La stimulation (médicamenteuse/électrique) de la conscience chez les patients en état de conscience altérée

Bertrand Hermann, MD, PhD

2 février, 2023

Journée EVC-EPR 2023

État Végétatif Chronique et État Pauci-Relationnel

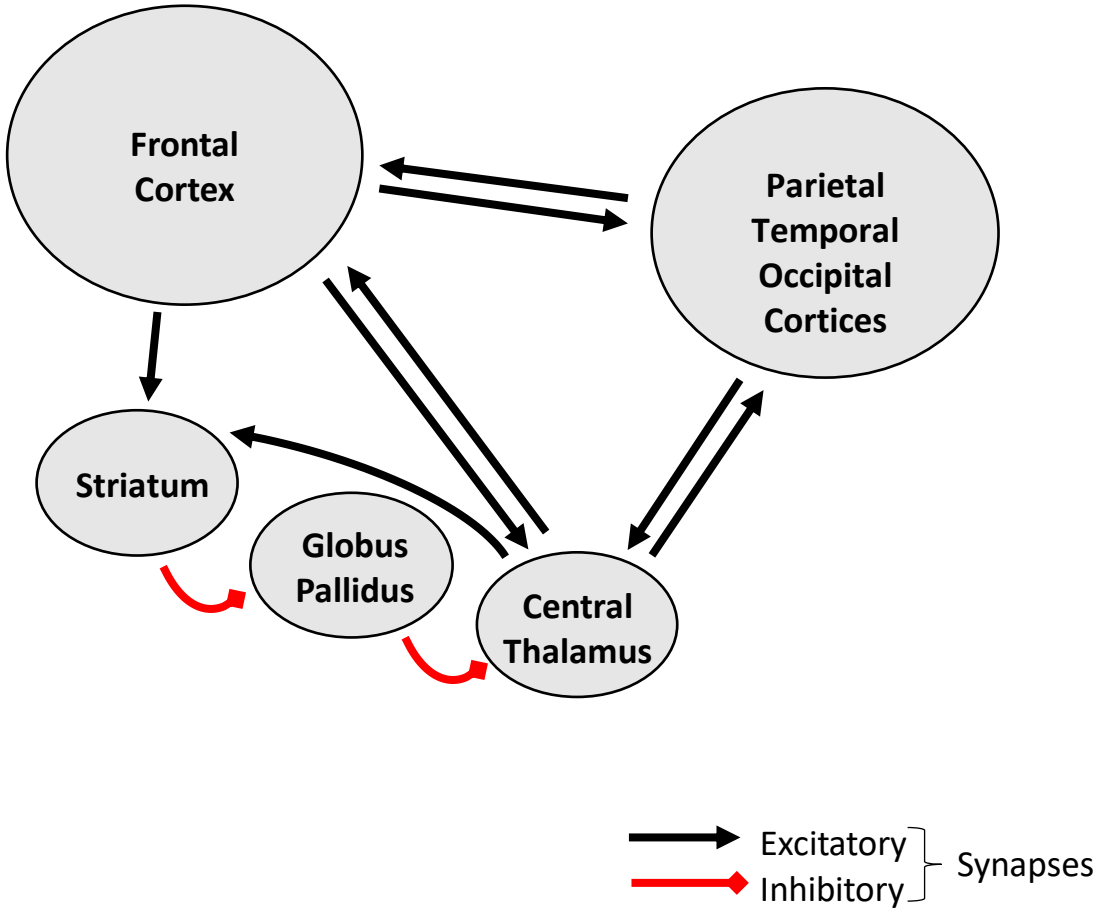
MÉDECINE PARIS CENTRE
Santé
Université de Paris

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS
AP-HP. Centre Université de Paris

Inserm
La science pour la santé
From science to health

Pas de conflit d’intérêt

MESOCIRCUIT HYPOTHESIS

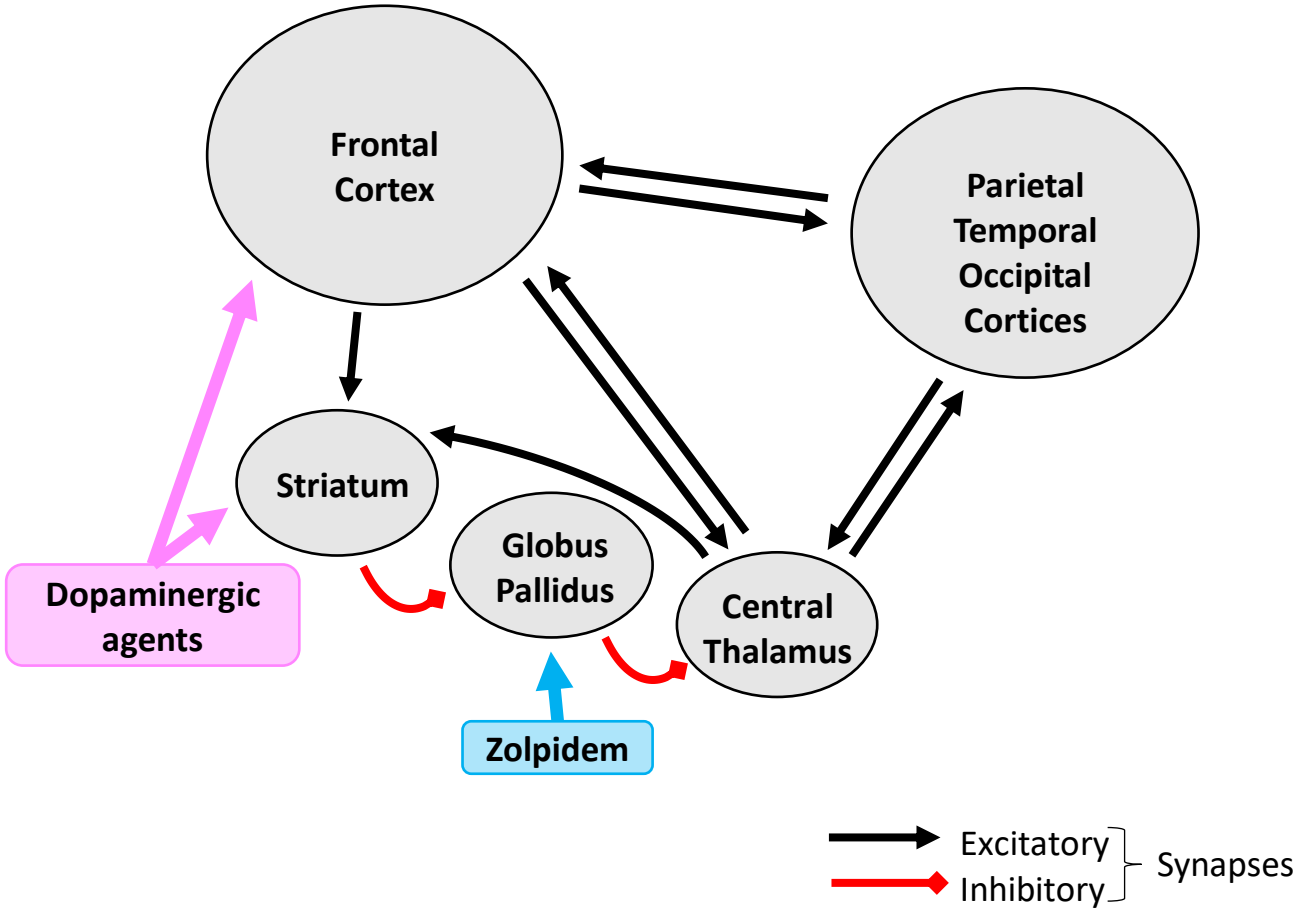


- Thalamo-cortical loops & consciousness
- Key role of the central thalamus in activating fronto-parietal cortices
- Striatal lesions are responsible for a inhibition of the central thalamus

→ unresponsiveness/unconsciousness

adapted from Thibaut et al., Lancet Neurol 2019

PHARMACOLOGICAL INTERVENTIONS



Pharmacological treatments

- Dopaminergic agents
- GABAergic agents

adapted from Thibaut et al., Lancet Neurol 2019

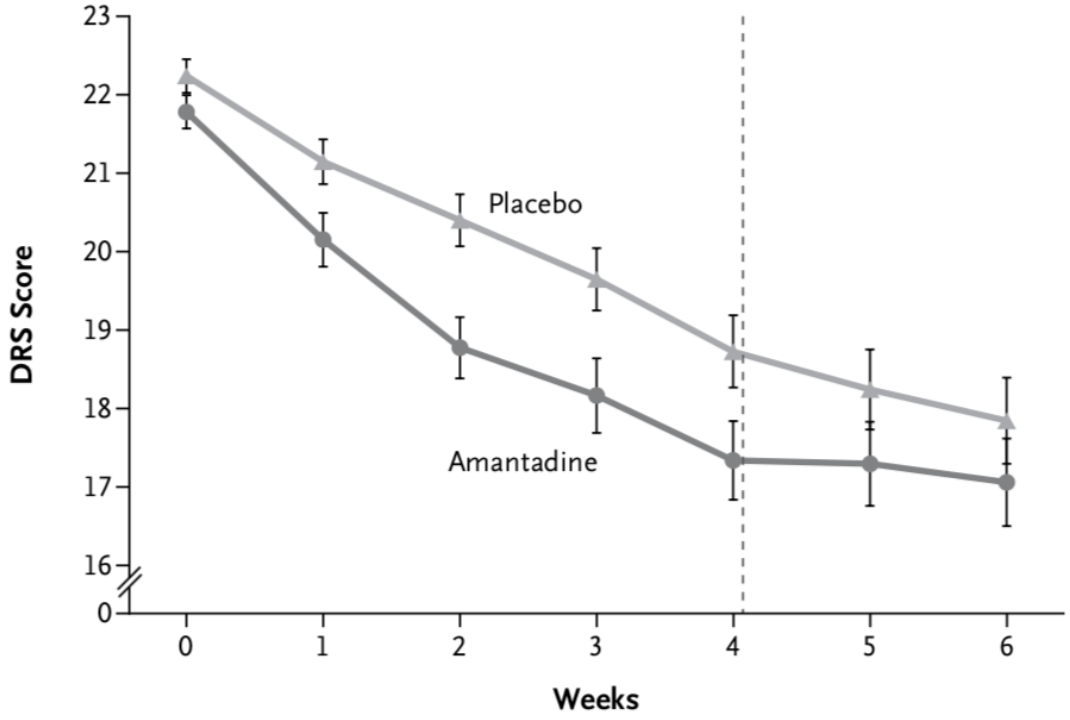
AMANTADINE

- Dopamine agonist & NMDA-antagonist

- Evidence in TBI
  - Randomized placebo-controlled trial
  - n = 184, subacute TBI
  - 4 weeks regimen (up to 200 mg/day)
  - 0,25 pt CRS-R/week

- Long-term effects ?
  - No effect on cognition at D28 and D60 after TBI
    Hammond, J Neurotrauma 2018

- Non traumatic brain injury (anoxia)?



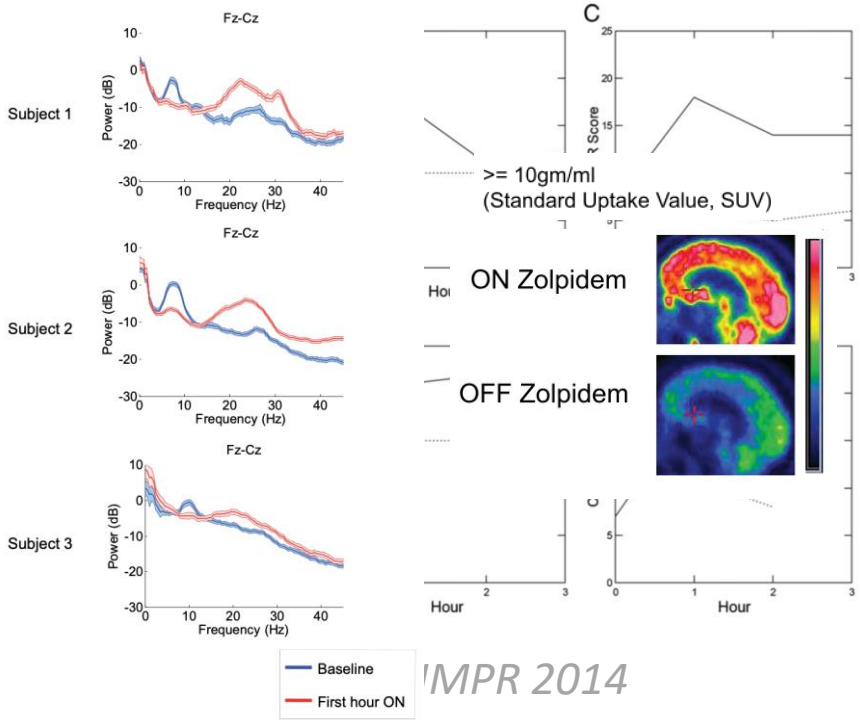
Giacino, NEJM 2012

Only recommended treatment in DoC
4-16 weeks after a traumatic brain injury

Giacino, Neurology 2018

ZOLPIDEM

- Hypnotic
- GABA agonist
- ~ 5% paradoxical effect
- Transient
- 10 mg, sometimes higher doses necessary
- Increase activity/metabolism in prefrontal areas



IMPR 2014

Williams, eLife 2013

Should probably be tested in all DoC patients

⚠ respiratory depression

OTHER DRUGS

Not enough evidence

- **Other dopamine agonists**
  - Apomorphine, Bromocriptine, Levodopa
  - Only case reports
  - Theoretical advantages over amantadine (mesocircuit hypothesis)

Fridman, Brain Inj 2009 & 2010

- **Other GABA agonists (BZD, Baclofen)**
- **Calcium channels blockers**
- **Various neurostimulants**

NIH U.S. National Library of Medicine

ClinicalTrials.gov

Find Studies

Home > Search Results > Study Record Detail

Treating Severe Brain-injured Patients With Apomorphine

ClinicalTrials.gov Identifier: NCT03623828

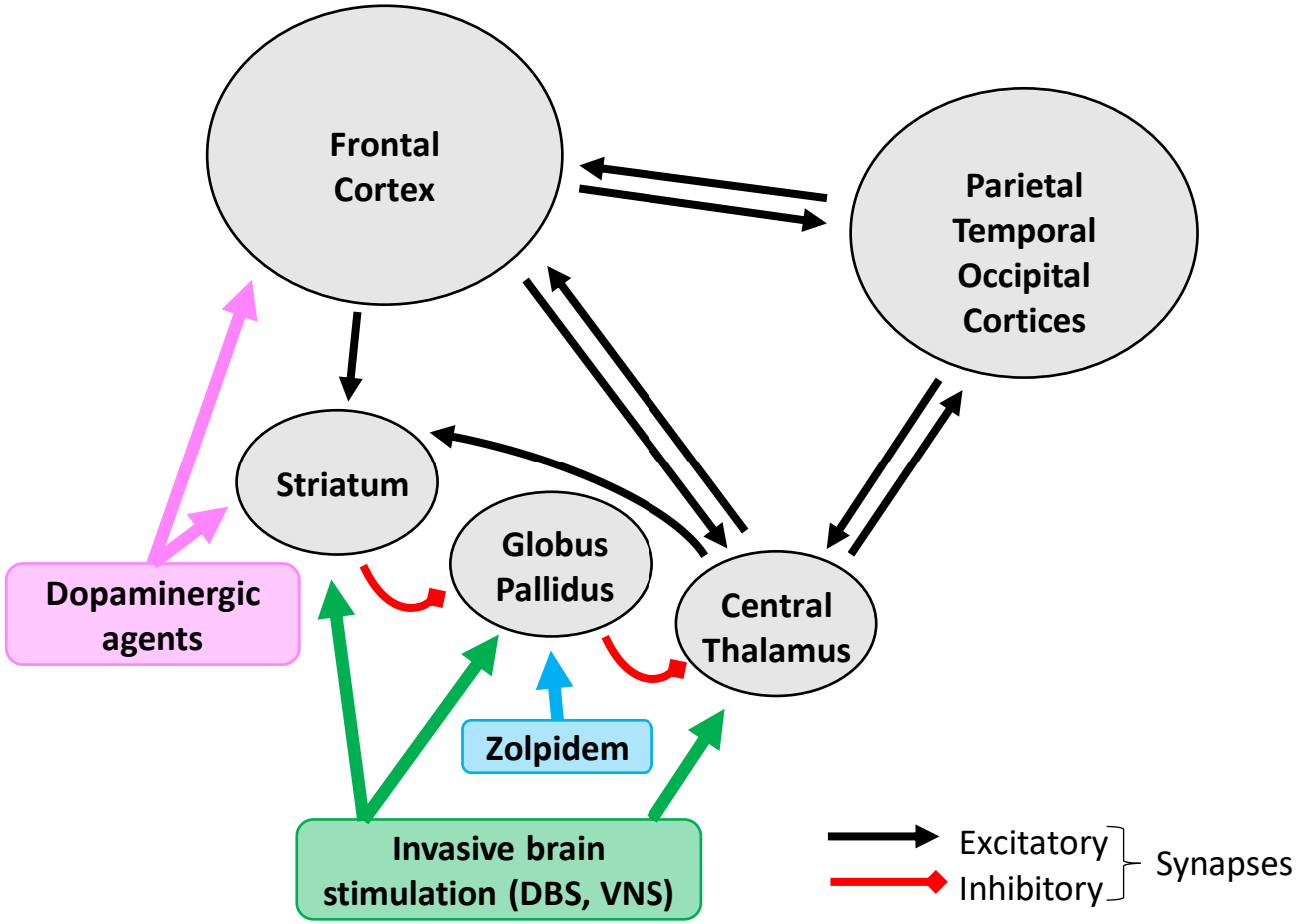
Recruitment Status : Recruiting

First Posted : August 9, 2018

Last Update Posted : January 10, 2020

See **Contacts and Locations**

INVASIVE BRAIN STIMULATION



adapted from Thibaut et al., Lancet Neurol 2019

Pharmacological treatments

- **Dopaminergic agents**
- **GABAergic agents**

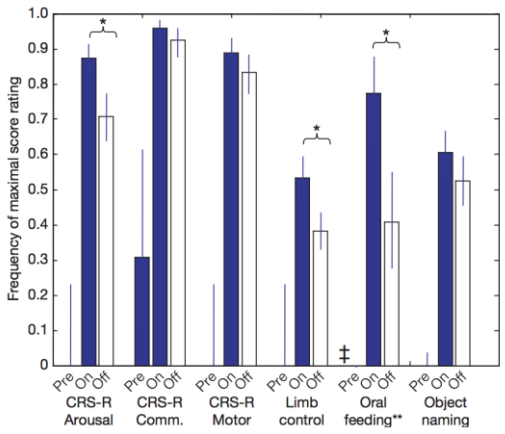
Brain stimulation

- **Invasive**
  - Deep brain stimulation (DBS)
  - Vagus nerve stimulation (VNS)

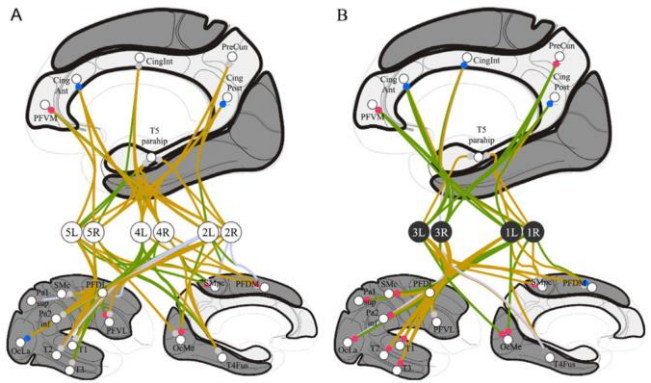
DEEP BRAIN STIMULATION (DBS)

- First report from 1968 ! *(McLardy, Trans. Am. Neurol. Assoc 1968)*

- Review of ten studies *(Bourdillon*, Hermann*, Front Neurosci 2019)*
  - 78 patients
  - Wide heterogeneity
    - Etiology
    - Site of stimulation : ARAS, central thalamus, intralaminar nuclei, pallidum
    - Intensity (50 Hz and 100 Hz)
    - Design with mostly open-label
  - Improvement in 30/67 UWS and 6/11 MCS
  - Confounding of spontaneous recovery (<1y)



Schiff, Nature 2007



Lemaire, ACTN 2018

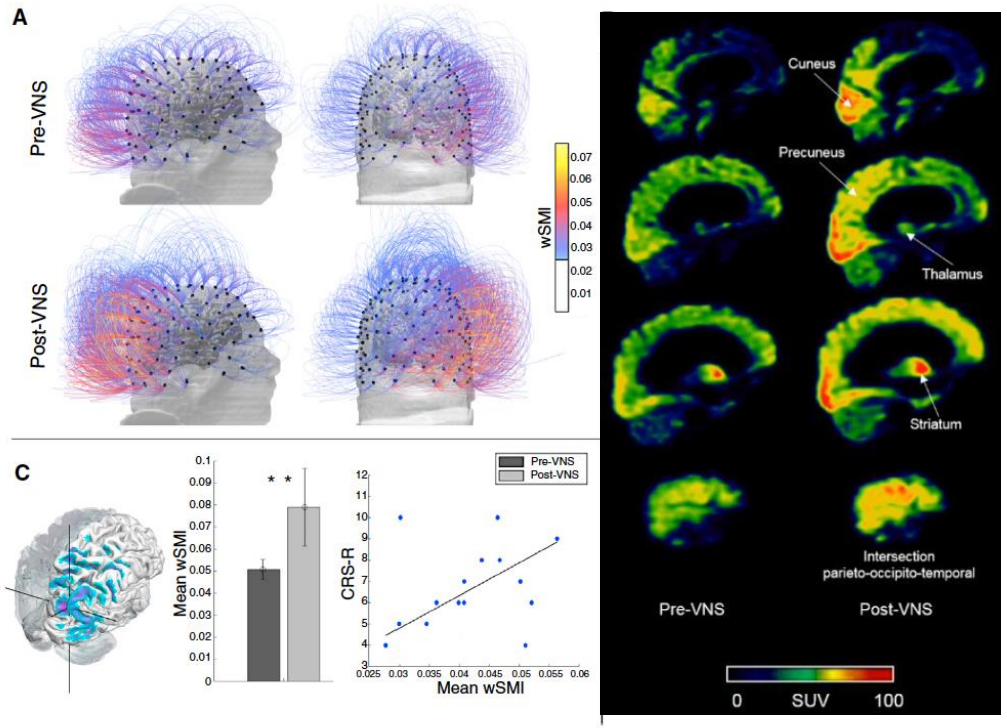
Need of double-blind design
Better patient selection ?
Invasivness

VAGUS NERVE STIMULATION (VNS)

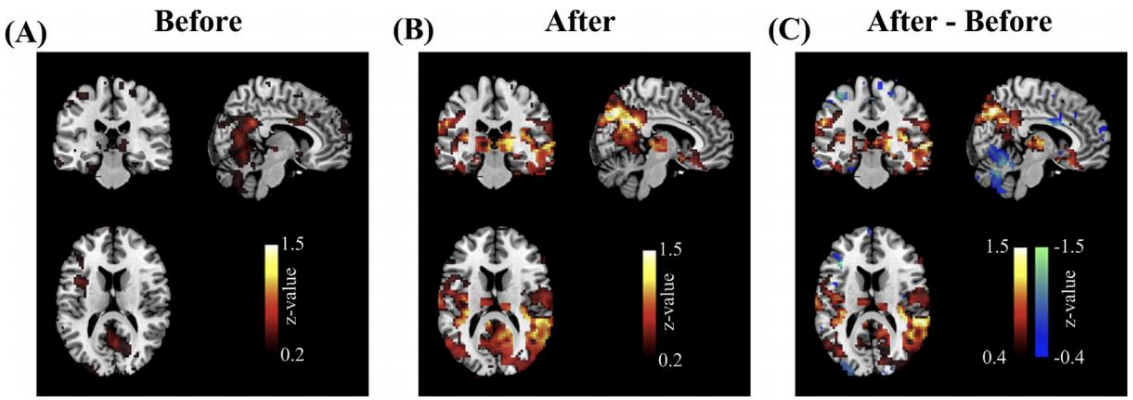
- **Surgically implanted**
  - One VS/UWS since 15 years
  - CRS-R 5 → 10
  - VS/UWS → MCS
  - Increased metabolism and posterior functional

- **Transcutaneous auricular VNS**
  - Similar changes
  - Increased precuneus/posterior cingulate resting state fMRI functional connectivity

Promising
Need more data

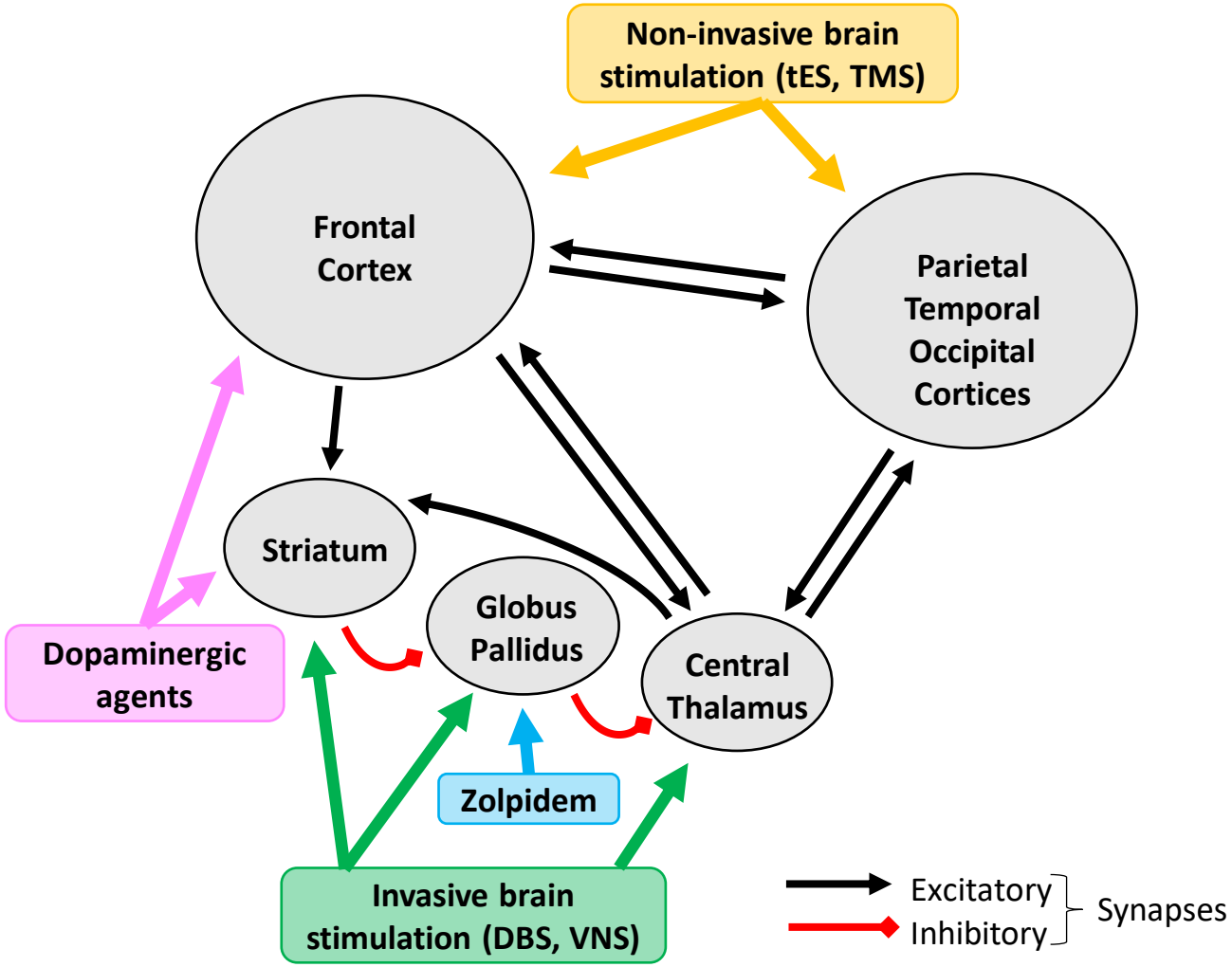


Corazzol, Current Biology 2017



Yu, Brain Stimulation 2018

NON-INVASIVE BRAIN STIMULATION



adapted from Thibaut et al., Lancet Neurol 2019

Drugs

- **Dopaminergic agents**
- **GABAergic agents**

Brain stimulation

- **Invasive**
  - Deep brain stimulation (DBS)
  - Vagus nerve stimulation (VNS)
- **Non-invasive**
  - Transcranial magnetic stimulation (TMS)
  - Transcranial electrical stimulation (tES)
  - Focused ultrasound

REPEATED TRANSCRANIAL MAGNETIC STIMULATION (rTMS)

Study	Design/Control	Population	Target/ Stimulation parameters	Behavioral effects	Electrophysiological effects	Side effects
Louise-Bender Pape et al., 2009	Case report/ None	1 VS/UWS patient	Right DLPFC/30 sessions over 6 weeks of 10 Hz rTMS (300 paired-pulse) at 110% RMT	No significant (trend) improvement of DOC Scale	Improvement of latencies of auditory brainstem evoked potentials	None
Piccione et al., 2011	Case report/ Median nerve stimulation	1 MCS patient	Left M1/2 sessions of 20 Hz rTMS (10 trains of 100 stimuli) at 90% RMT	Increased CRS-R score lasting 6 h after stimulation	Increase of absolute and relative power in delta, alpha and gamma band	None
Manganotti et al., 2013	Open-label/ None	6 patients (3 VS/UWS and 3 MCS)	Left or right M1/1 session of 20 Hz rTMS (10 trains of 100 stimuli) at 120% RMT	Improvement of consciousness in only 1 patient	Increase of absolute and relative power in delta, alpha and gamma band and reactivity in the responding patient	None
Pape et al., 2014	Open-label/ None	2 patients	Right DLPFC/30 sessions over 6 weeks of 10 Hz rTMS (300 paired-pulse) at 110% RMT	Not assessed	Not assessed	One epileptic
Xie et al., 2015	Open-label/ Case-control	20 patients (2 coma, 11 VS/UWS, 7 MCS) of which 10 were stimulated	Right DLPFC/28 sessions over 28 days of 5 Hz rTMS	6 out of 10 patients stimulated showed CRS-R improvement persisting at 4 weeks	Increase of alpha power and decrease of delta power	Not reported
Naro et al., 2015a	Not randomized/ Sham	10 patients (all VS/UWS) and 10 healthy controls	Right DLPFC/1 session of 10 Hz rTMS (1000 pulses) at 90% RMT	No significant group effect but small short-lasting improvement in 3 patients on the motor subscale of the CRS-R	No significant effect at the group level, but some short-lasting modulation of motor evoked potentials in the 3 responding patients	None
Cincotta et al., 2015	Cross-over RCT/ Sham	11 patients (all VS/UWS)	Left M1/5 sessions over 5 days of 20 Hz rTMS (1000 pulses) at 90% RMT	No significant differences in CRS-R scores between stimulation and sham	No significant changes on EEG (Synek classification)	None
Liu et al., 2016	Cross-over RCT/ Sham	10 patients (5 VS/UWS, 5 MCS)	Left M1/1 session of 20 Hz rTMS (1000 pulses) at 100% RMT	No behavioral effect	Significant changes in hemodynamic parameters (mean and peak velocity of middle cerebral artery) on transcranial doppler only in MCS	None
Bai et al., 2017	Case report/ None	1 MCS patient	Left DLPFC/ 20 sessions over 20 days of 10 Hz rTMS (1000 pulses) at 90% RMT	Improvement of CRS-R after 20 sessions	Concomitant improvement of perturbational complexity index, global mean field power and motor evoked potential.	None
Xia et al., 2017	Prospective/ Not controlled	16 patients (11 VS/UWS and 5 MCS)	Left DLPFC/ 20 sessions over 20 days of 10 Hz rTMS (1000 pulses) at 90% RMT	Improvement of CRS-R score in all MCS patients and 4/11 VS/UWS persisting 10 days after stimulation.	None	None
Xia et al., 2017	Prospective/ Not controlled	18 patients (12 had repeated sessions for 20 days)	Left DLPFC/ 20 sessions over 20 days of 10 Hz rTMS (1000 pulses) at 90% RMT	Overlapping population with the previous study. No statistical testing.	Decreased low-frequency band power and increased high-frequency band power, especially in MCS	None
He et al., 2018	Cross-over RCT/ Sham	6 patients (3 VS/UWS, 2 MCS and 1 EMCS)	Left M1/5 sessions over 5 days of 20 Hz rTMS (1000 pulses) at 100% RMT	No significant differences in CRS-R. One patient improved after real stimulation.	Increase delta, theta, alpha and beta power spectra in the responding patient.	Not reported
Liu et al., 2018	Cross-over RCT/ Sham	7 patients (2 VS/UWS and 5 MCS)	Left M1/5 sessions over 5 days of 20 Hz rTMS (1000 pulses) at 100% RMT	No significant changes of CRS-R scores	No significant changes in functional connectivity on EEG	None

- Mostly uncontrolled trials
- Small sample sizes
- Heterogeneity
  - Patients
  - Site
  - Frequency
  - Numbers of session
- Risk of seizure
- Logistically difficult

No evidence
Maybe not the best NIBS tool in this population

Bourdillon, Hermann* et al., Front Neurosci 2019*

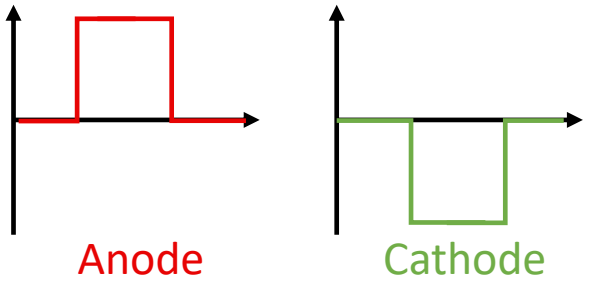
TRANSCRANIAL ELECTRIC STIMULATION (tES)

Common principles

- Low intensity currents (~2 mA) applied to the scalp
- Safety
- Online effects and after-effects

tDCS

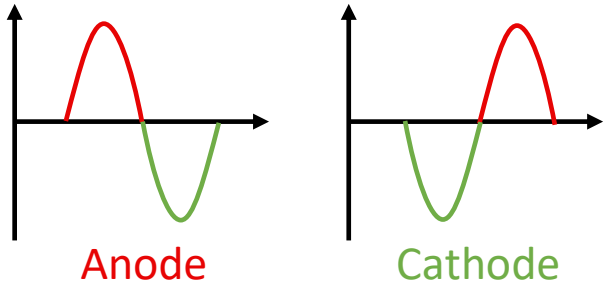
transcranial direct current stimulation



Excitation Inhibition

tACS

transcranial alternating current stimulation



Entrainment

TRANSCRANIAL DIRECT CURRENT STIMULATION (tDCS)

- **Proof of concept**
  - n=10
  - titration (sham, 1 mA, 2 mA)
  - left dorsolateral prefrontal (DLPFC) or precentral cortex
  - 4/10 patients improved

ORIGINAL ARTICLE

Transcranial Direct Current Stimulation Effects in Disorders of Consciousness

Angelakis, ACRM 2014

- **First randomized double-blind study**
  - n = 55 patients
  - One session 2 mA session L-DLPFC
  - 13/30 MCS and 2/25 VS/UWS improved

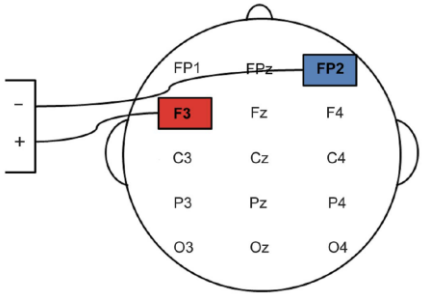
tDCS in patients with disorders of consciousness

Sham-controlled randomized double-blind study

Thibaut, Neurology 2014

Table 2 Treatment effects (i.e., change in CRS-R total score) for patients in VS/UWS and MCS

	Difference tDCS – sham	Median	p 25	p 75	p Value
VS/UWS	0.3 ± 1.4	0	0	0	0.952
MCS	1.6 ± 2.5	1.5	0	4	0.003



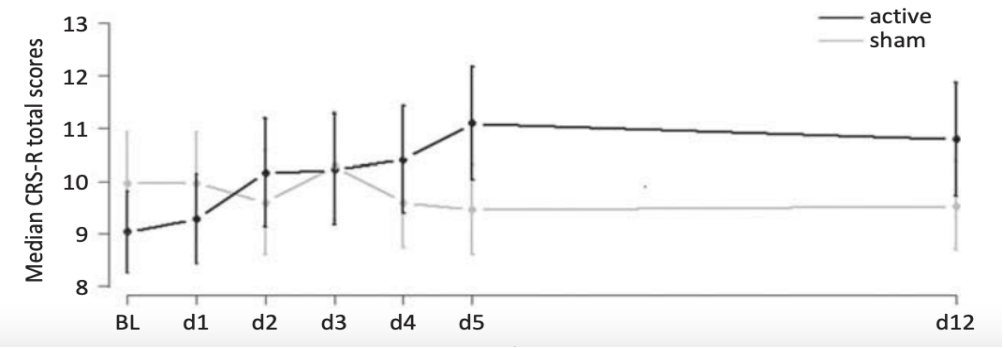
TRANSCRANIAL DIRECT CURRENT STIMULATION (tDCS)

- **Repeated sessions**

ORIGINAL ARTICLE

Controlled clinical trial of repeated prefrontal tDCS in patients with chronic minimally conscious state

Aurore Thibaut[a,b], Sarah Wannez[a], Anne-Francoise Donneau[c], Camille Chatelle[a,d], Olivia Gosseries[a], Marie-Aurélie Bruno[a], and Steven Laureys[a]

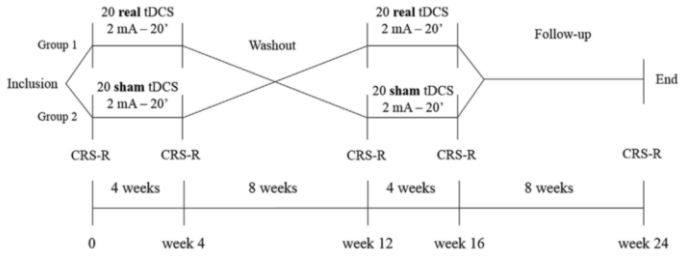


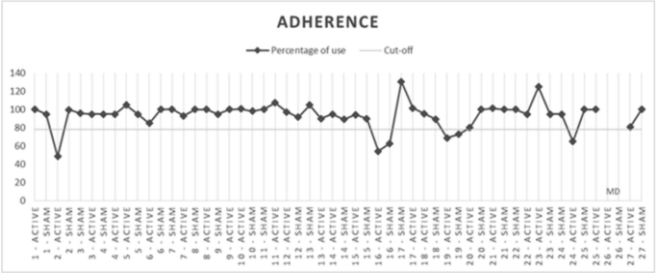
Thibaut, Brain Inj 2017

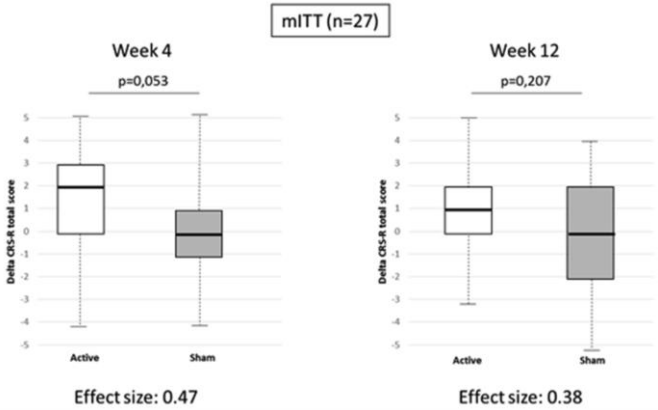
- **Home-based 4-weeks tDCS**

Randomized controlled trial of home-based 4-week tDCS in chronic minimally conscious state

Géraldine Martens, MSc [a, *], Nicolas Lejeune, MD [a, b], Anthony Terrence O'Brien, MD [c], Felipe Fregni, MD, PhD [c], Charlotte Martial, MSc [a], Sarah Wannez, MSc [a], Steven Laureys, MD, PhD [a, **, 1], Aurore Thibaut, PhD [a, c, 1]







Martens, Brain Stim 2018

SUMMARY: tDCS STUDIES IN DOC ON BEHAVIOR

Single-session

- *Thibaut et al., Neurology 2014 (n=55)*
- *Bai et al., Neuroimage Clinical 2017 (n=17)*
- *Bai et al., Int J Neurosci 2018 (n=18)*

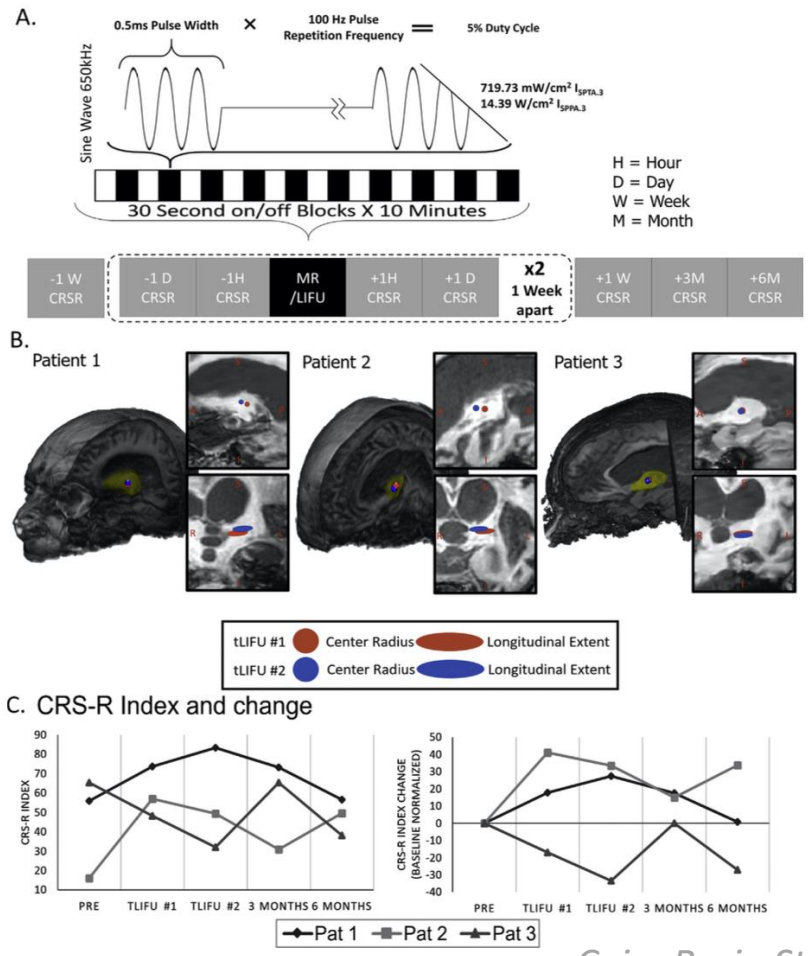
Repeated sessions

- *Angelakis et al., ACRM 2014 (n=10)*
- *Thibaut et al., Brain Injury 2017 (n=16)*
- *Estraneo et al., J Neurol Sci 2017 (n=13)*
- *Zhang et al., Front Neurol 2017 (n=26)*
- *Martens et al., Brain Stim 2018 (n=27)*
- *Cavinato et al., Clin Neurophysiol 2019 (n=24)*
- *Wu et al., Neural Plast 2019 (n=10)*
- *Martens, NeuroImage Clinical 2020 (n=46)*

- Best evidence to date, but still some inconsistent restults
- MCS > VS/UWS
- Transient improvement
- Repeated > single sessions
- Most studies with prefrontal stimulation

OTHER STIMULATION TOOLS ?

Focused ultrasounds



Cain, Brain Stim 2021

Towards other minimally- or non-invasive brain stimulation tools ?

Olfactory nerve stimulation ?

From Nose to Brain: Un-Sensed Electrical Currents Applied in the Nose Alter Activity in Deep Brain Structures

Weiss, Cereb Cortex 2016

EXPLAINING THE HETEROGENEITY OF TREAMENT EFFECT

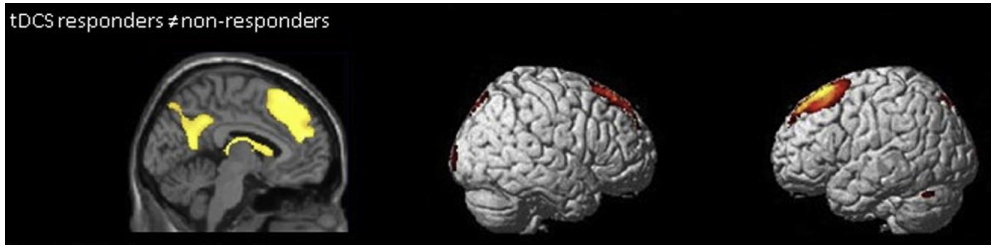
Many factors influence treatment effects and notably NIBS

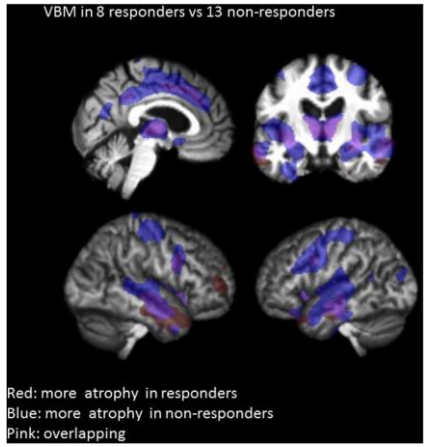
tES-specific

- Number of session
- Site
- Montage
- Intensity
- Duration

Non-specific

- Task
- Drugs (Ca2+ & Na-channel blocker ?)
- Genetic (BDNF)
- **Brain networks and structural anatomy**

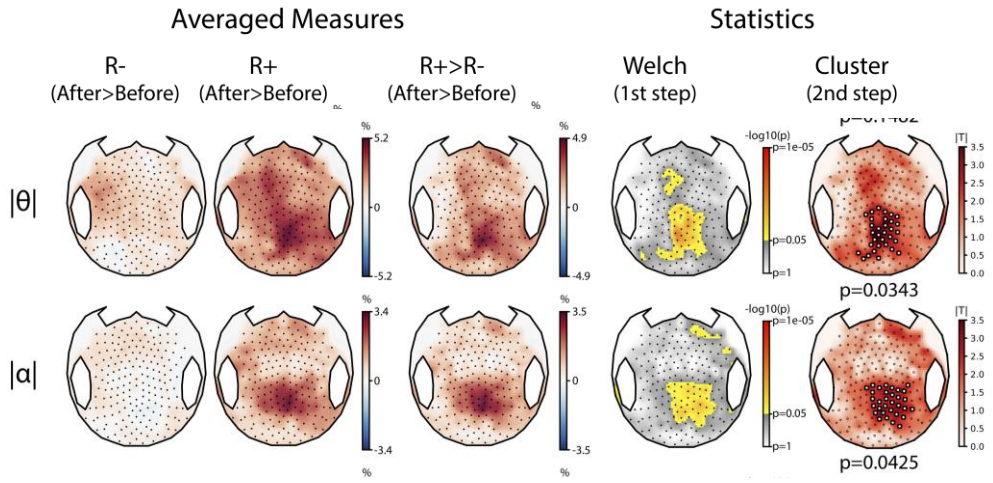


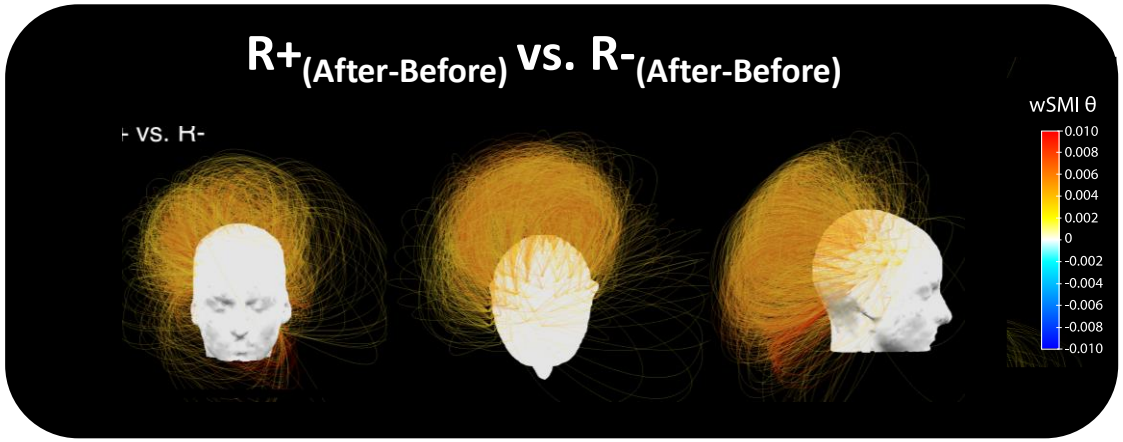


Thibaut, Brain Stim 2018

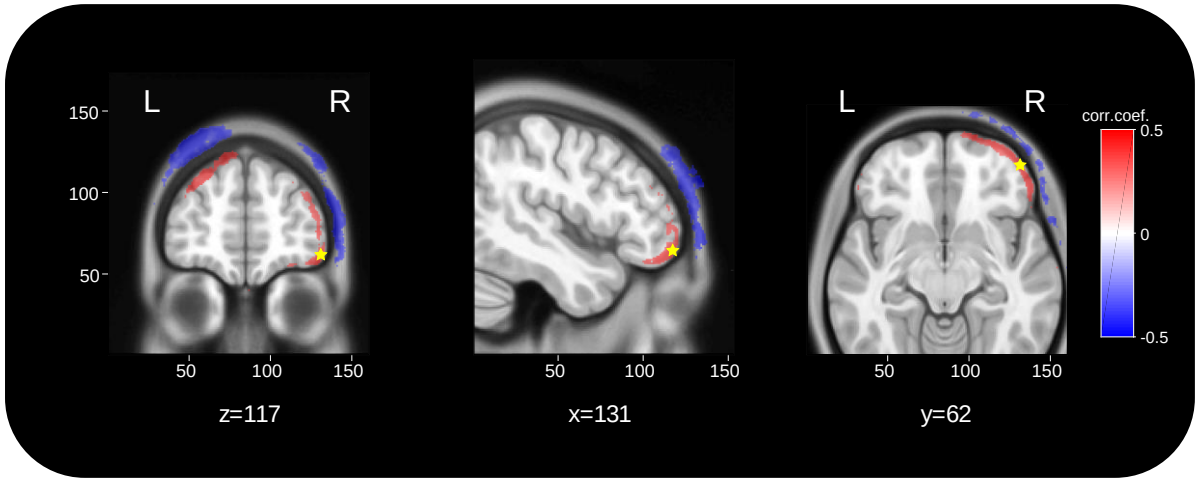
BRAIN ACTIVITY & RESPONSE TO tDCS

Spectral power & connectivity





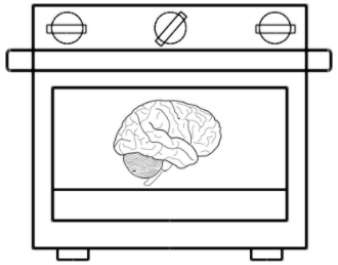
Electric fields modeling



Hermann, Scientific Reports 2020

TOWARDS INDIVIDUALIZED STIMULATION

Modeling of electric fields



Realistic,
v**O**lumetric **A**pproach
to **S**imulate **T**ranscranial
electric stimulation

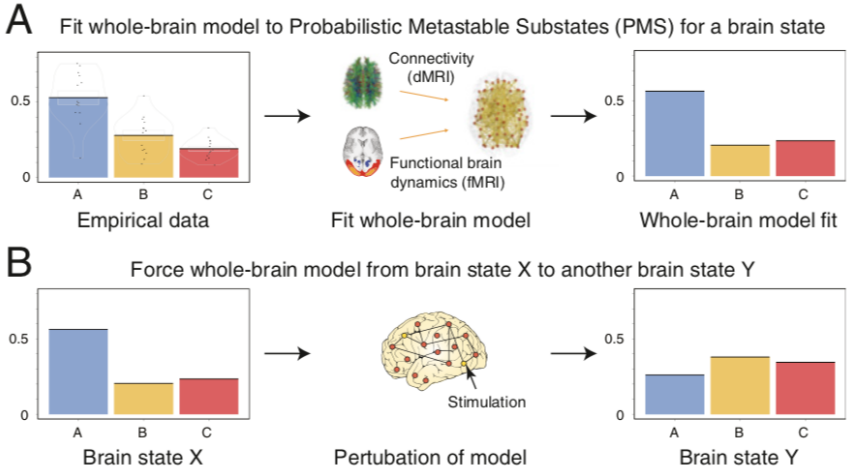
Huang et al., J Neural Eng 2019

Measures of brain activity during stimulation

Whole-brain modeling & simulation of brain-state transition

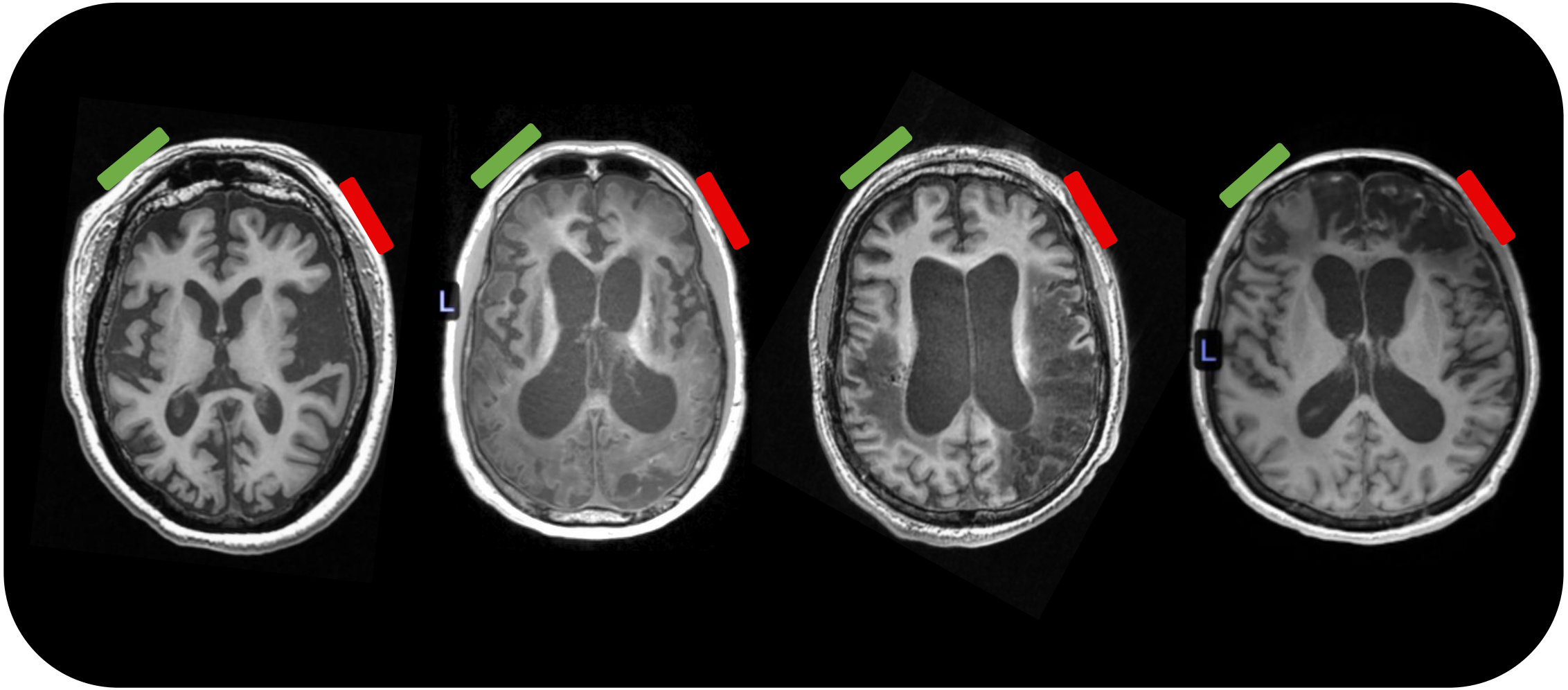
Awakening: Predicting external stimulation to force transitions between different brain states

Gustavo Deco[a,b,c,d,e,1], Josephine Cruzat[a,b], Joana Cabral[f,g,h], Enzo Tagliazucchi[i,j], Helmut Laufs[j,k], Nikos K. Logothetis[l,m,1], and Morten L. Kringelbach[f,g,h,1]

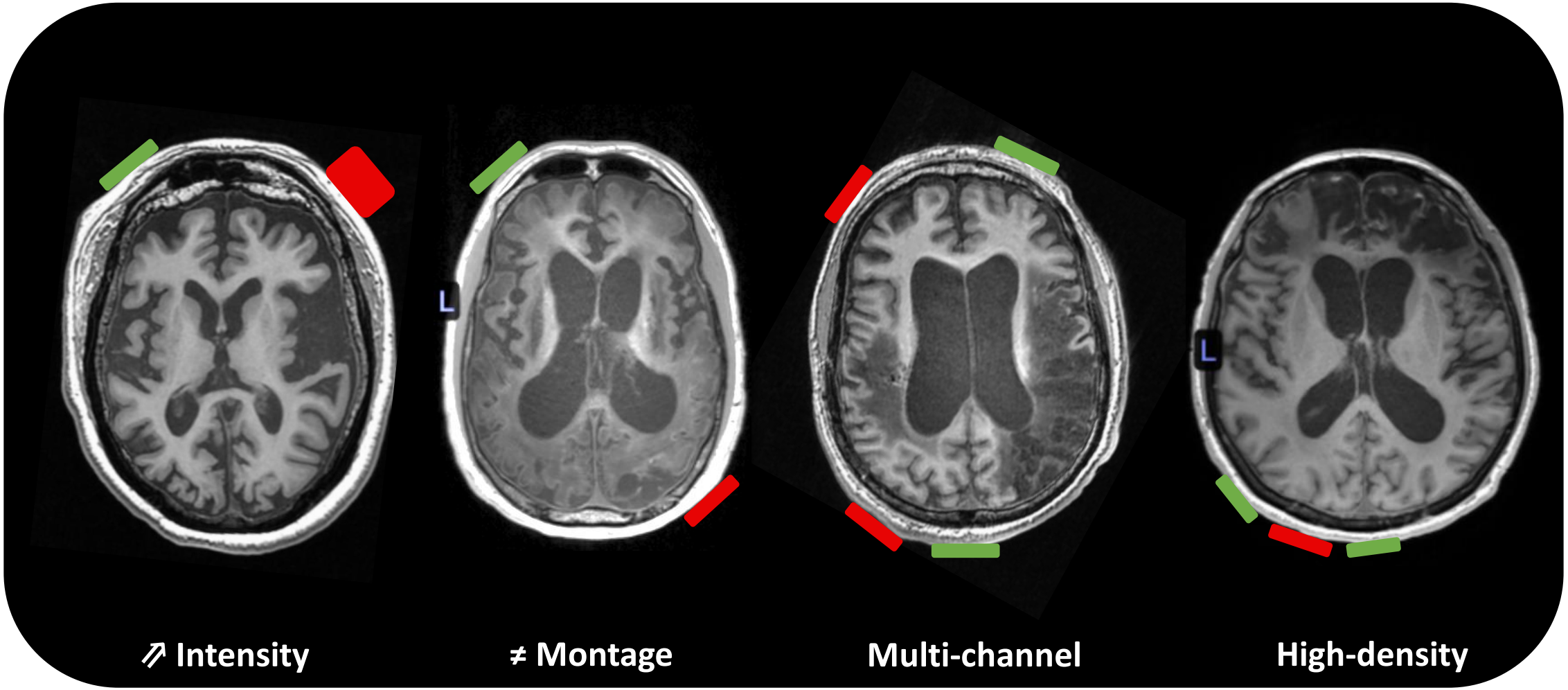


Deco, PNAS 2019

FROM ONE-SIZE-FITS-ALL….



… TO PERSOLANIZED STIMULATION !



TAKE-HOME MESSAGE

- **The only recommended treatment in DoC is Amantadine in TBI**
- **No guidelines for other treatments**
- **Zolpidem should (probably) be tested in all chronic DoC patients**
- **Most promising treatment so far is transcranial direct current stimulation (tDCS)**
  - MCS > UWS / Repeated sessions / Left dorsolateral prefrontal cortex
- **Need to understand (and reduce) treatment effects heterogeneity**
  - Investigate treatment effects through measures of brain activity
  - Personalized stimulation
  - Minimally invasive stimulation ? (VNS, FUS, …)

Journée EVC-EPR 2023

État Végétatif Chronique et État Pauci-Relationnel

Merci pour votre attention

MÉDECINE PARIS CENTRE
Santé
Université de Paris

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS
AP-HP. Centre Université de Paris

Inserm
La science pour la santé
From science to health

SUMMARY: tDCS STUDIES IN DOC ON BEHAVIOR

Study	Design/ Control	Population	Stimulation parameters	Behavioral effect	Electrophysiological effect	Side effects
Angelakis et al., 2014	Prospective/ Sham	10 patients (7 VS/UWS, 3 MCS)	5 sessions (20 min) of sham, 1 and 2 mA anodal L-DLPFC or L-SMC tDCS (F3/C3- Fp2; 25 cm2-35cm2)	CRS-R increase in the 3 MCS patients	Not assessed	None
Thibaut et al., 2014	Cross-over RCT/ Sham	55 patients (25 VS/UWS, 30 MCS)	Single session (20 min) of 2 mA anodal L-DLPFC tDCS (F3-Fp2; 35 cm^2)	Significant increase of CRS-R only in MCS patients.	Not assessed	None
Naro et al., 2015a	Cross-over RCT/ Sham	25 patients (12VS/UWS, 10 MCS, 2 EMCS)	Single session (10 min) of 1 mA anodal orbito-frontal cortex (Fp-Cz; 25–35 cm^2)	No effect	Changes in M1 excitability and premotor-motor connectivity in some DoC patients assessed by TMS	None
Naro et al., 2016b	Cross-over RCT/ Sham	20 patients (10 VS/UWS and 10 MCS)	Single session (20 min) of 2 mA cerebellar 5 Hz oscillatory tDCS (medial cerebellum-left buccinator muscle; 16 cm^2)	Improvement of CRS-R in MCS patients.	Increase in fronto-parietal coherence and power in theta and gamma band in MCS patients	None
Bai et al., 2017	Cross-over RCT/ Sham	18 patients (9 VS/UWS, 9 MCS)	Single session (20 min) of 2 mA anodal L-DLPFC (F3-Fp2; 25 cm^2)	No effect	Changes in cortical excitability assessed by TMS-EEG	Not reported
Bai et al., 2017	Cross-over RCT/ Sham	17 patients (9 VS/UWS, 8 MCS)	Single session (20 min) of 2 mA anodal L-DLPFC (F3-Fp2; 25 cm^2)	No effect	Increase fronto-parietal coherence in the theta band in MCS	Not reported
Zhang et al., 2017	Parallel RCT/ Sham	26 patients (11 VS/UWS, 15 MCS)	20 sessions (20 min) of 2 mA anodal L-DLPFC (F3-Fp2; 35 cm2) over 10 consecutive days	Significant improvement in CRS-R in MCS patients	Increased P300 amplitude in MCS during an auditory oddball paradigm	None
Thibaut et al., 2017	Cross-over RCT/ Sham	16 patients (all MCS)	5 sessions (20 min) of 2 mA anodal L-DLPFC (F3-Fp2; 35 cm^2) over 5 days	Significant improvement of CRSR [in 9/16 (56%)] at 5 days, persisting at 12 days.	Not assessed	None
Huang w. et al., 2017	Cross-over RCT/ Sham	27 patients (all MCS)	5 sessions (20 min) of 2 mA anodal posterior parietal cortex tDCS (Pz-Fp2; unknown)	Significant improvement of CRS-R after 5 days of stimulation, but no persistence at 10 days.	Not assessed	None
Estraneo et al., 2017	Cross-over RCT/ Sham	13 patients (7 VS/UWS, 6 MCS)	5 sessions (20 min) of 2 mA anodal L-DLPFC F3-Fp2; 35 cm^2) over 5 days	No effect on CRS-R after single or repeated sessions	Improvement of background rhythm in some patients	None
Martens et al., 2018	Cross-over RCT/ Sham	27 patients (all MCS) in rehabilitation facilities or at home.	20 sessions (20 min) of 2 mA anodal L-DLPFC F3-Fp2; 35 cm^2) over 4 weeks	No significant effect, but trend toward CRS-R improvement after 4 weeks, lasting at 12 weeks	Not assessed	One epileptic seizure

Bourdillon, Hermann* et al., Front Neurosci 2019*