

Non-invasive brain stimulation in post-comatose patients with disorders of consciousness

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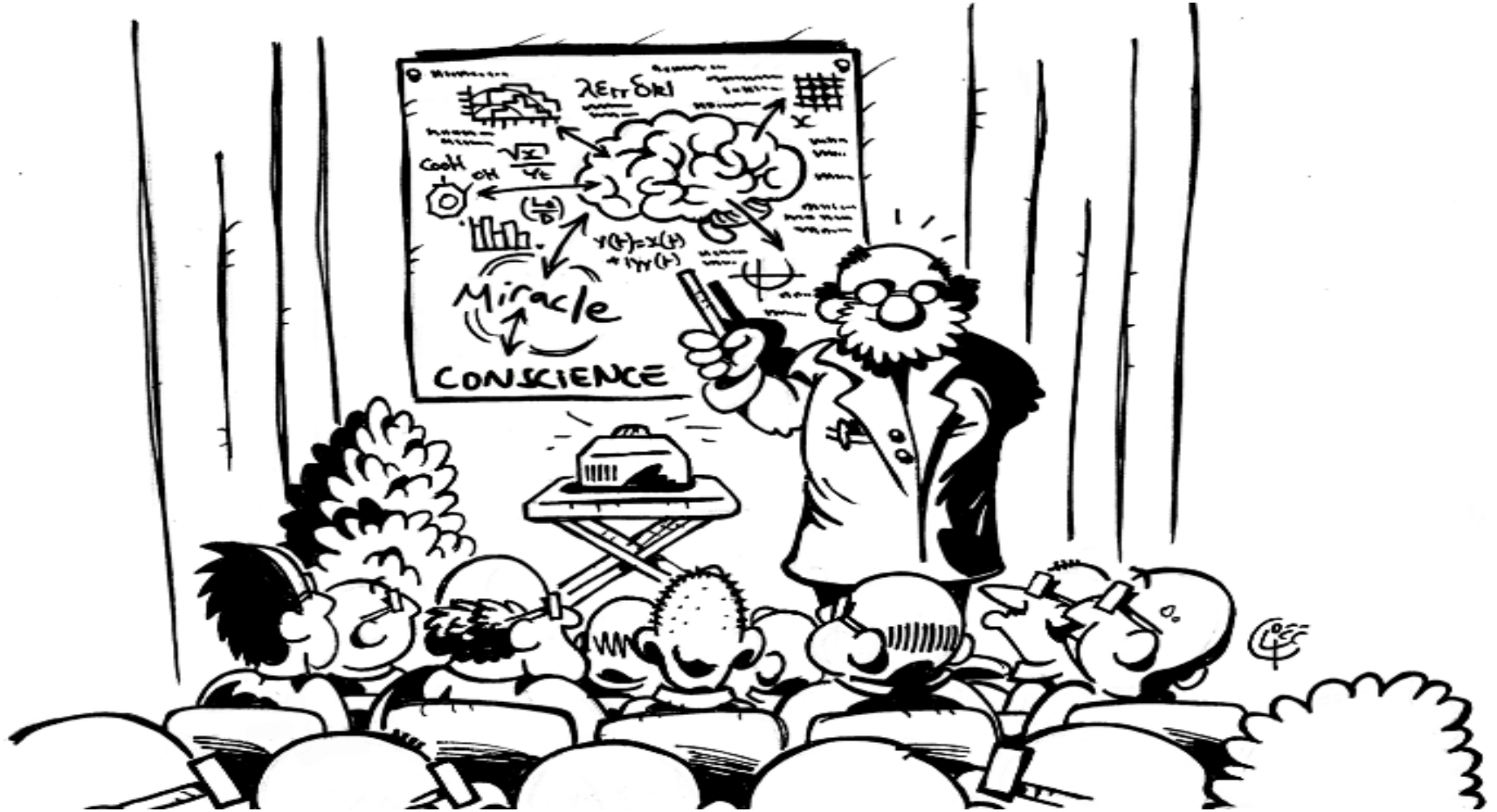
neuromodulationcenter.org





1. Definition of « disorders of consciousness »
(DOC)
2. NIBS as therapeutic tools
(tDCS, rTMS)
3. NIBS as diagnostic tool
(TMS-EEG)

What's consciousness?



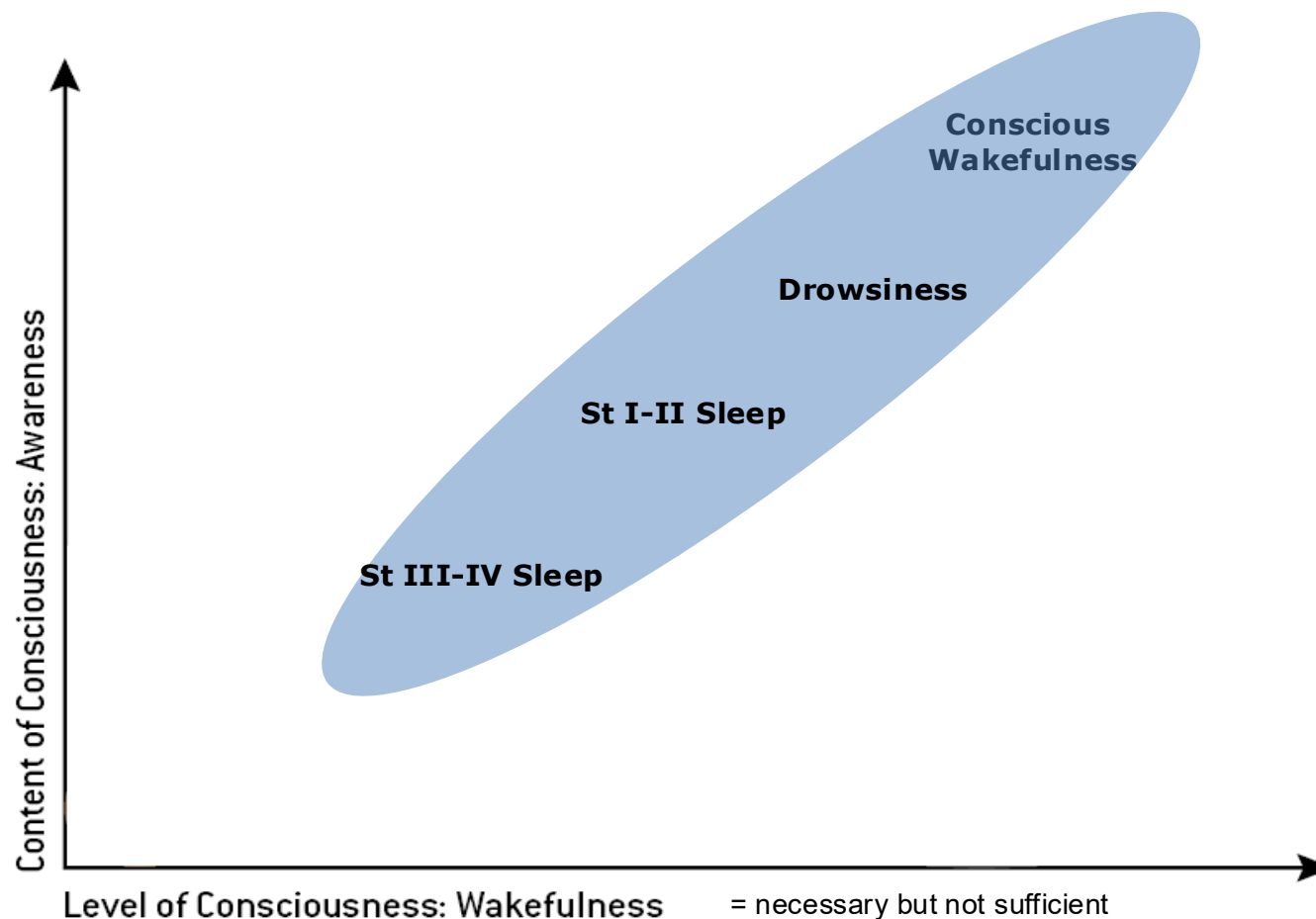


Arousal & awareness



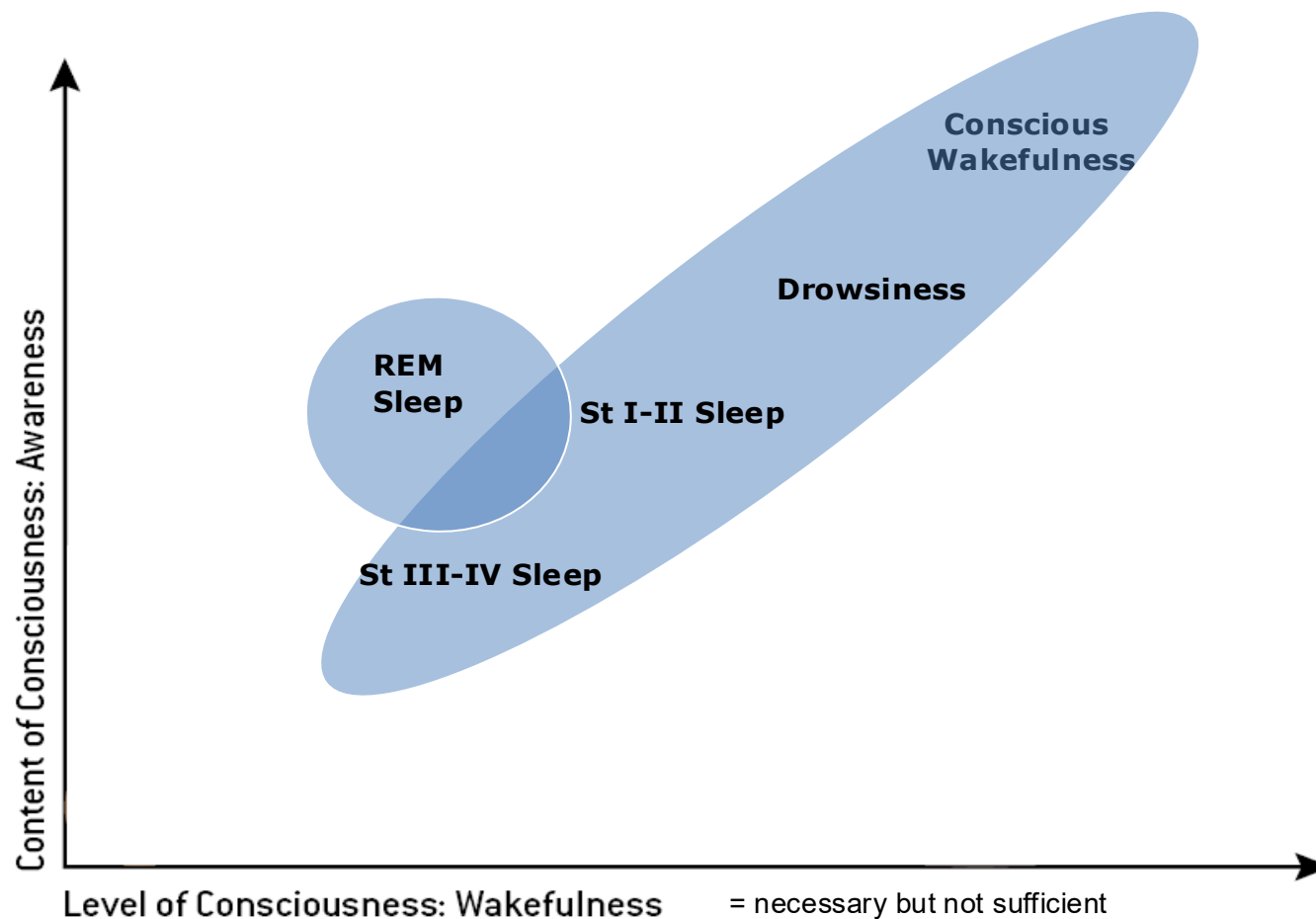


Arousal & awareness



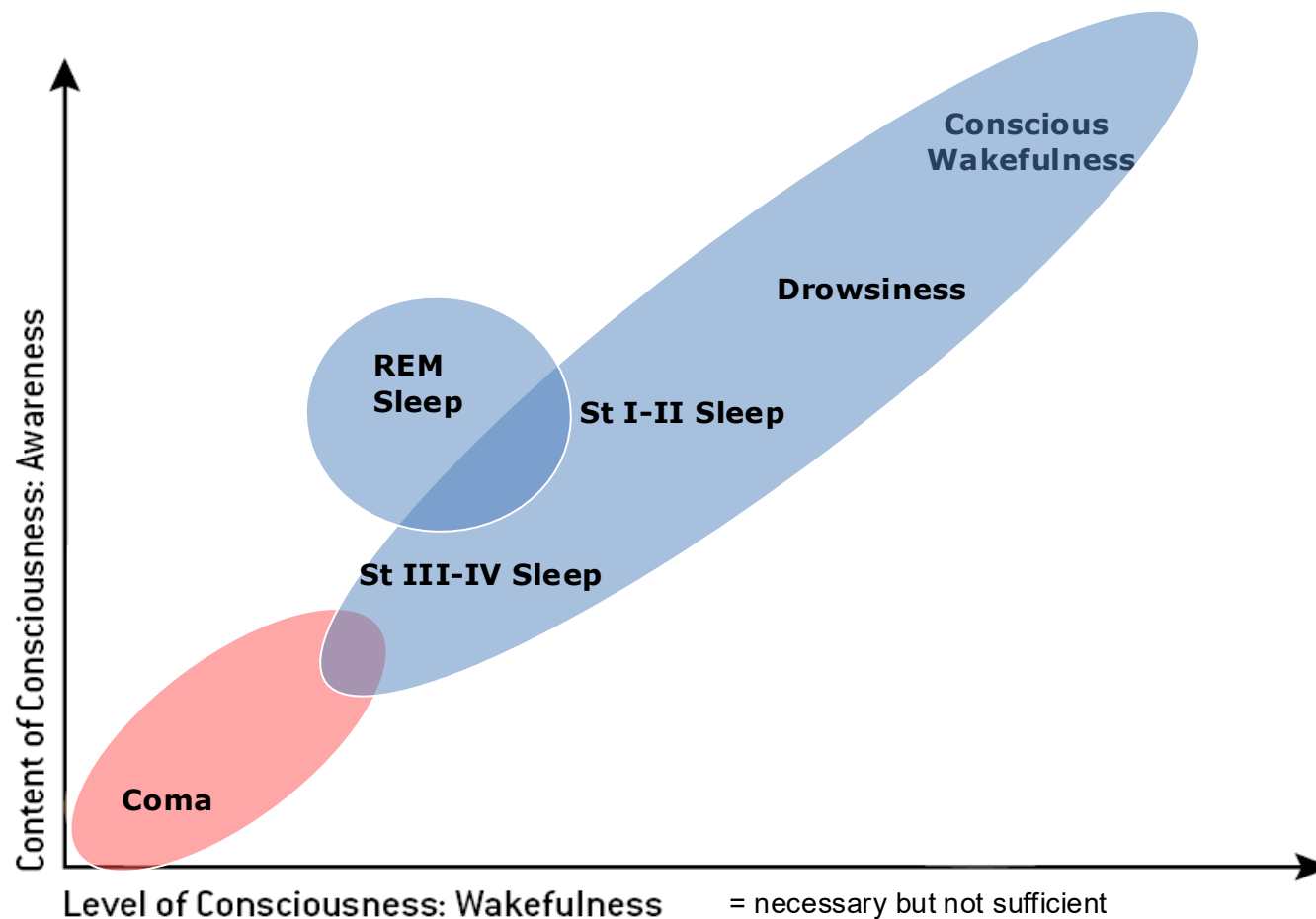


Arousal & awareness



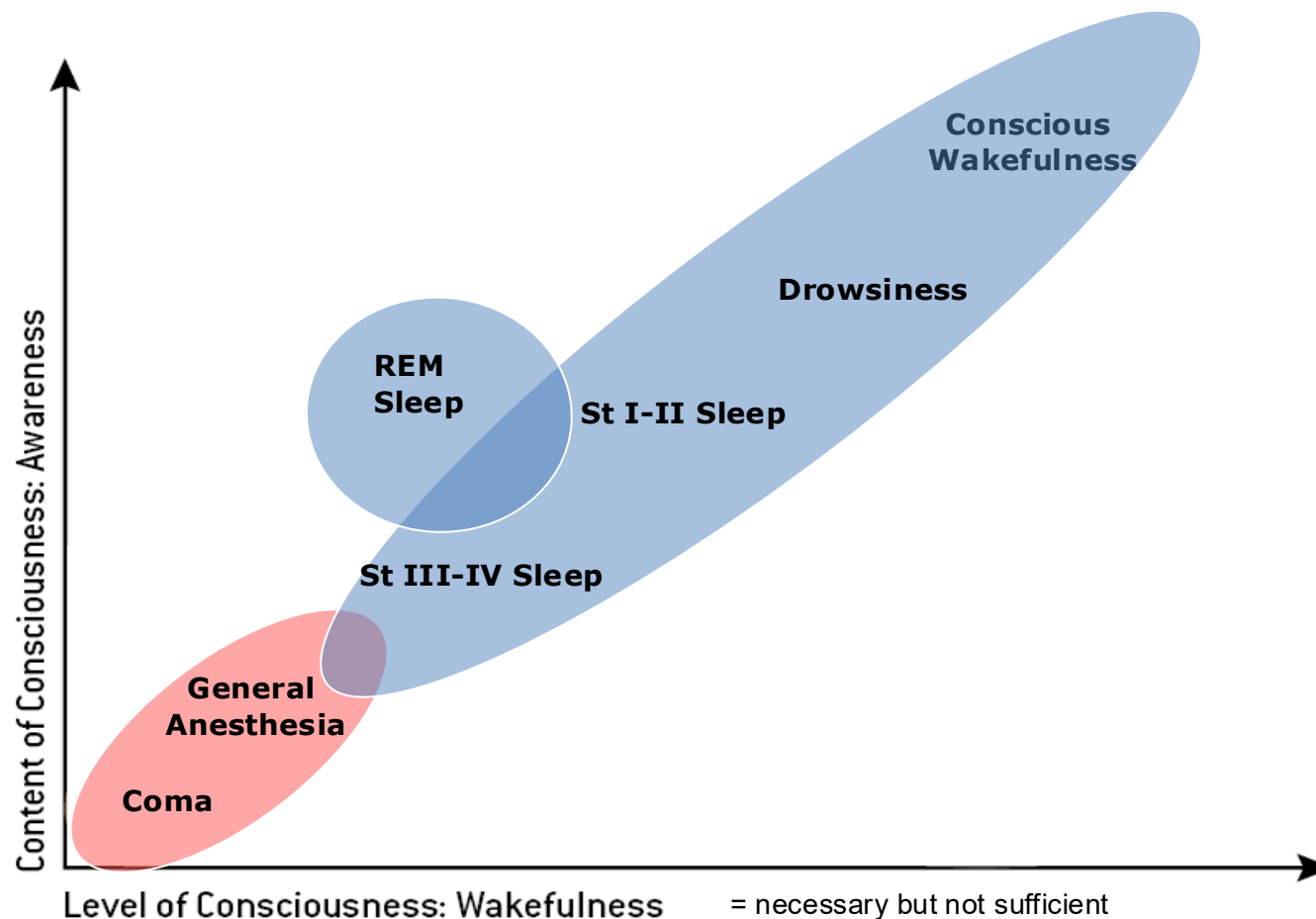


Arousal & awareness



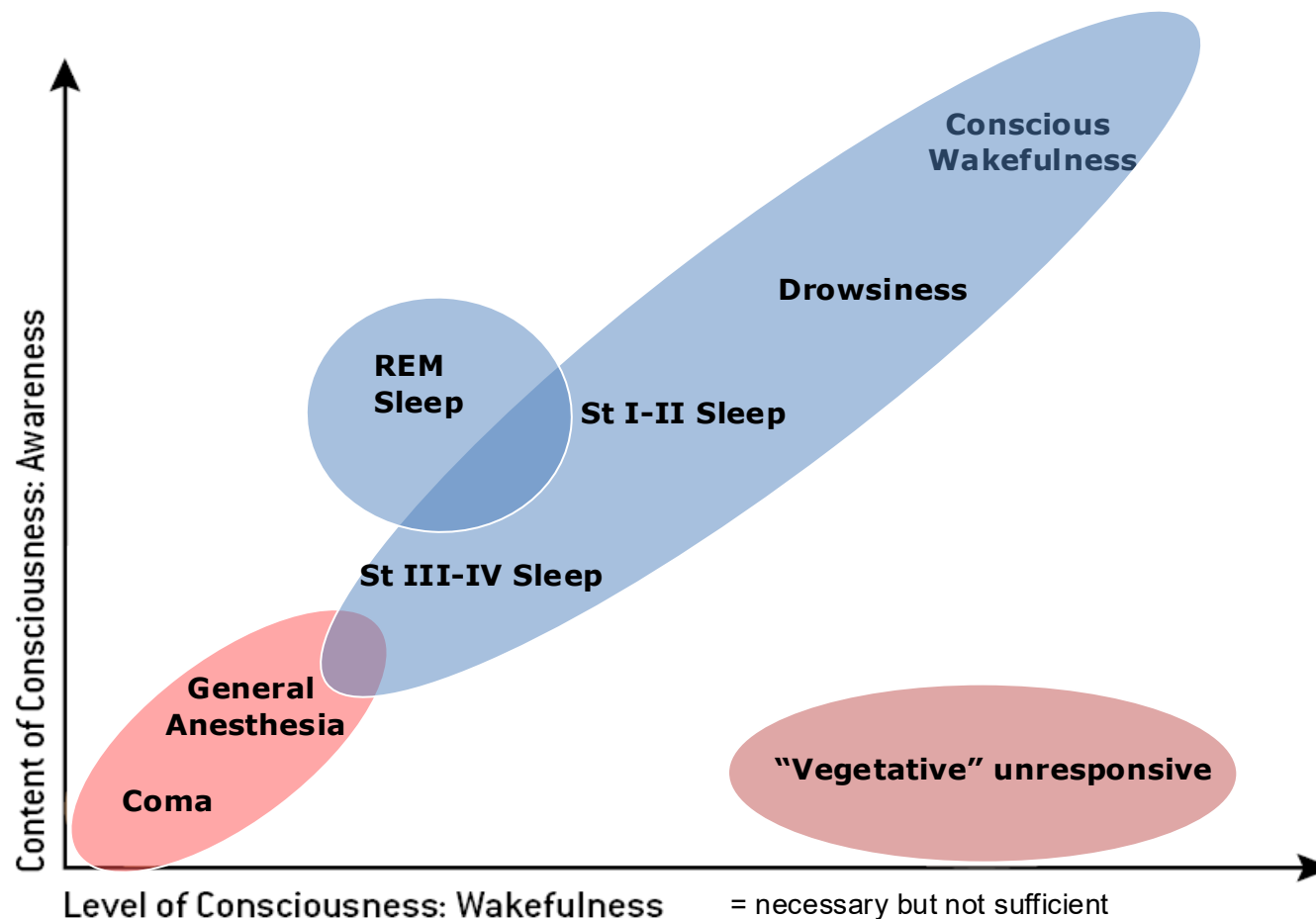


Arousal & awareness



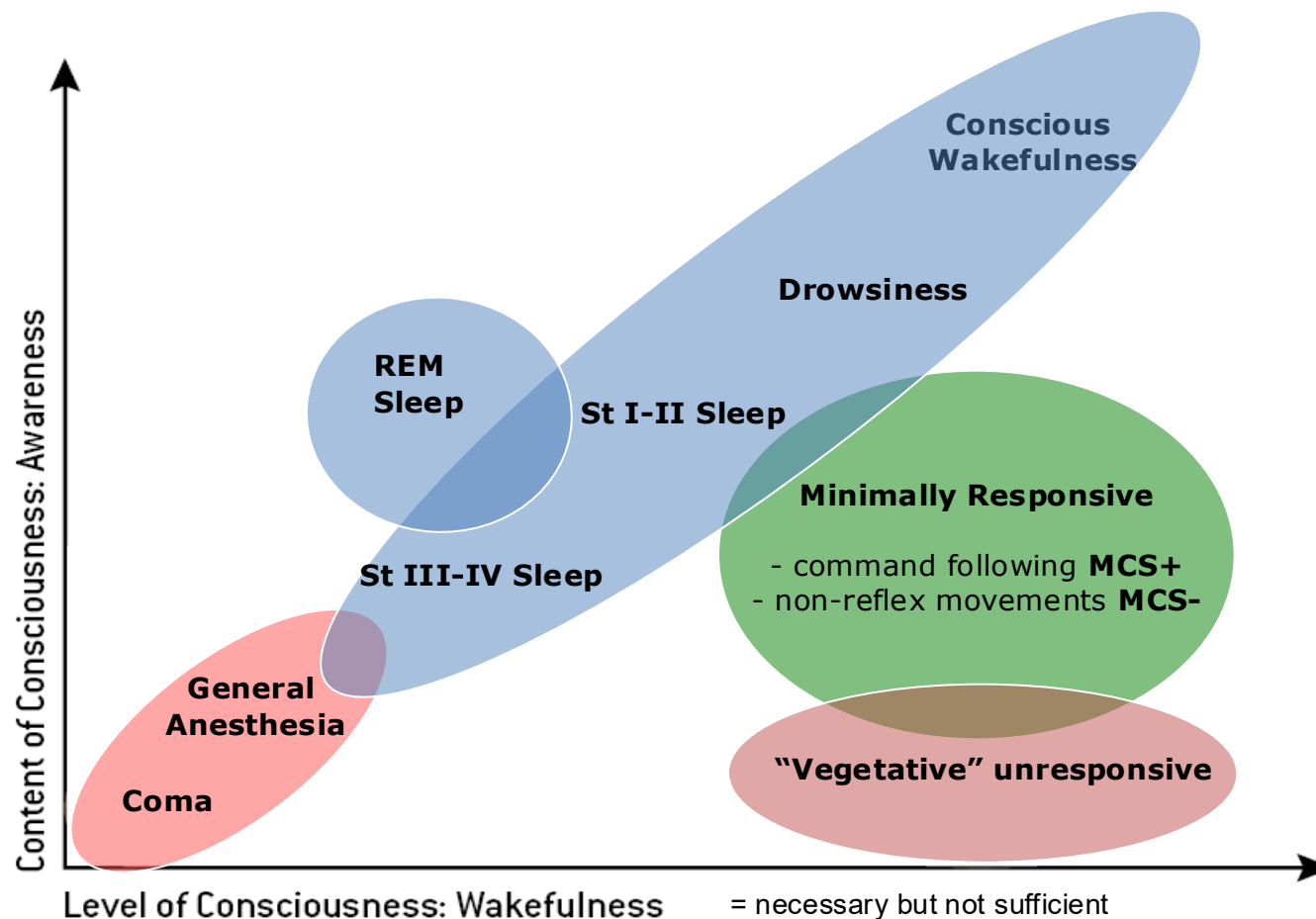


Arousal & awareness





Arousal & awareness



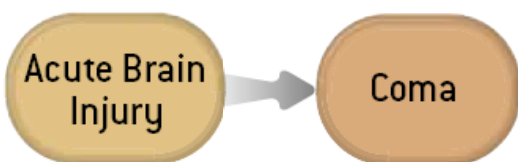


Clinical entities of DOC

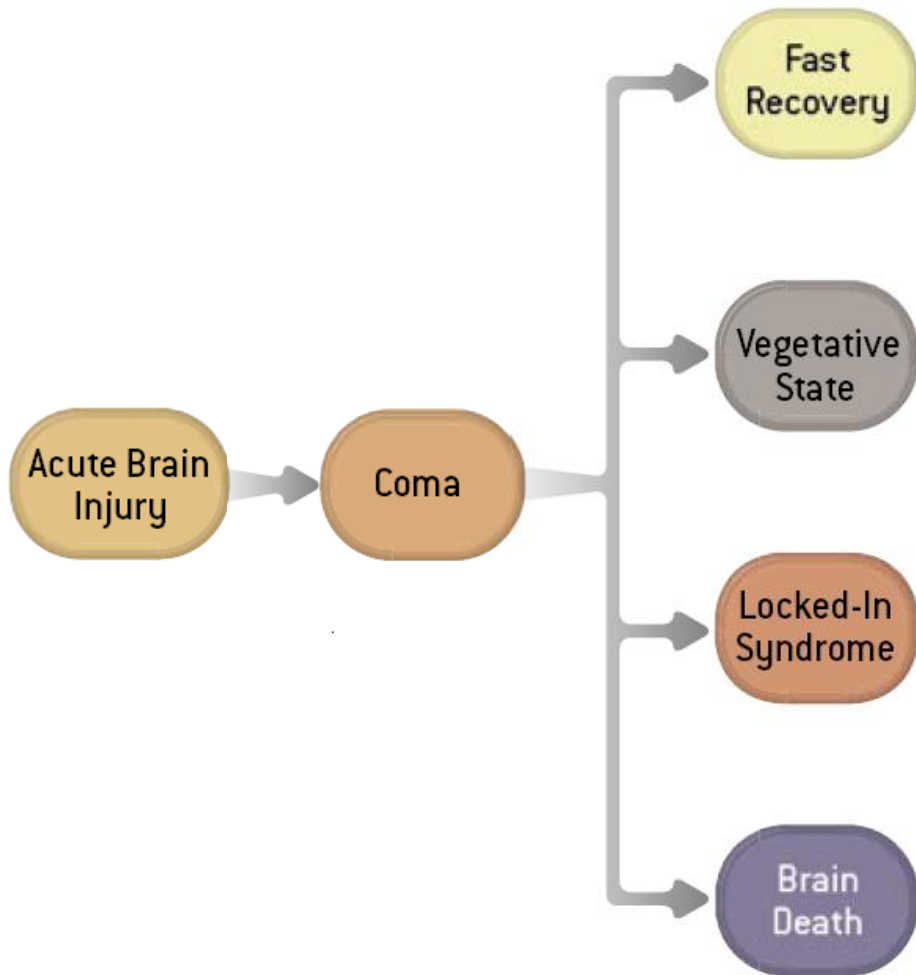
Acute Brain
Injury



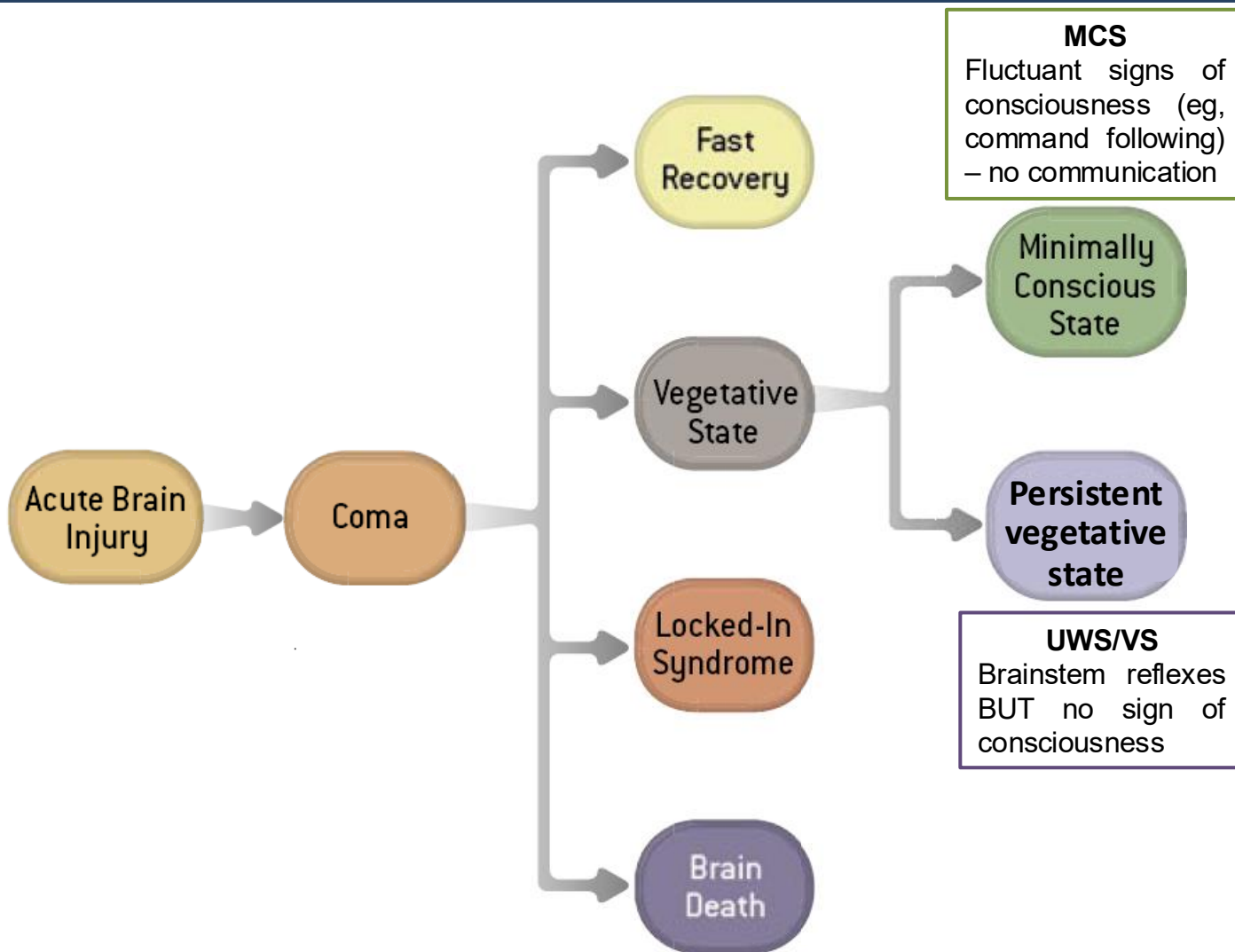
Clinical entities of DOC



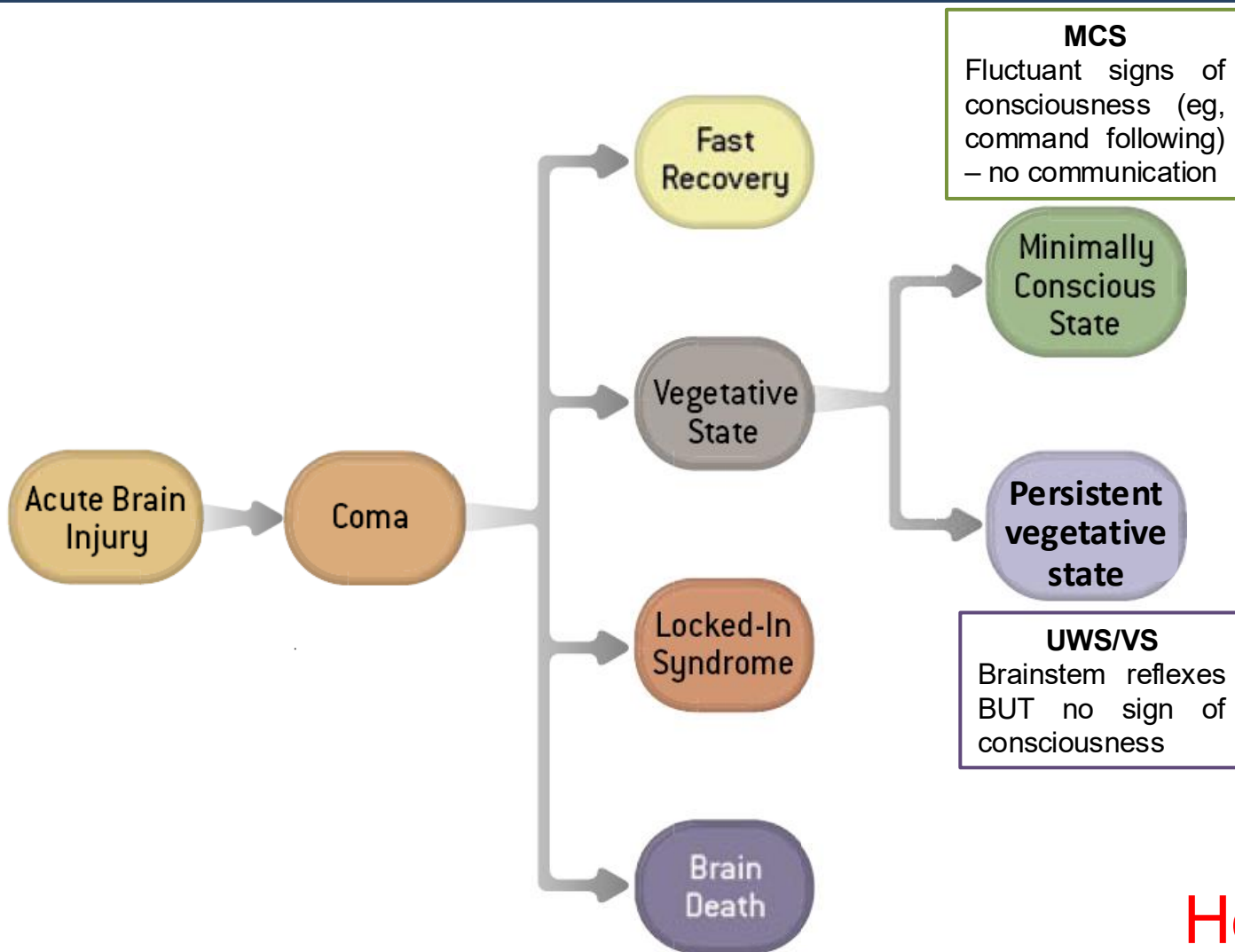
Clinical entities of DOC



Clinical entities of DOC



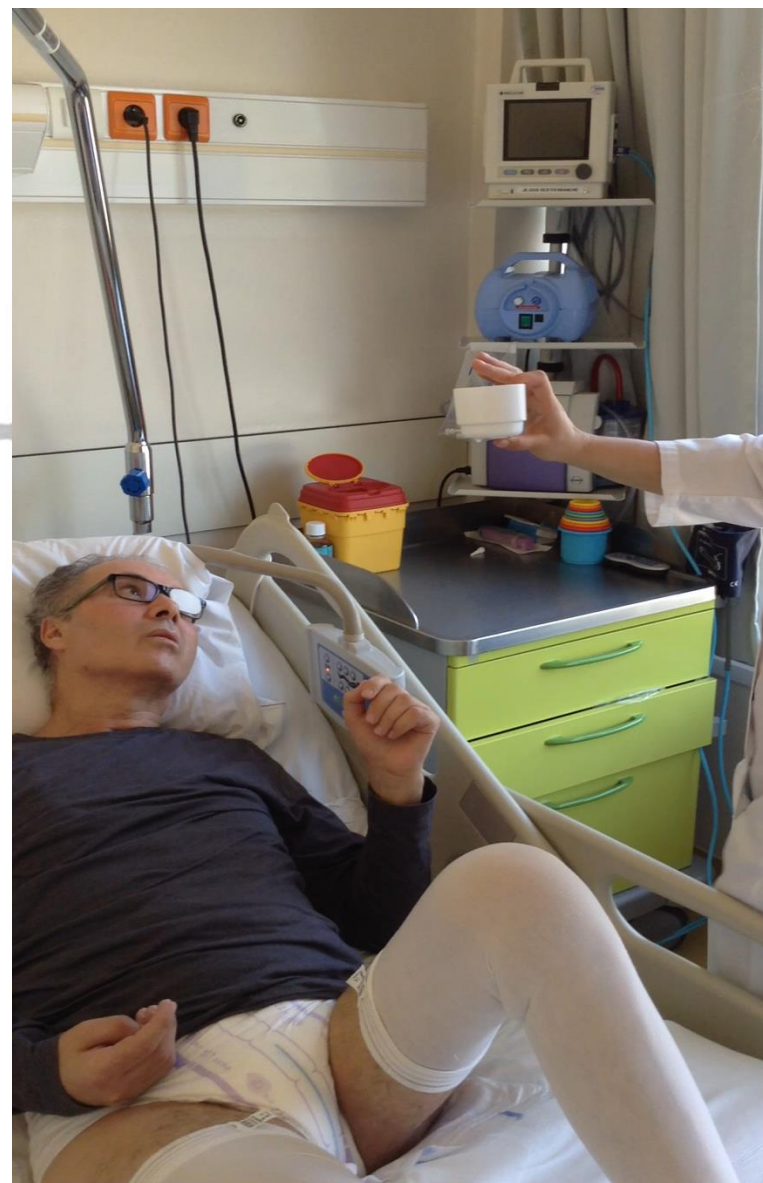
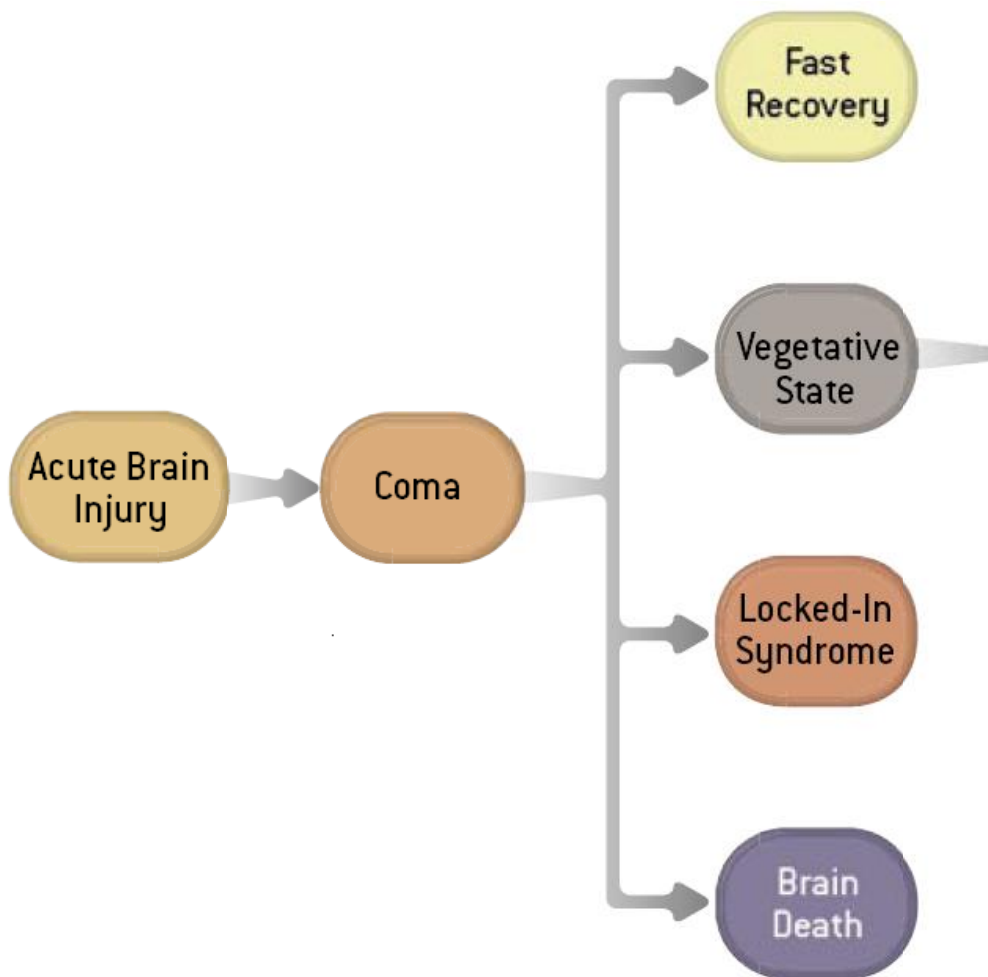
Clinical entities of DOC



How to improve recovery ?



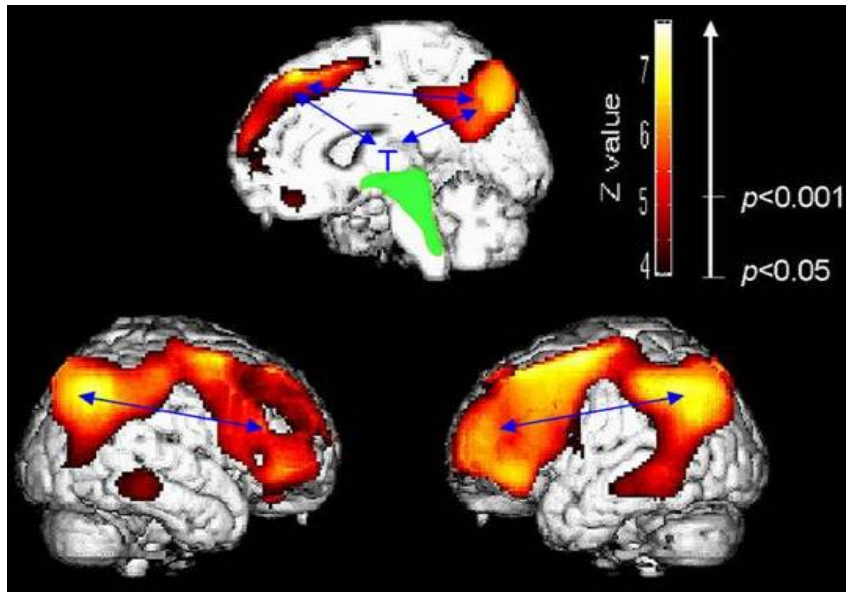
Clinical entities of DOC



Consciousness

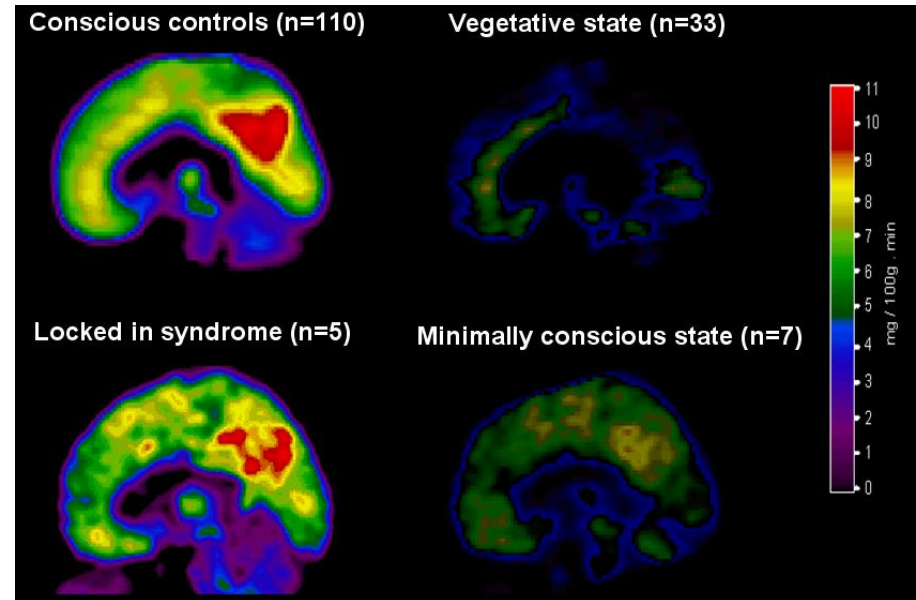
Fronto-parietal network

Brain regions & networks for consciousness recovery



Laureys et al, *Neuroimage*, 1999

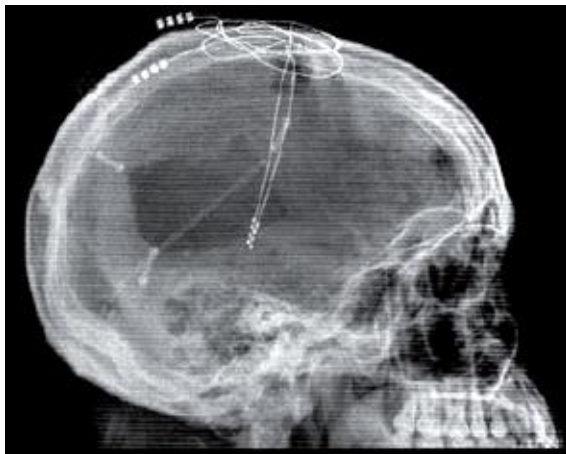
Fronto-parietal network



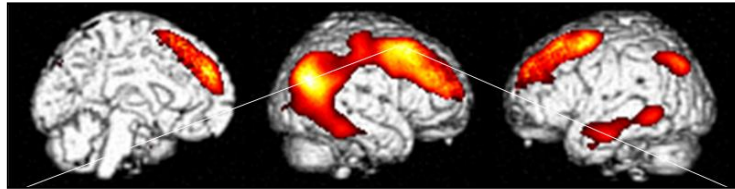
Laureys et al, *Lancet Neurology*, 2004

Precuneus

What are the therapeutic options for patients with disorders of consciousness?

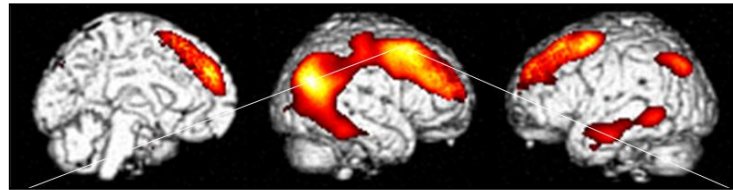


- Amantadine – RCT – 184 TBI (Giacino et al, *NEJM*, 2012)



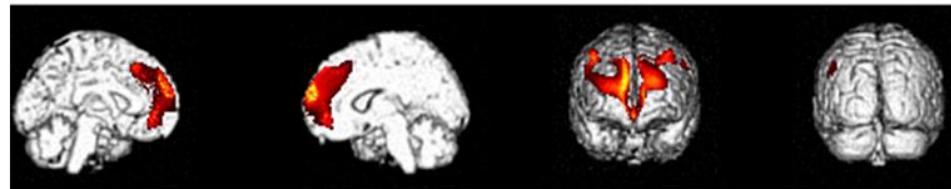
Schnakers et al, 2008

- Amantadine – RCT – 184 TBI (Giacino et al, *NEJM*, 2012)



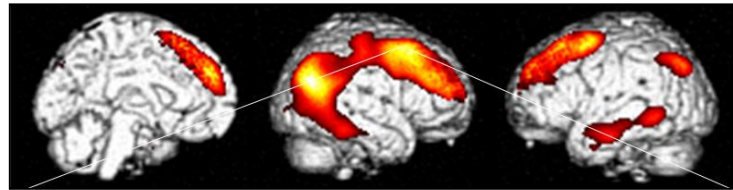
Schnakers et al, 2008

- Zolpidem
5-7% responders



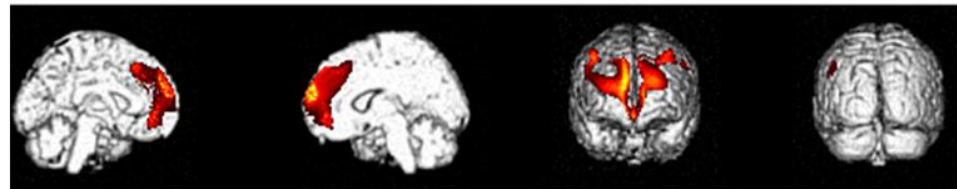
Chatelle et al, 2014, Thonnard et al, 2014

- Amantadine – RCT – 184 TBI (Giacino et al, *NEJM*, 2012)



Schnakers et al, 2008

- Zolpidem
5-7% responders

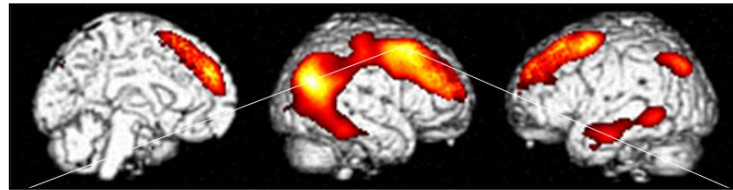


Chatelle et al, 2014, Thonnard et al, 2014

- Apomorphine

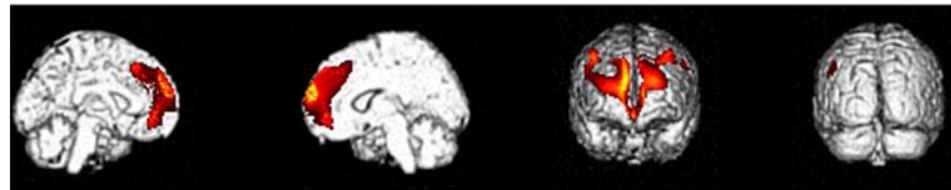
Drugs

- Amantadine – RCT – 184 TBI (Giacino et al, *NEJM*, 2012)



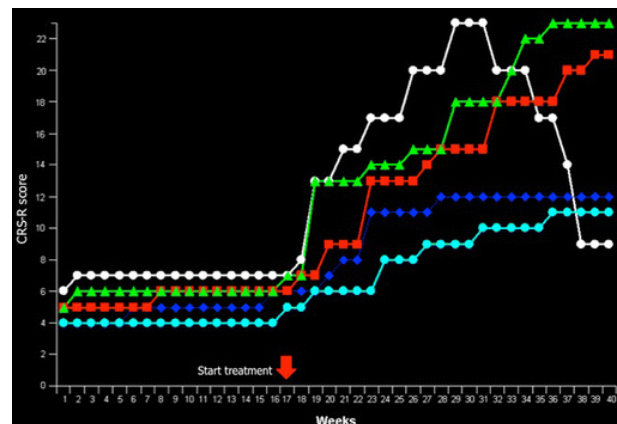
Schnakers et al, 2008

- Zolpidem
5-7% responders



Chatelle et al, 2014, Thonnard et al, 2014

- Apomorphine
- Baclofen

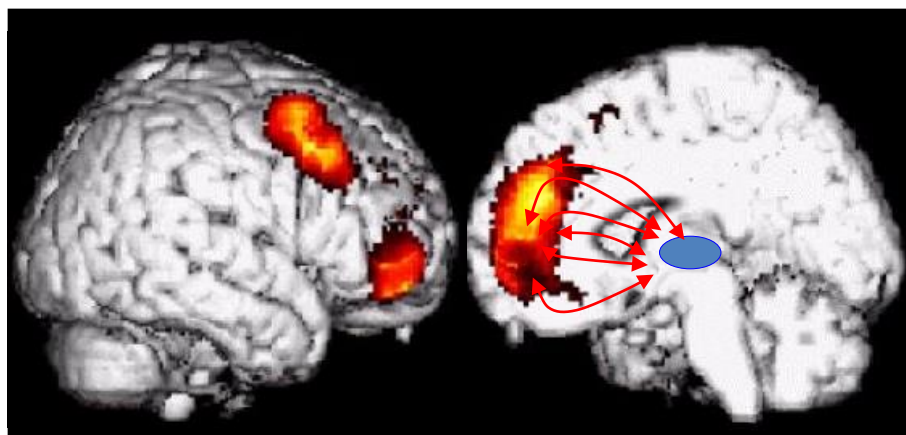


Sara et al, 2009; Pistoia et al, 2014

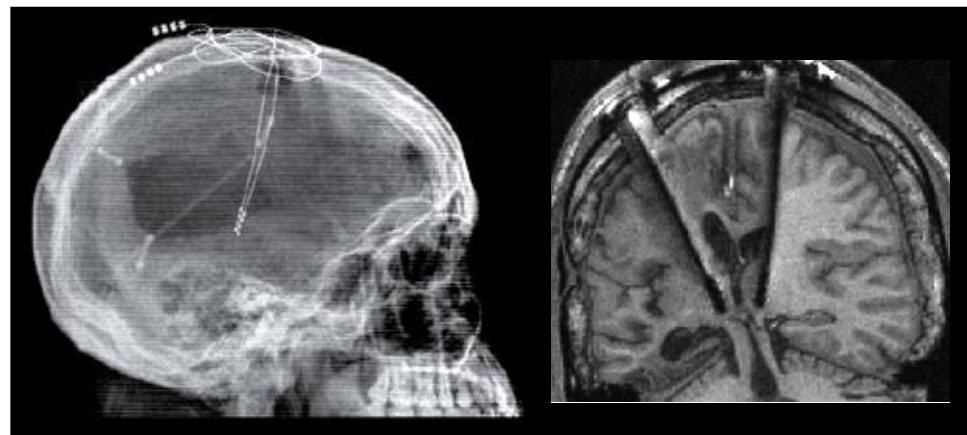


Deep Brain Stimulation

Intralaminar nuclei “reconnections” in spontaneous recovery from “vegetative” unresponsive state



Laureys et al, *Lancet* 2000

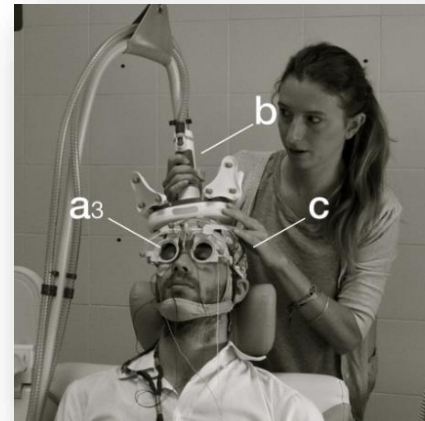


Schiff et al, *Nature* 2007

MCS → emerged – prolonged effects
sustained attention, intelligible words, functional objects use

No RCT & side-effects

Non-invasive brain stimulation



Recent RCTs on NIBS in DOC

NIBS	N	TSO	Procedure	Results	Effect sizes
tDCS Thibaut et al, 2014	55 25 TBI, 30 non-TBI 30 MCS, 25 UWS	1 week to 19 years	Single session (20 minutes) of active and sham stimulation over the left DLPFC with CRS-R before and after tDCS	13/30 patients in MCS and 2/25 patients in UWS clinically improved (recovery of visual pursuit or command following). At the group level, clinical improvement (2 points on the CRS-R) for MCS patients. No side-effects observed.	For MCS (n=30): d=0.38
tDCS Thibaut et al, 2017	16 11 TBI, 5 non-TBI 16 MCS	> 3months	5 sessions of active and sham tDCS (20 minutes a day) over the DLPFC. CRS-R performed before, after 5 days of tDCS and at 1-week follow-up	9/16 responders. Clinical improvement maintained up to one week after the end of the stimulation. No side-effects observed.	After tDCS: d=0.43 ; at 1week follow-up: d=0.57
tDCS Estraneo et al, 2017	13 1 TBI, 12 non-TBI 7 UWS, 6 MCS	> 3months	5 days of active and sham tDCS over the DLPFC (20 min/day). EEG and CRS-R at baseline, after 5 days and 3-month follow-up	Behavioral (CRS-R total score) and EEG changes in 5/13 patients (3 in MCS and 2 in UWS). At the group level, no statistical difference between the two groups. No information on side-effects.	/

NIBS	N	Time since injury	Procedure	Results	Effect sizes
tDCS Zang et al, 2017	26 12 TBI, 14 non-TBI 11 UWS, 15 MCS	1 to 18 months	20 sessions of tDCS over DLPFC for 20 days		
tDCS Martens et al, 2018	27 12 TBI, 15 non-TBI 27 MCS	10 months to 14 years	20 sessions of tDCS over DLPFC by 8 weeks, 1 tDCS (20 sessions) up.		
tDCS Huang et al, 2017	33 20 TBI, 13 non-TBI 33 MCS	> 3months	5 sessions of tDCS over DLPFC after 5 days up		
tRNS Mancuso et al, 2017	9 1 TBI, 9 non-TBI 9 UWS	30 days to 4 months	5 sessions of tRNS over DLPFC at baseline, 1 at 3-day follow-up		
rTMS Cincotta et al, 2015	11 2 TBI, 9 non-TBI 11 UWS	9 to 85 months	5 sessions of active or sham 20 Hz rTMS for 10 minutes (1000 pulses in 5 trains) over left M1. EEG and CRS-R before and after rTMS	No behavioral or EEG improvements. No side-effects observed.	/
rTMS Liu et al, 2016	10 4 TBI, 6 non-TBI 5 UWS, 5 MCS	1 to 28 months	One session of active or sham 20-Hz rTMS over M1 for 10 minutes (1000 pulses in 20 trains). CRS-R and CBF velocity of the MCA before and after rTMS	No behavioral (CRS-R) changes Temporary increase in peak systolic velocity and mean flow velocity of the left MCA for MCS. No effects in UWS or in sham group. No side-effects observed.	/
rTMS He et al, 2018	6 4 TBI, 2 non-TBI 3 UWS, 2 MCS, 1 EMCS	1 to 28 months	5 sessions of active or sham 20-Hz rTMS over M1 (1000 pulses in 20 trains). CRS-R and EEG before, after rTMS and 1-week follow-up	No treatment effect on the CRS-R nor on the EEG. Clinical improvement in 1 patient (up to 1-week follow-up - UWS became MCS- paralleled by EEG power spectra improvement. No information on side-effects.	/

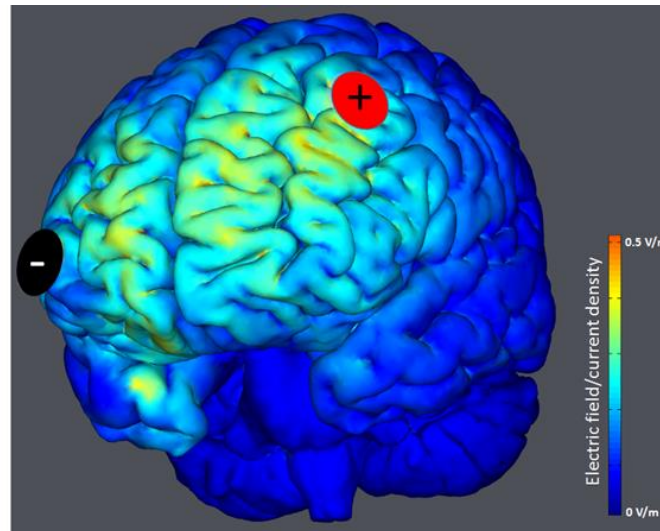
Past 5 years:

tDCS → 6 RCTs (170 pts) – 5 DLPFC & 1 M1 - 1 to 20 sessions – ES: 0.38 – 2.22

tRNS → 1 RCT (9 pts) – DLPFC – no clinical/neurophysiological effects

rTMS → 3 RCTs (27 pts) – M1 – 20 Hz – no clinical/neurophysiological effects

Transcranial Direct Current Stimulation (tDCS)



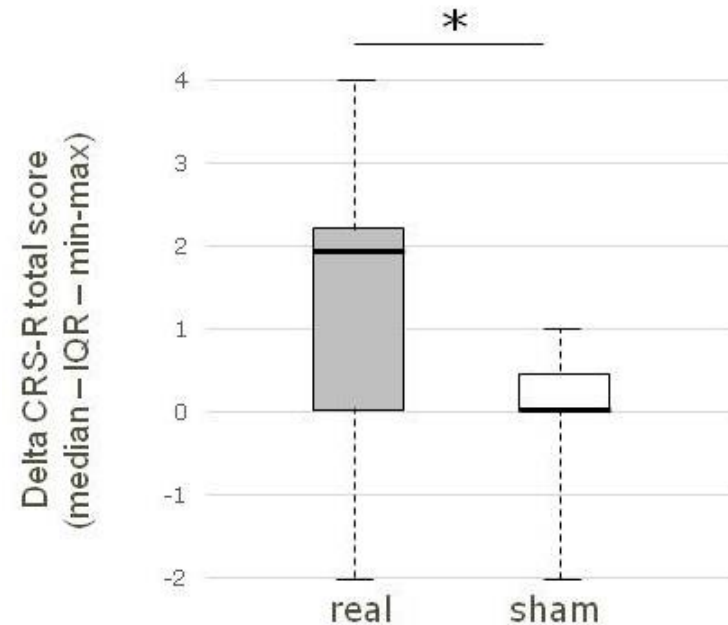
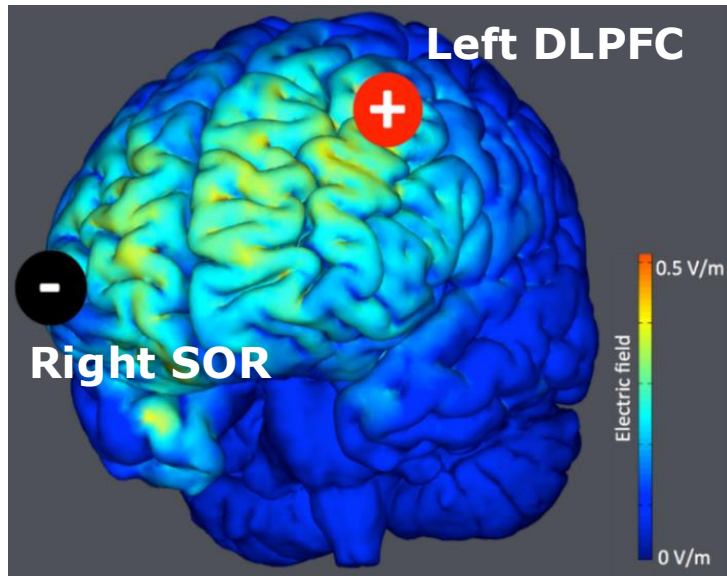
tDCS single session

ARTICLES

tDCS in patients with disorders of consciousness

Sham-controlled randomized double-blind study

Crossover RCT (n=55)



MCS
n=30

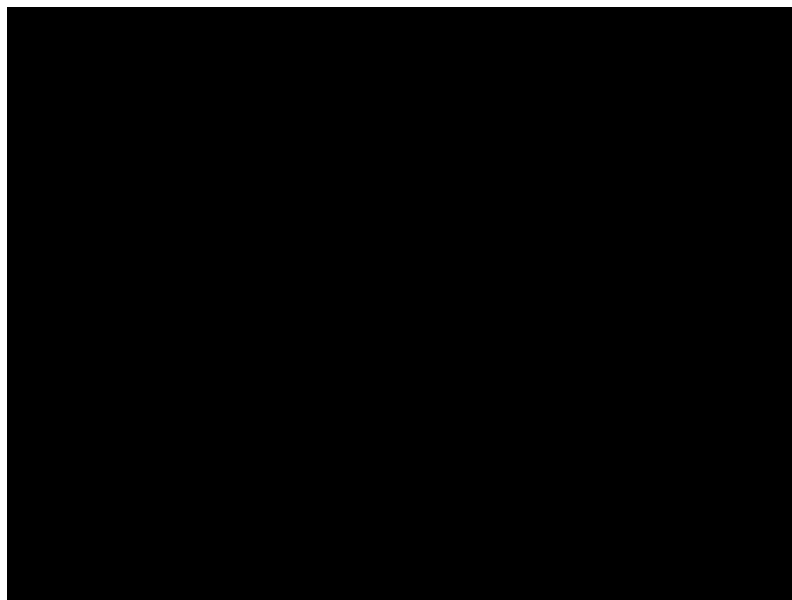
- ➔ No adverse events
- ➔ Clinical improvement in MCS only
- ➔ 13/30 responders (5 >1y post-insult)



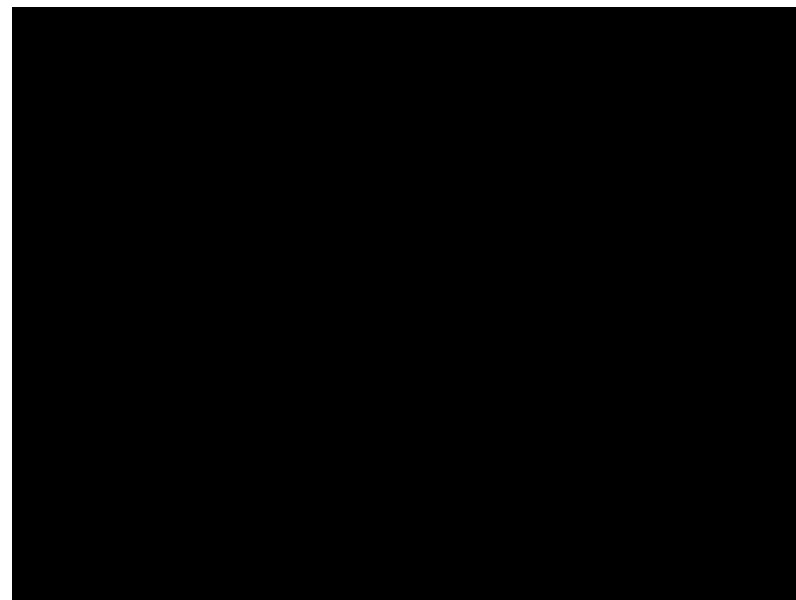
tDCS single session

29 years old male, 12 years post-TBI

Functional use of objects



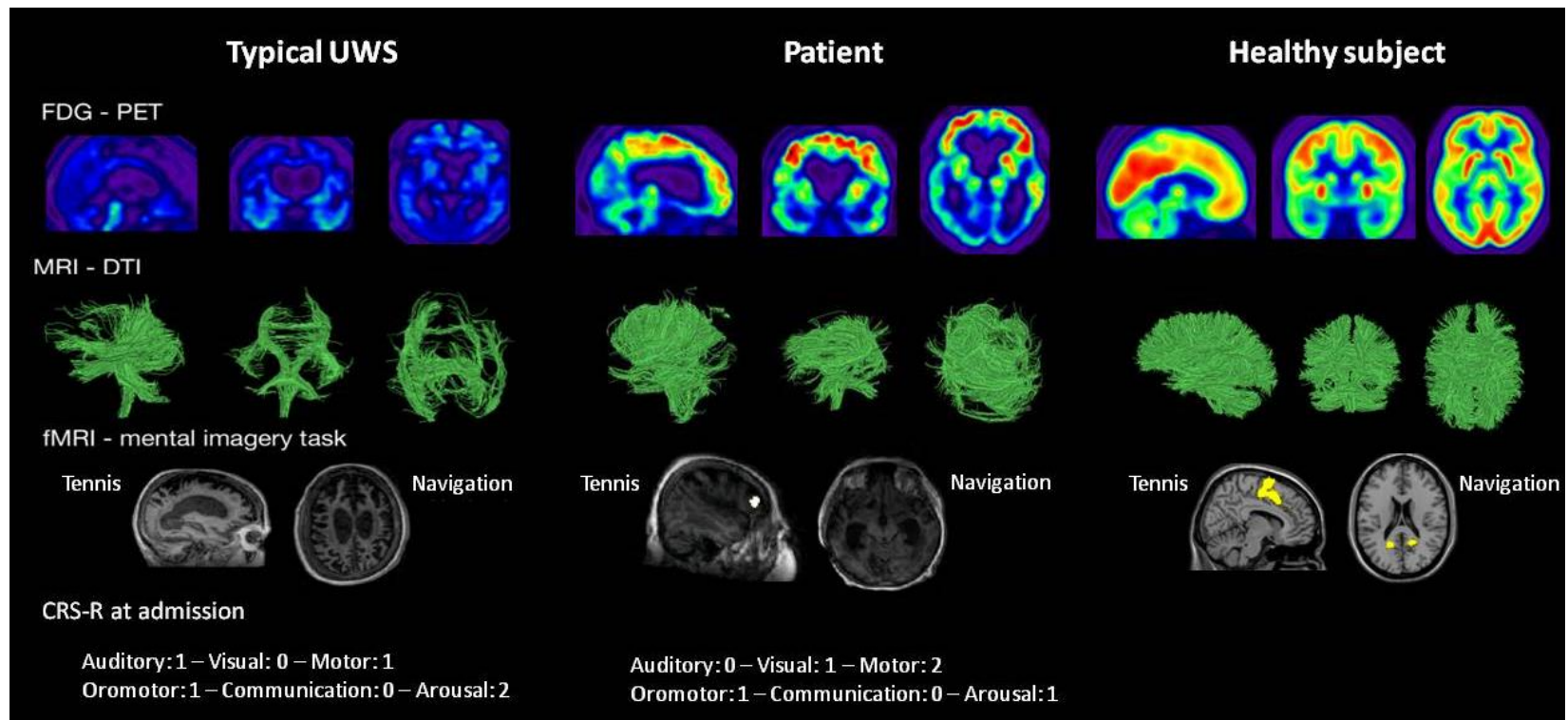
Before tDCS



After tDCS

Unveil covert consciousness

- 67yo woman in UWS for 4y after subarachnoid hemorrhage
- Out of 7 CRS-R, 1 localization to pain
- Consistent response to command only after tDCS
- Neuroimaging consistent with MCS*



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



Predicting clinical response

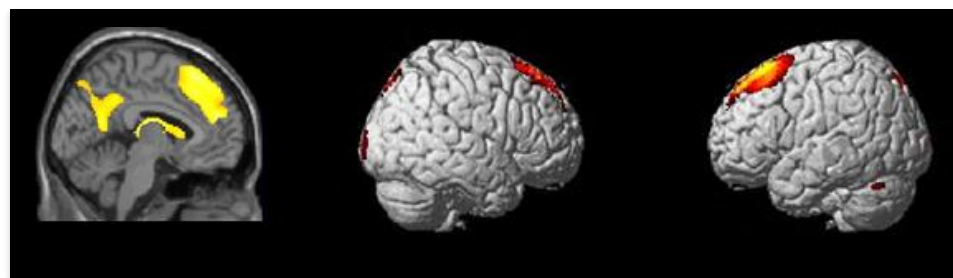
tDCS responders $\neq$ non-responders



Predicting clinical response

tDCS responders $\neq$ non-responders

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

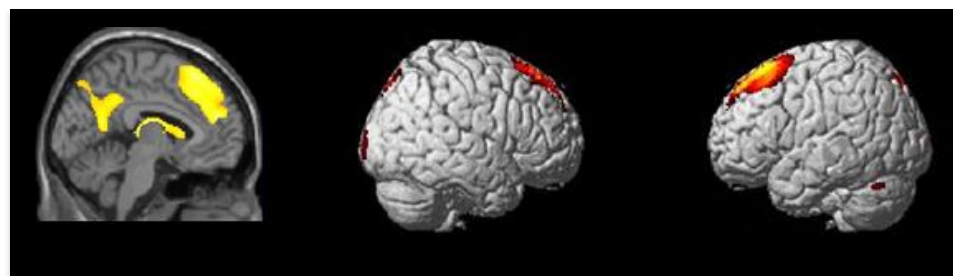




Predicting clinical response

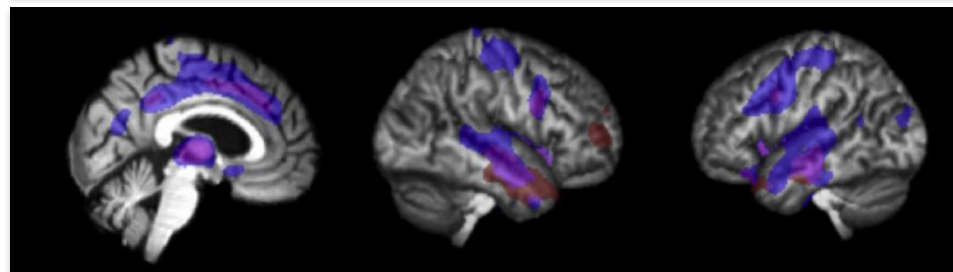
tDCS responders $\neq$ non-responders

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



Grey matter atrophy (MRI)

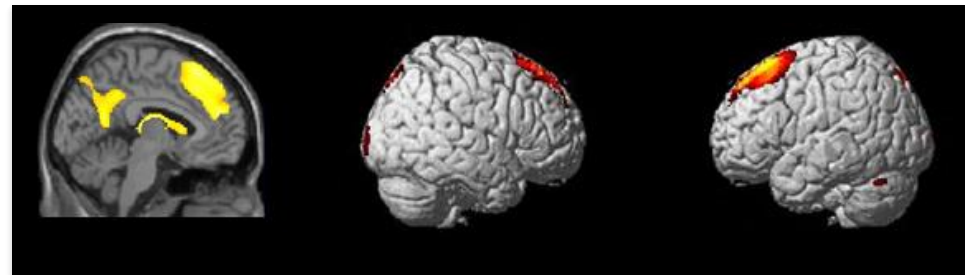
Grey matter atrophy
in responders ●
in non-responders ●



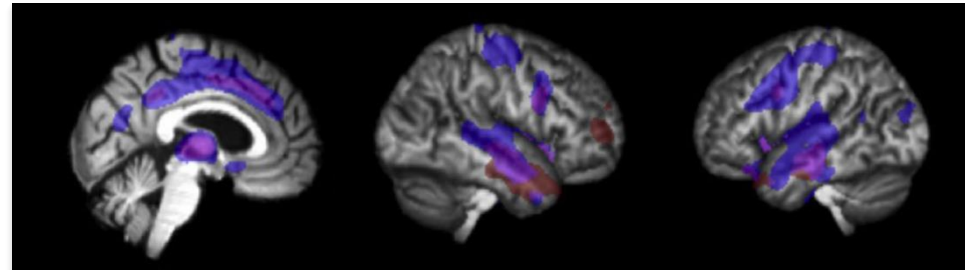
Predicting clinical response

tDCS responders $\neq$ non-responders

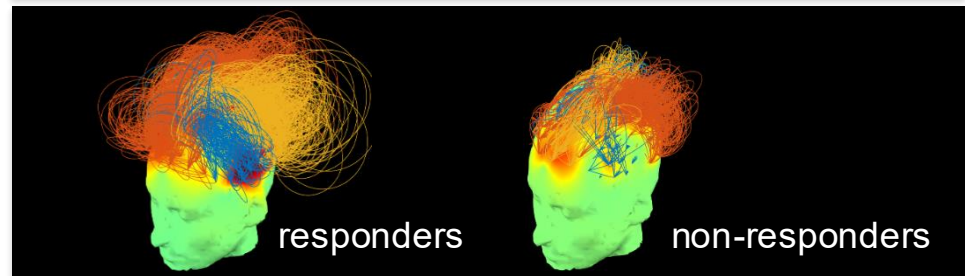
Brain metabolism (PET-scan)
 $\neq$ responders & non-responders ●



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

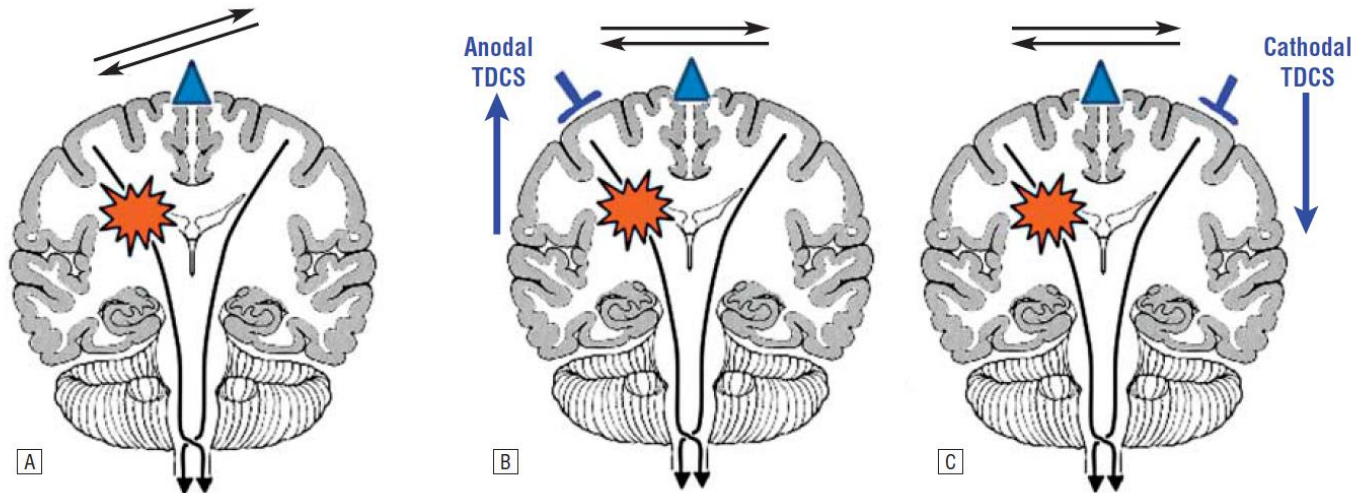


Brain connectivity (hd-EEG)
theta centrality



Predicting clinical response

Severe brain-injured patients $\neq$ stroke or moderate TBI



Schaulg, Renga, Nair, *JAMA Neurology*, 2008

Stroke: stimulate affected hemisphere / inhibit unaffected

TBI: stimulate affected brain region

DOC: extensive brain lesion $\rightarrow$ tDCS (partially) **preserved area**



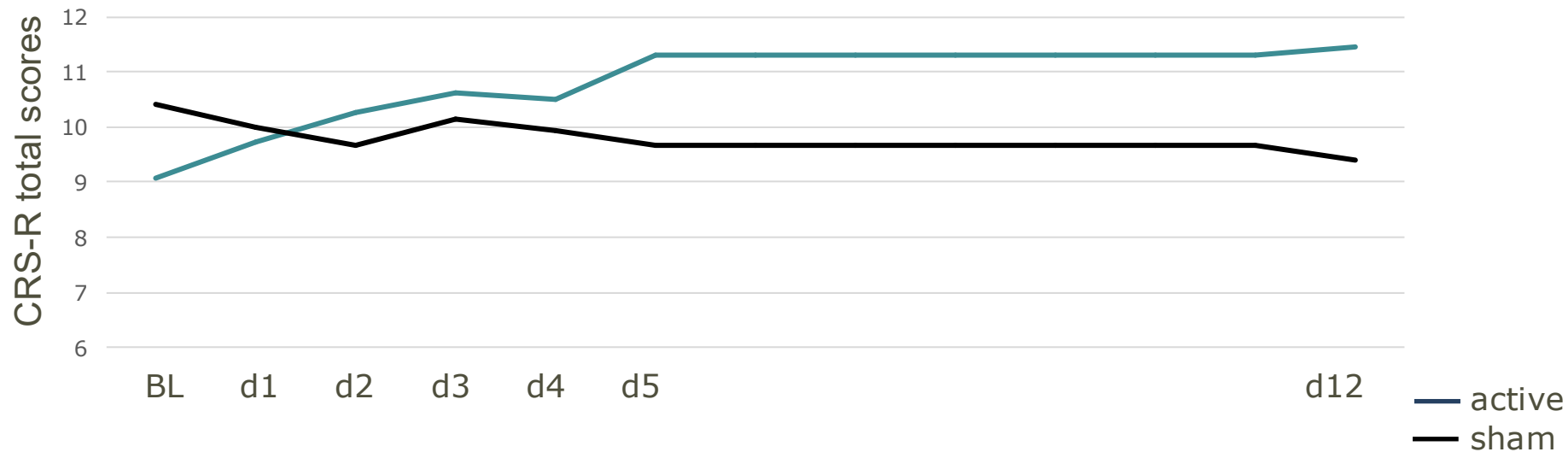
Repeated tDCS

Double-blind crossover RCT (16 chronic MCS)
5 sessions – 20 min prefrontal tDCS

Repeated tDCS

Double-blind crossover RCT (16 chronic MCS)
5 sessions – 20 min prefrontal tDCS

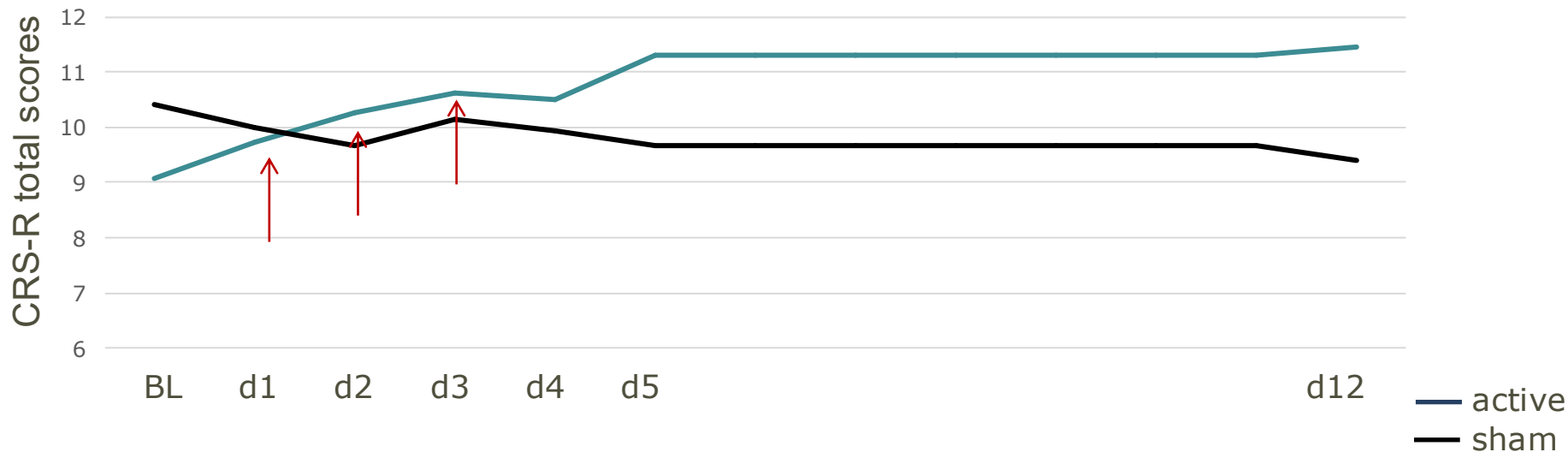
➔ Active session: significant time evolution



Repeated tDCS

Double-blind crossover RCT (16 chronic MCS)
5 sessions – 20 min prefrontal tDCS

➔ Active session: significant time evolution



Some patients responded after 1, 2 or 3 days of tDCS

↗ responders (9/16 – 56%) & ↗ duration of the effects (1 week)

Repeated tDCS



Archives of Physical Medicine and Rehabilitation

journal homepage: www.archives-pmr.org

Archives of Physical Medicine and Rehabilitation 2014;95:283-9



ORIGINAL ARTICLE

Transcranial Direct Current Stimulation Effects in Disorders of Consciousness



Efthymios Angelakis, PhD,^{a,b} Evangelia Liouta, MSc,^{a,b} Nikos Andreadis, PhD,^a Stephanos Korfiatis, MD,^{a,b} Periklis Ktonas, PhD,^a George Stranjalis, MD, PhD,^{a,b} Damianos E. Sakas, MD, PhD^{a,b}

From the ^aHellenic Center for Neurosurgical Research "Prof. Petros Kokkalis," Athens; and ^bEvangelismos Hospital, Department of Neurosurgery, Medical School, National and Kapodistrian University of Athens, Athens, Greece.

5 sessions over DLPFC
7 UWS and 6 MCS - chronic
→ Moderate clinical effects
→ Changes of EEG
background in patients who improved clinically

5 sessions over M1 or DLPFC
7 UWS and 3 MCS - chronic
→ All MCS showed clinical improvement immediately after treatment

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journal homepage: www.elsevier.com/locate/jns



Repeated transcranial direct current stimulation in prolonged disorders of consciousness: A double-blind cross-over study



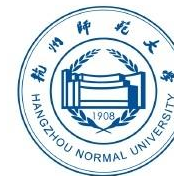
Anna Estraneo^{a,*}, Angelo Pascarella^a, Pasquale Moretta^a, Orsola Masotta^a, Salvatore Fiorenza^a, Grazia Chirico^a, Emanuela Crispino^a, Vincenzo Loreto^a, Luigi Trojano^{a,b}

^a Neurorehabilitation Unit and Research Lab. for Disorder of Consciousness, Mangeri ICS, Telesse Terme, Italy

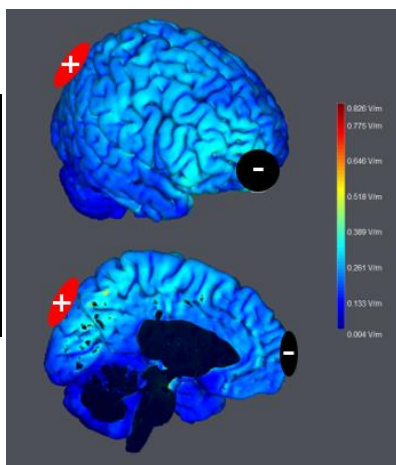
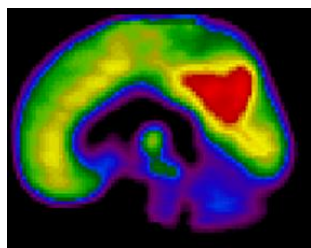
^b Neuropsychology Lab., Dept. of Psychology, Second University of Naples, Caserta, Italy



tDCS – Precuneus



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Brain Stimulation

journal homepage: <http://www.journals.elsevier.com/brain-stimulation>



Repeated stimulation of the posterior parietal cortex in patients in minimally conscious state: A sham-controlled randomized clinical trial

RCT crossover – 5 sessions

33 MCS >3 months post-insult
(57 ± 11 y; 20 TBI)

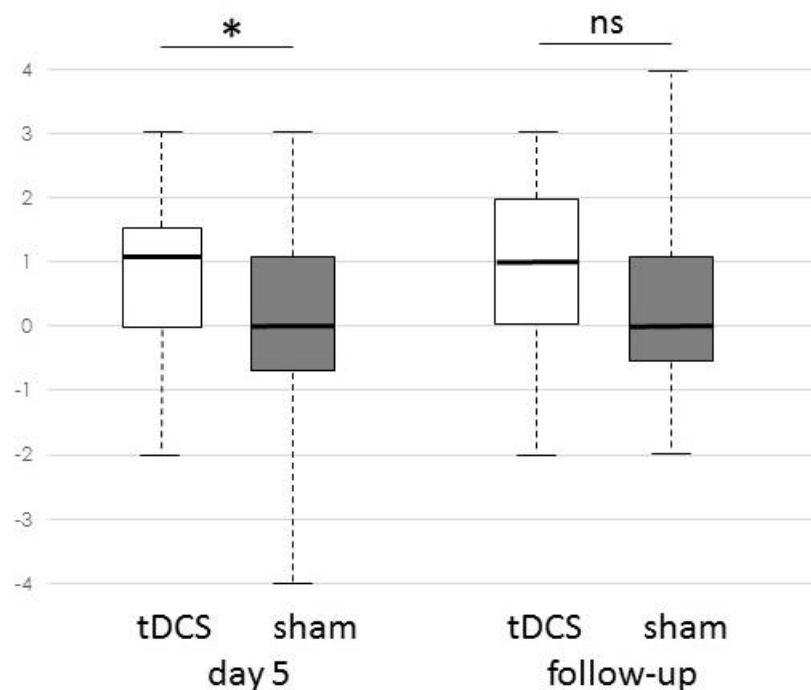
9 responders (27%)

Sub-acute > chronic

No effect at follow-up

Effect size : 0.31

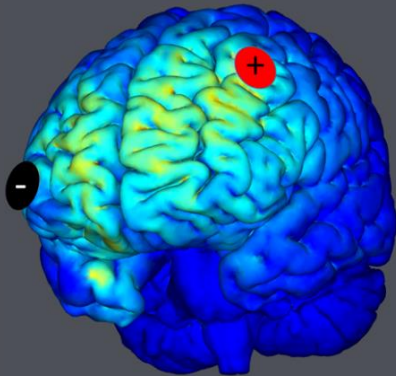
Delta CRS-R total score
(IQR – min/max)



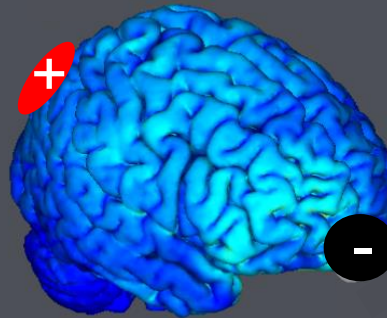
□ tDCS
■ sham

Stimulating different brain areas

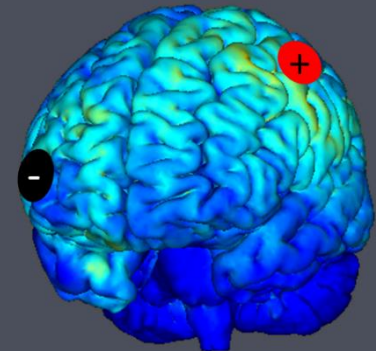
Prefrontal ↗



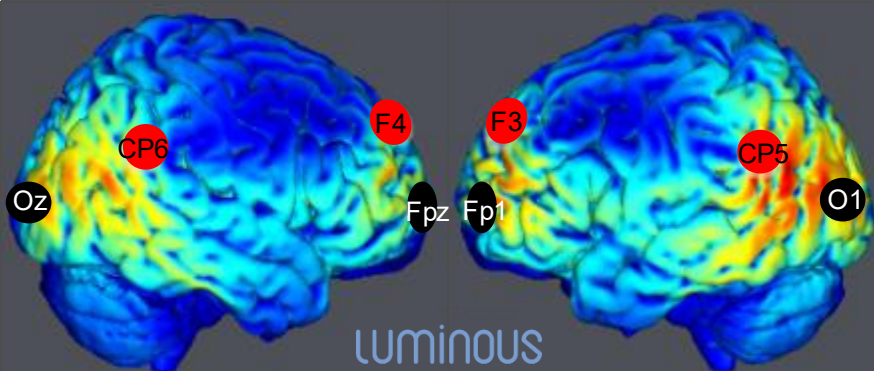
Precuneus ↘



Motor ≡



Multichannel frontoparietal ≡

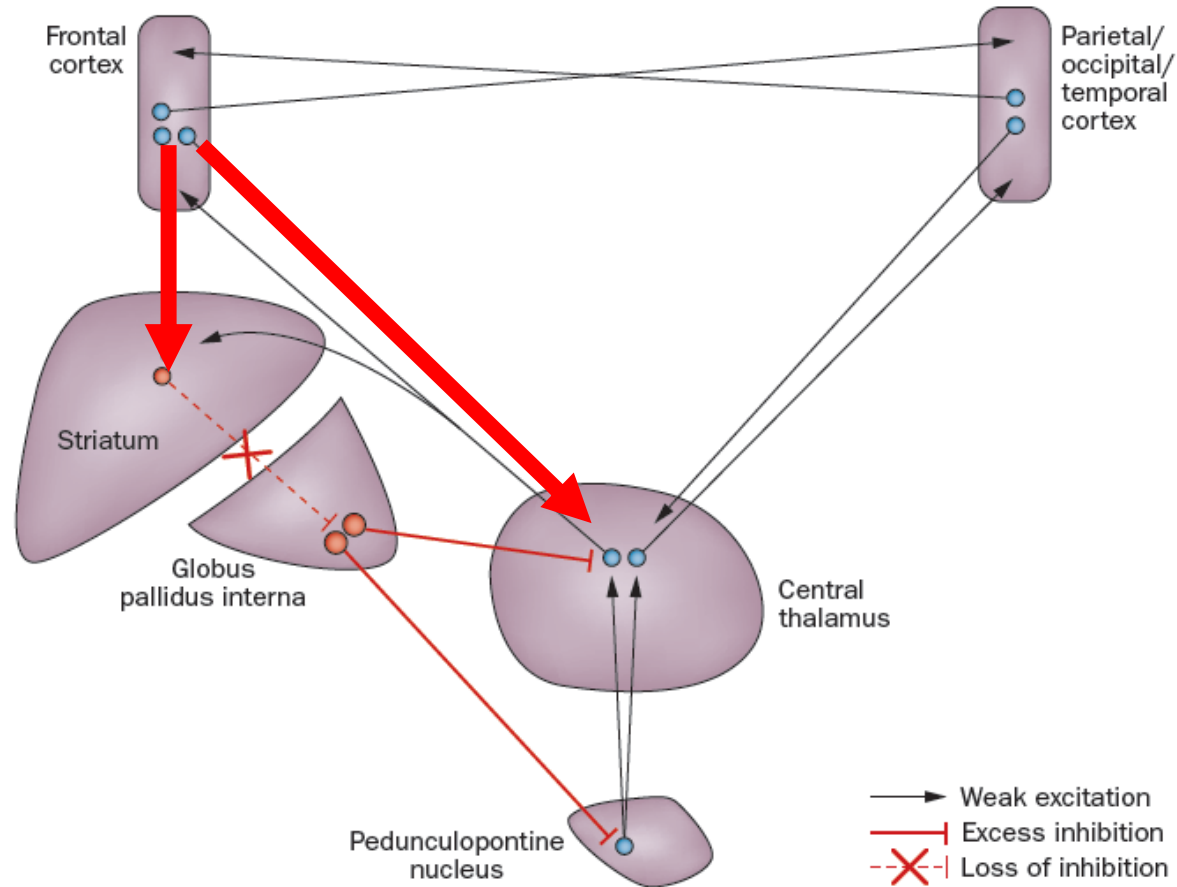


Group level: Prefrontal
tDCS best area to target

Single-subject level:
Patient's tailored montage

tDCS - mesocircuit

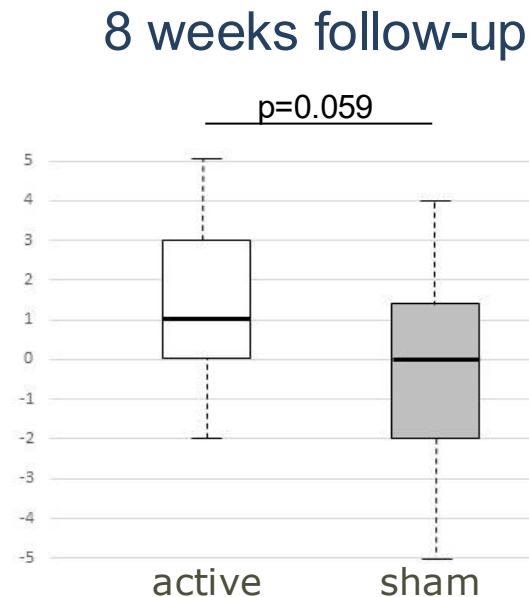
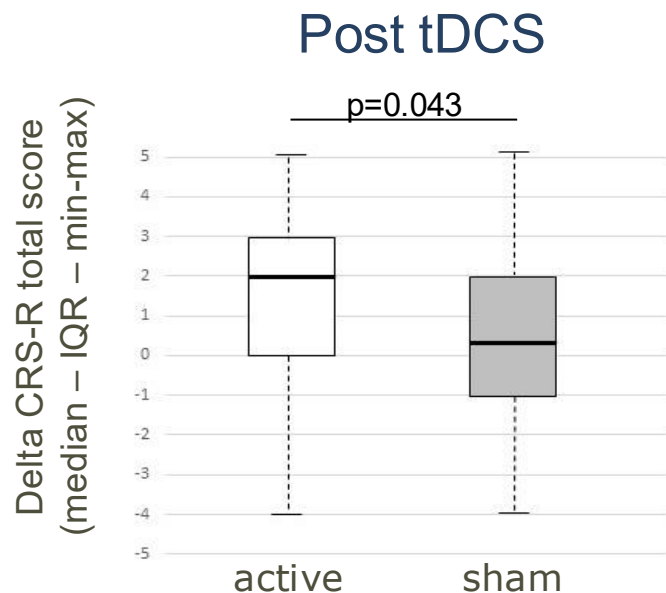
Prefrontal tDCS better than targeting other areas?



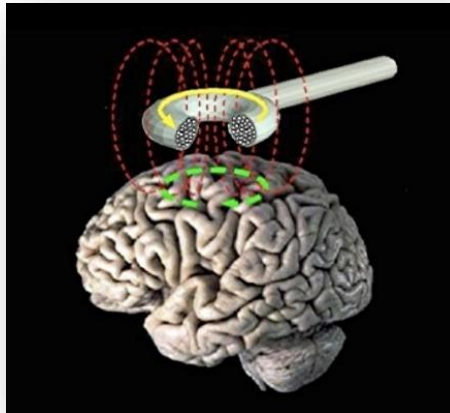
Clinical translation



- Feasibility of tDCS for daily use
 - By relatives/caregivers (20 sessions)
 - 27 MCS patients – compliance: $93 \pm 14\%$
 - No clinical effects
- 22 MCS patients received $\geq 80\%$ tDCS sessions
- Significant effects & trend at 8-week follow-up – no AE



Repeated Transcranial Magnetic Stimulation (rTMS)



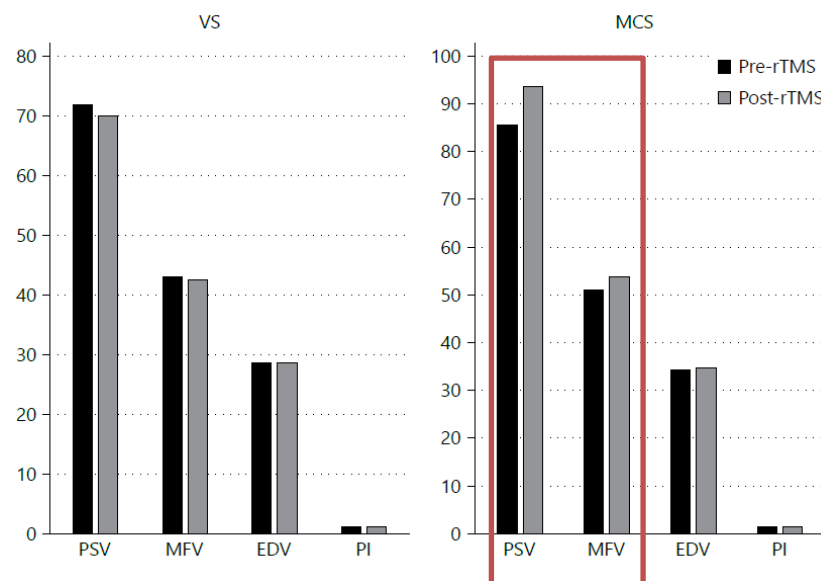


- 5 days of 20Hz M1-rTMS in 11 UWS patients
No behavioral & neurophysiological changes

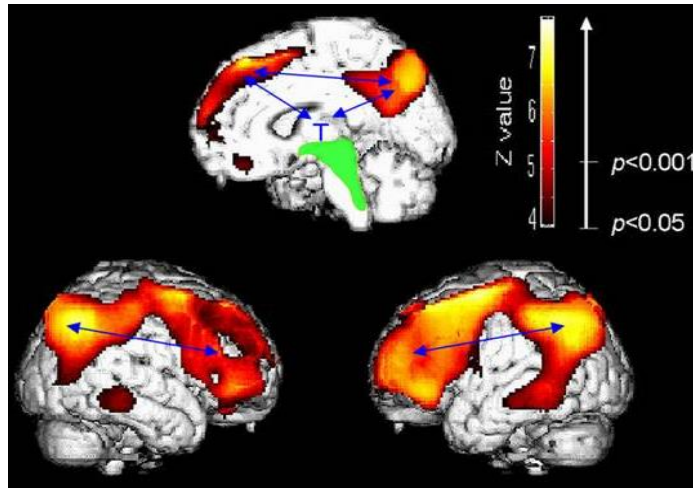
- Single session of 20Hz rTMS on M1 in 5 UWS & 5 MCS
No behavioral changes
↗ in CBF in MCS

- 5 sessions of 20Hz rTMS on M1 in 3 UWS & 3 MCS
One patient improved (EEG)

- DLPFC rTMS – case-reports – promising behavioral improvements



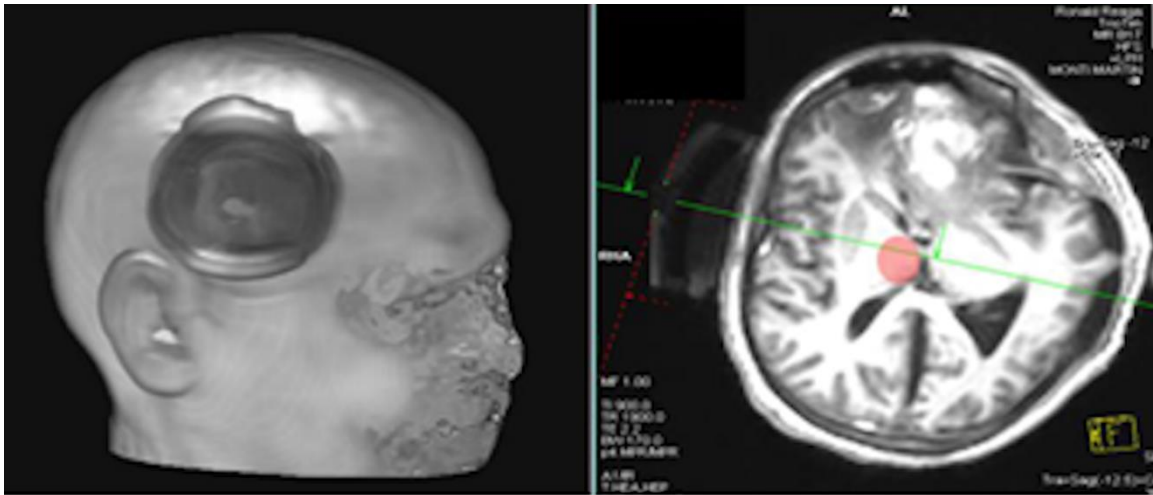
Stimulating the thalamus



LIFUP

Low Intensity Focal Ultrasound Pulses

- Non-invasive (safe) as tDCS
- Capable of stimulating thalamus as DBS



Case report

25 yo male, 19 days post-TBI

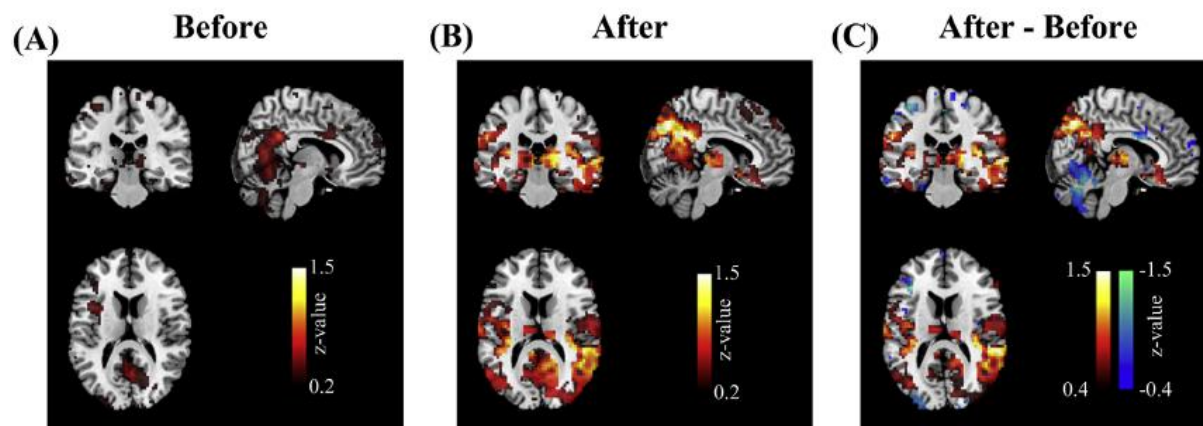
100Hz (pulse width 0.5s) – 10 sonications of 30s

→ CRS-R 15 to 17 (motor related behavior)

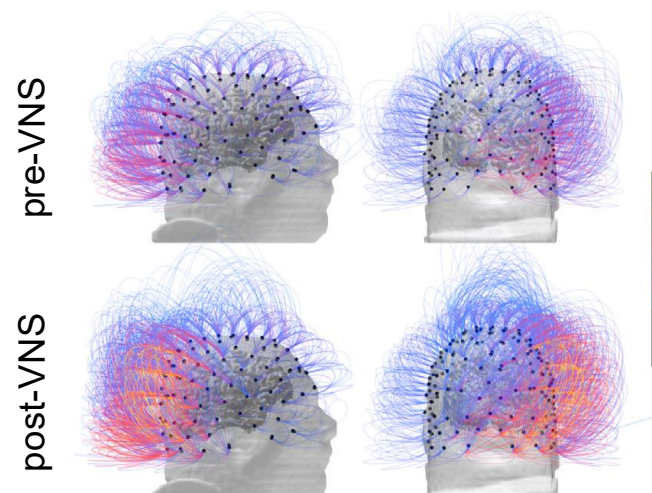
→ 3 days later emergence

- Transcutaneous auricular vagus nerve stimulation - taVNS (4-6mA, 20Hz) – case-report (73 yo, 50 days post-ARCA)

UWS → MCS



- Invasive VNS (max 1.5mA)
Case-report – 15 years post-TBI
1 month of stimulation
UWS → MCS



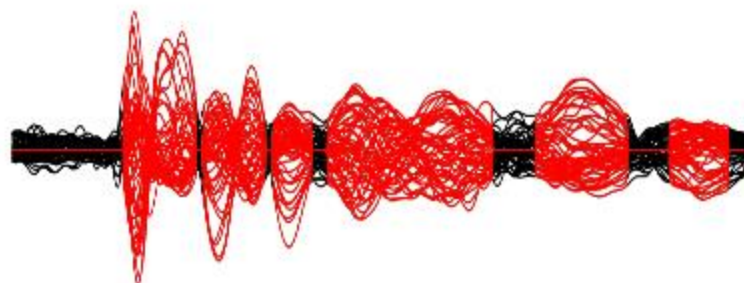
TMS-EEG



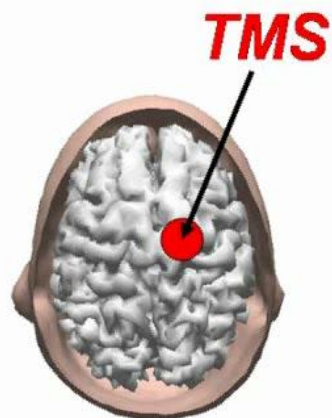


TMS-EEG in healthy subjects

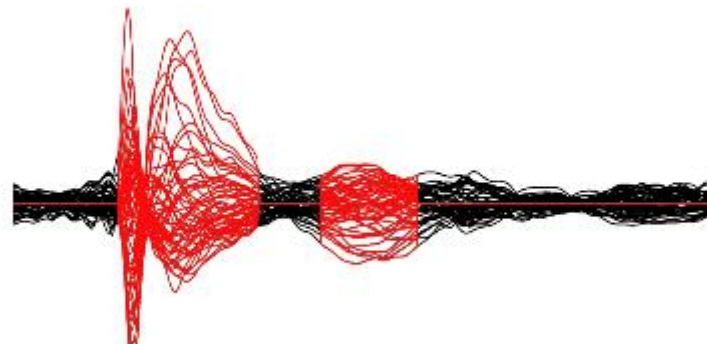
Wakefulness



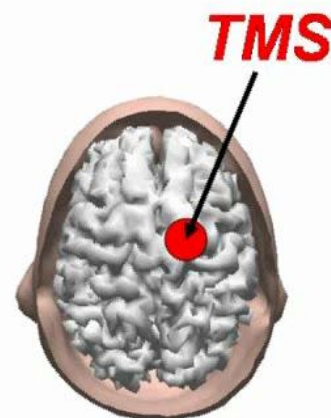
0 ms



Deep sleep



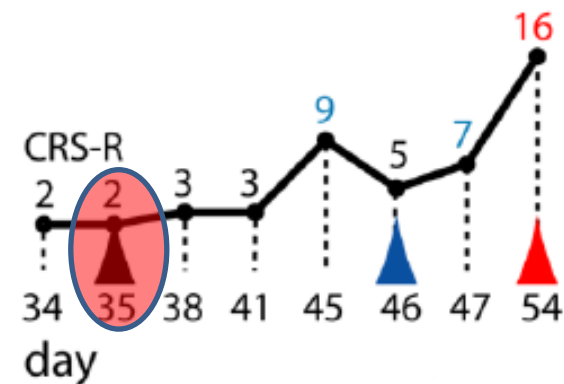
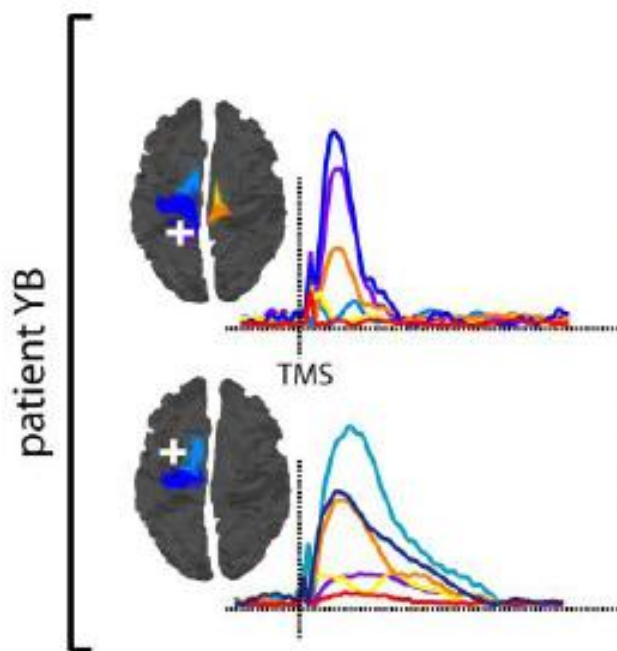
0 ms





TMS-EEG in comatose patients

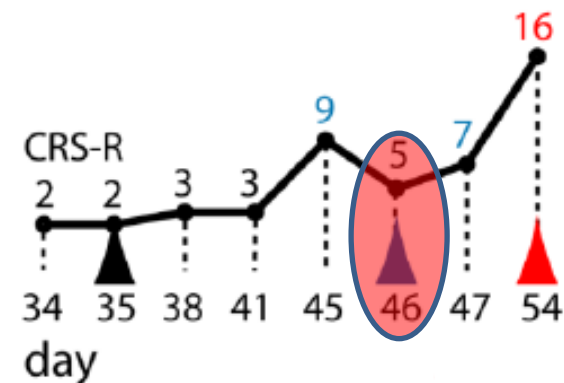
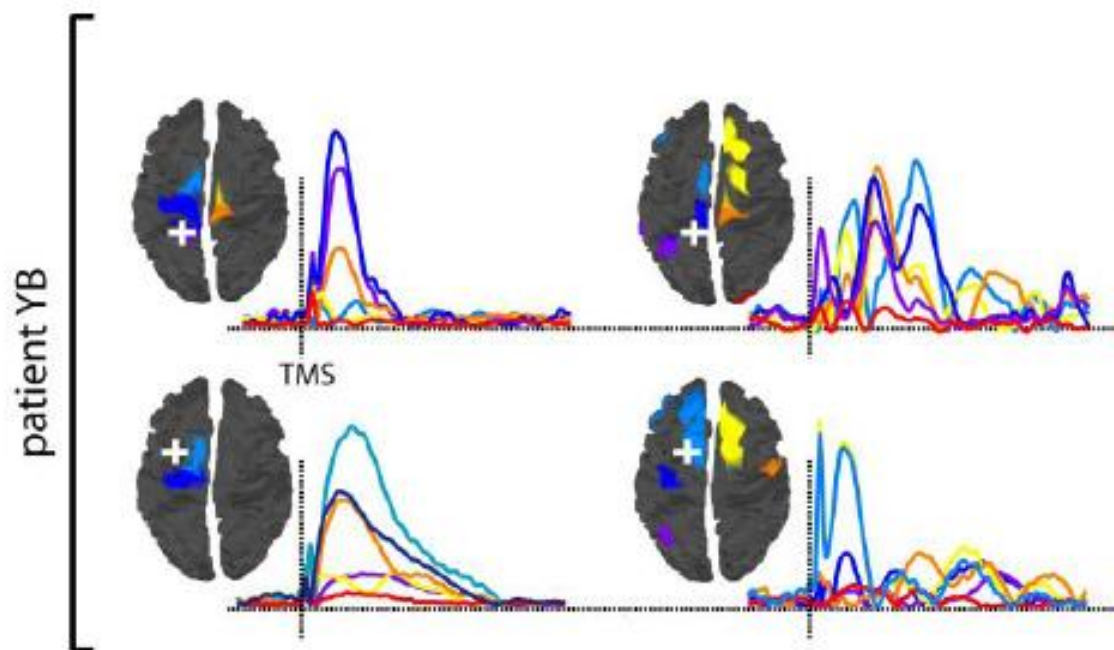
Unresponsive state





TMS-EEG in comatose patients

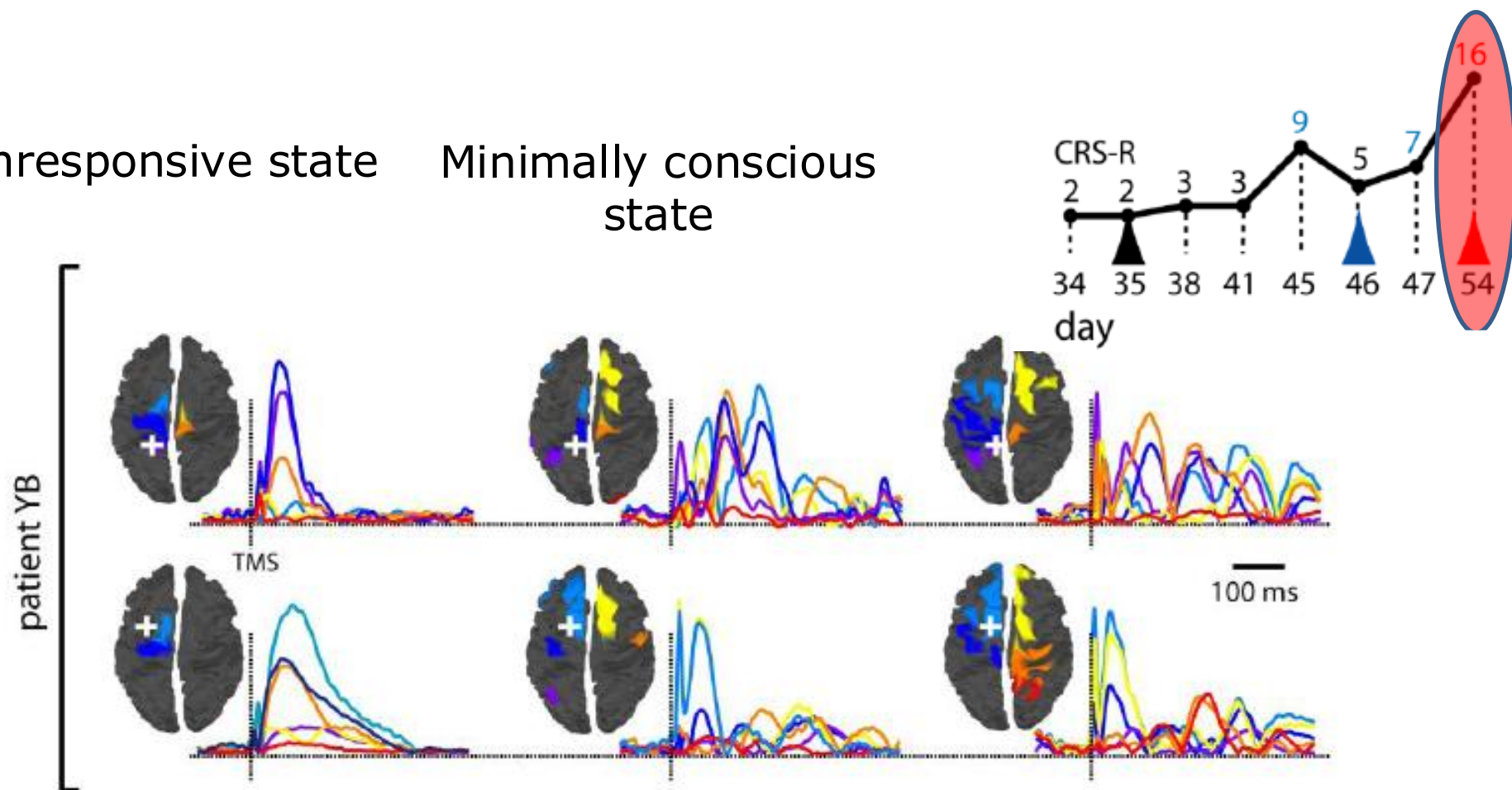
Unresponsive state Minimally conscious state





TMS-EEG in comatose patients

Unresponsive state Minimally conscious state



Perturbational complexity index

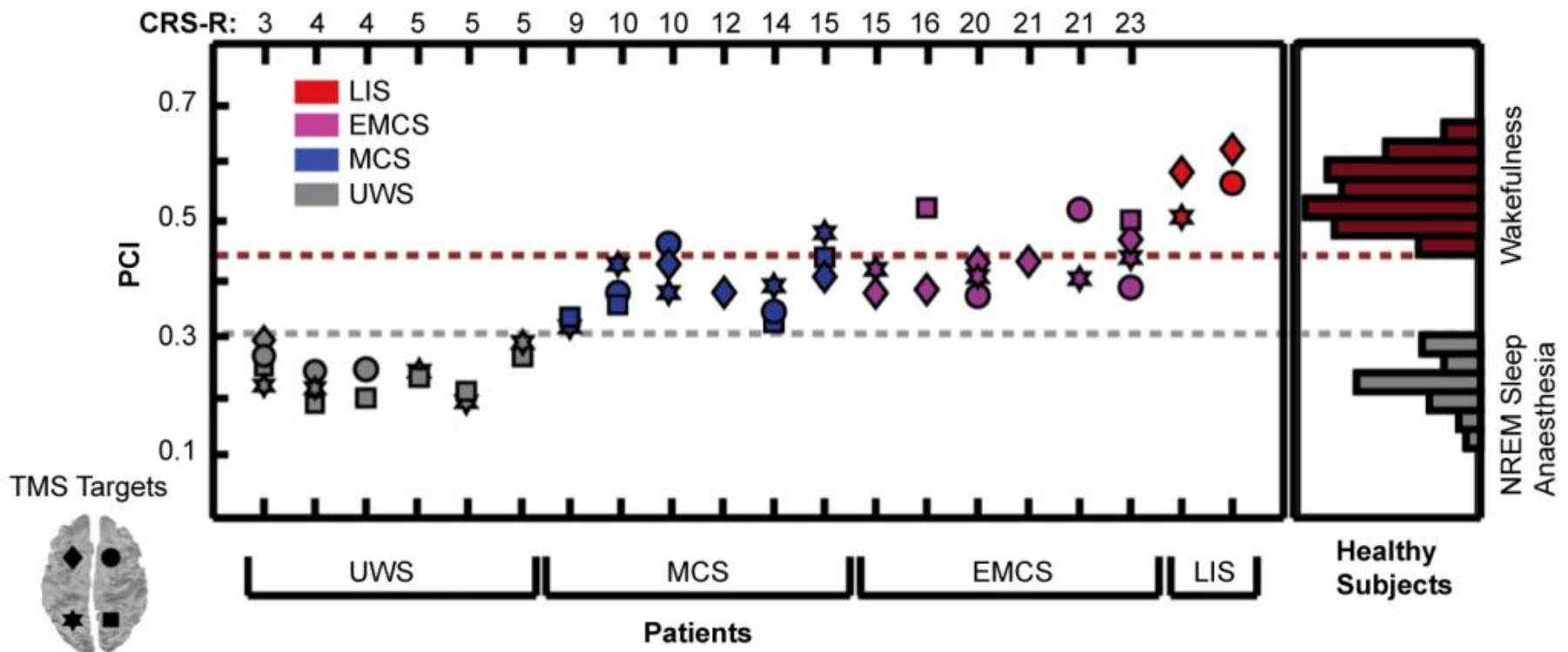
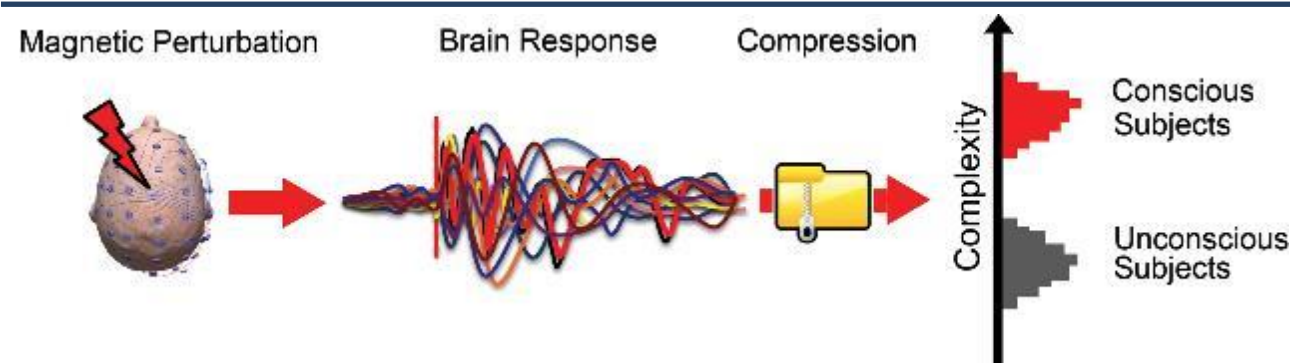


A Theoretically Based Index of Consciousness Independent of Sensory Processing and Behavior

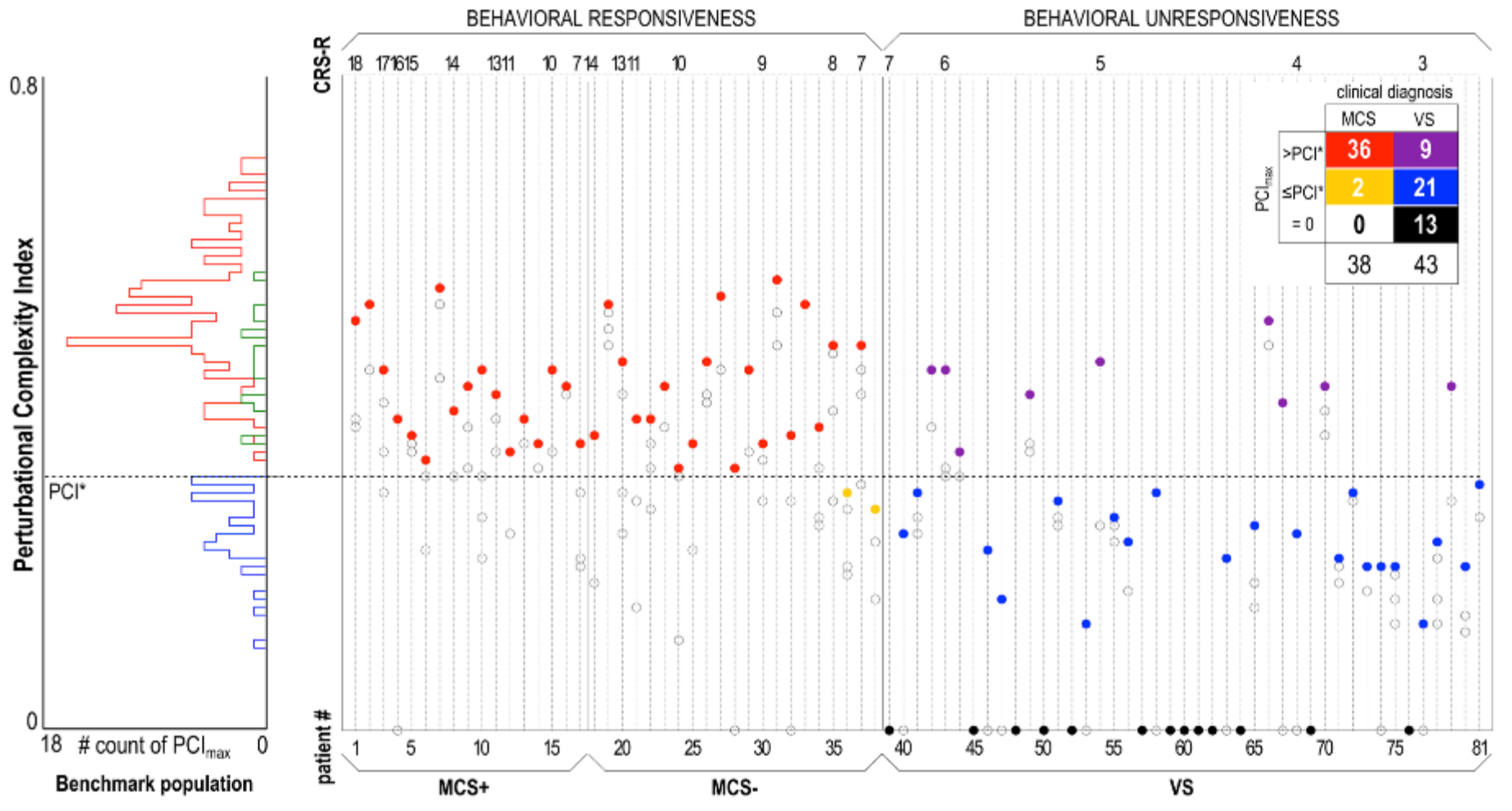
Casali et al., *Science Translational Medicine* (2013)

PCI → measures the ability of thalamo-cortical circuits to integrate information
(no motor or sensitive processing or subjects' participation)

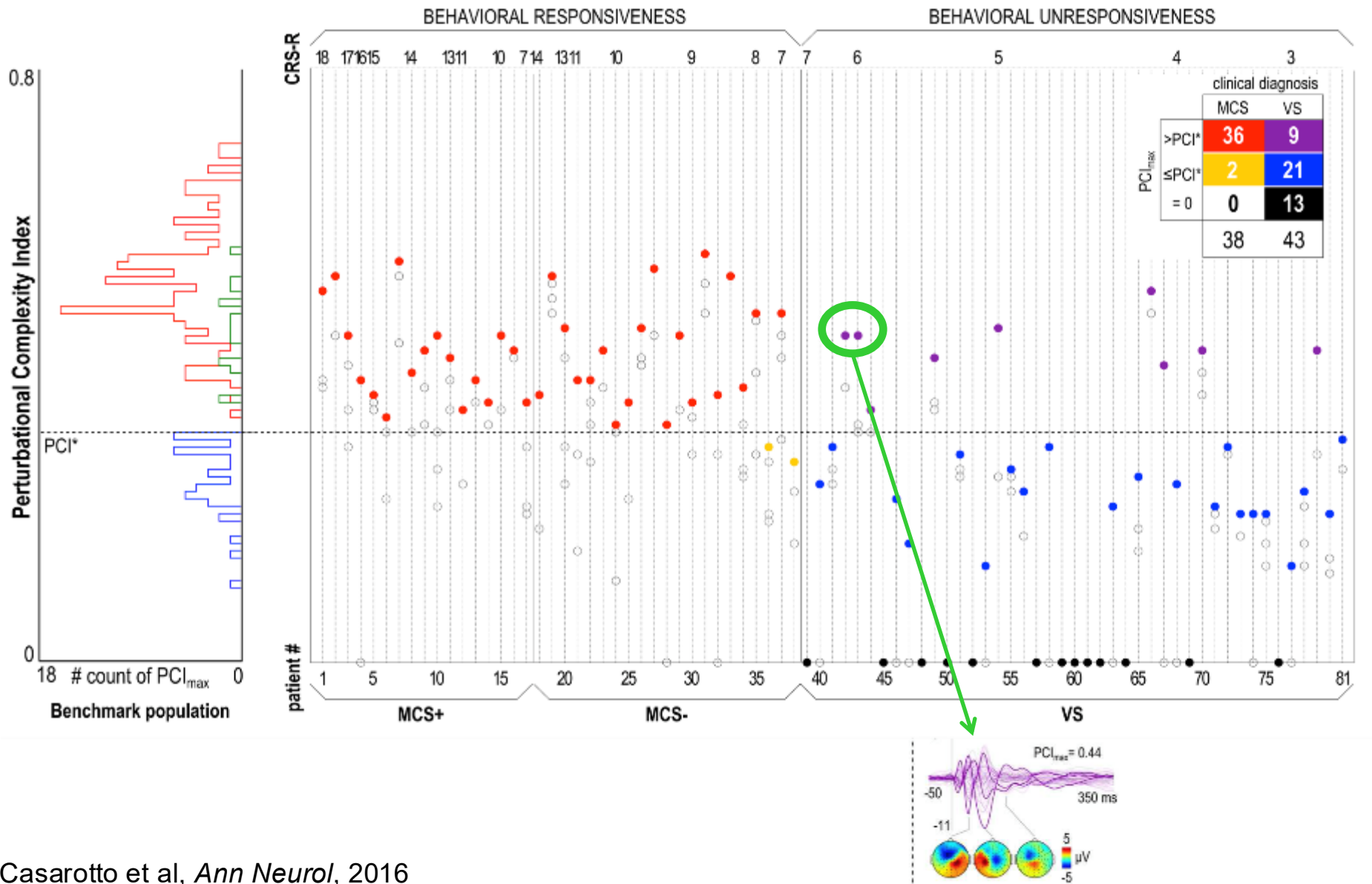
Perturbational complexity index in comatose patients



Perturbational complexity index in comatose patients



Perturbational complexity index in comatose patients

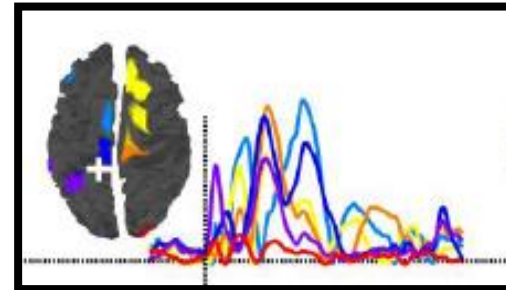
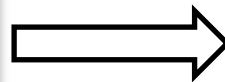


NIBS

- ▶ tDCS is safe in severely brain-injured patients
- ▶ **Prefrontal** tDCS & repeated sessions
- ▶ Need patients' tailored montage based on individual lesions
- ▶ DLPFC rTMS, LIFUP, VNS & taVNS → to be tested in RCT

TMS-EEG

- ▶ TMS-EEG & PCI are reliable diagnostic tools for *conscious/unconscious* post-coma patients at the **single subject level**



THANK YOU

COMA

SCIENCE GROUP



Studying Consciousness
in the electrical brain



James S. McDonnell Foundation

