



# Restoring consciousness through neuromodulation: Scientific & clinical advances

October 20<sup>th</sup> 2025



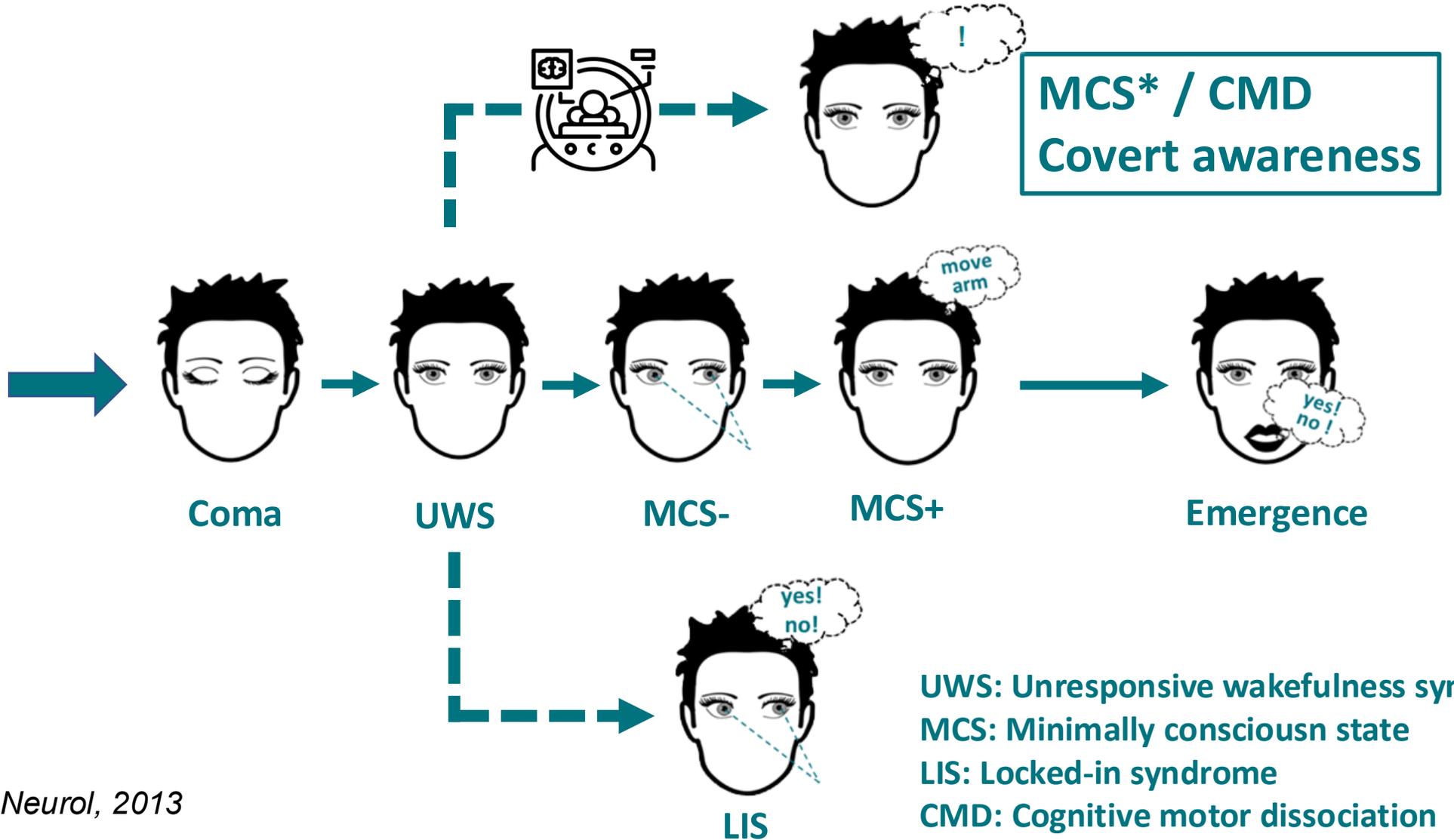
**Fondazione  
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Onlus**

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University Hospital of Liege

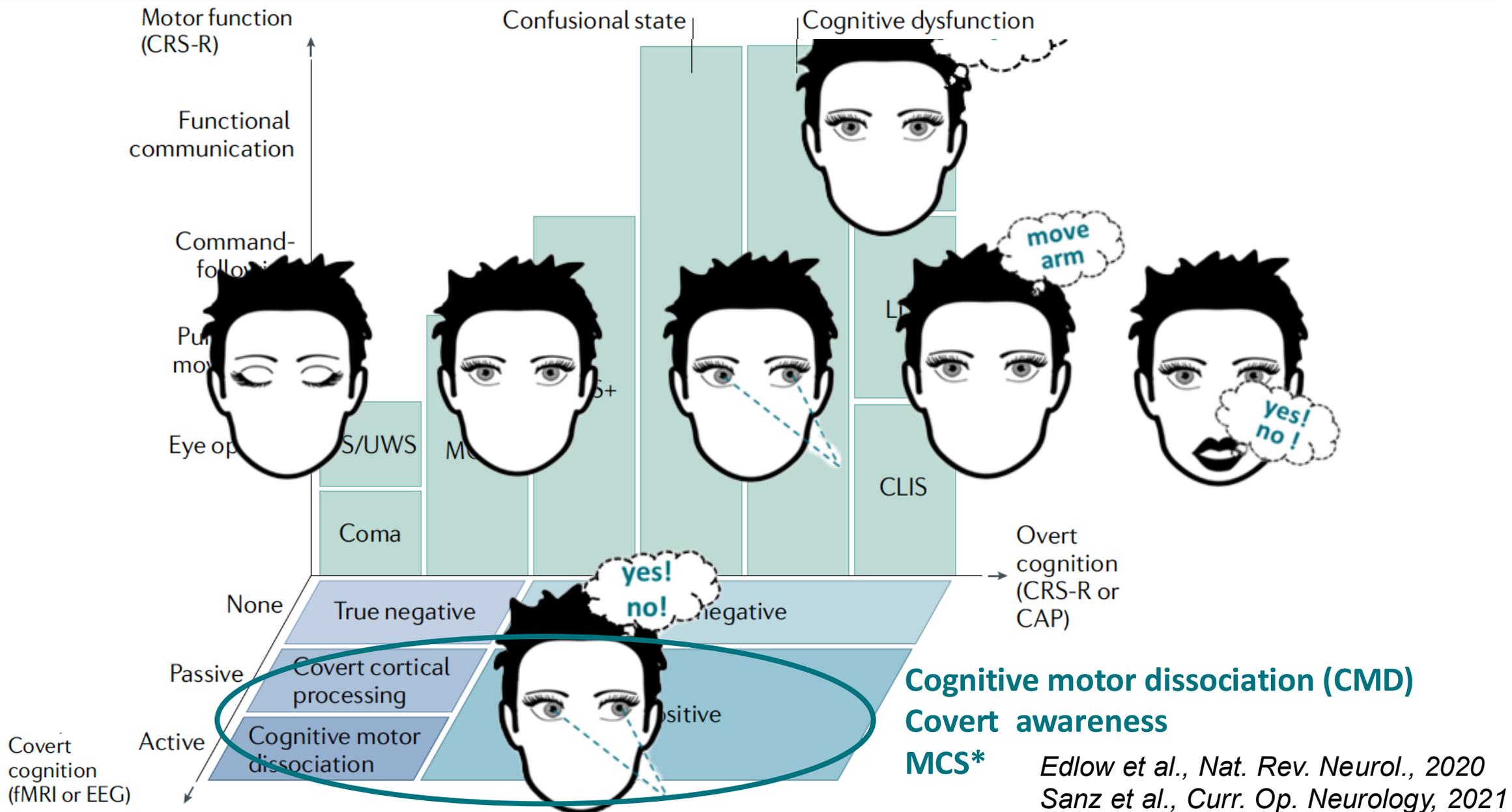
# Disorders of consciousness

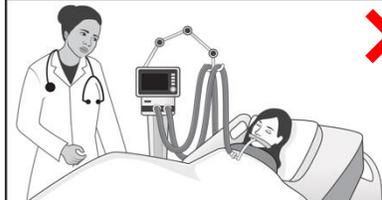
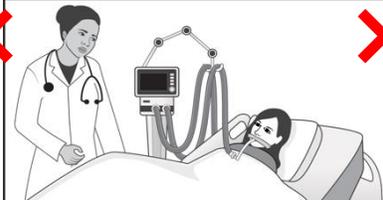
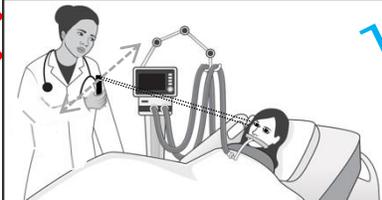
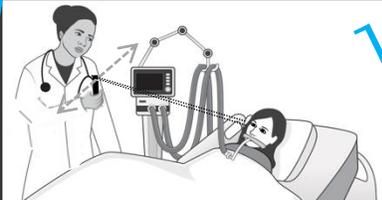
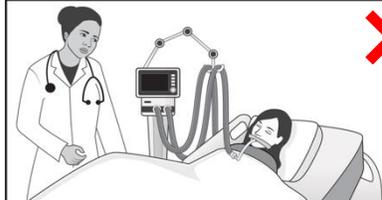
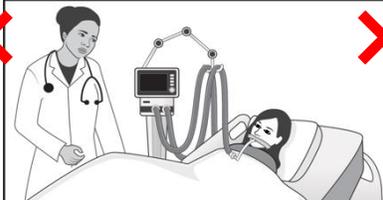
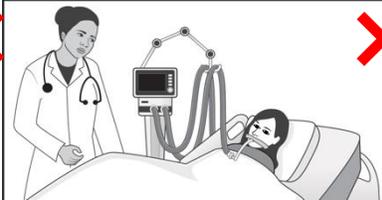
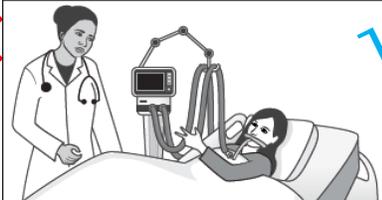
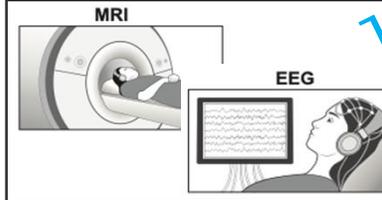
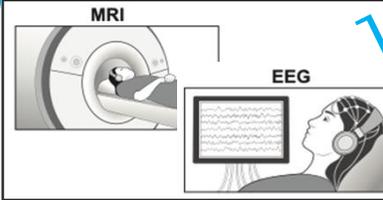
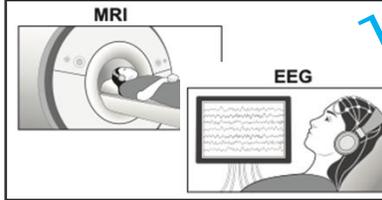
## Trauma

Anoxia  
Hemorrhage  
Metabolic  
Infection  
Inflammation



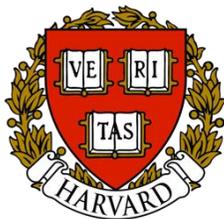
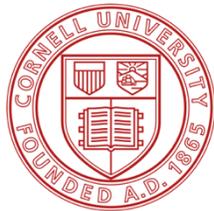
UWS: Unresponsive wakefulness syndrome  
MCS: Minimally conscious state  
LIS: Locked-in syndrome  
CMD: Cognitive motor dissociation



Clinical diagnosis		COMA	VS/UWS	MCS-	MCS+
Neurobehavioral assessment	Arousal	 ❌	 ✅	 ✅	 ✅
	Low-level purposeful behavior	 ❌	 ❌	 ✅	 ✅
	Response to command	 ❌	 ❌	 ❌	 ✅
EEG/fMRI assessment	Response to command (EEG/fMRI)	 ❌	 ❌	 ✅	 ✅

*Cognitive Motor Dissociation (CMD)*

6 centres – EU & USA (2006-2023)

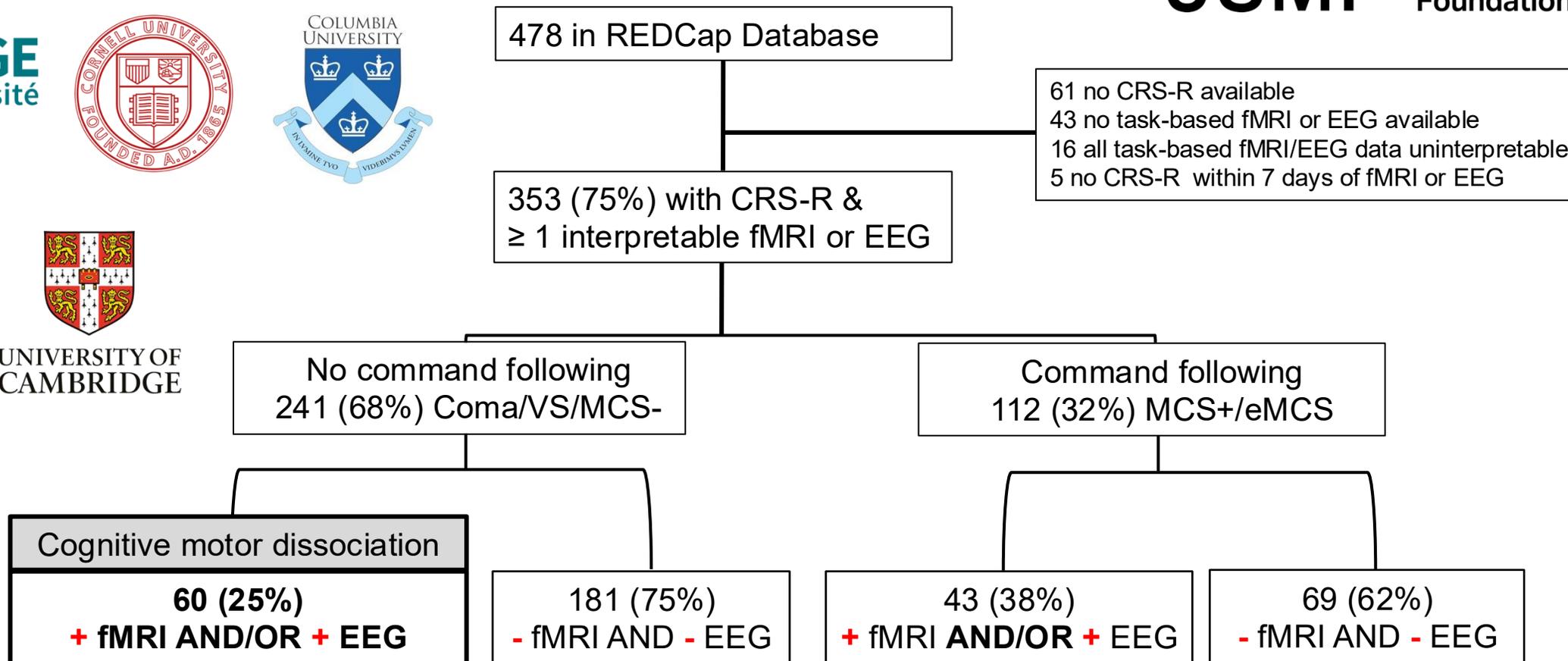


UNIVERSITY OF CAMBRIDGE



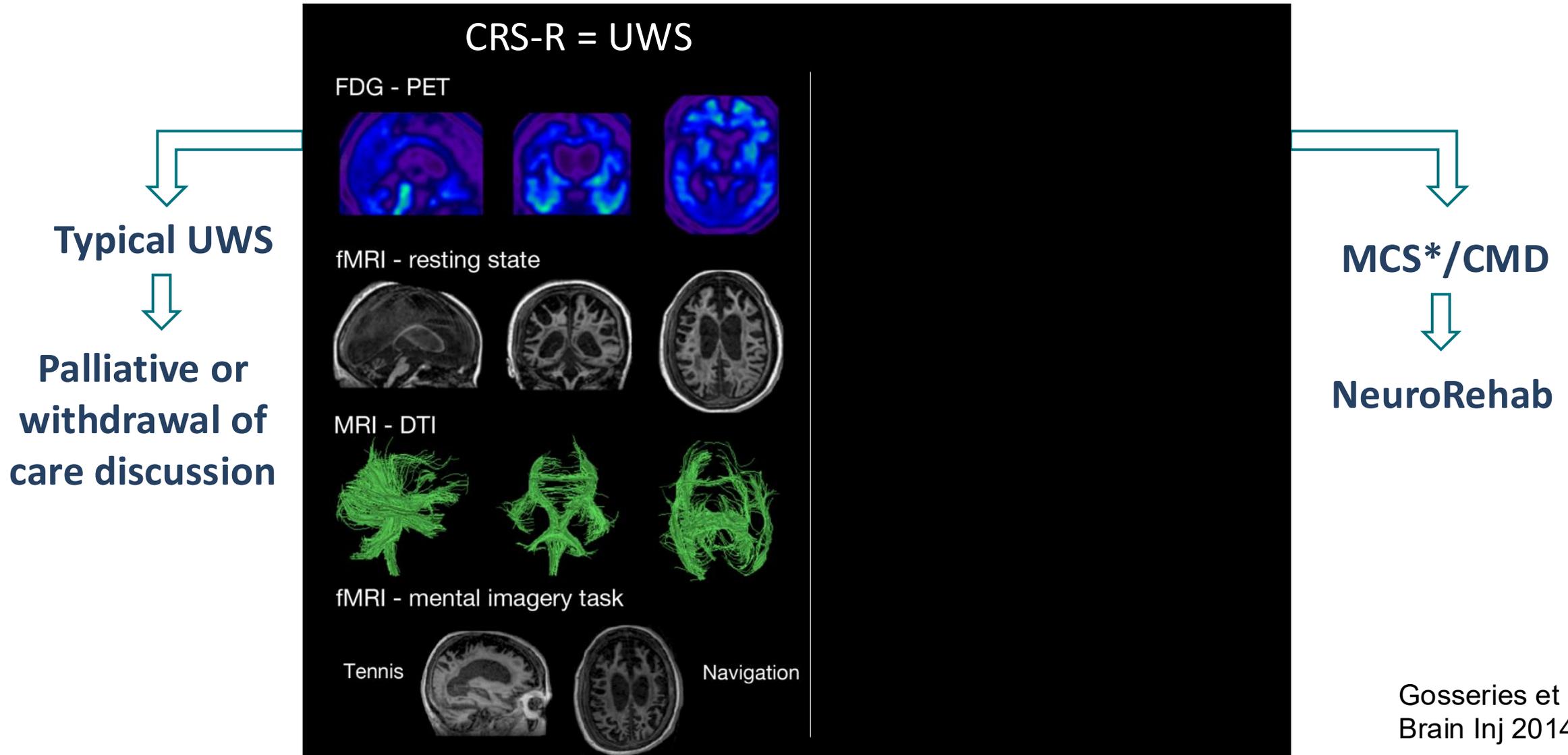
**JSMF**

James S. McDonnell Foundation



↗ TBI, ↘ age, ↗ TSO  
↗ fMRI + EEG

## Multimodal assessments for an accurate diagnosis



## Management of DoC patients



- **Absence of communication**
- Lack of interaction with environment
- Severe motor disability (e.g., spasticity)
- Constantly bedridden
- Fatigability
- Aphasia, blindness, deafness, ...

➔ **Limit access to active interventions**

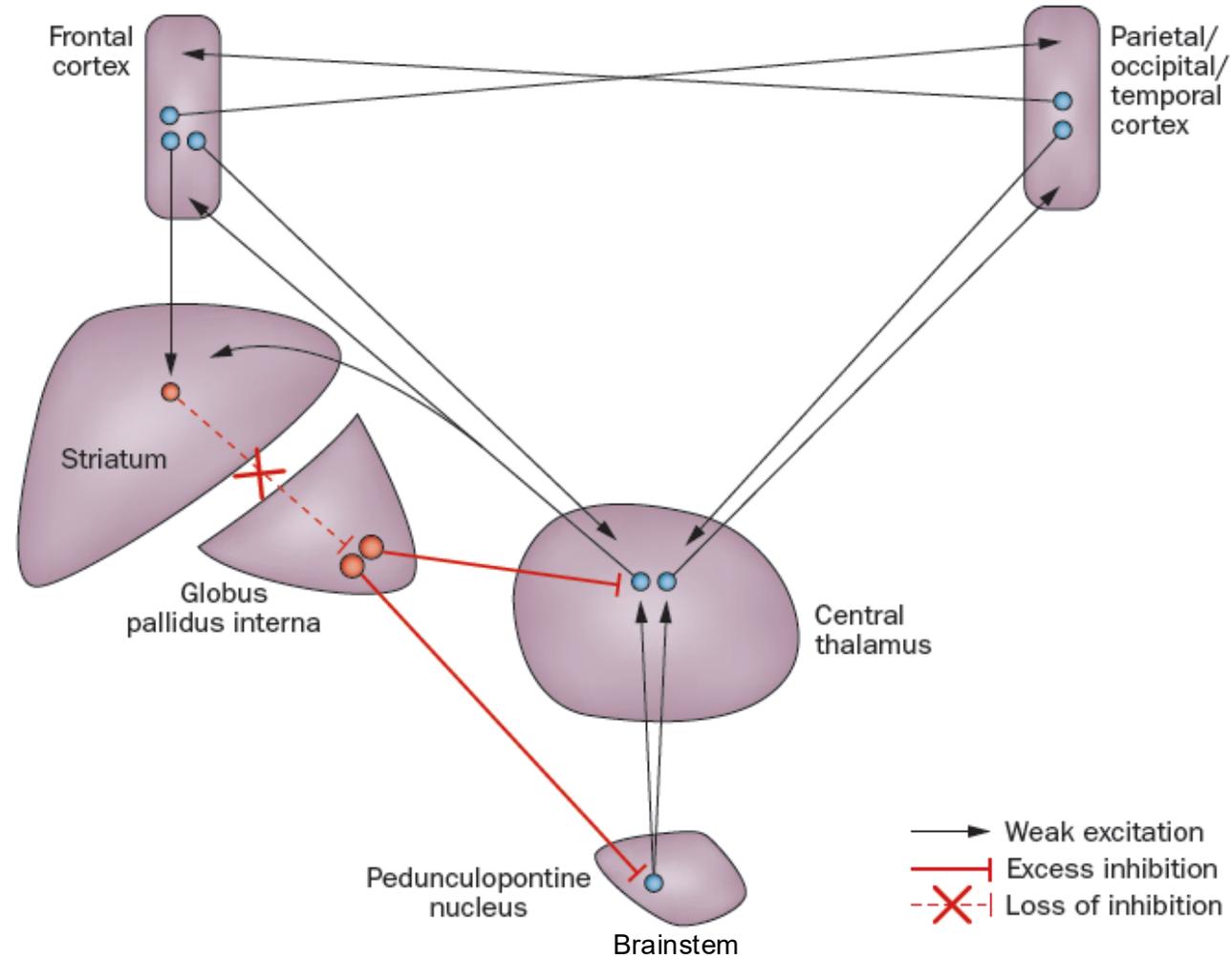
# Studied interventions

CURING C<sup>o</sup>MA<sup>®</sup>

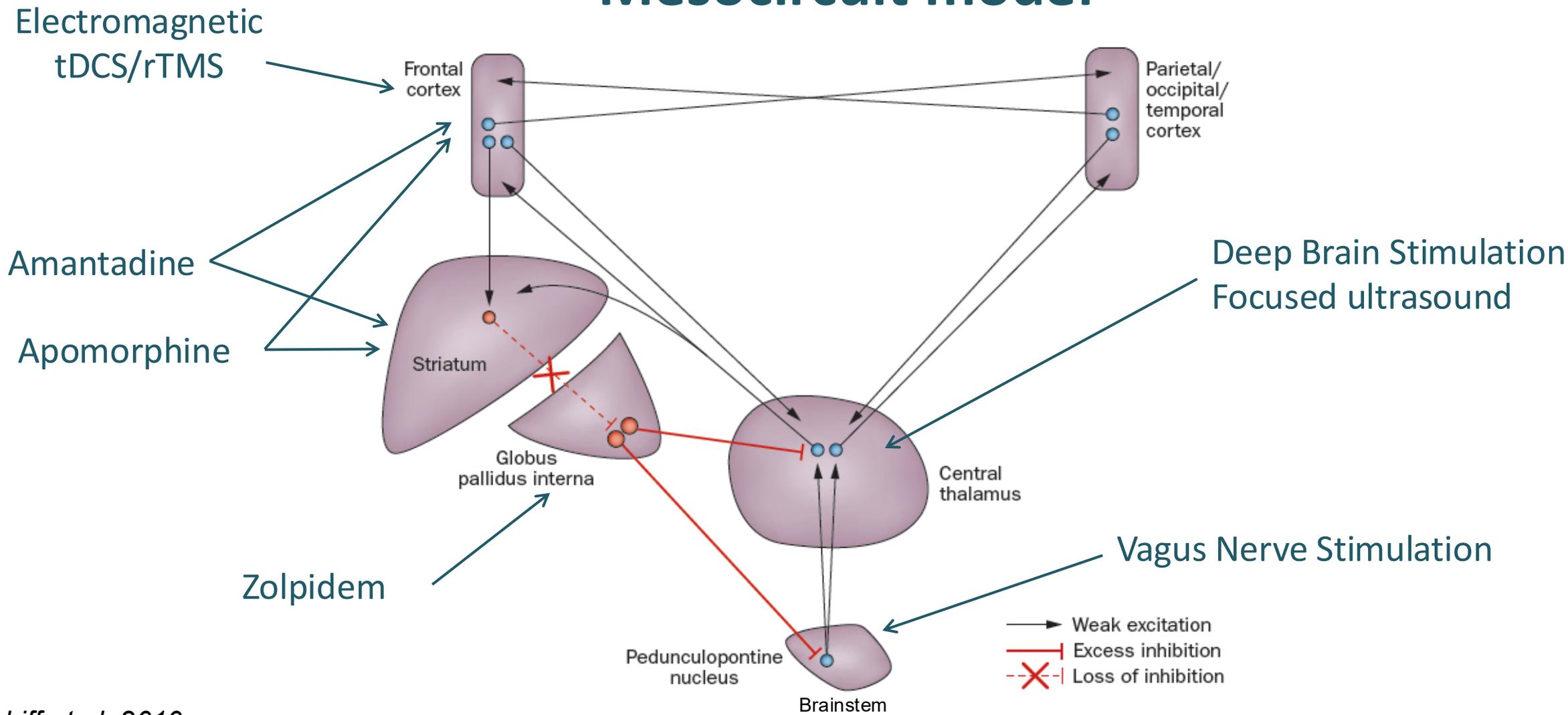


Class	Pharmacologic	Electromagnetic	Mechanical	Sensory	Regenerative
<b>Best evidence</b>	RCT (amantadine)	RCT (tDCS, TMS)	Case series	RCT (auditory)	Phase 1 trials (stem cells)
<b>Efficacy</b>	Faster rate of recovery	Improvement 30-50% MCS patients (frontal tDCS)	Improvement in 1/1 acute & 2/3 chronic patients	Behavioral + fMRI improvements	Possibly faster recovery
<b>Safety</b>	+	DBS – tDCS, TMS, taVNS: ++	++	Tactile, auditory: +++ Vestibular: ++	Unknown
<b>Limits</b>	Delayed action, drug tolerance, transient effects	DBS: invasive tDCS, TMS, taVNS: moderate transient effects	Early development	Tactile, auditory: uncertain effects, Vestibular: early development	Early development
<b>Ongoing trials</b>	4	10	1	5	0

# Mesocircuit model



# Mesocircuit model



# Amantadine

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Placebo-Controlled Trial of Amantadine for Severe Traumatic Brain Injury

Joseph T. Giacino, Ph.D., John Whyte, M.D., Ph.D., Emilia Bagiella, Ph.D., Kathleen Kalmar, Ph.D., Nancy Childs, M.D., Allen Khademi, M.D., Bernd Eifert, M.D., David Long, M.D., Douglas I. Katz, M.D., Sooja Cho, M.D., Stuart A. Yablon, M.D., Marianne Luther, M.D., Flora M. Hammond, M.D., Annette Nordenbo, M.D., Paul Novak, O.T.R., Walt Mercer, Ph.D., Petra Maurer-Karattup, Dr.Rer.Nat., and Mark Sherer, Ph.D.

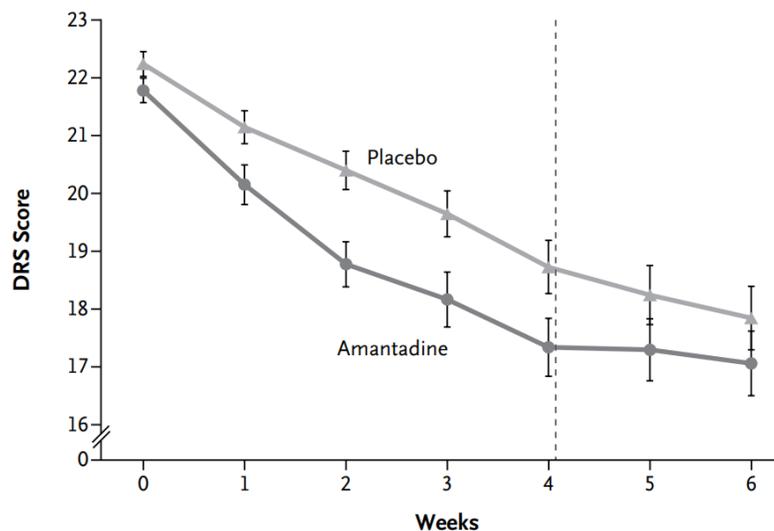
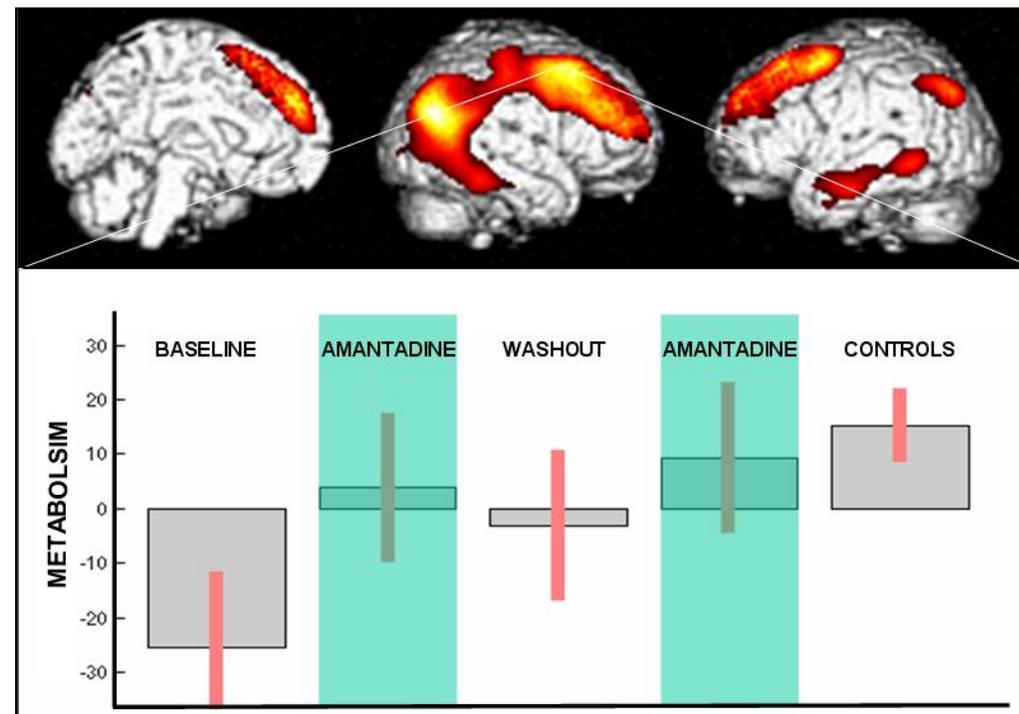


Figure 1. Mean Disability Rating Scale (DRS) Scores during the 6-Week Assessment Period, According to Study Group.

Giacino et al, NEJM, 2012



Schnakers et al, JNNP, 2008

➔ Ongoing multimodal multicenter RCT

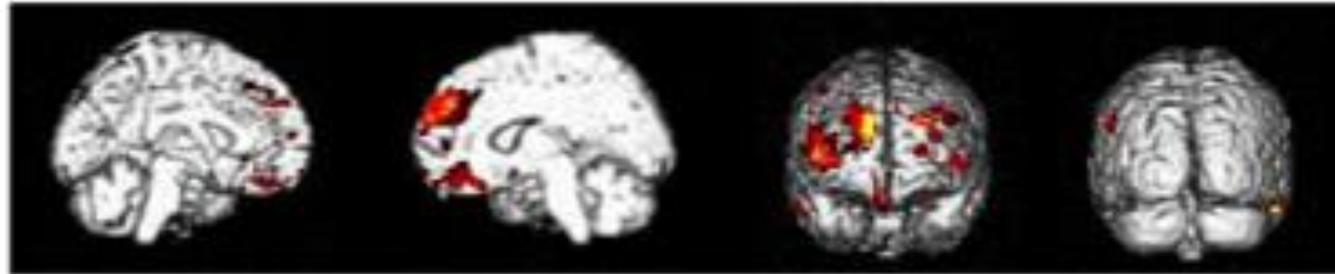


A. Gillet

# Zolpidem

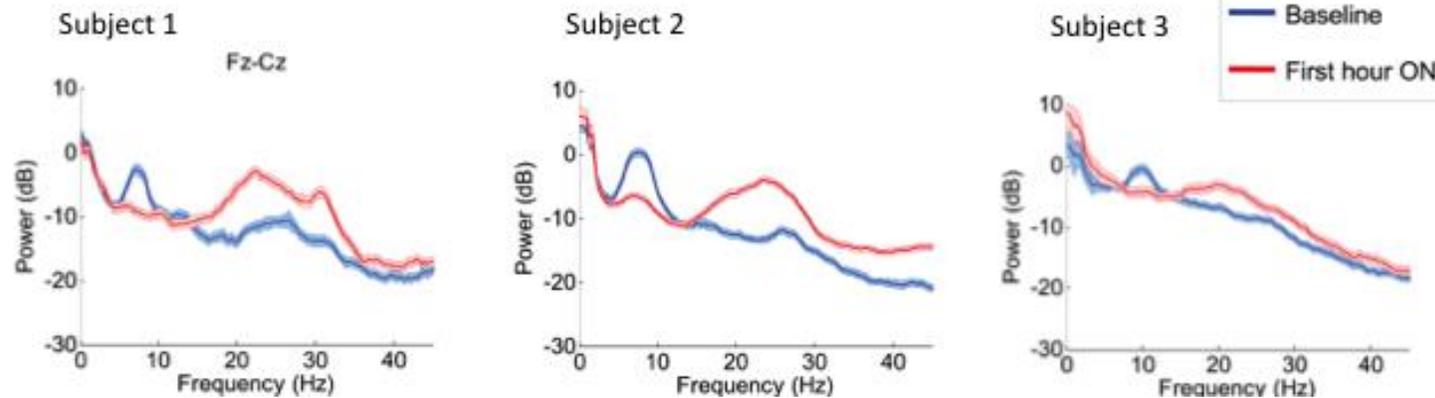
- Brain metabolism in responders (~5% of DoC patients)

Zolpidem  
> Placebo



N=3

- Brain electrical activity in responders



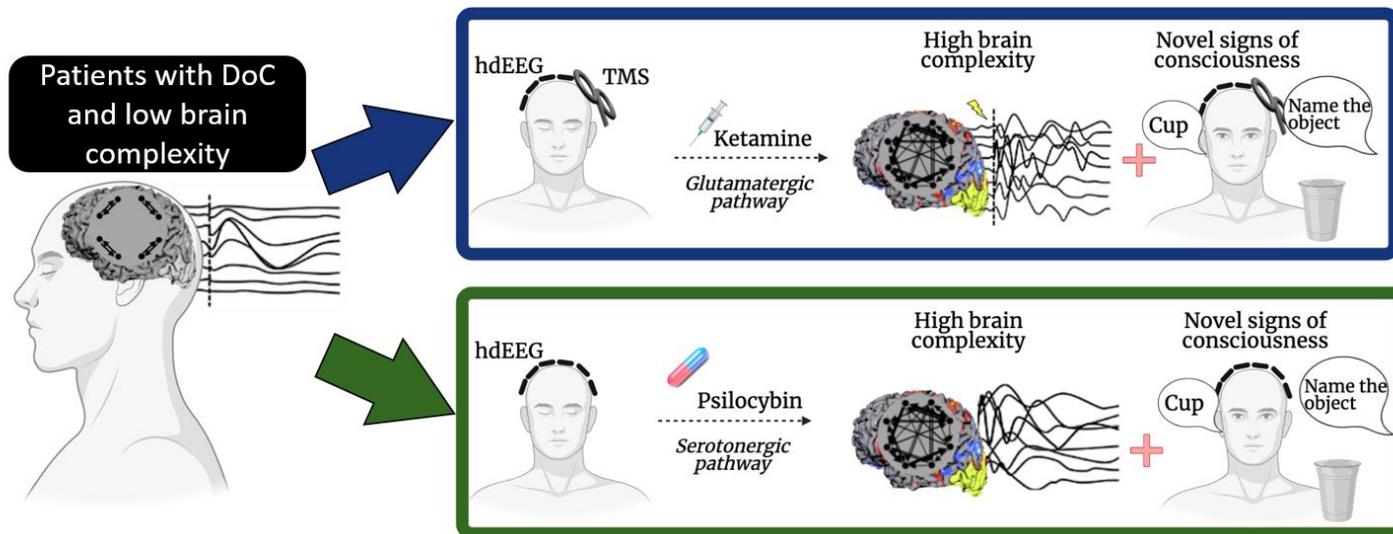
N=3



Fatemeh  
Seyfzadeh

➔ Ongoing RCT

# Psychedelics to treat DoC ?



**Ketamine**  
NMDAR antagonist

**Psilocybin**  
serotonin agonist



O. Gosseries



N. Lejeune



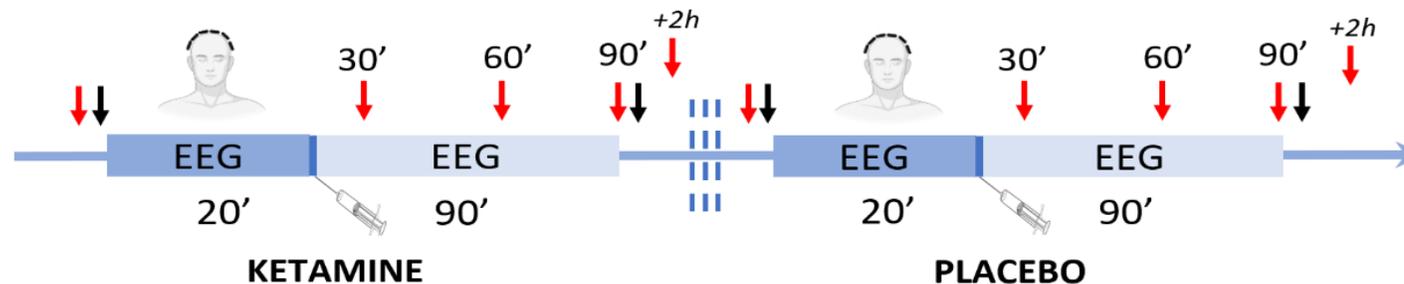
C. Martial



V. Bonhomme

1st pilot : reduced spasticity & responsiveness

Cardone et al. iScience 2024



# Neuromodulation : how to approach the system?

## Top-down stimulations

Transcranial electrical stimulation (tES)

Repetitive transcranial magnetic stimulation (rTMS)

## Central stimulations

Deep brain stimulation (DBS)

Low intensity focused ultrasound (LIFU)

## Bottom-up stimulations

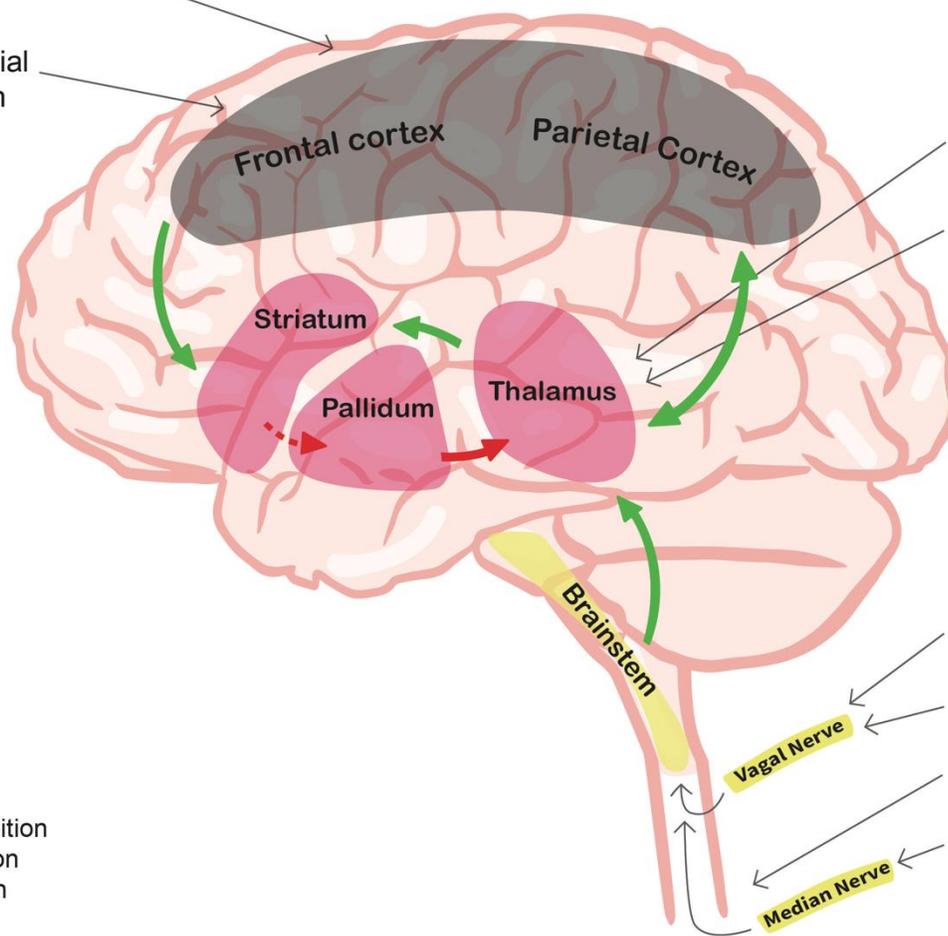
Transauricular vagal nerve stimulation (tVNS)

Vagal nerve stimulation (VNS)

Spinal cord stimulation (SCS)

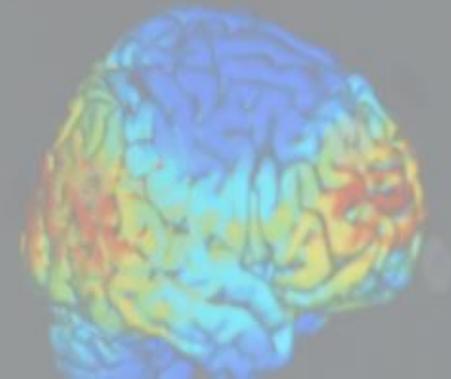
Median nerve stimulation (MNS)

→ Excess of Inhibition  
- - - Loss of Inhibition  
→ Weak excitation



- Top-down stimulations
- Central stimulations
- Bottom-up stimulations

# TOP-DOWN APPROACHES



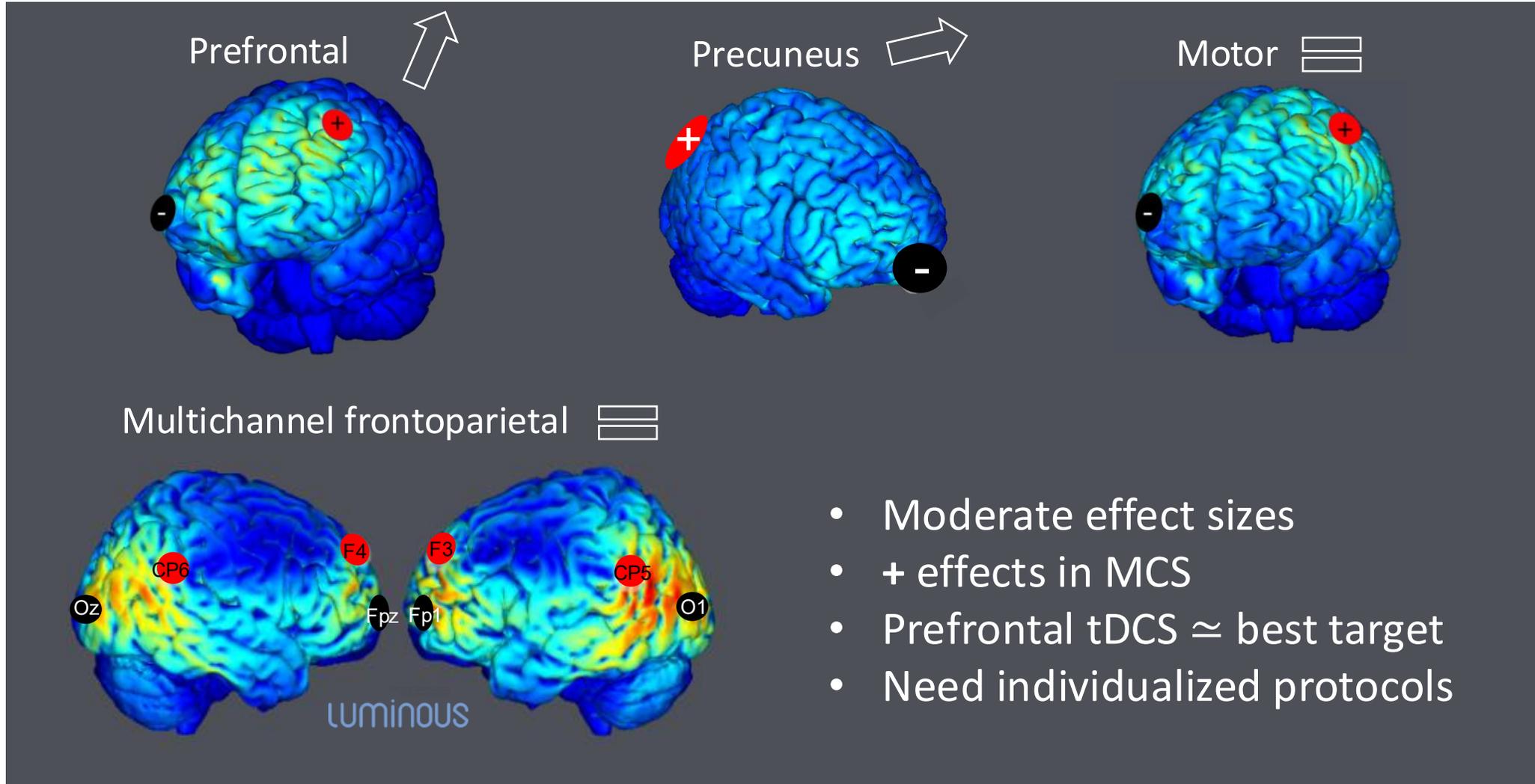
# Transcranial Direct Current Stimulation (tDCS)



G. Martens

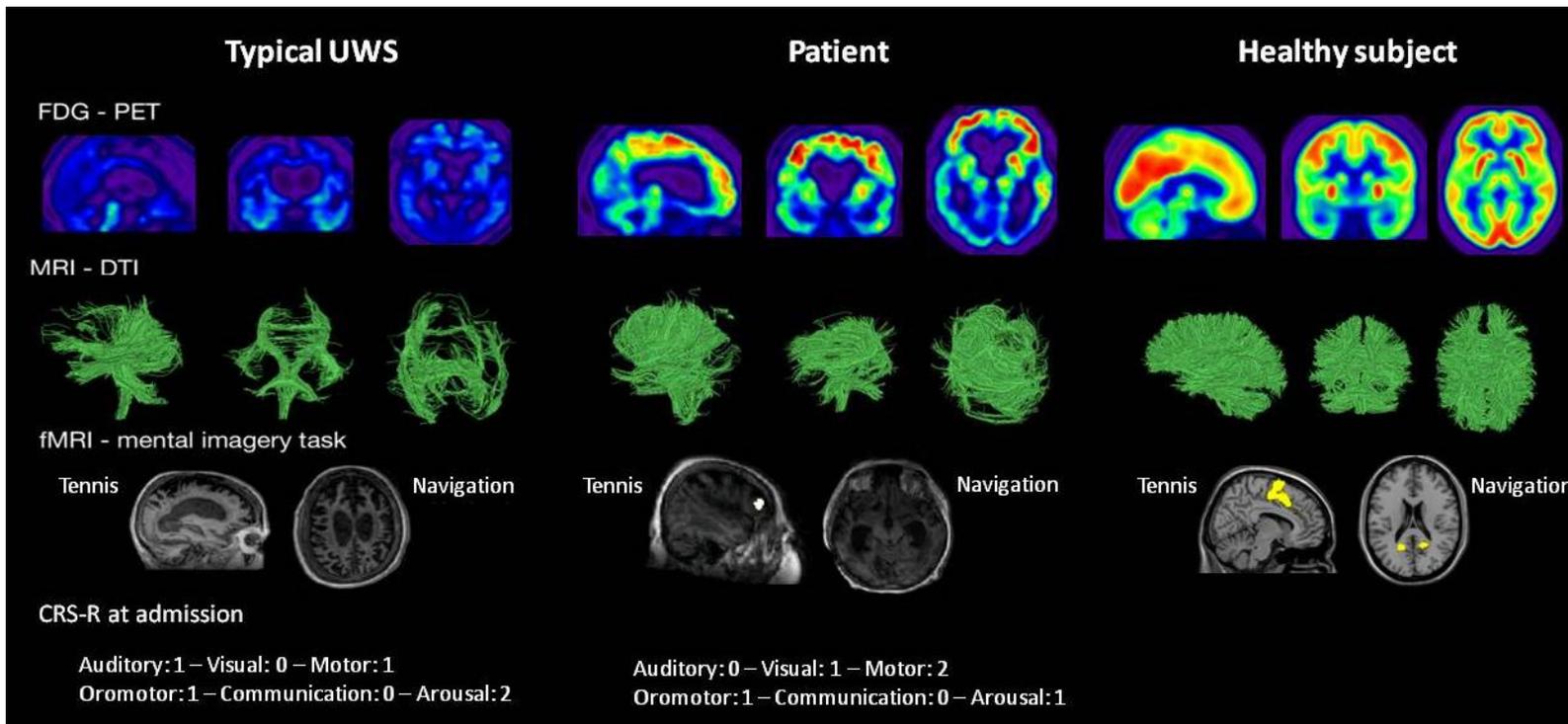


A. Barra



- Moderate effect sizes
- + effects in MCS
- Prefrontal tDCS  $\simeq$  best target
- Need individualized protocols

## tDCS & Cognitive Motor Dissociation



- 67yo woman in UWS for 4y after subarachnoid hemorrhage
- Out of 7 CRS-R, 1 L to P
- **Consistent response to command only after tDCS**

➔ tDCS may facilitate motor execution of command when cognitive functions are (partially) preserved

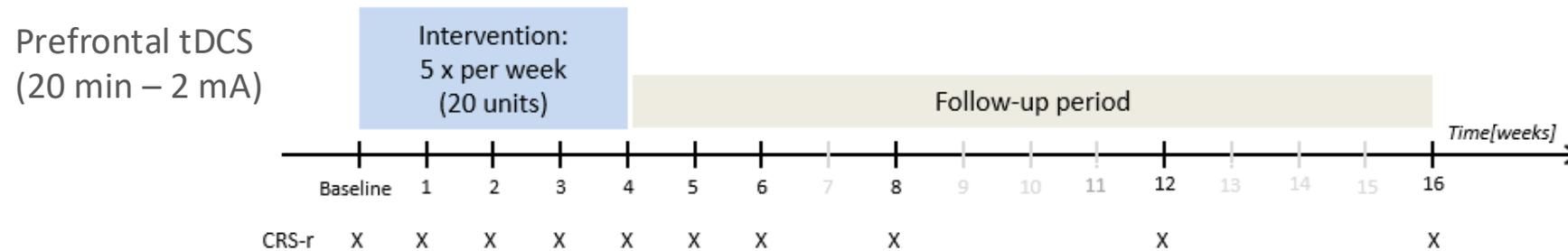
## tDCS multicenter trial



- Are 4 weeks of prefrontal tDCS more effective than sham in improving consciousness in patients with DoC while being in rehabilitation?
- Is there a difference between TBI/nTBI and UWS/MCS?
- Can the effect last over time (3 months follow-up)?

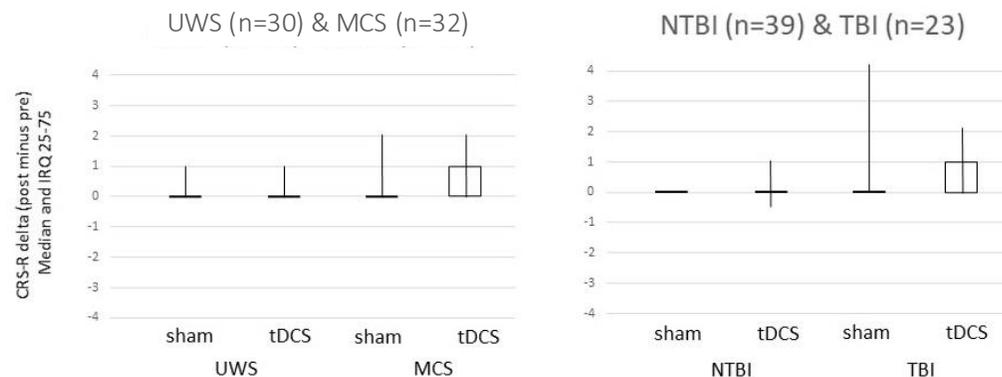
# tDCS multicenter trial

→ 62 patients: 32 MCS, 23 TBI, 33 active tDCS, age:  $44 \pm 14$  yo, TSO:  $37 \pm 24$ w.

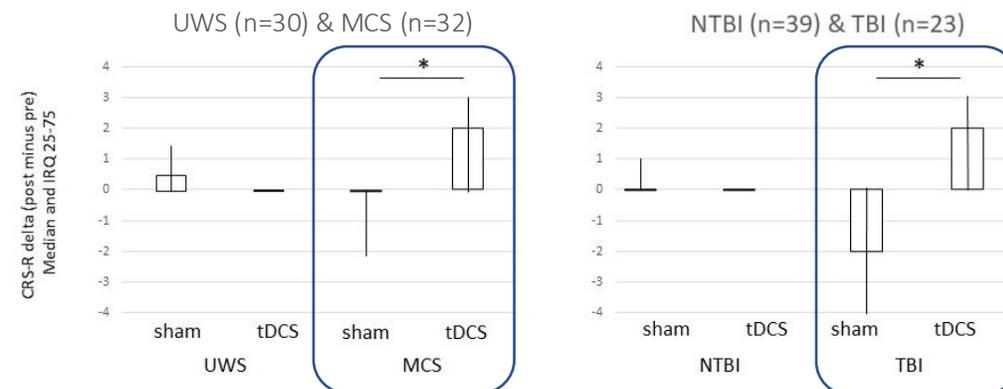


- No clinical effects at the group level
- Improvement at 3-month follow-up for MCS & TBI

4 weeks of tDCS



3 month follow-up



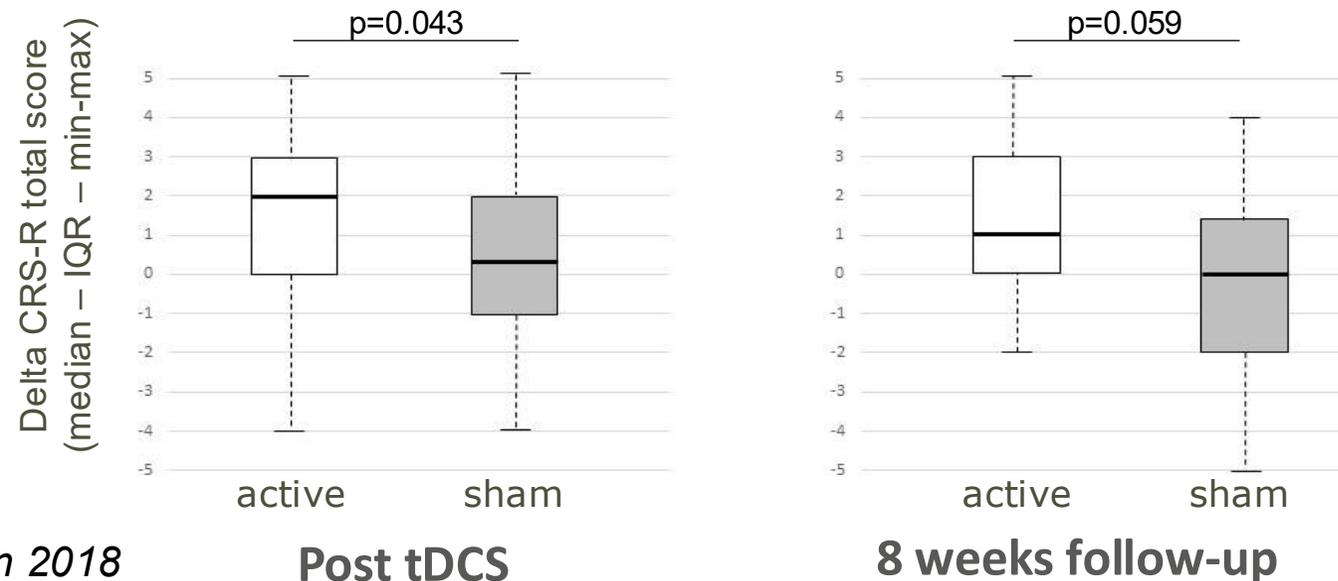
## tDCS clinical translation



G. Martens

Feasibility of prefrontal tDCS for daily use – 20 sessions by relatives/caregivers

- 27 MCS patients – adherence:  $93 \pm 14\%$
- No clinical effects
- 22 MCS patients received  $\geq 80\%$  tDCS sessions
- Significant effects & trend at 8-week follow-up – no AE

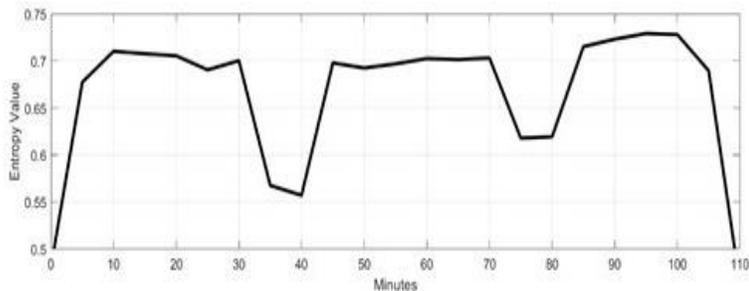




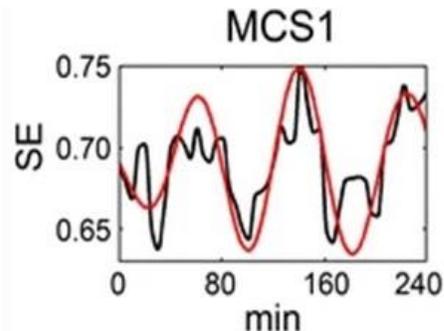
# Timing of stimulation – closed loop tDCS

A. Barra G. Martens

3 pilots 6h EEG



Spectral entropy in Pilot\_01

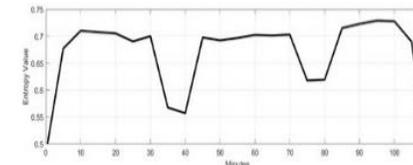


Spectral entropy from Piarulli et al. 2016



Recording

Stimulation



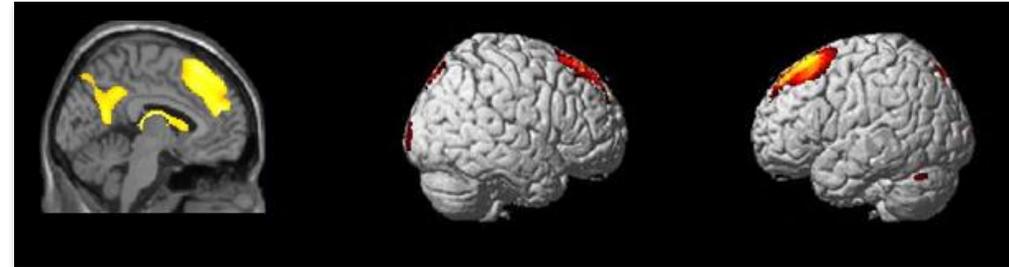
➔ Pilot study completed



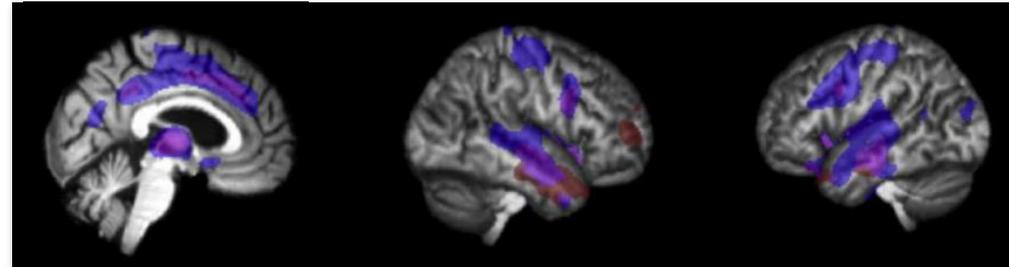
## Predicting clinical response

tDCS responders  $\neq$  non-responders

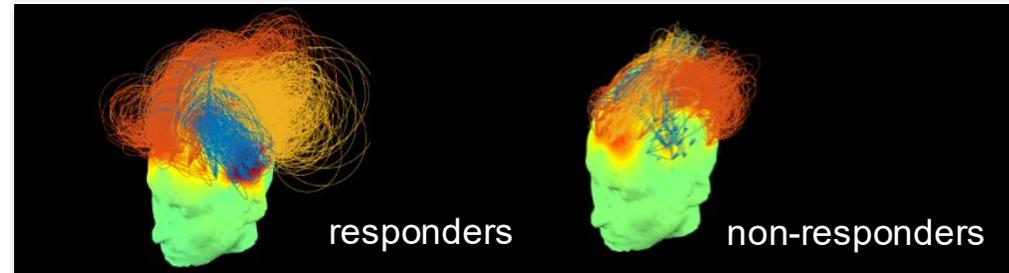
Brain metabolism (PET-scan)  
 $\neq$  responders & non-responders



Grey matter atrophy (MRI)  
in responders ●  
in non-responders ●

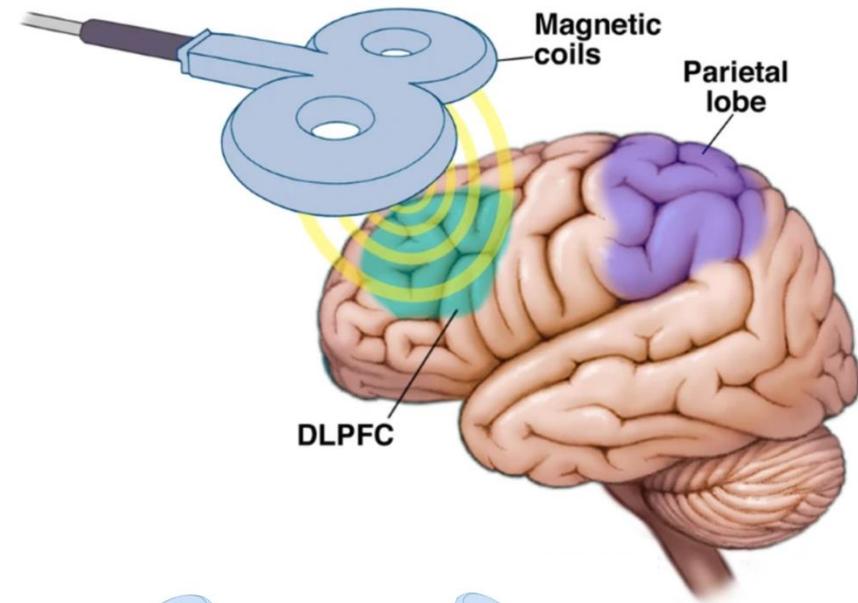


Brain connectivity (hd-EEG)  
theta centrality

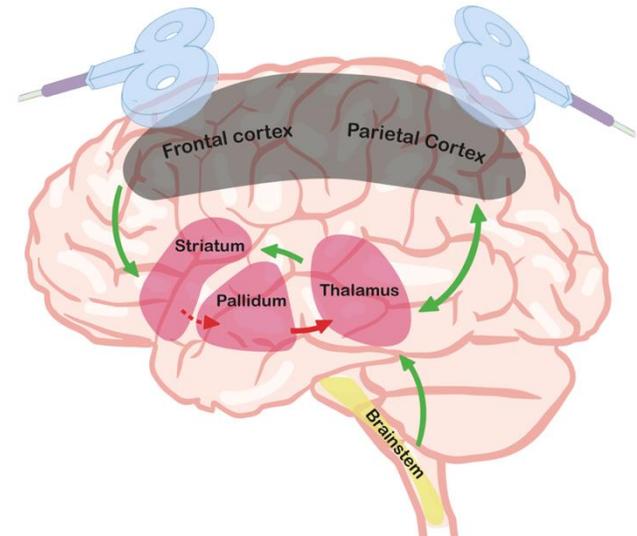


➔ Partially preserved brain areas (structural & functional)

# Transcranial Magnetic Stimulation (TMS)



- **Motor cortex** : no behavioral improvement (RCT)
- **DLPFC** : behavioral improvement + alpha power increase (open-label & sham controlled single blinded)
- **Angular Gyrus** : behavioral improvement in MCS not in UWS (open-label)

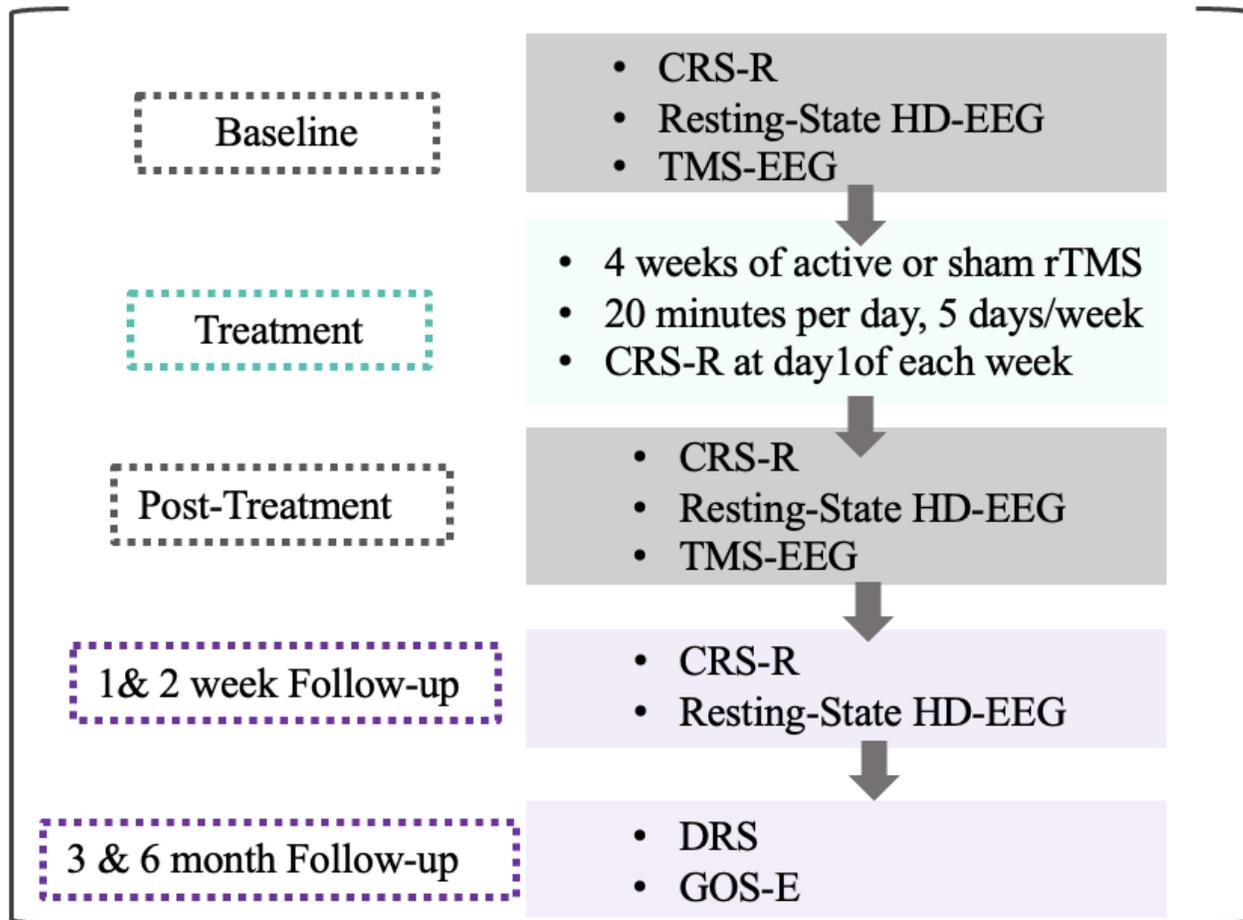


**Ongoing RCT : Angular Gyrus & DLPFC rTMS in prolonged DoC** *Vitello et al., Frontiers Neurol 2023*

*Xie et al, 2012, Cincotta et al, Cortex, 2015; Liu et al, Eur Neurol, 2016; Xia et al, 2017; He et al, Neural Plasticity, 2018, Legostaeva et al, 2019*

# Transcranial Magnetic Stimulation (TMS)

Double-blind RCT in 90 patients with prolonged DoC



O. Gosseries

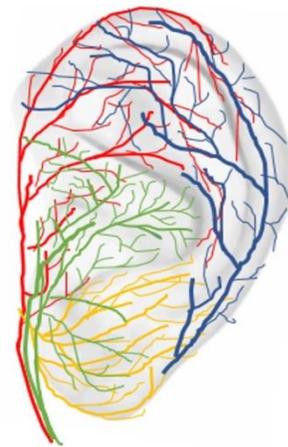


M. Vitello



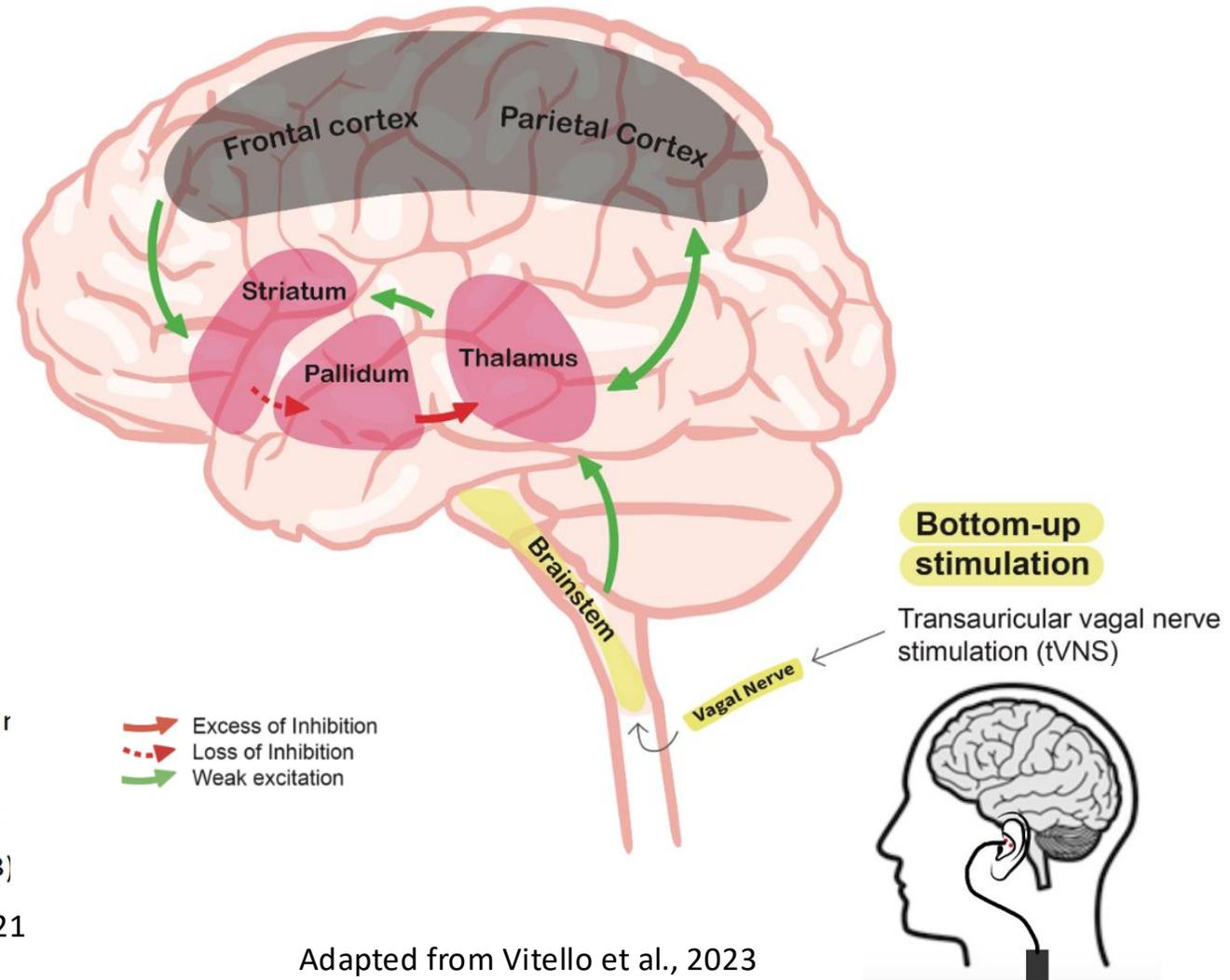
# BOTTOM-UP APPROACHES

# Transcutaneous Vagal Nerve Stimulation (tVNS)



- Auricular branch of the vagus r
- Auriculo-temporal nerve (V3)
- Lesser occipital nerve (C2-C3)
- Greater occipital nerve (C2-C3)

Adapted from Dumoulin et al. 2021

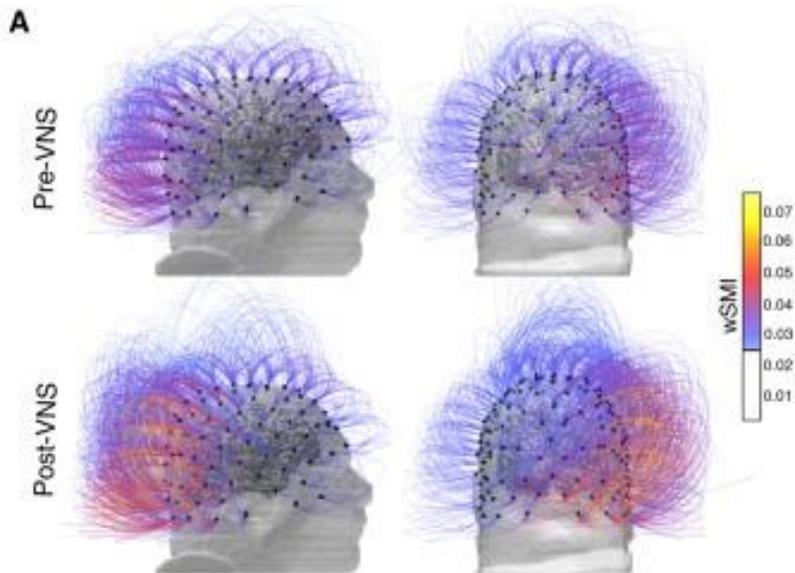


Adapted from Vitello et al., 2023

# Vagal Nerve Stimulation (VNS)

## Invasive VNS

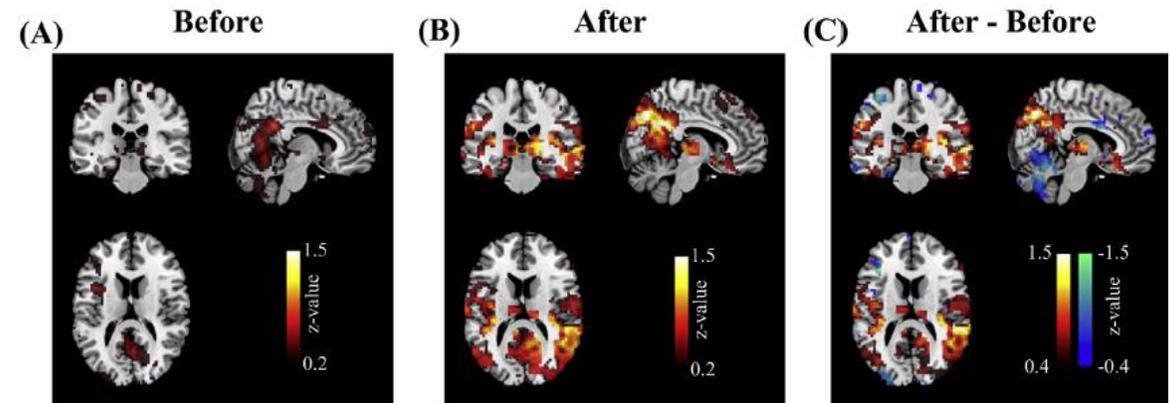
➔ Case report: 1 month of VNS  
UWS to MCS but no RCT so far



Corazzol et al, *Curr Biology*, 2017

## Non-Invasive transcutaneous VNS (tVNS)

➔ Case series and open label studies  
Recent RCTs in prolonged DoC



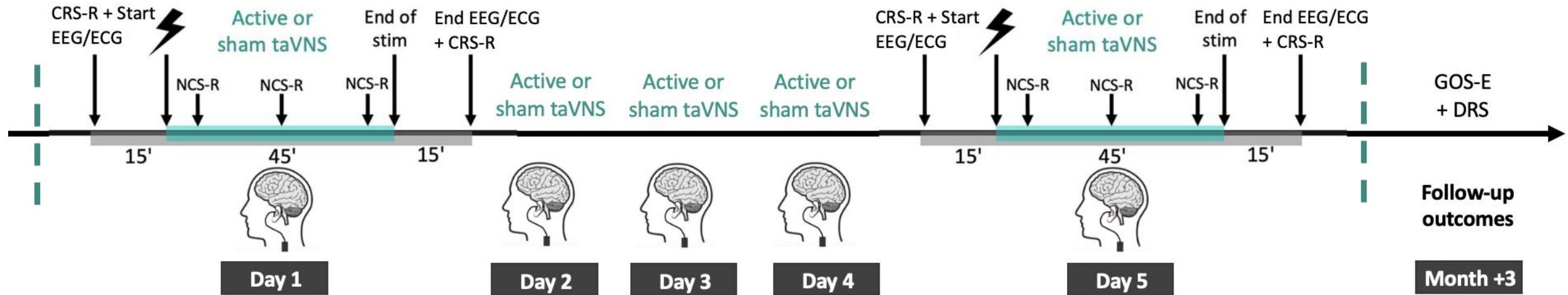
Yu et al, *Brain Stimul*, 2017; Hakon et al, *Neuromodulation*, 2020 ; Noe et al, *Brain Stimul*, 2021, Zhou et al. *Frontiers Neurosci.* 2023, Zhou et al. *Frontiers Neurol*, 2023

# Transcutaneous Vagal Nerve Stimulation (tVNS)



M. Vitello

➔ Double-blind randomized controlled clinical trial in **44 acute patients**



⚡ 5 days of 45 minutes (3mA, 200-300µs current width, 25Hz) taVNS vs Sham (earlobe)



# Transcutaneous Vagal Nerve Stimulation (tVNS)



M. Vitello

44 patients : 22 active & 22 sham  
23 MCS, 9 TBI, 20 females,  $\pm$  21d post-injury

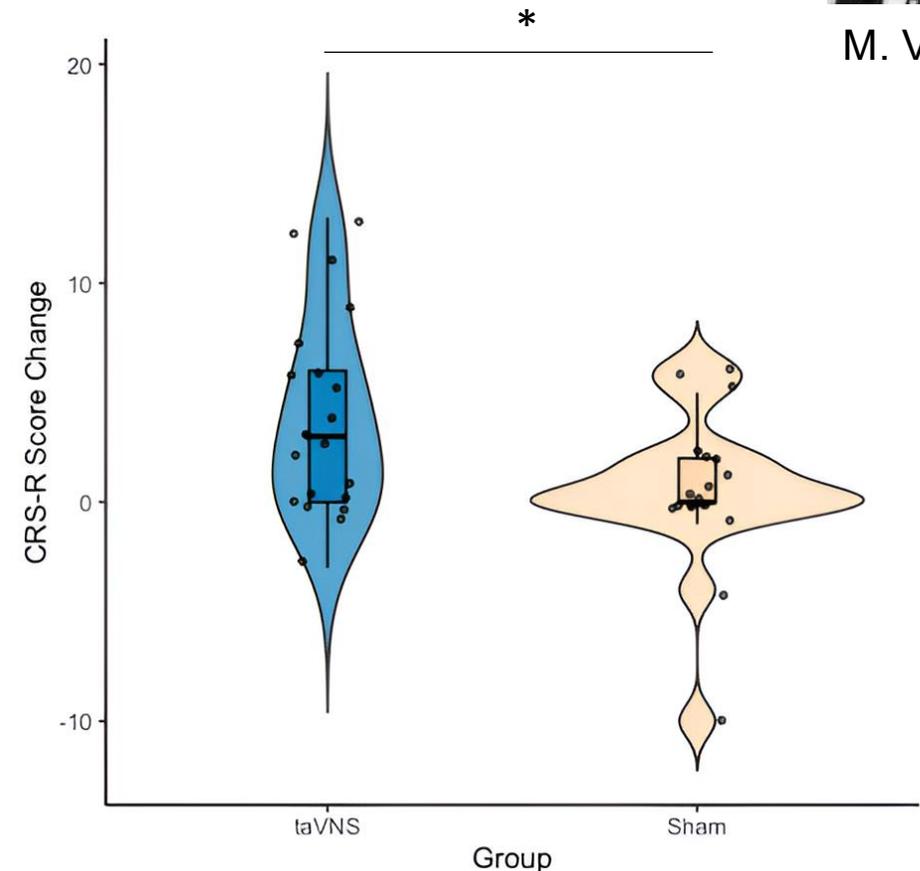
No serious adverse event – NCS-R <4  
Good adherence (91%)

## Significant treatment effects

**CRS-R increase** : taVNS (3 [0-6]) vs sham (0 [0-2])

No changes on EEG (power, connectivity)

No changes at 3-month follow-up (DRS, GOSE)



p-value = 0.03244

## Patient 11: Responder 3

---

- 18 yo patient with acquired brain injury due to severe TBI, 18 days since onset
- Diagnosed **MCS+** at day 1 (reproducible response to command)
- Improved to **eMCS** at day 5 (functional use of objects and functional communication)
- + Contingent behaviors : afraid of the EEG cap and cried when his mom entered the room



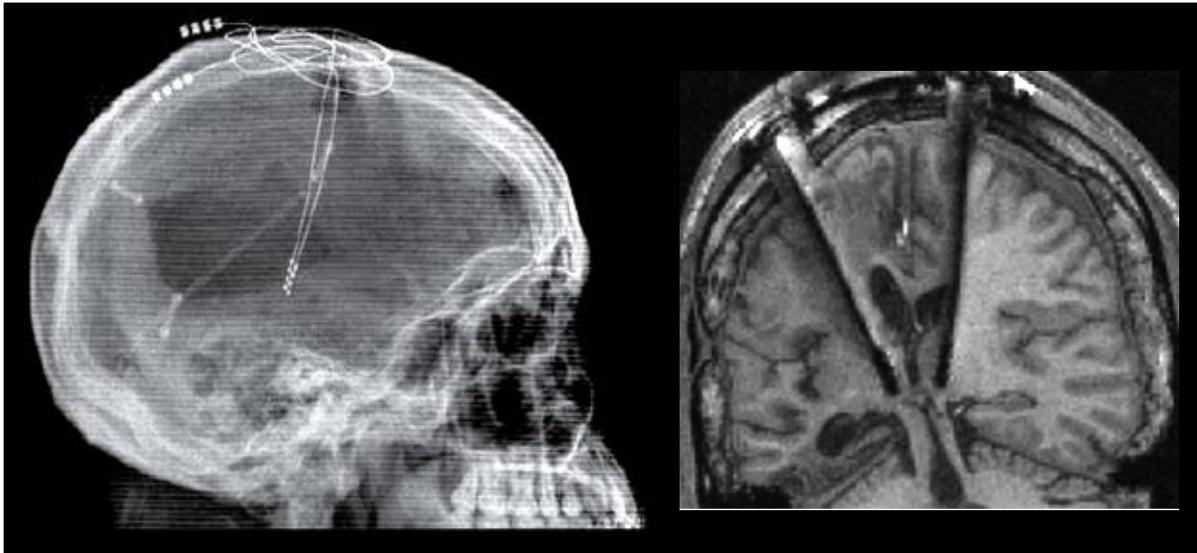
M. Vitello

# CENTRAL APPROACHES

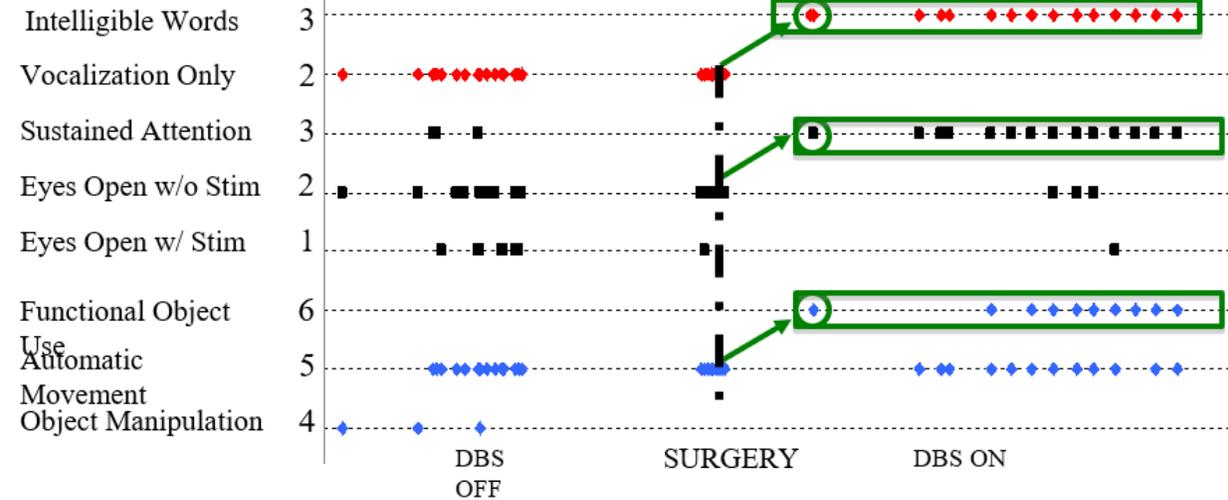


# Deep Brain Stimulation (DBS)

Intralaminar nuclei “reconnections” in spontaneous recovery from unresponsive state



CRS-R Scores

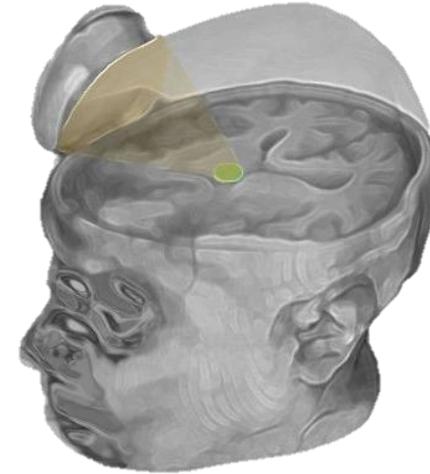
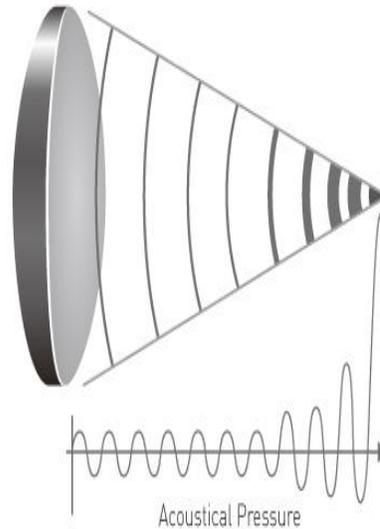
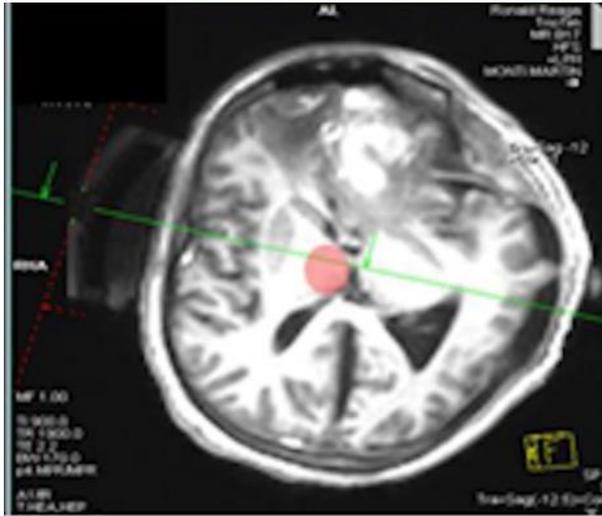


➔ Case-report : MCS ➔ emerged – prolonged effects

➔ No RCT & complications

# Low Intensity Focused Ultrasounds (LIFU)

→ Target thalamus non-invasively



## Case report – acute

25 yo male, 19 days post-TBI  
CRS-R 15 to 17 (motor related behavior)  
→ 3 days later emergence

## Series of cases – prolonged

3 patients – stroke, CA, TBI  
MCS > 1y post-injury  
→ 2/3 improved  
→ 1/3 up to 6m follow-up

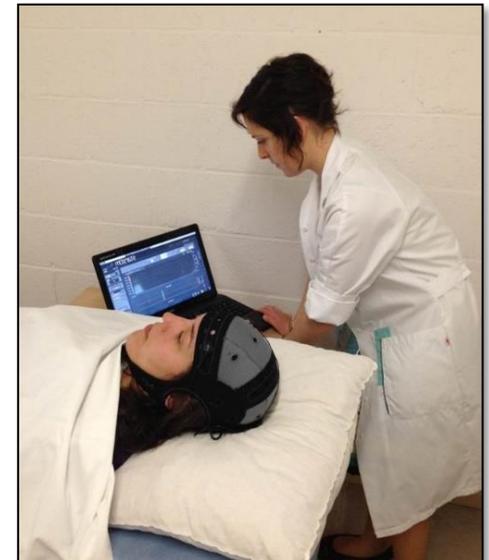
# Conclusions

## Top-down approaches

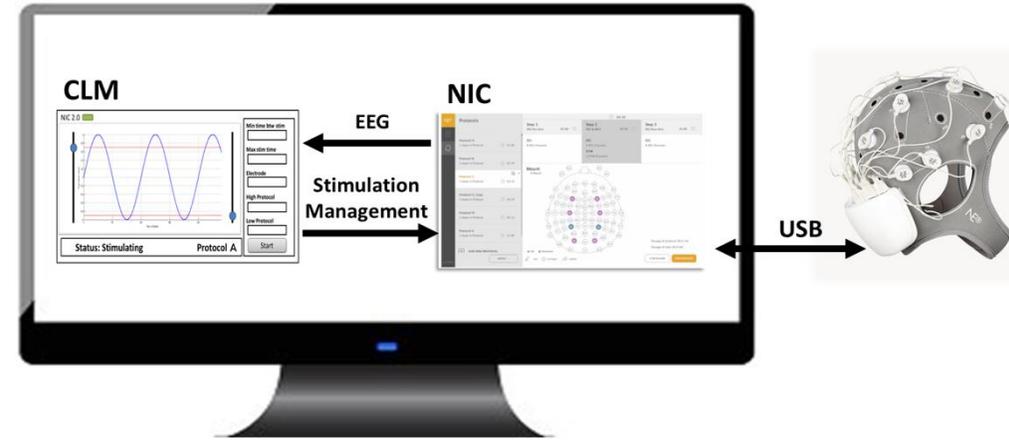
- tDCS is safe in severely brain-injured patients
- **Prefrontal tDCS**
  - consistent **moderate** clinical improvement
  - repeated sessions
  - TBI & MCS
- rTMS : M1 vs prefrontal & AG

## Bottom-up & central approaches

- DBS promising but invasive
- LIFU promising – need RCT
- taVNS feasible in ICU & promising

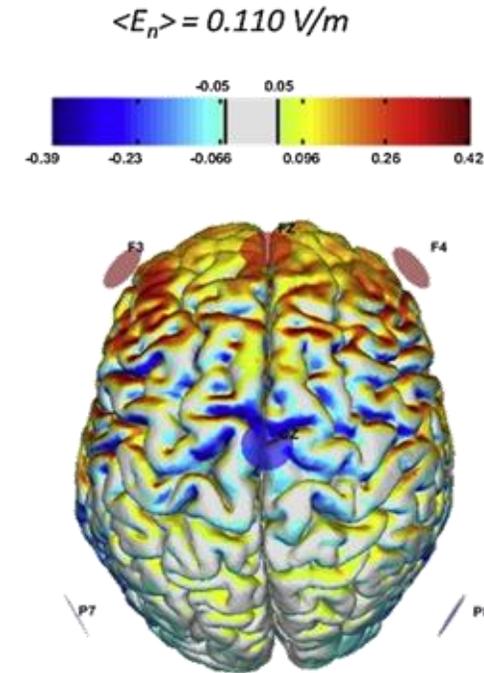


- Timing of stimulation



Closed-loop system

- Timing of stimulation
- Patients' tailored stimulation



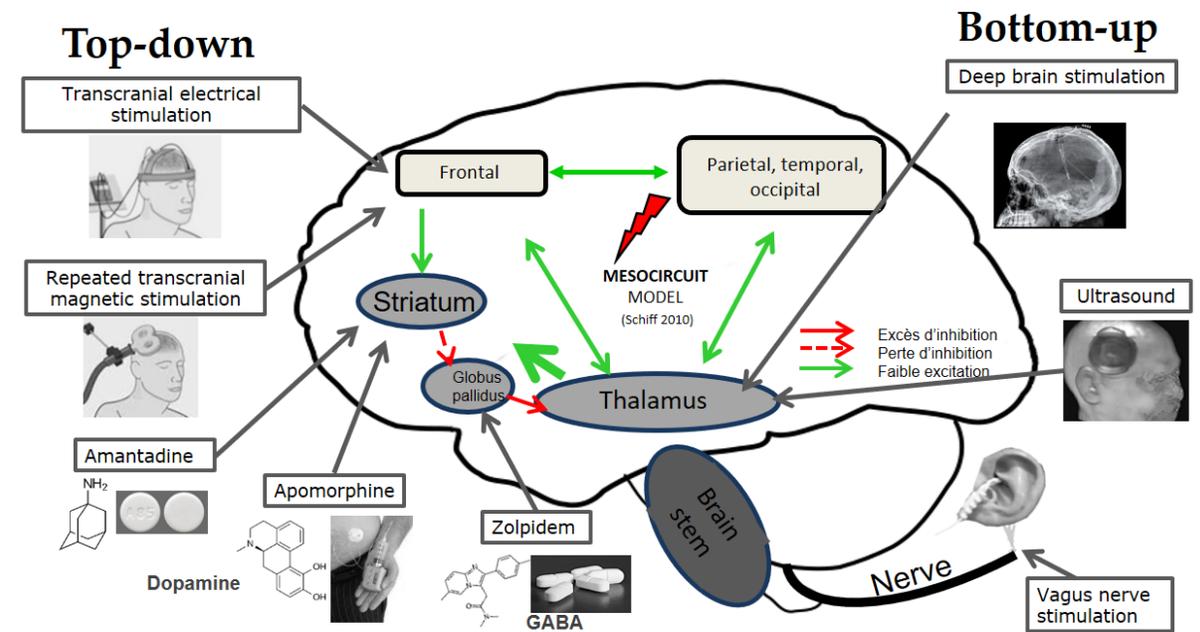
Individualized montage  
Patients' brain lesion (T1)

*Biagi et al. In prep*

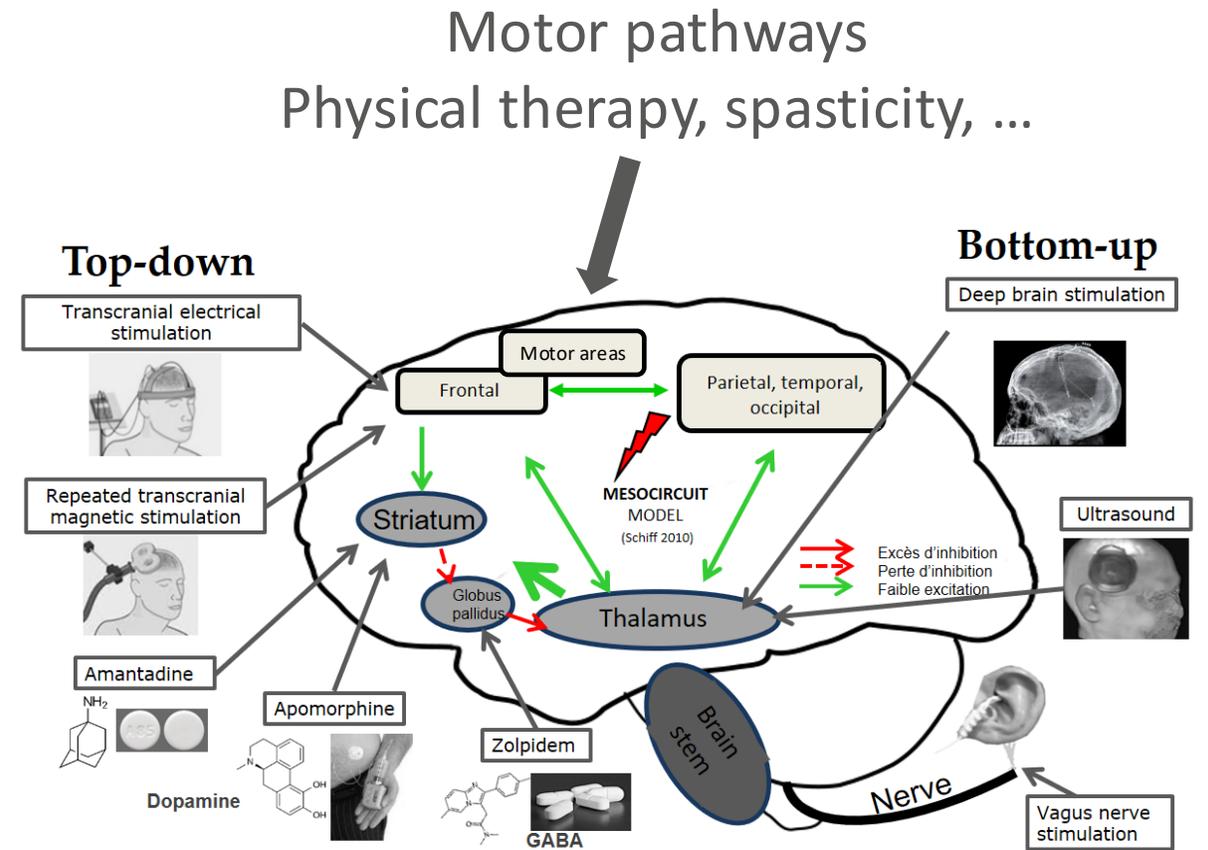
*Thibaut & Martens, Nature Rev Neurol, 2024*

- Timing of stimulation
- Patients' tailored stimulation
- tACS, taVNS, LIFUP, ...

Combination of therapies  
Top-down & bottom-up



- Timing of stimulation
- Patients' tailored stimulation
- tACS, taVNS, LIFUP, ...
- Consciousness >< motor



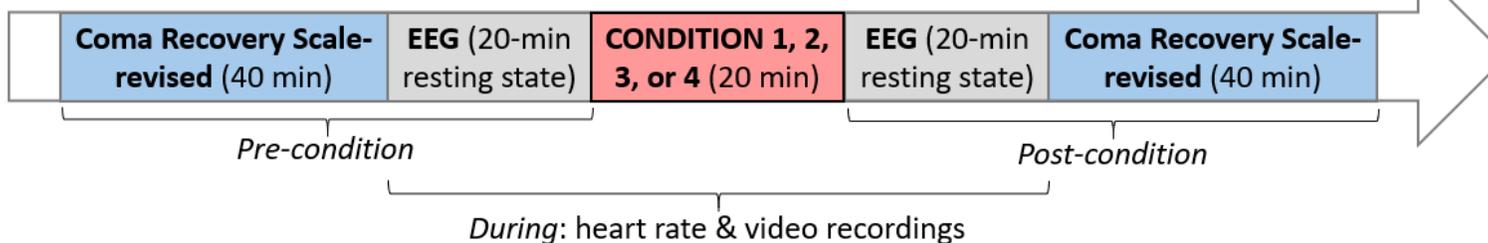
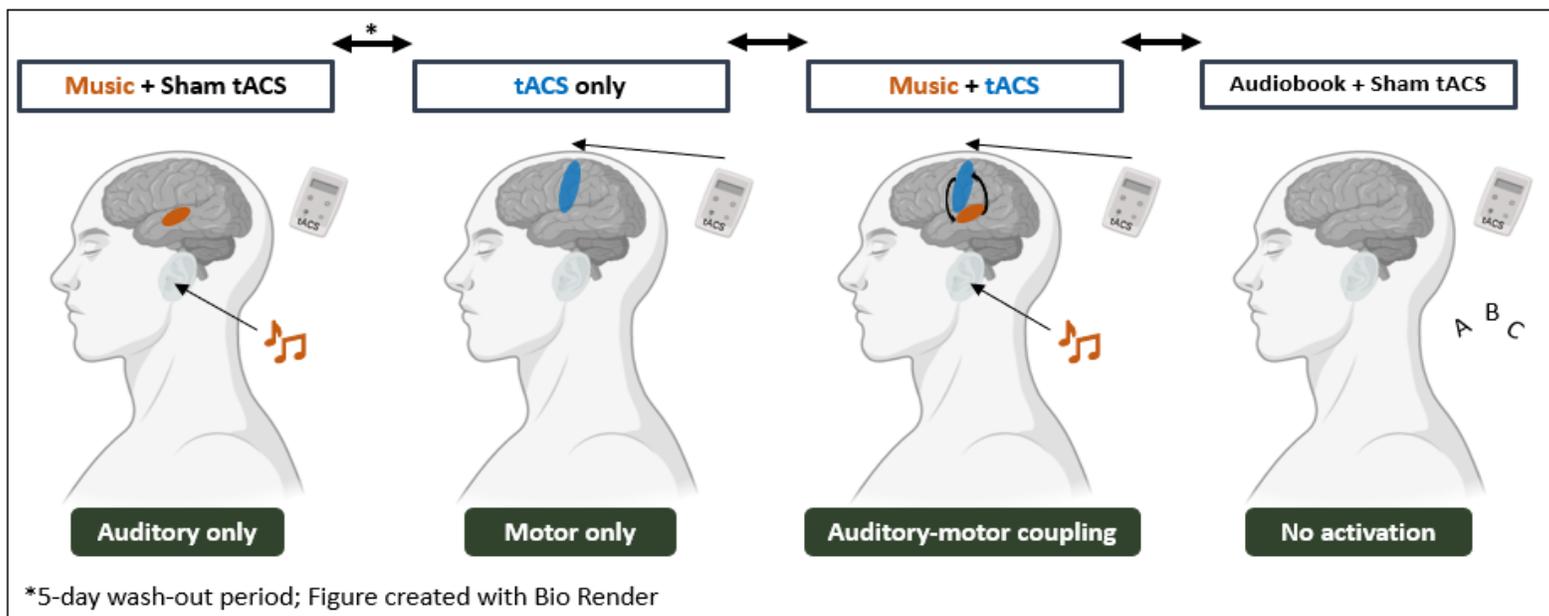
## Synergistic music & tACS stimulations in prolonged DoC

test auditory-motor coupling – music & M1-tACS – on recovery of consciousness

Multicentre,  
randomised,  
sham-controlled,  
4-arm, crossover,  
single-session trial

Synchronized tACS  
+ music  
100beats/min

35 pDOC  
35 HC



M. Poncelet





LIÈGE université  
GIGA institute  
CONSCIOUSNESS

NeuroRecovery Lab  
ADVANCING NEUROREHABILITATION THROUGH NEUROMODULATION



Thank you



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