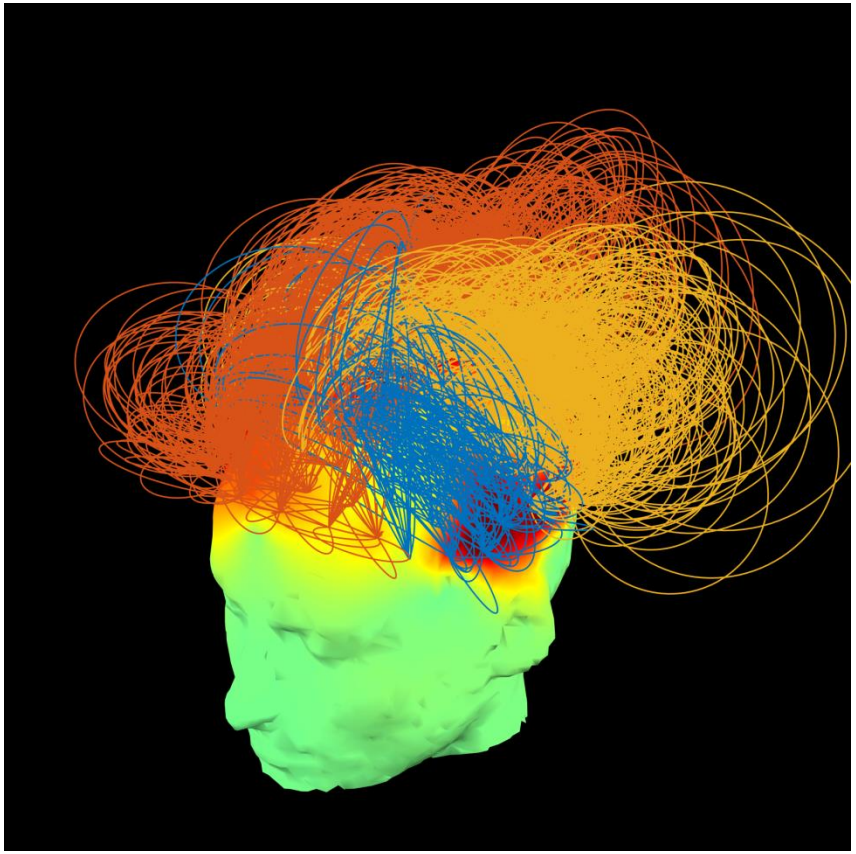


Thibaut *et al.*, Brain Stimulation 2015

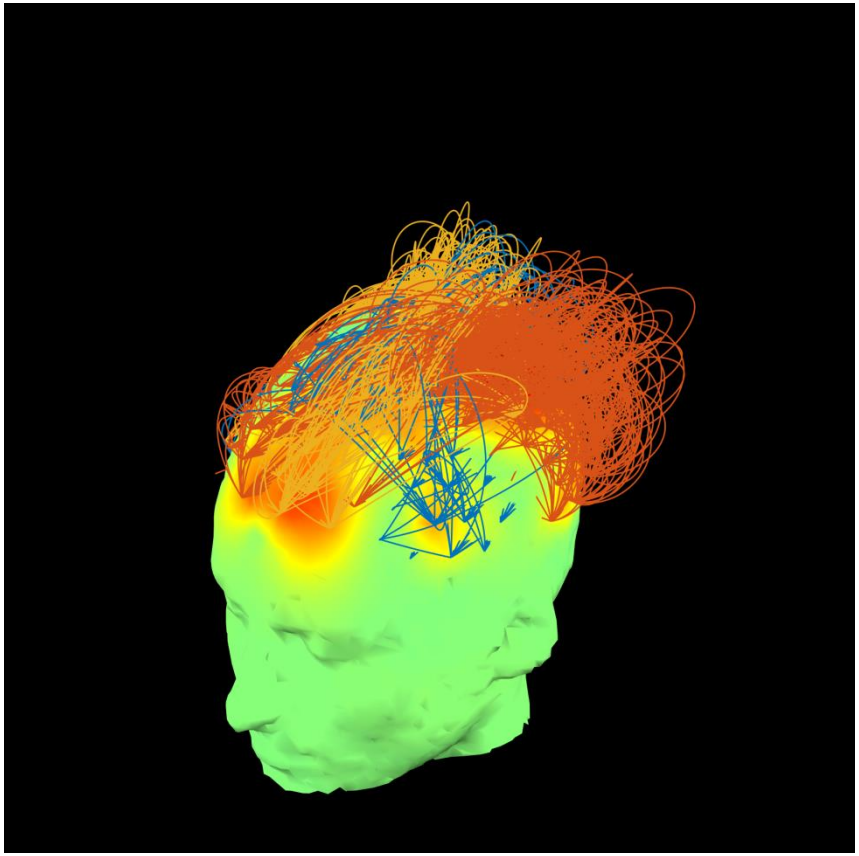
Neural correlates of responsiveness

Brain connectivity – theta band

8 tDCS responders



14 tDCS non-responders

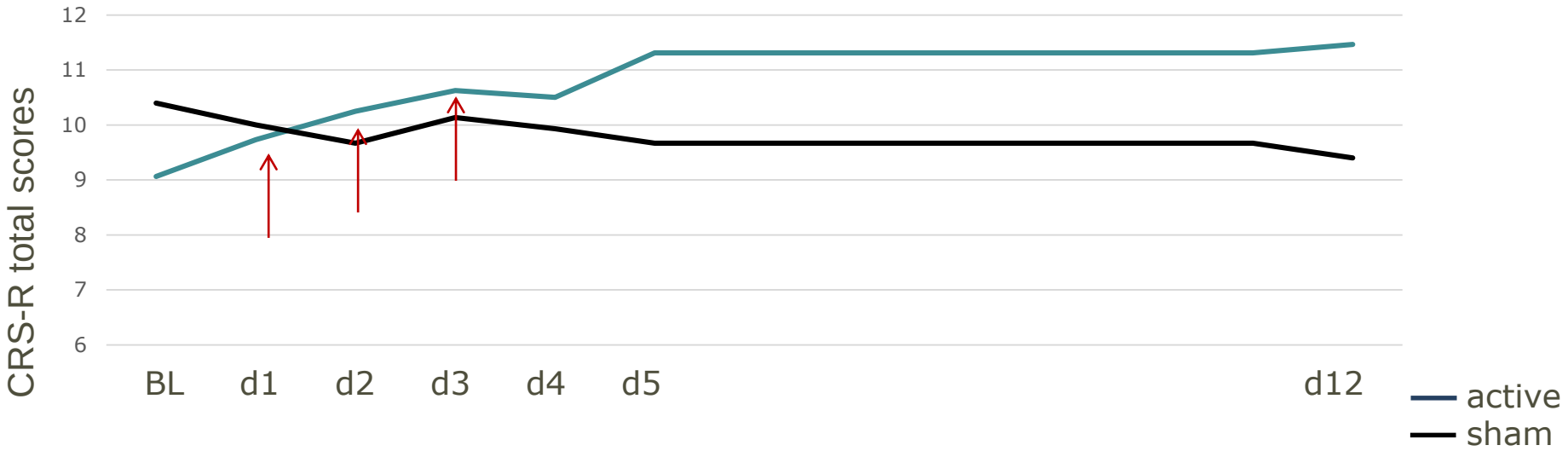


Thibaut et al., Brain Stimulation 2018

Repeated tDCS

Double-blind crossover RCT (16 chronic minimally conscious pts)
5 sessions – 20 min prefrontal tDCS

➔ Active session: significant time evolution ($p<0.001$)



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

↗ responders (9/16 – 56%) & ↗ duration of the effects (1 week)

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

Thibaut *et al.*, Brain Injury 2017

Repeated tDCS

ACRM
AMERICAN CONGRESS OF REHABILITATION MEDICINE

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 Korfias, MD,[a,b] Periklis Ktonas, PhD,[a] George Stranjalis, MD, PhD,[a,b] Damianos E. Sakas, MD, PhD[a,b]

From the [a]Hellenic Center for Neurosurgical Research "Prof. Petros Kokkalis," Athens; and [b]Evangelismos Hospital, Department of Neurosurgery, Medical School, National and Kapodistrian University of Athens, Athens, Greece.

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

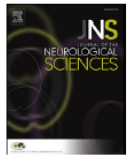
5 sessions over DFPLC
7 VS and 6 MCS - chronic
➔ Moderate clinical effects
➔ Changes of EEG background in patients who improved clinically

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



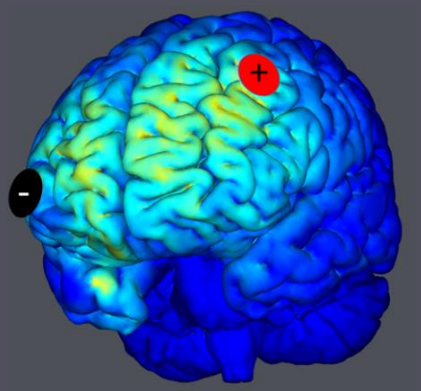
Repeated transcranial direct current stimulation in prolonged disorders of consciousness: A double-blind cross-over study

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]

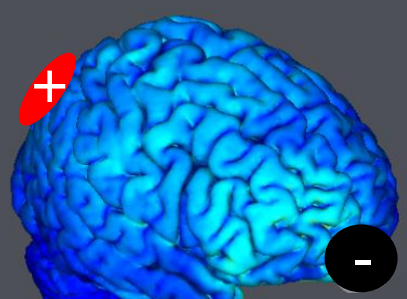
[a] *Neurorehabilitation Unit and Research Lab. for Disorder of Consciousness, Maugeri ICS, Telese Terme, Italy*
[b] *Neuropsychology Lab., Dept. of Psychology, Second University of Naples, Caserta, Italy*

Stimulating different brain regions

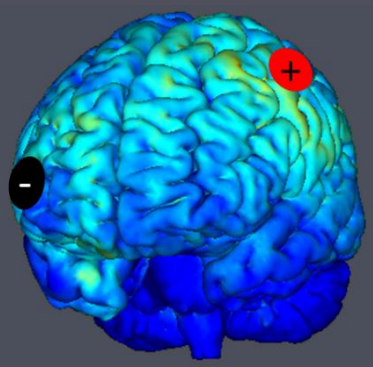
Prefrontal



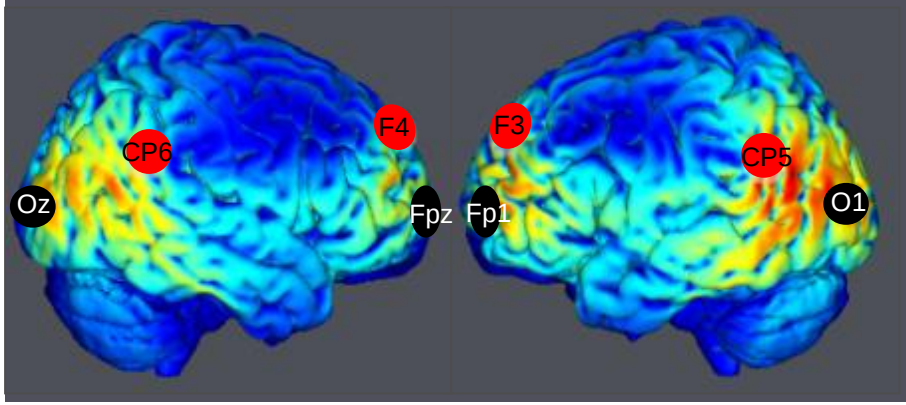
Precuneus



Motor



Multichannel frontoparietal



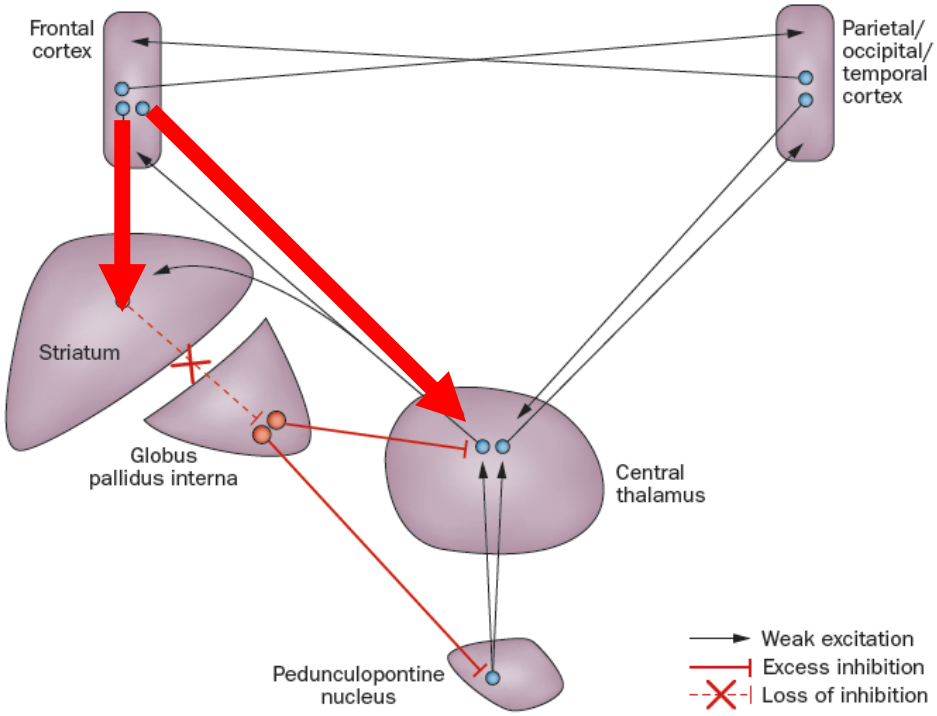
Group level: Prefrontal tDCS best area to target

Single-subject level: Patient's tailored montage

Thibaut et al, 2014, 2017
Huang et al, 2017
Martens et al, submitted, Thibaut et al, submitted

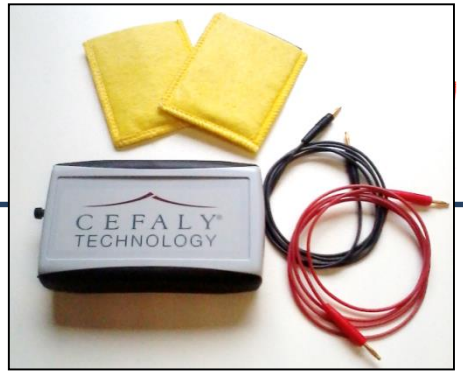
tDCS - mesocircuit

Prefrontal tDCS better than targeting other areas?

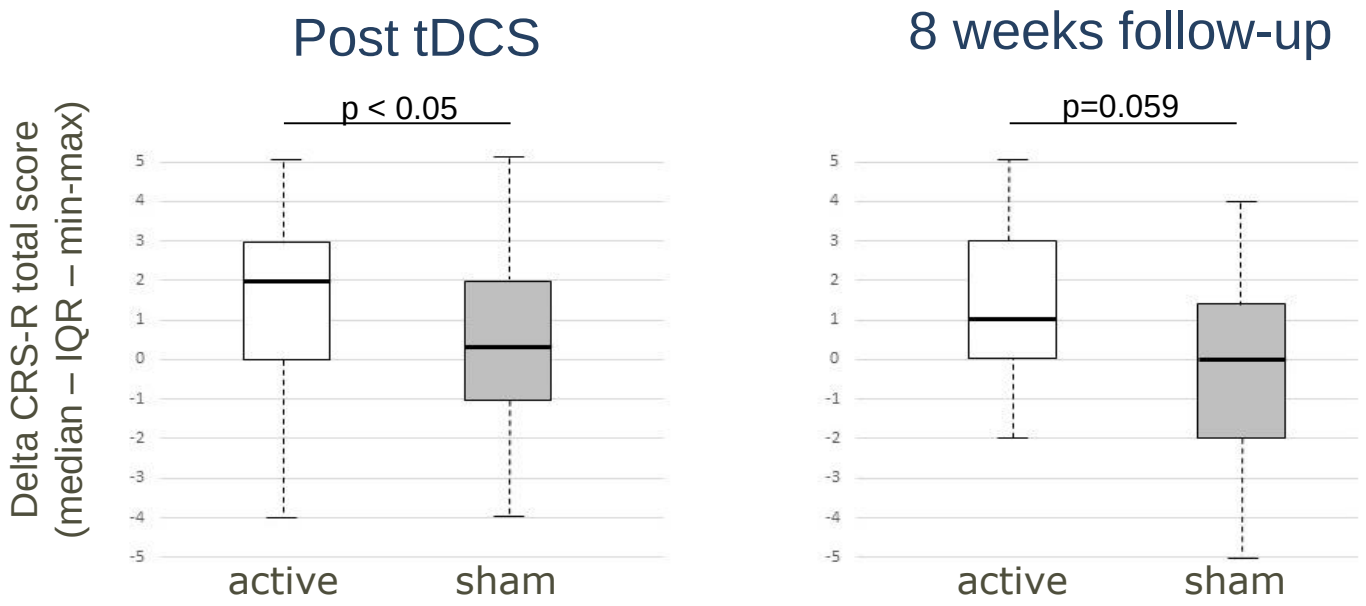


Schiff, JAMA, 2010
Giacino, Fins, Laureys, Schiff, *Nature Rev Neurol* 2014

Clinical translation



- Feasibility of tDCS for daily use
  - By relatives/caregivers (20 sessions)
- 27 MCS patients completed the study – compliance: **93±14%**
  - No clinical effects
- 22 MCS patients received ≥80% tDCS sessions
  - Significant effects & trend at 8-week follow-up – no AE



Martens et al, Brain Stim 2018

Conclusions

Pharmacological treatments

- Amantadine in TBI ➔ other etiologies?
- Zoplidem – 5% ➔ phenotype of responders
- Apomorphine ➔ randomized clinical trials

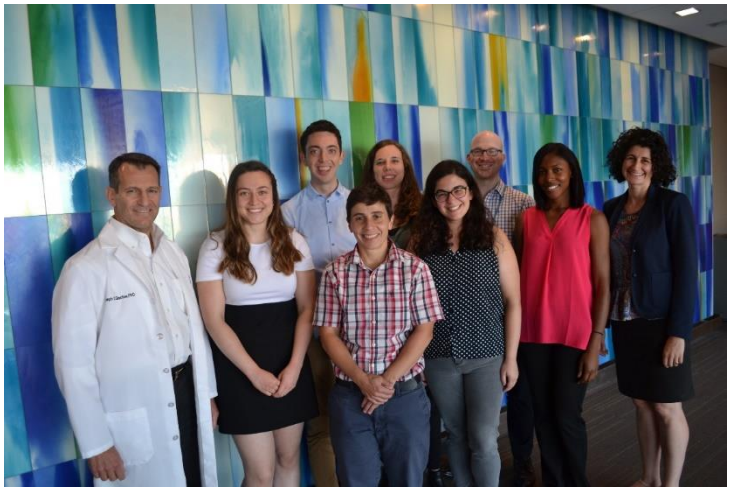
DBS

- Promising but invasive & no randomized clinical trials

NIBS

- tDCS is safe in severely brain-injured patients
- **Prefrontal** tDCS ➔ consistent clinical improvement
- Repeated tDCS ➔ increase duration of the effects
  ➔ increase number of responders
- Need patients' tailored montage based on individual brain lesions

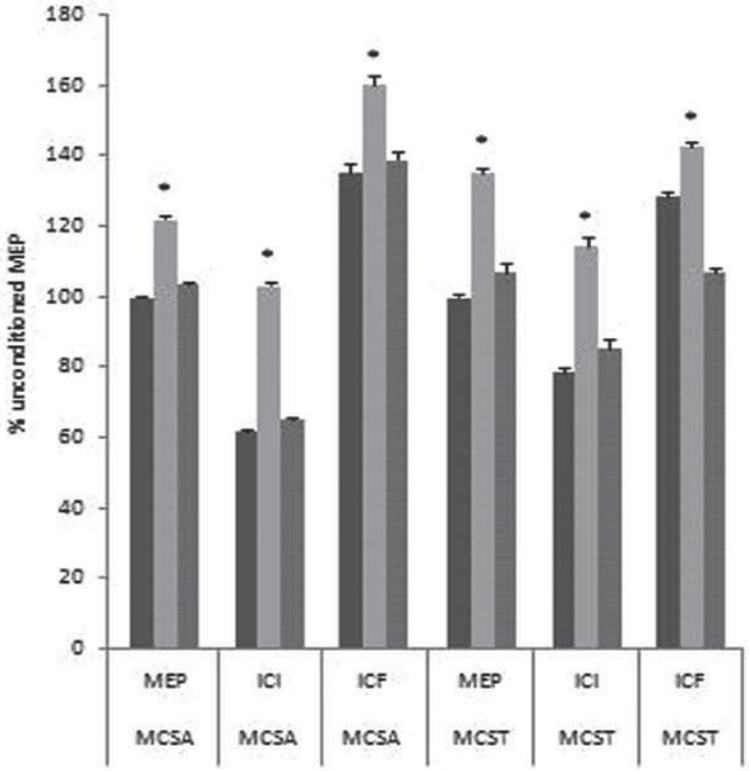
THANK YOU

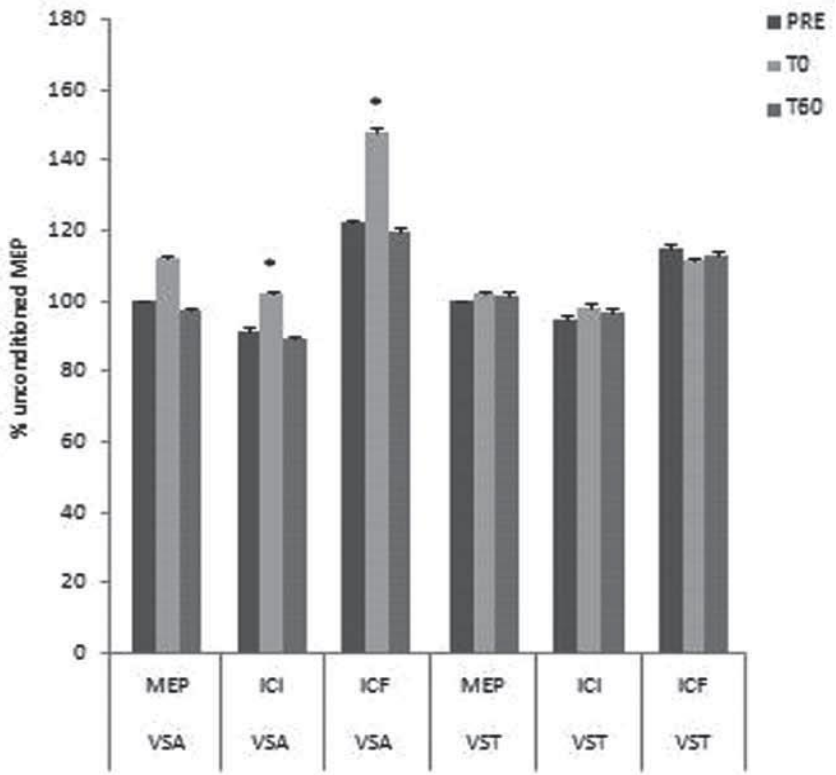


geraldine.martens@ulg.ac.be
gmartens@partners.org

Additional slides

tDCS – diagnostic tool?



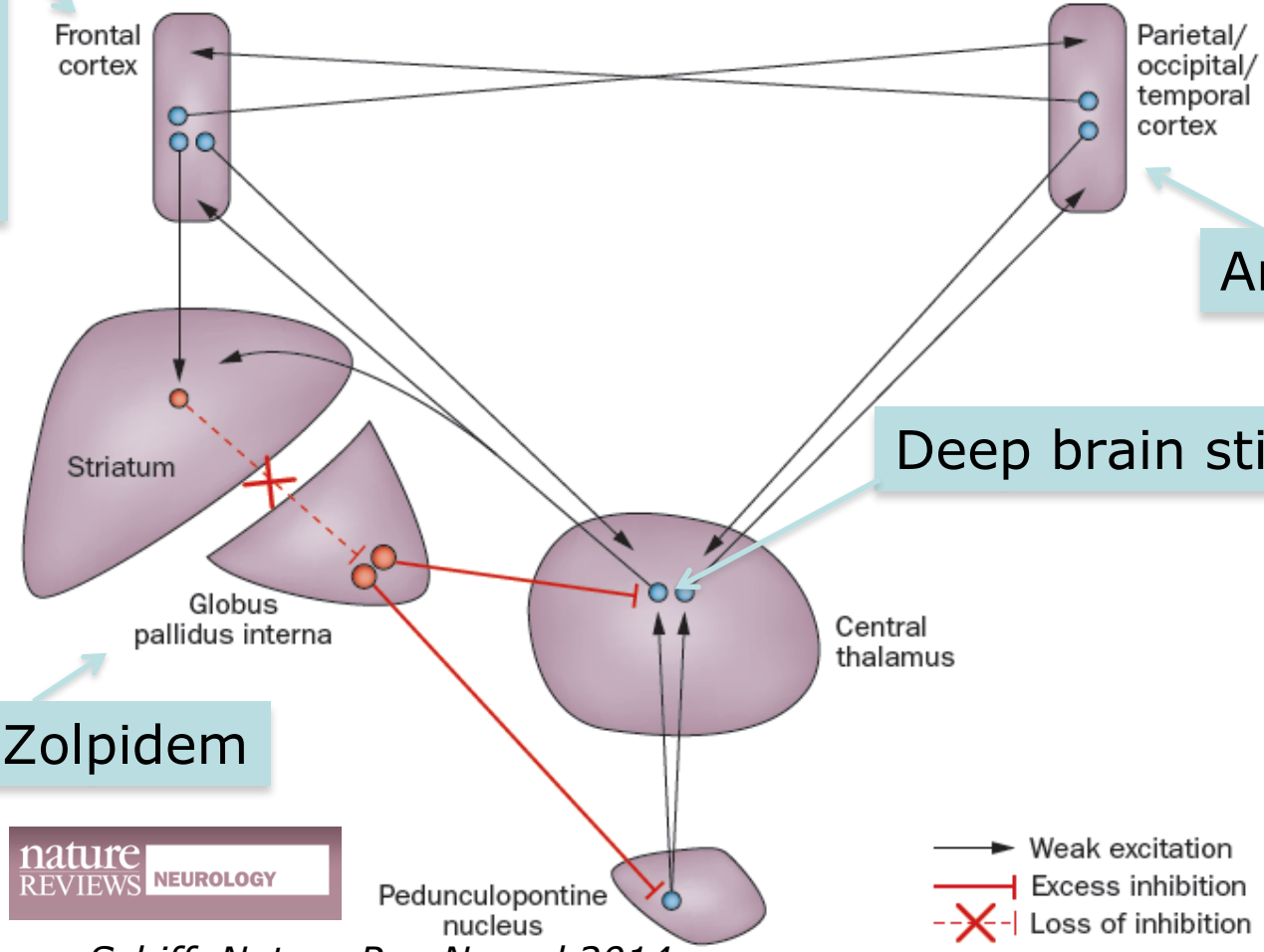


↗ LIS, EMCS & MCS & **4 VS/UWS**

Naro et al, Restor Neurol Neurosci 2015

Mesocircuit model

transcranial Direct Current Stimulation



Amantadine

Deep brain stimulation

Zolpidem

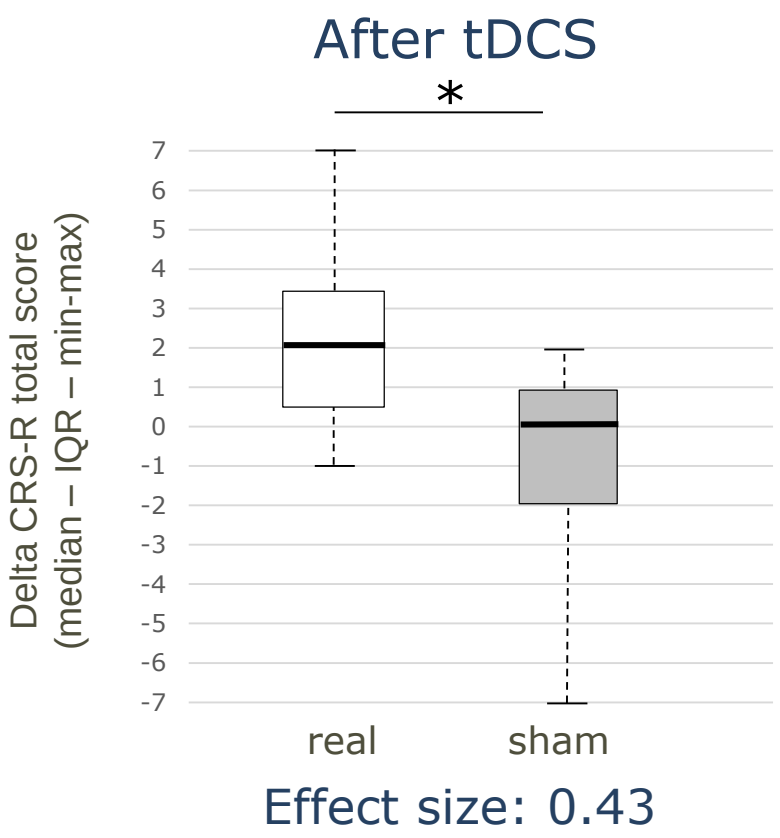
nature REVIEWS NEUROLOGY

Giacino, Fins, Laureys, Schiff, Nature Rev Neurol 2014

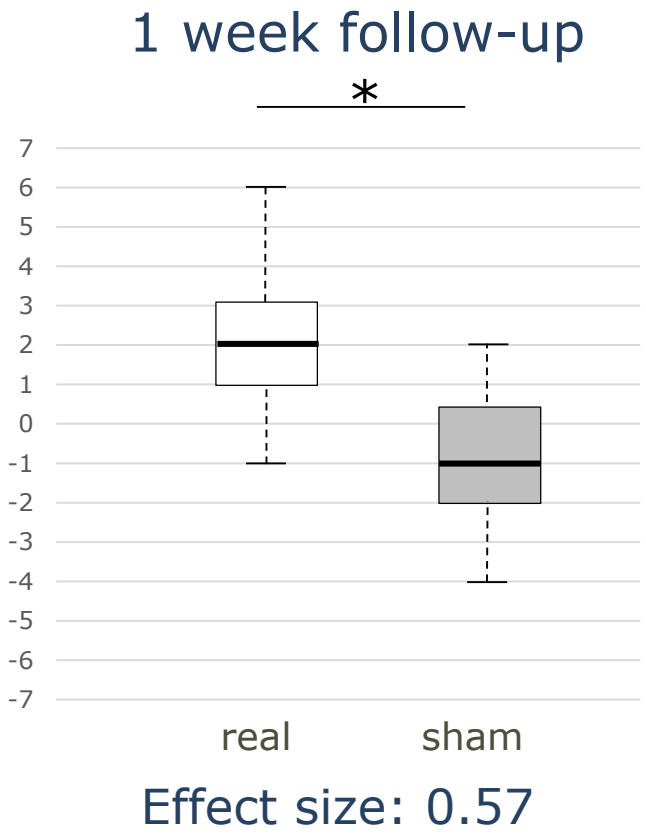
Repeated tDCS

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



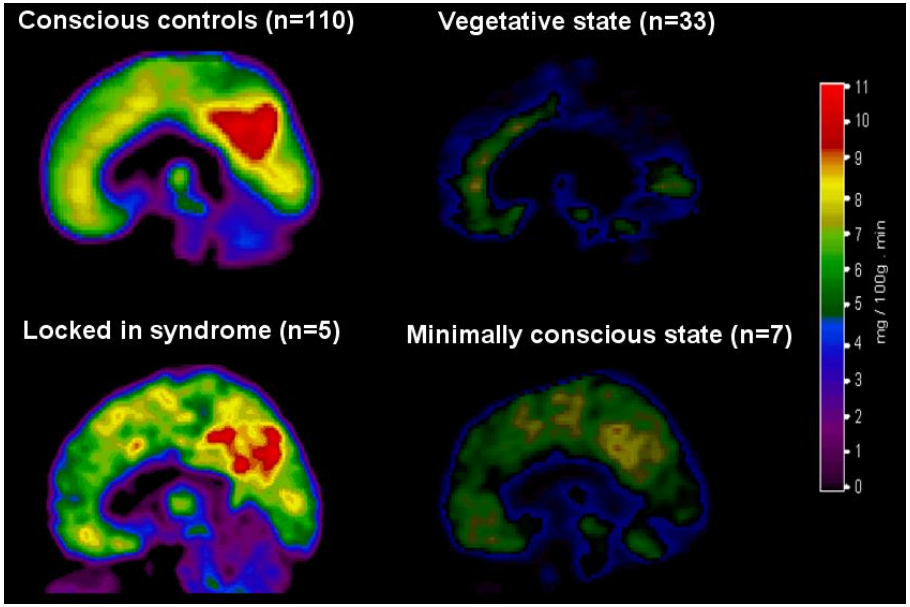
Effect size: 0.57

* $p<0.05$

Thibaut *et al.*, Brain Injury, 2017

Targeting other areas?

Precuneus: critical hub for consciousness



Laureys et al, Lancet Neurology, 2004

Anode: posterior parietal cortex
Cathode: right SOR

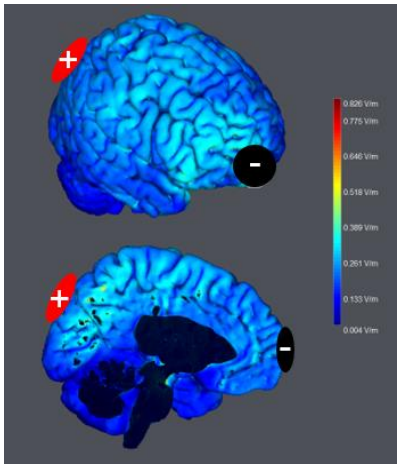
2mA; 20min

5 tDCS sessions

Active and sham – 5d washout

Huang et al, Bain Stimulation, 2017

tDCS – Precuneus



Contents lists available at ScienceDirect

Brain Stimulation

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

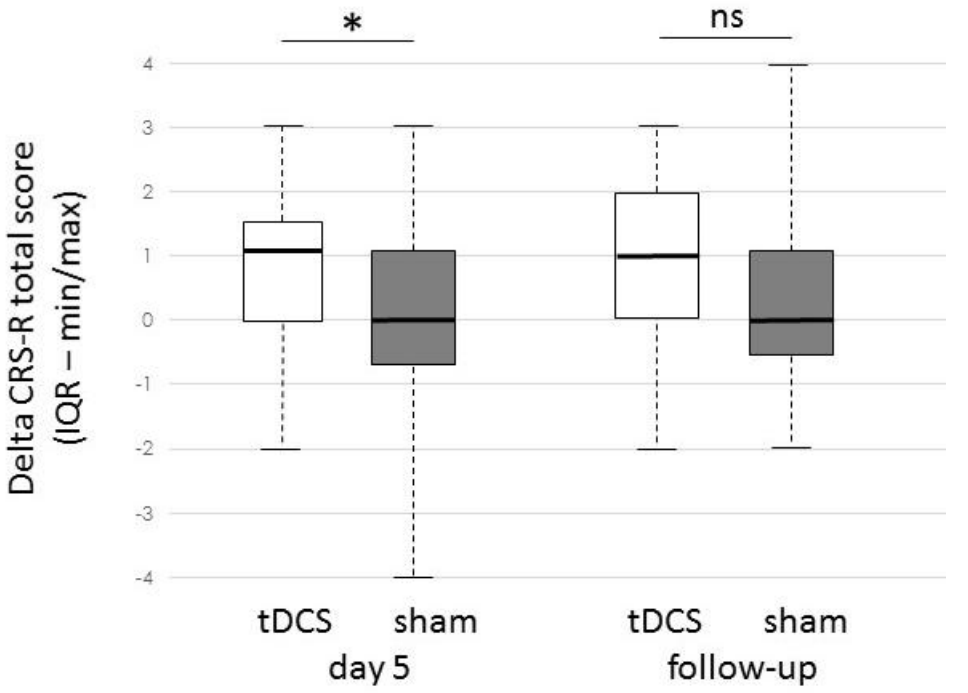
Repeated stimulation of the posterior parietal cortex in patients in minimally conscious state: A sham-controlled randomized clinical trial

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

9 responders (27%)
Sub-acute > chronic

No effect at 5day follow-up

Effect size : 0.31



Huang, … Thibaut, Bain Stimulation, 2017

tDCS – motor cortex

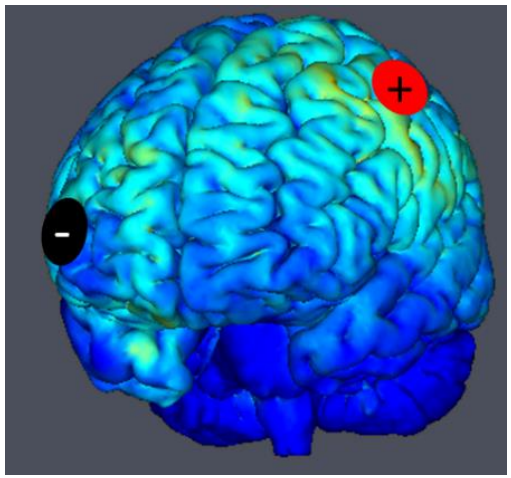
Motor cortex: common
& efficient tDCS target

For patients with DOC?

→ Immobilization, paresis…

→ Improve behavioral responsiveness

→ Covert consciousness



Martens et al., submitted

JFK COMA RECOVERY SCALE - REVISED ©2004
Record Form

Patient: Date:								
AUDITORY FUNCTION SCALE								
4 - Consistent Movement to Command *								
3 - Reproducible Movement to Command *								
2 - Localization to Sound								
1 - Auditory Startle								
0 - None								
VISUAL FUNCTION SCALE								
5 - Object Recognition *								
4 - Object Localization: Reaching *								
3 - Visual Pursuit *								
2 - Fixation *								
1 - Visual Startle								
0 - None								
MOTOR FUNCTION SCALE								
6 - Functional Object Use †								
5 - Automatic Motor Response *								
4 - Object Manipulation *								
3 - Localization to Noxious Stimulation *								
2 - Flexion Withdrawal								
1 - Abnormal Posturing								
0 - None/Flaccid								
OROMOTOR/VERBAL FUNCTION SCALE								
3 - Intelligible Verbalization *								
2 - Vocalization/Oral Movement								
1 - Oral Reflexive Movement								
0 - None								
COMMUNICATION SCALE								
2 - Functional: Accurate †								
1 - Non-Functional: Intentional *								
0 - None								
AROUSAL SCALE								
3 - Attention								
2 - Eye Opening w/o Stimulation								
1 - Eye Opening with Stimulation								
0 - Unarousable								
TOTAL SCORE								

Denotes emergence from MCS †
Denotes MCS *

Kalmar & Giacino, 2004

tDCS – motor cortex

Motor cortex: common
& efficient tDCS target

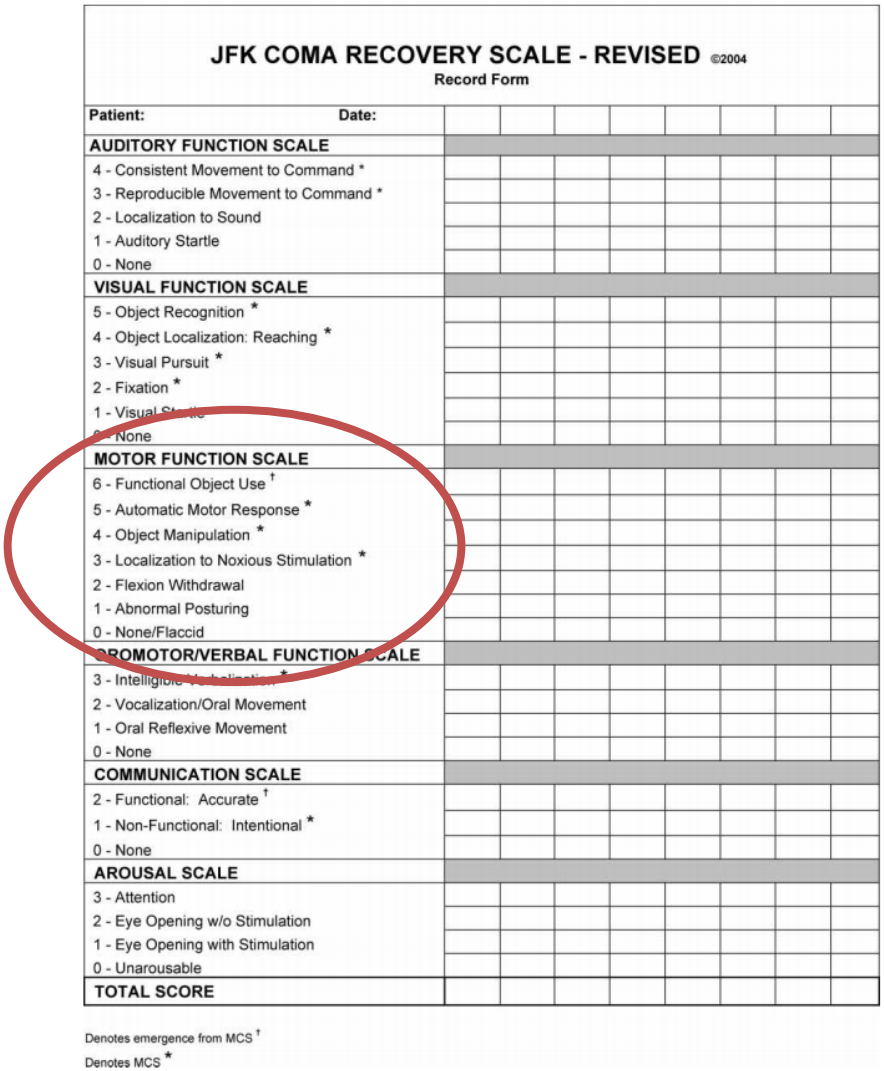
For patients with DOC?
→ Immobilization, paresis…
→ Improve behavioral responsiveness
→ Covert consciousness

Group level (n=10): no significant improvement (p=0.55; ES=0.10)

Single-subject level: 2 responders

Single stimulation & small sample size

Martens et al., submitted



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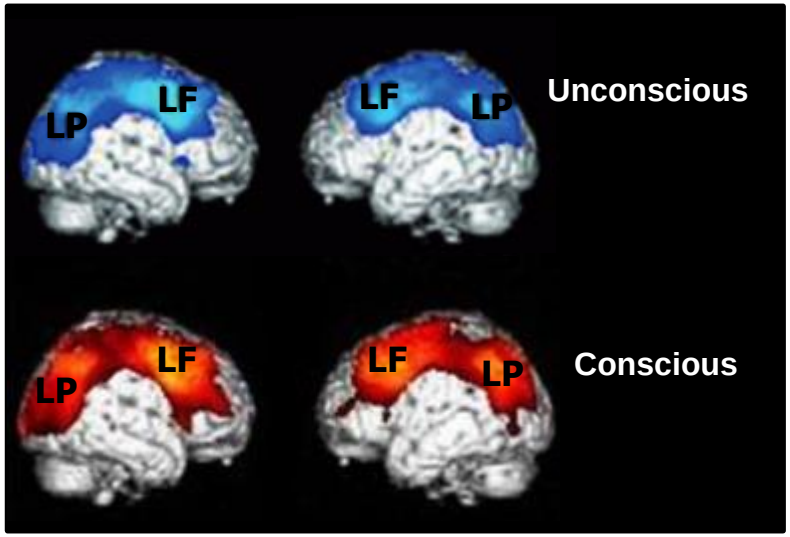
Denotes emergence from MCS †
Denotes MCS *

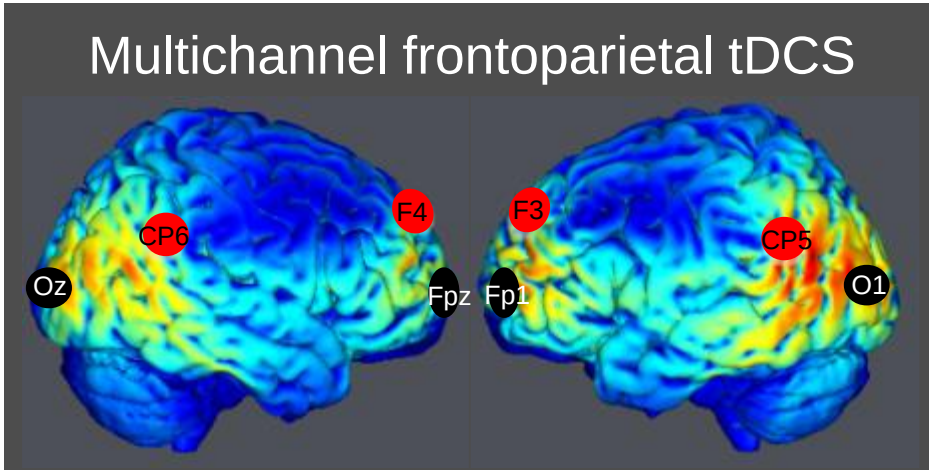
Kalmar & Giacino, 2004

Fronto-parietal multichannel tDCS

Frontoparietal network
External awareness network
Critical for consciousness recovery

➔ Stimulation of the external awareness network bilaterally

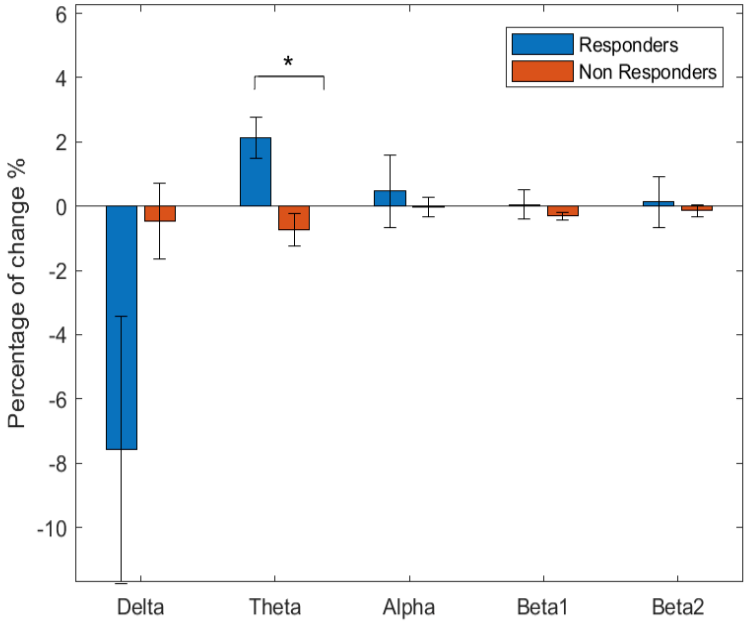




Thibaut et al., J Rehab Med, 2011

Fronto-parietal multichannel tDCS

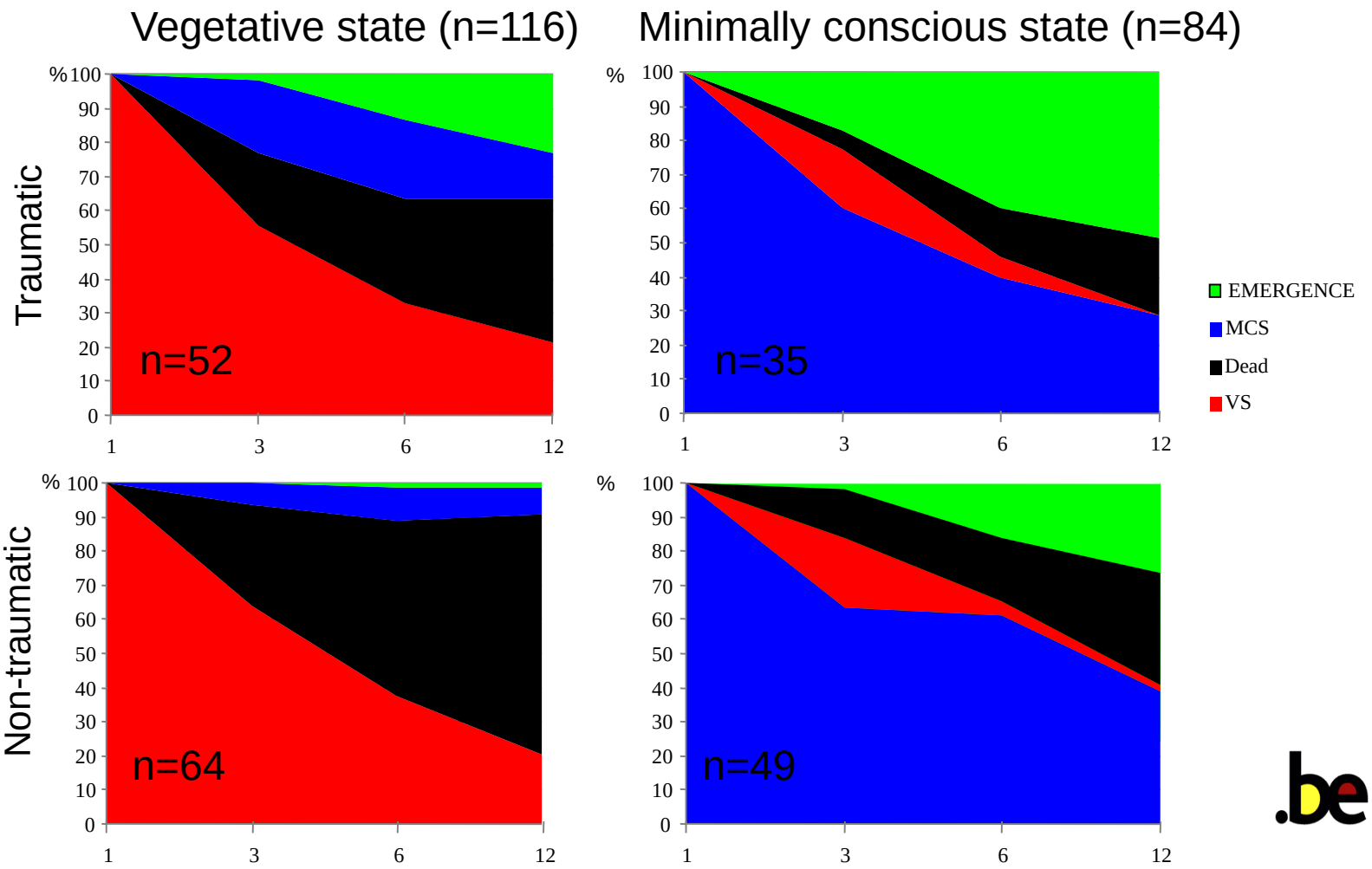
46 patients with prolonged DOC. VS and MCS, TBI and non-TBI
4 anodes and 4 cathodes – 1mA; 20min
Single stimulation – active & sham
Behavioral & EEG assessments



- Group level: no improvement
  1 mA not enough?
  1 session not enough?
- 6 responders (13%) mostly TBI
- EEG in responders: increase in theta complexity after active tDCS - no changes after sham tDCS

Martens et al., in prep

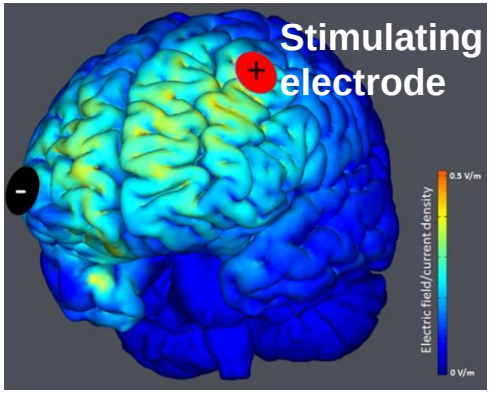
Prognostic



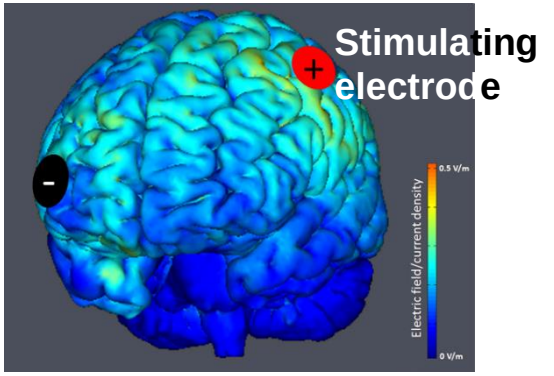
Bruno et al, Coma and disorders of consciousness, Eds Schnakers and Laureys, 2012

transcranial Direct Current Stimulation - tDCS

Prefrontal stimulation



Motor stimulation



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

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

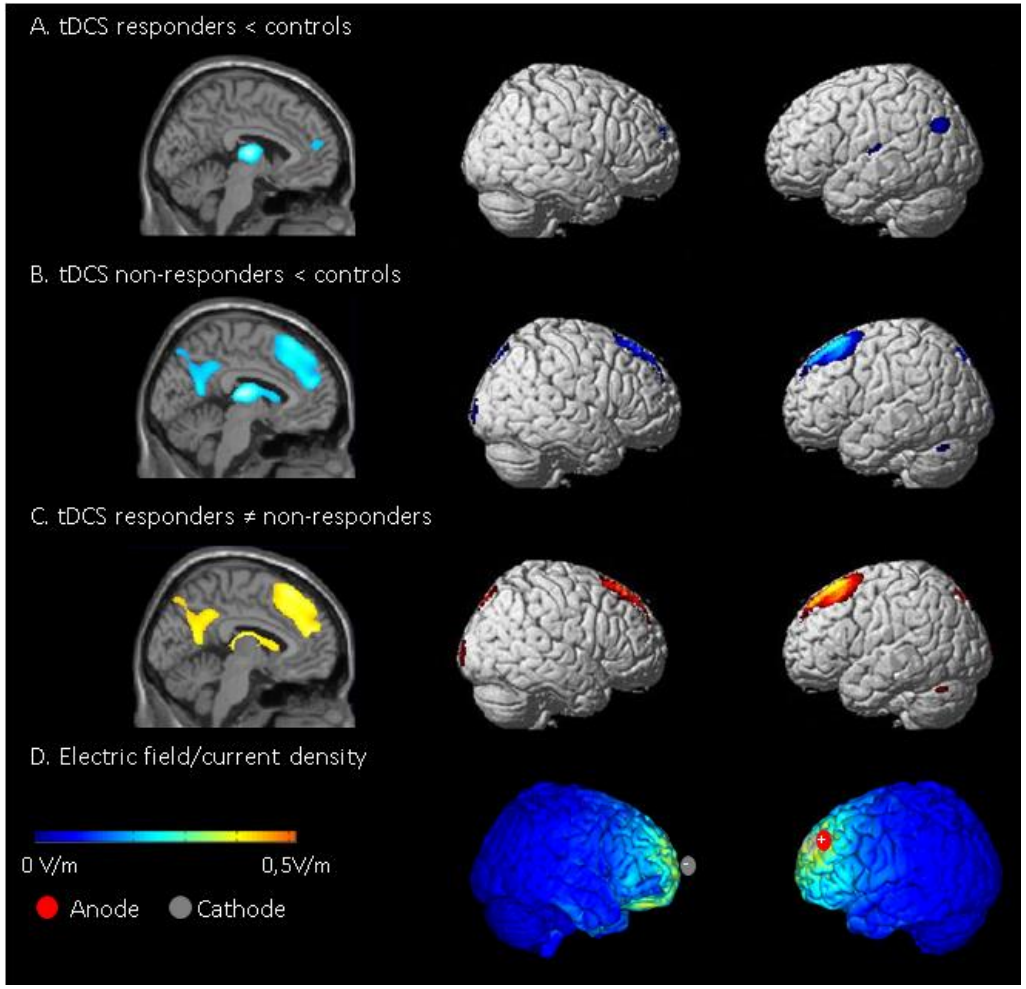
➔ *Long term effects*
Neural excitability & plasticity (LTP-LTD)
Ion channels (Na^+, Ca^{2+})
NMDA receptors

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

Neural correlates

- hypometabolic
- preservred

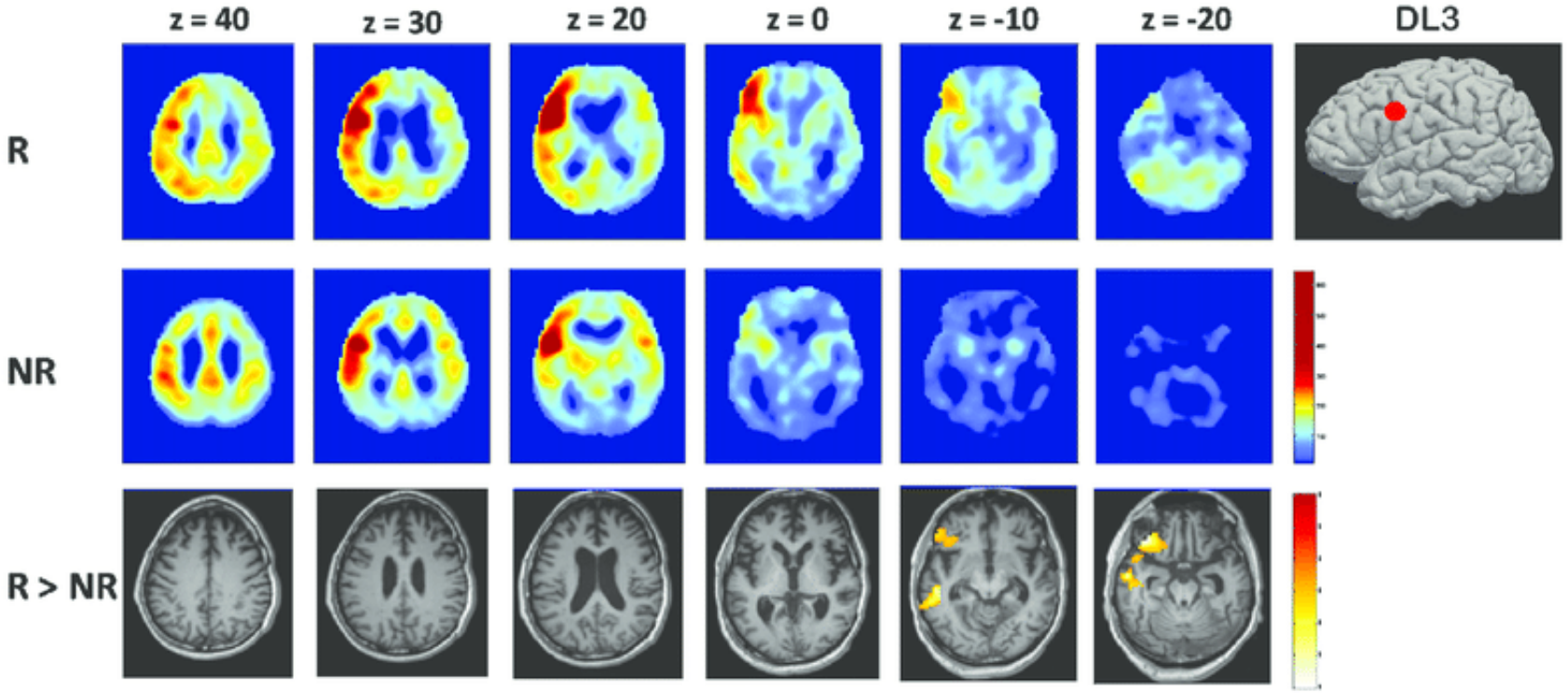
  p<0.05



Thibaut *et al.*, Brain Stimulation 2015

Neural correlates

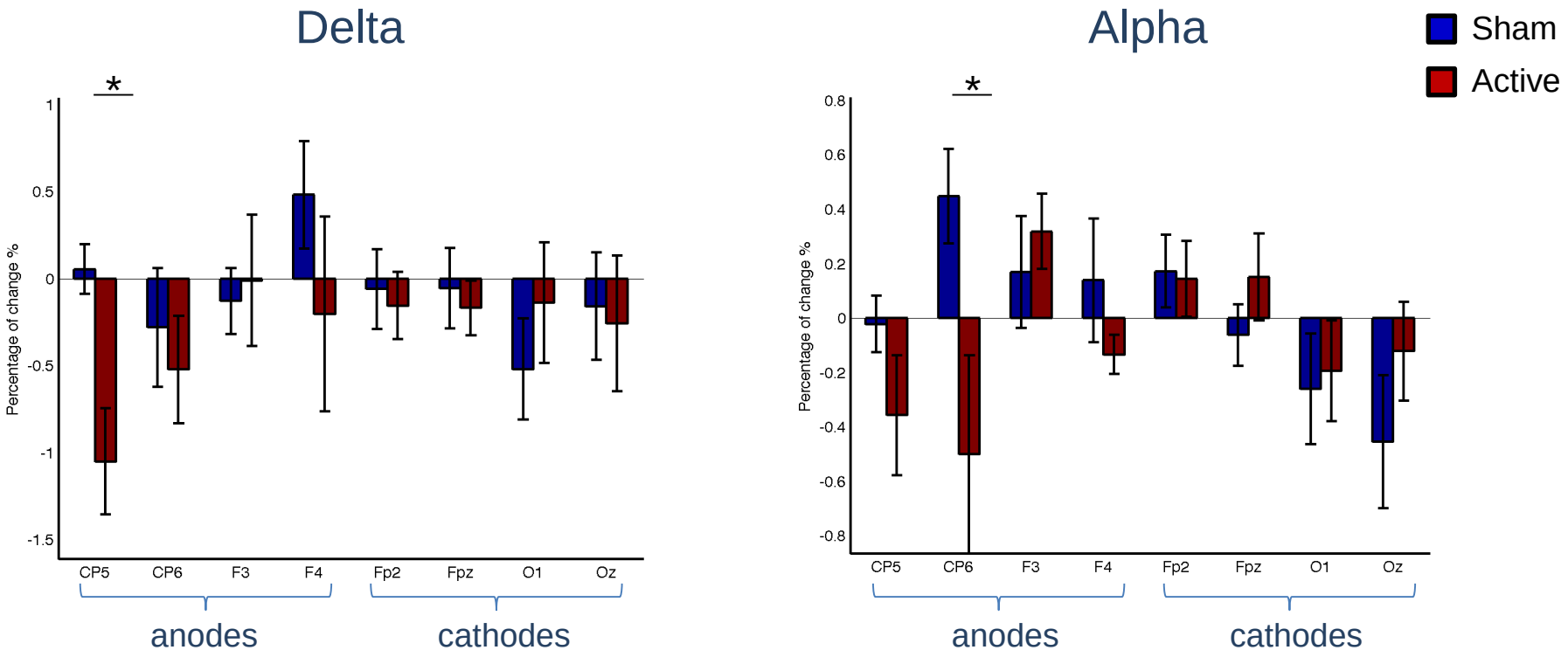
fMRI 16 chronic MCS – 6 tDCS responders



Cavaliere et al. 2016 Frontiers Cell Neurosci

Fronto-parietal multichannels tDCS

Measure of complexity: LZW estimation per band and electrode
Percentage of change = (Post_LZW – Pre_LZW)/Pre_LZW*100 %)



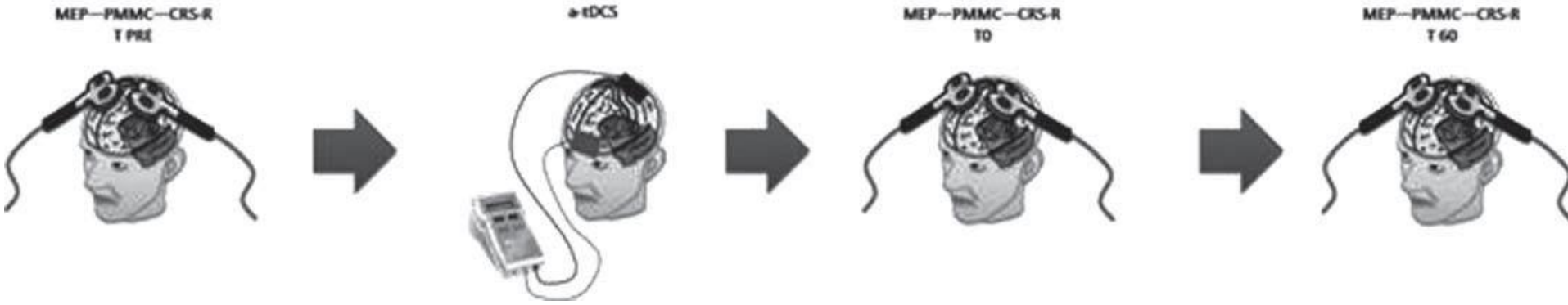
LZW significantly decreases with tDCS under anodes, indicating that **complexity decreases with tDCS** in these bands

➔ more structure in the data following tDCS?

tDCS – diagnostic tool?

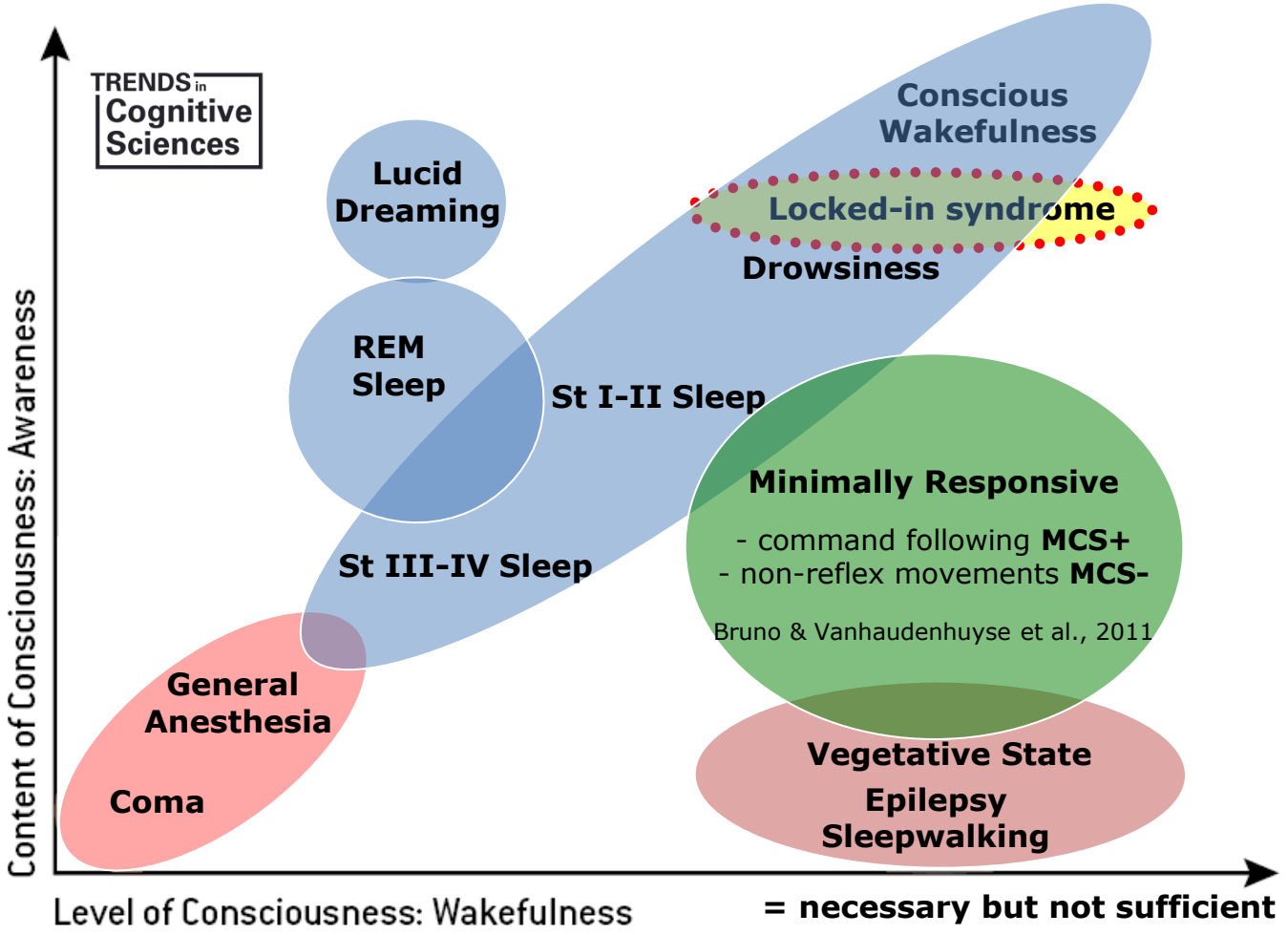
tDCS & TMS

25 chronic DOC (12 VS/UWS; 10 MCS; 2 EMCS;1 LIS)
Anode: OFC (Fpz) & cathode: Cz
TMS: MEP, RMT, ICI, ICF



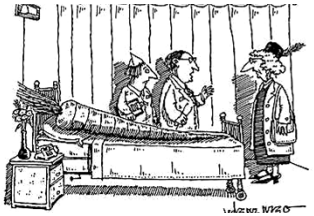
Naro et al, Restor Neurol Neurosci 2015

What is consciousness?



Laureys, Trends in Cognitive Sciences, 2005

Unresponsive Wakefulness Syndrome
Laureys et al., 2010



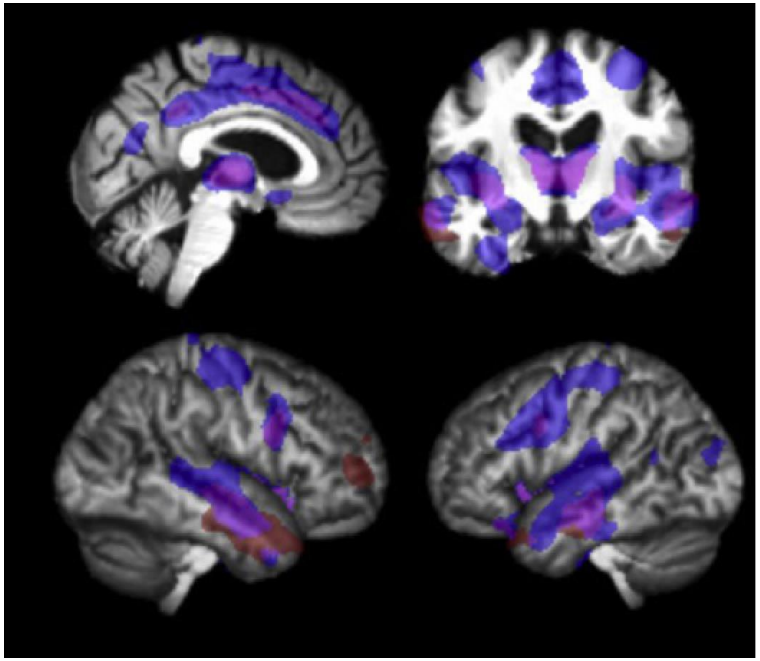
"There's nothing we can do… he'll always be a vegetable."

Why tDCS in DOC?

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

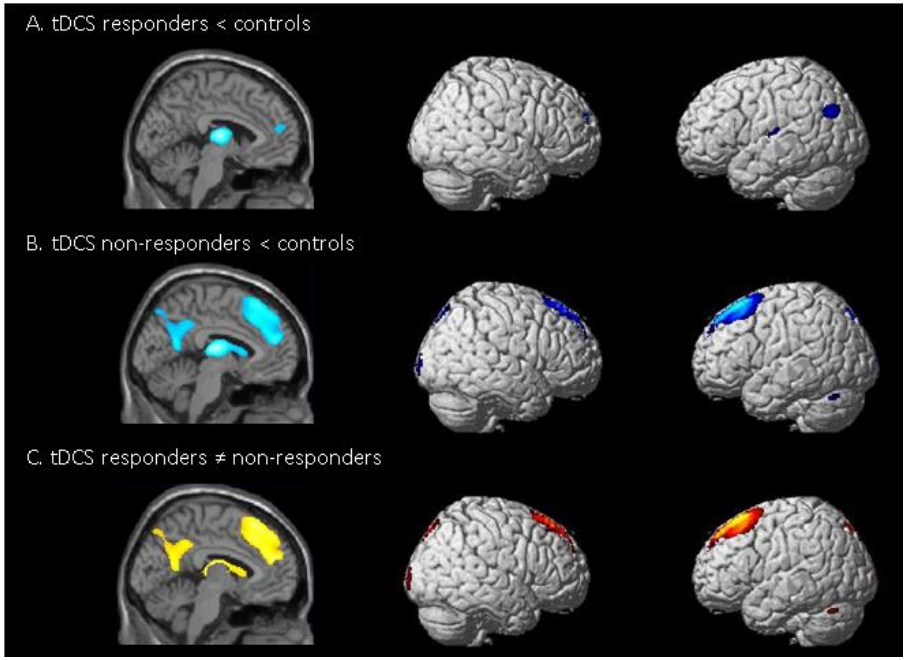
Neural correlates

Grey matter atrophy – VBM



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

Brain metabolism – PET-scan



- hypometabolic
- preservred

Thibaut *et al.*, Brain Stimulation 2015