

The role of multimodal imaging in the diagnosis and prognosis of DoC patients

Instituto “Carlo Besta”

October 13th 2023

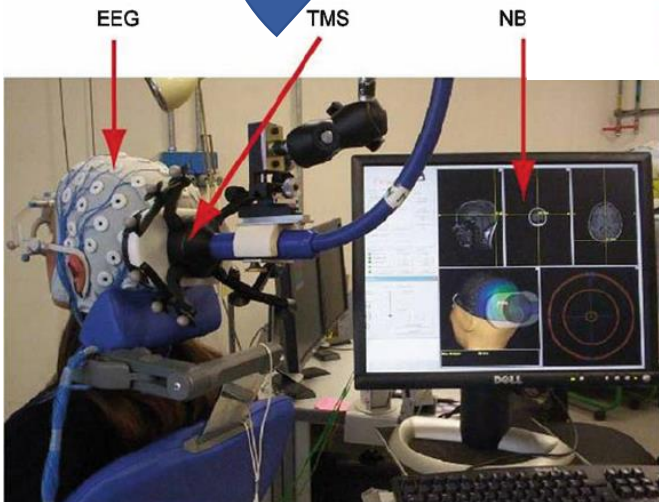
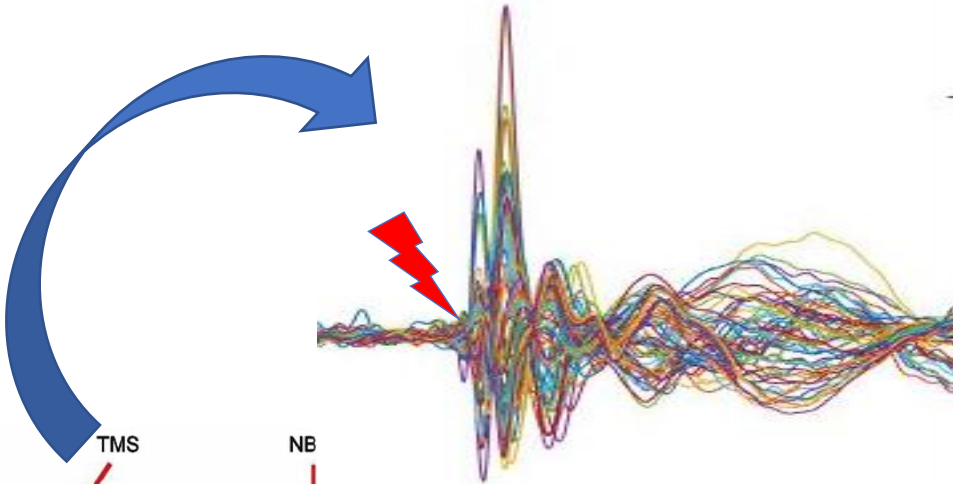
*Paolo Cardone
PhD Student
FNRS Aspirant
GIGA-Doctoral School*

Often, not real multimodal

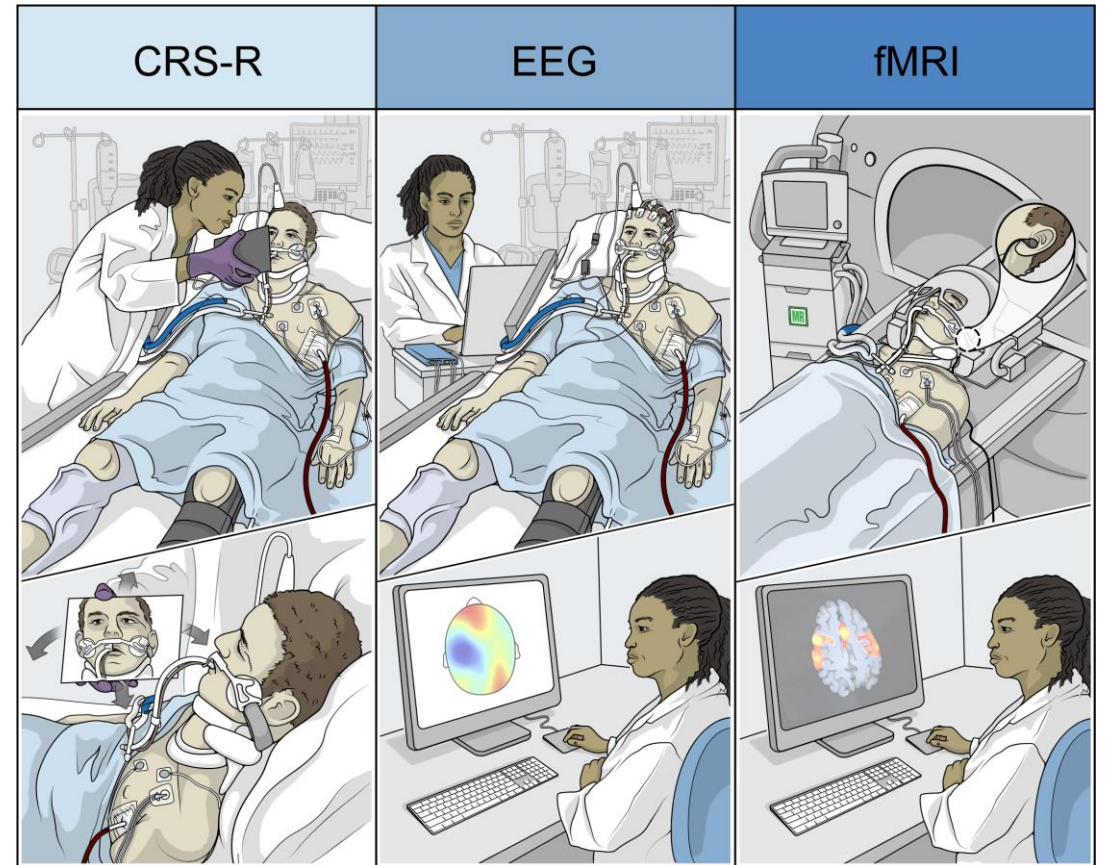


Real multimodal

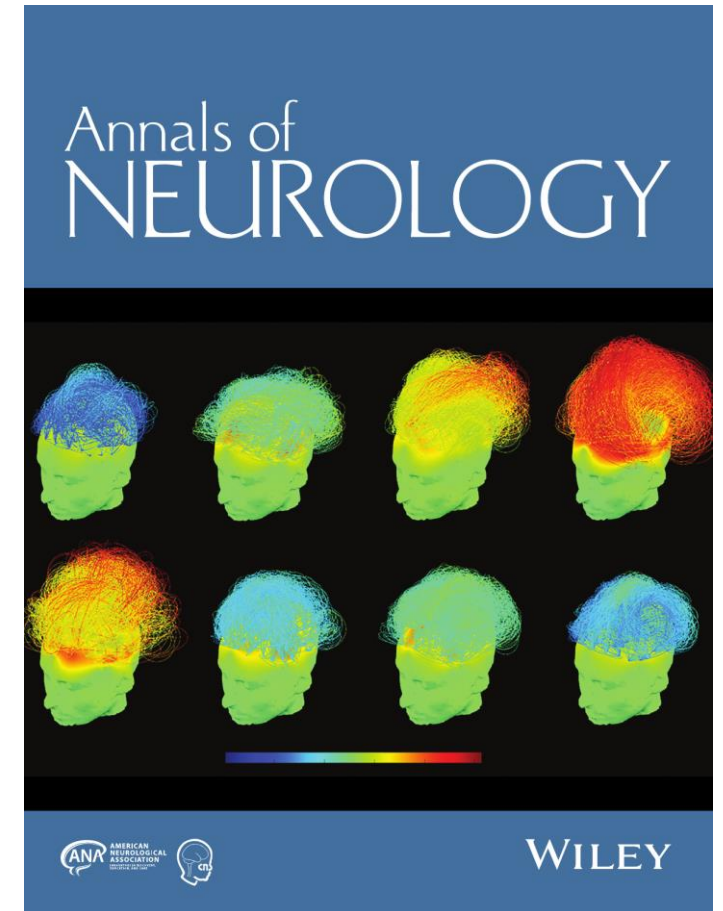
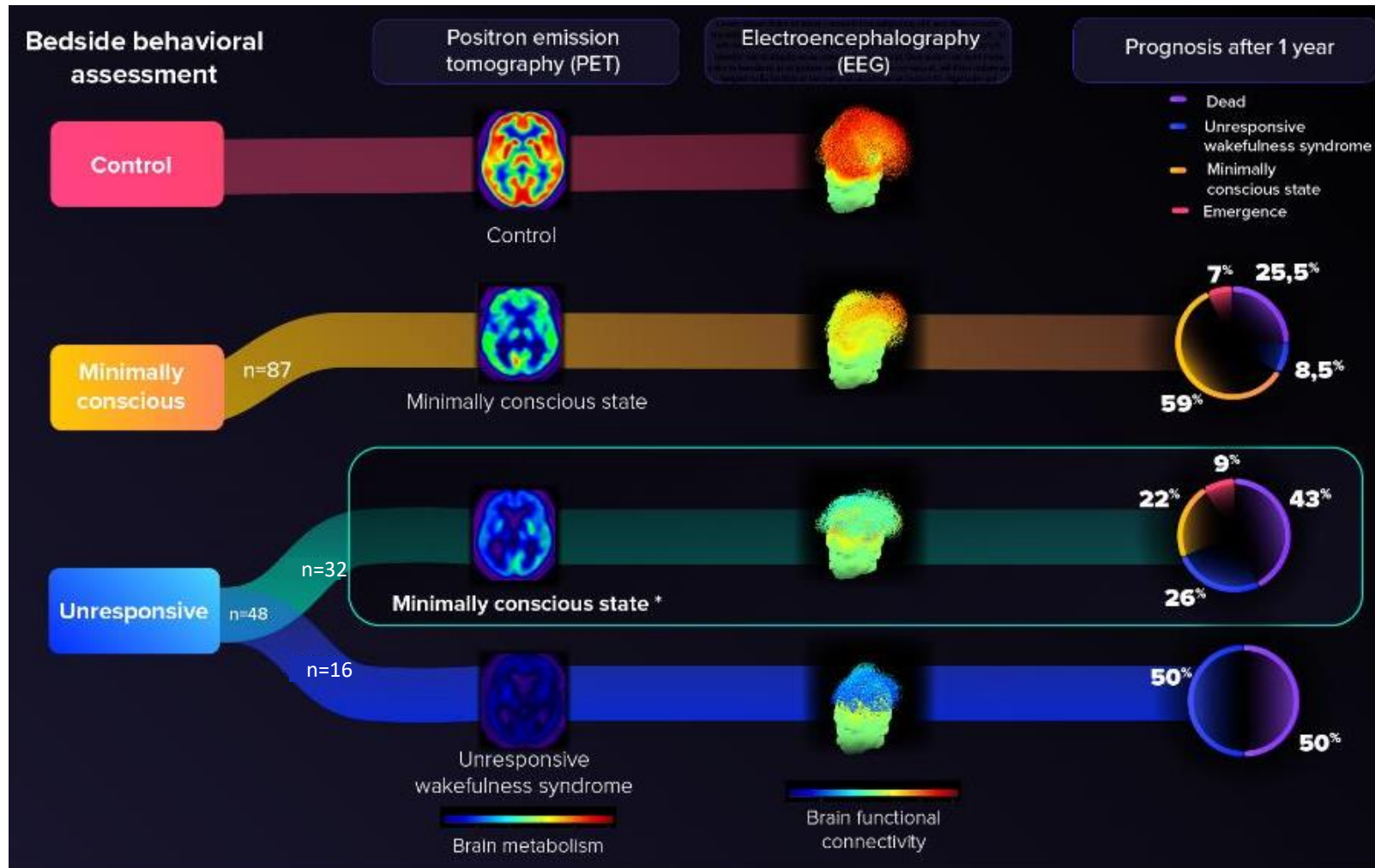
TMS-EEG



“Compounded” unimodal



More conscious than expected?





Inferring consciousness



Stimulus

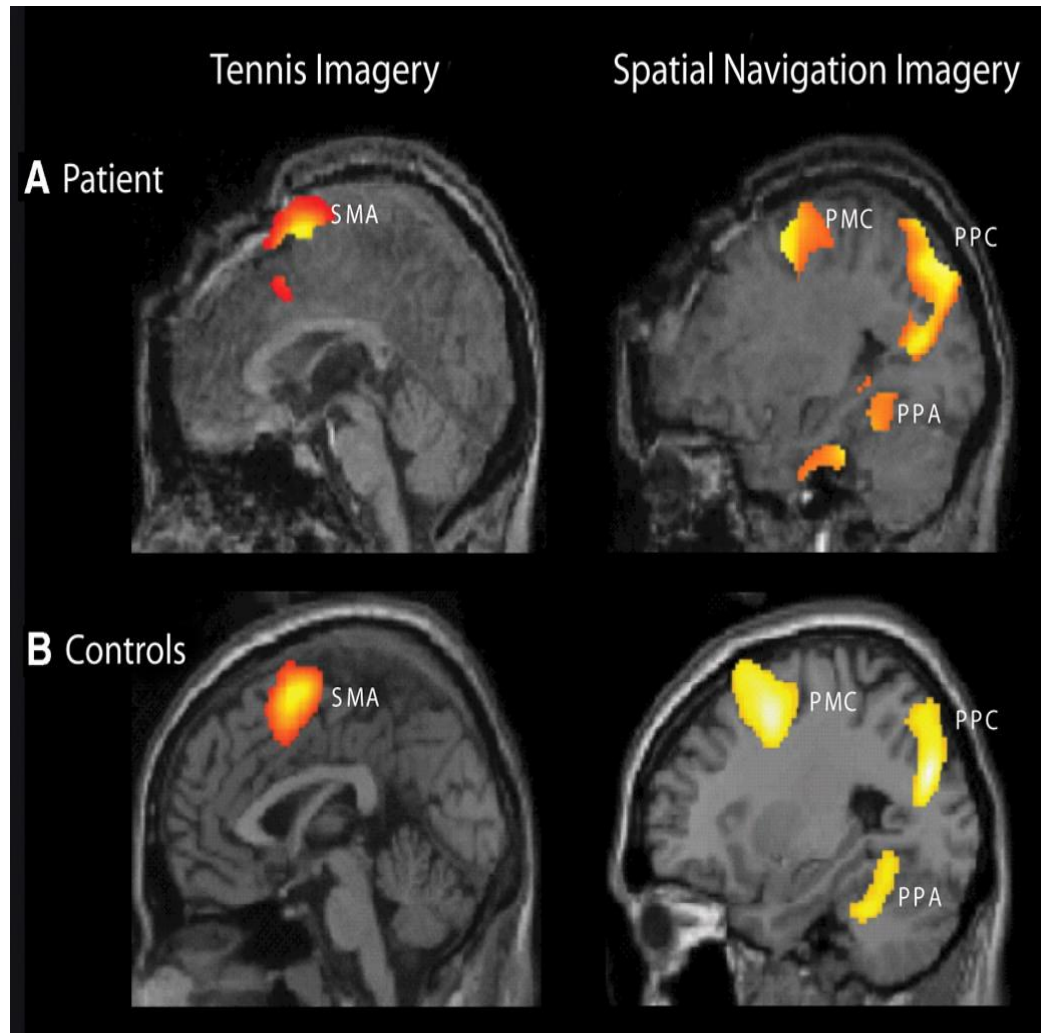


Response

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



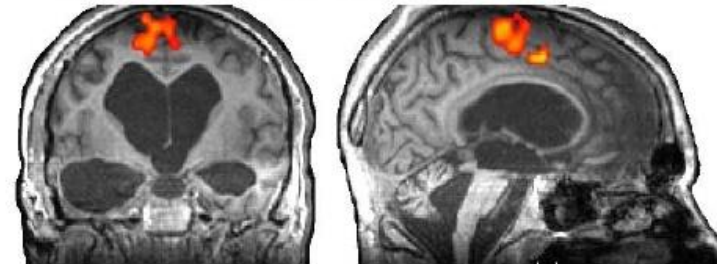
Active paradigm - fMRI



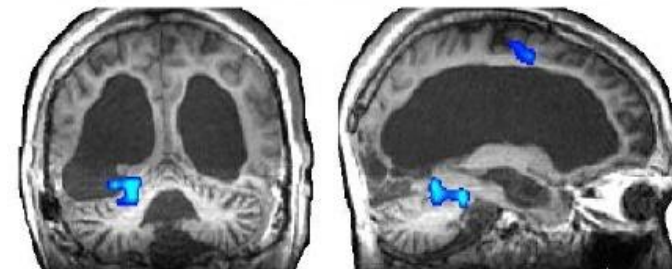
Owen et al., *Science*, 2006

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

“VEGETATIVE”
UNRESPONSIVE
PATIENT

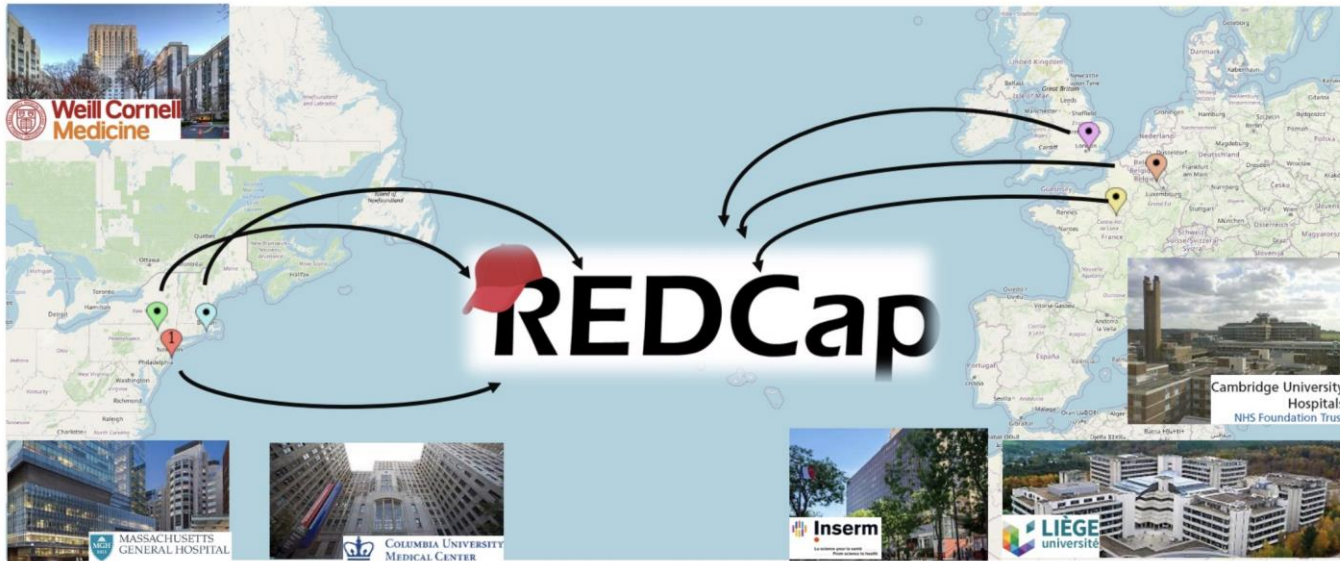


Basis for brain-
computer
interface (BCI)

Opens a door for
communication



Active tasks in DoC – McDonnell



- Multicentric study to gather larger-to-date cohort of patients with active tasks
- At least 1 in 4 unresponsive patients is conscious



Inferring consciousness, again



Stimulus

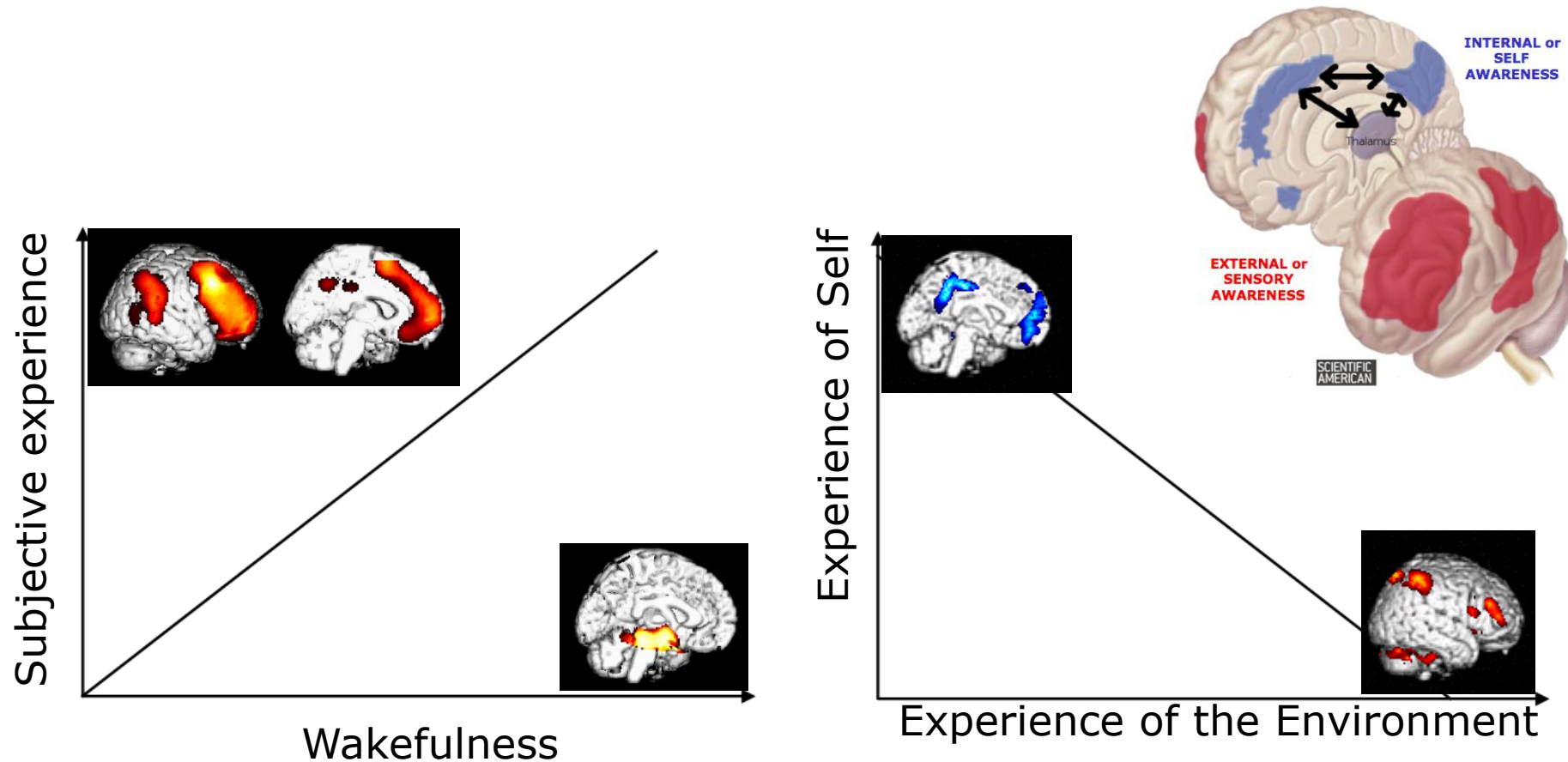


Response

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



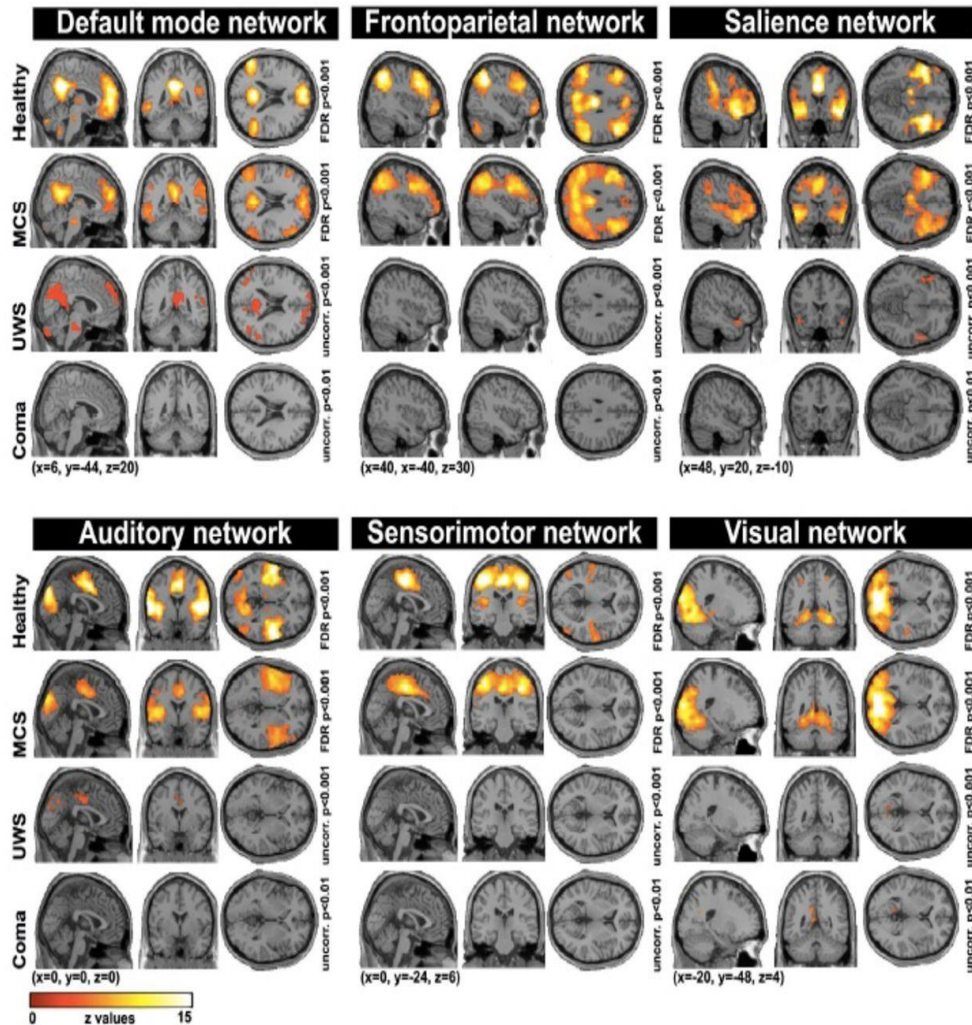
Internal and external awareness networks



Boly et al, *Ann NY Acad Sci*, 2009

Vanhaudenhuyse & Demertzi et al, *J Cogn Neurosci*, 2011

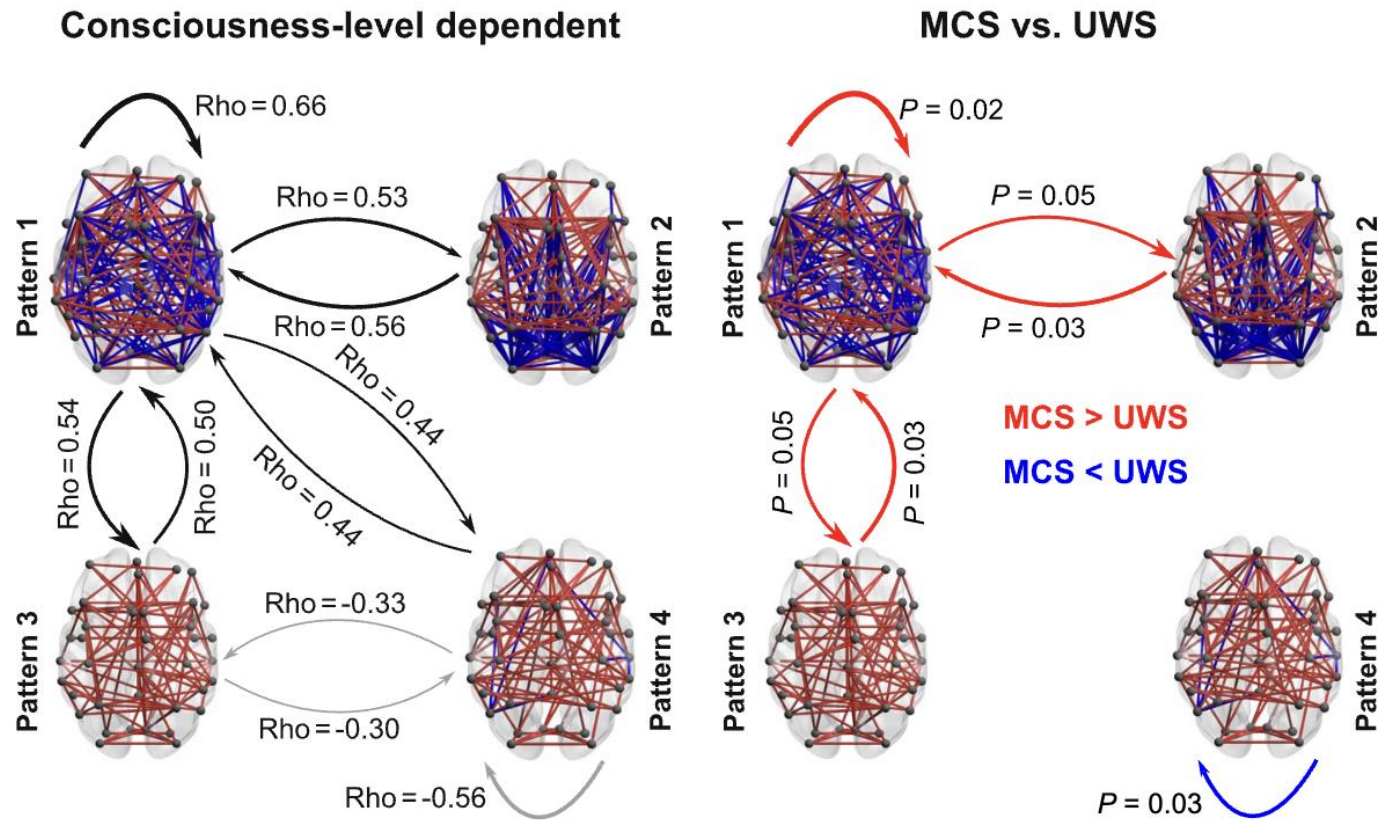
Resting state fMRI – Preserved networks



- MCS patients present preserved functional network differentiation
 - Anticorrelation of DMN and TPN emerges only in EMCS
- Static difference of functional organization

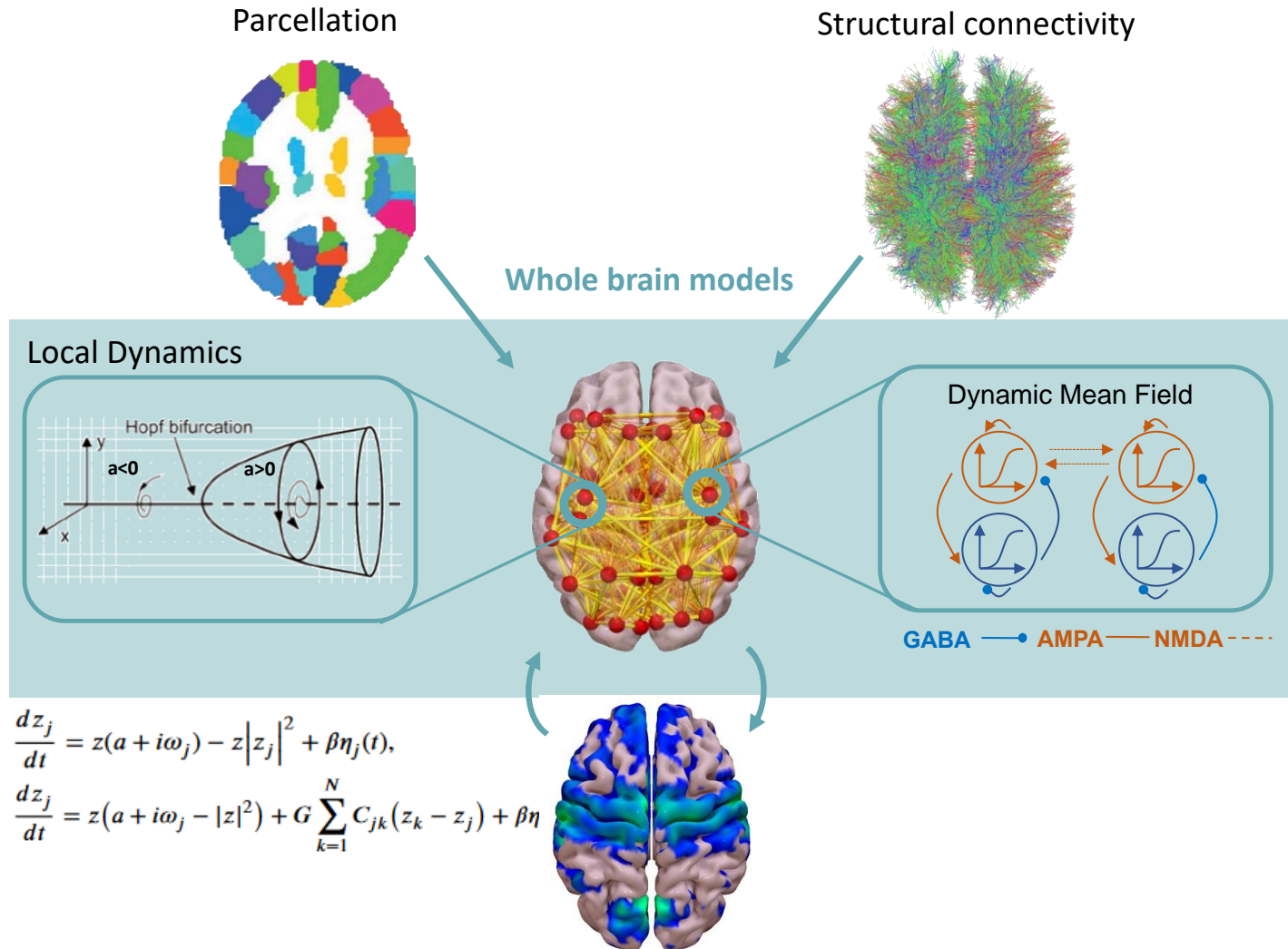


Resting state fMRI – Dynamics



- Markov chain applied on fMRI in chronic DoC
- Discernable evolution over time of activity pattern between conscious and unconscious patients

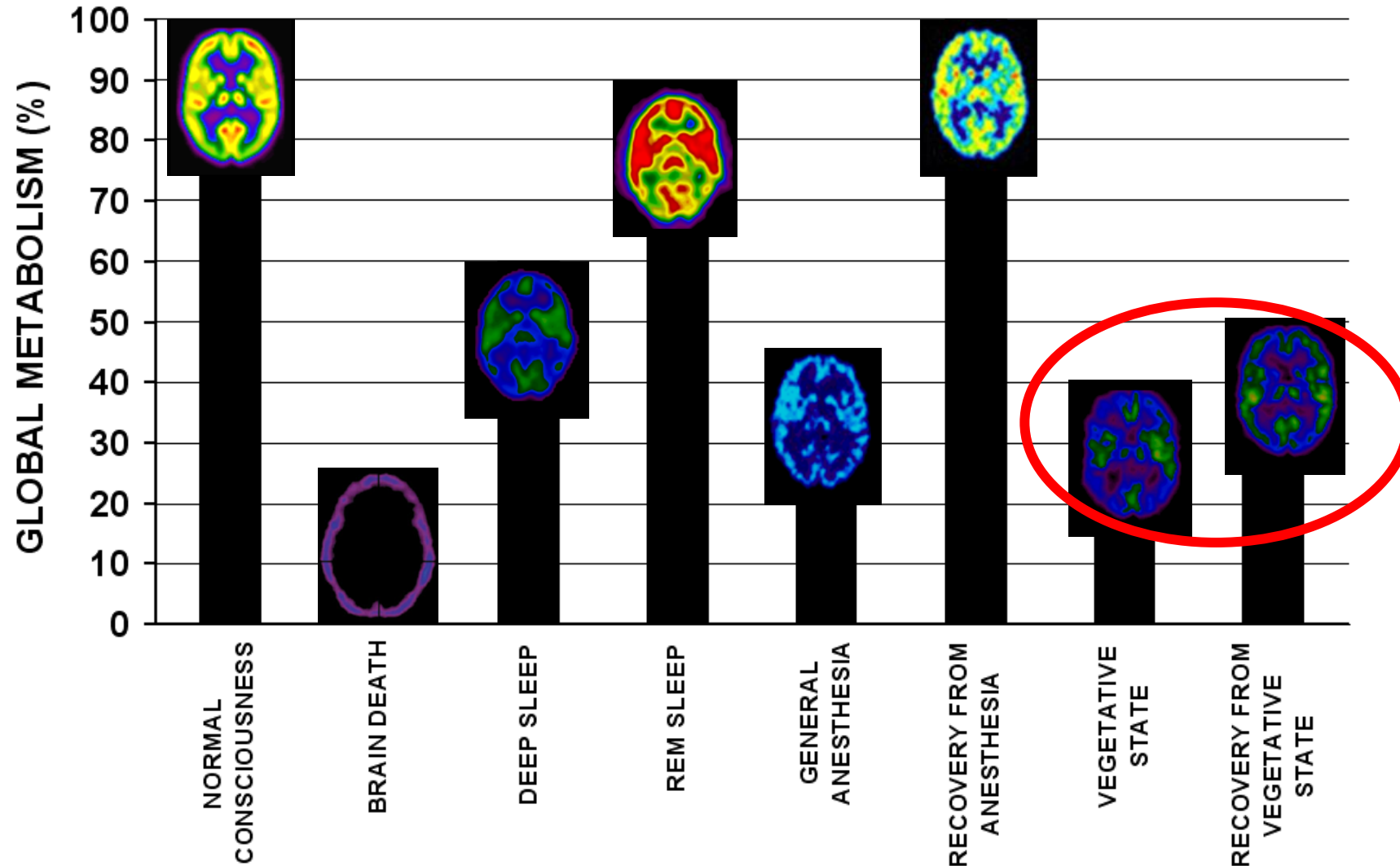
Modelling and fMRI



- “Phase-0 experiments” for challenging or impossible studies
- In-silico biomarkers of responsiveness to a treatment



Global brain metabolism and consciousness



PET difference between MCS and UWS

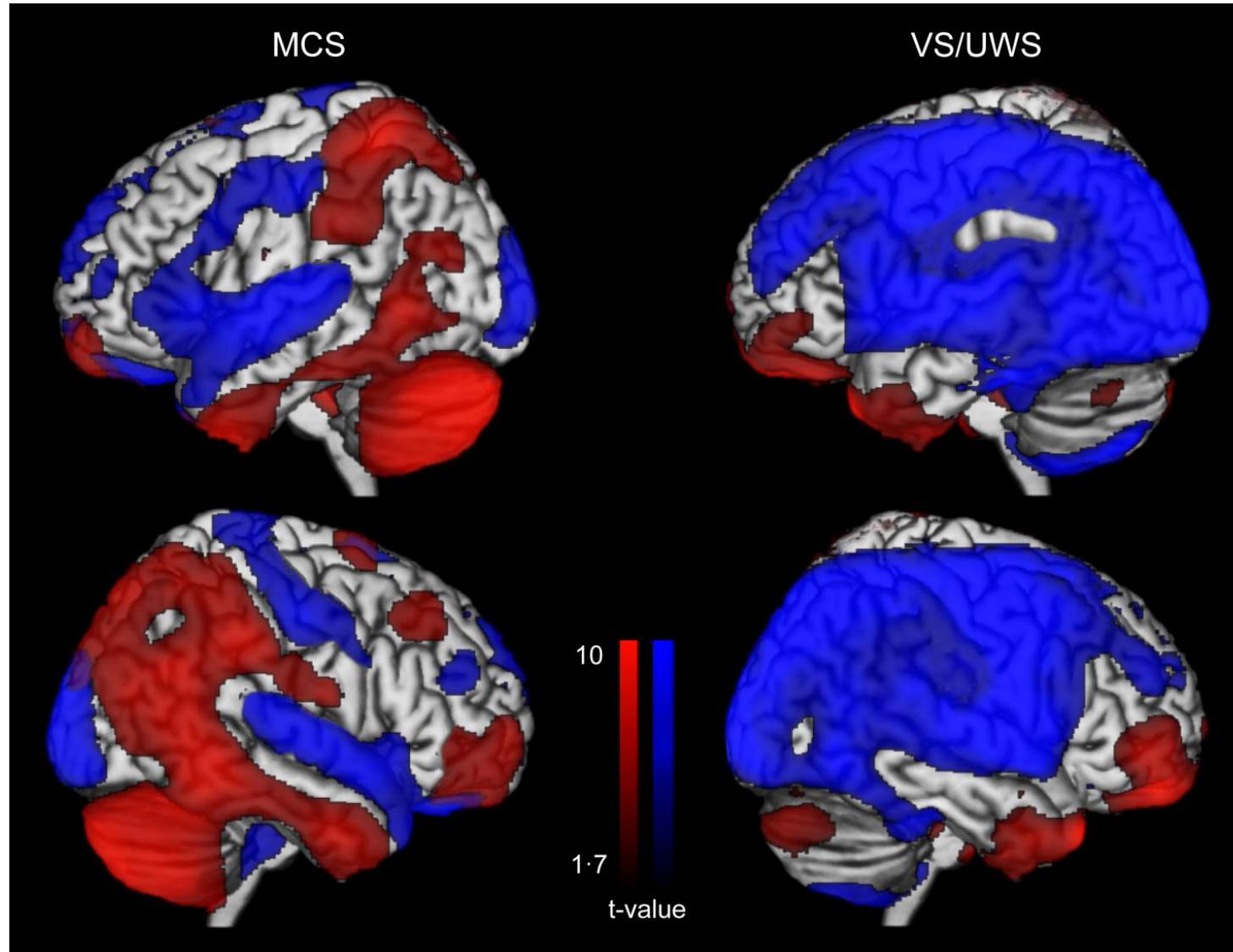


130 patients

81 MCS

41 VS/UWS

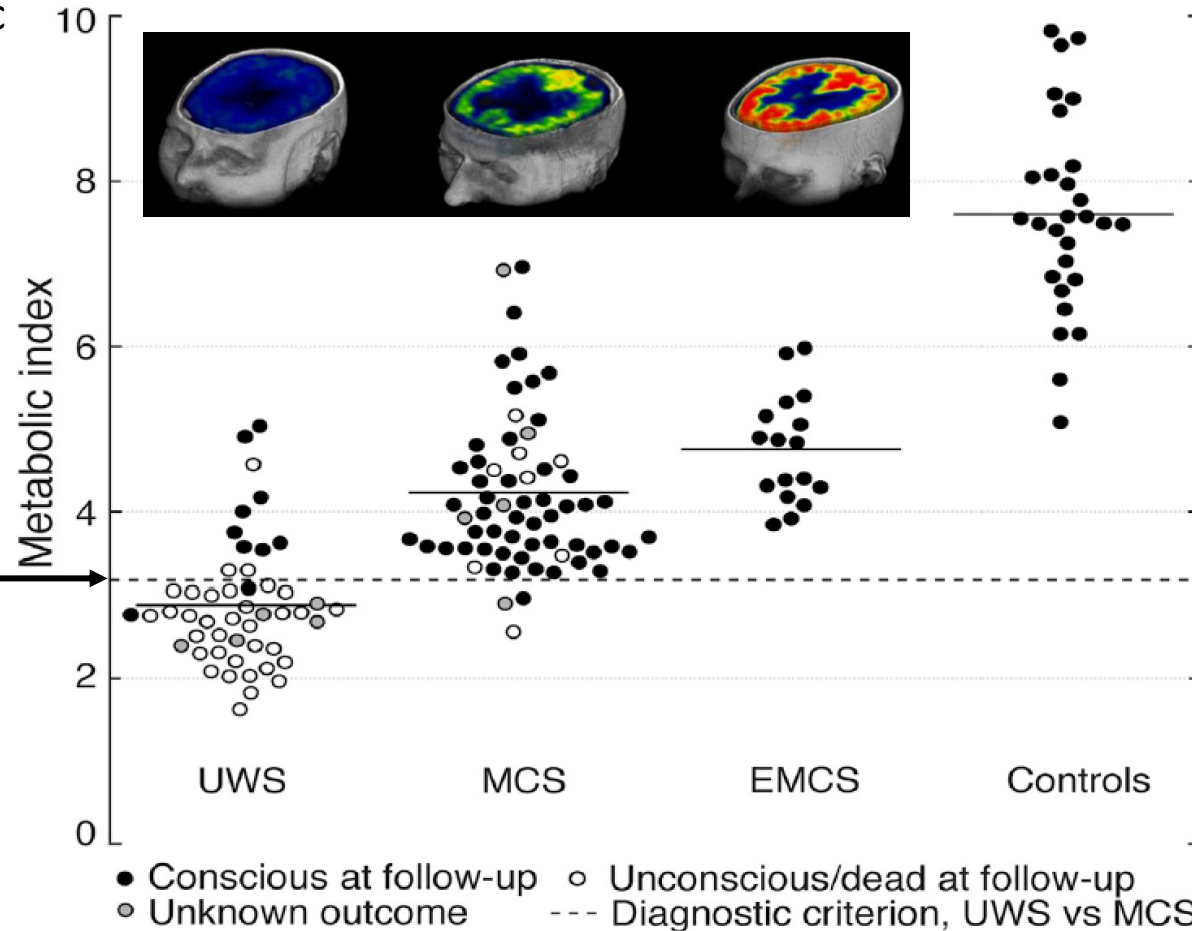
4 LIS





Minimal energy dispense for consciousness

Minimal Energetic Requirement



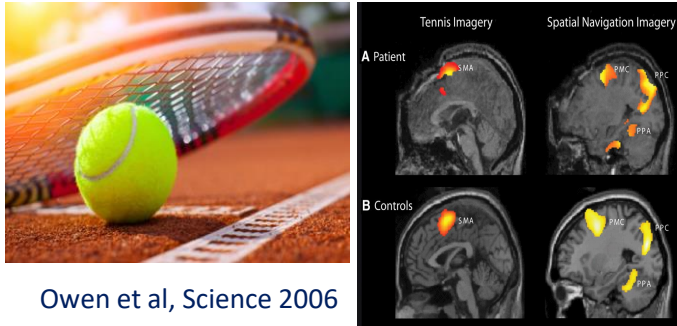
Pipeline used in the lab



tinyurl.com/DOC-TOOLBOX

European Academy of Neurology recommendations

Active fMRI



Owen et al, Science 2006

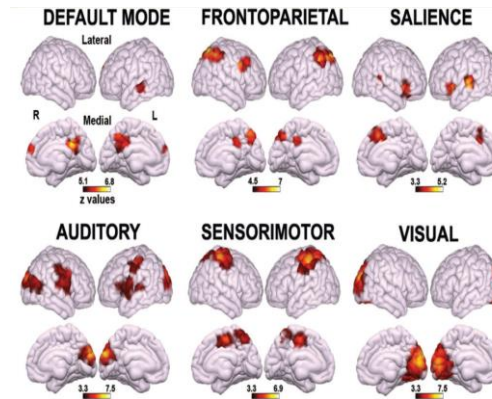
Recommendation:
consider active fMRI paradigms as part of multimodal assessment in patients without command following

Moderate evidence, weak recommendation

20 publications

Kondziella et al, Eur J Neurol, 2020

Resting state fMRI



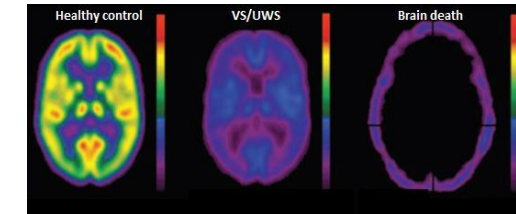
Demertzi et al, Brain 2015

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

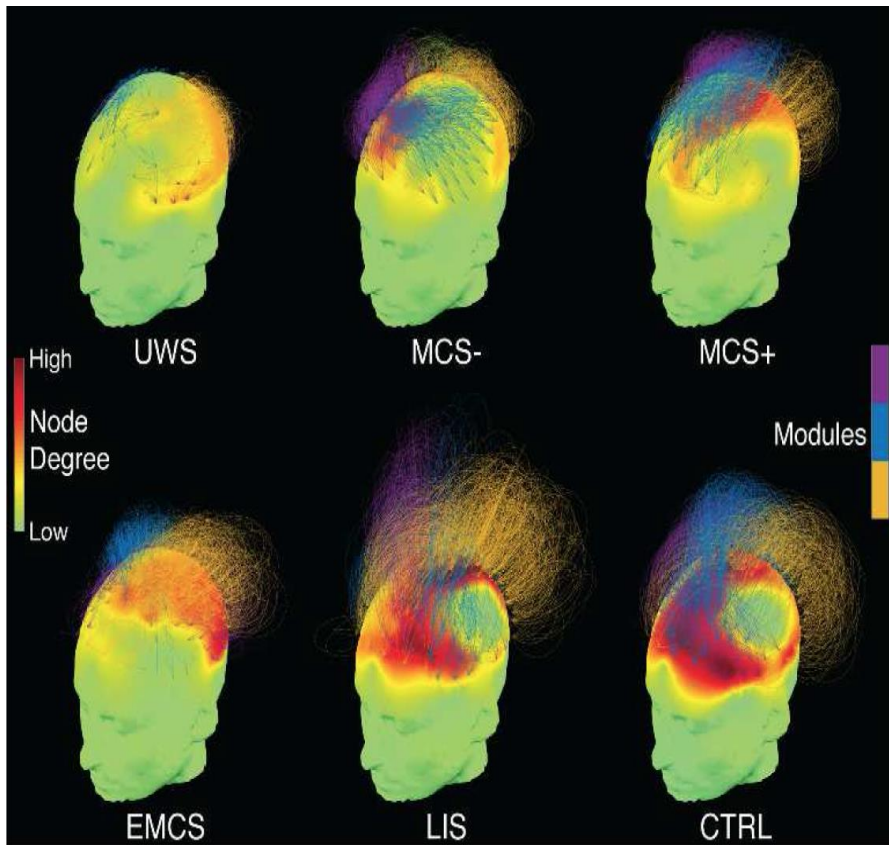
Low evidence, weak recommendation

5 publications



Resting state EEG

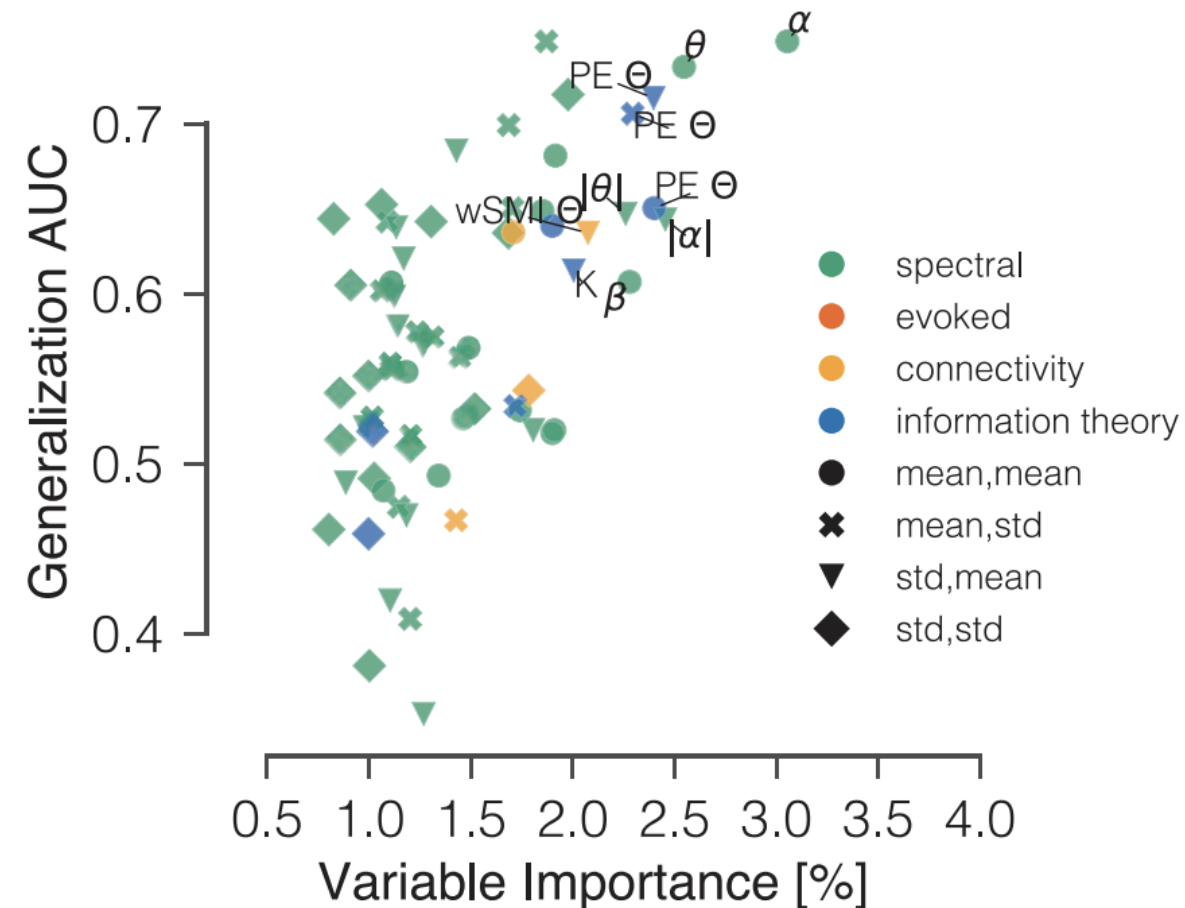
Alpha band connectivity



- Stronger alpha connectivity in MCS patients compared to UWS
- Alpha centrality (graph-based metric) has a clinical impact



Comparing EEG markers



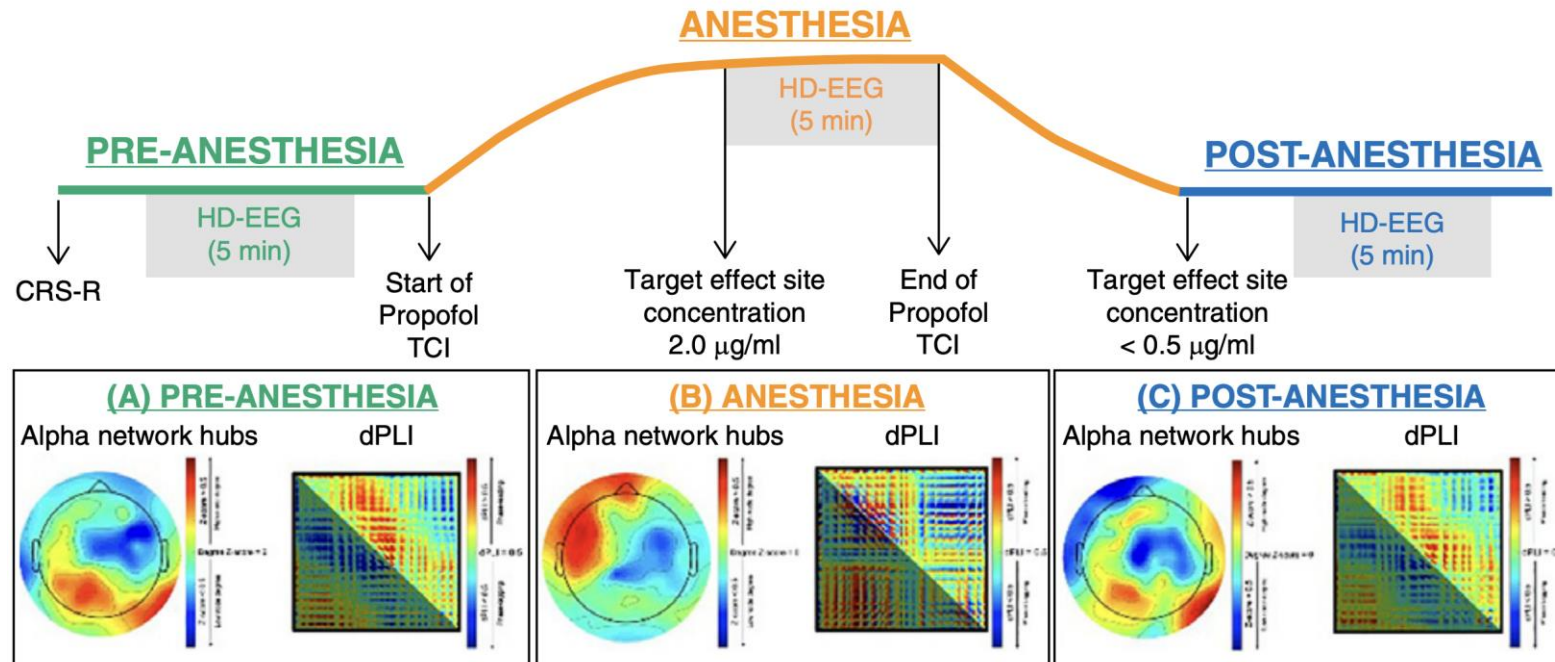
Large population: 327 DoC; 66 HC

Random-forest classifier to rank the most-informative markers:

- Alpha-band power
- Theta-band connectivity
- Time series complexity measures



EEG and anaesthesia – Pharmacological perturbation



- Reconfiguration of alpha after propofol
 - Sensibility of the brain to pharmacological perturbation
- Possible to use in the acute setting

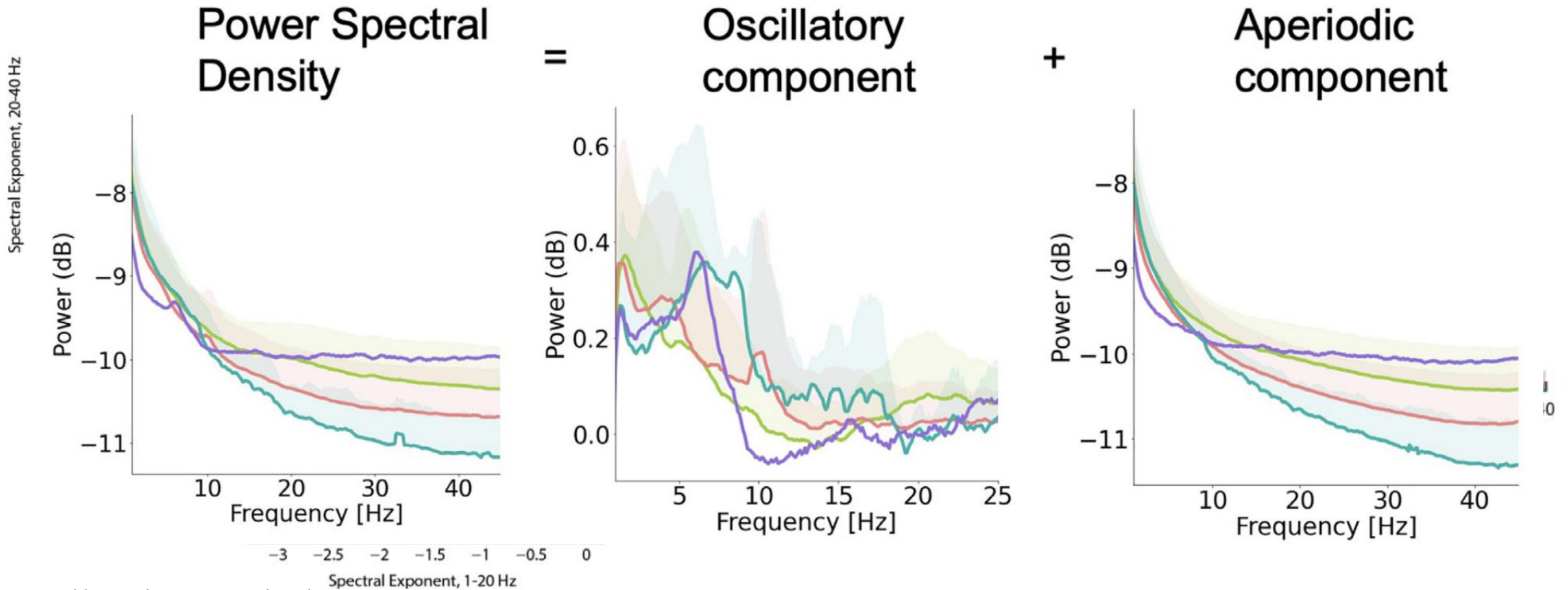
Duclos, Maschke, Mahdid, et al, *Am J Respir Crit Care Med*, 2021

Maschke et al, *Front. Hum. Neuro.*, 2022

Maschke et al, *NeuroImage*, 2023



PDS slope: diagnosis and prognosis

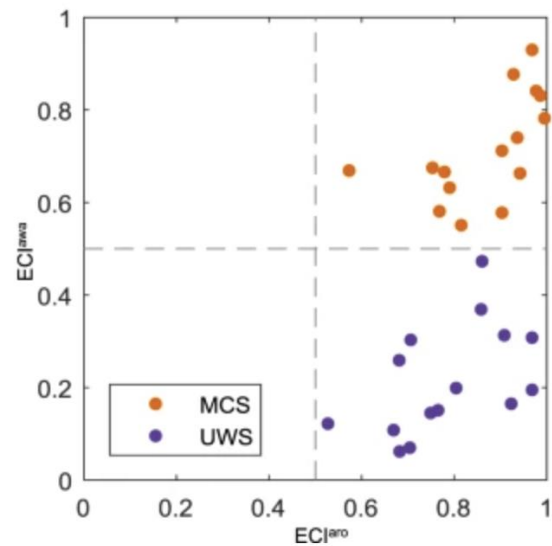
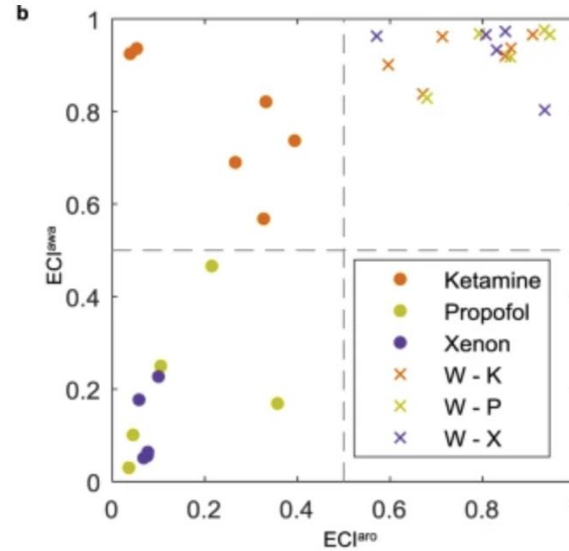
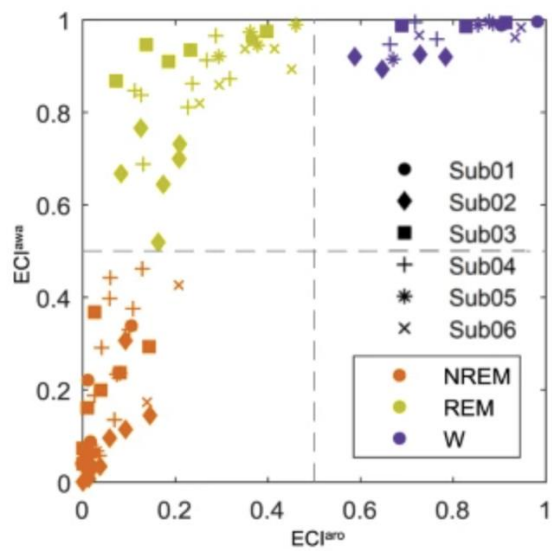


Maschke, Duclos, Owen et al et al, *NeuroImage*, 2023

Colombo et al, *Neuroimage*, 2019

Kustermann et al, *Resuscitation*, 2019

Explainable Consciousness Indicator (ECI)



d

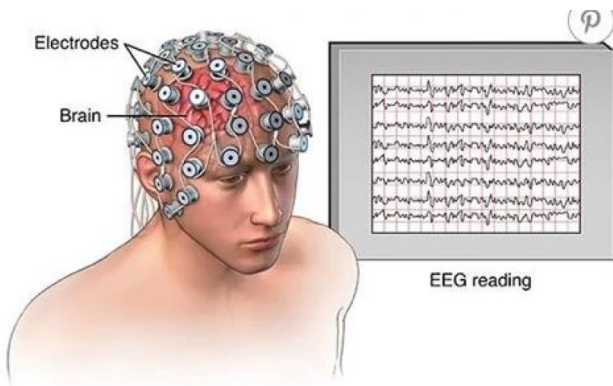
Condition	Measure	ECI ^{aro}		ECI ^{awa}	
		Low	High	Low	High
Sleep	AUC	1.0	1.0	1.0	1.0
	Sensitivity	1.0	1.0	1.0	1.0
	Specificity	1.0	1.0	1.0	1.0
Anesthesia	AUC	1.0	1.0	0.995	0.995
	Sensitivity	1.0	1.0	1.0	0.980
	Specificity	1.0	1.0	0.980	1.0
Patients with DoC	AUC	-	-	1.0	1.0
	Sensitivity	-	-	1.0	1.0
	Specificity	-	-	1.0	1.0

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



EEG coupled with Transcranial Magnetic Stimulation (TMS-EEG)

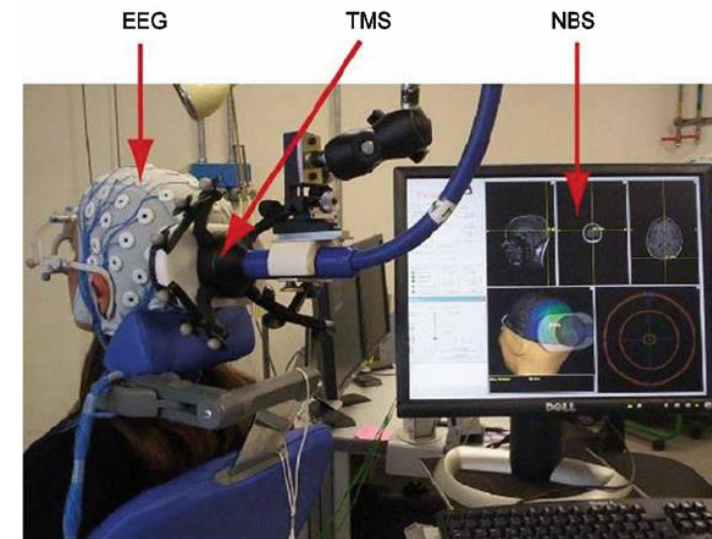
Electroencephalography (EEG)



Transcranial Magnetic Stimulation (TMS)



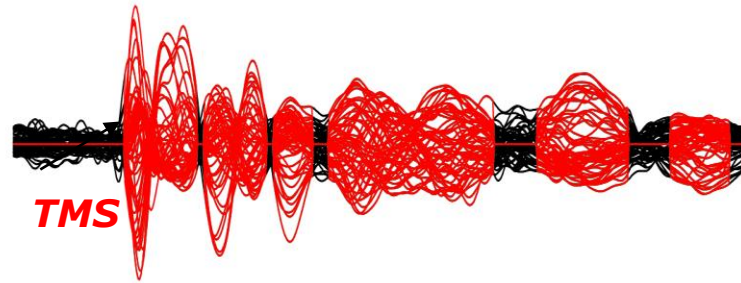
TMS-EEG



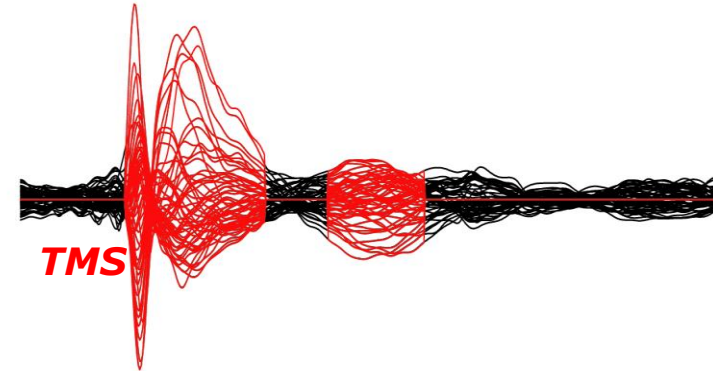


TMS-Evoked Potentials & Consciousness

Conscious

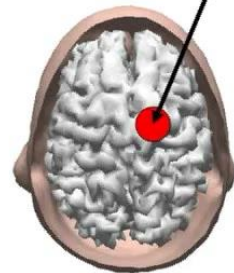


Unconscious



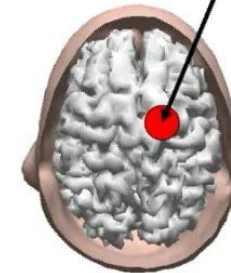
0 ms

TMS



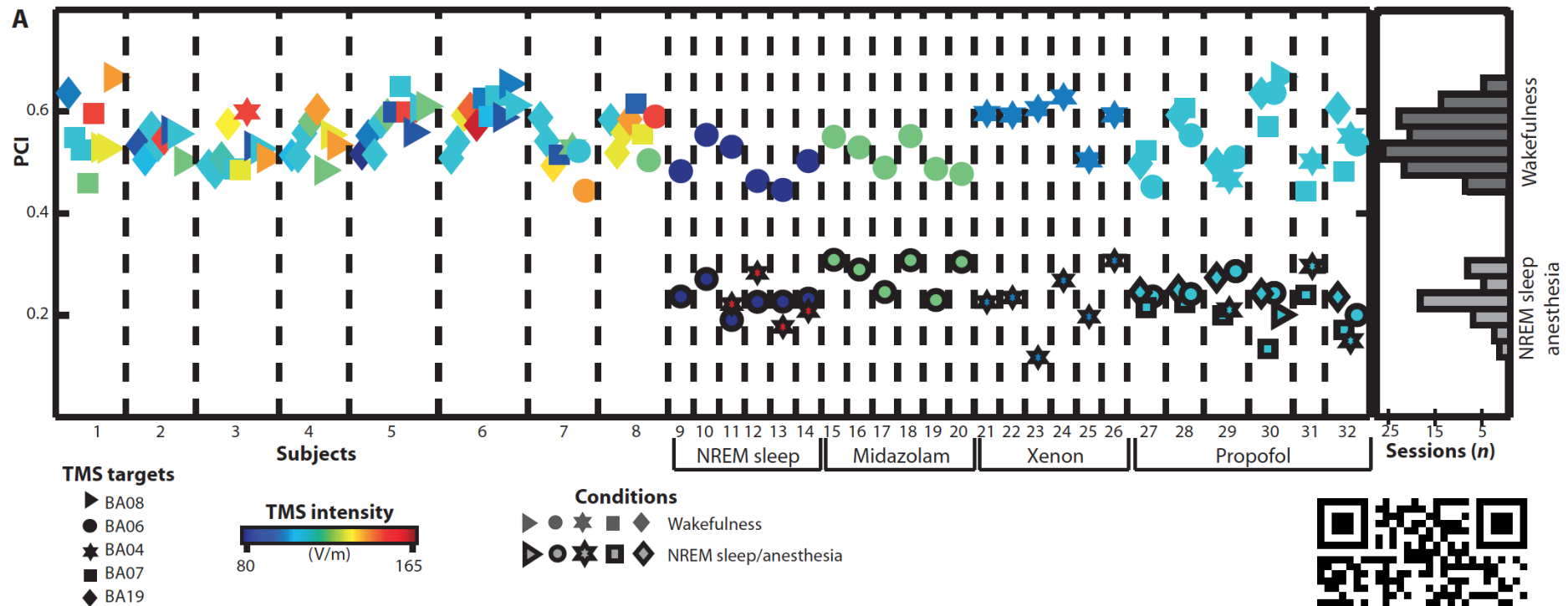
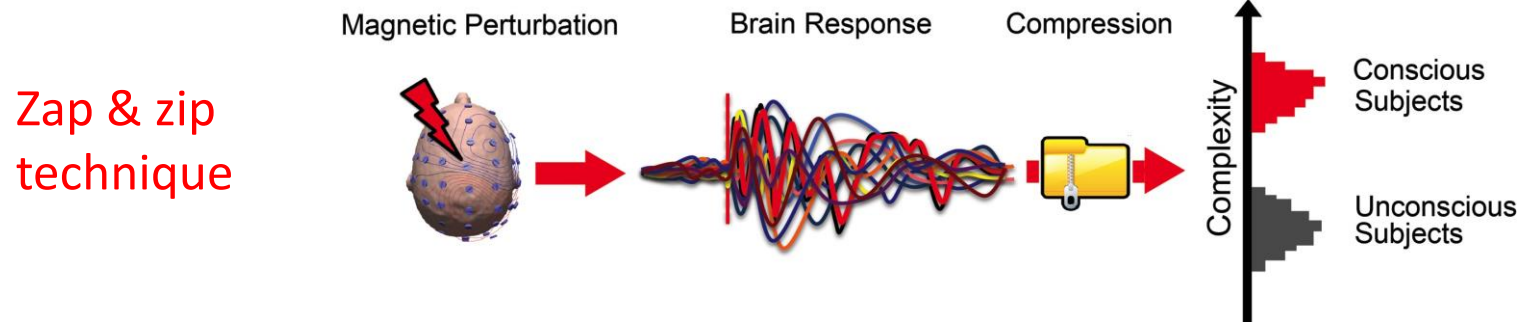
0 ms

TMS



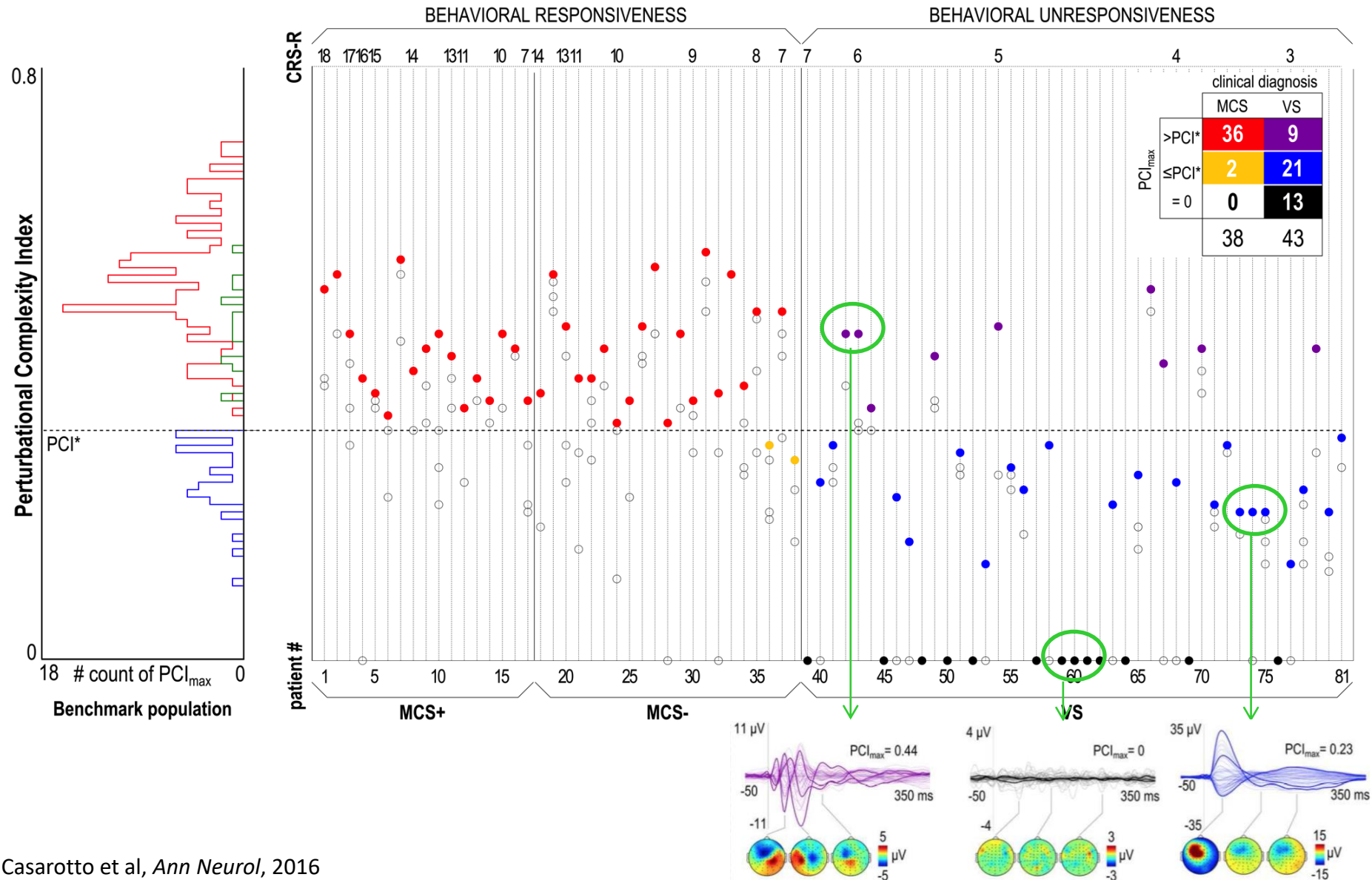


Perturbational Complexity Index (PCI)



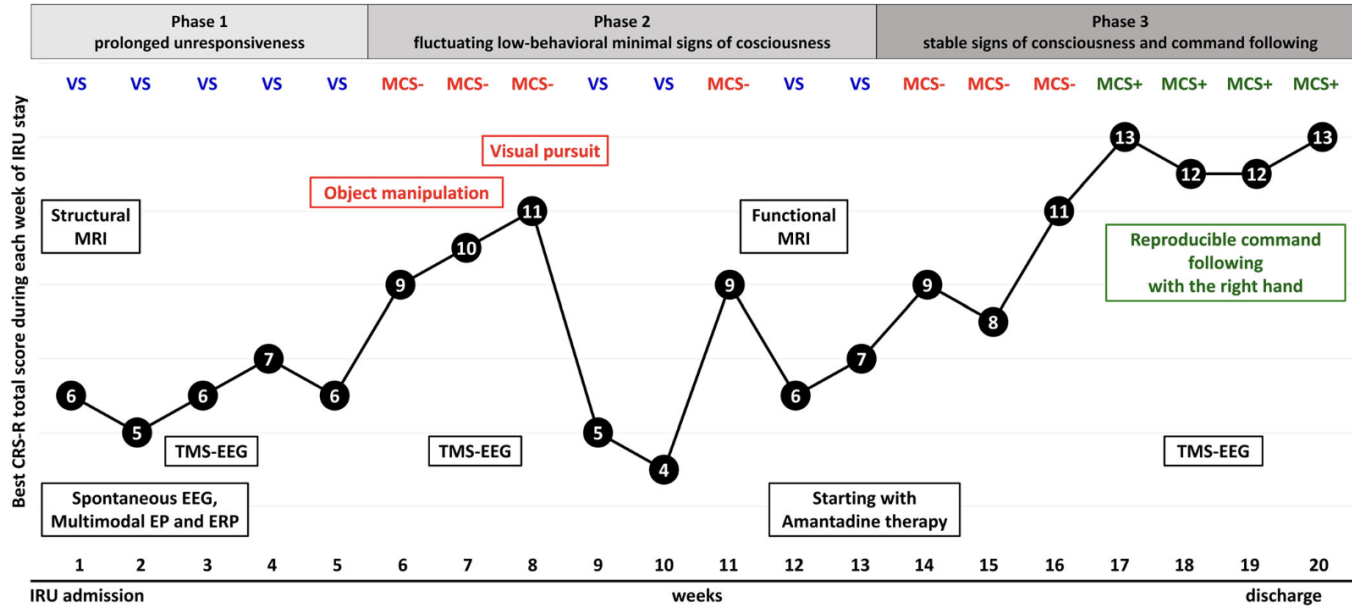


PCI in DoC

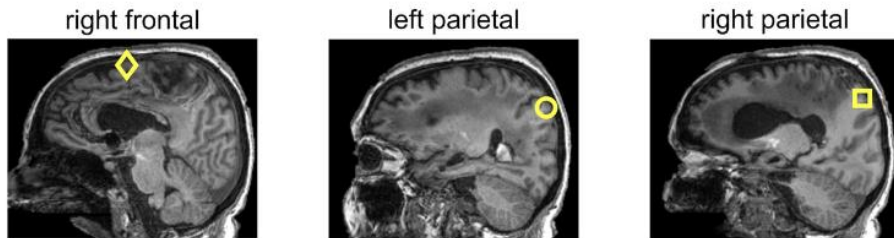




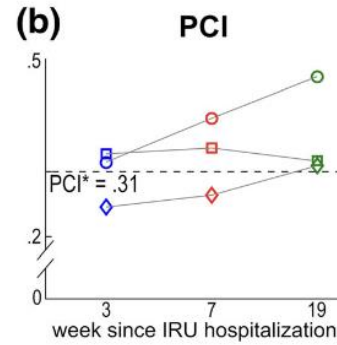
Case-study: akinetic mutism



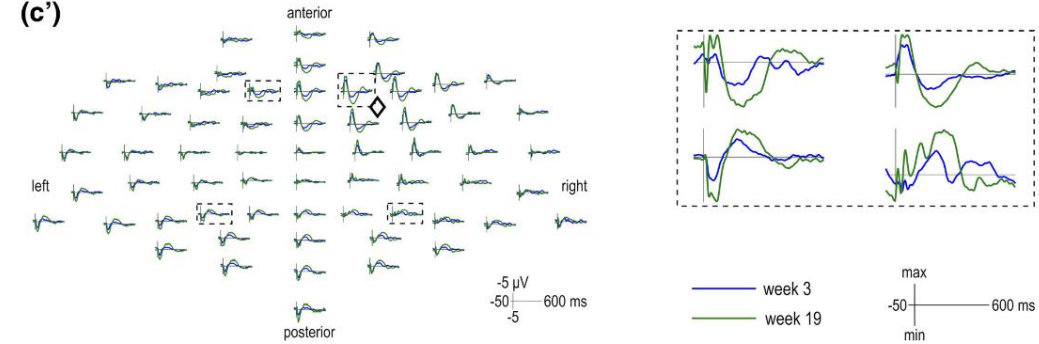
(a)



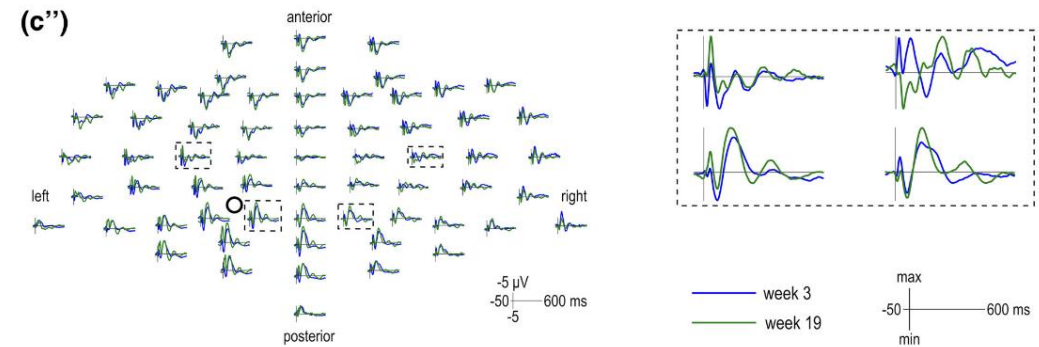
(b)

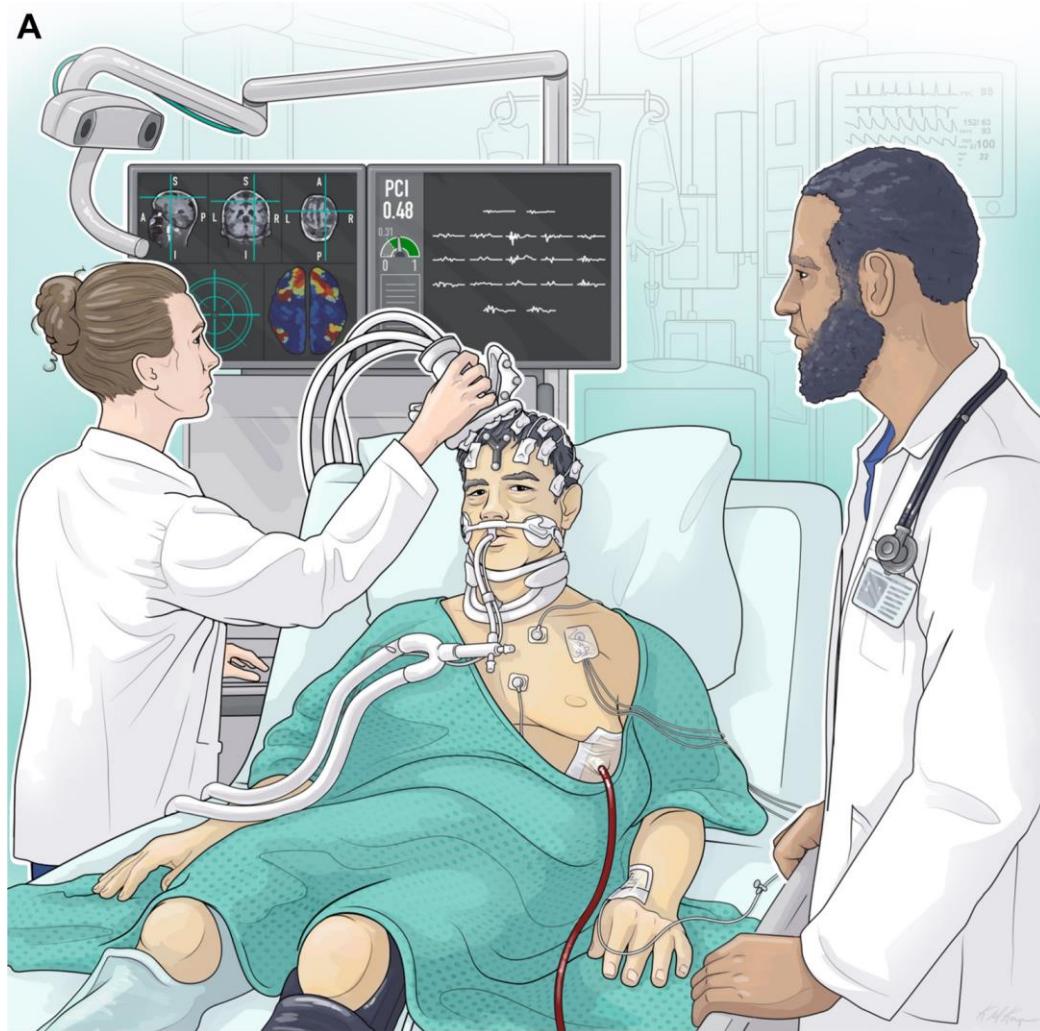


(c')



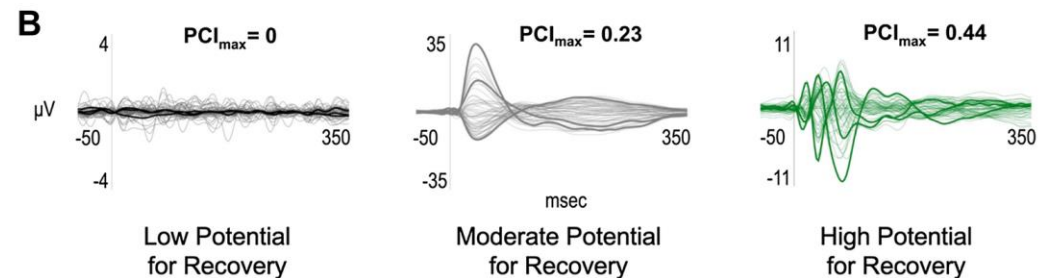
(c'')





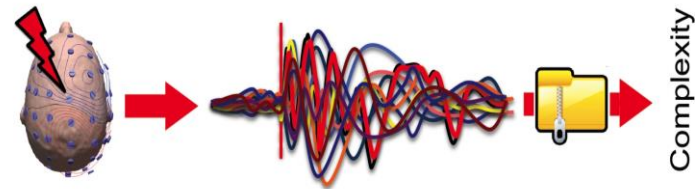
TMS-EEG in the ICU

- Feasibility of TMS-EEG to be investigated in the acute setting
- Future investigation looking at implantation in ICU
 - Diagnostic and prognostic value





European Academy of Neurology recommendations



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

Weak evidence, weak recommendation

6 publications

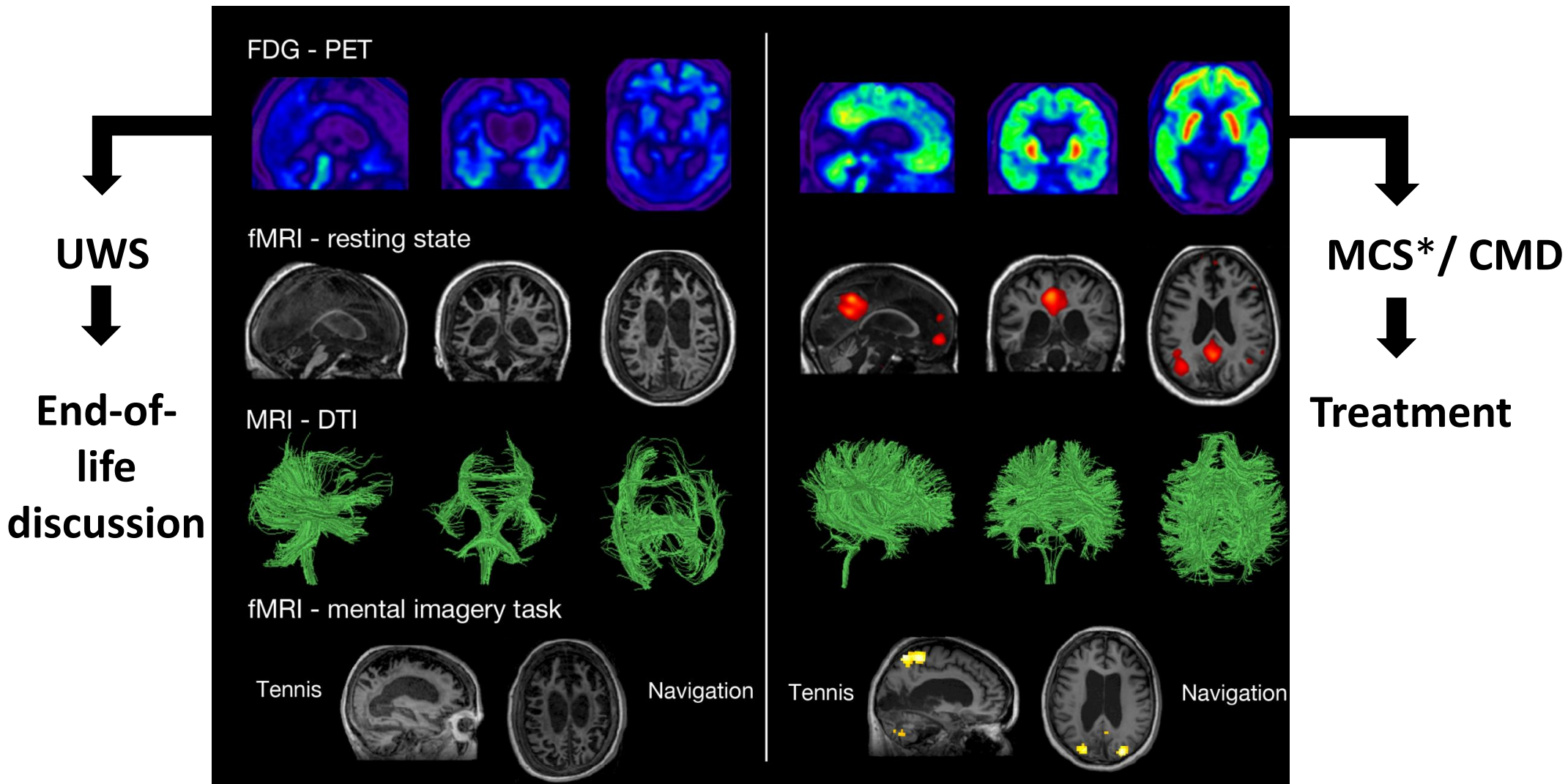


Recommendation: consider **quantitative** high density

Moderate evidence, weak recommendation

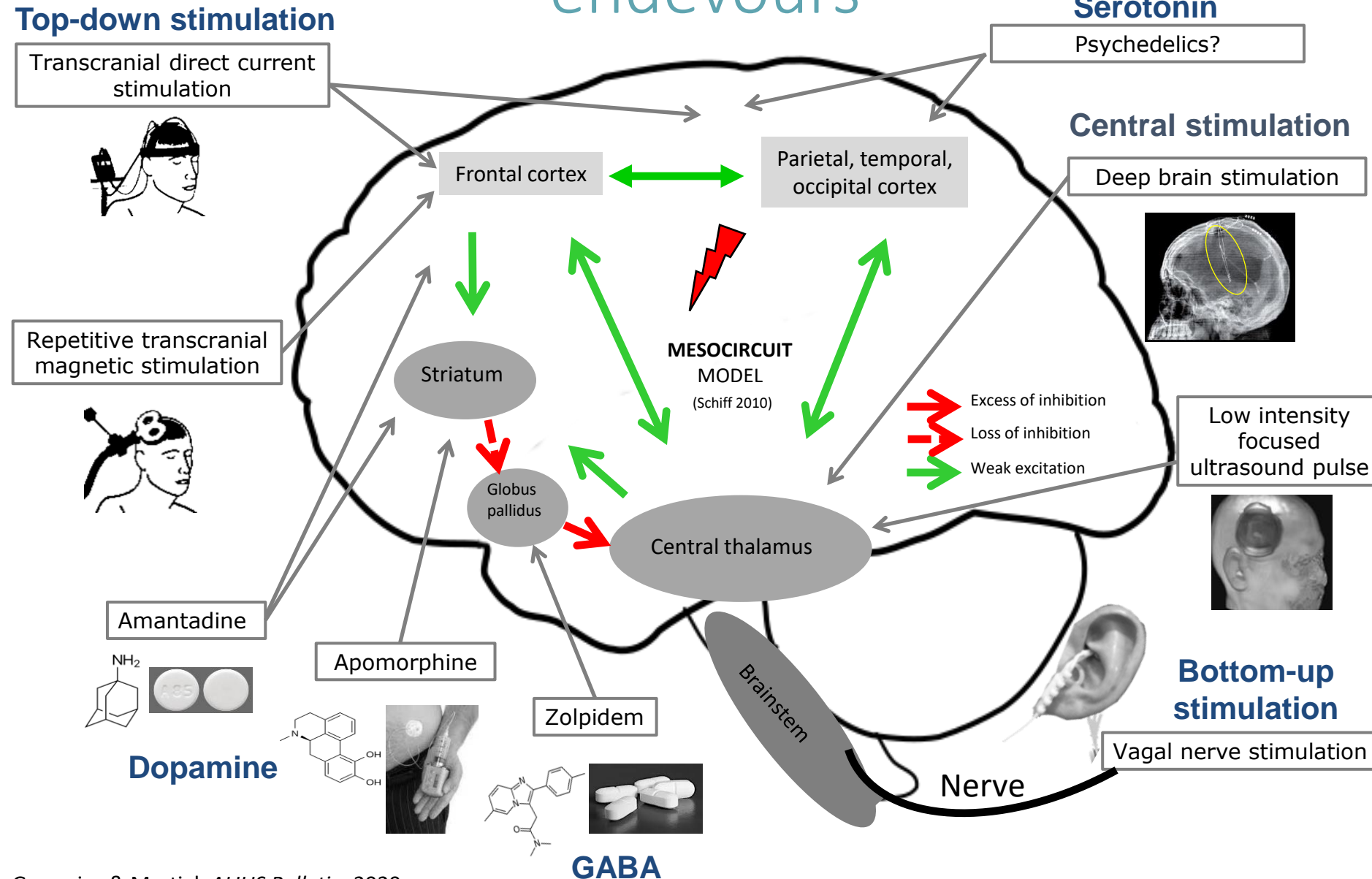
6 publications

Two scenarios



MCS* = non-behavioral minimally conscious state
CMD = cognitive-motor dissociation

Treatments in DoC: current landscape and new endeavours





Key points and take home messages

1. Multimodal treatment is a viable way to assess consciousness in patients with DoC
 - MRI has shown potential in the chronic phase
 - EEG relatively more accessible in the acute phase
 - PET is having a new surge of investigations
2. Multimodal imaging could pinpoint to biomarkers for pharmacological responsiveness or good prognosis
3. Presence of consciousness in one evaluation is more important than absence in several ones



Acknowledgments



Pr. Olivia
Gosseries



Dr. Charlotte
Martial

Patients & families!

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