Novel treatments for disorders of consciousness ?

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Motor disorder: spasticity

➔ Exageration of myotatic reflex leading to an unvoluntary muscle contraction after muscle stretching or a permanant muscle contraction

Aggravating factors: Velocity of stretching
Fatigue and stress

Side effects: Muscle retraction (↘ sarcomeres)
Irreversible stiffness of joints
Vicious positions and pain

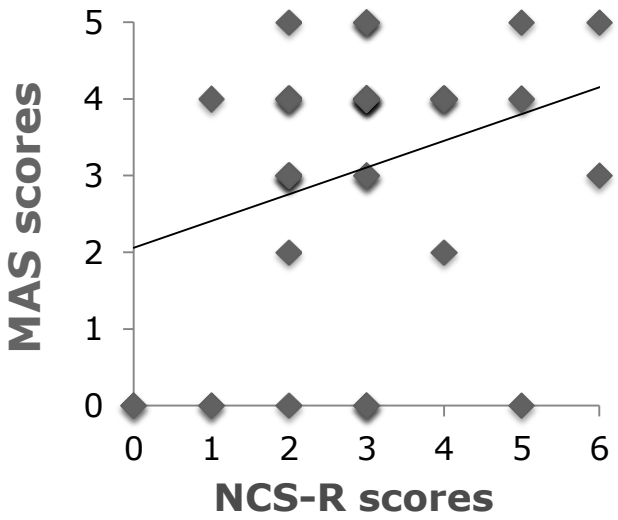
Physiopathology is complicated
No clear treatment guidelines yet

Thibaut et al, *Brain Injuy,* 2013

Spasticity in DOC

Assess spasticity (MAS*) in VS/UWS and MCS (n= 65)

- **88%** (n=57) showed spasticity
  60% (n=39) had severe spasticity (MAS≥3)
- **Time since insult**: positively correlated with MAS scores
- **Pain** (*Nociception Coma Scale Revised*) : positive correlation



* MAS=Modified Ashworth Scale

Thibaut et al, *submitted*

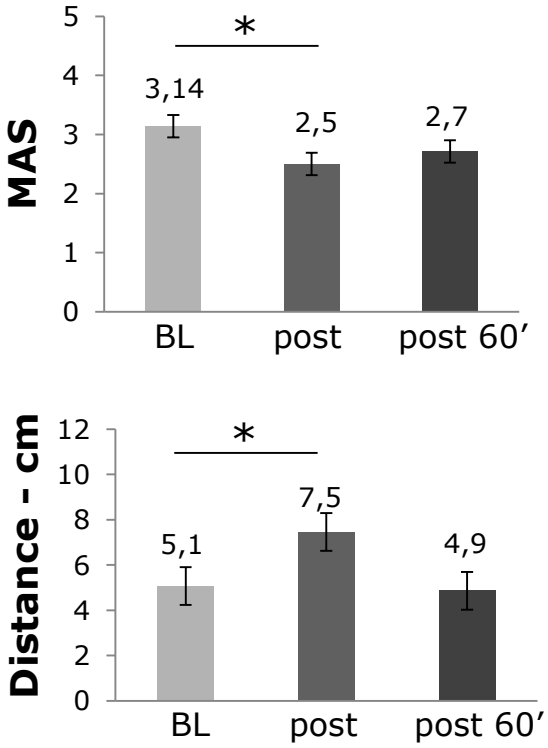
Soft splints

- **AIM:** Test the efficacy of soft splints on spastic upper limb to reduce spasticity in chronic VS/UWS & MCS
- **Avantages:**
  - Easy to apply
  - Patient can be alone
  - Soft and confortable
  - Several hours/day

Thibaut et al, *submitted*

Soft splints

- **AIM:** Test the efficacy of soft splints on spastic upper limb to reduce spasticity in chronic VS/UWS & MCS (n=17)
- **Avantages:**
  - Easy to apply
  - Patient can be alone
  - Soft and confortable
  - Several hours/day
- **Clinical benefits:**
  - Spasticity decrease on fingers flexors
  - Increase of hand opening

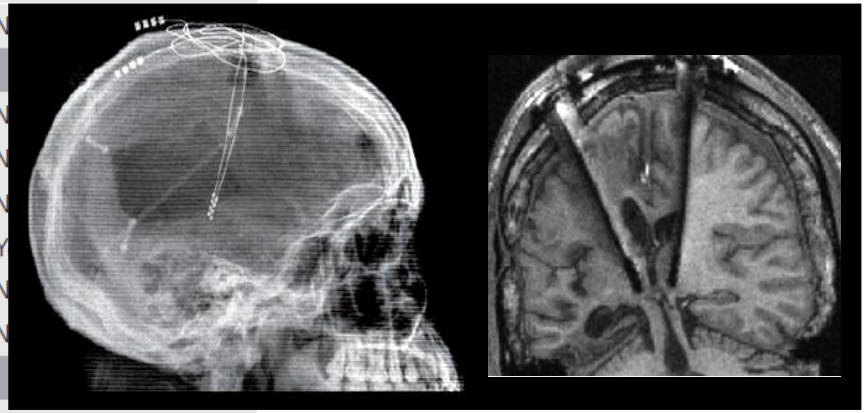


Thibaut et al, *submitted*

Current treatments

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	Positive
	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	N	
Nonbenzodiazepine sedative					
Zolpidem	Cohen (2008)	1 anoxic	Lethargic	N	
	Shames (2008)	1 anoxic	MCS	N	
	Singh (2008)	1 TBI	MCS	N	
	Brefel-Courbon (2007)	1 hypoxic	Akinetic mutism	Y	
	Clauss (2006)	2 TBI, 1 anoxic	VS	N	
	Clauss (2000)	1 TBI	Semi-comatose	N	
GABA agonist					
Baclofen	Sarà (2007)	1 non-TBI	VS	No	Positive

Deep Brain Stimulation (DBS) Intralaminar nuclei stimulation induces "recovery" from MCS



Adapted from Demertzi et al, *Expert Rev Neurotherapeutics*, 2008
Giacino et al, NEJM, 2012
Schiff et al, Nature, 2007

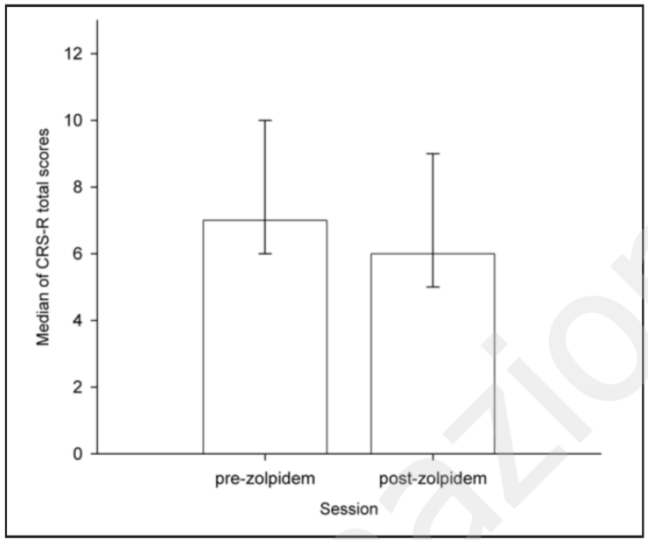
Zolpidem

Effect of Zolpidem in chronic disorders of consciousness: a propective open label study

60 patients (32 MCS, 35±15y, 18 wo, 37 TBI, 4±5.5 y post insult)

Open label study

- 12 patients improved but no diagnostic change
- 1 patient : MCS ➔ EXIT
  Placebo control: no effect anymore
- At the group level: no effect



Thonnard et al., *Functional Neurology*, 2014

Why direct current?

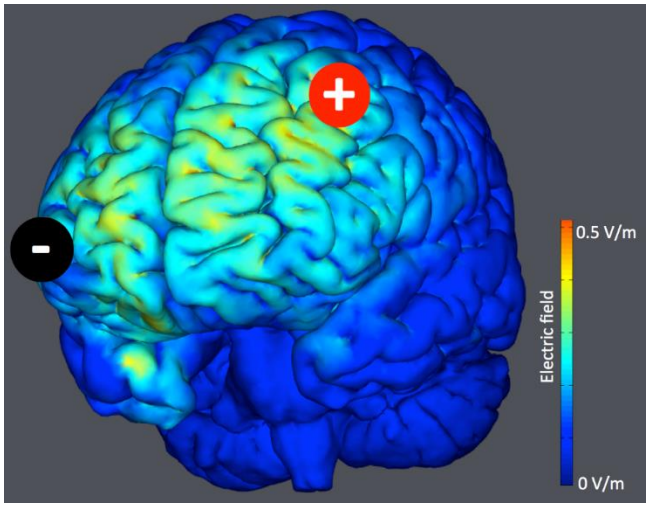
Stimulation	Population	Effects	Authors
Motor cortex	Healthy subjects	Dexterity	Boggio et al. Neurosci Lett, 2006
	Hemiplegic patients	Dexterity and strength	Hummel et al. Lancet, 2006
	Spastic patients	Spasticity & ADL (activity of daily life)	Wu et al., Arch Phys Med Rehabil 2012
Prefrontal cortex	Healthy subjects	Memory	Marshall et al. J Neurosci, 2004
	Alzheimer's patients	Memory	Ferrucci et al. Neurology, 2008
	Stroke patients	Attention	Jo et al. Am J Phys Med Rehabil, 2009
	Aphasic patients	Language	Baker et al. Stroke, 2010

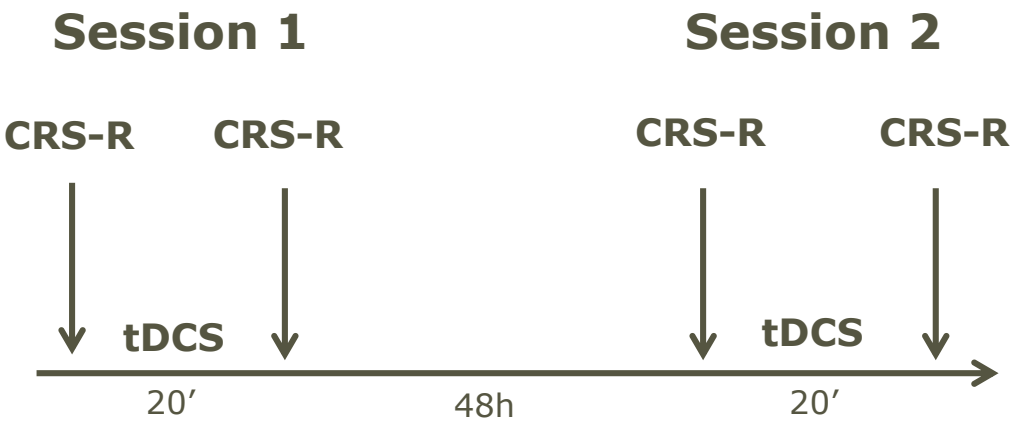
➔ Cheap & easy to use

Thibaut et al, Rev Neurol, 2013

Methods

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

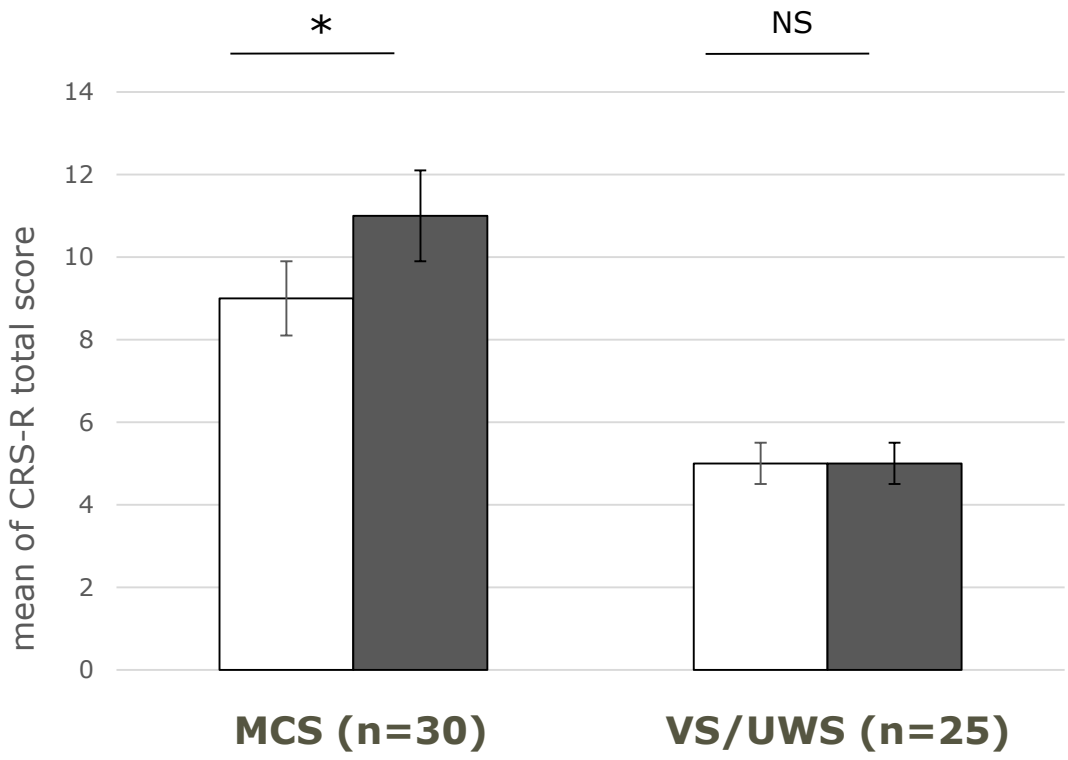




Thibaut et al, *Neurology, 2014*

Results

- 55 patients (16f, 43±18y)
- 25 VS/UWS, 30 MCS
- 25 TBI, 30 NTBI
- 20 subacute, 35 chronic (>3m)



* p<0.001

Thibaut et al, *Neurology, 2014*

Results

15 responders

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

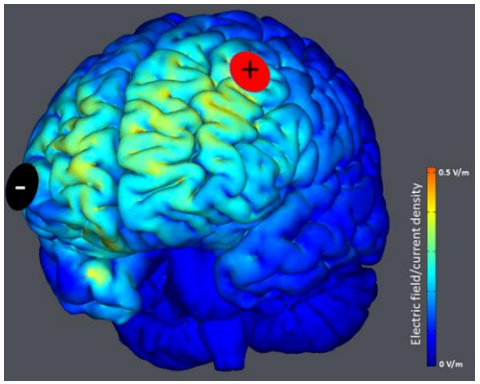
- 2 UWS; acute
- 13 MCS (5>1y post insult) ➔ 43% of MCS

- 2 UWS ➔ MCS (acute)
- 2 MCS ➔ EXIT (acute)

Neurophysiology

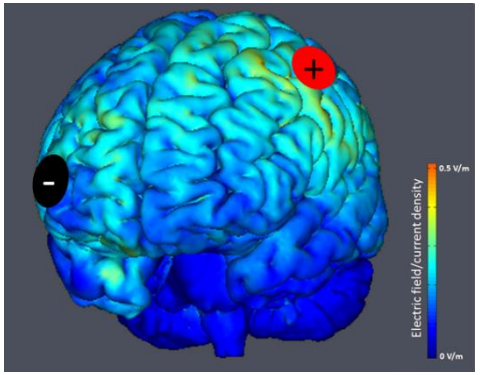
Prefrontal stimulation

- ↗ of DMN connectivity (rsfMRI)
- ↗ of α rhythm (EEG)



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)

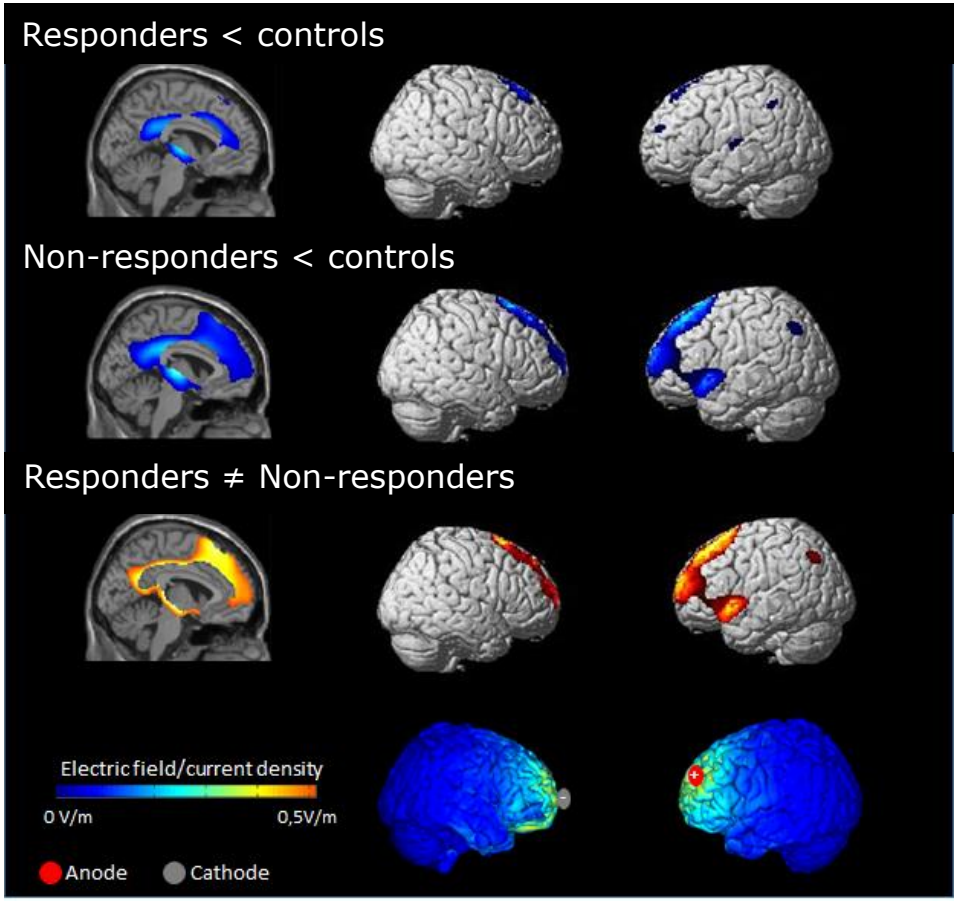


Keeser et al., J Neurosci, 2011
Lang et al., Eur J Neurosci, 2005
Polania, Nitsche and Paulus, HBM, 2010

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 compare to non responders



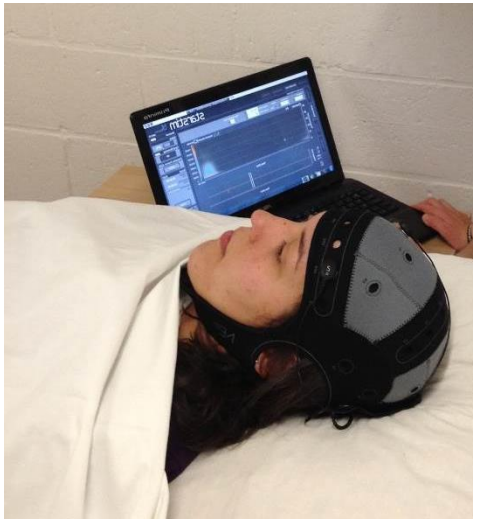
FWE corrected

Thibaut et al, *in prep*

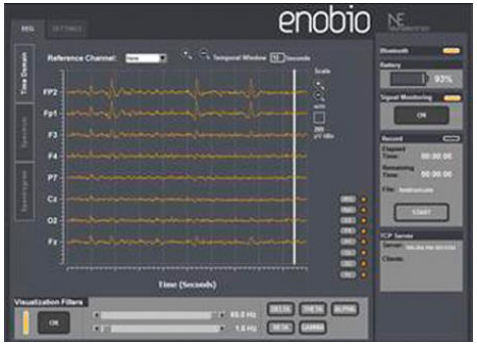
Motor tDCS

88% of patients with DOC are spastic
Spasticity (MAS) correlates with NCS-r
(Thibaut et al, *submitted)*

➔How to decrease spasticity?



- Cathodal tDCS: C3/C4
- 1 mA – 20 minutes
- 2 sessions (real/sham)
- MAS and CRS-R before and after
- tDCS coupled with 8 electrodes EEG
- Record cortical activity before and after

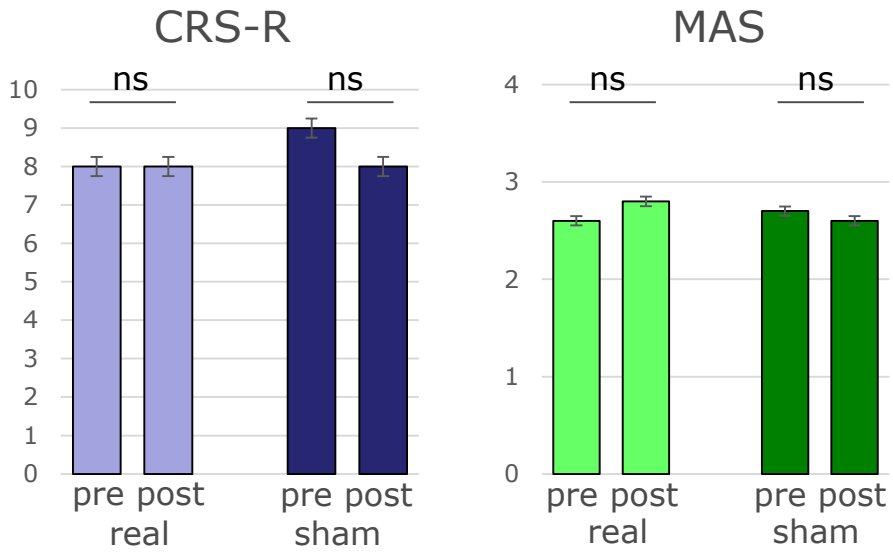


Motor tDCS

15 chronic patients (7 MCS, 40±15y, 8wo, 7 TBI)

Results

➔ no significant differences
= Spasticity (MAS)
= CRS-R
EEG: analyses in progress

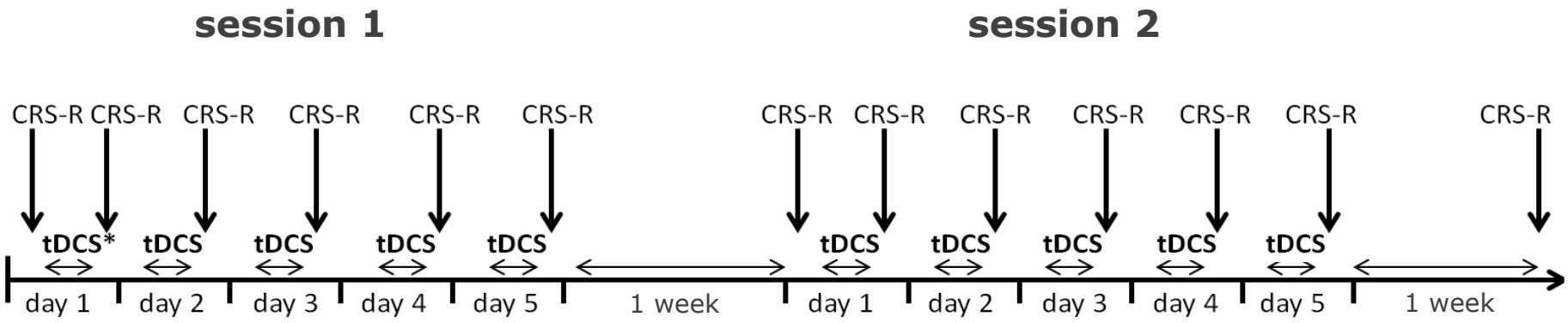


Cathodal tDCS decrease motor response?
Chronic patients with fixed joints?

Repeated tDCS

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

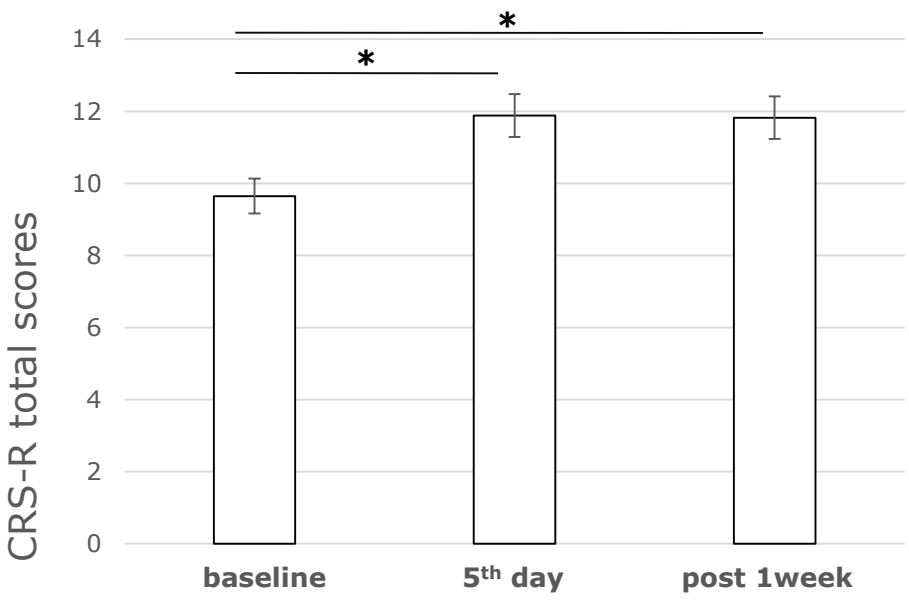
Daily stimulations (5days) (Fregni et al., *Pain*, 2006)
Improvement and extension of benefits
Randomized sham controlled double blind study

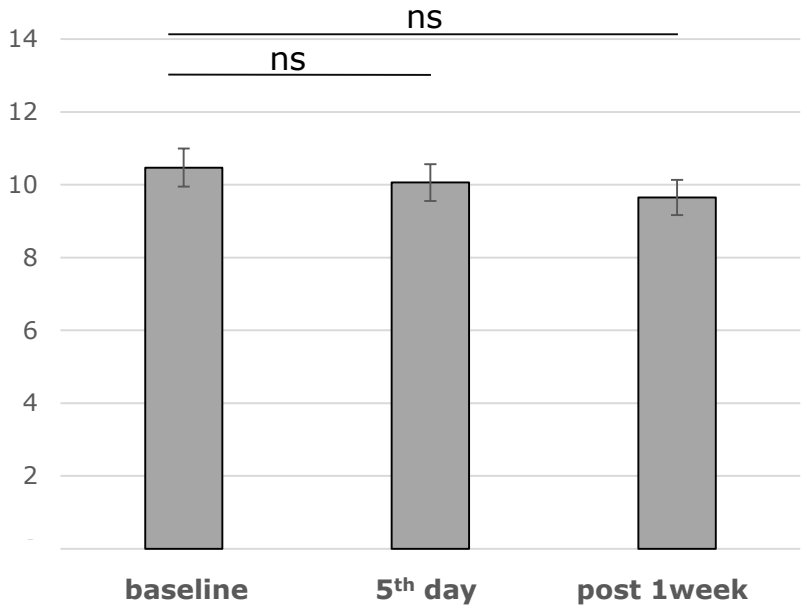


*tDCS = 20minutes

Repeated tDCS

Chronic MCS – N=21 (4 excluded)





➔ 10 responders (out of 17 patients)

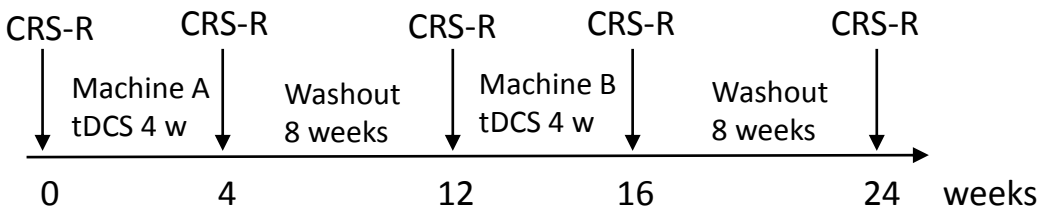
* <0.025

rtDCS in chronic patients

Repeated tDCS in chronic patients at home or nursing home (multicentric study)

Protocol:

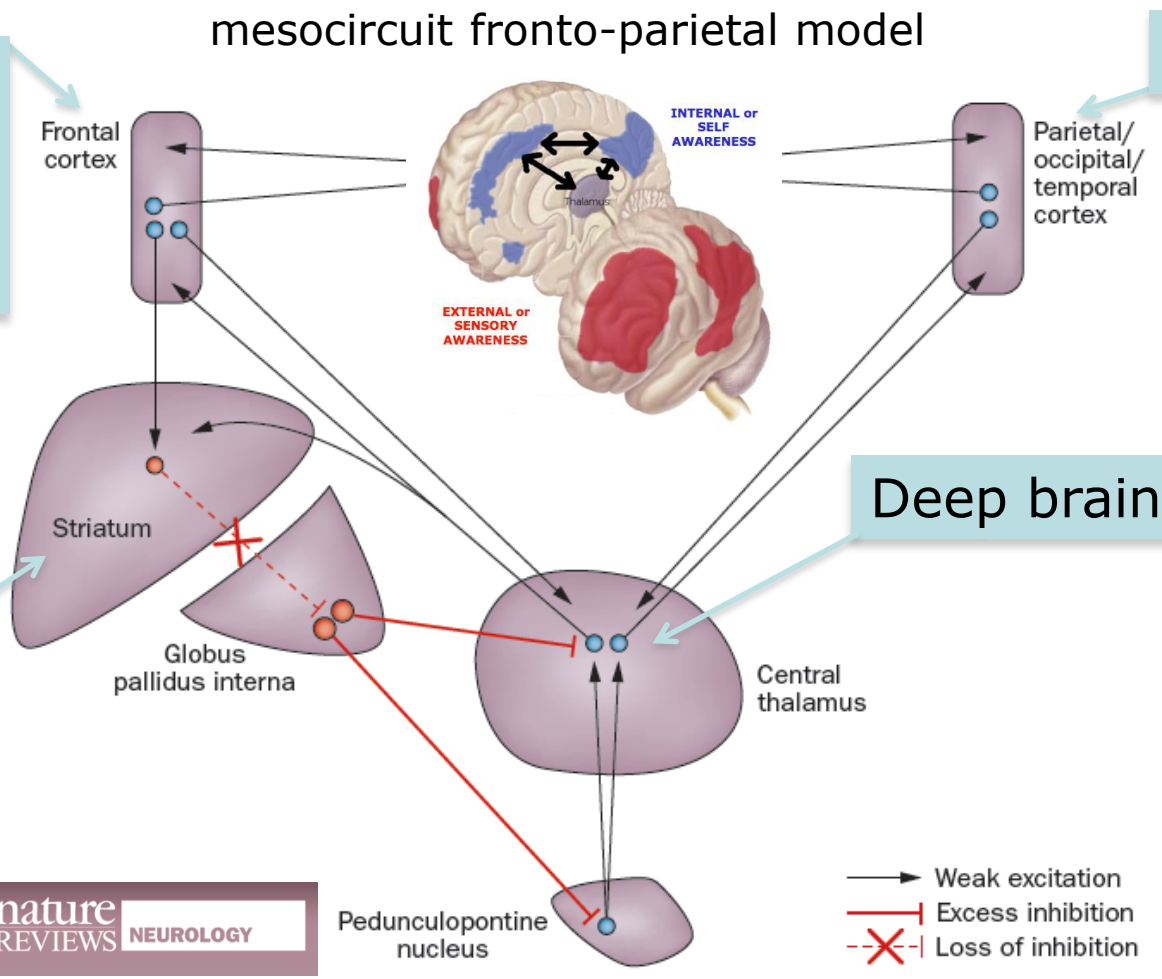
- tDCS over the prefrontal dorsolateral cortex, 2 mA, 20 min
- 5 days per week during 4 weeks (2 tDCS sessions – real & sham)
- Stimulations made by the family (video)
- Assessment: CRS-R before – after 4 weeks – two month later
- Double blind randomized study (2 months of washout)
- Chronic MCS patients (> 1y post insult) at home/nursing home



Consciousness ≈ connectivity

transcranial Direct Current Stimulation

amantadine

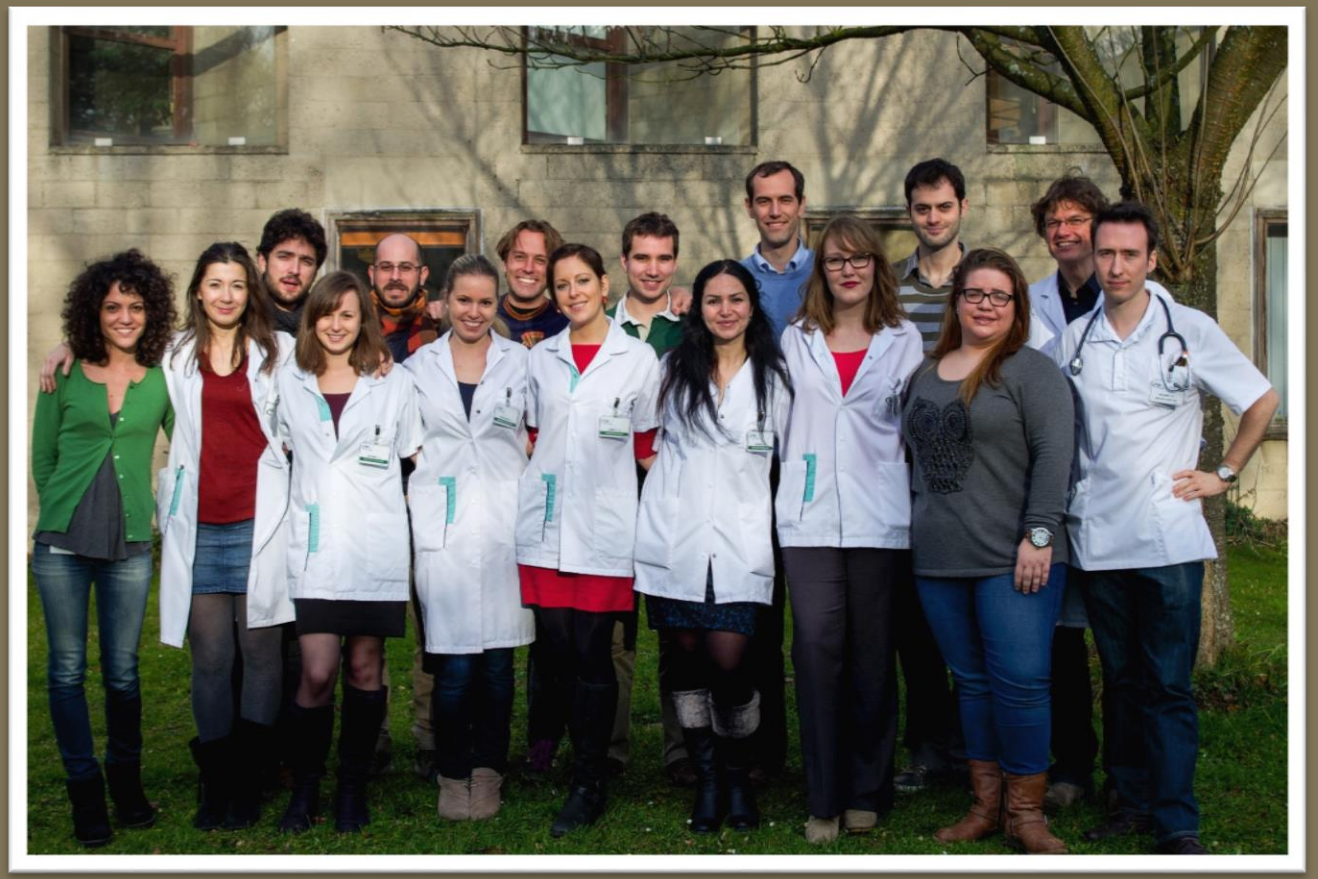


Deep brain stimulation

zolpidem

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

THANK YOU



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