EEG in prolonged disorder of consciousness (vegetative state and minimally conscious state)

Anna Estraneo, MD

Neurology Unit, General Hospital, Nola,

Don Gnocchi Foundation, Florence, Italy

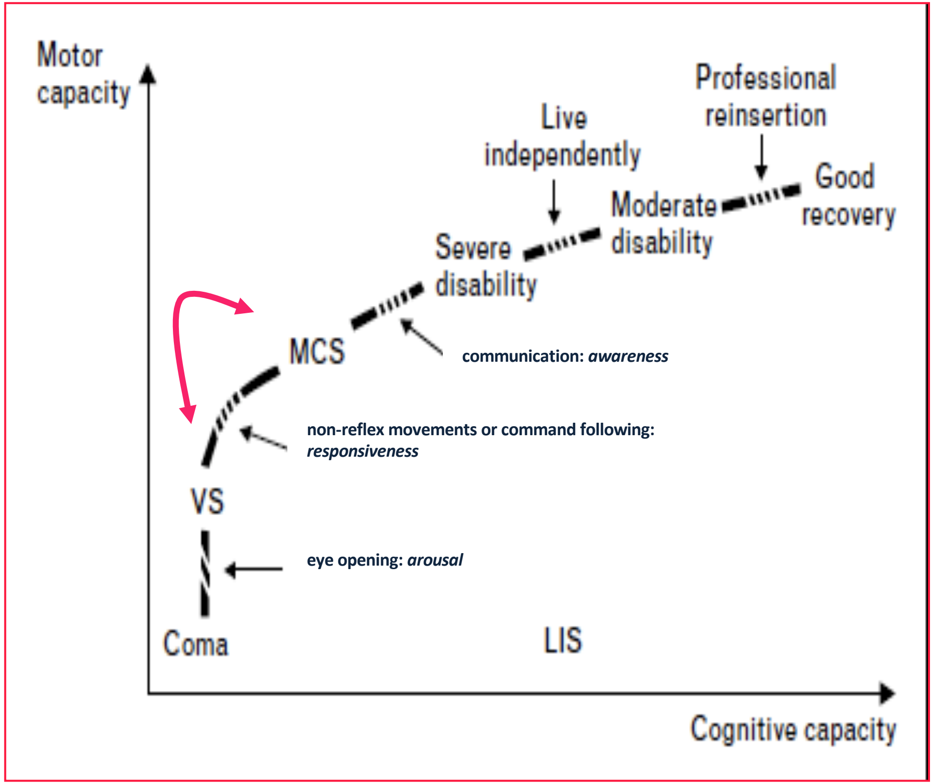
aestraneo@gmail.com

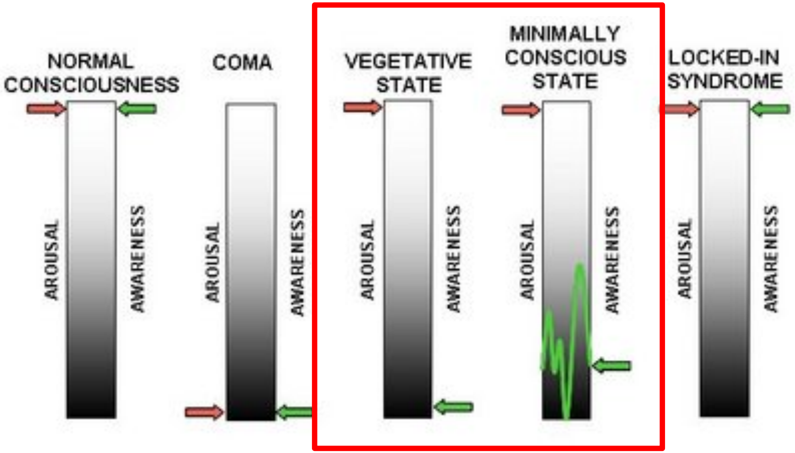
La dr.ssa Estraneo Anna dichiara l'assoluta autonomia dei contenuti scientifici del proprio intervento ed indipendenza da interessi economici commerciali con possibili aziende sponsorizzatrici.

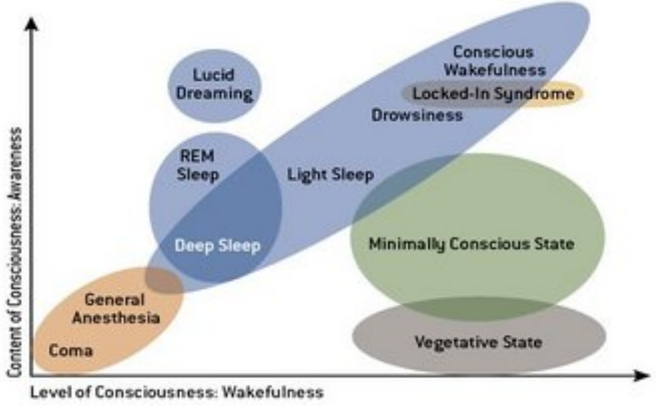
EEG in VS and MCS

- Which patient
- EEG and PE in clinical diagnosis
- EEG and PE in prognostication
- EEG and seizure

Prolonged disorders consciousness

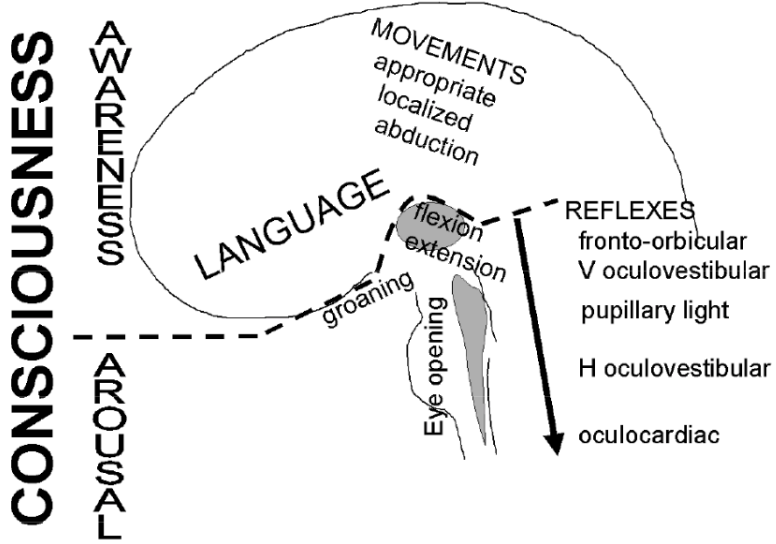


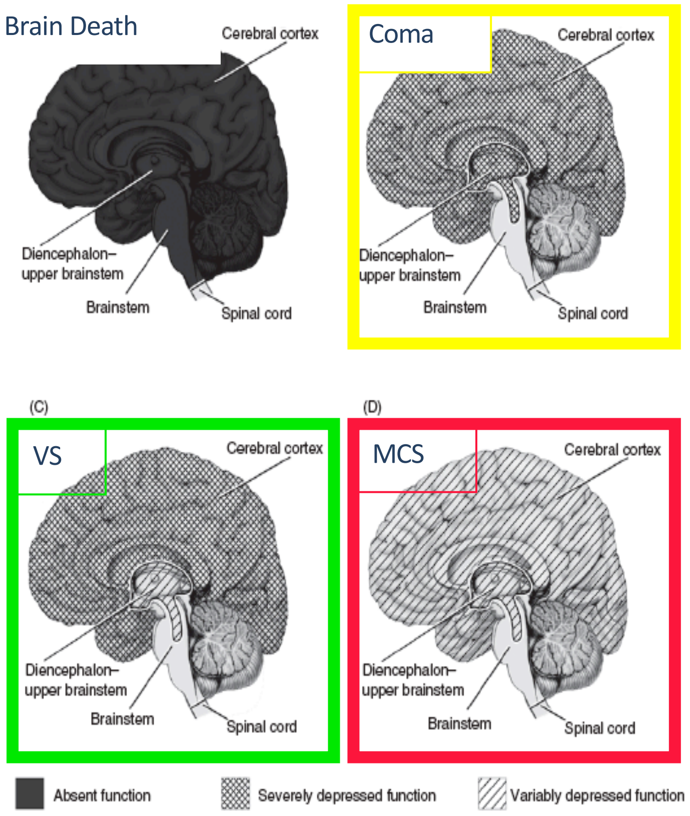




Laureys, 2005

Consciousness components





Laureys, 2002

Laureys and Tononi, 2009

Vegetative state/unresponsive wakefulness syndrome

- State of deep, unarousable unconsciousness (no intentional behavioral responses)
- Presence of arousal: patients with spontaneous eyes opening or in response to multisensorial stimuli

- *Possible clinical (reflexive) behaviors:*
- grimace in response to painful stimuli,
- stereotyped withdrawal responses of the limbs,
- no localizing responses or discrete defensive movements
- vocalization
- sound localization

Minimally conscious state


Special Article

AMERICAN ACADEMY OF NEUROLOGY

CME

The minimally conscious state

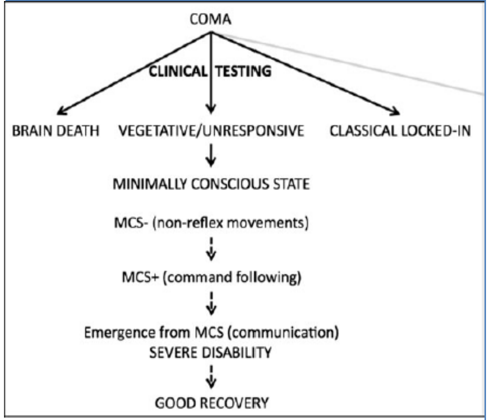
Definition and diagnostic criteria

J.T. Giacino, PhD; S. Ashwal, MD; N. Childs, MD; R. Cranford, MD; B. Jennett, MD; D.I. Katz, MD; J.P. Kelly, MD; J.H. Rosenberg, MD; J. Whyte, MD, PhD; R.D. Zafonte, DO; and N.D. Zasler, MD

Inconsistent, but reproducible or sustained (long enough to be differentiated from reflexive behaviors) cognitively mediated behaviors:

- ✓ Following simple commands.
- ✓ Gestural or verbal yes/no responses (regardless of accuracy).
- ✓ Intelligible verbalization.
- ✓ Purposeful behavior to relevant environmental stimuli including:
  - pursuit eye movement or sustained fixation to moving or salient stimuli
  - appropriate smiling or crying to the linguistic or visual emotional stimuli
  - vocalizations or gestures in direct response to the linguistic content of questions
  - reaching for objects that demonstrates a clear relationship between object location and direction of reach
  - touching or holding objects in a manner that accommodates the size and shape of the object

Subcategorizing MCS patients



- **MCS+** is defined by the presence of:
  - command following, or
  - intelligible verbalization or
  - gestural or verbal yes/no responses

- **MCS-** patients only show minimal levels of behavioural interaction, with non-reflex movements such as:
  - orientation to noxious stimuli, or
  - pursuit eye movements in response to moving or salient stimuli, or
  - movements or affective behaviors in relation to relevant stimuli (e.g., appropriate smiling or crying, vocalizations or gestures)

Bruno et al., J Neurol, 2011

Emergence from MCS

1) Verbal or non-verbal functional communication

2) Functional object use: appropriate use of at least two different objects

Giacino, Neurology 2002

Sources of diagnostic error:

- Aphasia
- Confusional state/post-traumatic amnesia *(Nakase-Richardson, Neurology, 2009)*
- Cognitive impairments

CLINICAL DIAGNOSIS CLINICAL SIGNS	COMA	VEGETATIVE STATE	MINIMALLY CONSCIOUS STATE
Awareness	Absent	Absent	Partial
Awakening	Absent	Present	Present
Motor Function	Reflex abnormal posturing	Abnormal posturing or flexion withdrawal to noxious stimuli	Localization to noxious stimulation Reaching for object
Auditory function	Absent	Auditory startle Localization to sound	Reproducible movements to command
Visual function	Absent	Visual startle	Sustained visual fixation Visual pursuit Object recognition
Communication	Absent	Absent/afinalistic vocalization	Inconsistent but intelligible verbalization

Clinical diagnosis of pDoC

JFK COMA RECOVERY SCALE - REVISED ©2004

Record Form

This form should only be used in association with the "CRS-R ADMINISTRATION AND SCORING GUIDELINES" which provide instructions for standardized administration of the scale.

Patient:	Diagnosis:	Etiology:
Date of Onset:	Date of Admission:	

Date																
Week	ADM	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
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																

Denotes emergence from MCS†

Denotes MCS*

1

(Giacino et al, 2004)

VS

- Auditory <=2 and
- Visual <=1 and
- Motor <=2 and
- Oro-motor/verbal <=2 and
- Communication = 0 and
- Arousal <=3

MCS

- Auditory = 3-4 **or**
- Visual = 2-5 **or**
- Motor = 3-5 **or**
- Oro-motor = 3 **or**
- Communication =or

EMERGENCE FROM MCS

- Motor = 6 **AND/OR**
- Communication = 2

Published Ahead of Print on August 8, 2018 as 10.1212/WNL.0000000000005926
SPECIAL ARTICLE

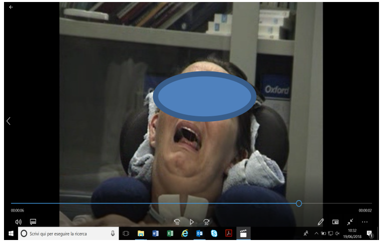
AMERICAN ACADEMY OF NEUROLOGY.

Practice guideline update recommendations summary: Disorders of consciousness

RECOMMENDED

Recommendation statement and level

Clinicians should identify and treat conditions that may confound accurate diagnosis of a DoC prior to establishing a final diagnosis (Level B based on feasibility and cost).



Subscore 1	Subscore 2	Possible Contributing Factors (When Scoring Errors Are Ruled Out)
Consistent command following (A4)*	Unarousable/no eye-opening (Ar0)*	Bilateral ptosis§; facial oedema§; eyelid apraxia§
Blink to threat (V1)*	Functional object use (M6)*	Bilateral optic nerve damage; Terson syndrome; cortical blindness
Blink to threat (V1)*	Functional communication (C2)*	
Visual fixation (V2)*	Unarousable (Ar0)*	Ptosis§; eyelid apraxia§
Object localization (V4)*	Unarousable (Ar0)*	
Object localization (V4)*	No motor response (M0)*	
Object recognition (V5)*	Abnormal posturing (M1)*	Severe spasticity
Object recognition (V5)*	Unarousable (Ar0)*	Ptosis§; eyelid apraxia§
Abnormal posturing (M1)*	Intelligible verbalization (Ve3)*	Severe spasticity
Functional object use (M6)*	Unarousable (Ar0)*	Ptosis§; eyelid apraxia§
Functional communication (C2)*	Unarousable (Ar0)*	
Reproducible command following (A3)†	Functional communication (C2)†	N/A‡
Consistent command following (A4)†	No visual response (V0)†	Bilateral optic nerve damage; Terson syndrome; cortical blindness
Consistent command following (A4)†	No motor response (M0)†	Quadriplegia
No visual response (V0)†	Functional communication (C2)†	Bilateral optic nerve damage; Terson syndrome; cortical blindness
Visual fixation (V2)†	Functional communication (C2)†	Third and fourth cranial nerve palsy; ocular apraxia; visual agnosia
Visual pursuit (V3)†	Functional communication (C2)†	Ocular apraxia; visual agnosia
Object localization (V4)†	Functional communication (C2)†	Visual agnosia, hemineglect
Object recognition (V5)†	No motor response (M0)†	Quadriplegia
No motor response (M0)†	Functional communication (C2)†	Quadriplegia
Abnormal posturing (M1)†	Functional communication (C2)†	Severe spasticity
Flexion withdrawal (M2)†	Functional communication (C2)†	Severe spasticity, hypertonus or hypotonus
Localization to pain (M3)†	Functional communication (C2)†	Apraxia
Object manipulation (M4)†	Functional communication (C2)†	Severe spasticity, hypertonus or hypotonus; apraxia
Automatic motor response (M5)†	Functional communication (C2)†	Object agnosia; apraxia
No verbal response (Ve0)†	Functional communication (C2)†	Facial nerve palsy/oromotor weakness
Oral reflexive movement (Ve1)†	Functional communication (C2)†	
Vocalization (Ve2)†	Functional communication (C2)†	
Functional communication (C2)†	Eyes open with stimulation (Ar1)†	N/A‡
Functional communication (C2)†	Eyes open without stimulation (Ar2)†	N/A‡

Chatelle et al., 2015

Appropriateness of diagnostic procedure

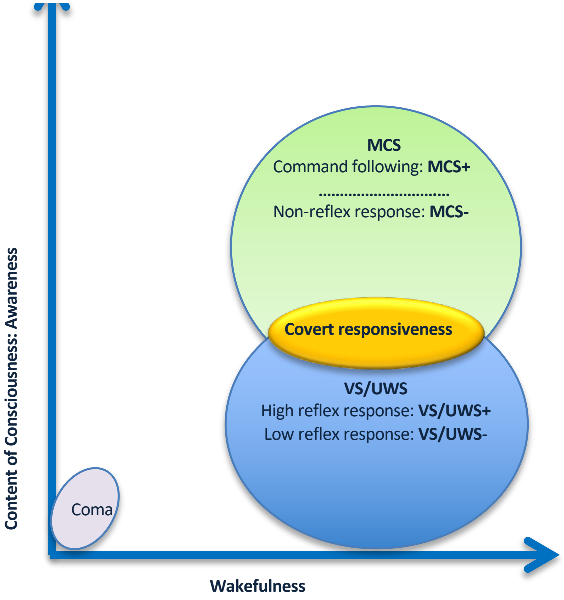
brain sciences

MDPI

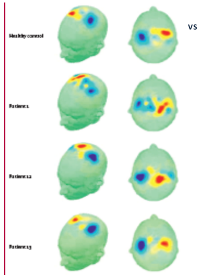
Article

Covert Cognition in Disorders of Consciousness: A Meta-Analysis

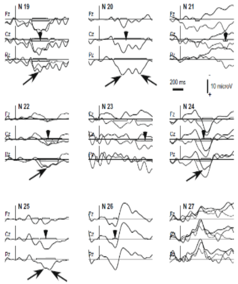
Caroline Schnakers [1,*], Michaela Hirsch [2], Enrique Noé [3], Roberto Llorens [3,4], Nicolas Lejeune [5], Vigneswaran Veeramuthu [6], Sabrina De Marco [7], Athena Demertzi [5], Catherine Duclos [8], Ann-Marie Morrissey [9], Camille Chatelle [5] and Anna Estraneo [10,11]



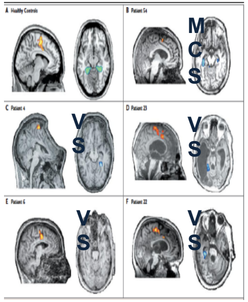
Modified from Laureys. 2005



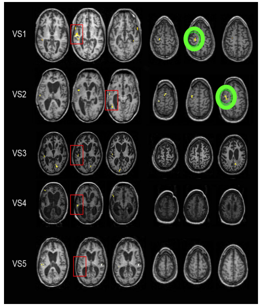
EEG response to motor imagery task. *Cruse, 2011*



P3 to the subject's own name *Fischer 2010*

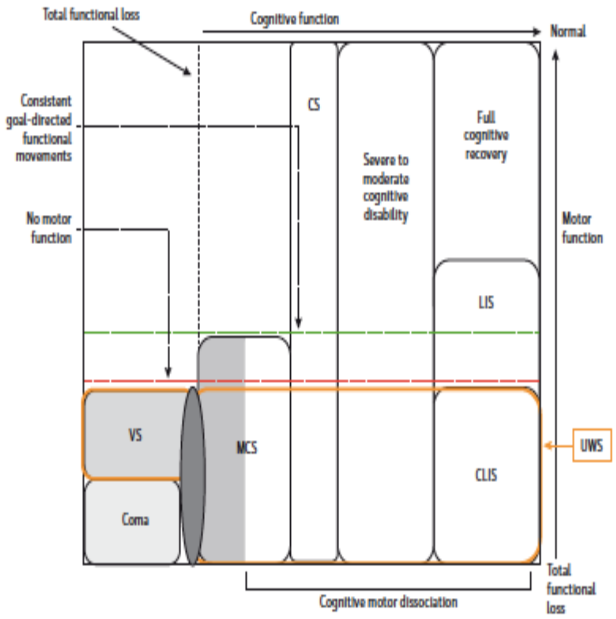


Motor or spatial imagery *Monti, 2010*

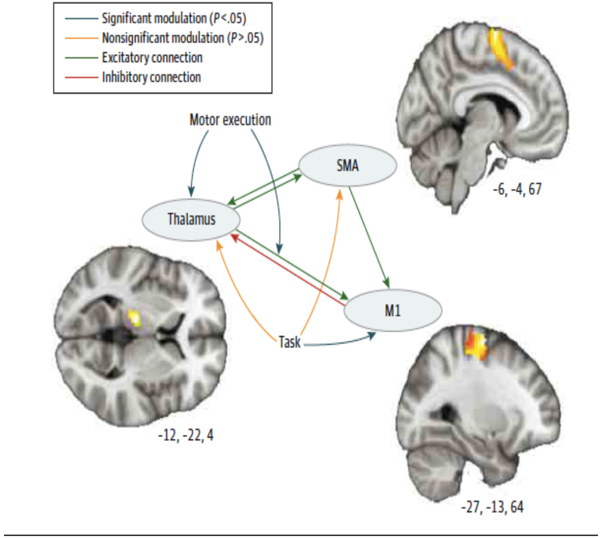


Activation to motor tasks in premotor area *Bekinschtein, 2010*

Cognitive-motor dissociation



Schiff, JAMA, 2015



Fernández-Espejo et al, *JAMA, 2015*

- ✓ Dissociation of measured bedside behavior (a lack of purposeful motor behavior) and fMRI or electrophysiologic evidence of command following
- ✓ Due to an underlying structural disruption between the motor cortex and the thalamus.

EEG in VS and MCS

- Which patient
- EEG and PE in clinical diagnosis
- EEG and PE in prognostication
- EEG and seizure

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Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Standard EEG in diagnostic process of prolonged disorders of consciousness

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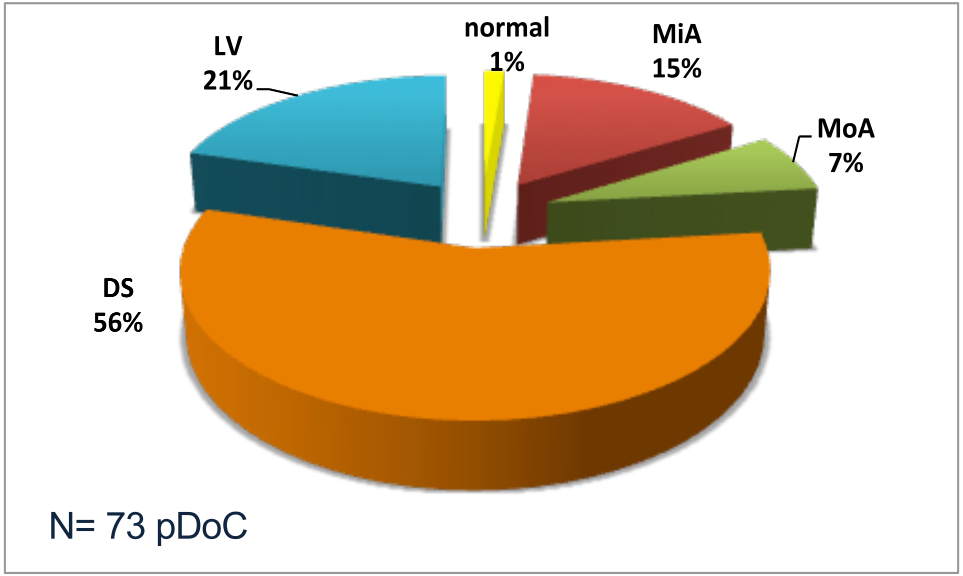
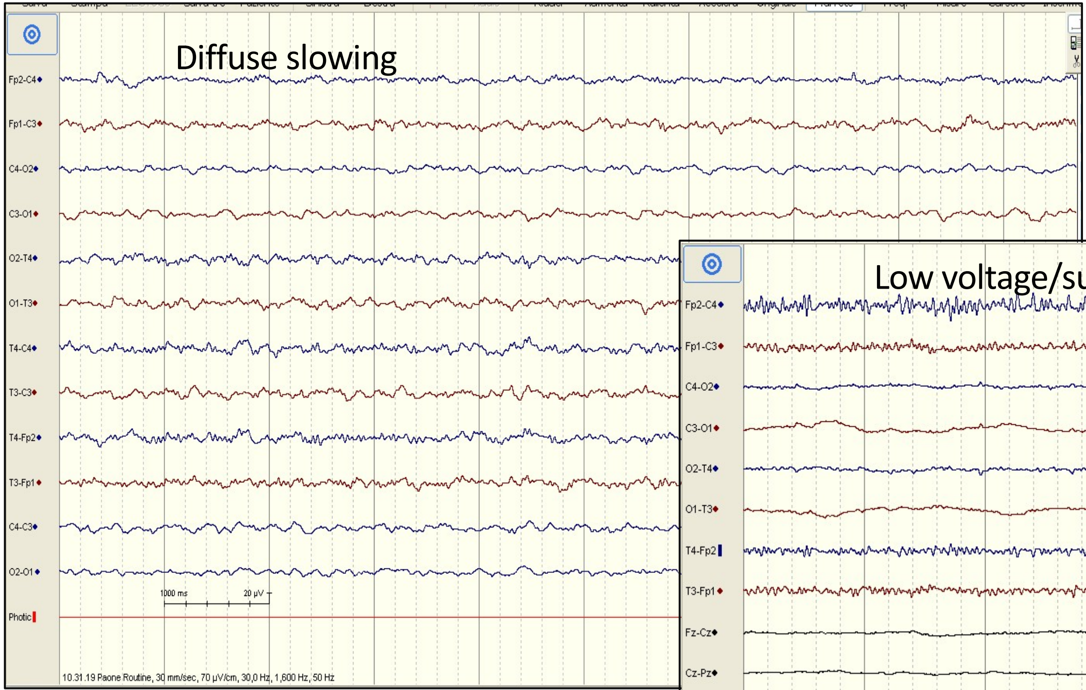
[b]Neuropsychology Lab., Dept. of Psychology, Second University of Naples, Viale Ellittico 31, 81100 Caserta, Italy

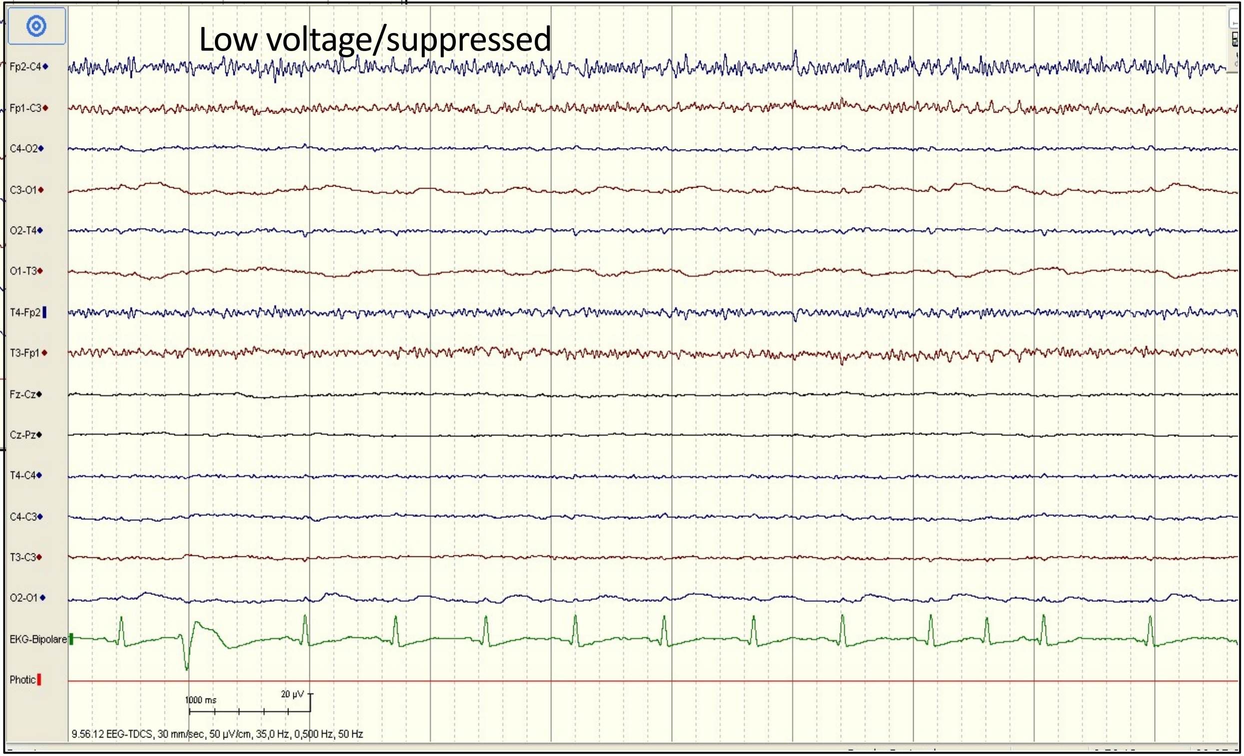
EEG findings in prolonged DoC



1. **Normal:** predominant α rhytms
2. **MiA** (Mildly abnormal): θ (≥20 µV), with frequent (10-49%) α
3. **MoA** (Moderately abnormal) θ/δ ≥20 µV, with rare (1-9%)) α
4. **DS** (Diffuse slowing): θ/δ ≥20 µV
5. **LV** (Low voltage): θ/δ <20 µV

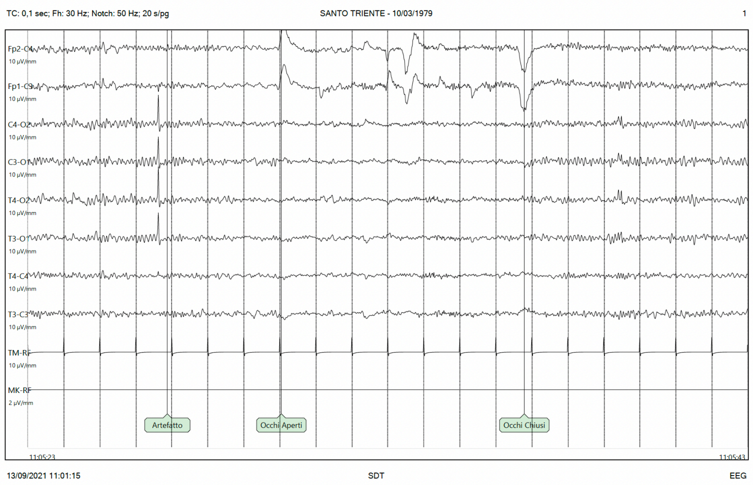
EEG findings in DoC





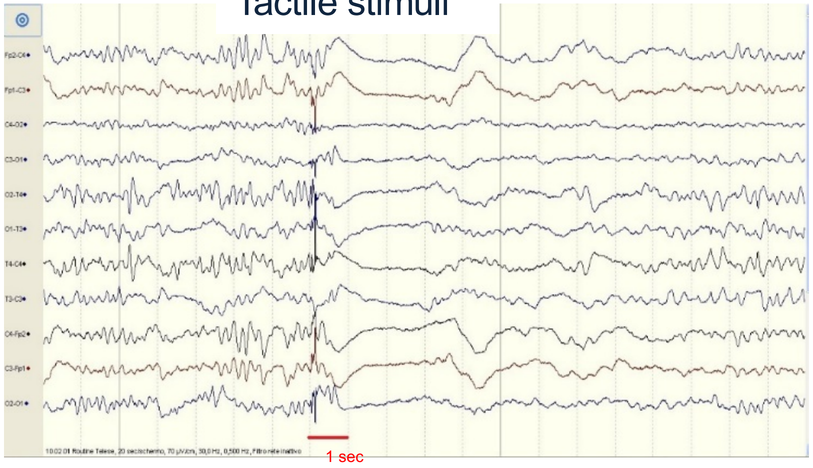
EEG reactivity analysis

Presence of reactivity: change in frequency and/or amplitude (or attenuation) of the background activity in the 3-sec EEG activity after (eye closing, tactile, painful and acoustic) stimuli, with respect to the 3 seconds before

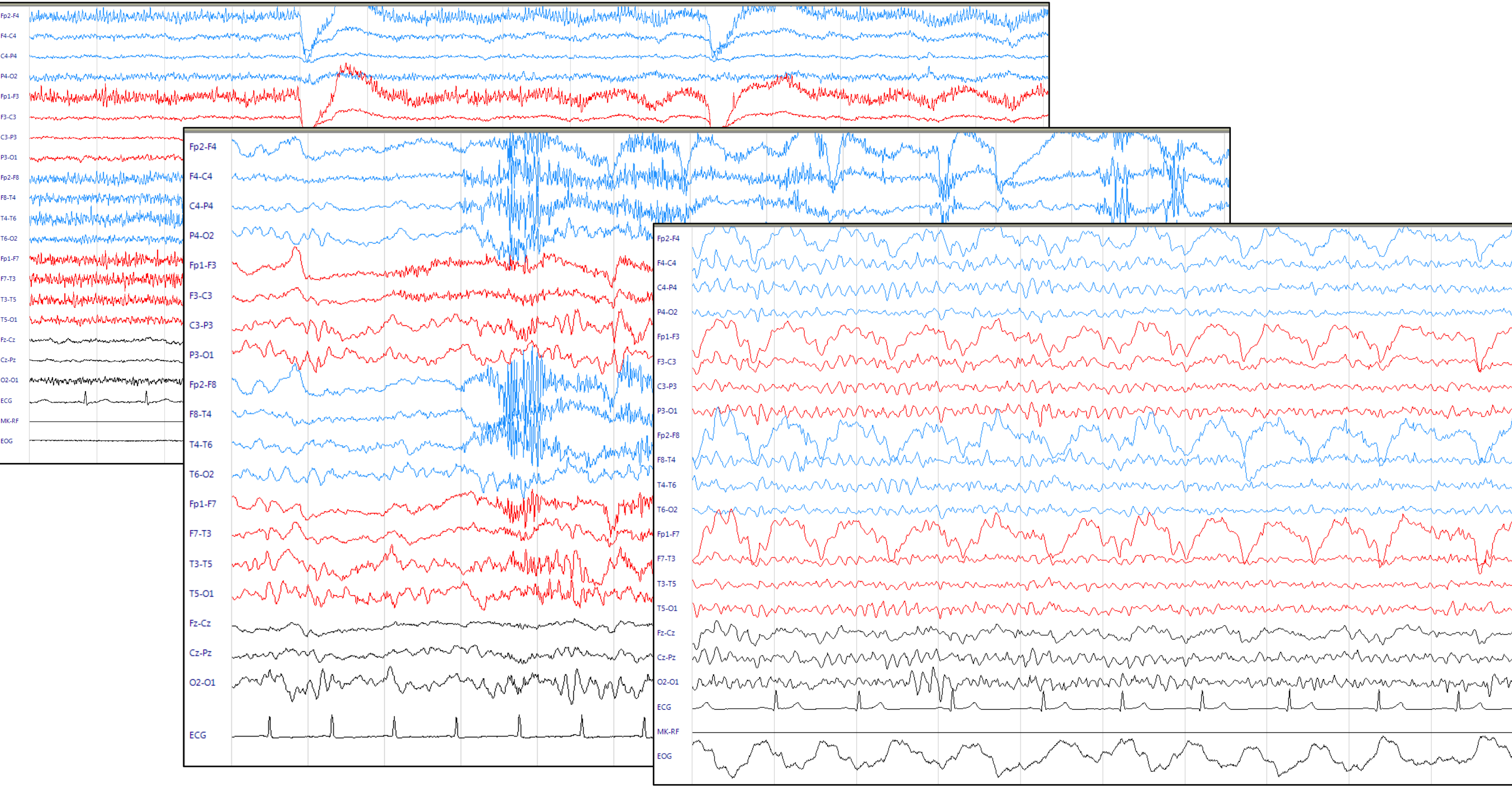


Auditory stimuli

Tactile stimuli



Issue in EEG recording in prolonged DoC



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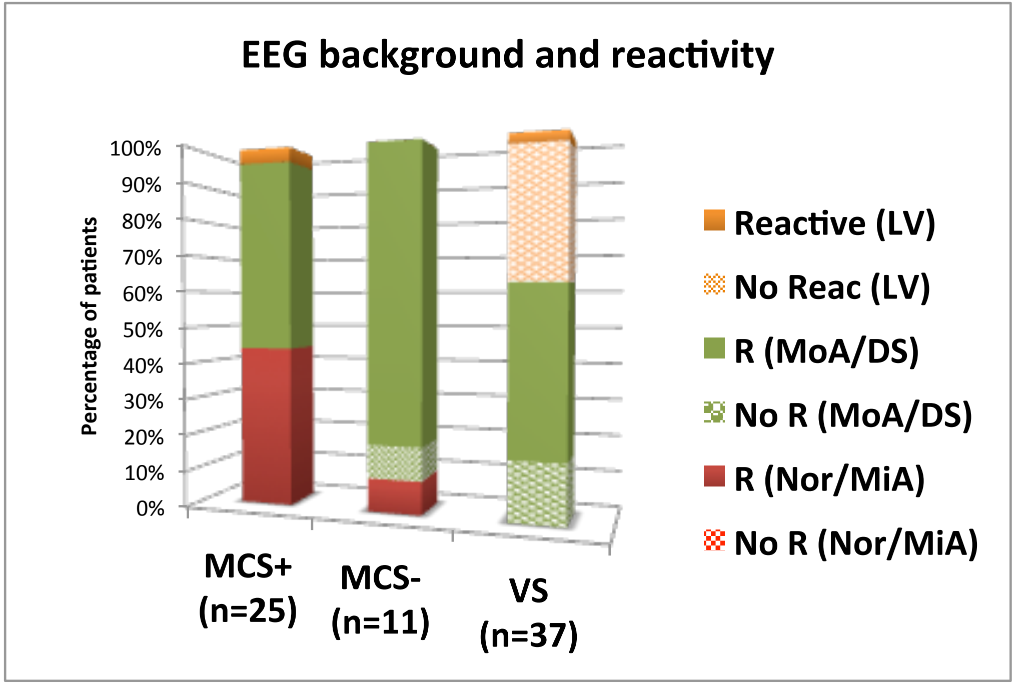
[b]Neuropsychology Lab., Dept. of Psychology, Second University of Naples, Viale Ellittico 31, 81100 Caserta, Italy

EEG background activity and reactivity as a function of clinical diagnosis

EEG categories	Predominant Background activity
Normal	predominant posterior alpha rhythm and of the anterior-posterior gradient (APG), without focal or hemispheric slowing or epileptiform abnormalities
Mildly abnormal	predominant posterior theta activity (≥20 µV), symmetric or not, with frequent (10-49% of recording) posterior alfa rhythms
Moderately abnormal	predominant posterior theta activity (≥20 µV), symmetric or not, poorly organized APG, even with rare (<1% of recording) or occasional (1-9% of recording) posterior alfa rhythms
Diffuse slowing	predominant diffuse theta or theta/ delta rhythms at amplitude ≥20 µV, without APG
Low-voltage	predominant EEG activity (theta or delta) <20 µV over most brain regions



Sensitivity= 0.91; Specificity= 0.54; Youden Index= 0.48

EEG background activity and reactivity differ between VS and MCS- or MCS+

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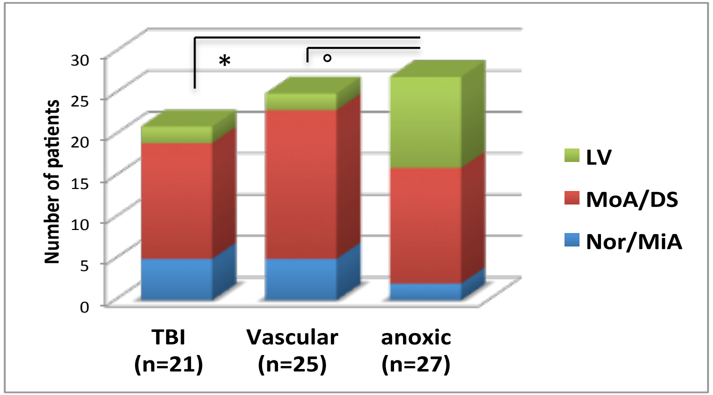
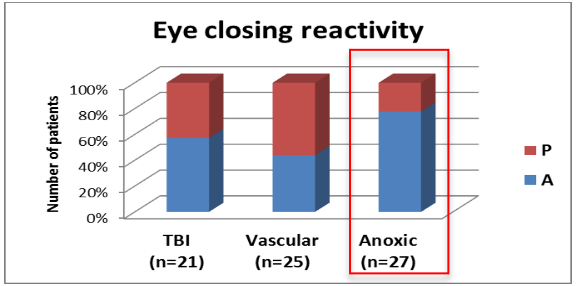
EEG findings in the 3 etiologies

EEG background activity and reactivity to eye opening and closing and to acoustic stimuli are more impaired in anoxic patients

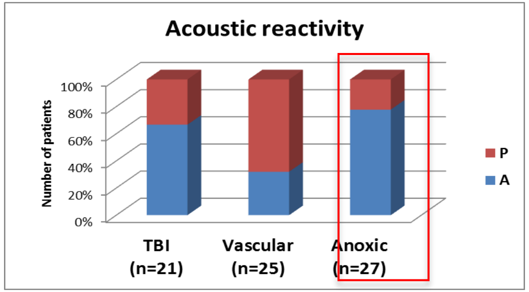
EEG and etiology



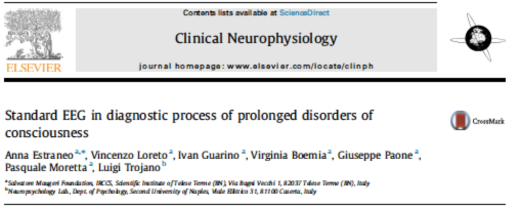
° Chi-square= 11.2, df= 2, p< .01
* Chi-square= 9.7, df= 2, p< .01



Chi square= 6.3, p< .043



Chi square= 11.97, p= .003



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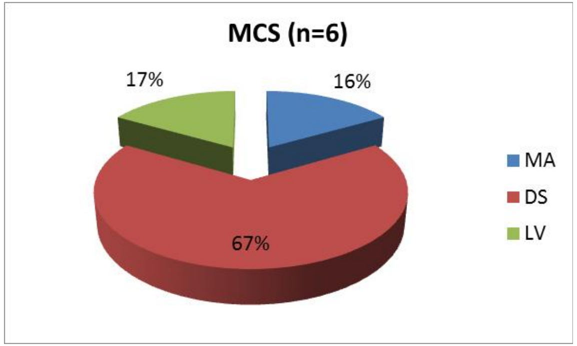
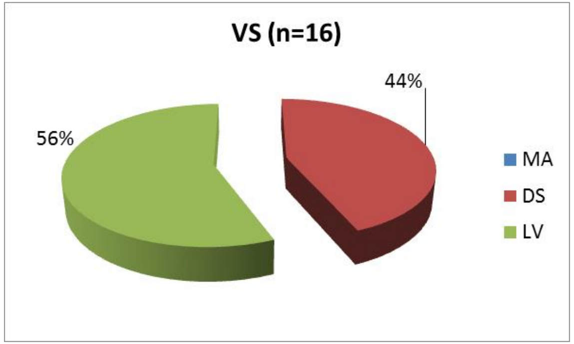
EEG findings
In prolonged DoC

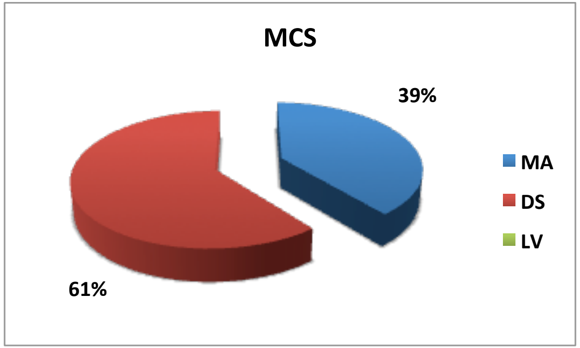
Anoxic (n= 22)

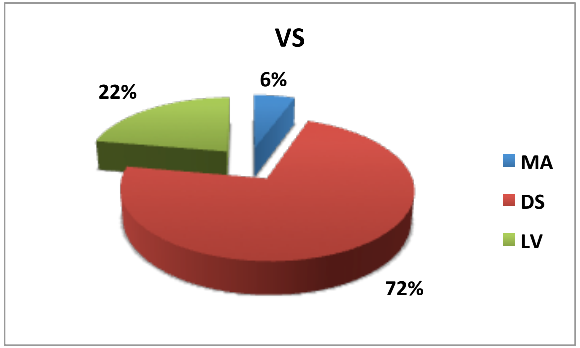




Chi square= 4.6, df= 2, p= .1

Non-Anoxic (n= 41)





Chi square= 9.98, df= 2, p= .007

EEG for identifying covert cognition

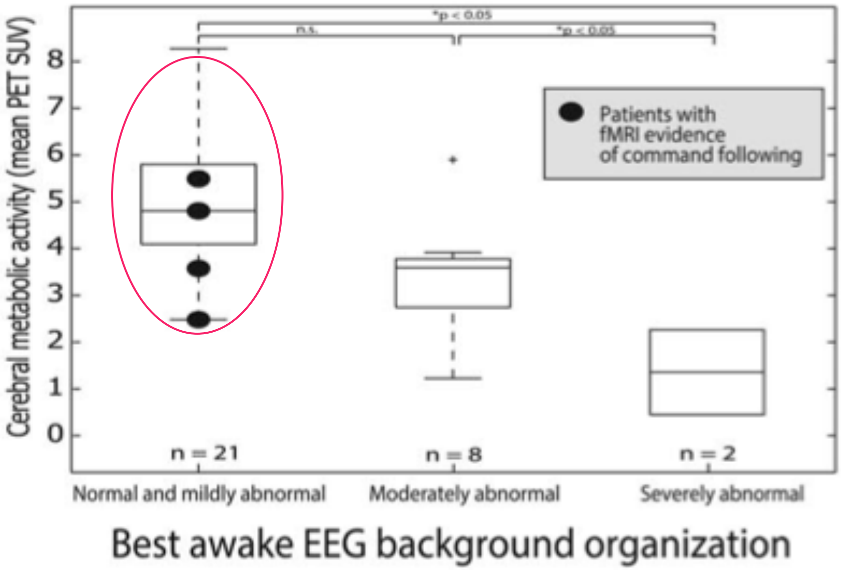
EEG classification (Forgacs et al., 2014):

1.Normal: dominant alpha rhythm, an amplitude difference <50% between hemispheres, with the expected AP gradient

2.Mildly abnormal: asymmetric or mildly slowed dominant rhythm (7-8Hz), not well organized AP gradient was, and/or mild degree of focal or hemispheric slowing

3. ***Moderately abnormal***: dominant theta (4–7Hz) posterior rhythms and/or focal or hemispheric theta/delta range

4. ***Severely abnormal***: dominant delta (<4Hz) over most of the brain areas



Forgacs et al, Ann Neur, 2014

Conventional visual assessment of EEG organization is an accurate **measure of overall brain integrity** and helps **to identify patients with covert cognition** by the presence of normal or near-normal EEG features.

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SPECIAL ARTICLE

AMERICAN ACADEMY OF NEUROLOGY.

Practice guideline update recommendations summary: Disorders of consciousness

In situations where there is continued ambiguity regarding evidence of conscious awareness despite serial neurobehavioral assessments, or where confounders to a valid clinical diagnostic assessment are identified, clinicians may use multimodal evaluations incorporating specialized functional imaging or electrophysiologic studies to assess for evidence of awareness not identified on neurobehavioral assessment that might prompt consideration of an alternate diagnosis (Level C based on assessment of benefit relative to harm, feasibility, and cost relative to benefit).

ean european academy of neurology

European Academy of Neurology guideline on the diagnosis of coma and other disorders of consciousness

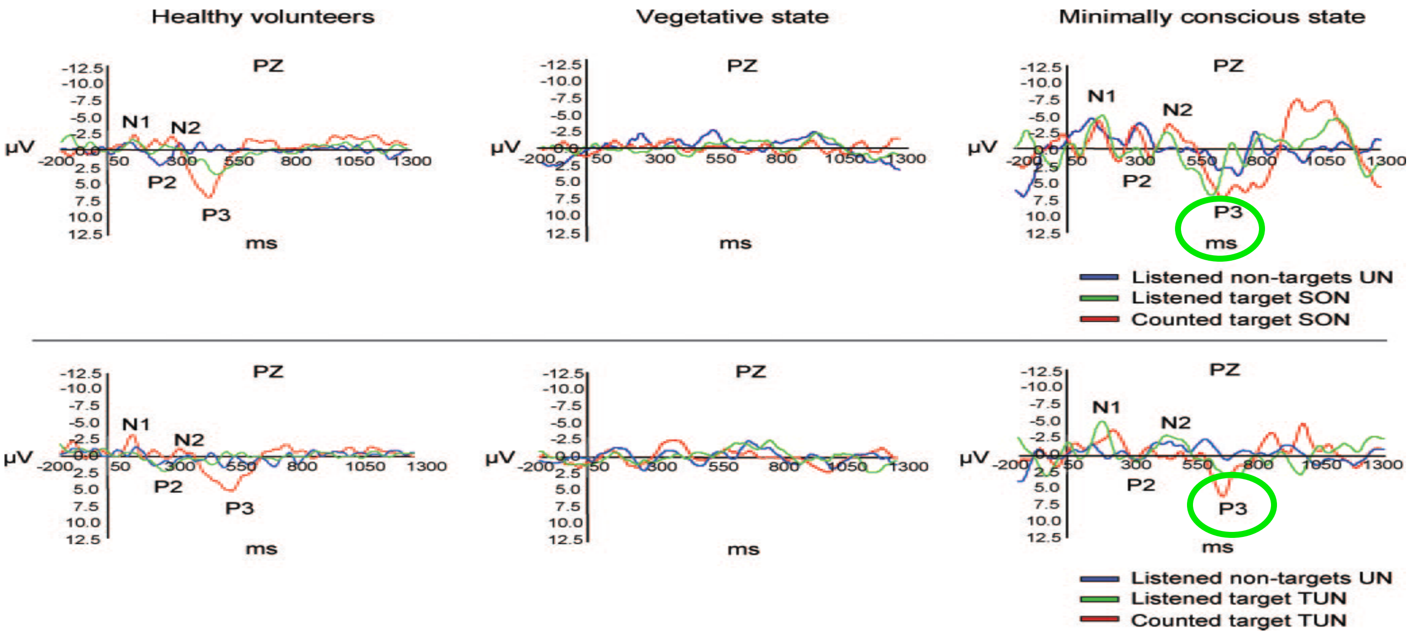
D. Kondziella[a,b,c], A. Bender[d,e], K. Diserens[f], W. van Erp[g,h], A. Estraneo[i,j], R. Formisano[k], S. Laureys[g], L. Naccache[l,m], S. Ozturk[n], B. Rohaut[l,m,o], J. D. Sitt[m], J. Stender[p], M. Tiainen[q], A. O. Rossetti[f,]*, O. Gosseries[g,]*, and C. Chatelle[g,r,]* on behalf of the EAN Panel on Coma, Disorders of Consciousness[†]

Paper=2; pts=117

Relative risk for detection of signs of covert consciousness with standard EEG as compared to clinical examination was **11.25** (95% CI 2.85-44.46; p=0.0006).

Visual analysis of clinical standard EEG may detect patients with preserved consciousness with high specificity but low sensitivity.

Diagnostic value of Event Related potentials



MCS patients presented a larger P3 to the patient's own name, in the passive and in the active conditions. The P3 to target stimuli was higher in the active than in the passive condition, suggesting voluntary compliance to task instructions like controls.

Schnakers,et al , Neurology, 2008

Published Ahead of Print on August 8, 2018 as 10.1212/WNL.0000000000005926
SPECIAL ARTICLE

AMERICAN ACADEMY OF NEUROLOGY

Practice guideline update recommendations summary: Disorders of consciousness

In situations where there is continued ambiguity regarding evidence of conscious awareness despite serial neurobehavioral assessments, or where confounders to a valid clinical diagnostic assessment are identified, clinicians may use multimodal evaluations incorporating specialized functional imaging or electrophysiologic studies to assess for evidence of awareness not identified on neurobehavioral assessment that might prompt consideration of an alternate diagnosis (Level C based on assessment of benefit relative to harm, feasibility, and cost relative to benefit).

ean european academy of neurology

European Academy of Neurology guideline on the diagnosis of coma and other disorders of consciousness

D. Kondziella[a,b,c], A. Bender[d,e], K. Diserens[f], W. van Erp[g,h], A. Estraneo[i,j], R. Formisano[k], S. Laureys[g], L. Naccache[l,m], S. Ozturk[n], B. Rohaut[l,m,o], J. D. Sitt[m], J. Stender[p], M. Tiainen[q], A. O. Rossetti[f,*], O. Gosseries[g,*], and C. Chatelle[g,r,*] on behalf of the EAN Panel on Coma, Disorders of Consciousness[†]

Paper=14; pts=1298

Relative risk for detection of signs of covert consciousness with ERP as compared to clinical examination was **1.49** (95% CI 1.27 to 1.75; $p < 0.0001$).

The sensitivity for all cognitive evoked potentials is low

regione campania aslnapoli3sud

Subgroup VS as function of neurophysiological data

Pat	Aetiology	Sex (M, F)	Age (years)	Time from coma onset (months)	CRS	PVS or MCS	SEP (1 normal, 2 reduced, 3 absent)	BAEP (1 normal, 2 delayed, 3 abnormal)	MLAEP (1 normal, 2 reduced, 3 absent)	N100 (Present)	MMN (Present)	nP3 (Present)	P3b (Present)
1	Anoxia	M	54	5	4	PVS	2	1	3	No	No	No	No
2	Anoxia	M	34	8	10	MCS	1	1	1	No	No	No	No
3	Anoxia	M	44	13	7	PVS	3	1	2	No	No	No	No
4	Anoxia	F	72	6	4	PVS	3	2	3	No	No	No	No
5	Anoxia	M	35	72	9	MCS	1	1	2	No	No	No	No
6	Anoxia	F	22	71	7	PVS	3	1	2	No	No	No	No
7	Anoxia	F	49	40	7	PVS	1	1	1	Yes	Yes	Yes	No
8	Anoxia	M	34	14	5	PVS	3	1	1	No	No	No	No
9	Anoxia	M	68	4	5	PVS	3	2	2	No	No	No	No
10	Anoxia	F	53	6	4	PVS	3	1	3	No	No	No	No
11	Anoxia	M	31	201	11	MCS	2	1	1	Yes	No	No	No
12	Anoxia	M	47	81	6	PVS	3	1	3	No	No	No	No
13	Anoxia	M	26	73	5	PVS	3	1	3	No	No	No	No
14	Anoxia	M	38	59	11	MCS	2	3	1	Yes	No	No	No
15	Anoxia	M	22	21	4	PVS	3	3	2	No	No	No	No
16	Anoxia	F	49	7	6	PVS	1	1	2	No	No	No	No
17	Anoxia	M	19	20	9	MCS	1	1		Yes	Yes	Yes	No
18	Anoxia	M	45	261	4	PVS	3	1	3	No	No	No	No
19	Encephalitis	M	48	13	11	MCS	1	1	1	Yes	Yes	Yes	No
20	TBI	M	24	15	7	PVS	2	2		Yes	No	Yes	Yes
21	TBI	M	52	37	10	MCS	1	1	1	No	No	No	No
22	TBI	F	44	59	9	MCS	1	1	1	Yes	No	Yes	No
23	TBI	M	48	12	11	MCS	2	3	1	Yes	No	No	No
24	Stroke	F	30	11	7	PVS	1	2	1	Yes	Yes	Yes	No
25	Stroke	M	56	8	14	MCS	1	2	1	Yes	Yes	Yes	Yes
26	Stroke	F	52	94	12	MCS	1	3	2	Yes	No	No	No
27	Stroke	F	49	11	5	PVS	1	1	1	Yes	No	No	No

1. **Authentic VS**
2. **Able to have sensations**
3. **Preserved island of cognition**

Fischer, et al 2010

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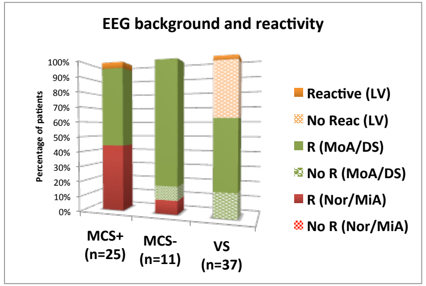
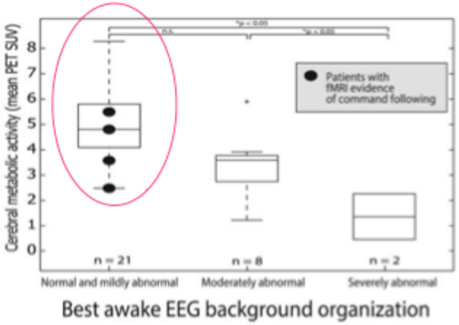
Practice guideline update recommendations summary: Disorders of consciousness

2e In situations where there is continued ambiguity regarding evidence of conscious awareness despite serial neurobehavioral assessments, or where confounders to a valid clinical diagnostic assessment are identified, clinicians may use multimodal evaluations incorporating specialized functional imaging or electrophysiologic studies to assess for evidence of awareness not identified on neurobehavioral assessment that might prompt consideration of an alternate diagnosis (Level C based on assessment of benefit relative to harm, feasibility, and cost relative to benefit).

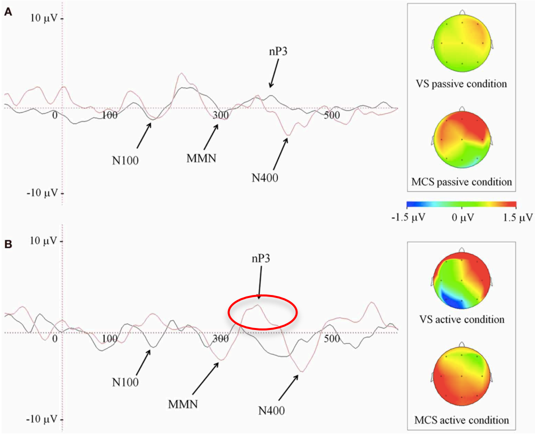


Estraneo et al., Clin Neuroph. 2016



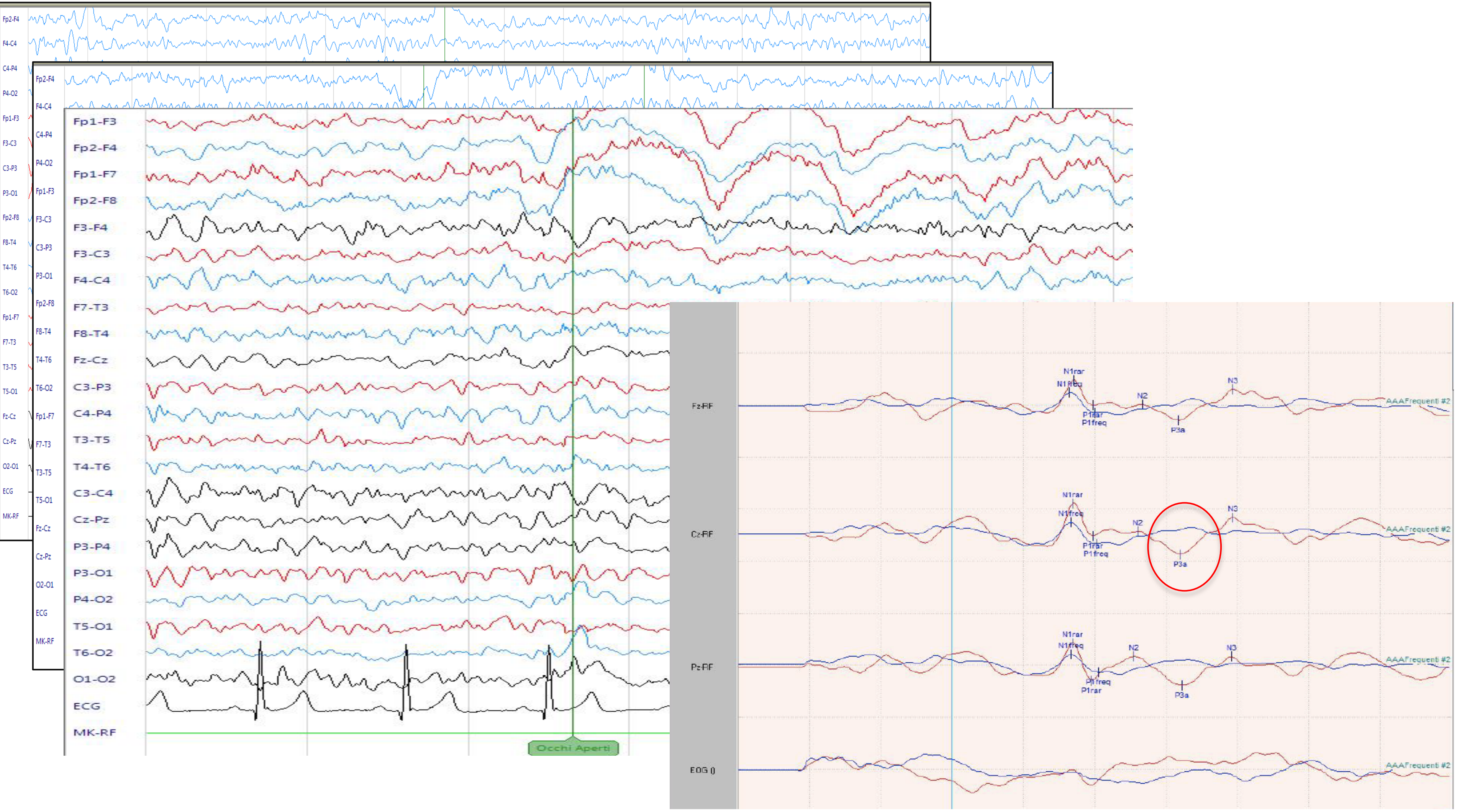
Forgacs et al, Ann Neur, 2014

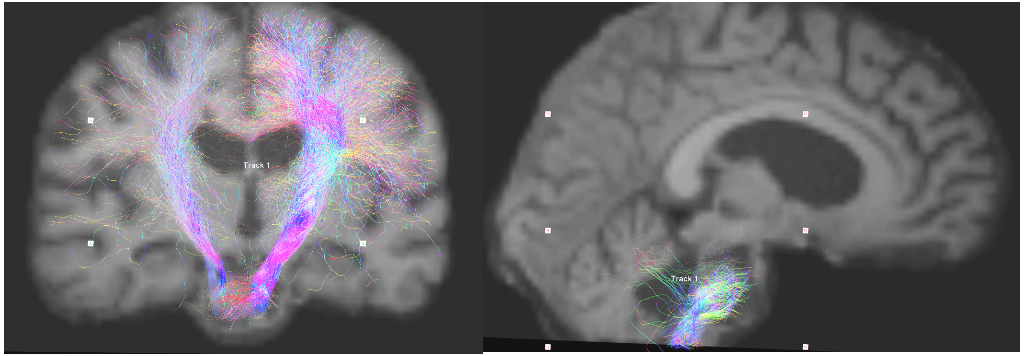
Active listening of patients'own name (nP3) in MCS

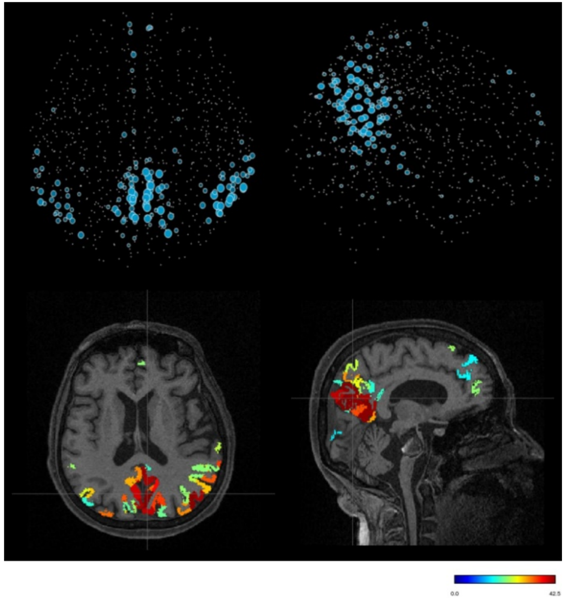


Risetti et al, 2010

- 36-year-old woman
- severe haemorragic stroke
- 5 mos post injury
- **CRS-R = 4 (VS)**


Fp1-F3
Fp2-F4
Fp1-F7
Fp2-F8
F3-F4
F3-C3
F4-C4
F7-T3
F8-T4
Fz-Cz
C3-P3
C4-P4
T3-T5
T4-T6
C3-C4
Cz-Pz
P3-P4
P3-O1
P4-O2
T5-O1
T6-O2
O1-O2
ECG
MK-RF
Occhi Aperti
Fz-RF
Cz-RF
Pz-RF
EOG ()
N1rar
N1freq
P1rar
P1freq
N2
P3a
N3
AAAFrequenti #2





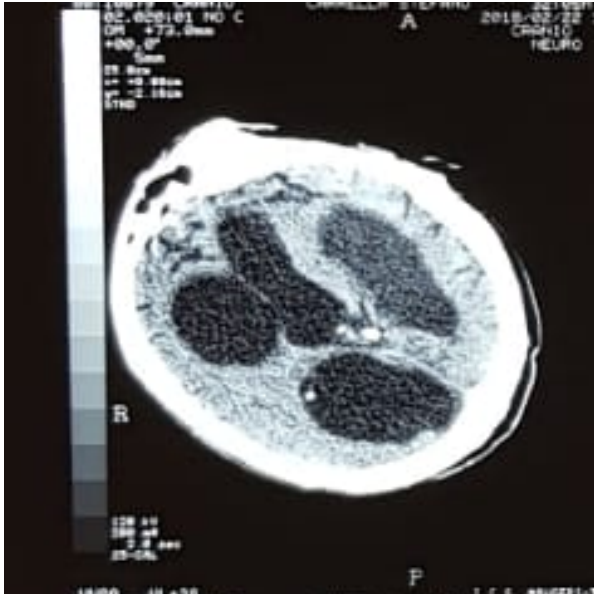
Locked-in syndrome
Clinical variants

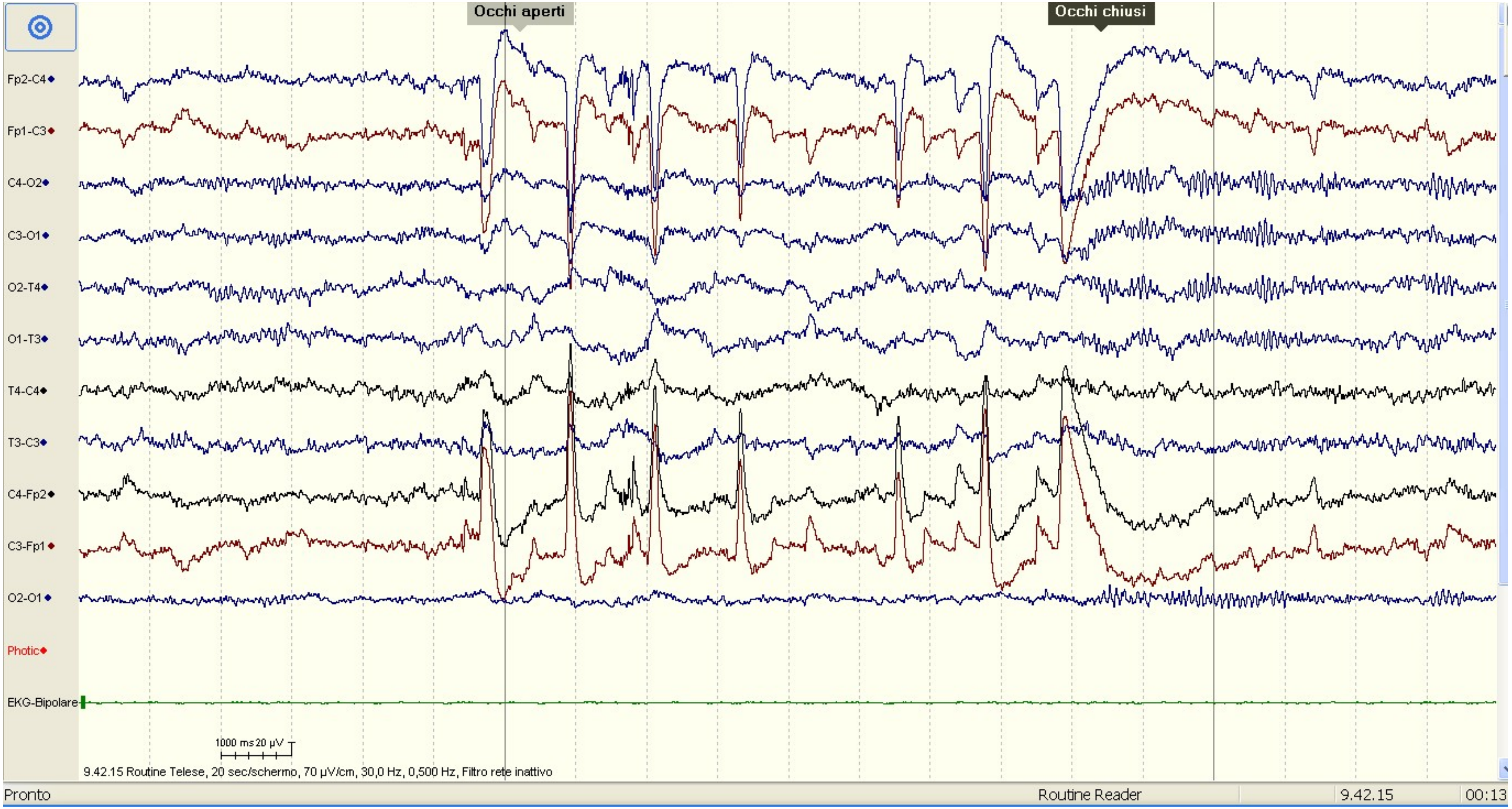
- Classical LIS: quadriplegia, anarthria, full consciousness, preserved vertical eye movements
- Incomplete LIS: variable residual intentional movements
- Total LIS: lack of any intentional response, full recovery of consciousness

Bauer et al., 1979

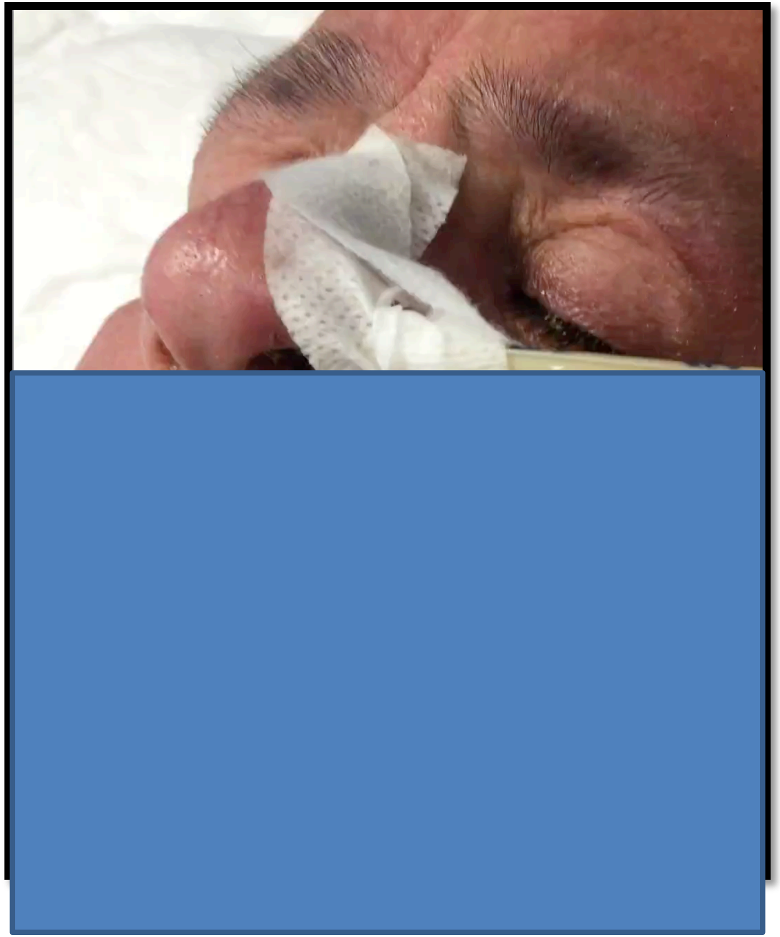
- 27-year-old man
- severe traumatic brain injury
- 23 mos after TBI

Chronic VS ?

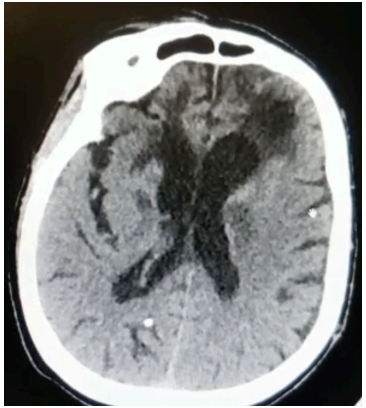




Chronic eMCS !



- ✓ 60-year-old man
- ✓ Epilepsy from age 4
- ✓ convulsive status epilepticus
- ✓ 21 days after SE



TC: 0,1 sec; Fh: 30 Hz; Notch: 50 Hz; 20 s/pg 1

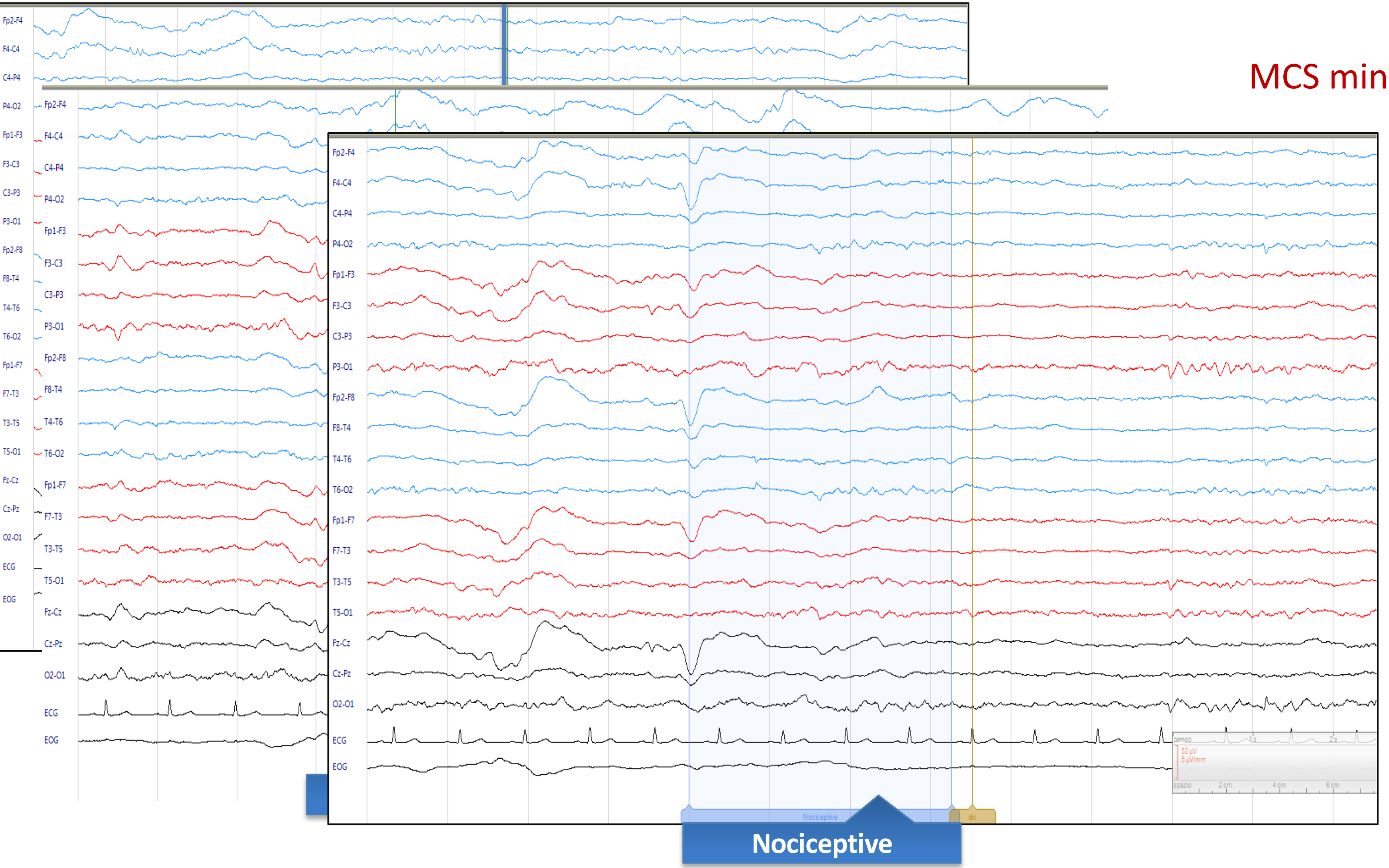
28/10/2021 11:07:26 SDT EEG

TC: 0,1 sec; Fh: 30 Hz; Notch: 50 Hz; 20 s/pg 1

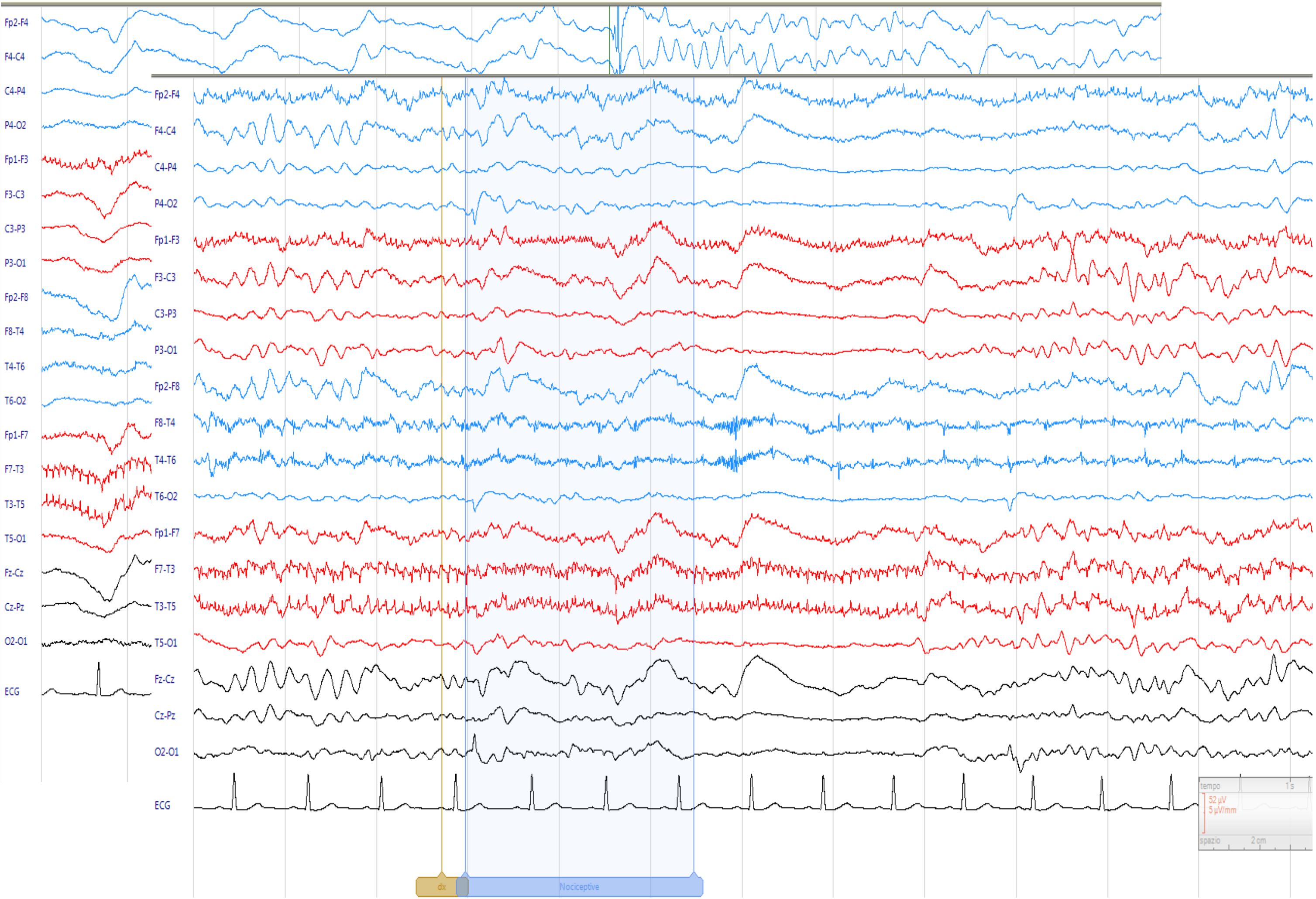
TC: 0,1 sec; Fh: 30 Hz; Notch: 50 Hz; 20 s/pg 1

28/10/2021 11:07:26 SDT EEG

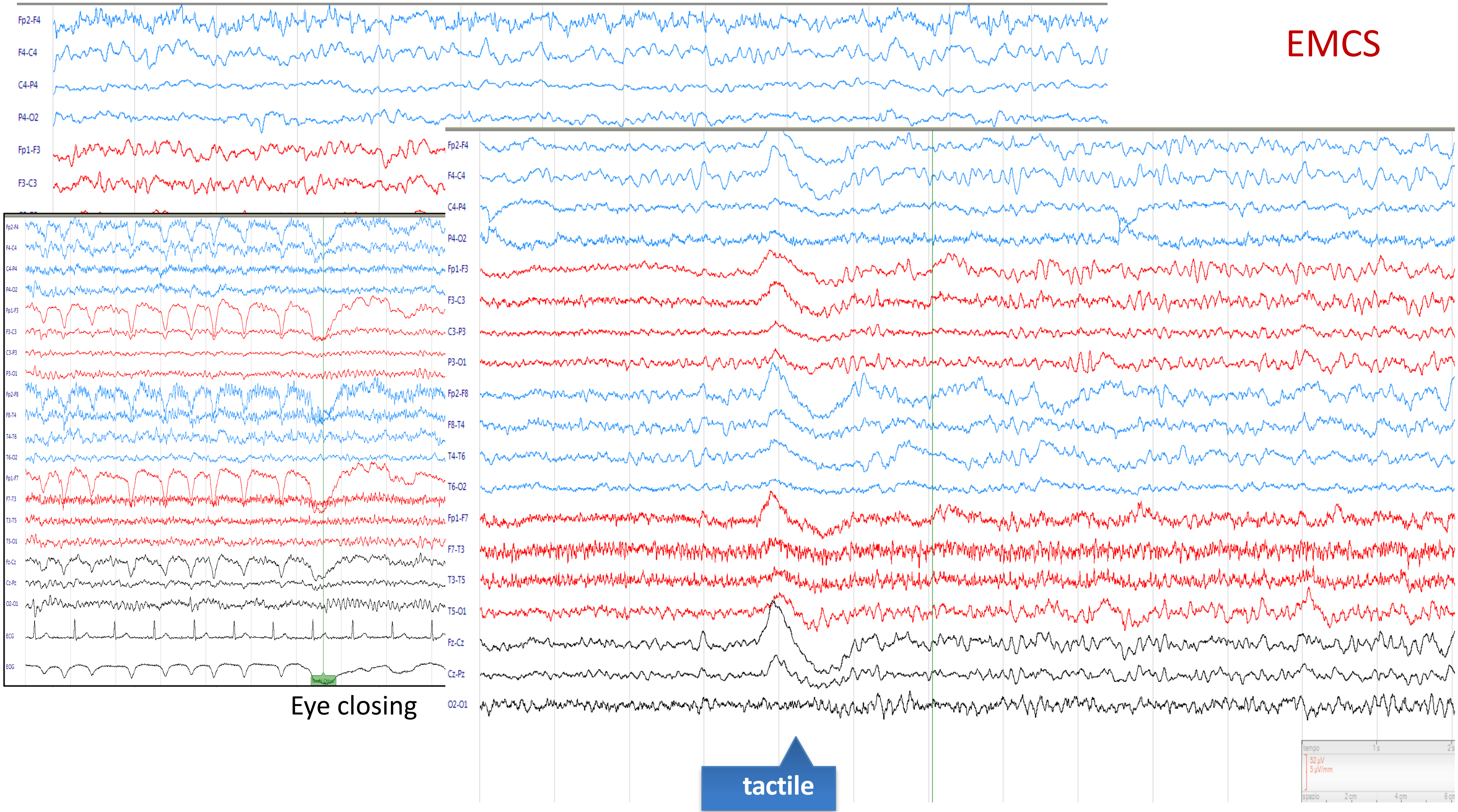
MCS minus



MCS plus


Fp2-F4
F4-C4
C4-P4
P4-O2
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp2-F8
F8-T4
T4-T6
T6-O2
Fp1-F7
F7-T3
T3-T5
T5-O1
Fz-Cz
Cz-Pz
O2-O1
ECG
dx
Nociceptive
tempo
1 s
52 µV
5 µV/mm
spazio
2 cm

EMCS


Fp2-F4
F4-C4
C4-P4
P4-O2
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp2-F8
F8-T4
T4-T6
T6-O2
Fp1-F7
F7-T3
T3-T5
T5-O1
Fz-Cz
Cz-Pz
O2-O1
ECG
EOG
Eye closing
tactile
tempo
1 s
2 s
52 µV
5 µV/mm
spazio
2 cm
4 cm
6 cm

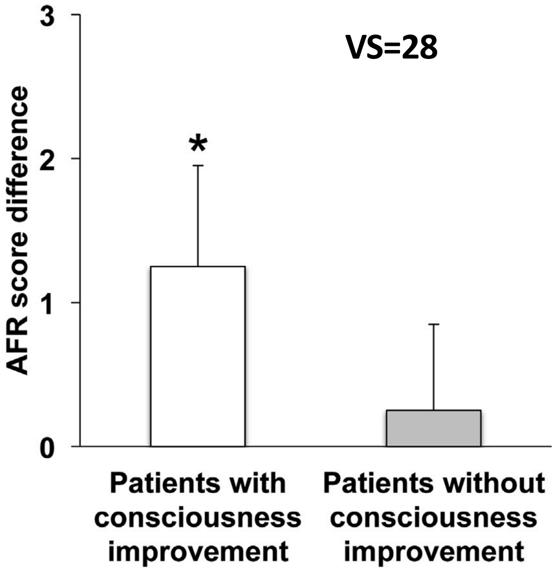
ACRM
AMERICAN CONGRESS OF REHABILITATION MEDICINE
Archives of Physical Medicine and Rehabilitation
journal homepage: www.archives-pmr.org
Archives of Physical Medicine and Rehabilitation 2017;98:665-72

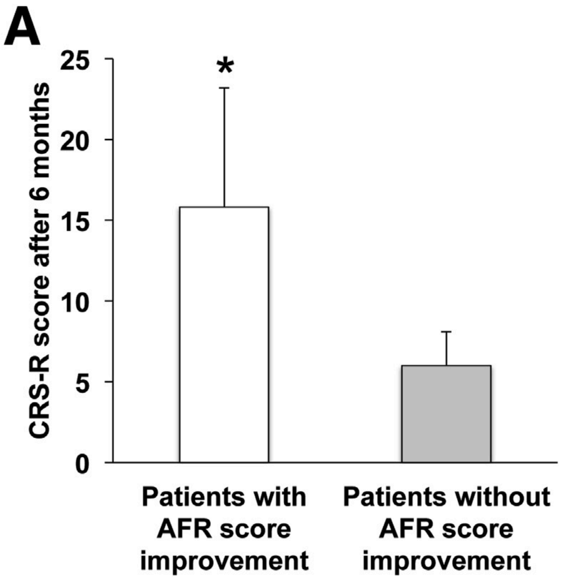
ORIGINAL RESEARCH

Changes in Standard Electroencephalograms Parallel Consciousness Improvements in Patients With Unresponsive Wakefulness Syndrome

Sergio Bagnato, MD, PhD,[a] Cristina Boccagni, MD,[a] Caterina Prestandrea, NphT,[a] Alexander A. Fingelkurts, PhD,[b] Andrew A. Fingelkurts, PhD,[b] Giuseppe Galardi, MD[a]

The transition from the theta to the alpha band was the most common frequency change in patients who recovered consciousness



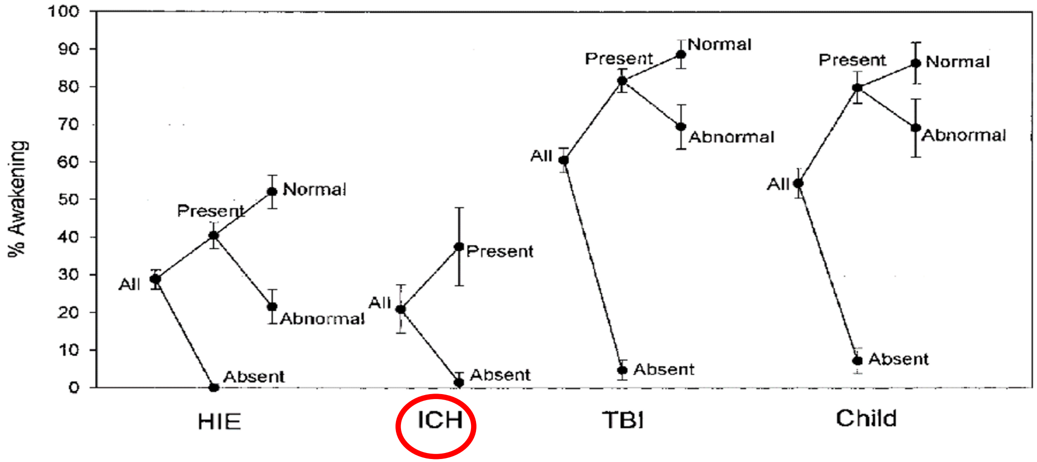


AFR= cumulative Amplitude-Frequency-Reactivity score

EEG in VS and MCS

- Which patient
- EEG and PE in clinical diagnosis
- EEG and PE in prognostication
- EEG and seizure

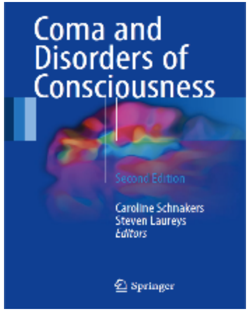
Prognostic value of SEP



Robinsons et al., 2005

Most available (neurophysiological) prognostic markers are collected in comatose state

Despite their clear utility, these simple measures are rarely recorded in most Intensive Care Units



Estraneo et. Al., Prognosis in DoC., In: Coma and DoC. 2018

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SPECIAL ARTICLE

AMERICAN ACADEMY OF NEUROLOGY

Practice guideline update recommendations summary: Disorders of consciousness

Nontraumatic, postanoxic VS/UWS: Clinicians should perform the CRS-R (Level B) and may assess SEPs (Level C based on feasibility) to assist in prognostication regarding recovery of consciousness at 24 months for patients in nontraumatic postanoxic VS/UWS.

Anna Estraneo, MD
Pasquale Moretta, PsyD
Vincenzo Loreto, MD
Bernardo Lanzillo, MD
Autilia Cozzolino, MD
Annamaria Saltalamacchia, NphT
Francesco Lullo, NphT
Lucio Santoro, MD
Luigi Trojano, MD

Predictors of recovery of responsiveness in prolonged anoxic vegetative state

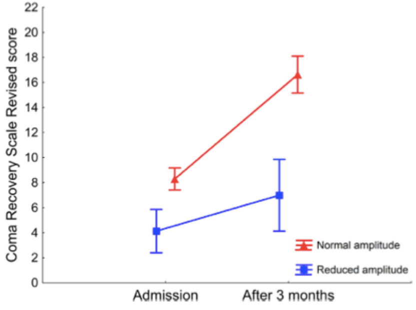
Neurology 2013;80:464–470

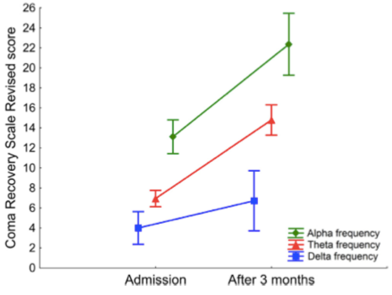
	reference	Odds-ratio	Lower 95%CI	Upper 95%CI	P
Age	≤50 years	.96	.65	1.06	.425
CRS-R	≥ 6	4.61	1.05	11643.58	.042
DRS	<25	0.69	.09	4.05	.585
PSH	Present	1.29	.02	972.17	.921
SEP	Present	17.88	1.37	6511.41	.026

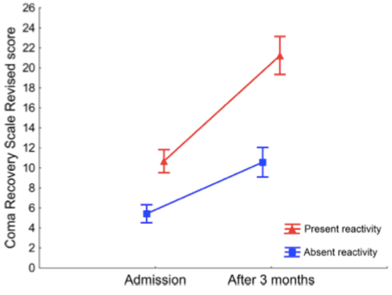
Estraneo et al. Neurology 2013

Prognostic value of EEG in prolonged DOC

n=106 traumatic, vascular, anoxic DoC (59 VS, 47 MCS). Outcome at 3 months







Reduced amplitudes => less improvement in CRS-R scores at 3 mos.

Delta, theta, and alpha frequencies => least, intermediate, and the greatest improvement in CRS-R scores, respectively.

EEG reactivity => greater improvements in CRS-R scores (*Bagnato, 2014*)

Prognostic value of EEG in prolonged DOC

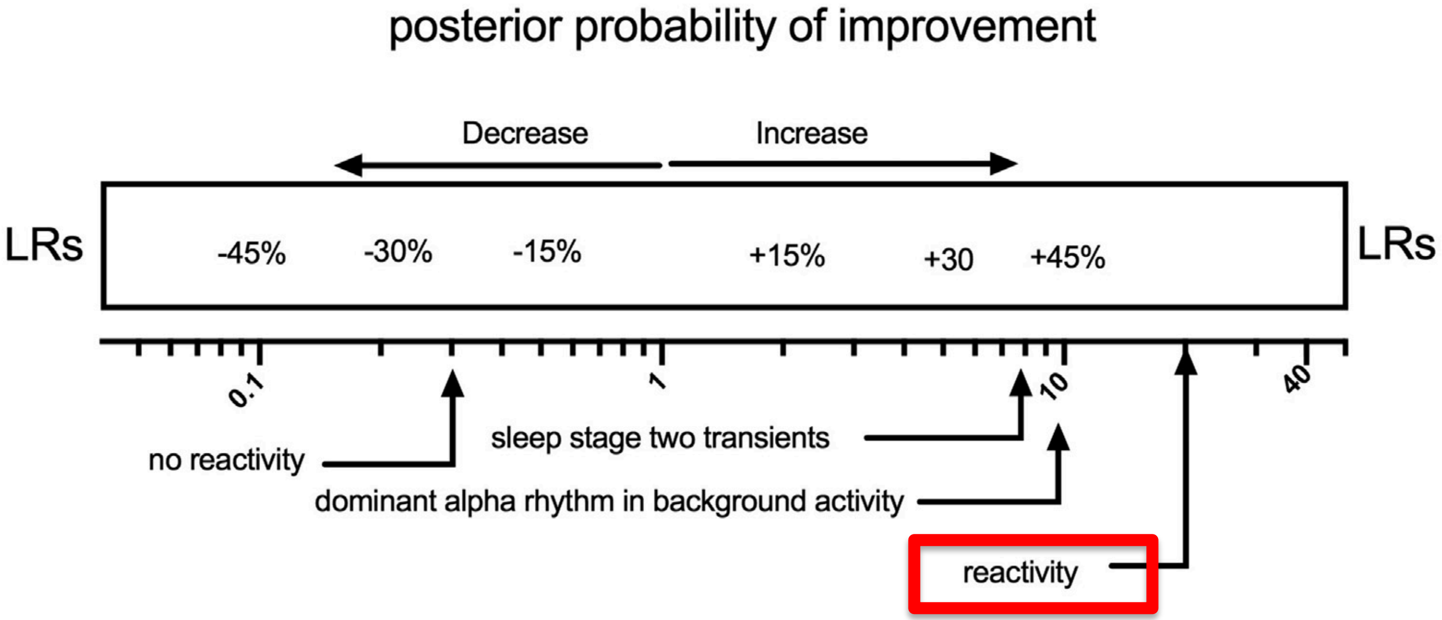
EEG parameters adapted from the American Clinical Neurophysiology Society's standardized critical care EEG Terminology, 2012

Background EEG				
Predominant background Frequency	**Beta** Frequencies >1β Hz	**Alpha** Ranges from 8 to 13 Hz	**Theta** Ranges from 4 to <8Hz	**Delta** Refers to frequencies <4 Hz
Voltage	**Normal** All activity >20 uV, measured in longitudinal bipolar with standard 10–20 electrodes from peak to trough	**Low Voltage** Most or all activity <20 uV measured in longitudinal bipolar with standard 10–20 electrodes from peak to trough (Attenuation refers to low voltage EEG but with most or all >10 uV)	**Suppression** Refers to all activity<10 uV >2uV	**Isoelectric** All activity 2 uV. No activity of brain origin is detectable at a sensitivity of 2 uV/mm: electrocerebral silence
Continuity	**Continuous** Normal or low-voltage EEG activity	**Nearly continuous** Refers to continuous EEG activity, but with occasional (<10% of the record) periods of attenuation (>10 uV) or suppression (<10 uV)	**Discontinuous** 10% to 49% of the record consisting of attenuation or suppression, as defined above	**Burst attenuation or Burst-suppression** >50% of the record consisting of attenuation or suppression, as defined above, with bursts alternating with attenuation or suppression
Reactivity	**Reactive** Change in cerebral EEG activity to intense auditory and/or noxious stimuli. This may include change in amplitude or frequency, including attenuation of activity. If the only form of reactivity is stimuli induced rhythmic or periodic discharges or appearance of only muscle activity or eye blink artifacts, does not qualify as reactive	**Non Reactive** No change in cerebral EEG activity after intense auditory and painful stimuli		

Scarpino et al., 2019

Prognostic value of EEG in prolonged DOC

N=102 DoC (61 VS, 41 MCS). Outcome: 6 mos after brain injury



EEG reactivity, alpha rhythm and presence of stage II sleep pattern => greater improvements in clinical diagnosis in VS patients only (*Scarpino et al, 2019*)

Prognostic value of EEG in prolonged DOC

EEG parameters adapted from the American Clinical Neurophysiology Society's standardized critical care EEG Terminology, 2012

Pattern	Prognostic value	score
Delta, Epileptic Dis, absence of reactivity and variability	Poor prognosis	0
Presence/Absence of APG, theta, A of II sleep patterns, A of Ep Dis, any item of EEG voltage, continuity and symmetry	No significant prognosis	1
alpha, Presence of EEG stage II sleep patterns, Presence of reactivity and variability).	Good prognosis	2

Scarpino et al., 2020

ARTICLE OPEN ACCESS

Multicenter prospective study on predictors of short-term outcome in disorders of consciousness

Anna Estraneo, MD, Salvatore Fiorenza, NphT, Alfonso Magliacano, PsyD, Rita Formisano, MD, Donatella Mattia, MD, PhD, Antonello Grippo, MD, Anna Maria Romoli, MD, Efthymios Angelakis, MD, Helena Cassol, MD, Aurore Thibaut, PhD, Olivia Gosseries, PhD, Gianfranco Lamberti, MD, Enrique Noé, MD, PhD, Sergio Bagnato, MD, PhD, Brian L. Edlow, MD, Camille Chatelle, PhD, Nicolas Lejeune, MD, Vigneswaran Veeramuthu, PhD, Michelangelo Bartolo, MD, PhD, Jlenia Toppi, PhD, Nathan Zasler, MD, Caroline Schnakers, PhD, and Luigi Trojano, MD, on behalf of IBIA DoC-SIG

Correspondence
Dr. Estraneo
aestraneo@gmail.com

Neurology® 2020;95:e1488-e1499. doi:10.1212/WNL.0000000000010254

Predictors of good clinical outcome at 6 months

IBIA DoCMA

DoC = 135; VS = 68; MCS = 67

Factor	Reference	β	OR	LCI 95%	UCI 95%	*p*	Bootstrapped-*p*	LASSO β
Age		**-1.32**	.26	.12	.54	**< .001**	**< .001**	**-.81**
Gender (M)	F	.85	2.35	.85	6.45	.09	.14	.60
Etiology (TBI)	Non-TBI	-.46	.62	.17	2.18	.46	.51	0
Time post injury		**-1.30**	.27	.14	.50	**< .001**	**< .001**	**-.85**
Diagnosis (MCS)	VS/UWS	-1.02	.36	.07	1.79	.21	.31	0
CRS-R		**1.29**	3.64	1.27	10.45	**.01**	**.04**	**.58**
DRS		-.35	.70	.37	1.32	.27	.34	-.17
EEG Background (Alpha)	Slow	.16	1.18	.41	3.36	.75	.75	.16
EEG-R Eye (Present)	Absent	**1.65**	5.21	1.45	18.75	**.01**	**.02**	**1.15**
EEG-R Acoustic (Present)	Absent	.92	2.51	.76	8.24	.12	.17	.57

Lower age, shorter time post-injury, higher CRS-R total score and presence of EEG eye opening reactivity predict better outcome (VS>MCS, VS or MCS to full consciousness)

IBIA DoCMA

Predictors of consciousness recovery at 24 months

DoC = 134; VS = 66 (24 improved); MCS = 68 (47 improved)

Factor	Reference	β	OR	LCI 95%	UCI 95%	*p*	Bootstrapped-*p*	LASSO β
Age		**-1.71**	**.18**	.08	.42	**<.001**	**.001**	**-0.05**
Gender (M)	F	**1.42**	**4.15**	1.26	13.60	**.02**	**.02**	**0.96**
Etiology (TBI)	Non-TBI	-.79	.45	.12	1.77	.26	.24	0
Time post-injury		**-1.50**	**.22**	.11	.47	**<.001**	**.001**	**-0.04**
Diagnosis (MCS)	VS/UWS	-1.04	.35	.06	2.08	.22	.29	0
CRS-R		**1.55**	**4.72**	1.38	16.17	**.01**	**.01**	**0.17**
NCS-R		.23	1.26	.70	2.26	.44	.47	0.02
DRS		-.49	.61	.30	1.24	.17	.25	-0.09
EEG Background (Alpha)	Slow	1.16	3.18	1.00	10.09	.05	.05	0.89
EEG-R Eye (Present)	Absent	**1.49**	**4.46**	1.18	16.83	**.03**	**.03**	**0.88**

Lower age, male gender, shorter time post-injury, higher CRS-R total score and presence of EEG eye opening reactivity predict better outcome (VS>MCS, VS or MCS to full consciousness)

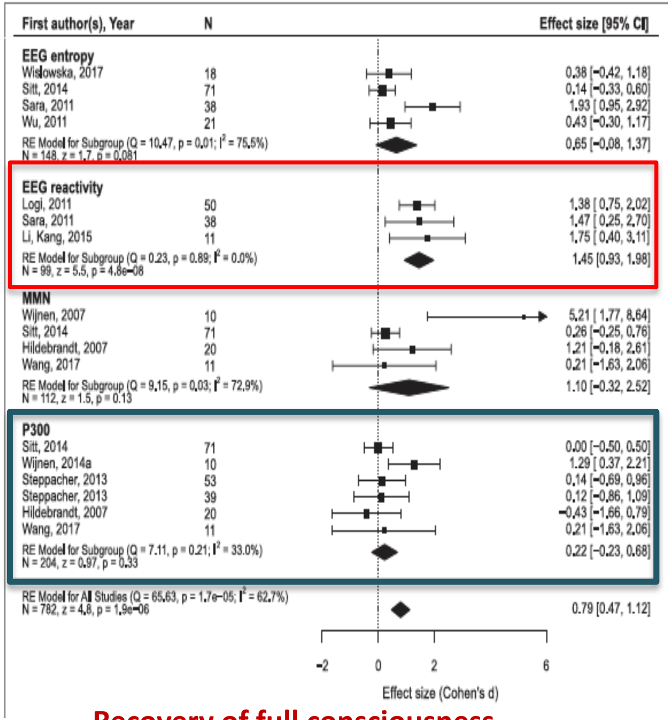
unpublished data-do not copy or distribute

frontiers in Neurology

EEG reactivity predicts minimal and full recovery of consciousness

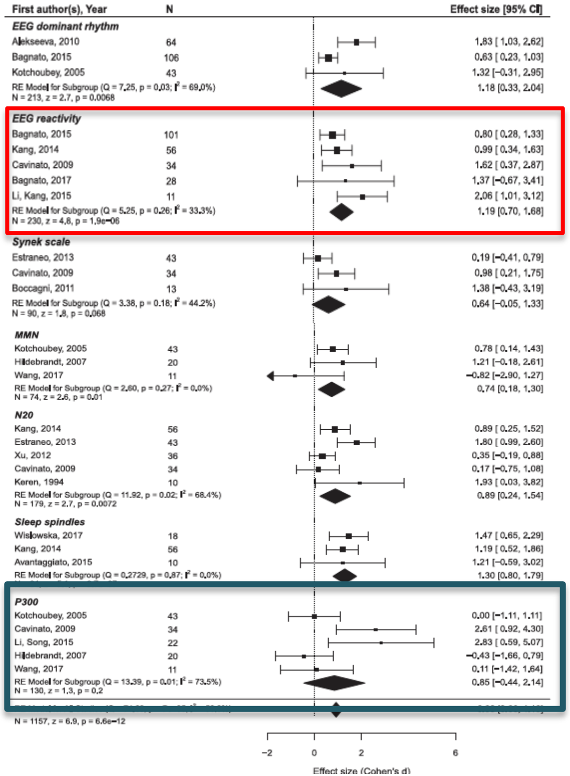
A Systematic Review and Meta-Analysis of the Relationship Between Brain Data and the Outcome in Disorders of Consciousness

Boris Kotchoubey[1] and Yuri G. Pavlov[1,2]*



Recovery of full consciousness

in VS and MCS



Minimal clinical improvement

VS =>MCS, MCS => EMCS

Received: 6 August 2021 | Accepted: 11 October 2021
DOI: 10.1111/ene.15143

european journal of neurology

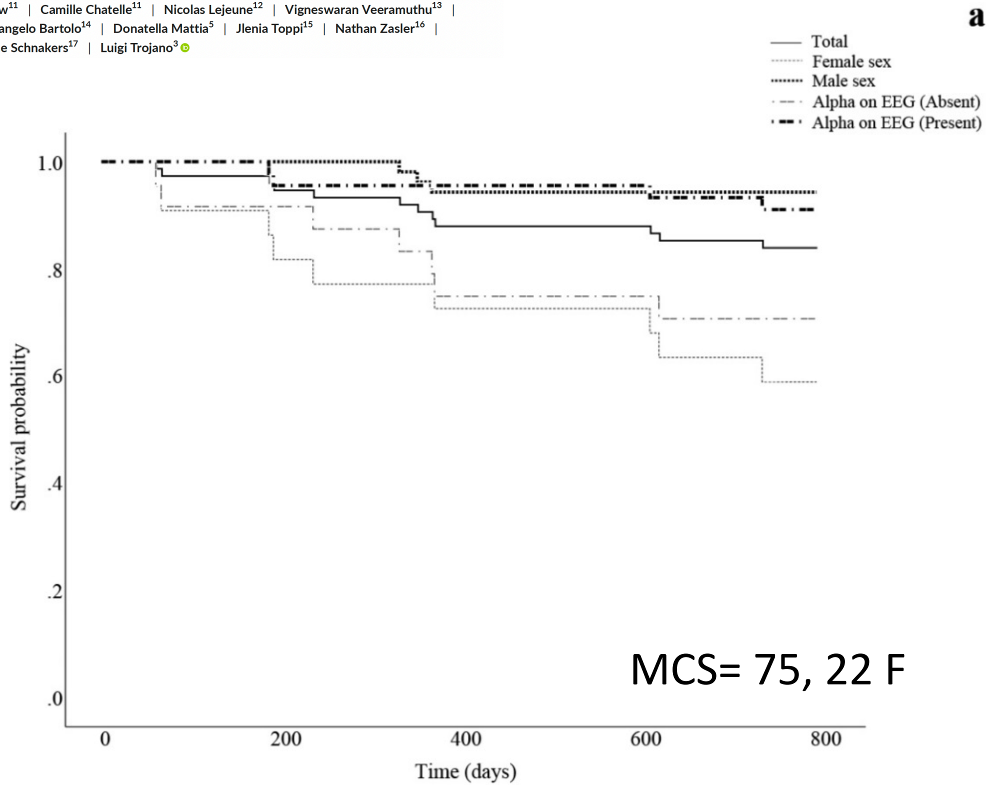
ORIGINAL ARTICLE

Risk factors for 2-year mortality in patients with prolonged disorders of consciousness: An international multicentre study

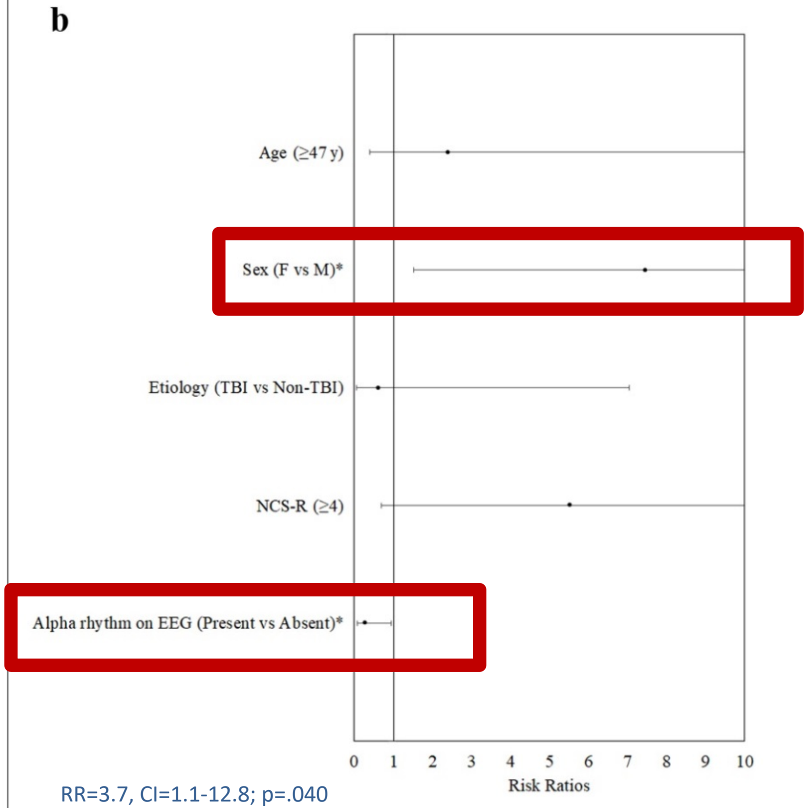
Anna Estraneo[1,2] | Alfonso Magliacano[1,3] | Salvatore Fiorenza[4] | Rita Formisano[5] | Antonello Grippo[1] | Efthymios Angelakis[6] | Helena Cassol[7] | Aurore Thibaut[7] | Olivia Gosseries[7] | Gianfranco Lamberti[8] | Enrique Noé[9] | Sergio Bagnato[10] | Brian L. Edlow[11] | Camille Chatelle[11] | Nicolas Lejeune[12] | Vigneswaran Veeramuthu[13] | Michelangelo Bartolo[14] | Donatella Mattia[5] | Jlenia Toppi[15] | Nathan Zasler[16] | Caroline Schnakers[17] | Luigi Trojano[3]

IBIA DoCMA

Survival curves and predictors in the MCS



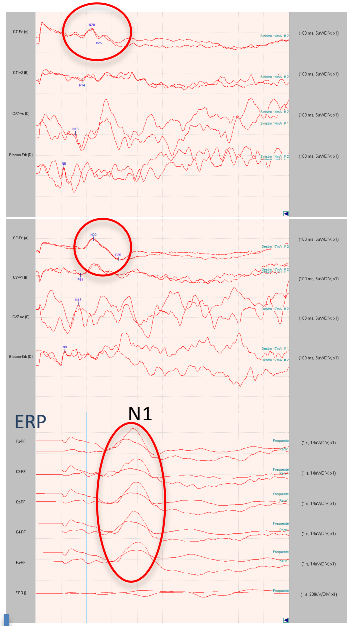
MCS= 75, 22 F



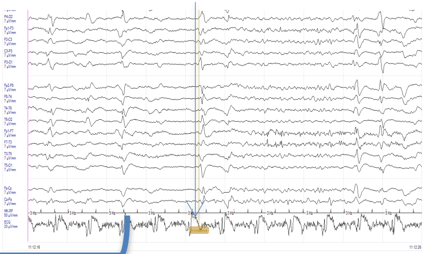
RR=3.7, CI=1.1-12.8; p=.040

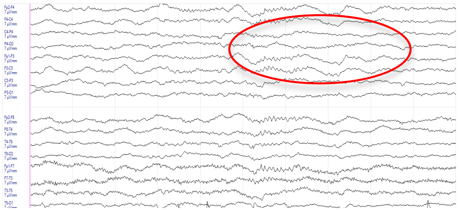
Prognostic value of Neurophysiology

SEP



Diffuse slowing: predominant diffuse theta ≥20 µV, reactivity to acoustic stimuli (with residual G-PEDS)





Mildly abnormal predominant posterior theta activity (≥20 µV), with frequent (10-49%) posterior alfa rhythms

Anoxic VS/UWS

MCS

Dec, 2016
(20 days post onset)

March, 2017

From Grippo Antonello

EEG in VS and MCS

- Which patient
- EEG and PE in clinical diagnosis
- EEG and PE in prognostication
- EEG and seizure

Epileptic seizures in acquired brain injury

Acute symptomatic seizure

- occur in close temporal relationship with acute brain insult (i.e. within 1 week after an acquired brain injury);
- due to a temporary lowering of epileptic threshold resulting from such acute cerebral insult;
- are not necessarily characterized by a tendency for recurrence, but their occurrence is generally associated with a poor outcome (higher mortality at 30 days)

40-52 % of pts with acute seizure experience a late unprovoked seizures (Berg, 1991)

Remote symptomatic seizure

- developed after one week from brain injury;
- in absence of a potentially responsible clinical conditions (*unprovoked seizures*);
- depend on a structural chronic changes (e.g. gliosis) of the brain

Hesdoffer, 2009; Beghi 2010

Brain Injury

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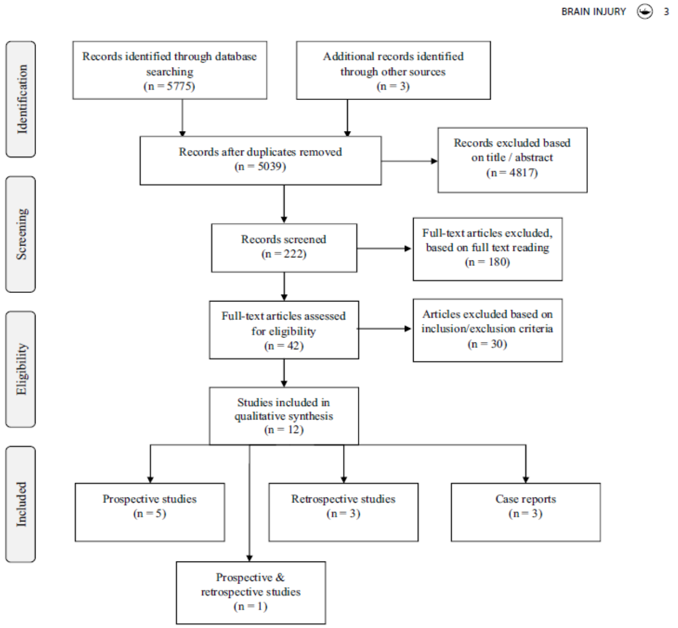
Epilepsy in prolonged disorders of consciousness: a systematic review

Nicolas Lejeune, Nathan Zasler, Rita Formisano, Anna Estraneo, Olivier Bodart, Wendy L. Magee & Aurore Thibaut



Epilepsy in prolonged DoC

- ✓ The occurrence of ES/PTE and EA in pDoC was poorly and inconsistently reported
- ✓ No conclusive data on
  - ✓ the effects of ASMs on recovery
  - ✓ the influence of any therapeutic interventions for consciousness recovery on seizure occurrence.

J Neurol (2016) 263:2048–2056
DOI 10.1007/s00415-016-8232-y

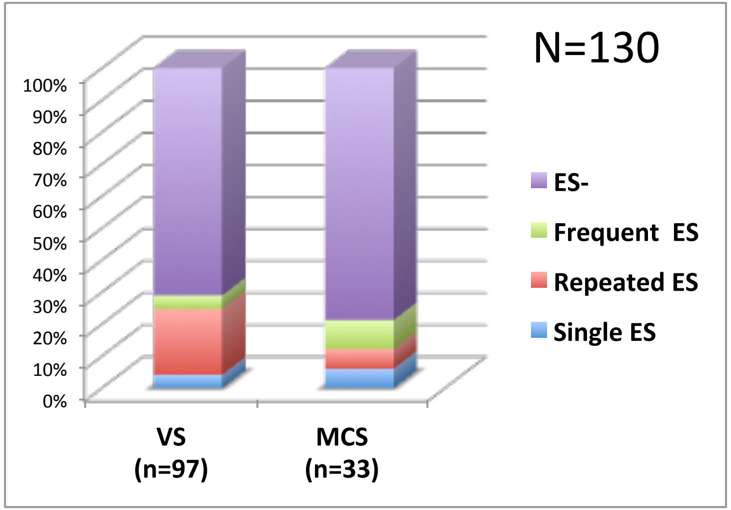
ORIGINAL COMMUNICATION

Long-term outcome of patients with disorders of consciousness with and without epileptiform activity and seizures: a prospective single centre cohort study

Angelo Pascarella[1] · Luigi Trojano[2] · Vincenzo Loreto[1] · Leonilda Bilo[3] · Pasquale Moretta[1] · Anna Estraneo[1]

Epileptic seizure as a function of clinical diagnosis and etiology

ES in **26.9%** DOC pts, without significant differences in the clinical diagnosis or etiology



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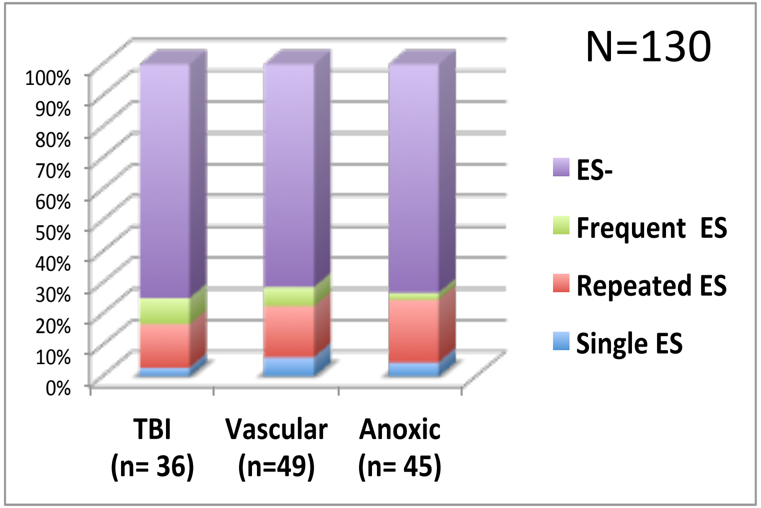

(chi-square <1)

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ORIGINAL COMMUNICATION

EA as a function of clinical diagnosis and etiology

Long-term outcome of patients with disorders of consciousness with and without epileptiform activity and seizures: a prospective single centre cohort study

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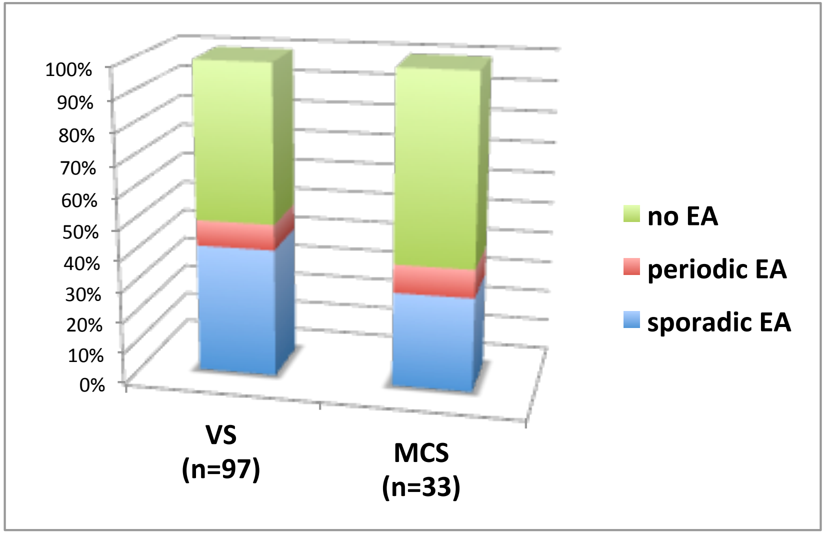
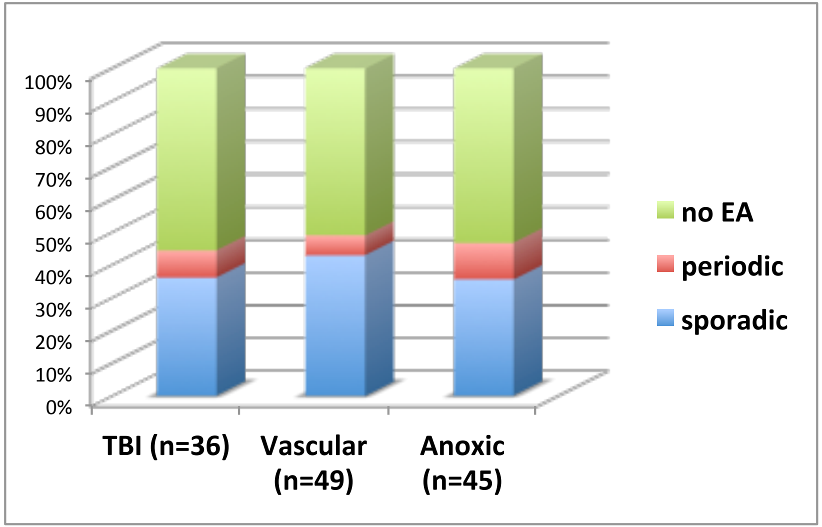
EA in **46.9%** of DOC pts, without significant differences in the clinical diagnosis or etiology





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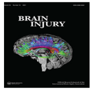

Brain Injury

Taylor & Francis

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Interictal epileptic activity categorization *(Hirsh, 2011)*

SPORADIC EA	
Generalized	bilateral, bisynchronous and symmetric pattern
Lateralized	unilateral and bilateral synchronous but asymmetric; includes focal, regional and hemispheric patterns
Bilateral independent	presence of 2 independent [asynchronous] lateralized patterns, one in each hemisphere
Multifocal	presence of at least three independent lateralized patterns with at least one in each hemisphere
PERIODIC PATTERN	
PLEDs biPLEDs GPEDs	Periodic lateralized epileptiform discharges Periodic bilateral epileptiform discharges Periodic generalized epileptiform discharges

SPORADIC EA FREQUENCY	
Abundant	≥ 1/10 seconds of EEG recording
Frequent	≥ 1/minute but < 1/10 seconds of EEG recording
Occasional	>1/30 minutes but < 1/minute of EEG recording
Rare	=1/30 minutes of EEG recording

EA recorded in at least one of two EEG whitin 15 days from admission

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CrossMark

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Epileptic activity in prolonged DoC

N=130

EA	*Total*	*Clinical diagnosis*		*Etiology*		
		VS	*MCS*	*TBI*	*Vascular*	*Anoxia*
N	61	48	13	16	24	21
Sporadic EA	50 (82.0)	40 (83.3)	10 (76.9)	13 (81.2)	21 (87.5)	16 (76.2)
Sporadic EA type						
Generalized	2 (4.0)	2 (5.0)	0 (0)	0 (0)	0 (0)	2 (12.5)
Lateralized	38 (76.0)	29 (72.5)	9 (90.0)	11 (84.6)	18 (85.7)	9 (56.2)
Bilateral independent	8 (16.0)	7 (17.5)	1 (10.0)	2 (15.4)	2 (9.5)	4 (2.5)
Multifocal	2 (4.0)	2 (5.0)	0 (0)	0 (0)	1 (4.8)	1 (6.3)
Sporadic EA quantification						
Abundant	9 (18.0)	8 (20.0)	1 (10.0)	4 (30.8)	1 (4.8)	4 (25.0)
Frequent	25 (50.0)	20 (50.0)	5 (50.0)	4 (30.8)	13 (61.9)	8 (50.0)
Occasional	11 (22.0)	10 (25.0)	1 (10.0)	3 (23.1)	4 (19.0)	4 (25.0)
Rare	5 (10.0)	2 (5.0)	3 (35.0)	2 (15.4)	3(14.3)	0 (0)
Periodic patterns	11 (18.0)	8 (16.7)	3 (23.1)	3 (18.8)	3 (12.5)	5 (23.8)
Periodic patterns type						
LPDs	7 (63.6)	5 (62.5)	2 (66.7)	3 (100)	1 (33.3)	3 (60.0)
GPDs	2 (18.2)	2 (25.0)	0 (0)	0	0 (0)	2 (40.0)
BIPDs	2 (18.2)	1 (12.5)	1 (33.3)	0	2 (66.7)	0 (0)

Most often non-generalized, whereas generalized EA (sporadic and periodic) were present only in anoxic patients

ES/EA and mortality of pDoC

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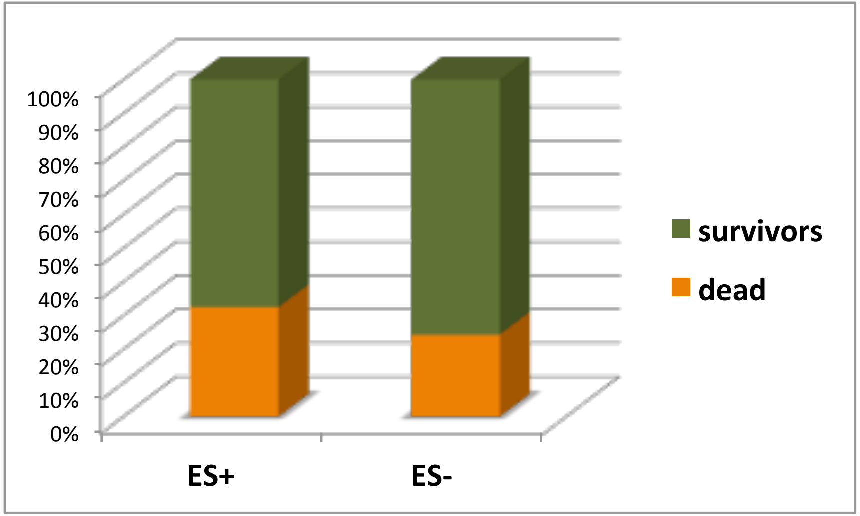

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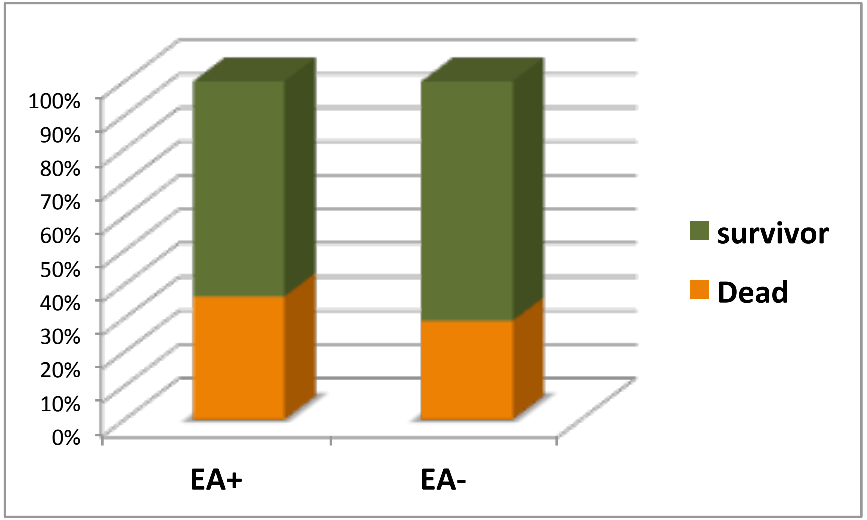

chi-square<1

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Archives of Physical Medicine and Rehabilitation
journal homepage: www.archives-pmr.org
Archives of Physical Medicine and Rehabilitation 2018;■■:■■■-■■■

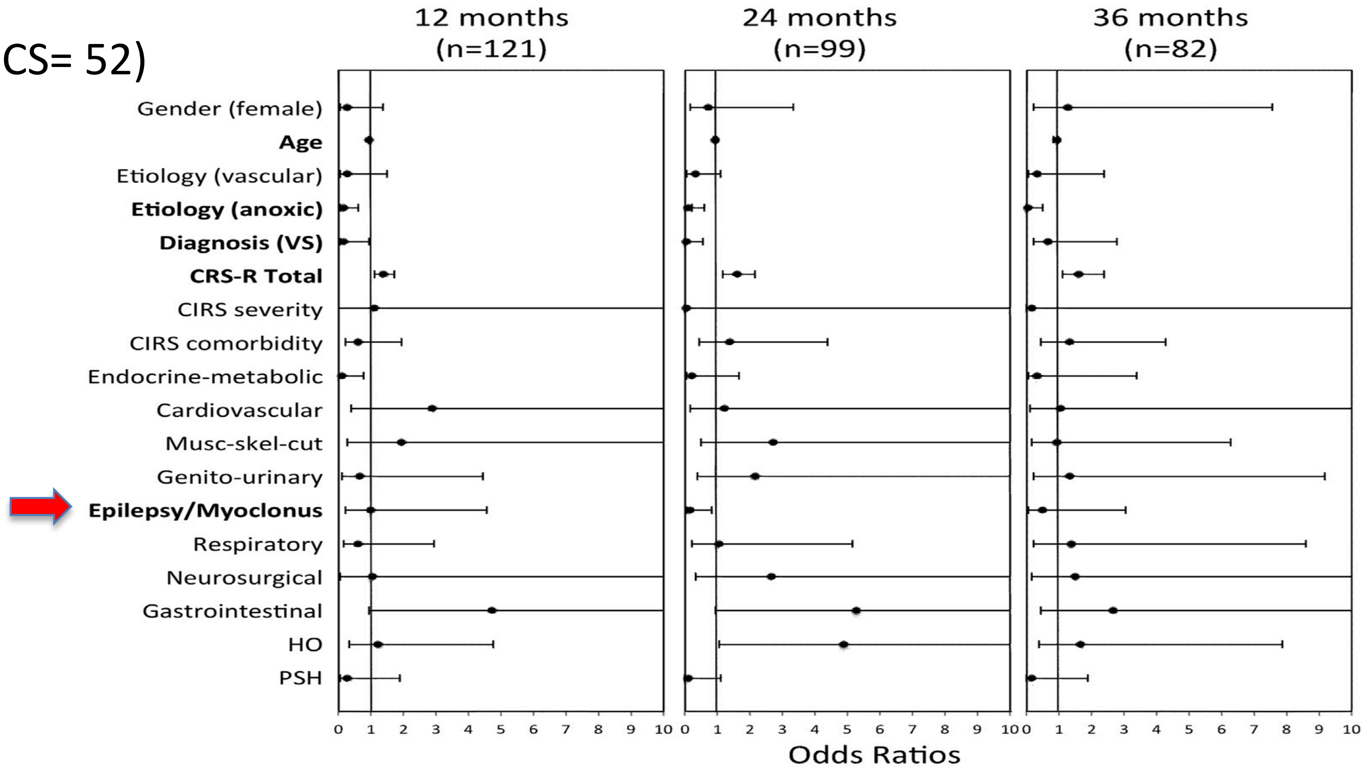
ORIGINAL RESEARCH

Do Medical Complications Impact Long-Term Outcomes in Prolonged Disorders of Consciousness?

Anna Estraneo, MD,[a] Vincenzo Loreto, MD,[a] Orsola Masotta, Psy,[a] Angelo Pascarella, MD,[a] Luigi Trojano, MD[a,b]

ES and EA and long-term consciousness recovery

DoC=194 (VS= 142; MCS= 52)



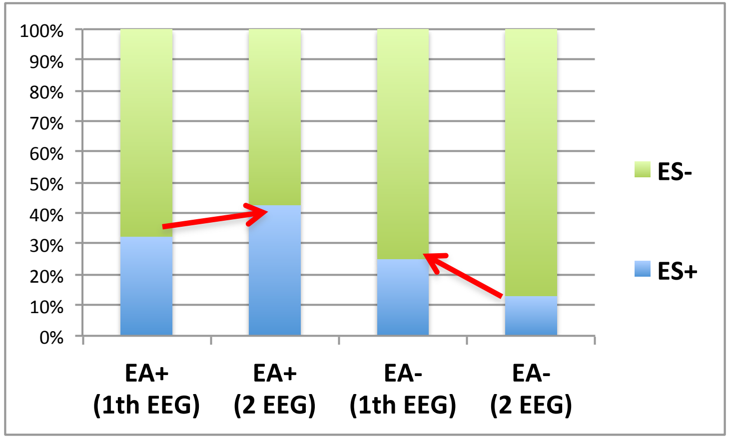
J Neurol (2016) 263:2048–2056
DOI 10.1007/s00415-016-8232-y
ORIGINAL COMMUNICATION

Epileptic seizure and epileptic abnormalities

Long-term outcome of patients with disorders of consciousness with and without epileptiform activity and seizures: a prospective single centre cohort study

Angelo Pascarella[1] · Luigi Trojano[2] · Vincenzo Loreto[1] · Leonilda Bilo[3] · Pasquale Moretta[1] · Anna Estraneo[1]

ES occurred in 26/61 (**42.6%**) patients with EA, and in only 9/69 (**13.0%**) DOC patients without EA on **two EEG** recorded at study entry



..whereas taking into account the first EEG at study entry, ES and EA co-occurred in 11/34 (32.3%) patients, and in 24/96 (25.0%) patients without EA

EEG to detect seizures in DoC

Brain Injury

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- ✓ **duration of EEG recording** has been shown to increase the chance to detect epileptic abnormalities (EA) (56% of EA were detected during the first hour, 94% within 48 hours) (18), **the repetition of 30-minute EEGs** every 6 hours allows seizure detection with an accuracy of 92%
- ✓ neither continuous EEG monitoring nor repeated EEG recordings are suitable for the long-term management of patients with DoC (due to movement artifacts on EEG, availability of human resources and equipment and time spent to analyze data among other reasons).

Concluding remarks

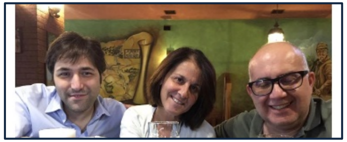
- ✓ Conventional EEG is easily available and repeatable at bedside
- ✓ Very severe EEG background activity (LV) and lack of EEG reactivity are most often found in VS patients and in anoxic DoC patients
- ✓ Normal or near normal EEG are more frequent in MCS, especially in MCS+, but the differences of EEG background and reactivity in the two subgroups of MCS patients are marginally significant
- ✓ In anoxic DOC patients EEG background activity is more impaired and provide less discriminative diagnostic information.

Concluding remarks

- ✓ Neurophysiological evaluation (standard EEG) could
  - detect negative influencing factors (eg. (Non) convulsive epileptic seizure, sleep activities)
  - monitor clinical evolution (EEG, ERP)
  - complement the diagnostic behavioral diagnosis (EEG, ERP)
  - provide prognostic information (EEG, SEP, ERP)
- ✓ Conventional EEG can provide useful diagnostic and prognostic information at group level (but not at individual level)
- ✓ Combining neurophysiological data and patients' clinical assessment could identify diagnostic and prognostic (sub) groups

Thank you for your attention

Anna Estraneo, MD
Campana Biagio, MD
De Bellis Francesco, Psy
Magliacano Alfonso Psy
Fiorenza Salvatore, TNFP
Spinola Marcella, log
Fasano Cinzia, log



Scientific collaborations

- Trojano L, Dept. Psychology, University Lugi Vanvitelli, Caserta, Italy
- Farisco M, Centro di Ricerche Genetiche Biogem di Ariano Irpino, Italy e Uppsala University, Sweden
- Soddu A., The University of Western Ontario, London ON, Canada
- Schnakers C, UCLA Department of Neurosurgery, Los Angeles, California (USA)
- Thibaut A, Gosseries O. Coma Science Group, Liège University, Belgium
- Molteni E, School of Biomedical Engineering & Imaging Sciences, King's College London, London, United Kingdom.
- Cavaliere C., SDN – Istituto di Ricerca Diagnostica e Nucleare, Napoli, Italy
- Formisano R., Fondazione Santa Lucia - IRCCS, Roma
- Noè E. Neurorehab – Valencia, Spain
- Eldow B. Harvard Medical School; Boston (USA)
- Cincotti F, Toppi J. Dept. of Computer, Control and Management Engineering, Sapienza University of Rome, Italy