

La neuropronostication : dernières avancées en matière de troubles de la conscience

GLEM meeting – 22/09/22

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FNRS Aspirant

GIGA-Doctoral School



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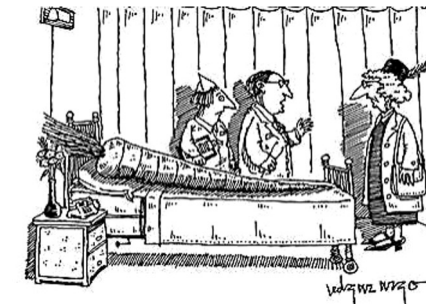
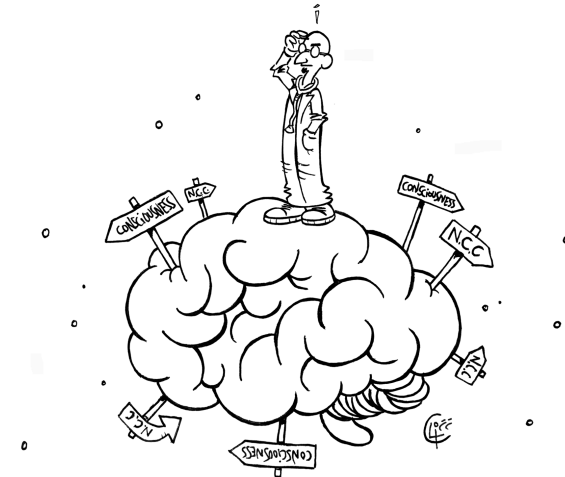
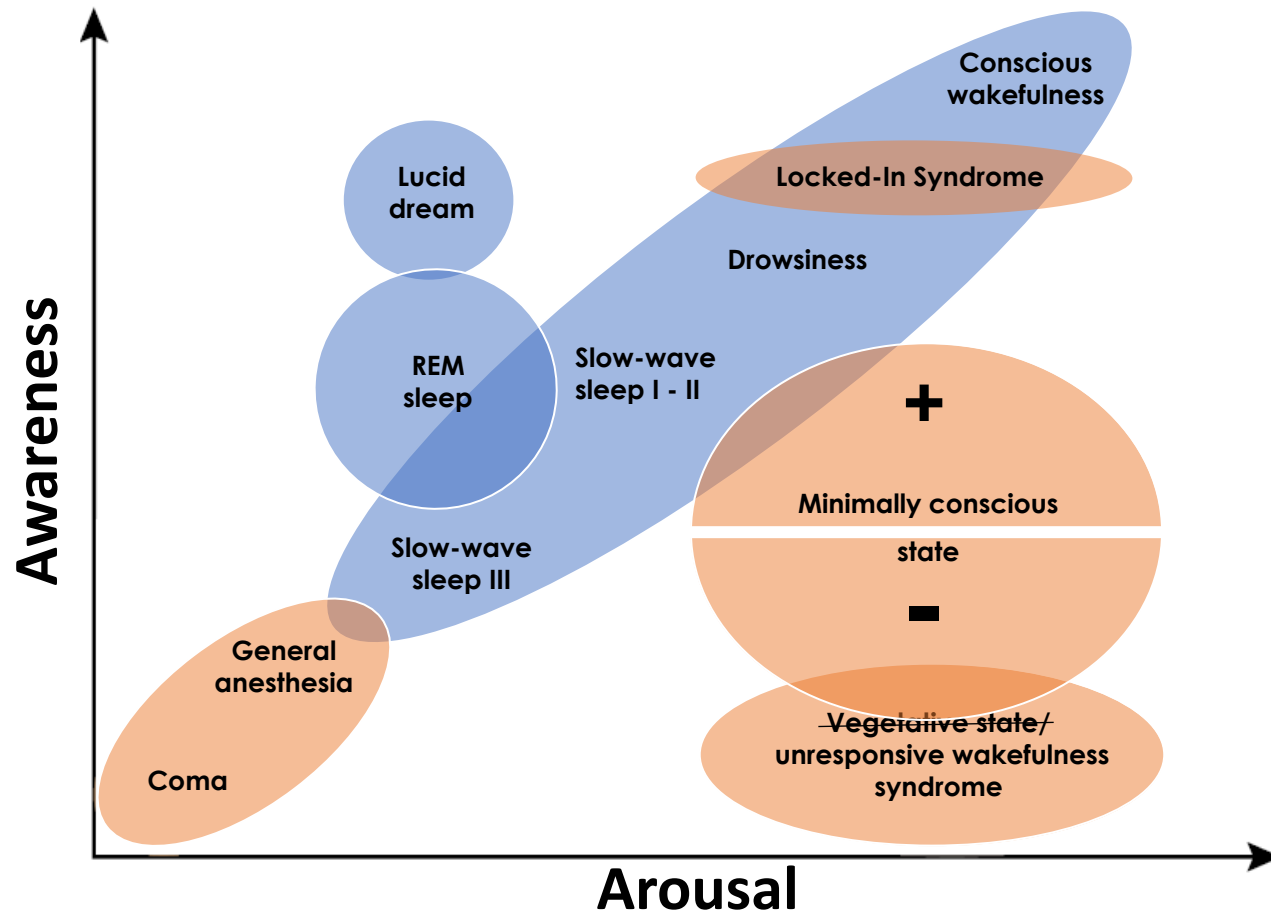
- Role for diagnosis & prognosis

4. Treatments

- Ongoing research



What is consciousness?

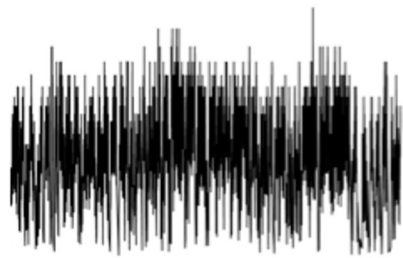


"There's nothing we can do... he'll always be a vegetable."



Inferring consciousness

- Behavioral based



Stimulus

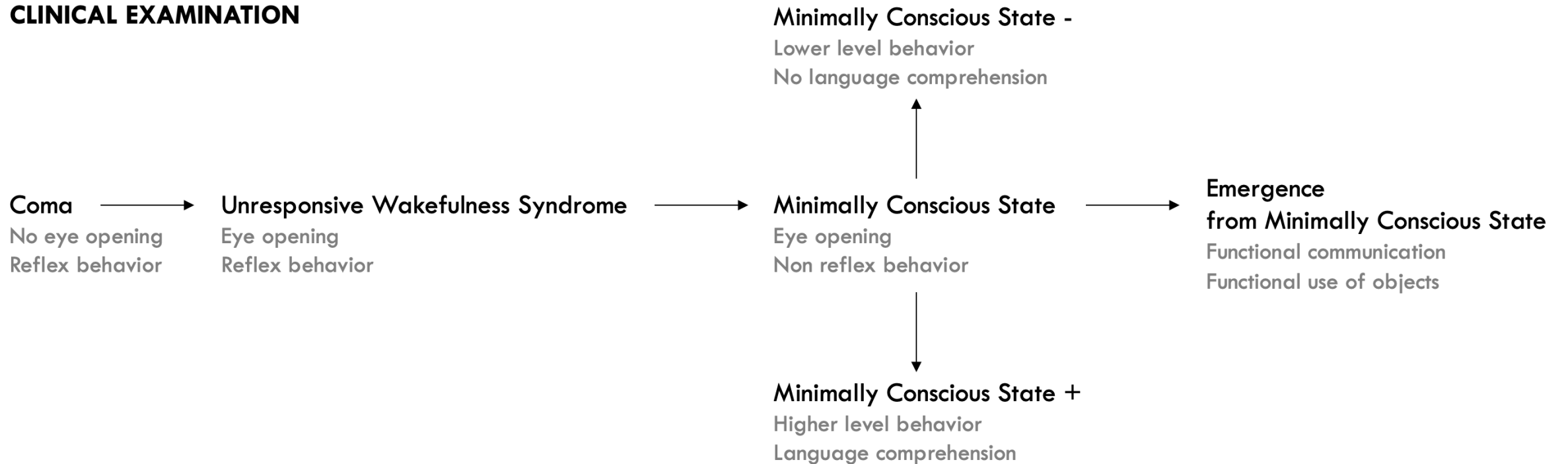


Response



Disorder of consciousness

CLINICAL EXAMINATION



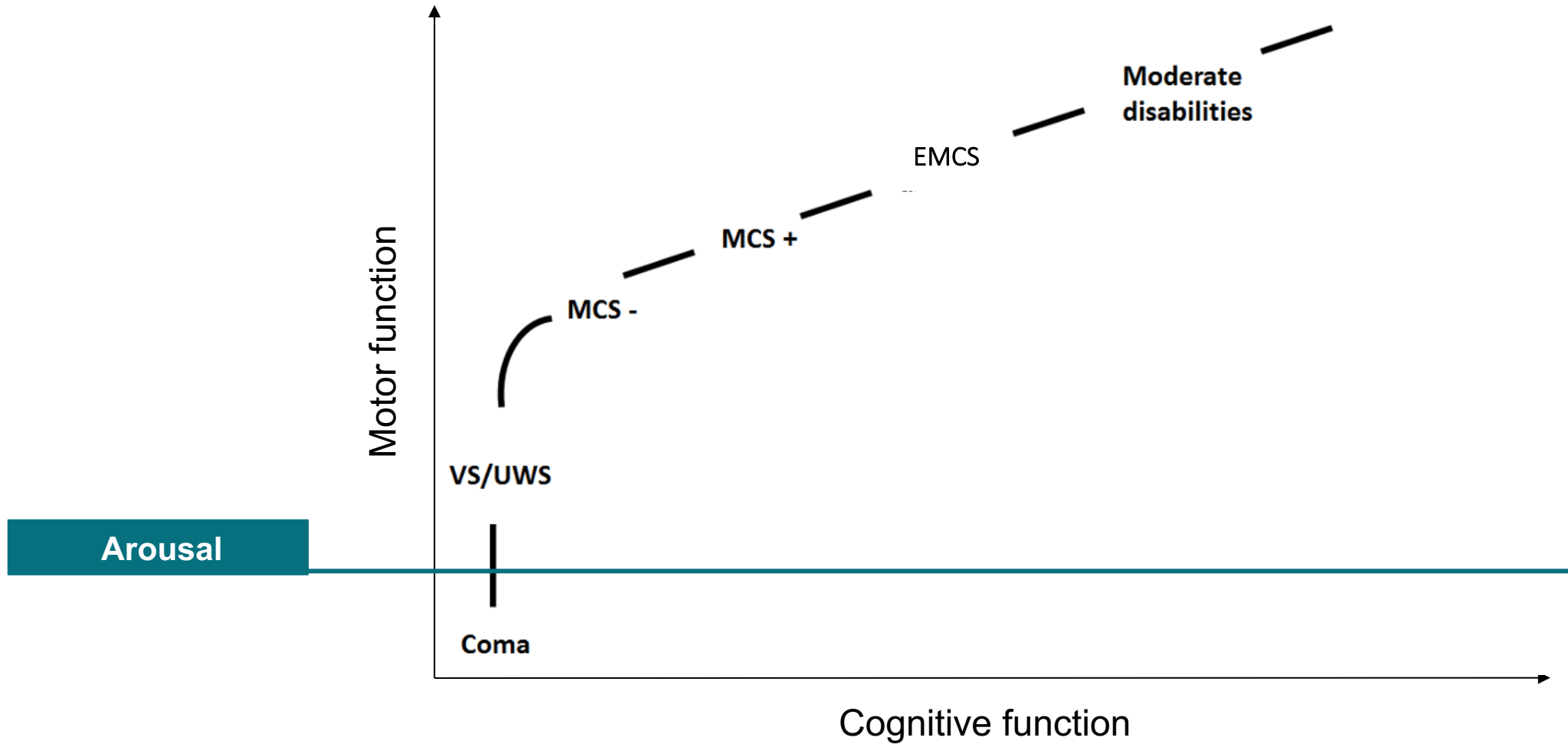
NEUROIMAGING EXAMINATION

Non-Behavioral Minimally Conscious State (*)

Dissociation between clinical evaluation and neuroimaging results showing preserved brain function

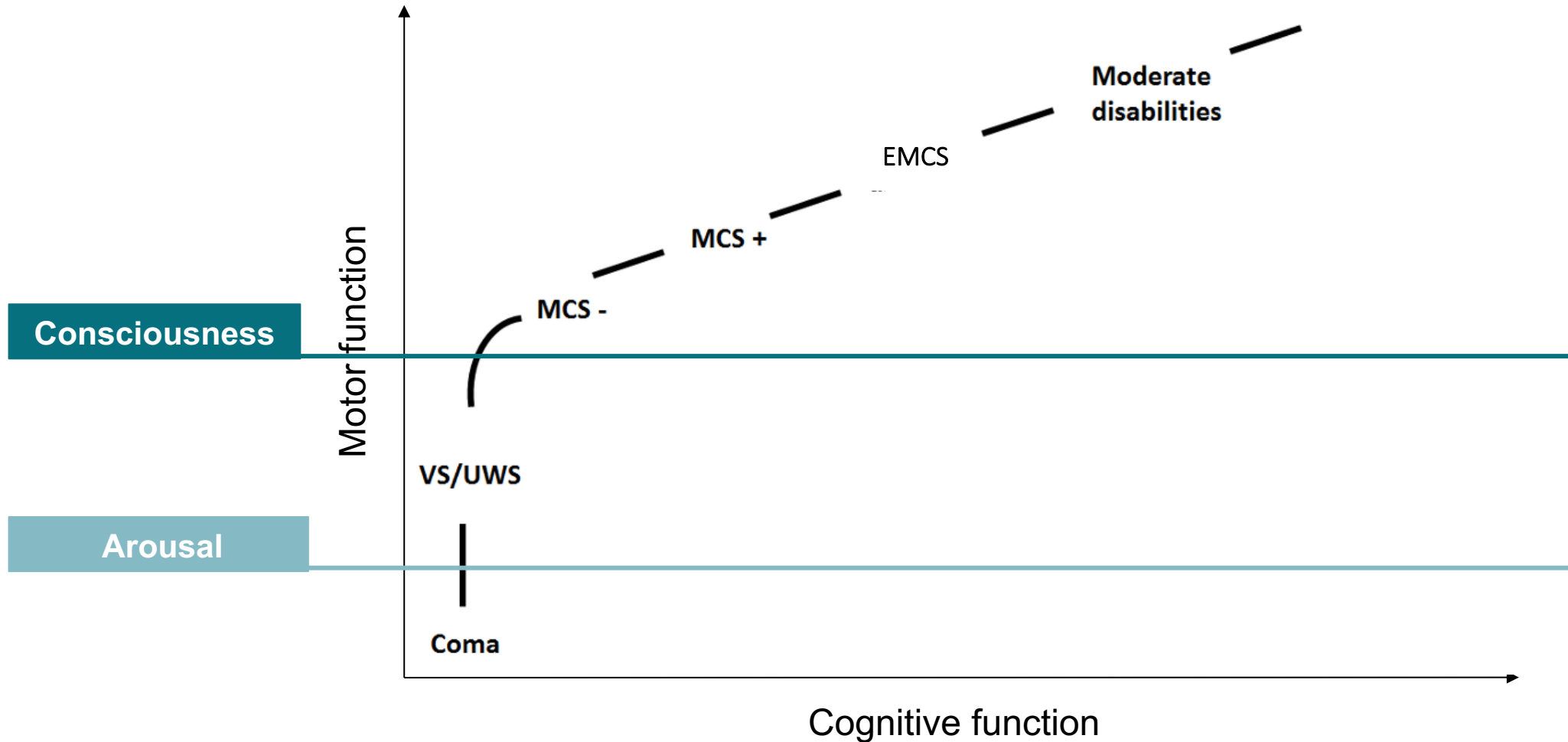


Clinical evolution



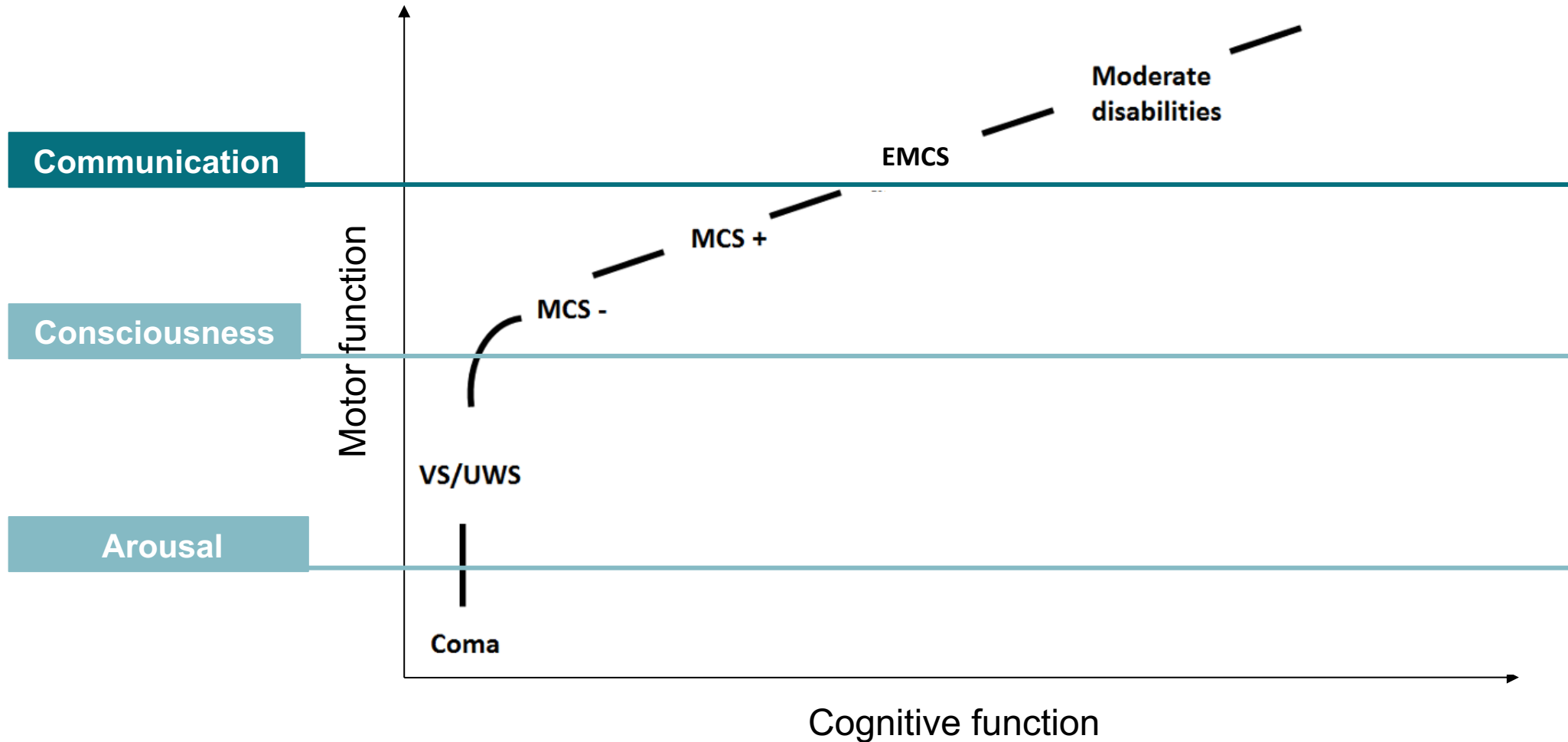


Clinical evolution





Clinical evolution





Misdiagnosis in DoC

126 post-coma patients

- 51 diagnosed in unresponsive wakefulness syndrome by clinical consensus
- 18 showed signs of consciousness by standardized scale



30-40% misdiagnosis after a coma

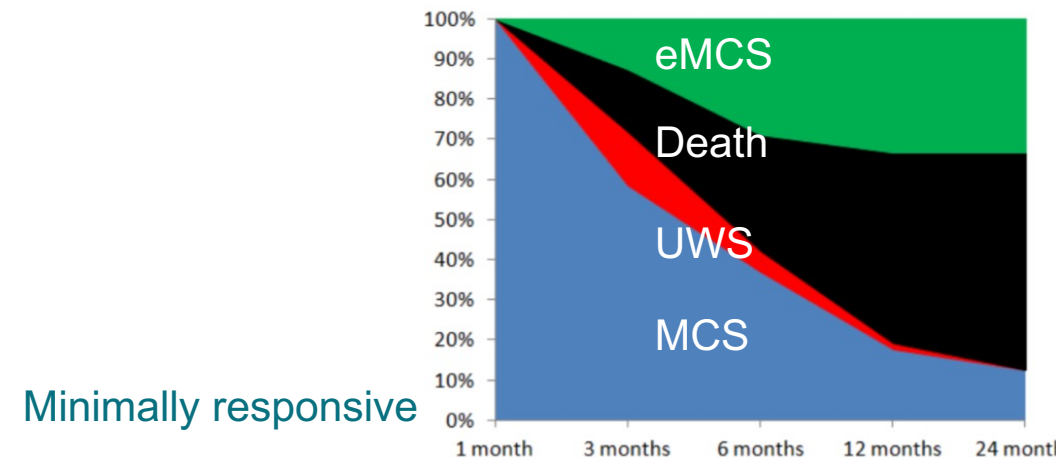
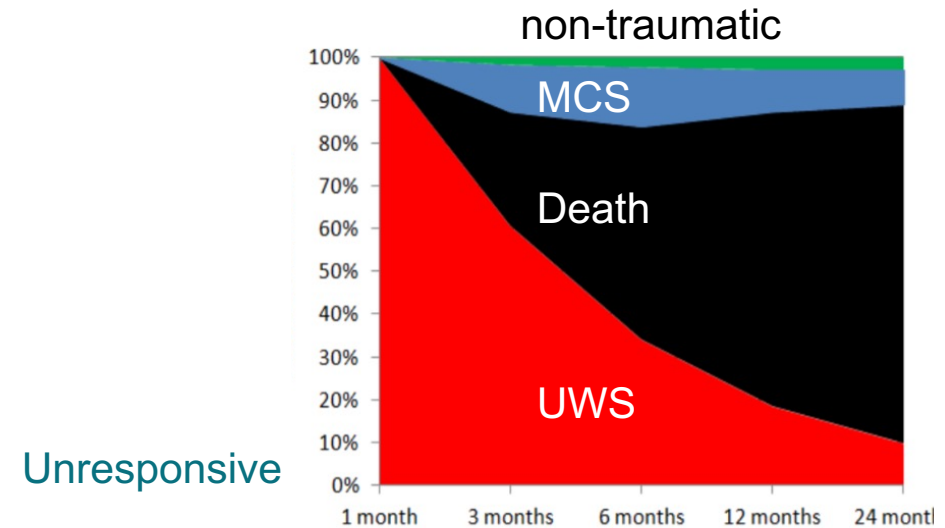


Why should we care?



Prognosis

Bruno et al, Coma and disorders of consciousness 2012 (p11-23)





Why should we care?



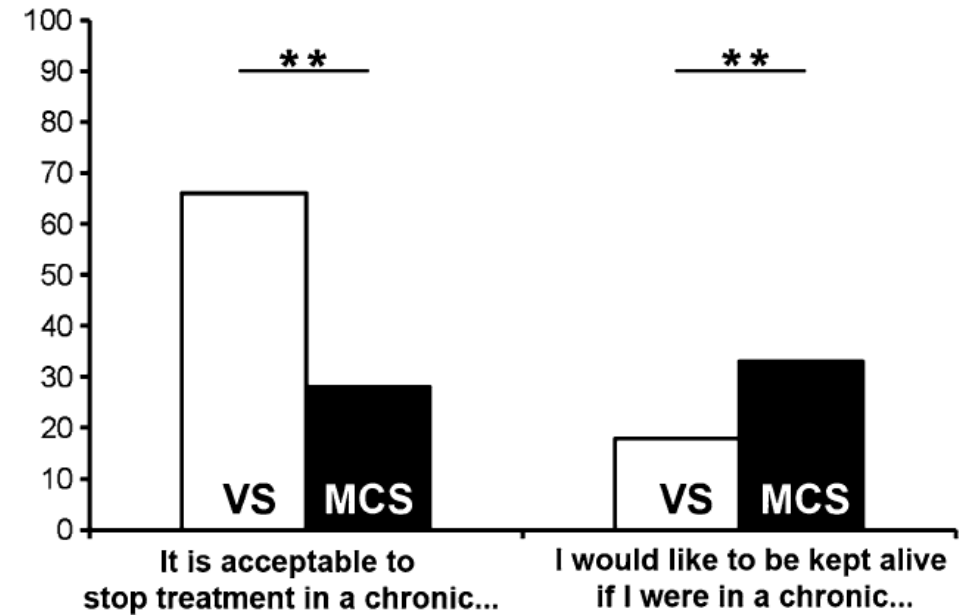
Prognosis

Bruno et al, Coma and disorders of consciousness 2012 (p11-23)



Ethics

Demertzi et al, *J Neurology* 2011





Why should we care?



Prognosis

Bruno et al, Coma and disorders of consciousness 2012 (p11-23)



Ethics

Demertzi et al, *J Neurology* 2011



Treatment

**Stay
tuned!**



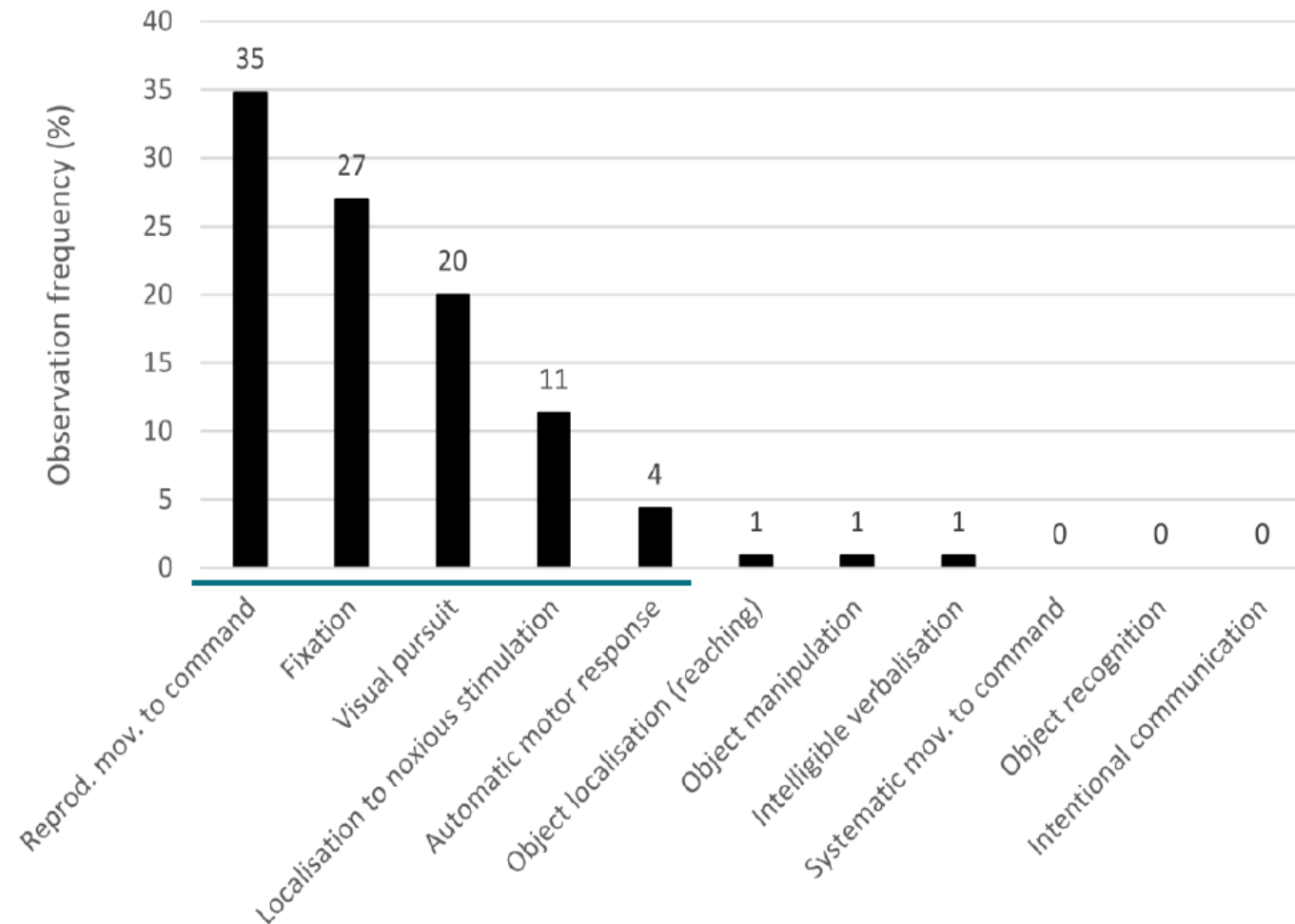
Coma Recovery Scale-Revised (CRS-R)

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									
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									
TOTAL SCORE									

- Subscales for different functions
 - Audition, vision, motor abilities, oro-motor abilities, communication, arousal
- Brainstem reflexes and contingent behaviors assessed
- Validate, standardized, hierarchical **but** long to administer and training needed



A fast version: SECONDS



Patient : Examiner : Date : Time :

Simplified Evaluation of CONsciousness Disorders (SECONDS)

Command 1: /3
2: /3
3: /3
Written command: /3
→ The patient responds at least twice for one of the commands (= score 6)

Code yes :
Code no :
Responses : .../5 o Verbal o Autobiographical
Correct : .../5 o Written o Situational
→ The patient responds (even incorrectly) to at least 3 questions (= score 7)
→ The patient correctly responds to the 5 questions (= score 8)

Horizontal : .../2 Vertical : .../2
o Spontaneous o Mirror o Manual eye-opening
→ The patient shows at least 2 visual pursuits of at least 2 seconds (= score 4)

Sup L : .../1 Sup R : .../1
Inf L : .../1 Inf R : .../1
o Spontaneous o Mirror o Manual eye-opening
→ The patient shows at least 2 visual fixations of at least 2 seconds (= score 3)

Localization: L : .../1 R : .../1
Anticipation: L : .../1 R : .../1
→ The patient touches the point of stimulation at least once with the non-stimulated hand (= score 2)
→ The patient shows 2 anticipations (= score 6)

Nb :
→ The patient shows at least one oriented behavior (= score 5)

0-25% / 25-50% / 50-75% / 75-100%
Spontaneously / Auditory / Tactile / Pain stimulations
→ The patient shows at least one eye-opening during the whole assessment (= score 1)

A. Observation

☐ **B. Command-following** (score 6)
3 x 3 spoken commands
10" interval between commands
(1 x 3 written command if 0/3)
Stop if 2 commands 3/3

☐ **C. Communication**
☐ **Intentional** (score 7)
☐ **Functional** (score 8)
Autobiographical questions
Name (no), birth date (yes), name (yes), birth date (no), children (yes/no)
If incorrect answer(s): Situational questions
Place (yes), wearing a hat (no), place (no), touching hand (yes), touching face (no)

☐ **D. Visual pursuit** (score 4)
Person/mirror, 30 cm from face
Each movement on horizontal or vertical axes = 4" (→ ← ↓ ↑)

☐ **E. Visual fixation** (score 3)
Person/mirror, 30 cm from face
Present stimulus in each quadrant

☐ **F. Pain localization** (score 2)
Inform patient
5" pressure on nail bed
1 trial on each hand

☐ **G. Oriented behaviors** (score 5)
E.g., scratching, grabbing sheets, holding bed, laughing or crying contextually,...

H. Arousal
☐ **Eye-opening** (score 1)
☐ **No arousal** (score 0)
Report the percentage of eye-opening time and administered stimulations

Diagnosis : Coma (0) / UWS (1) / MCS- (2-5) / MCS+ (6-7) / EMCS (8)
Additional index point : ... /100



Behavioural assessment – what we need?



Clinician

- Standardized scales
- Repeated assessments
- Assessment modalities



Patient

- Paralysis
- Aphasia
- Agnosia
- Deafness or blindness
- Fluctuating awareness
- Pain
- Medical complication
- Sedation
- Lack of cooperation

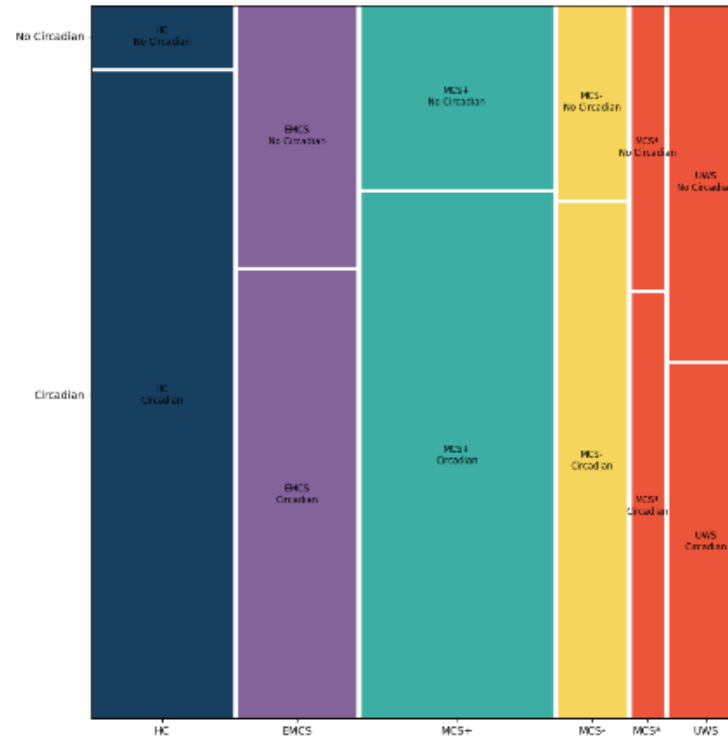
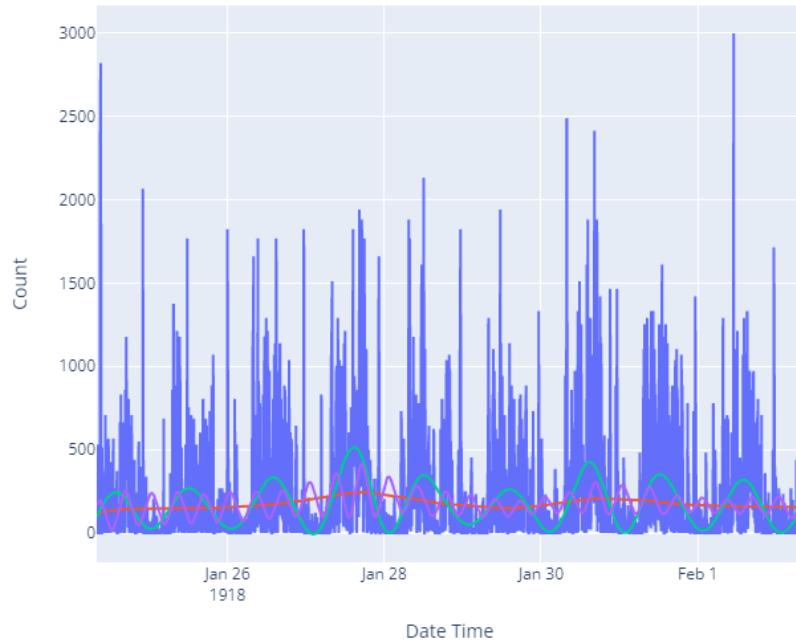




New conscious behaviour - actigraphy



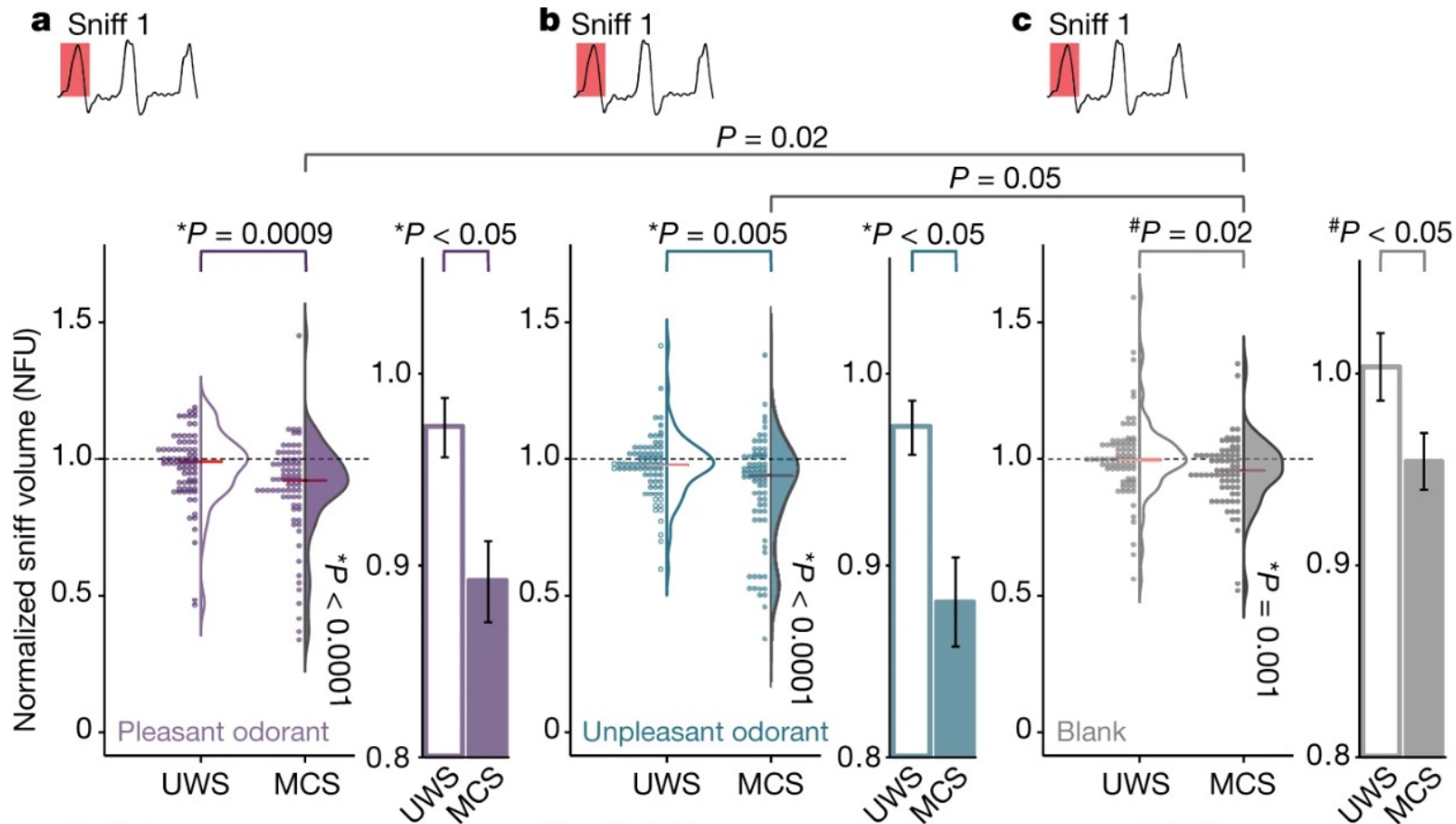
Work by Glenn Van der Lande



- Actigraphy to detect spontaneous movement
- Difference between circadian and ultradian rhythms



New conscious behaviour - respiration



- Sniff response to pleasant/unpleasant odorant
- Ongoing studies on spontaneous pattern of respiration



Other signs of consciousness



Eye opening resistance

Van Ommen et al, *J Neurology*, 2018



Auditory localization

Carrière et al, *Brain comm* 2020



Oral feeding

Melotte et al, *J Neurology*, 2018 & Melotte et al, *APRM*, 2020



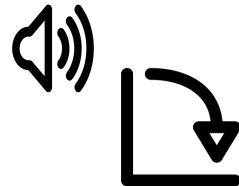
Grimaces

Chatelle et al, *APMR*, 2018



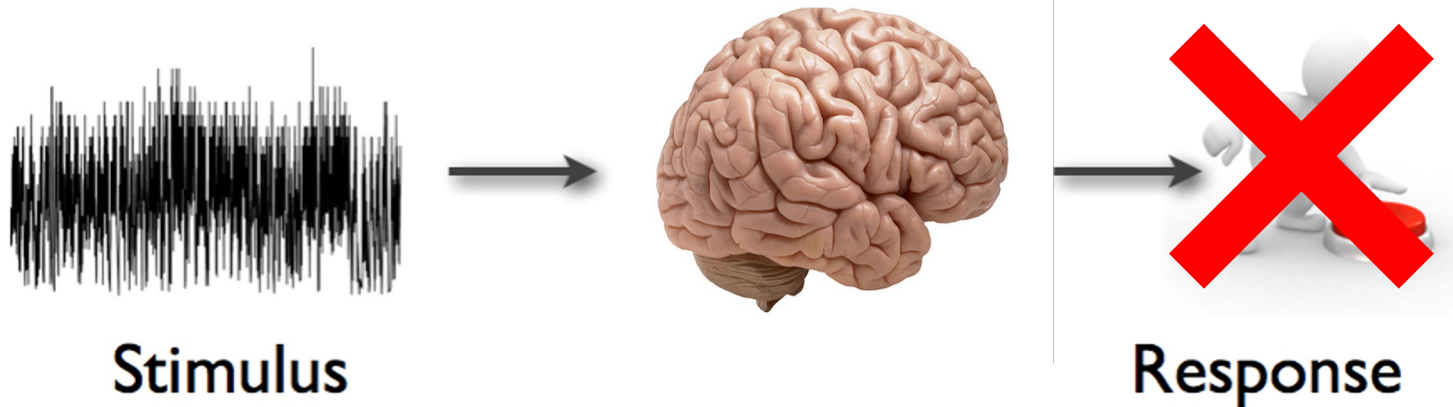
Auditive habituation

Hermann et al, *Brain*, 2020





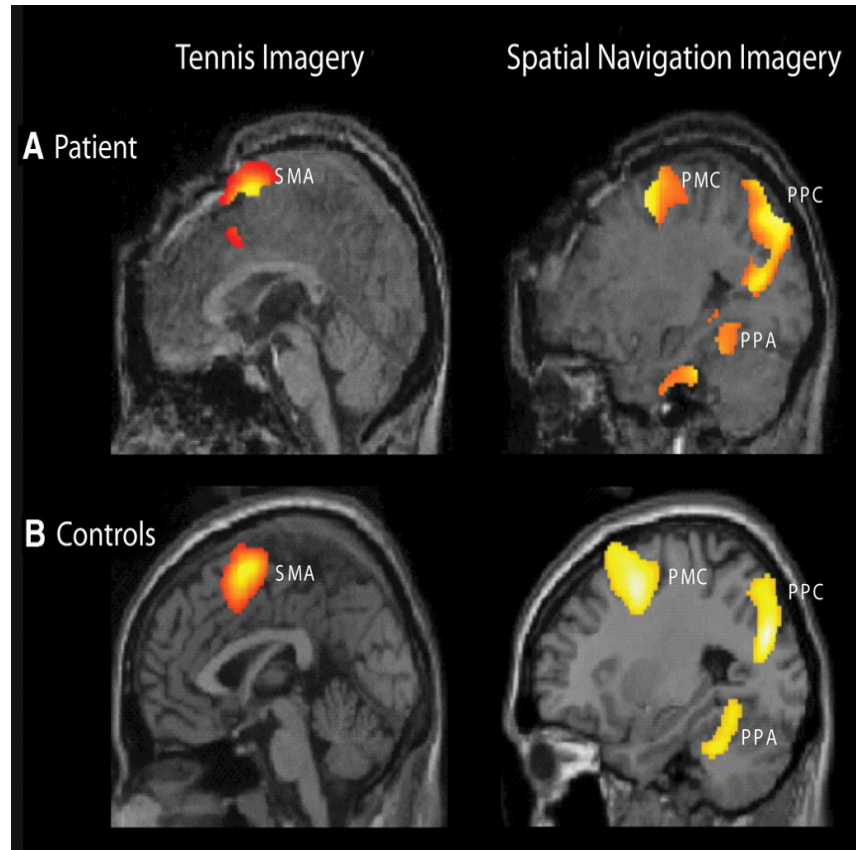
Inferring consciousness – Part 2



- Behavioral based
 - Population constraints
- Elimination of any behavioural output
 - Active and passive paradigms



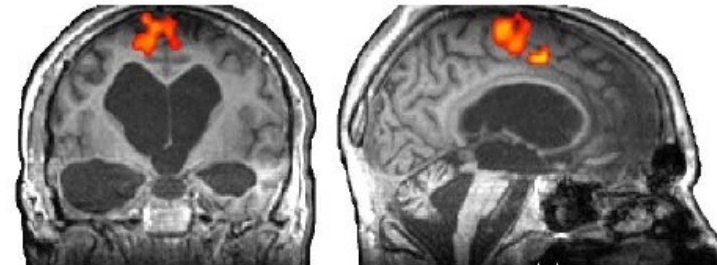
Active paradigm - fMRI



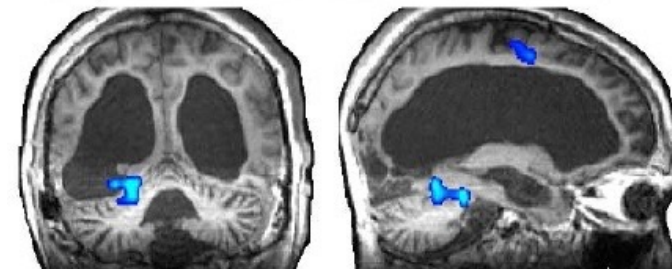
Owen et al., *Science*, 2006

Imagine **Tennis** to answer 'YES'
Imagine **Navigating** to answer 'NO'

Is your father's name Alexander ?



Is your father's name Thomas ?



Monti & Vanhaudenhuyse et al, *New England J Med*, 2010

Horki et al, *Front Hum Neurosci*.2014

Edlow et al, *Brain*, 2017;

Bodien et al, *Front Neurol*, 2017

Haugg et al, *Front Neurol*, 2018



Active paradigm - EEG

“MOVE YOUR FOOT”



“MOVE YOUR HAND”



**HEALTHY
CONTROL
SUBJECTS**

**Basis for brain-
computer interface
(BCI)**

**“VEGETATIVE”
UNRESPONSIVE
PATIENT**



**Opens a door for
communication**



Inferring consciousness – Part 3



Stimulus

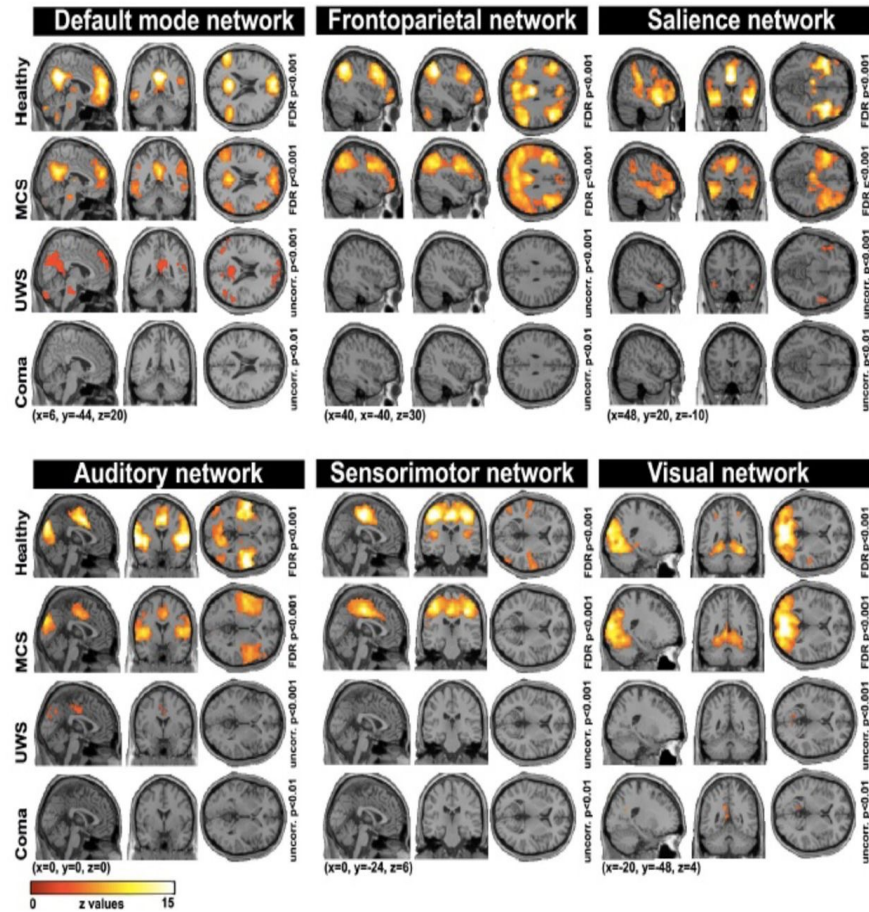


Response

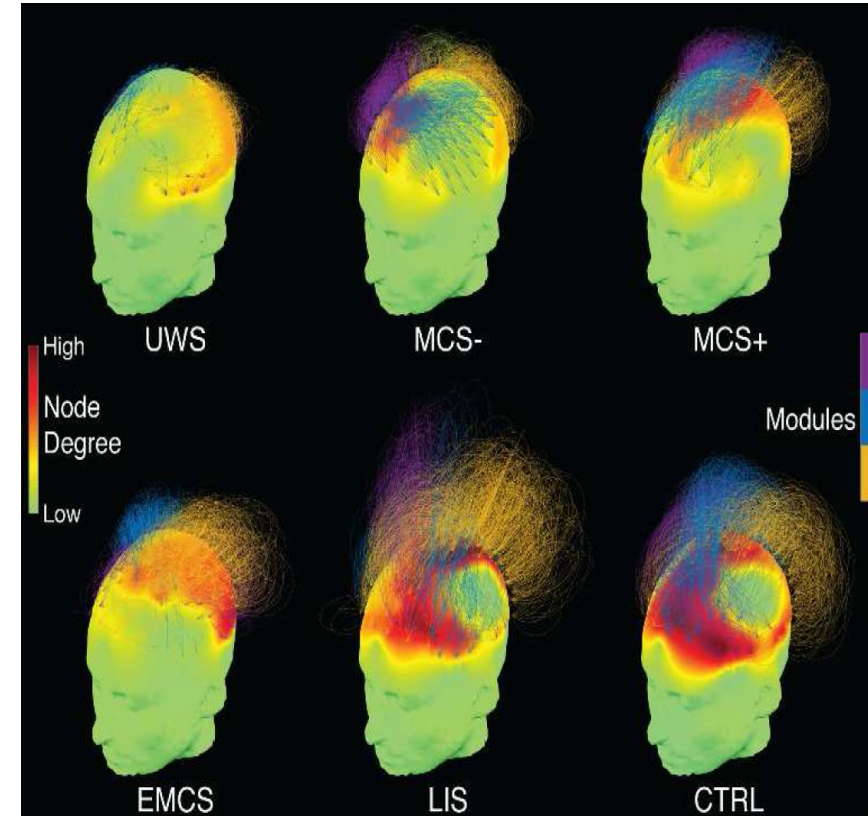
- Behavioral based
 - Population constraints
- Elimination of any behavioural output
 - Active and passive paradigms
- Elimination of inputs
 - No task



Resting state fMRI and EEG



Alpha band connectivity



Vanhaudenhuyse et al, *Brain*, 2010

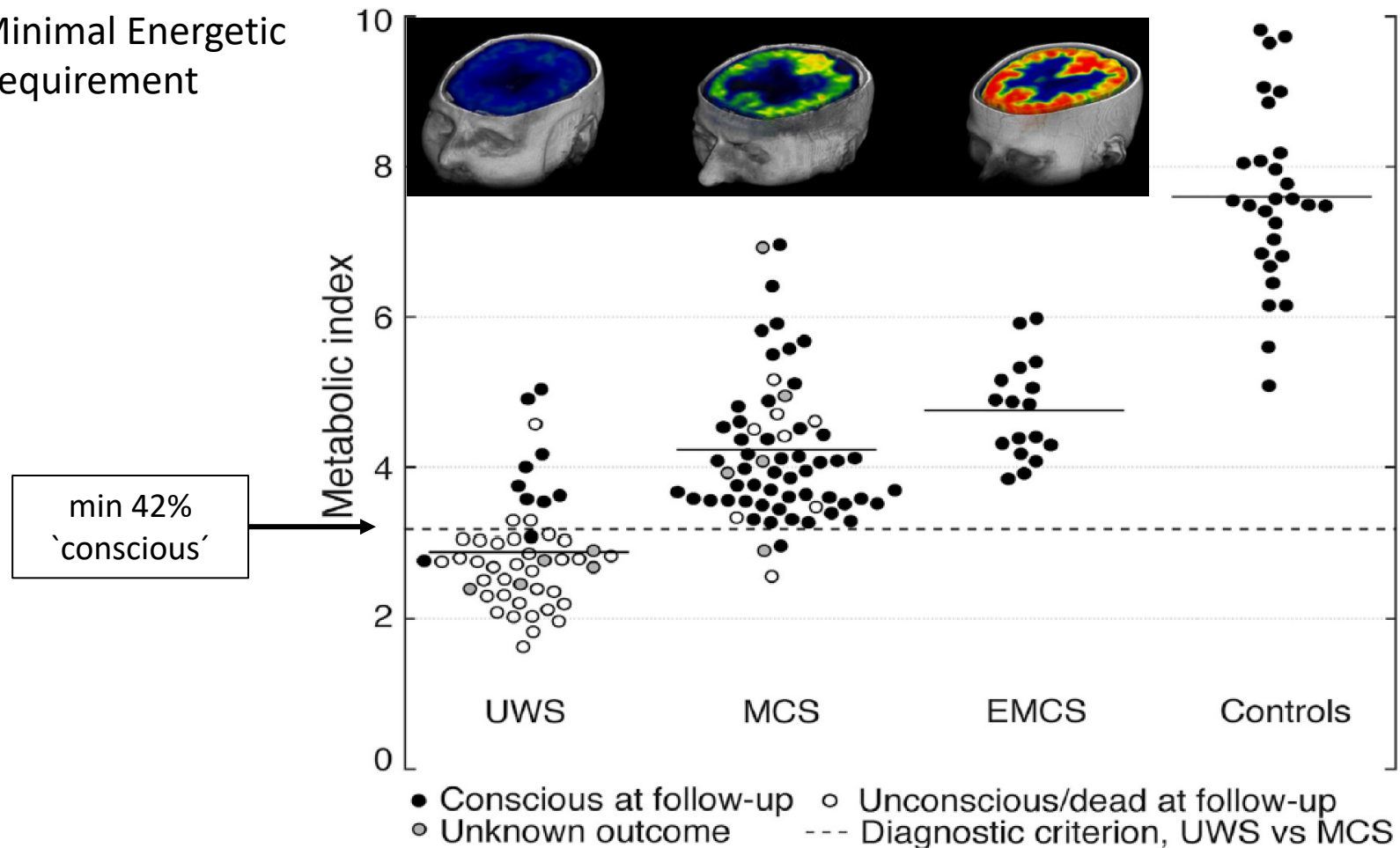
Demertzi et al, *Brain*, 2015; *Adv Science* 2019

Chennu et al, *Brain*, 2017



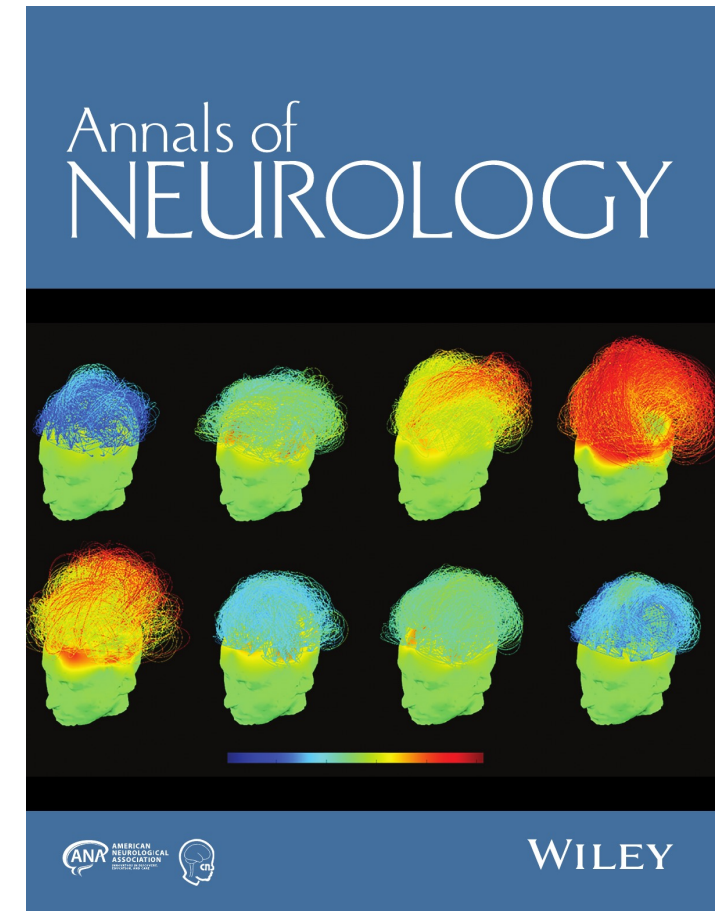
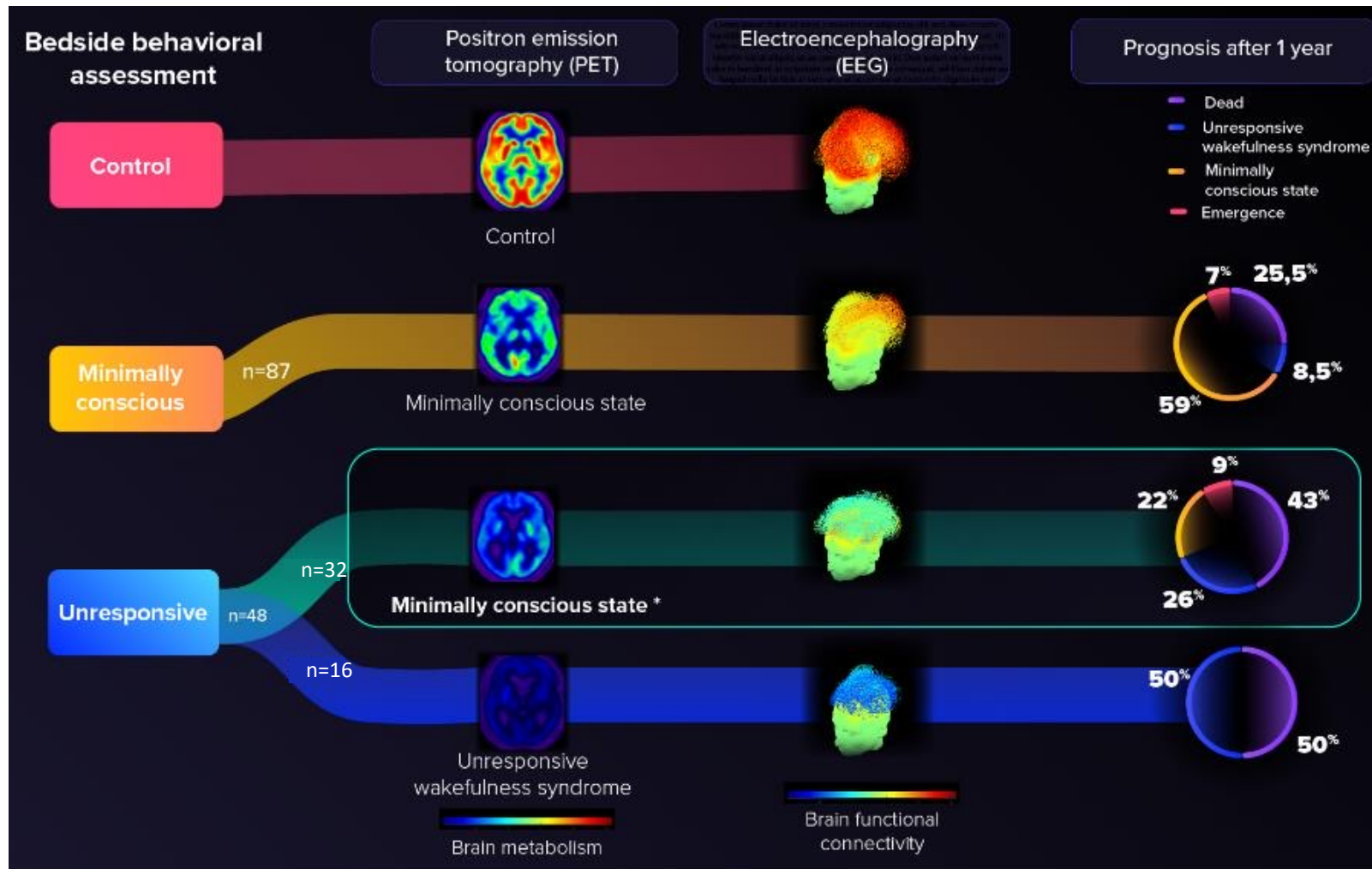
Resting state PET

Minimal Energetic Requirement





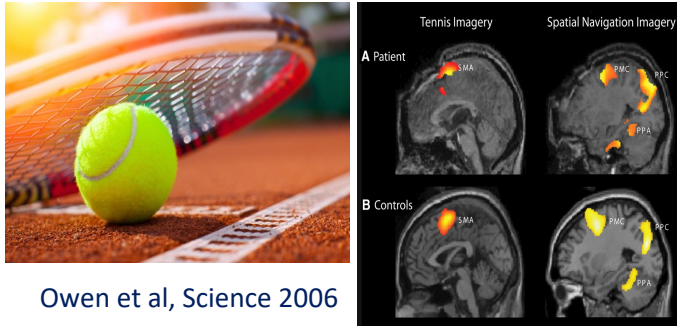
More conscious than expected?





European Academy of Neurology recommendations

Active fMRI



Owen et al, Science 2006

Recommendation:

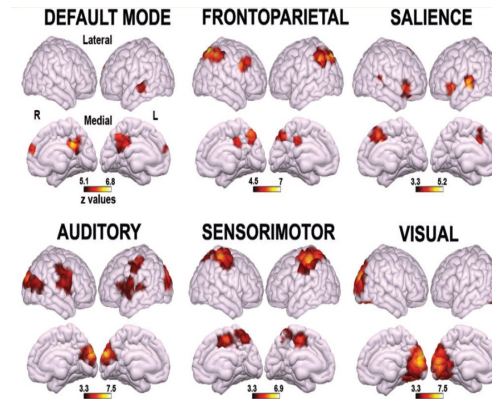
consider active fMRI paradigms as part of multimodal assessment in patients without command following

Moderate evidence, weak recommendation

20 publications

Kondziella et al, Eur J Neurol, 2020

Resting state fMRI



Demertzi et al, Brain 2015

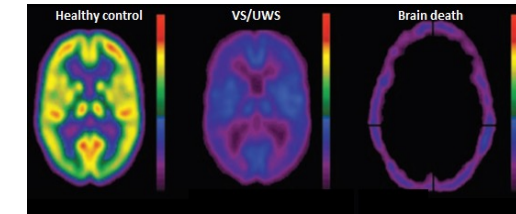
Recommendation:

If clinical MRI is indicated, add resting state fMRI as part of multimodal assessment

Low evidence, weak recommendation

6 publications

Brain metabolism – PET



Laureys et al, Lancet Neurol, 2004

Recommendation:

Resting state FDG PET should be considered as part of multimodal assessment in unresponsive patients

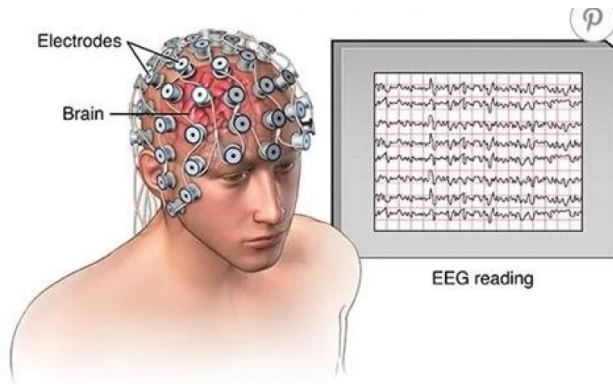
Low evidence, weak recommendation

5 publications



EEG coupled with Transcranial Magnetic Stimulation (TMS-EEG)

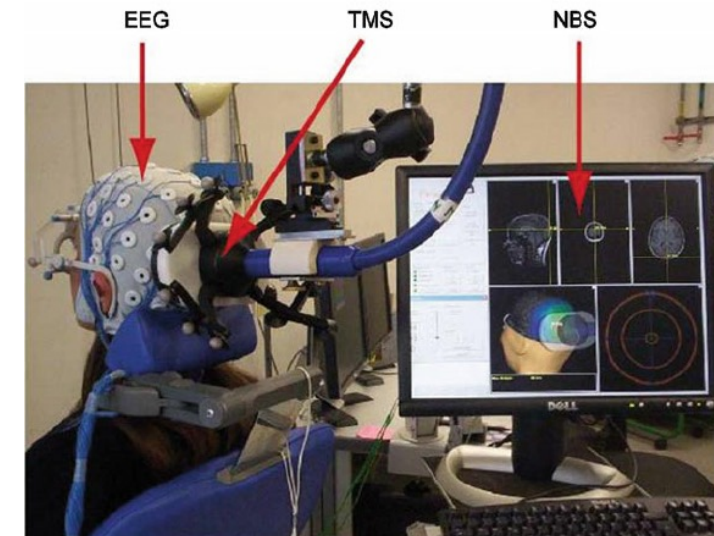
Electroencephalography (EEG)



Transcranial Magnetic Stimulation (TMS)



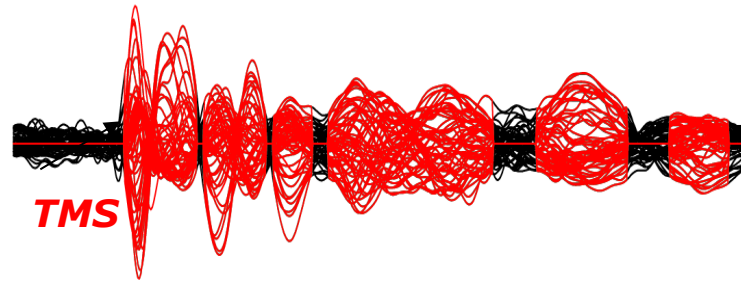
TMS-EEG





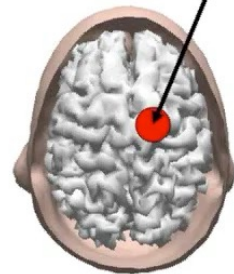
TMS-Evoked Potentials & Consciousness

Conscious

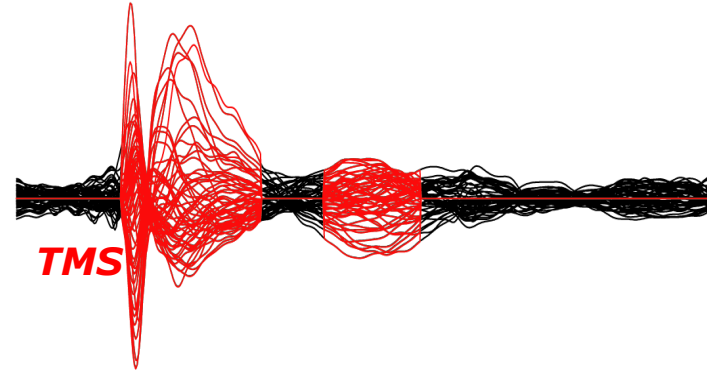


0 ms

TMS

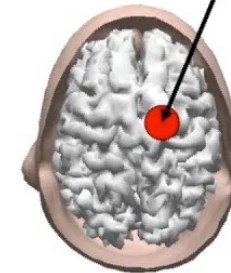


Unconscious



0 ms

TMS





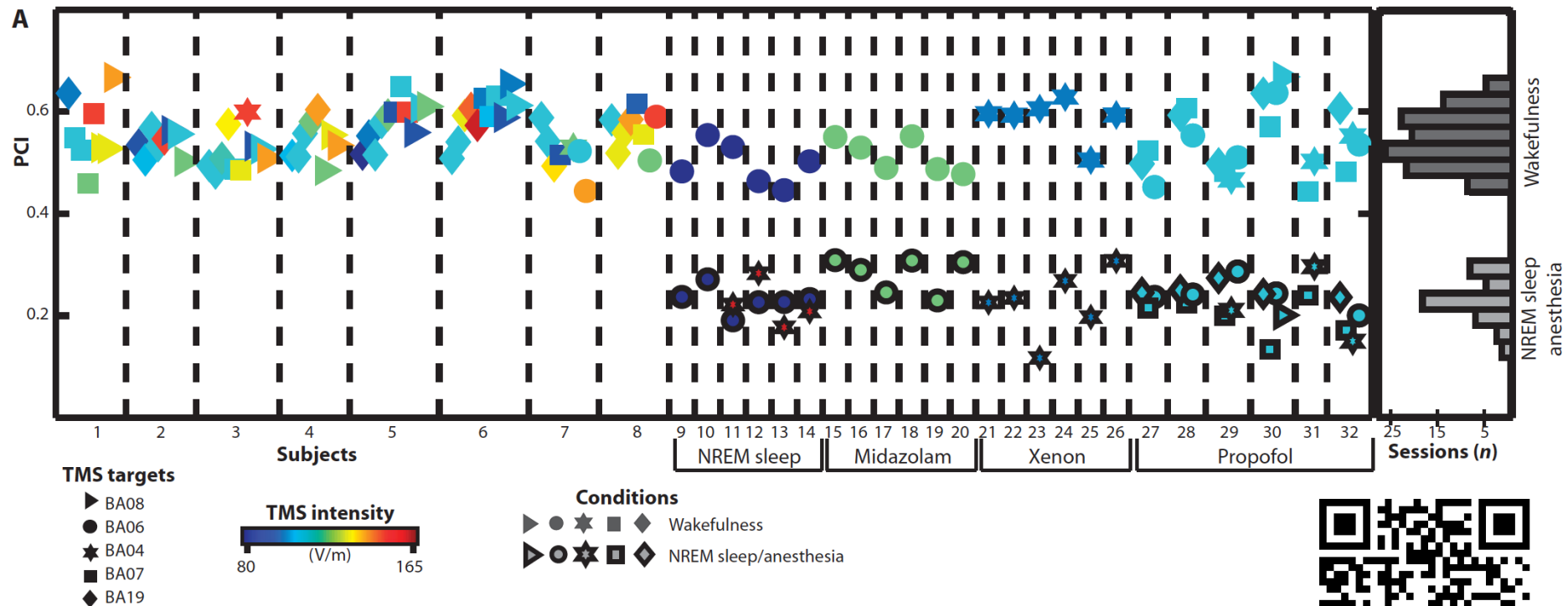
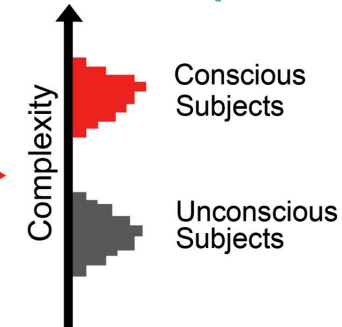
Perturbational Complexity Index (PCI)

Zap & zip
technique

Magnetic Perturbation

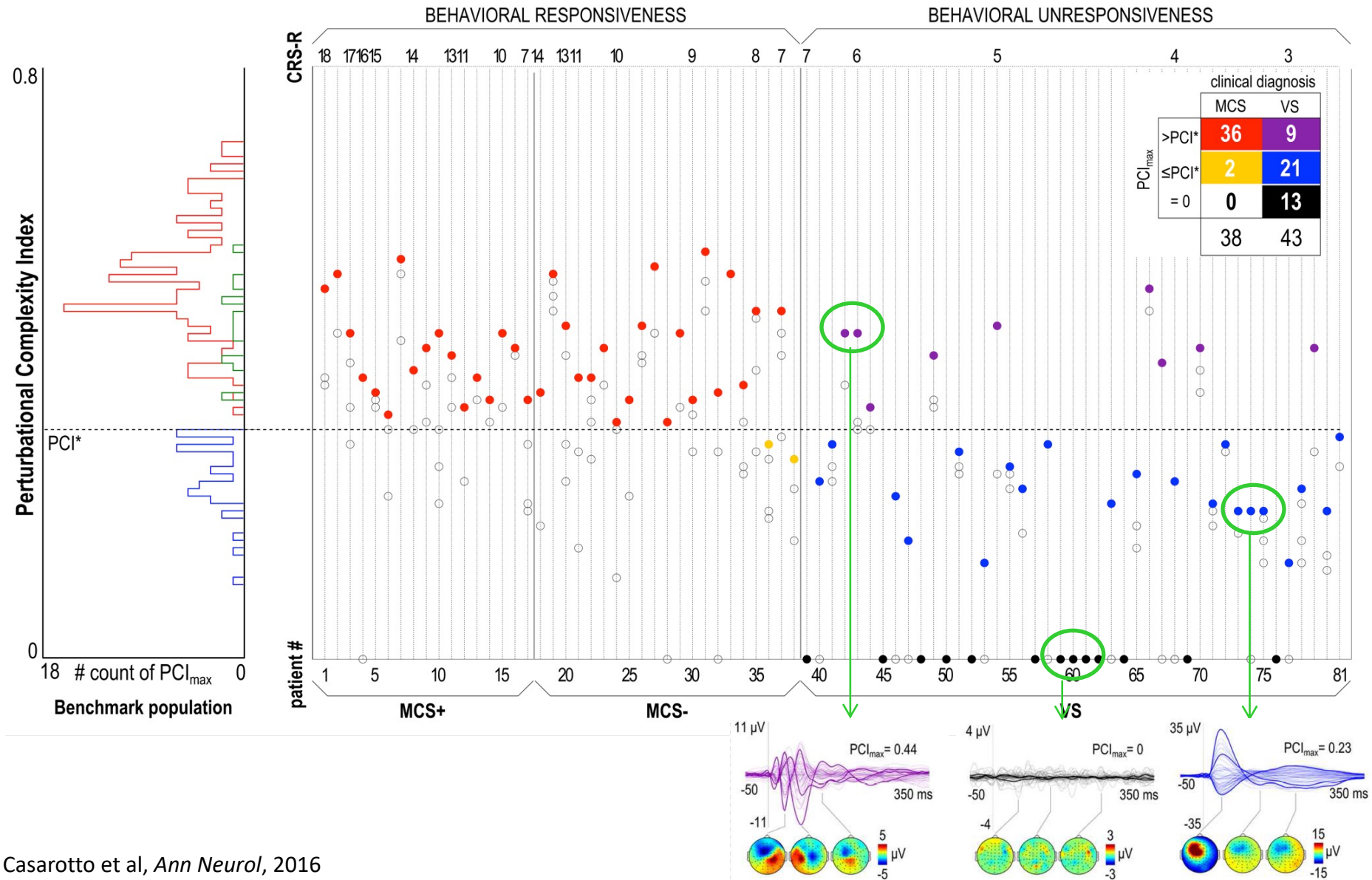
Brain Response

Compression



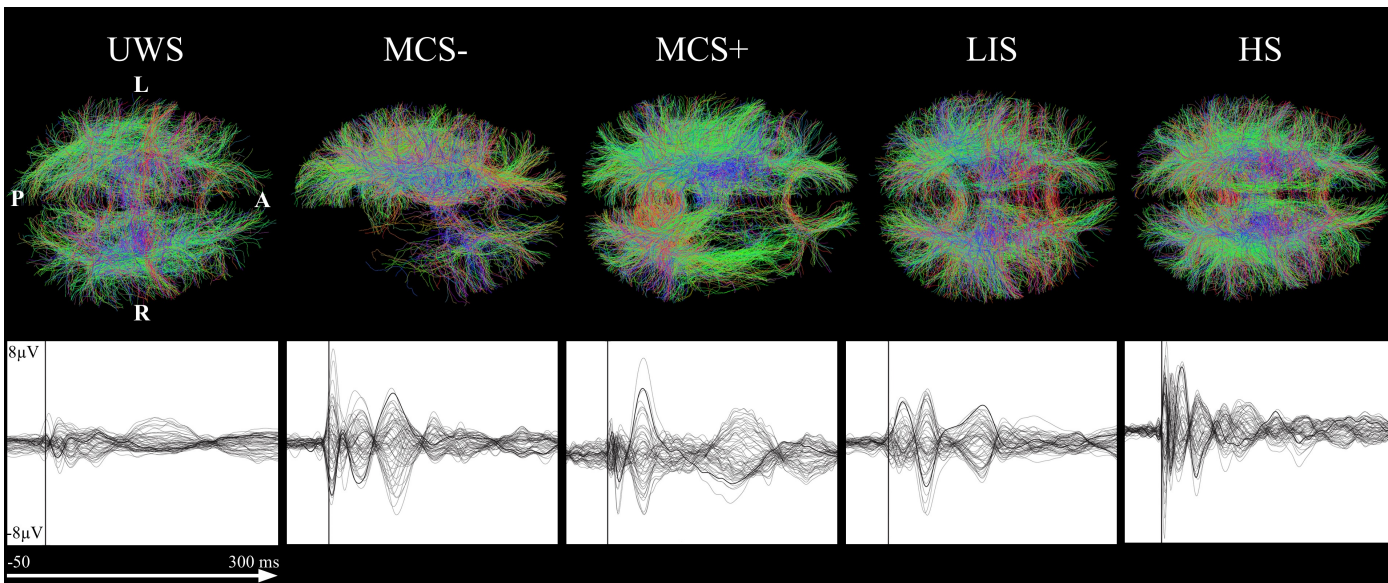


PCI in DoC

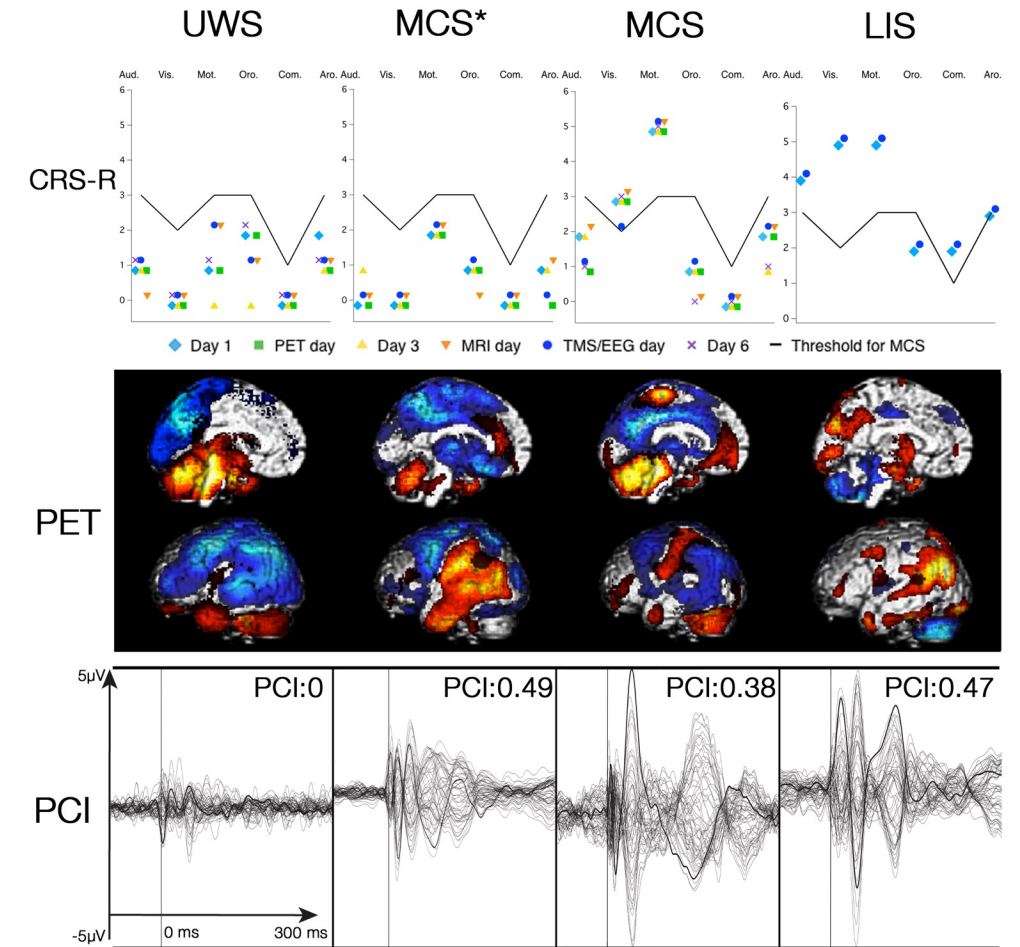




Complexity and multimodal assessment



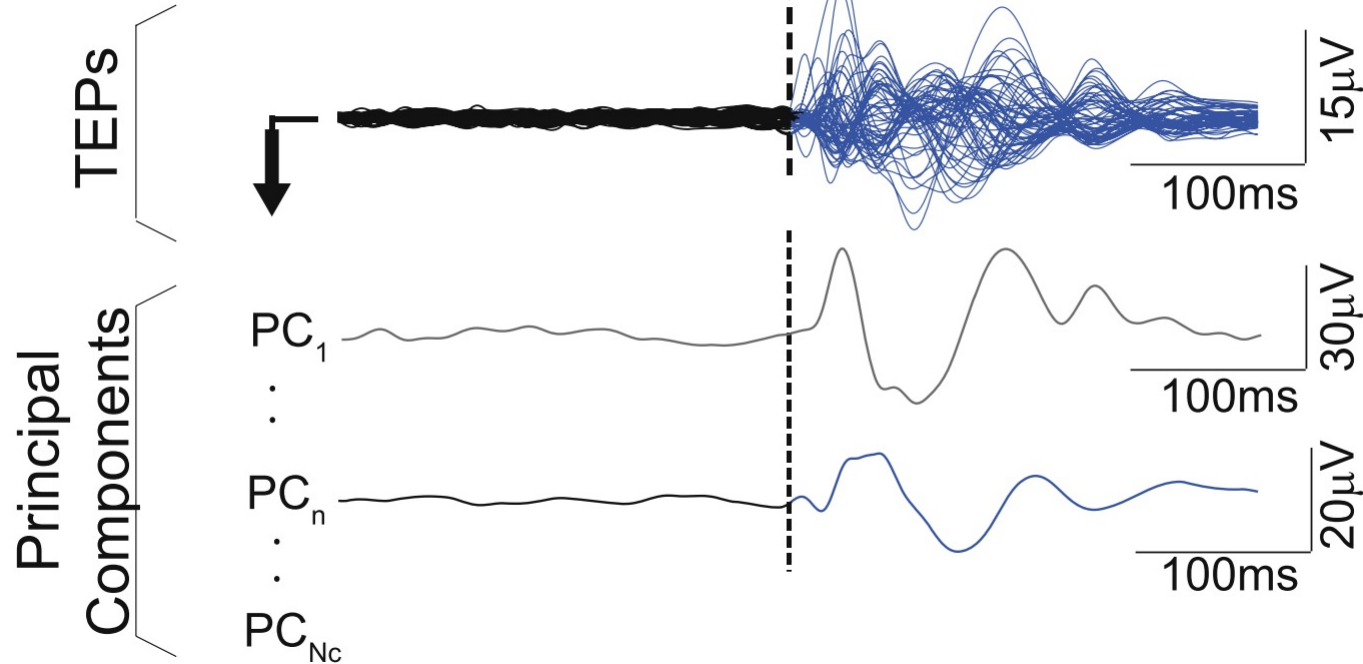
Bodart et al, *Brain Stimul*, 2018



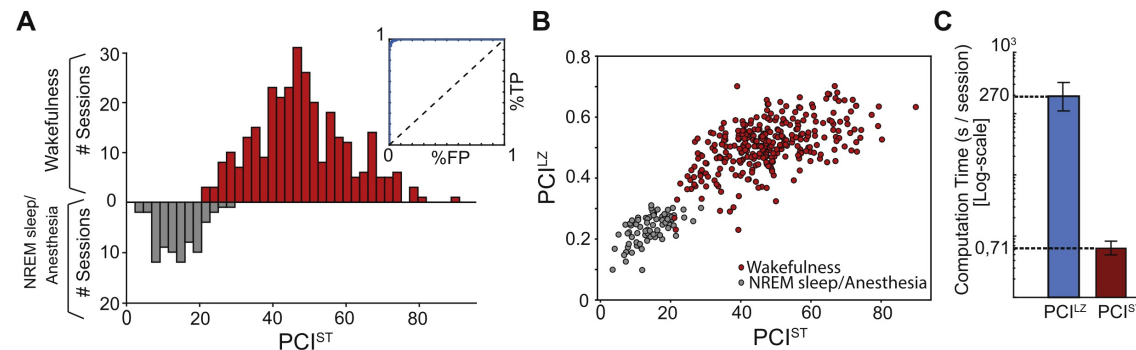
Bodart et al, *Neuroimage Clin*, 2017



PCI State Transition

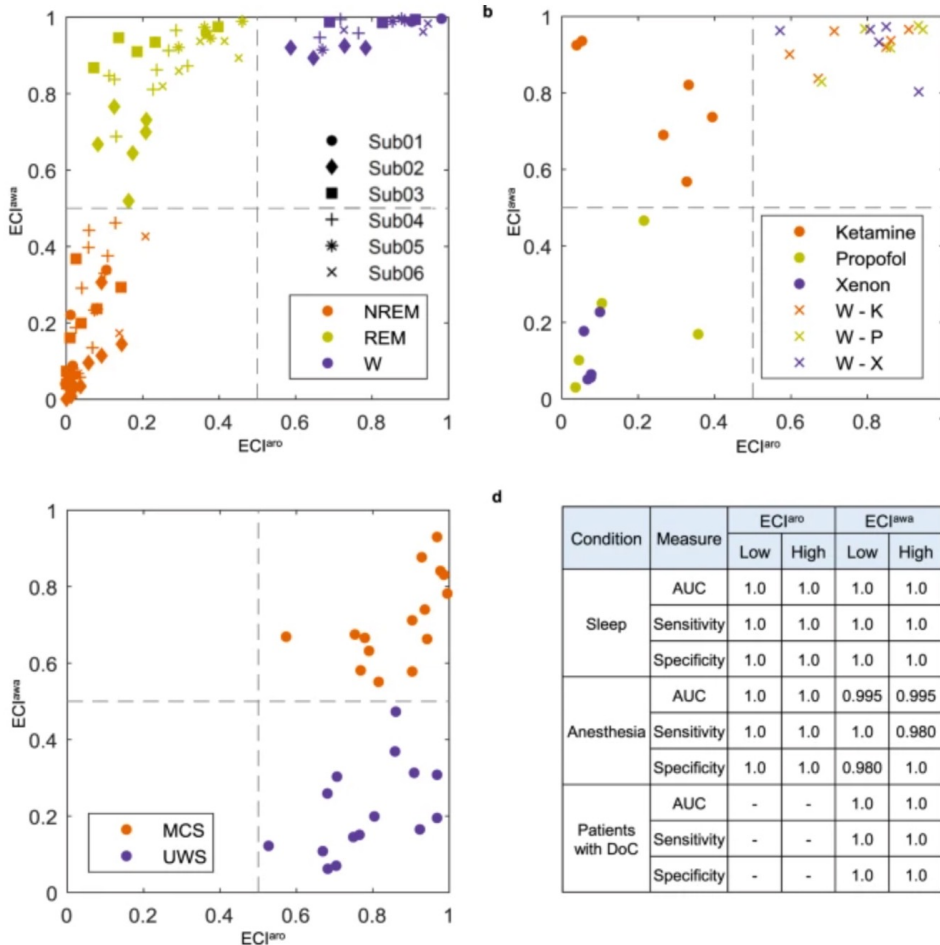


- Faster to compute
- More generalizable (used for intracranial recordings as well)





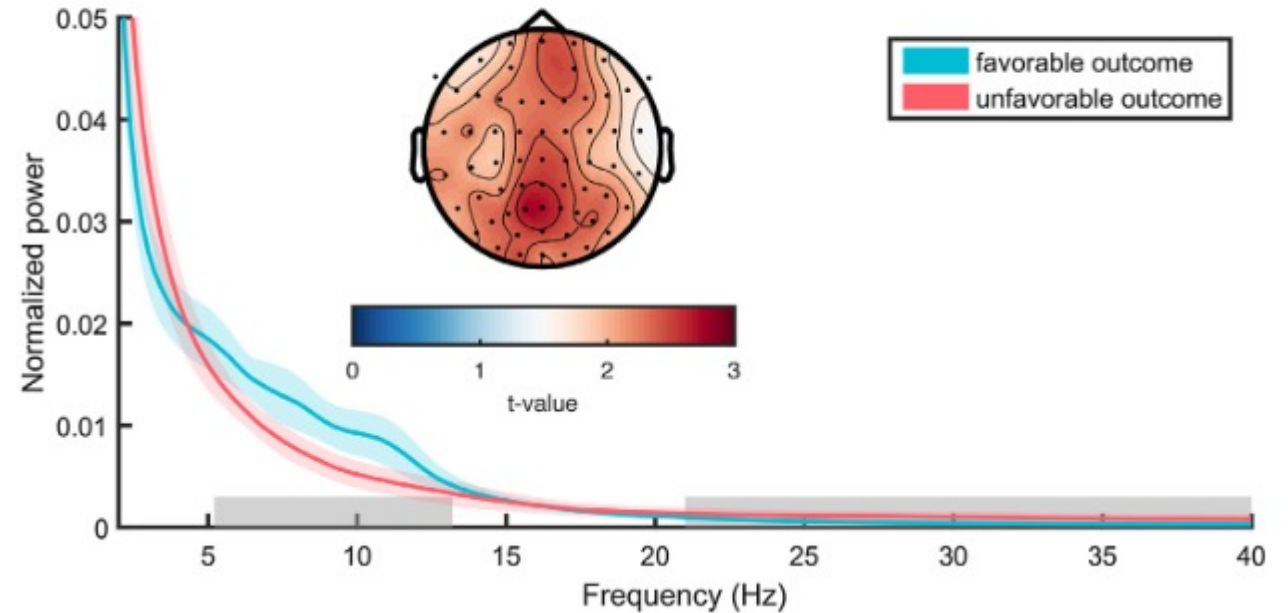
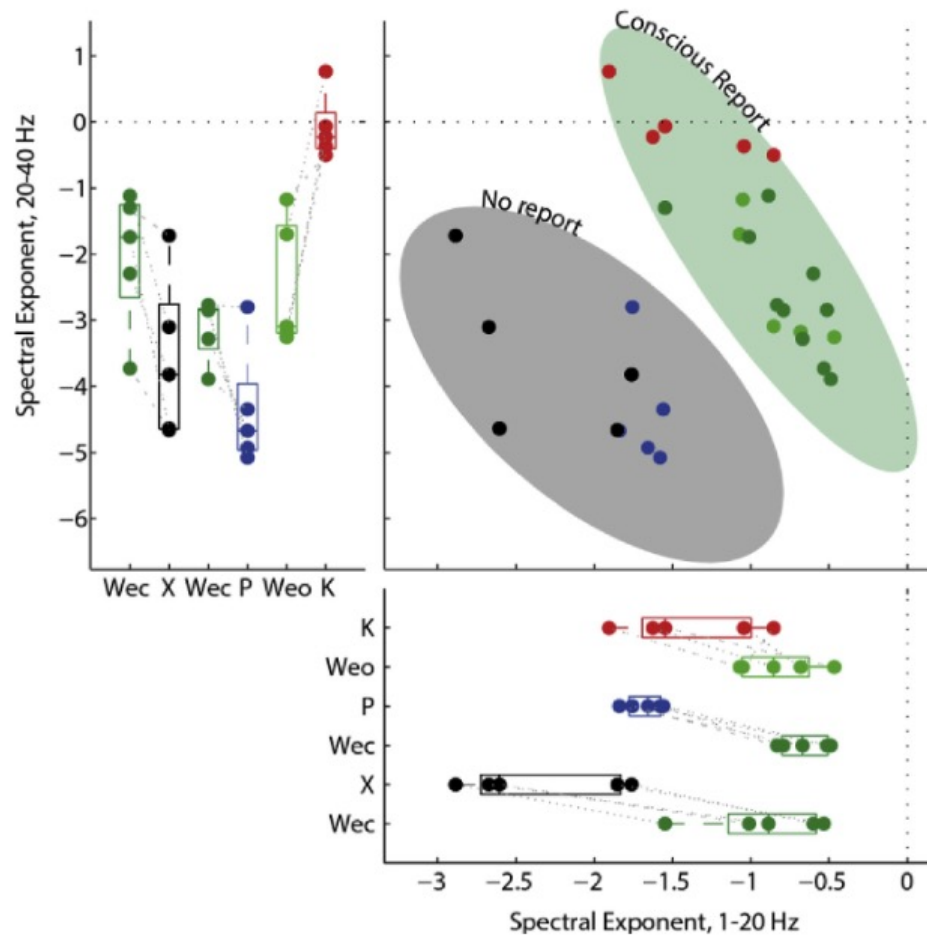
Explainable Consciousness Indicator (ECI)



- Multidimensional: difference between awareness and arousal
- Applicable to raw EEG without any perturbation

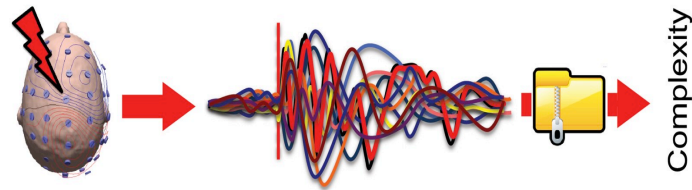


Power spectrum: diagnosis and prognosis





European Academy of Neurology recommendations



Recommendation: consider **TMS**-EEG to differentiate unresponsive from minimally conscious

Weak evidence, weak recommendation

6 publications



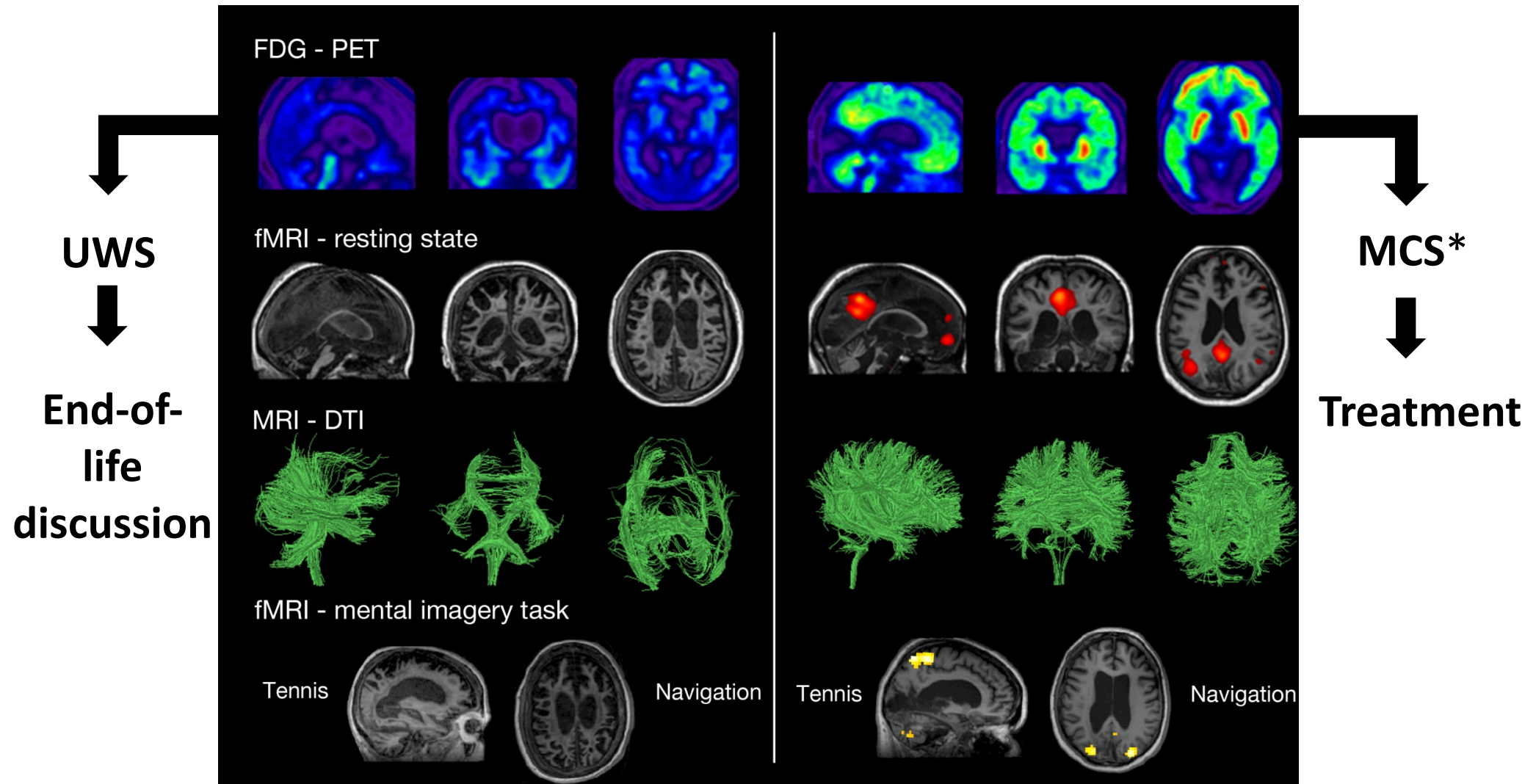
Recommendation: consider **quantitative** high density

Moderate evidence, weak recommendation

6 publications

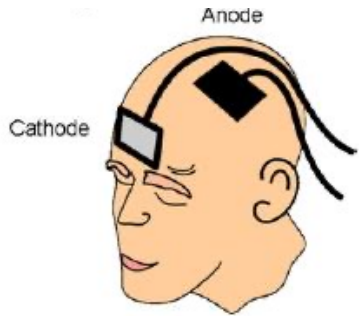


Two scenarios

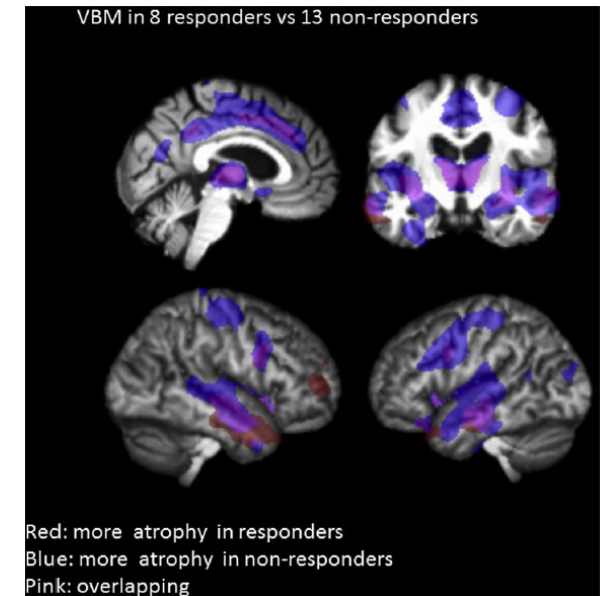
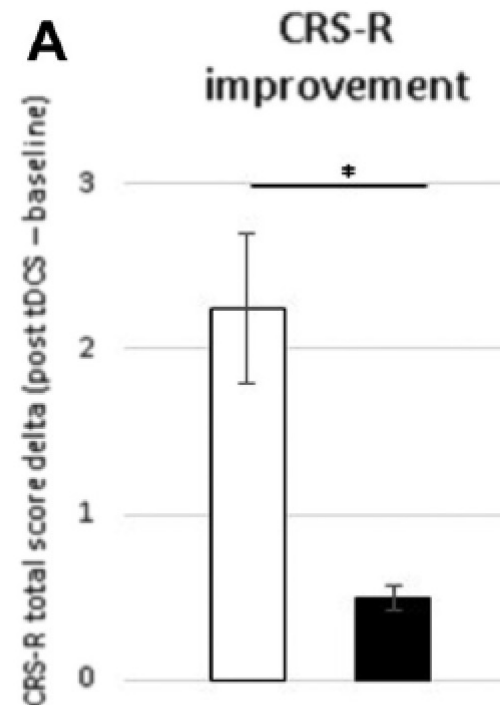
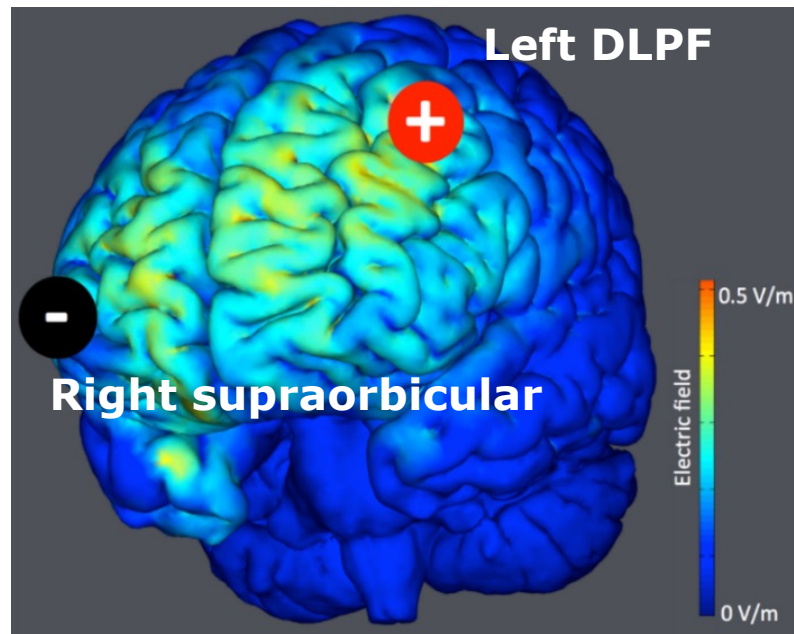




NIBS - tDCS



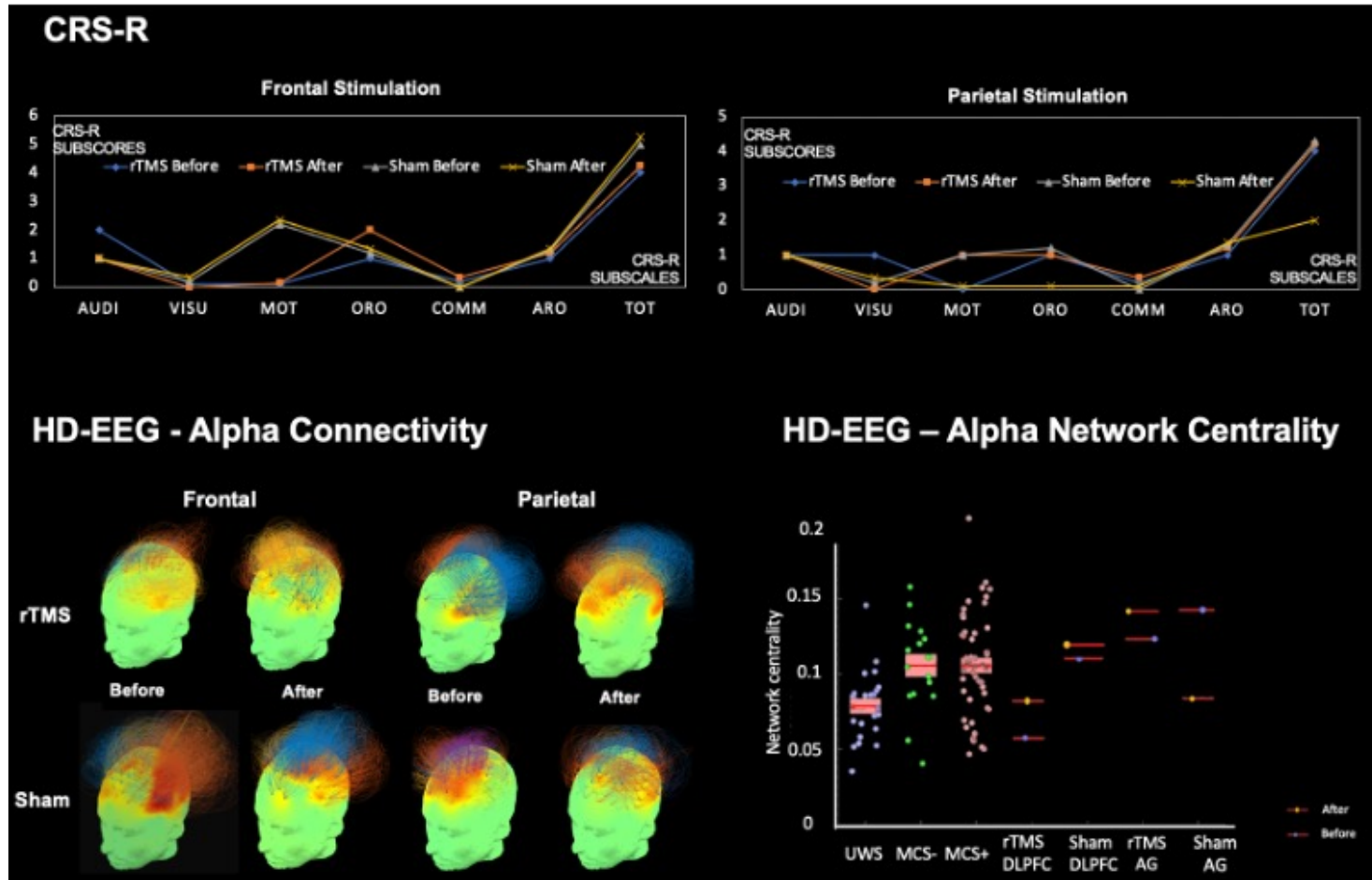
Crossover RCT (n=55)





Work by Marie Vitello

NIBS - repetitive TMS



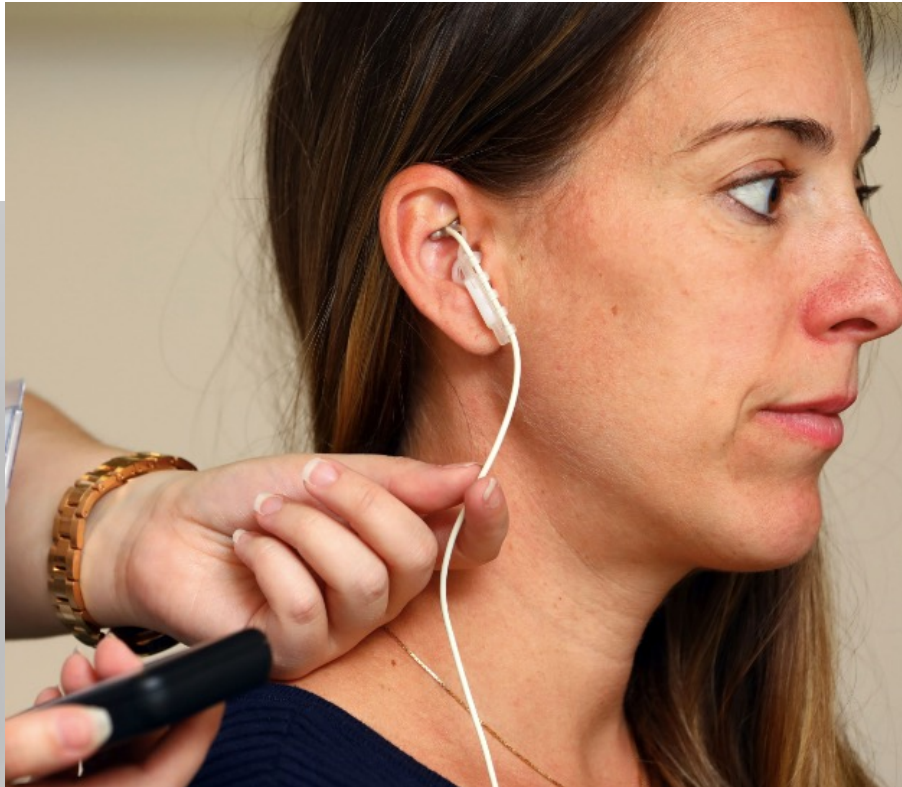
- Protocol of stimulation:
 - With or without sham
 - Dorsolateral PreFrontal Cortex; Angular Gyrus
- Change on connectivity in the alpha band after stimulation



NIBS - taVNS

Work by Marie Vitello

- transcutaneous auricular Vagal Nerve Stimulation (taVNS)
- Clinical trial in the intensive care unit
- Promising preliminary results!





Pharmacological treatment - Apomorphine

CLINICAL STUDY PROTOCOL ARTICLE

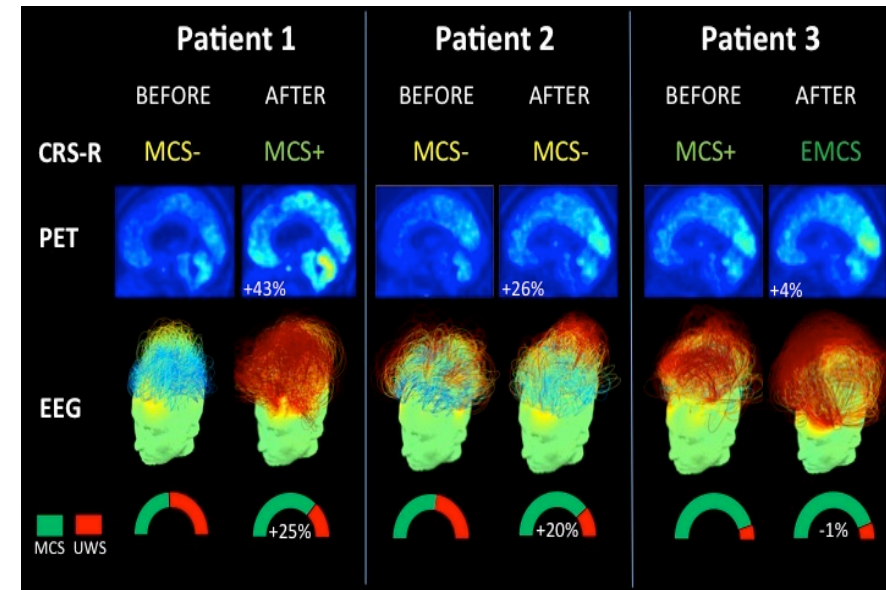
Front. Neurol., 19 March 2019 | <https://doi.org/10.3389/fneur.2019.00248>

Treating Disorders of Consciousness With Apomorphine: Protocol for a Double-Blind Randomized Controlled Trial Using Multimodal Assessments



Sanz et al, *Front Neurol*, 2019

Pilot study results

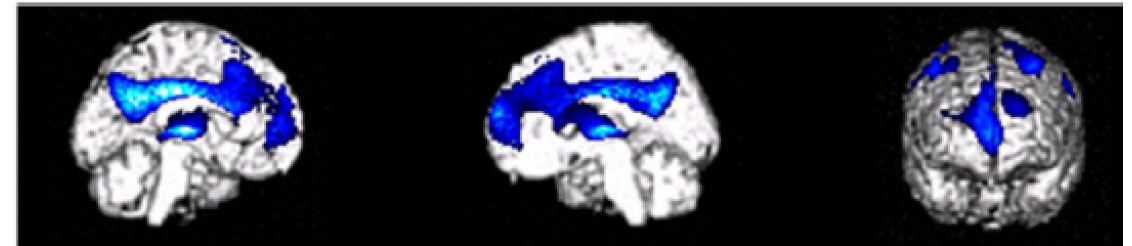




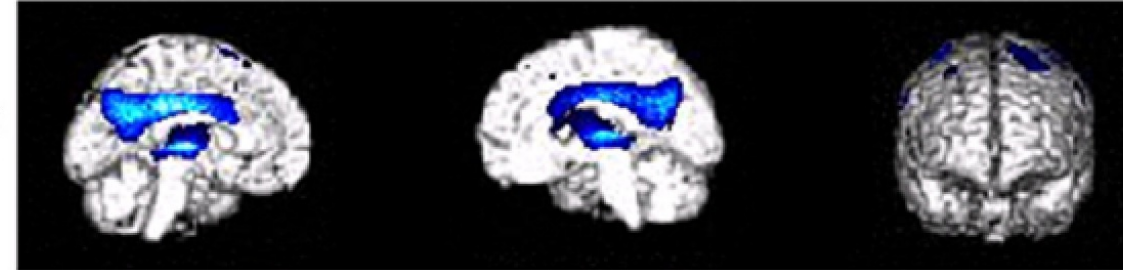
Pharmacological treatment - Zolpidem



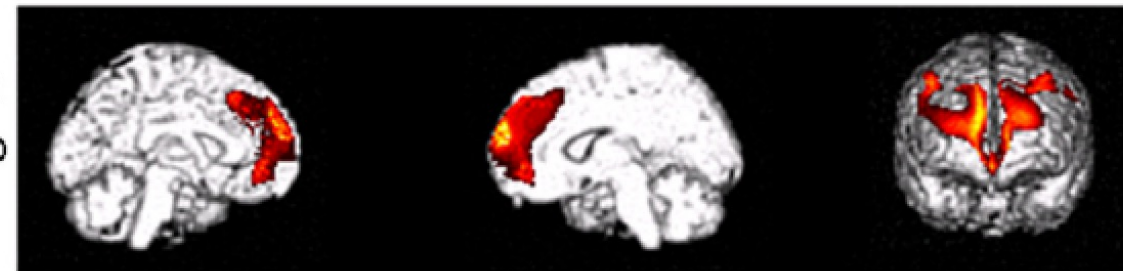
Placebo
impaired



Zolpidem
impaired

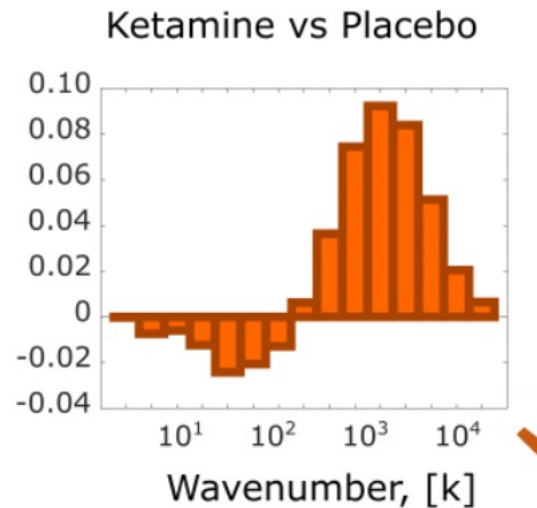
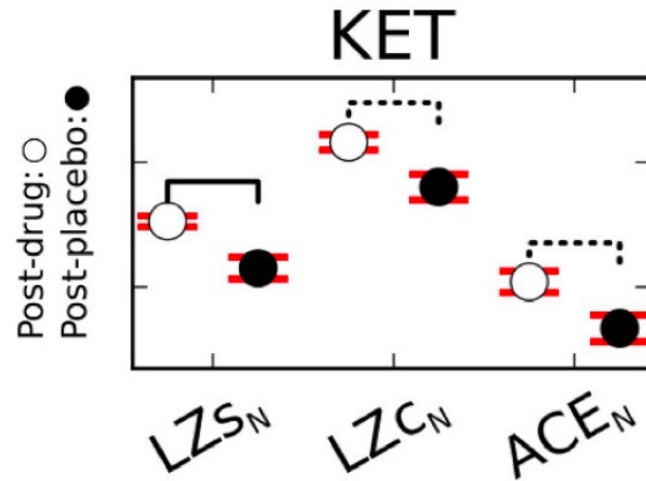


Zolpidem
> Placebo





Could we increase complexity?



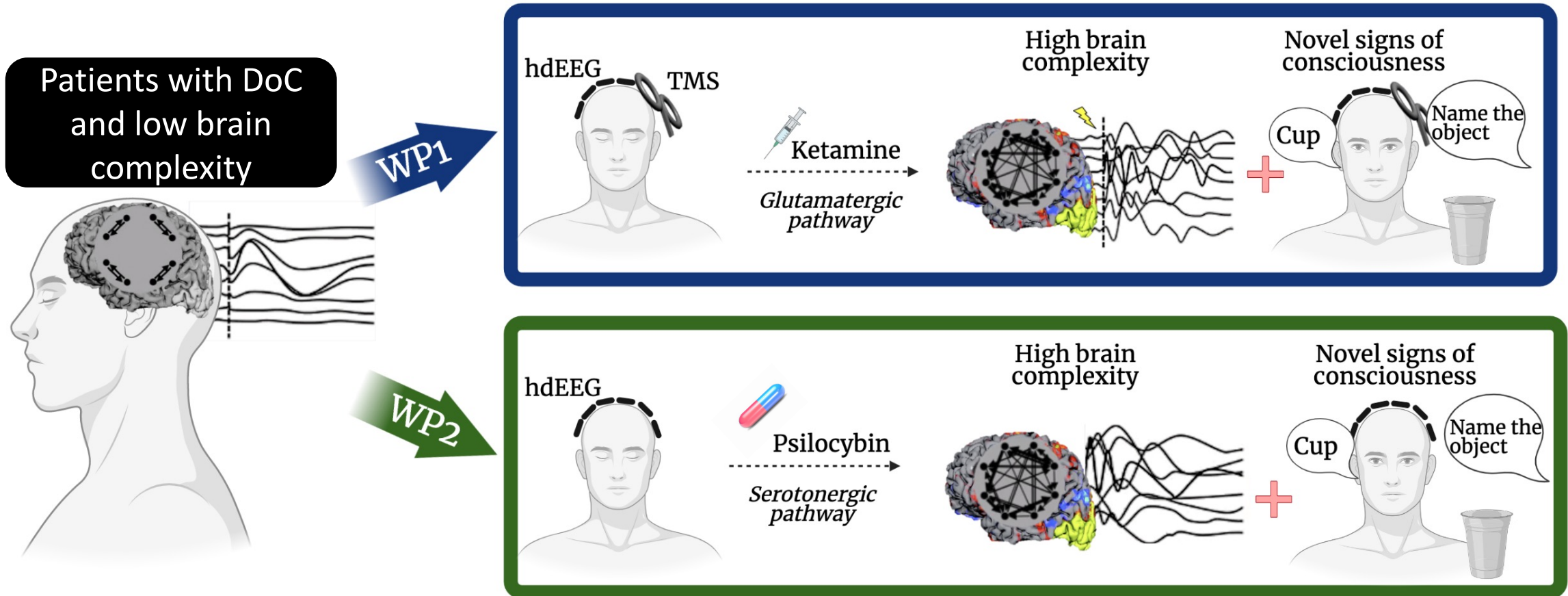
- In healthy participants psychedelics increase complexity
- Results replicate through different modalities and studies
 - Analogous for psilocybin

Schartner et al. ,*Sci. Rep.*, 2017

Luppi et al.. *BioRxiv*, 2020



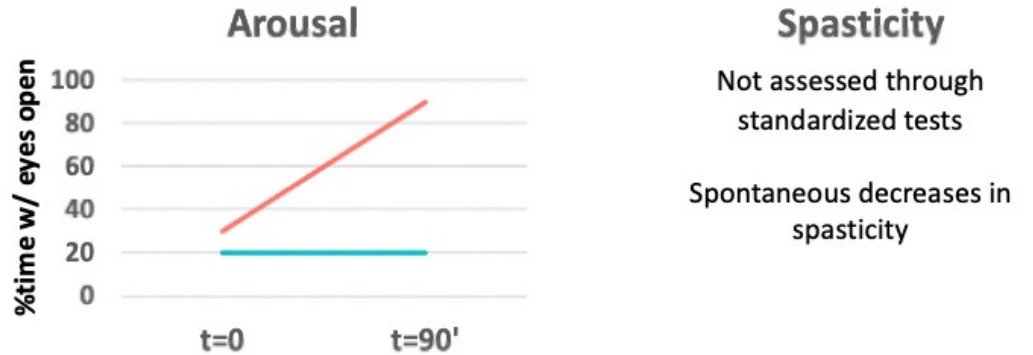
Pharmacological treatment - Psychedelics



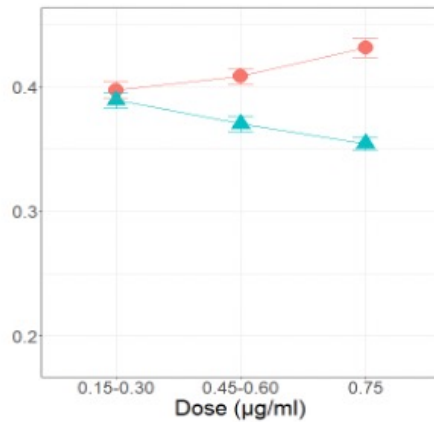


Preliminary results - Ketamine

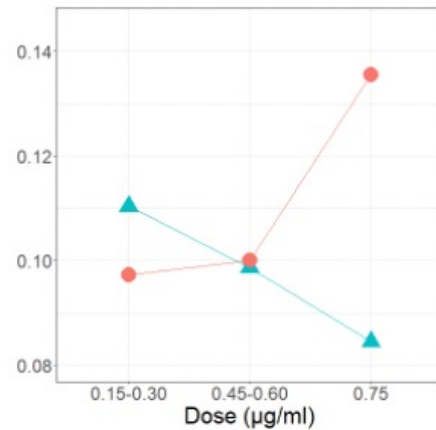
50yo male, stroke, 7m since injury, MCS-



Lempel-Ziv complexity



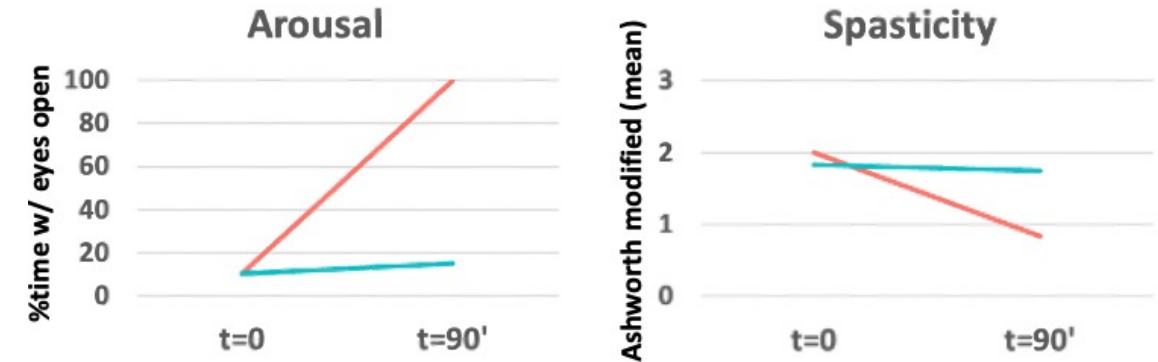
Alpha connectivity



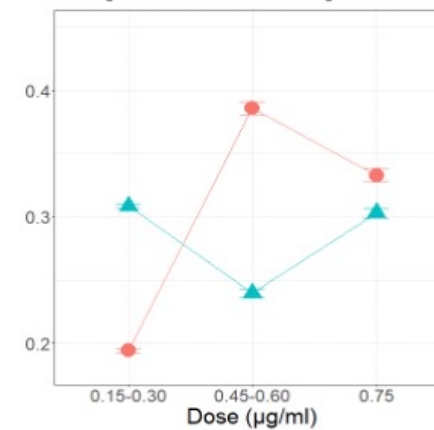
— Ketamine — Placebo

Increased arousal and LZC
No change in diagnosis

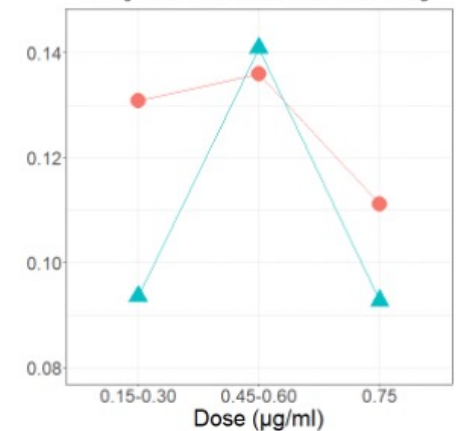
32yo male, TBI, 13y since injury, UWS



Lempel-Ziv complexity



Alpha connectivity



— Ketamine — Placebo

Increased arousal and decreased spasticity
No change in diagnosis but one response to command



Model of DoC and treatments!

Top-down stimulation

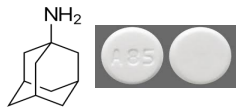
Transcranial direct current stimulation



Repetitive transcranial magnetic stimulation

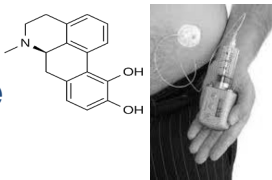


Amantadine

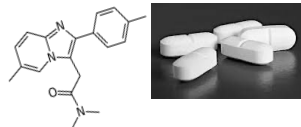


Dopamine

Apomorphine



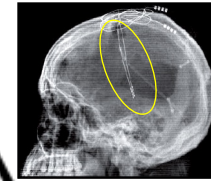
Zolpidem



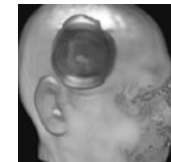
GABA

Central stimulation

Deep brain stimulation

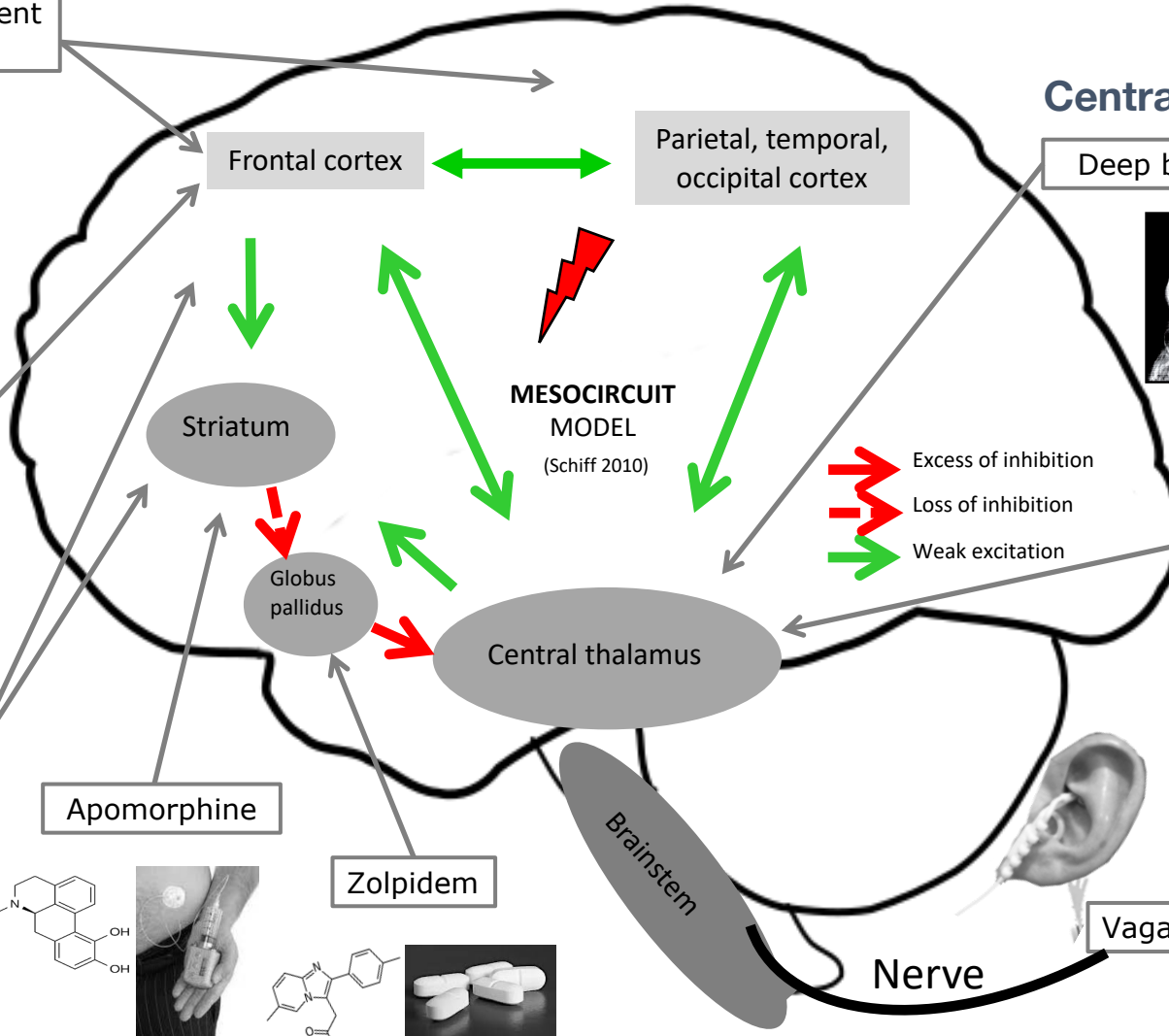


Low intensity focused ultrasound pulse



Bottom-up stimulation

Vagal nerve stimulation



What's next?



Key points and take home messages

1. Consciousness is experience, not responsiveness
2. Behavioral assessment is useful but limited
3. Neuroimaging is a necessary tool to be implemented
4. Valuable treatment available, and more on the way!

Don't judge a book by its cover!



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Gosseries



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Studying Consciousness
in the electrical brain

