What about treatments for patients with disorder of consciousness

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September 18, 2013

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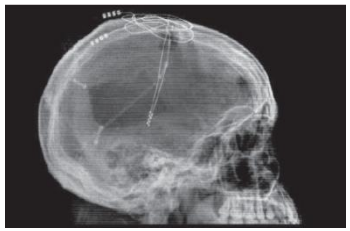
Treatment in DOC

1. Curative

- Cognitive functions
- Motility

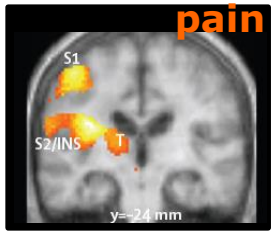
1. Pharmacological treatment
2. Deep brain stimulation
3. Transcranial direct current stimulation (tDCS)



2. Palliative

Decrease side effects & improve comfort

4. Pain
5. Spasticity



Pharmacological treatments

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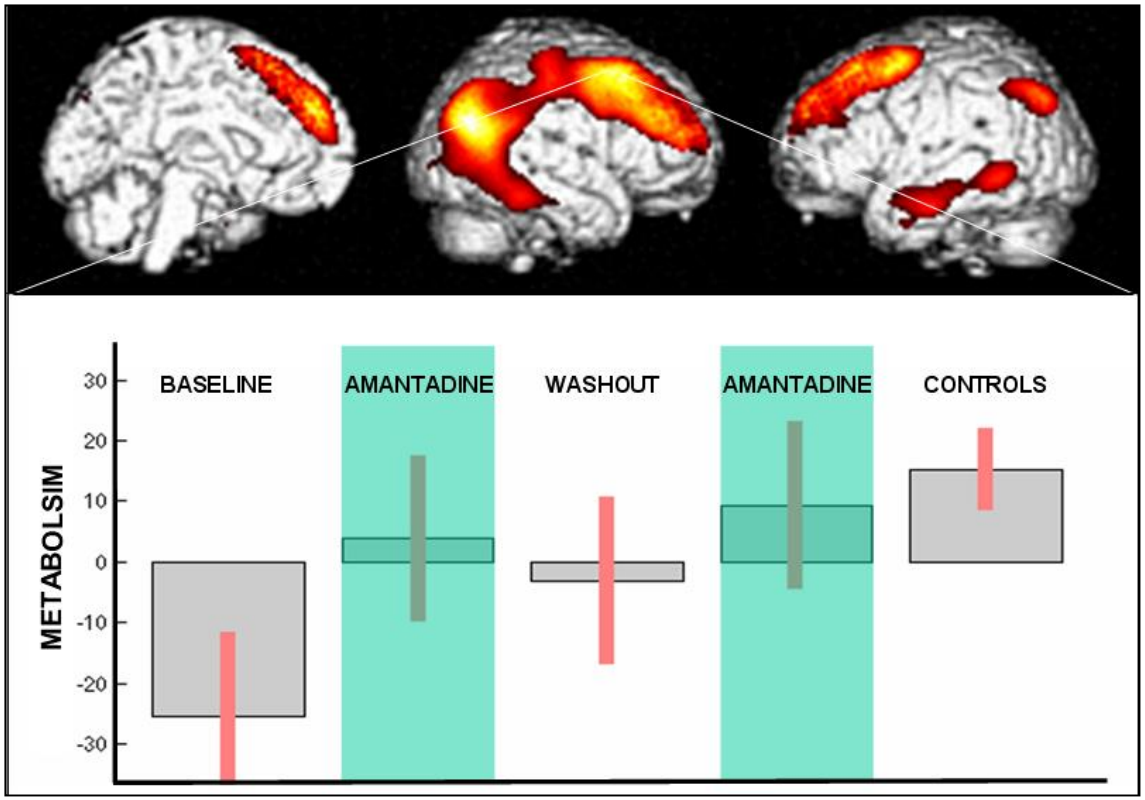
Pharmacological treatments

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)

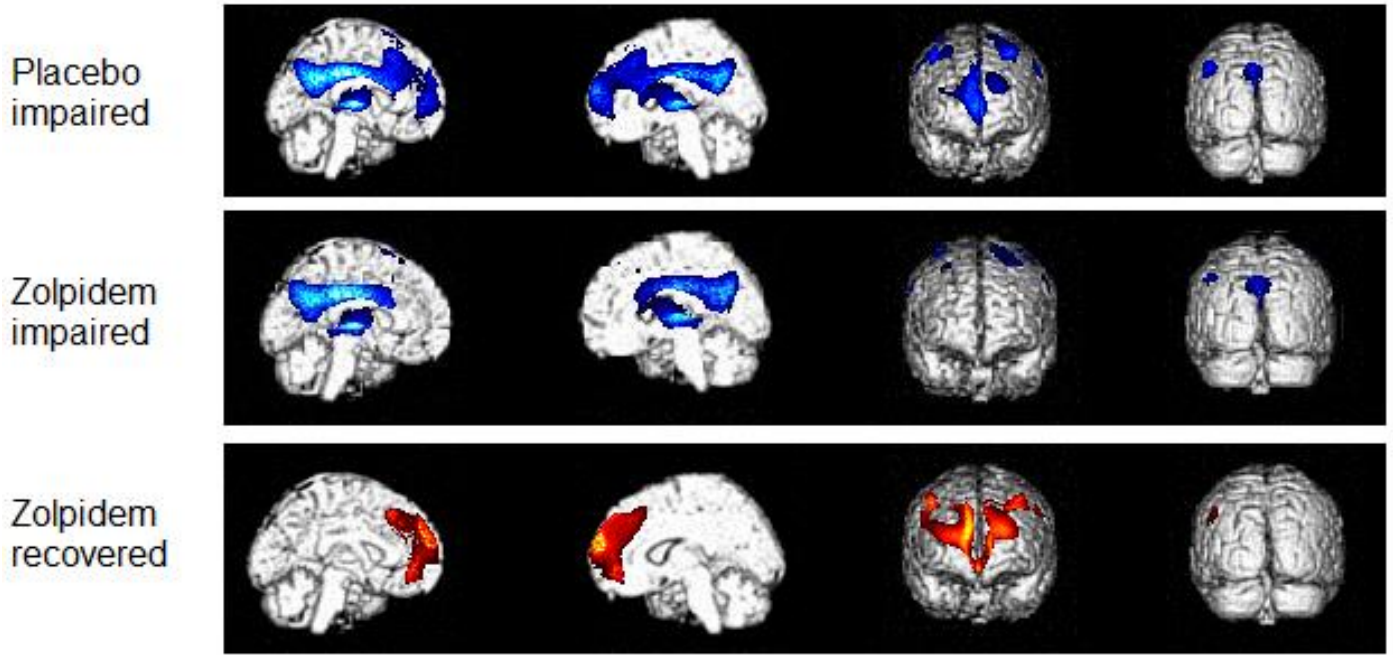


Schnakers et al, *JNNP,* 2008

Zolpidem

Sedative-hypnotic agent (insomnia)

Indirect agonist of $GABA_A$ receptors



Chatelle & Thibaut, et al., *submitted*

Deep brain stimulation

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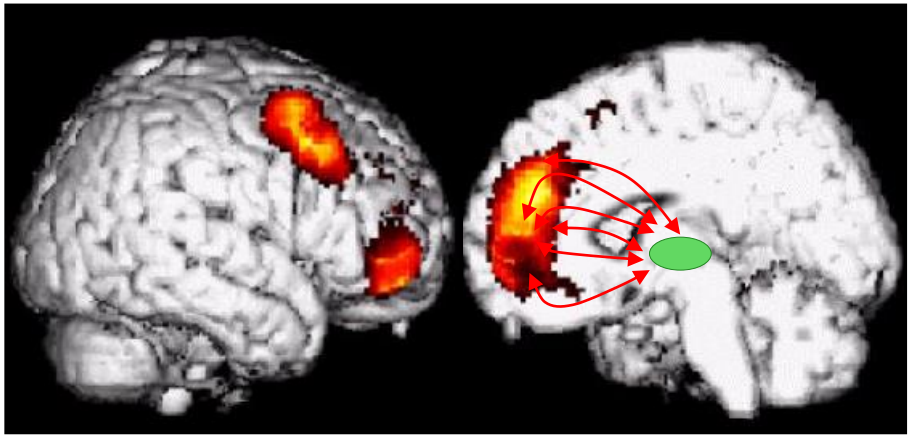
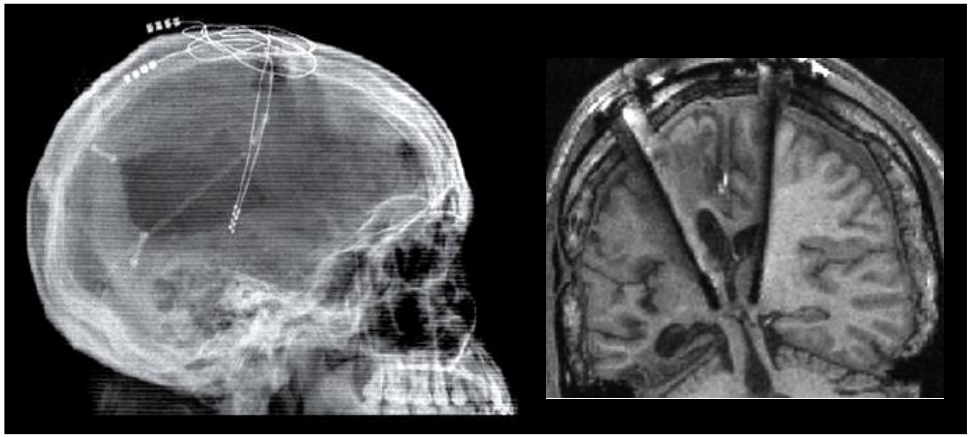
Curative treatment: Deep brain stimulation?

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

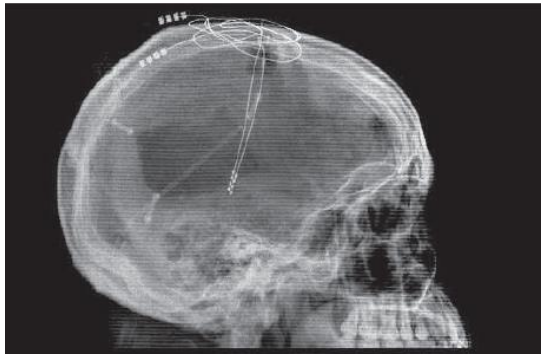


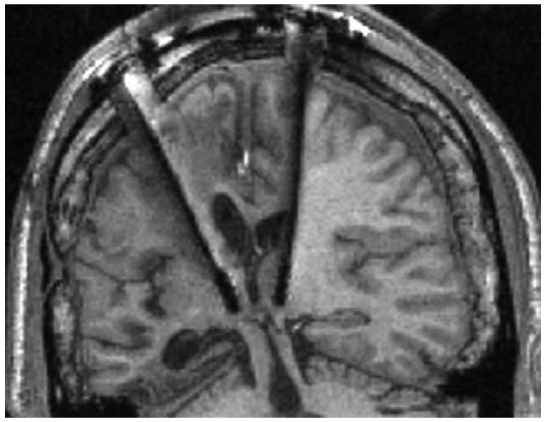
Intralaminar nuclei stimulation induces "recovery" from minimally responsive state

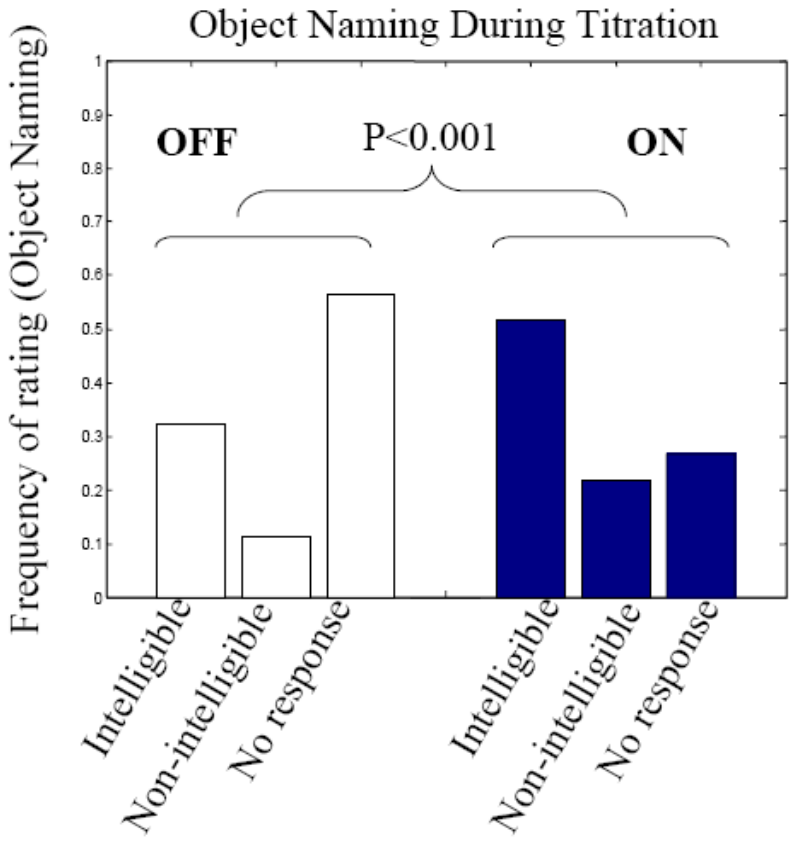


Laureys et al, *Lancet,* 2000
Schiff et al, *Nature*, 2007

Curative treatment: Deep brain stimulation?







MCS ➔ emerged

Schiff et al, *Nature,* 2007

Transcranial direct current stimulation (tDCS)

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Why direct current?

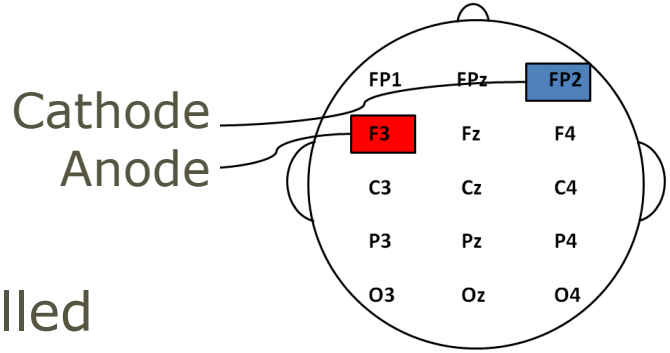
Stimulation	Population	Effects	Authors
Motor cortex	Healthy subjects	Dexterity	Boggio et al. Neurosci Lett, 2006
	Hemiplegic patients	Dexterity and strength	Hummel et al. Lancet, 2006
	Spastic patients	Spasticity & ADL (activity of daily life)	Wu et al., Arch Phys Med Rehabil 2012
Prefrontal cortex	Healthy 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

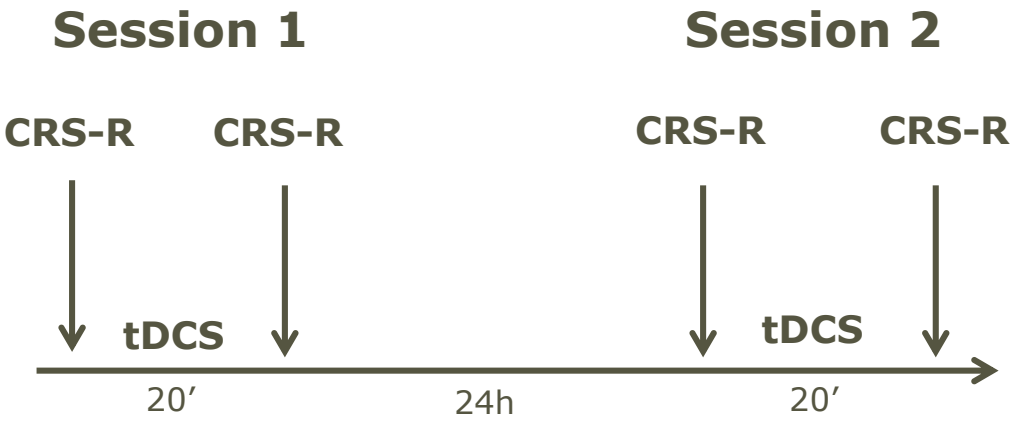
Cheap & easy to use

Thibaut et al, Rev Neurol, 2013

Methods

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





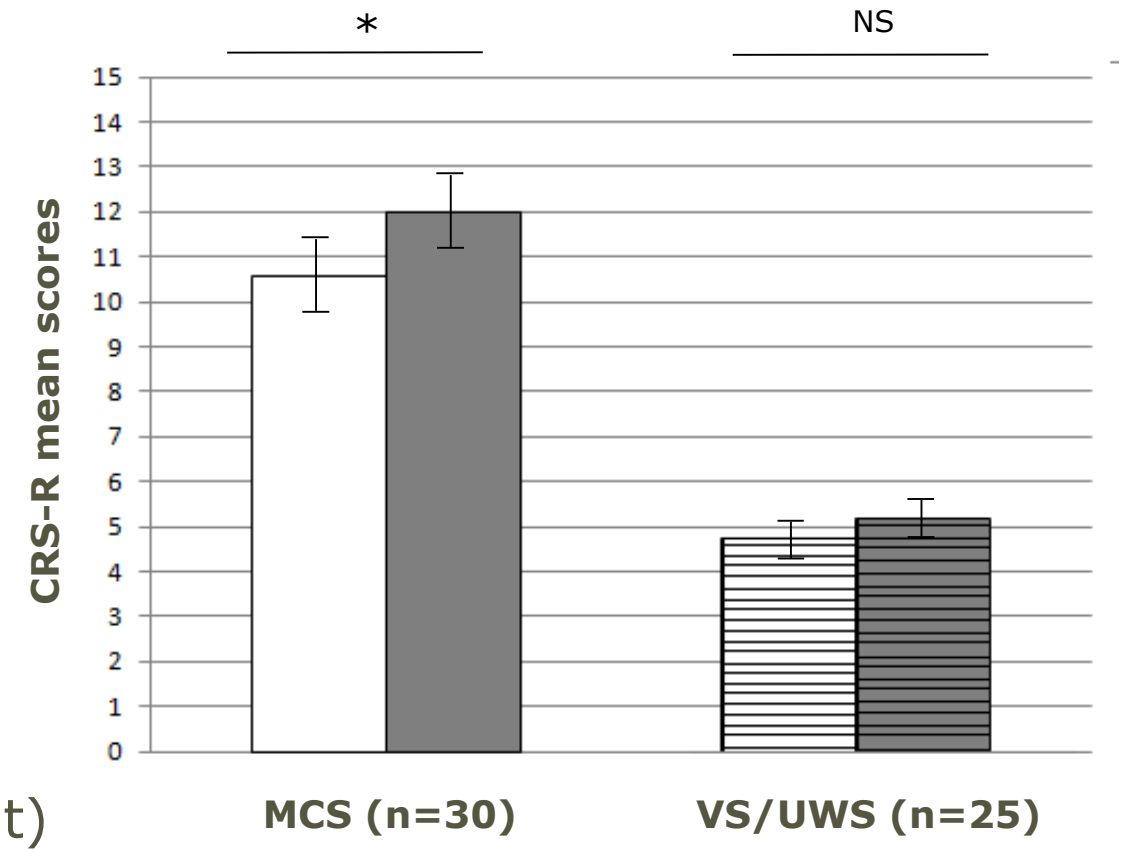
Results

- 55 patients (43±18y; 25 VS/UWS, 30 MCS; 25 TBI; 35 chronic (>3 months)

- **15 responders**

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

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

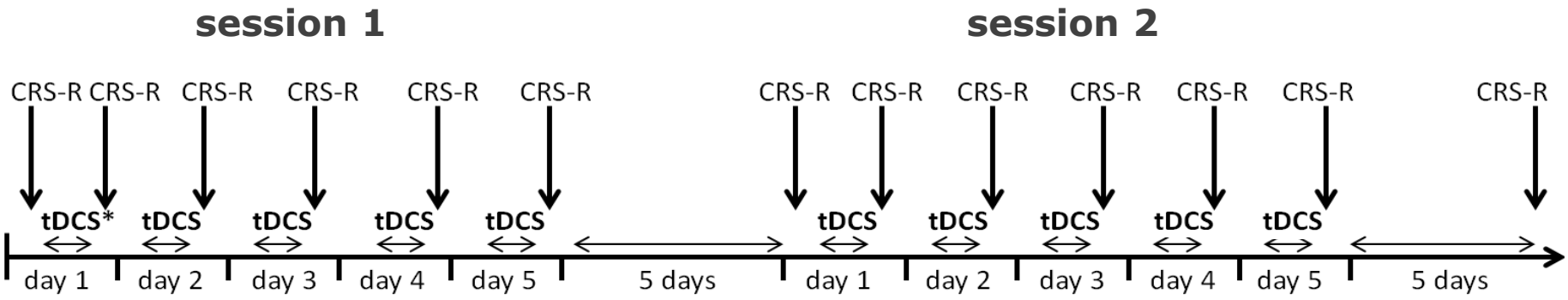


Thibaut et al, *submitted*

tDCS – long term

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



*tDCS = 20minutes

Pain in DOC

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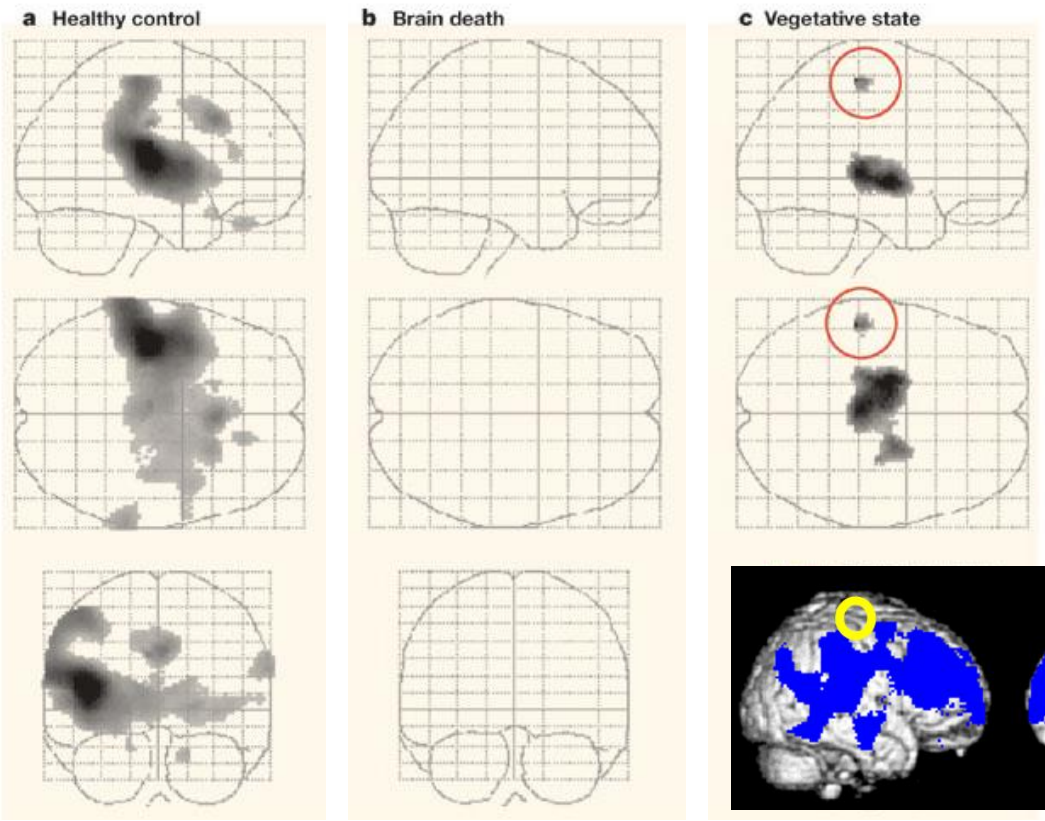
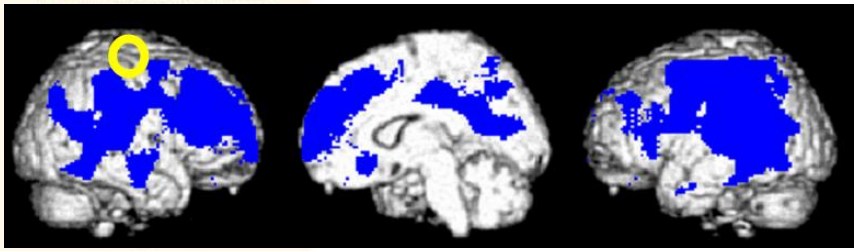
Pain in brain death & VS/UWS

Noxious electrical stimulation

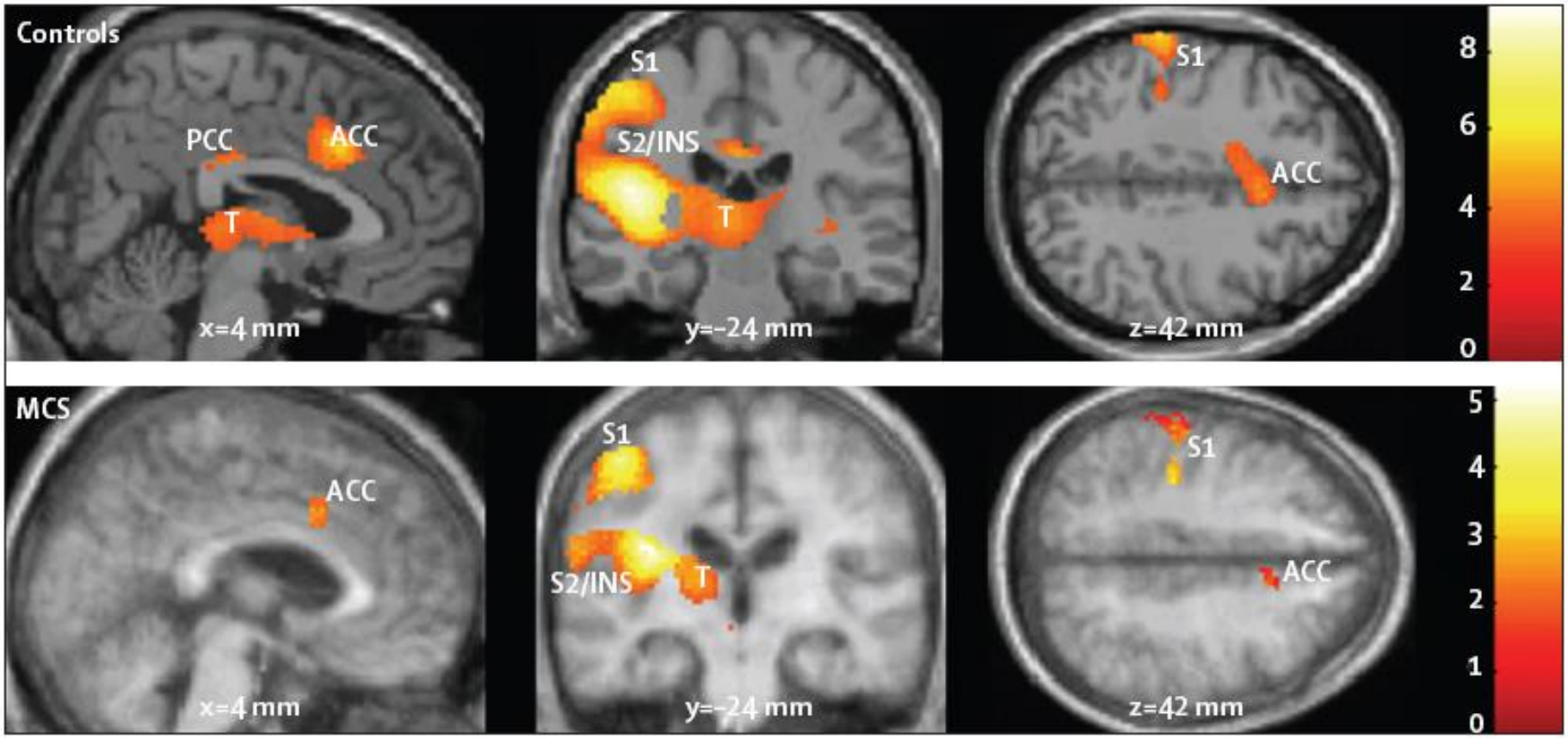


Low level disconnected cortical activation



Laureys et al, *Neuroimage,* 2002
Laureys, *Nature Reviews Neuroscience,* 2005

Pain in minimally conscious state



Boly et al, *Lancet Neurology,* 2008

BUT…

Subject number	Sex	Age	ACC	AI	S2	S1	Thalamus	PI	Cerebellum
1	F	52	–	–	+	+	–	–	+
2	F	29	–	+	+	+	+	+	+
3	M	46	–	–	+	–	+	–	+
4	M	29	+	+	+	+	+	+	+
5	F	31	+	+	+	+	+	+	+
6	F	35	+	+	+	–	–	+	–
7	M	32	+	+	+	+	+	+	–
8	M	62	–	–	+	–	–	+	–
9	F	47	–	–	–	+	–	+	–
10	M	52	–	–	+	+	–	+	–
11	F	58	–	–	+	+	–	–	–
12	M	48	+	+	+	+	–	–	–
13	F	28	+	+	+	+	+	+	+
14	M	33	–	+	+	+	–	+	+
15	M	54	–	–	+	–	–	–	–

Acc ai = ***

Markl et al. *Brain & Behavior,* 2013

Nociception and pain

Nociception Coma Scale - Revised

Motor response
3 – Localization to noxious stimulation
2 – Flexion withdrawal
1 – Abnormal posturing
0 – None/flaccid

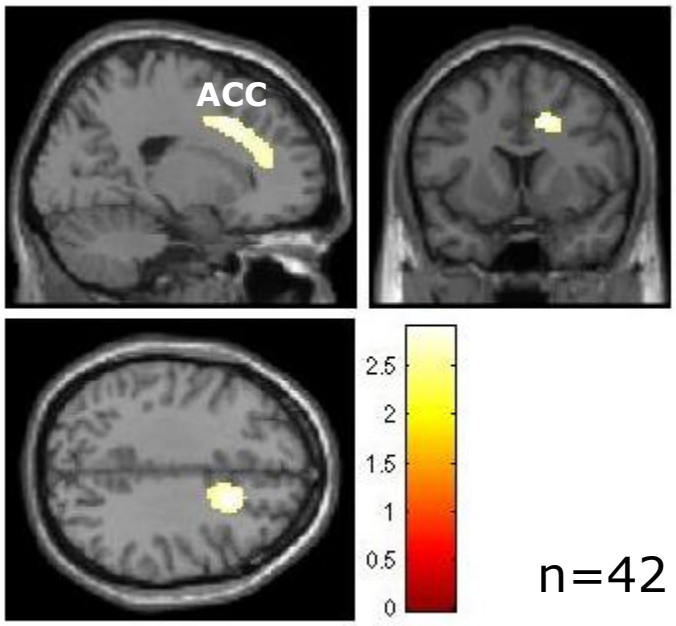
Verbal response
3 – Verbalisation (intelligible)
2 – Vocalisation
1 – Groaning
0 – None

Facial expression
3 – Cry
2 – Grimace
1 – Oral reflexive movement/startle response
0 – None

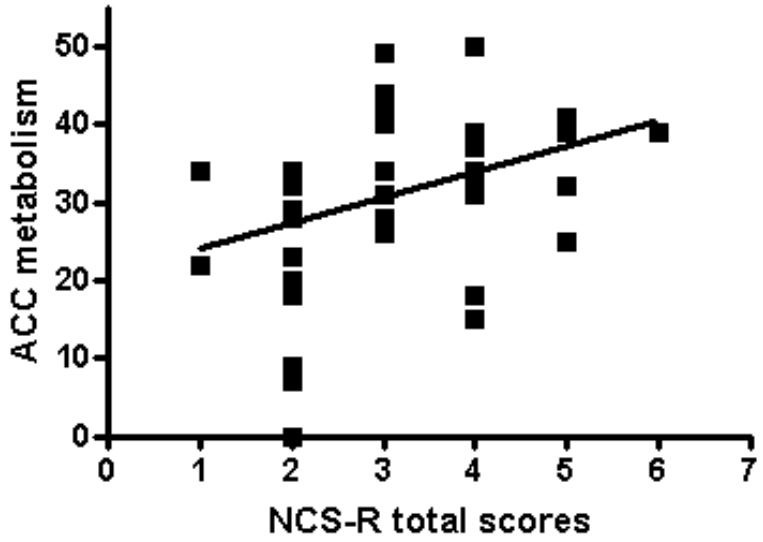
Score >3/9 = analgesic treatment

Chatelle et al, *JNNP,* 2012

NCS-R and brain metabolism



n=42



Correlation between brain metabolism in anterior cingulate cortex (ACC – pain matrix) and Nocicetion Coma Scale Revised

Chatelle, Thibaut et al, NNR, 2013

Spasticity in DOC

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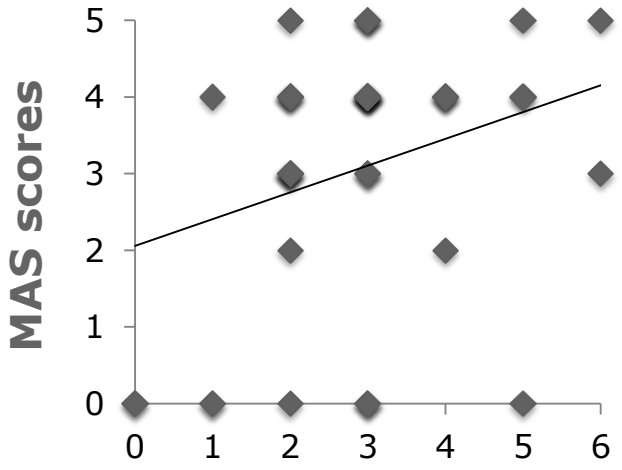
Spasticity in DOC

Assess spasticity (MAS*) in VS/UWS and MCS (n= 57)

- **84%** showed spasticity
  67% 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, *in prep*

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

- **Clinical benefits:**
  - Spasticity decrease on fingers flexors
  - Increase of hand opening
  - Better improvement for patients without tendon retraction

Thibaut et al, *in prep*

Conclusion

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Conclusion

- Current treatments: Amantadine, Zolpidem, (+ other drugs and DBS)
- **tDCS** could improve **cognitive** and **motor** functions of severe brain injured patients
- Pain ➔ Nociception Coma Scale-Revised (antalgics: >3)
- Chronic patients ➔ improve their **comfort** and treat **spasticity**

Needs

Clear therapeutic guidelines for acute and chronic patients with DOC

Best chance to recover good quality of life

« Habla con ella » Pedro Almodovar

THANK YOU

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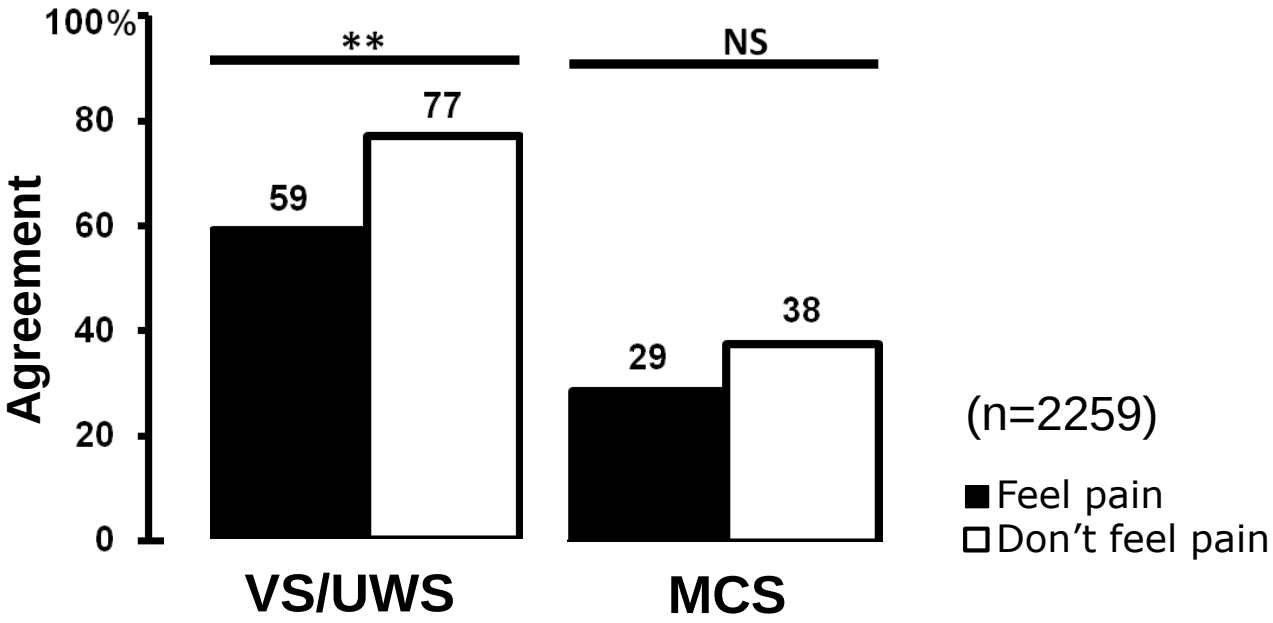
Artificial nutrition as a

Pain Perception in Disorders of Consciousness: Neuroscience, Clinical Care, and Ethics in Dialogue

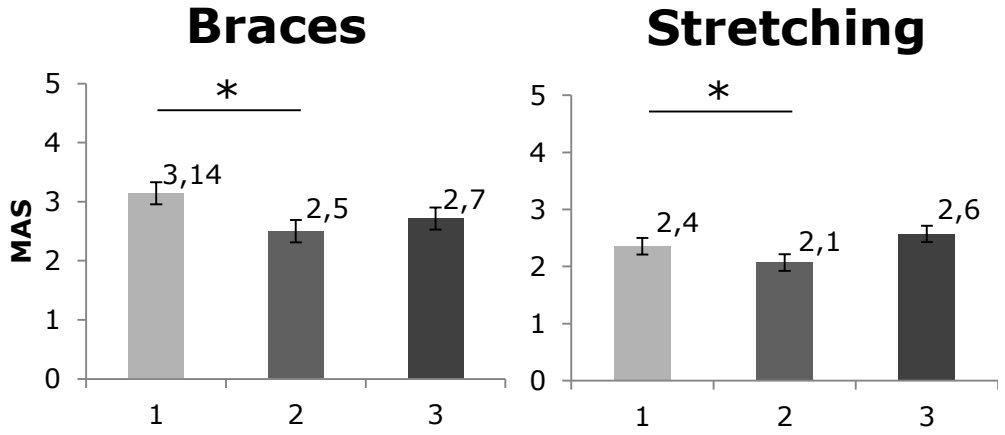
A. Demertzi · E. Racine · M-A. Bruno · D. Ledoux · O. Gosseries · A. Vanhaudenhuyse · M. Thonnard · A. Soddu · G. Moonen · S. Laureys



Demertzi & Racine et al, *Neuroethics* 2012
Kuehlmeyer et al. *J Neurol*, 2011

Study: soft braces

- **AIM:** Test the efficacy of soft braces on spastic upper limb to reduce spasticity in chronic VS/UWS & MCS
- **Clinical benefits:**
  - Spasticity decrease on fingers flexors
  - Increase of hand opening
  - Better improvement for patients without tendon retraction



Thibaut et al, *in prep*

tDCS - Motor

Cognitive effects ⊕

Motor effects ?

Parameters:

2 mA – 20 min

M1 (C3/C4)

1. **Anodal** (↗ motricity)
   Improve stroke patients strenght and dexterity (Hummel et al., 2006)

2. **Cathodal** (↘ spasticity)
   Decrease spasticity of stroke patients (Vandermeeren et al., 2013)