How to cure cognitive sequelae after brain injury: any hope for the future?

Focus Meeting 2023 - ESAIC

November 27th 2023

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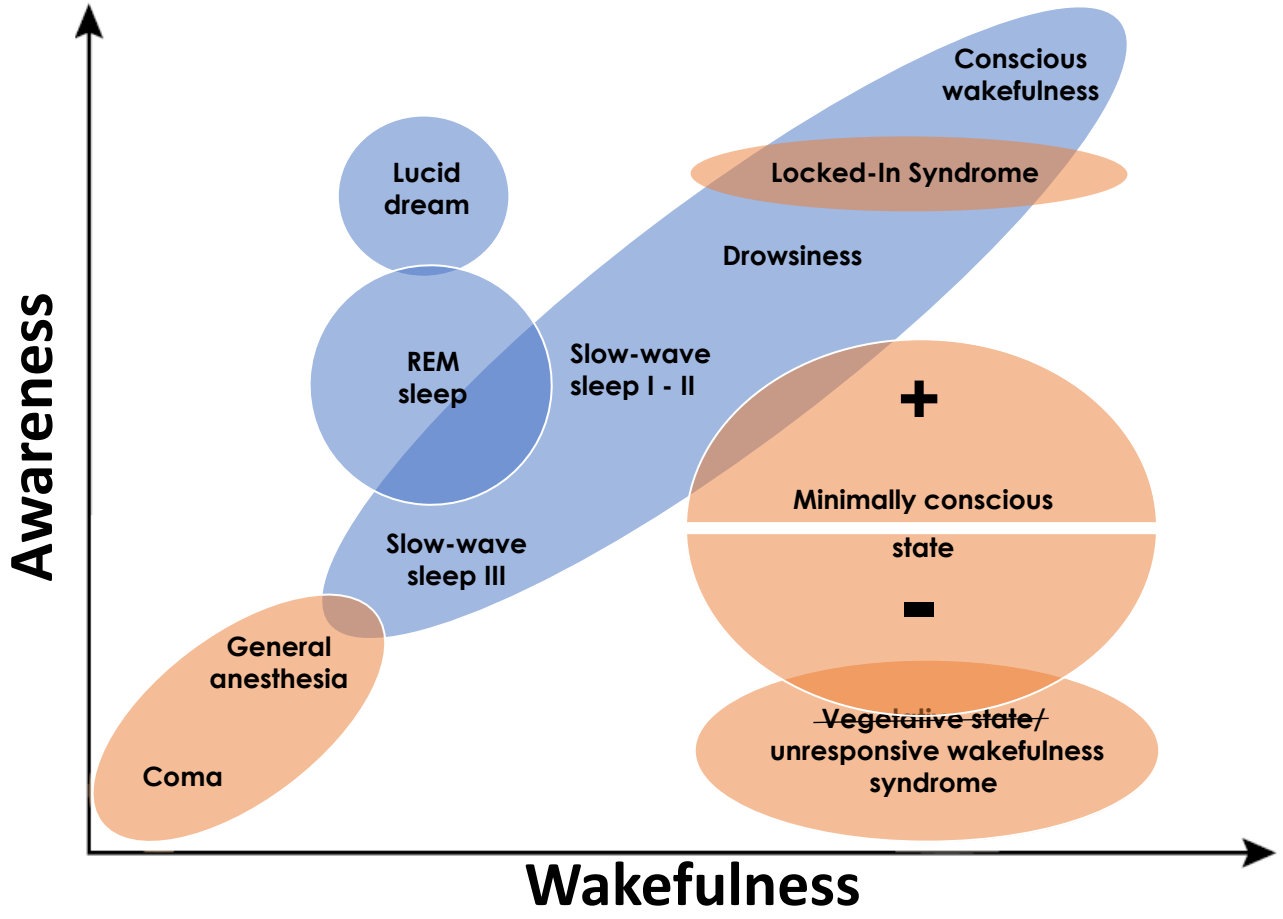
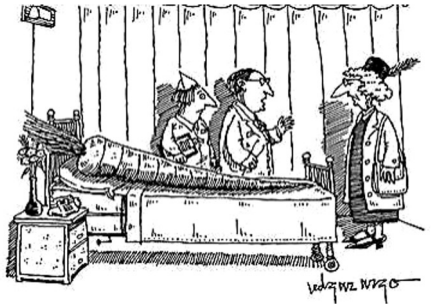
PhD Student
FNRS Aspirant
GIGA-Doctoral School

What is consciosuness?

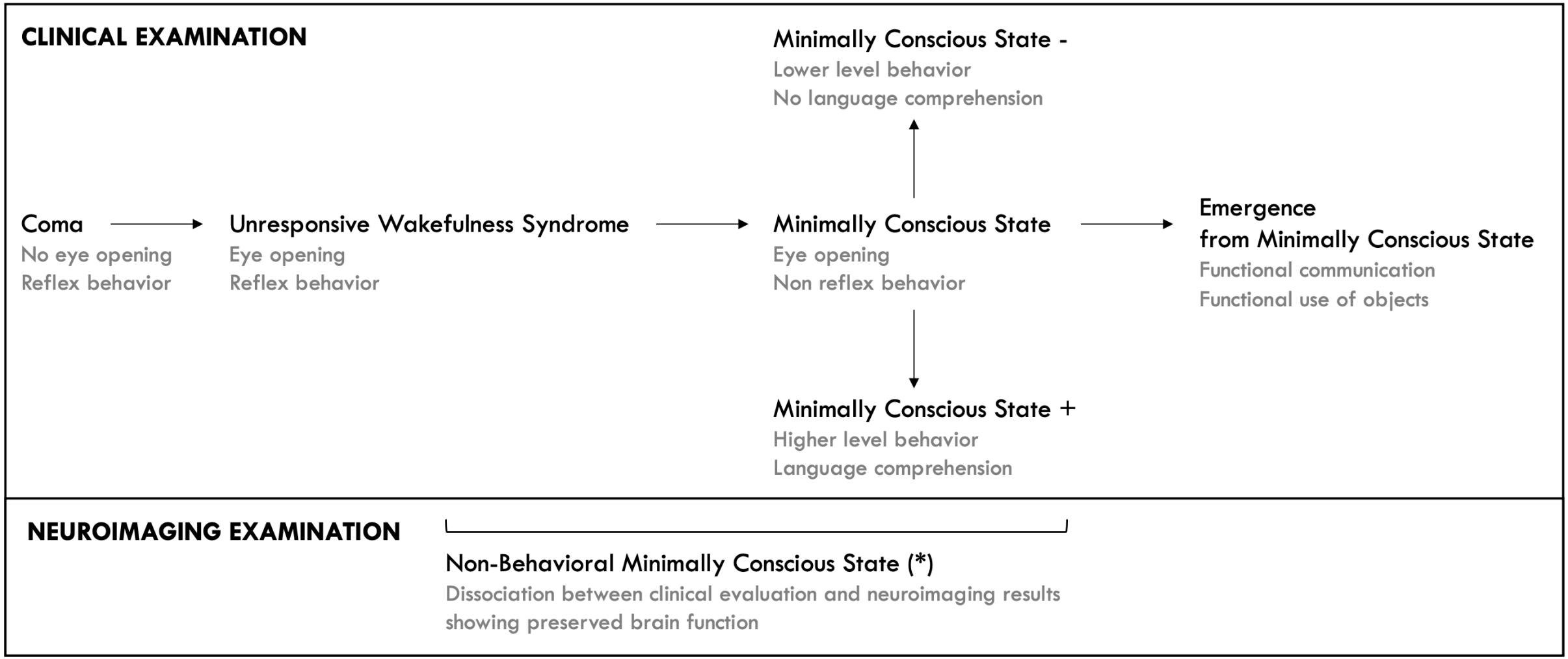


Laureys, *Trends in Cognitive Sciences*, 2005



"There's nothing we can do… he'll always be a vegetable."

Disorder of consciousness

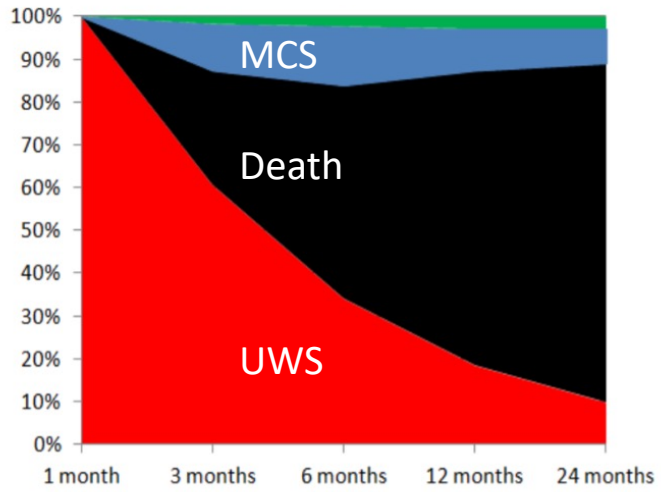


Bodart, Gosseries & Laureys, *Semin Neurol*, 2013

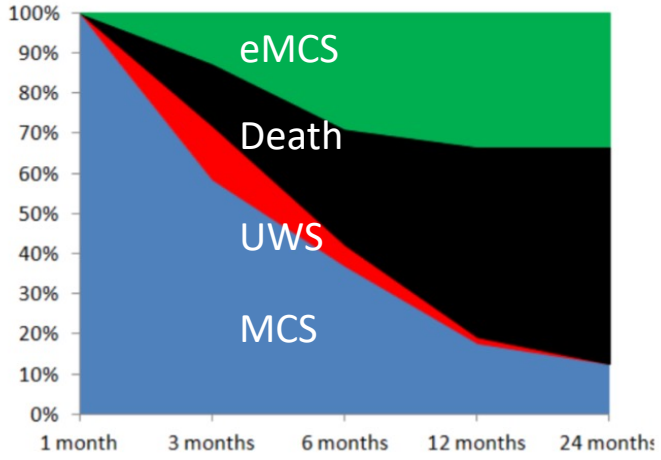
Relevance of appropriate diagnosis

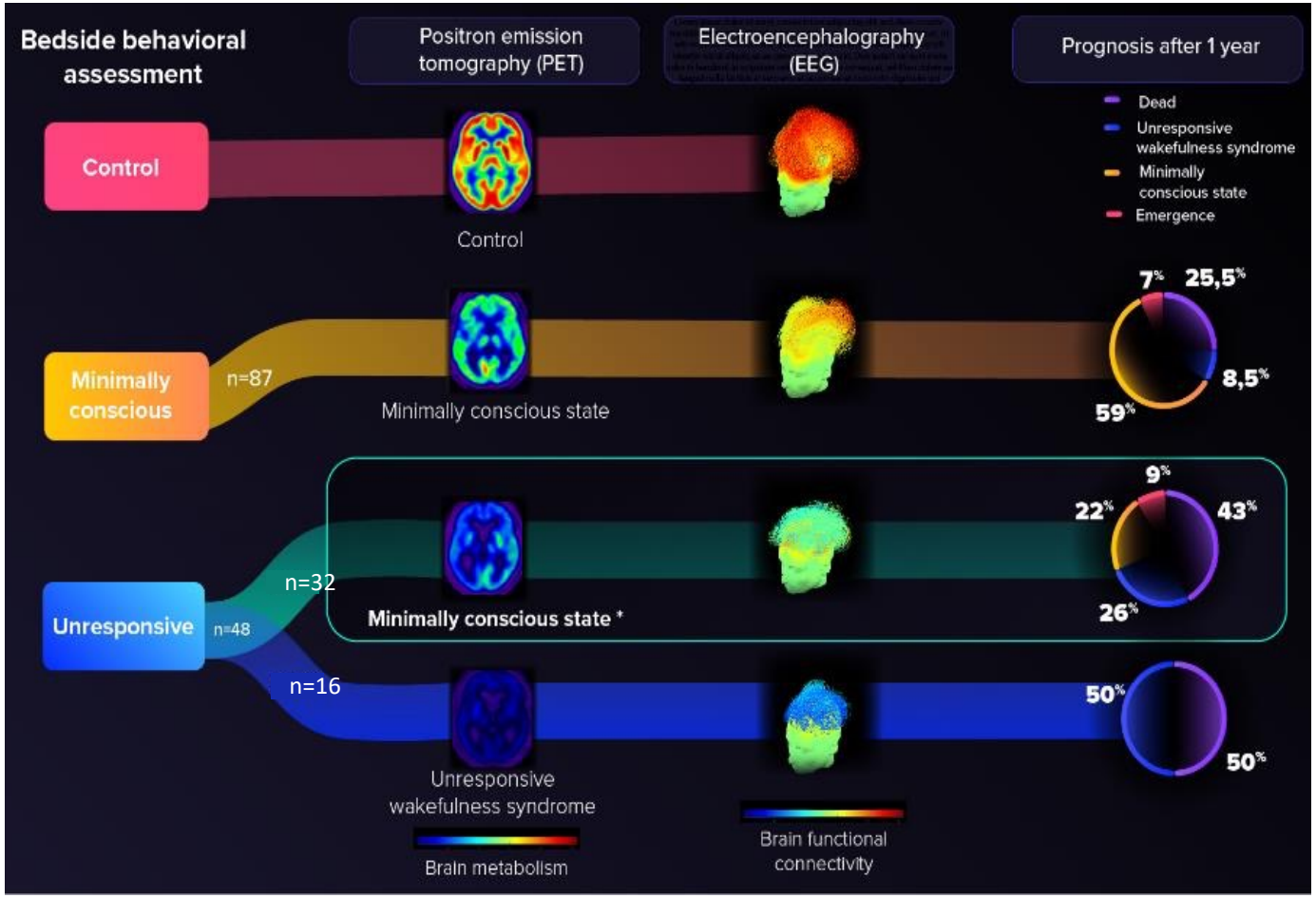
non-traumatic

Unresponsive



Minimally responsive



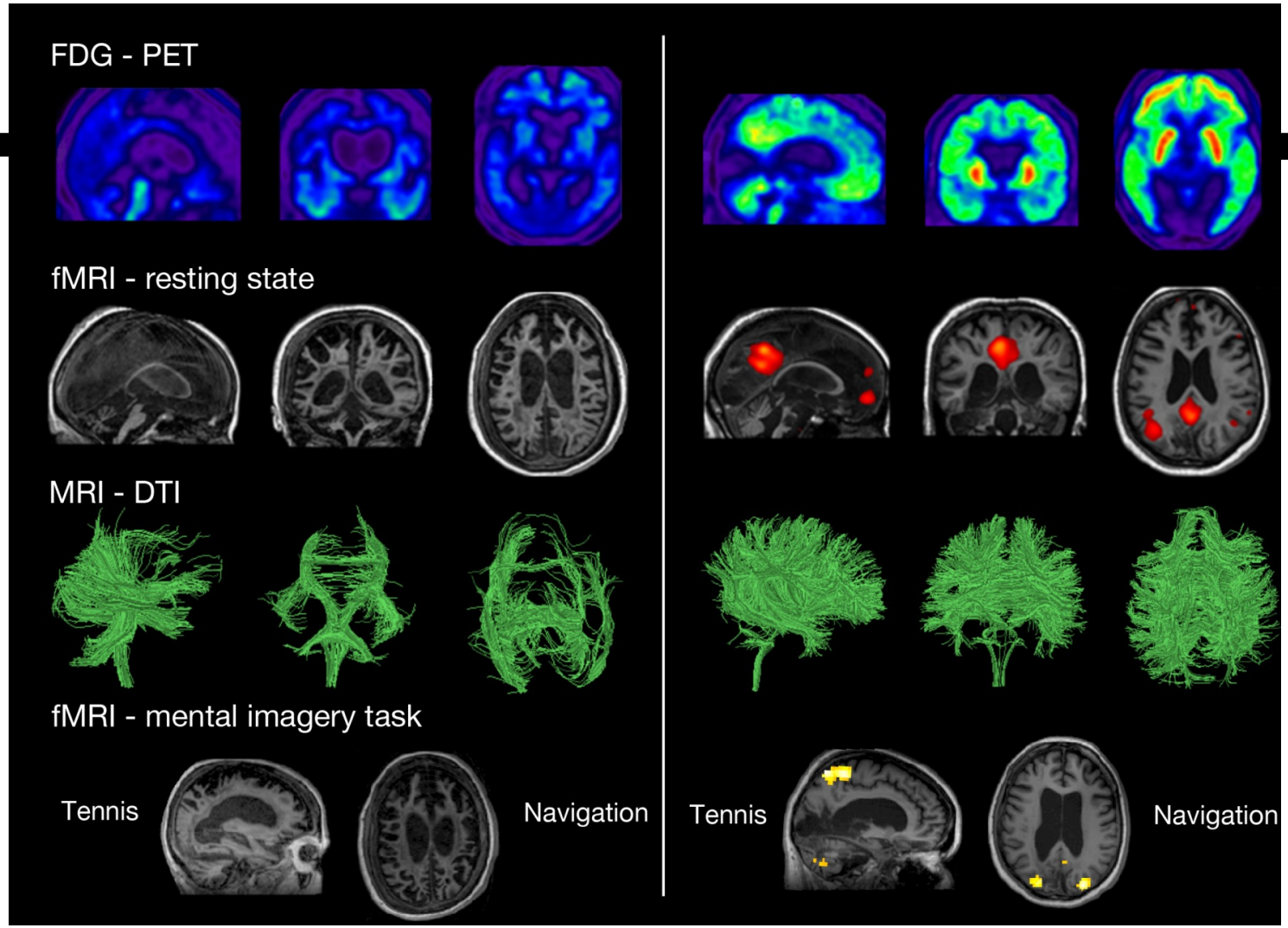


Thibaut & Panda et al, *Annals Neurol.* 2021

Two scenarios

UWS

Dime prognosis



MCS or MCS*

Treatment

MCS* = non-behavioral minimally conscious state

Gosseries et al, *Brain Injury*, 2014

Available treatments

CURING COMA®

Class	Pharmacologic	Electromagnetic	Mechanical	Sensory	Regenerative
Best evidence	RCT (amantadine)	RCT (tDCS, TMS)	Case series	RCT (auditory)	Phase 1 trials (stem cells)
Efficacy	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
Safety	+	DBS – tDCS, TMS, taVNS: ++	++	Tactile, auditory: +++ Vestibular: ++	Unknown
Limits	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
Ongoing trials	4	10	1	5	0

➔ need of precision medicine approach & large RCTs

Edlow, Sanz* et al., 2021*

PHARMACOLOGICAL TREATMENTS

Amandatine

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.

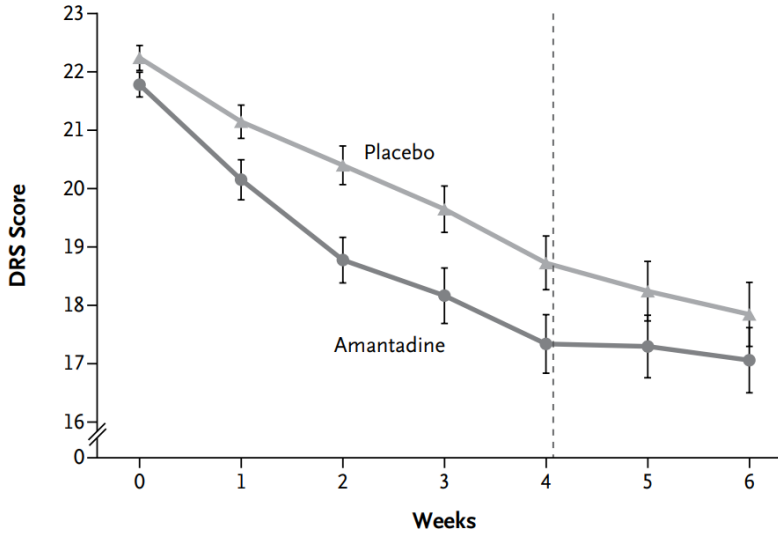
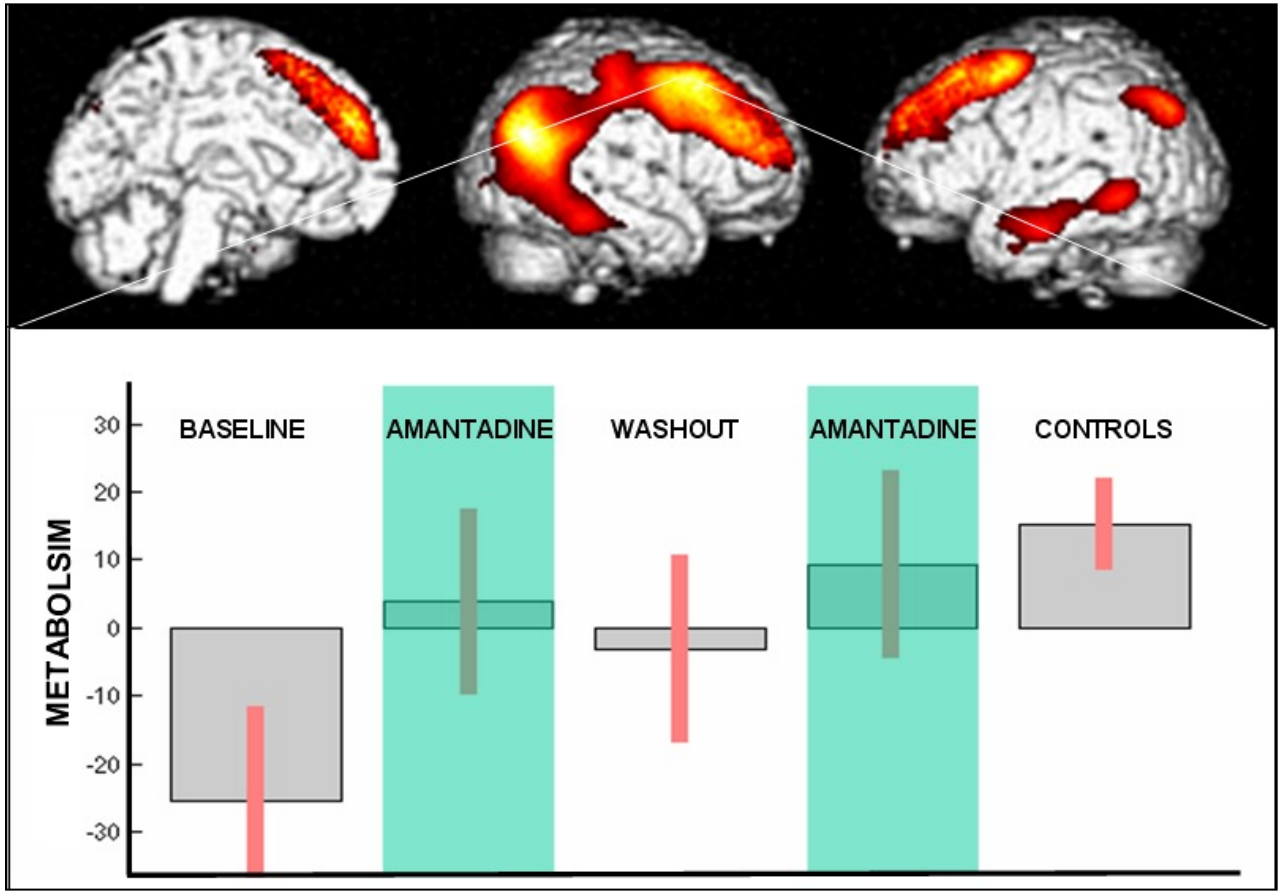


Figure 1. Mean Disability Rating Scale (DRS) Scores during the 6-Week Assessment Period, According to Study Group.

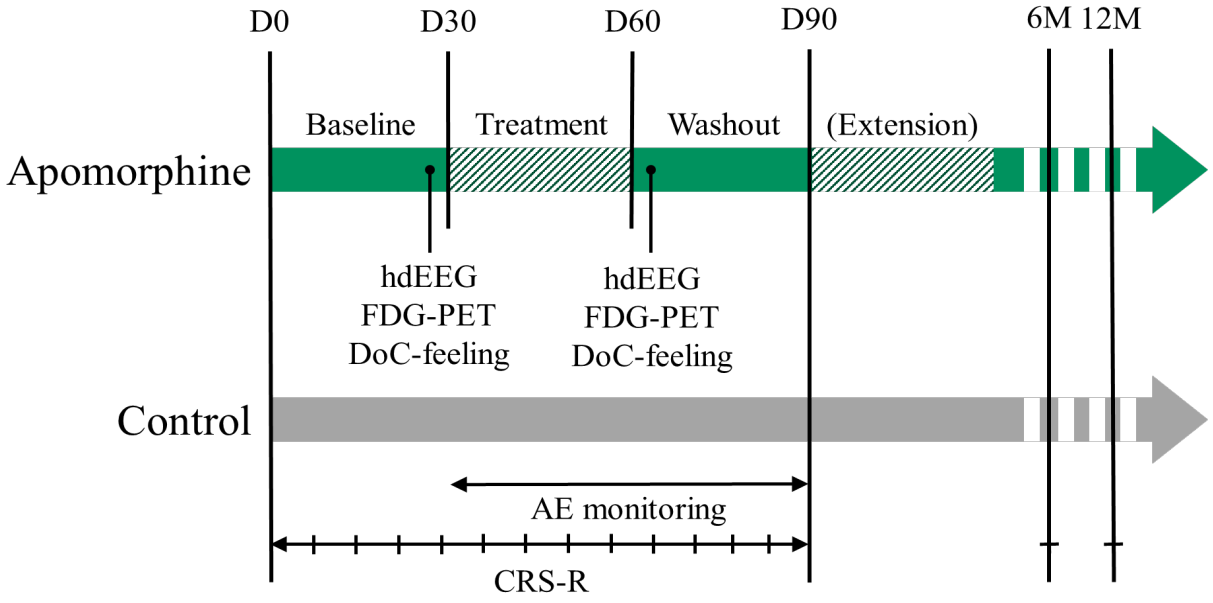
Increased metabolism in DLPFC, temporal, parietal, right sensorimotor areas

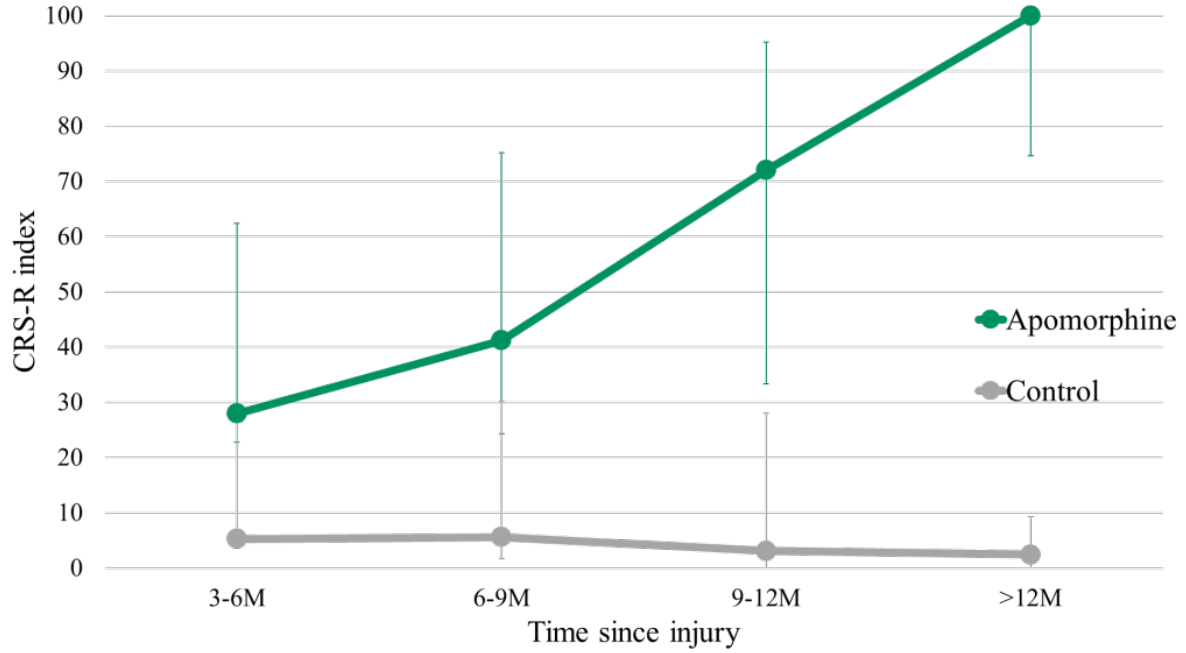


Giacino et al, 2012, Schnakers et al, 2008


Apomorphine

Open-label controlled study





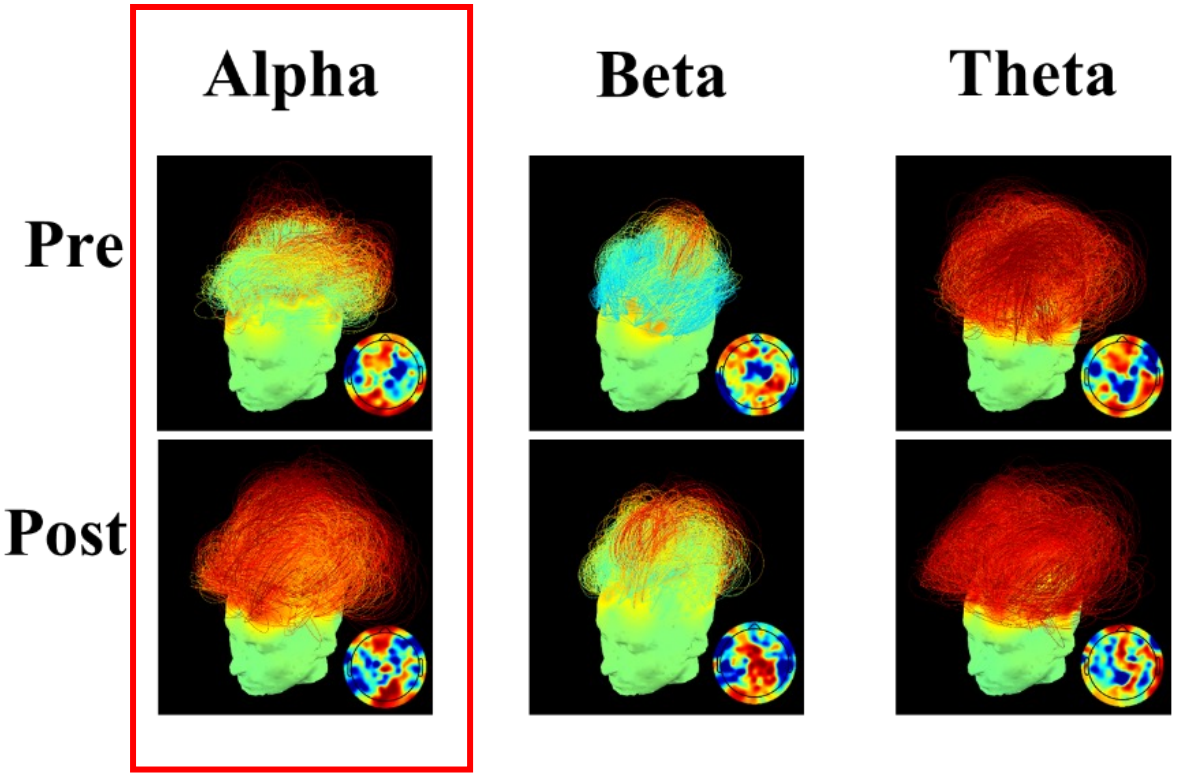
- 30 days of subcutaneous infusion (12h/day continuous)
- Multimodal assessments
- Apomorphine (n=6) & control groups (n=7)

- Better recovery in active group at 12 months

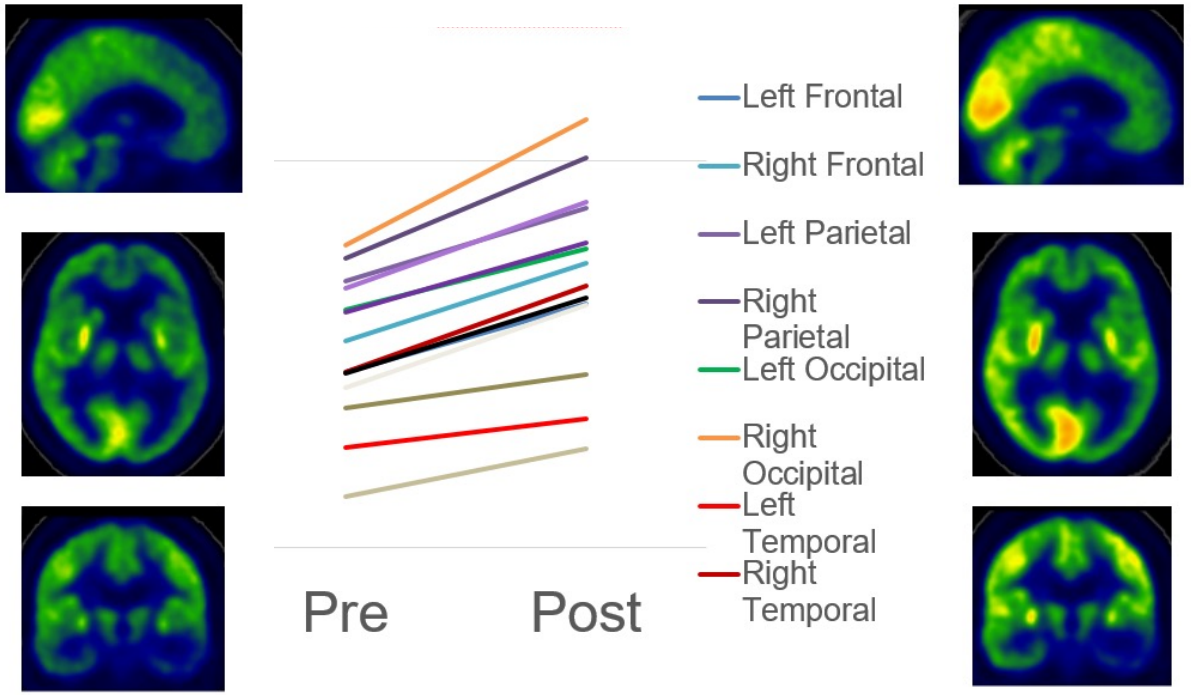
Sanz et al., Front Neurol 2019 &
Sanz, Szymkowicz et al, Submitted


Apomorphine

High-density EEG



Brain metabolism (FDG-PET)

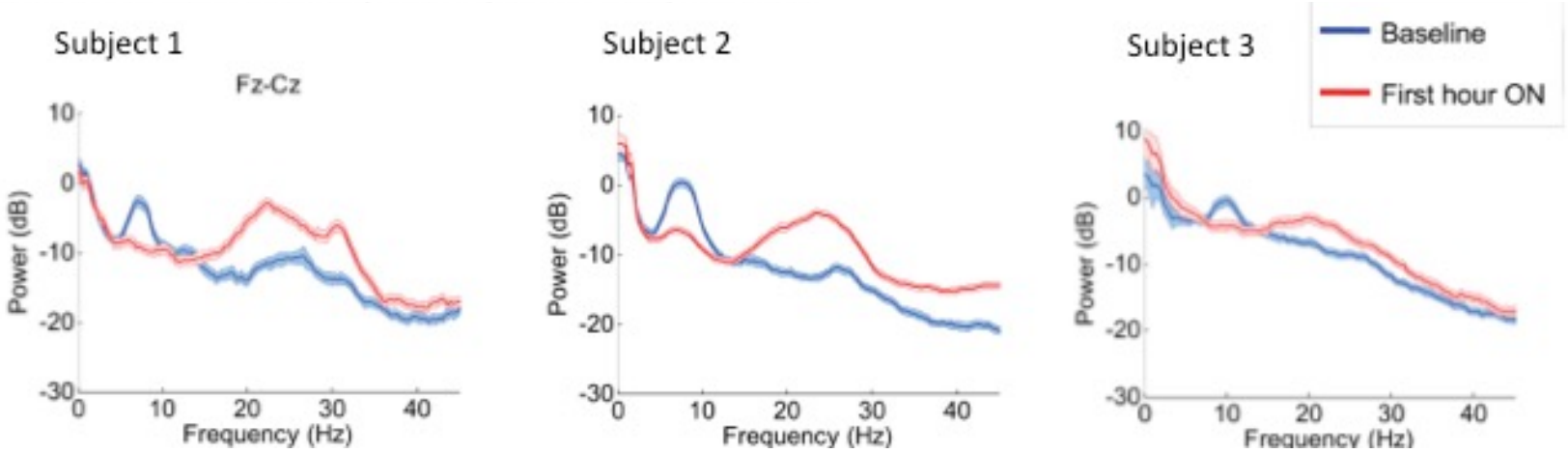


➔ Ongoing multicenter randomized controlled trial

Sanz et al., Front Neurol 2019 & Sanz & Szymkowicz et al, Submitted

Zolpidem

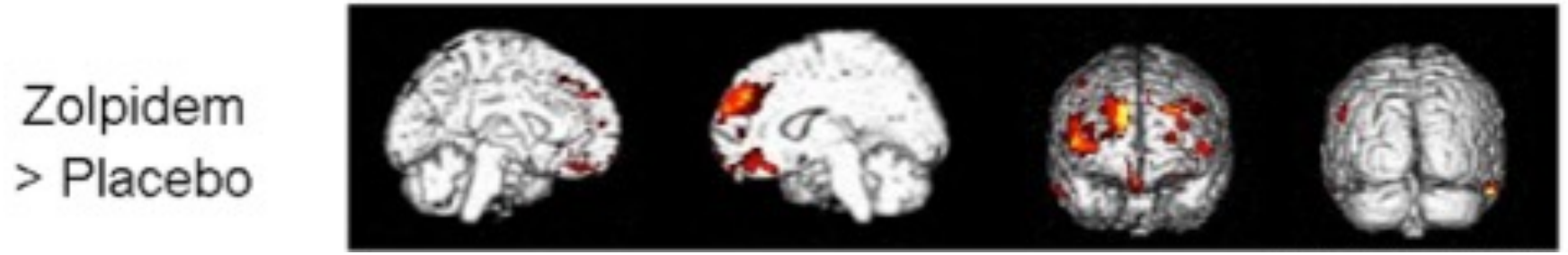
- Brain electrical activity in responders (~5% of DoC patients)



N=3

- Brain metabolism in responders

Increased metabolism in mesiofrontal and prefrontal cortex



N=3

Williams et al, Elife, 2013; Chatelle et al, Front Hum Neurosci, 2014

Zolpidem

fMRI

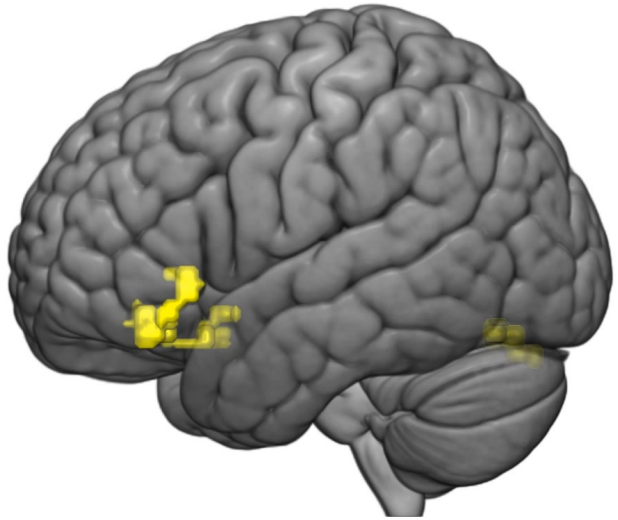
15 MCS & 5 EMCS

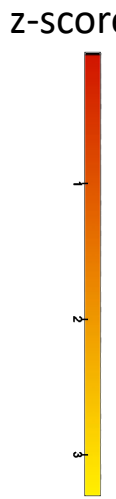
10 mg

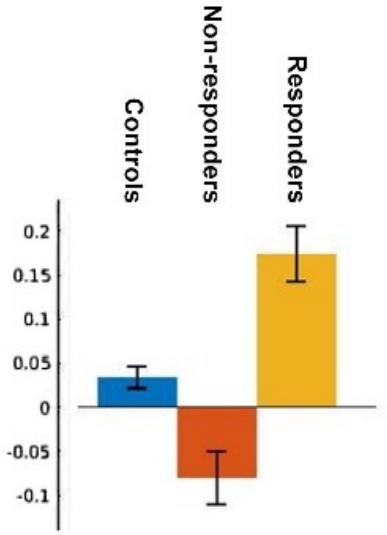
9 responders
new CRS-R behavior
never observed before

11 non-responders

SEED - THALAMUS



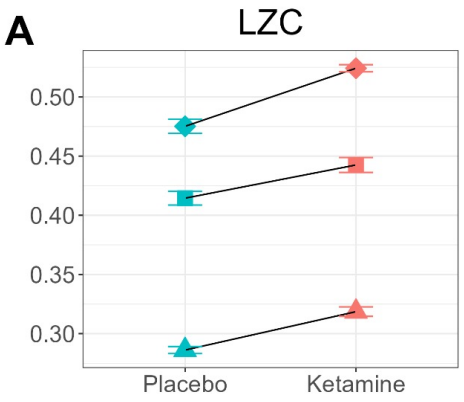


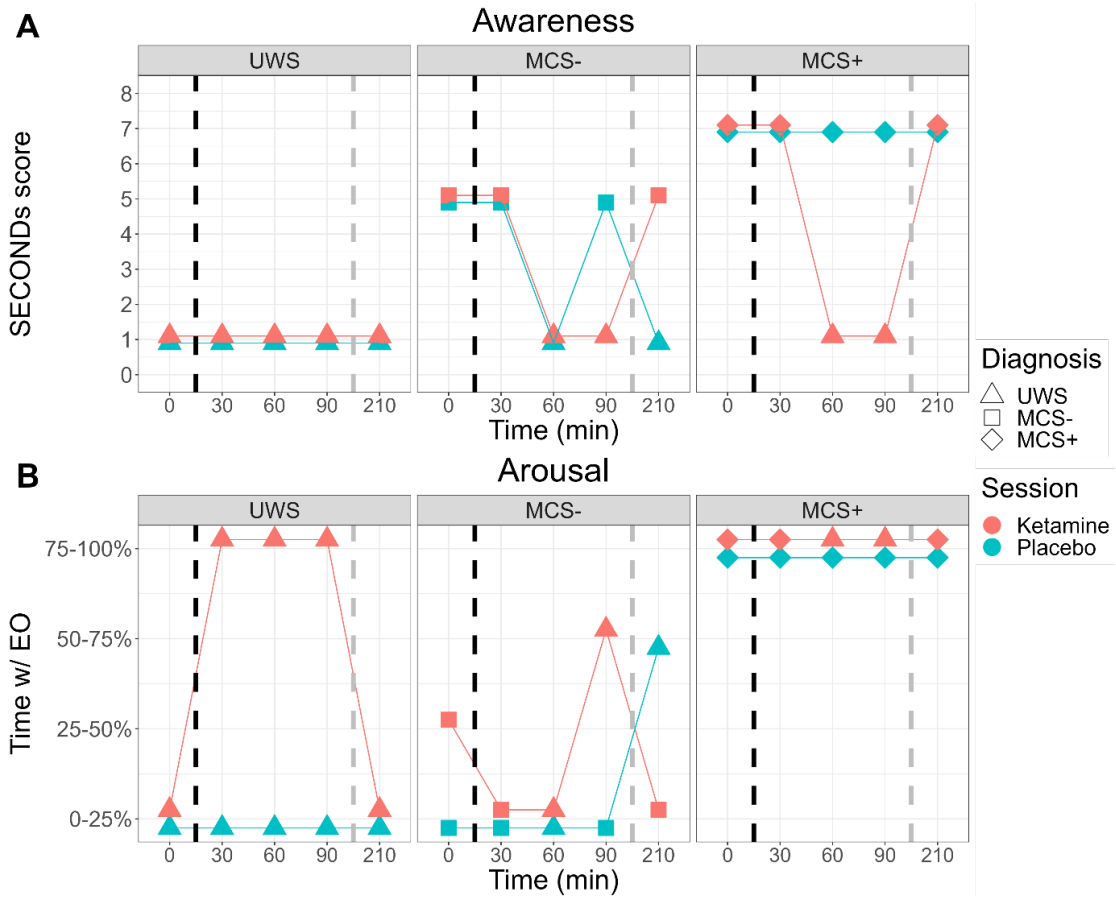


connectivity between **thalamus** and **left fronto-insular +** temporo-parieto-occipital areas

Ippoliti et al., in preparation

Ketamine





- Sub-anesthetic dose of ketamine
- Increased brain complexity
- More time awake, but no new overt behaviour

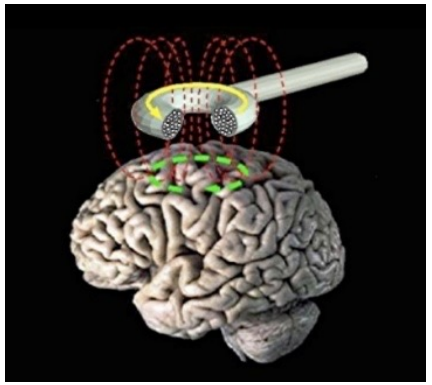
Cardone et al., in submission

NON-PHARMACOLOGICAL TREATMENTS

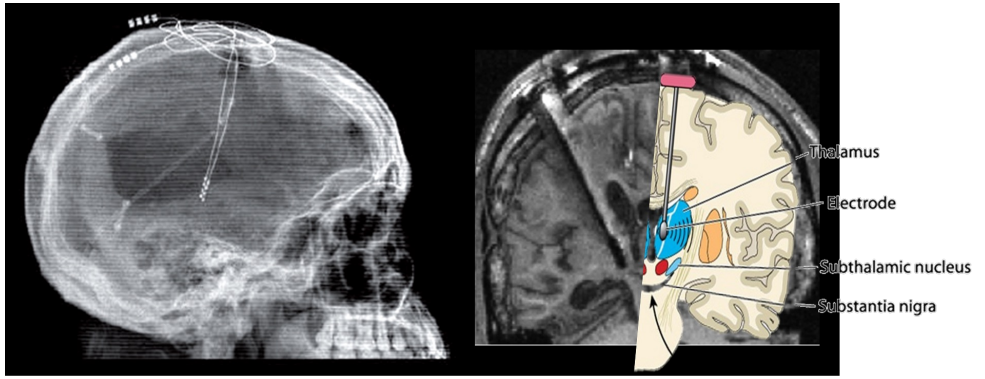
Non-pharmacological treatments

tDCS

rTMS

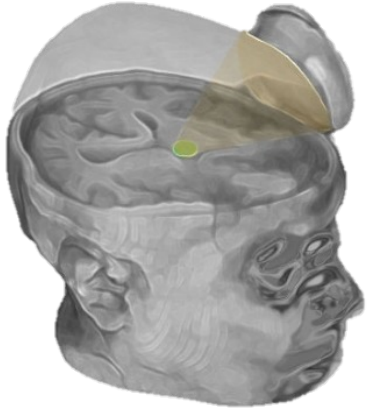


DBS

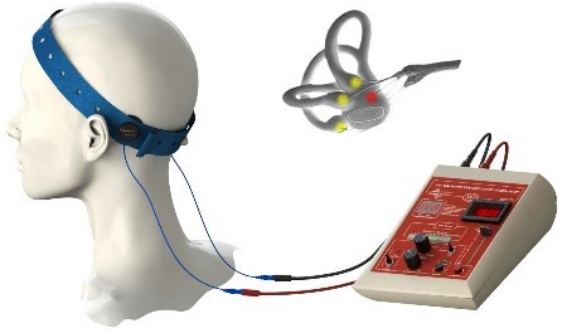


taVNS

LIFUP



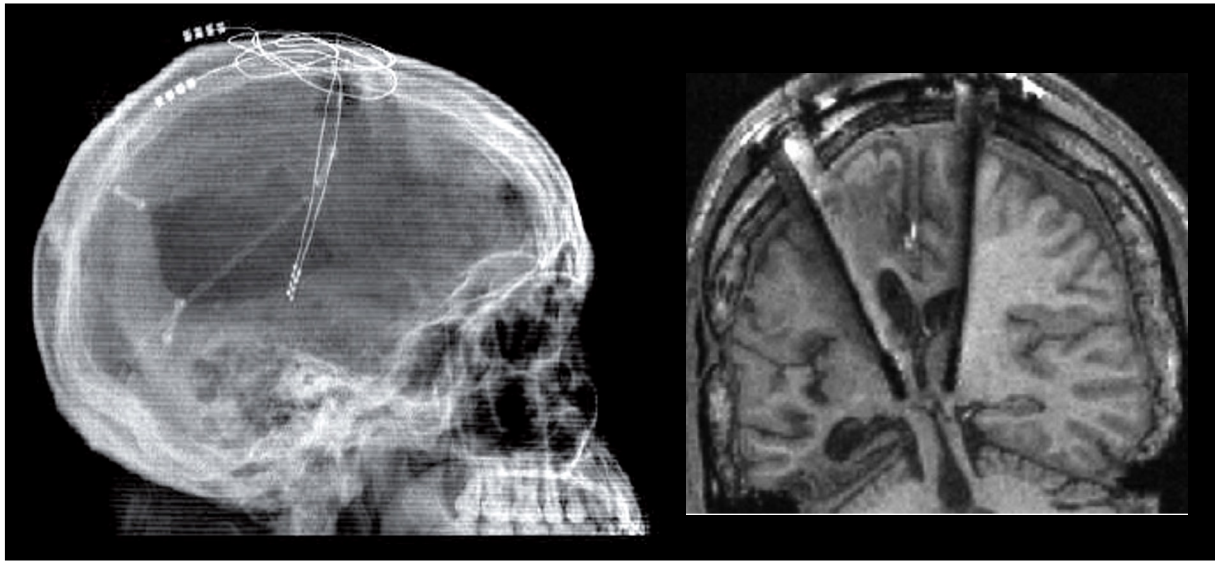
Vestibular

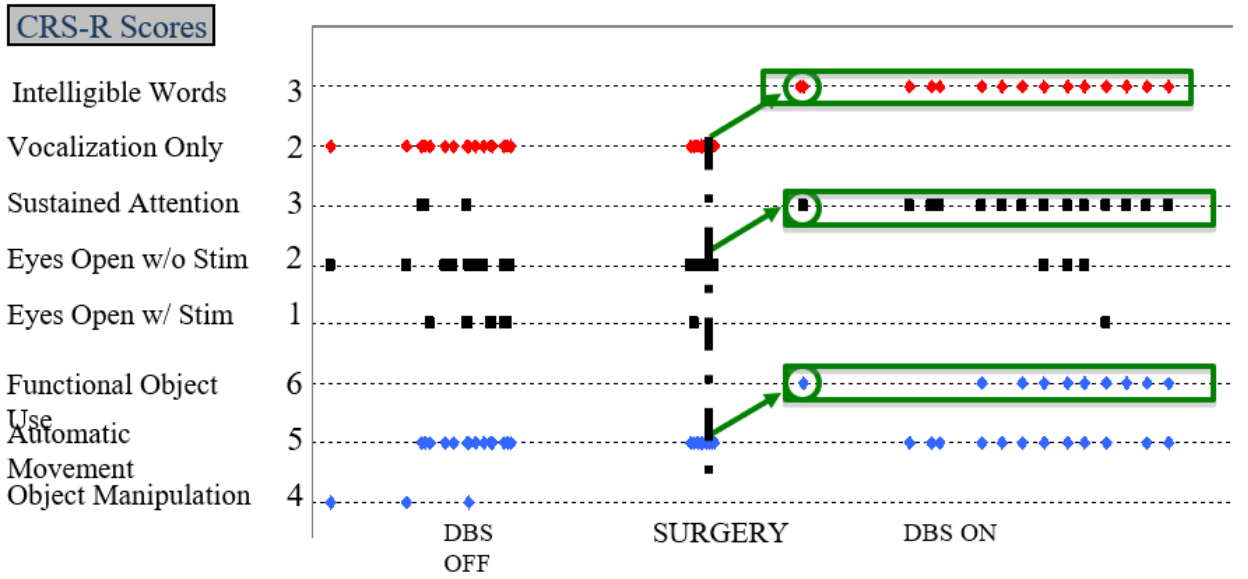


Sensory stimulation

Deep Brain Stimulation

Intralaminar nuclei “reconnections” in spontaneous recovery from unresponsive state





Case-report : MCS ➔ emerged – prolonged effects

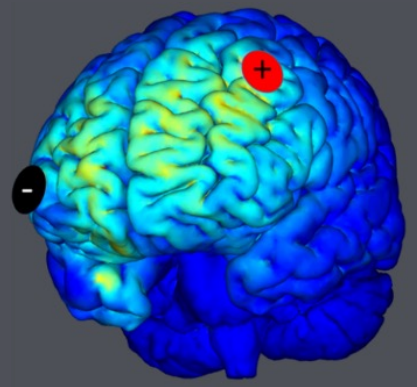
sustained attention, intelligible words, functional objects use

No RCT & side-effects

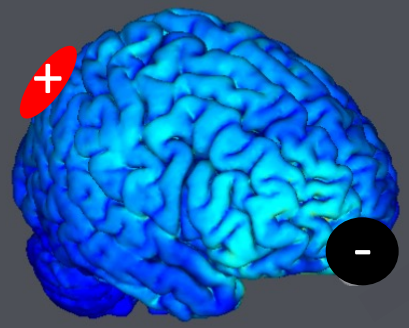
Schiff et al, Nature 2007

Transcranial direct current stimulation (tDCS)

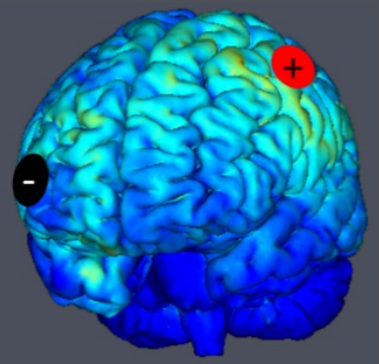
Prefrontal



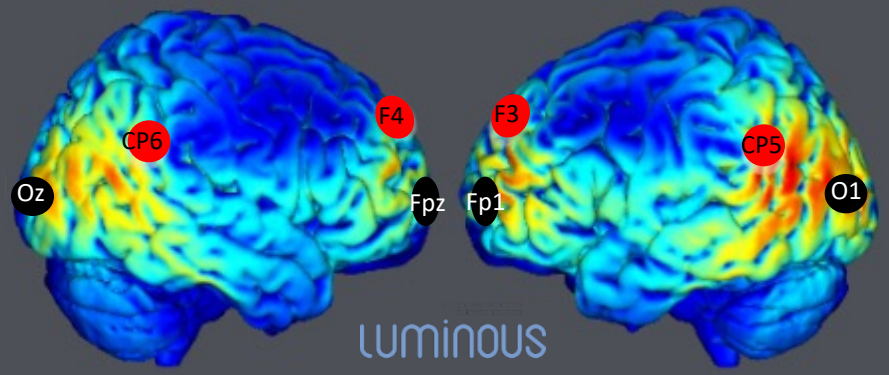
Precuneus



Motor



Multichannel frontoparietal



➔ + effects in MCS & prefrontal tDCS = best target

➔ need for multicenter trials & individualized treatments

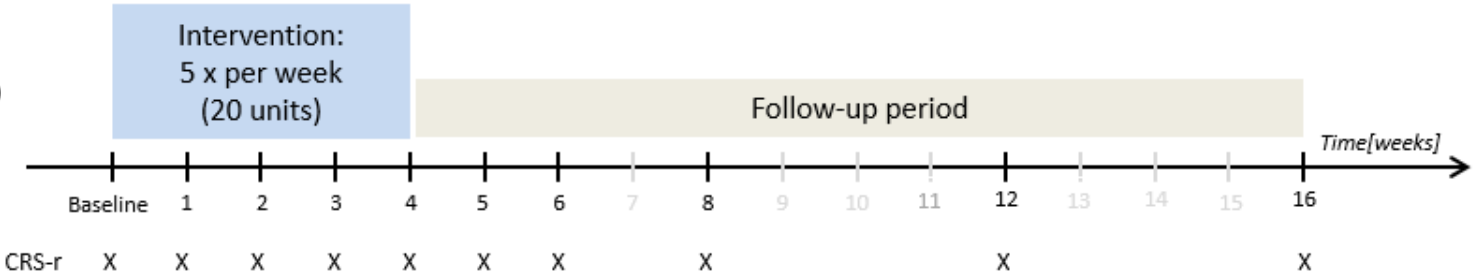
Thibaut et al, 2014, 2017; Huang et al, 2017; Martens et al, 2018; Martens et al, 2019 , Martens et al, 2020

tDCS multicentric trial

DoCMA

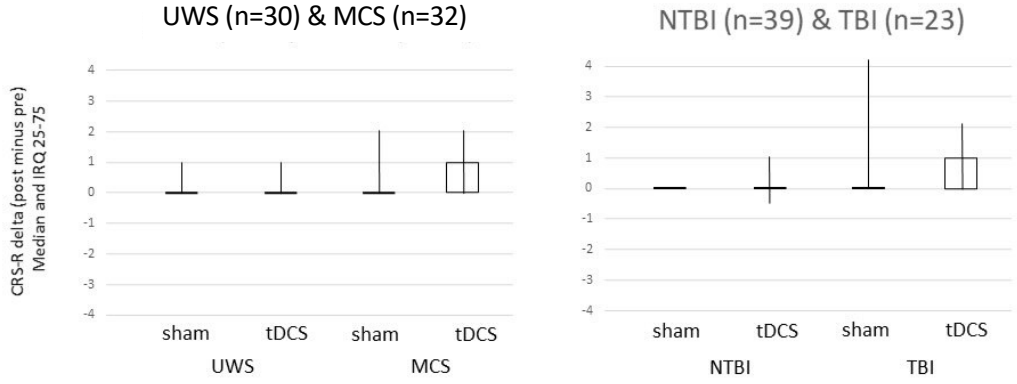
➔ 62 patients: 32 MCS, 23 TBI, 33 active tDCS, age: 44±14 yo, TSO: 37±24w.

Prefrontal tDCS
(20 min – 2 mA)

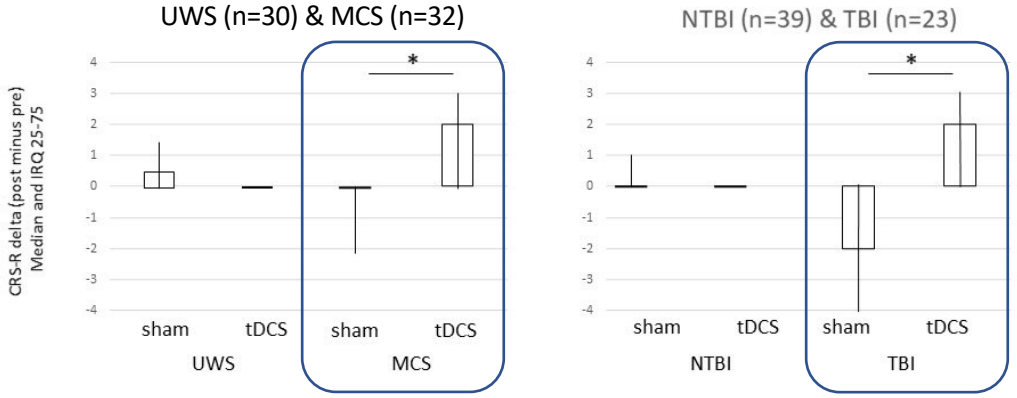


- No clinical effects at the group level
- Improvement at 3-month follow-up for MCS & TBI

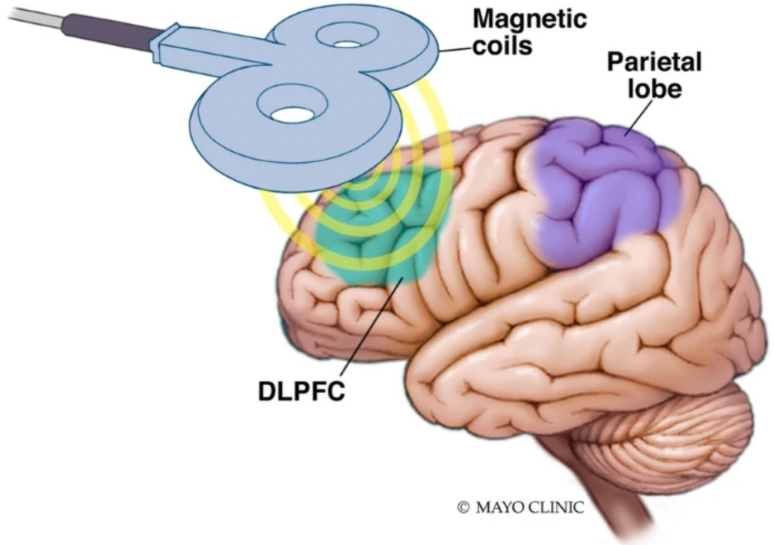
4 weeks of tDCS



3 month follow-up



Transcranial magnetic stimulation (TMS)



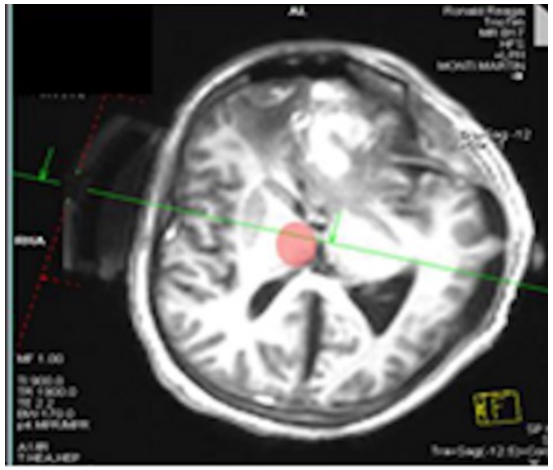
- **Motor cortex** : no behavioral improvement (RCT)
- **DLPFC** : behavioral improvement + alpha power increase (open-label & sham controlled single blinded)
- **AG** : behavioral improvement in MCS not in UWS (open-label)

➔ **Ongoing RCT** : AG & DLPFC rTMS in prolonged DoC

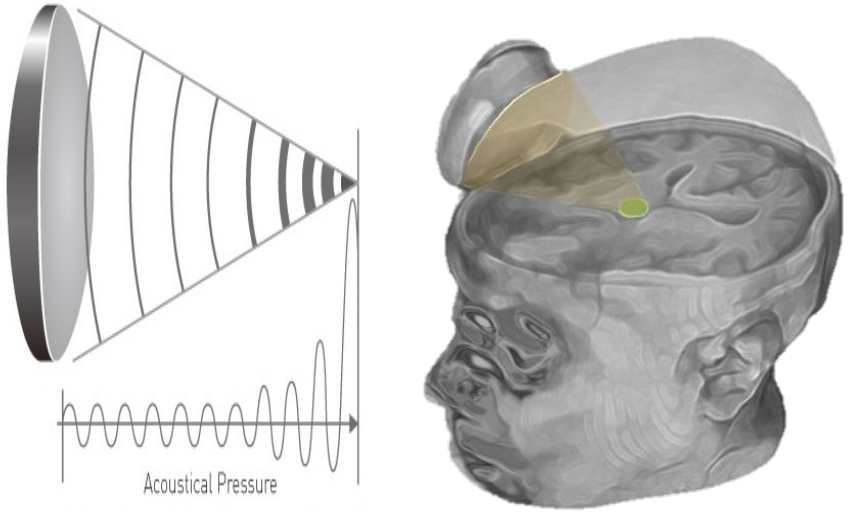
Xie et al, 2012, Cincotta et al, Cortex, 2015; Liu et al, Eur Neurol, 2016; Xia et al, 2017; He et al, Neural Plasticity, 2018, Legostaeva et al, 2019; Vitello & Rosenfelder* et al., Front Neurol, 2023*

Low Intensity Focal Ultrasound Pulses

Safe as tDCS, deep as DBS



Target thalamus



<u>Case report – acute</u>

25 yo male, 19 days post-TBI

CRS-R 15 to 17 (motor related behavior)

➔ 3 days later emergence

<u>Series of cases – chronic</u>

3 patients – stroke, CA, TBI

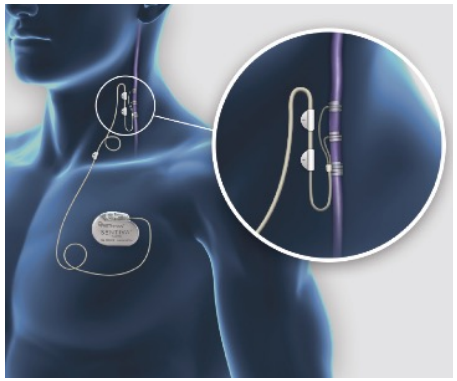
MCS > 1y post-injury

➔ 2/3 improved

➔ 1/3 up to 6m follow-up

Monti et al, Brain Stimul 2016, Cain et al, Brain Stimul 2021

Vagal Nerve stimulation

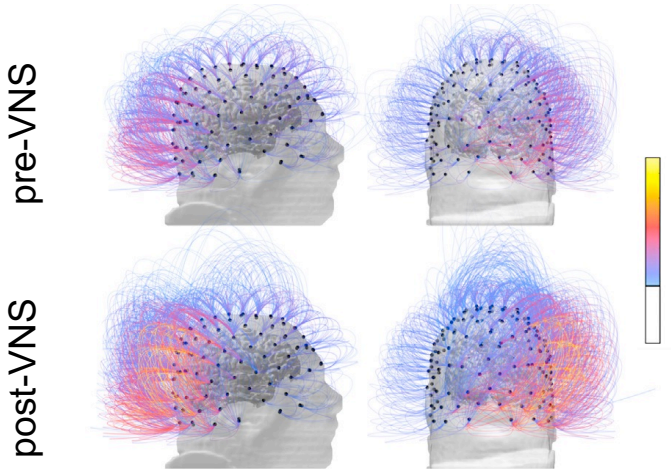


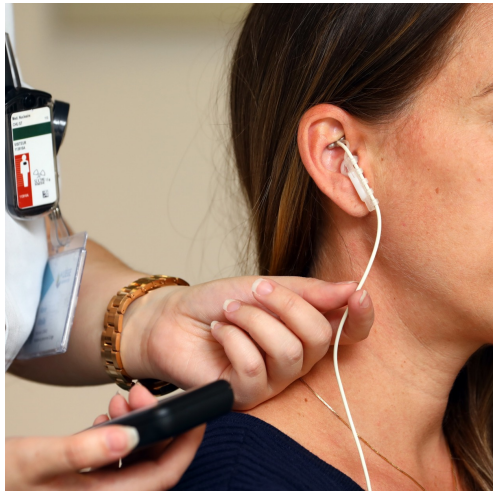
- **Invasive VNS (max 1.5mA)**

Case report

1 month of stimulation, UWS ➔ MCS

No RCT



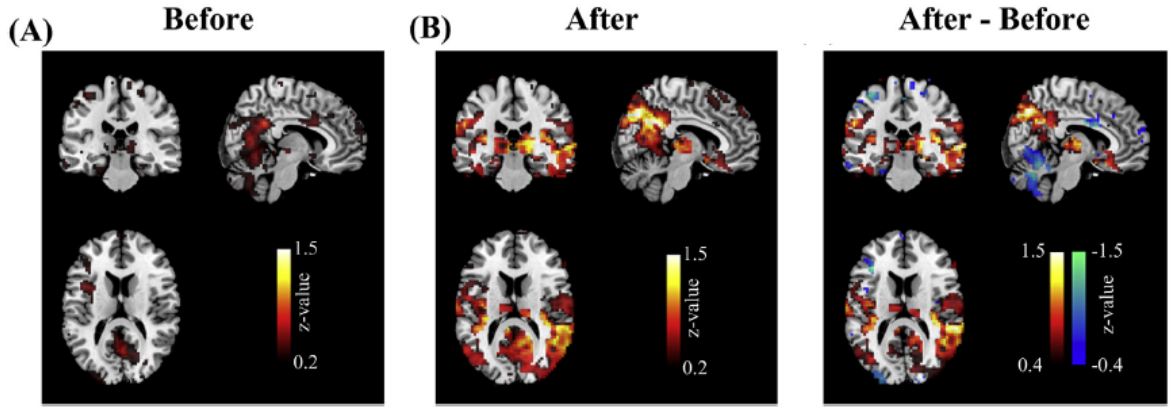


- **Non-invasive vagal nerve stimulation - taVNS**

Case series

heterogenous behavioral

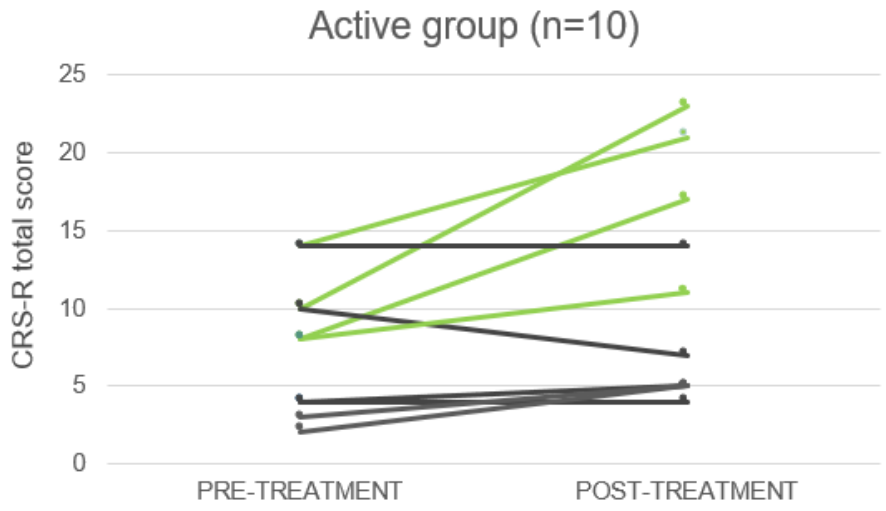
and neuroimaging effects

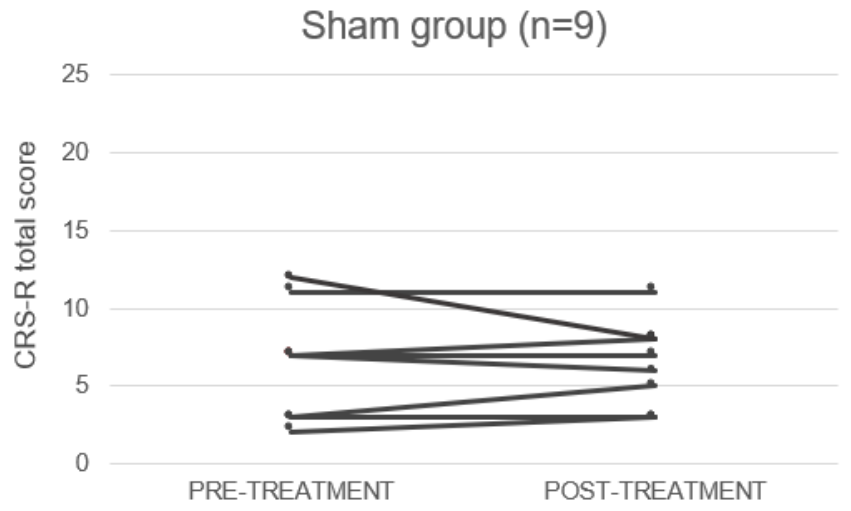


Yu et al, Brain Stimul, 2017; Corazzol et al, Curr Biology, 2017 ; Hakon et al, Neuromodulation, 2020 ; Noe et al, Brain Stimul, 2021

Vagal Nerve stimulation

Behavioral results



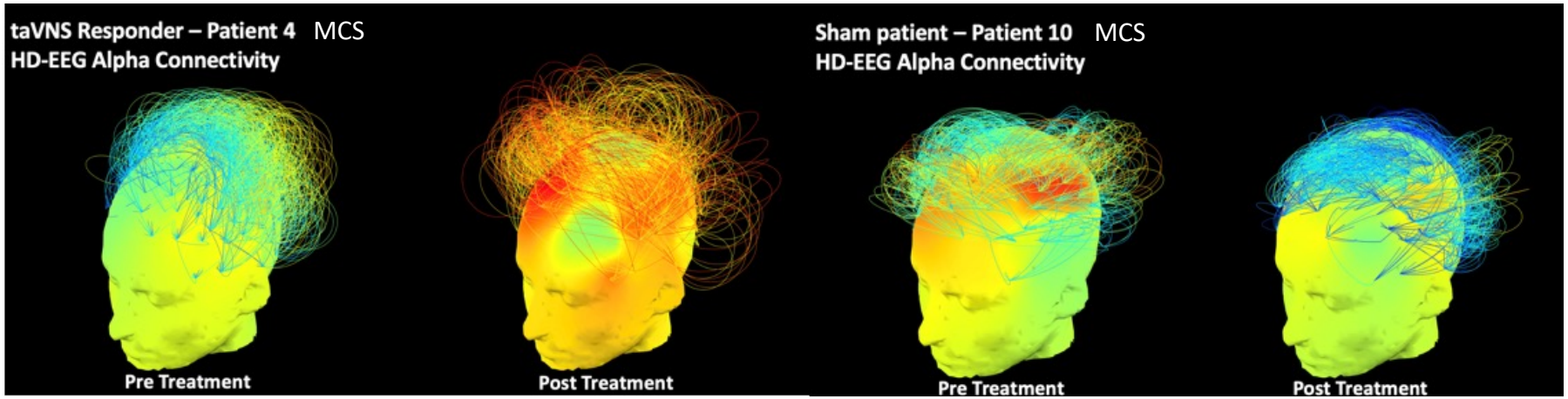


Responders

Non responders

Hd-EEG

α connectivity



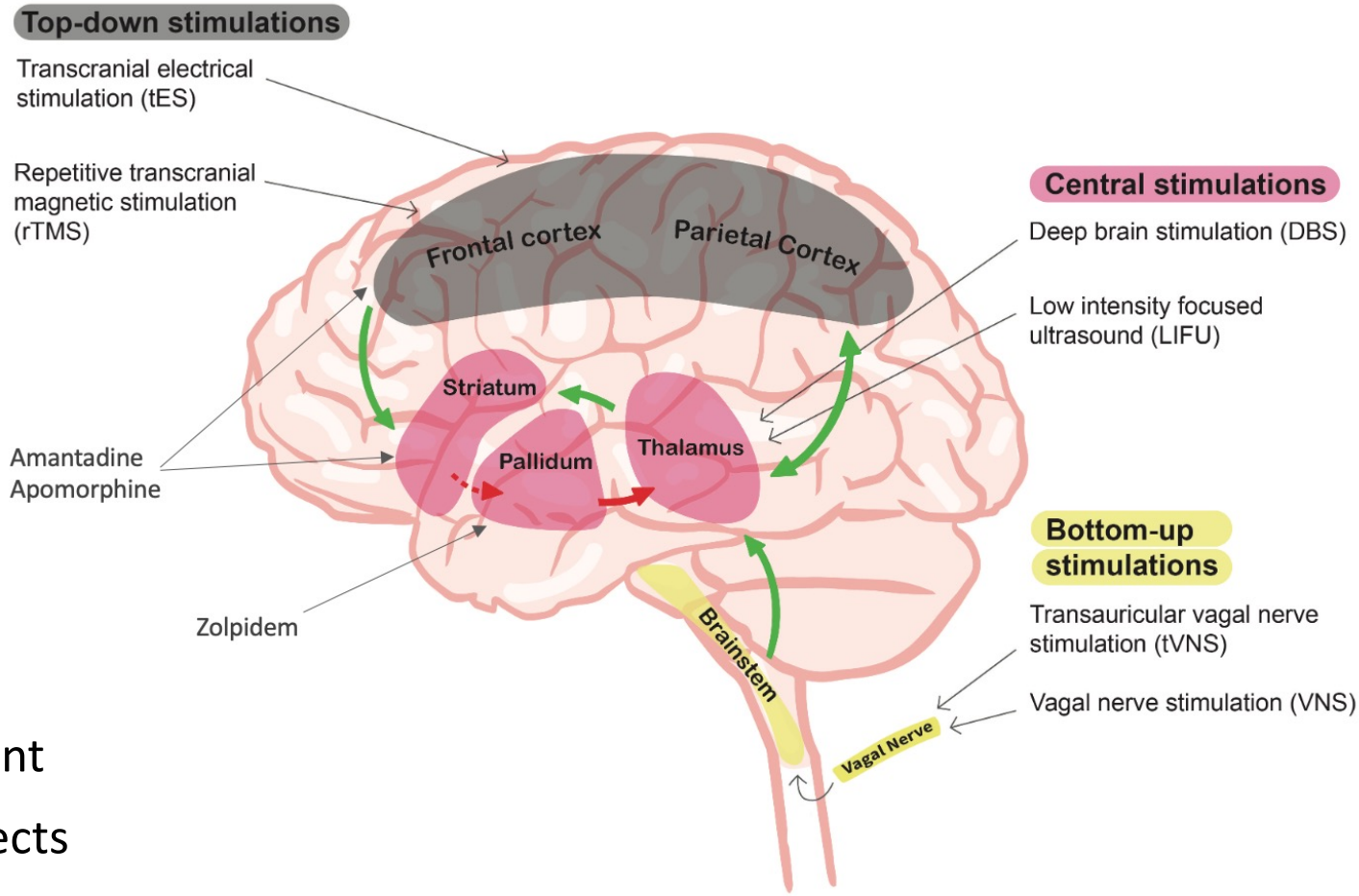
Conclusion: which treatment?

Pharmacological treatments

- Amantadine in TBI ➔ other etiologies?
- Apomorphine ➔ randomized clinical trials
- Zolpidem – 5% ➔ phenotype of responders
- Ketamine & psychedelics?

Brain Stimulations

- DBS: Promising but invasive & no randomized clinical trials
- tDCS is safe in severely brain-injured patients
- **Prefrontal** tDCS ➔ consistent clinical improvement
- Repeated tDCS ➔ increased duration of the effects
  ➔ increased number of responders
- Novel approaches ➔ taVNS, rTMS LIFUP & more



Key points and take home messages

1. DoC is a dramatic disorders, with very few treatments available
2. At the moment, amantadine and tDCS (?) show positive results. Other solutions are invasive
3. New investigations focus on pharmacological (e.g.) and non-pharmacological treatments

Acknowledgments

Pr. Olivia Gosseries

Dr. Charlotte Martial

Patients & families!

For more information:
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