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)

Neuroimaging

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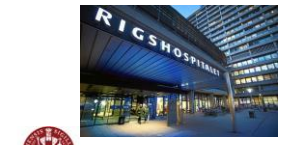

UNIVERSITY OF COPENHAGEN

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

-

Neuroimaging

Daniel Kondziella
Copenhagen

Conflicts of interests: none

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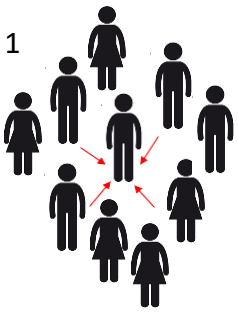
How to make an EAN guideline

1



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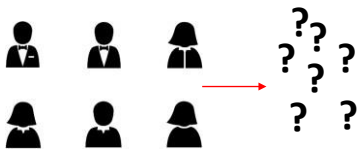

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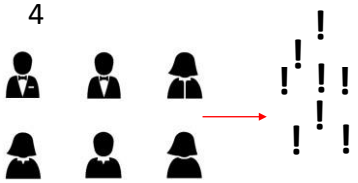

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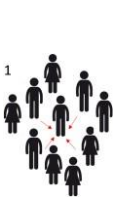

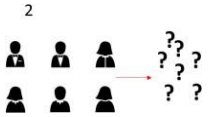

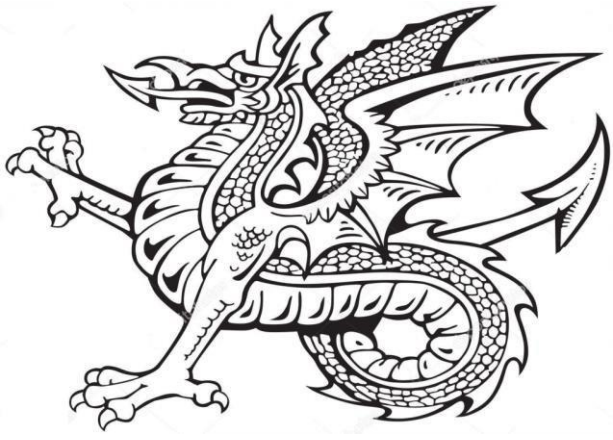

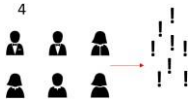

The GRADE approach

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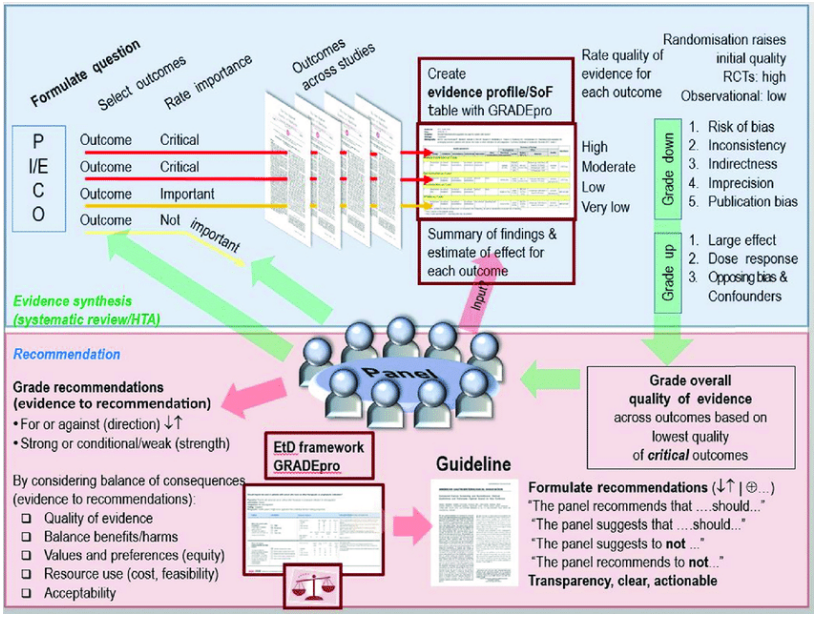
Grading of Recommendations Assessment, Development and Evaluation (GRADE)



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

From left to right: Johan Stender (DK), Willemijn van Erp (NL), Andreas Bender (GER), Olivia Gosseries (BE), Camille Chatelle (BE), Benjamin Rohaut (FR), Serefnur Ozturk (TR), Karin Diserens (CH), Daniel Kondziella (DK), Lionel Naccache (FR), Marjaana Tiainen (FI), Jacobo Sitt (FR) (standing); Andrea O. Rossetti (CH), Anna Estraneo (IT), Rita Formisano (IT), Steven Laureys (BE) (insert)

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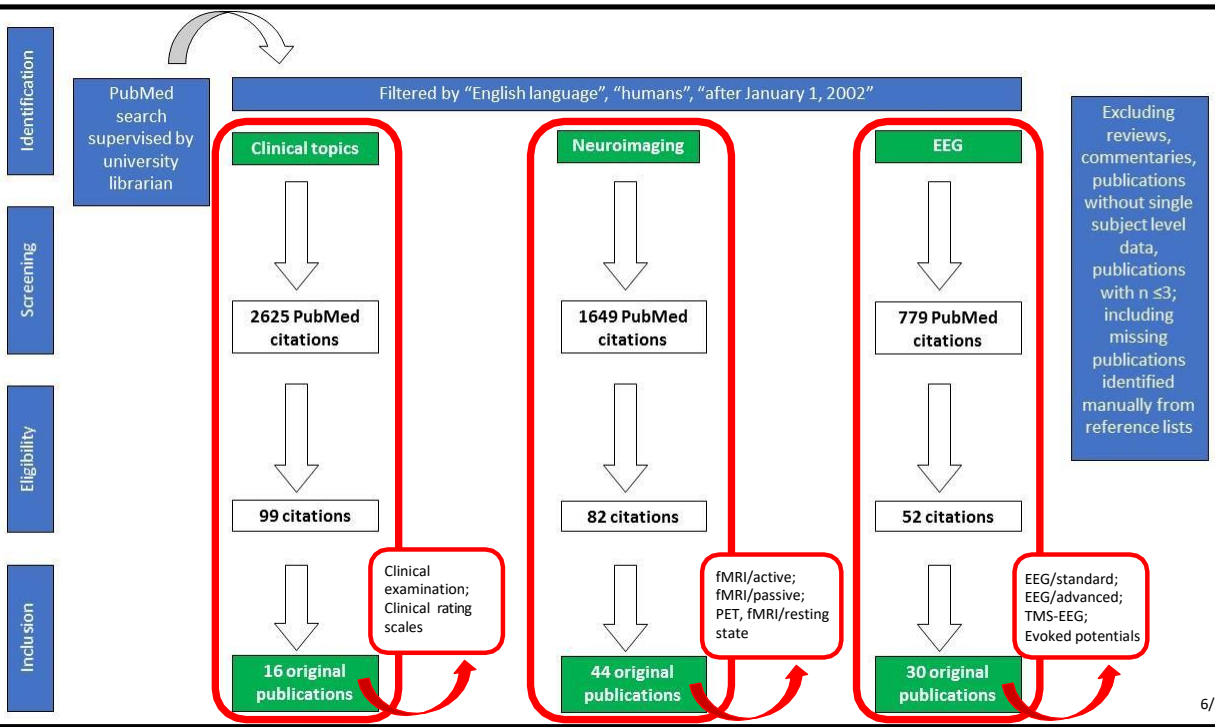

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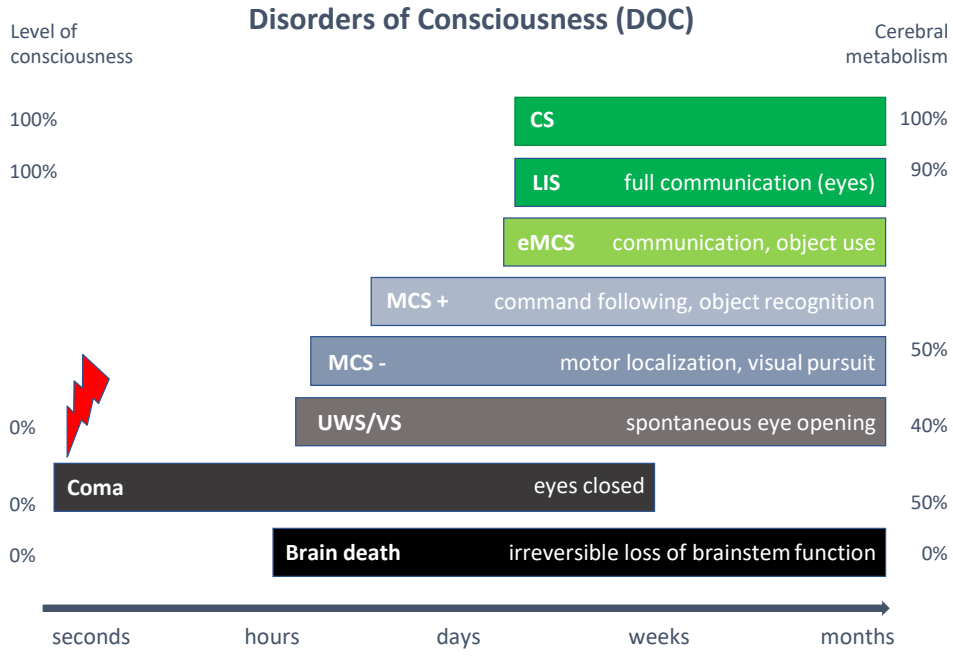

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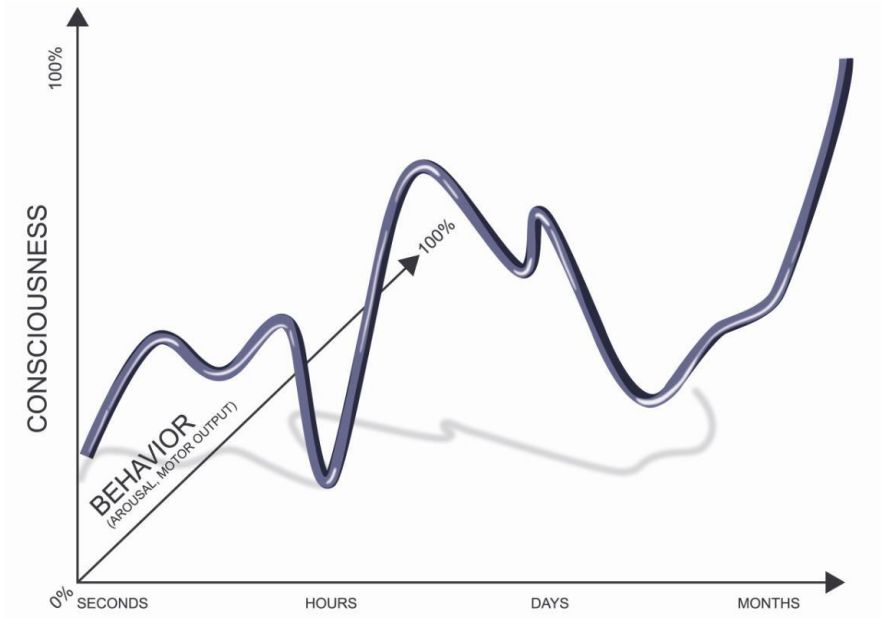

Kondziella et al. J Neurol Neurosurg Psychiatry 2016

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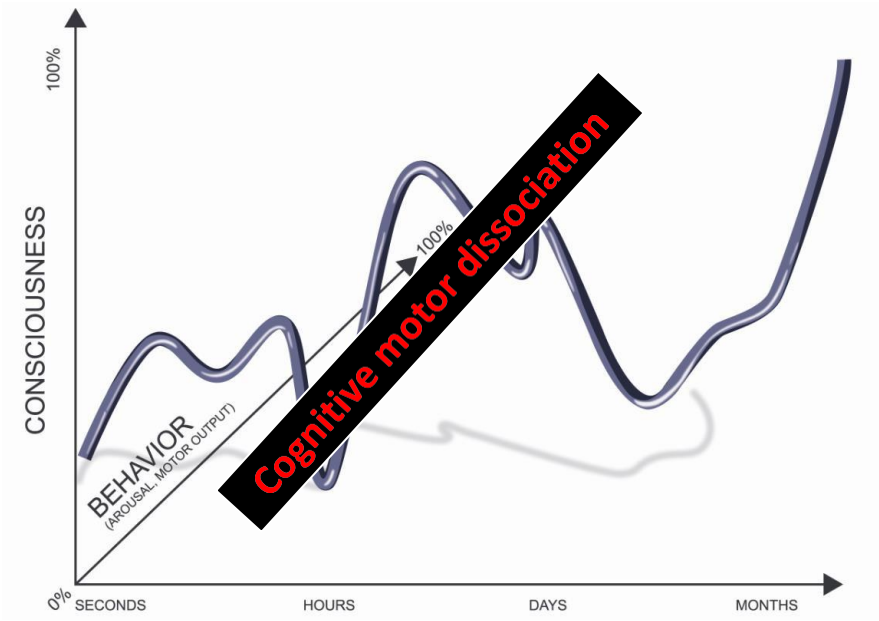
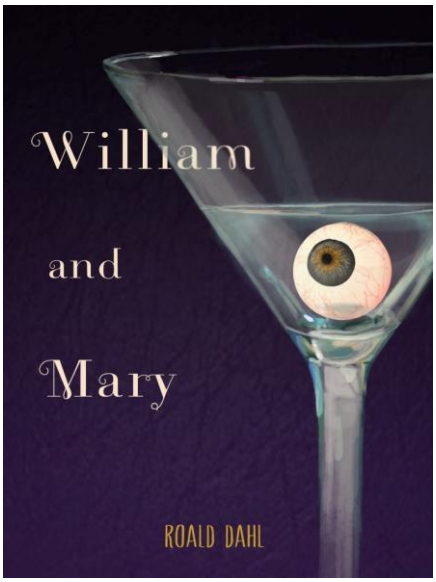


Kondziella et al. J Neurol Neurosurg Psychiatry 2016

Cognitive motor dissociation

Schiff. JAMA Neurol 2015



Roald Dahl. William and Mary. In: Kiss Kiss, by Roald Dahl. A. A. Knopf, Inc. 1960

Kondziella. J Neurol Sci 2017

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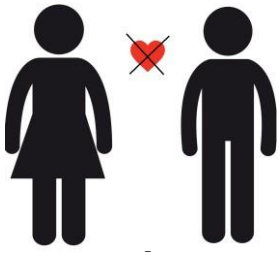

Roald Dahl. William and Mary. In: Kiss Kiss, by Roald Dahl. A. A. Knopf, Inc. 1960

Kondziella. J Neurol Sci 2017

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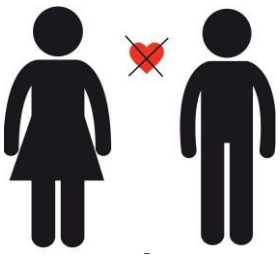

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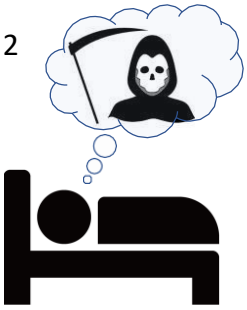

Roald Dahl. William and Mary. In: Kiss Kiss, by Roald Dahl. A. A. Knopf, Inc. 1960

Kondziella. J Neurol Sci 2017

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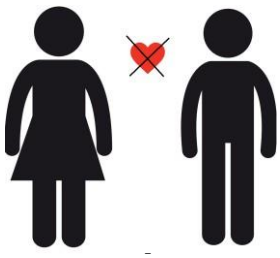

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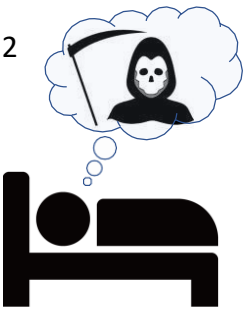

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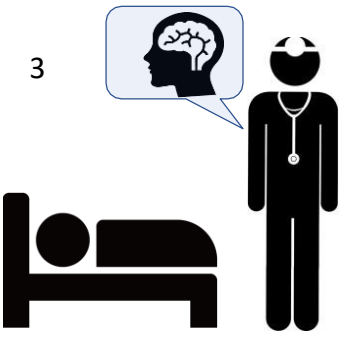

Roald Dahl. William and Mary. In: Kiss Kiss, by Roald Dahl. A. A. Knopf, Inc. 1960

Kondziella. J Neurol Sci 2017

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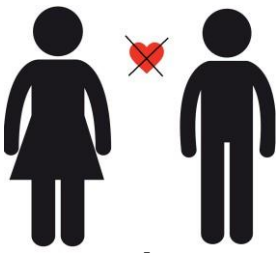

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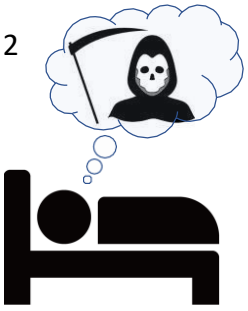

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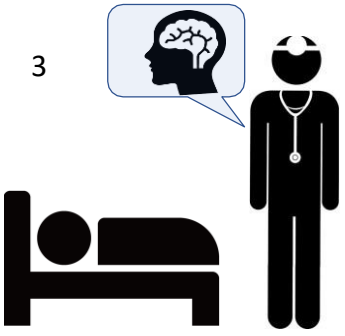

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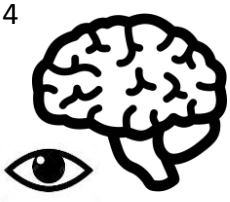

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Kondziella. J Neurol Sci 2017

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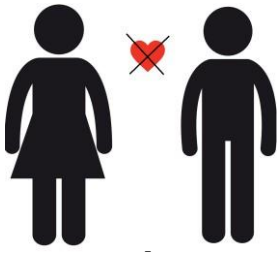

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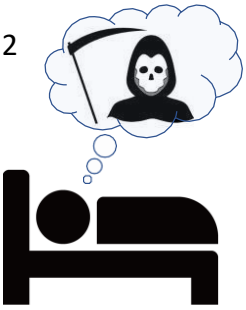

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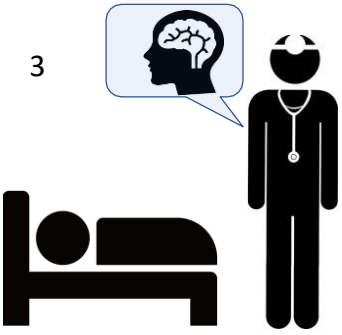

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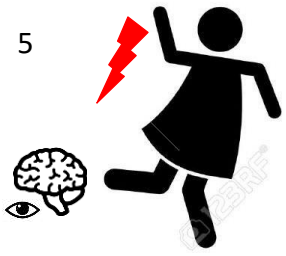

Roald Dahl. William and Mary. In: Kiss Kiss, by Roald Dahl. A. A. Knopf, Inc. 1960

Kondziella. J Neurol Sci 2017

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high specificity

active paradigms
command following (fMRI, EEG)

passive paradigms
cogntive ERPs (EEG), TEMS-EEG
cortical connectivity (fMRI, EEG, PET)

resting state
brain networks (fMRI), metabolims (PET)
cortical connectivity (EEG)

high sensitivity

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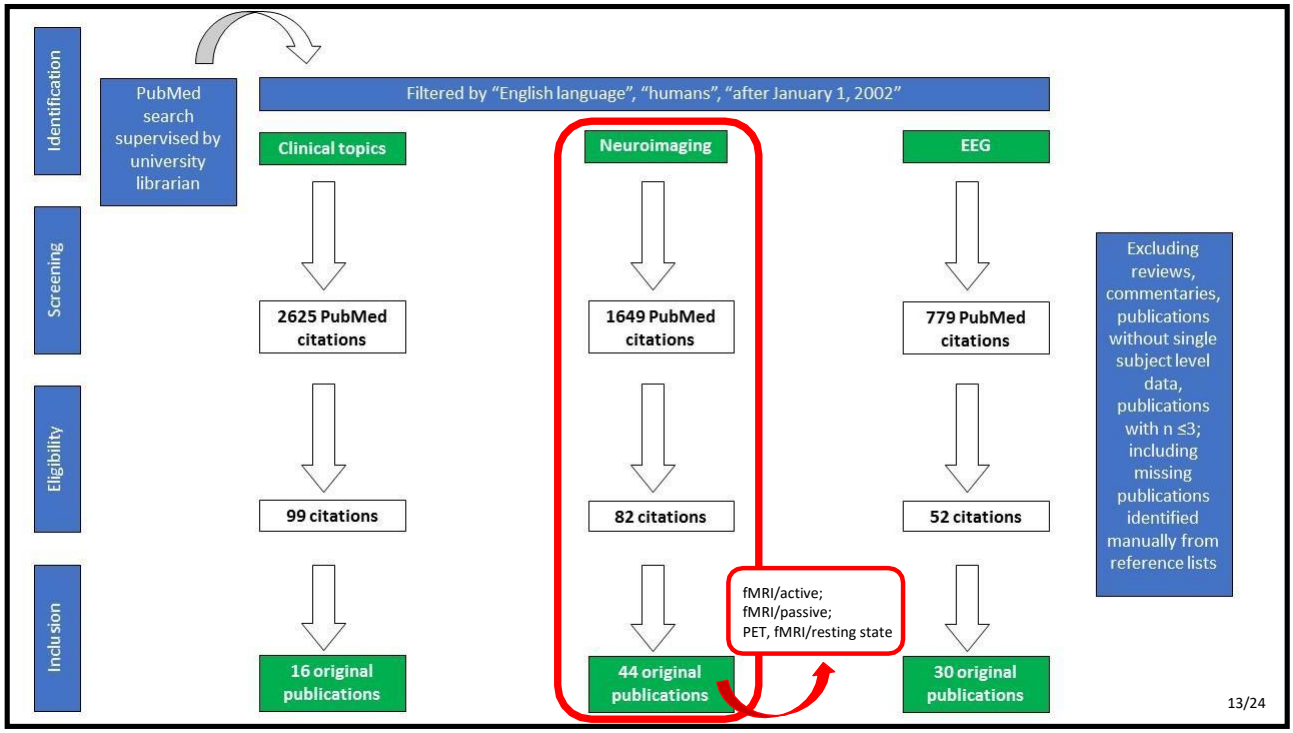
Identification
Screening
Eligibility
Inclusion
PubMed search supervised by university librarian
Filtered by "English language", "humans", "after January 1, 2002"
Clinical topics
Neuroimaging
EEG
2625 PubMed citations
1649 PubMed citations
779 PubMed citations
99 citations
82 citations
52 citations
16 original publications
44 original publications
30 original publications
fMRI/active;
fMRI/passive;
PET, fMRI/resting state
Excluding reviews, commentaries, publications without single subject level data, publications with n ≤3; including missing publications identified manually from reference lists
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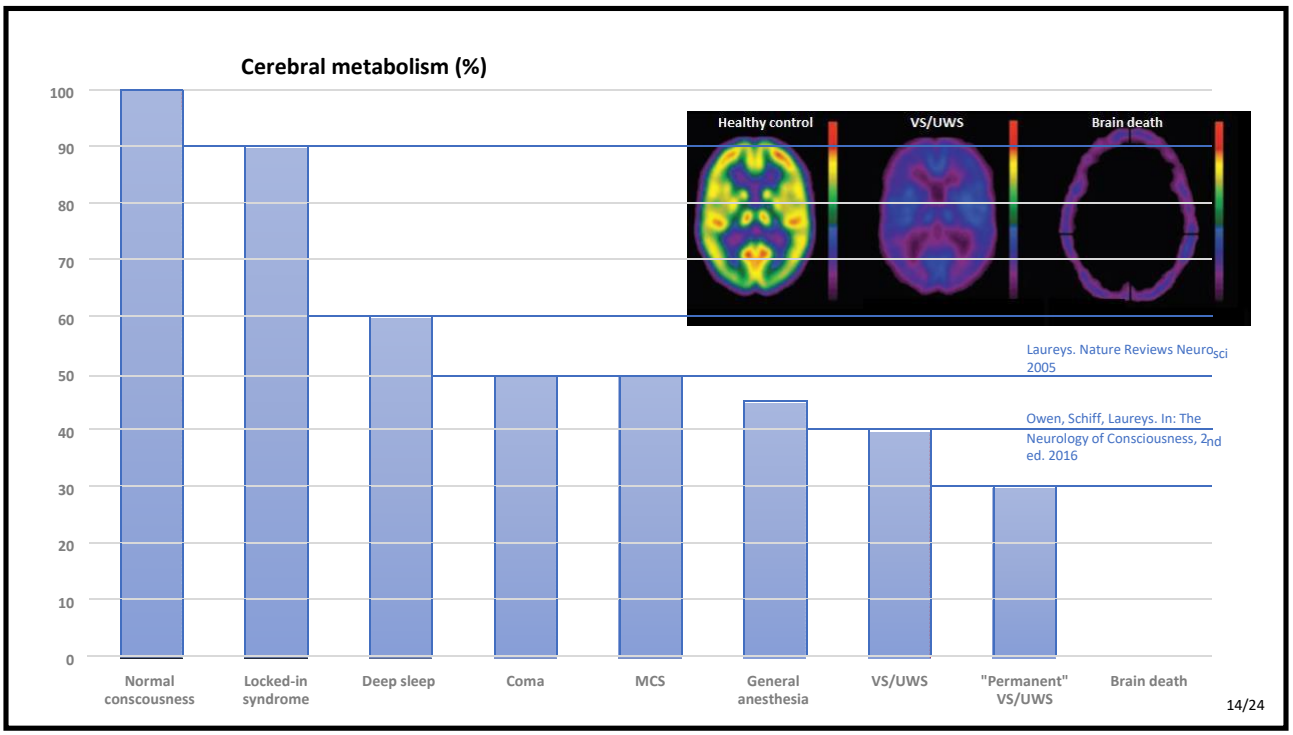
Cerebral metabolism (%)
100
90
80
70
60
50
40
30
20
10
0
Healthy control
VS/UWS
Brain death
Laureys. Nature Reviews Neurosci 2005
Owen, Schiff, Laureys. In: The Neurology of Consciousness, 2nd ed. 2016
Normal conscousness
Locked-in syndrome
Deep sleep
Coma
MCS
General anesthesia
VS/UWS
"Permanent" VS/UWS
Brain death
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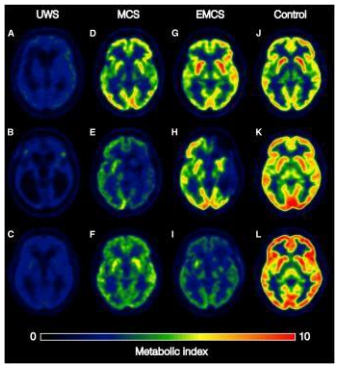
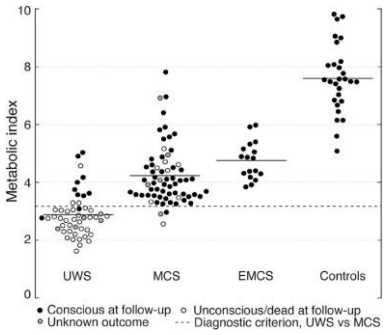
FDG-PET (single subject level)

Stender et al.
Curr Biol 2016



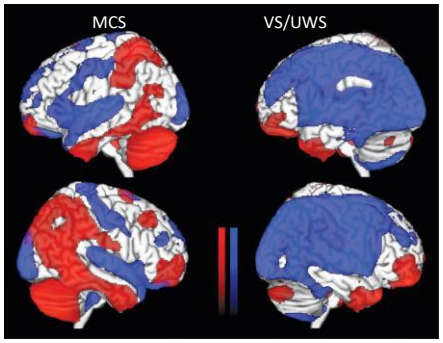


FDG-PET (group level)

Stender et al. Lancet 2014

Areas with decreased metabolism

Areas with preserved metabolism



Recommendation: "Resting state FDG PET should be considered as part of multimodal assessment in unresponsive patients *(low evidence, weak recommendation)."*

5 publications (n=341 patients)

RR for intrinsic cortical activity in MCS vs. coma or VS/UWS: 3.14 (95% CI 2.40-4.12; p<0.0001)

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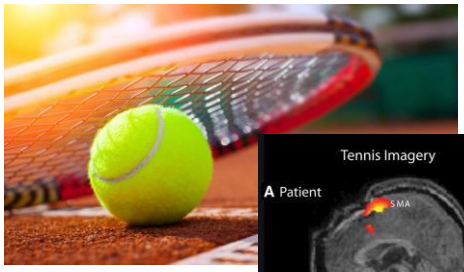

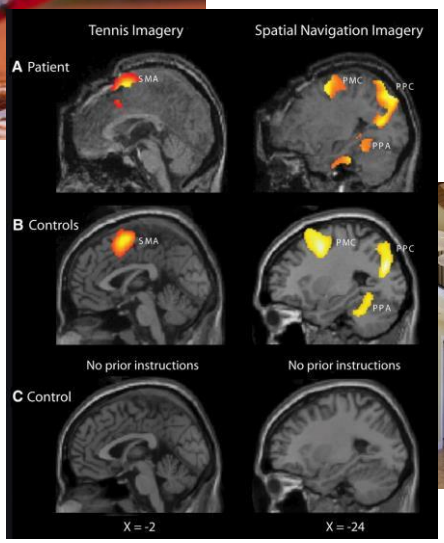

Owen et al. Science 2006

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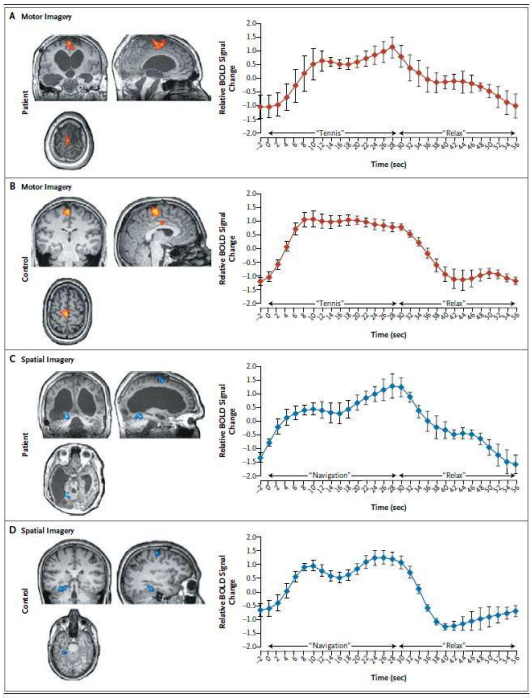

Monti et al. NEJM 2010

Recommendation: "We suggest considering active fMRI paradigms as part of multimodal assessment in patients without command following at the bedside (*moderate evidence, weak recommendation*)."

20 publications (n=343)

RR for command following in MCS vs. coma or VS/UWS: 1.60 (95% CI 1.16-2.20; p=0.0037)

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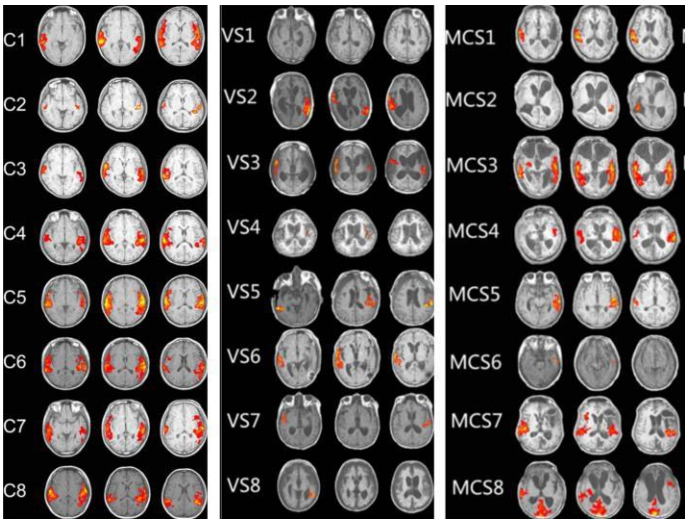
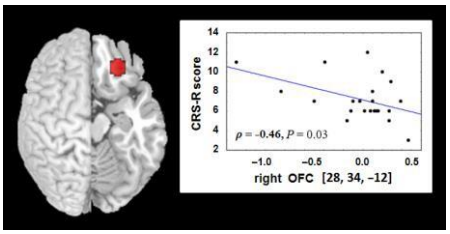


"Subject's own name"

Wang et al. BMC Medicine 2015



Olfaction

Nigri et al. Eur J Neurol 2016

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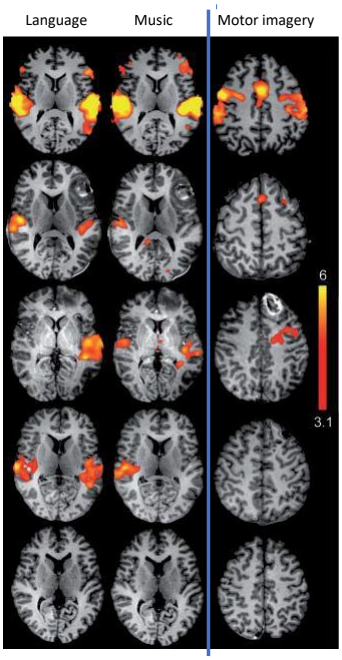
CRS-R Diagnosis	fMRI/EEG Diagnosis
Healthy subject	Healthy subject
MCS+	MCS+
VS/UWS	CMD
MCS-	HMD
Coma	Coma



Edlow et al. Brain 2017

Recommendation: "Given the small effect and the heterogeneity of the employed paradigms, we only recommend using passive fMRI paradigms within research protocols (*low evidence, weak recommendation*)."

16 publications (n=313)

RR for preserved connectivity in MCS vs. coma or VS/UWS: 1.69 (95% CI 1.38-2.07; p=0.0001)

Recommendation: "We recommend using salient stimuli for examination of DoC patients by fMRI (*very low evidence, weak recommendation*)."

9 publications (n=167)

RR for preserved intrinsic activity or command following in MCS following salient stimuli as compared to coma or VS/UWS: 1.23-2.32; p<0.0011

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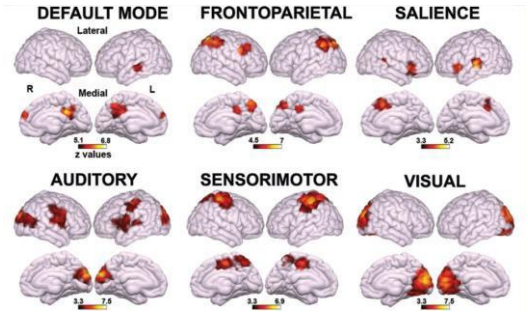
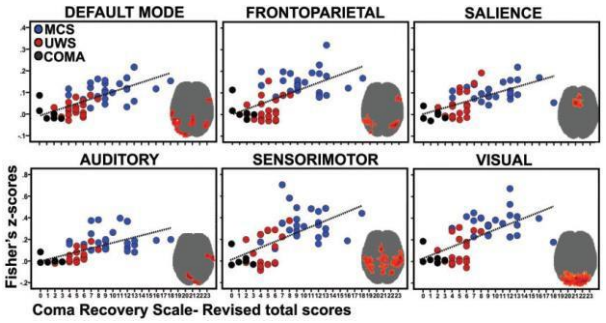
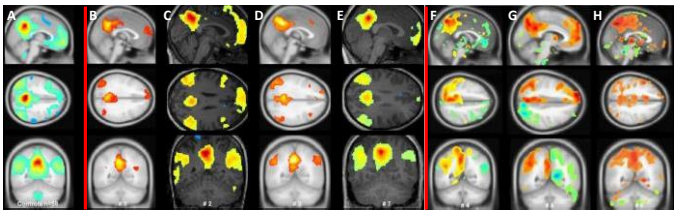




Demertzi et al. Brain 2015



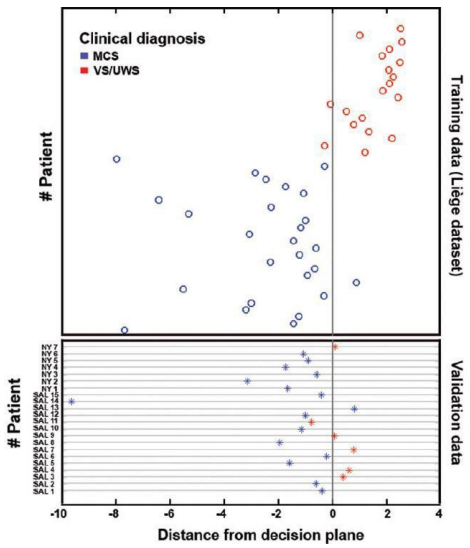
58 healthy volunteers

Good outcome in 4 patients with preserved default mode network (DMN)

Poor outcome in 3 patients without preserved DMN

Kondziella et al. Neurocrit Care 2017

20/24



Recommendation: "If a standard clinical (structural) MRI is indicated, we recommend adding a resting state fMRI sequence as part of multimodal assessment (*low evidence, weak recommendation*)."

6 publications (n=218)

RR for intrinsic cortical activity with resting state fMRI in MCS as compared to coma or VS/UWS: 2.45 (95% CI 1.81-3.33; p<0.0001)

Recommendation: "The DMN is just one of several resting state fMRI networks that may be used to complement the behavioral assessment in patients with DoC (*low evidence, weak recommendation*)."

6 publications (n=236)

RR for intrinsic activity in MCS as compared to coma or VS/UWS: 2.28 (95% CI 1.70-3.07 p<0.0001)

Demertzi et al. Brain 2015

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Active paradigms (fMRI/EEG)

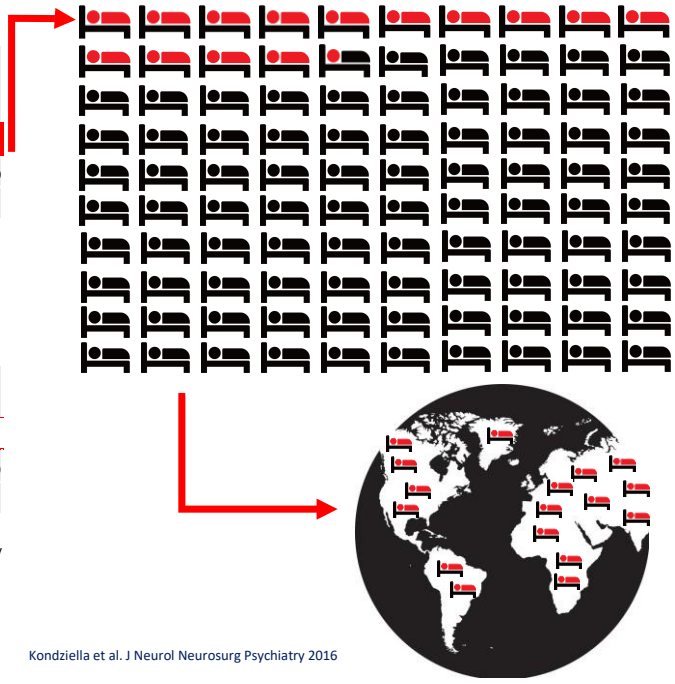
	command following	no command following	total	
VS	42	250	292	
MCS	98	205	303	32%
			595	

MCS patients more likely than VS patients to show command following (**odds ratio 2.85**; 95% CI 1.9-4.27; p<0.0001)

Passive paradigms (fMRI/EEG)

	cortical connetivity	cortical connetivity	total	
VS	91	261	352	
MCS	134	109	243	55.1%
			595	

MCS patients more likely than VS patients to show preserved cortical connectivity (**odds ratio 3.53**; 95% CI 2.49-4.99; p<0.0001)



Kondziella et al. J Neurol Neurosurg Psychiatry 2016

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Conclusions

- Neuroimaging can detect covert consciousness, including cognitive motor dissociation (CMD)
- Cerebral metabolism (FDG-PET) is a reliable marker of consciousness
- Passive and resting state fMRI is less specific but more sensitive than active fMRI
- Active fMRI paradigms based on e.g. motor imagery may reveal CMD in ca. 15% of clinically unresponsive patients
- Worldwide, 10.000s of patients believed to be in a VS/UWS are probably awake and aware

Thank you!