

Motor tDCS in patients with Disorders of Consciousness

Géraldine MARTENS, PhD student

Coma Science Group
University of Liege, Belgium



Neurorehabilitation Lab
Spaulding-Harvard TBI Model System
Boston, USA



www.giga.ulg.ac.be

www.comascience.org

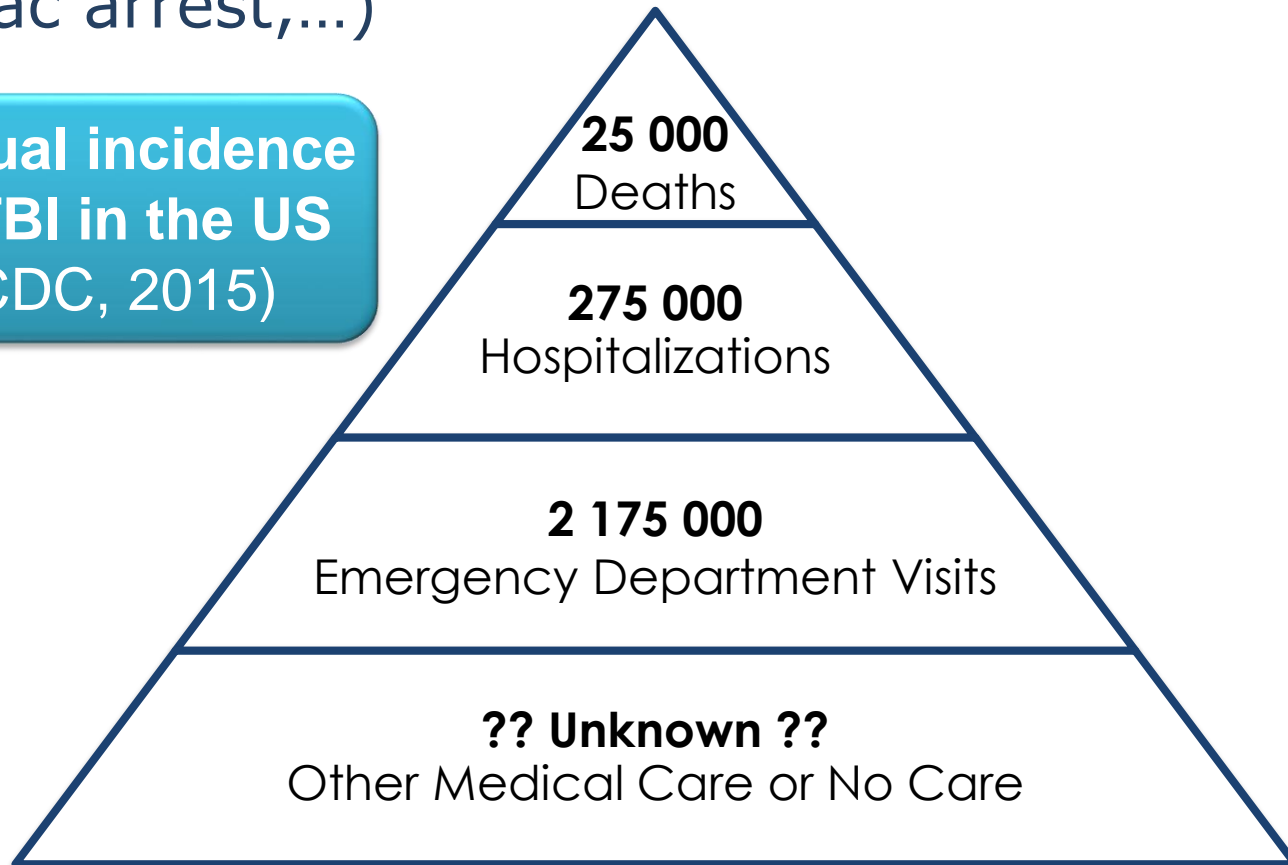
srhneurorehabilitationlab.org



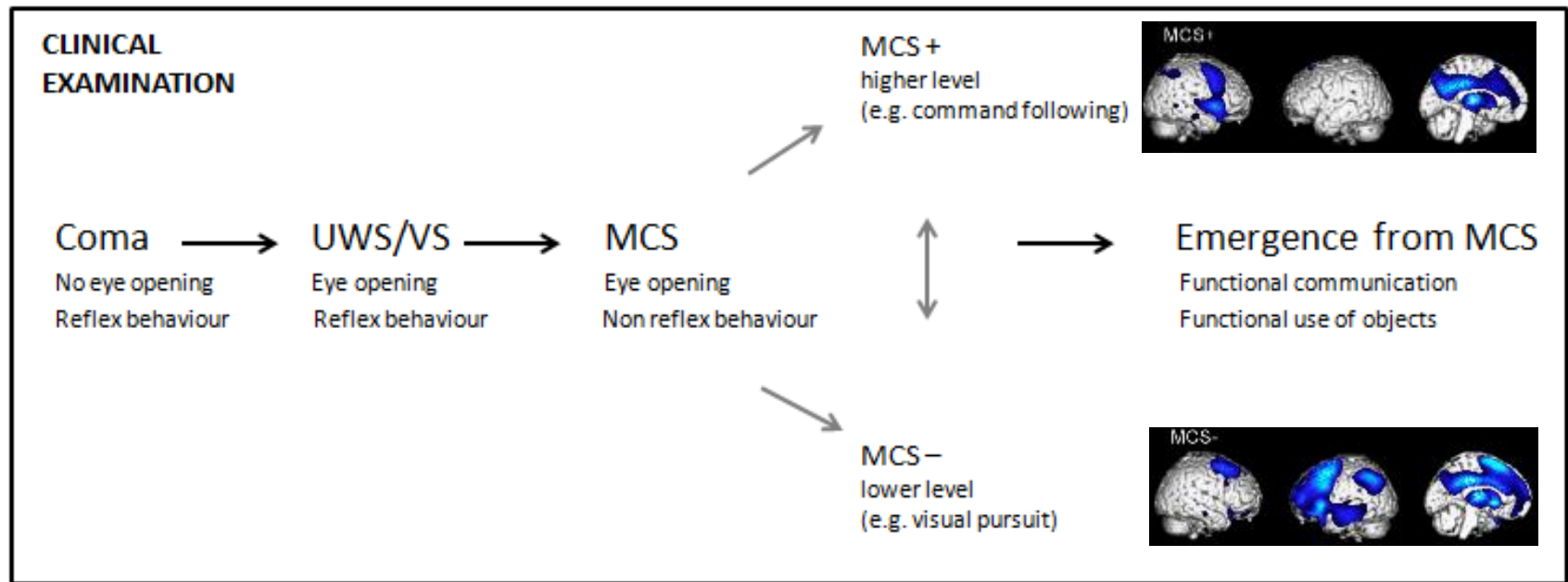
Severe brain injury

- Traumatic etiologies (TBI - e.g., car accident, fall, gunshot,...)
- Non-traumatic etiologies (nTBI - e.g., stroke, cardiac arrest,...)

**Annual incidence
of TBI in the US
(CDC, 2015)**



Disorders of Consciousness



UWS=unresponsive wakefulness syndrome

VS=vegetative state

MCS=minimally conscious state



Clinical diagnosis

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 †

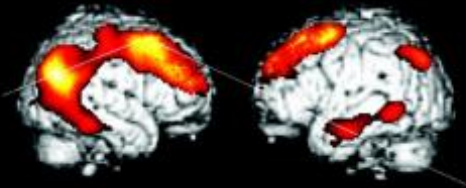
Denotes MCS *



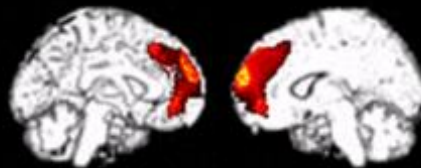
Therapeutic options

Pharmacological interventions

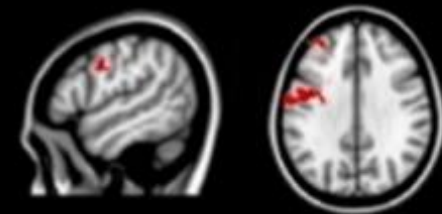
Amantadine



Zolpidem

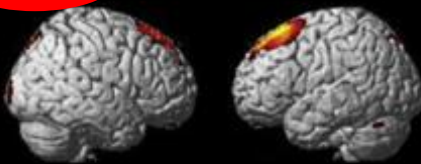


Music therapy

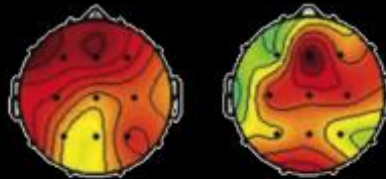


Brain stimulations

tDCS



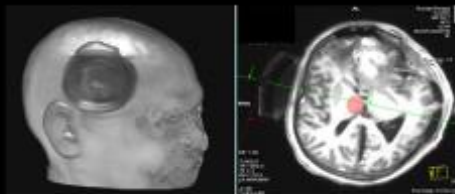
rTMS



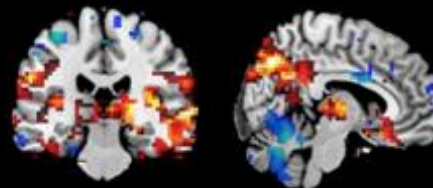
DBS



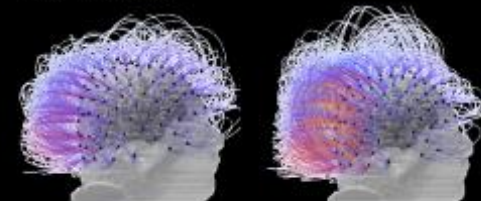
LIFUP



Non invasive taVNS

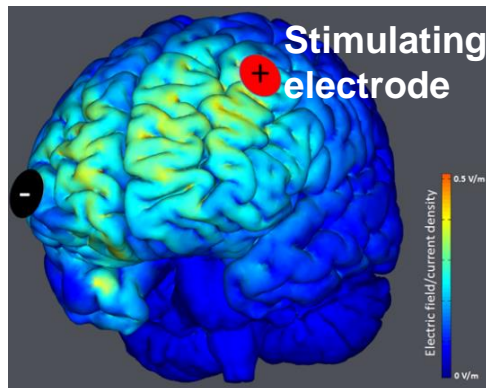


Invasive VNS



transcranial Direct Current Stimulation - tDCS

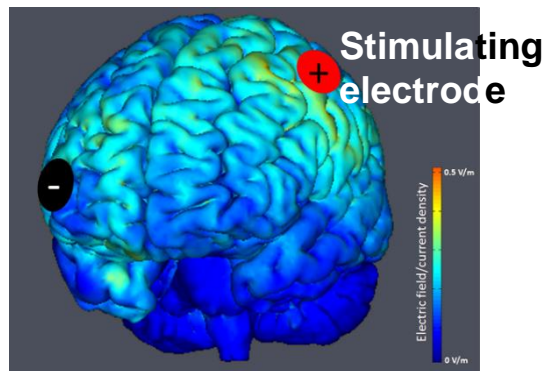
Prefrontal stimulation



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 in DoC?

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

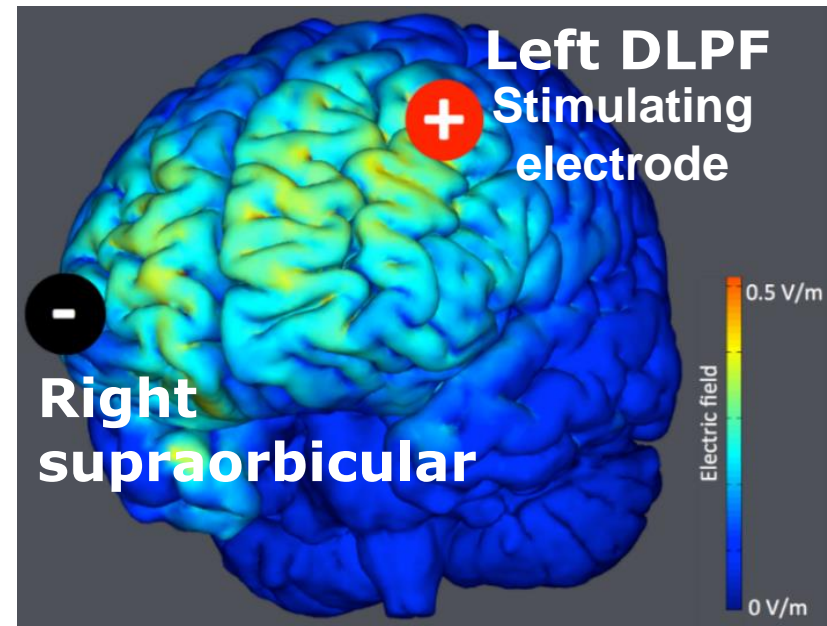
tDCS single session

ARTICLES

tDCS in patients with disorders of consciousness

Sham-controlled randomized double-blind study

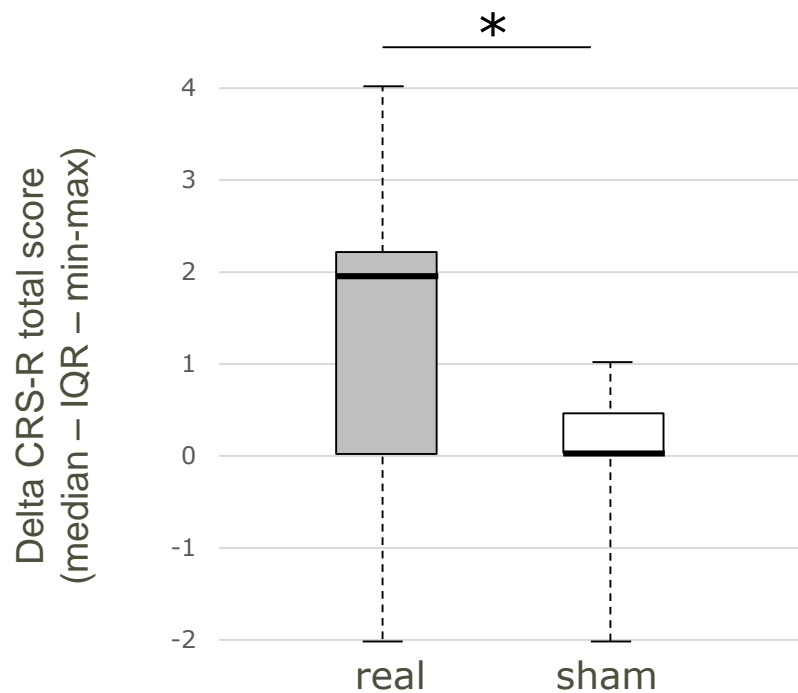
- Randomized, double blind, sham controlled, cross-over study
- Single stimulation – 2 mA; 20 min
- Prefrontal stimulation
- Coma Recovery Scale-R (CRS-R)
- 55 patients included (43 ± 18 y)
25 VS/UWS & 30 MCS
35 chronic (>3m) & 20 acute
25 TBI & 30 nTBI





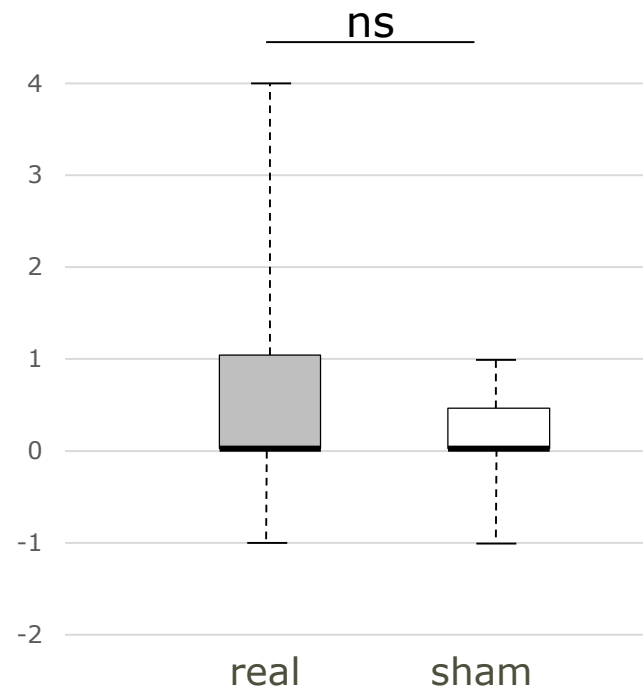
tDCS single session

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

- 15/55 responders (13 MCS – 5 chronic; 2 UWS)
- Change of diagnosis: 3 MCS → EMCS; 2 UWS → MCS

SUBSCALES	RECOVERY	PATIENTS (n)
AUDITORY	Systematic command following	1
	Reproducible command following	4
	Localization to sounds	1
VISUAL	Object recognition	2
	Object localization	1
	Visual pursuit	5
MOTOR	Functional use of object	1
	Automatic motor reaction	2
	Object manipulation	3
OROMOTOR	Vocalisation	3
COMMUNICATION	Functional communication	2
AROUSAL	Without stimulation	2



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 critical brain regions

Motor cortex

Precuneus

Fronto-parietal network

→ Can tDCS be used in clinical setting?

Translational study

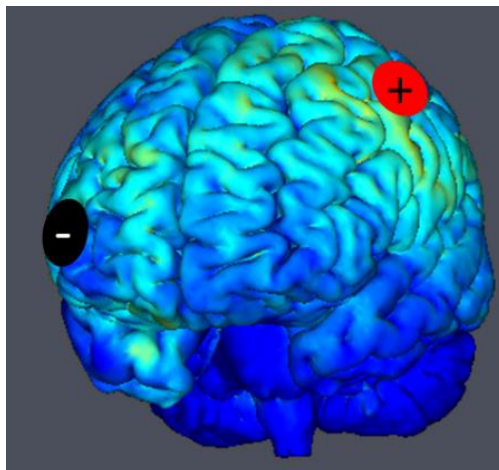


Targeting other areas?

Motor cortex: common & efficient tDCS target

For DOC patients?

- Immobilization, paresis...
- **Covert consciousness**
- Improve behavioral responsiveness



Patient:		Date:									
JFK COMA RECOVERY SCALE - REVISED ©2004 Record Form											
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											
PROMOTOR/VERBAL FUNCTION SCALE											
3 - Intelligible Vocalization *											
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 *

Targeting other areas?

Motor cortex stimulation

- Randomized, double blind, sham controlled, cross-over study
- Single stimulation – 2 mA; 20 min (active and sham)
- Motor cortex stimulation (C3 or C4)
- Coma Recovery Scale-R (CRS-R)
- 10 patients included (49 ± 22 y)
4 VS/UWS & 6 MCS
4 chronic (>3m) & 6 acute
5 TBI & 5 nTBI



Motor cortex stimulation

- Group level: no significant improvement ($p=0.55$; $ES=0.10$)
- Limitations
 - single session
 - small sample size
 - confounding factors (spasticity, flaccidity,...)
- Single-subject level: ?

Motor cortex stimulation

ID	Age (gender)	Etiology	Time Since Injury (days)	Baseline Diagnosis	tDCS Allocation	CRS-R Total Score			
						Before Active	After Active	Before Sham	After Sham
P1	24 (M)	TBI	286	UWS	active/sham	4	4	4	4
P2	32 (M)	non-TBI	150	MCS	sham/active	20	20	18	22
P3	68 (M)	TBI	45	MCS	sham/active	6	7	4	7
P4	70 (M)	non-TBI	12	MCS	active/sham	7	7	6	9
P5	74 (M)	non-TBI	24	UWS	sham/active	2	2	2	2
P6	21 (M)	TBI	1332	MCS	sham/active	9	9	13	8
P7	51 (F)	TBI	42	MCS	active/sham	18	18	15	17
P8	19 (M)	TBI	218	MCS	sham/active	8	11	8	7
P9	64 (M)	non-TBI	28	UWS	sham/active	6	7	5	7
P10	68 (F)	non-TBI	39	UWS	active/sham	4	4	4	4

Motor cortex stimulation

ID	Age (gender)	Etiology	Time Since Injury (days)	Baseline Diagnosis	Conscious Behaviors Recovered	
					After Active	
P1	24 (M)	TBI	286	UWS	/	
P2	32 (M)	non-TBI	150	MCS	/	
P3	68 (M)	TBI	45	MCS	/	}
P4	70 (M)	non-TBI	12	MCS	/	
P5	74 (M)	non-TBI			/	
P6	21 (M)				/	
P7	51 (F)	TBI	42	MCS	/	
P8	19 (M)	TBI	218	MCS	Object Localization	
P9	64 (M)	non-TBI	28	UWS	Visual Pursuit	
P10	68 (F)	non-TBI	39	UWS	/	

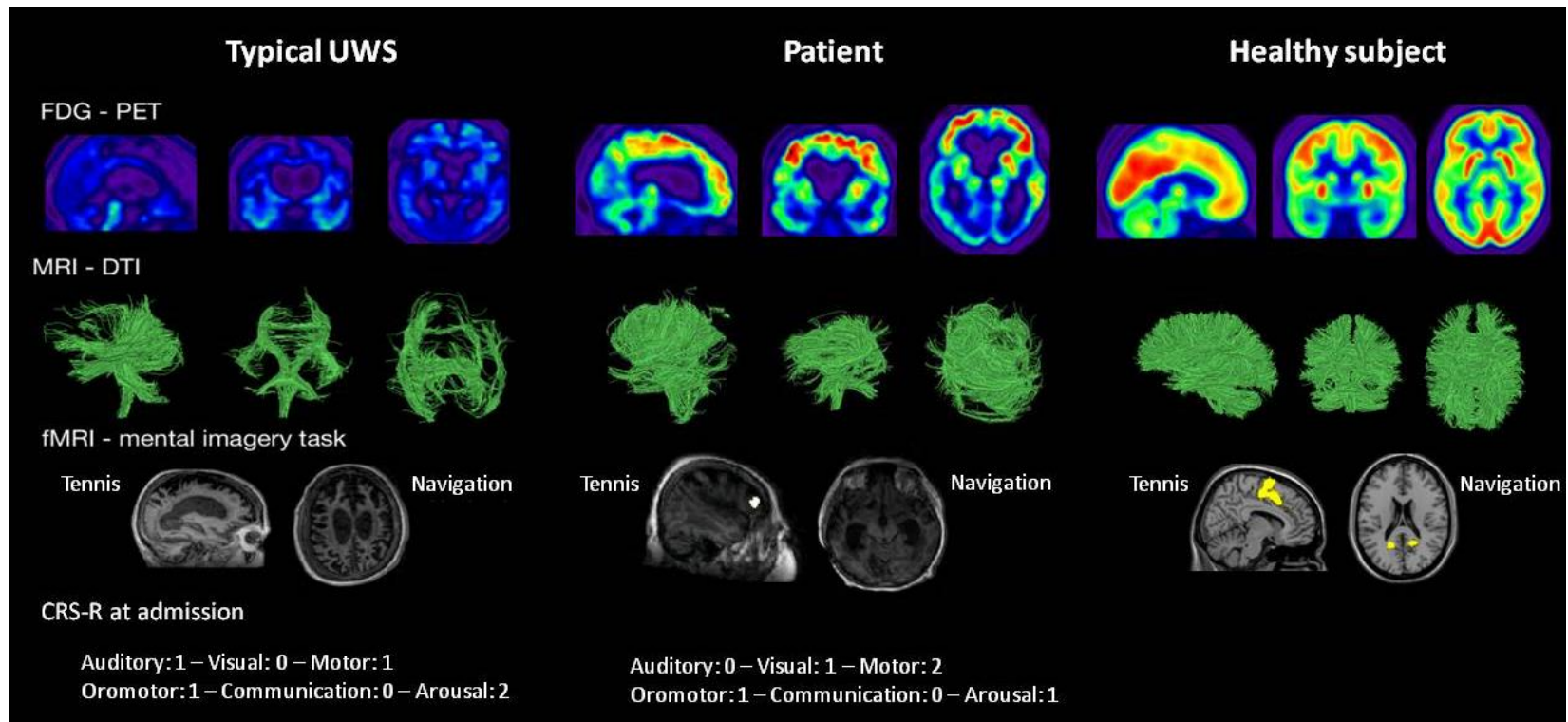
« sham responders »

MCS

?

tDCS to unveil covert consciousness

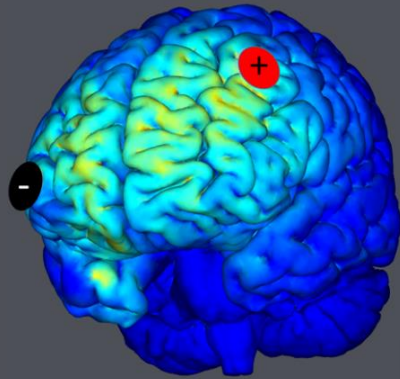
- 67yo woman in UWS for 4 years after a subarachnoid hemorrhage
- Out of 8 standardized CRS-R she showed 1 localization to pain
- She demonstrated reproducible response to command only after tDCS
- Neuroimaging exams were consistent with the diagnosis of MCS*



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

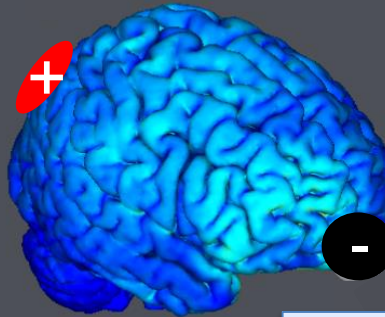
Stimulating different areas

Prefrontal ↗



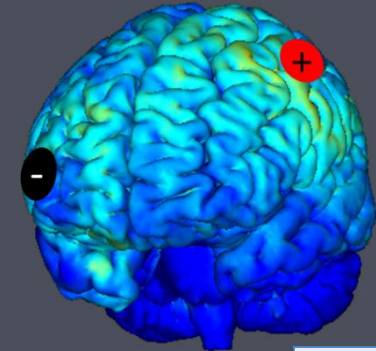
N=55

Precuneus ↘



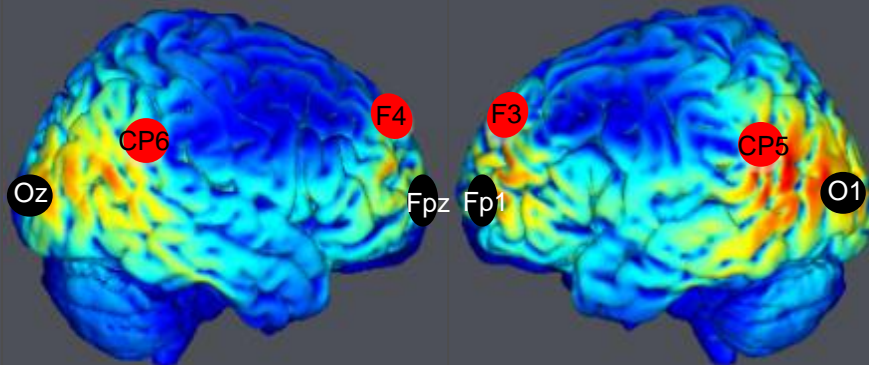
N=33

Motor ≡



N=10

Multichannel frontoparietal ≡



N=46

Prefrontal tDCS
best area to target



Conclusions

- **Prefrontal** tDCS → reproducible clinical improvements
- **Motor** tDCS → effects less remarkable
- Patients with cognitive-motor dissociation may benefit from tDCS

Next?

- Neurophysiological correlates of tDCS
- Patients' tailored montage – based on patients' brain lesion
- Treatments combination

THANK YOU



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



James S. McDonnell Foundation



Subscales



Real

Subject	BL real	Auditive	Visual	Motor	Verbal	Commu nication	Arousal	Post real	Auditive	Visual	Motor	Verbal	Commu nication	Arousal
1	4	1	0	0	1	0	2	4	1	0	0	1	0	2
2	20	3	4	6	3	1	3	20	3	4	6	3	1	3
3	6	0	1	3	1	0	1	7	0	1	3	1	0	2
4	7	0	3	1	1	0	2	7	0	3	1	1	0	2
5	2	0	0	0	1	0	1	2	0	0	0	1	0	1
6	9	1	3	1	1	1	2	9	1	3	1	1	1	2
7	18	3	3	5	3	1	3	18	3	3	5	3	1	3
8	8	1	3	1	1	0	2	11	1	4	2	2	0	2
9	6	1	1	1	1	0	2	7	1	3	1	1	0	1
10	4	0	0	2	1	0	1	4	0	0	2	1	0	1

Sham

BL sham	Auditive	Visual	Motor	Verbal	Commu nication	Arousal	Post sham	Auditive	Visual	Motor	Verbal	Commu nication	Arousal
4	1	0	0	1	0	2	4	1	0	0	1	0	2
18	3	3	5	3	1	3	22	4	5	6	3	1	3
4	0	0	1	1	0	2	7	3	1	1	0	0	2
6	0	1	2	1	0	2	9	0	3	3	1	0	2
2	0	0	0	1	0	1	2	0	0	0	1	0	1
13	1	3	5	1	1	2	8	1	3	1	1	0	2
15	3	3	4	3	0	2	17	3	3	4	3	1	3
8	1	3	1	1	0	2	7	1	2	1	1	0	2
5	1	1	1	1	0	1	7	2	1	1	1	0	2
4	0	0	2	1	0	1	4	0	0	2	1	0	1

tDCS response



Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: www.brainstimjrn.com



8 tDCS responders
13 tDCS non-responders

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



Aurore Thibaut^{a,*}, 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

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

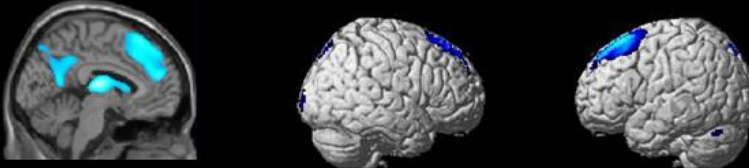
Brain metabolism – PET-scan

Grey matter atrophy – VBM

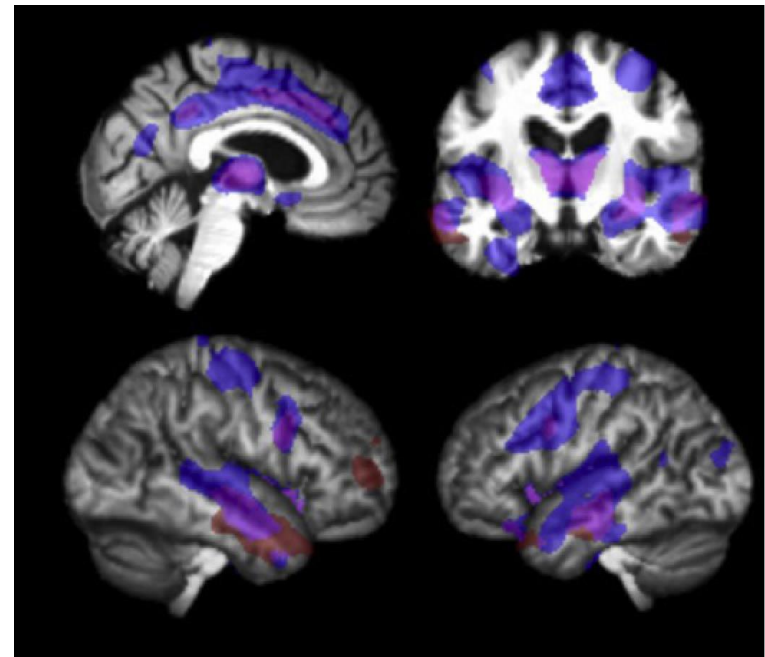
A. tDCS responders < controls



B. tDCS non-responders < controls

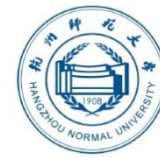


C. tDCS responders ≠ non-responders

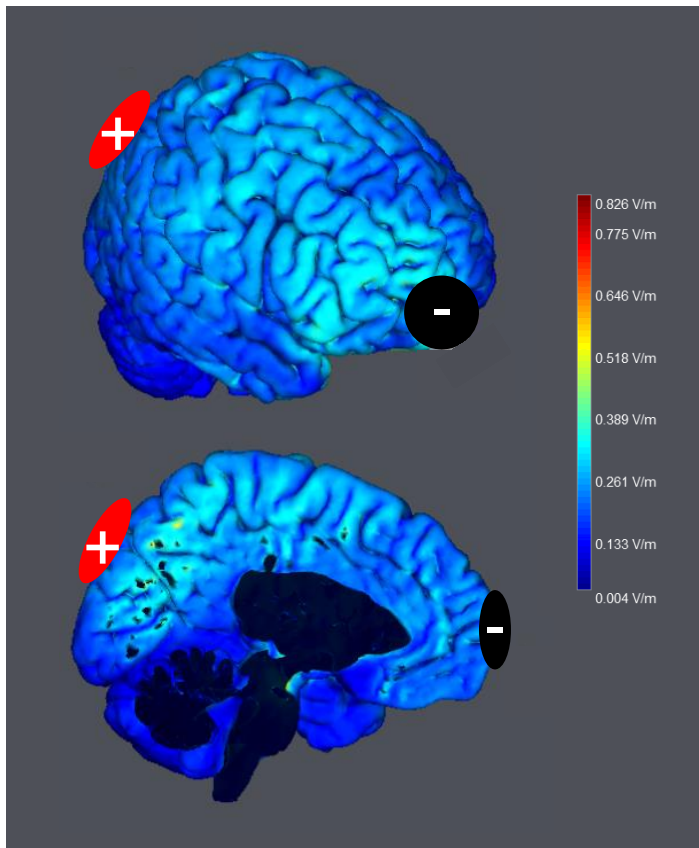




tDCS – Precuneus



Precuneus: critical hub for consciousness



Anode: posterior parietal cortex
Cathode: right SOR

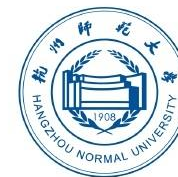
2mA; 20min

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>



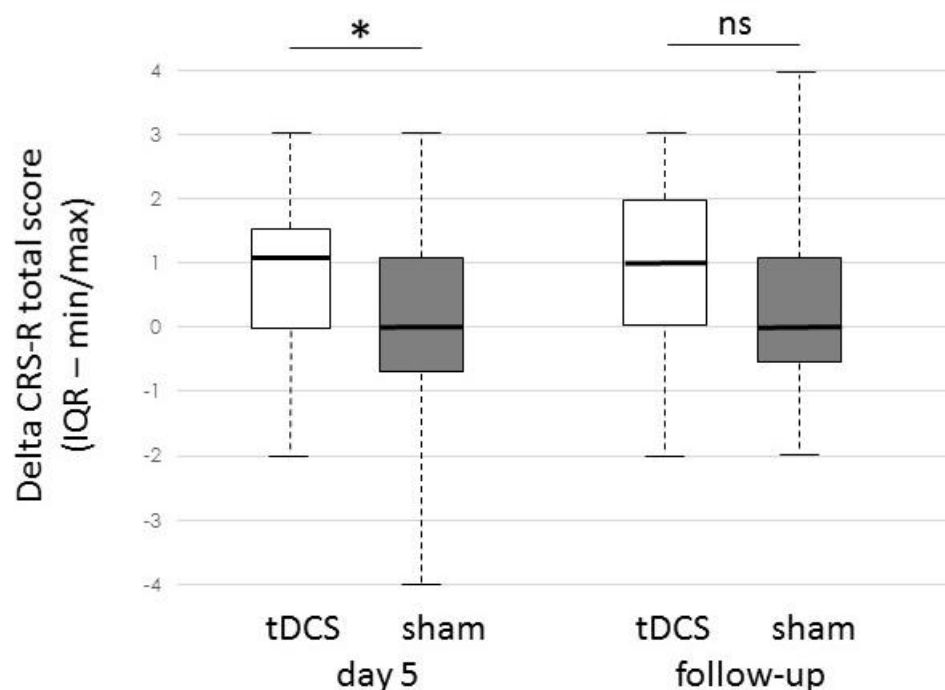
Repeated stimulation of the posterior parietal cortex in patients in minimally conscious state: A sham-controlled randomized clinical trial

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

9 responders (27%)
Sub-acute > chronic

No effect at 5d follow-up

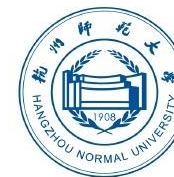
Effect size : 0.31



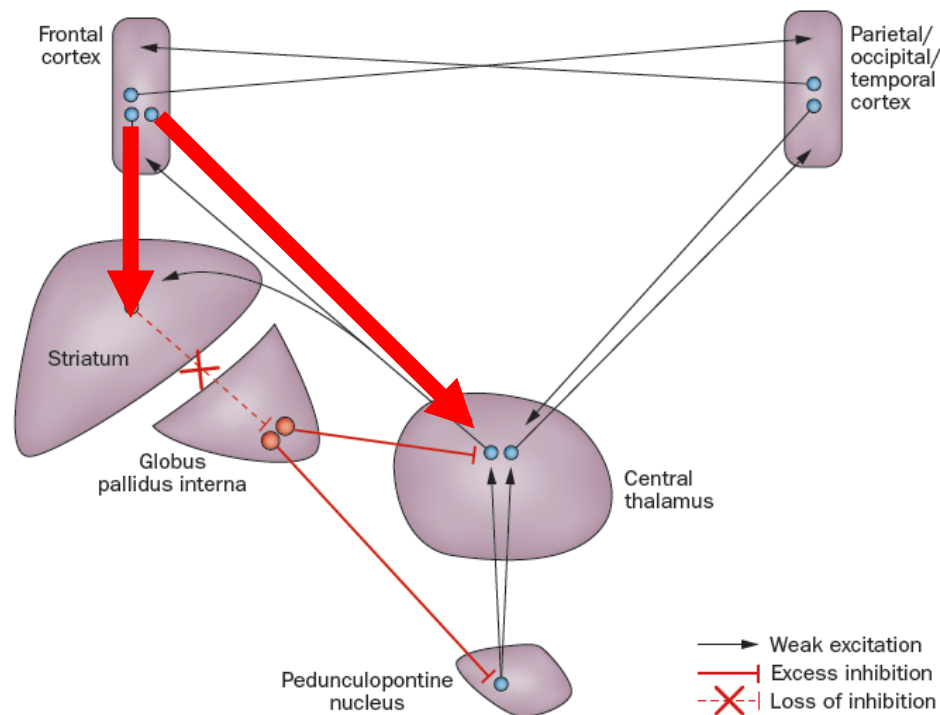
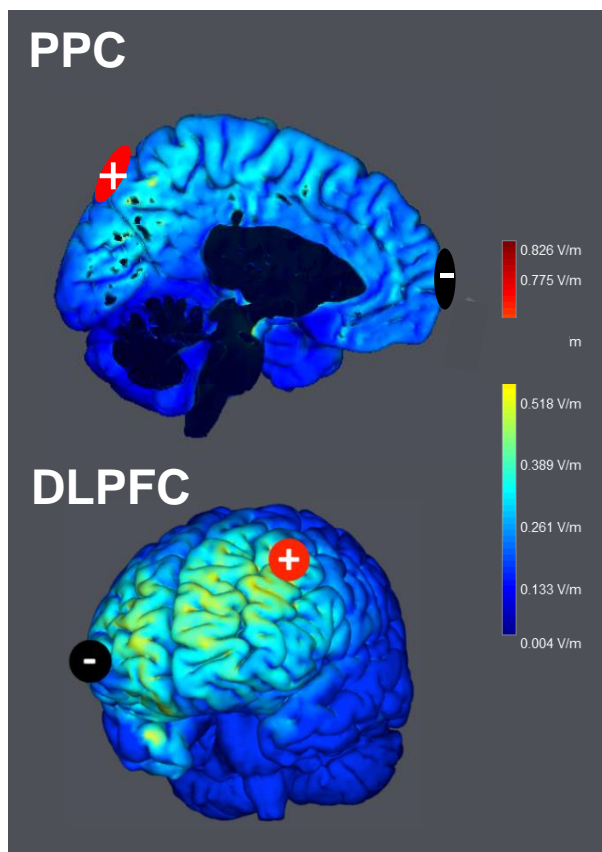
□ tDCS
■ sham



tDCS – Precuneus



Prefrontal tDCS better than posterior parietal tDCS?

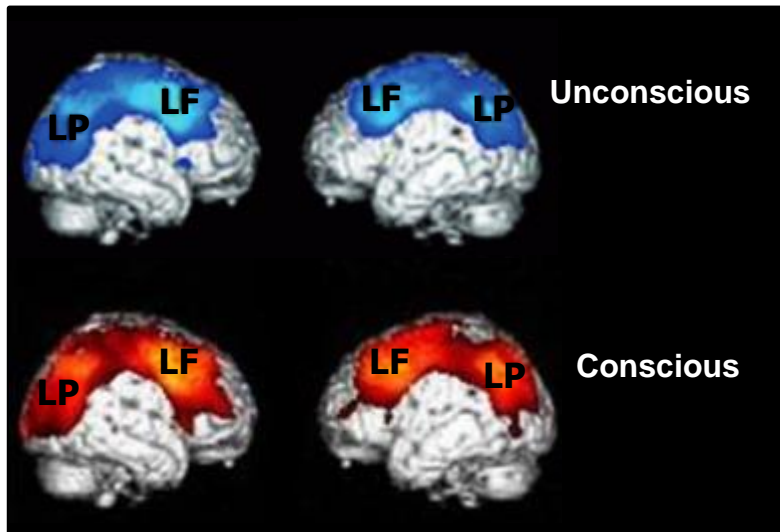


Huang, ... Thibaut, Bain Stimulation, 2017

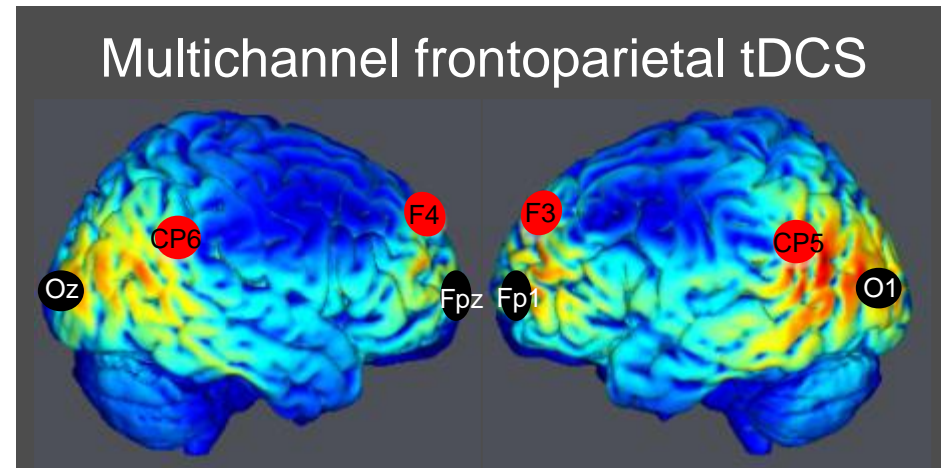
Giacino, Fins, Laureys, Schiff, *Nature Rev Neurol* 2014

Frontoparietal network
External consciousness network
Critical for consciousness recovery

→ Stimulation of the external consciousness network bilaterally



- Hypometabolic areas
- Preserved areas



Fronto-parietal multichannel tDCS

46 patients (23MCS, 17UWS, 6EMCS; 22TBI, 24nTBI; >1month)

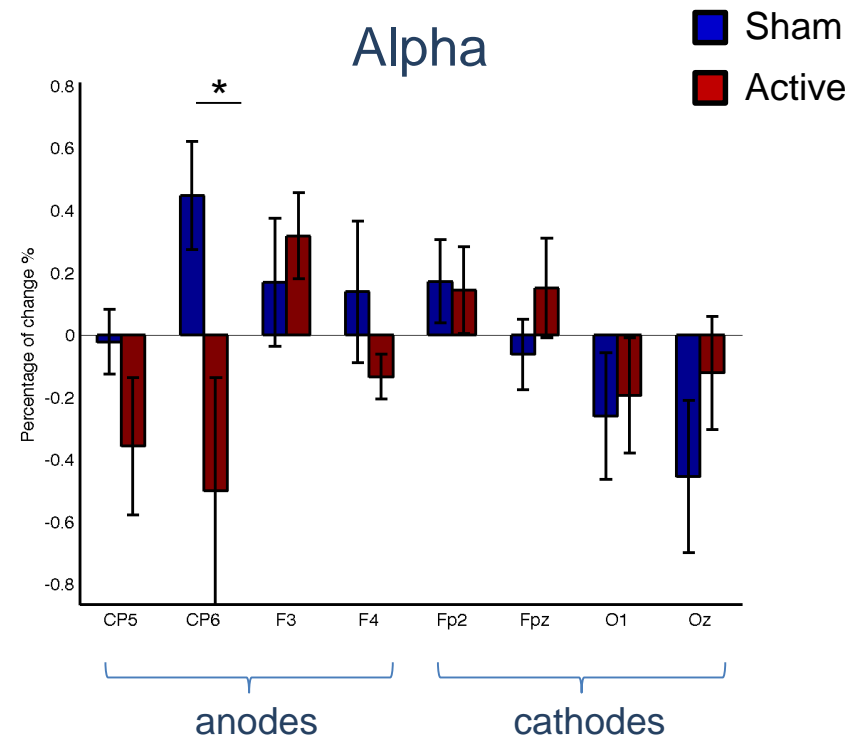
4 anodes and 4 cathodes – 1mA; 20min

Single stimulation – active & sham

CRS-R & EEG

- No side-effects
- 5 responders: all MCS TBI
- Group level: no effect behavioral effects
 - ➔ inter-hemispheric competition?
 - ➔ 1mA per electrodes not enough?

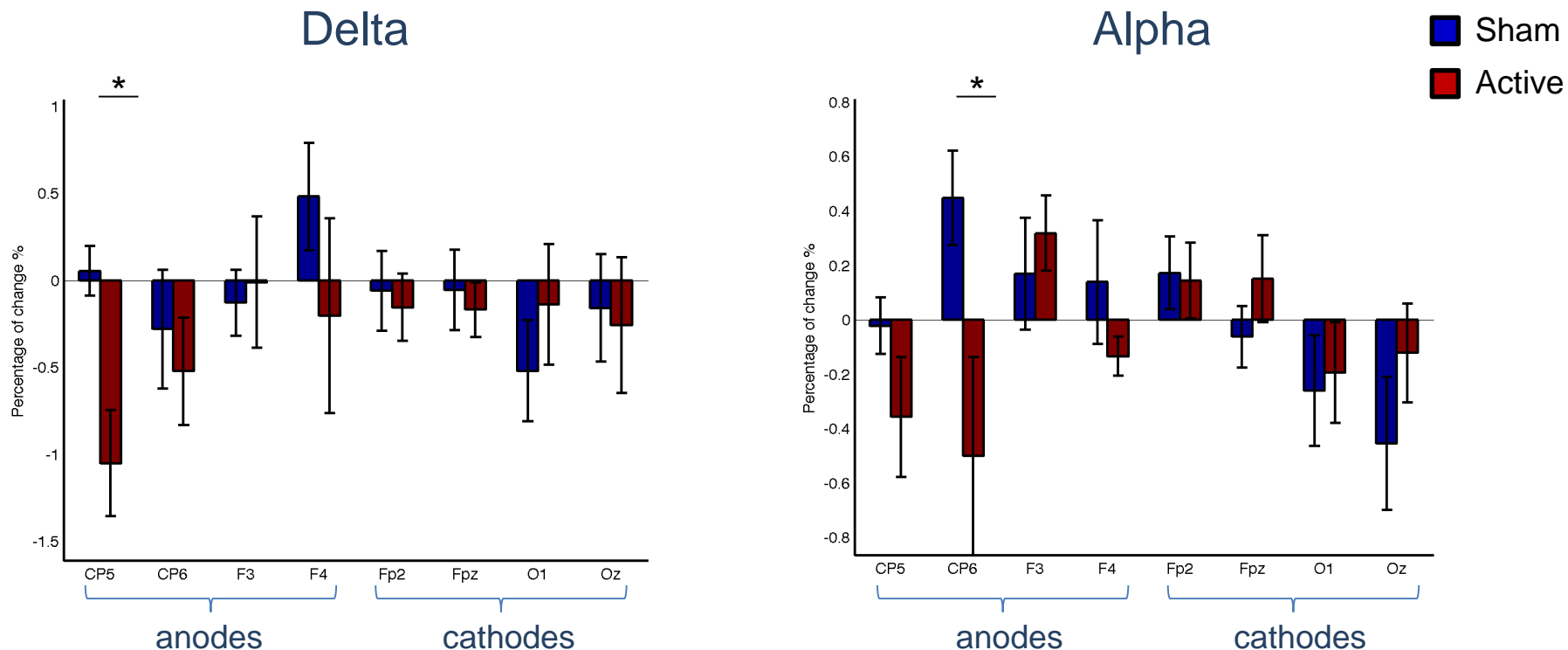
Measure of complexity (LWZ)





Measure of complexity: LZW estimation per band and electrode

Percentage of change = $(\text{Post_LZW} - \text{Pre_LZW}) / \text{Pre_LZW} * 100 \%$



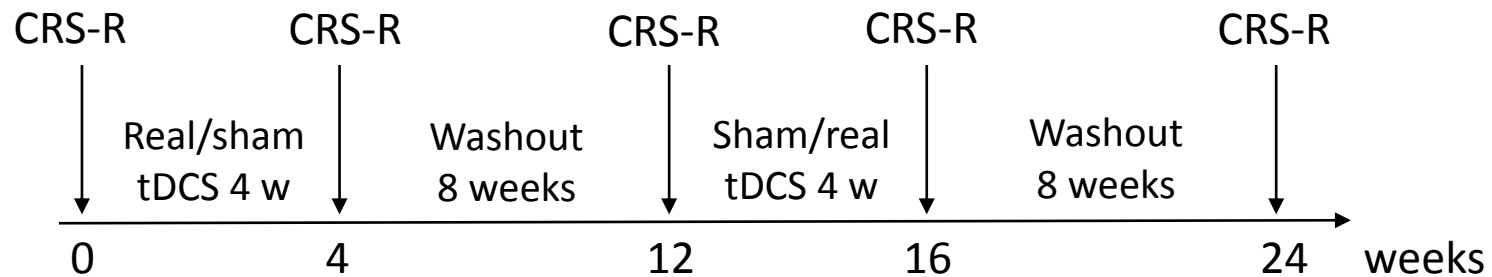
LZW significantly decreases with tDCS under anodes, indicating that **complexity decreases with tDCS** in these bands
→ more structure in the data following tDCS?



Clinical translation



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





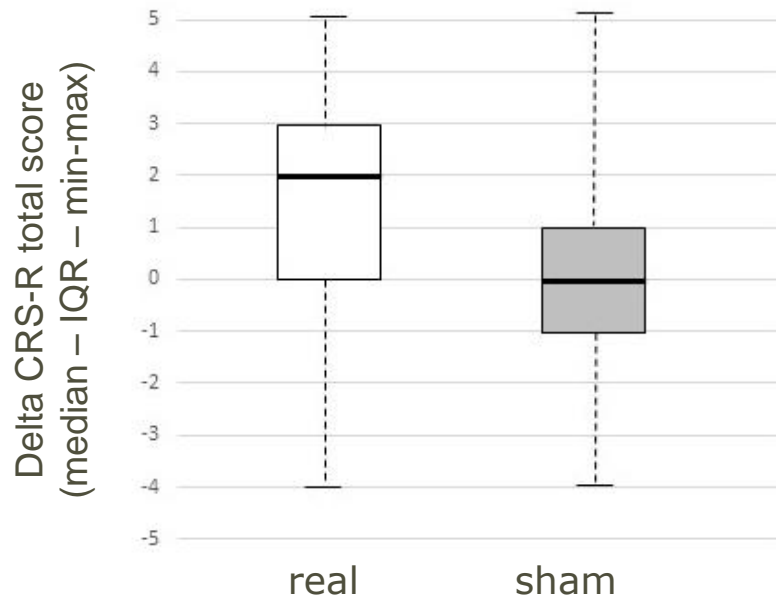
Clinical translation

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

Compliance: $93 \pm 14\%$

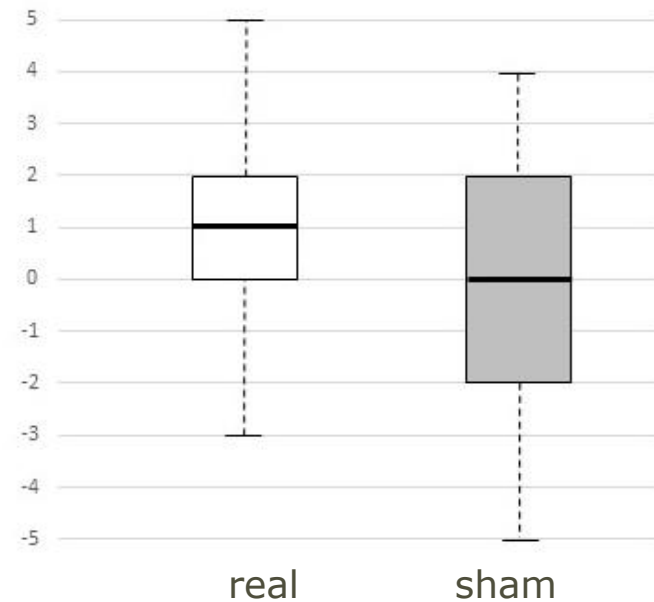
Post tDCS

$p=0.052$ – $d=0.46$



8 weeks follow-up

ns



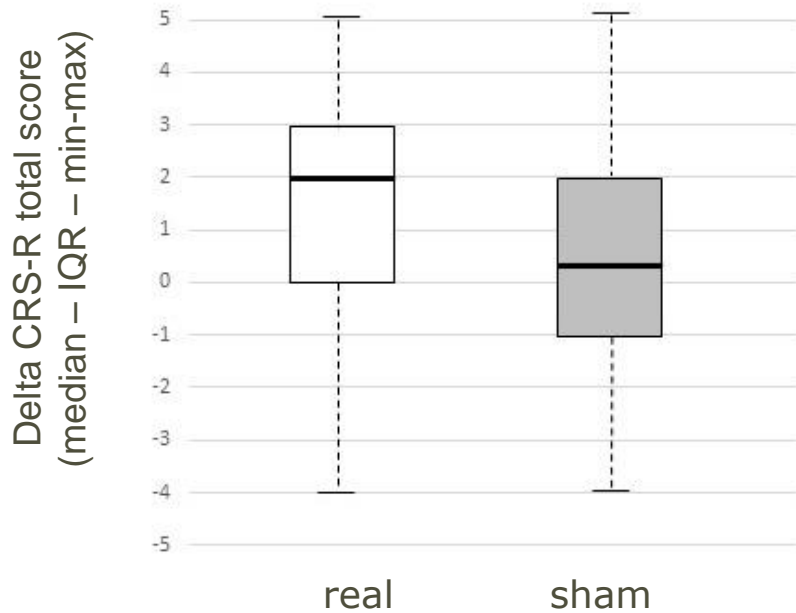


Clinical translation

22 patients received at least 80% of tDCS sessions

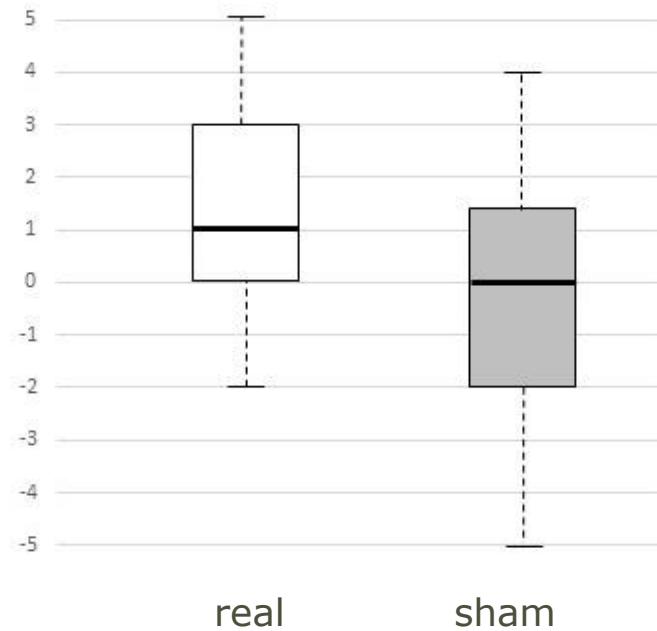
Post tDCS

$p=0.042$ – $d=0.56$



8 weeks follow-up

$p=0.059$



➔ Relevant clinical improvement: >80% tDCS sessions

tDCS to unveil covert consciousness



Assessments :	E1	E2	E3	E5	E6	E7	E8	BL tDCS	Post tDCS	BL sham	Post sham
AUDITORY FUNCTION SCALE											
4 - Consistent Movement to Command*											
3 - Reproducible Movement to Command*									X		
2 - Localization to Sound											
1 - Auditory Startle		X	X	X				X		X	X
0 - None	X				X	X	X				
VISUAL FUNCTION SCALE											
5 - Object Recognition*											
4 - Object Localization: Reaching*											
3 - Pursuit Eye Movements*											
2 - Fixation*											
1 - Visual Startle	X	X	X	X	X		X	X	X	X	X
0 - None						X					
MOTOR FUNCTION SCALE											
6 - Functional Object Use											
5 - Automatic Motor Response*											
4 - Object Manipulation*											
3 - Localization to Noxious Stimulation*				X							
2 - Flexion Withdrawal	X		X		X	X	X		X	X	
1 - Abnormal Posturing		X						X			X
0 - None/Flaccid											
OROMOTOR/VERBAL FUNCTION SCALE											
3 - Intelligible Verbalization*											
2 - Vocalization/Oral Movement		X				X		X			
1 - Oral Reflexive Movement	X		X	X			X		X	X	X
0 - None					X						
COMMUNICATION SCALE											
2 - Functional: Accurate											
1 - Non-Functional: Intentional*											
0 - None	X	X	X	X	X	X	X	X	X	X	X
AROUSAL SCALE											
2 - Eye Opening w/o Stimulation							X		X		X
1 - Eye Opening with Stimulation	X	X	X	X	X	X		X		X	
0 - Unarousable											
TOTAL SCORE	5	6	6	7	4	5	6	6	9	6	6

