Patients with disorders of consciousness: how to treat them?

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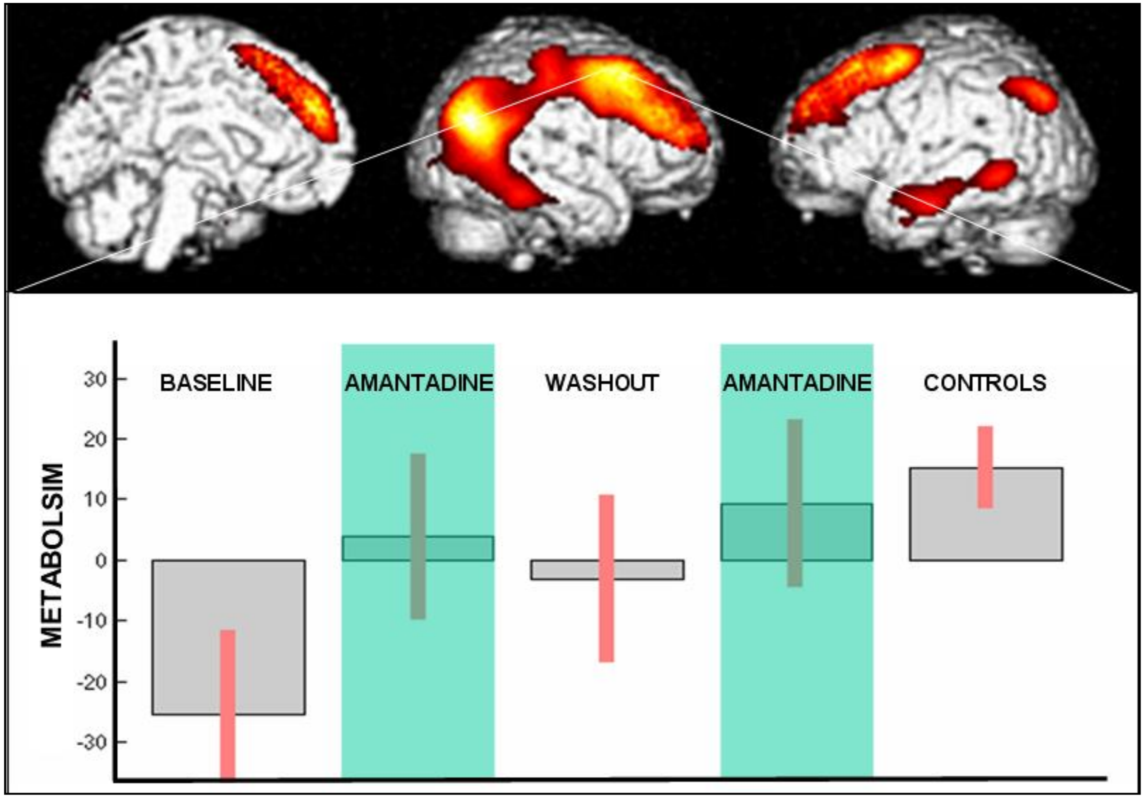
Pharmacological treatments

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	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

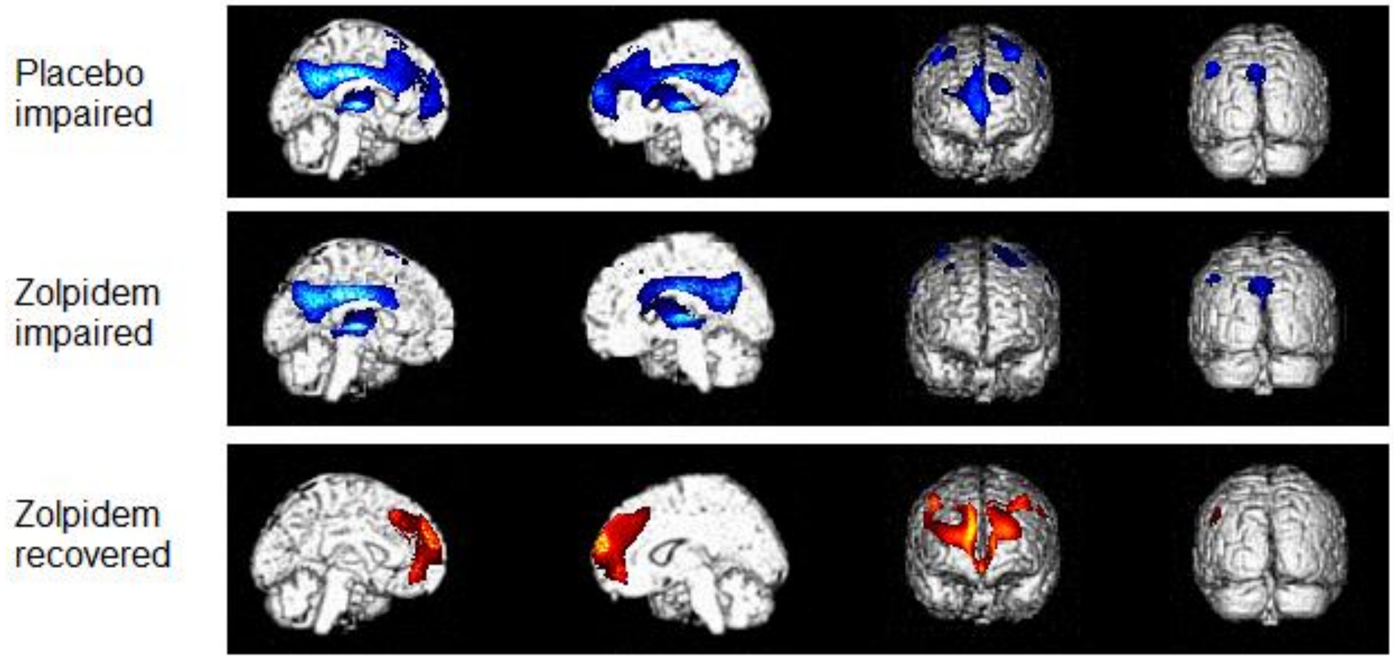
Dopaminergic agent (Parkinson)



Zolpidem

Sedative-hypnotic agent (insomnia)

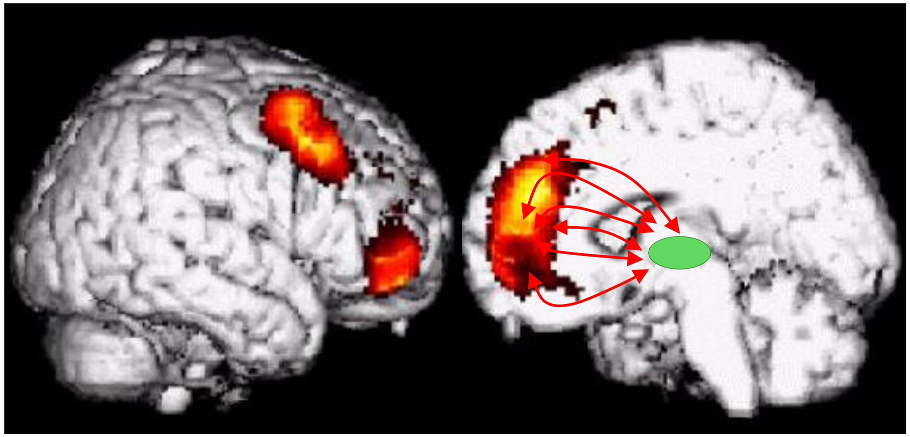
Indirect agonist of $GABA_A$ receptors



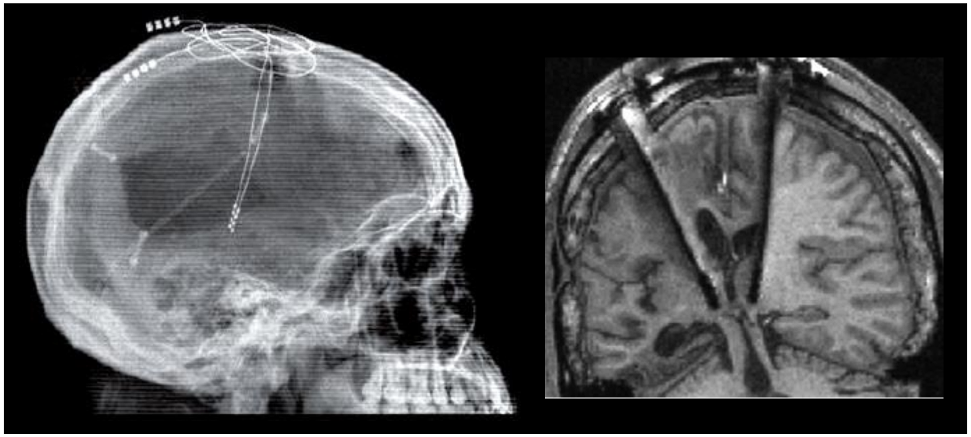
Chatelle & Thibaut, et al., 2014

Deep brain stimulation

Recovery of consciousness = recovery of thalamo-cortical (prefrontal) connectivity



Intralaminar nuclei stimulation induces "recovery" from minimally responsive state



Laureys et al, *Lancet,* 2000
Schiff et al, *Nature*, 2007

Transcranial direct current stimulation

- Amantadine: risk of epileptic seizure
- Zolpidem: rare cases
- Deep brain stimulation: invasive surgery

➔ new non-invasive and non-pharmacological technique

Transcranial direct current stimulation (tDCS)

Anode : ↗ excitability

Cathode: ↘ excitability

Transcranial direct current stimulation

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

tDCS presumed mode of action

Short term effects (Nitsche et al., J Physiol 2000)

Modification of neuronal excitability (action potential)

Long term effects (Nitsche et al., Neuroscientist 2010)

Action on opening of ion channels (Na^{+}, Ca^{2+})

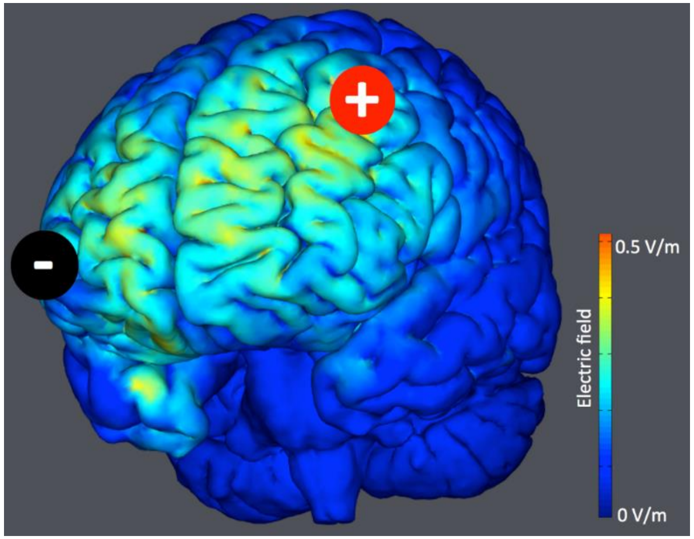
Increase NMDA receptors excitability

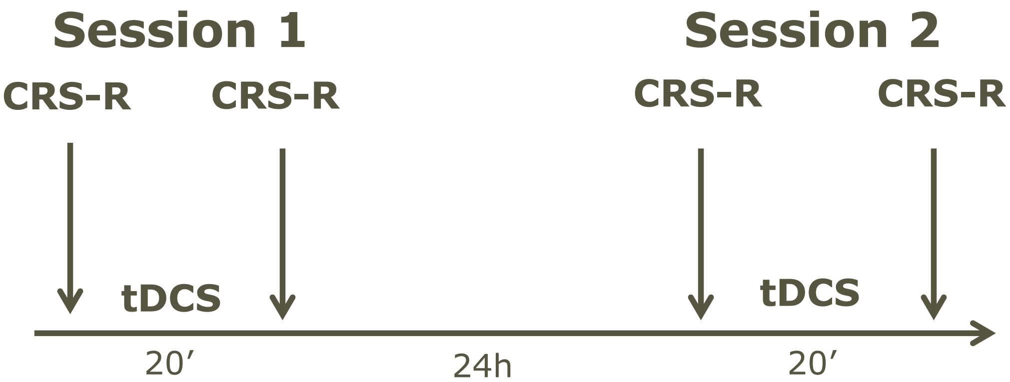
⇨ improve neuronal excitability & plasticity?

Thibaut et al., Rev Neurol, 2013

Pilot study – single tDCS

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

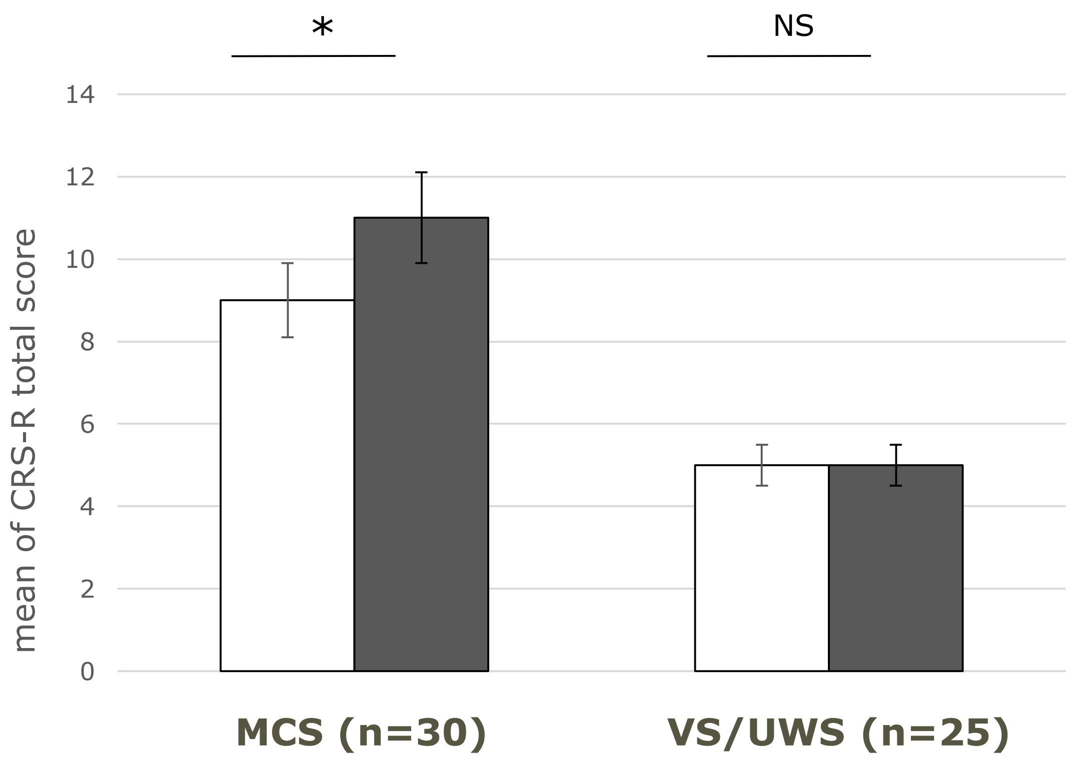




Thibaut et al, Neurology, 2014

Results – single tDCS

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



* p<0.001

Thibaut et al, Neurology, 2014

Results - single tDCS

15 responders

Sign of consciousness after tDCS and not before tDCS or before and after sham

- 2 UWS; acute
- 13 MCS (5>1y post insult)

3 MCS became EMCS
2 UWS became MCS

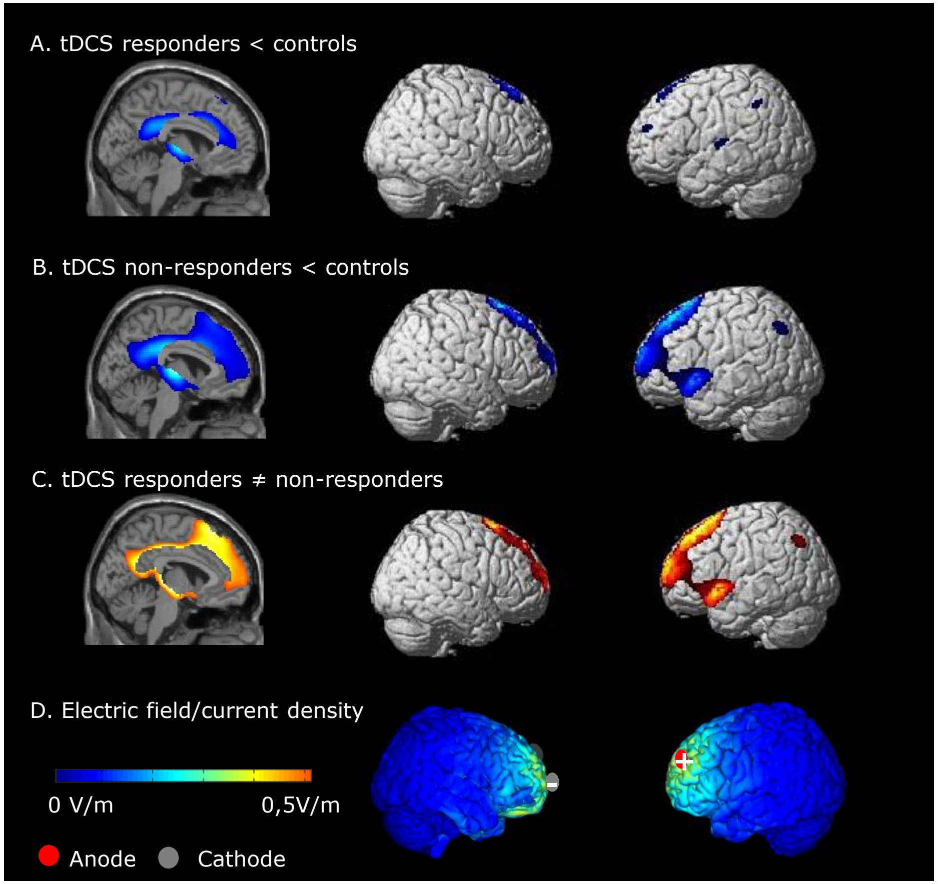
Thibaut et al, Neurology, 2014

Responders vs Non-responders : PET

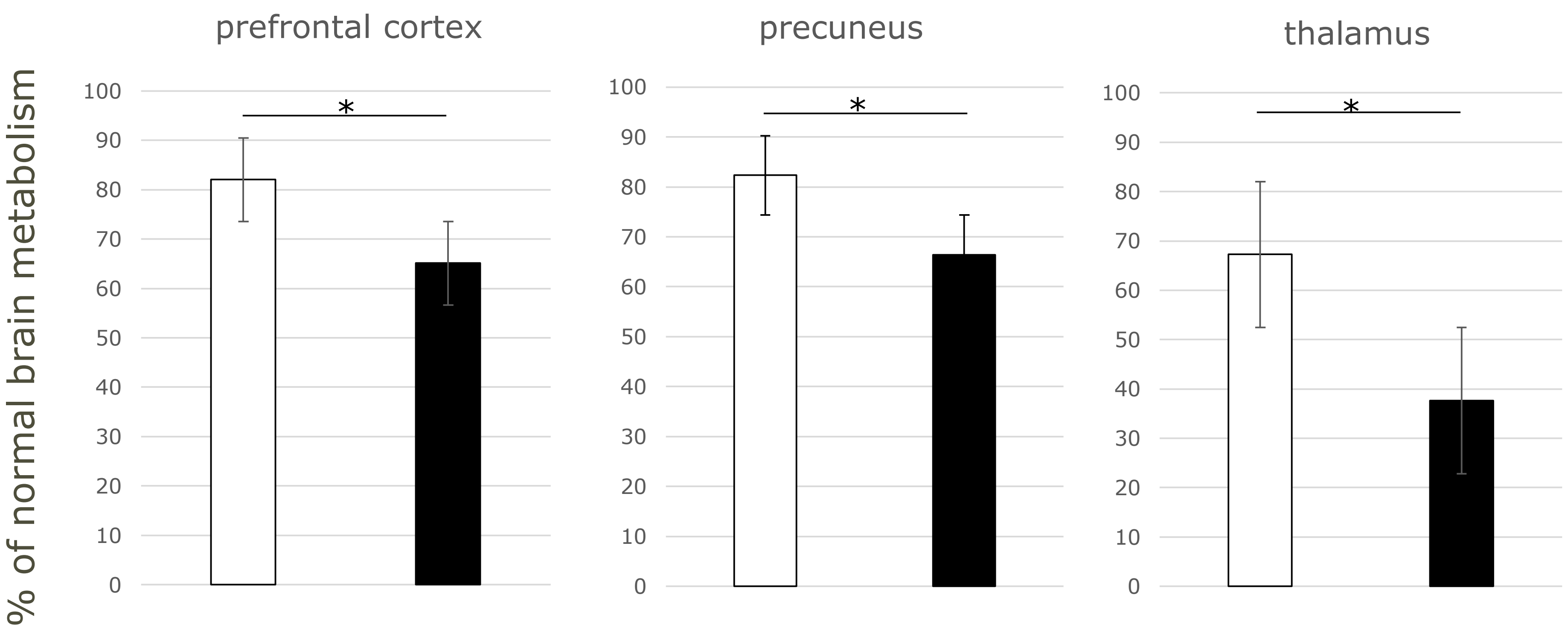
Responders (n=8) vs non-responders (n=13)

Less hypometabolism

1. Stimulated area (left prefrontal cortex)
2. Long distance cortical area (precuneus)
3. Long distance sub-cortical area (thalamus)



Responders vs Non-responders : PET



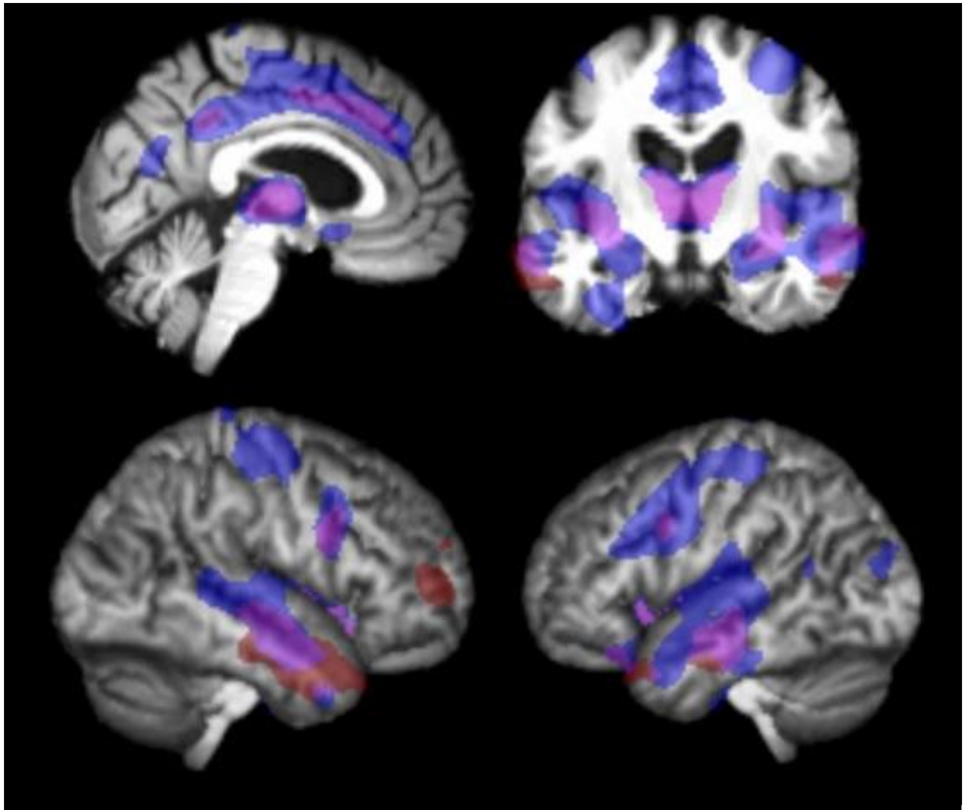
Thibaut & Di Perri et al., submitted

Responders vs Non-responders : VBM

Responders (n=8) vs non-responders (n=13)

Less atrophy in:

1. Stimulated area (left prefrontal cortex)
2. Midline (mesiofrontal/ACC, PCC/precuneus)
3. Temporo-parietal cortex
4. Thalamus



Red: atrophy in responders
Blue: atrophy in non-responders
Pink: overlapping

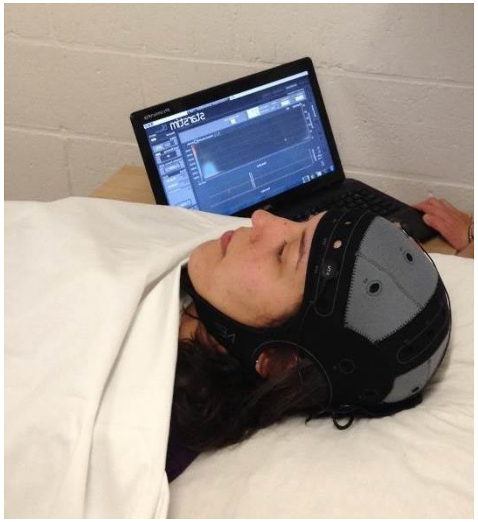
Thibaut & Di Perri et al., submitted

Motor tDCS

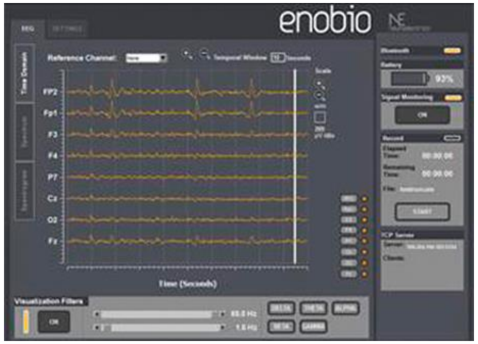
89% of patients with DOC are spastic
Spasticity (MAS) correlates with NCS-R
(Thibaut et al, *in press)*

➔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



NE
neuroelectrics ®

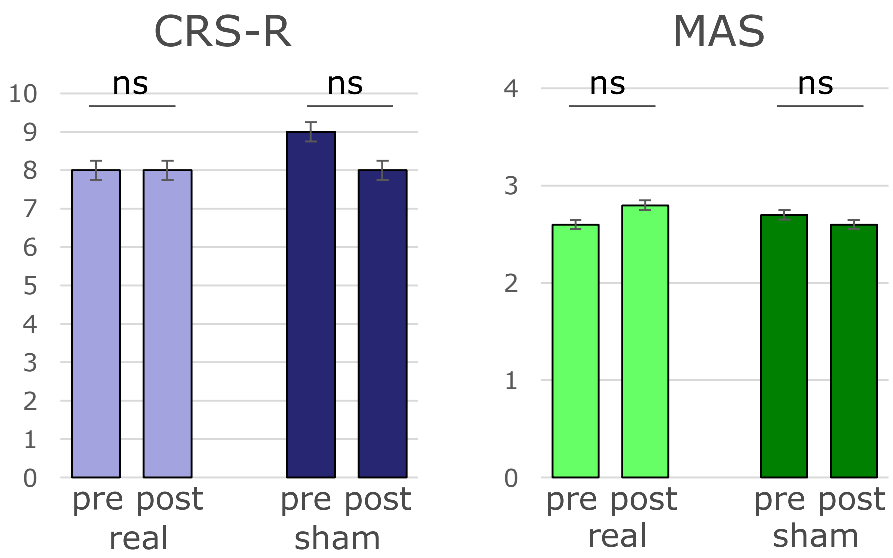


Motor tDCS

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

Results
Group level : no ≠
Subject level: 1 patient ↘ MAS

EEG: 1 responder : ↘ beta

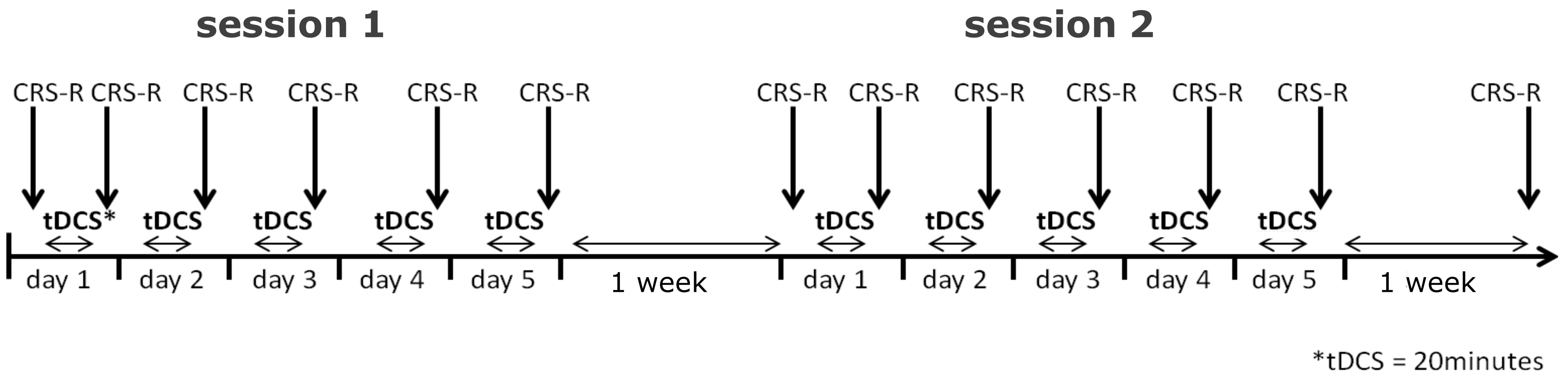


Cathodal tDCS decrease motor response?
Chronic patients with fixed joints?

Repeated tDCS

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

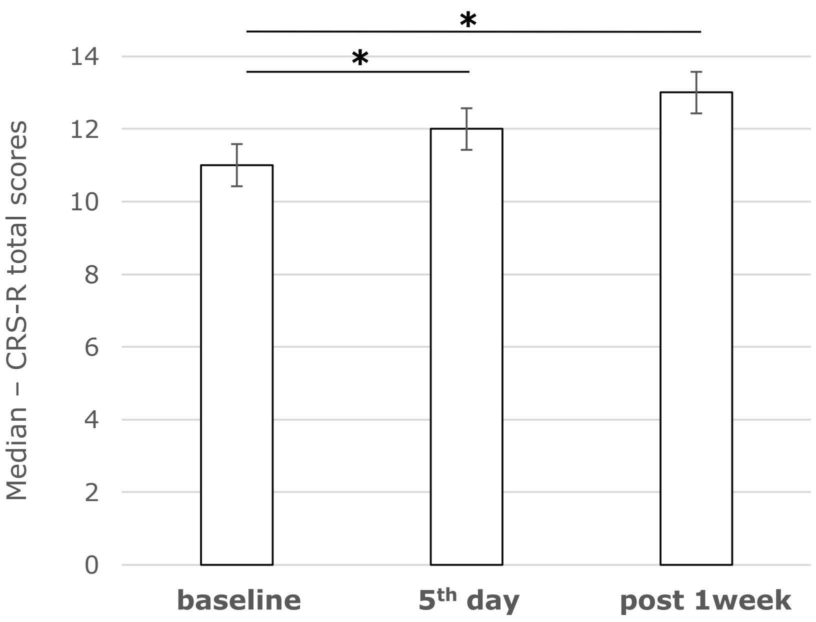
Daily stimulations (5days) (Antal et al., J Pain Symptom Manage 2010)
Improvement and extension of benefits
Randomised sham controlled double blind study

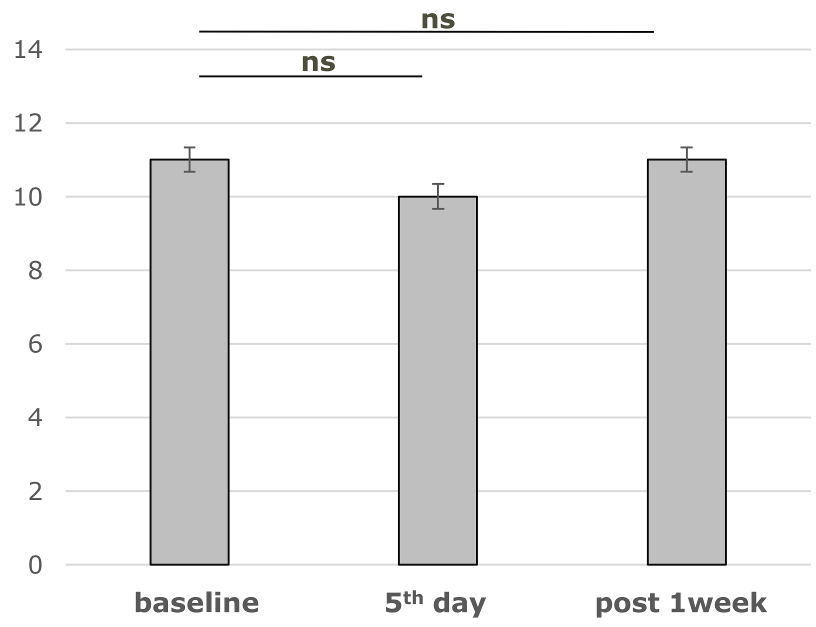


In prep

Repeated tDCS : results

Chronic MCS – N=24 (4 excluded)
(age: 47±16 years; time: 78±95 months; 12 TBI, 8 non-TBI)

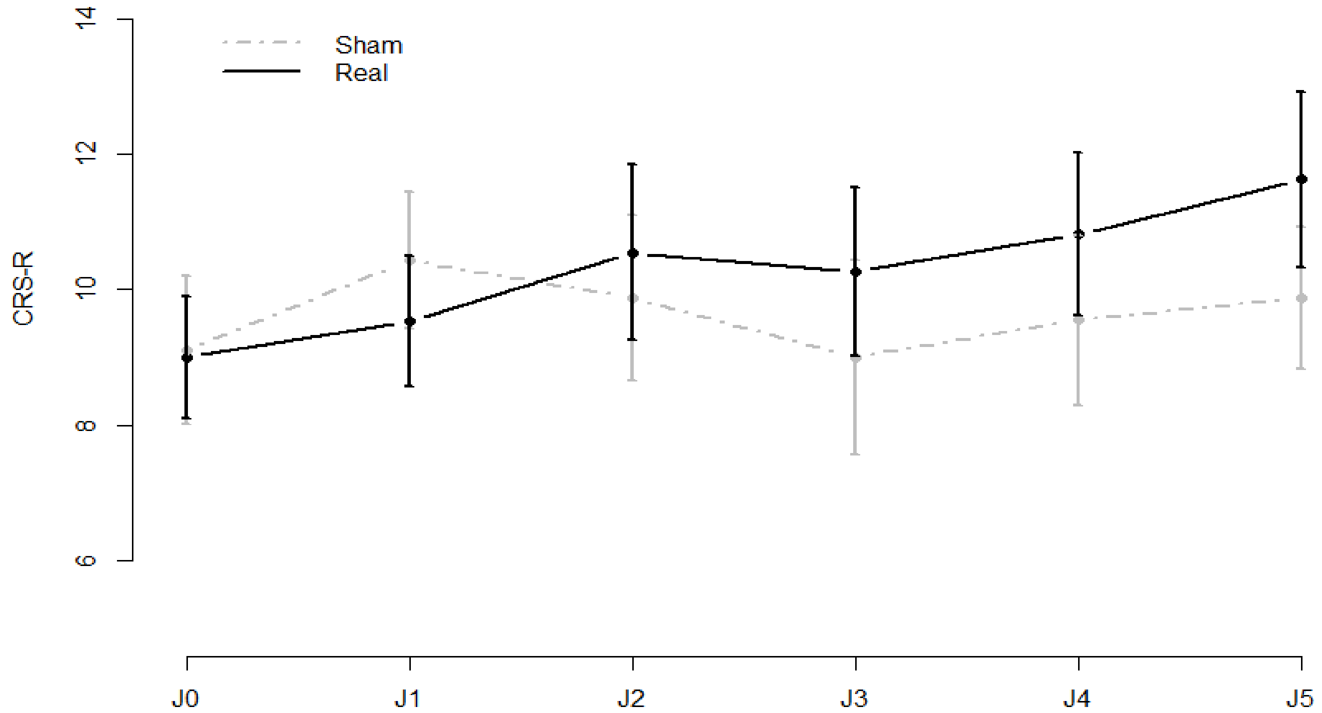




* $p \leq 0.05$

Repeated tDCS : results

- ➔ 50% responders (10/20)
  - ➔ 5 patients responded after 1 tDCS
  - ➔ 5 patients responded after 2, 3 or 4 tDCS

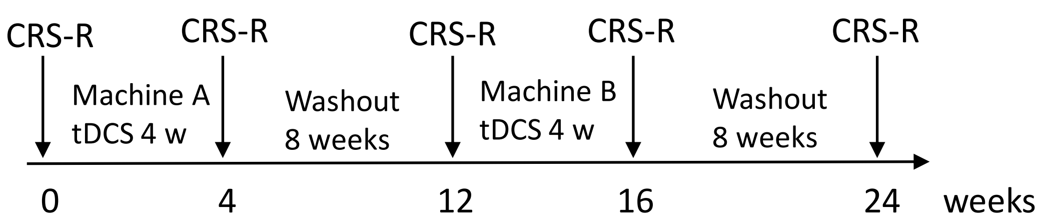


rtDCS in chronic patients

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



Thank you!

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