Progrès dans la compréhension de la conscience et applications aux personnes en états de la conscience altérée

Journée EVC-EPR 2023

État Végétatif Chronique et État Pauci-Relationnel

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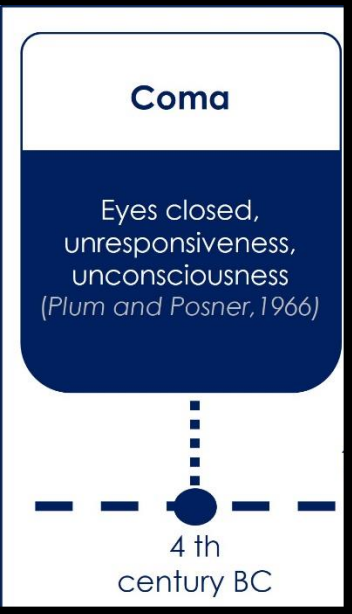
Trois questions au sujet des “DoC patients”:

- *Survol historique & conceptuel : ➔ évaluer un patient “chronique” en 2023*

- *Vocabulaire : VS/UWS ; MCS/CMS*

- *Proposition de structuration des évaluations & thérapeutiques innovantes*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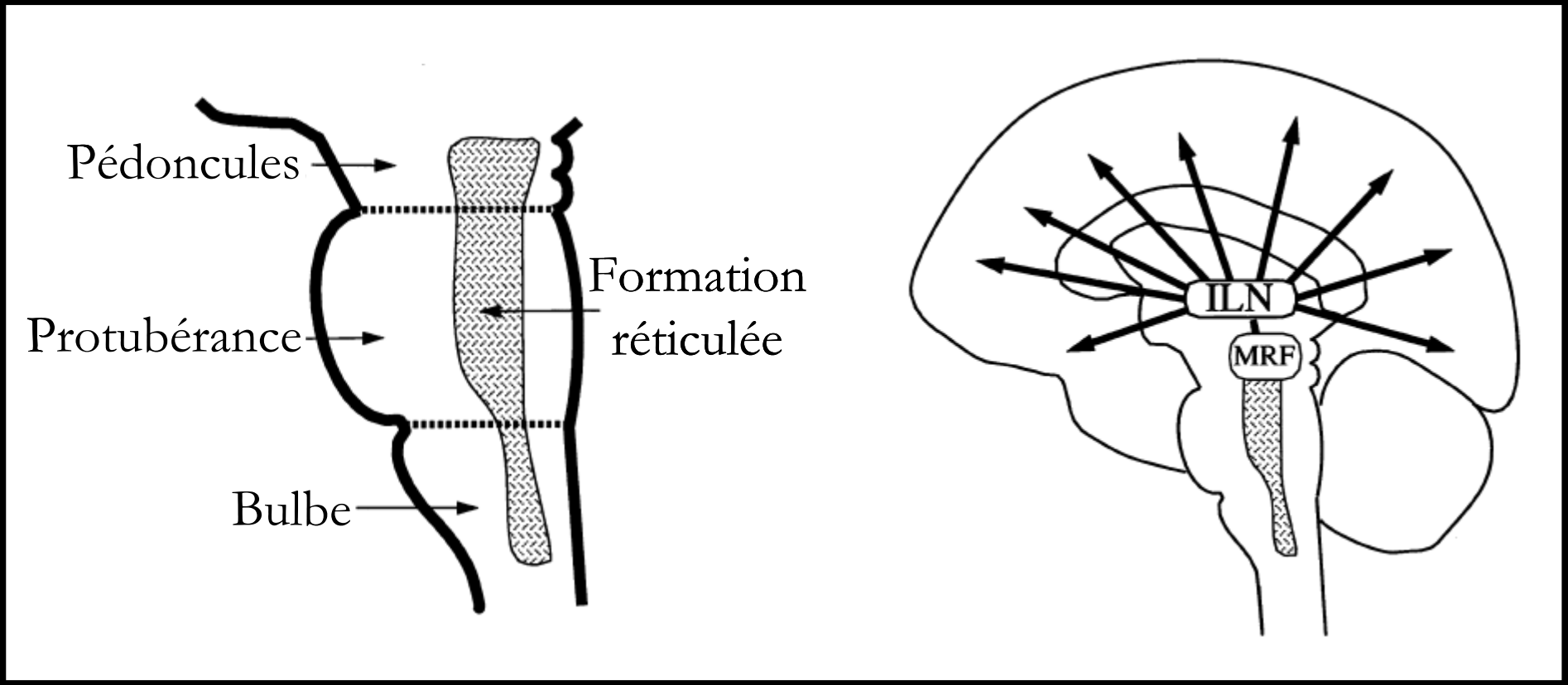
COMATOSE : VIGILANCE/AROUSAL is a necessary condition of conscious states



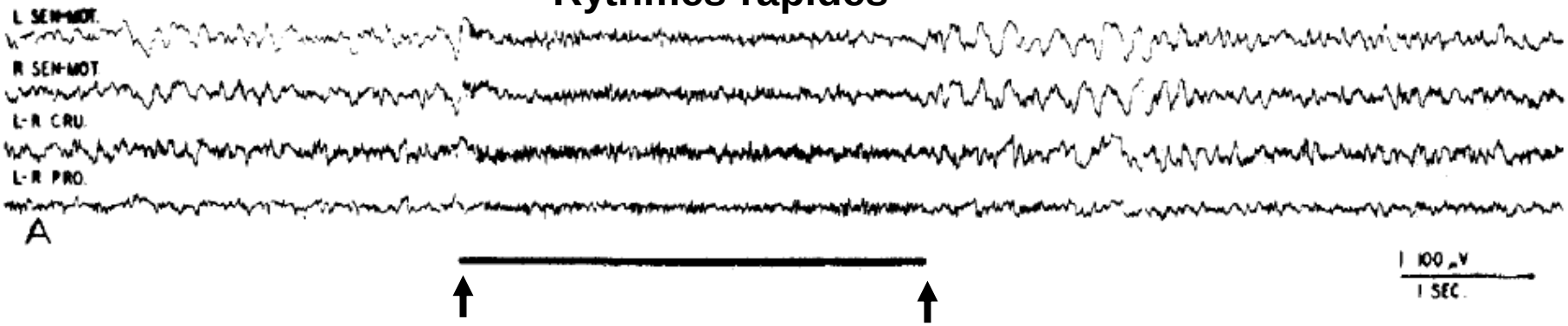
ARAS and cortical arousal

- Expériences de Moruzzi & Magoun chez le chat anesthésié (1949)
- Préparation « encéphale isolé » Bremer
- Lésions (coma irréversible)

Etat anesthésié
Amples ondes lentes

Eveil
Désynchronisation
Rythmes rapides

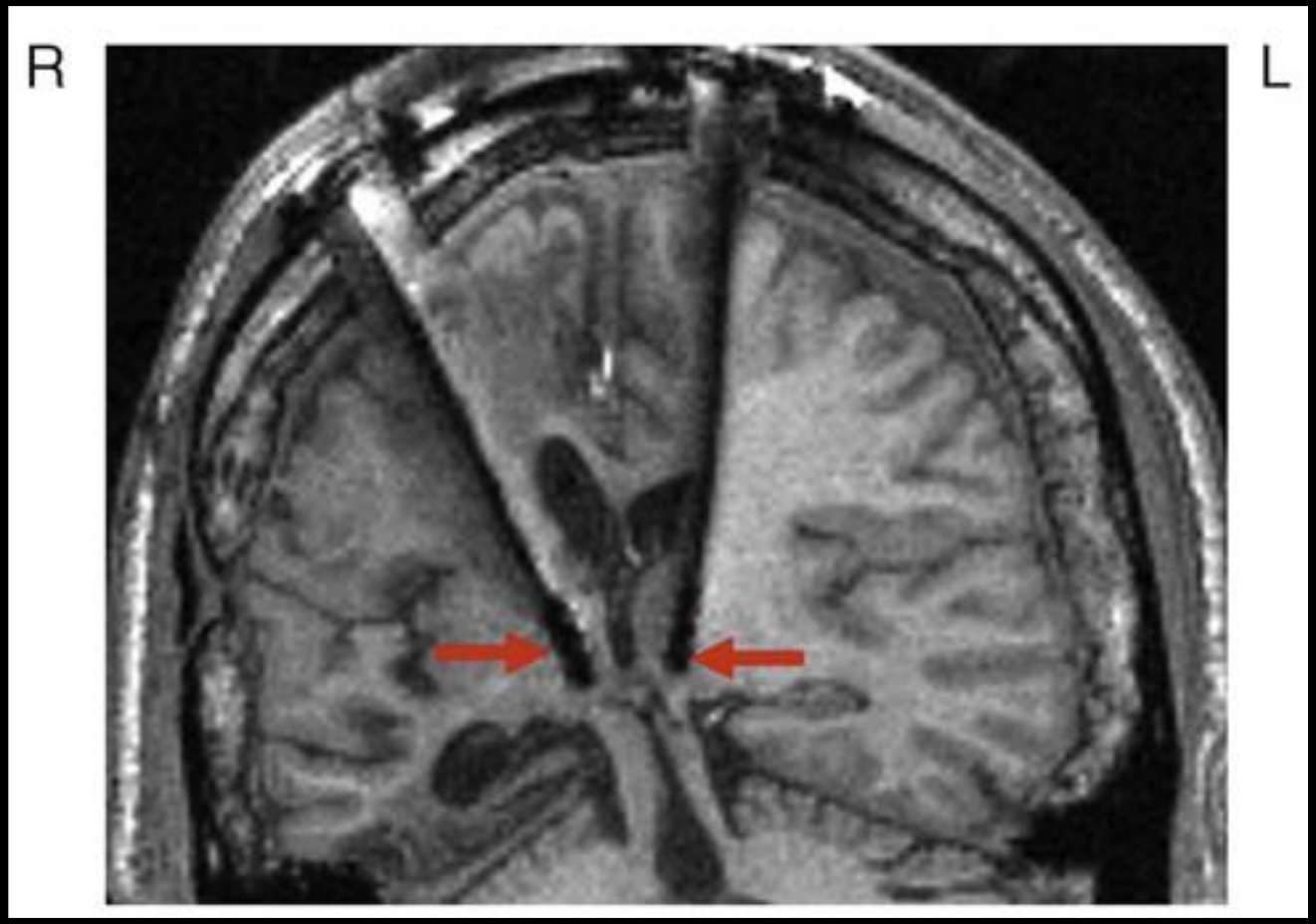
Etat anesthésié
Amples ondes lentes

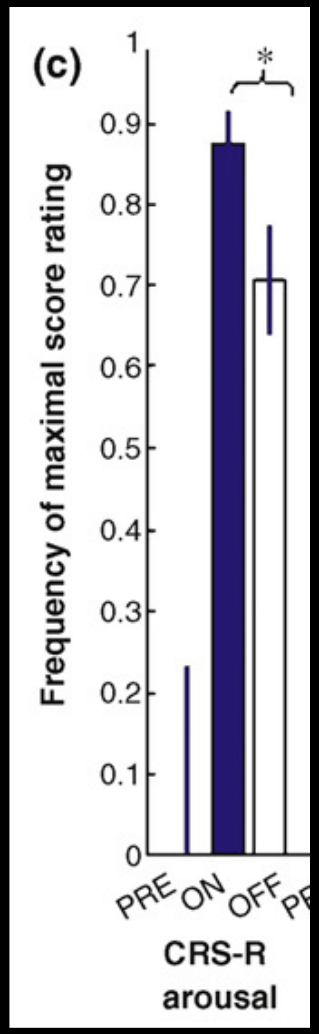


Stimulation électrique de la FRAA
Niveau bulbaire

ARAS and cortical arousal

From cats to humans





Homme de 38 ans avec trouble de l'éveil depuis 6 ans (Schiff et al., Nature 2007)

ARAS and cortical arousal

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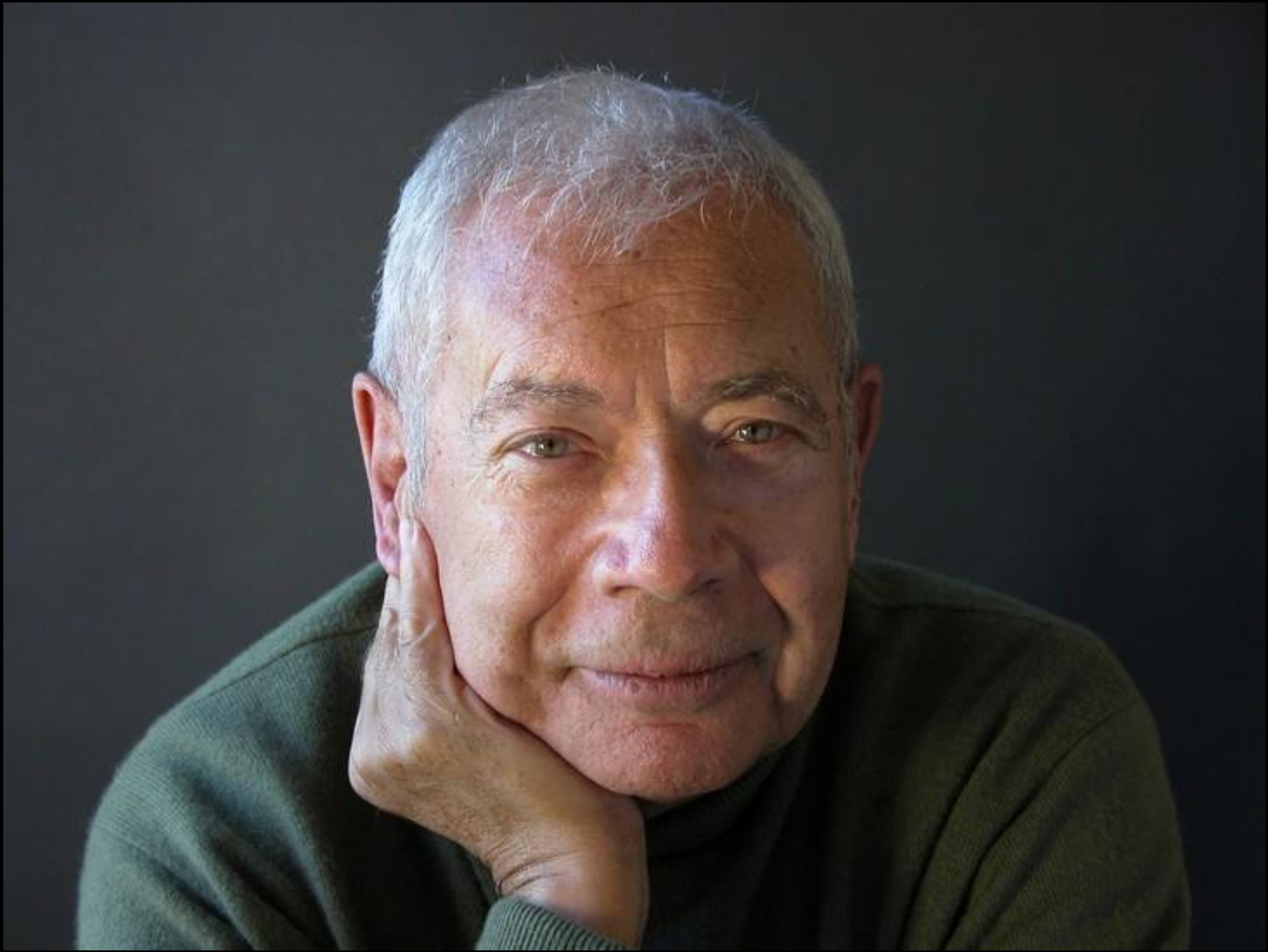
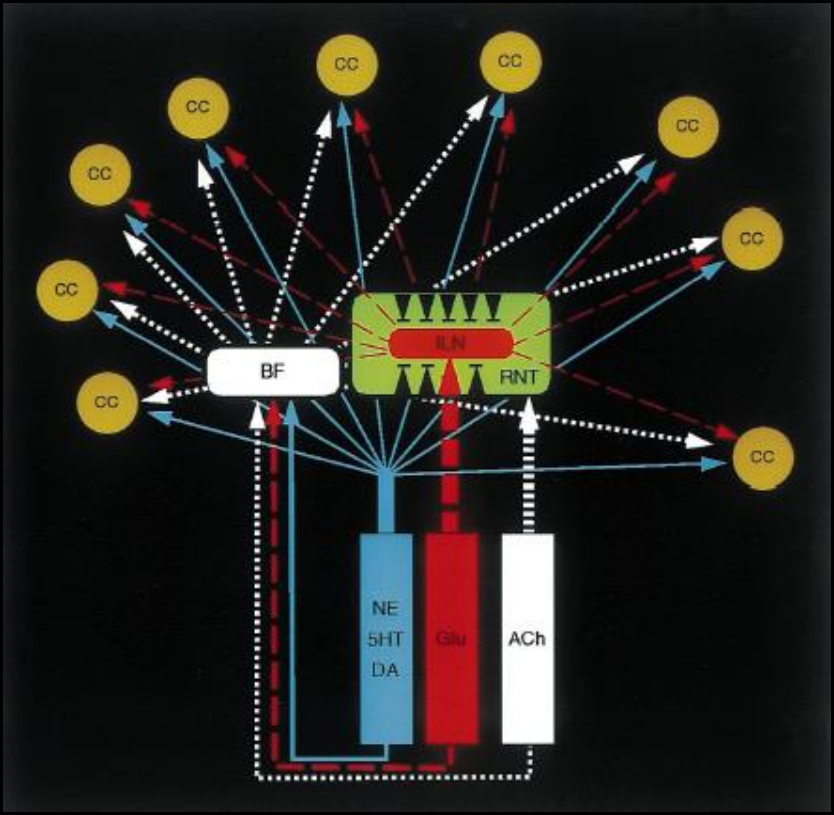


ARAS 2.0



Depuis 1949 : <u>Version complexifiée de la théorie réticulaire de l'éveil</u>

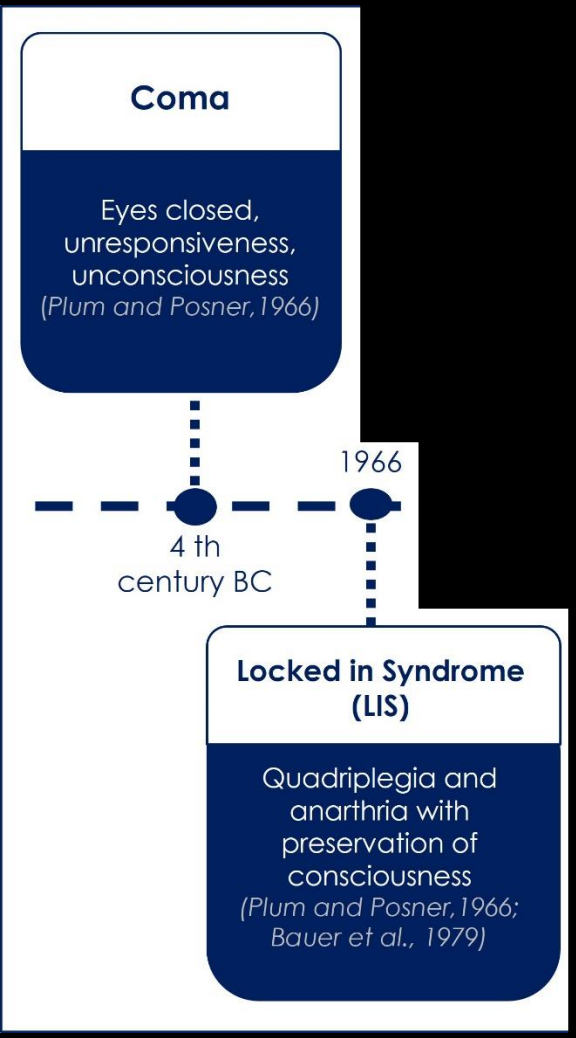
➔ Un ensemble très hétérogène de noyaux

➔ Riche intégration intéroceptive et extéroceptive

➔ Une neurochimie complexe

➔ Une conception homéostasique de l'éveil

Parvizi & Damasio, Cognition 2001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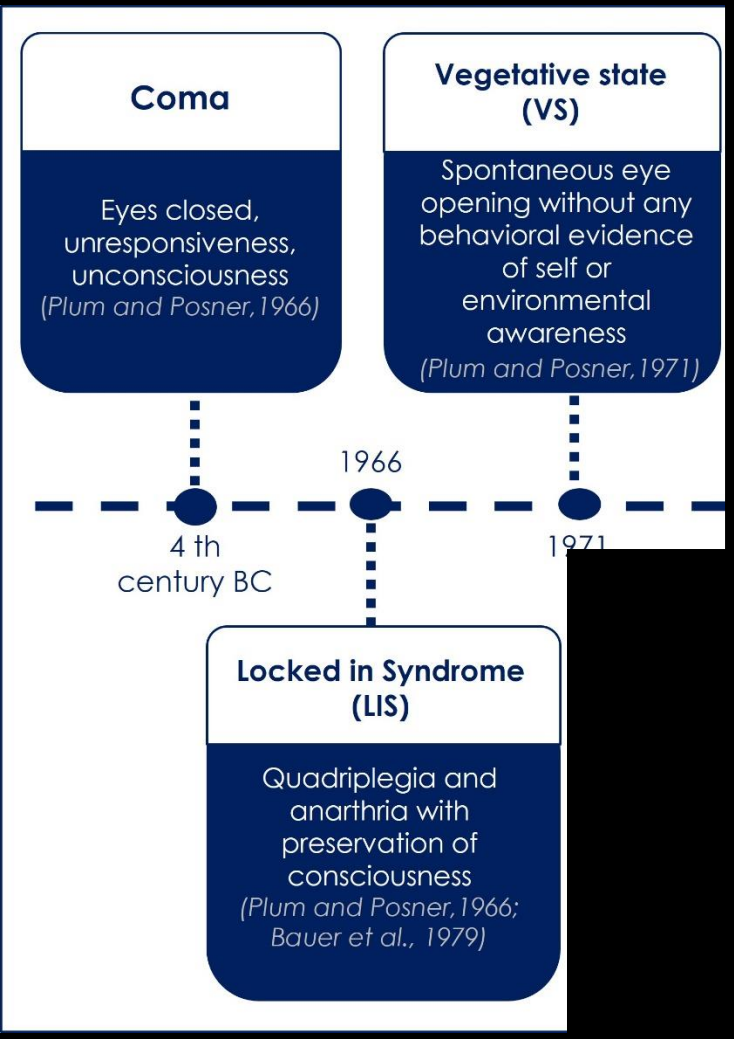
« Locked-in » syndrome :

oculo-motor codes

➔CS can be dissociated from behavior

➔ Looking for CS in brain activity…

➔(to be followed)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  ➔ ne pas confondre fonctions végétatives avec vie végétale +++

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- ***Imprécis et inexact :*** ***activités corticales locales & 30-40% d’erreurs (BHV), et 30% sans activité cérébrale***

Etat “ végétatif ” ➔ Pédagogie+++

(famille & medias)

- ***CONFUSION sémantique : fonctions végétatives preservées versus conscience abolie***
  ➔ ne pas confondre fonctions végétatives avec vie végétale +++

- ***Imprécis et inexact : activités corticales locales & 30-40% d’erreurs (BHV), et 30% sans activité cérébrale***

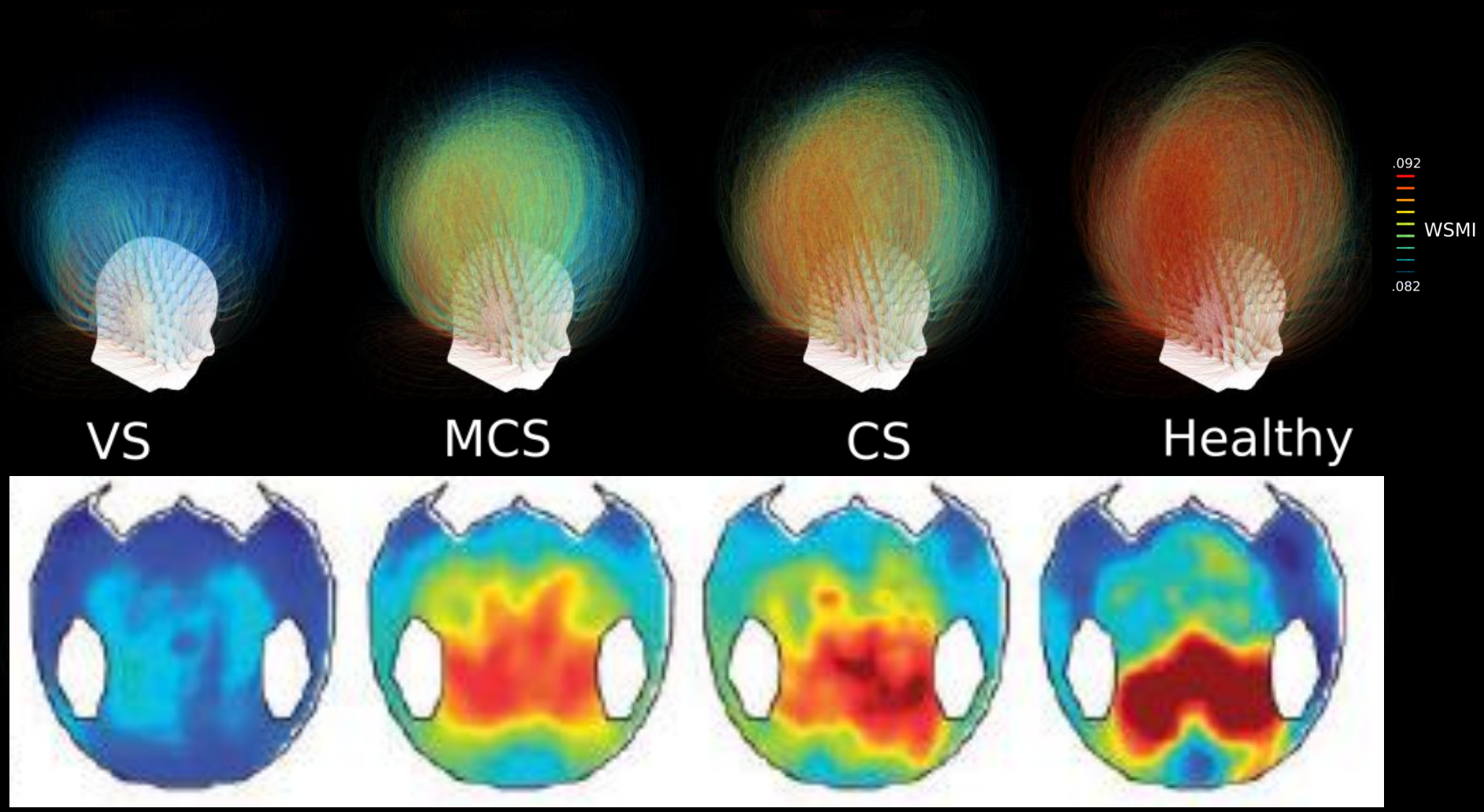
- ***Initiative UWS/Syndrome d’éveil non répondant : louable (syndrome/empirique) mais expression complexe, et induction d’un biais vers representation le plus souvent inexacte d’un patient VS sur le modèle d’un patient “LIS”) : le pb n’est pas que la réponse***

Cortical arousal is a necessary but not sufficient condition for CS

- ➔ Spontaneous eye-opening but no evidence of CS
- ➔ Sleep-wake cycles (or at least fluctuations)
- ➔ ARAS and brainstem are functional
- ➔ Islets of cortical areas are functional during periods of arousal

➔Arousal and consciousness can be dissociated

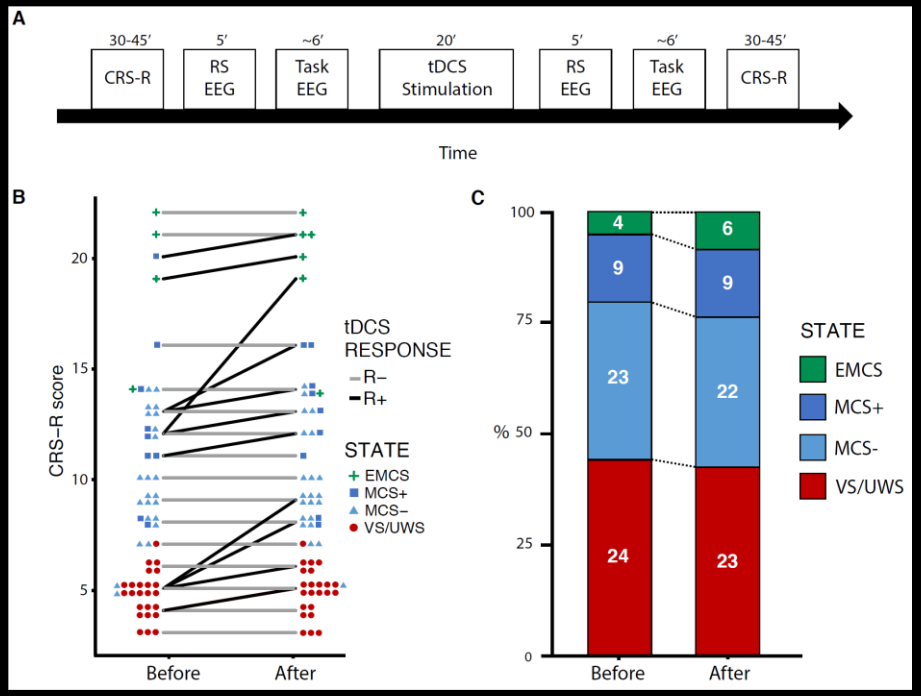
➔Consciousness requires long-distance cortico-cortical functional connectivity

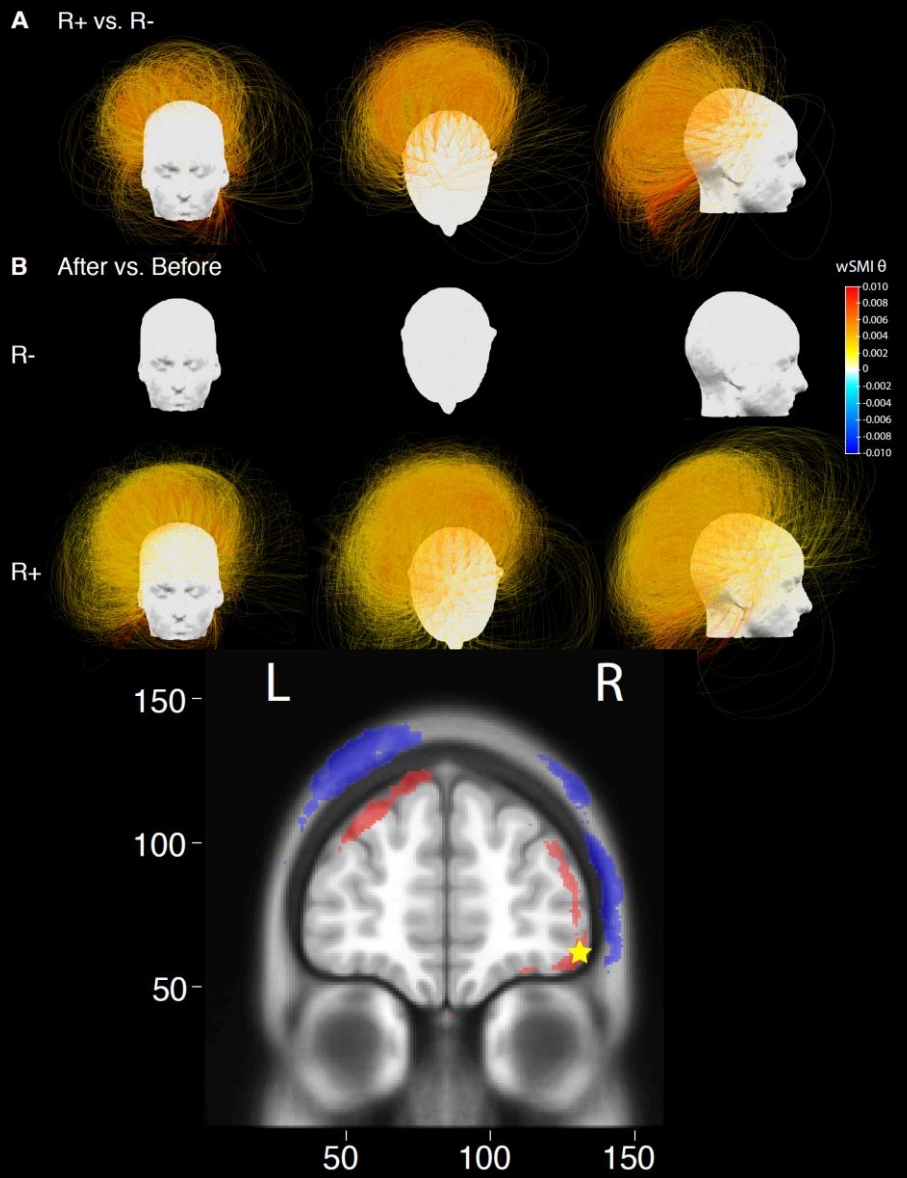


King, Sitt… Naccache, Dehaene, Current Biology 2013

➔Consciousness requires long-distance cortico-cortical functional connectivity

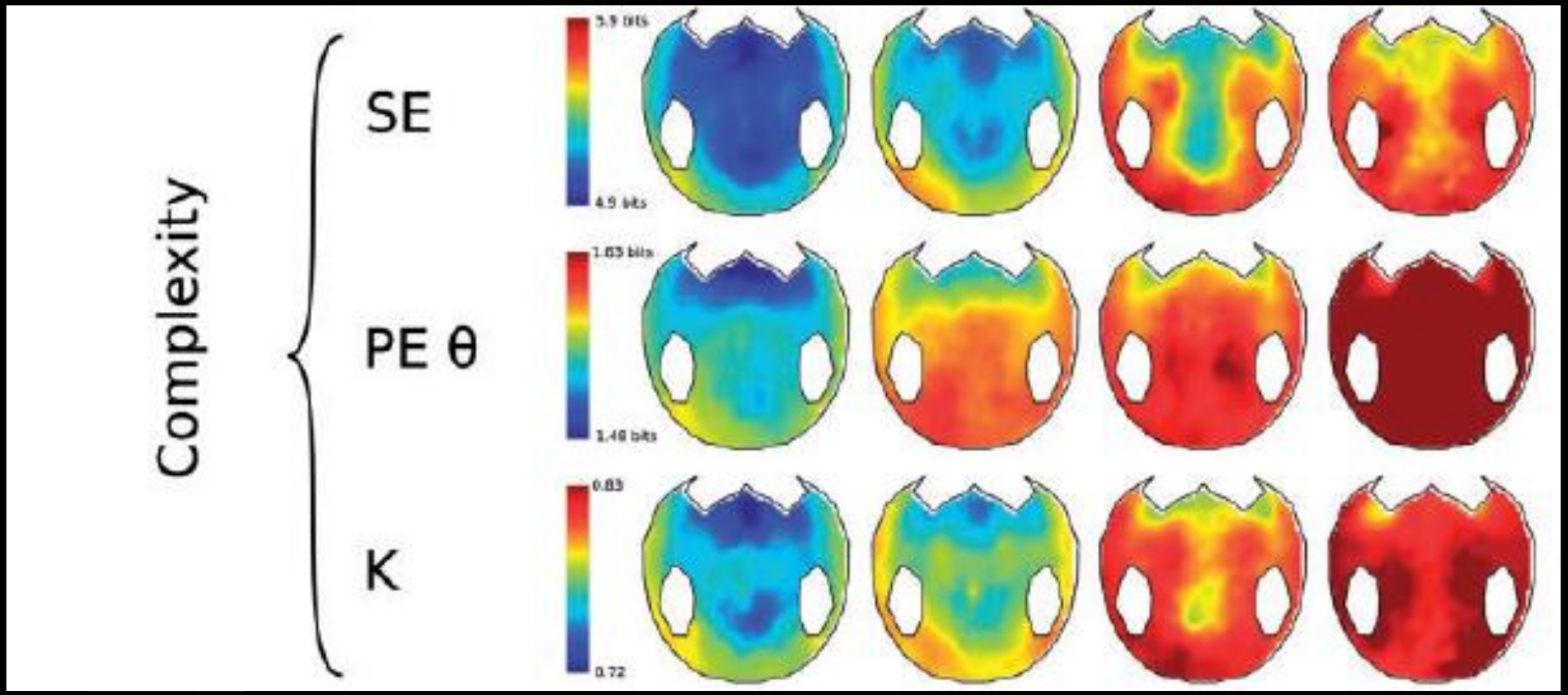
PFC tDCS of DOC patients: improvements of CS correlate with increases of FC





Hermann,… Sitt, Naccache, Sci. Reports 2020

Cortical activity is complex during conscious states



VS MCS CS CS HV

Sitt, King,… & Naccache, Brain 2014

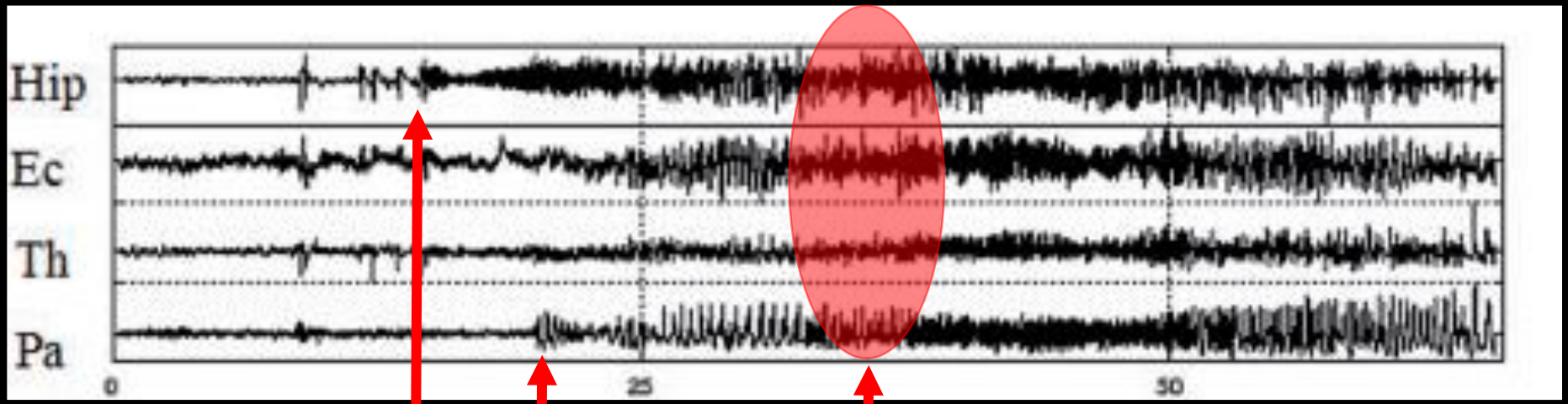
➔ Consciousness requires a complex and coherent long-distance connectivity

. Loss of consciousness due to an excess of connectivity with a loss of complexity and differentiation

➔ Complex partial & Absence epilecitc seizures

Loss of consciousness

The rich, complex and coherent conscious brain-scale conversation turns suddenly to…



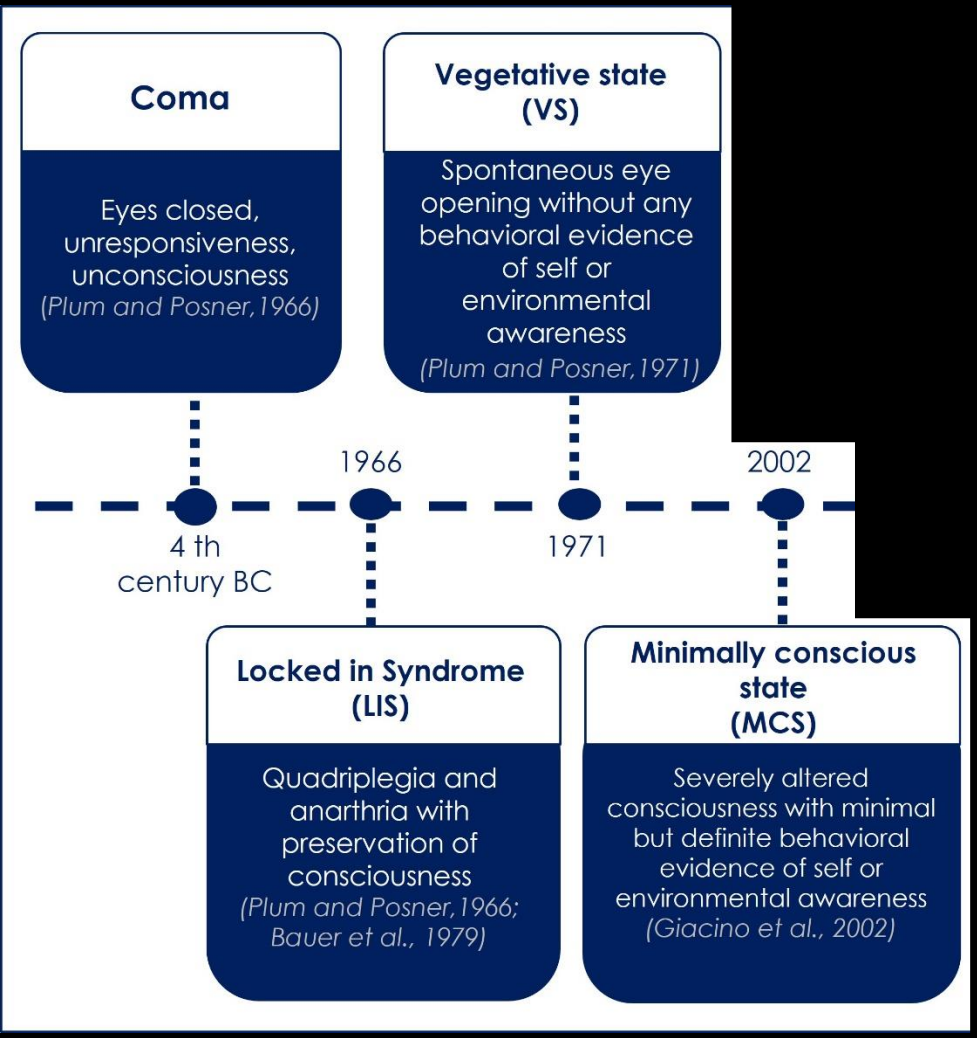
a too coherent, poor & undifferentiated communication

Seizure onset in a local brain circuit

Seizure propagates to other brain circuits

Seizure reaches the conscious global workspace

Arthuis,… Naccache, Bartolomei, Brain 2009
Bartolomei & Naccache, Behav. Neurol. 2011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Severely altered consciousness with minimal but definite behavioral evidence of self or environmental awareness
(Giacino et al., 2002)

‘Gold-standard’ of MCS diagnosis: the CRS-R

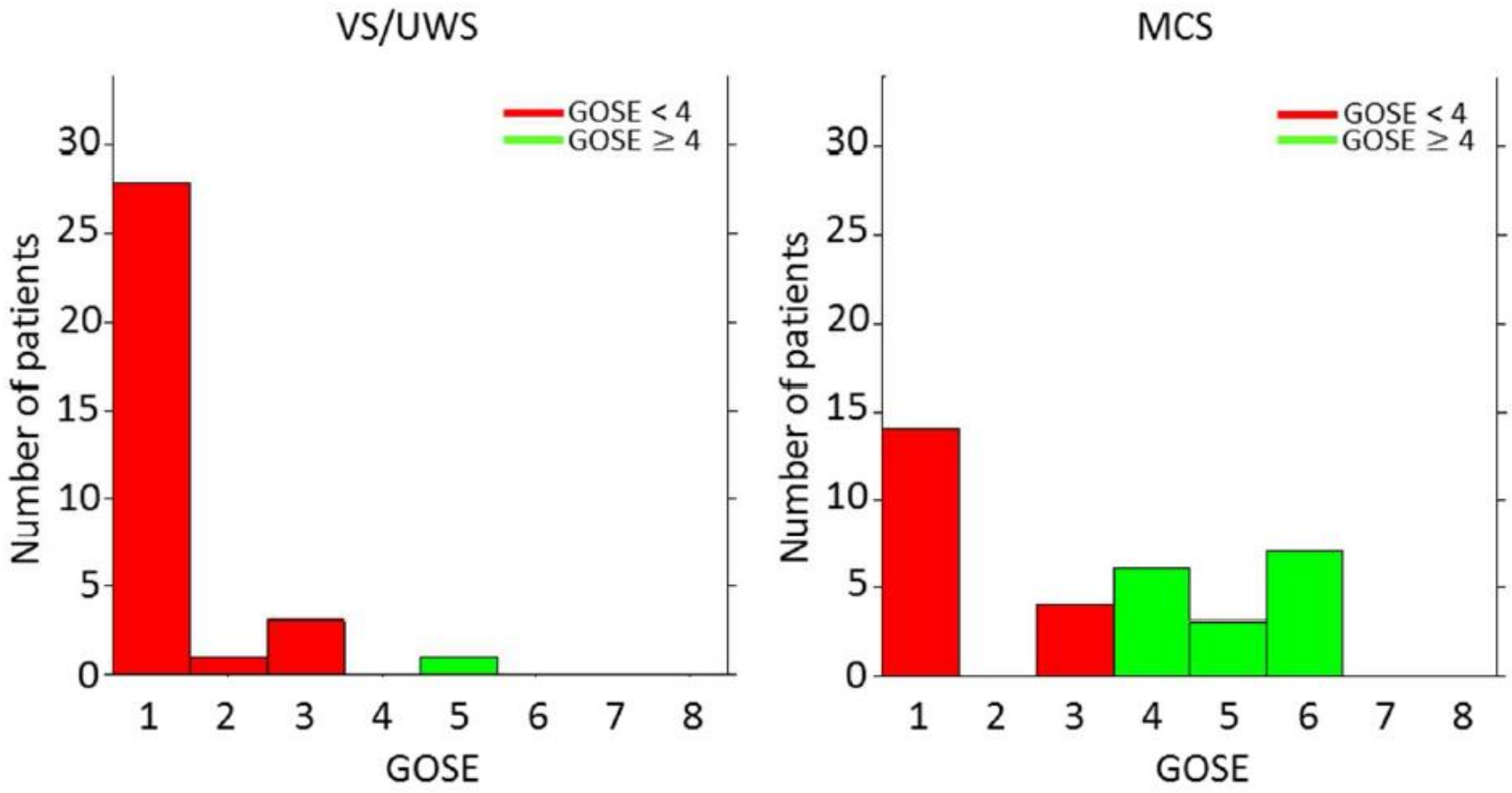
“cognitively mediated behavior occurs inconsistently, but is reproducible or sustained long enough to be differentiated from reflexive behavior”

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

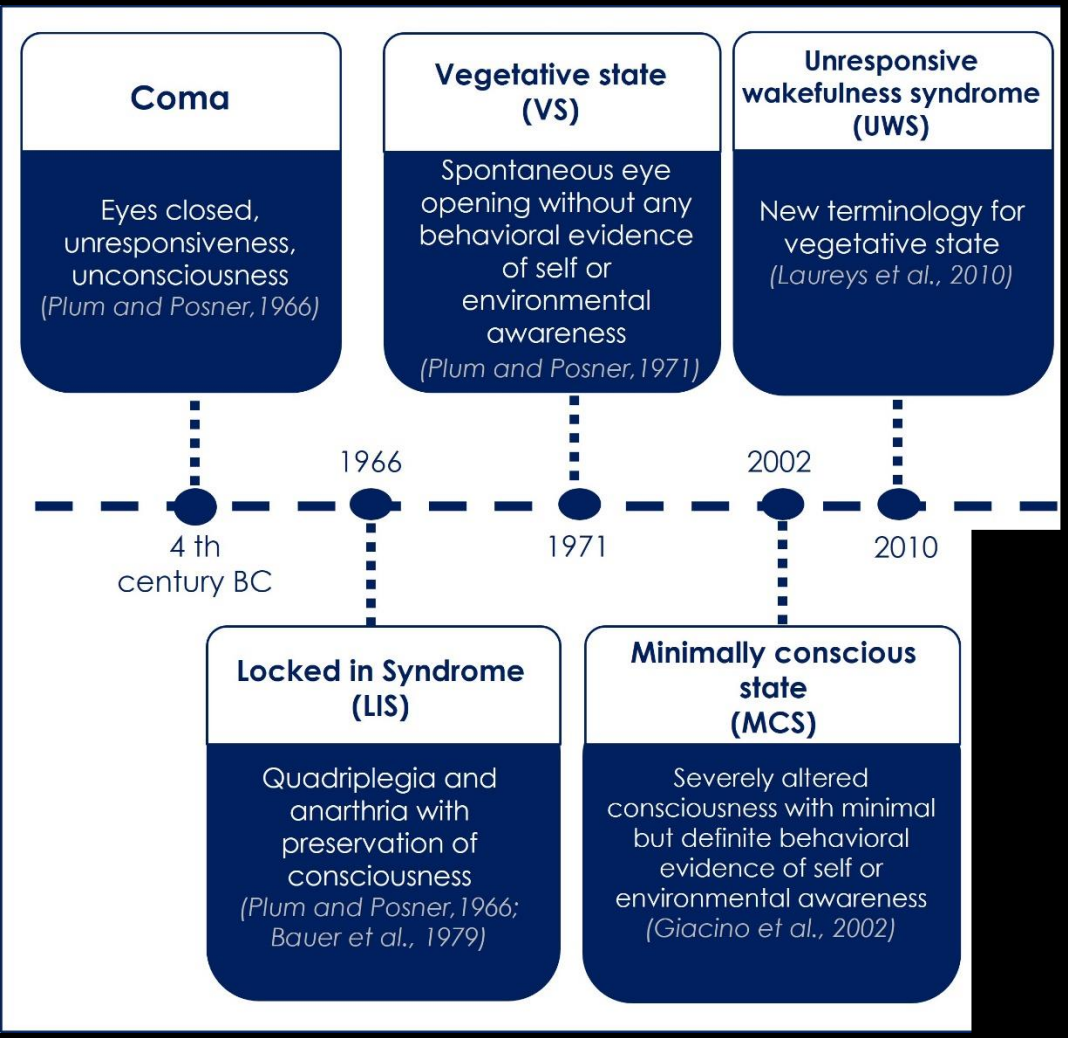
AUDITORY FUNCTION SCALE
4 - Consistent Movement to Command *
3 - Reproducible Movement to Command *
2 - Localization to Sound
1 - Auditory Startle
0 - None
VISUAL FUNCTION SCALE
5 - Object Recognition *
4 - Object Localization: Reaching *
3 - Visual Pursuit *
2 - Fixation *
1 - Visual Startle
0 - None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

Kalmar & Giacino., Neuropsychol. Rehab. 2005
Giacino et al. Neurology 2002

These purely behavioral labels are useful



Luauté et al. Neurology 2010
Faugeras,… Naccache, Brain Injury 2018
Perez… Naccache, Frontiers in Neurology 2021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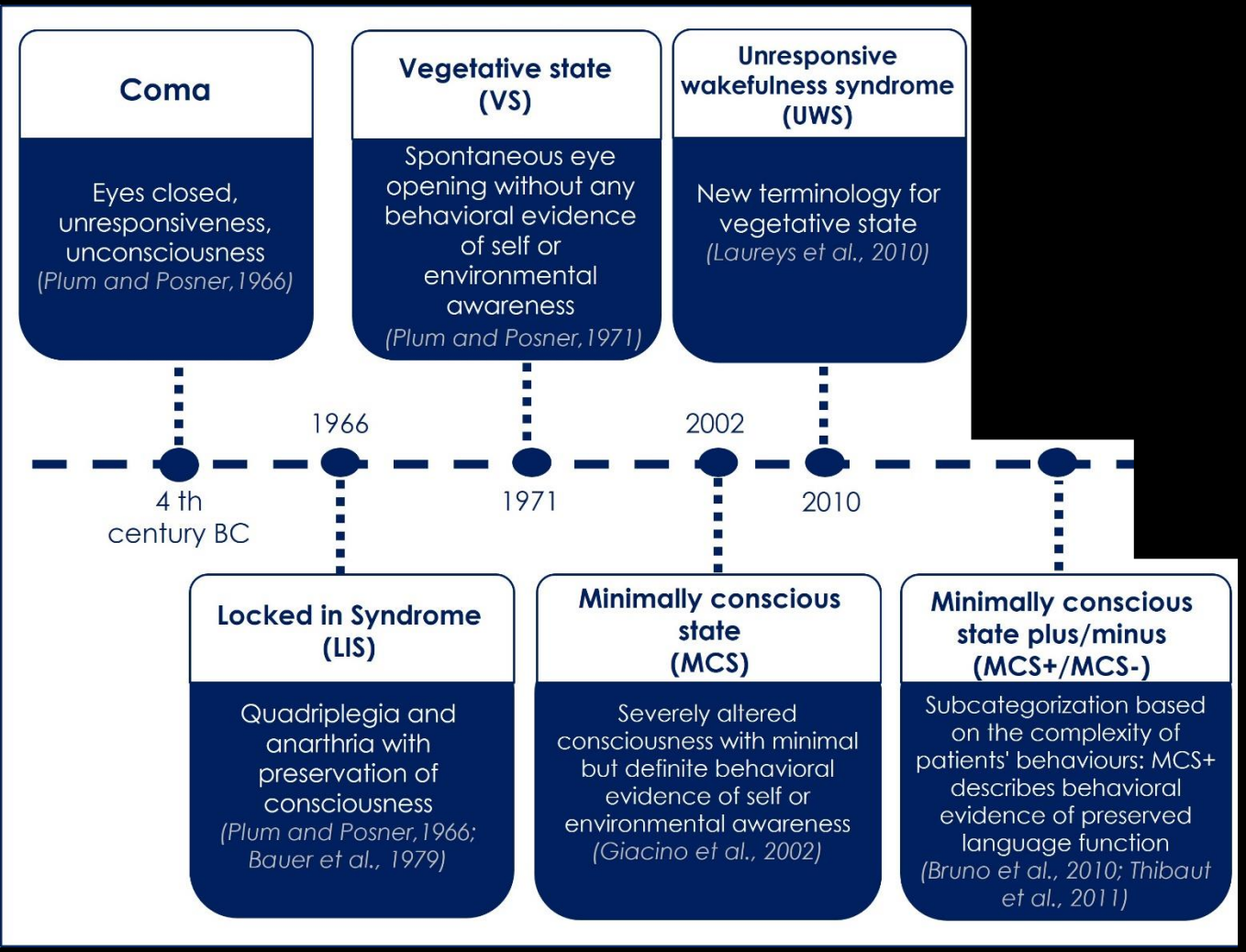
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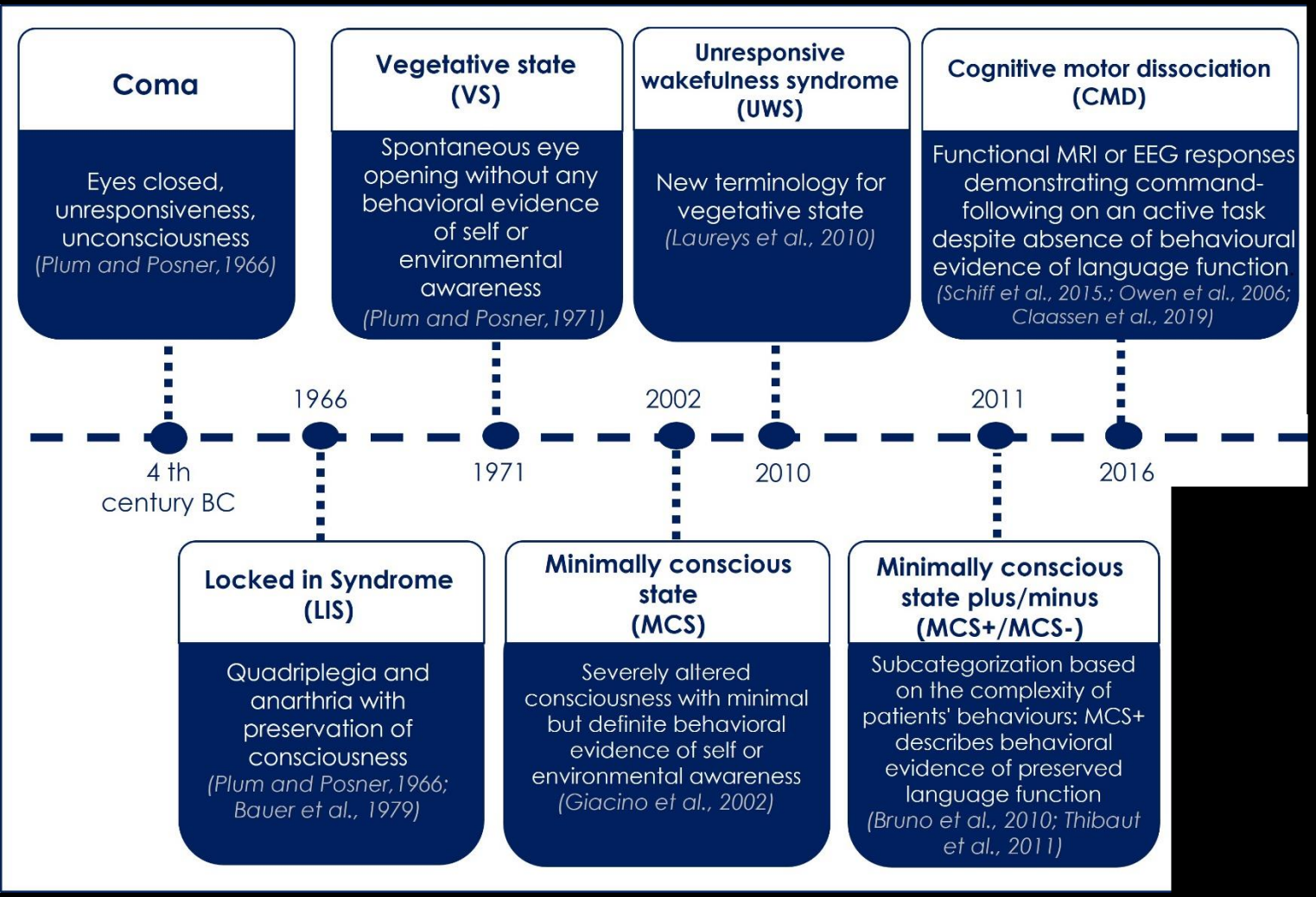
Subcategorization based on the complexity of patients' behaviours: MCS+ describes behavioral evidence of preserved language function
(Bruno et al., 2010; Thibaut et al., 2011)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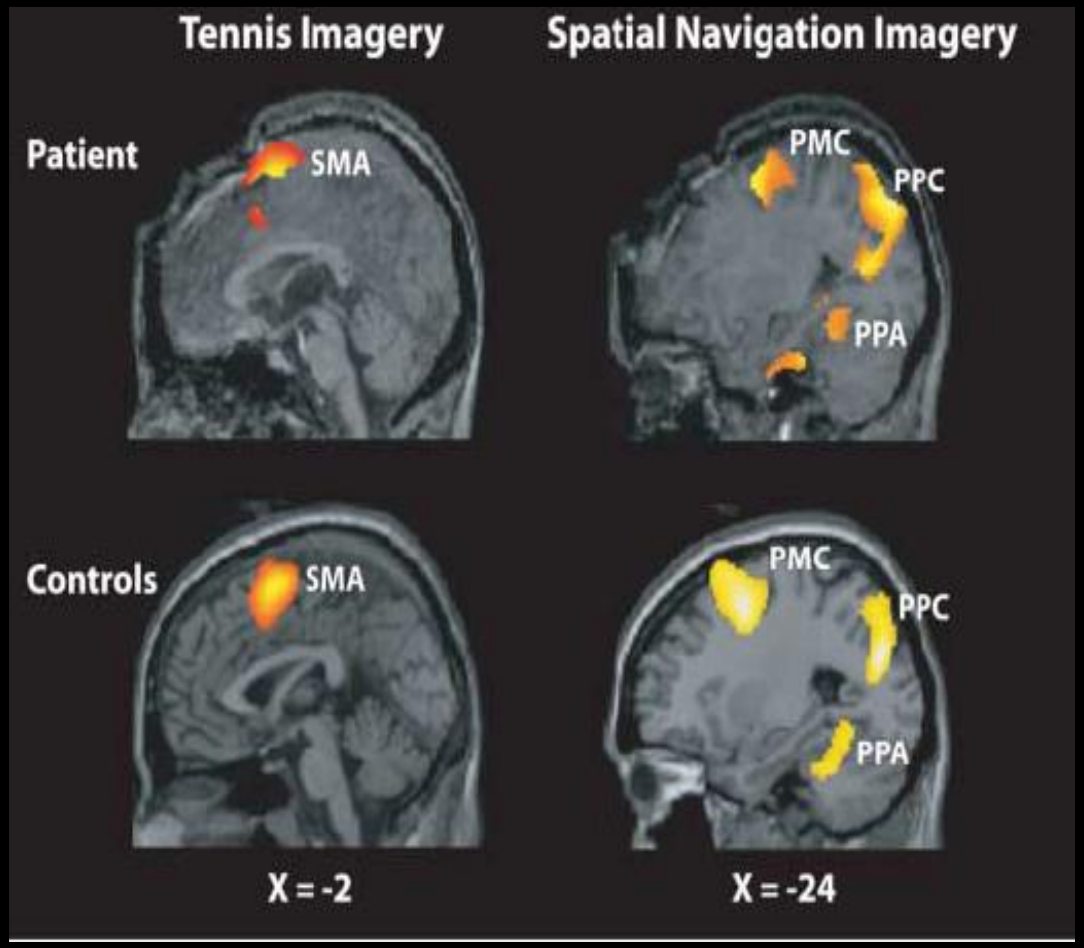
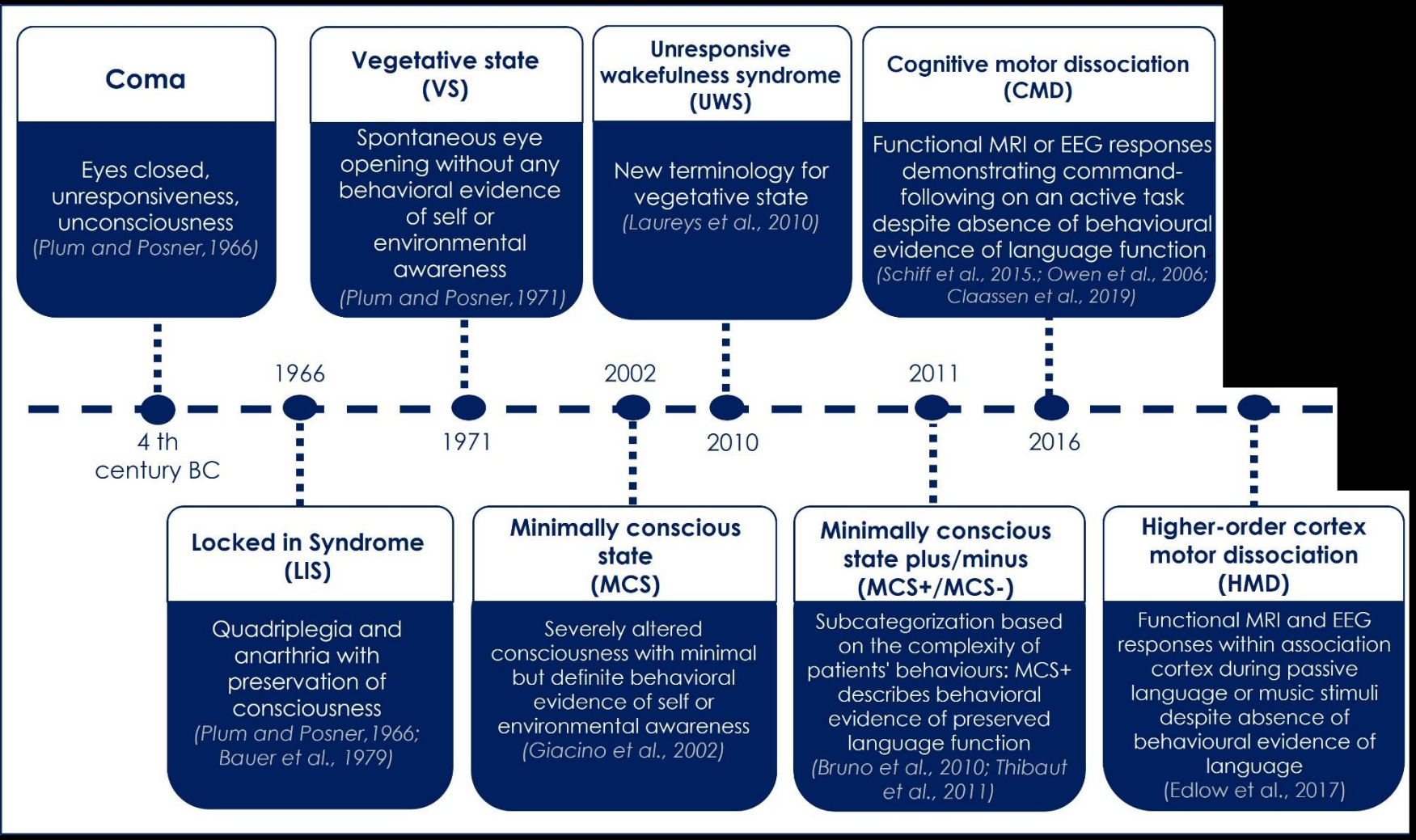
➔ **BHV : no R2C or functional communication (no LIS)**
➔ **Brain activity: R2C & functional communication**



Owen et al., Science 2006
Cruse et al., Lancet 2011
Goldfine et al., Clinical Neurophysiol. 2011
Claassen,… & Rohaut, NEJM 2019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Higher-order cortex motor dissociation (HMD)
Functional MRI and EEG responses within association cortex during passive language or music stimuli despite absence of behavioural evidence of language
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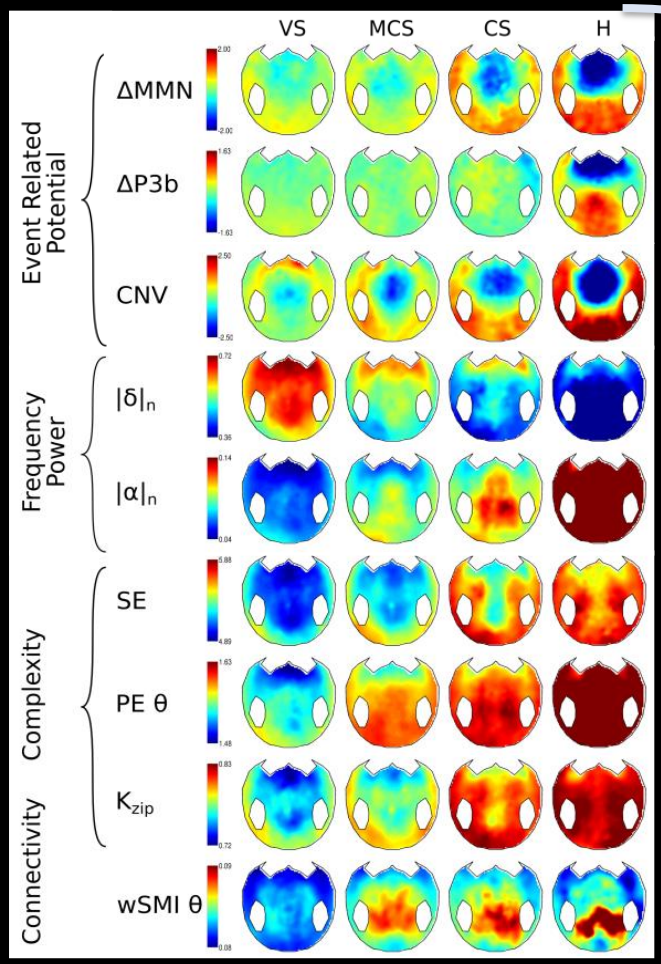
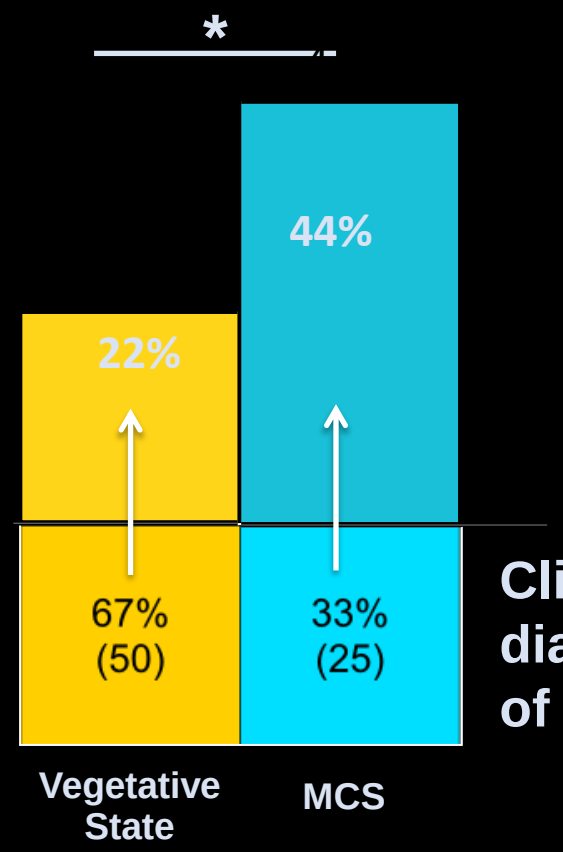
➔ ~15-30% of clinically VS/UWS are MCS according to brain activity

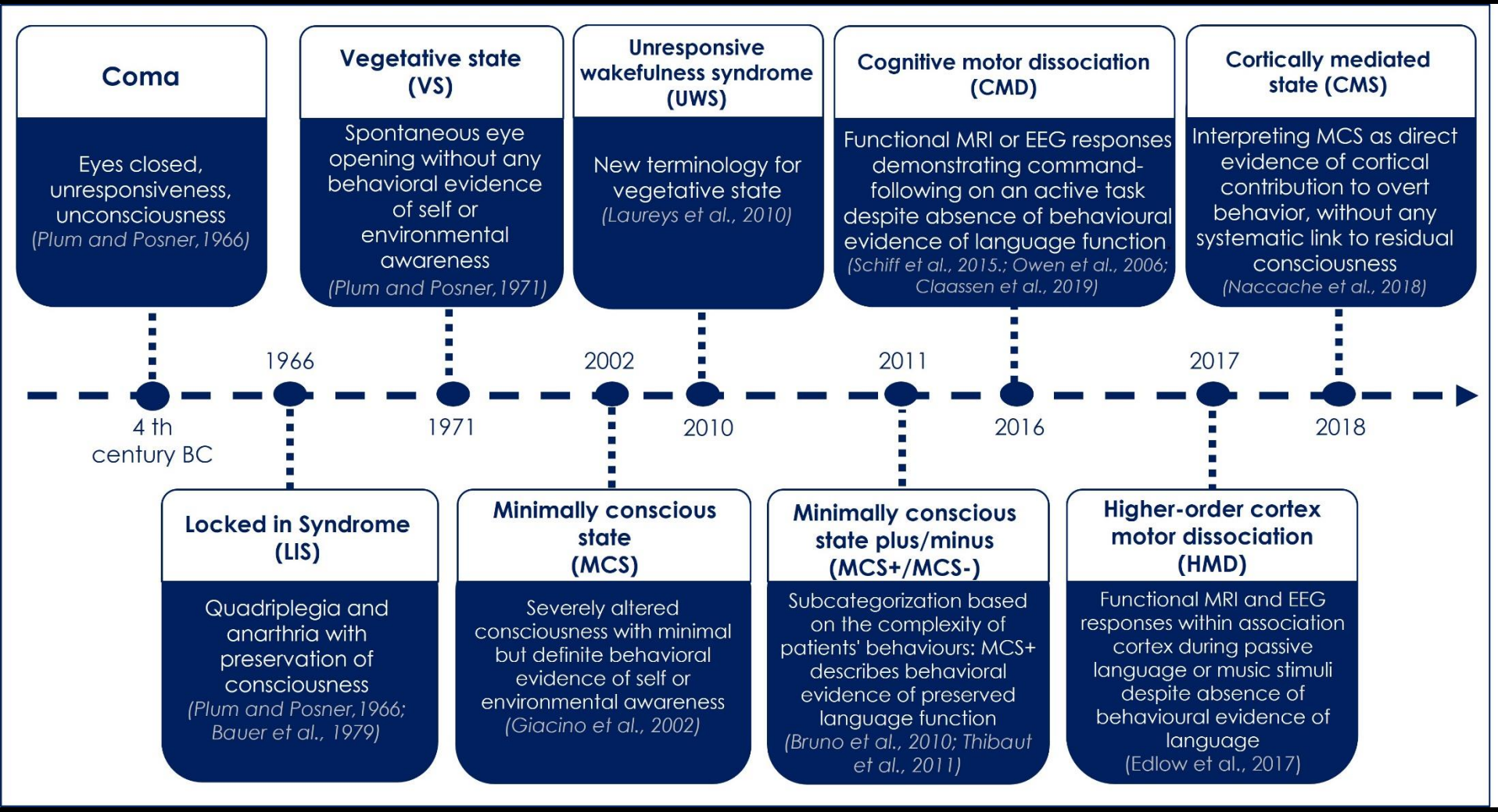




Clinical diagnosis of VS

EEG-based algorithmic diagnosis

Sitt, King,…, Dehaene, Naccache, Brain 2014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Cortically mediated state (CMS)
Interpreting MCS as direct evidence of cortical contribution to overt behavior, without any systematic link to residual consciousness
(Naccache et al., 2018)
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- ***Vocabulaire : VS/UWS ; MCS/CMS***

	Item	Cortically Mediated Behavior?
AUDITORY FUNCTION		
4	Consistent movement to command	YES
3	Reproducible movement to command	YES
2	Localization to sound	NO
1	Auditory startle	NO
0	None	X
VISUAL FUNCTION		
5	Object recognition	YES
4	Object localization: reaching	YES
3	Visual pursuit	YES
2	Fixation	DEBATED
1	Visual startle (blink to threat)	NO
0	None	X
MOTOR FUNCTION		
6	Functional object use	YES
5	Automatic motor response	YES
4	Object manipulation	YES
3	Localization to noxious stimulation	YES
2	Flexion withdrawal	NO
1	Abnormal posturing	NO
0	None/Flaccid	X
OROMOTOR FUNCTION		
3	Intelligible verbalization	YES
2	Vocalization/Oral movement	DUBIOUS
1	Oral reflexive movement	NO
0	None	X
COMUNICATION		
2	Functional: accurate	YES
1	Non functional: intentional	YES
0	None	X
AROUSAL		
3	Attention	DUBIOUS
2	Eye opening without stimulation	NO
1	Eye opening with stimulation	NO
0	Unarousable	X

Cortical networks

Brainstem: Superior olivary complex

Brainstem: cochlear nucleus/LLN/caudal pontine reticular nucleus (PnC)

Cortical network: occipito-parietal-FEF

Occipital cortex?

Brainstem: tectobulbar fibers / rostral colliculi of the midbrain

Cortex

Spinal cord reflex & sometimes higher

Subcortical responses (Jackson): decortication / decerebration

Cortex : language networks

Loose criterion: from subcortical to cortical involvement (phonological networks)

Brainstem

Cortex

Loose criterion: mostly cortex but?

Brainstem Reticular Formation (ARAS)

Brainstem Reticular Formation (ARAS)

Naccache, Brain 2018

So, stating that a patient is in a MCS means, - with 100% certitude -, that some his/her overt behaviors are cortically-driven.

➔ CRS-R criterion used to define MCS actually define a Cortically Mediated State (CMS)

Naccache, Brain 2018

Why is it confusing to label MCS ‘MCS’?

- ➔ Presence of cortical processing does not guarantee conscious state

Why is it confusing to label MCS 'MCS'?

'Minimally conscious state' includes the adjective 'conscious'

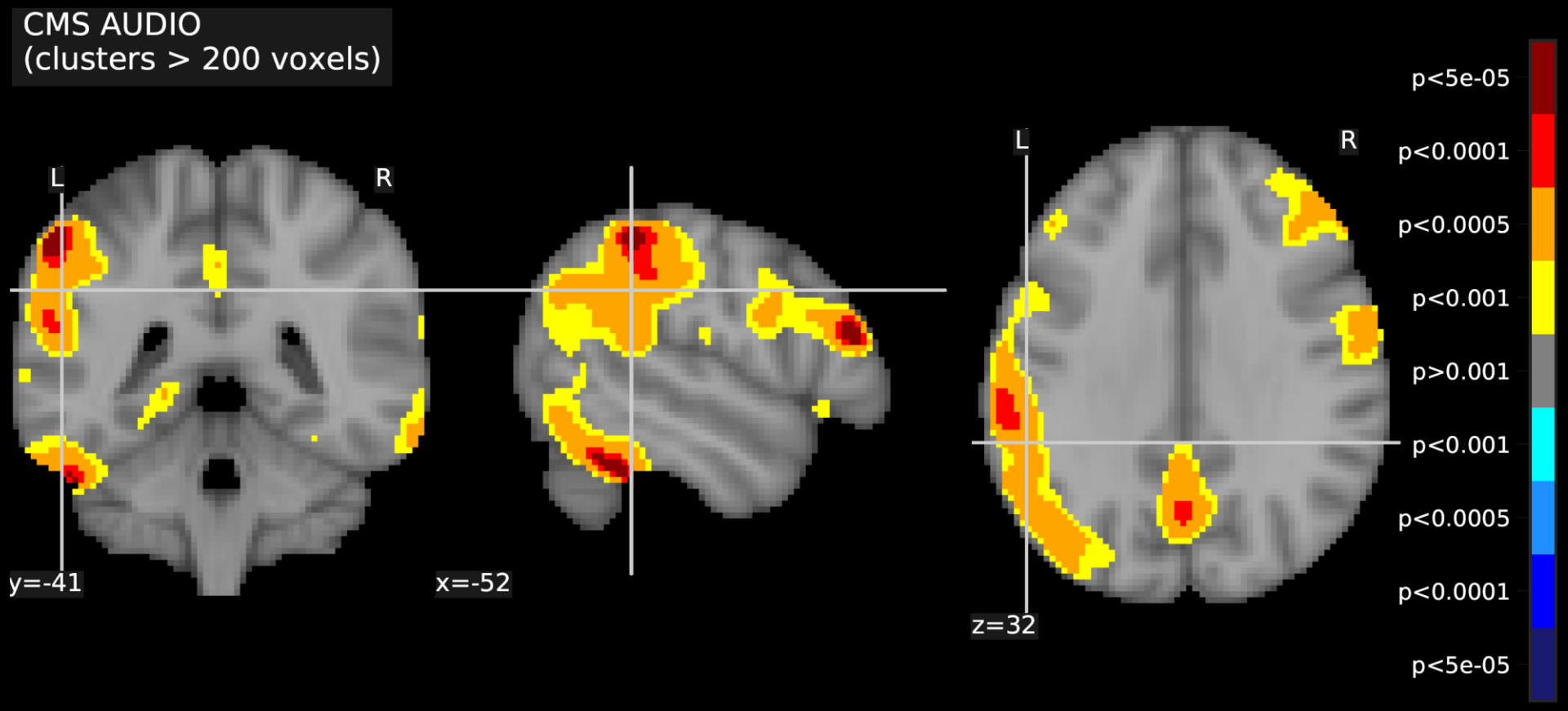
➔ Caregivers / Families / Society (media-framing)

➔ Bias to interpret subjectively MCS ~LIS patients (self-conscious) whereas many patients are scored MCS only on 'fixation' or 'visual pursuit' items !

➔ Being CMS does not mean being conscious but increases the probability to be conscious and to recover consciousness

Naccache, Brain 2018

➔Imaging specific CMS networks with resting state PET

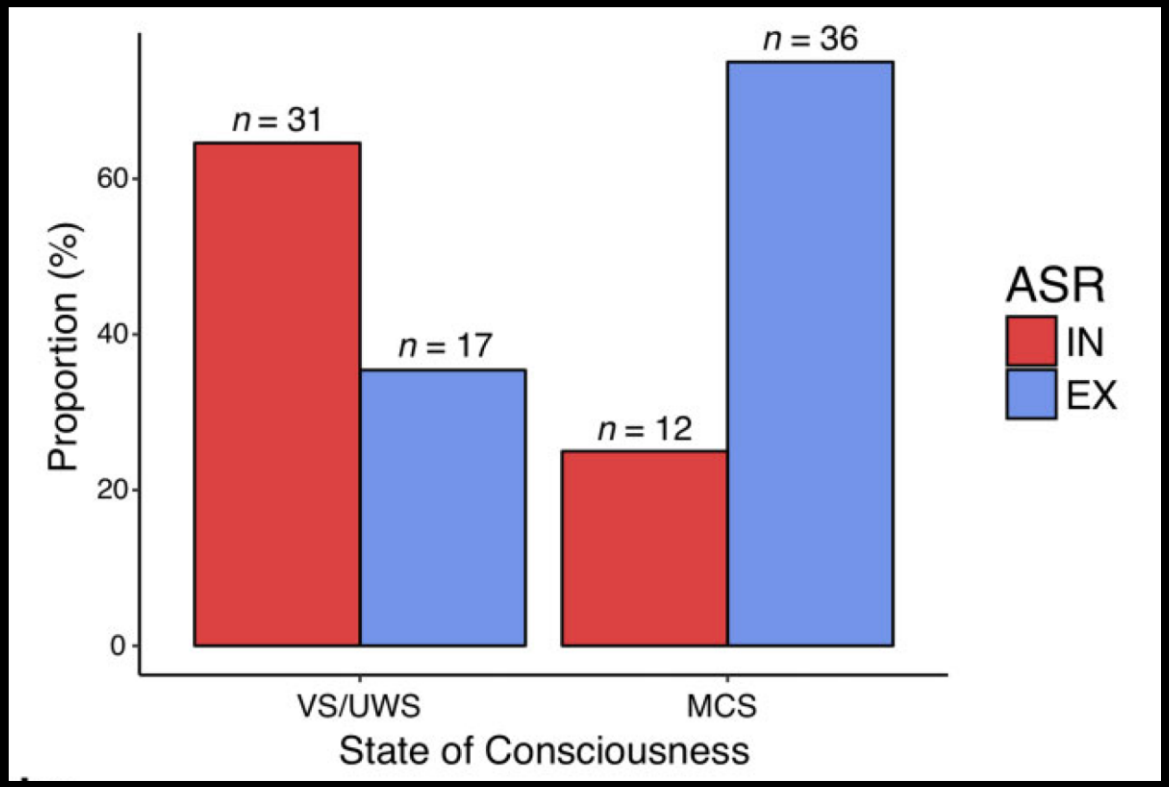


Hermann,… et Naccache, Neurosc. of Consciousness 2022

Importance, limits and caveats of the use of *Disorders of Consciousness* to theorize consciousness

➔ Develop also new BHV measures

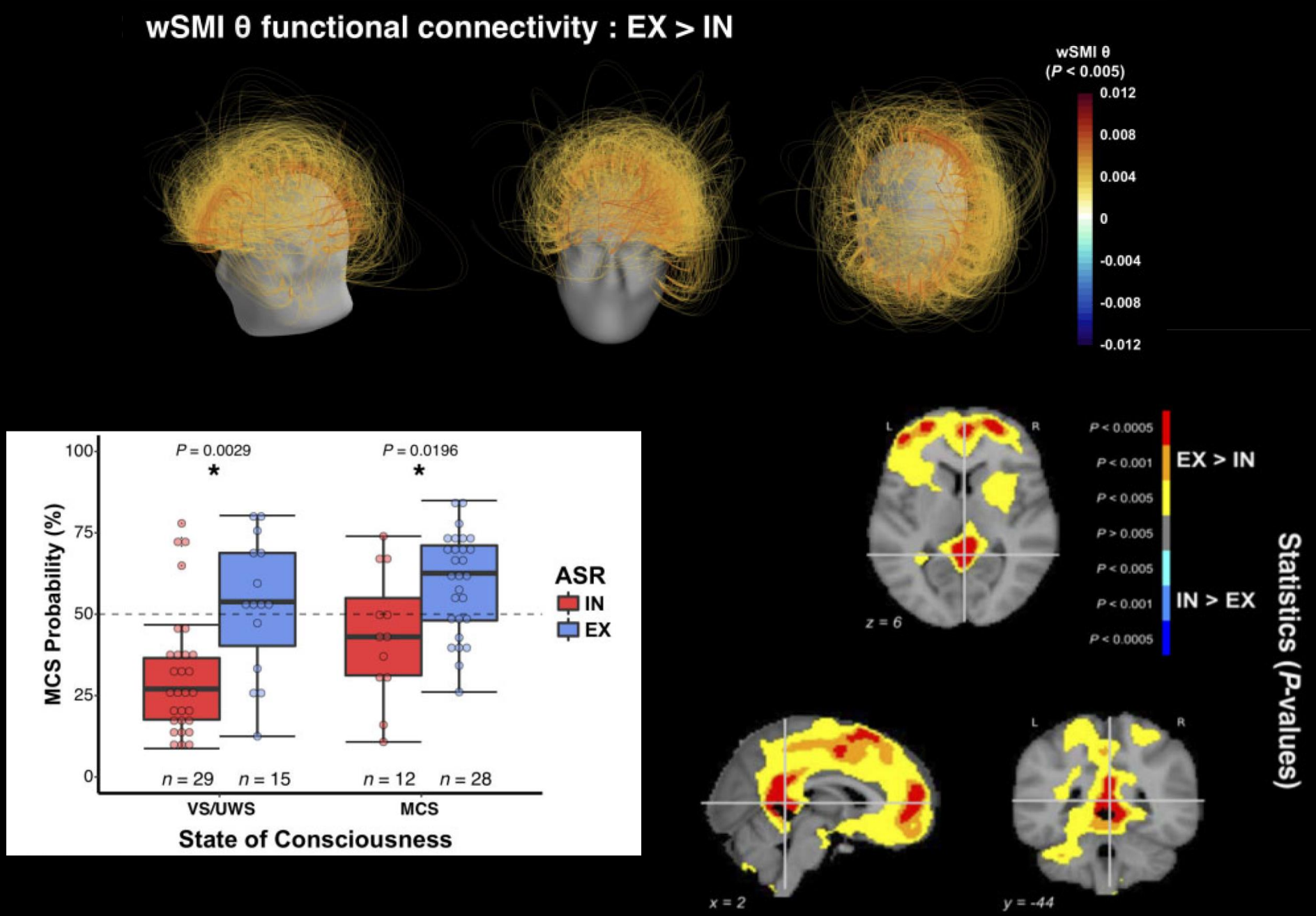
Habituation of auditory startle is a new powerful and behavioral sign of CMS easy to assess at bedside



	Pr (%)	AUC [95% CI]
Habituation of auditory startle reflex		
Exhaustible	55	0.70 [0.60–0.79]
Auditory		
Reproducible (3)	9	0.59 [0.54–0.66]
Systematic (4)	5	0.55 [0.51–0.6]
Visual		
Fixation (2)	6	0.56 [0.52–0.61]
Pursuit (3)	25	0.75 [0.68–0.82]
Localization (4)	2	0.52 [0.5–0.55]
Recognition (5)	5	0.55 [0.51–0.59]
Motor subscale		
Localization (3)	7	0.57 [0.53–0.62]
Manipulation (4)	2	0.52 [0.5–0.55]
Automatic (5)	16	0.66 [0.59–0.72]
Oromotor and verbal subscale		
Verbalization (3)	1	0.51 [0.5–0.53]
Communication subscale		
Intentional (1)	8	0.58 [0.53–0.64]

Acc = accuracy; AUC = area under the ROC curve; N
value; Pr = prevalence; Sen = sensitivity; Sp = specific

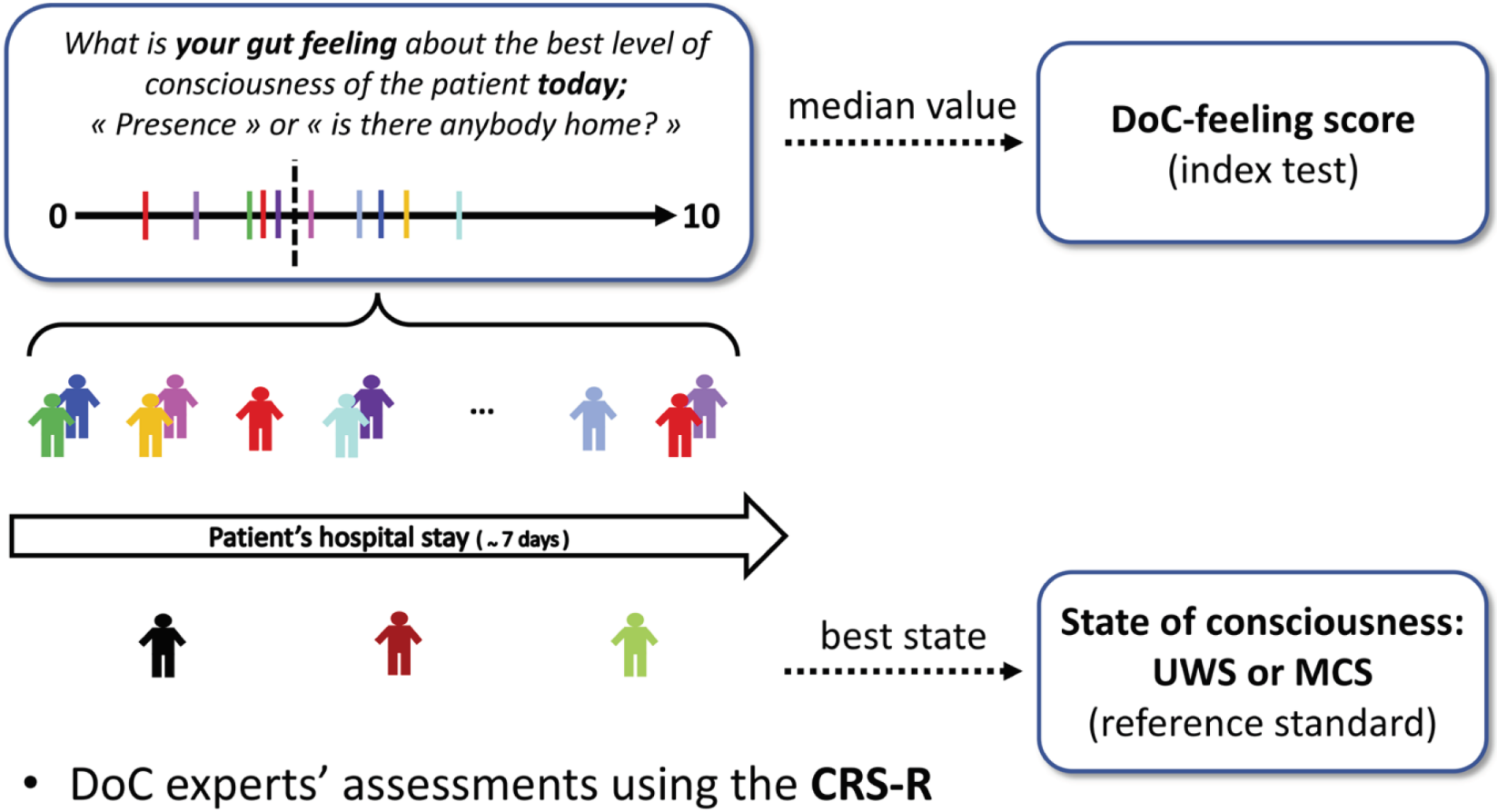
Hermann, Ben Salah … Naccache, Brain 2020



Hermann, Ben Salah … Naccache, Brain 2020

Integrate the expertise of nurses & nurses assistants : 'DOC Feeling' A visual analog scale of conscious state

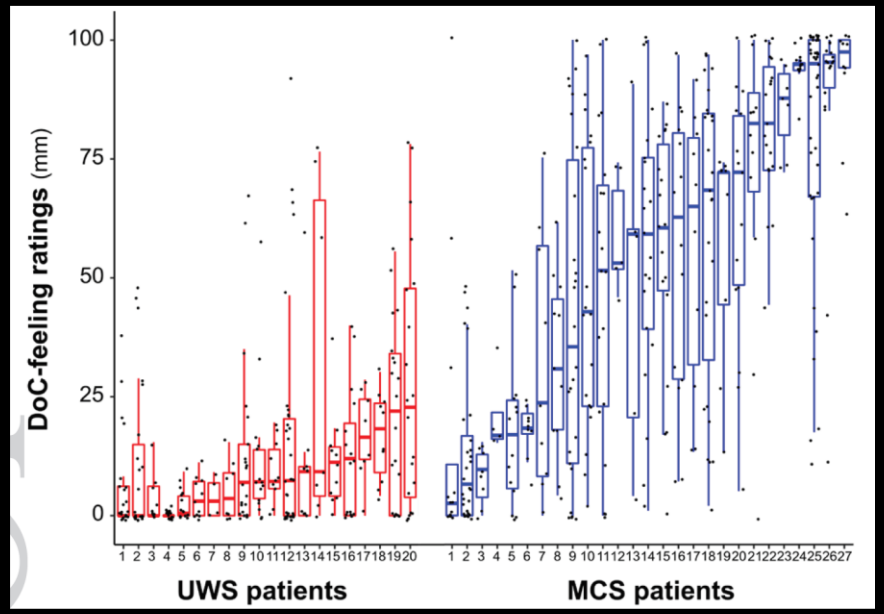
- Nursing staff assessments using the **DoC-feeling scale**

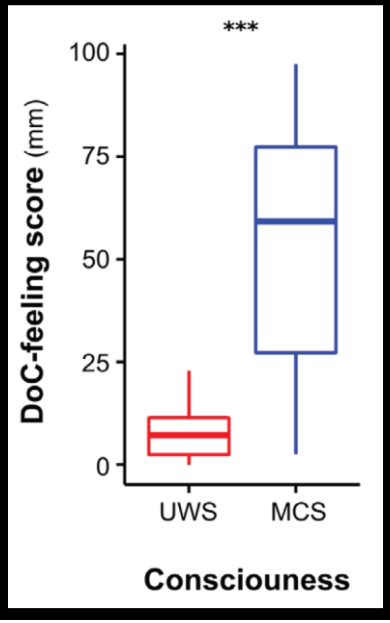


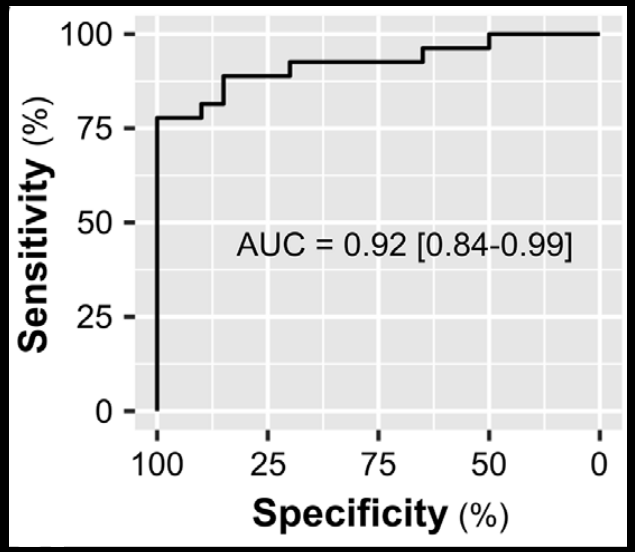
- DoC experts' assessments using the **CRS-R**

Hermann et al., BMJ Open 2019

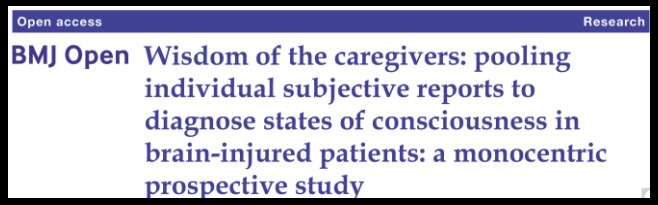
Integrate the expertise of nurses & nurses assistants : 'DOC Feeling' A visual analog scale of conscious state







Cutoff (mm)	Se (%)	Sp (%)
23.3	78 [58-91]	100 [83-100]
18.3	81 [62-94]	90 [68-99]
16.7	**89 [71-98]**	**85 [62-97]**
9.5	93 [76-99]	70 [46-88]
5.1	96 [81-99]	40 [19-64]
1.5	100 [87-100]	25 [8-49]


Open access Research

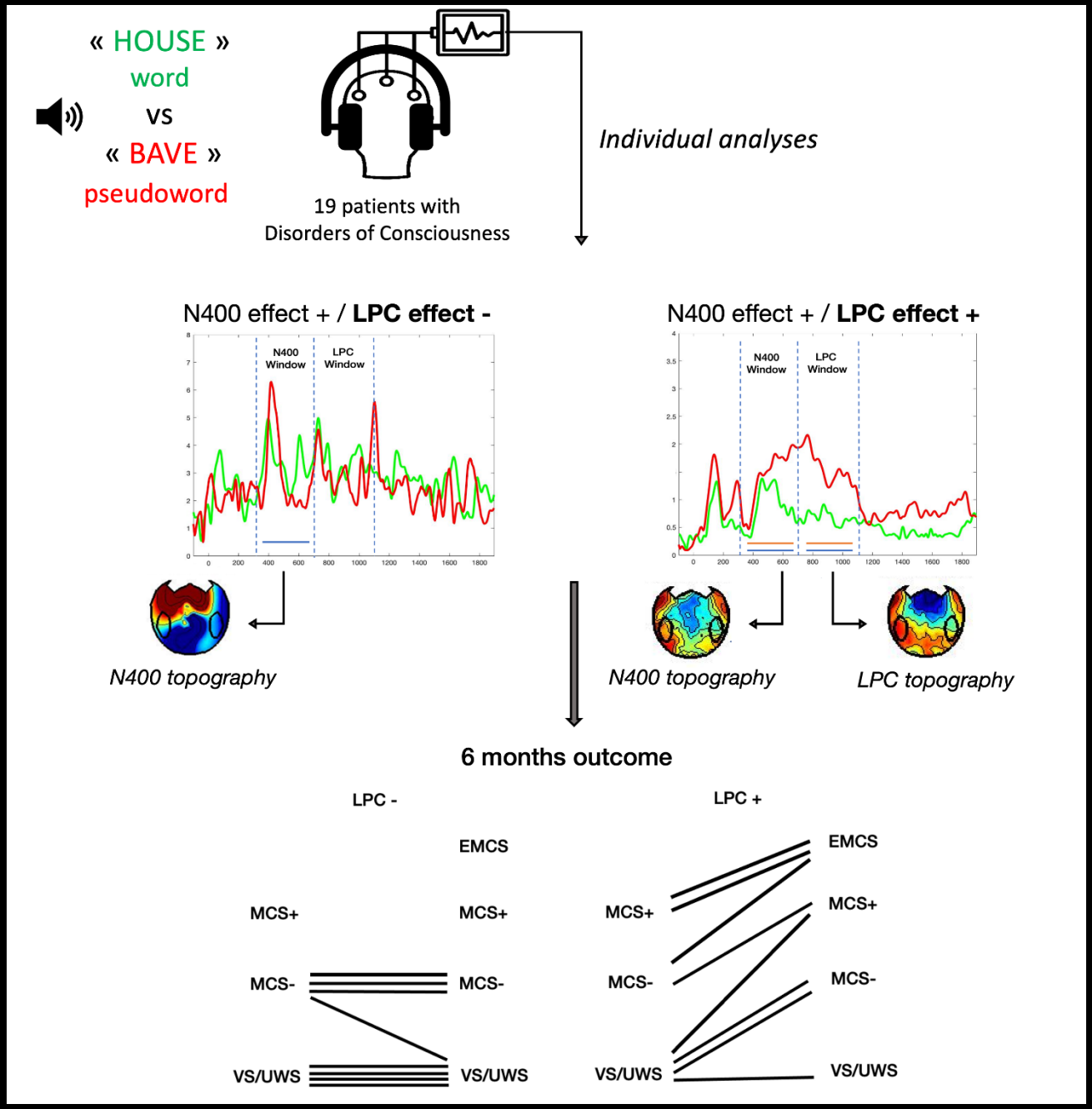
BMJ Open Wisdom of the caregivers: pooling individual subjective reports to diagnose states of consciousness in brain-injured patients: a monocentric prospective study

Hermann et al., BMJ Open 2019

En 2023 :

➔ Expertise Clinique (CRSr répétées et autres mesures) +++

➔ Necessité d’inclure des données de structure et d’activité cérébrale dans la definition de l’état clinique



Ben Salah, Marois, … & Naccache, Annals of Neurology 2023

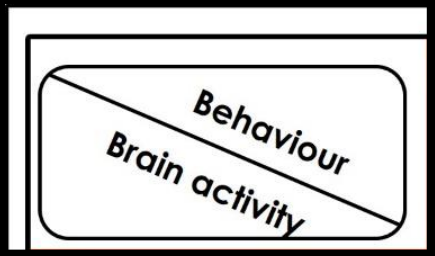
Evidence of unconsciousness

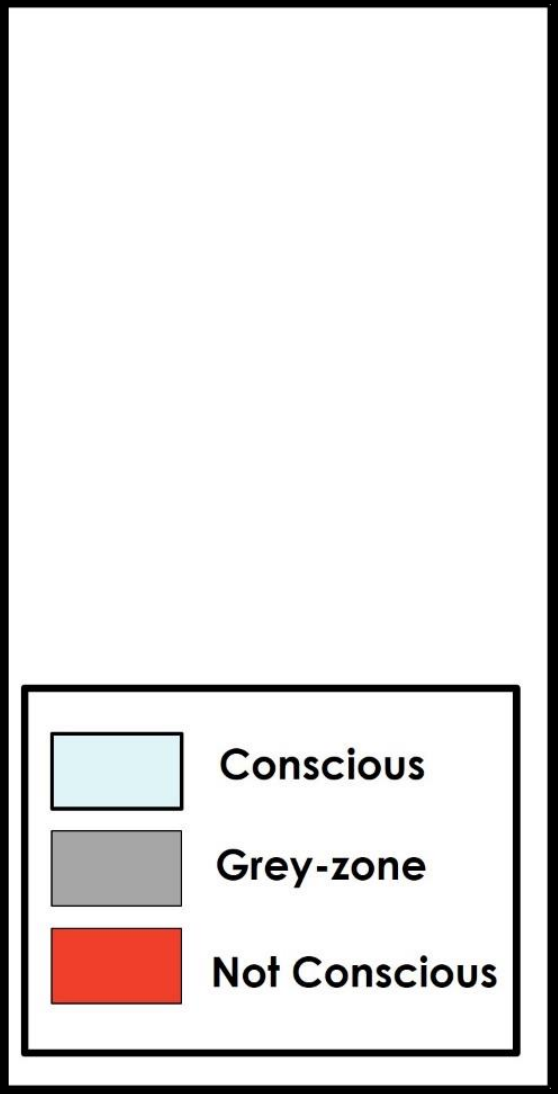
Evidence of consciousness

State #	State name	Source of evidence
1a	Comatose state	Behavior and functional brain-imaging
1b	Comatose state	Behavior
2a	VS / UWS	Behavior and functional brain-imaging
2b	VS / UWS	Behavior
3a	Cortically Mediated State	Functional brain-imaging
3b	Cortically Mediated State	Behavior
4a	Conscious state	Functional brain-imaging
4b	Conscious state	Behavior

Naccache, Brain 2018

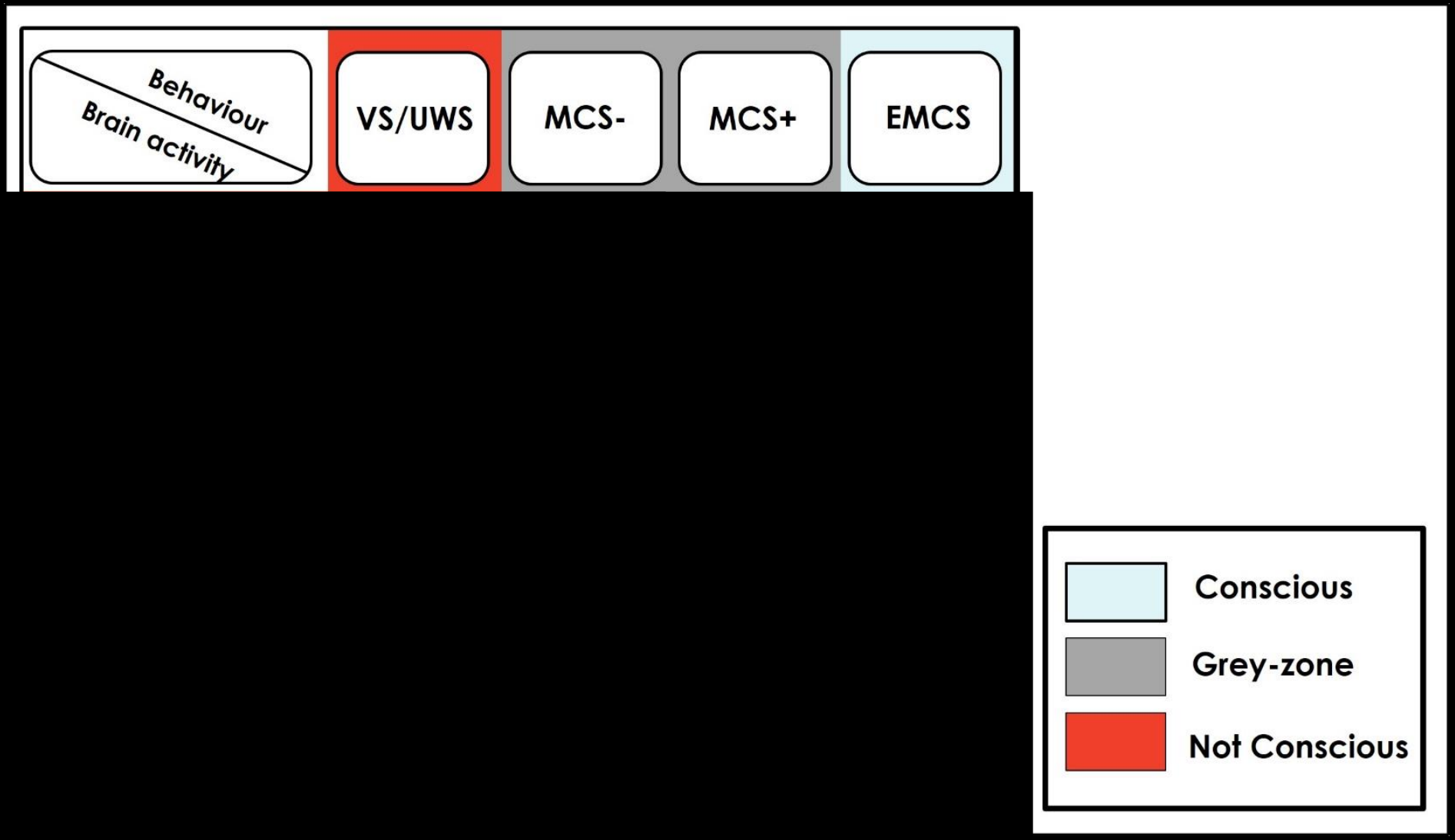
Toward the integration of BHV and brain activity





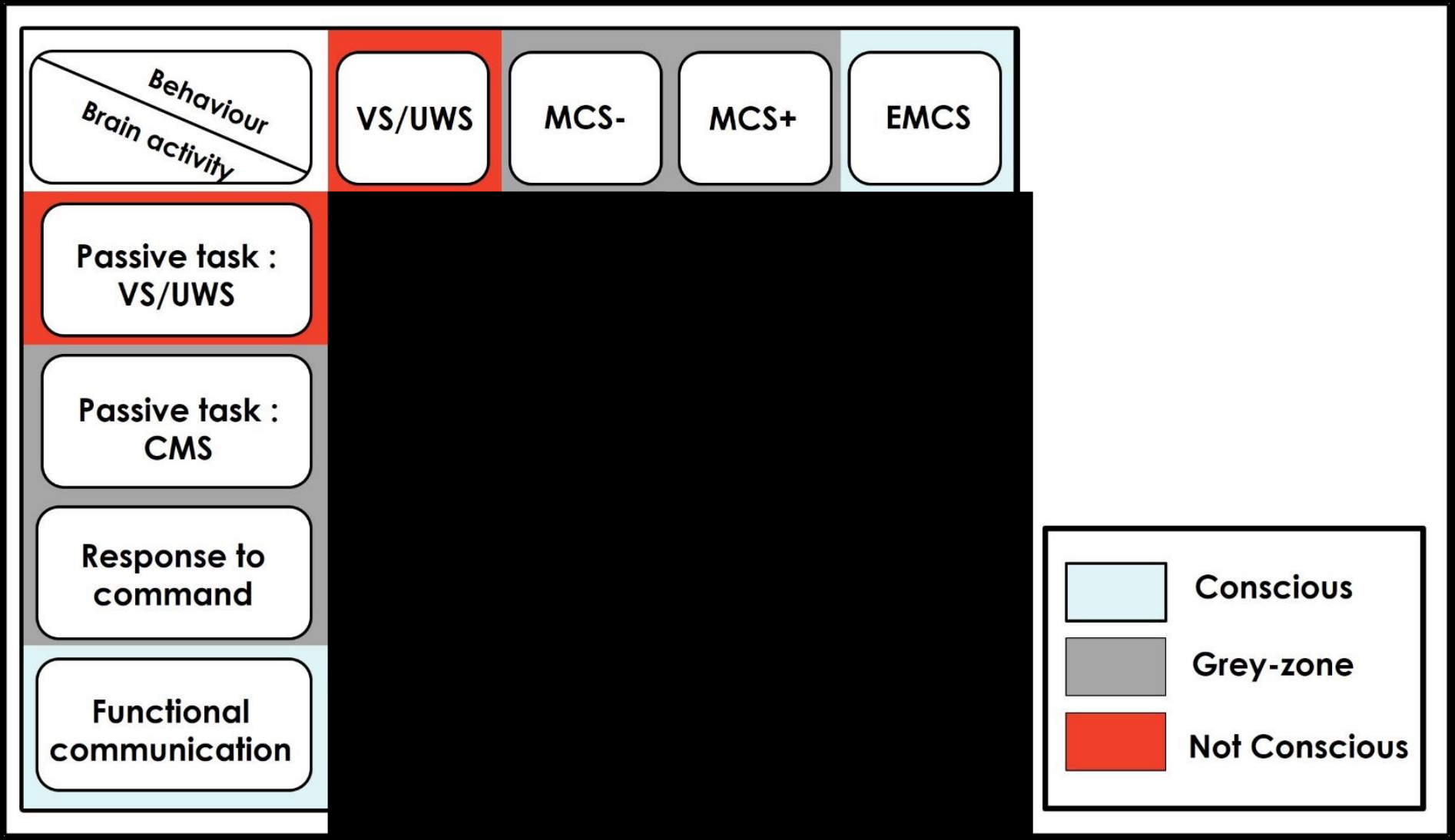
Hermann, Sangare,… Naccache, Neurosc. of Consc. 2022

Toward the integration of BHV and brain activity



Hermann, Sangare,… Naccache, Neurosc. of Consc. 2022

Toward the integration of BHV and brain activity



Hermann, Sangare,… Naccache, Neurosc. of Consc. 2022

Toward the integration of BHV and brain activity

Behaviour / Brain activity	VS/UWS	MCS-	MCS+	EMCS
Passive task : VS/UWS				CS 4b
Passive task : CMS				CS 4b
Response to command				CS 4b
Functional communication	CS 4a	CS 4a	CS 4a	CS 4b

Conscious

Grey-zone

Not Conscious

Hermann, Sangare,… Naccache, Neurosc. of Consc. 2022

Toward the integration of BHV and brain activity

Behaviour / Brain activity	VS/UWS	MCS-	MCS+	EMCS
Passive task : VS/UWS	VS/UWS 2a			CS 4b
Passive task : CMS				CS 4b
Response to command				CS 4b
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- Conscious
- Grey-zone
- Not Conscious

Hermann, Sangare,… Naccache, Neurosc. of Consc. 2022

Toward the integration of BHV and brain activity

Behaviour / Brain activity	VS/UWS	MCS-	MCS+	EMCS
Passive task : VS/UWS	VS/UWS 2a	MCS- CMS 3b	MCS+ CMS 3b	CS 4b
Passive task : CMS	HMD MCS* CMS 3a	HMD? CMS 3b	MCS+ CMS 3b	CS 4b
Response to command	CMD MCS* CMS 3a	CMD CMS 3b	MCS+ CMS 3b	CS 4b
Functional communication	CS 4a	CS 4a	CS 4a	CS 4b

Conscious

Grey-zone

Not Conscious

Hermann, Sangare,… Naccache, Neurosc. of Consc. 2022

Trois questions au sujet des “DoC patients”:

- ***Survol historique & conceptuel : ➔ évaluer un patient “chronique” en 2023***

- ***Vocabulaire : VS/UWS ; MCS/CMS***

- ***Proposition de structuration des évaluations & thérapeutiques innovantes***

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Neurology and Intensive Care

Toward a coherent structuration of disorders of consciousness expertise at a country scale: A proposal for France

L. Naccache [a,b,c,d,*], *J. Luauté* [e,f], *S. Silva* [g,h], *J.D. Sitt* [a,b], *B. Rohaut* [a,b,d]

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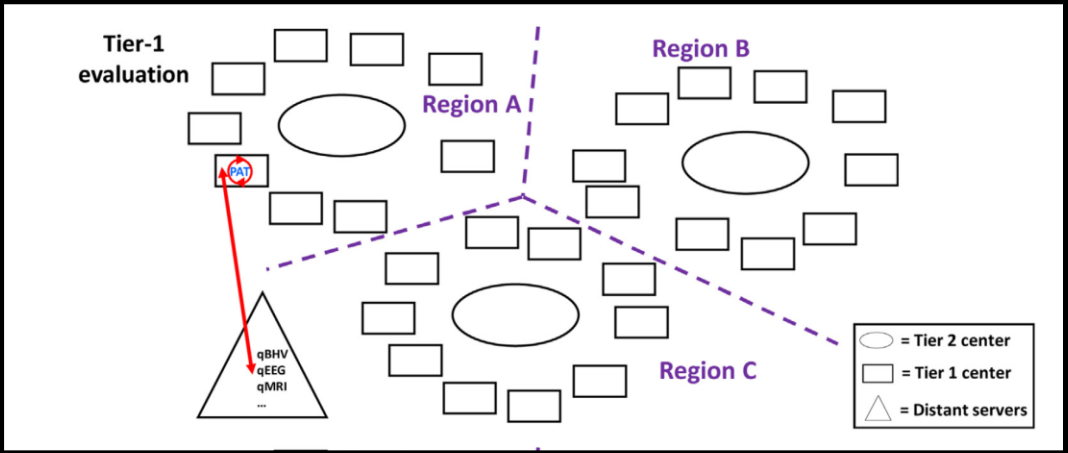
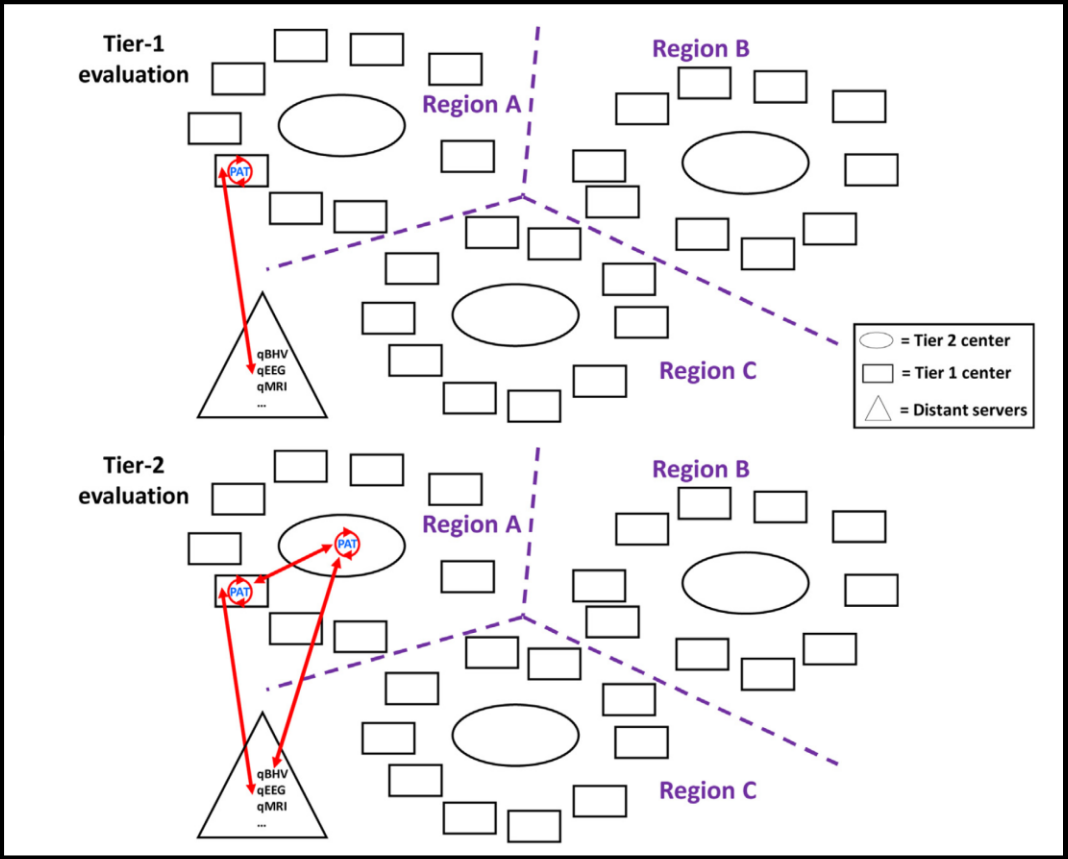
[b] *Sorbonne université, UPMC Univ Paris 06, faculté de médecine Pitié-Salpêtrière, Paris, France*
[c] *AP–HP, hôpital groupe hospitalier Pitié-Salpêtrière, DMU neurosciences, department of clinical neurophysiology, Paris, France*
[d] *AP–HP, hôpital groupe hospitalier Pitié-Salpêtrière, DMU neurosciences, department of neurology, Neuro ICU, Paris, France*
[e] *Service de médecine physique et réadaptation, hôpital Henry-Gabrielle, Hospices Civils de Lyon, Saint-Genis Laval, France*
[f] *Équipe « Trajectoires », centre de recherche en neurosciences de Lyon, Inserm UMR-S 1028, CNRS UMR 5292, université de Lyon, université Lyon 1, Bron, France*
[g] *Intensive Care Unit, Purpan University Hospital, 31000 Toulouse, France*
[h] *Toulouse NeuroImaging Center (ToNIC lab) URM UPS/INSERM 1214, 31000 Toulouse, France*


Tier-1
evaluation
Region A
Region B
Region C
PAT
qBHV
qEEG
qMRI
...
= Tier 2 center
= Tier 1 center
= Distant servers


Tier-1
evaluation
Region A
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Tier-2
evaluation
Region A
Region B
Region C
PAT
PAT
qBHV
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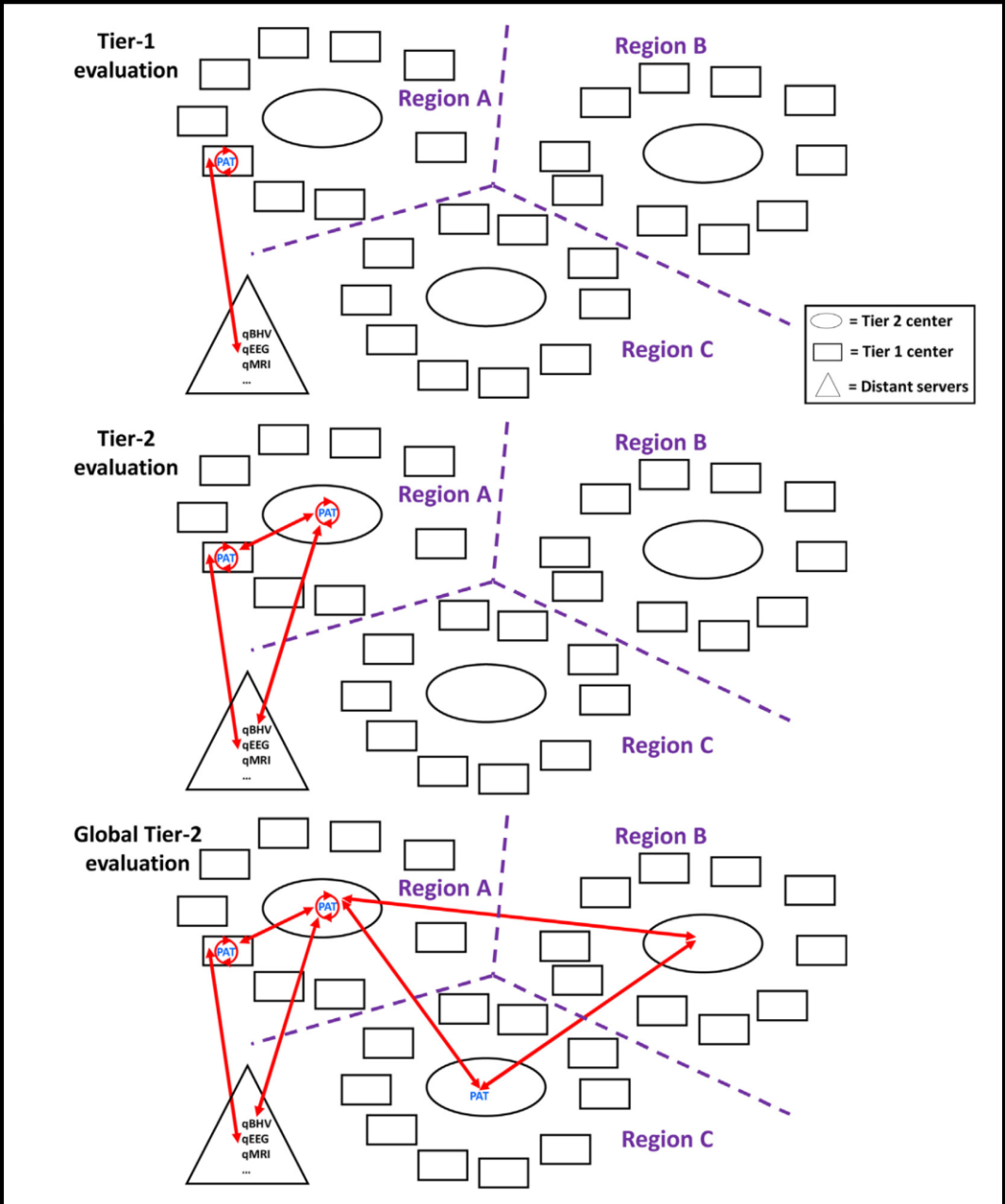
...


Tier-1 evaluation
Region A
Region B
Region C
PAT
qBHV
qEEG
qMRI
...
= Tier 2 center
= Tier 1 center
= Distant servers
Tier-2 evaluation
Region A
Region B
Region C
PAT
PAT
qBHV
qEEG
qMRI
...
Global Tier-2 evaluation
Region A
Region B
Region C
PAT
PAT
PAT
qBHV
qEEG
qMRI
...

PICNIC Lab & Salpetrière teams

Vignette clinique #1

<u>Patient TAXXX:</u> Patient de 84 ans admis il y a 4 ans pour coma fébrile » / Pneumopathie aiguë

<u>Appelés, par confrères réanimateurs pour avis neurologique:</u> IRM cérébrale normale
➔ Cause du coma?

<u>Evaluation clinique:</u> Abolition de tous les réflexes tendineux
Mouvement volontaires de flexion de la tête sur le tronc. Code de communication fonctionnelle
➔ Patient paralysé mais conscient! Syndrome de Guillain-Barré sévère

Vignette clinique #1

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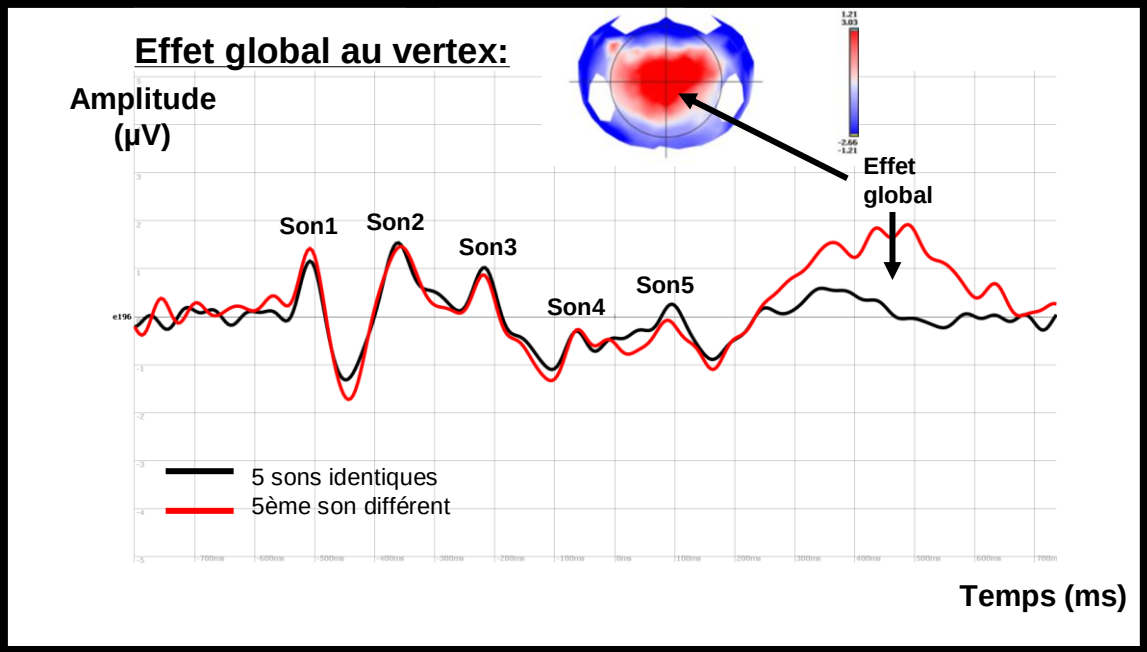
Evaluation EEG: Conscient



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Evaluation EEG: Conscient!

Bonne évolution: plusieurs mois de réanimation, autonome, se souvient des sons!

Vignette clinique #2

Patiente RV113: Patiente de 54 ans avec hémorragie sous-arachnoïdienne en février 2013 sur rupture anévrysme et vasospasmes multiples prédominant à gauche

Appelés, 2 ans ½ plus tard par confrère EVC-EPR pour évaluation

Evaluation clinique: CRS-R = 20/23 (MCS) [3 3 5 3 1 3]

Evaluation EEG: MCS

Vignette clinique #2

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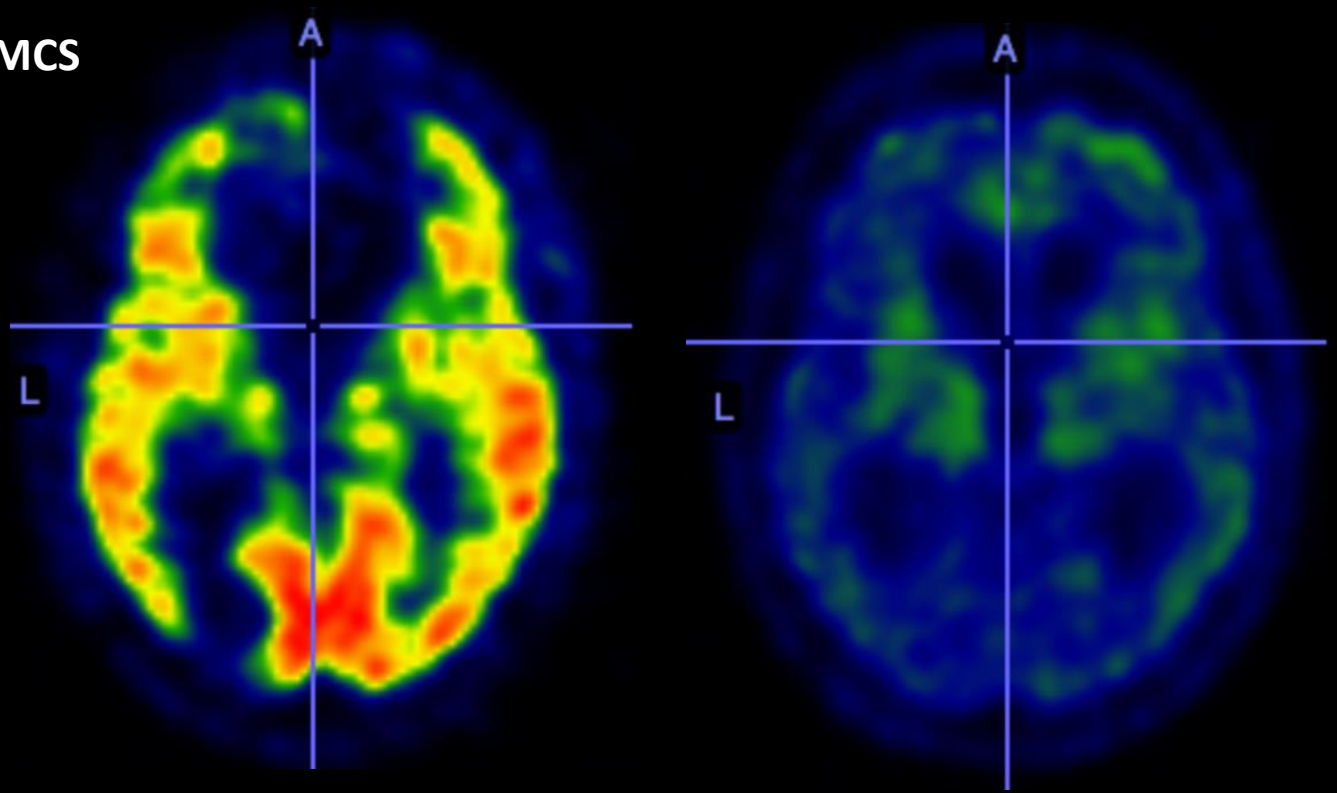
Evaluation clinique: CRS-R = 20/23 (MCS) [3 3 5 3 1 3]

Evaluation EEG: MCS

Evaluation PET: MCS



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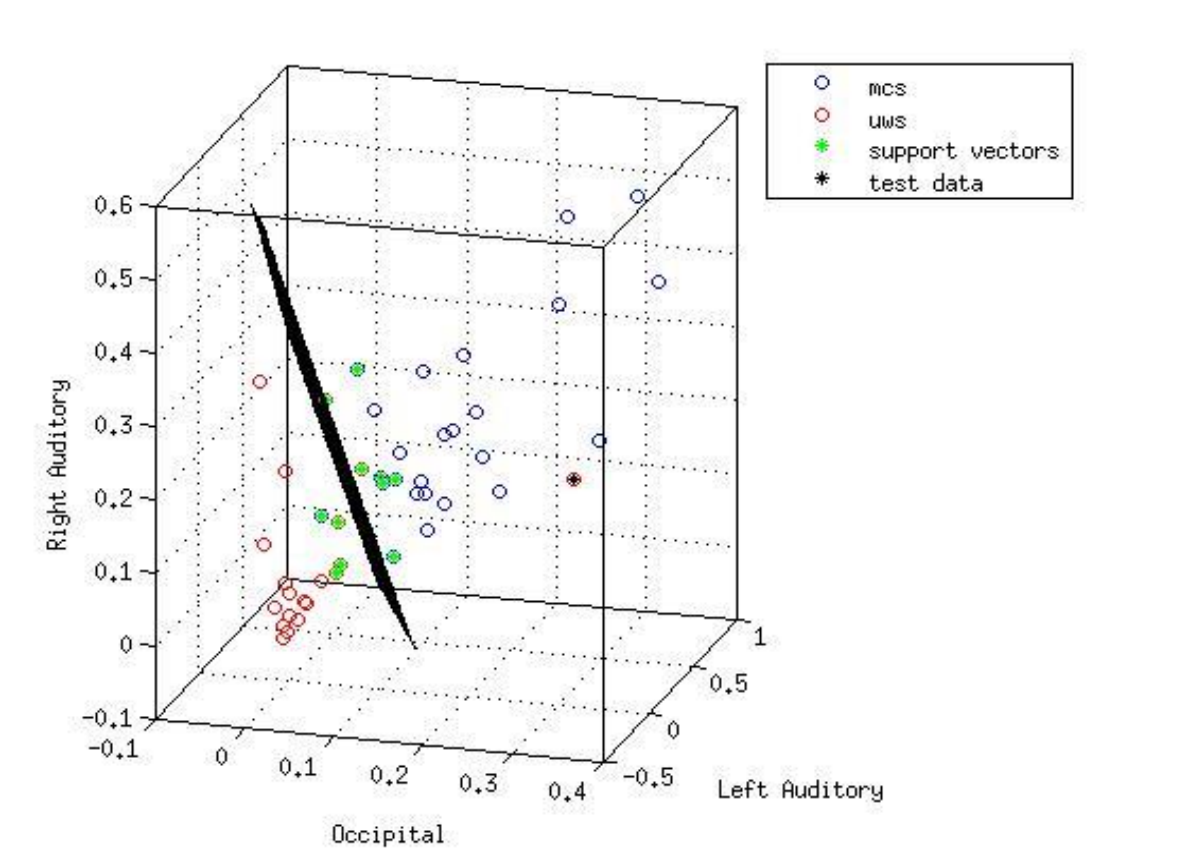
Evaluation EEG: MCS

Evaluation PET: MCS

IRM: **.structurelle: séquelles**
.fonctionnelle: MCS



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Evaluation EEG: MCS

Evaluation PET: MCS

IRM: **.structurelle: séquelles ischémiques bilatérales étendues**
.fonctionnelle: MCS

tDCS: passe en état conscient (EMCS) avec communication fonctionnelle ! [3 3 5 3 2 3]

→Patiente consciente avec handicaps moteurs et cognitifs
→Projet tDCS

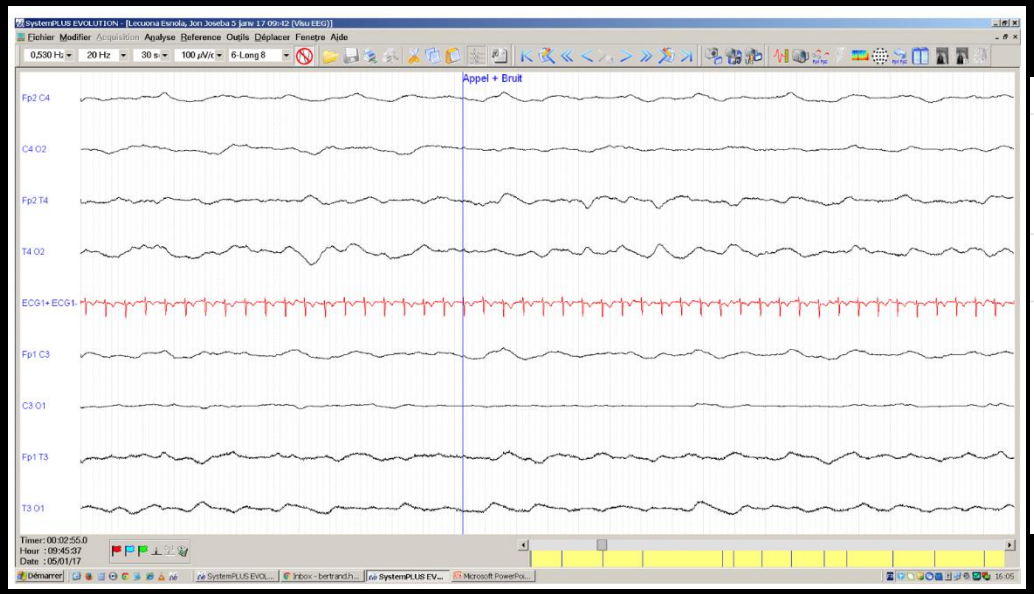
Vignette clinique #3

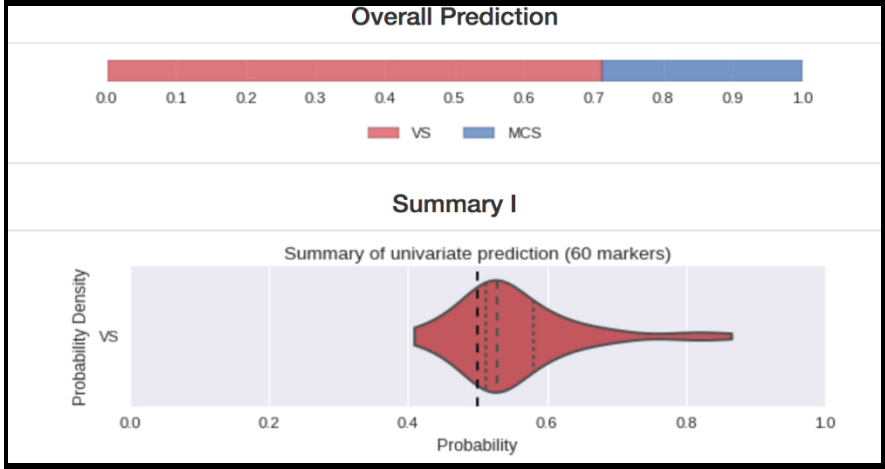
<u>Patient LJ120:</u> 33 ans / Chirurgie sarcome thoracique / arrêt cardiaque par obstruction de sonde d'intubation post-opératoire le 22/12/2016

<u>Appelés, le 10 janvier 2017 par</u> Réanimateurs car : « ouveture des yeux sans autre comportement évident »

<u>Evaluation clinique:</u> CRS-R = 3/23 (VS) [0 0 1 1 0 1]

<u>Evaluation EEG:</u> lent aréactif / pas d'effet local ni global / VS





Vignette clinique #3

Patient LJ120: 33 ans / Chirurgie sarcome thoracique / arrêt cardiaque par obstruction de sonde d'intubation post-opératoire le 22/12/2016

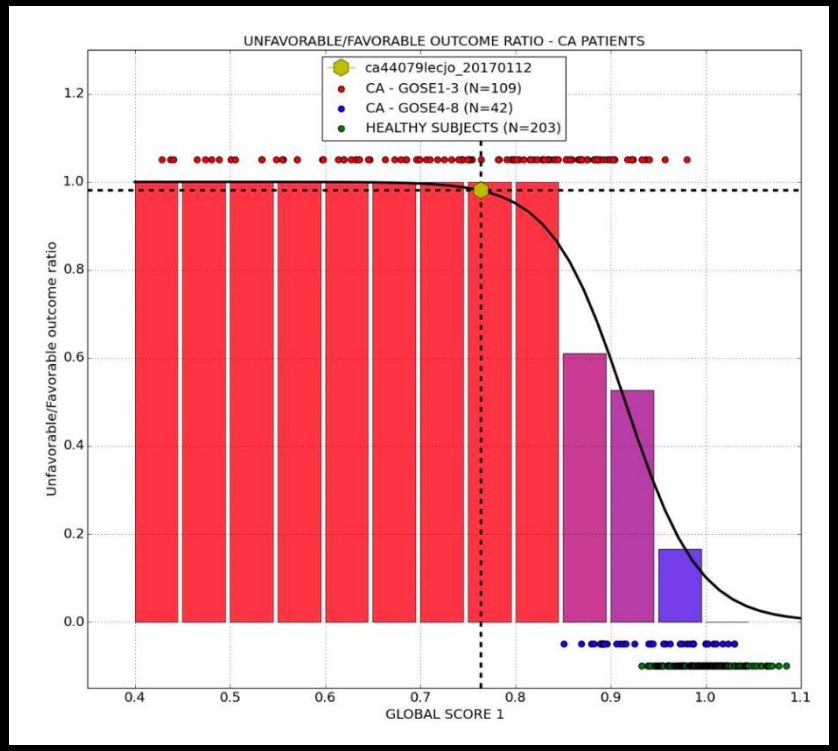
Appelés, le 10 janvier 2017 par Réanimateurs car : « ouveture des yeux sans autre comportement évident »

Evaluation clinique: CRS-R = 3/23 VS) [0 0 1 1 0 1]

Evaluation EEG: lent aréactif / pas d'effet local ni global / VS

Evaluation PET: -

IRM: structurelle DTI : sédation



Vignette clinique #3

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Appelés, le 10 janvier 2017 par Réanimateurs car : « ouveture des yeux sans autre comportement évident »

Evaluation clinique: CRS-R = 3/23 VS) [0 0 1 1 0 1]

Evaluation EEG: lent aréactif / pas d'effet local ni global / VS

Evaluation PET: -

IRM: structurelle DTI : sédation

Test Stilnox: négatif

tDCS: -

➔ Patient VS après arrêt cardiaque à 3 semaines de l'arrêt cardiaque. Retour Hôpital d'origine. Pas progression clinique à 1 mois. LATA avec accord de la famille

Vignette clinique #4

Patient AA121: 31ans / Défenestration volontaire mi-décembre 2016 TC sévère et polytraumatismes / coma initial

Appelés, le 9 janvier 2017 par Réanimateurs car : « suit du regard mais aucune communication ni réponse aux ordres simples »

Evaluation clinique: CRS-R = 13/23 (MCS) [2 3 5 1 0 2] et découverte d'une utilisation fonctionnelle des objets

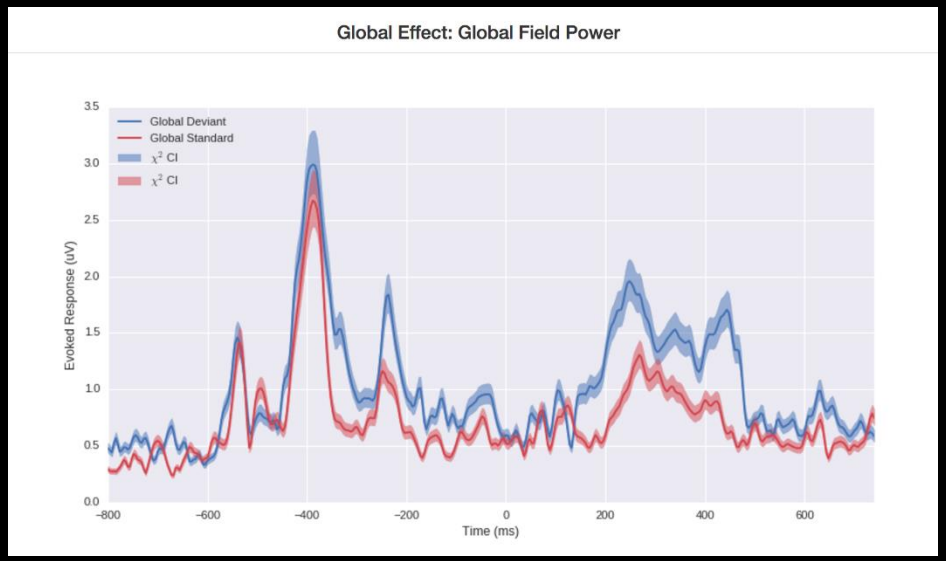
Vignette clinique #4

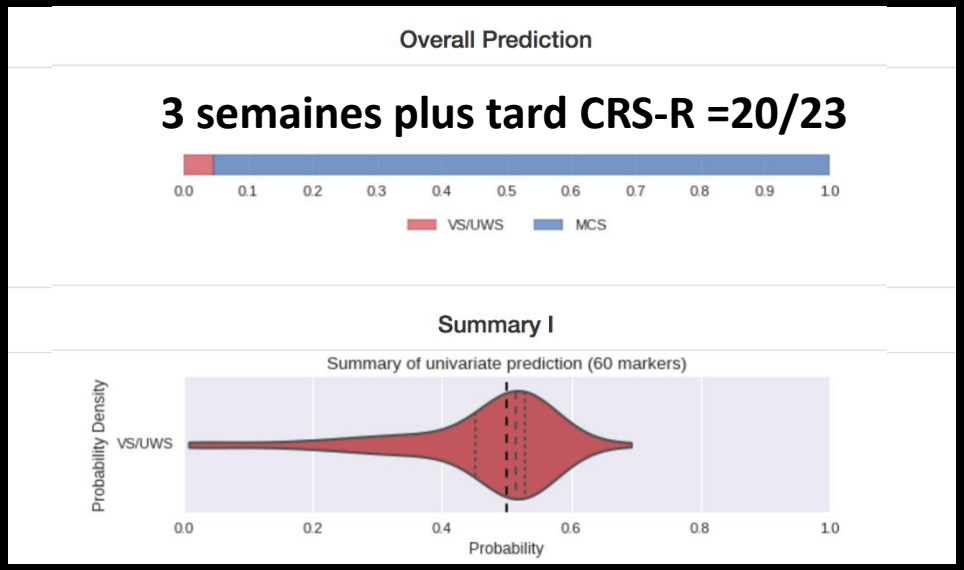
<u>Patient AA121:</u> 31ans / Défenestration volontaire mi-décembre 2016 TC sévère et polytraumatismes / coma initial

<u>Appelés, le 9 janvier 2017 par</u> Réanimateurs car : « suit du regard mais aucune communication ni réponse aux ordres simples »

<u>Evaluation clinique:</u> CRS-R = 13/23 (MCS) [2 3 5 1 0 2] et découverte d'une utilisation fonctionnelle des objets

<u>Evaluation EEG:</u> effet global / MCS



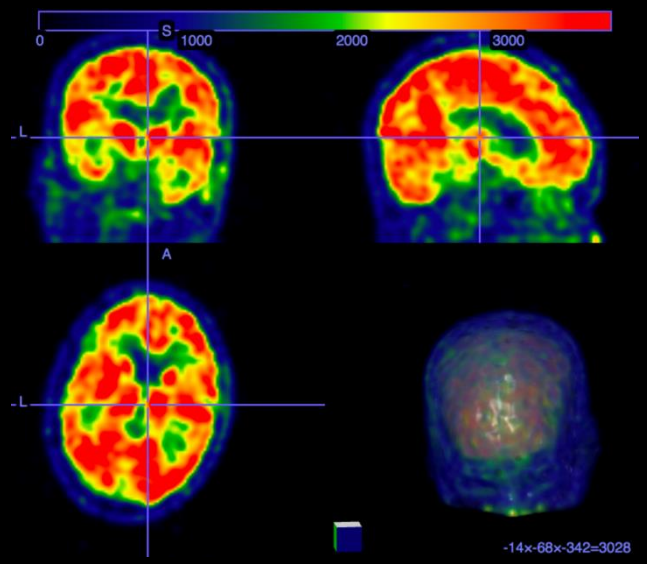
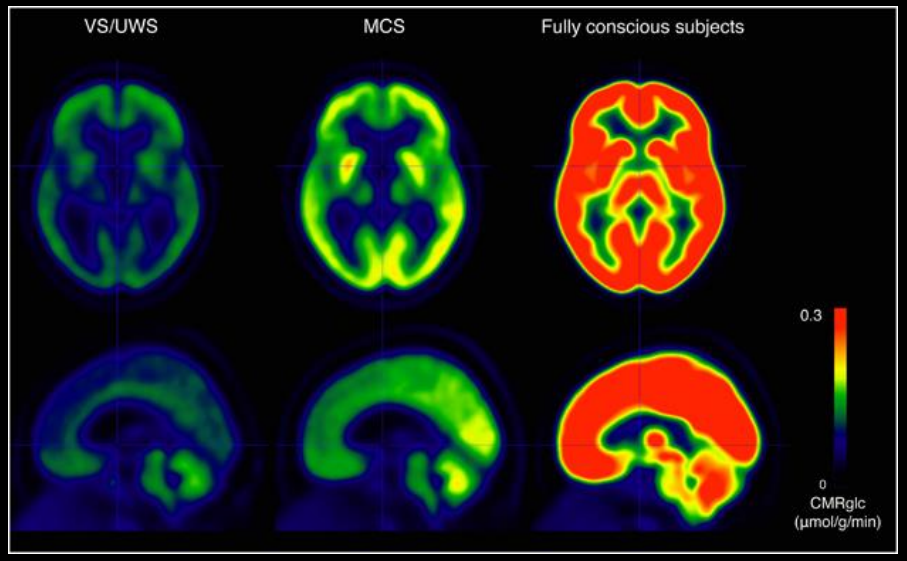


Vignette clinique #4

<u>Patient AA121:</u> 31ans / Défenestration volontaire mi-décembre 2016 TC sévère et polytraumatismes / coma initial

<u>Appelés, le 9 janvier 2017 par</u> Réanimateurs car : « suit du regard mais aucune communication ni réponse aux ordres simples »

<u>Evaluation clinique:</u> CRS-R = 13/23 (MCS) [2 3 5 1 0 2] et découverte d'une utilisation fonctionnelle des objets

<u>Evaluation EEG:</u> effet global / MCS

<u>Evaluation PET:</u> MCS ou mieux