Transcranial Direct Current Stimulation (tDCS) in patients with disorders of consciousness

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Cyclotron research centre

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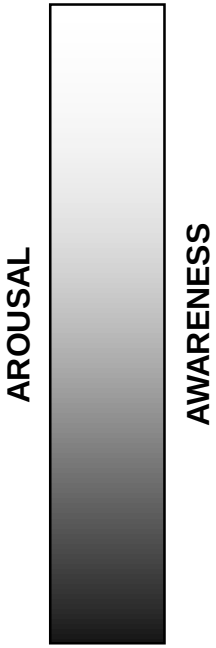
Disorders of consciousness

NORMAL CONSCIOUSNESS



Laureys, Owen and Schiff, Lancet Neurology, 2005

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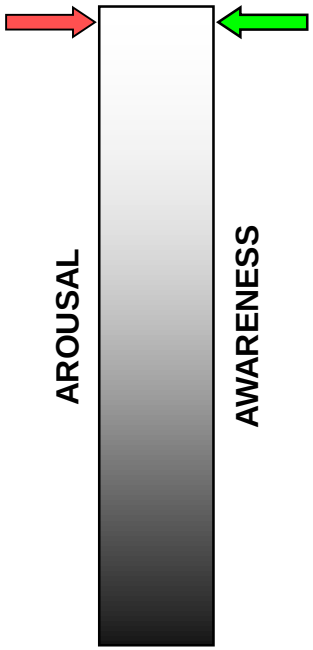

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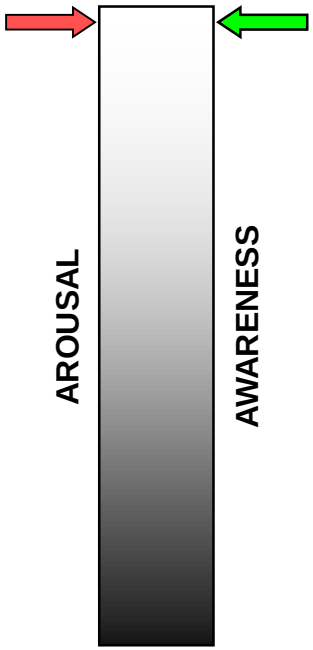

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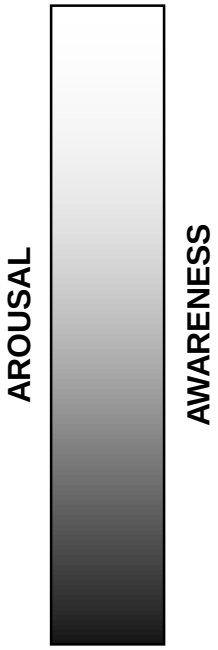

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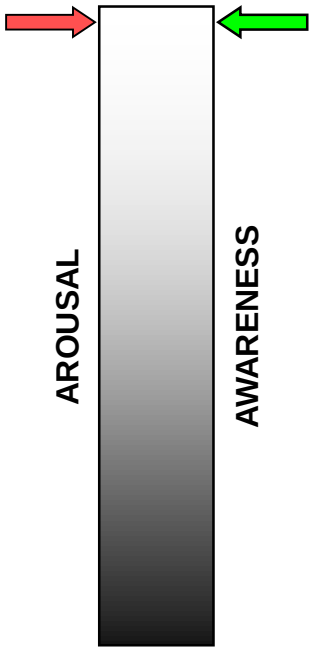

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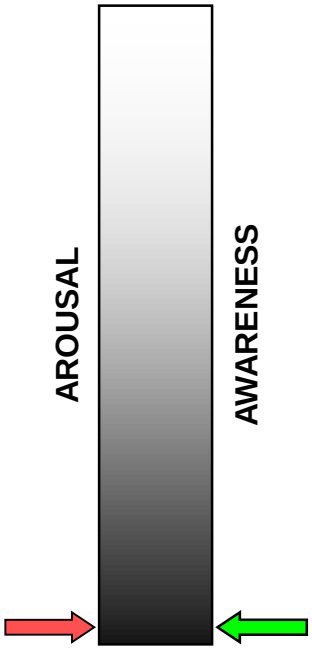

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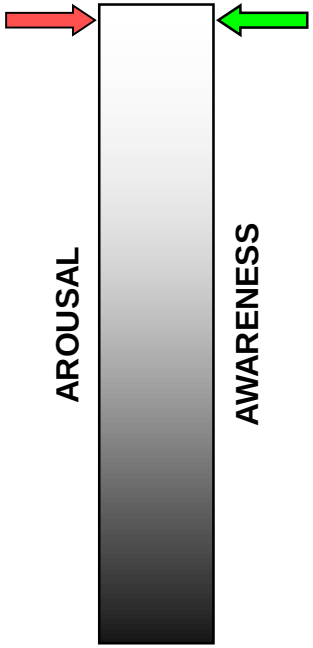

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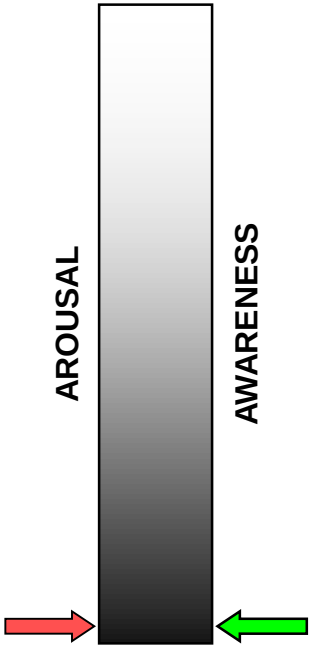
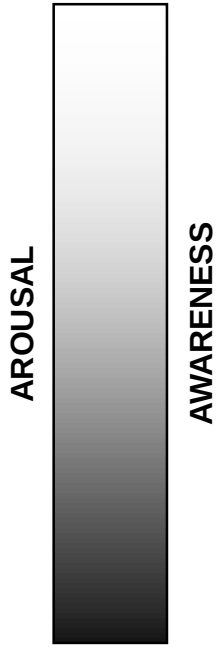


VEGETATIVE STATE/ UNRESPONSIVE WAKEFULNESS SYNDROME



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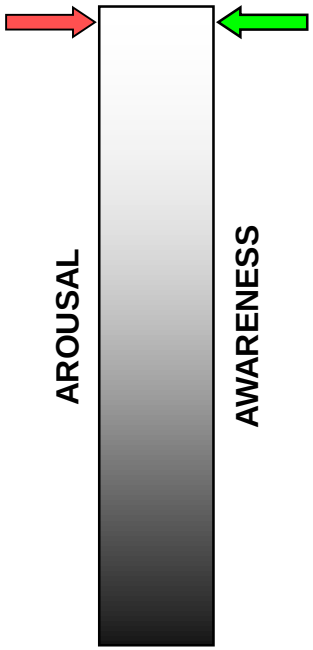

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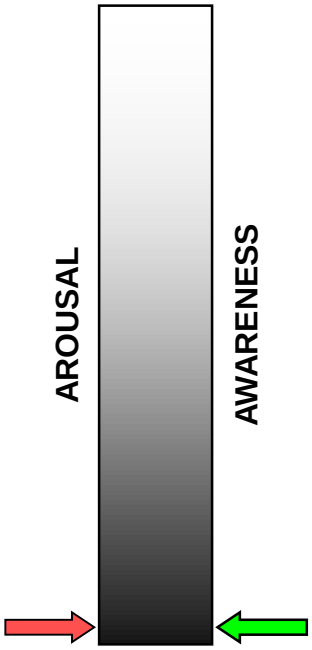

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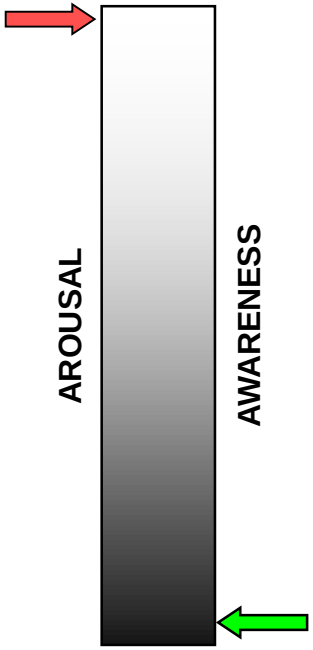

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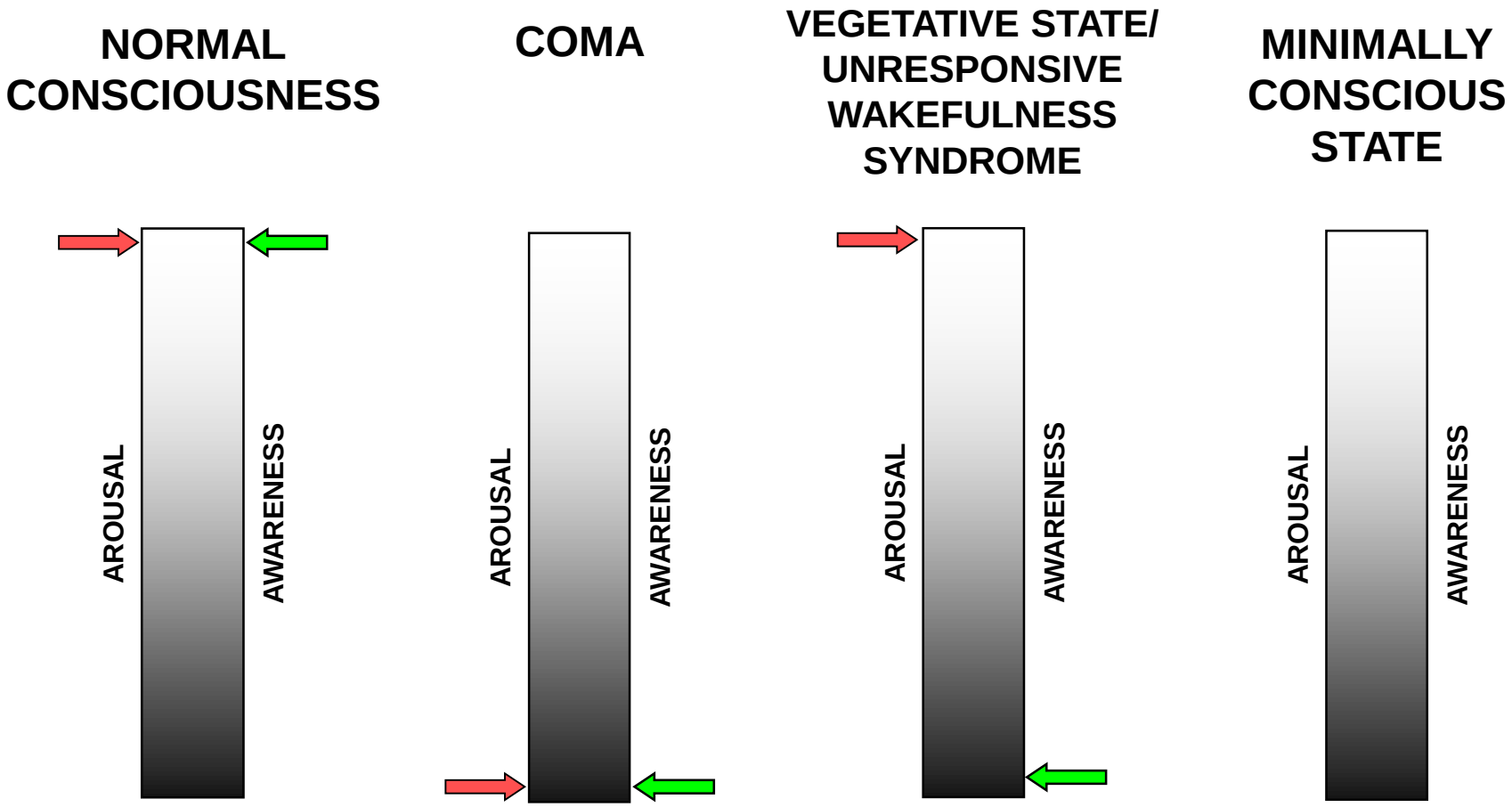

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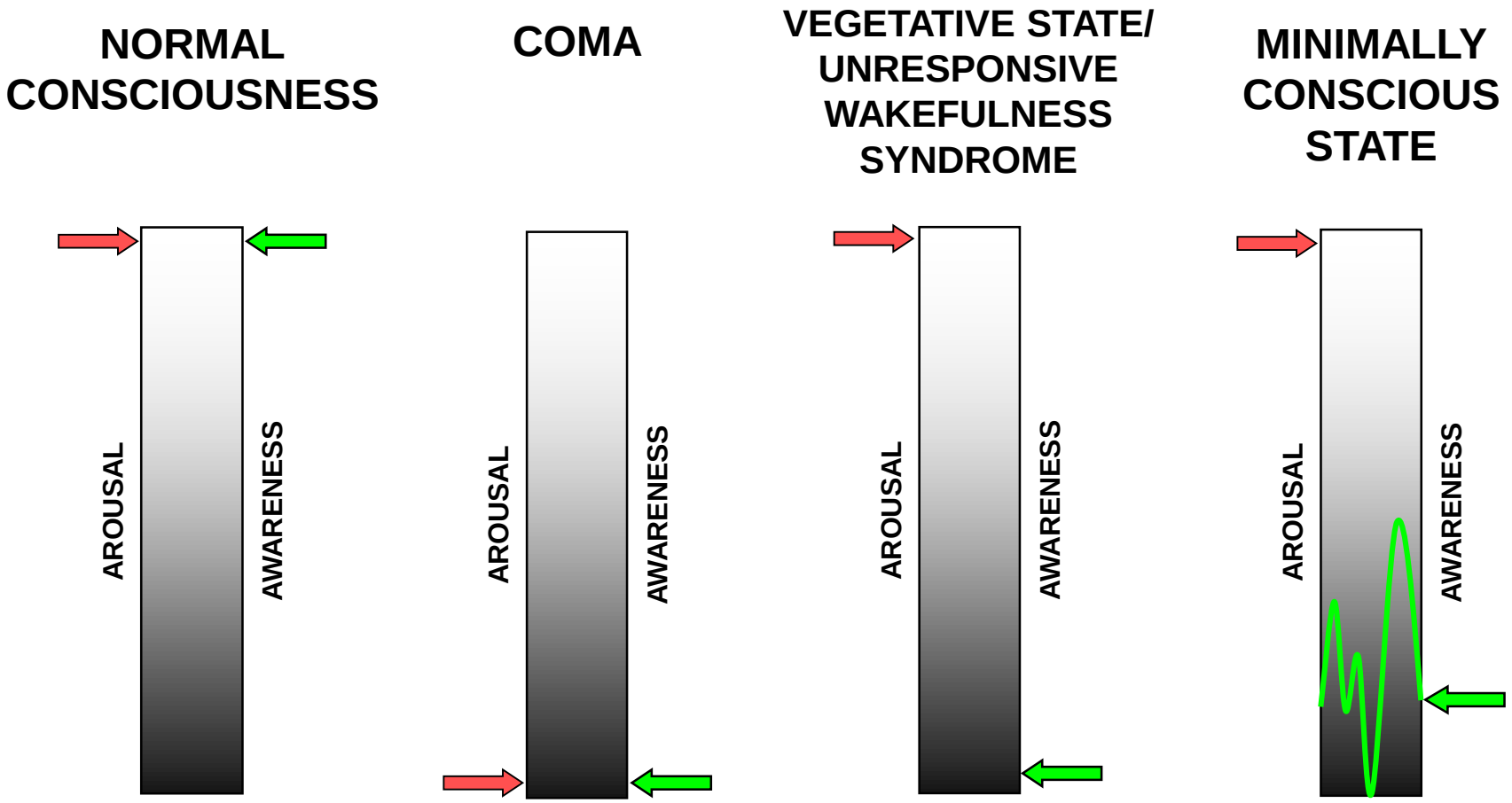

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Clinical entities

Laureys, Scientific American, 2007

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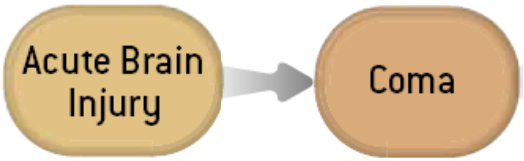

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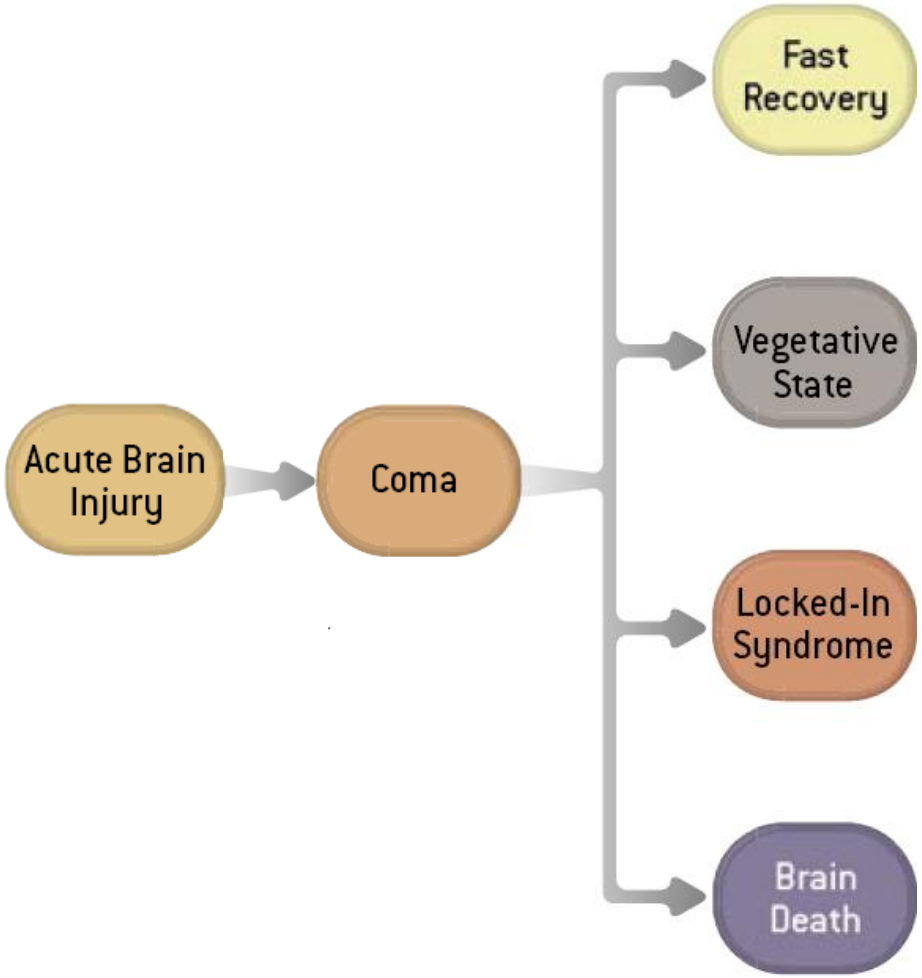

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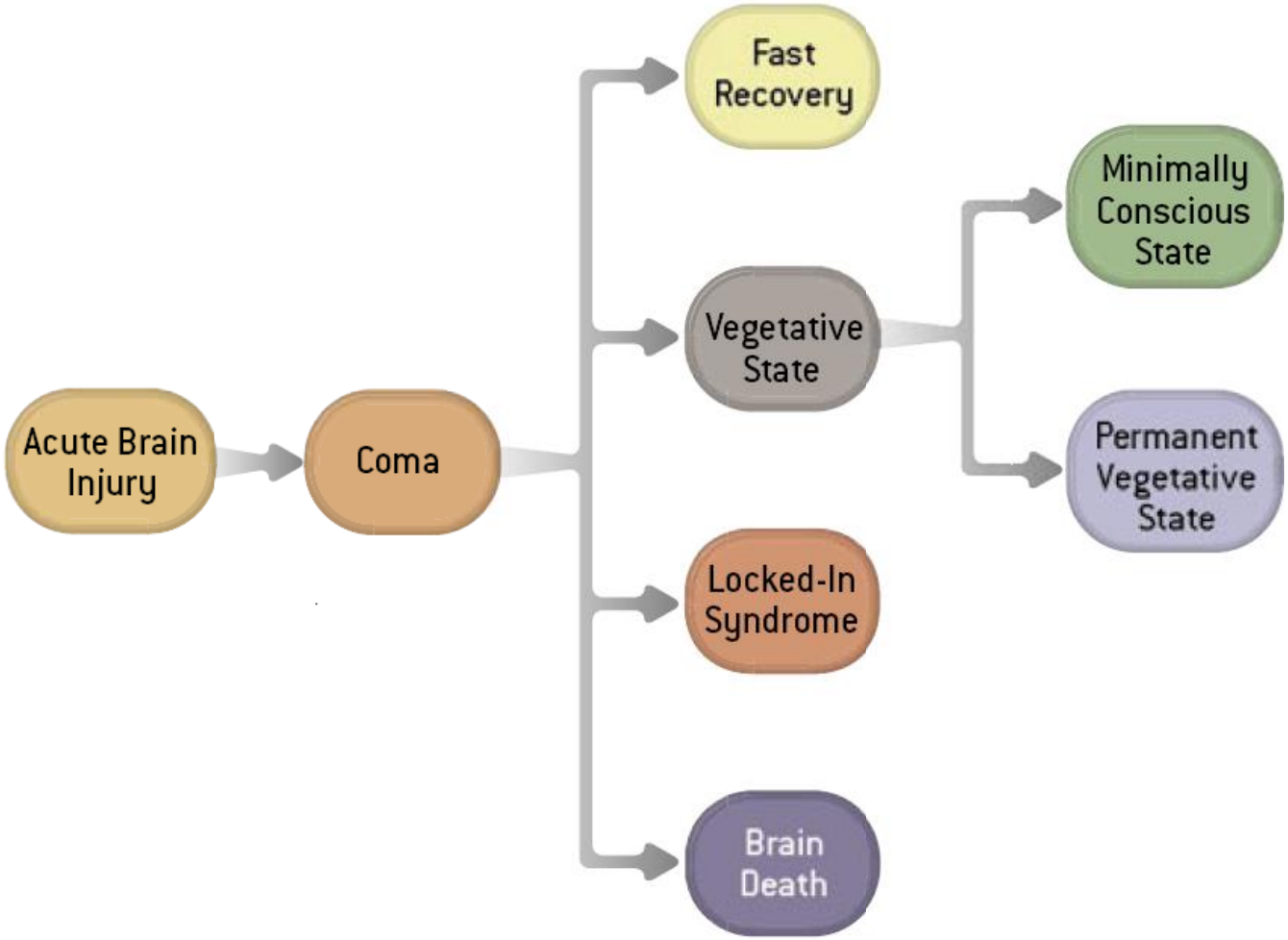

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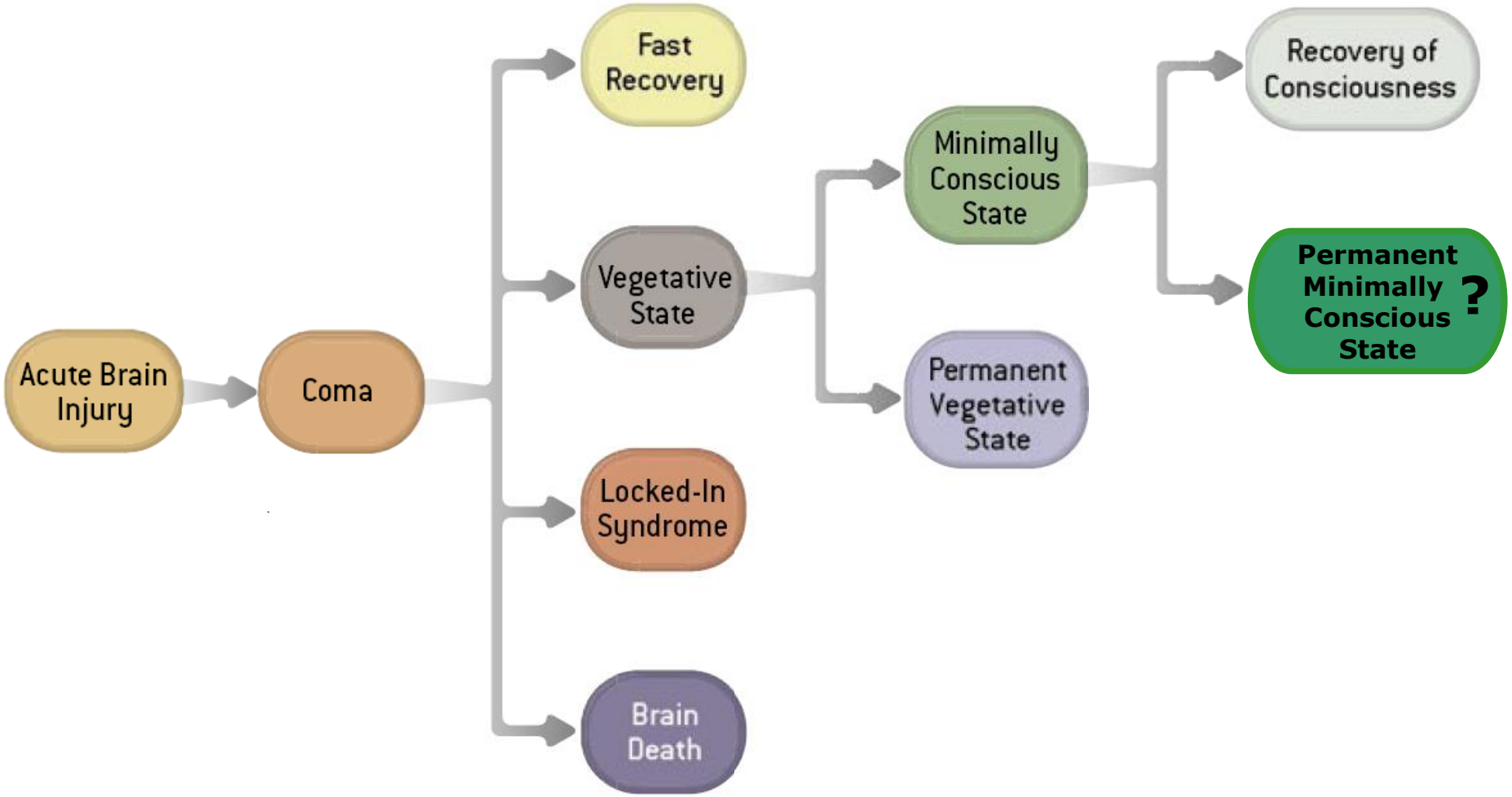

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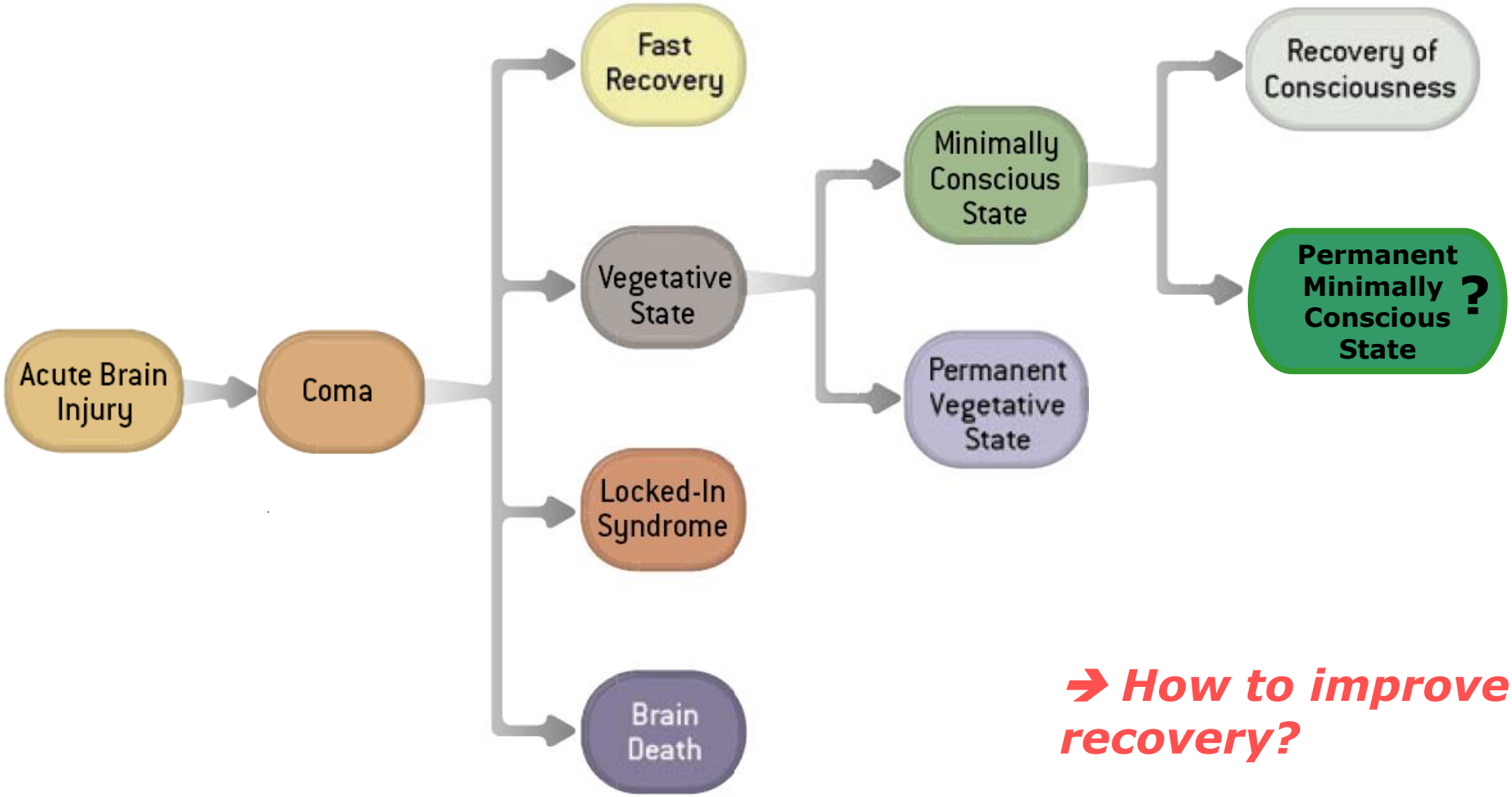


➔ ***How to improve recovery?***

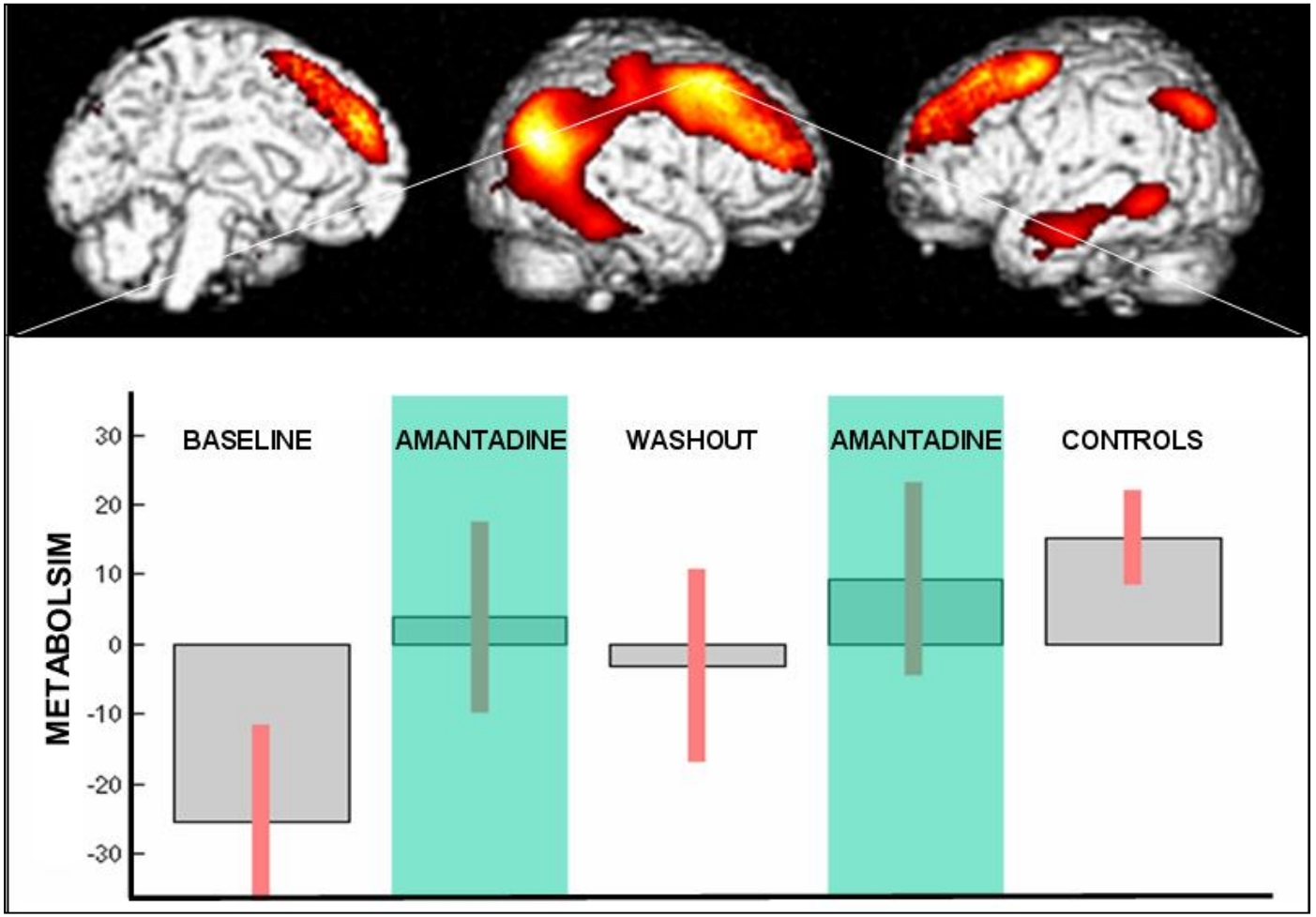
Laureys, Scientific American, 2007

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

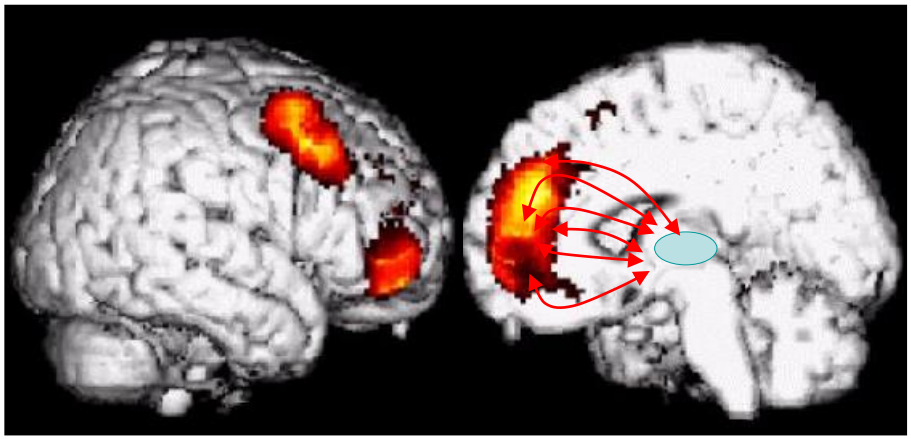
Pharmacological treatment



Schnakers et al
J Neurol Neurosurg Psychiatry 2008

Consciousness ≈ thalamo-cortical

Intralaminar nuclei "reconnections" in spontaneous recovery from "vegetative" unresponsive state



Laureys et al, *Lancet* 2000

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

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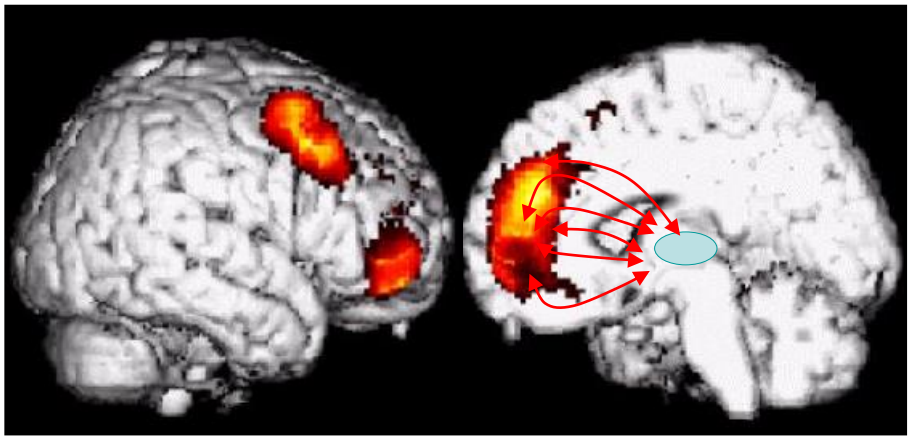
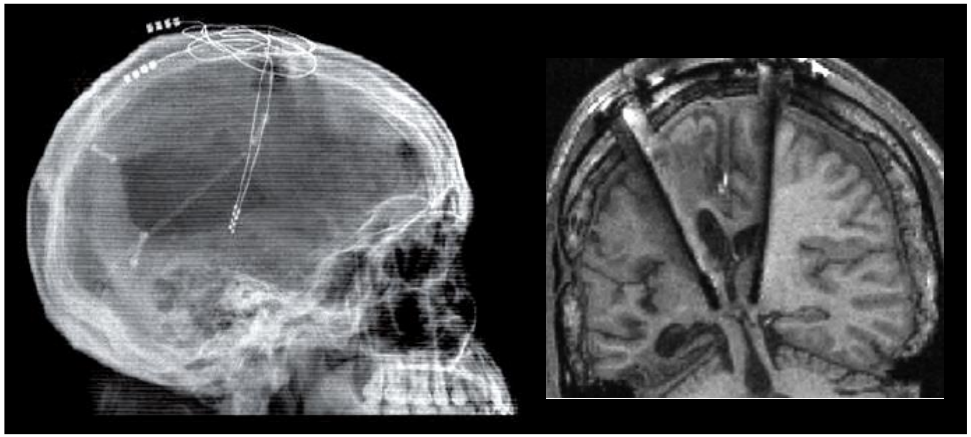


Laureys et al, *Lancet* 2000

Intralaminar nuclei stimulation induces "recovery" from minimally responsive state



Schiff et al, *Nature* 2007

MCS ➔ emerged

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

tDCS presumed mode of action

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

Modification of neuronal excitability (action potential)

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)

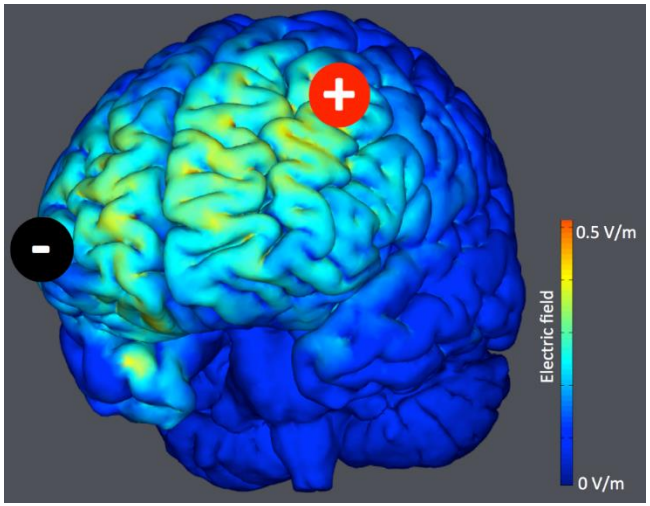
Action on opening of ion channels (Na^+, Ca^{2+})

Increase NMDA receptors excitability

⇨ improve neuron excitability

Methods

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



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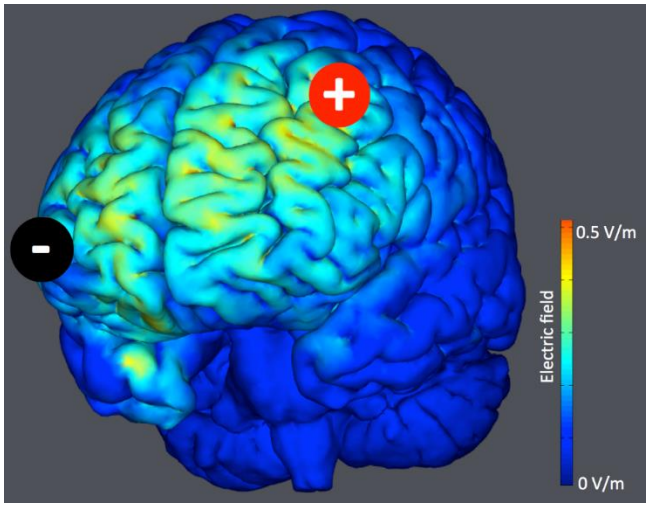
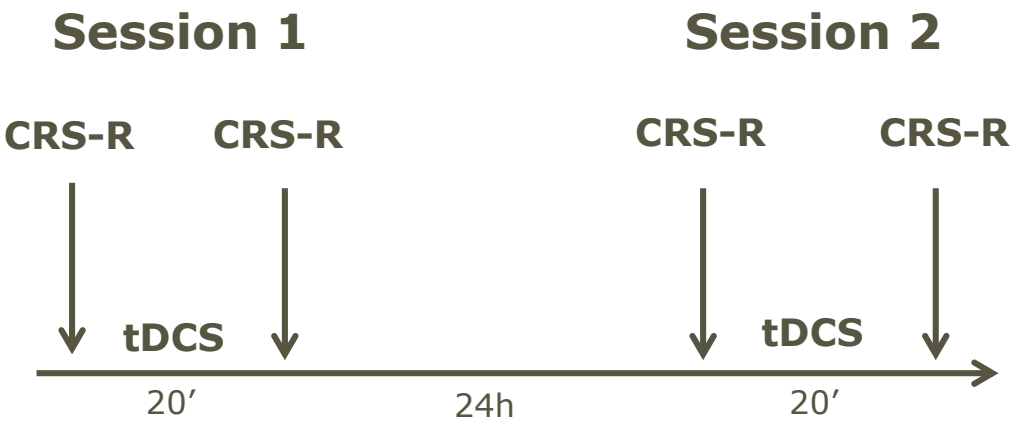
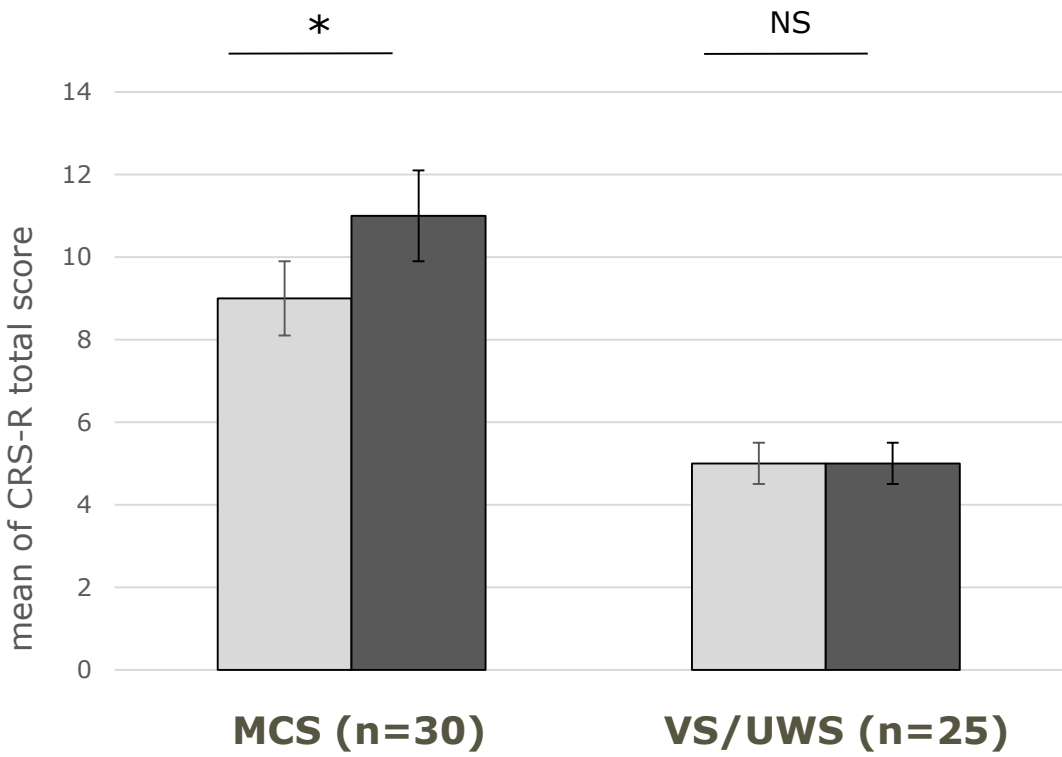




Thibaut et al, *Neurology, 2014*

Results

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



* p<0.001

Thibaut et al, *Neurology, 2014*

Results

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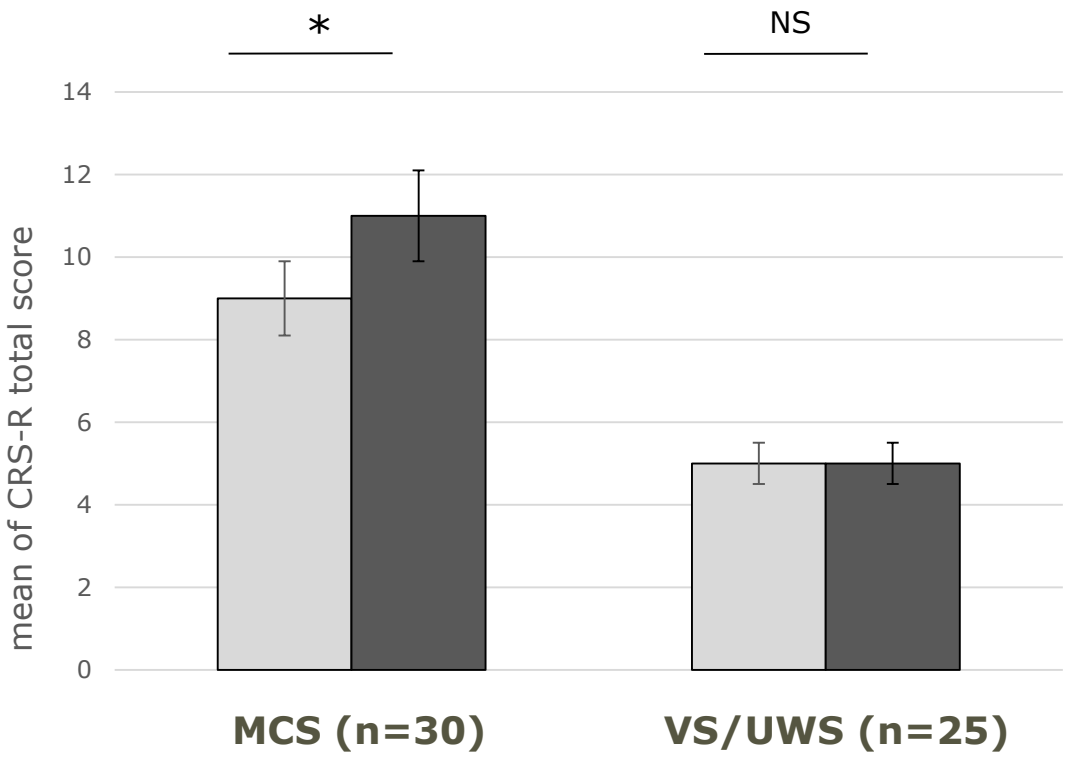
- 25 TBI, 30 NTBI
- 35 chronic (>3 months)

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)



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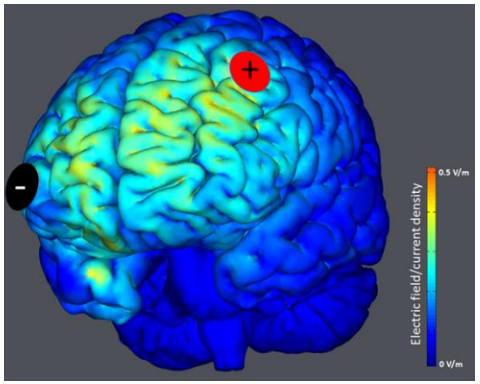
Neurophysiology

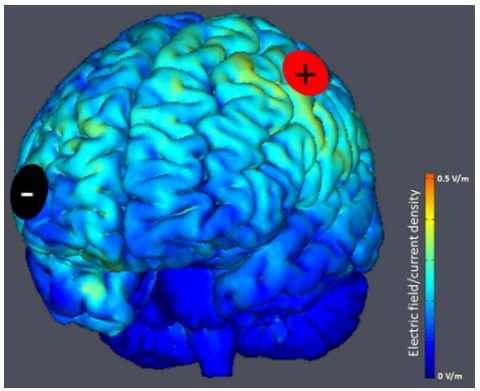
Prefrontal stimulation

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



Motor stimulation

- rCBF ↗ in the left M1, right prefrontal cortex, right S1 (PET-scan)
- Functional connectivity ↗ within premotor, motor and sensorimotor areas (EEG)

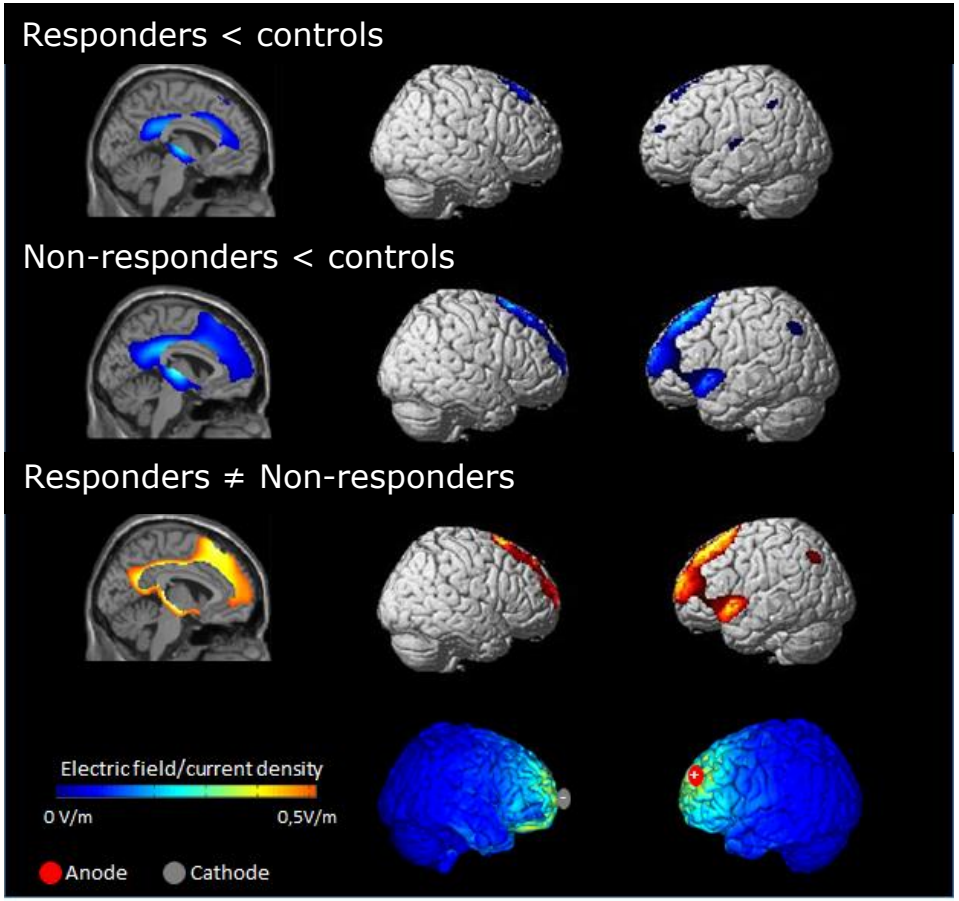


Keeser et al., J Neurosci, 2011
Lang et al., Eur J Neurosci, 2005
Polania, Nitsche and Paulus, HBM, 2010

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



Thibaut et al, *in prep*

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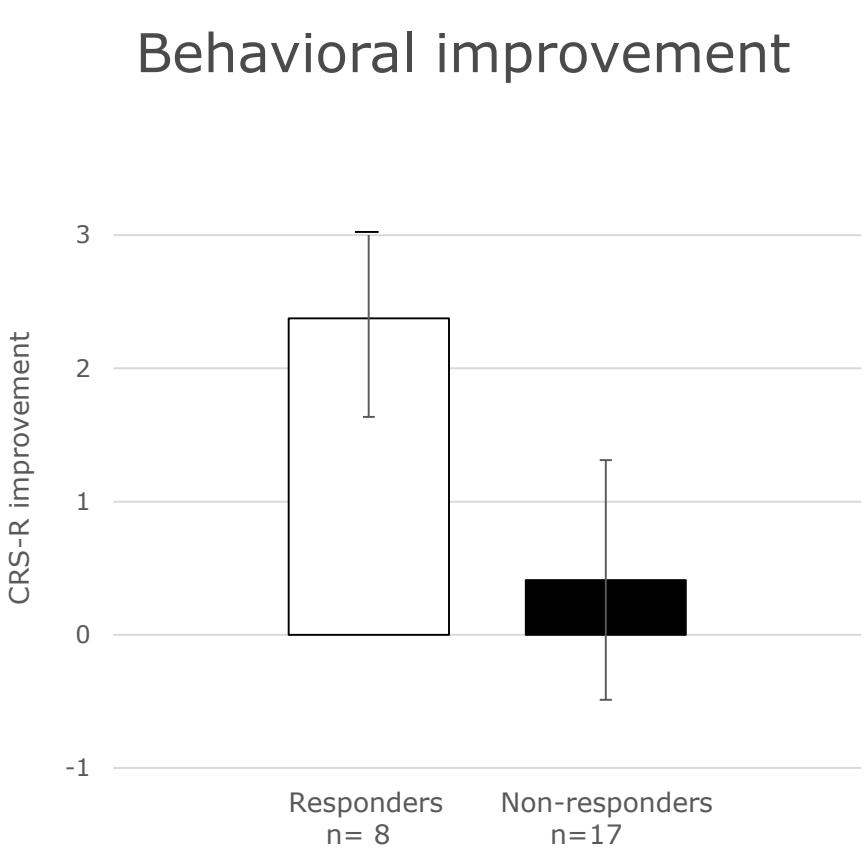

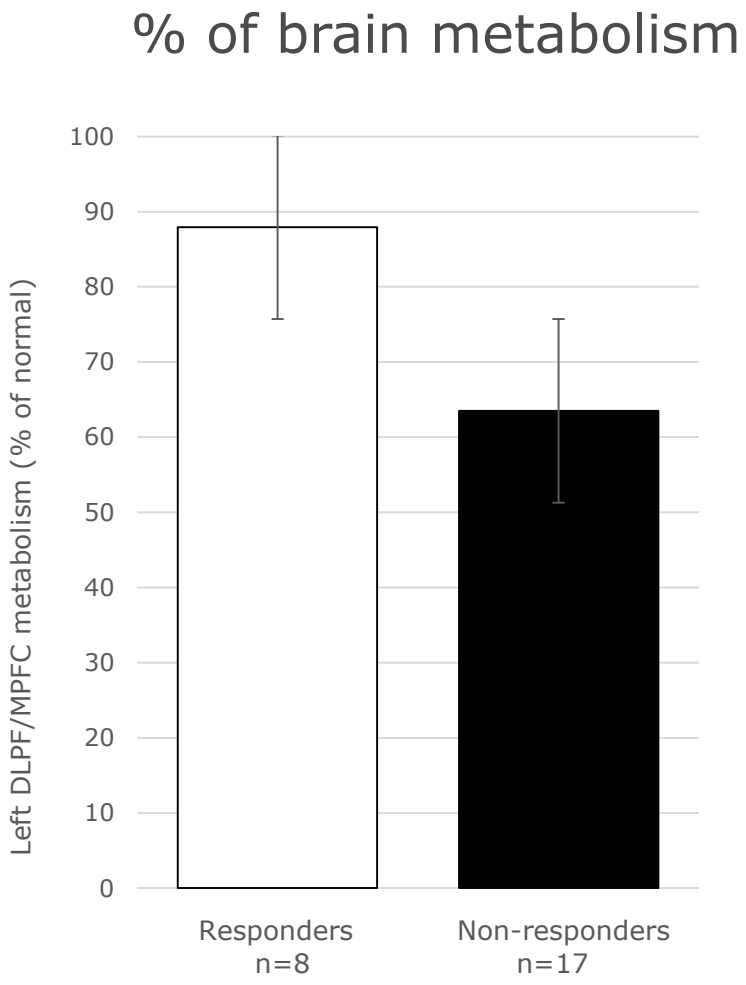

Thibaut et al, *in prep*

Repeated tDCS

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

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Daily stimulations (5days) (Fregni et al., *Pain*, 2006)
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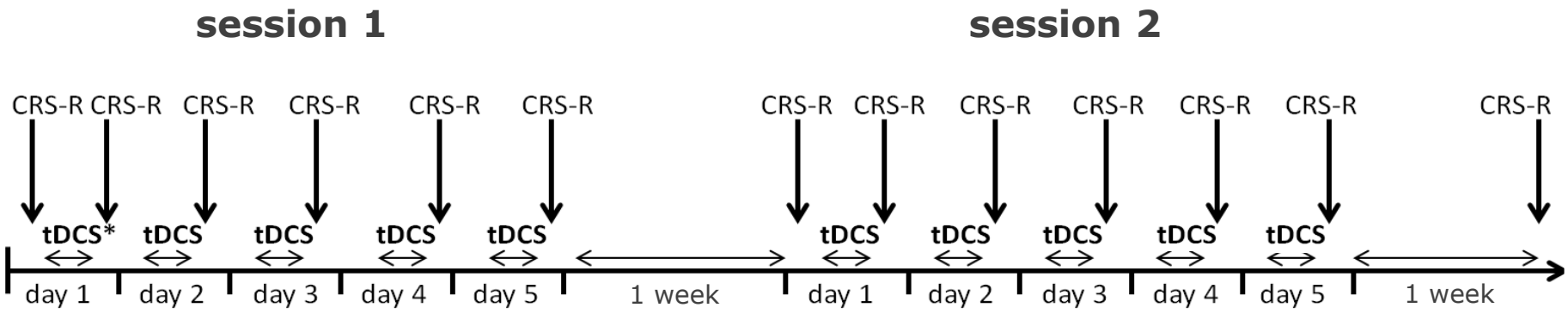
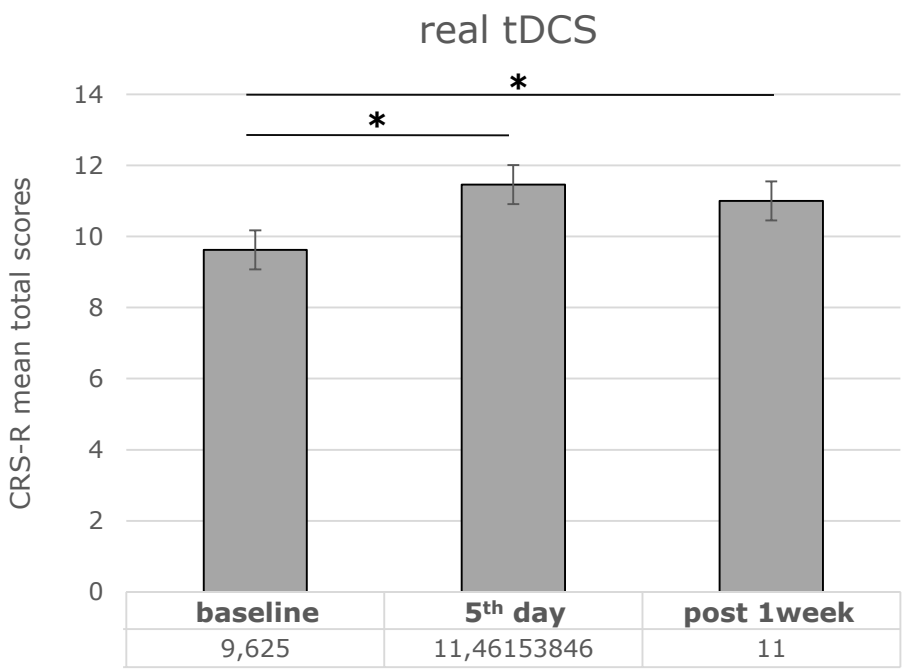
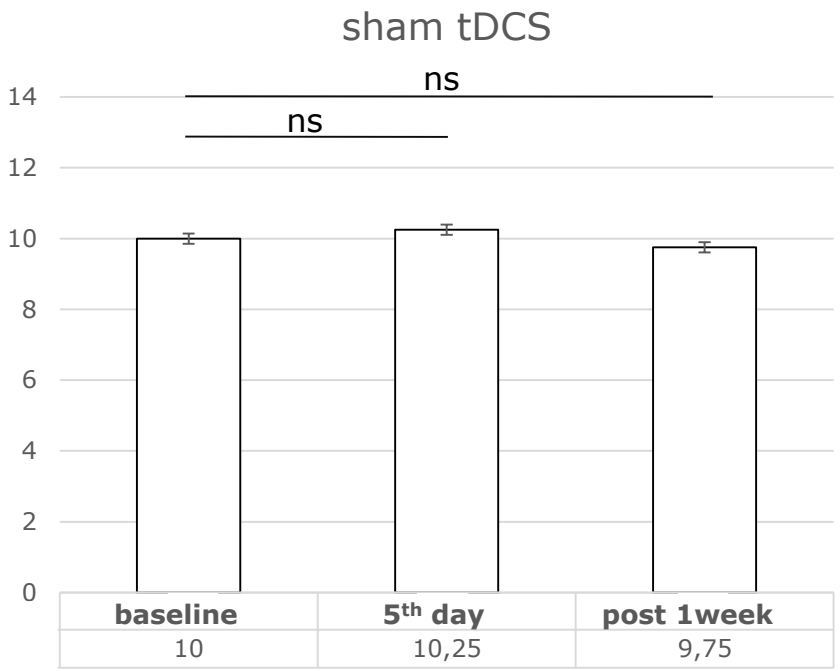


*tDCS = 20minutes

Repeated tDCS

Chronic MCS – N=13





➔ 7 responders (out of 13 patients)

* <0.025

rtDCS in chronic patients

Repeated tDCS in chronic patients at home or nursing home

CEFALY®

Protocol:

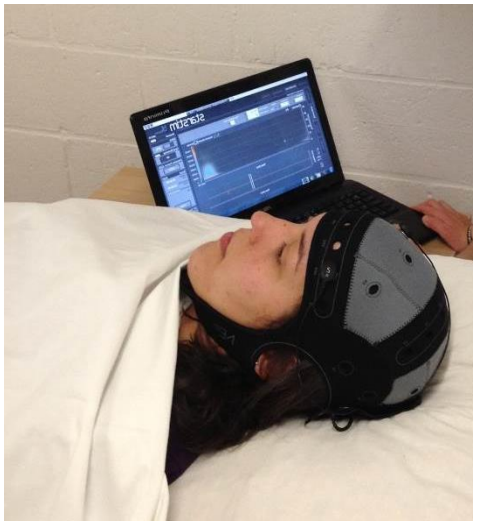
- tDCS over the prefrontal dorsolateral cortex
- 5 days per week during 4 weeks (2 tDCS sessions – real & sham)
- Stimulations made by the family (video)
- Assessment: CRS-R before – after 4 weeks – one month later
- Double blind randomized study (2 months of washout)
- Chronic patients (> 1year post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

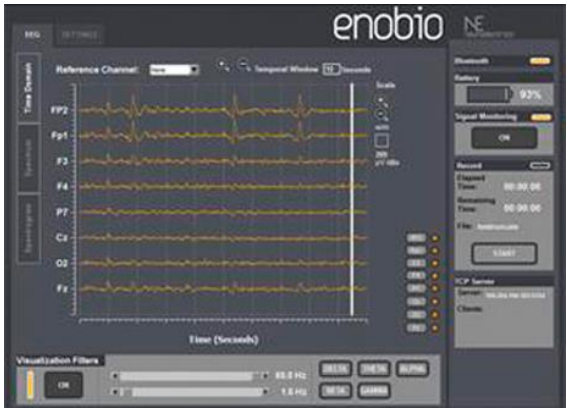
rtDCS in chronic – EEG

tDCS coupled with 8 electrodes EEG

Record cortical activity before, during and after the stimulation

Electrodes: record and stimulate

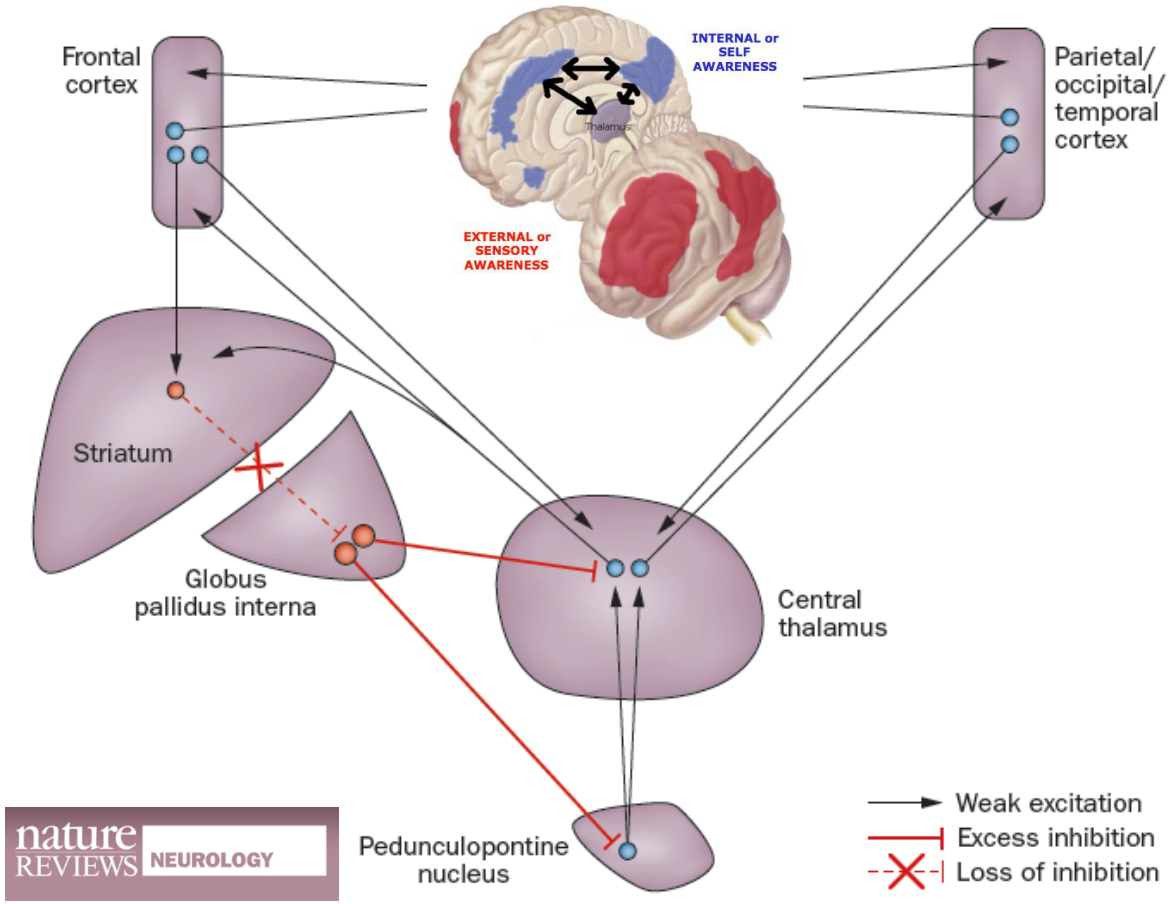




➔ Understand the underlying neurophysiological effect of tDCS on a *damage* or *preserved* area

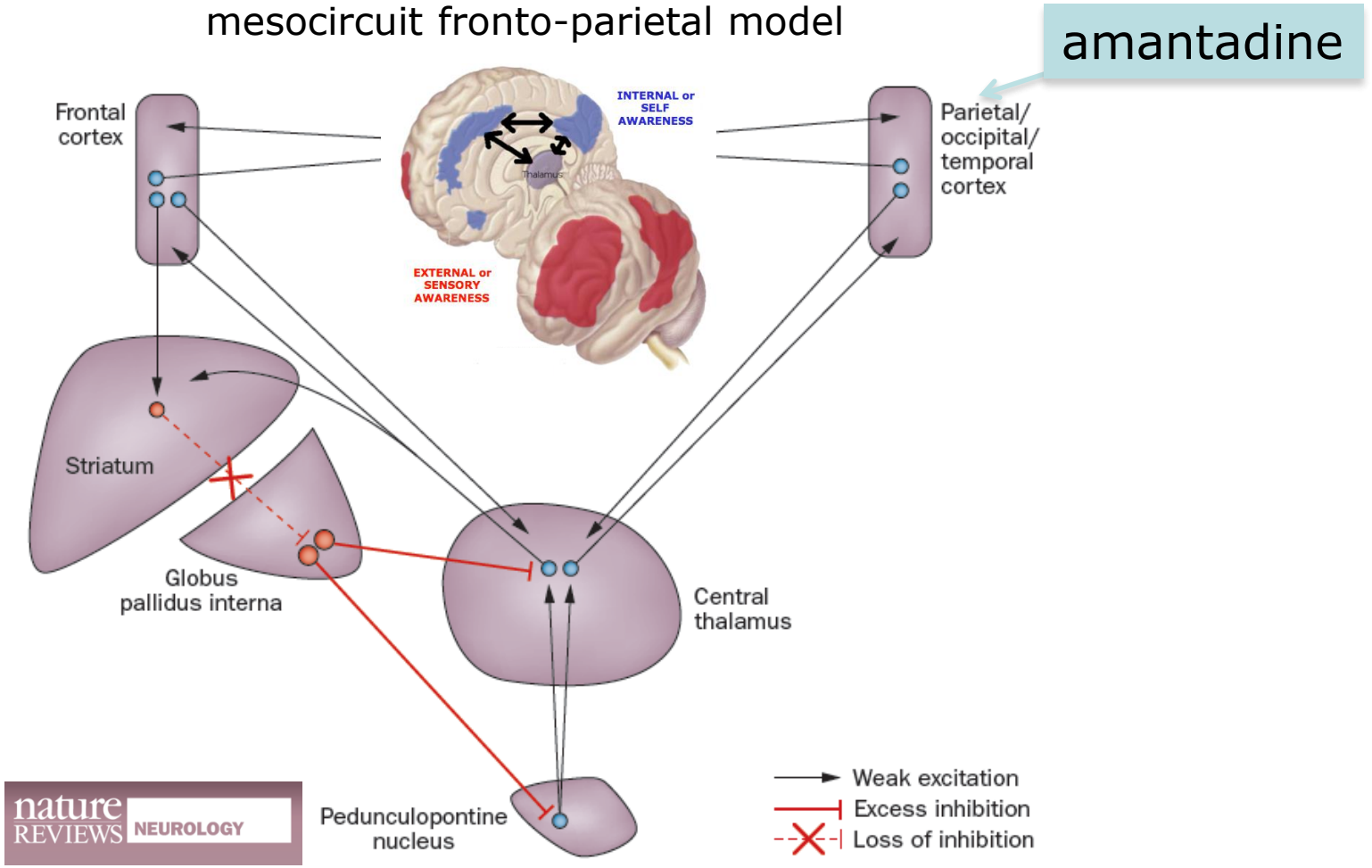
Consciousness ≈ connectivity

mesocircuit fronto-parietal model



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

Consciousness ≈ connectivity



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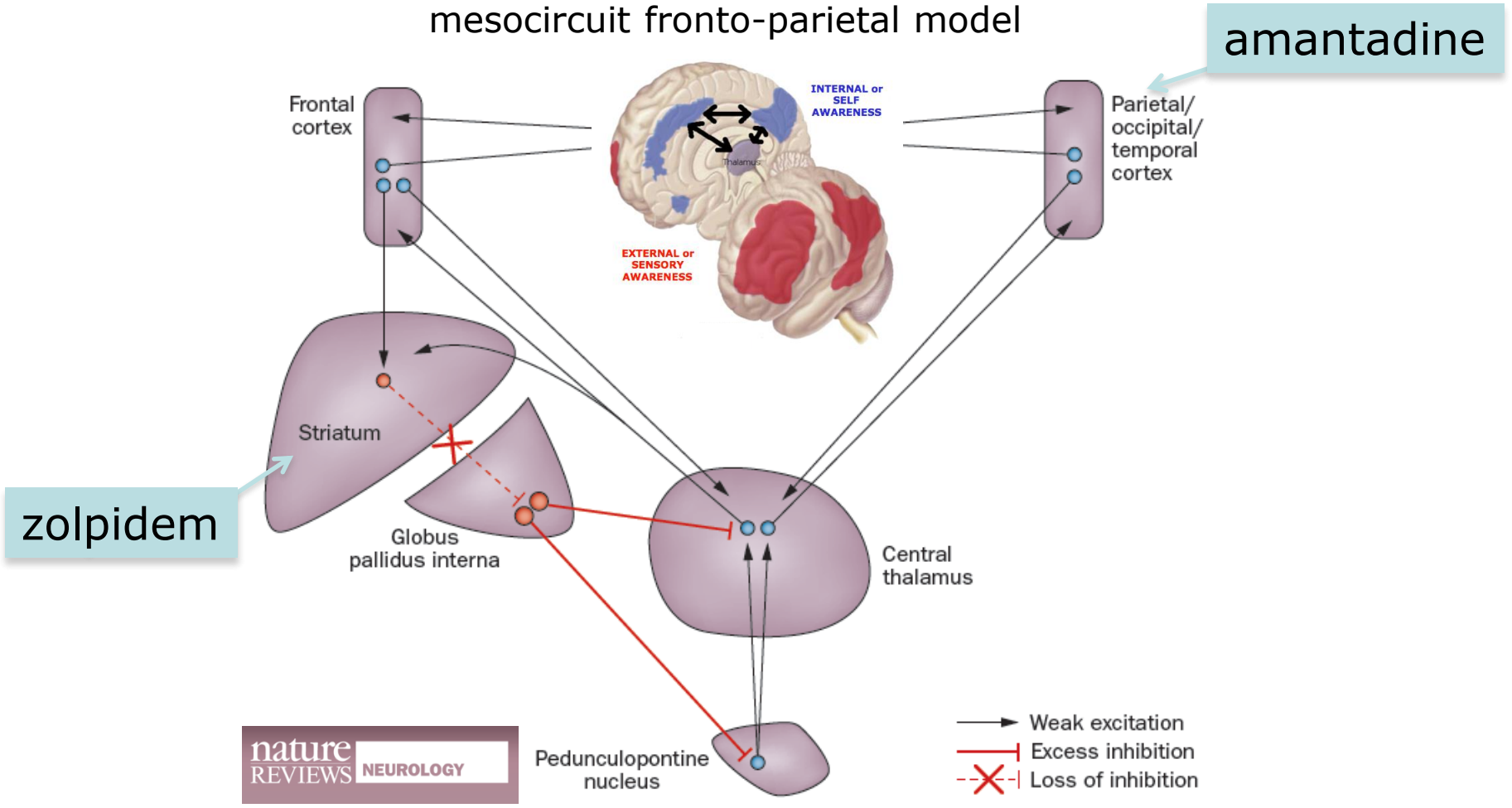

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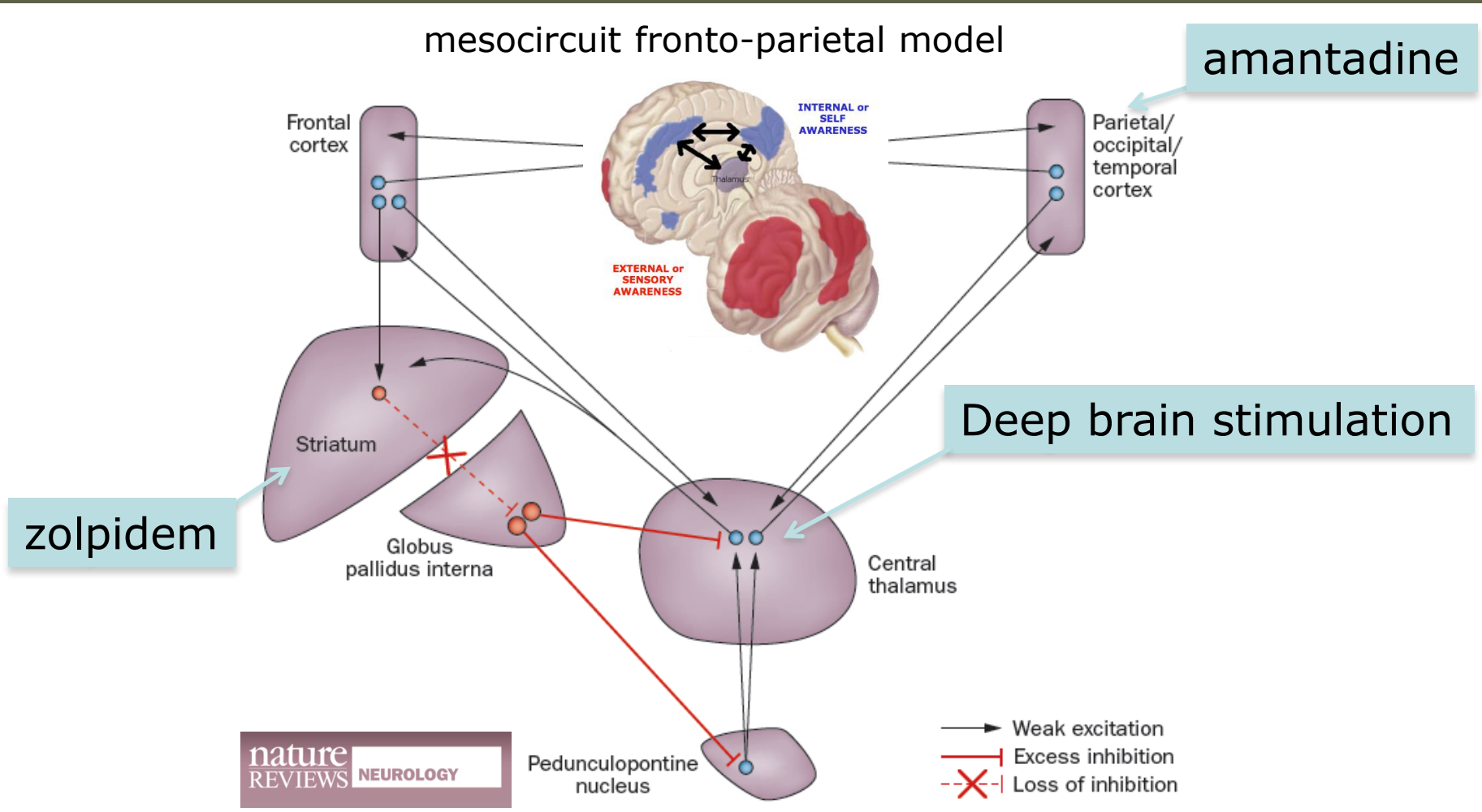
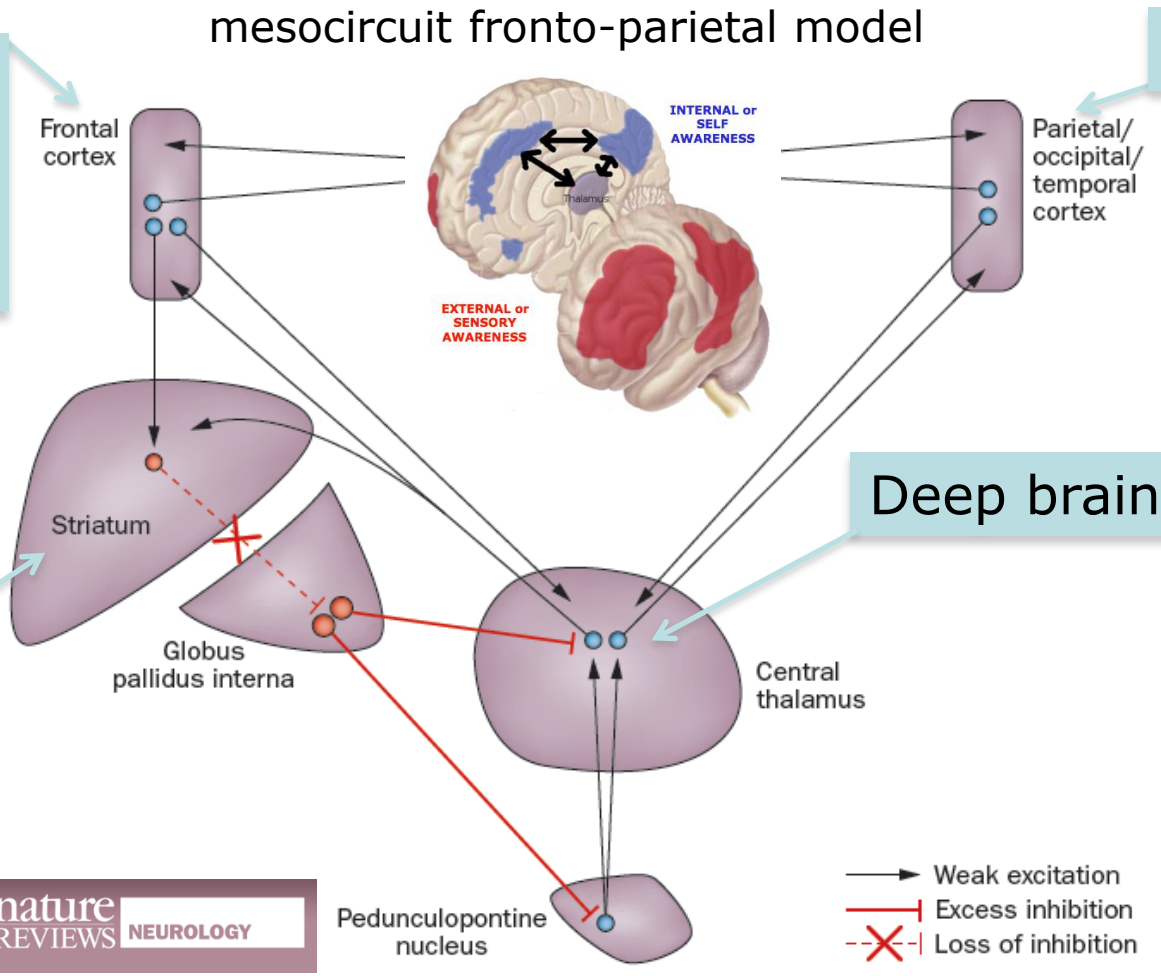


Giacino, Fins, Laureys, Schiff, *Nature Rev Neurol* 2014

Consciousness ≈ connectivity

transcranial Direct Current Stimulation

amantadine

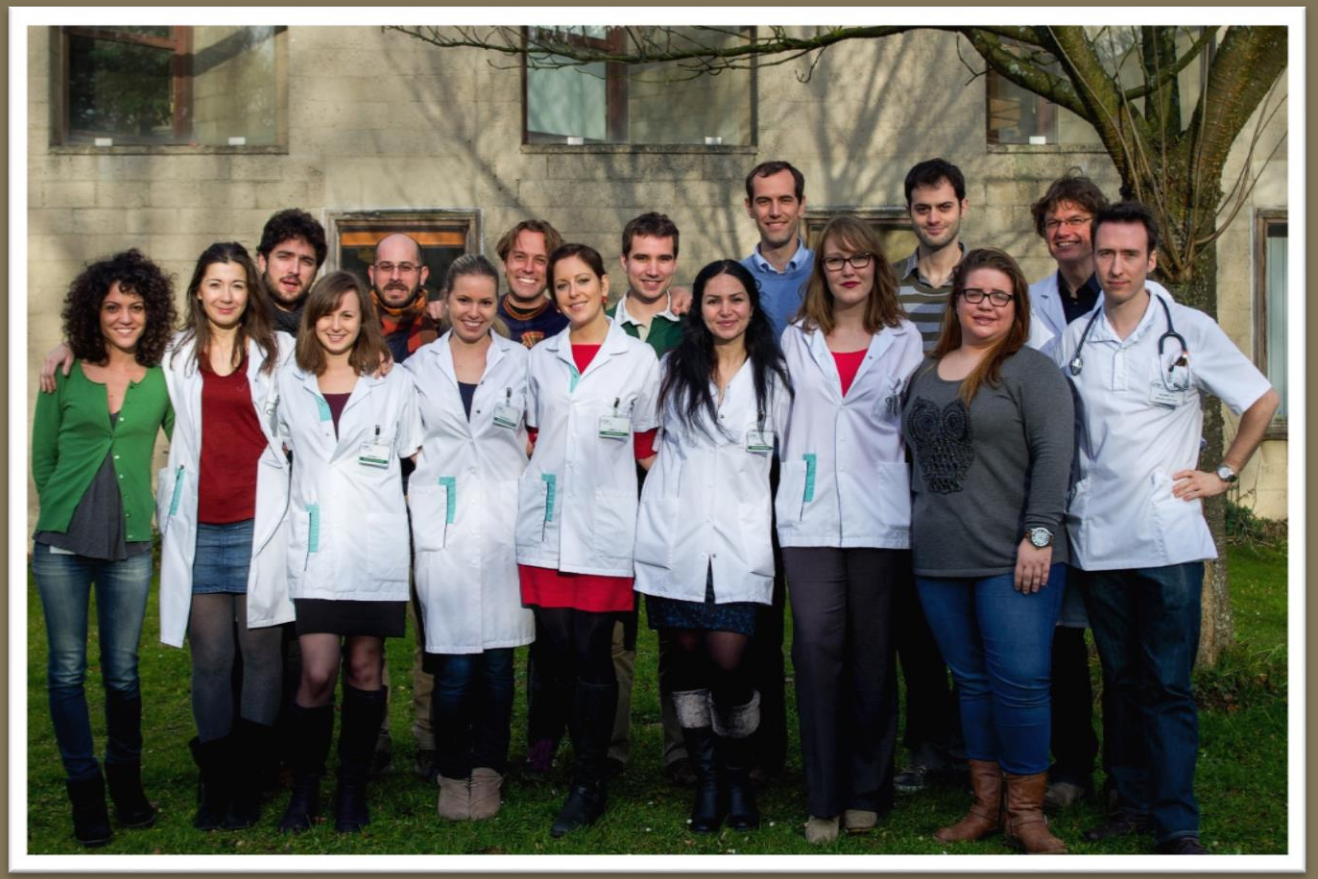


Deep brain stimulation

zolpidem

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

THANK YOU



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DECODER BCI and Detection of Consciousness

IUAP

FNRS Fonds National de la Recherche Scientifique

Critisisms

Limitations:

- Short term effect (after 1-2h patients return to their initial state)
- Moderate clinical change
- Unknown neurophysiological effects on DOC

Hummel et al., Lancet 2006

Clinical improvement

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)

2 VS/UWS ⊃ MCS

Visual pursuit

Response to command

2 MCS ⊃ EXIT

Functional communication

Functional use of objects

Conclusion

- A single stimulation transiently improves CRS-R scores
- Preserved metabolism in the stimulated area is requested
- 5 days of tDCS increase the lasting of the effects

- ➢ Could daily stimulations be helpful for patient's recovery?
- ➢ Could tDCS be implemented in daily clinical practice?

Future: tDCS could help patients with disorders of consciousness (acute or chronic) to increase their interaction with their environment

tDCS – advantages

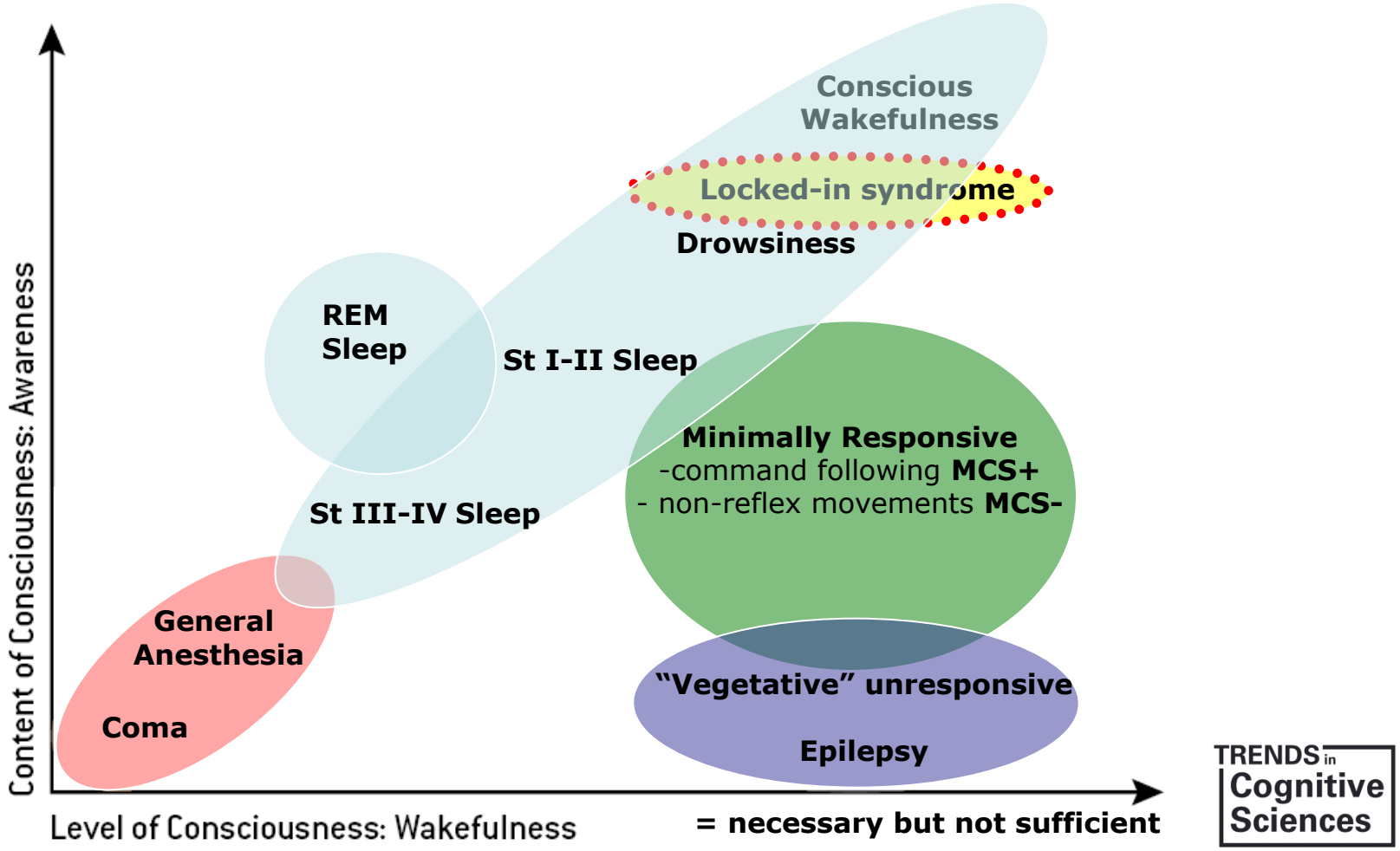
DBS and **Amantadine** improve cognitive functions of patients with disorder of consciousess

But side effects

tDCS $\Longrightarrow$ improve cognition of patients in minimally conscious state without risk of brain damage or seizure

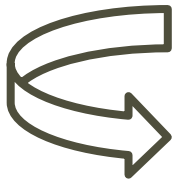
Schiff et al., Nature 2008
Giacino et al., New Eng J Med, 2012
Thibaut et al., Neurology 2014

Reducing consciousness to 2D



Laureys, *Trends in Cognitive Sciences*, 2005

tDCS - Motor



Cognitive effects ⊕

Motor effects ?

Parameters:

2 mA – 20 min

Cathode: M1 (C3&C4)

(↘spasticity)

Anode: DLPF (F3&F4)

(↗ signs of consciousness)

1. **Behavioral** assessments: CRS-R & Ashworth
2. **EEG**

Hummel et al., Lancet, 2006
Vandermeeren Y et al., Acta Neurol Bel, 2013