

Curative and palliative treatments for patients with disorder of consciousness

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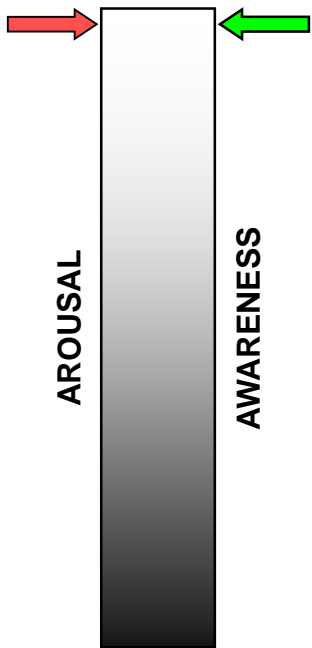
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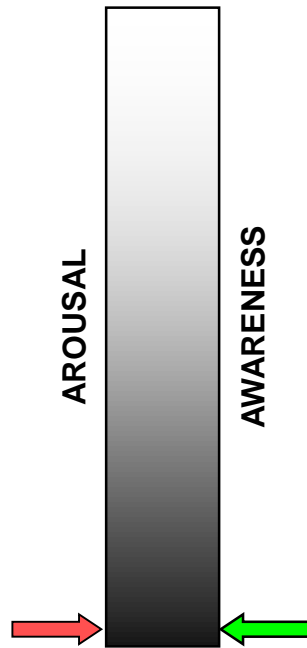
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Consciousness

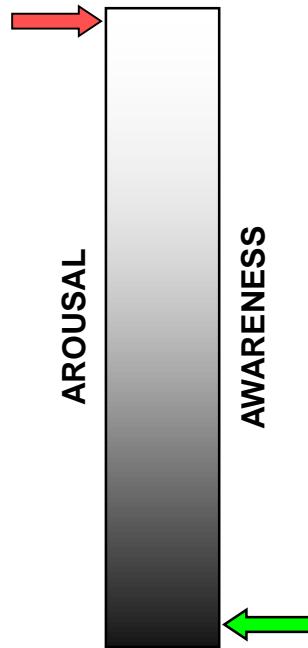
NORMAL CONSCIOUSNESS



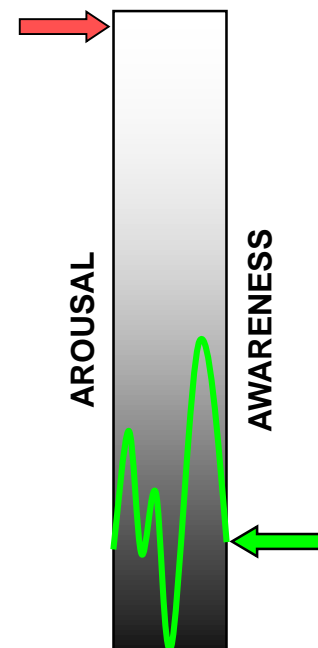
COMA



VEGETATIVE STATE



MINIMALLY CONSCIOUS STATE



Coma Recovery Scale-Revised

Patients in VS and MCS : correct 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									

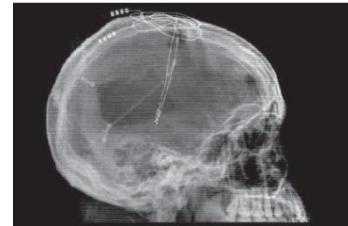
Denotes emergence from MCS †
Denotes MCS *

Treatment in DOC

1. Curative

- Cognitive function
- Physical function

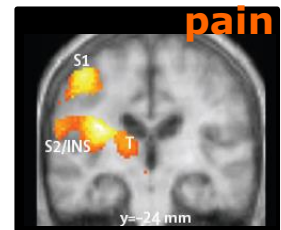
1. Pharmacological
2. Deep brain stimulation
3. Transcranial direct current stimulation (tDCS)



2. Palliative

- Decrease side effects
& improve comfort

4. Pain
5. Spasticity



Curative treatments

Pharmacological



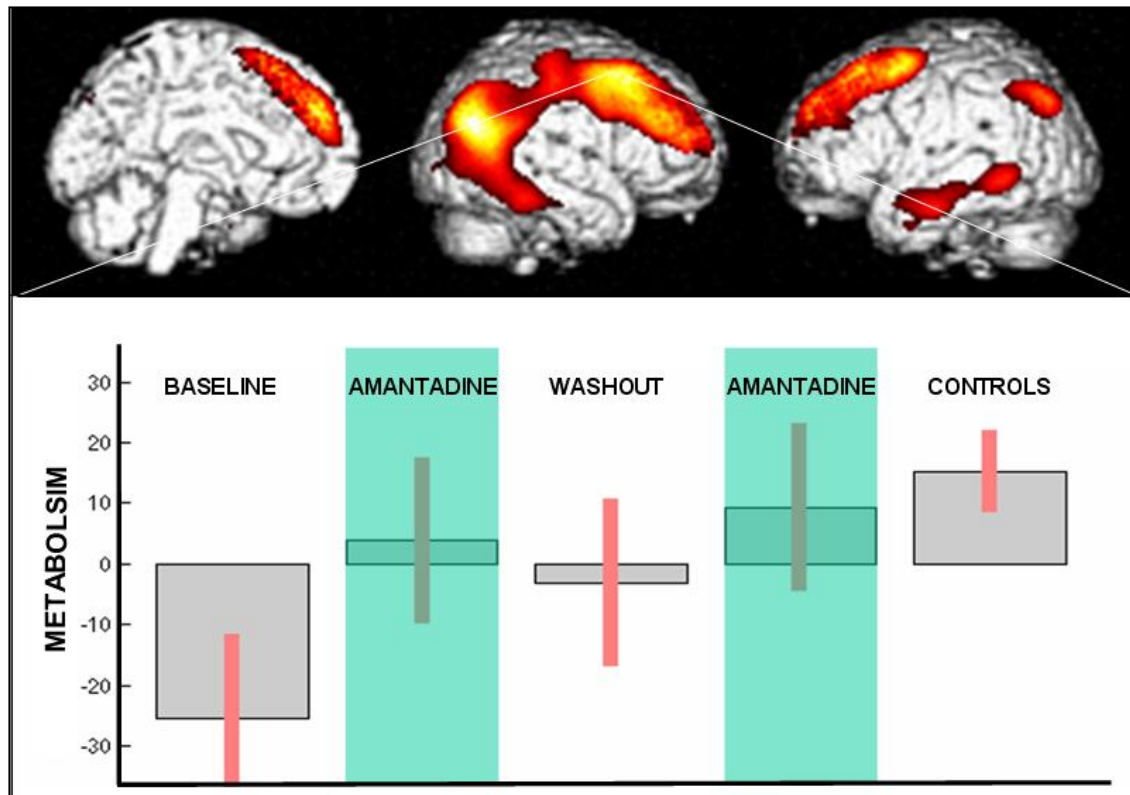
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Pharmacological treatment

Drugs	Study (first author, year)	Number of patients and etiology	Diagnosis	Placebo control	Reported functional outcome
<i>Dopaminergic agents</i>					
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
<i>Nonbenzodiazepine sedative</i>					
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
<i>GABA agonist</i>					
Baclofen	Sarà (2007)	1 non-TBI	VS	No	Positive

Amantadine

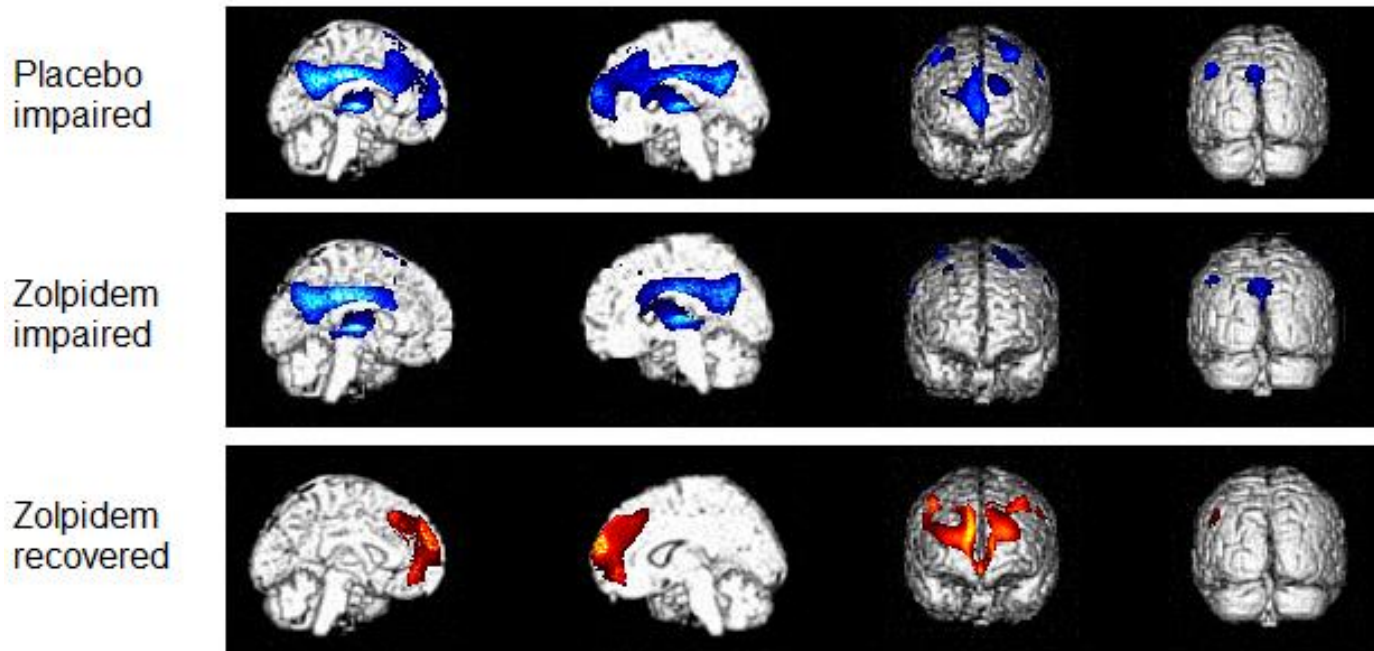
Dopaminergic agent (Parkinson)



Zolpidem

Sedative-hypnotic agent (insomnia)

Indirect agonist of GABA_A receptors



Curative treatments

Deep brain stimulation

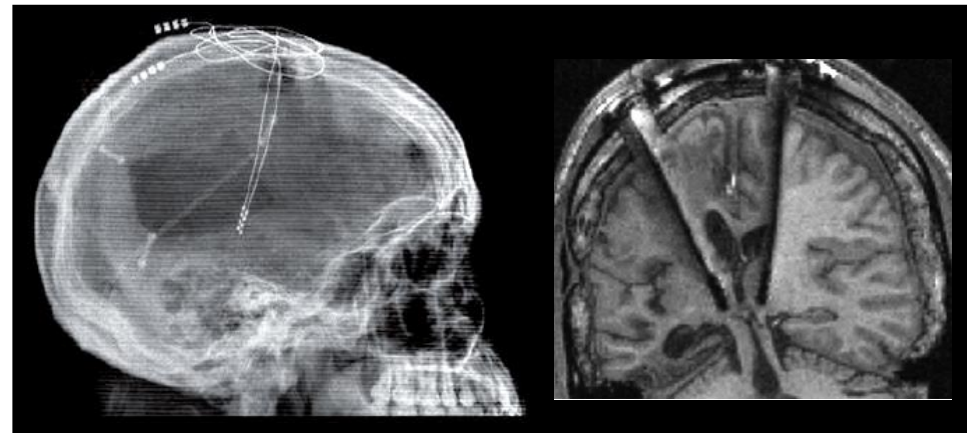
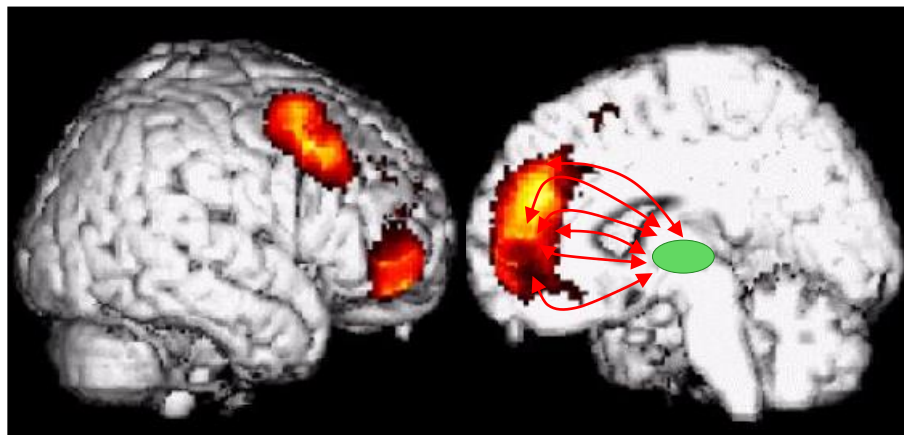


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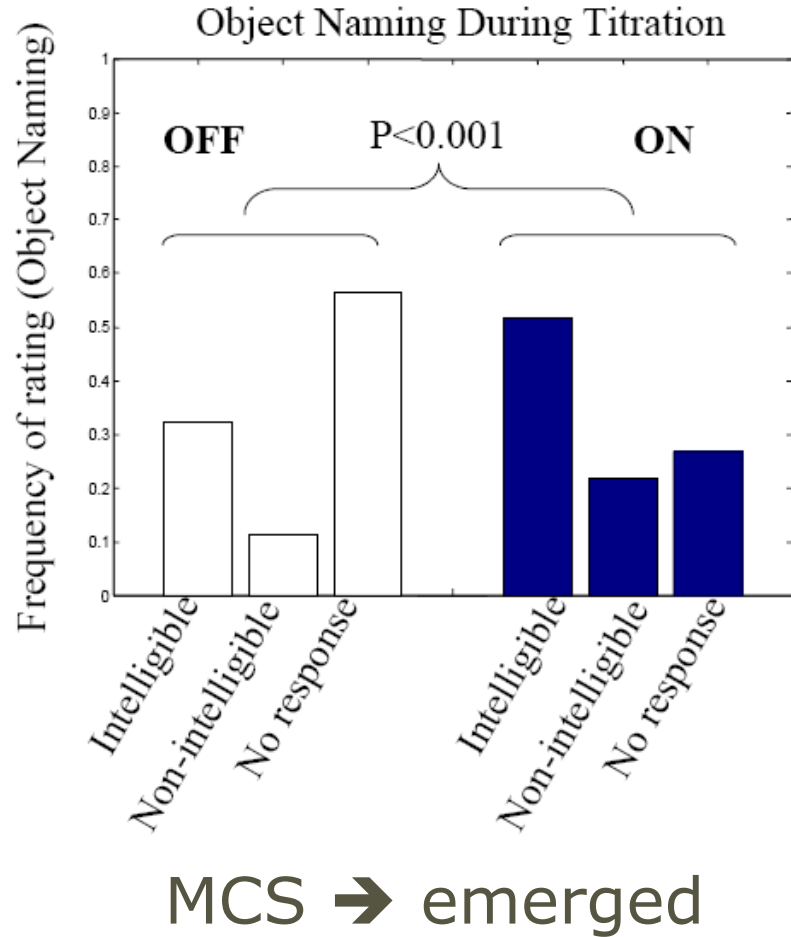
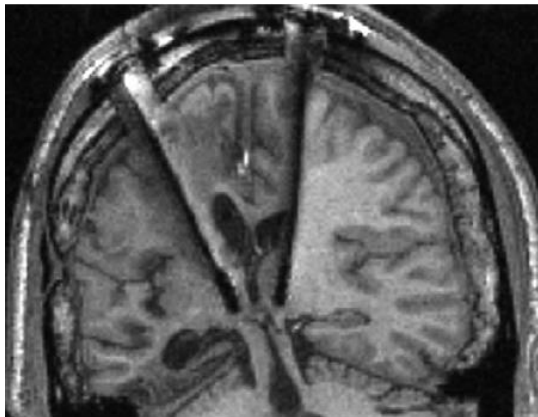
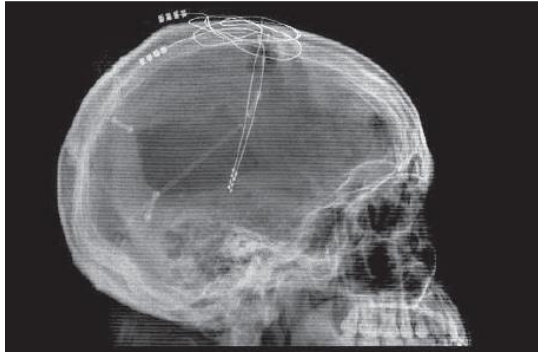
Curative treatment: Deep brain stimulation?

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

Intralaminar nuclei stimulation
induces "recovery" from
minimally responsive state



Curative treatment: Deep brain stimulation?



Curative treatments

Transcranial direct current stimulation (tDCS)



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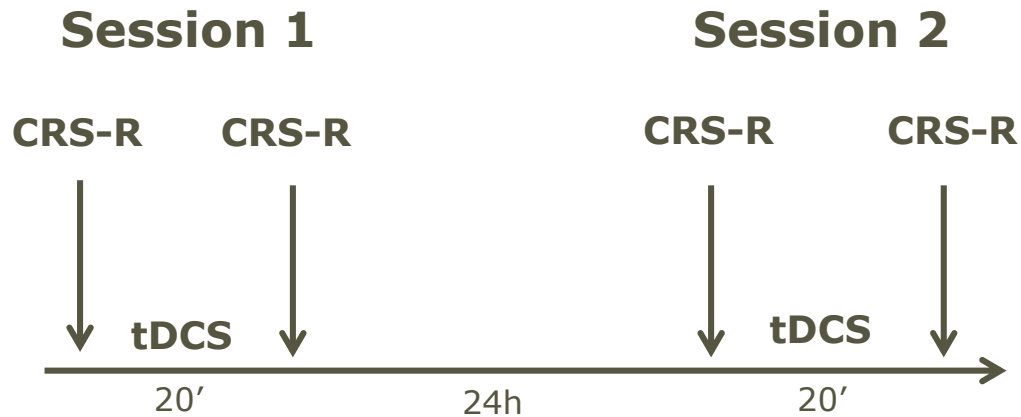
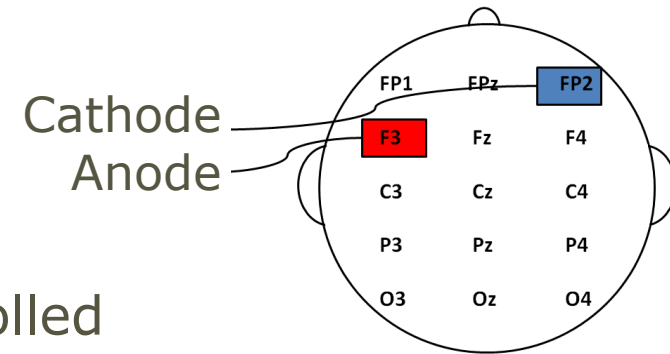
Why direct current?

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

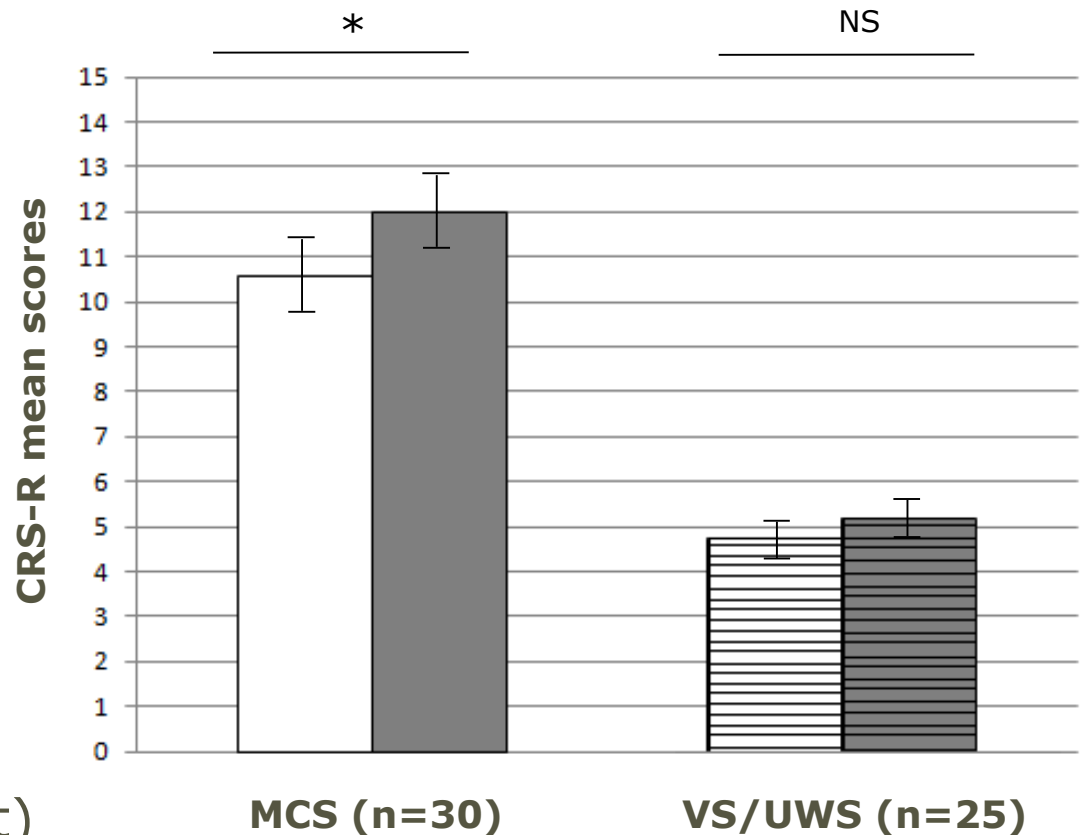
Methods

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



* $p < .05$

tDCS – long term

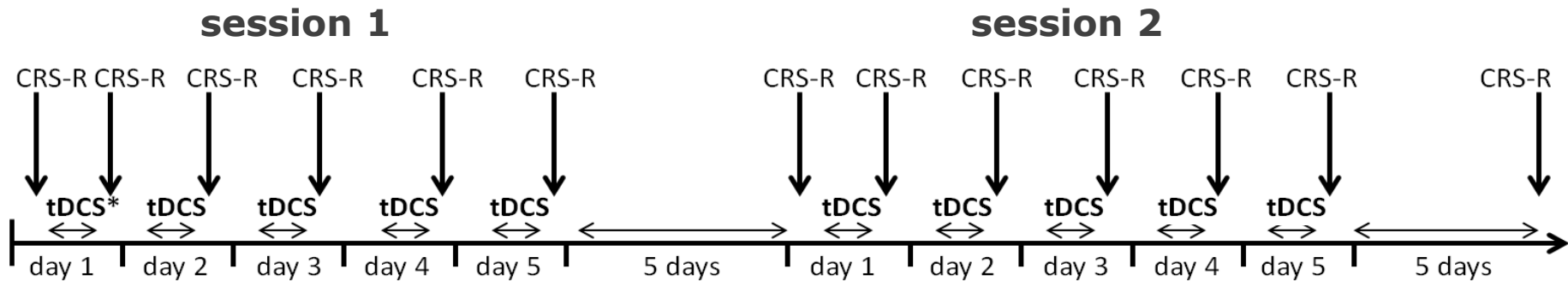
Effects last \pm 90 minutes (Hummel et al., Lancet 2006)

→ 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

Prefrontal & precuneus stimulations

Palliative treatments

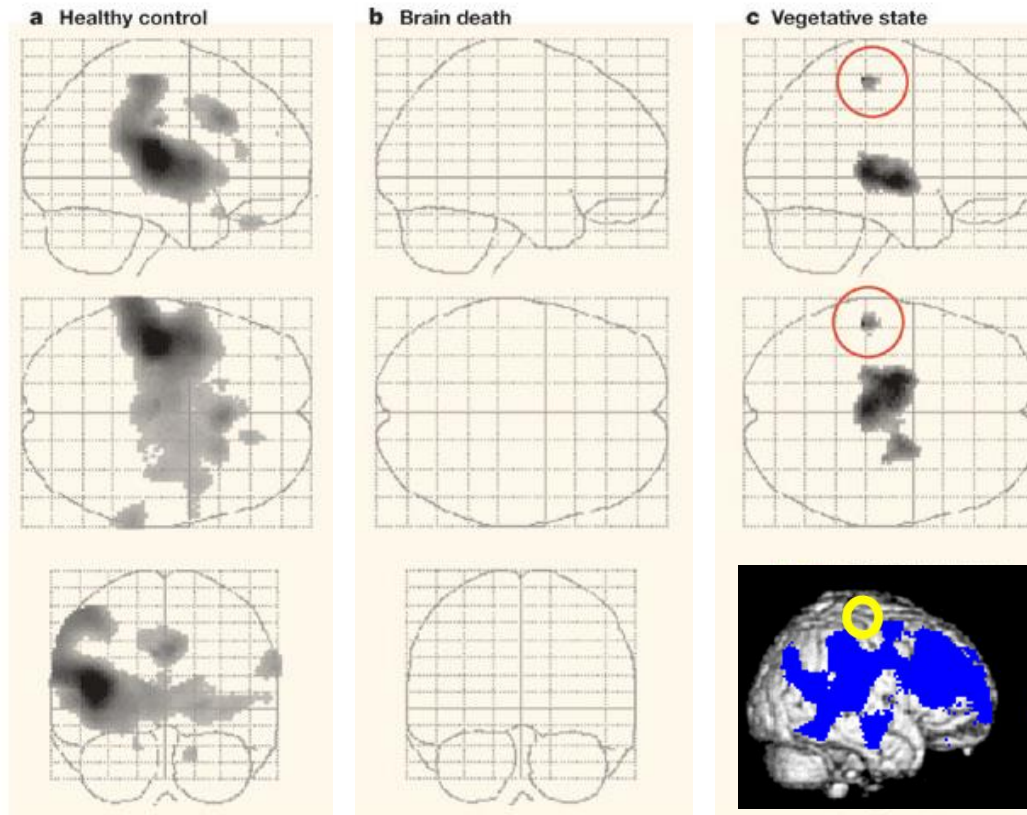
*Pain in disorders of
consciousness*



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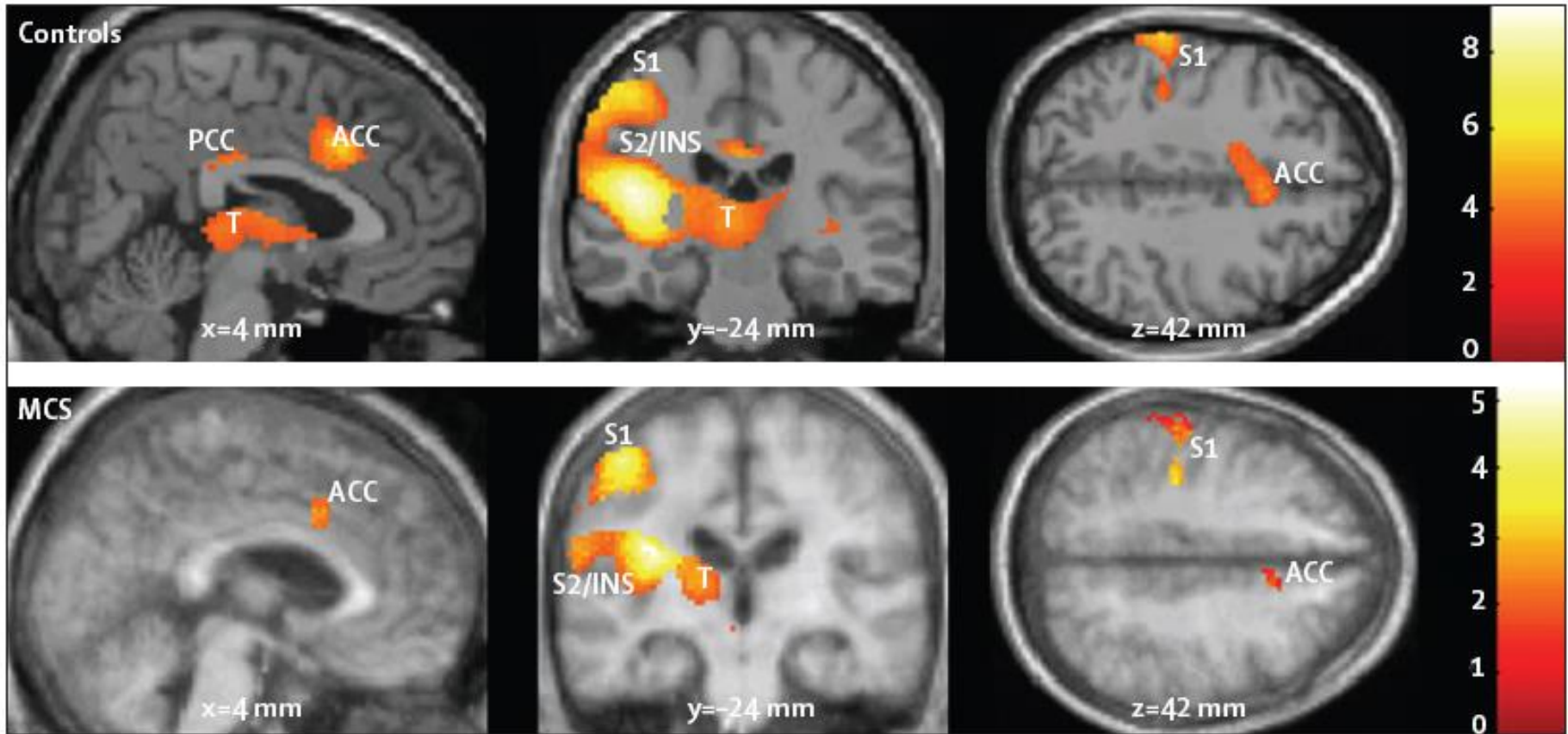
Pain in brain death & VS/UWS

Noxious electrical stimulation



Low level
disconnected
cortical activation

Pain in minimally conscious state



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 = anterior cingulate cortex

AI = anterior insula

S1/S2 = primary and secondary somatosensory areas

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

Palliative treatments

Spasticity



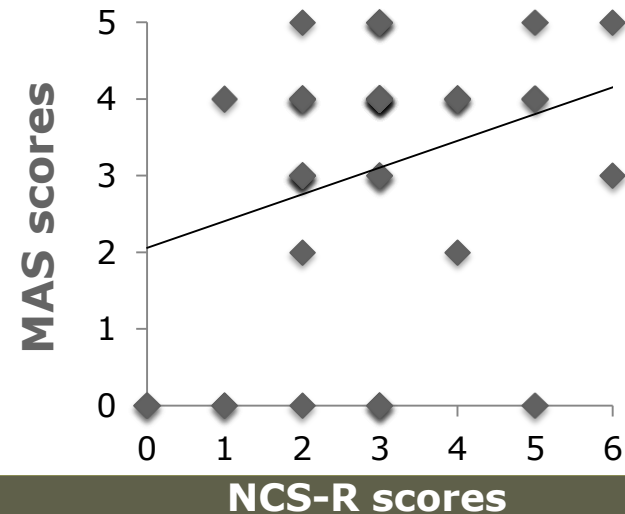
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Spasticity in DOC

Spasticity assessment (MAS*) in VS/UWS and MCS (n=57)

- **84%** showed spasticity
67% had severe spasticity (MAS \geq 3)
- **Time since insult:** positively correlated with MAS scores
- **Pain** (*Nociception Coma Scale Revised*) : positive correlation

* MAS=Modified Ashworth Scale



Drugs

Drug	Dose	Mechanism of action	Side effects
Diazepam	5-20 mg 3 times daily	Increases the affinity of GABA for the GABA _A receptor complex leading to an increase in presynaptic inhibition and reduction of synaptic reflexes	Sedation, weakness, hypotension, adverse gastrointestinal effects, memory trouble, confusion, depression and ataxia
Clonazepam	0.5-1.00 once daily (bed time)	Same as above	Weakness, hypotension, ataxia, disco-ordination, sedation, depression and memory impairment. Prolonged use could increase the risk of addiction
Baclofen	5-20 mg 3-4 times daily	Centrally acting GABA analogue. Binds to GABA _B receptor at the presynaptic terminal and thus inhibits the muscle stretch reflex	Daytime sedation, dizziness, weakness, fatigue, nausea; lowers seizure threshold Withdrawal seizures and hallucinations with abrupt discontinuation
Tizanidine	4-36 mg daily	Imidazole derivative, with agonist action on alpha-2 adrenergic receptors in central nervous system	Dry mouth, sedation, dizziness, mild hypotension, weakness (less common than with baclofen) Liver enzymes should be monitored
Dantrolene	25-100 mg 4 times daily	Interferes with the release of calcium from the sarcoplasmic reticulum of the muscle	Generalized muscle weakness, mild sedation, dizziness, nausea, diarrhoea, Hepatotoxicity
Phenol/alcohol	30 mg/kg	Chemical denervation of the muscles	Burning and dysesthesias. Damage of the sensory nerves with pain
Botox	10-15 units/kg	Inhibit the release of acetylcholine at the neuromuscular junction	minimal side effects. Rarely, children may become unusually floppy for a few days or weeks after high doses of Botox.
Intrathecal baclofen	25-1000 mg daily	Binds to GABA _B receptor at the presynaptic terminal and inhibits the muscle stretch reflex	Decreased ambulation speed and muscle weakness

Physical therapy

- Stretching is very important to keep physiological amplitude of patient's articulations
 - Every day on each articulation
- Massage could relax patient (but not sufficient)
- Be careful about irritative sources (bedsores, infections, etc)
 - → pain, stress and fatigue increase spasticity
- Splints to hands and feet could be beneficial



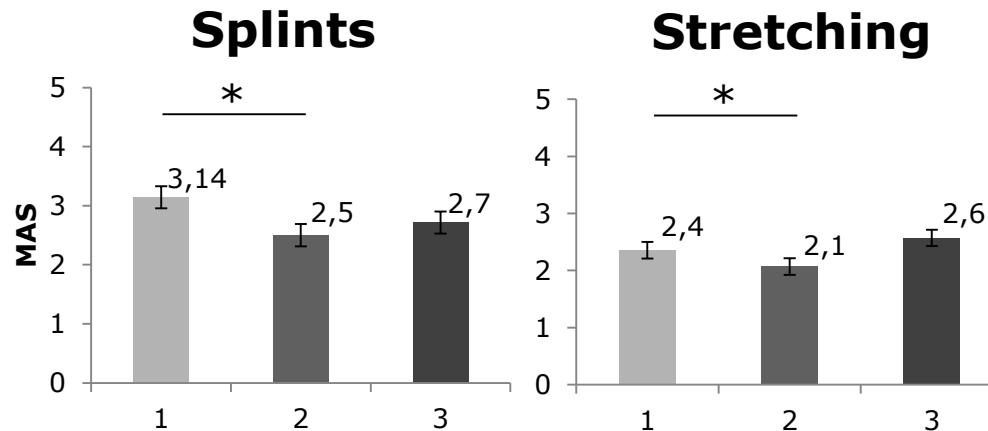
Soft splints

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



Soft splints

- **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



Conclusions



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Conclusions

- Current treatments: **Amantadine**, Zolpidem, (+ other drugs?)
- **Deep Brain Stimulation**
- **tDCS** could improve **cognitive** function in severe brain injured patients
- **Pain** → Nociception Coma Scale-Revised
- Chronic patients → improve their **comfort** and treat **spasticity**

Conclusions

- To treat **spasticity**
 - **Botox : localized hypertonicity**
 - **Intrathecal baclofen pump : generalized hypertonicity**
 - **Baclofen, Diazepam, etc**
 - **Physical therapy: stretching & massage every day**
 - **Soft braces**
 - **!! Remove irritative causes**

THANK YOU



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