



Pharmacological and non-pharmacological neuromodulation treatments after severe brain injury

Aurore THIBAUT, PhD

GIGA-Consciousness

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Neuromodulation Center

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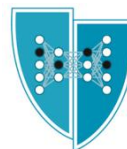
Harvard Medical School, Boston, USA



www.giga.ulg.ac.be

www.comascience.org

neuromodulationcenter.org



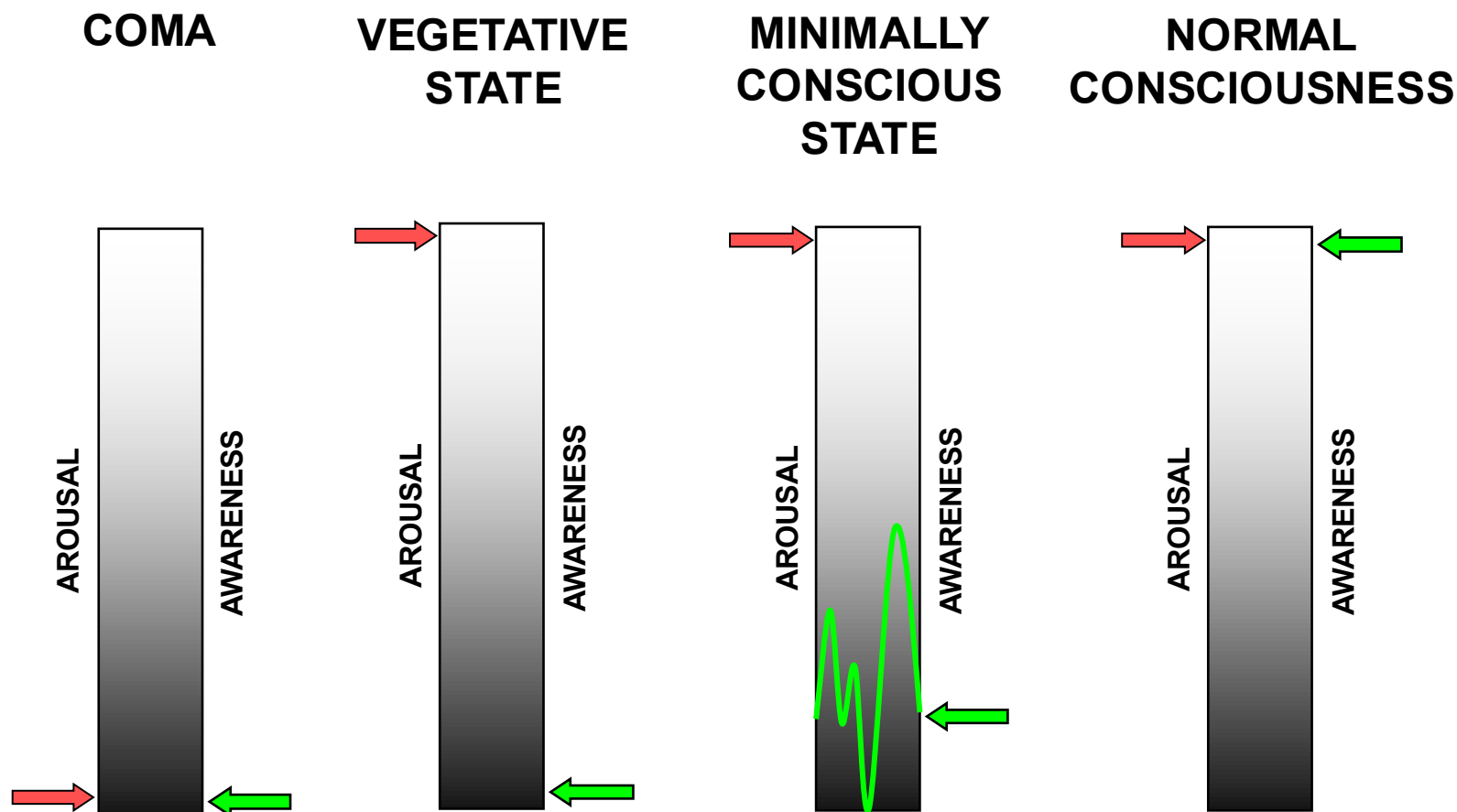
HARVARD
MEDICAL SCHOOL



Disorder of consciousness: definitor



Clinical entities



Laureys et al, Lancet Neurol, 2004; the European Task Force on Disorders of Consciousness, BMC Med, 2010

Disorders of consciousness

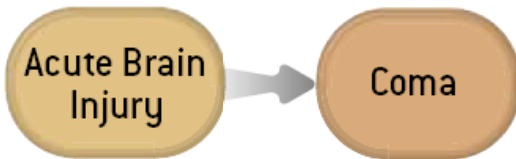
Clinical entities



Acute Brain
Injury

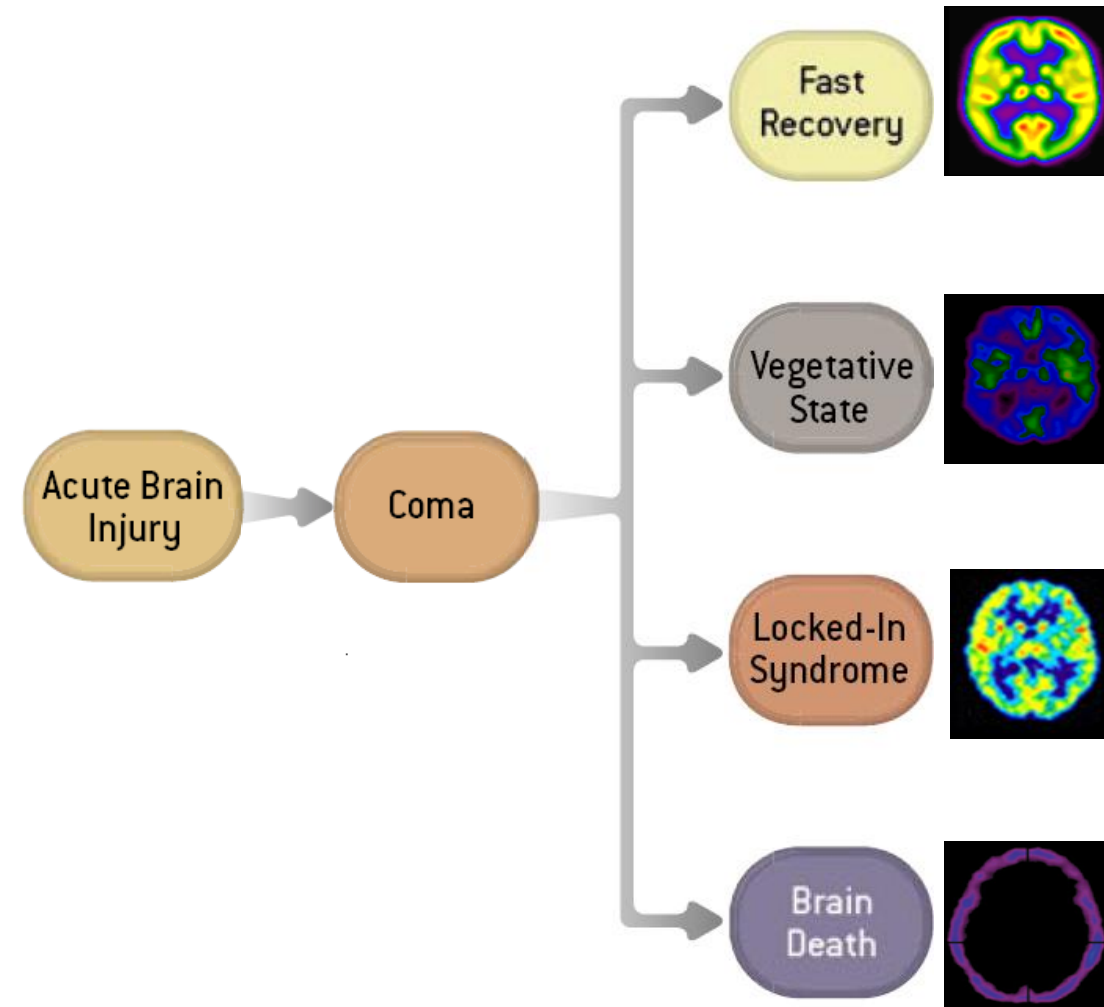
Disorders of consciousness

Clinical entities



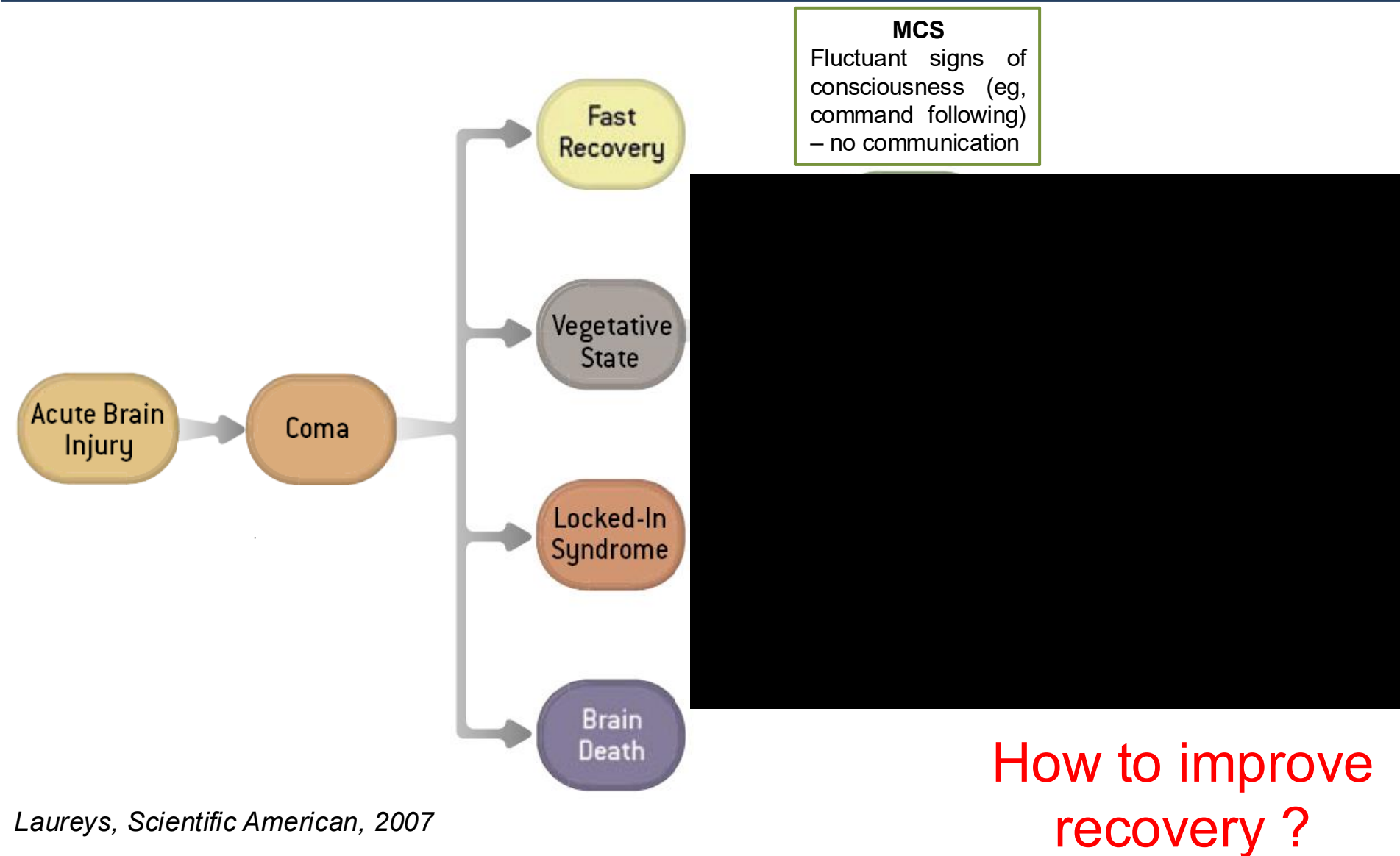
Disorders of consciousness

Clinical entities



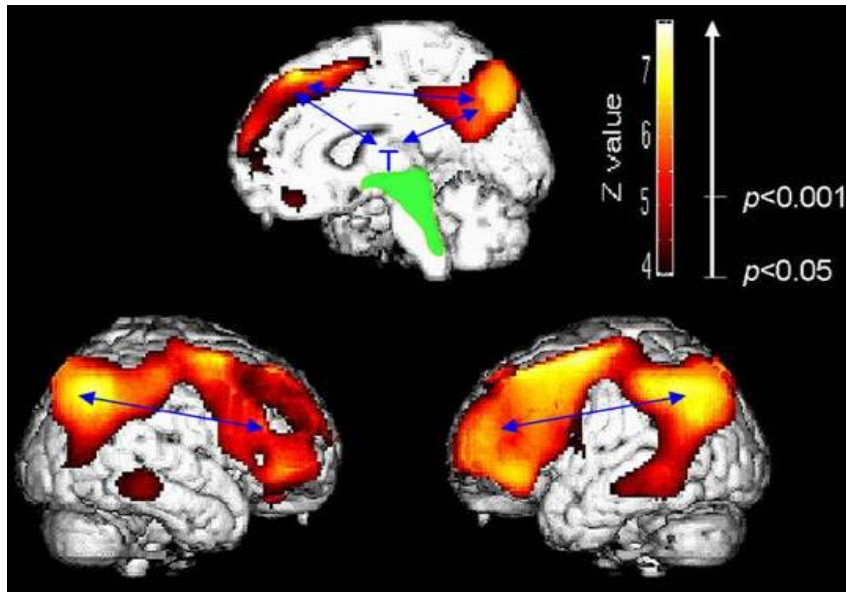
Disorders of consciousness

Clinical entities



Consciousness network

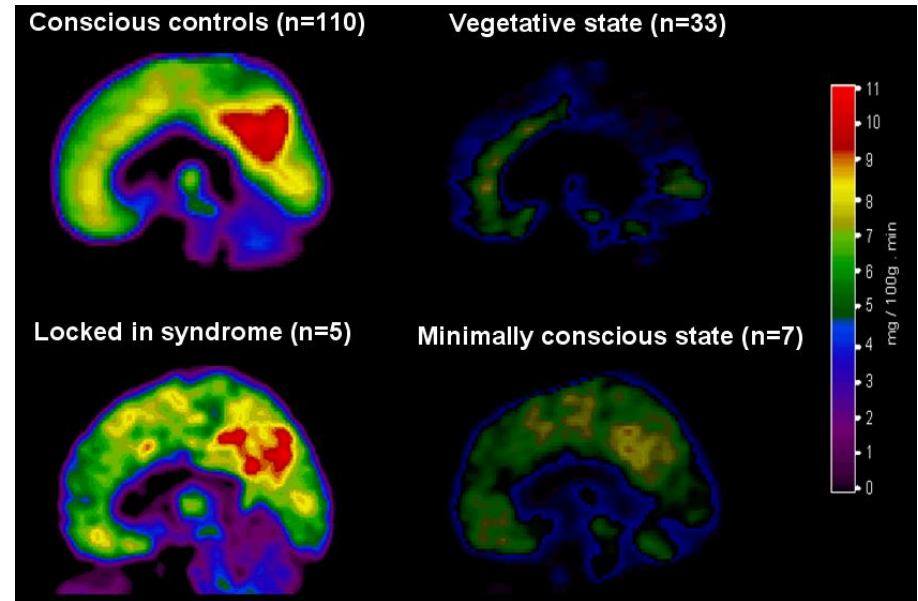
Fronto-parietal network



Laureys et al, Neuroimage 1999
Thibaut et al, Rehab Med, 2012
Stender et al, Lancet, 2014

Lateral: external awareness / environment
Medial: internal awareness / self

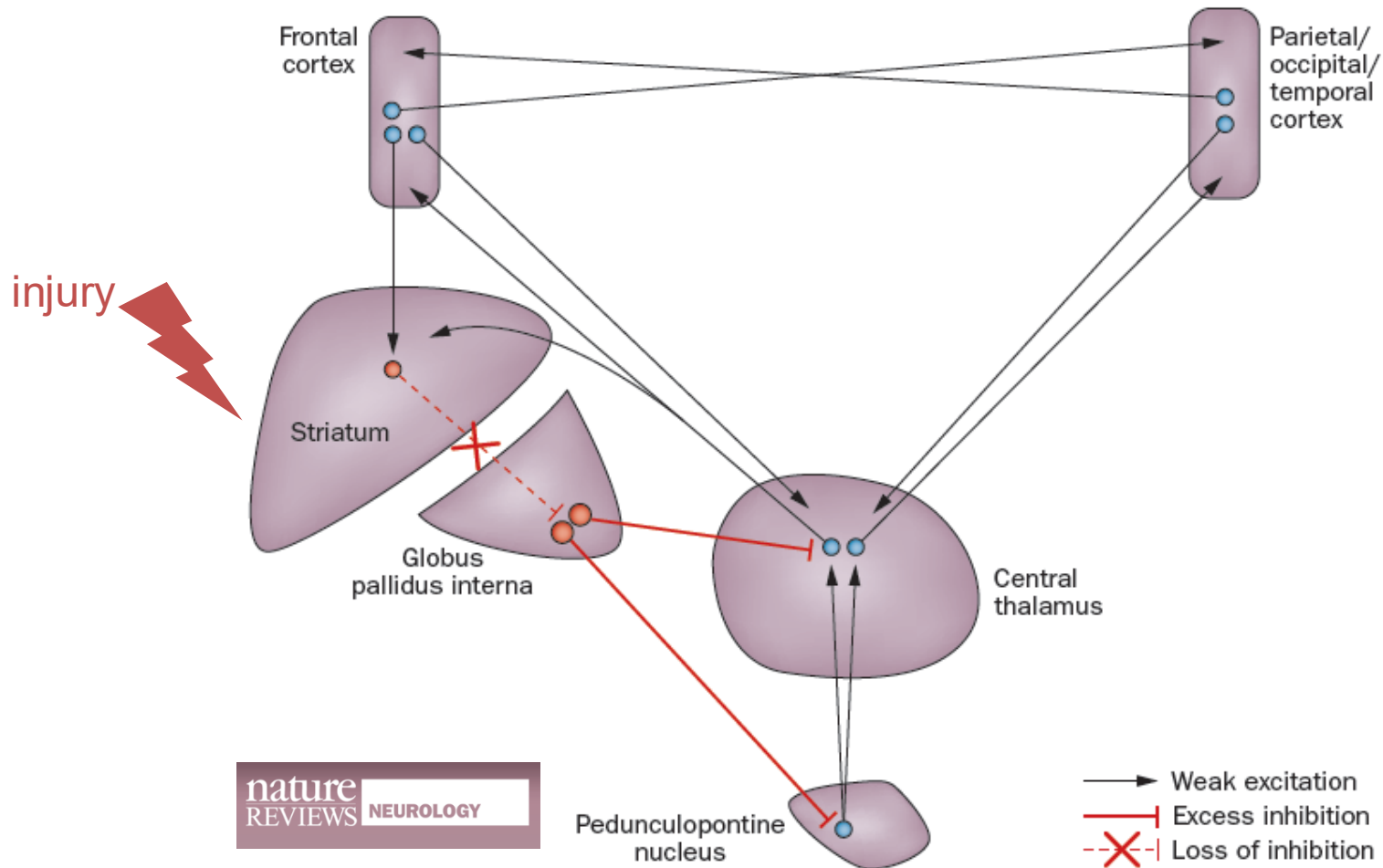
Precuneus



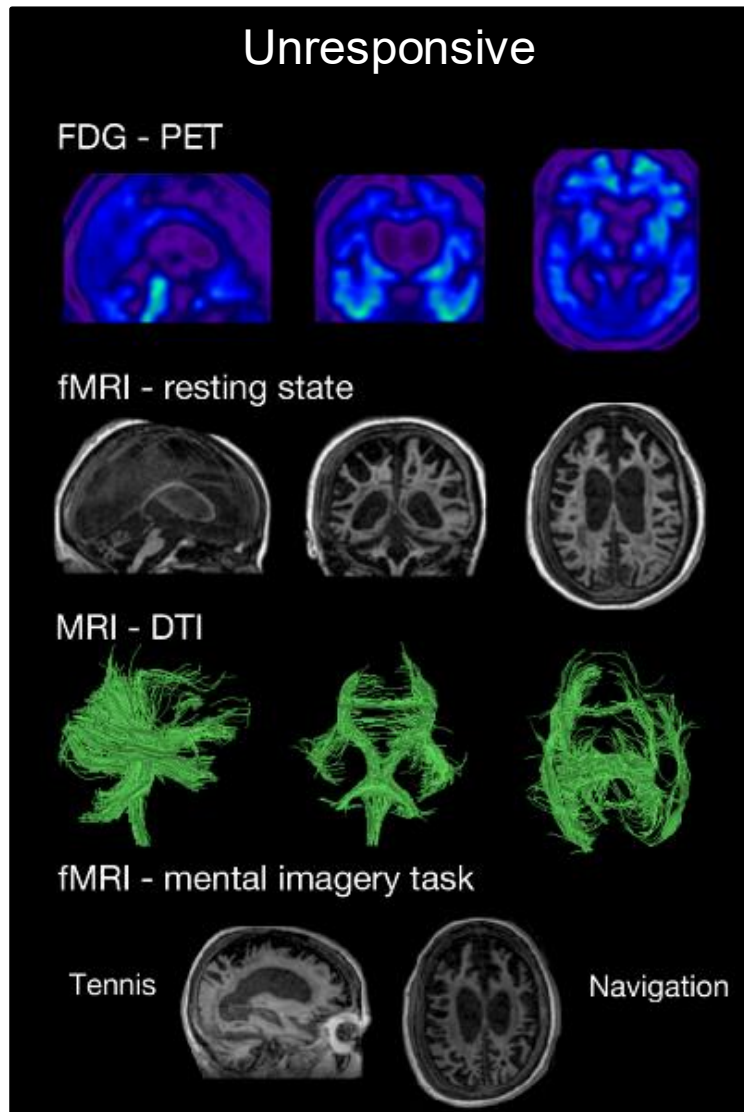
Laureys et al, Lancet Neurology, 2004

Precuneus – self awareness

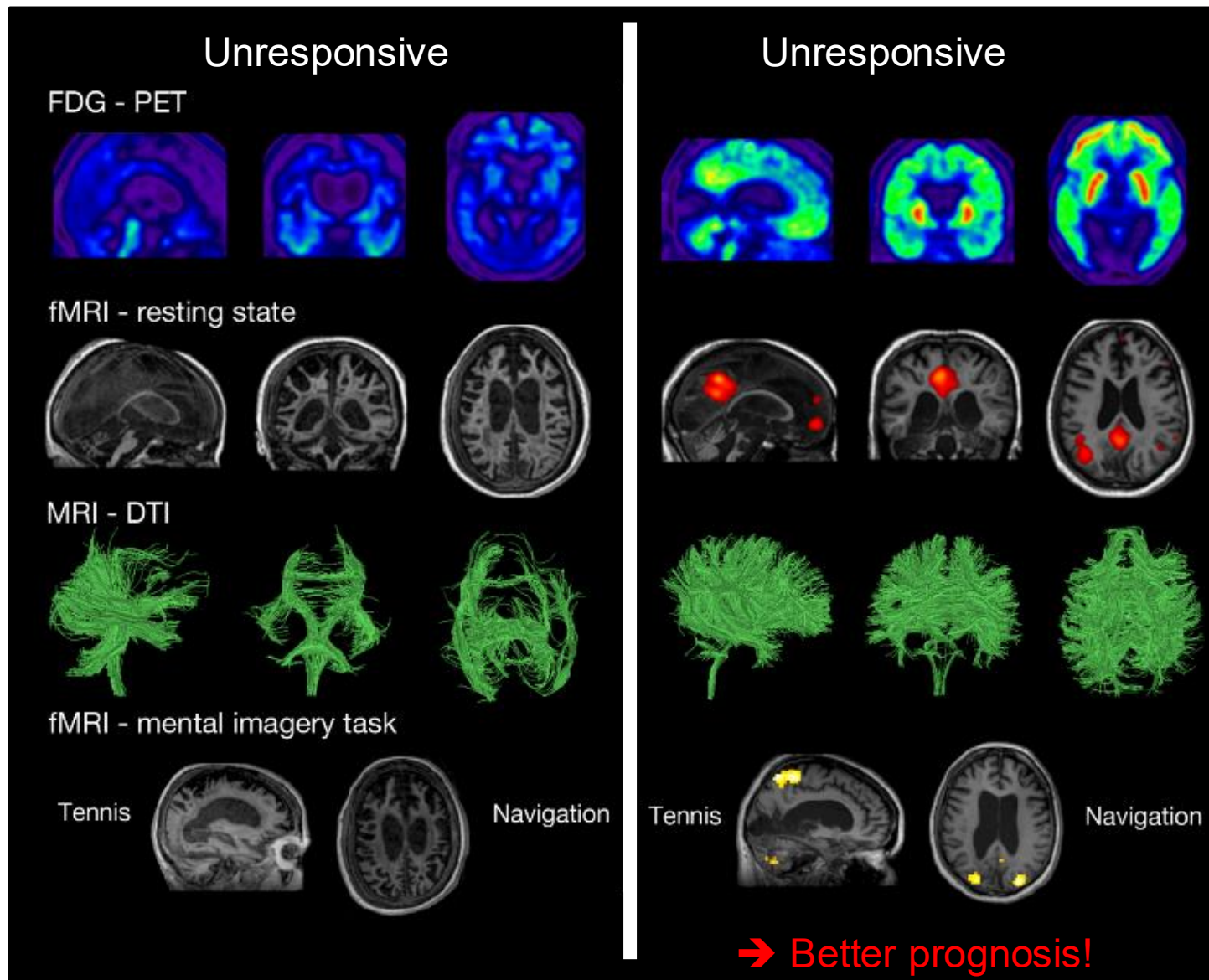
Mesocircuit model



Multimodal assessments case reports



Multimodal assessments case reports



Specificities of therapeutic interventions for DOC patients

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



➔ No active rehabilitative interventions

« Hable con Ella »
Pedro Almodóvar



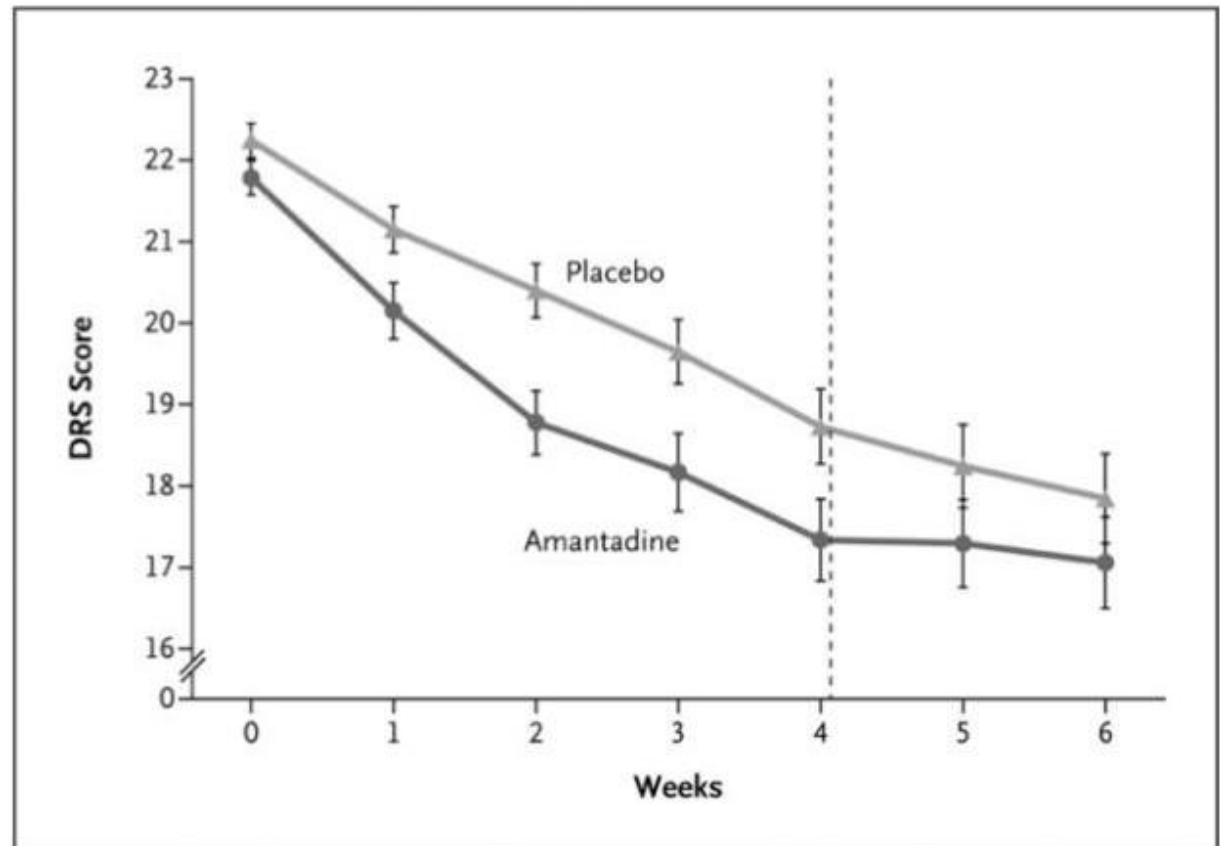
Pharmacological interventions

Pharmacological interventions

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

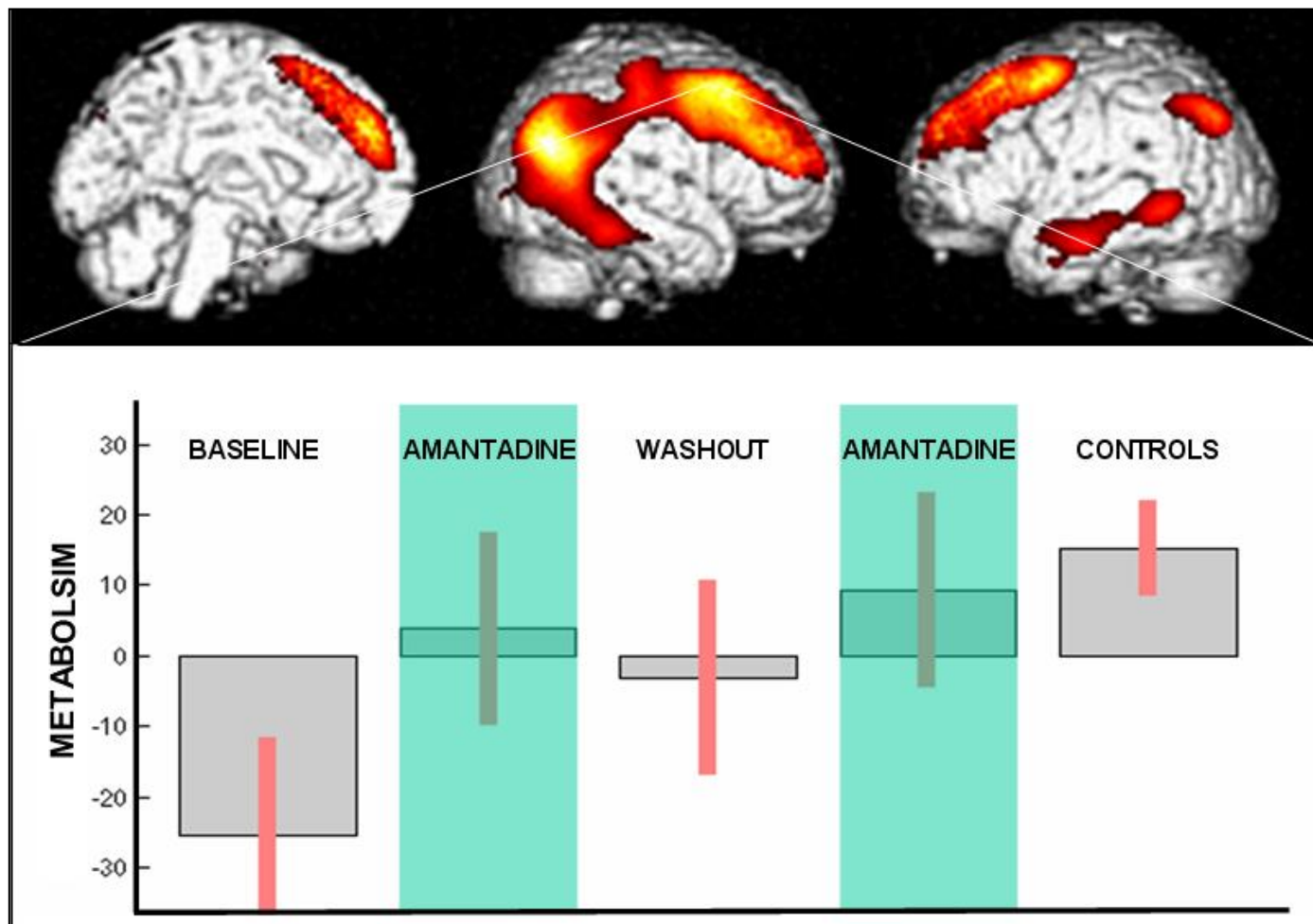
Amantadine

- Dopaminergic agent (Parkinson)
- Enteral administration, 6 weeks treatment (200mg/2*day)
- Side effects (seizure)





Amantadine



Zolpidem

- GABAergic agent
 - Enteral/oral administration (10mg)
 - No side effects (sleep)
-
- 5% responders dramatic effects!
 - 20% (12/60) improved behaviors after zolpidem but in only 1 patient changed of diagnosis (regained functional communication)

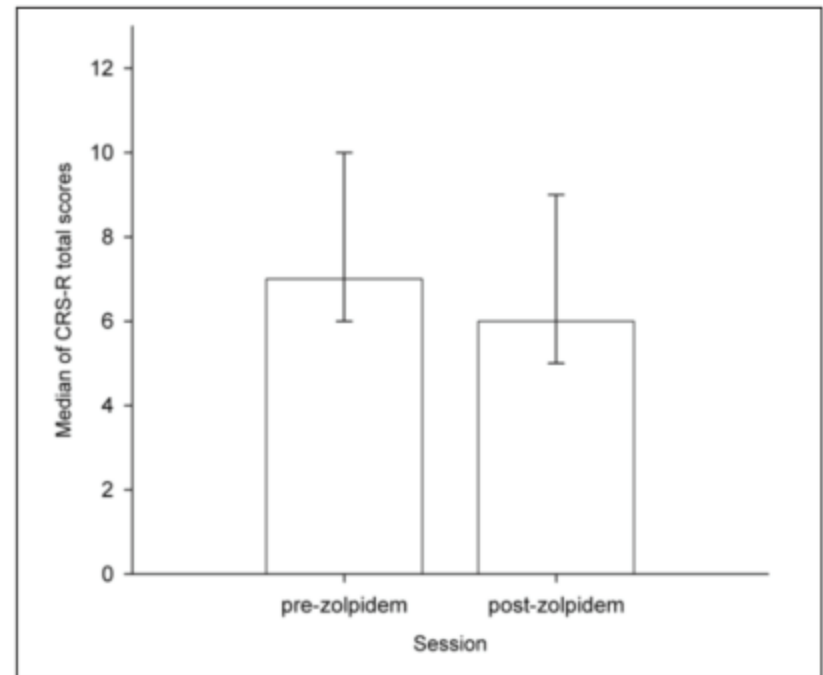
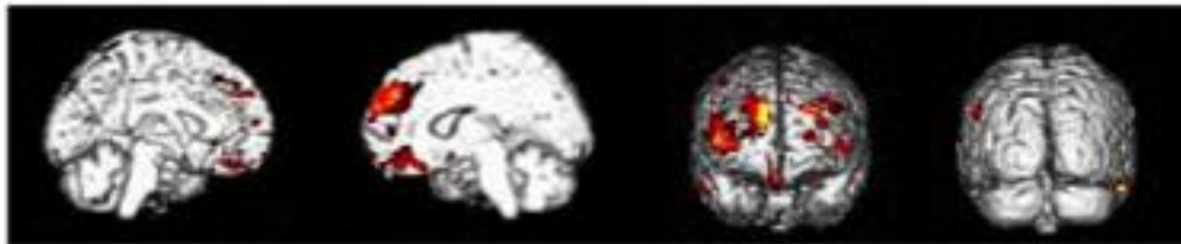


Figure 1 - Significant decrease of CRS-R total scores (ranging from 0 to 23) after zolpidem intake (interquartile range represented by errors bars) in the entire sample (n=60).

Zolpidem

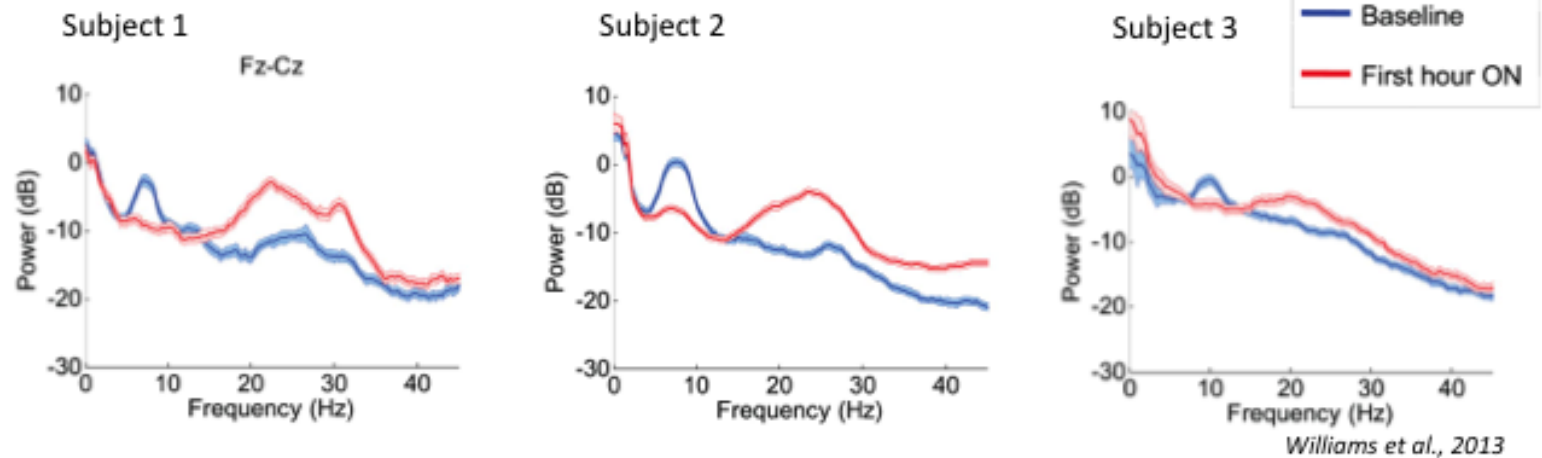
A. Brain metabolism in zolpidem responders

Zolpidem
> Placebo



N=3

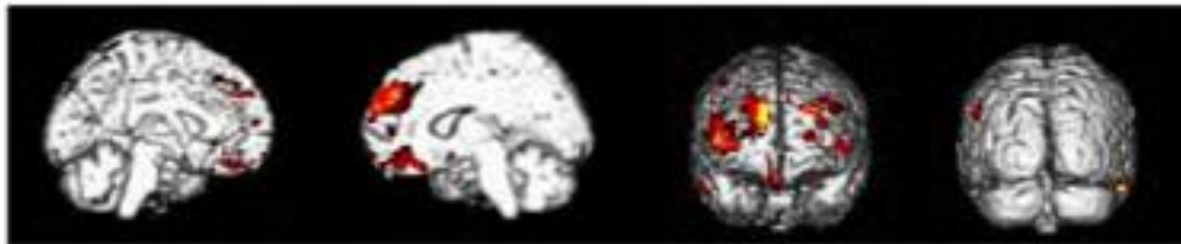
B. Brain electrical activity in zolpidem responders



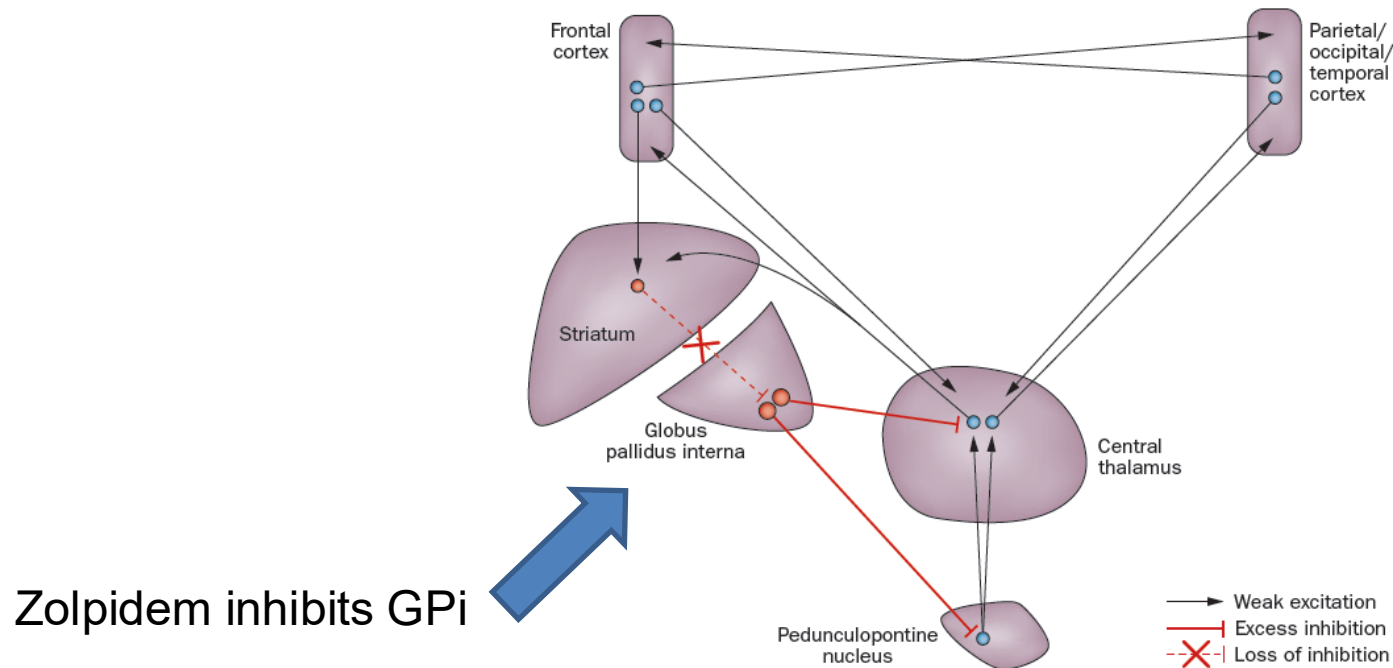
Zolpidem

A. Brain metabolism in zolpidem responders

Zolpidem
> Placebo



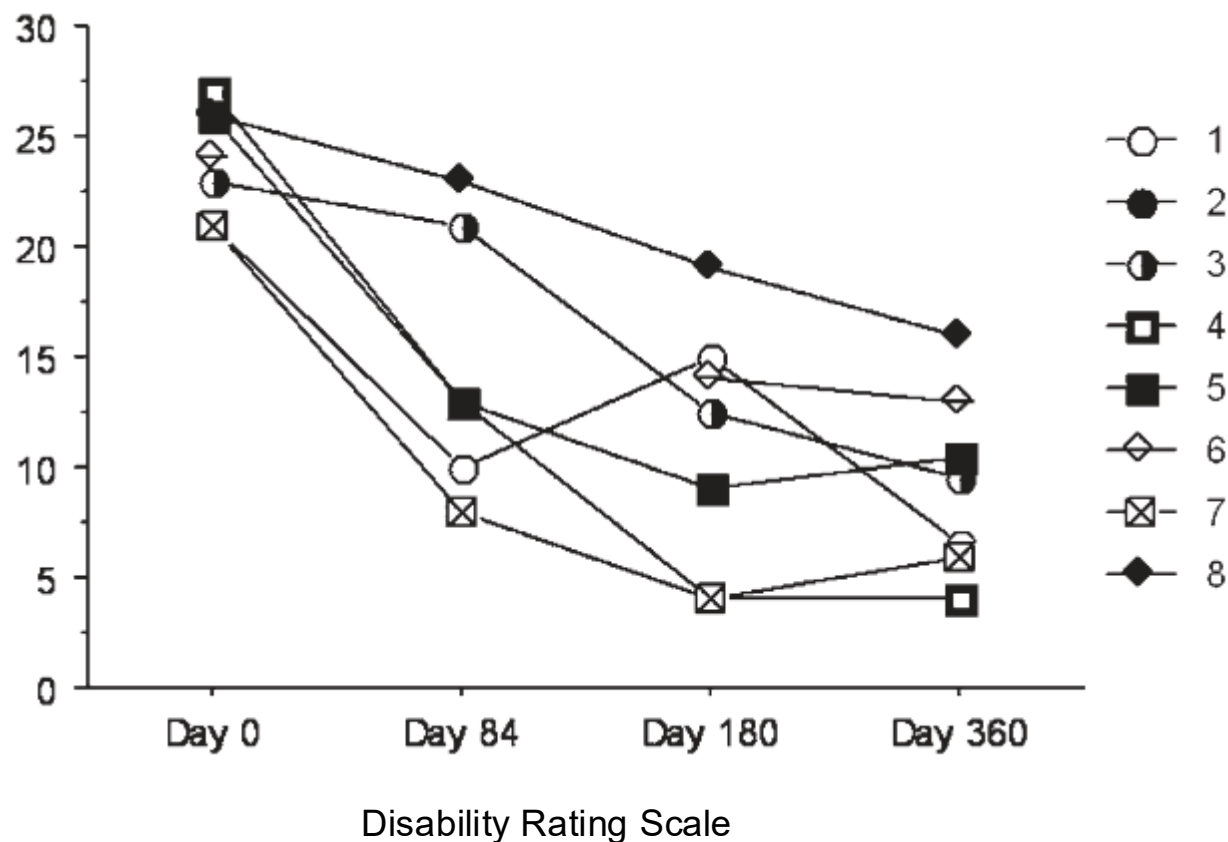
N=3





Apomorphine

- Dopaminergic agent
- Subcutaneous administration (12h/day)
- Only case studies
- Side effects



Pharmacological treatments

conclusion



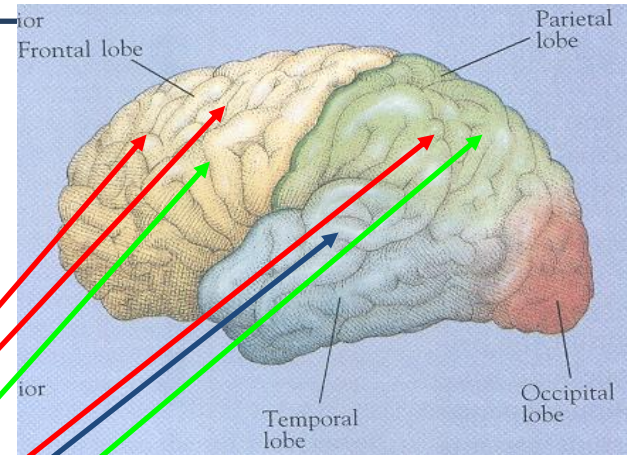
- Only a few pharmacological treatments
- Side effects / abituation
- Next:

Apomorphine multimodal trial

Zolpidem responders phenotype

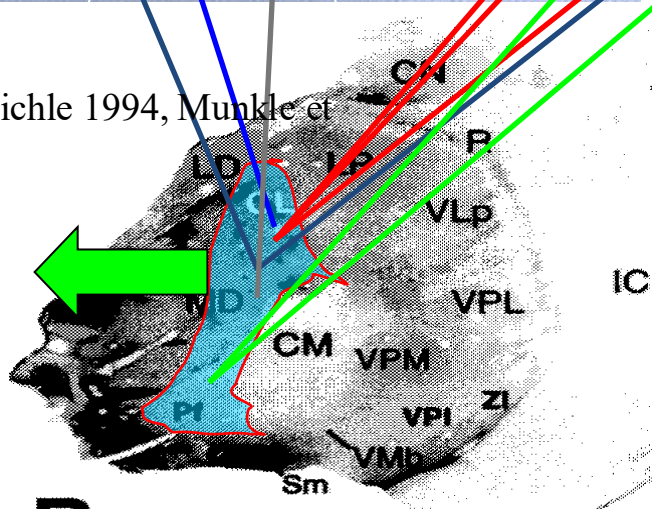


Central Thalamic Deep Brain Stimulation

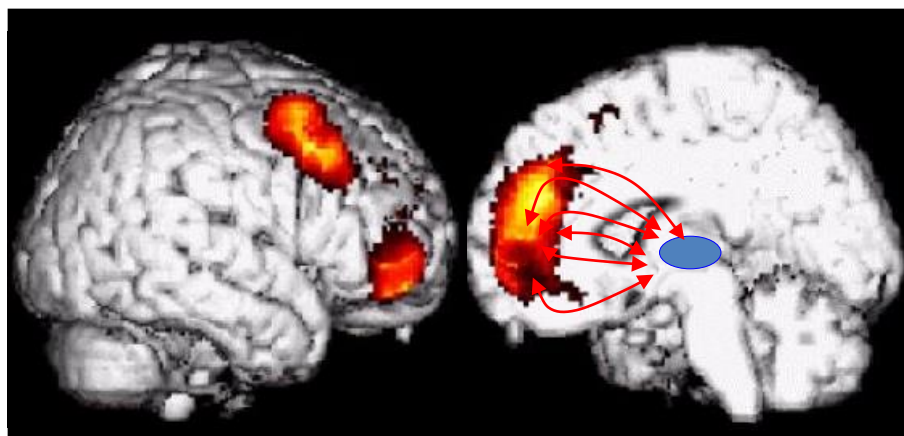


Adapted from:
Posner and Raichle 1994, Munkle et al. 2000.

Striatum

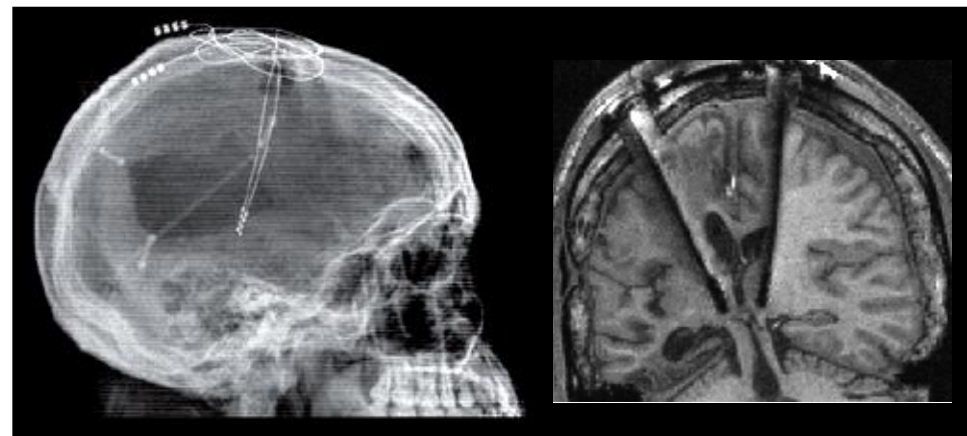


Intralaminar nuclei “reconnections”
in spontaneous recovery from
“vegetative” unresponsive state



Laureys et al, *Lancet* 2000

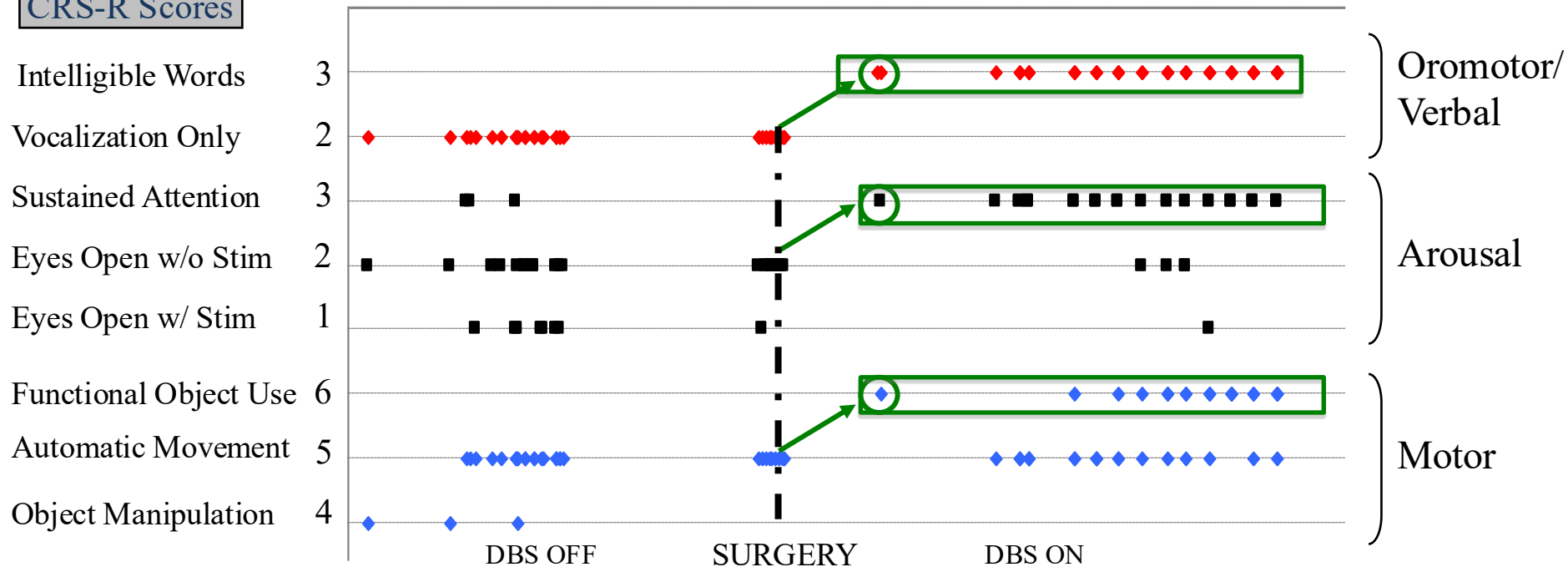
Intralaminar nuclei stimulation
induces “recovery” from
minimally responsive state



Schiff et al, *Nature* 2007

Deep Brain Stimulation

CRS-R Scores



MCS → emerged – prolonged effects

- *sustained attention*
- *intelligible words*
- *functional objects use*

Deep Brain Stimulation

conclusion

- DBS modulates specific cognitive and behavioral functions (arousal, functional limb movement, swallowing).
- Evidence of DBS carryover effects
- Limitations:
 - Strict inclusion criteria (e.g., no thalamic lesion)
 - Invasive
 - No randomized controlled study



Non-invasive brain stimulations

tDCS

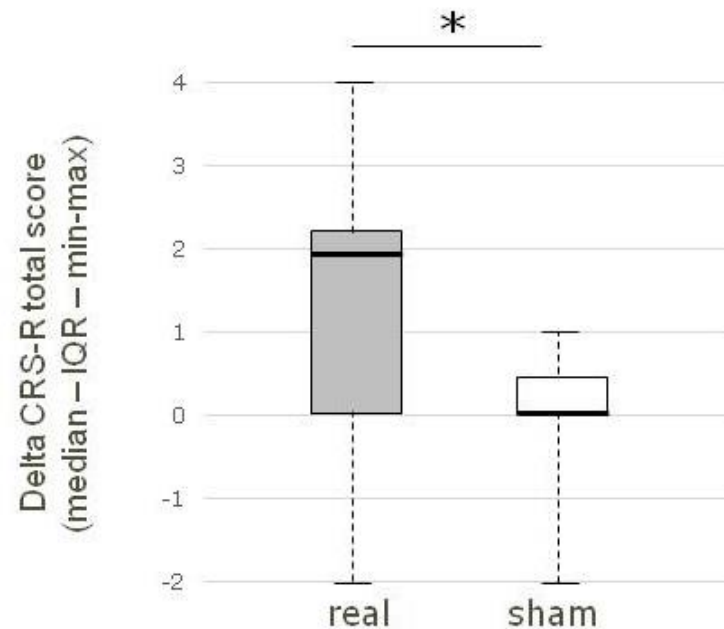
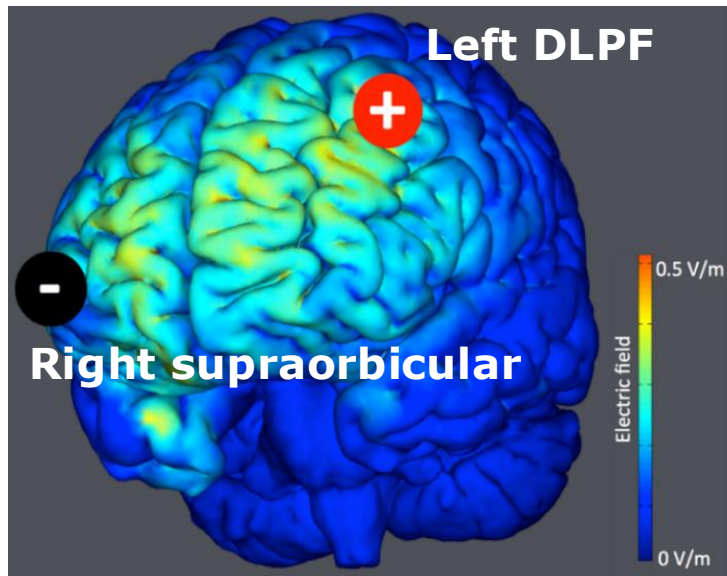
tDCS single session

ARTICLES

tDCS in patients with disorders of consciousness

Sham-controlled randomized double-blind study

Crossover RCT (n=55)

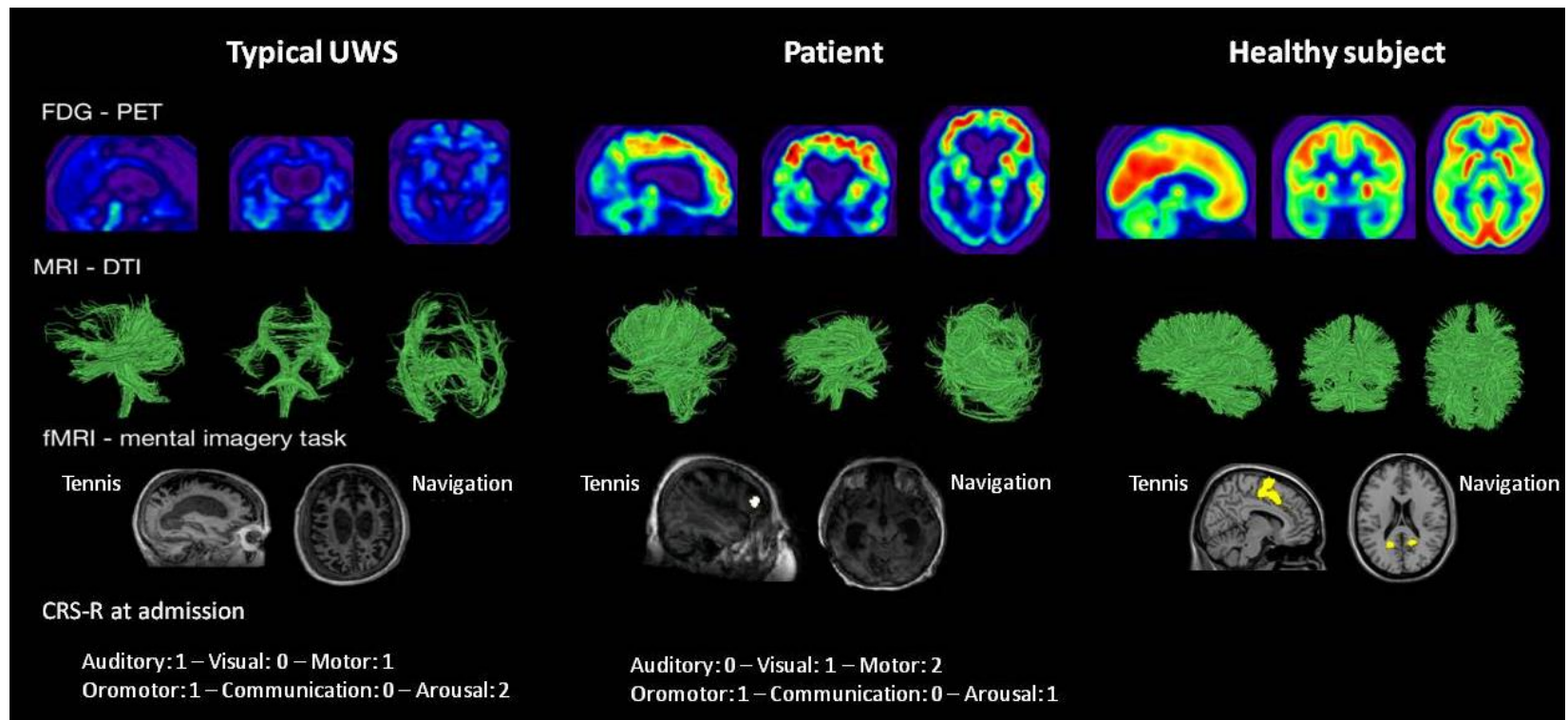


MCS
n=30

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

tDCS to unveil covert consciousness

- 67yo woman in UWS for 4 years after a subarachnoid hemorrhage
- Out of 7 standardized CRS-R she showed 1 localization to pain
- She demonstrated consistent response to command only after tDCS
- Neuroimaging exams were consistent with the diagnosis of MCS*



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

Neural correlates of responsiveness

Brain Stimulation 8 (2015) 1116–1123



Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: www.brainstimjrn.com



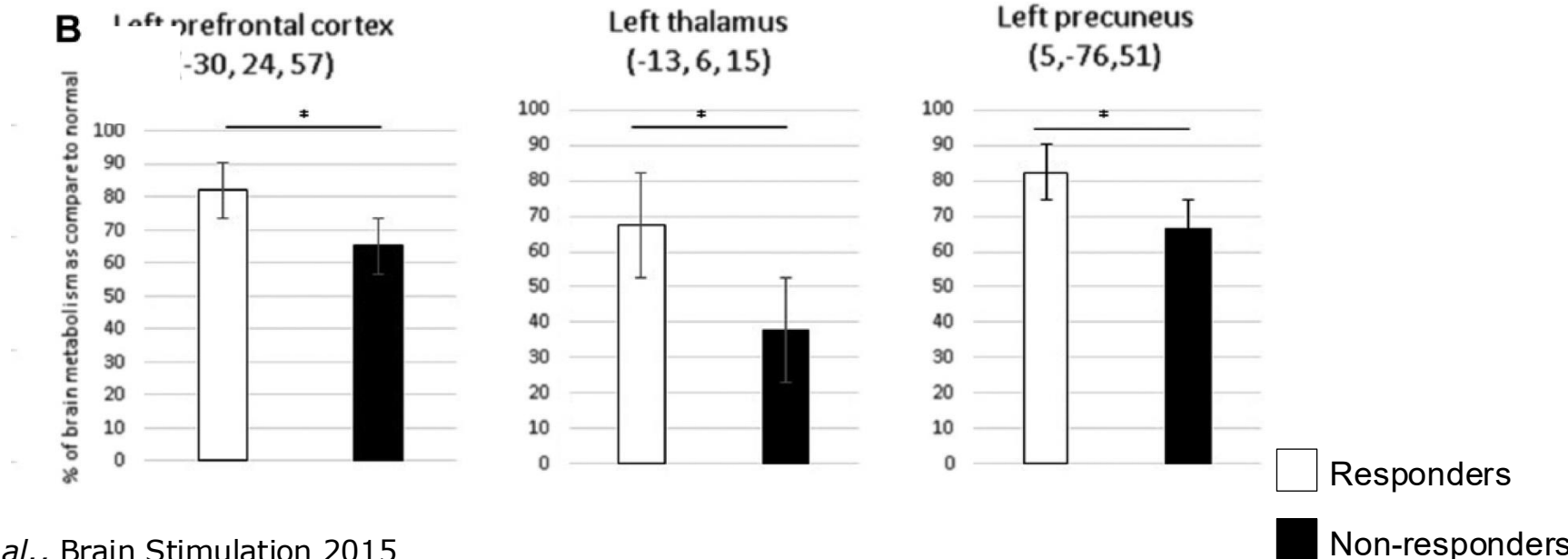
Clinical Response to tDCS Depends on Residual Brain Metabolism and Grey Matter Integrity in Patients With Minimally Conscious State



8 tDCS responders versus 13 tDCS non-responders

Aurore Thibaut^{a,*,1}, Carol Di Perri^{a,1}, Camille Chatelle^{b,c}, Marie-Aur lie Bruno^a, Mohamed Ali Bahri^d, Sarah Wannez^a, Andrea Piarulli^{a,e}, Claire Bernard^f, Charlotte Martial^a, Lizette Heine^a, Roland Hustinx^f, Steven Laureys^a

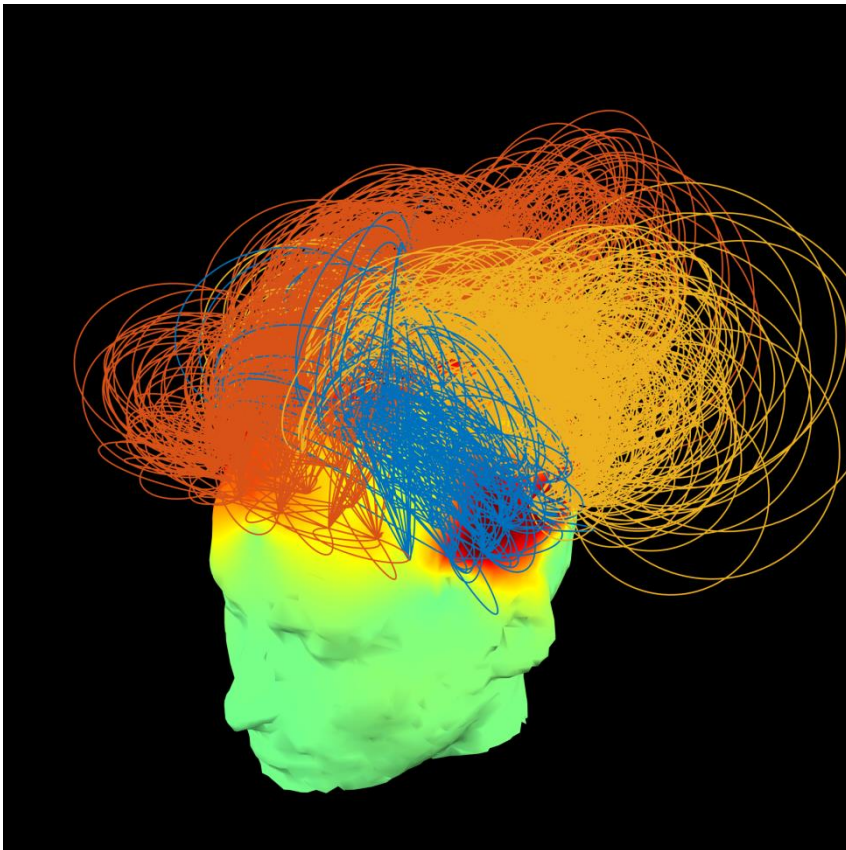
Regional brain metabolism



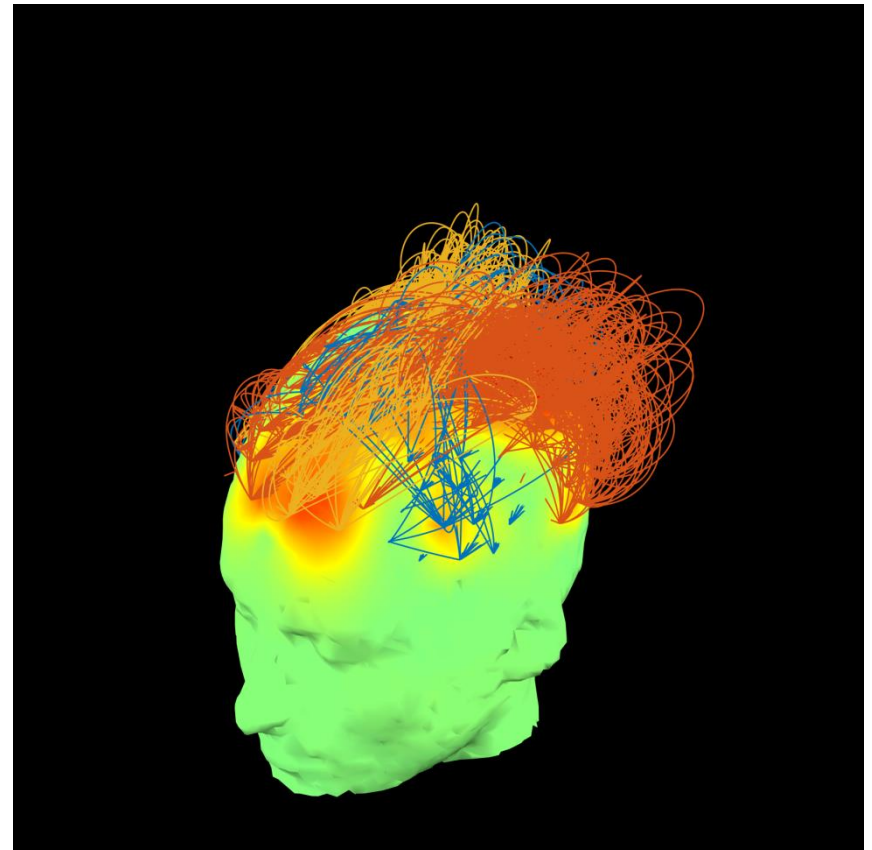
Neural correlates of responsiveness

Brain connectivity – theta band

8 tDCS responders



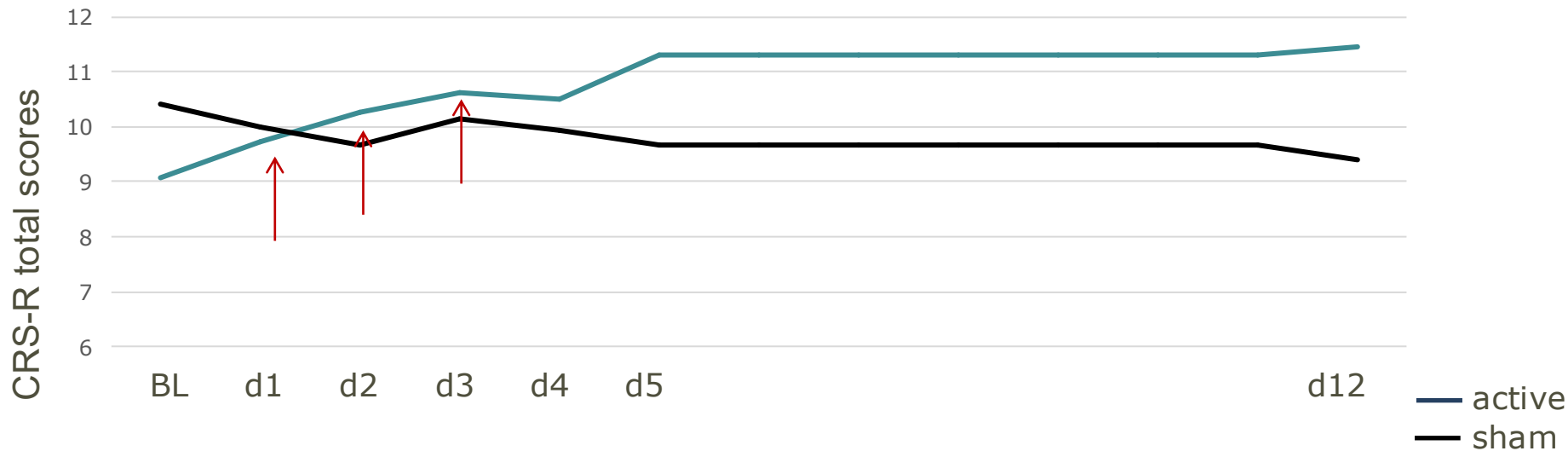
14 tDCS non-responders



Repeated tDCS

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

➔ Active session: significant time evolution ($p < 0.001$)



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

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

Single stim: 43% responders – effect size : 0.38 versus 0.57

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 DFPLC
7 VS and 6 MCS - chronic
→ Moderate clinical effects
→ Changes of EEG background
in patients who improved
clinically

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

Journal of the Neurological Sciences 375 (2017) 464–470



Contents lists available at ScienceDirect

Journal of the Neurological Sciences

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



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



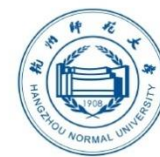
Anna Estraneo^{a,*}, Angelo Pascarella^a, Pasquale Moretta^a, Orsola Masotta^a, Salvatore Fiorenza^a, Grazia Chirico^a, Emanuela Crispino^a, Vincenzo Loreto^a, Luigi Trojano^{a,b}

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

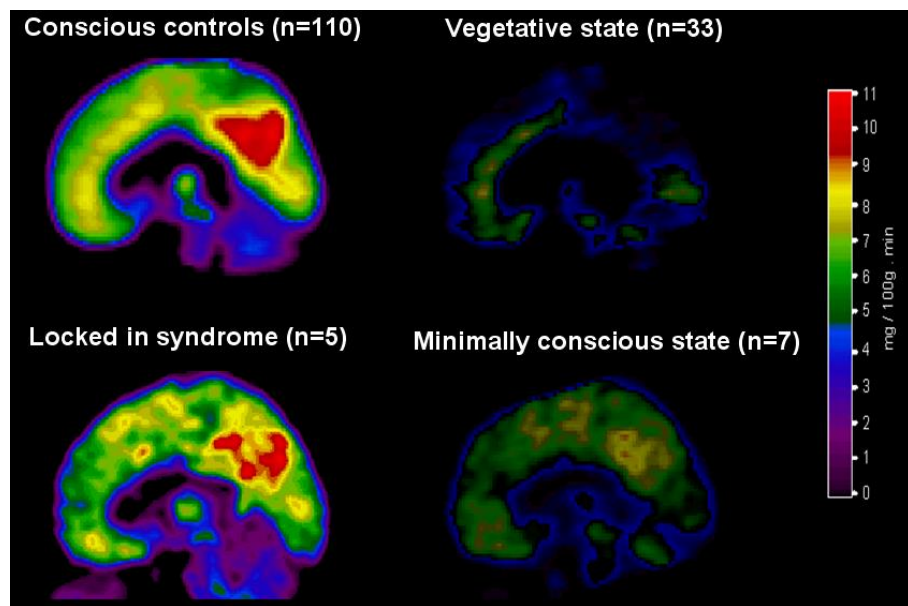
^b Neuropsychology Lab., Dept. of Psychology, Second University of Naples, Caserta, Italy



Targeting other areas?



Precuneus: critical hub for consciousness



Anode: posterior parietal cortex
Cathode: right SOR

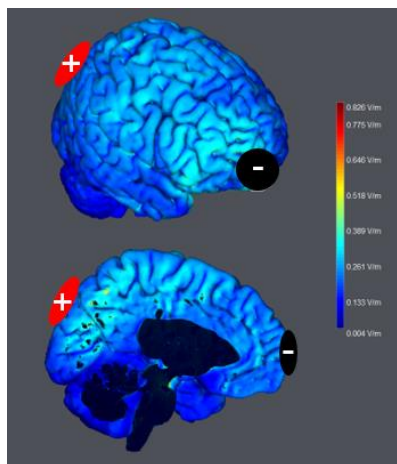
2mA; 20min

5 tDCS sessions

Active and sham – 5d washout

Laureys et al, Lancet Neurology, 2004

tDCS – Precuneus



Contents lists available at ScienceDirect

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

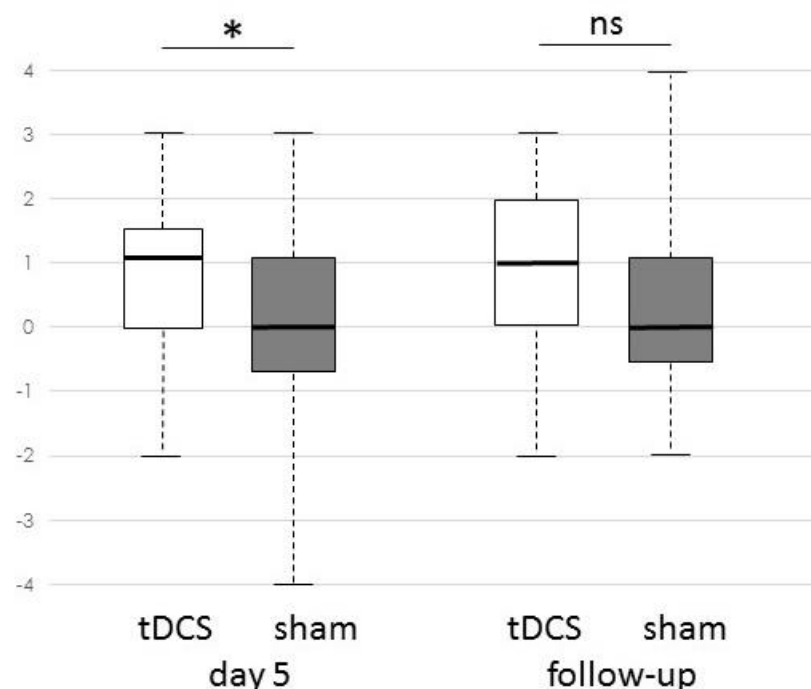
33 MCS >3 months post-insult
(57 ± 11 y; 20 TBI)

9 responders (27%)
Sub-acute > chronic

No effect at 5day follow-up

Effect size : 0.31

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



□ tDCS
■ sham



tDCS – motor cortex

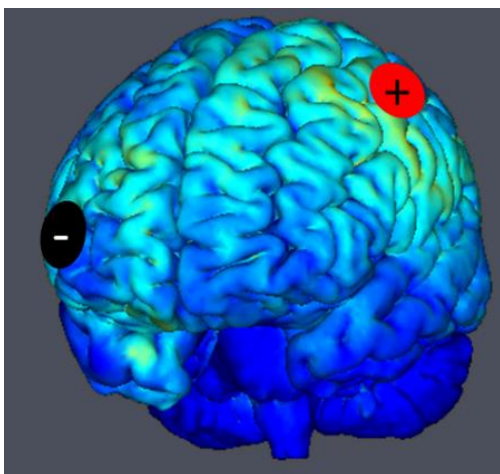
Motor cortex: common
& efficient tDCS target

For patients with DOC?

→ Immobilization, paresis...

→ Improve behavioral responsiveness

→ Covert consciousness



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												
SEMIMOTOR/VERBAL FUNCTION SCALE												
3 - Intelligible Vocalization *												
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 *



tDCS – motor cortex

Motor cortex: common
& efficient tDCS target

For patients with DOC?

→ Immobilization, paresis...

→ Improve behavioral responsiveness

→ Covert consciousness

Group level (n=10): no significant
improvement (p=0.55; ES=0.10)

Single-subject level: 2 responders

Single stimulation & small sample size

JFK COMA RECOVERY SCALE - REVISED ©2004										
Record Form										
Patient:	Date:									
AUDITORY FUNCTION SCALE										
4 - Consistent Movement to Command *										
3 - Reproducible Movement to Command *										
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TOTAL SCORE										

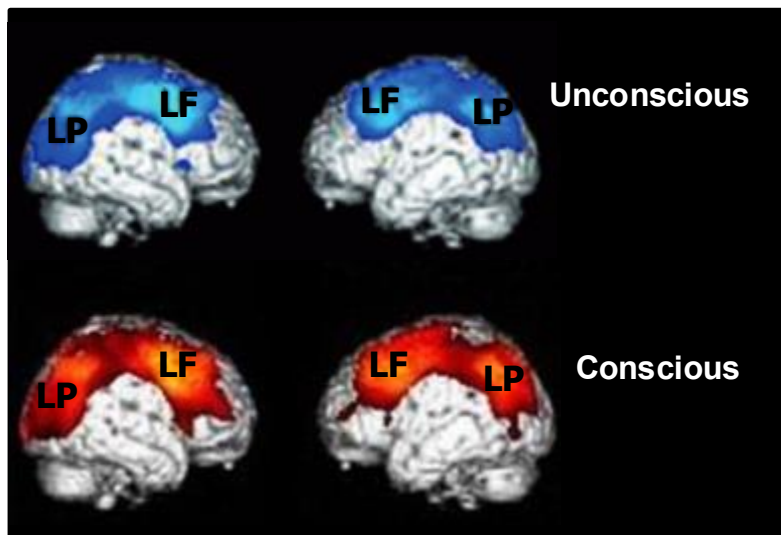
Denotes emergence from MCS †

Denotes MCS *

Fronto-parietal multichannel tDCS

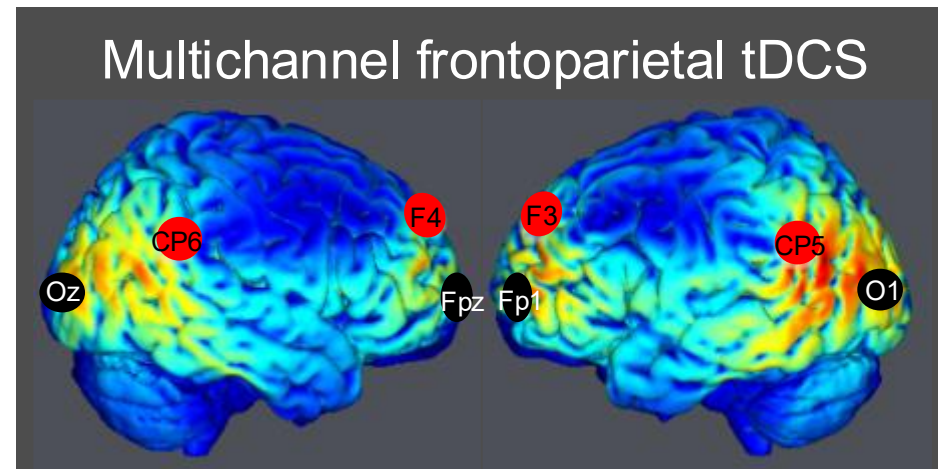
Frontoparietal network
External awareness network
Critical for consciousness recovery

→ Stimulation of the external awareness network bilaterally



● Hypometabolic areas

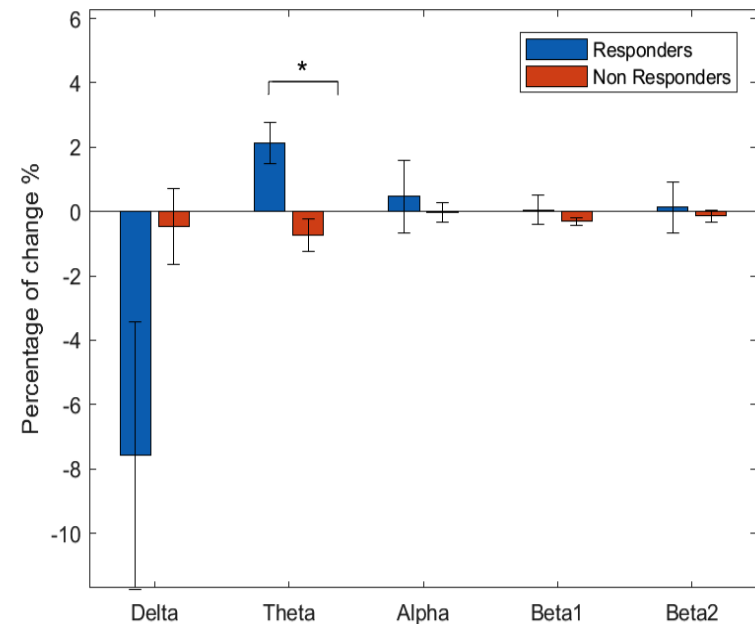
● Preserved areas



Fronto-parietal multichannel tDCS

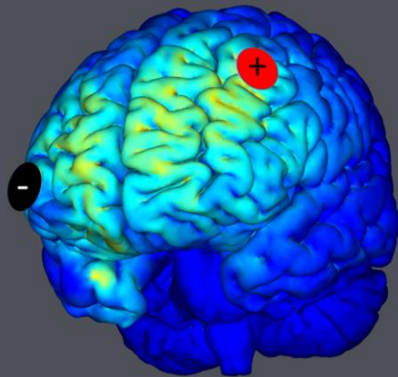
46 patients with prolonged DOC. VS and MCS, TBI and non-TBI
4 anodes and 4 cathodes – 1mA; 20min
Single stimulation – active & sham
Behavioral & EEG assessments

- Group level: no improvement
1 mA not enough?
1 session not enough?
- 6 responders (13%) mostly TBI
- EEG in responders: increase in theta complexity after active tDCS - no changes after sham tDCS

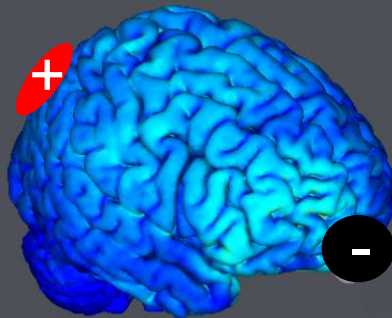


Stimulating different brain regions

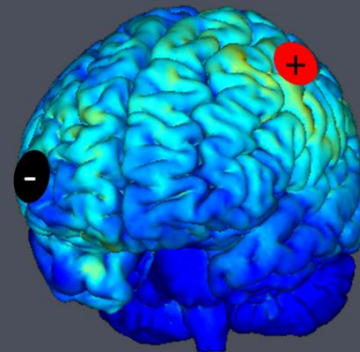
Prefrontal ↗



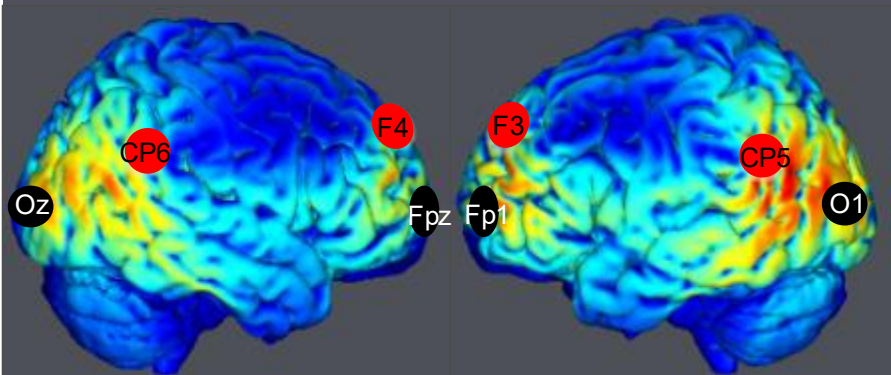
Precuneus →



Motor ≡



Multichannel frontoparietal ≡



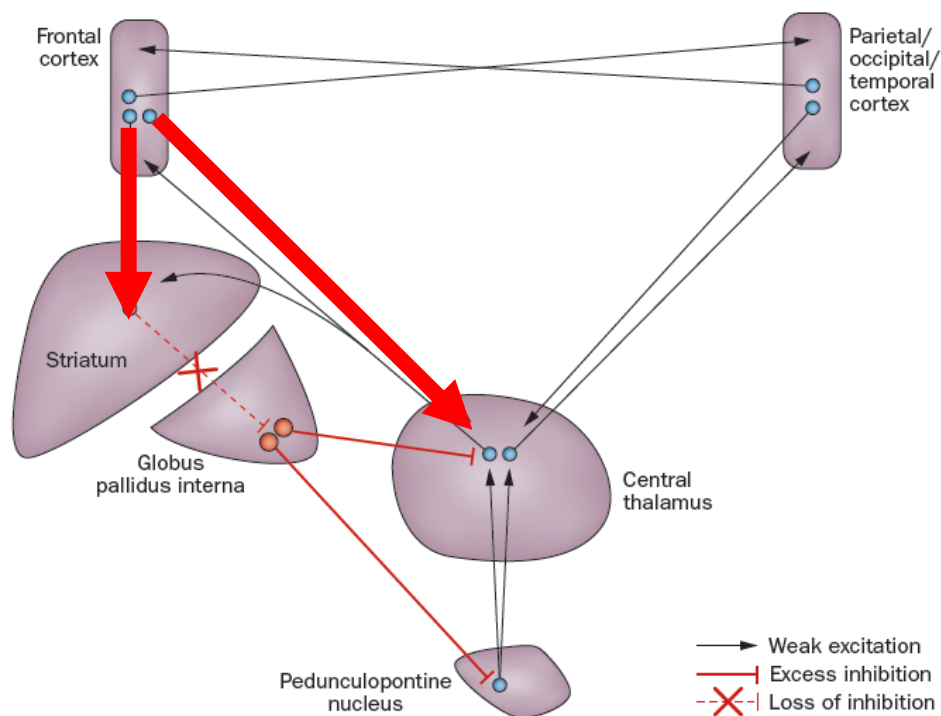
Group level: Prefrontal tDCS best area to target

Single-subject level:
Patient's tailored montage



tDCS - mesocircuit

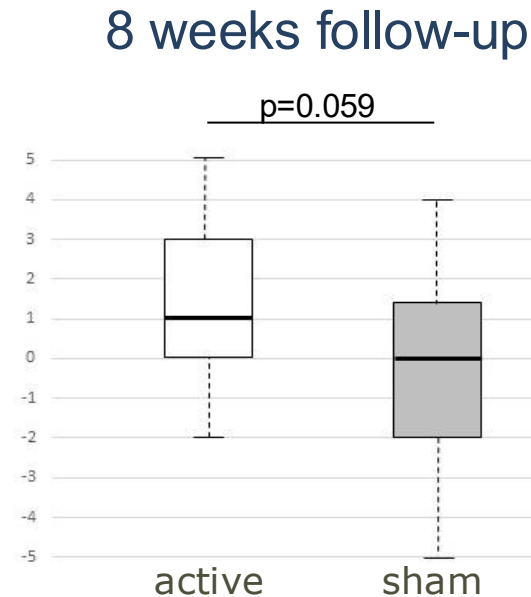
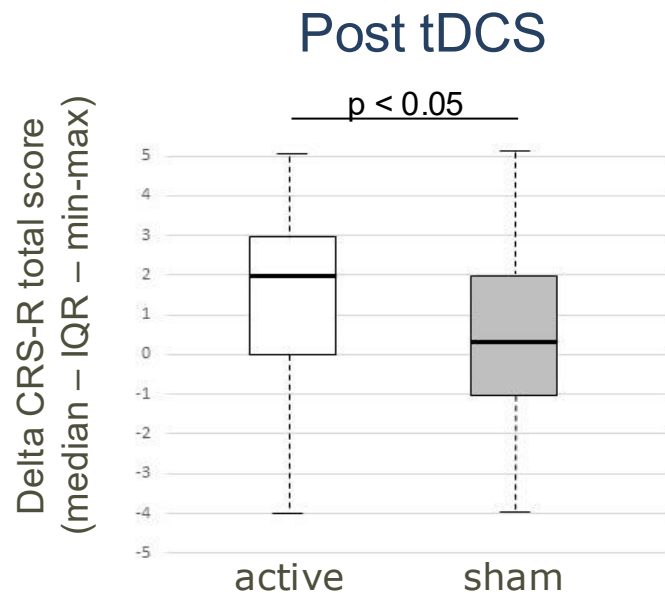
Prefrontal tDCS better than targeting other areas?



Clinical translation



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



Pharmacological treatments

- Amantadine in TBI → other etiologies?
- Zoplidem – 5% → phenotype of responders
- Apomorphine → randomized clinical trials

DBS

- Promising but invasive & no randomized clinical trials

NIBS

- tDCS is safe in severely brain-injured patients
- **Prefrontal** tDCS → consistent clinical improvement
- Repeated tDCS → increase duration of the effects
→ increase number of responders
- Need patients' tailored montage based on individual brain lesions

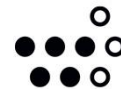
THANK YOU



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