Management of severe brain injury: focus on neurobehavioral diagnosis and neuromodulation

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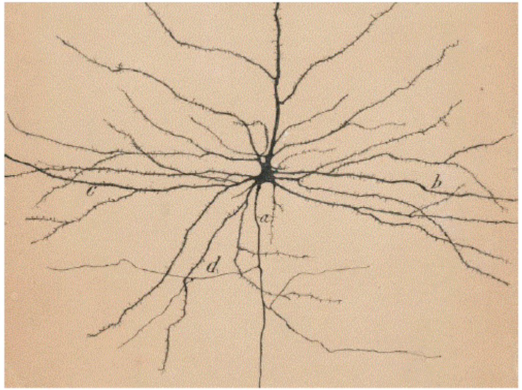
LIÈGE université

Under the supervision of
Prof Steven LAUREYS,
Coma Science Group,
GIGA-Consciousness

LIÈGE université GIGA Consciousness

NON-INVASIVE BRAIN STIMULATION IN POST-COMATOSE STATES

Géraldine Martens



THESE PRESENTEE EN VUE DE L'OBTENTION DU GRADE DE

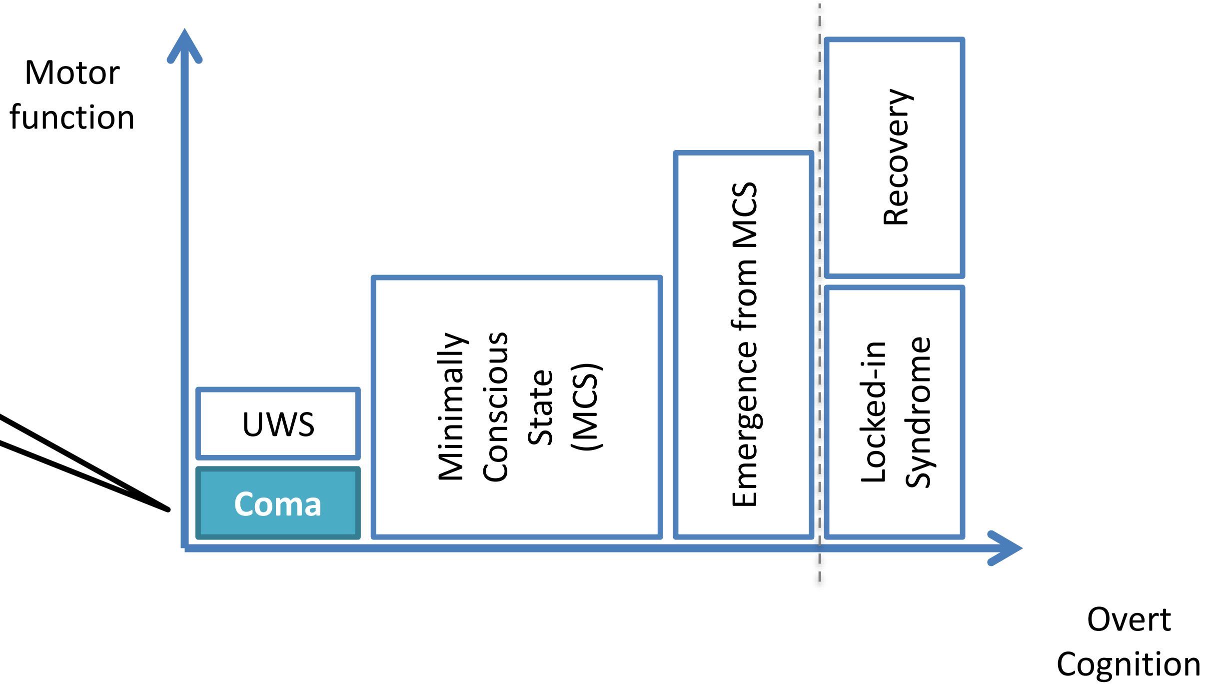
Docteur en Sciences de la Motricité

Année académique 2019-2020

Disorders of Consciousness (DOC)

- After severe brain injury (traumatic, vascular, anoxic…)
- Several clinical entities

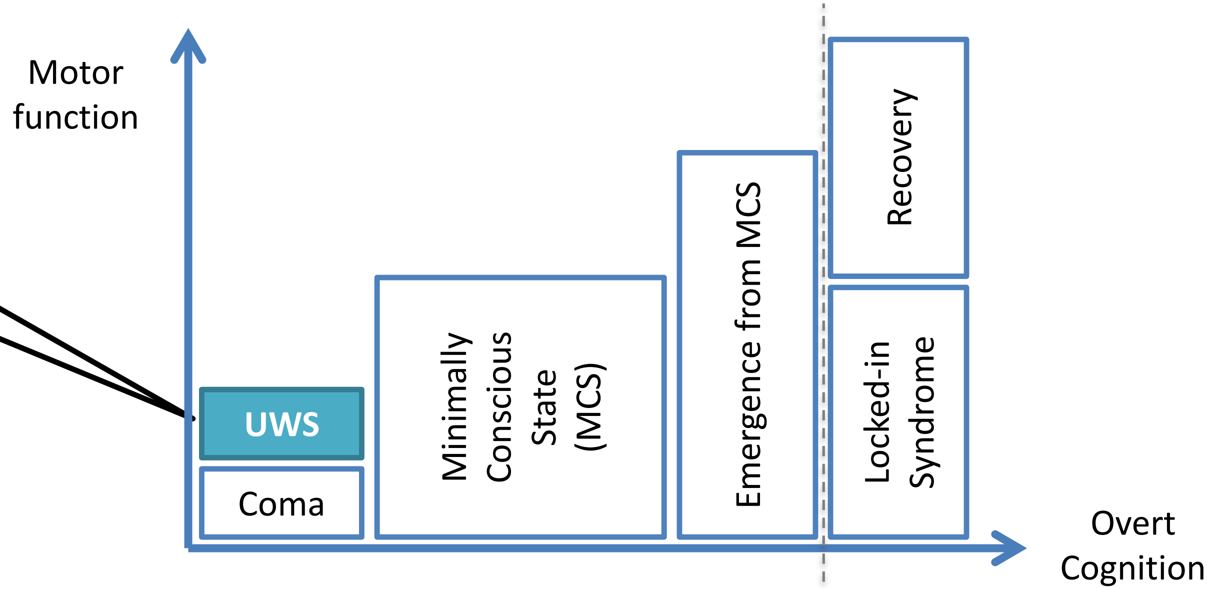
Coma
No eye-opening
Reflex behaviors



Edlow et al. (2017)

Disorders of Consciousness (DOC)

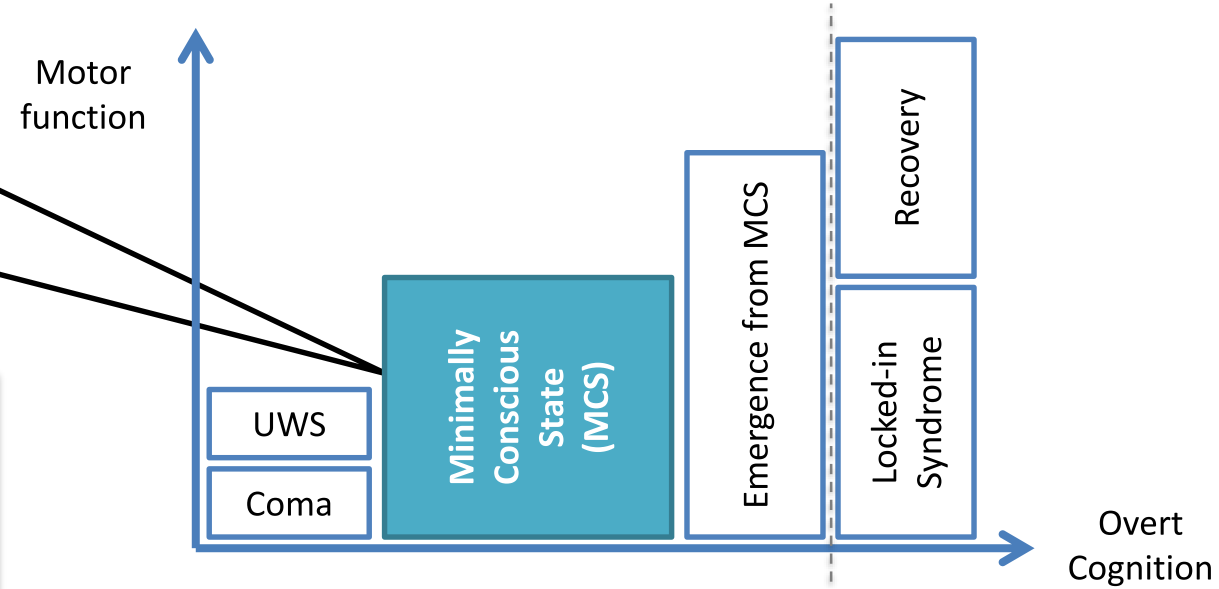
Unresponsive Wakefulness Syndrome
Eye-opening
Reflex behaviors



Edlow et al. (2017)

Disorders of Consciousness (DOC)

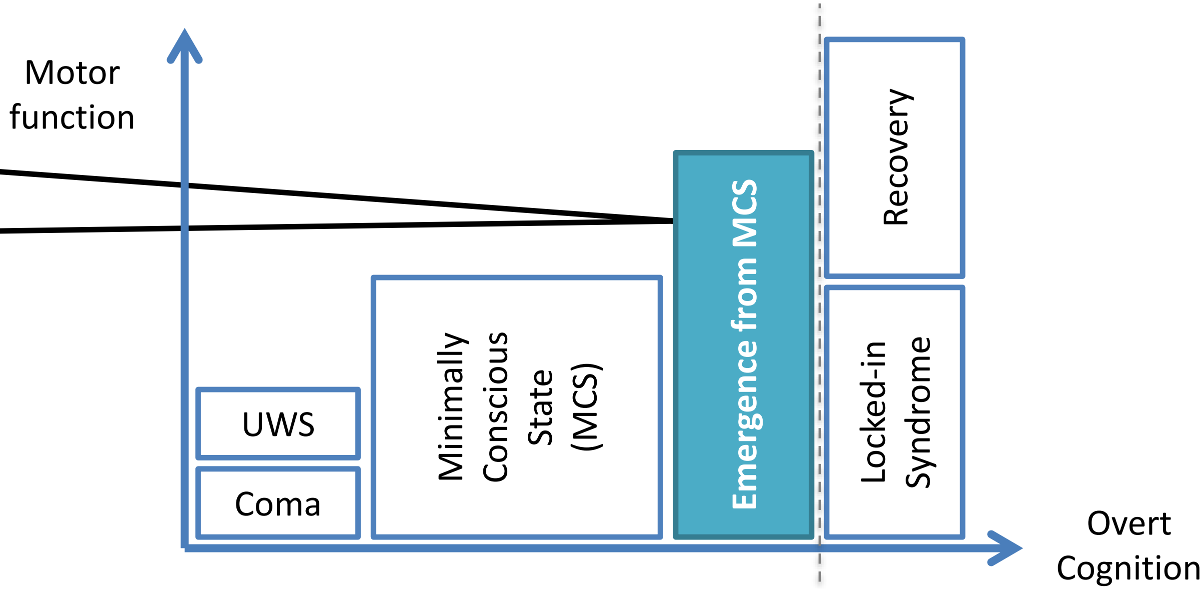
Minimally Conscious State
Non-reflex behaviors (signs of consciousness)
MCS+: language-related
MCS-: not language-related



Edlow et al. (2017)

Disorders of Consciousness (DOC)

Emergence
Functional object use
Functional communication



➔ 40% misdiagnosis rate

Schiff (2010)

Diagnosis: bedside

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

JFK COMA RECOVERY SCALE - REVISED ©2004

- Current gold standard for DOC

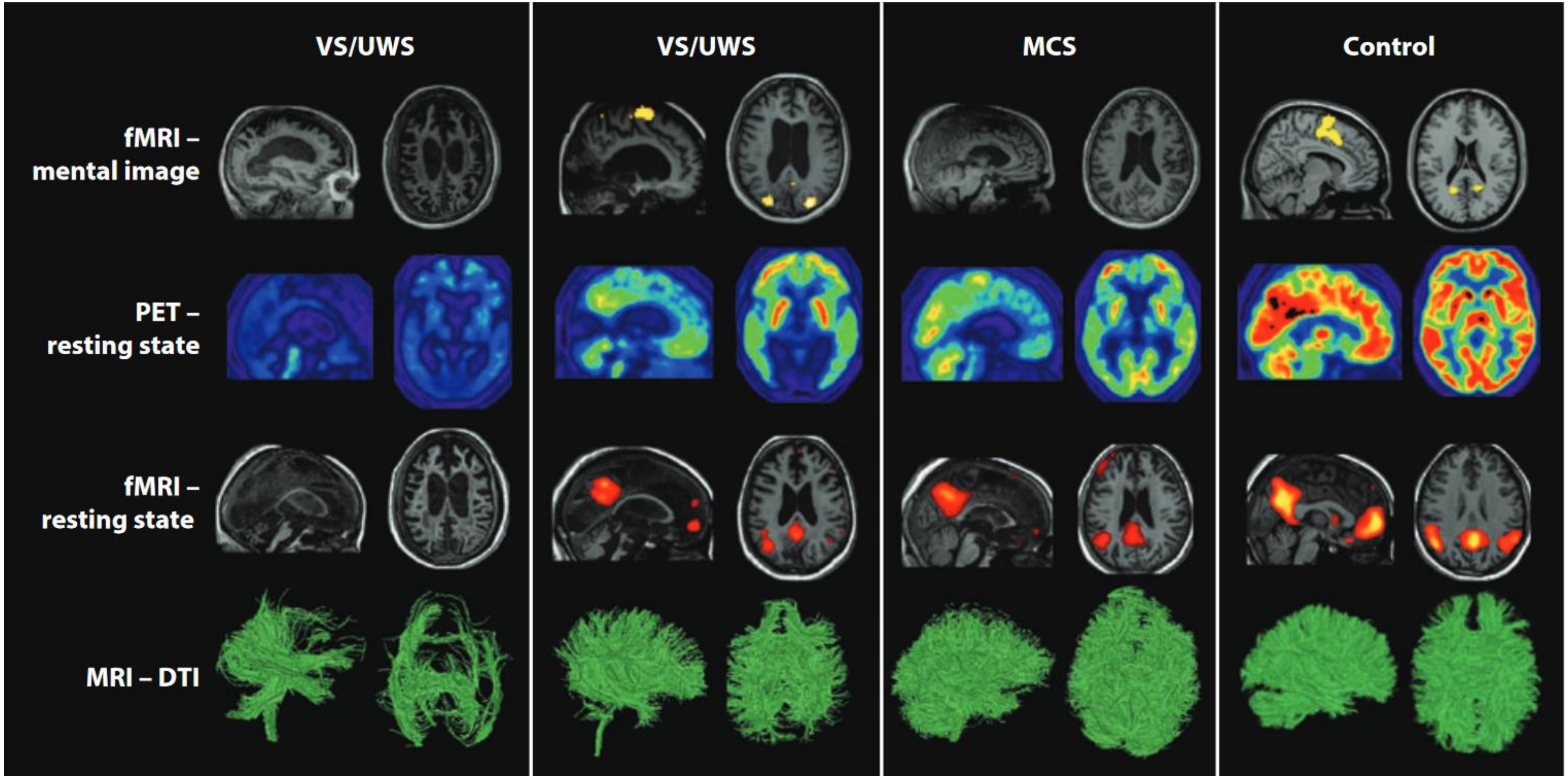
OROMOTOR/VERBAL FUNCTION SCALE
3 - Intelligible Verbalization *
2 - Vocalization/Oral Movement
1 - Oral Reflexive Movement
0 - None
COMMUNICATION SCALE
2 - Functional: Accurate †
1 - Non-Functional: Intentional *
0 - None
AROUSAL SCALE
3 - Attention
2 - Eye Opening w/o Stimulation
1 - Eye Opening with Stimulation
0 - Unarousable

Denotes emergence from MCS†

Denotes MCS *

Giacino et al. (2004)
Seel et al. (2010)

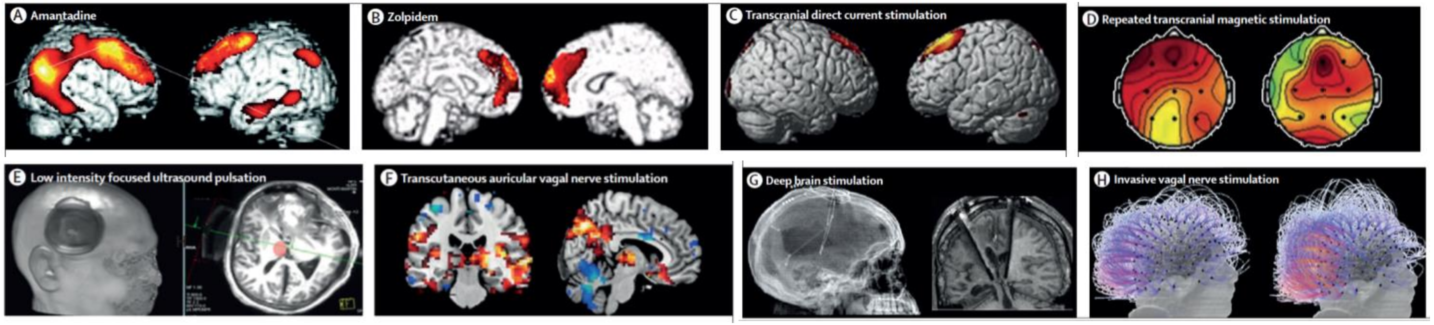
Diagnosis: neuroimaging



Gosseries et al. (2014)

Treatment options

- Conventional **rehabilitation**: physical/occupational/speech/music therapies
- **Pharmacological**: amantadine, zolpidem, apomorphine…
- **Neurostimulation**: deep brain stimulation (surgical), vagal nerve stimulation (surgical), repeated transcranial magnetic stimulation
- **Neuromodulation**: transcranial direct/alternating/pulsed current stimulation, focused ultrasound pulsation, transauricular vagal nerve stimulation



Thibaut et al. (2019)

Treatment options

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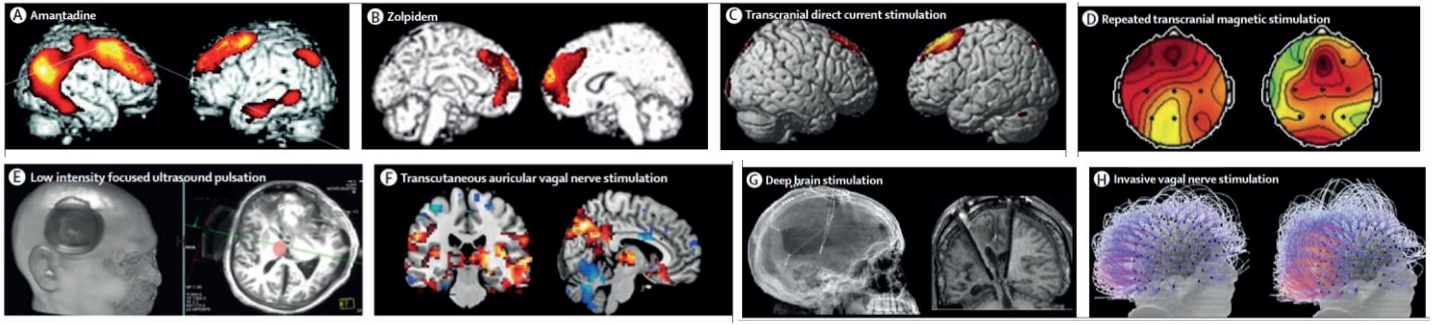


Thibaut et al. (2019)

Transcranial direct current stimulation (tDCS)

- Modulates neural excitability using low density direct current (1 – 2 mA)

➔ *Membrane polarization*

Anode: ↗ excitability

Cathode: ↘ excitability

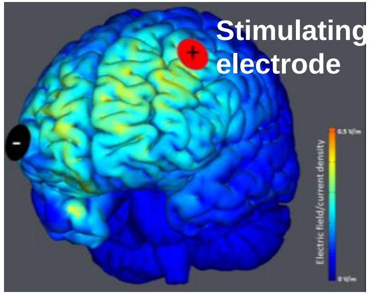
➔ *Long term effects*

Neural excitability & plasticity (LTP-LTD)

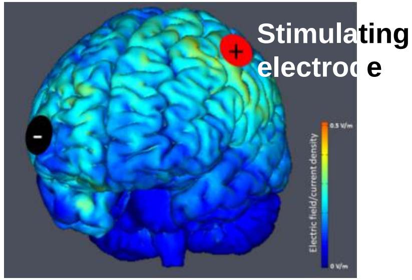
Ion channels (Na^+, Ca^{2+})

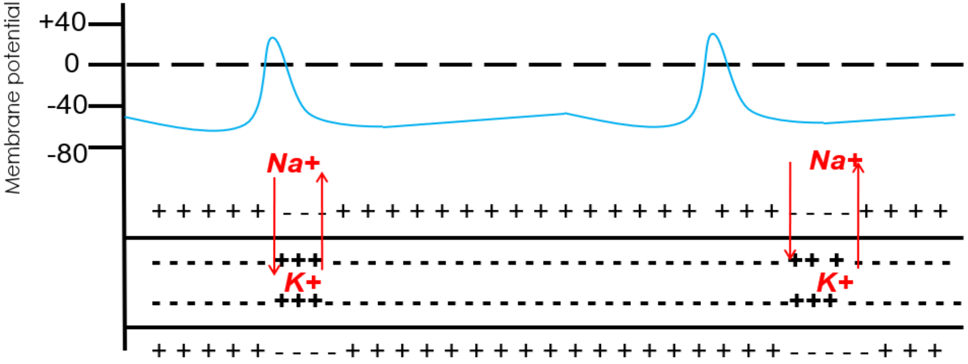
NMDA receptors

Prefrontal stimulation



Motor stimulation

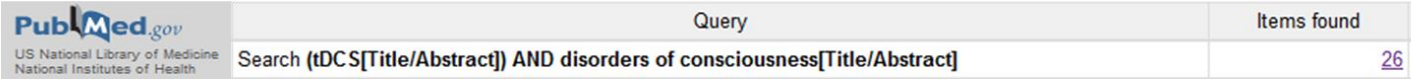




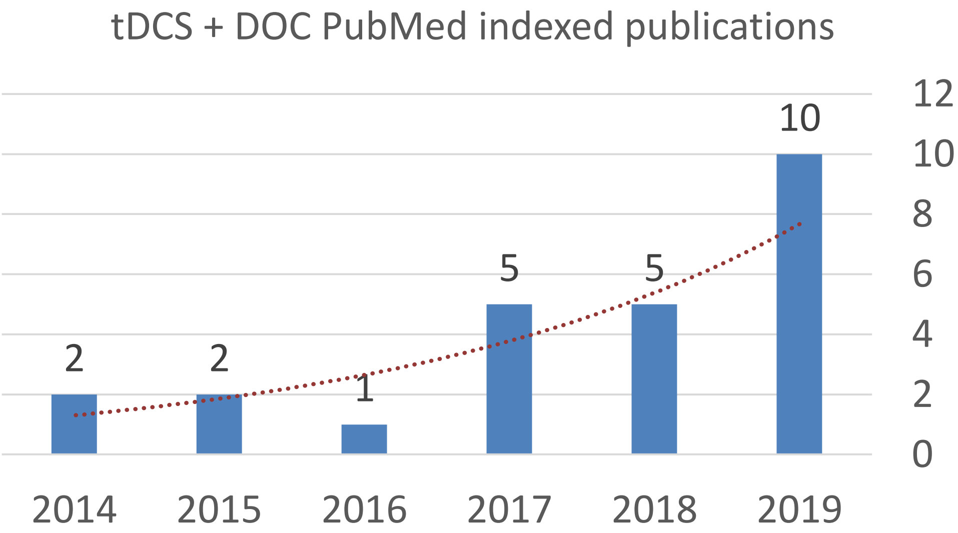
Nitsche et al. (2010)
Thibaut et al. (2014)

tDCS for DOC?

- Indications in pain, depression; used in stroke, Parkinson, Alzheimer
- Easy to apply, safe, painless, affordable, reliable **sham** condition



02/2020



Fregni et al. (2007)
Nitsche et al. (2009)
Elsner et al. (2016)
Boggio et al. (2006)
Ferrucci et al. (2008)

tDCS for DOC?

- Significantly increases level of consciousness (CRS-R total score)
- **Left dorsolateral prefrontal cortex** (DLPFC)
- More responders in MCS population
- Repeated sessions (5) more efficient & well tolerated

Thibaut et al. (2019)
Antal et al. (2017)

Contents

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Annals of Physical & Rehabilitation Medicine
SOFMER

Original article

Which behaviours are first to emerge during recovery of consciousness after severe brain injury?

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Part 1
Diagnosis at the bedside

Study 1. Behavioral markers of consciousness recovery

Study 2. Recovery of intentional and functional communication

Part 2
tDCS as a treatment

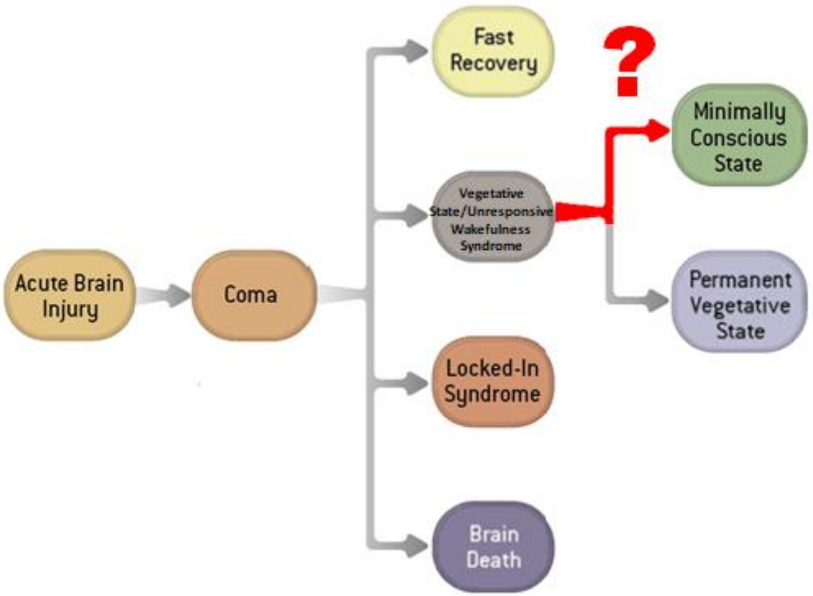
Study 3. Home-based long term tDCS

Study 4. Motor tDCS

Study 5. Multifocal frontoparietal tDCS

Study 1: Objectives

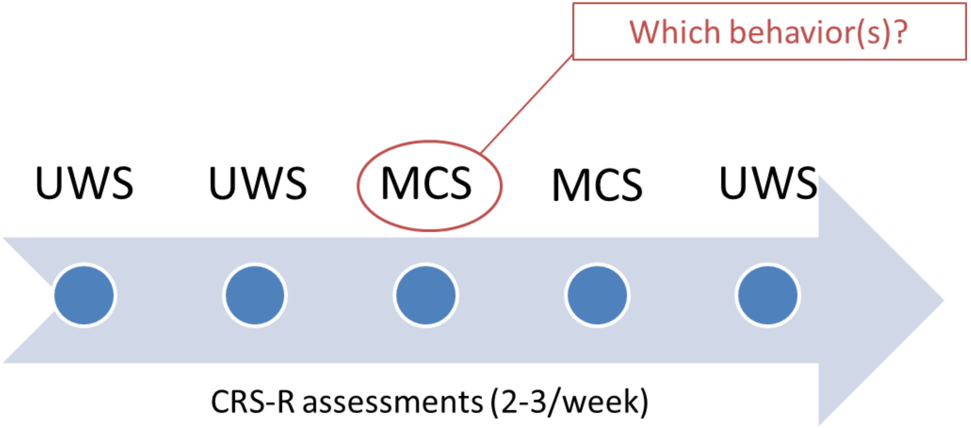
- Estimate the **time course** to recovery of consciousness in the subacute phase
- Determine which behavioral signs of consciousness are first to emerge at **transition** from unconscious (coma, UWS) to conscious (MCS, EMCS) states



Laureys (2007)

Study 1: Methods

- Retrospective observational study
- Patients admitted unconscious (coma/UWS); transitioned to consciousness (MCS/EMCS) *during their rehab stay*

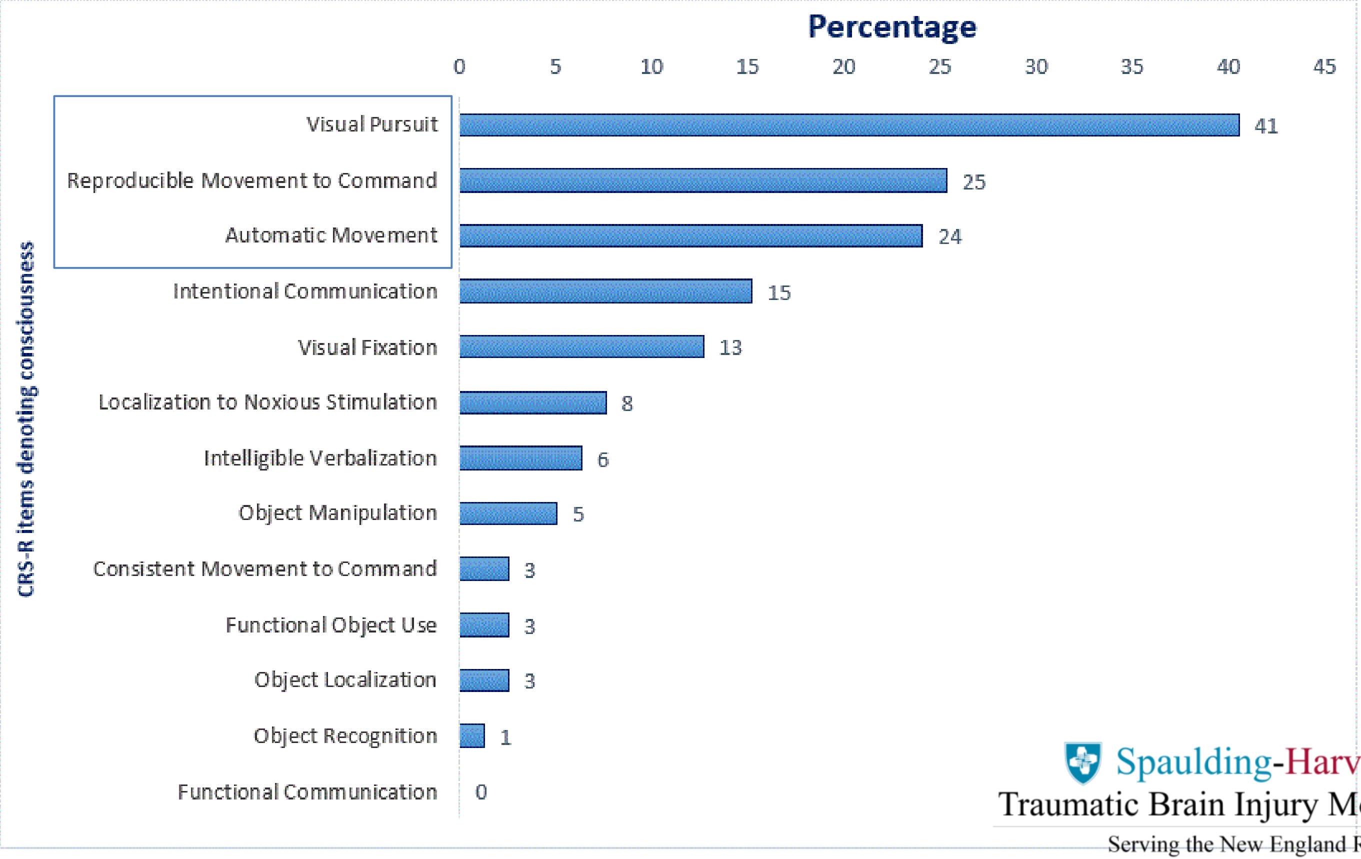


Study 1: Results

	TBI	Non-TBI	TBI and Non-TBI	TBI vs non-TBI comparison
N (male)	34 (25)	45 (26)	**79** (51)	p=0.705 [b]
Age	33 [a] [23 – 53]	57 [33 – 64]	48 [25.5 – 61]	***p=0.002*** [c]
Days from injury to rehab admission	28.5 [20.25 – 35.5]	25 [20 – 36]	26 [20 – 36]	p=0.454 [c]
Days from injury to recovery of consciousness	41 [29 – 50]	46 [35 – 63]	44 [33 – 59]	p=0.517 [c]

[a]=Median [interquartile range]; [b]=Fisher's exact test; [c] =Wilcoxon Rank Sum test

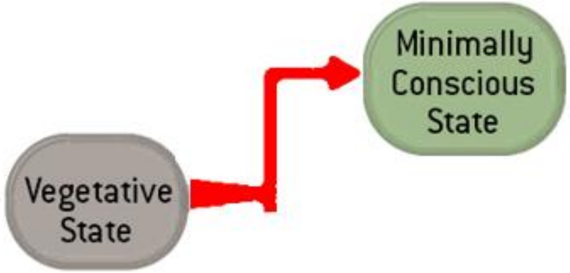
Study 1: Results



Spaulding-Harvard
Traumatic Brain Injury Model System
Serving the New England Region

Study 1: Conclusions

- Top 3 transition markers (sensitivity of assessments)
- ~6 weeks to transition (TBI & nTBI)
- Limitations: low sample size, single-site study (selection bias), retrospective analysis



Visual Pursuit
Reproducible Movement to Command
Automatic Movement

ELSEVIER
Archives of Physical Medicine and Rehabilitation
Available online 28 February 2020
In Press, Journal Pre-proof

Temporal profile of recovery of communication in patients with disorders of consciousness following severe brain injury

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2 Coma Science Group, GIGA-Consciousness, University of Liège, Liège, Belgium
3 Centre du Cerveau[2] - Centre intégré pluridisciplinaire de l'étude du cerveau, de la cognition et de la conscience, University Hospital of Liège, Liège, Belgium
4 Laboratory for Neuroimaging in Coma and Consciousness, Massachusetts General Hospital, Boston, MA

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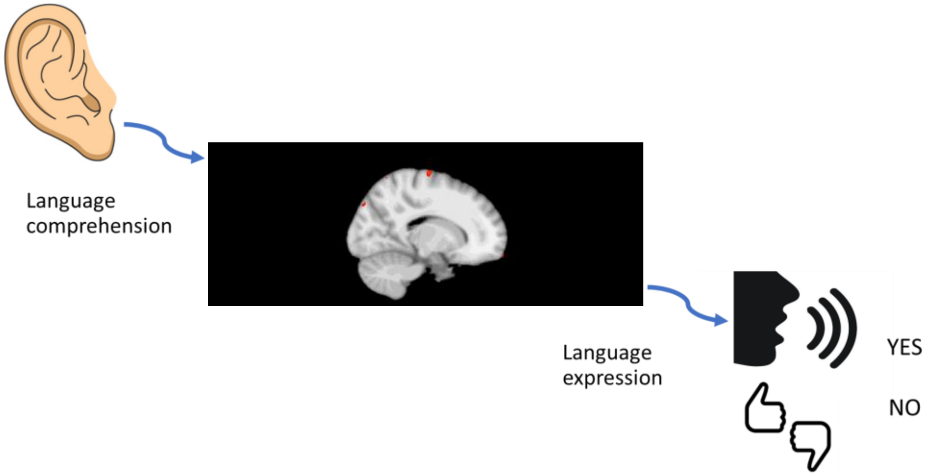
Study 2: Objectives

- Communication = critical milestone recovery trajectory
- Most valued outcome for caregivers
- Facilitates autonomy and therapeutic interventions

➔ **How long after injury?**



Binder et al. (1997)
Lee et al. (1996)

Study 2: Methods

- Characterize the time-course of recovery of **intentional** and **functional communication** after severe brain injury

COMMUNICATION SCALE
2 - Functional: Accurate †
1 - Non-Functional: Intentional *
0 - None

Denotes emergence from MCS†

Denotes MCS*

6/6 questions accurately

≤ 2/6 questions (in)accurately

- Patients admitted non-communicative, followed for 8 weeks (standardized DOC rehab program)

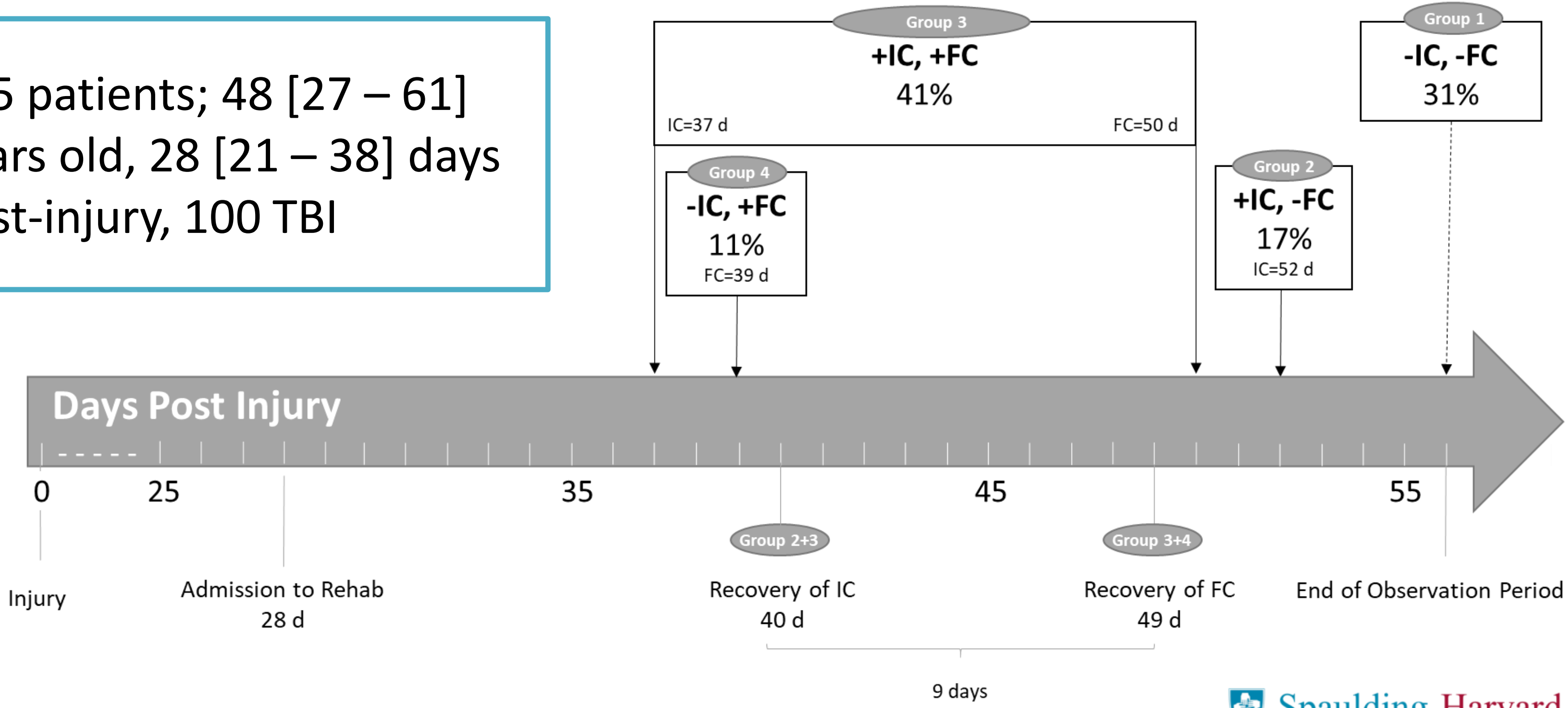
REDCap Research Electronic Data Capture

Observational retrospective

Spaulding-Harvard Traumatic Brain Injury Model System
Serving the New England Region

Study 2: Results

175 patients; 48 [27 – 61] years old, 28 [21 – 38] days post-injury, 100 TBI



IC = Intentional Communication (≤ 2/6 questions (in)accurately)
FC = Functional Communication (6/6 questions accurately)

Study 2: Conclusions

- ~70% of non-communicative patients admitted to rehab recover communication
- Potential for late recovery of communication
- May help inform clinical treatment planning and caregiver expectations
- Limitations: single-site study (selection bias), retrospective analysis

Part 1
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Brain Stimulation 11 (2018) 982–990
Contents lists available at ScienceDirect
Brain Stimulation
journal homepage: http://www.journals.elsevier.com/brain-stimulation

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]

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[b] Centre Hospitalier Neurologique William Lennox, Saint-Luc University Clinics, Université Catholique de Louvain, Belgium
[c] Neuromodulation Center, Spaulding Rehabilitation Hospital, Harvard Medical School, Boston, MA, USA

Study 3: Objectives

- Prefrontal tDCS (MCS patients) – repeat sessions

BRAIN INJURY
2017, VOL. 31, NO. 4, 466–474
http://dx.doi.org/10.1080/02699052.2016.1274776

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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-Au… and Steven Laureys[a]

[a]Coma Science Group, GIGA-research, University of Liège, Liège, Belgium; [b]Spaulding Neuromodulation Center, Spaulding Rehabil… Harvard Medical School, Boston, MA, USA; [c]Biostatistics, Department of Public Health, University of Liège, Liège, Belgium; [d]Labora… NeuroImaging of Coma and Consciousness, Massachusetts General Hospital, Boston, MA, USA

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

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

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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, Maugeri ICS, Telese Terme, Italy
[b] Neuropsychology Lab., Dept. of Psychology, Second University of Naples, Caserta, Italy

frontiers in Neurology

ORIGINAL RESEARCH
published: 21 November 2017
doi: 10.3389/fneur.2017.00620

Transcranial Direct Current Stimulation in Patients with Prolonged Disorders of Consciousness: Combined Behavioral and Event-Related Potential Evidence

Ye Zhang, Weiqun Song, Jubao Du, Su Huo, Guixiang Shan and Ran Li*

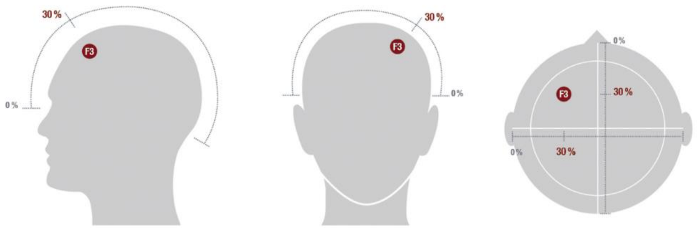
Department of Rehabilitation Medicine, Xuan Wu Hospital, Capital Medical University, Beijing, China

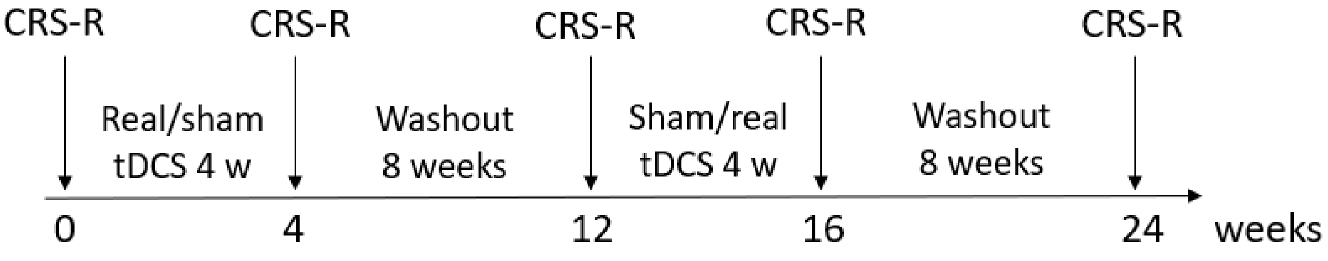
- Increase the amount of sessions, tackle transportation issues

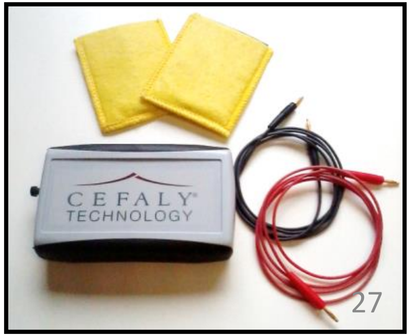
➔ Investigate **behavioral effects**, **safety** and **feasibility** of **long term home-based prefrontal tDCS**

Study 3: Methods

- Chronic MCS patients at home or in rehabilitation facilities
- Relatives/caregivers training
- tDCS lDLPFC 20 min 2 mA 5x/week



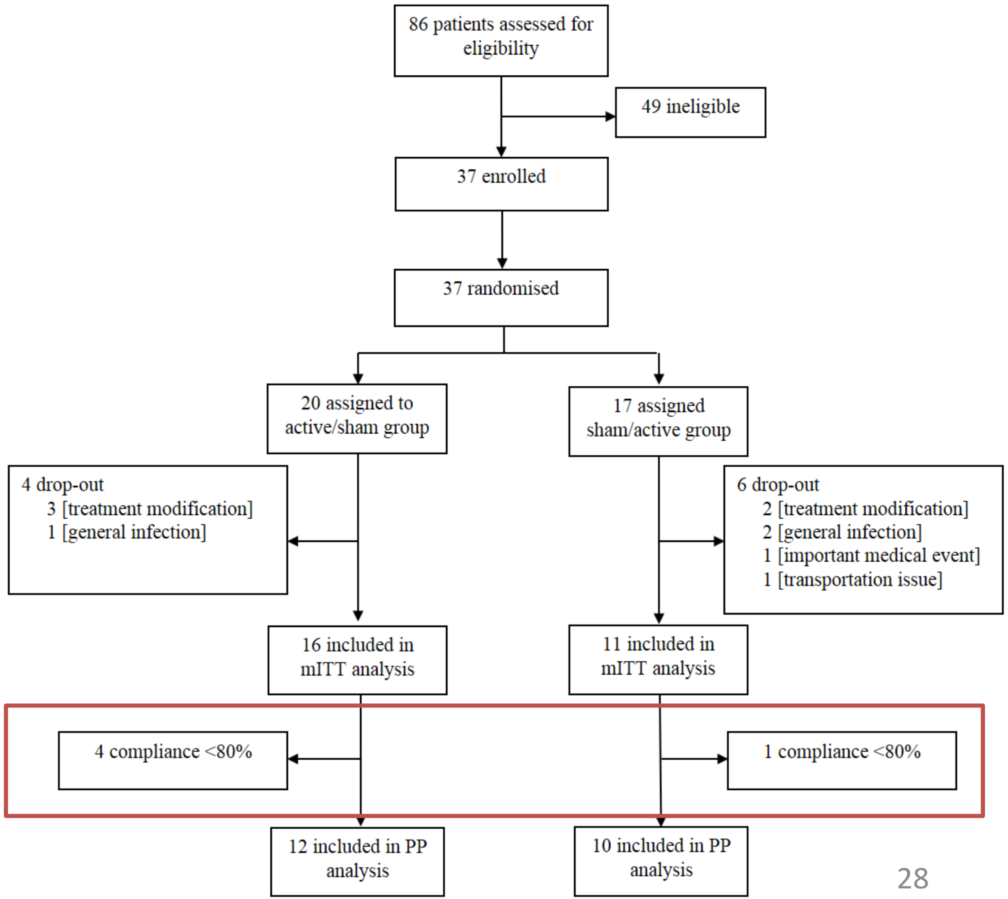




Double-blind crossover sham controlled

Study 3: Results

- Compliance: 93±14%
- 5 patients compliance <80%
- Modified Intention To Treat (mITT) analysis: 27 patients
- Per Protocol (PP) analysis: 22 patients



Thibaut et al. (2017)

Study 3: Results

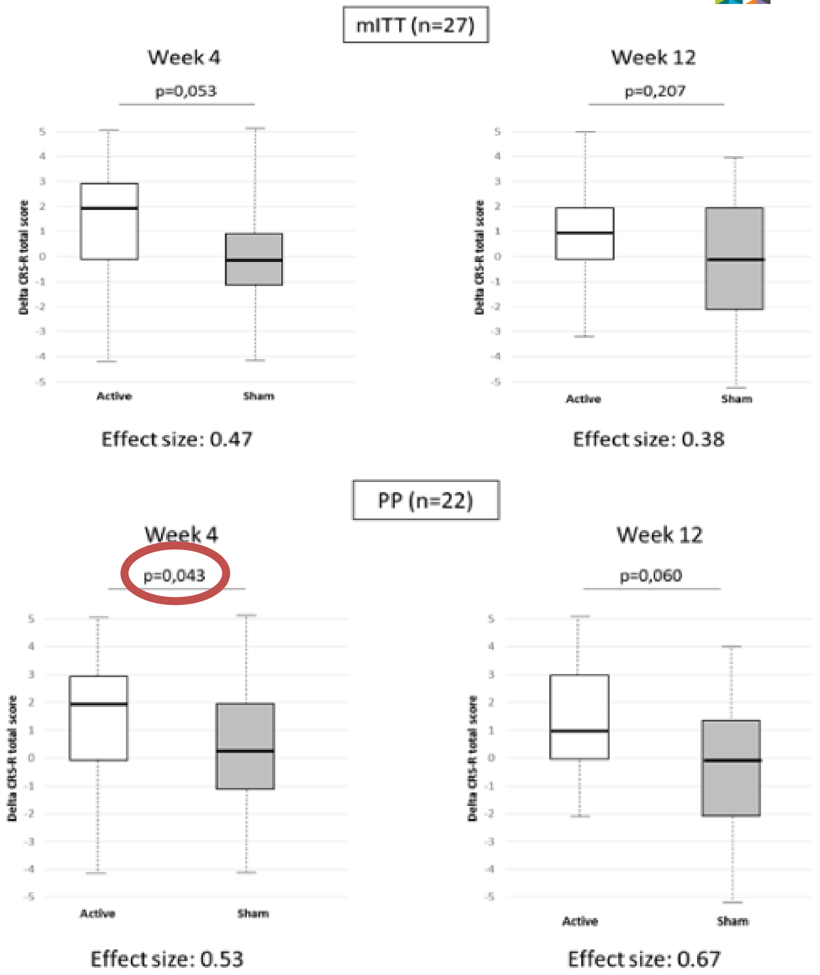
- 27 chronic MCS patients completed the study (mITT)

CRS-R: Trend for treatment effect

- 22 MCS patients received ≥80% tDCS sessions (PP)

CRS-R significant treatment effect
& trend at 8-week follow-up

- Safety: no severe adverse event reported



Wilcoxon Matched Paired tests

Study 3: Conclusions

- Home-based long term prefrontal tDCS efficient to improve behavioral responsiveness in chronic MCS
- Need for continuous neuromodulation
- Feasible to train non-professionals
- Safe if complying with security guidelines for remote tDCS
- Limitations: periodic assessments, dropouts

Charvet et al. (2015)

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BRAIN INJURY
2019, VOL. 33, NOS. 13–14, 1679–1683
https://doi.org/10.1080/02699052.2019.1667537

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Check for updates

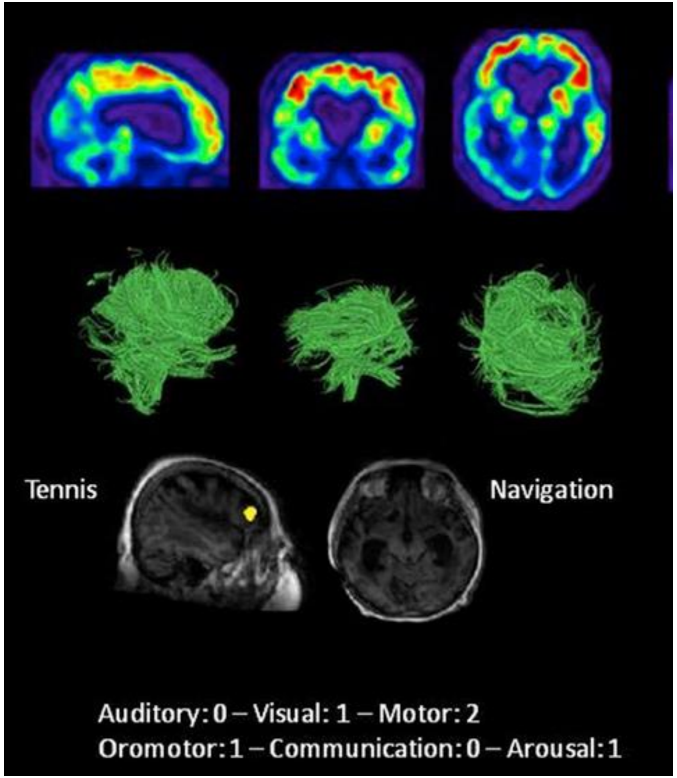
Single tDCS session of motor cortex in patients with disorders of consciousness: a pilot study

Géraldine Martens[a,b], Felipe Fregni[c], Manon Carrière[a,b], Alice Barra[a,b], Steven Laureys[a,b#], and Aurore Thibaut[a,b,c#]

[a]Coma Science Group, GIGA Consciousness, University of Liege, Liège, Belgium; [b]Centre du Cerveau[2] - Centre intégré pluridisciplinaire de l'étude du cerveau, de la cognition et de la conscience, University Hospital of Liège, Liège, Belgium; [c]Harvard Medical School, Neuromodulation Center, Spaulding Rehabilitation Hospital, Boston, MA, USA

Study 4: Objectives

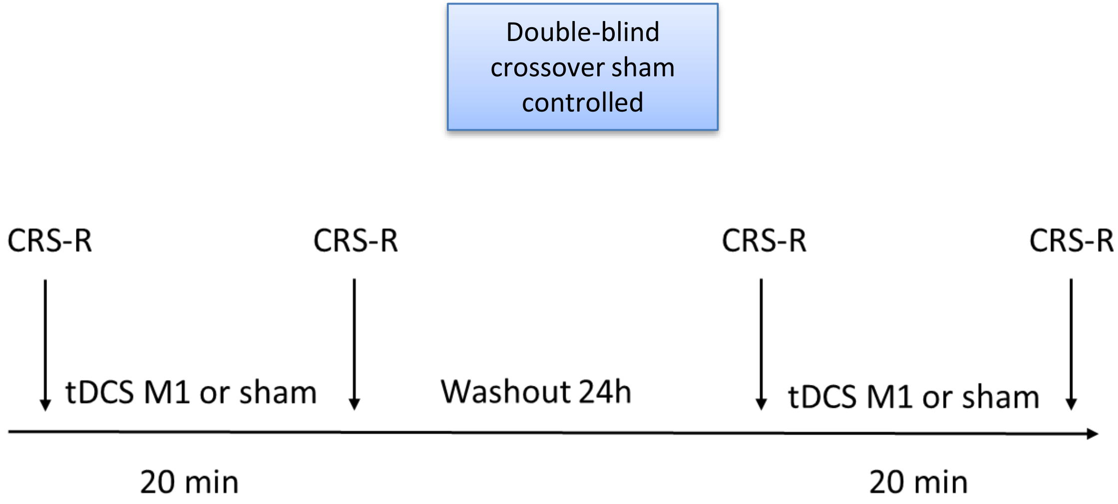
- Target **motor cortex** (consciousness ↔ motor output)
- *Cognitive motor dissociation* (CMD)
- Investigate behavioral effects (CRS-R) of **motor tDCS** in DOC
- Investigate effects on CRS-R subscales independently

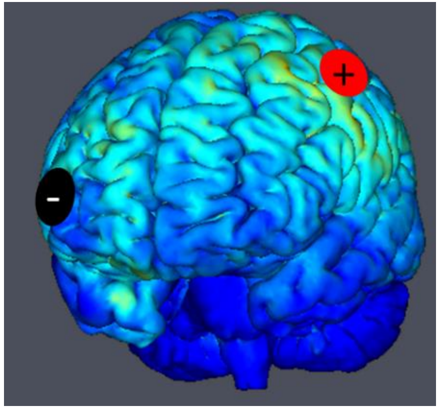


Thibaut et al. (2018)

Study 4: Methods

- Acute & chronic UWS/MCS patients
- tDCS M1 (most affected side) 20 min 2 mA 1x





Study 4: Results

10 patients; 58 [26 – 68] years old, 44 [31 – 201] days post-injury, 5 TBI; 4 UWS, 6 MCS

	CRS-R Total Score			
	Before Active	After Active	Before Sham	After Sham
Median [IQR]	6,5 [4,5 - 8,8]	7 [4,8 - 10,5]	5,5 [4,0 - 11,8]	7 [4,8 - 8,8]

Wilcoxon Matched Paired tests

- Group level: no significant improvement (no treatment effect for total score AND for each CRS-R subscale)
- Single-subject level: 2 responders (recovered object localization and visual pursuit)

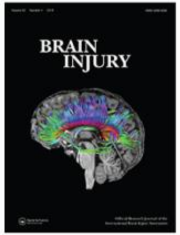
Study 4: Conclusions

- Less efficient than prefrontal tDCS
- Limitations: pilot study (small sample size), single session
- Contradictory with another open-label study in 10 chronic MCS TBI (80% responders) but bilateral anodal M1 tDCS

Bilateral M1 anodal transcranial direct current stimulation in post traumatic chronic minimally conscious state: a pilot EEG-tDCS study

Sofia Straudi, Valentina Bonsangue, Sonia Mele, Laila Craighero, Andrea Montis, Felipe Fregni, Susanna Lavezzi & Nino Basaglia ...show less

Pages 490-495 | Received 04 Mar 2018, Accepted 02 Jan 2019, Published online: 11 Jan 2019



- Needs further investigation with a priori sample size estimation and larger subgroups

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NeuroImage: Clinical 28 (2020) 102426

Contents lists available at ScienceDirect

NeuroImage: Clinical

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Behavioral and electrophysiological effects of network-based frontoparietal tDCS in patients with severe brain injury: A randomized controlled trial

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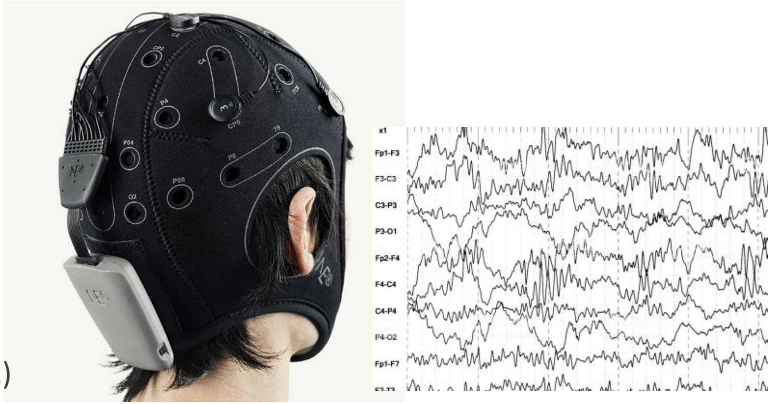
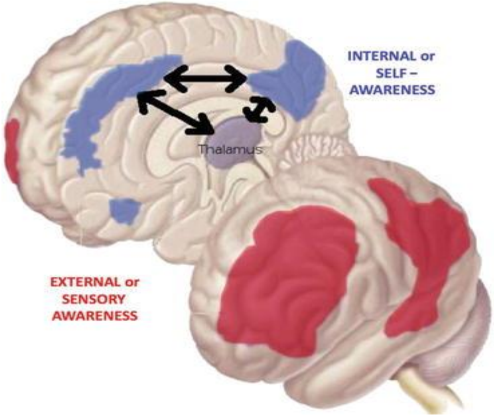
Study 5: Objectives

- Frontoparietal **network**: external awareness
- Multifocal stimulation (vs. single-site)
- Electrophysiological effects?
- Investigate the behavioral and EEG effects of **multifocal frontoparietal tDCS** in chronic DOC (UWS, MCS, EMCS)



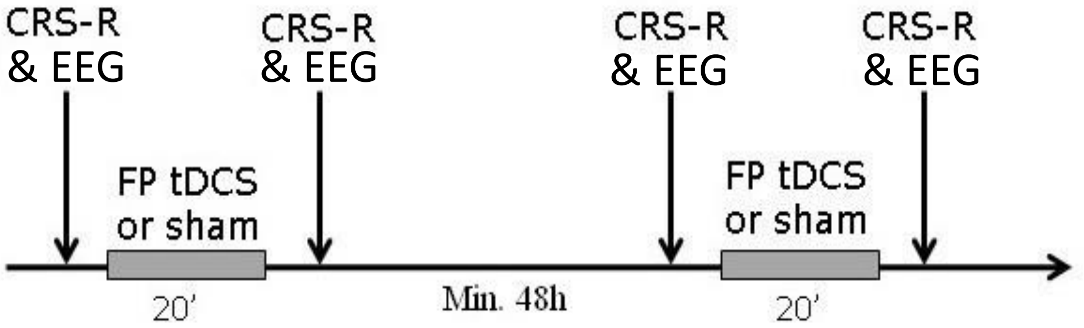


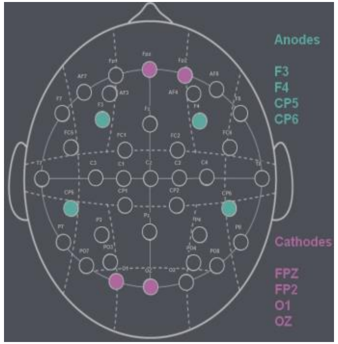
Vanhaudenhuyse et al. (2011)

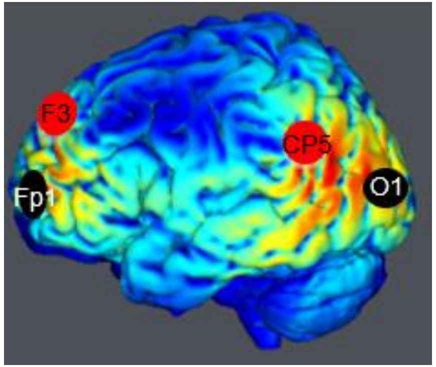
Study 5: Methods

- tDCS FP 20 min 4x1mA 1x

Double-blind crossover sham controlled







Study 5: Results

46 patients; 46 [35 – 59] years old, 12 [5 – 47] months post-injury, 22 TBI; 17 UWS, 23 MCS, 6 EMCS

- No behavioral treatment effect at the group level neither in diagnosis/etiology subgroups
- No electrophysiological treatment effect

Study 5: Results

46 patients; 46 [35 – 59] years old, 12 [5 – 47] months post-injury, 22 TBI; 17 UWS, 23 MCS, 6 EMCS

- Individual level: **three** types of behavioral response

tDCS+ : increase after active tDCS (n=7; 4 MCS-3 EMCS; 6 TBI)

tDCS= : no change (n=32; 17 UWS-13 MCS-2 EMCS; 13 TBI)

tDCS- : decrease after active tDCS (n=7; 6 MCS-1 EMCS; 3 TBI)

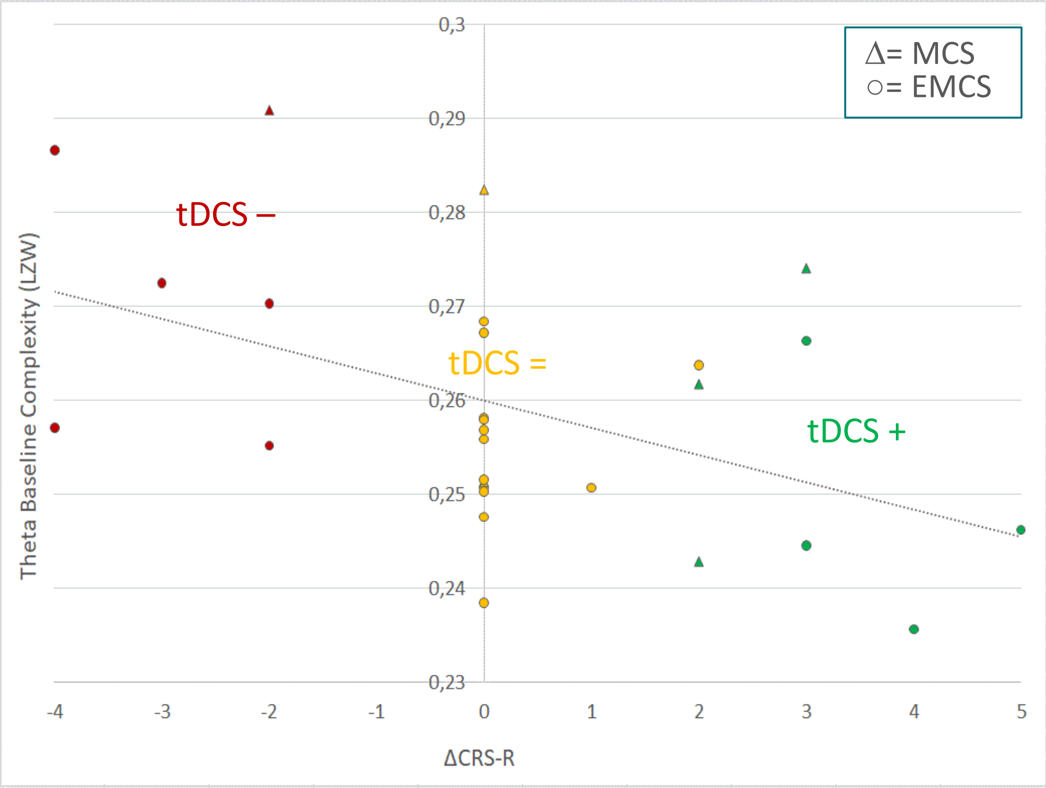
Study 5: Results

- Significant correlation between CRS-R score change & baseline theta complexity (rho= -0.429; p=0.02) in conscious patients (MCS/EMCS)

tDCS- : decrease after active tDCS

tDCS= : no change

tDCS+ : increase after active tDCS



Spearman correlation

Study 5: Conclusions

- Frontoparietal multifocal: less efficient
- Individual level: 15% responders
- **BUT** 15% lose conscious behaviors!
- Baseline theta complexity as biomarker for responsiveness
- Responders? – behavioral fluctuation
- Limitations: montage? Single session, burdensome protocol

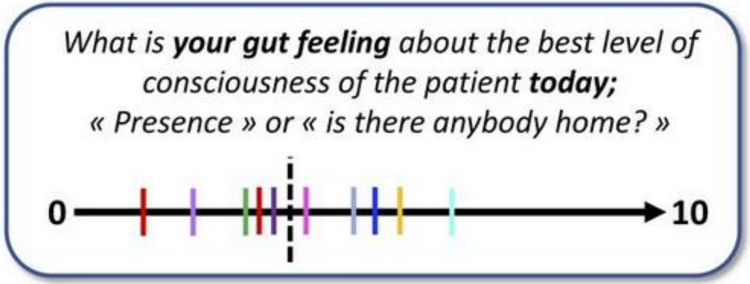
Conclusions: behavioral recovery

- Visual pursuit = prevalent marker of transition to consciousness (within 6 weeks)
- Repeat the CRS-R assessments

- 69% of non-communicative patients admitted to rehab recover communication over 6-7 weeks
- Potential for late recovery of communication

Perspectives: behavioral recovery

- Track down behavioral recovery in acute settings (ICU)
- Investigate relationships between trajectory of recovery and long-term outcome
- Simplify the behavioral assessment: shorter scales (SECONDs, CRS-R FAST)
- Involve the caregivers: DoC-feeling



Hermann et al. (2019)

Conclusions: tDCS as a treatment option

- Repeated prefrontal tDCS in home-based setting: **efficient**, feasible and safe – strong adjuvant to current treatment approaches
- Motor tDCS: less efficient
- Frontoparietal multifocal: less efficient but baseline theta complexity could be a biomarker for responsiveness

Prefrontal repeated tDCS = best option so far

Future directions

- Brain-state dependent stimulation
- Patient tailored stimulation – individual montage modelling based on prior neuroimaging
- Combination with other therapeutic interventions: physical therapy, occupational therapy
- Combination with pharmacological interventions (e.g., NMDA receptor agonists)

Nair et al. (2011)
Dehem et al. (2018)

Take Home Messages for clinicians

- Track visual pursuit, response to command & automatic movement in UWS
- Consider potential for communication recovery within 6 weeks post-injury during acute decisioning
- Consider tDCS in therapeutic arsenal
- Favor left prefrontal stimulation & repeated sessions
- Expect greater response rates in MCS
- Caregivers can be safely involved in delivering tDCS remotely

THANK YOU!

COMA
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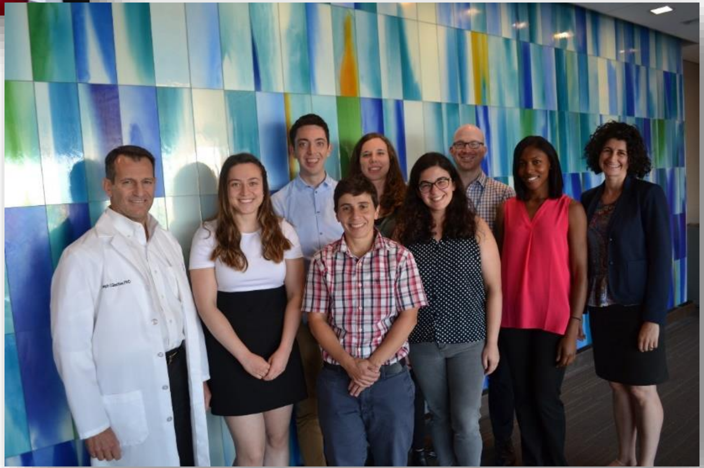
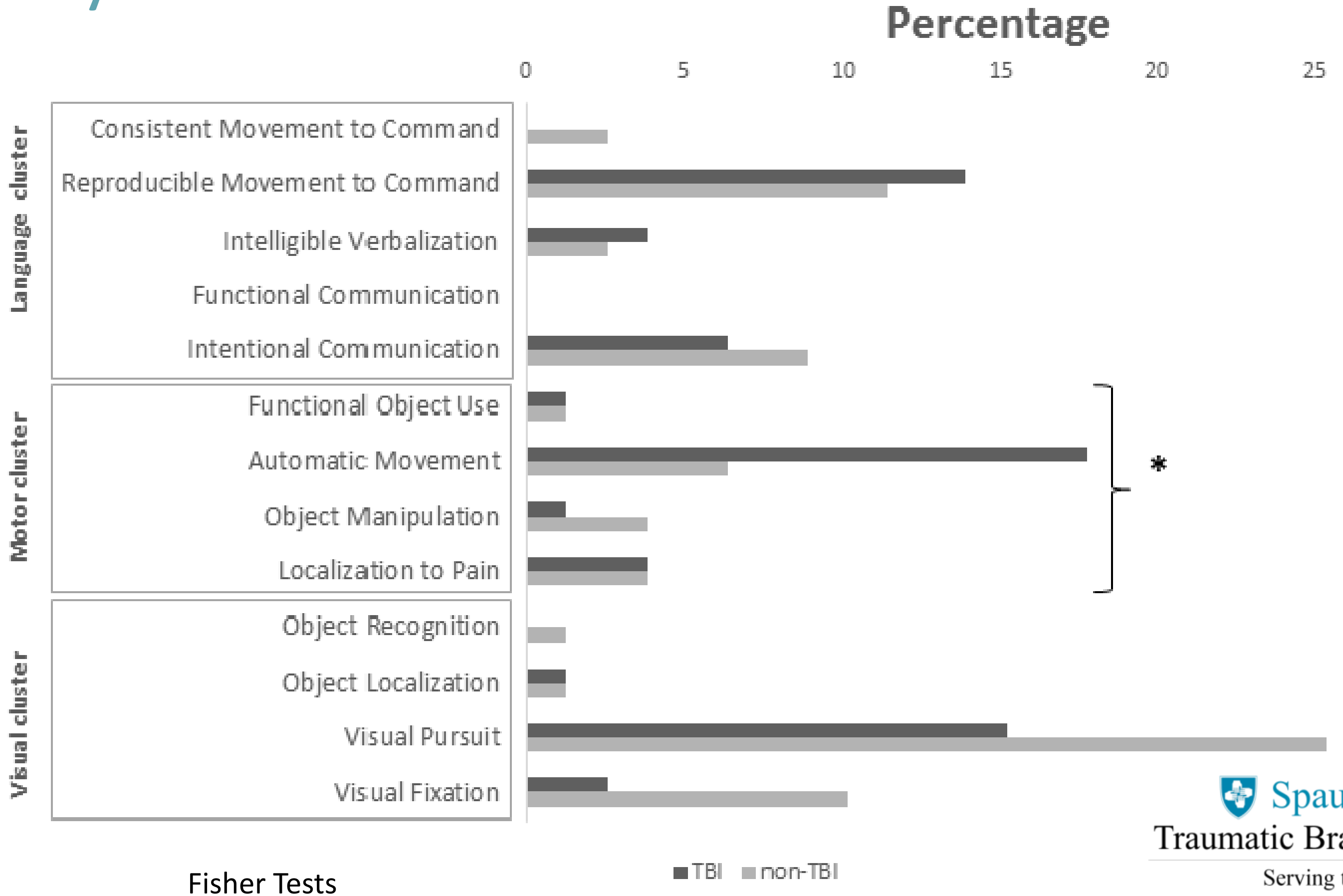


List of publications

- **Martens, G.**, Bodien, Y. Thomas, A., & Giacino, J. Temporal profile of recovery of communication in patients with disorders of consciousness following severe brain injury. *Archives of Physical Medicine and Rehabilitation.* doi:10.1016/j.apmr.2020.01.015
- **Martens, G.**, Bodien, Y., Sheau, K., Christoforou, A., & Giacino, J. T. (2019). Which behaviours are first to emerge during recovery of consciousness after severe brain injury? *Annals of physical and rehabilitation medicine*. doi:10.1016/j.rehab.2019.10.004
- **Martens, G.**, Fregni, F., Carrière, M., Barra, A., Laureys, S., & Thibaut, A. (2019). Single tDCS session of motor cortex in patients with disorders of consciousness: a pilot study. *Brain Injury*, 1-5.
- **Martens G.**, Deltombe T., Foidart-Dessalle M., Laureys S., & Thibaut A. (2018). Clinical and electrophysiological investigation of spastic muscle overactivity in patients with disorders of consciousness following severe brain injury. *Clinical Neurophysiology*, 130(2), 207-213.
- **Martens, G.**, Lejeune, N., O'Brien, A. T., Fregni, F., Martial, C., Wannez, S., Laureys, S. & Thibaut, A. (2018). Randomized controlled trial of home-based 4-week tDCS in chronic minimally conscious state. *Brain stimulation*, 11(5), 982-990.
- **Martens, G.**, Laureys, S., & Thibaut, A. (2017). Spasticity management in disorders of consciousness. *Brain sciences*, 7(12), 162.
- Bodien, Y., **Martens, G.**, Ostrow, J., Sheau, K., Giacino, J. (2020). Cognitive Impairment, Clinical Symptoms and Functional Disability in Patients Emerging from the Minimally Conscious State. *NeuroRehabilitation*. 46(1), 65-74.

ADDITIONAL SLIDES

Study 1: Results TBI vs Non-TBI



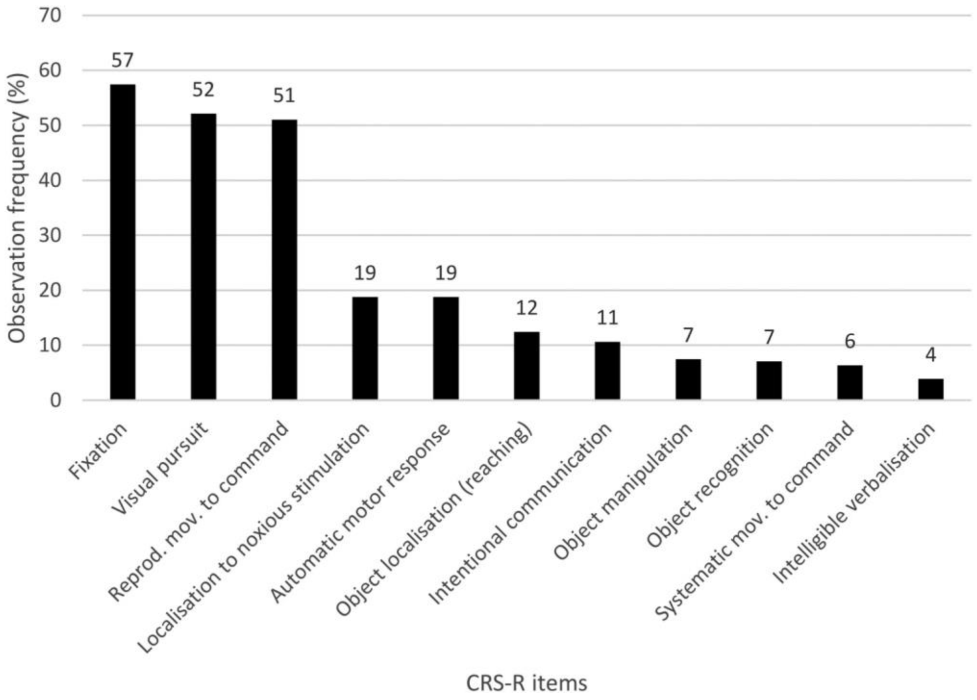
Fisher Tests

Spaulding-Harvard Traumatic Brain Injury Model System
Serving the New England Region

Prevalence of coma-recovery scale-revised signs of consciousness in patients in minimally conscious state

Sarah Wannez, Olivia Gosseries, Deborah Azzolini, Charlotte Martial, Helena Cassol, Charlène Aubinet, Jitka Annen, Géraldine Martens, Olivier Bodart, Lizette Heine, Vanessa Charland-Verville, Aurore Thibaut, Camille Chatelle, Audrey Vanhaudenhuyse, Athena Demertzi, Caroline Schnakers, Anne-Françoise Donneau & Steven Laureys ...show less

Pages 1350-1359 | Received 01 Oct 2016, Accepted 16 Mar 2017, Published online: 11 Apr 2017



Transcranial direct current stimulation (tDCS)

- Modulates neural excitability using low density direct current (1 – 2 mA)

➔ *Membrane polarization*

Anode: ↗ excitability

Cathode: ↘ excitability

The calcium blocker Flunarizine reduced the effects of anodal motor tDCS

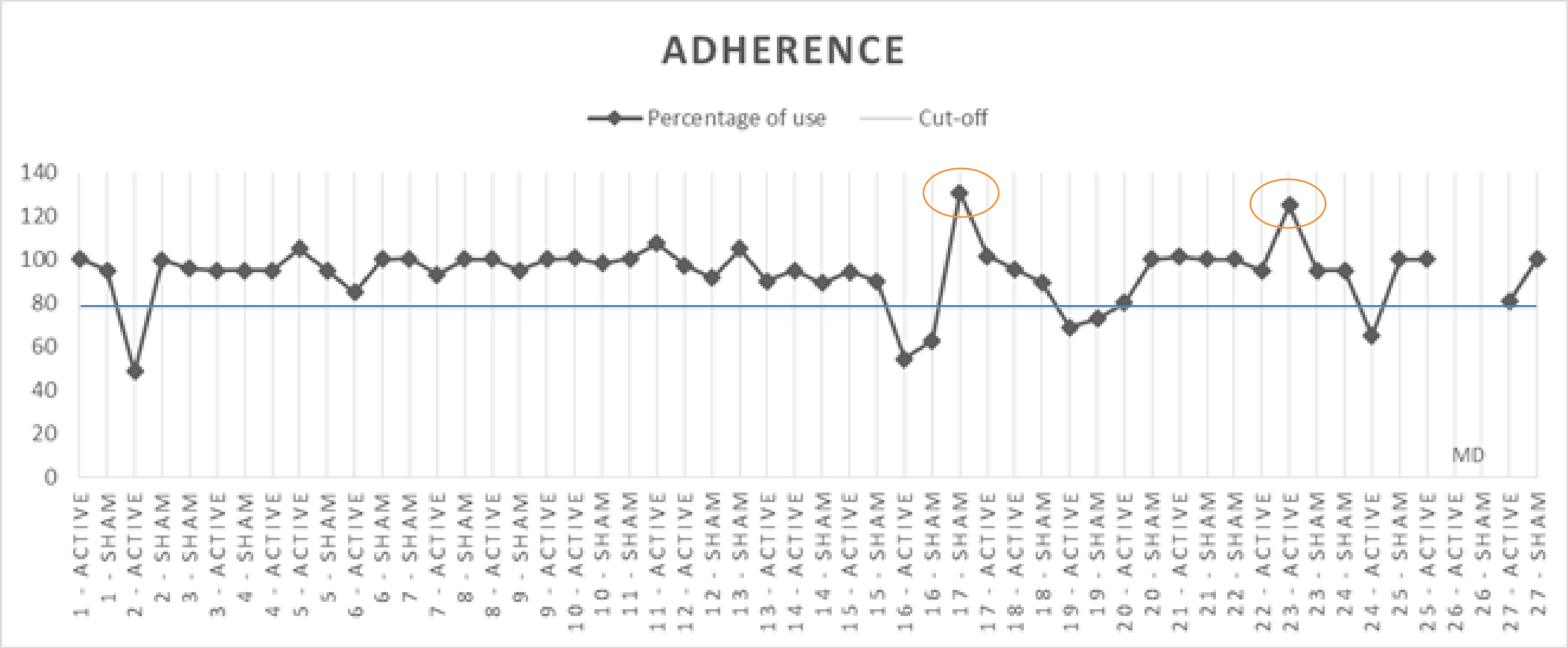
The sodium blocker Carbamezipine abolished the effect of anodal motor tDCS

The NMDA receptor agnosit d-cycloserine increased the duration of the effects

Nitsche et al. (2003)

Study 3: Results

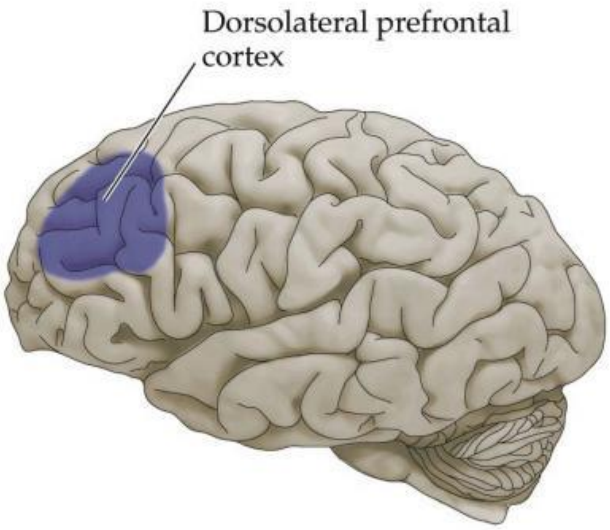
- Compliance: 93±14%



Why the left DLPFC?

- Involved ++ in attention and working memory
- Integrates inputs from associative cortices
- Hub of motor control and planning network

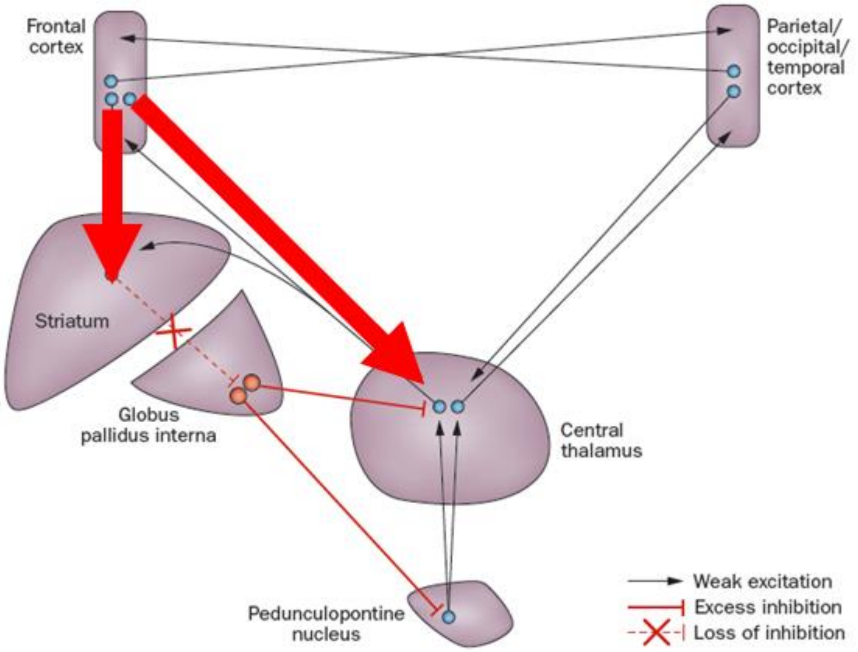
- Right DLPFC: arousal and attention



Devinsky and D'Esposito (2004)
Heekeren et al. (2006)
Sturm and Willmes (2001)

Why prefrontal tDCS?

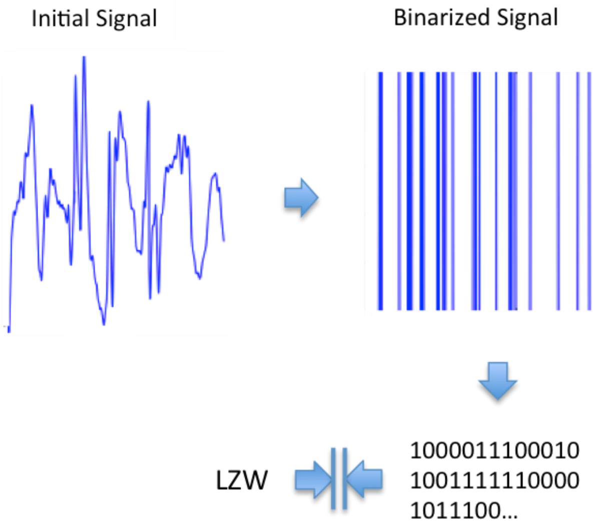
- Mesocircuit hypothesis



Schiff et al. (2010)

LZW Complexity

- Estimate of algorithmic complexity
- Depicts 'randomness' of the neural signal
- ➔ Integrity of inter-neural connectivity
- Decreases under anesthesia, sleep (less brain oscillations)
- Increases under psychoactive drugs (ketamine)
- Decreased in DOC vs HC
- Increased in MCS/EMCS vs UWS



Martens et al. (submitted)

Closed loop EEG pilot patient

- Fluctuations in spectral entropy