

Coma, is my patient really unconscious? Lessons from behavior and neuroimaging studies

Aurore THIBAUT, PhD

Coma Science Group
GIGA-Consciousness
University of Liege, Belgium

www.giga.ulg.ac.be
www.comascience.org



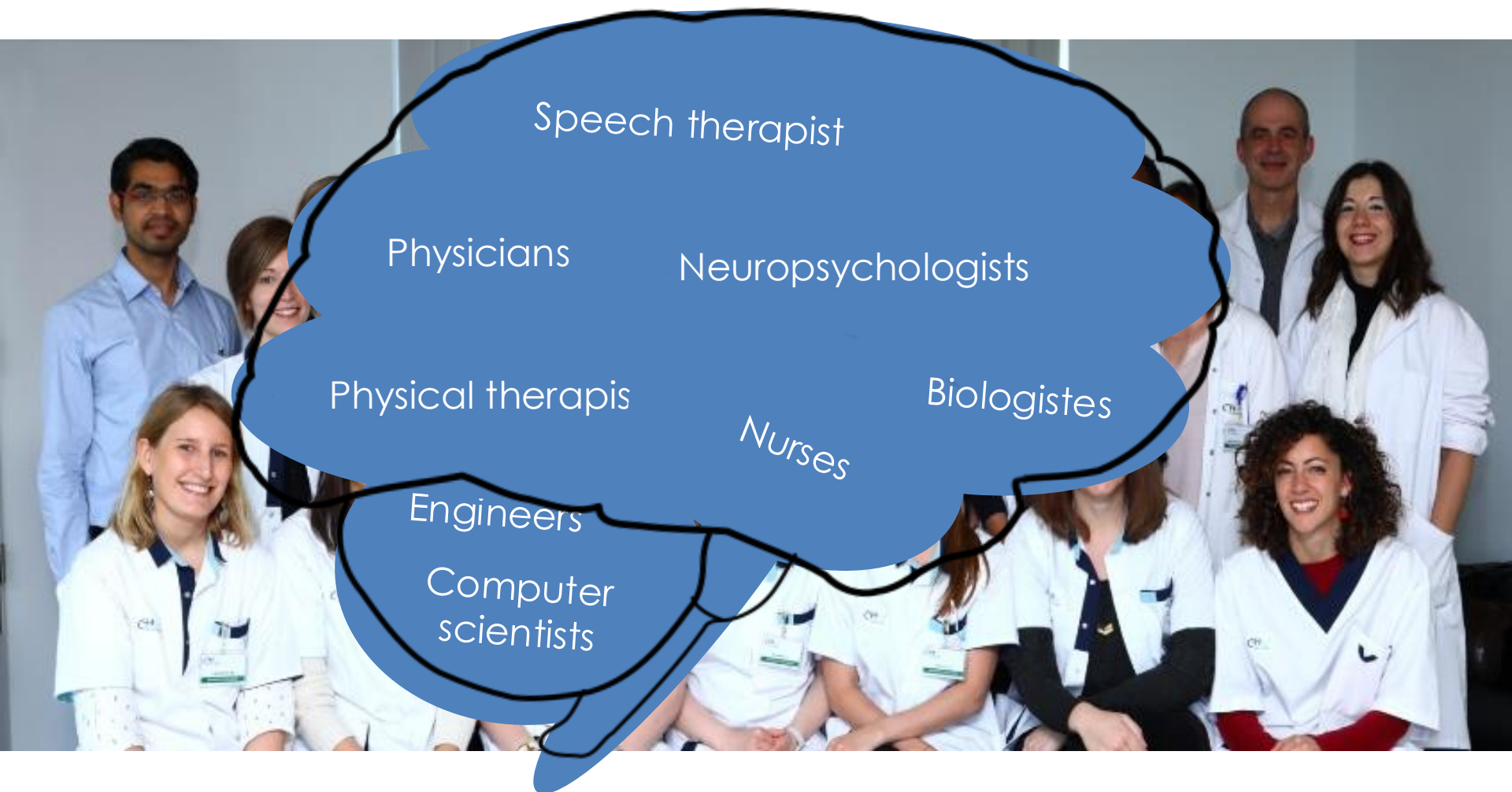
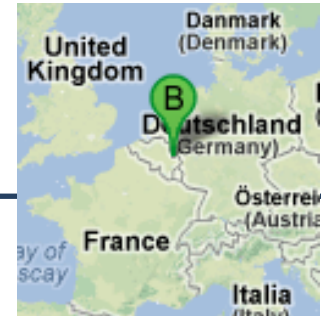


Disclosure

- No relevant financial or non-financial interest to disclose.

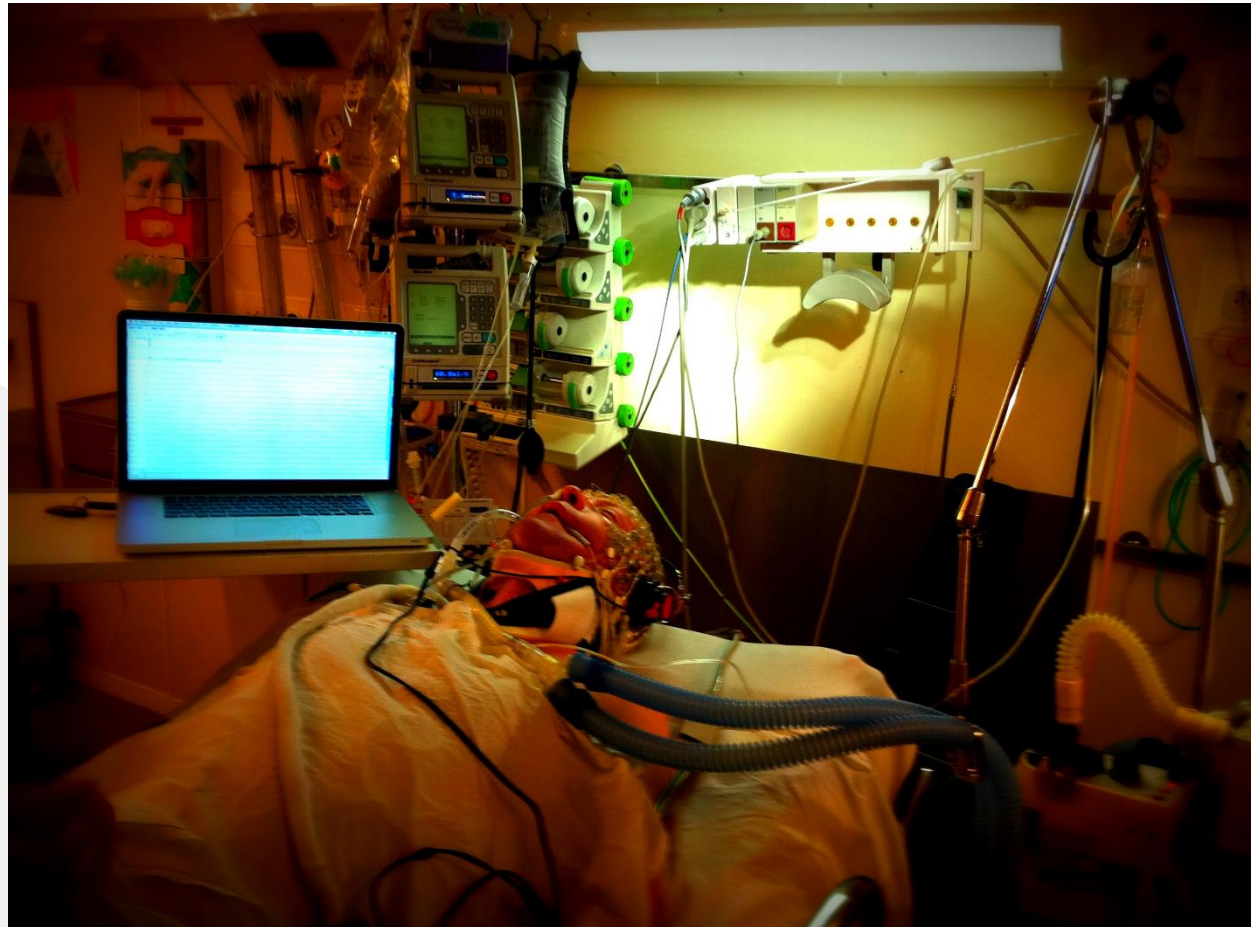


GIGA-Consciousness Coma Science Group



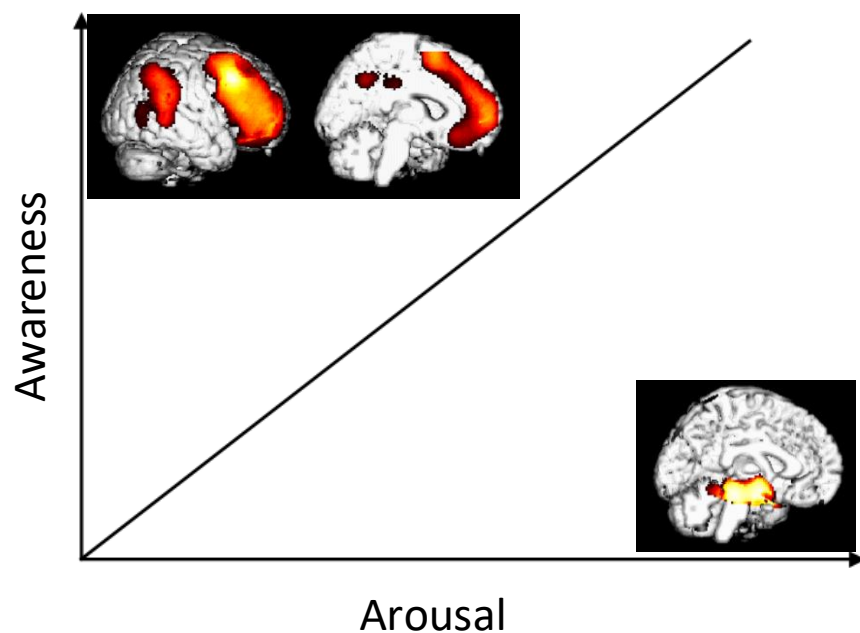
- **Disorders of consciousness**
- **Behavioural diagnosis**
- **Brain imaging**
- **Treatment**

DISORDERS OF CONSCIOUSNESS





Measuring consciousness



What happens after a coma?

CLINICAL EXAMINATION

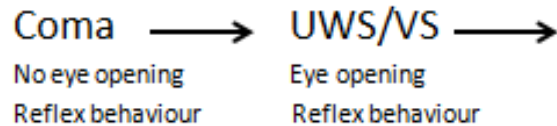
Coma →

No eye opening

Reflex behaviour

What happens after a coma?

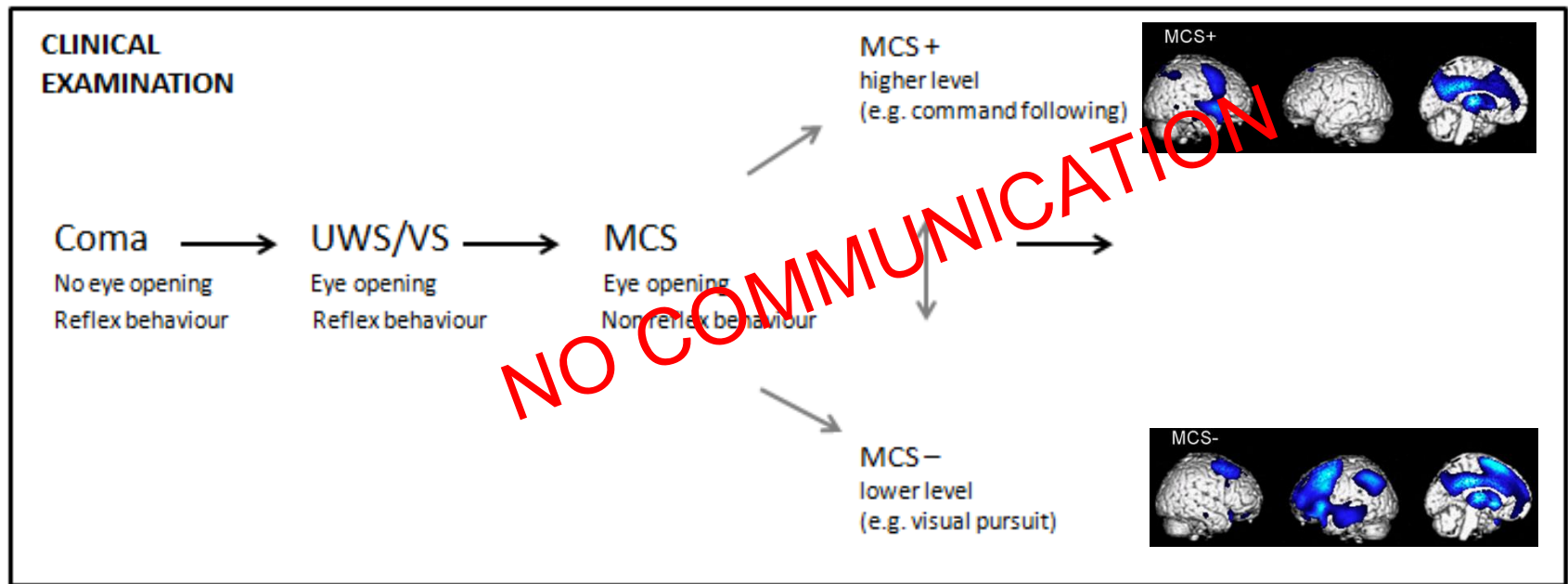
CLINICAL EXAMINATION



UWS=unresponsive wakefulness syndrome

VS=vegetative state

What happens after a coma?

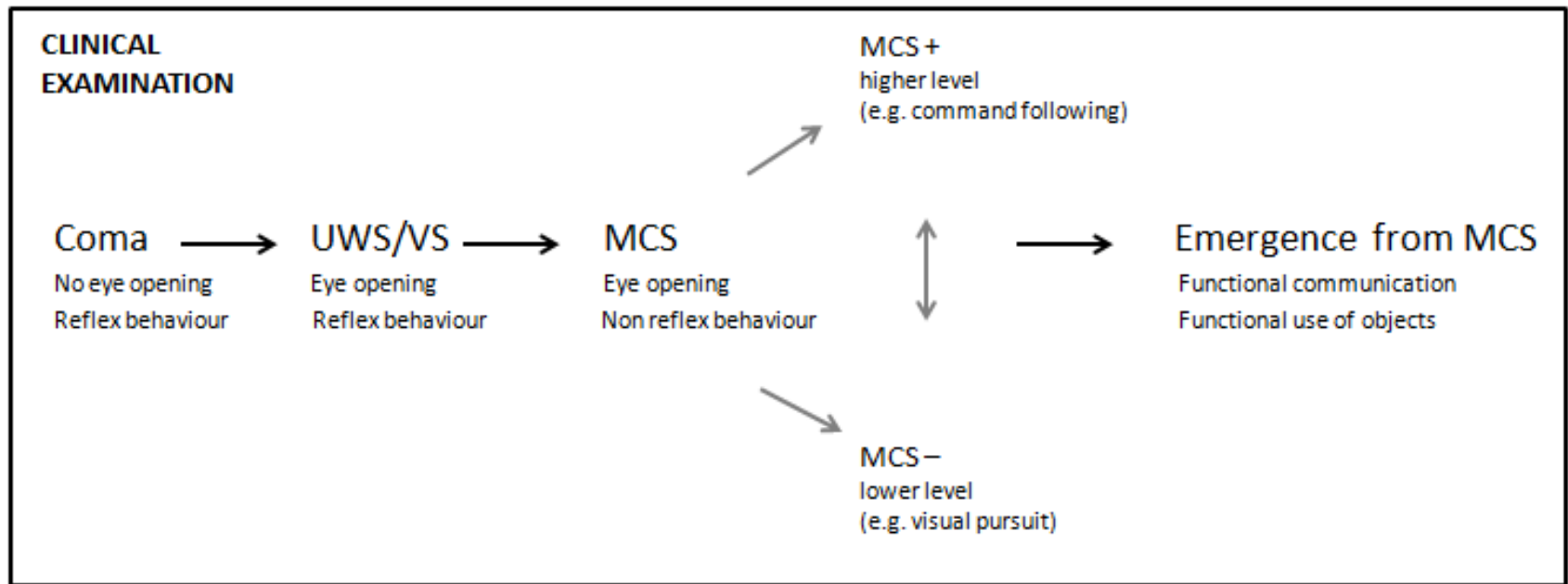


UWS=unresponsive wakefulness syndrome

VS=vegetative state

MCS=minimally conscious state

What happens after a coma?

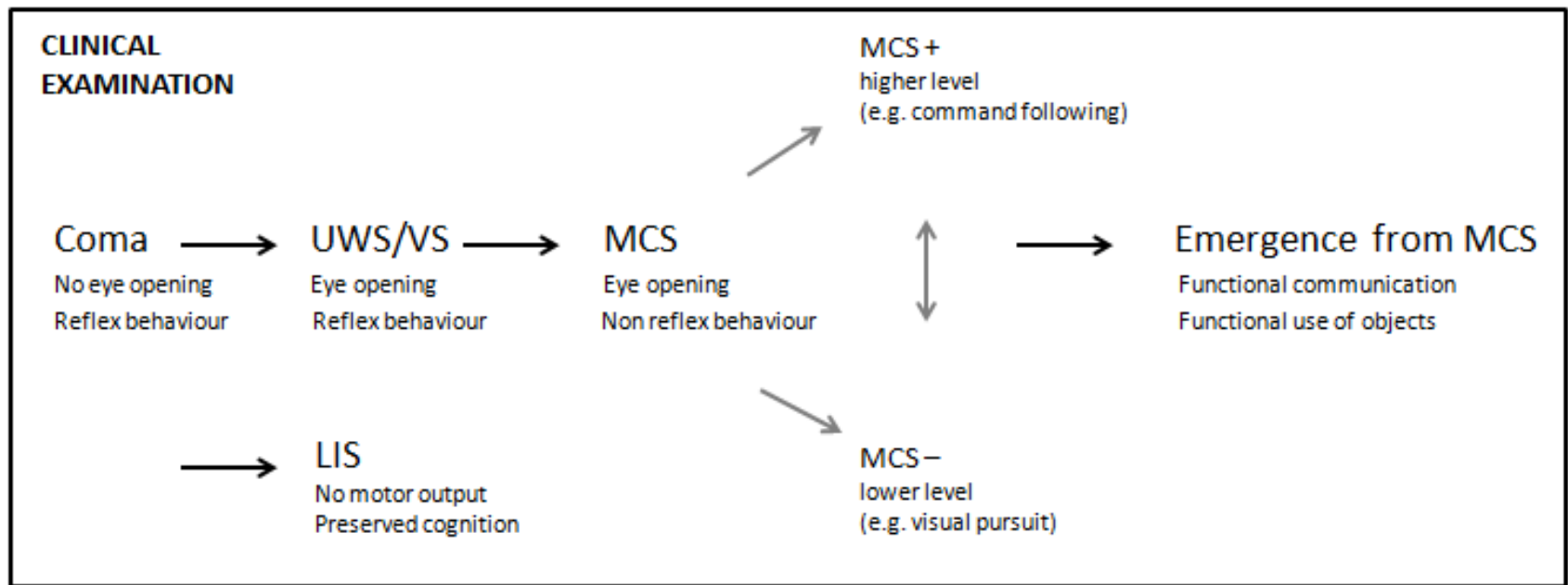


UWS=unresponsive wakefulness syndrome

VS=vegetative state

MCS=minimally conscious state

What happens after a coma?



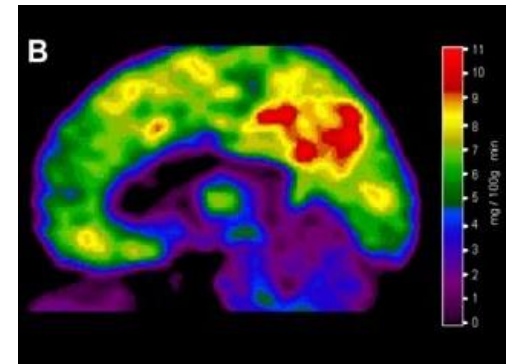
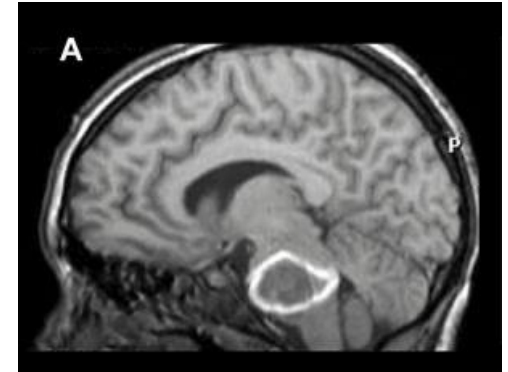
UWS=unresponsive wakefulness syndrome

VS=vegetative state

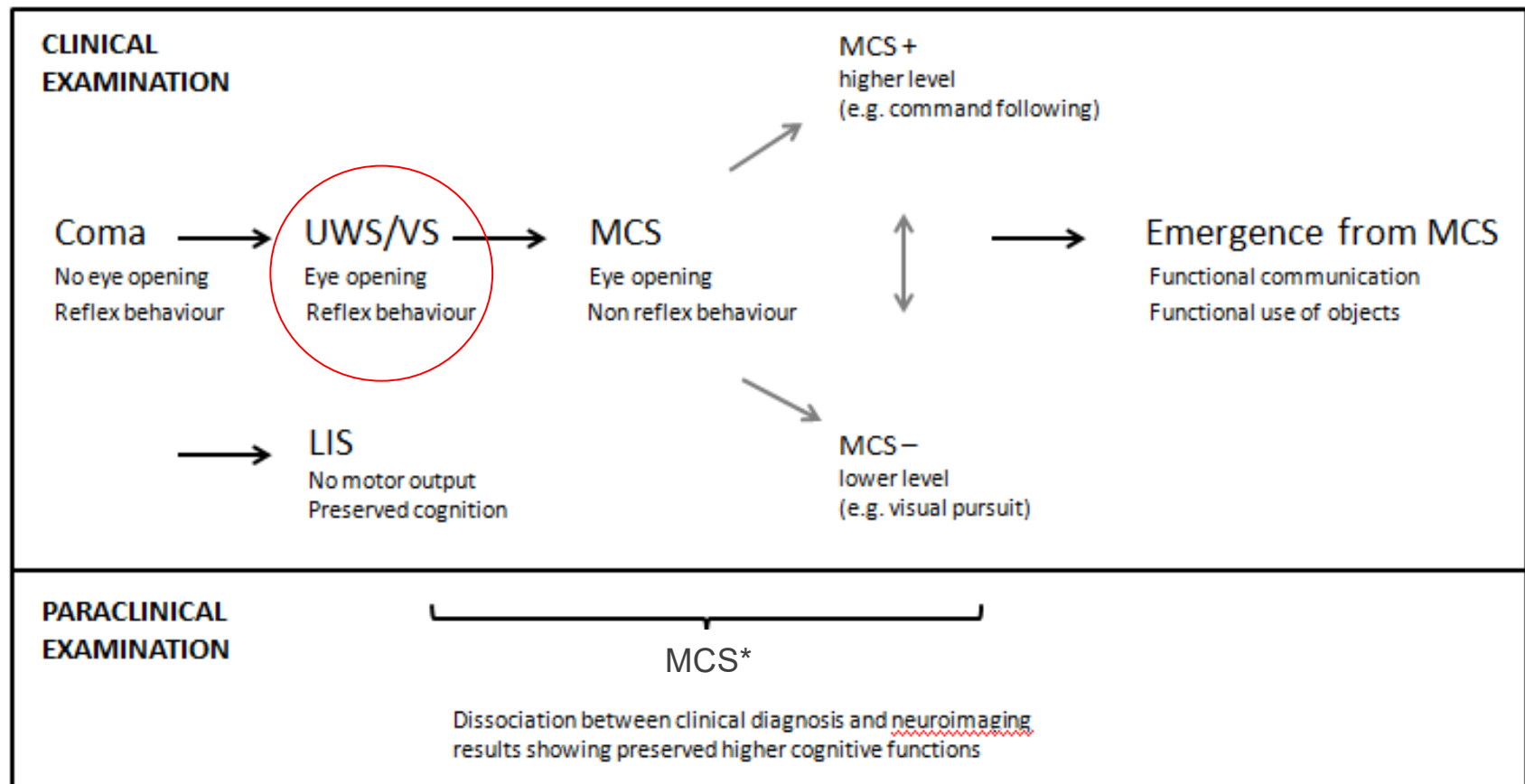
MCS=minimally conscious state

LIS=locked-in syndrome

Locked-in syndrome



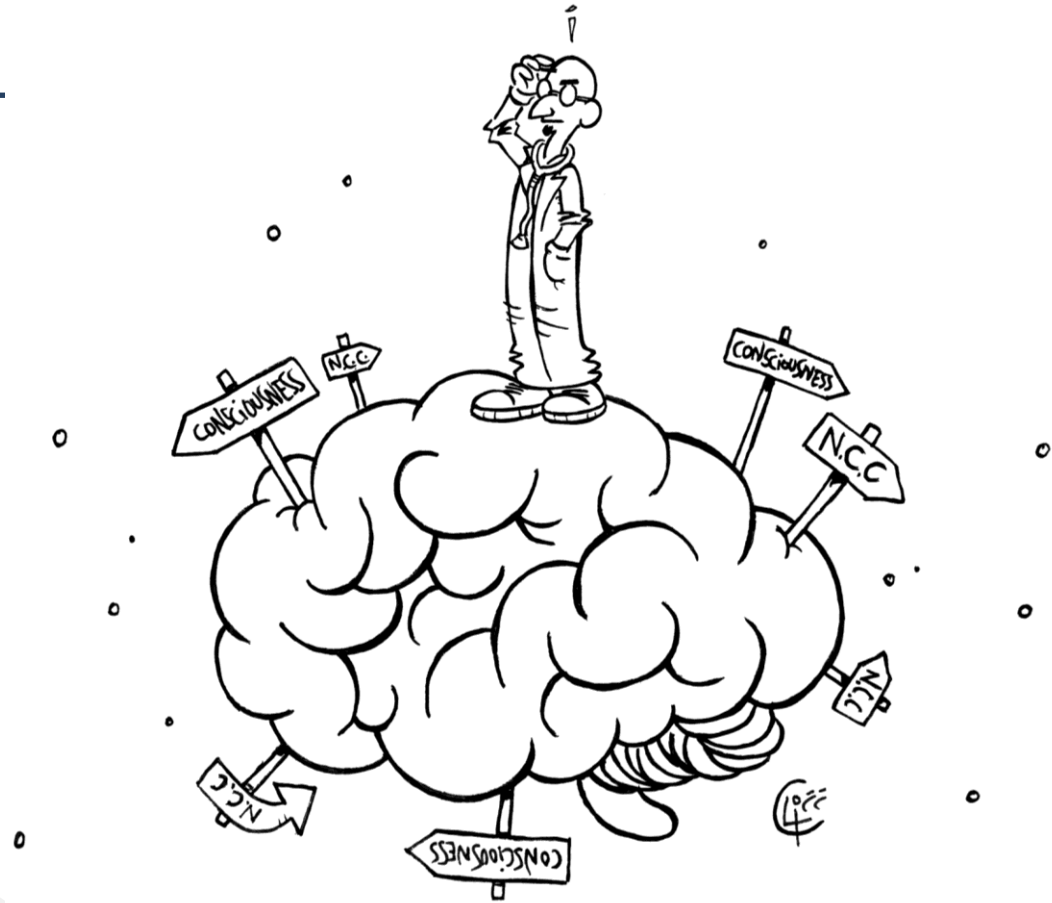
What happens after a coma?



MCS*=non-behavioral minimally conscious state

The absence of proof is not the proof of absence!

Behaviours



Diagnostic error

N=126 post-comatose patients

- 51 clinical consensus diagnosis
‘vegetative state’

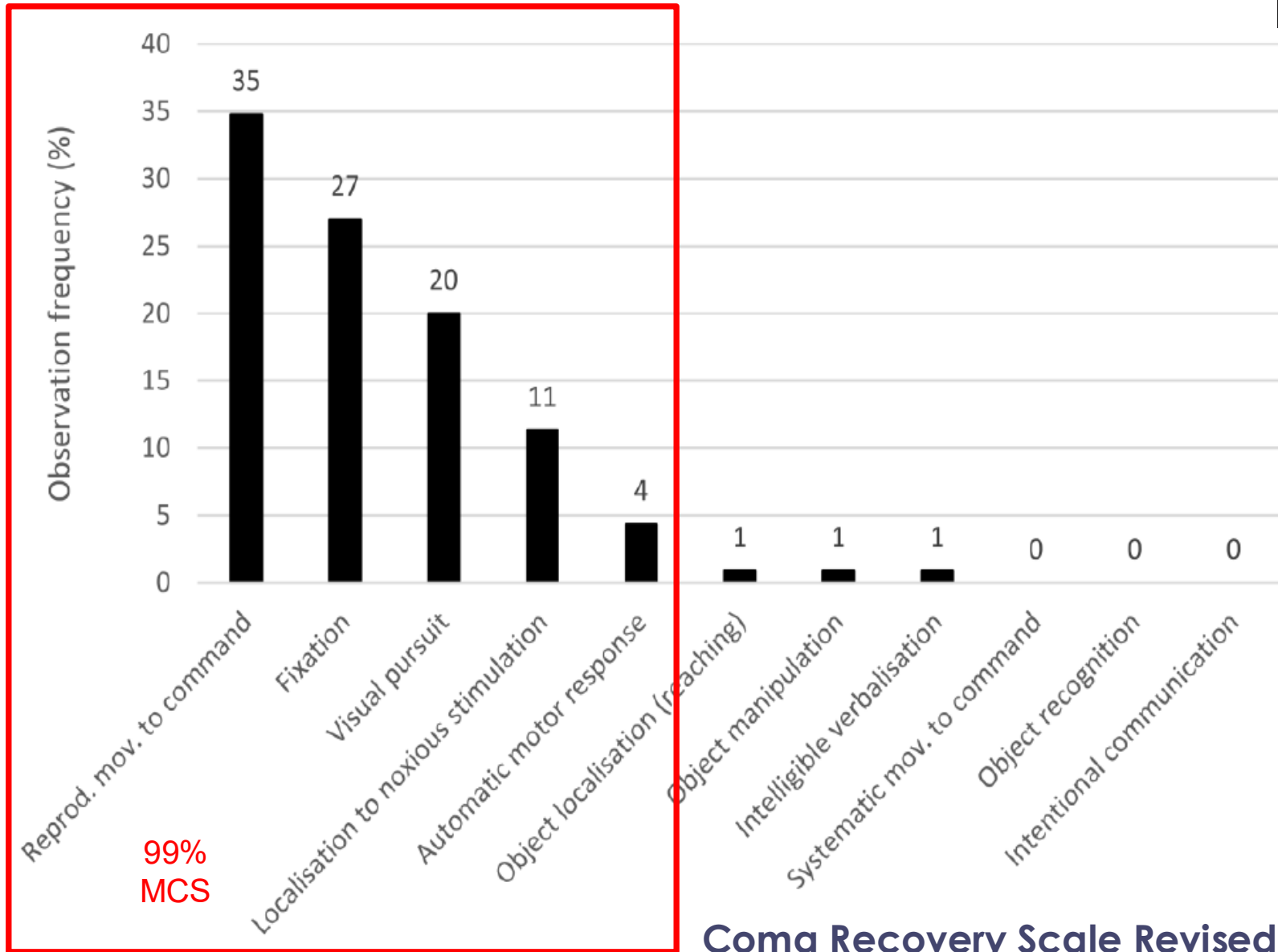
- 18 signs of awareness

(Coma Recovery Scale – Revised)

↪ **30 - 40% potential
misdiagnosis**

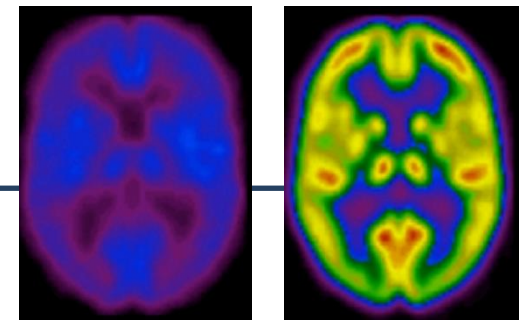
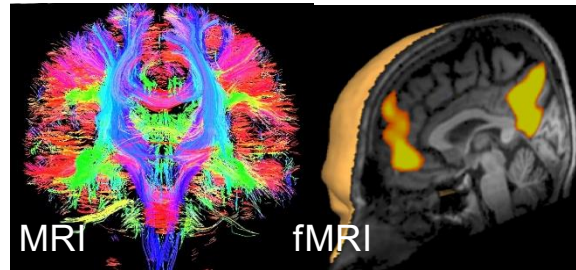
JFK COMA RECOVERY SCALE - REVISED ©2004										
Record Form										
Patient:	Date:									
AUDITORY FUNCTION SCALE										
4 - Consistent Movement to Command *										
3 - Reproducible Movement to Command *										
2 - Localization to Sound										
1 - Auditory Startle										
0 - None										
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										
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										

Signs of consciousness



Coma Recovery Scale Revised (CRS-R)

Neuroimaging

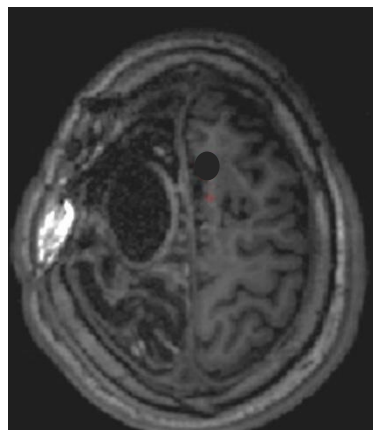
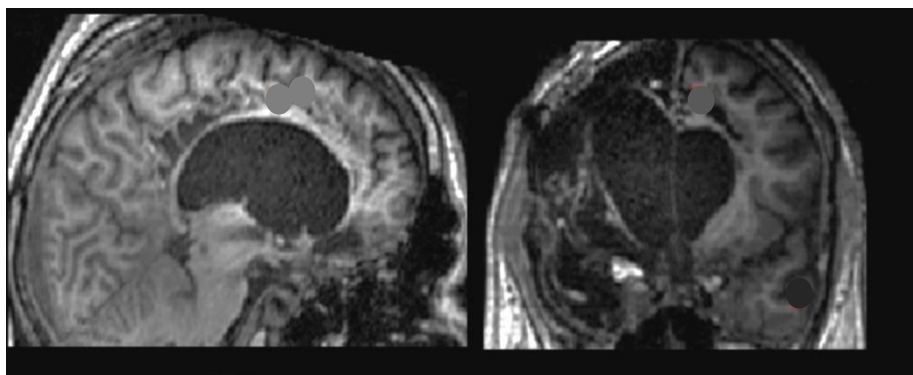




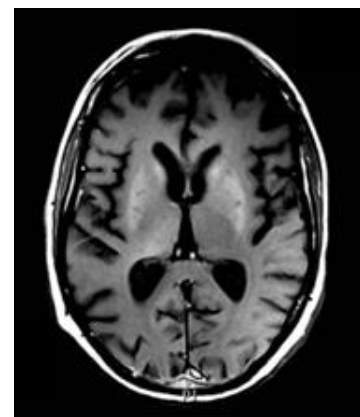
Consciousness $\neq$ structure

MRI T1

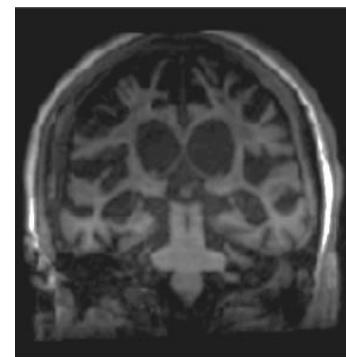
Trauma



Anoxia



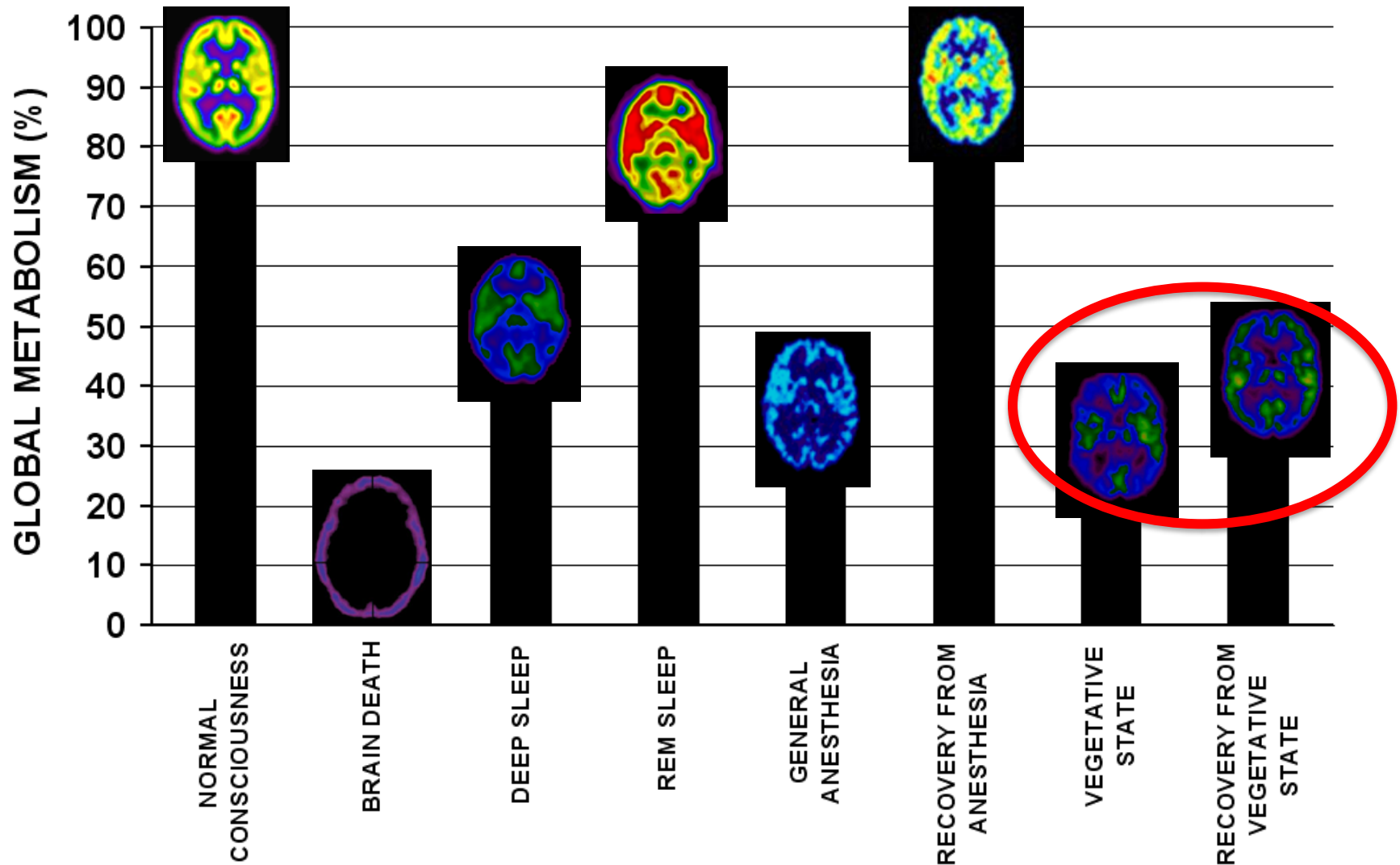
Acute



Chronic

Consciousness $\neq$ global brain function

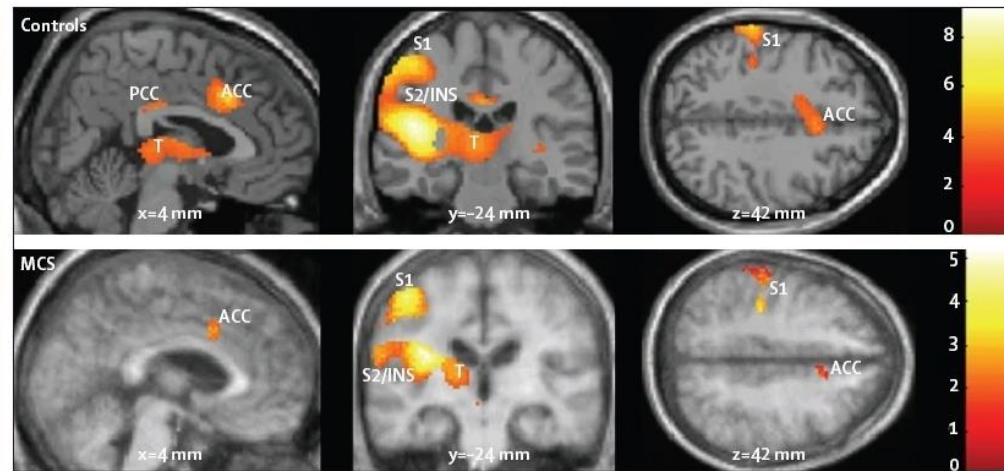
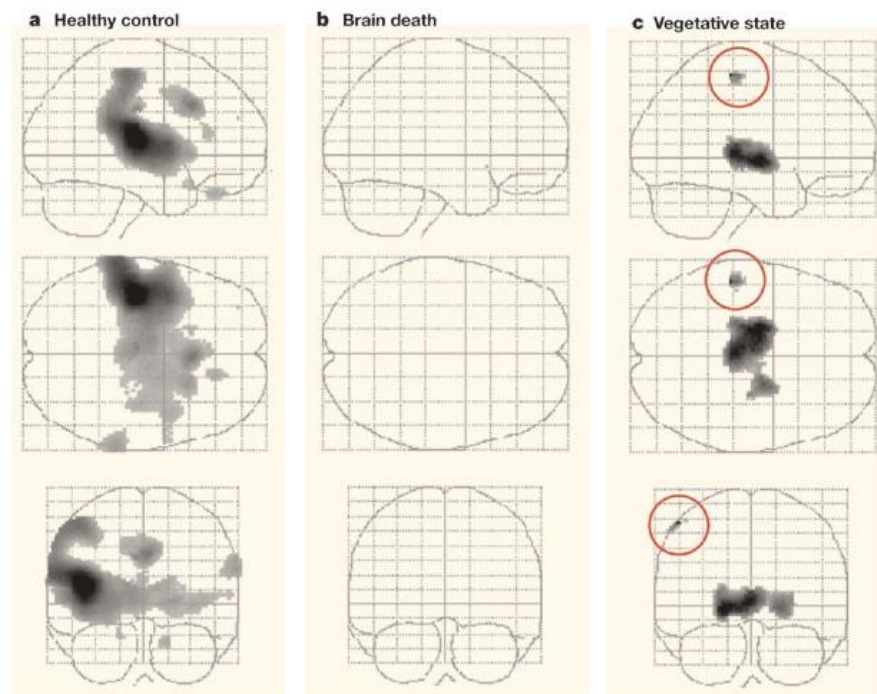
FDG-PET



Consciousness $\neq$ primary cortex

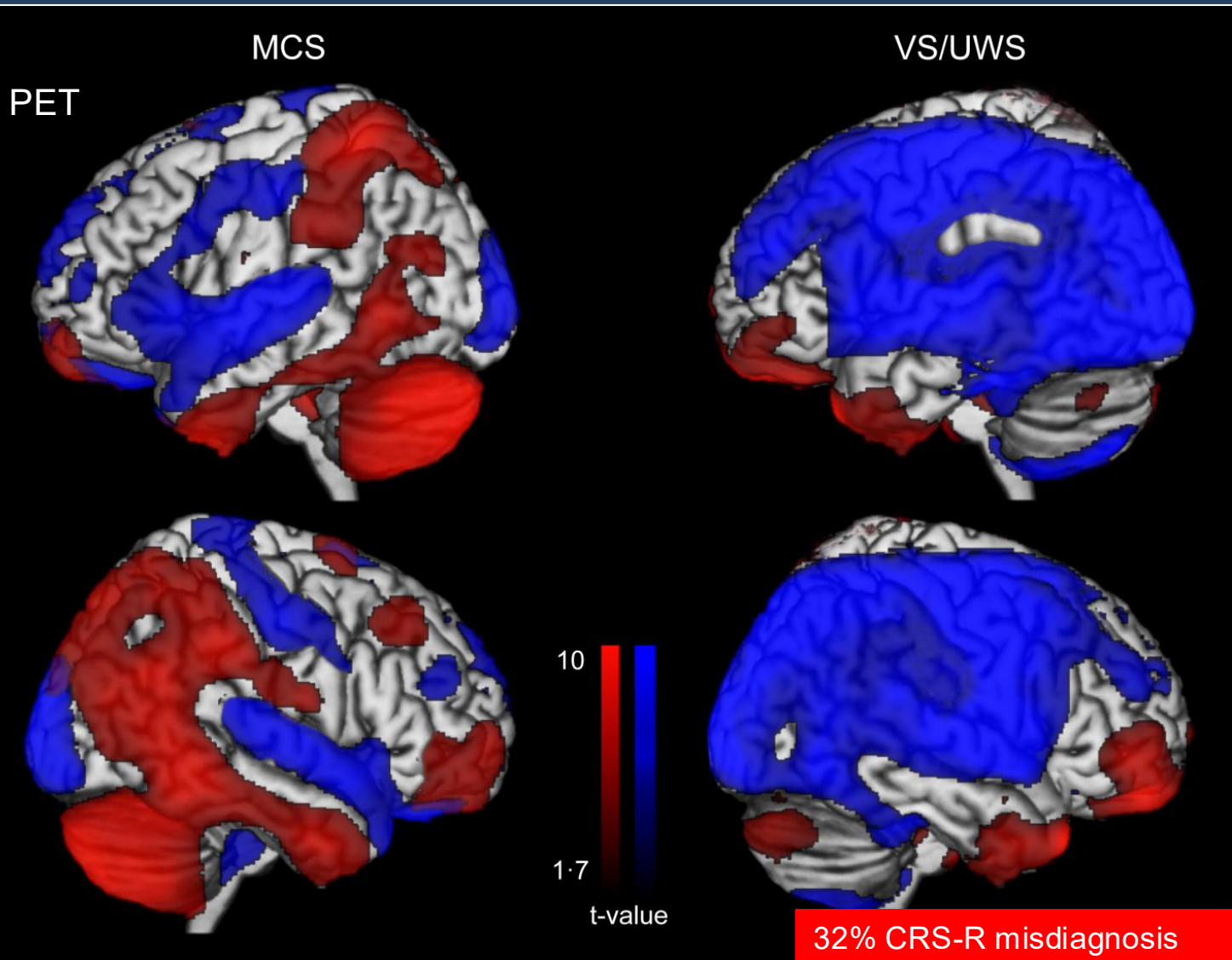
FDG-PET

Noxious electrical stimulation



Consciousness $\approx$ fronto-parietal areas

FDG-PET



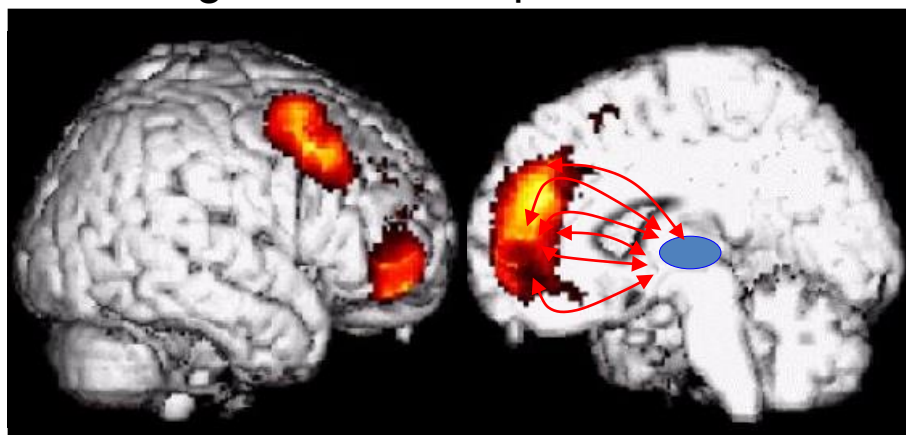
130 patients

81 MCS
41 UWS
4 LIS



Consciousness $\approx$ thalamo-cortical

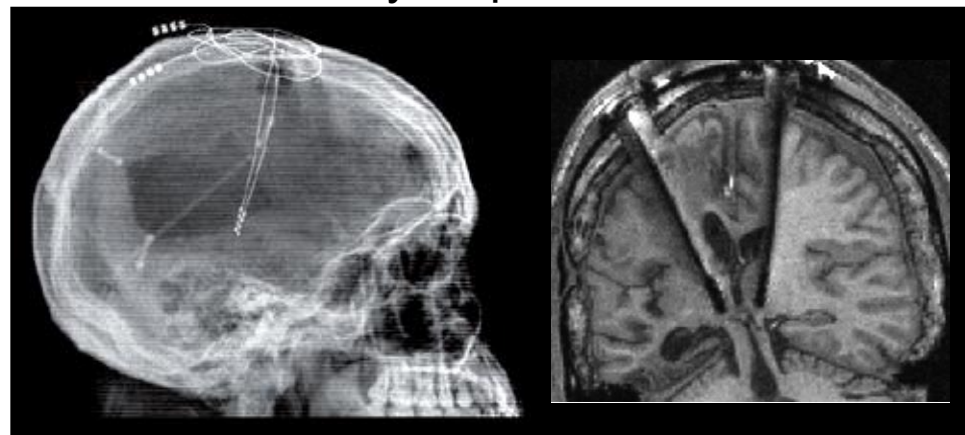
Intralaminar nuclei “reconnections”
in spontaneous recovery from
“vegetative” unresponsive state



FDG-PET

Laureys et al, *Lancet*, 2000

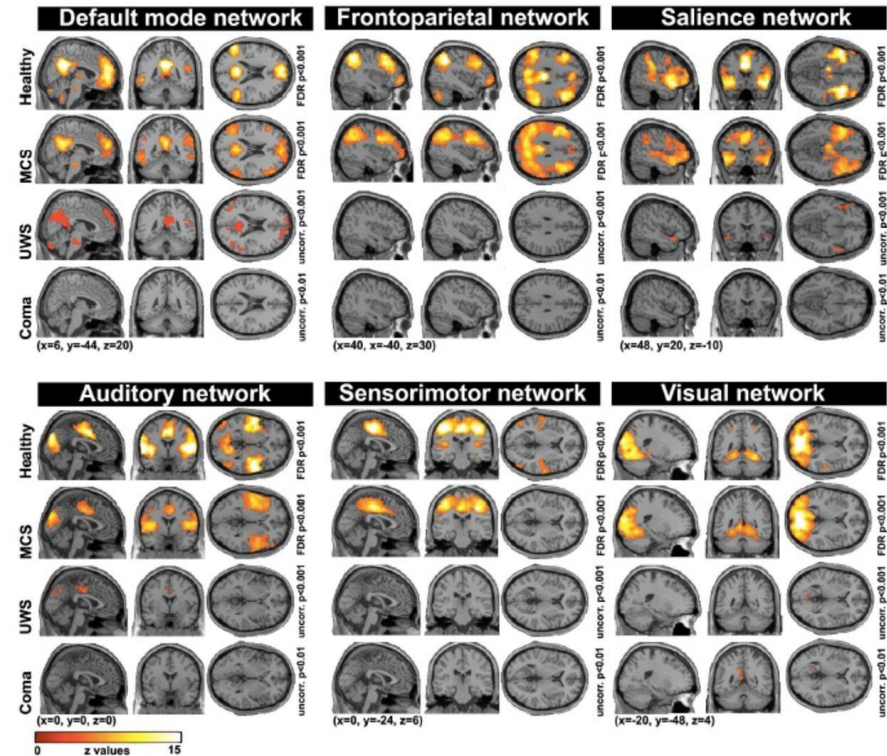
Intralaminar nuclei stimulation
induces “recovery” from
minimally responsive state



Schiff et al, *Nature*, 2007

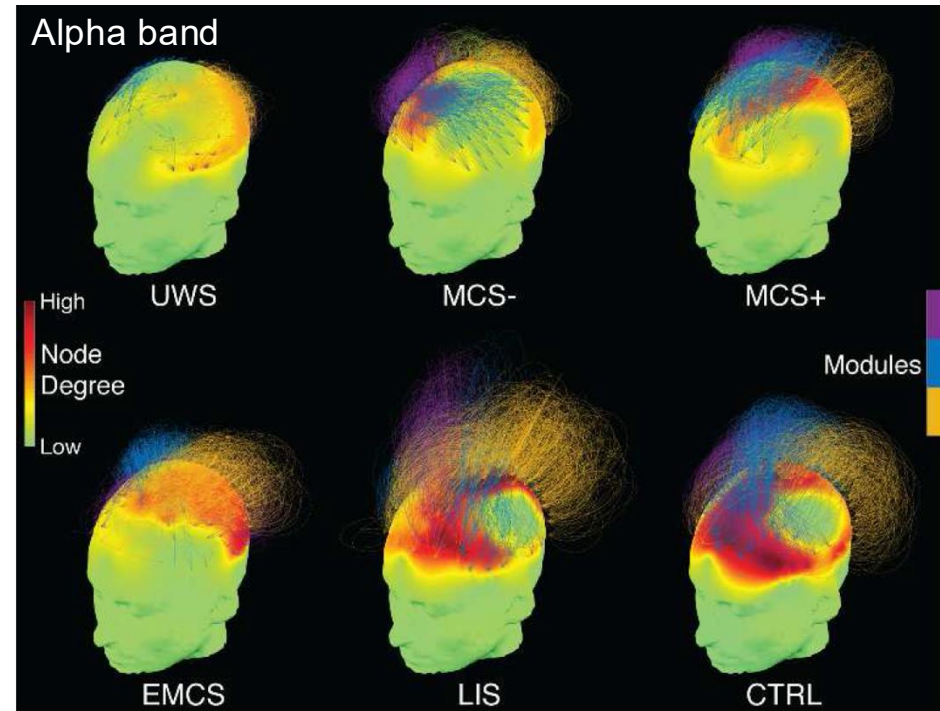
Consciousness $\approx$ connectivity

Resting state fMRI



Vanhaudenhuyse et al, *Brain*, 2010
Demertzi et al, *Brain*, 2015

Resting state EEG



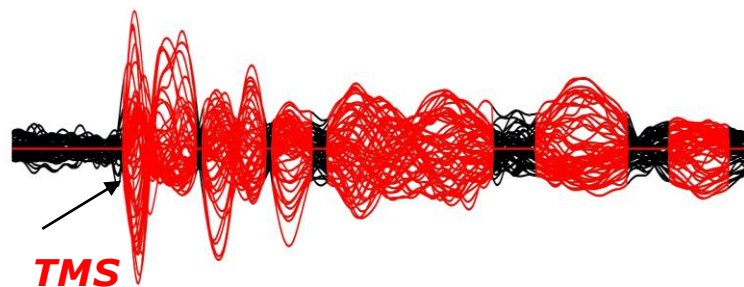
Chennu et al, *Brain*, 2017



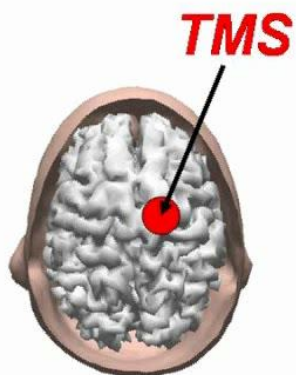
Consciousness $\approx$ complexity

TMS-EEG

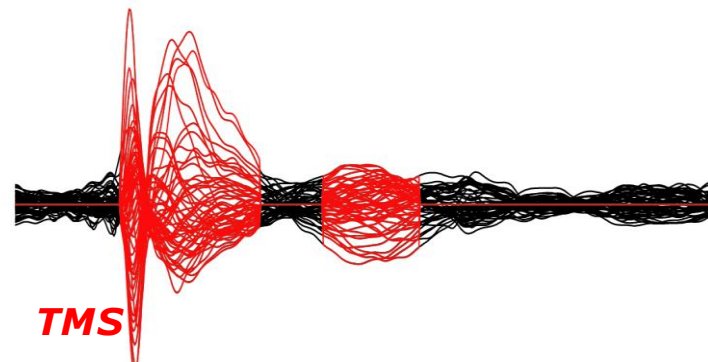
Conscious



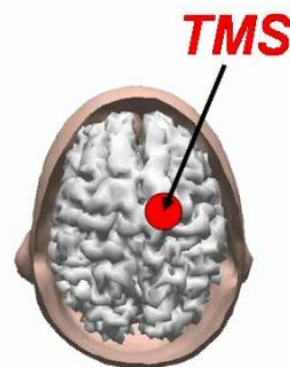
0 ms



Unconscious



0 ms



Perturbational complexity index



Magnetic Perturbation

Brain Response

Compression



Conscious
Subjects

Unconscious
Subjects

BEHAVIORAL RESPONSIVENESS

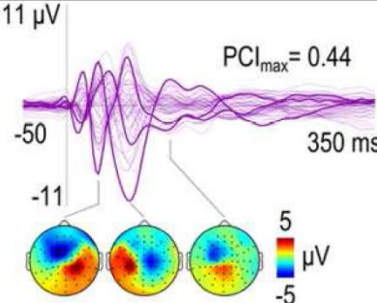
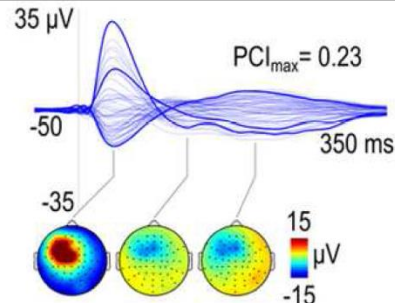
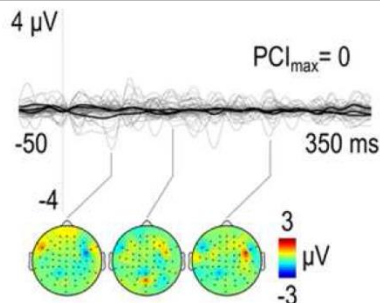
BEHAVIORAL UNRESPONSIVENESS

CRS-R

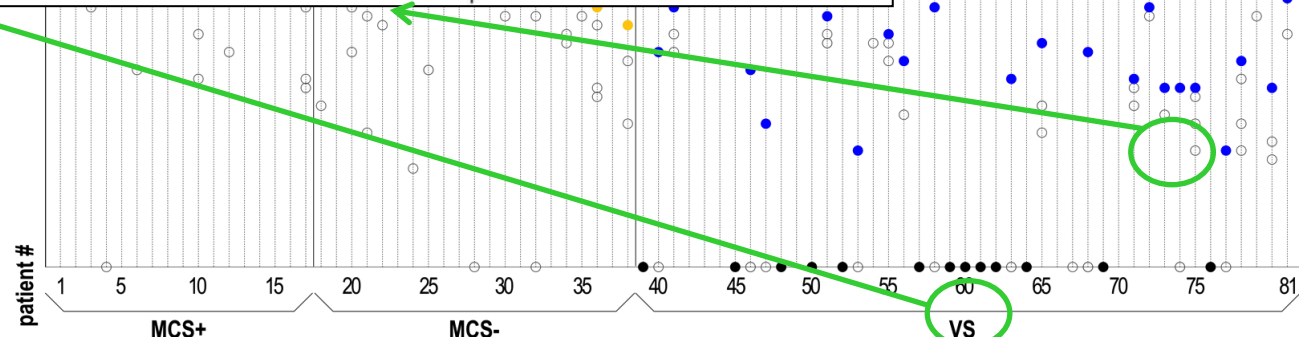
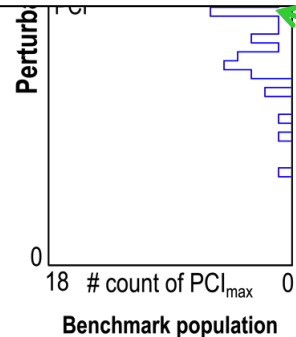


0.8

TMS-evoked potentials



PCI _{max}	clinical diagnosis	
	MCS	VS
>PCI*	36	9
≤PCI*	2	21
= 0	0	13
	38	43



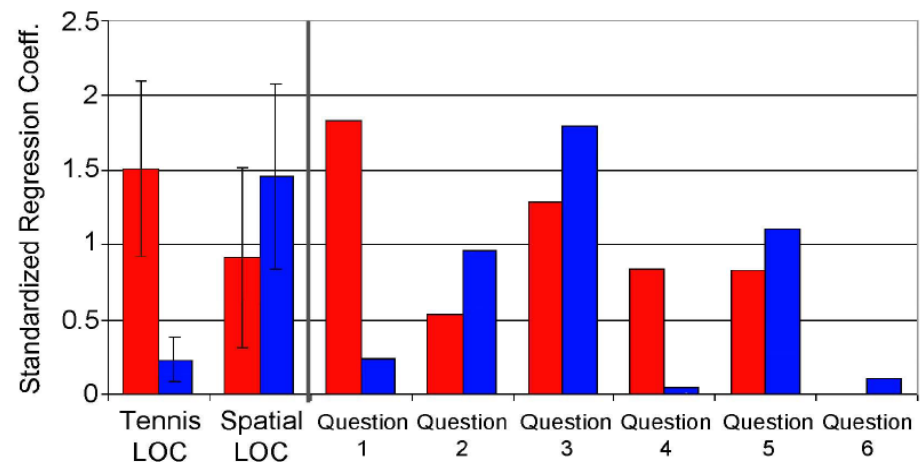
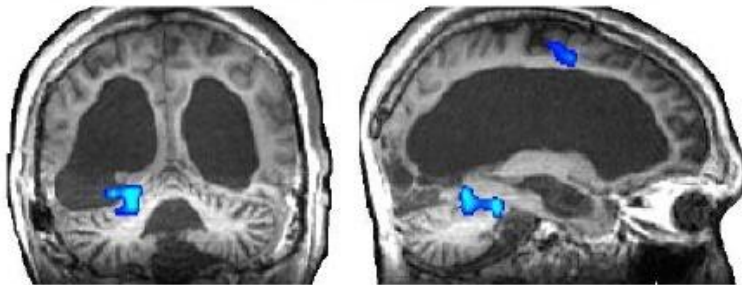
fMRI active paradigms $\approx$ communication

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

Is your father's name Alexander ?



Is your father's name Thomas ?



EEG active paradigms $\approx$ communication

"MOVE YOUR FOOT"



"MOVE YOUR HAND"



HEALTHY
CONTROL
SUBJECT

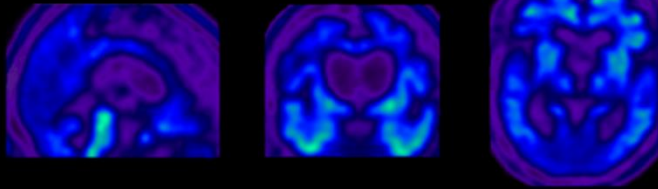
"VEGETATIVE"
UNRESPONSIVE
PATIENT



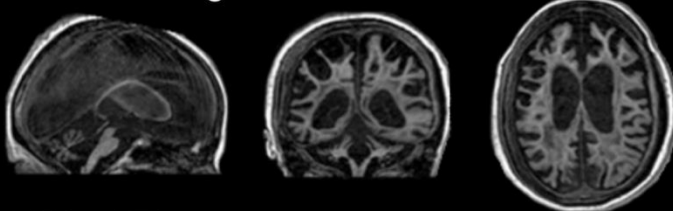
Consciousness $\neq$ responsiveness



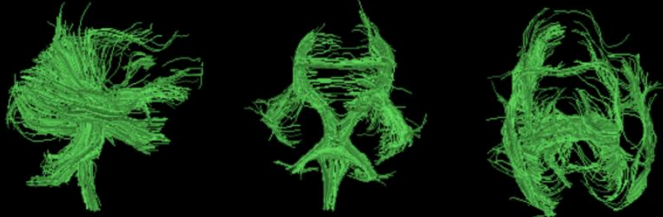
FDG - PET



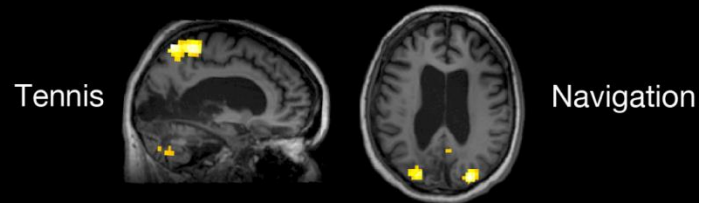
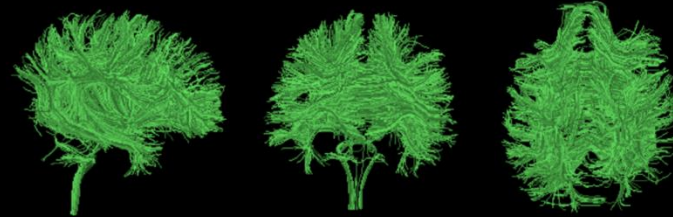
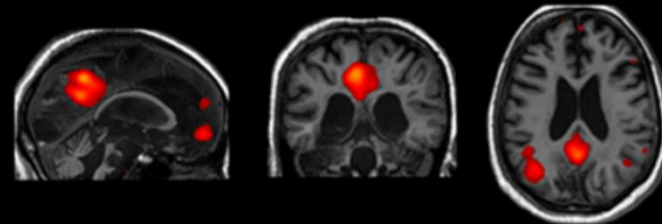
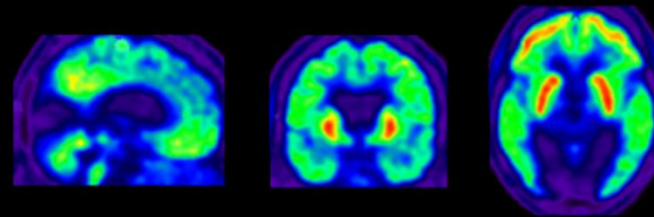
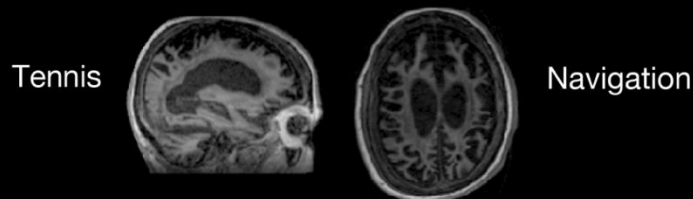
fMRI - resting state



MRI - DTI



fMRI - mental imagery task



UWS



End-of-life
discussion



MCS*

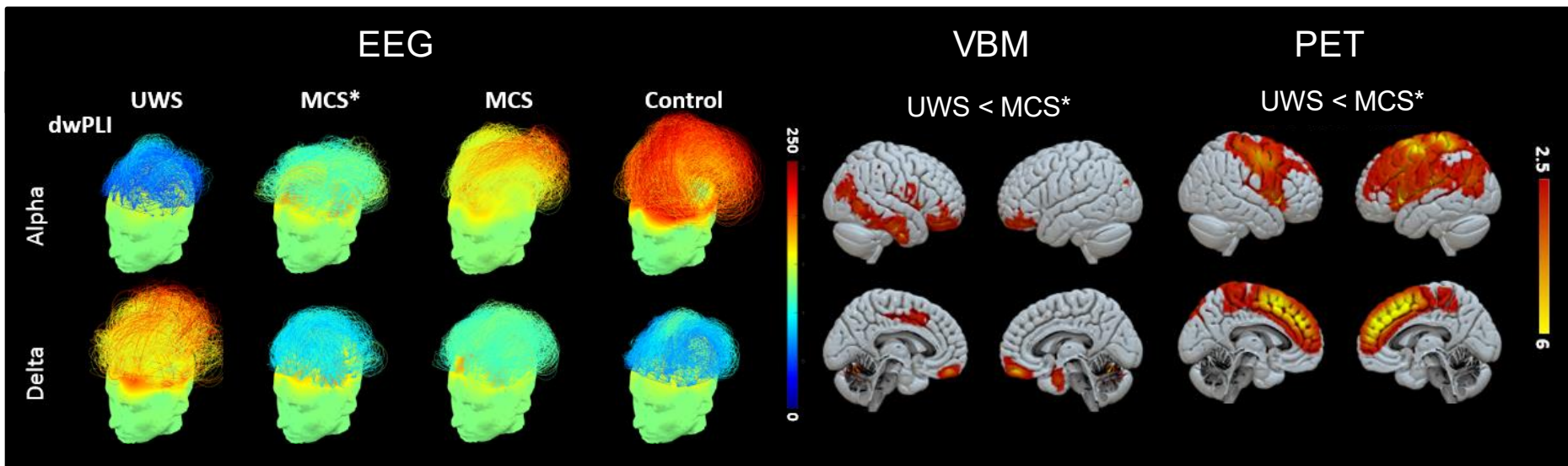
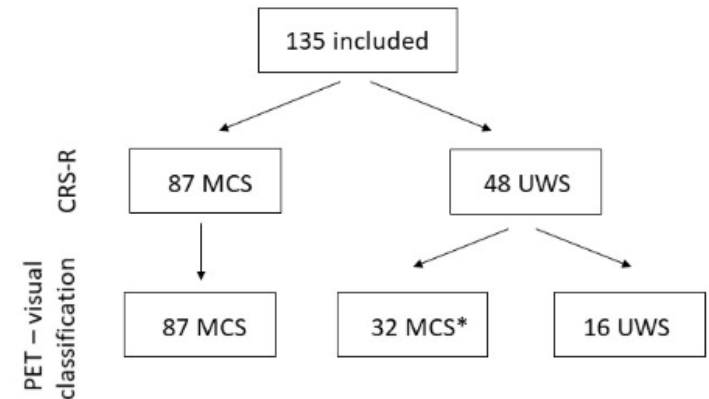
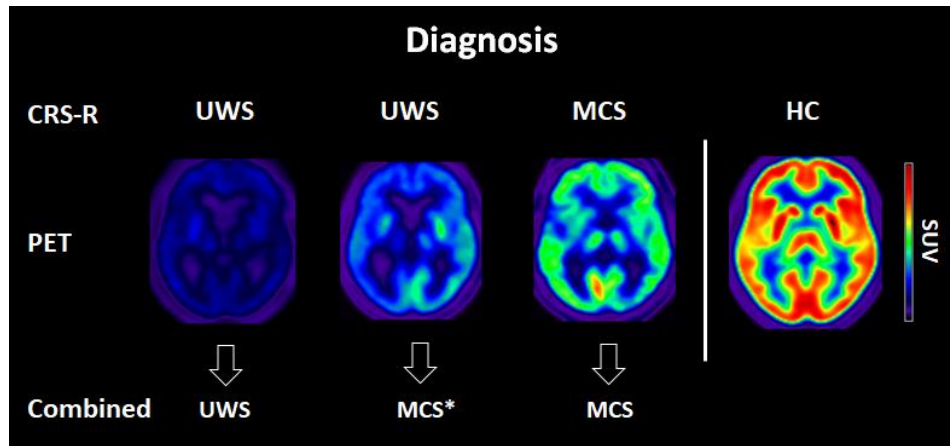


Stimulation

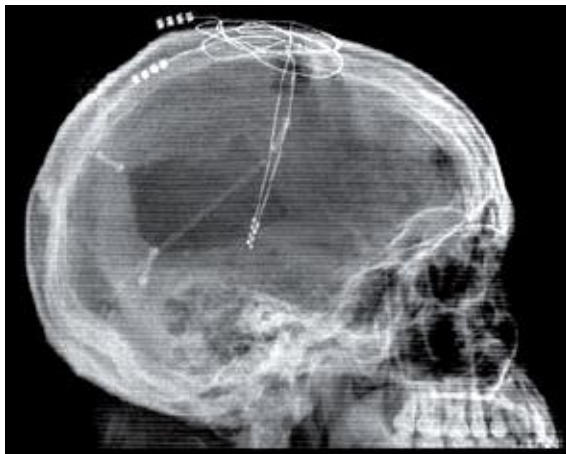
UWS = unresponsive wakefulness syndrome

MCS* = non-behavioral minimally conscious state

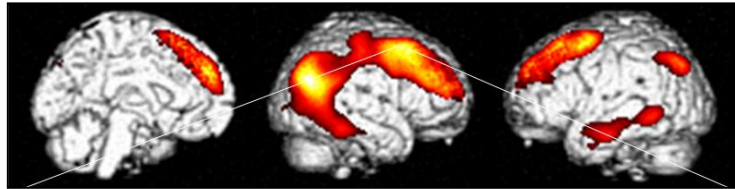
Covert cognition



What are the therapeutic options for patients with disorders of consciousness?

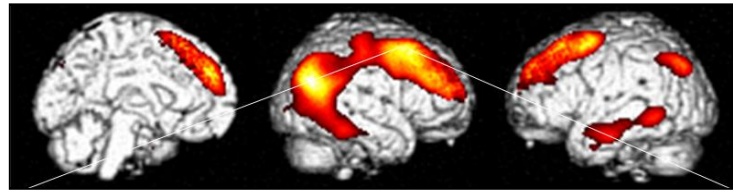


- Amantadine – RCT – 184 TBI (Giacino et al, *NEJM*, 2012)



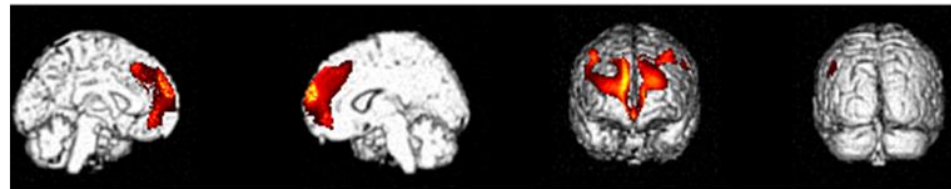
Schnakers et al, 2008

- Amantadine – RCT – 184 TBI (Giacino et al, *NEJM*, 2012)



Schnakers et al, 2008

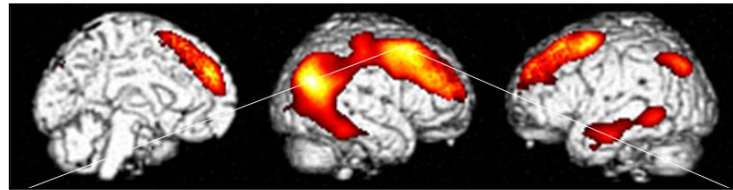
- Zolpidem
5-7% responders



Chatelle et al, 2014, Thonnard et al, 2014

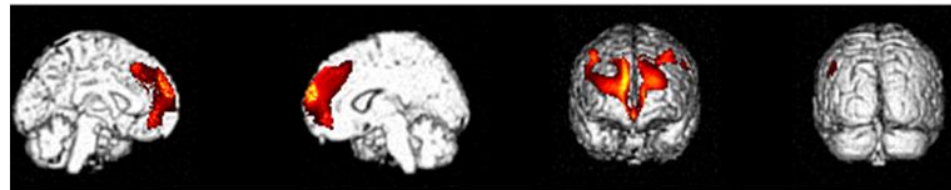
Drugs

- Amantadine – RCT – 184 TBI (Giacino et al, *NEJM*, 2012)



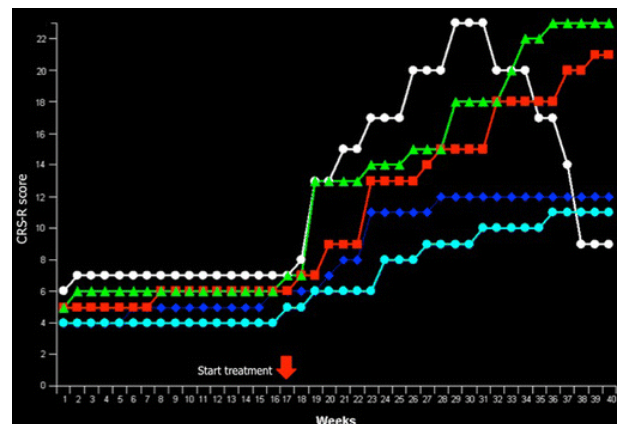
Schnakers et al, 2008

- Zolpidem
5-7% responders



Chatelle et al, 2014, Thonnard et al, 2014

- Apomorphine
- Baclofen

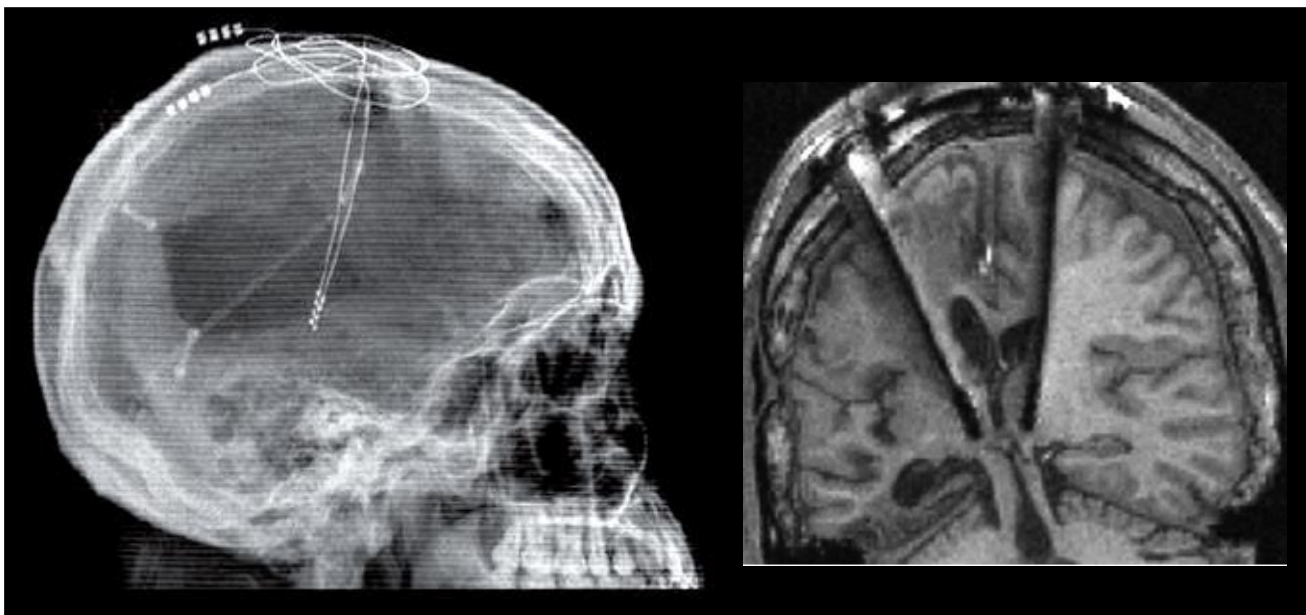


Sara et al, 2009; Pistoia et al, 2014



Deep Brain Stimulation

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



MCS → emerged – prolonged effects
sustained attention, intelligible words, functional objects use

No RCT & side-effects

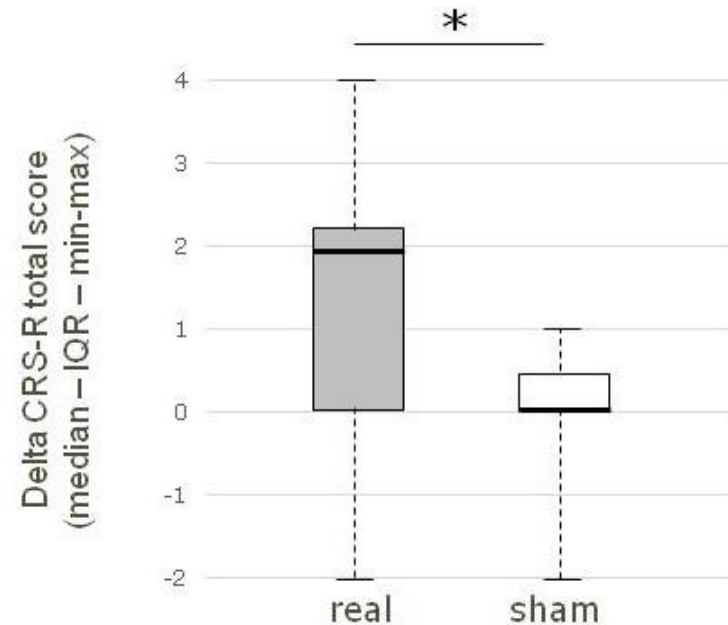
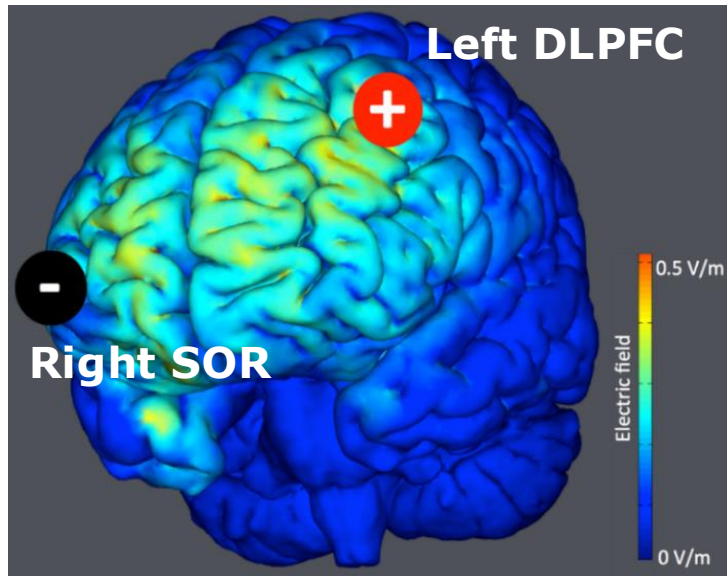
tDCS single session

ARTICLES

tDCS in patients with disorders of consciousness

Sham-controlled randomized double-blind study

Crossover RCT (n=55)

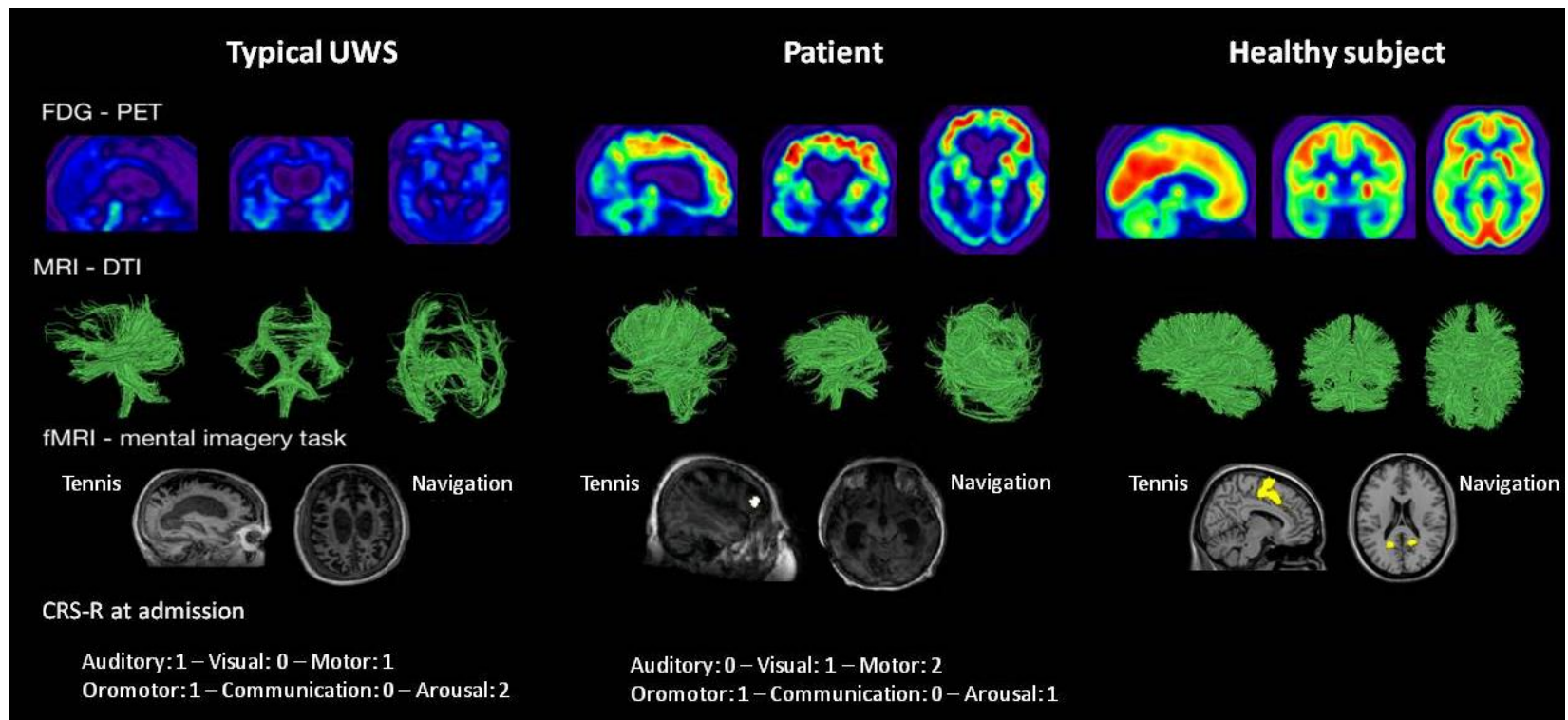


MCS
n=30

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

Unveil covert consciousness

- 67yo woman in UWS for 4y after subarachnoid hemorrhage
- Out of 7 CRS-R, 1 localization to pain
- Consistent response to command only after tDCS
- Neuroimaging consistent with MCS*

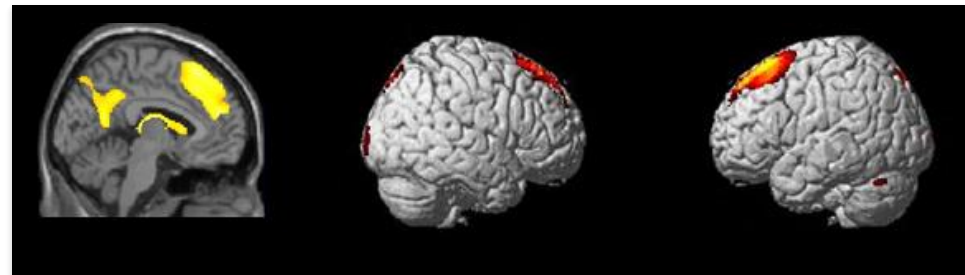


➔ tDCS may facilitate motor execution of command when cognitive functions are preserved

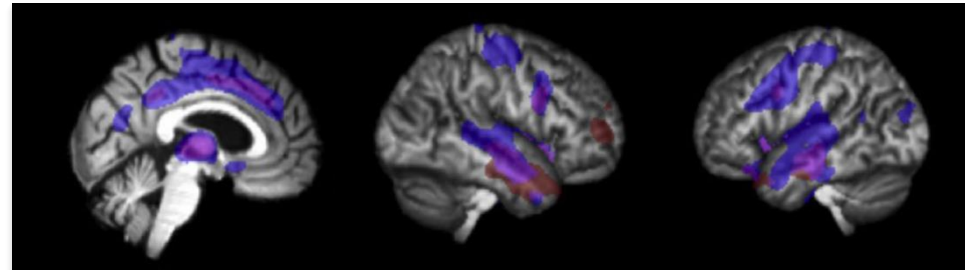
Predicting clinical response

tDCS responders $\neq$ non-responders

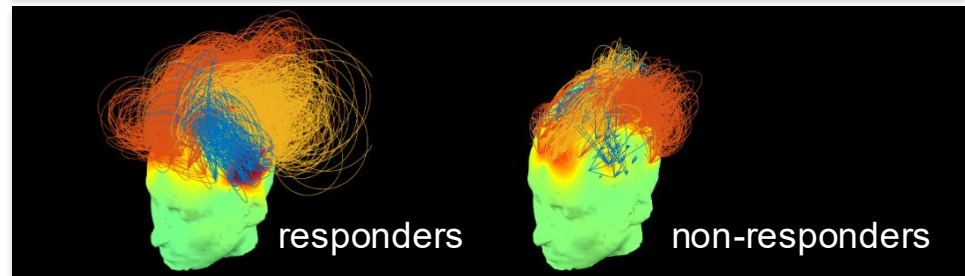
Brain metabolism (PET-scan)
 $\neq$ responders & non-responders ●



Grey matter atrophy (MRI)
Grey matter atrophy
in responders ●
in non-responders ●

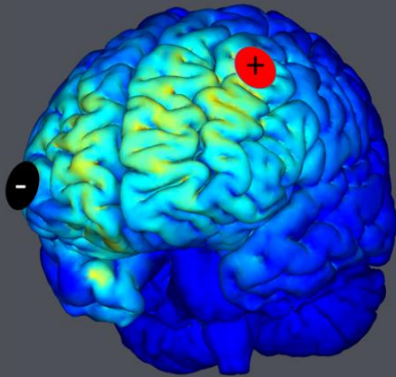


Brain connectivity (hd-EEG)
theta centrality

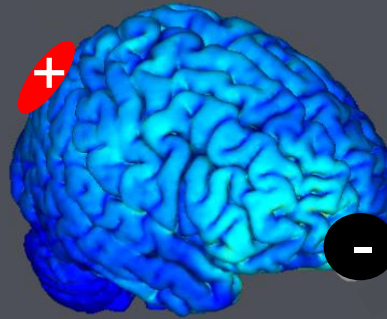


Stimulating different brain areas

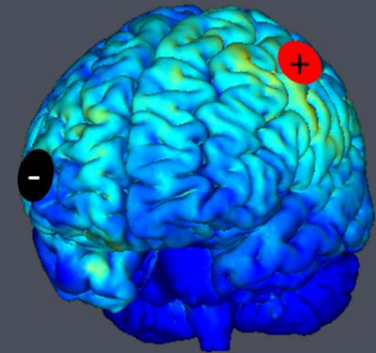
Prefrontal ↗



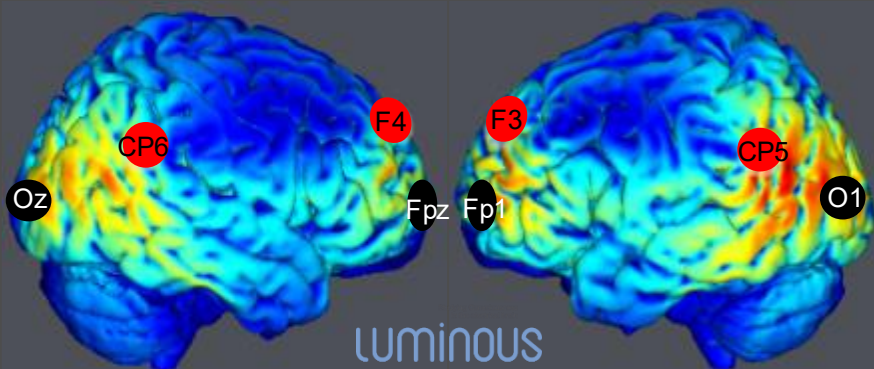
Precuneus ↘



Motor ≡



Multichannel frontoparietal ≡



Group level: Prefrontal
tDCS best area to target

Single-subject level:
Patient's tailored montage



Conclusion

- ✓ Consciousness $\neq$ behavioral responsiveness
 - $\neq$ global brain function
 - $\neq$ primary cortices
- $\approx$ emergent property of collective critical neural network dynamics, involving a fronto-parietal network & thalamo-cortical loop (connectivity & complexity)
- ✓ Diagnostic use
 - $\approx$ 40% misdiagnosis $\rightarrow$ multimodal imaging
- ✓ Therapeutic use
- ✓ Ethical challenges $\rightarrow$ don't judge a book by its cover!

THANK YOU

COMA
SCIENCE GROUP



Studying Consciousness
in the electrical brain



James S. McDonnell Foundation

