5th Congress of the European Academy of Neurology

Oslo, Norway, June 29 - July 2, 2019

Teaching Course 14

Diagnosing coma and disorders of consciousness – pearls and pitfalls from a new EAN guideline (Level 1 or 2)

Electrophysiology

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EAN Guideline
on the Classification of
Coma and other Disorders of Consciousness

-

Electrophysiology

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Disclosures

- French public funding:
  - Poste d'accueil Inserm (PhD)
  - Assistance Publique Hôpitaux de Paris (Posdoc)
- Foundation funding:
  - Philippe foundation (Posdoc)
  - Amical des Anciens Internes en Médecine des Hôpitaux de Paris & Syndicat des CCA des Hôpitaux de Paris (Posdoc)
- Investigator for MRI-Coma, VALSE, MYACORT
- Site PI for ProReTro

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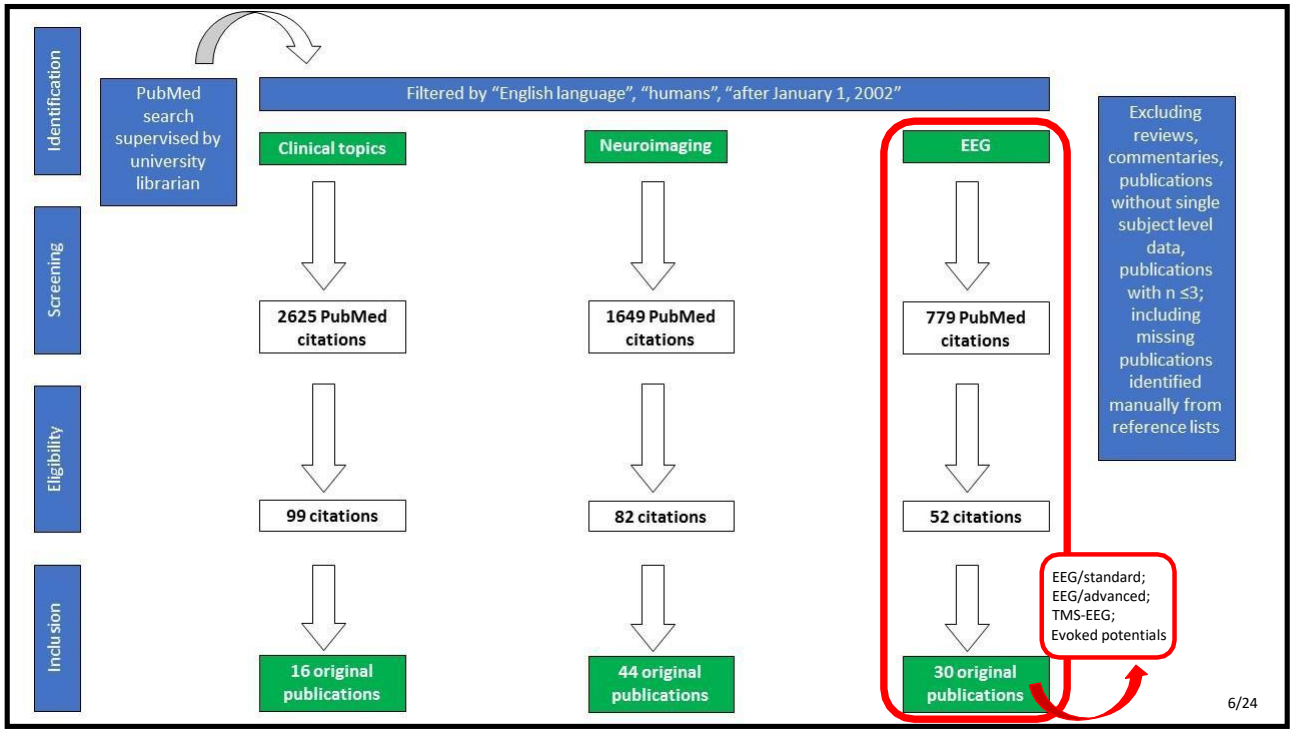
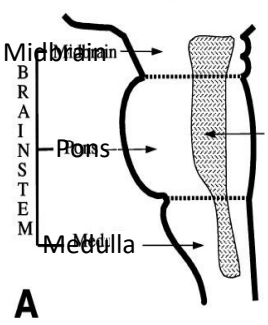


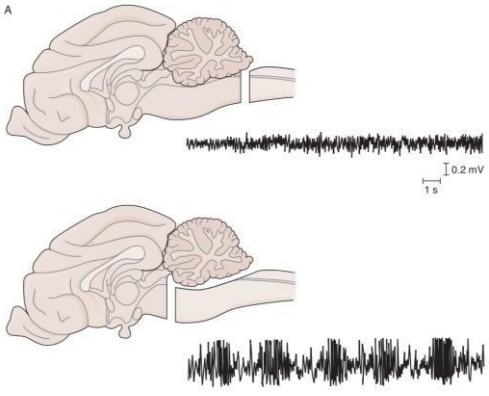
EEG and consciousness:

… a long story!



Ascending reticular activating system (ARAS)

Bremer in the 30s, Moruzzi, Magoun in the 50s



Plum and Posner's Diagnosis of Stupor and Coma 2007

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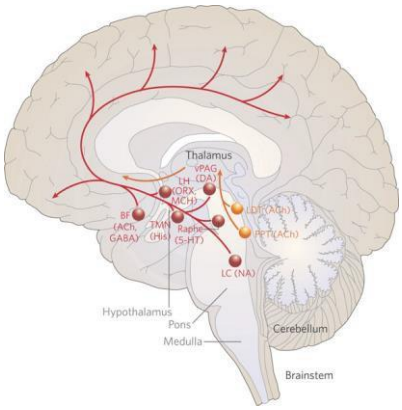
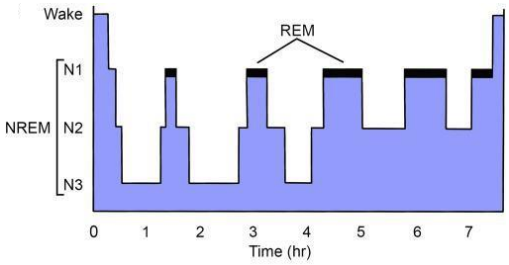
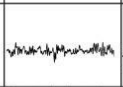
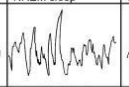
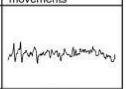
EEG and consciousness:

… a long story!



Saper et al., *Nature*. 2005



	Wake	NREM sleep	REM sleep
Psychological features	Varying amounts of alertness and attentiveness	Unconscious, or bland thoughts	Vivid, story-like dreams
Physiological features	Sympathetic tone variable	Sympathetic tone low; roving eye movements in light NREM sleep	Sympathetic tone variable; bursts of fast saccadic eye movements
EEG pattern (5 sec)			
Developmental changes	Short wake bouts in infants and young children	Deep NREM sleep abundant in children, but gradually decreases across adulthood	Abundant in infants, steady levels across adulthood; NREM-REM cycle short in infants

Review: Scammell TE, Arrigoni E, Lipton JO. *Neuron*. 2017

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Question 1/6: Can visual analysis of clinical standard EEG differentiate coma and VS/UWS from MCS?

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EEG background classification:

- "**Normal":** posterior dominant symmetric rhythm of 8–12 Hz ("**alpha**"), with and antero-posterior gradient and no focal or hemispheric slowing
- **"Mildly abnormal":** asymmetric and/or mildly **slowed** posterior dominant rhythm antero-posterior gradient not well organized and/or mild degree of focal or hemispheric slowing
- **"Moderately abnormal":** dominance of **theta** (4–7Hz) posterior rhythms and/or presence of moderate degree of focal or hemispheric slowing
- **"Severely abnormal":** dominance of **delta** (< 4Hz) waves over most of the brain areas

Forgacs PB, et al. *Ann Neurol* 2014

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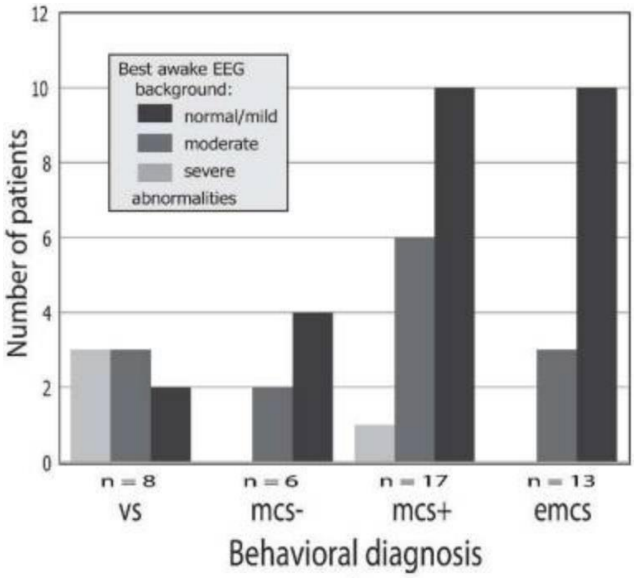

		Behavioral diagnosis		
		MCS/EMCS	VS	total
Awake EEG background	normal/mild	24	2	26
	mod & severe	12	6	18
total		36	8	44

*Fisher's exact test (one tailed) p=0.039

CMD: 3 MCS patients with CMD (fMRI), all with none/mild EEG background

Forgacs PB, et al. *Ann Neurol* 2014

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EEG reactivity :

1. eye opening and (forced) eye closing
2. tactile stimuli (wiping on the back of right and left forearm with cotton wool)
3. noxious stimulation (pressing fingernail beds on each hand)
4. acoustic stimulation (hand clapping)
5. Intermittent Photic Stimulation (IPS; 1 to 20Hz)

Estraneo A, et al. *Clin Neurophysiol* 2016

	EEG reactivity	VS (n = 37)	MCS– (n = 11)	MCS+ (n = 25)	Chi-square	p
1	Eye opening and closing	9 (24.3)	6 (54.5)	14 (56.0)	7.44	.024
2	Tactile	10 (27.0)	4 (36.4)	11 (44.0)	1.93	.38
3	Acoustic	9 (24.3)	7 (63.6)	14 (56.0)	8.9	.012
4	Nociceptive	7 (18.9)	5 (45.5)	9 (36.0)	3.88	.14
5	IPS	14 (37.8)	8 (72.7)	23 (92.0)	19.18	<.001
	EOC + Ac + IPS	3 (8.1)	5 (45.5)	10 (40.0)	11.18	.004
	At least one reactivity	18 (48.6)	10 (90.9)	25 (100)	21.96	<.001

Estraneo A, et al. *Clin Neurophysiol* 2016

Question 1/6: Can visual analysis of clinical standard EEG differentiate coma and VS/UWS from MCS?

Recommendation :

- 2 studies / 117 patients
- RR = 11.25 (95% CI 2.85-44.46)
- **Visual analysis of clinical standard EEG seems to detect patients with preserved consciousness with high specificity but low sensitivity (*low evidence, moderate recommendation*)**

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Question 2/6: Does sleep EEG, as opposed to clinical examination, help to distinguish coma and VS/UWS from MCS ?

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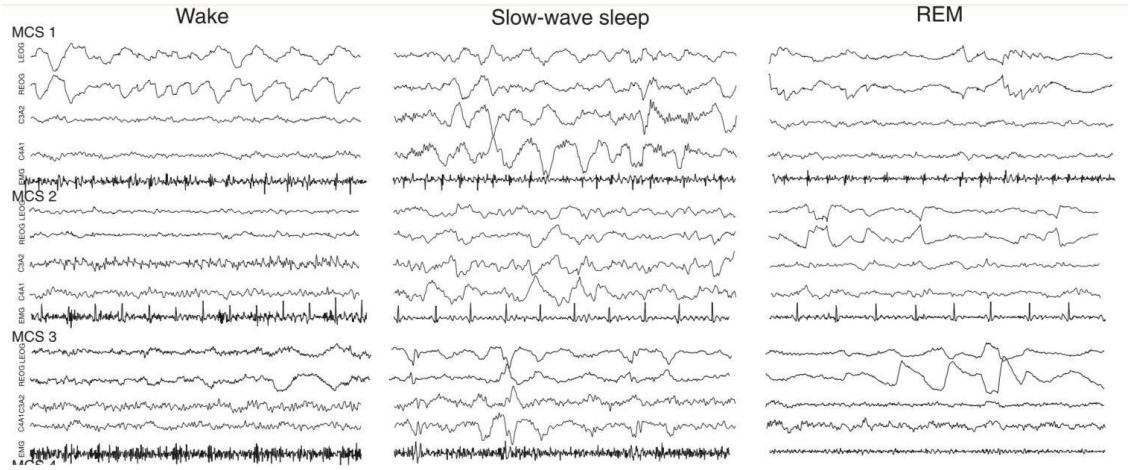

Landsness E, et al. *Brain* 2011

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Question 2/6: Does sleep EEG, as opposed to clinical examination, help to distinguish coma and VS/UWS from MCS ?

Recommendation :

- 6 studies / 153 patients
- RR = 1.55 (95% CI 1.24 to 1.94)
- **We recommend sleep EEG for the differentiation between VS/UWS and MCS as a part of multimodal assessment (*low evidence, weak recommendation*)**

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Question 3/6: Can high-density EEG (≥ 32 electrodes) with computational techniques, as compared to clinical examination, differentiate coma and VS/UWS from MCS?

Question 4/6: Can non-visual (i.e. numerical) analysis of clinical standard EEG (<32 electrodes) differentiate coma and VS/UWS from MCS ?

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Two main approaches when applying machine learning to DoC patients

Group approach

-> estimating signs of consciousness by analyzing measurement data obtained from multiple subjects

Individual approach

-> detecting changes in brain activation during functional tasks in a unique subjet

Review: Noirhomme G, et al. *Neuroimage* 2017

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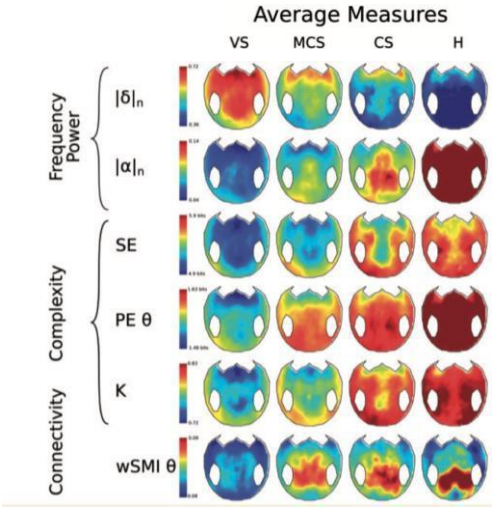
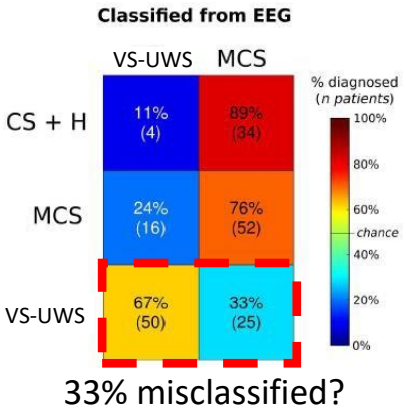
Example of a group approach:

VS-UWS / MCS classification (256 electrodes)





33% misclassified?

Sitt JD, King J-R, et al. *Brain* 2014

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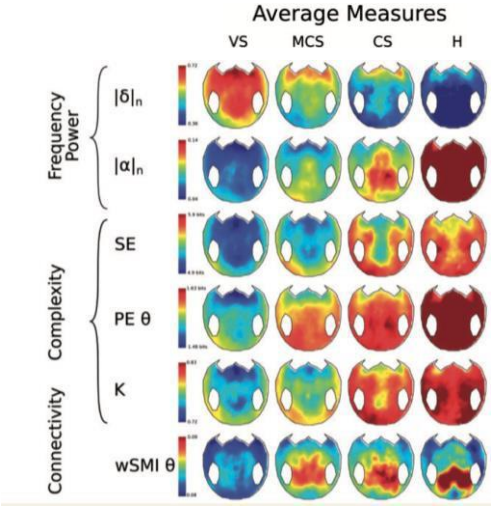
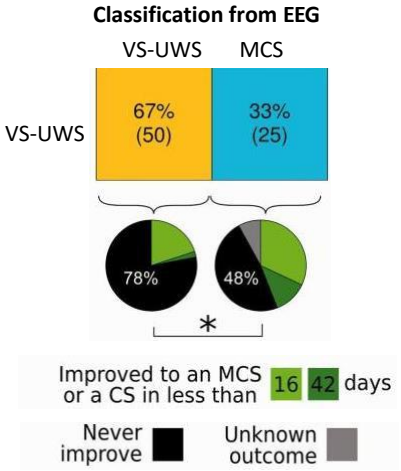
Example of a group approach:

VS-UWS / MCS classification (256 electrodes)





Sitt JD, King J-R, et al. *Brain* 2014

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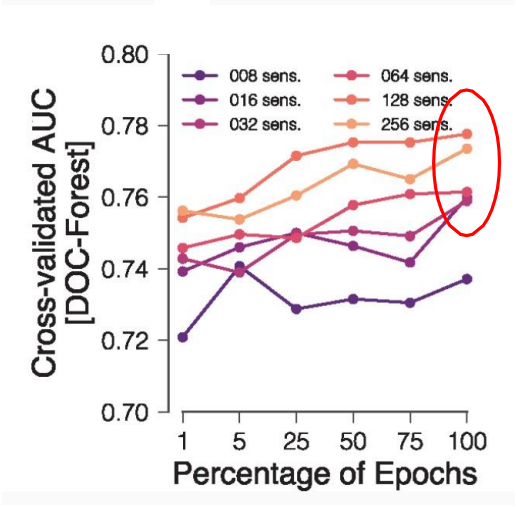

Multivariate classifiers seem to perform well when applied to **≥ 16 electrodes** EEG recordings (simulation)

Engemann, DA, Faimondo F et al. *Brain* 2018

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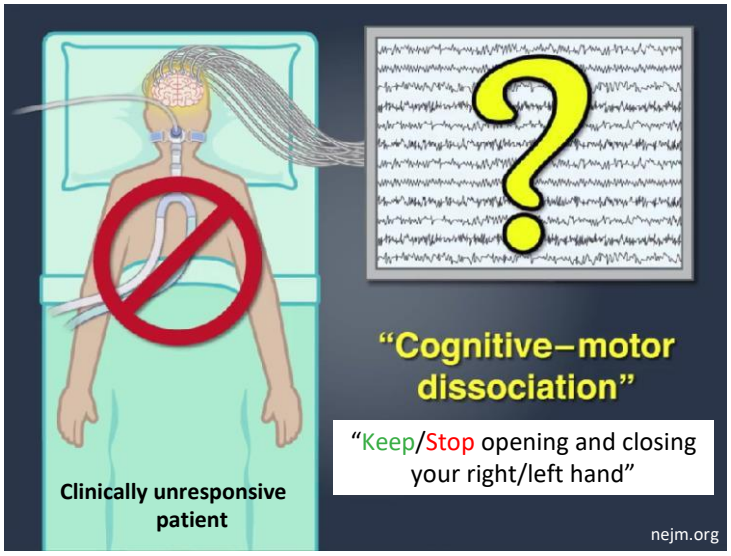
Example of an individual approach:
Motor Command Protocol to probe CMD



- Cruse D, et al. *Lancet* 2011 (n=3/16)
- Goldfine, et al. *Clin. Neurophysiol* 2011 (n=1/2 MCS)
- Cruse D, et al. *Neurology* 2012 (n=5/23)
- Edlow B, et al. *Brain* 2017 (n=0/13 [4/8 with fMRI])
- Curley WH, et al. *Brain* 2018 (n=9/21)
- Claassen J, et al. *NEJM* 2019 (n=16/104)

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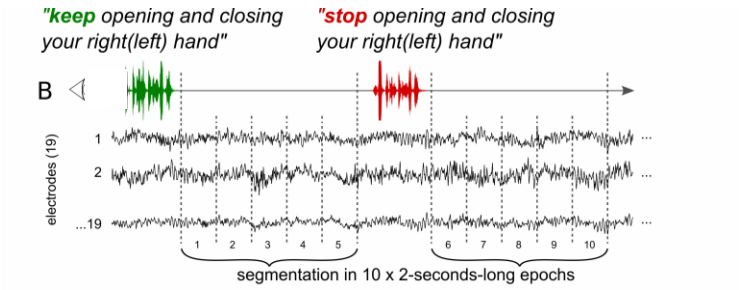
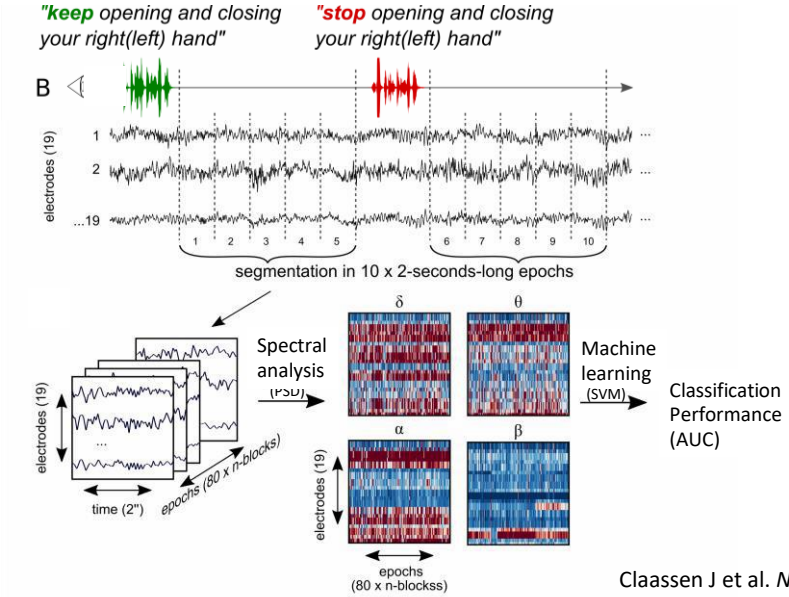
Motor Command Protocol



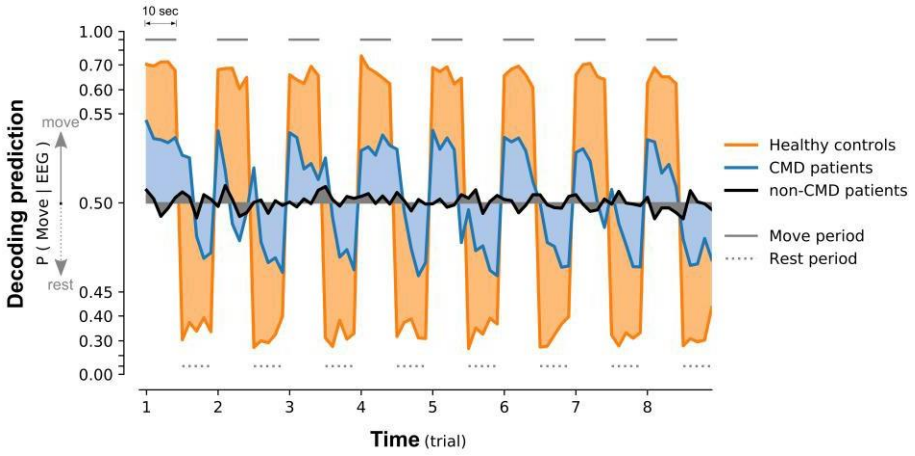
Claassen J et al. *NEJM* 2019

Motor Command Protocol



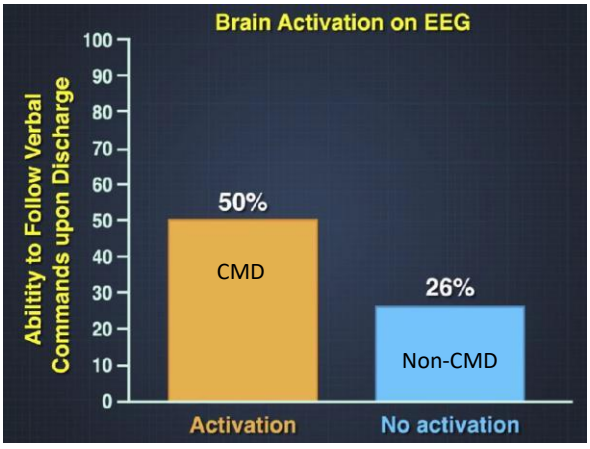
Claassen J et al. *NEJM* 2019

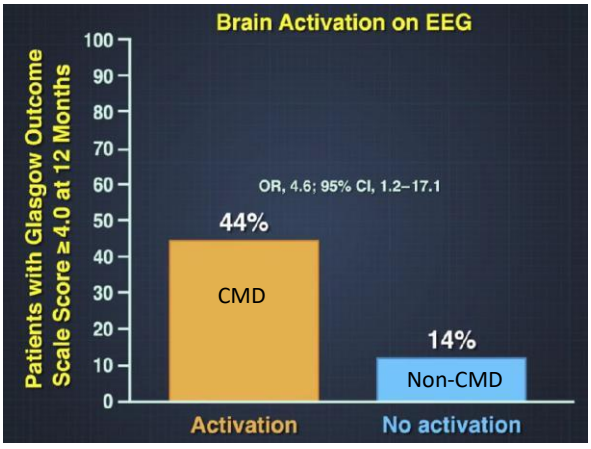
Prospective single center study (Columbia Neuro-ICU)
16/104 (15%) patients detected as CMD



Claassen J et al. *NEJM* 2019

CMD at the acute phase is associated with ouctome





Claassen J et al. *NEJM* 2019

Question 3/6: Can high-density EEG (e.g. ≥32 electrodes) with computational techniques, as compared to clinical examination, differentiate coma and VS/UWS from MCS?

Recommendation :

- 6 studies / 337 patients
- RR = 2.21 (95% CI 1.72 to 2.82)
- **It is recommended to consider quantitative analysis of high-density EEG for the differentiation between VS/UWS and MCS as part of multimodal assessment (*moderate evidence, weak recommendation*)**

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Question 4/6: Can non-visual (i.e. numerical) analysis of clinical standard EEG (<32 electrodes) differentiate coma and VS/UWS from MCS?

Recommendation :

- There were no eligible studies
- **Non-visual (i.e. numerical) analysis of standard EEG cannot yet be recommended for the differentiation between VS/UWS and MCS (*very low evidence, weak recommendation*)**

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Question 5/6: Can cognitive evoked potentials, as compared to clinical examination, differentiate coma and VS/UWS from MCS ?

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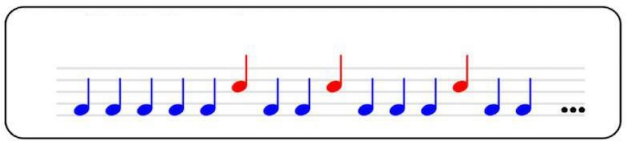
Cognitive evoked potentials: the *oddball* paradigm



- Näätänen, R. *Biological Psychology* 1975
- Squires, N. K., Squires, K. C., & Hillyard, S. A. *Electroencephalography and Clinical Neurophysiology* 1975

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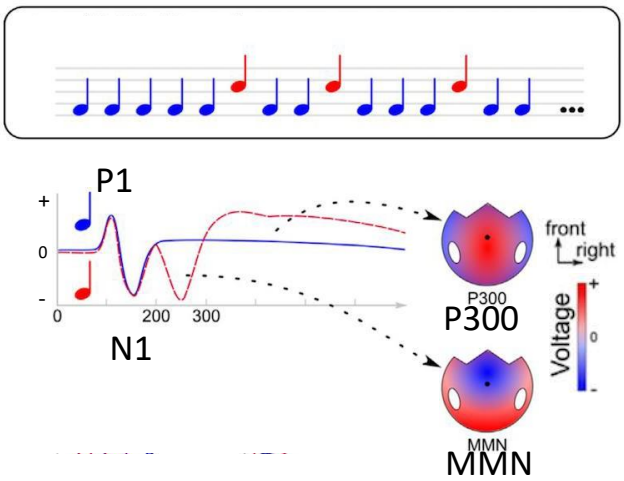

-> “Neural correlate of detection of novelty”

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Predictive value in coma:

- Kane, N.M., et al. *Lancet* 1993
- Fischer, C., et al. *Clin Neurophysiol* 1999
- Fischer, C., et al. *Neurology* 2004
- Naccache, L., et al. *Clinical Neurophysiology* 2005
- Fischer C et al. *Crit Care Med* 2006
- Daltrozzo et al . *Clin Neurophysiology* 2007
- Vanhaudenhuyse A et al . *Neurocrit Care* 2008
- Tzovara A et al. *Brain* 2013

MMN + ➔ Awakening (better than VS/UWS) = 90%

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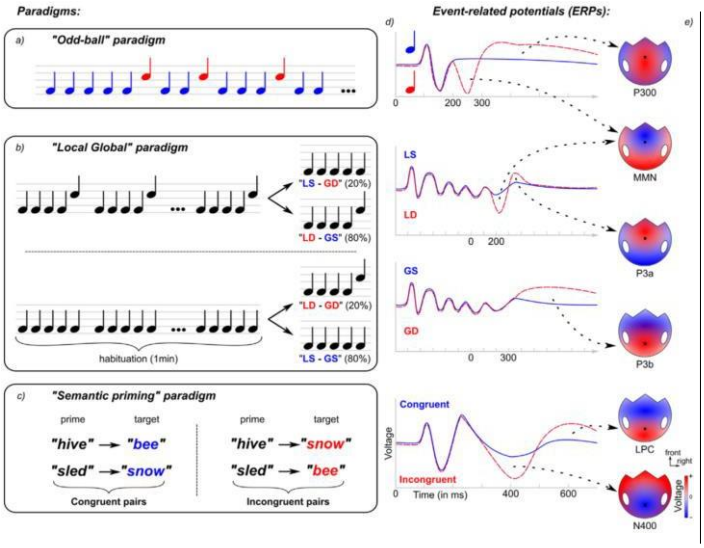
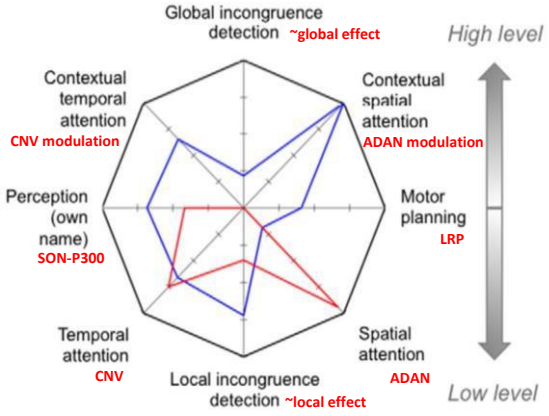
Many other ERP paradigms than the oddball !!!



Rohaut B & Naccache L. *Rev Neurol* 2017



Sergent C, et al. Neuroimage 2017

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Question 5/6: Can cognitive evoked potentials, as compared to clinical examination, differentiate coma and VS/UWS from MCS ?

Recommendation :

- 14 studies / 1298 patients
- RR 1.49 (95% CI 1.27 to 1.75)
- **Cognitive evoked potentials for the differentiation between VS/UWS and MCS might be considered as part of multimodal assessment (*low evidence, weak recommendation*)**

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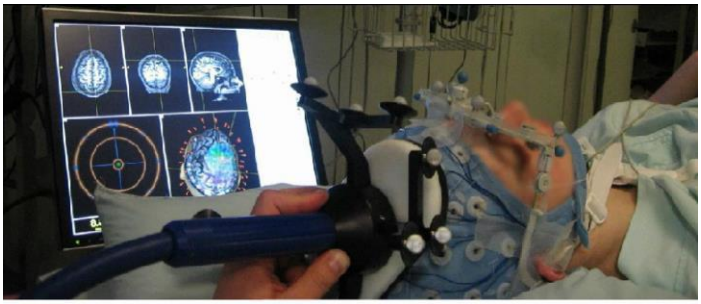
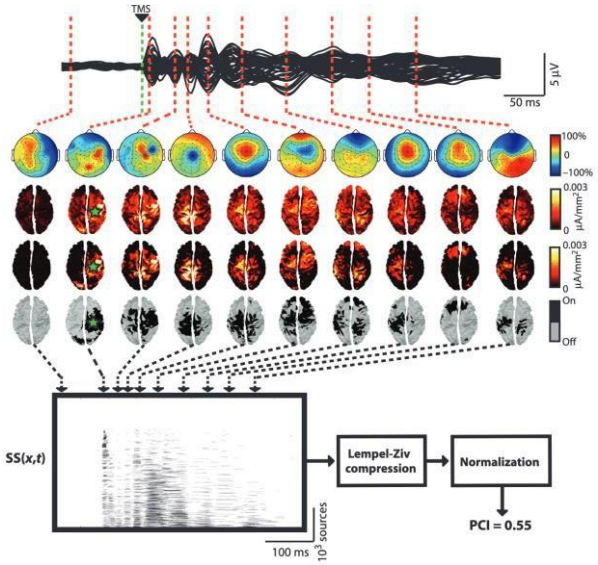
Question 6/6: Do EEG paradigms using TMS, as opposed to clinical examination, help to distinguish coma and VS/UWS from MCS ?



Credit: Casali AG



The Perturbational Complexity Index (PCI)

<u>Marker integrating 2 dimensions related with consciousness</u>

- **Differentiation**: ability to activate many functionally specialized modules of the thalamocortical system
- **Integration**: ability of this modules to interact rapidly and effectively

Casali AG, Gosseries O, Rosanova M, et al.. *Science Transl Med* 2013

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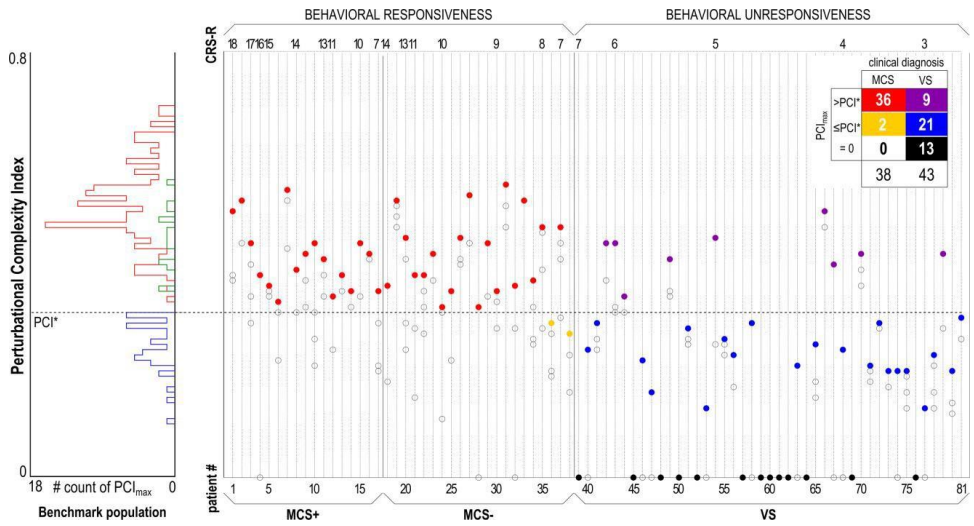

Casarotto S, et al. *Ann Neurol*. September 2016

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Question 6: Do EEG paradigms using TMS, as opposed to clinical examination, help to distinguish coma and VS/UWS from MCS?

Recommendation :

- 6 studies / 173 patients
- RR =5.40 (95% CI 3.29- 8.87).
- **We recommend considering TMS-EEG for the differentiation between VS/UWS and MCS as part of multimodal assessment (*low evidence, weak recommendation*)**

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Case example 1

- 65-year old man
- Scheduled digestive surgery
- Post-surgery complication (peritonitis, septicshock)
- Delayed awakening after sedation withdrawal
- No sign of awareness

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Next-of-kin consent obtained. Rohaut B, Raimondo F, et al *Brain inj* 2017

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Case vignette

- no visual pursuit, no fixation, no blink to visual threat
- no command following (spoken)
- pupillary, corneal and cough reflexes preserved
- oculocephalic and caloric responses abolished
- no startle reflex
- facial diplegia, no movement to nociceptive stimuli
- tendon reflexes present

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Coma Recovery Scale revised (CRS-R)

	Date	
	Week	ADM
AUDITORY FUNCTION SCALE		
4 - Consistent Movement to Command *		
3 - Reproducible Movement to Command *		
2 - Localization to Sound		
1 - Auditory Startle		
0 - None		X
VISUAL FUNCTION SCALE		
5 - Object Recognition *		
4 - Object Localization: Reaching *		
3 - Visual Pursuit *		
2 - Fixation *		
1 - Visual Startle		
0 - None		X

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

CRS-R = 4 [0 0 1 1 0 2]

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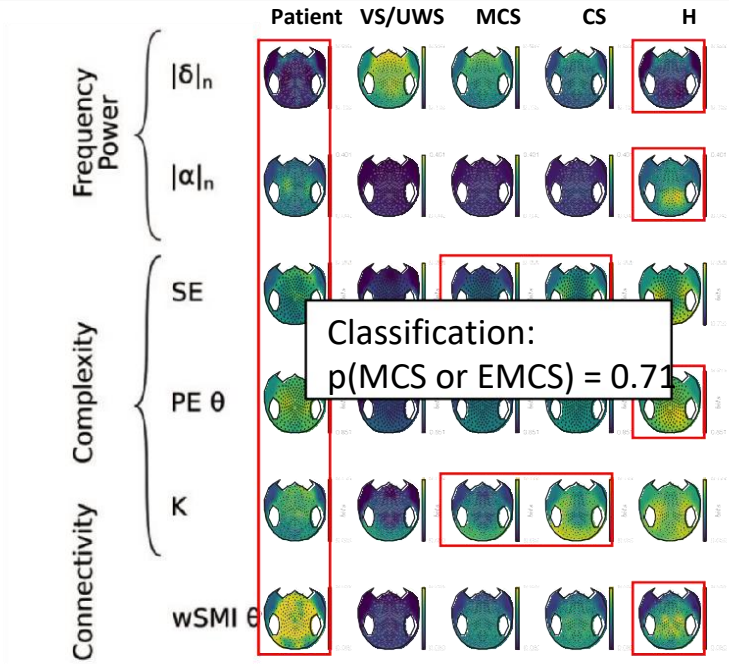
EEG (8 electrodes bedside): background activity consisted in a posterior and symmetrical theta band (4-6Hz) activity, slightly reactive to passive eye-opening/closing, but neither to auditory nor to nociceptive stimulation

-> **“mildly abnormal”**



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Next-of-kin consent obtained. Rohaut B, Raimondo F, et al *Brain inj* 2017

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Is this patient in a MCS ?

How to test if he is in a better state ?

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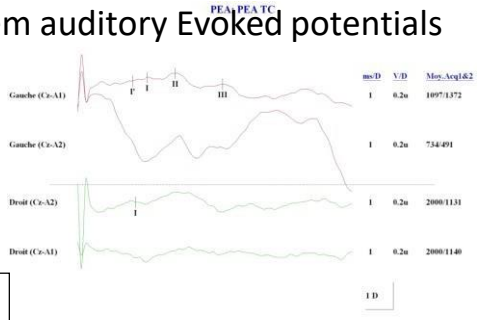
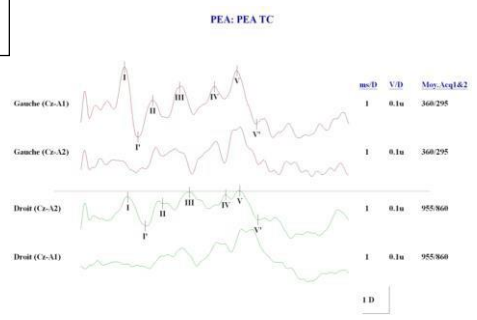
Brainstem auditory Evoked potentials

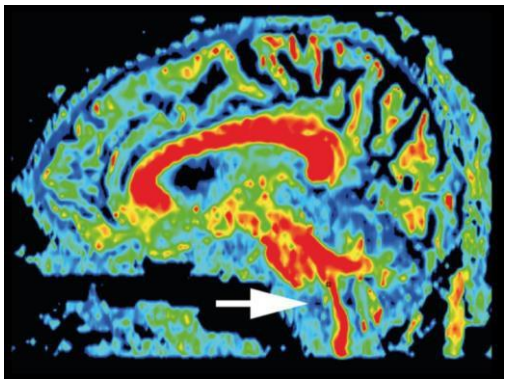
Case



I cochlear nerve
II cochlear nuclei
III superior olive
IV lateral lemniscus

Normal responses





MRI-DTI: Supra tentorial WM preserved. Interruption of the corticospinal track at the junction between the pons and the medulla

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Next-of-kin consent obtained. Rohaut B, Raimondo F, et al *Brain inj* 2017

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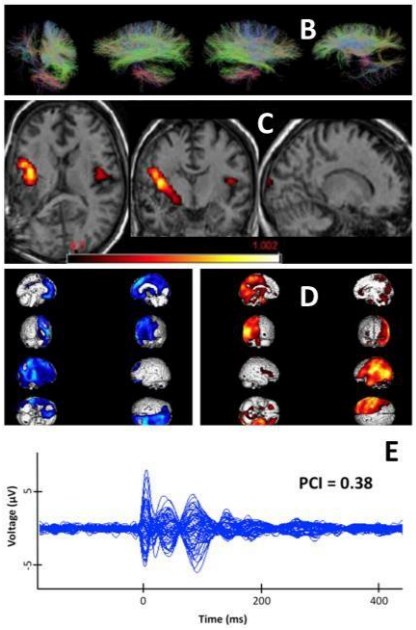
Case example 2

- 27-year old woman with a history of focal epilepsy was admitted with headache, confusion and rapid loss of consciousness due to a right ICH from a parietal arteriovenous malformation
- VS/UWS and referred for multimodal consciousness evaluation 13 weeks later.
- **Repeated neurological examinations** (n=6): spontaneous eye opening with preserved blink reflex to visual threat, no fixation or visual pursuit, absence of spontaneous movements other than myoclonic tremor in the right lower limb, auditory startle, stereotyped extensor posturing and grimacing following nociceptive stimuli, and preserved oral reflexes = **VS/UWS**
- Structural MRI revealed right temporo-parietal cortical atrophy and ischemic damage to the left cerebral peduncle and mesencephalon (presumably from right-sided mass effect with herniation of the left cerebral peduncle against the tentorium, i.e., Kernohan's notch).

COMA RECOVERY SCALE - REVISED					A	
AUDITORY FUNCTION SCALE						
4 - Consistent Movement to Command						
3 - Reproducible Movement to Command						
2 - Localization to Sound						
1 - Auditory Startle	X	X	X	X	X	X
0 - None						
VISUAL FUNCTION SCALE						
5 - Object Recognition						
4 - Object Localization: Reaching						
3 - Pursuit Eye Movements						
2 - Fixation						
1 - Visual Startle			X			
0 - None	X	X		X	X	X
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	X	X	X	X	X	X
0 - None/Flaccid						
OROMOTOR/VERBAL FUNCTION SCALE						
3 - Intelligible Verbalization						
2 - Vocalization/Oral Movement						
1 - Oral Reflexive Movement	X	X	X	X	X	X
0 - None						
COMMUNICATION SCALE						
2 - Functional: Accurate						
1 - Non-Functional: Intentional						
0 - None	X	X	X	X	X	X
AROUSAL SCALE						
2 - Eye Opening w/o Stimulation						
1 - Eye Opening with Stimulation	X	X	X	X	X	X
0 - Unarousable						
TOTAL SCORE	4	4	5	4	4	4
DIAGNOSIS	UWS	UWS	UWS	UWS	UWS	UWS



- **MRI-DTI :** decreased FA, consistent with axonal damage and decreased fiber intensity in the right cerebral hemisphere
- **resting state fMRI:** auditory network relatively preserved
- **PET:** hypometabolism (blue) involving the right hemisphere, including the thalamus, as well as the left prefrontal region; preserved metabolism (red) in the brainstem, the cerebellum, and large parts of the left cerebral hemisphere, including the left thalamus
- **TMS-EEG:** PCI =f 0.38 consistent with some degree of preserved consciousness
- **EEG:** right hemispheric background slowing in the theta range and lack of epileptiform activity (moderately abnormal")

Next-of-kin consent obtained. Figures courtesy of Aurore Thibaut, Olivier Bodart, Lizette Heine and Olivia Gosseries from the Coma Science Group, Liège, Belgium 51

- Patient clinically VS-UWS
- PET scan and TMS-EEG suggesting MCS
- At 12-month follow-up the patient evolved towards MCS with severe disability (Glasgow Outcome Scale-Extended score 3)

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Thank you!