


Tutorial

Resting state fMRI as a means to assess the consciousness after severe brain injury

1st Summer School
Interdisciplinary Research on Brain Network Dynamics

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The problem

Patients cannot express themselves



Hable con ella 2002, Pedro Almodóvar

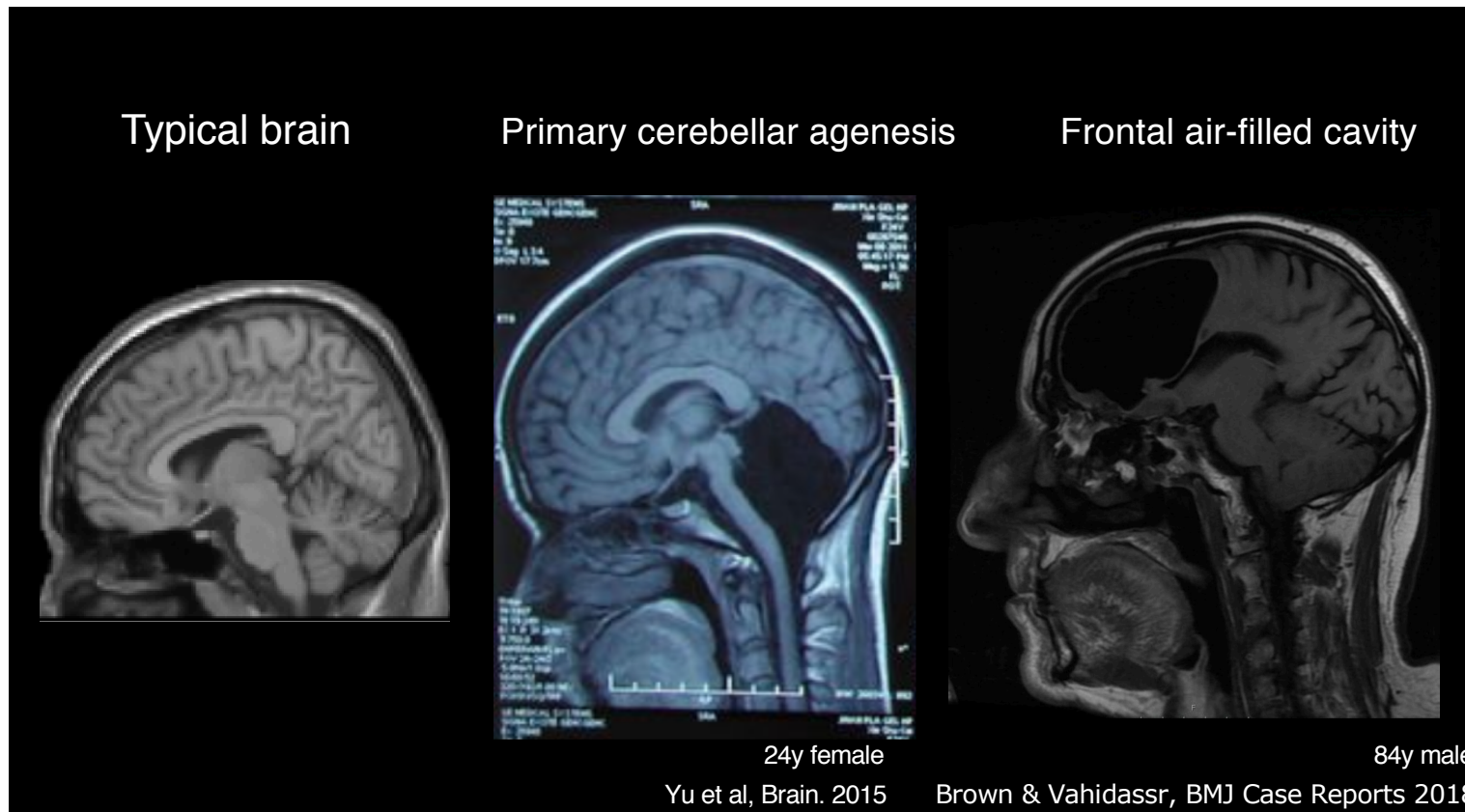


How can we evidence C in the absence of communication?
What is the minimum information we need?



How can we be conscious? (1)

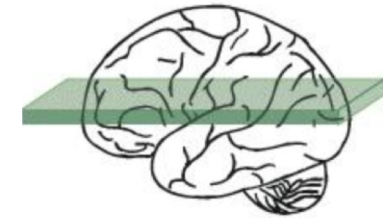
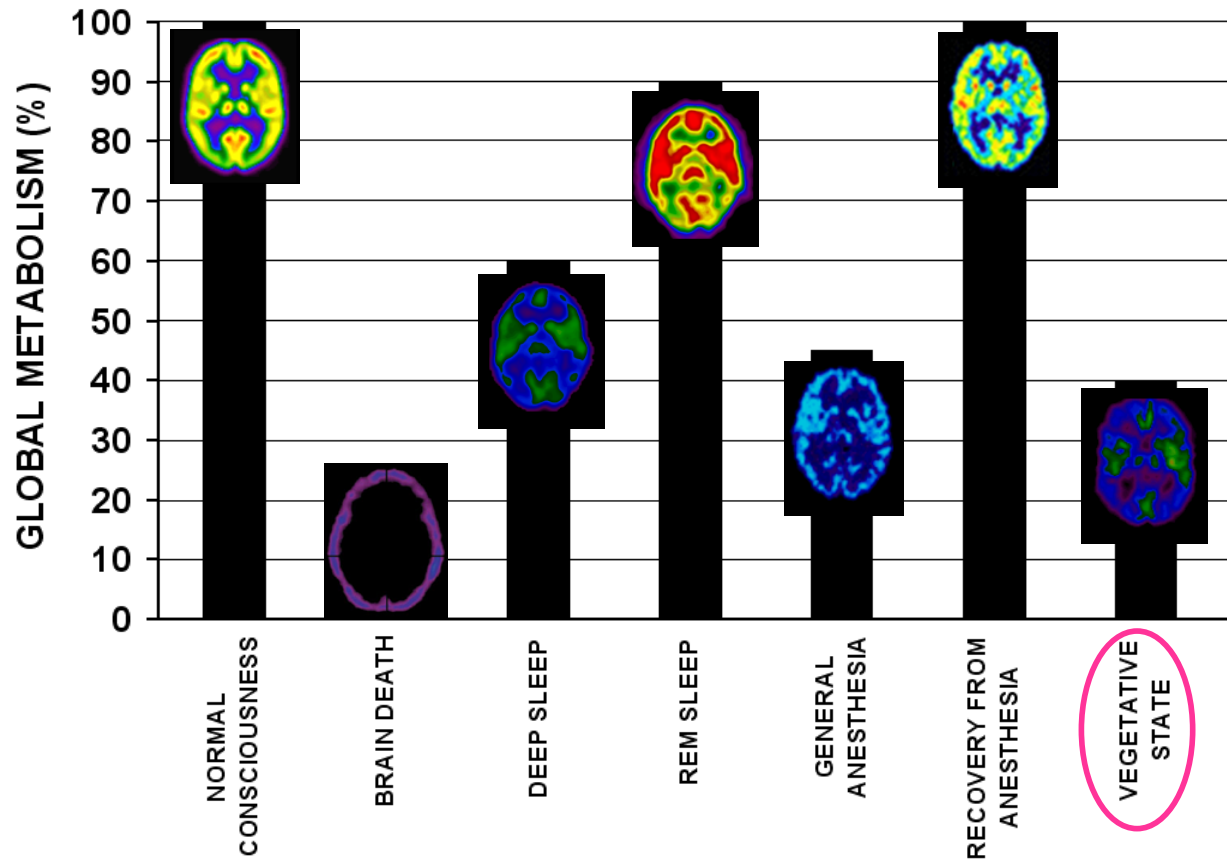
We need a brain (all of it?)





How can we be conscious? (2)

We need a functional brain





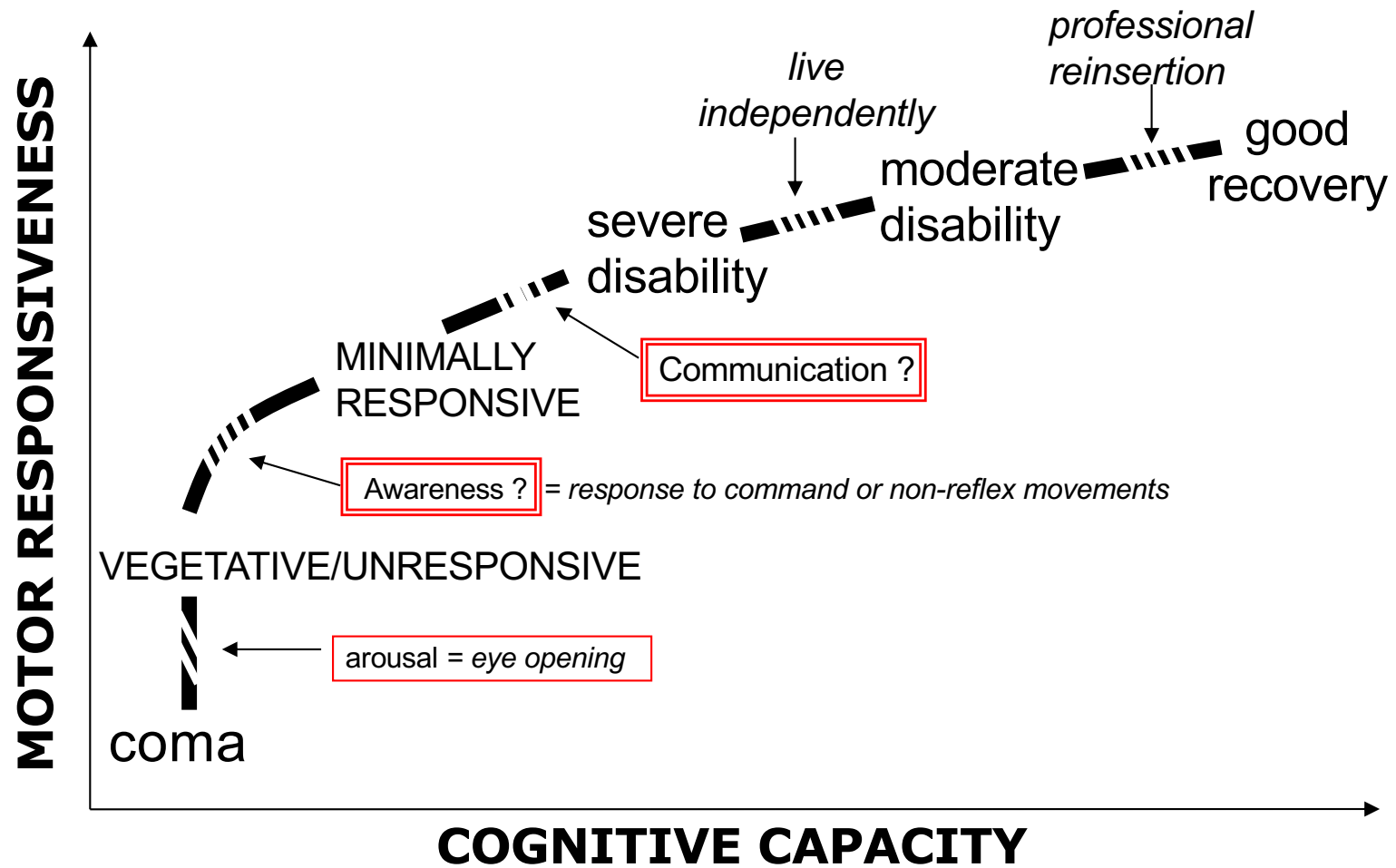
Is she conscious?



Terry Schiavo °1963,
vegetative 1990, † 2005 USA



Behavioural signs of C





We cannot always trust behavior

Standardized assessment

n=103 post-comatose patients

45 Clinical diagnosis of VS

18 Coma Recovery Scale MCS



40% misdiagnosed

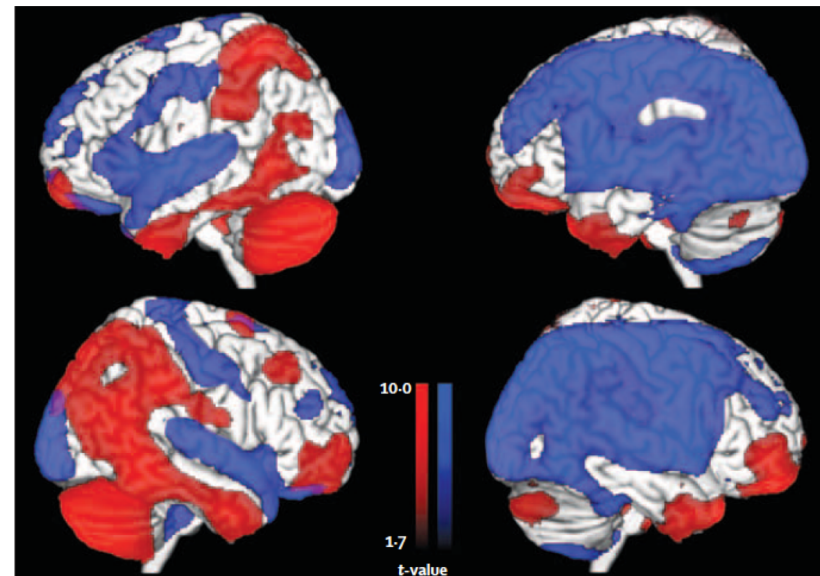
Schnakers et al, *Ann Neurol* 2006; *BMC Neurol* 2009

Neuroimaging

	Coma Recovery Scale-Revised results		
	UWS	MCS	Total
Clinical consensus diagnosis			
¹⁸F-FDG PET			
VS/UWS	24 (21%)	5 (4%)	29 (26%)
MCS	12 (11%)	71 (63%)	83 (74%)
Total	36 (32%)	76 (68%)	112 (100%)

UWS=unresponsive wakefulness syndrome. MCS=minimally conscious state.

Table 2: Diagnostic results by modality



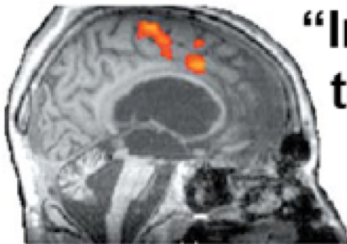

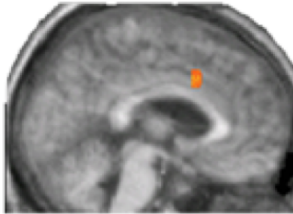

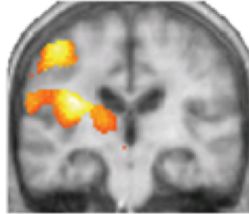
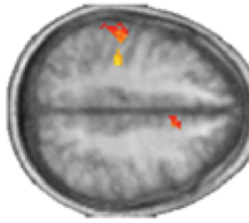
Stender & Gosseries et al, *Lancet* 2014



Neuroimaging paradigms

Owen et al, Science 2006
Monti & Vanhaudenhuyse et al, NEJM 2010

Boly et al, Lancet Neurol 2008

Active paradigms	Passive paradigms
 <p data-bbox="638 576 1048 683">“Imagine playing tennis”</p>	 <p data-bbox="1131 1102 1458 1145">median nerve</p> 
 <p data-bbox="638 901 1048 1077">“Imagine visiting the rooms of your house”</p>	
	

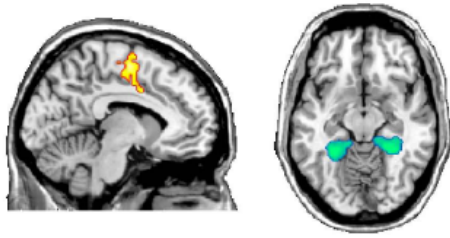
Heine, Di Perri, Soddu, Laureys, Demertzi
In: *Clinical Neurophysiology in Disorders of Consciousness*, Springer-Verlag 2015

Demertzi & Laureys, In: *I know what you are thinking: brain imaging and mental privacy*, Oxford University Press 2012

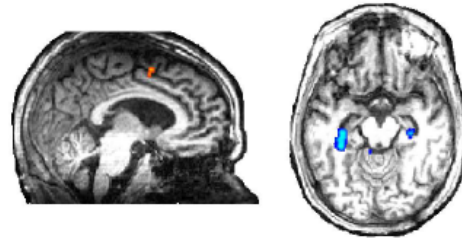


Neuroimaging to find “hidden minds”

Healthy Controls

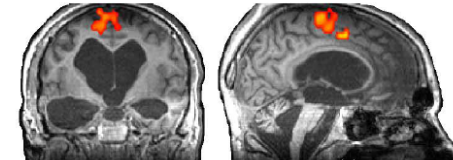


L25 TBI

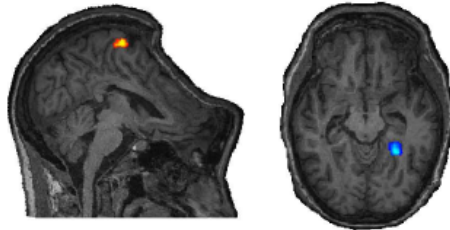


Imagine **Tennis** to answer 'YES'
Imagine **Navigating** to answer 'NO'

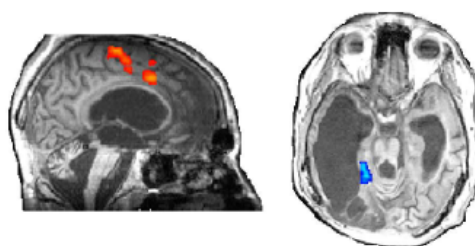
Is your father's name Alexander ?



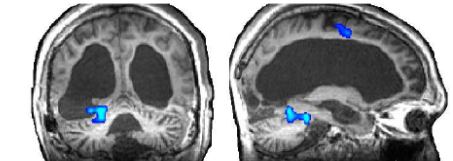
C04 TBI



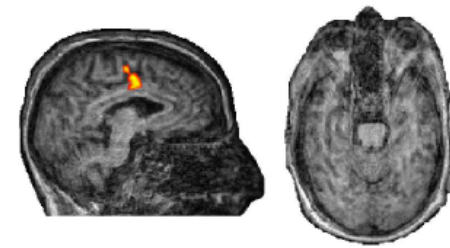
L23 TBI



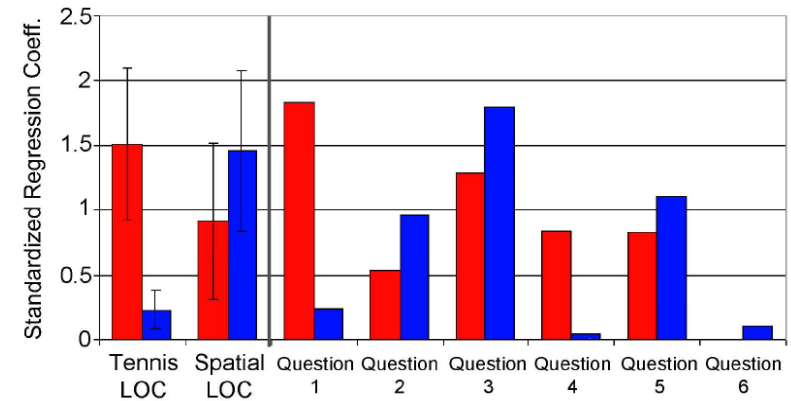
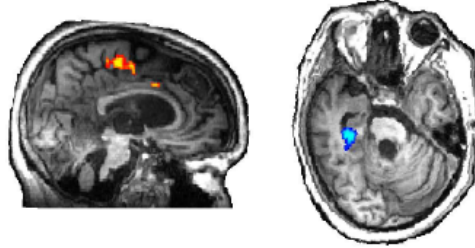
Is your father's name Thomas ?



C06 TBI



L22 TBI





Some numbers...

- The human brain is approximately 2% of body's weight
- 80% of this energy for neuronal signalling
→ most of consumed energy used for function
- Stimulus & performance-evoked changes in brain energy consumption are surprisingly small (typically <5%)



While conscious awareness is a low bandwidth phenomenon and therefore energetically inexpensive, it is dependent upon a very complex, dynamically organized, non-conscious state of the brain that is achieved at great expense



A control state?

Cognitive psychology: Mental chronometry (measures the time required to complete specific mental operations isolated by the careful selection of task and control states

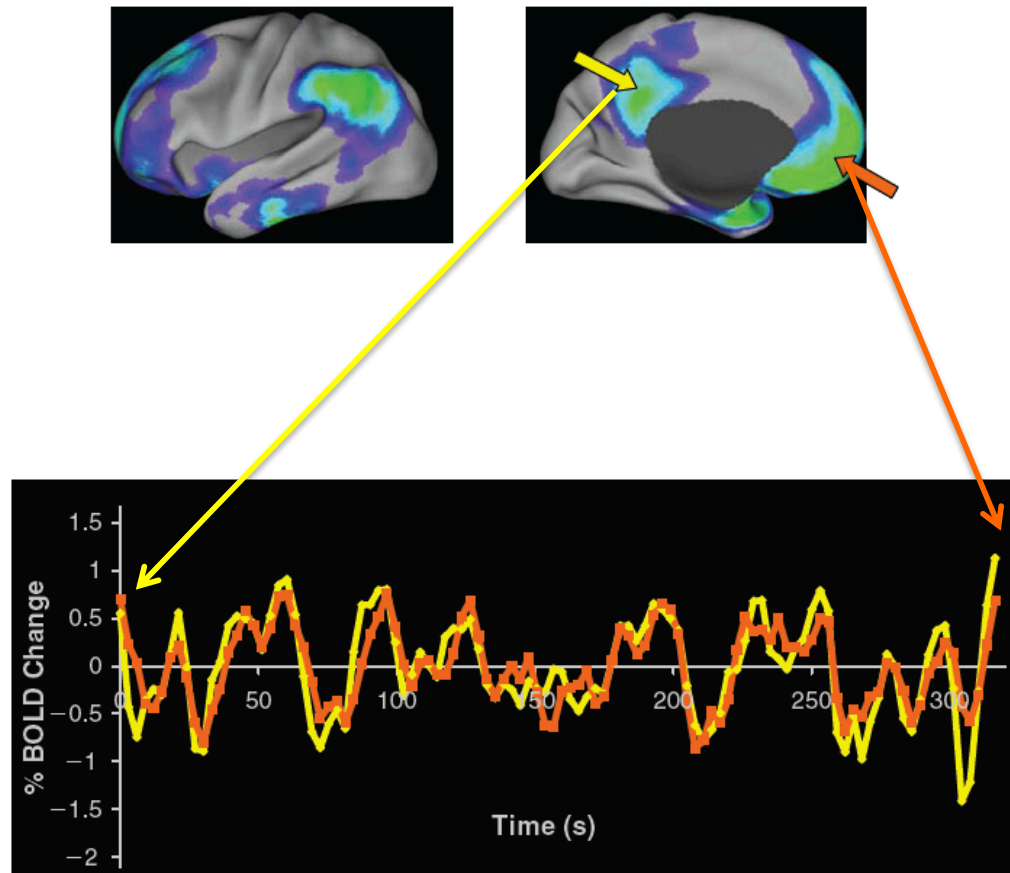


fMRI: Subtracting functional images acquired in a task state from ones acquired in a control state



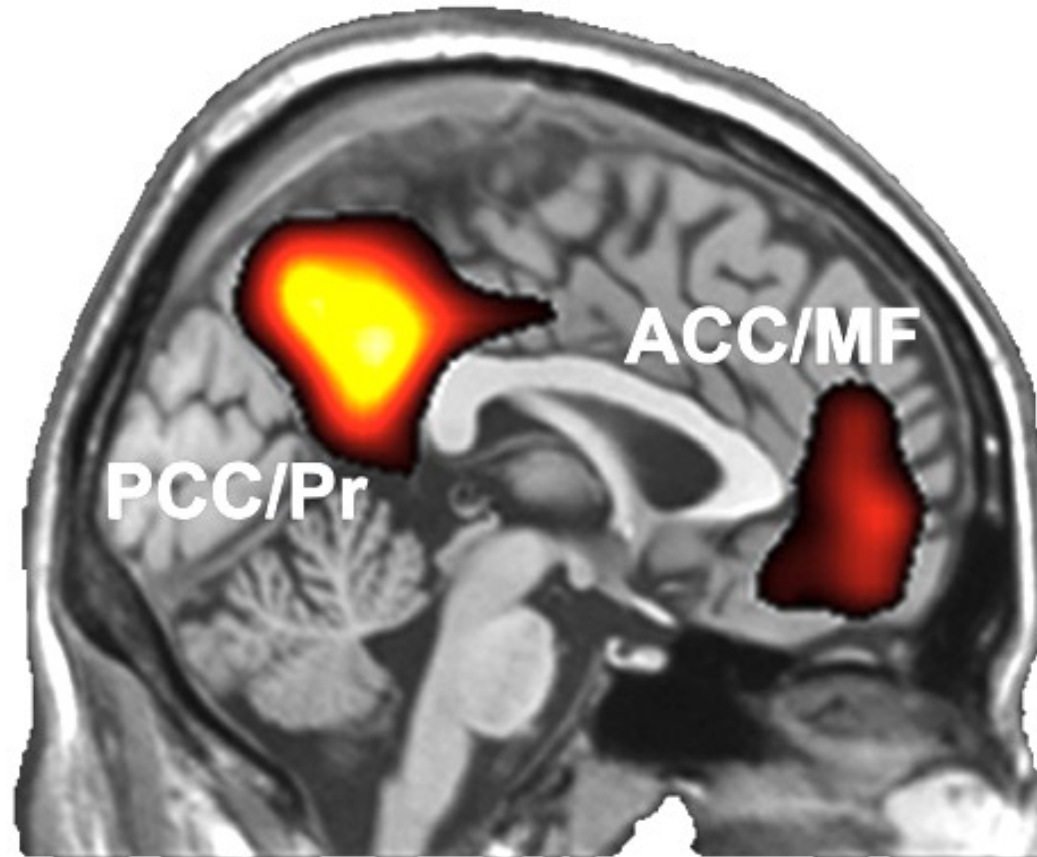
Task deactivations

Task performance - Rest (fixation/eyes closed) → **Deactivations**





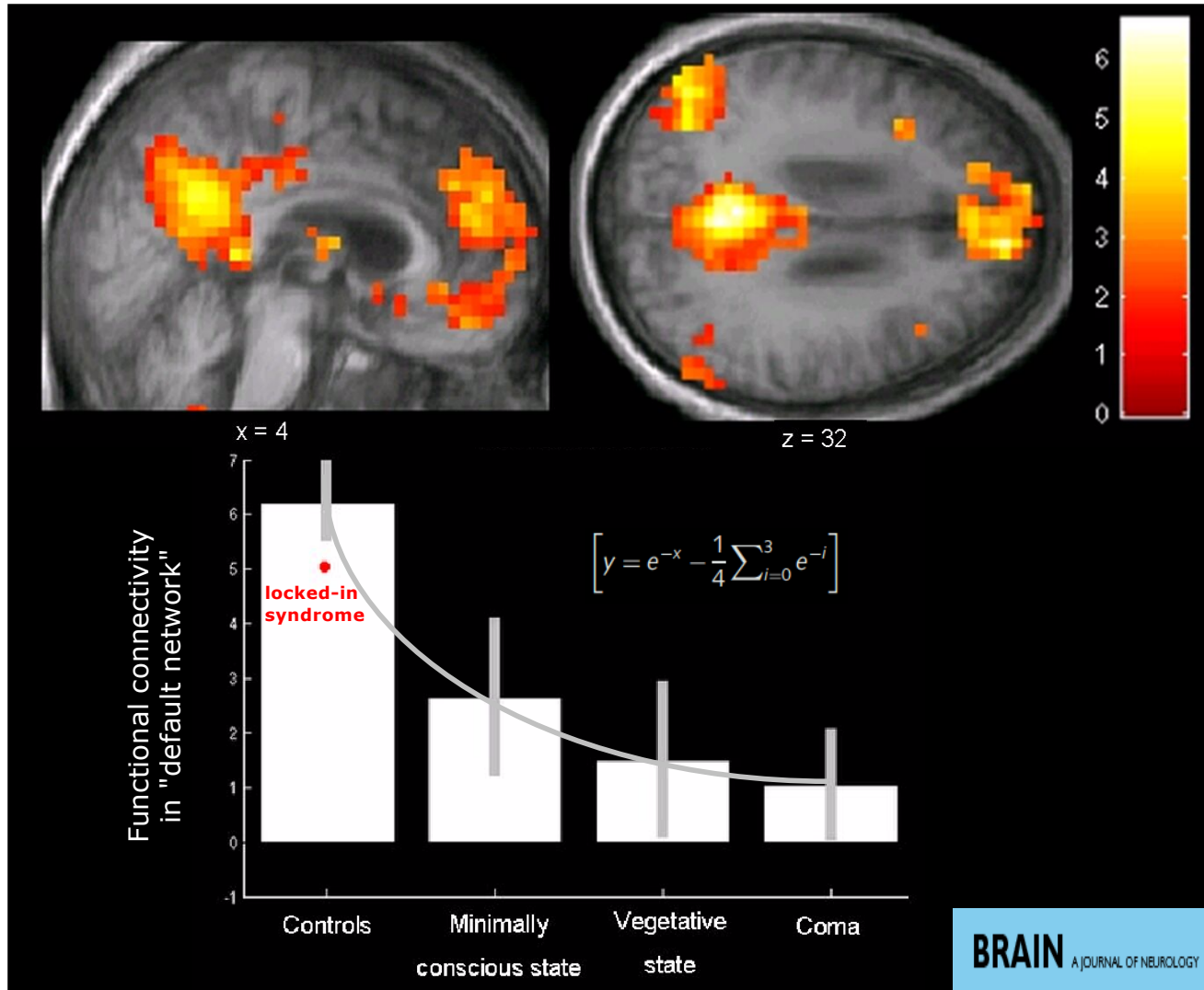
The brain's default mode at rest



Demertzi & Whitfield-Gabrieli, in: Neurology of Consciousness 2nd ed. 2015
Demertzi, Soddu, Laureys, Curr Opin Neurobiology 2013
Demertzi et al, Front Hum Neurosci 2013
Raichle et al, PNAS 2001

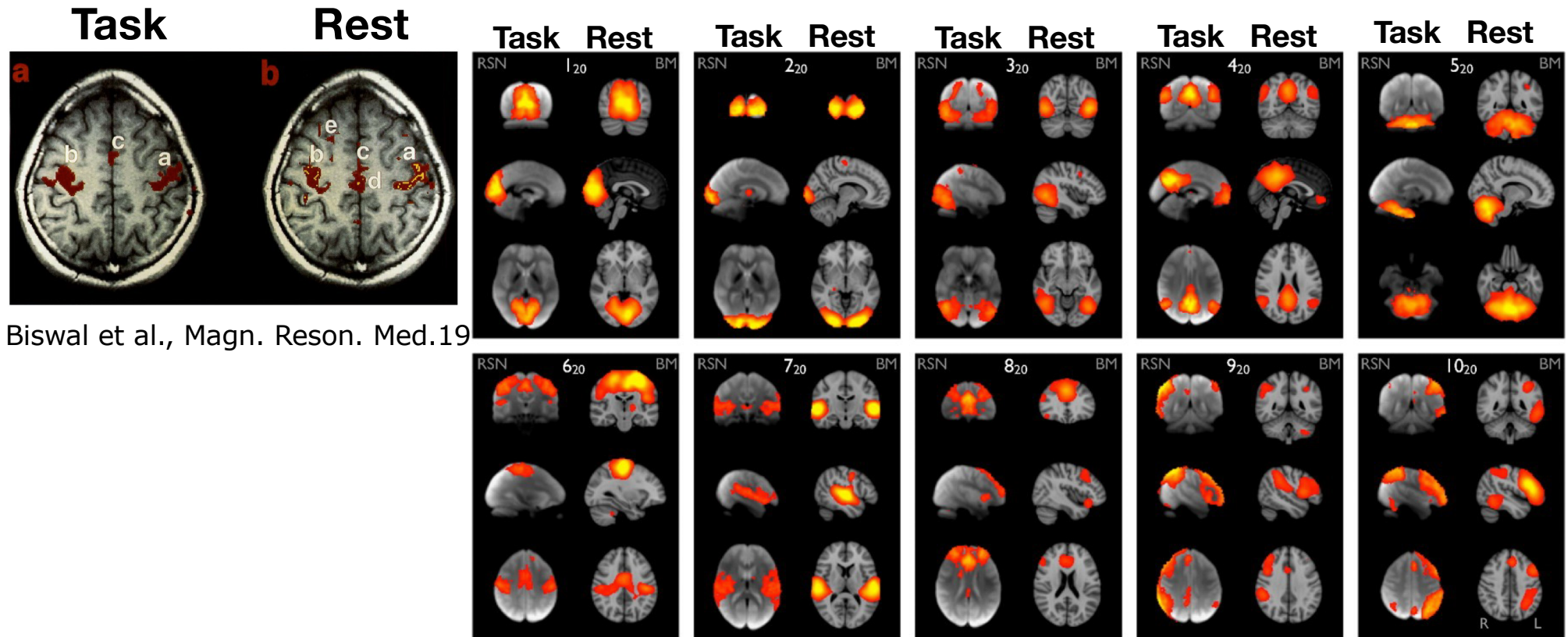


Default mode network in DOC





Intrinsic Connectivity Networks

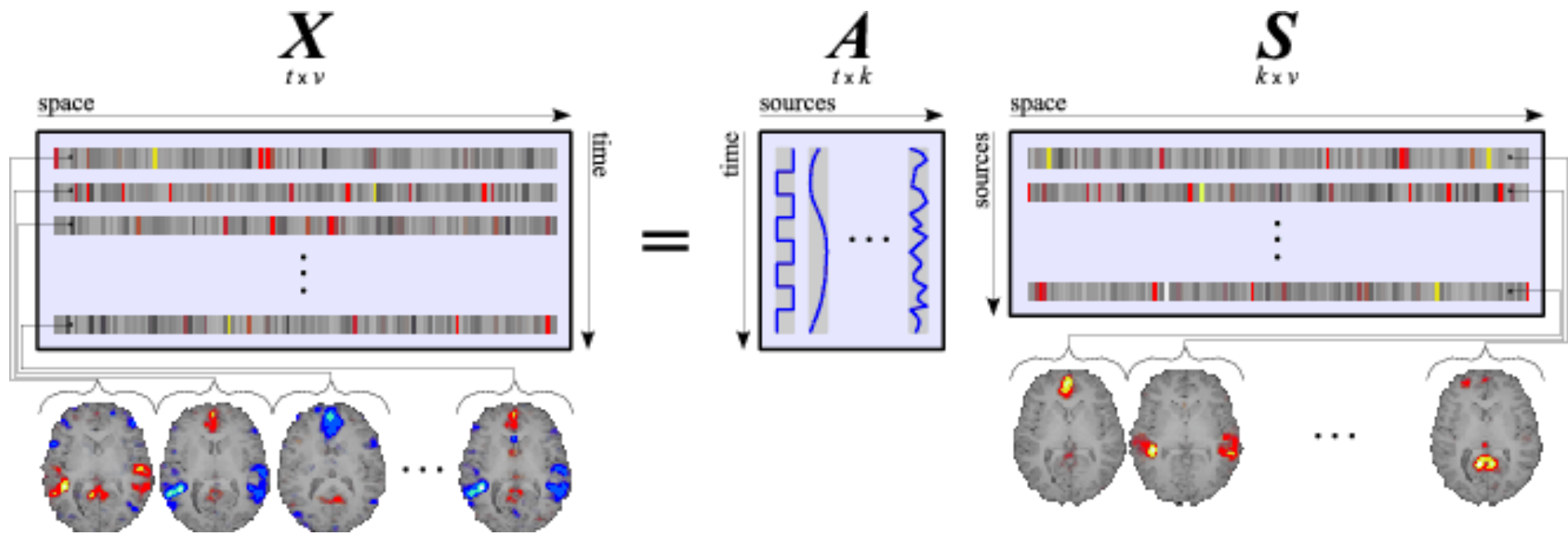


Biswal et al., Magn. Reson. Med. 19

Smith et al, PNAS 2009

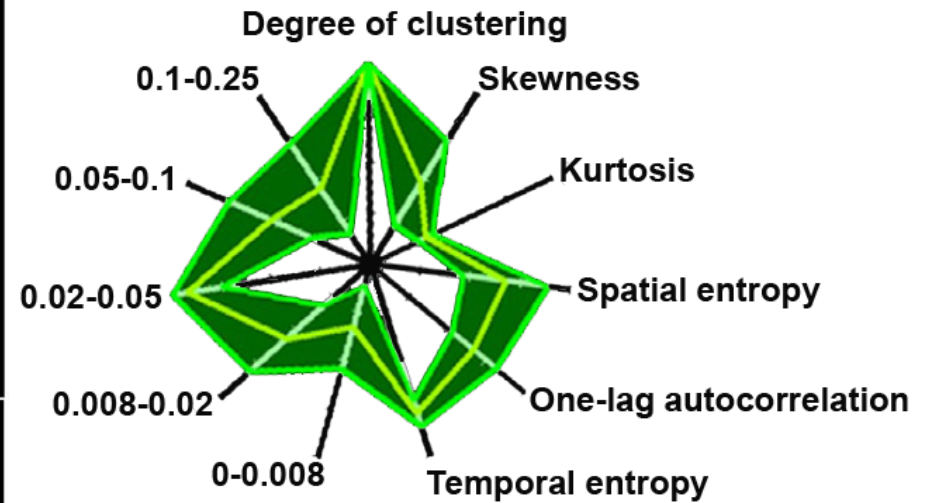
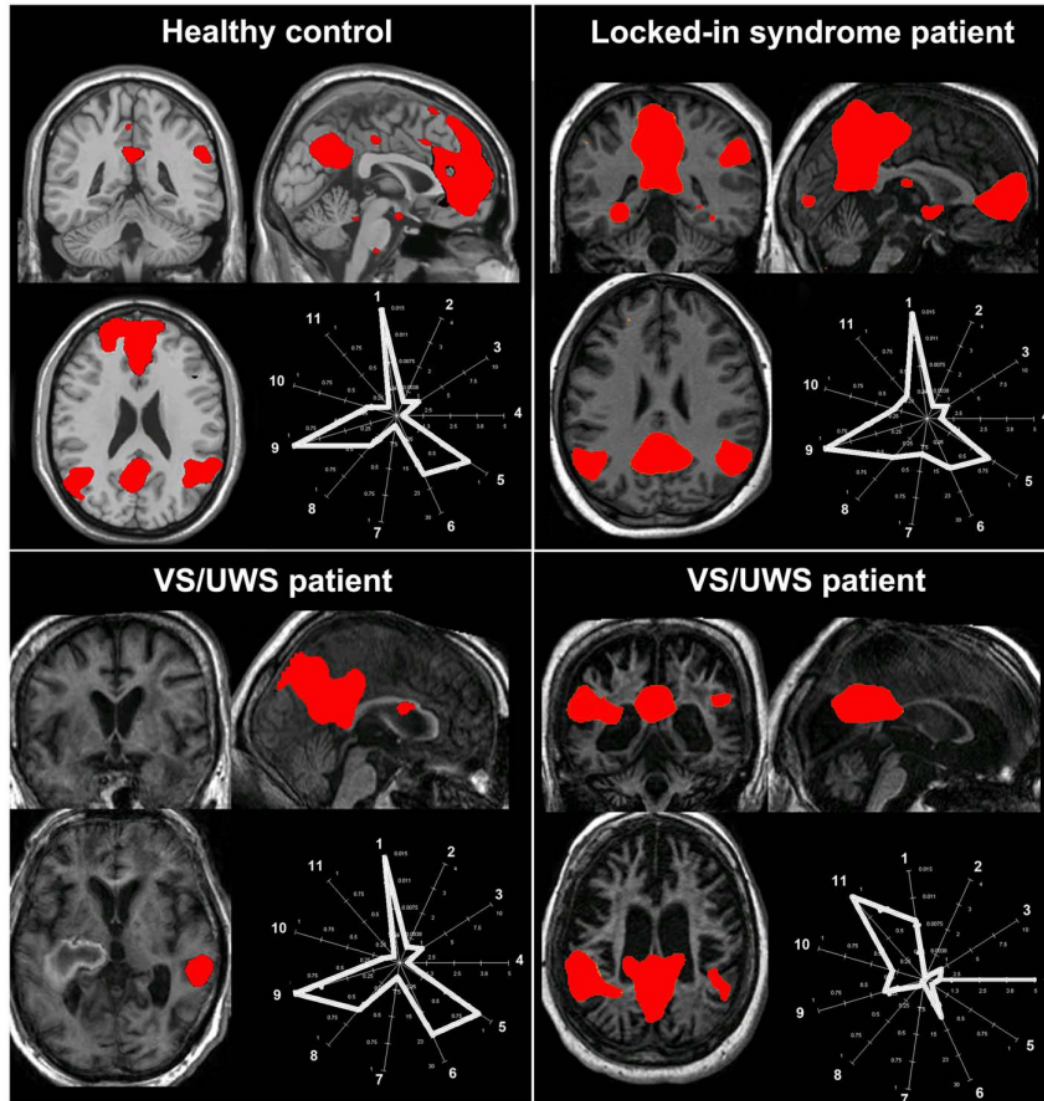


Independent component analysis (ICA)



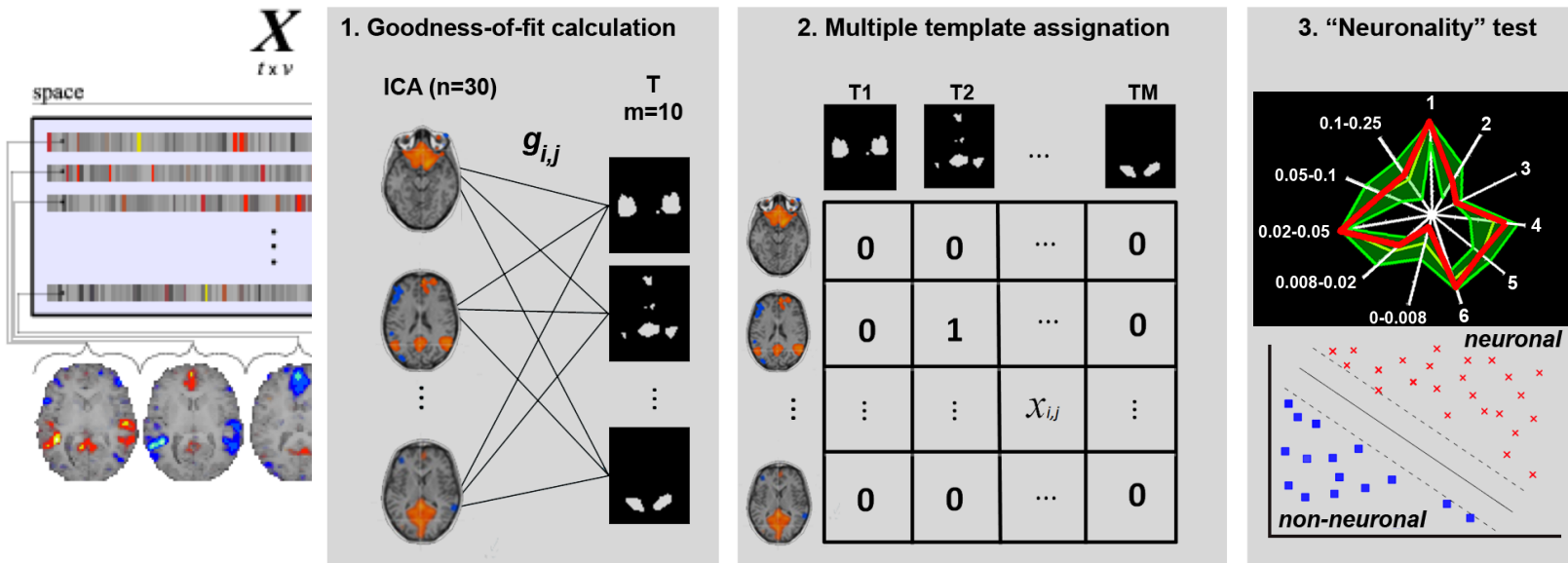
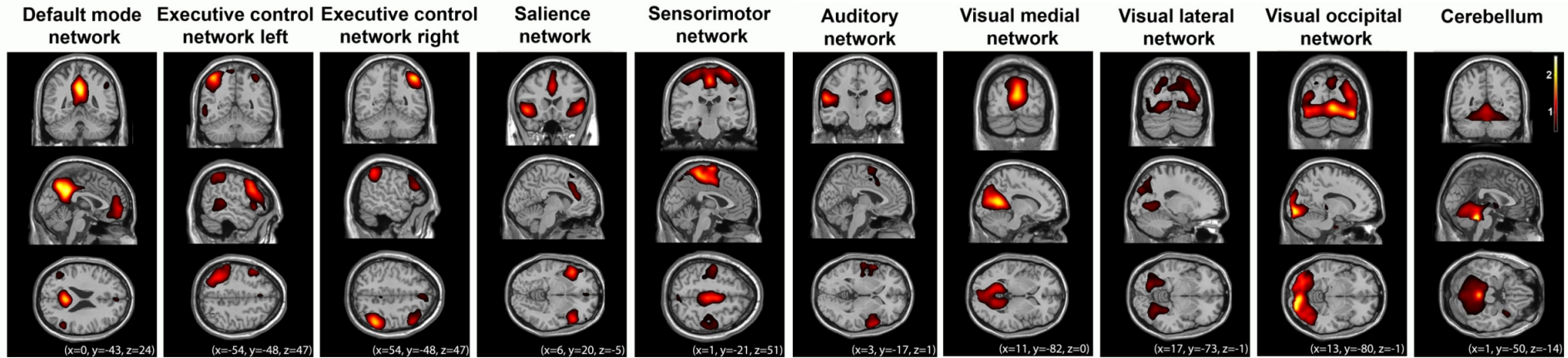


A challenge...





Systems-level intrinsic connectivity

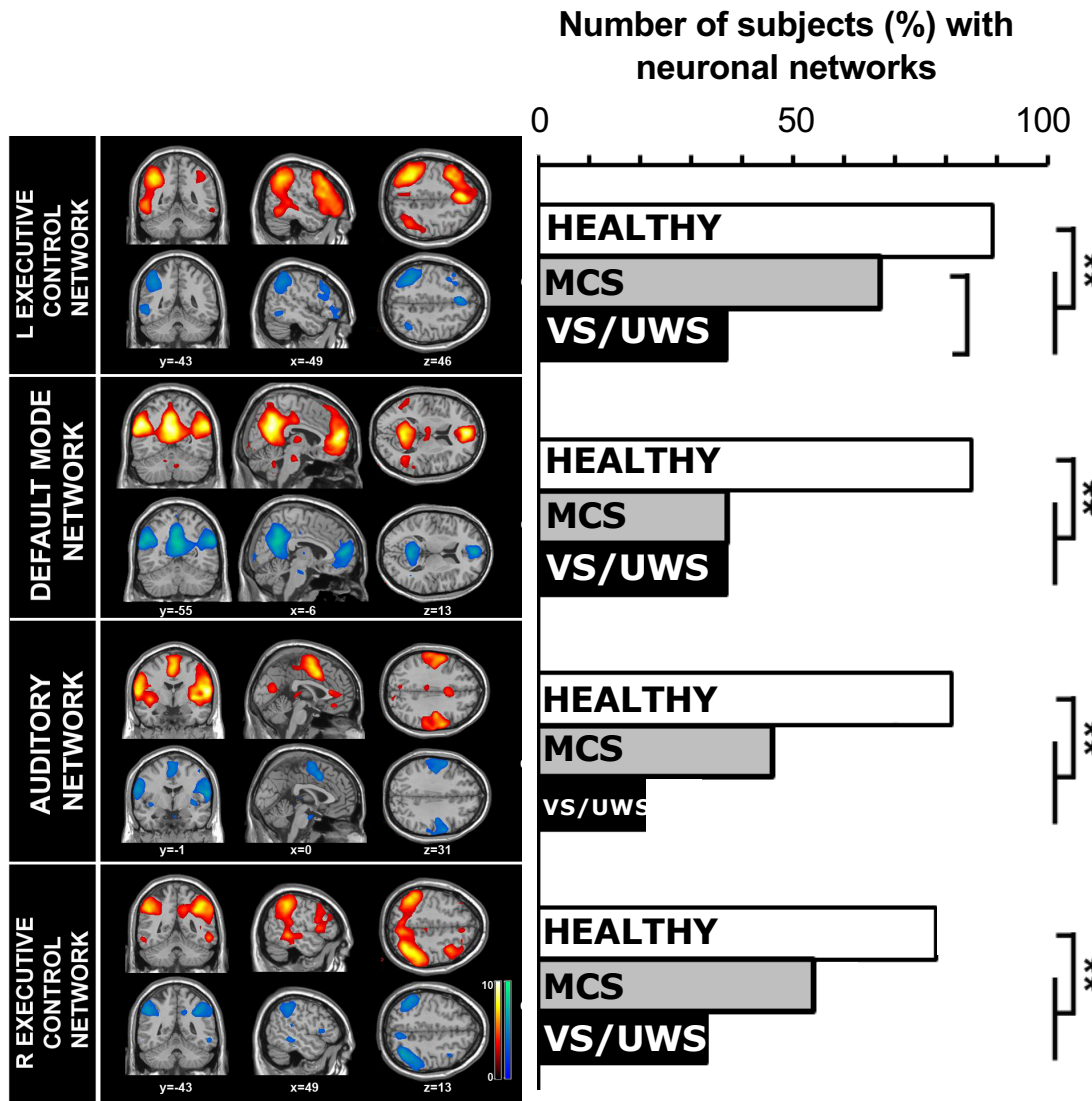


Demertzi & Gómez et al, Cortex 2014

Heine et al, Front Psychol 2012; Smith et al, PNAS 2009; Beckmann et al, Phil. Trans. R. Soc. B 2005



Fewer “neuronal” networks in DOC

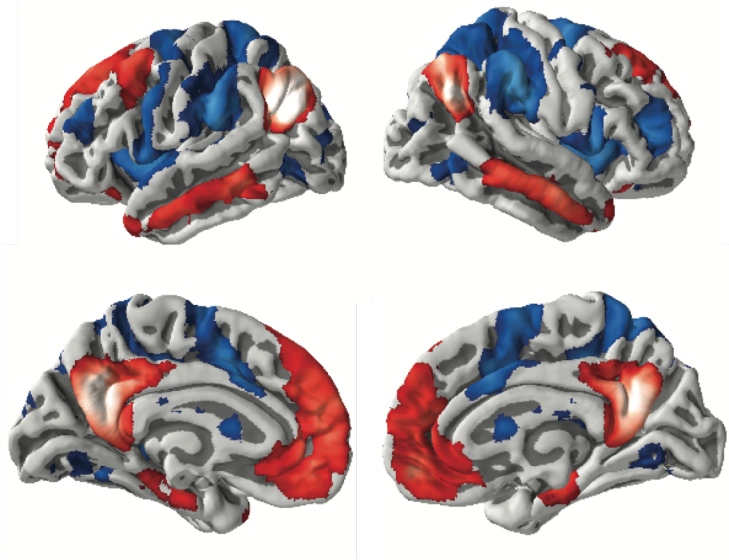


Single-patient classification

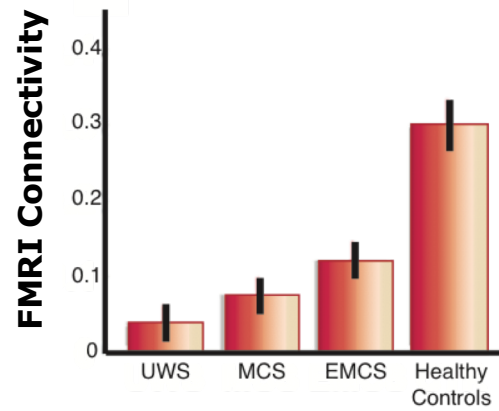
Performance measures	Accuracy	TPR healthy	TPR patients	Selected RSNs
	Healthy vs. all patients			
Neuronal	85.3	.82	.87	Auditory, DMN



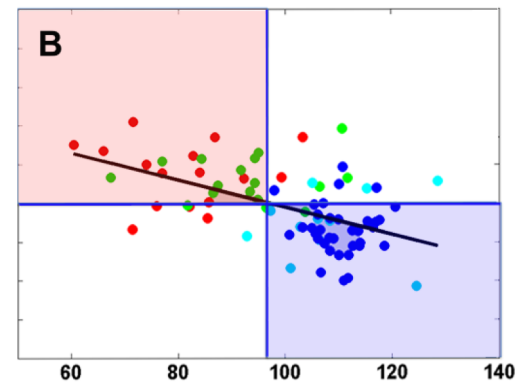
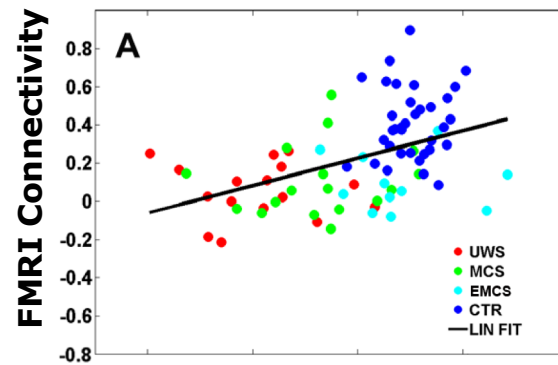
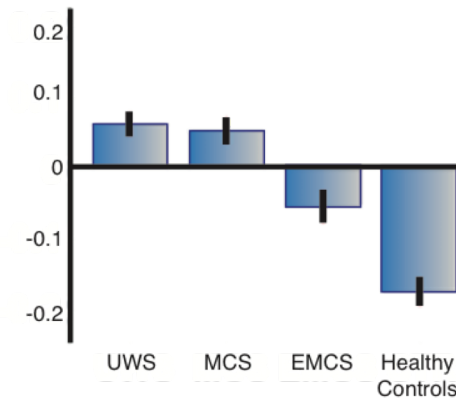
Effect of pathology



DMN CORRELATIONS



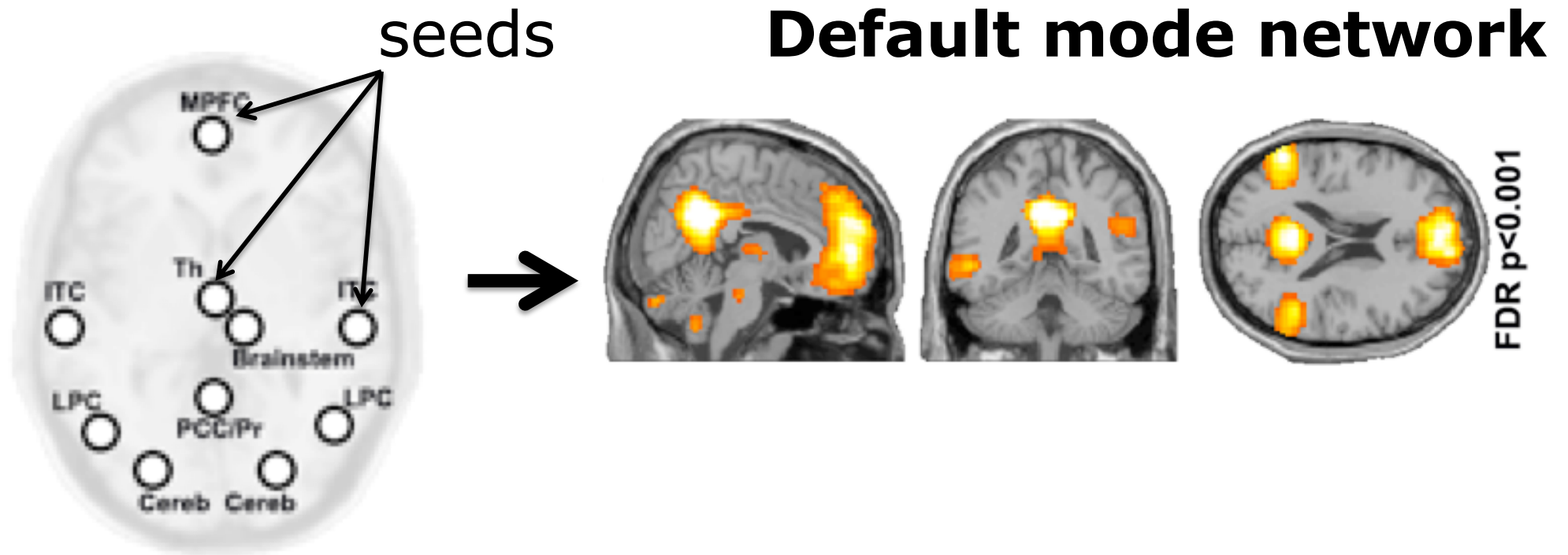
DMN ANTICORRELATIONS



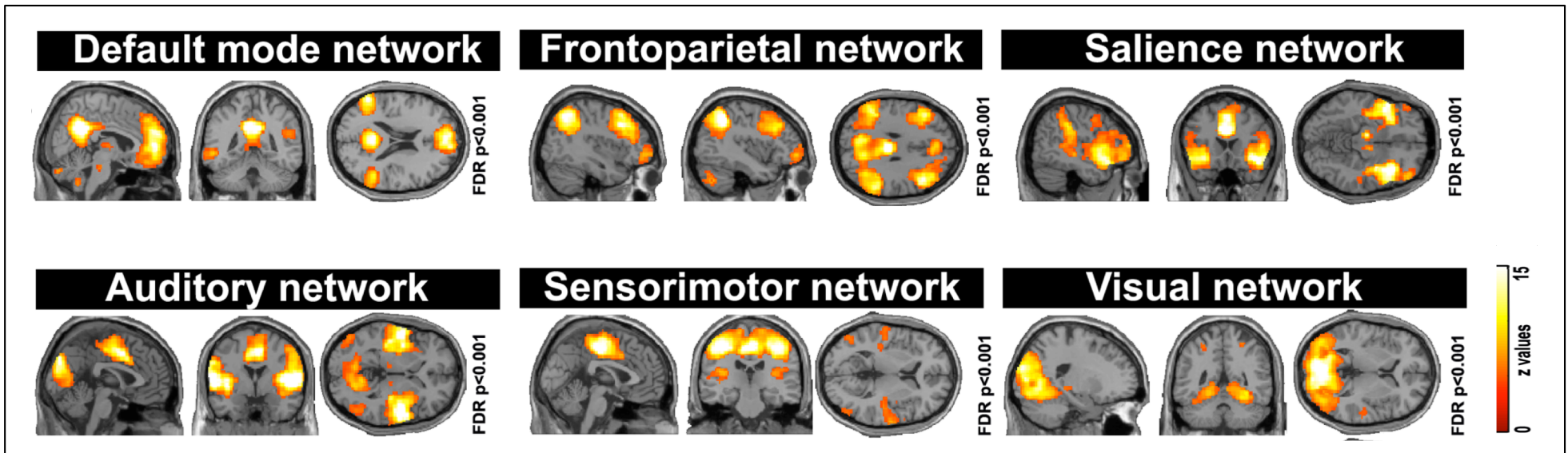
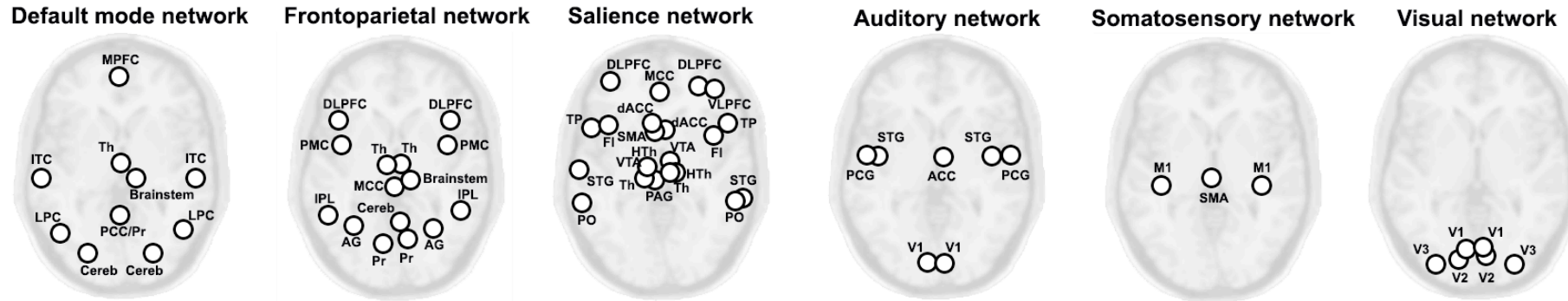
Brain metabolism



Seed-based functional connectivity

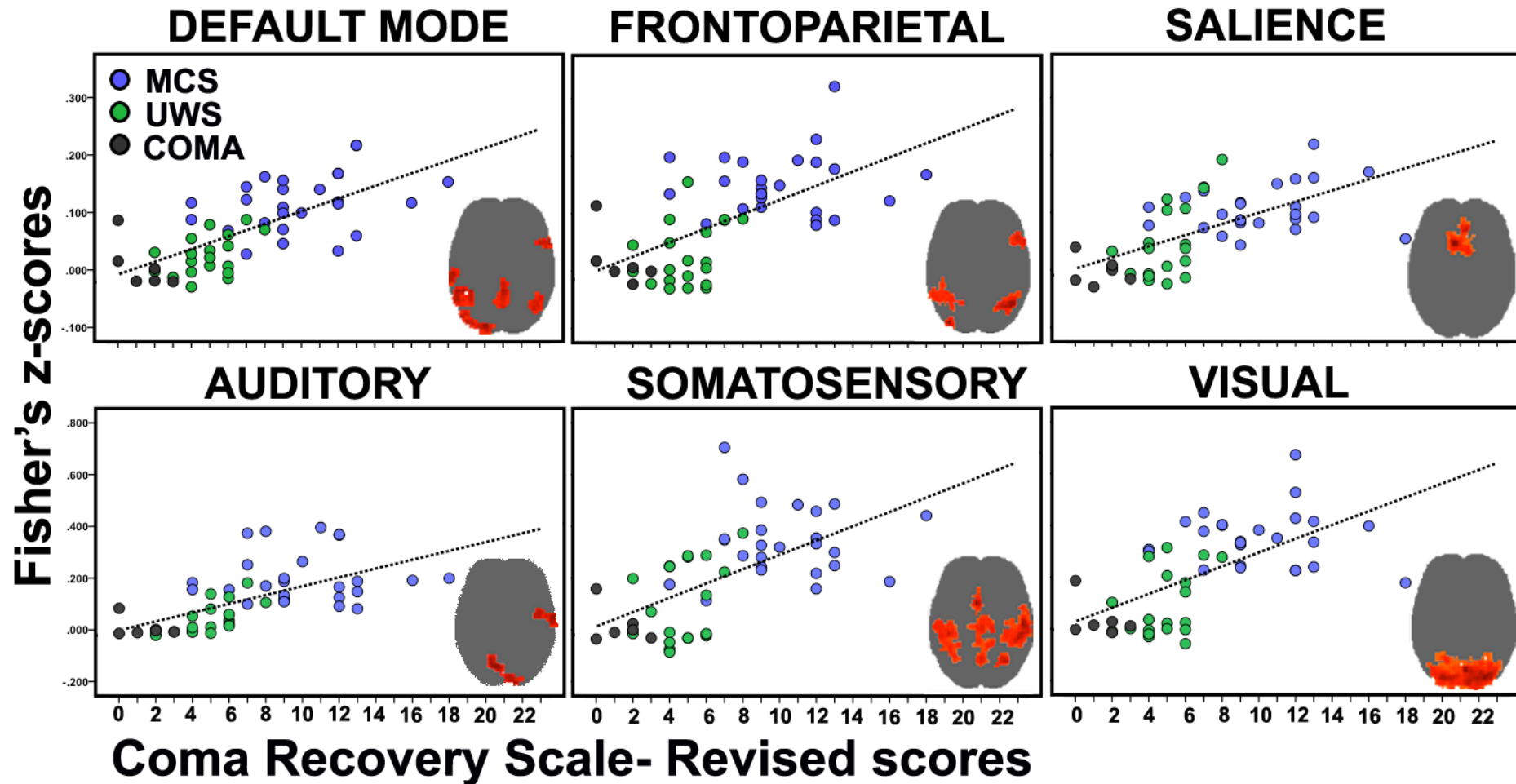


Seed-based functional connectivity





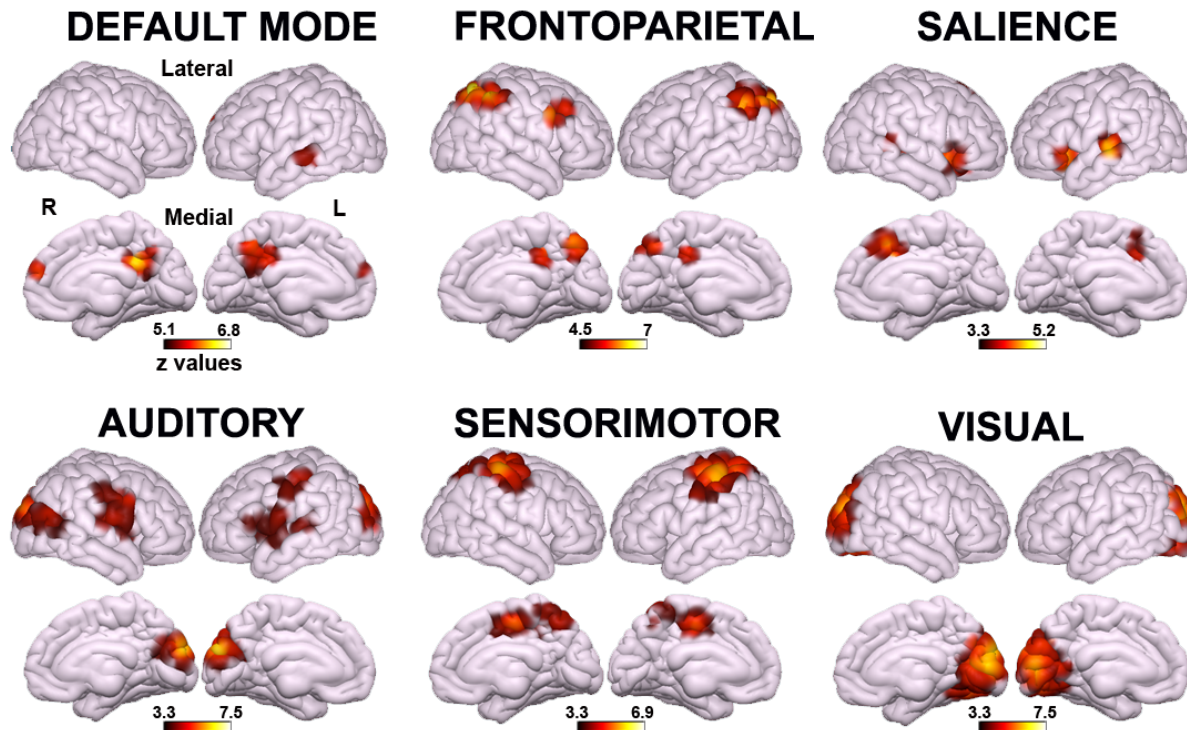
Connectivity reflects C state





Which network discriminates best?

MCS > VS/UWS

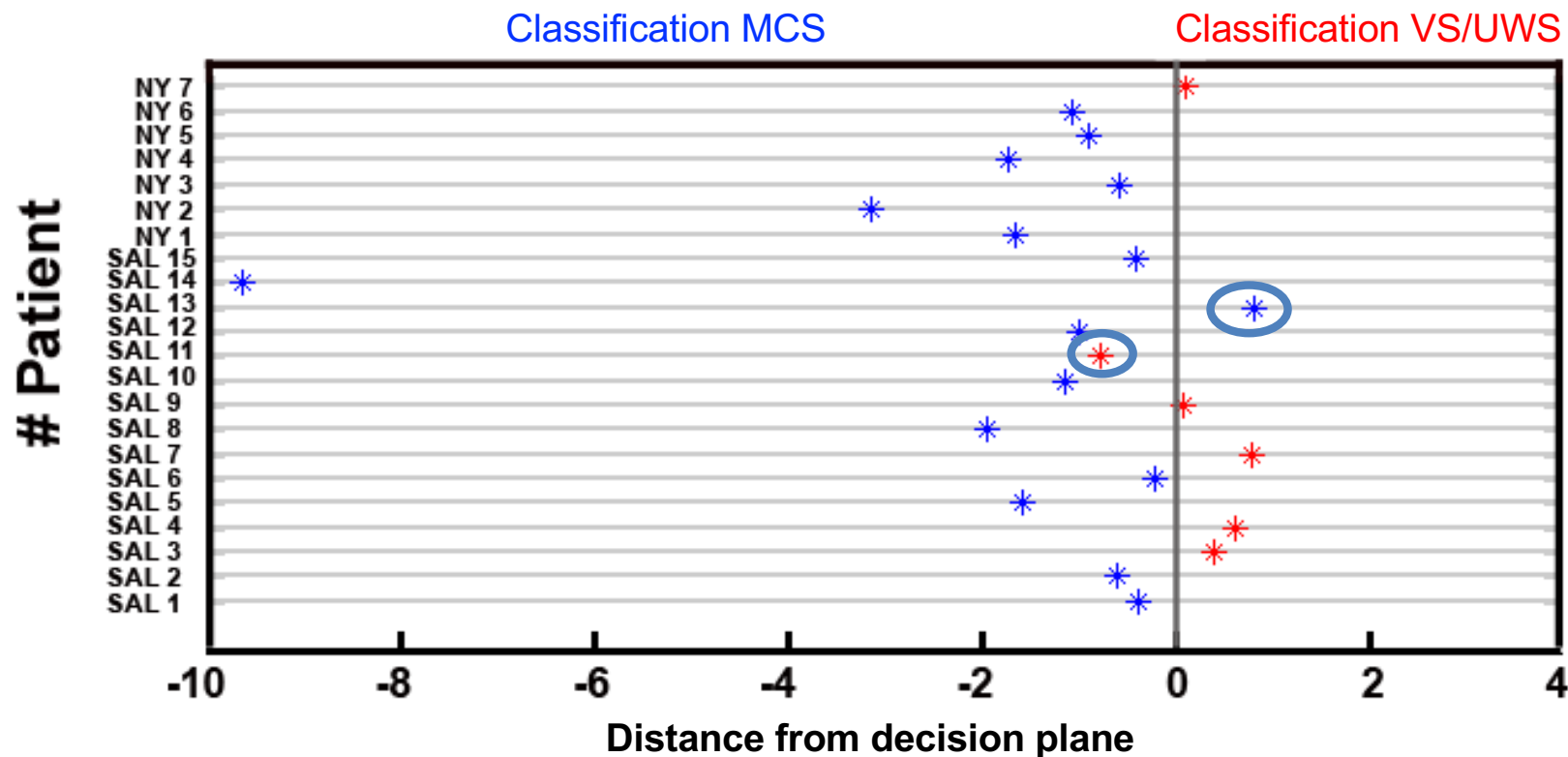
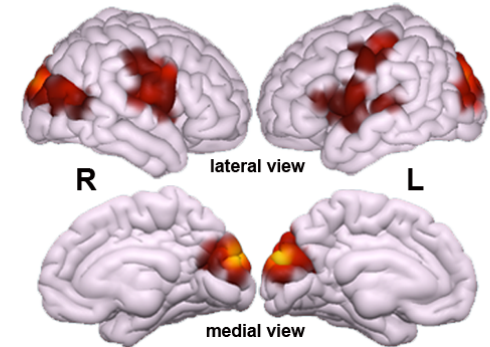


FWE $p < 0.05$ (cluster-level)

Network	Feature selection criterion (t-test)			Single-feature classification		
	t value	Rank	p value	TP MCS	TN VS/UWS	Accuracy
Auditory	8.32	1	<.001	25	18	43/45
Visual	7.79	2	<.001	23	15	38/45
Default mode	6.95	3	<.001	23	15	38/45
Frontoparietal	6.82	4	<.001	23	15	38/45
Salience	6.21	5	<.001	24	15	39/45
Sensorimotor	5.87	6	<.001	24	13	37/45

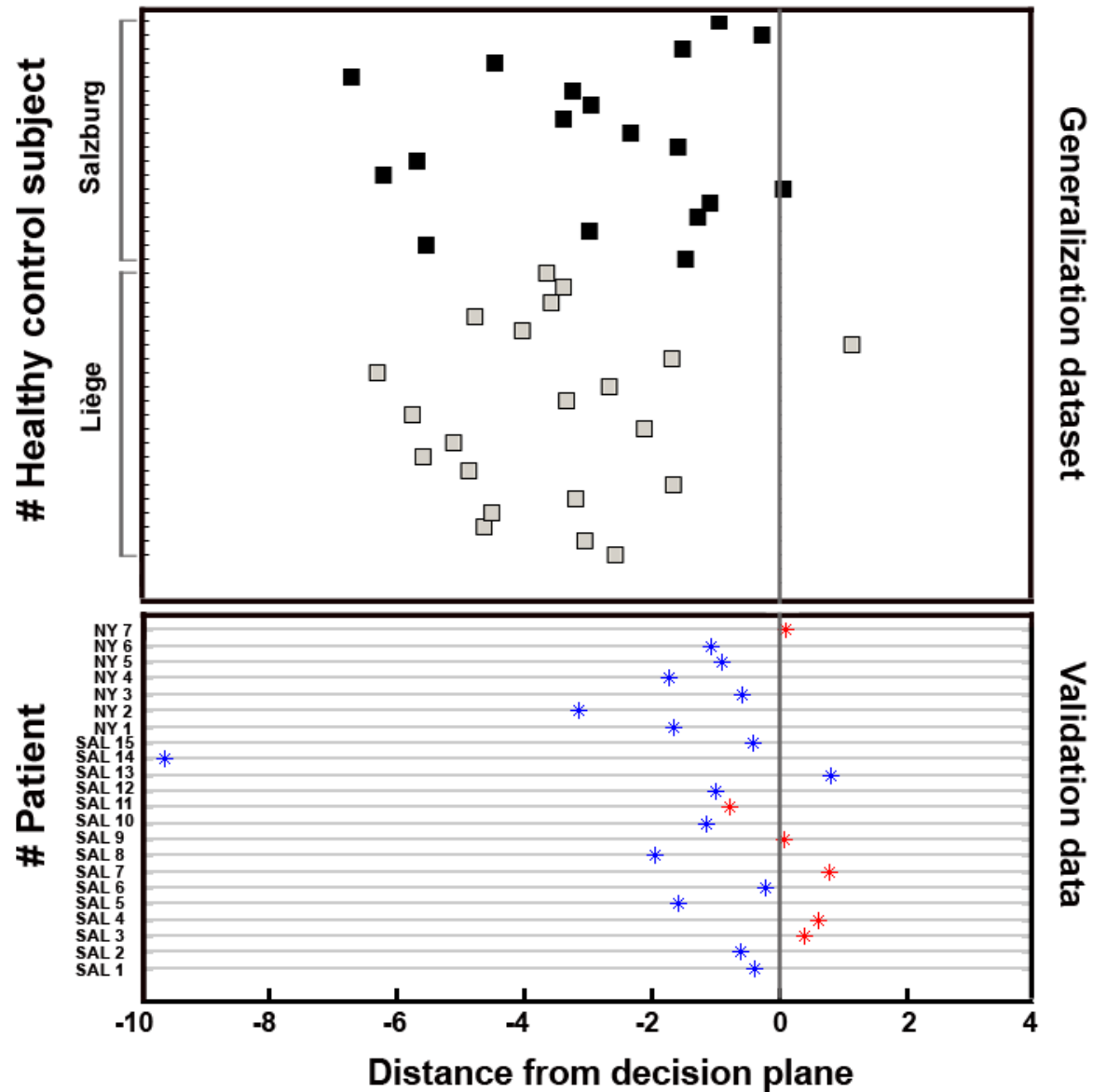
Crossmodal connectivity classifies DOC

- Training set: 45 DOC (26 MCS, 19 VS/UWS)
 - 14 trauma, 28 non-trauma, 3 mixed
 - 34 patients assessed >1m post-insult
- Test set: **16 MCS**, **6 VS/UWS** (M_{age} : 43y, 15 non-trauma; all chronic), from 2 different centers





Classifier generalizes to healthy





Why does it matter?



The American Journal of Bioethics, 8(9): 3–12, 2008

Target Article

Neuroimaging and Disorders of Consciousness: Envisioning an Ethical Research Agenda

Joseph J. Fins, Weill Medical College of Cornell University*

Judy Illes, University of British Columbia*

James L. Bernat, Dartmouth Medical School**

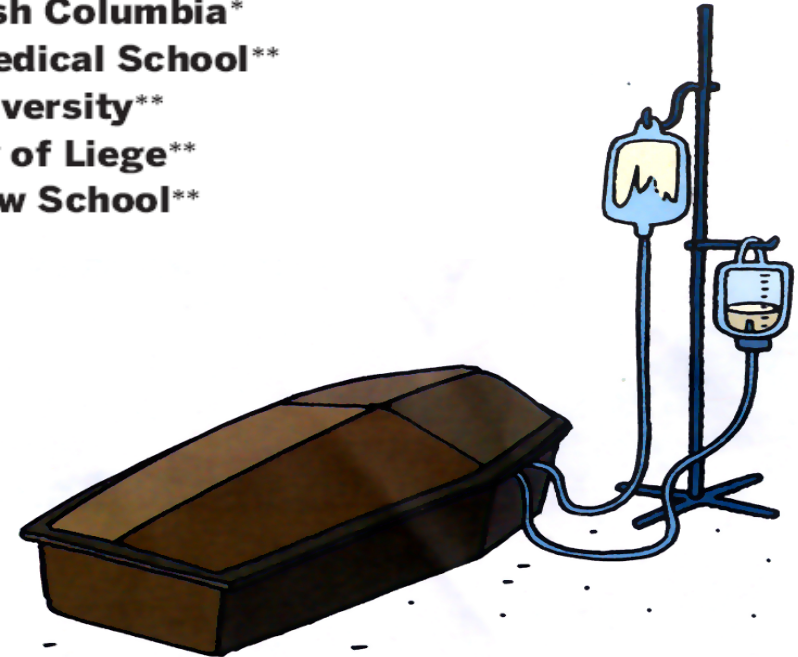
Joy Hirsch, Columbia University**

Steven Laureys, University of Liege**

Emily Murphy, Stanford Law School**

*Co-lead authors.

**Equal authors in alphabetical order.



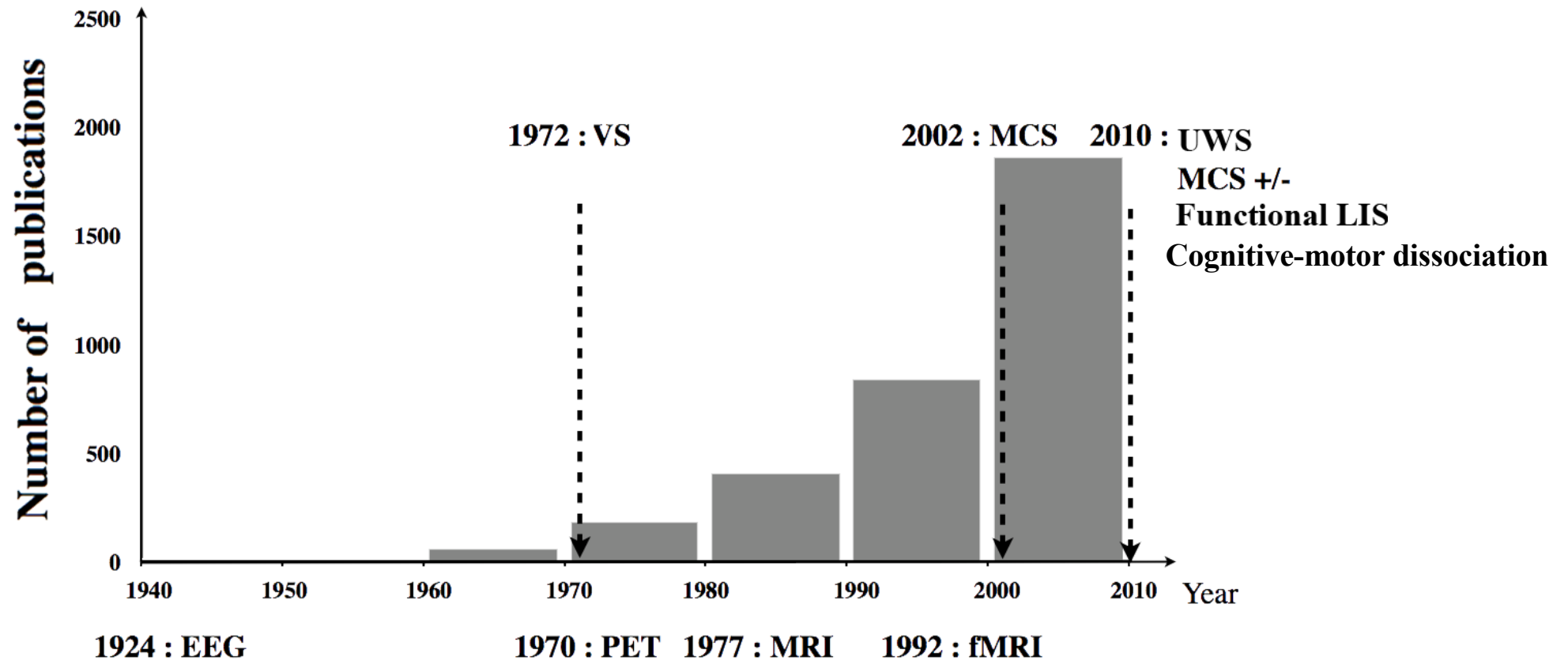


Balancing costs-benefits

Results of Tests	Beneficial Effects	Harmful Effects
- brain activity than neurological examination	Relatives: decisions to limit life-sustaining treatment	Relatives: may lose hope, purpose, and meaning in life
+ brain activity than neurological examination	Clinical management: may be intensified by the chance of further recovery	Relatives: false hopes
Same as neurological examination	Clinicians & relatives: may be affirmed in their decision about the level of treatment	Clinicians & relatives: may be disappointed & treatment cost/effectiveness may be poor

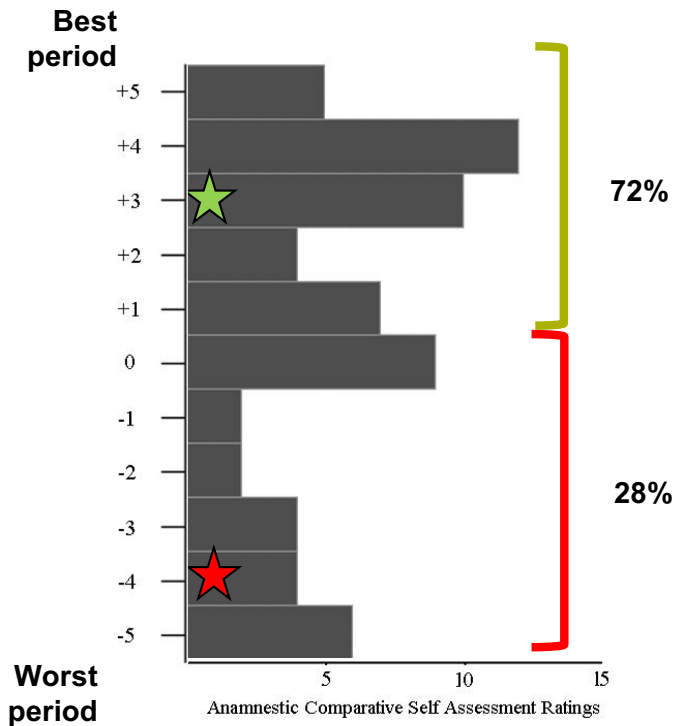


Benefit for science

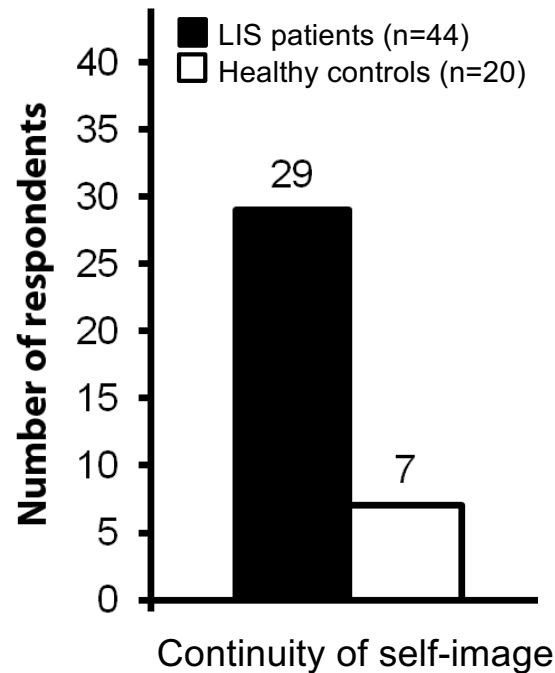




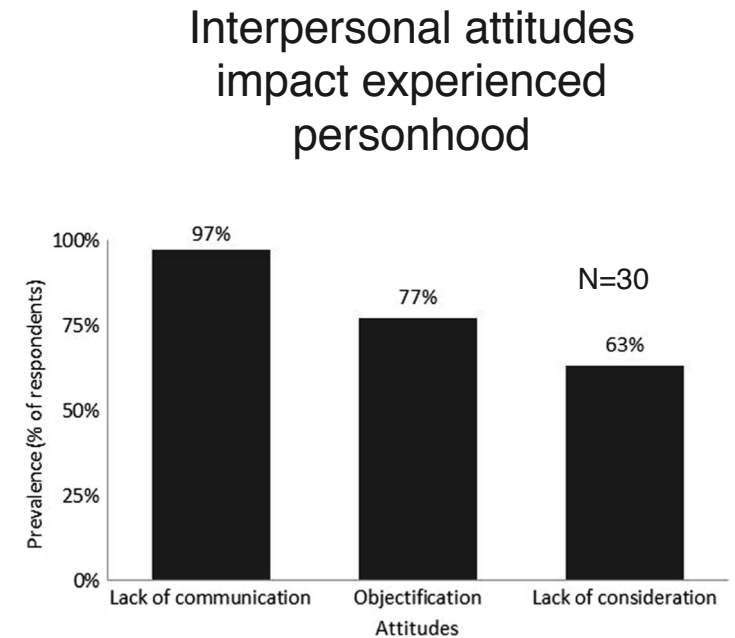
Benefit for patients?



Bruno et al, *Br Med J Open* 2011



Nizzi & Demertzi et al, *Conscious & Cogn* 2012



Nizzi, Blandin, Demertzi *NeuroEthics* 2018



Benefit for caregivers?

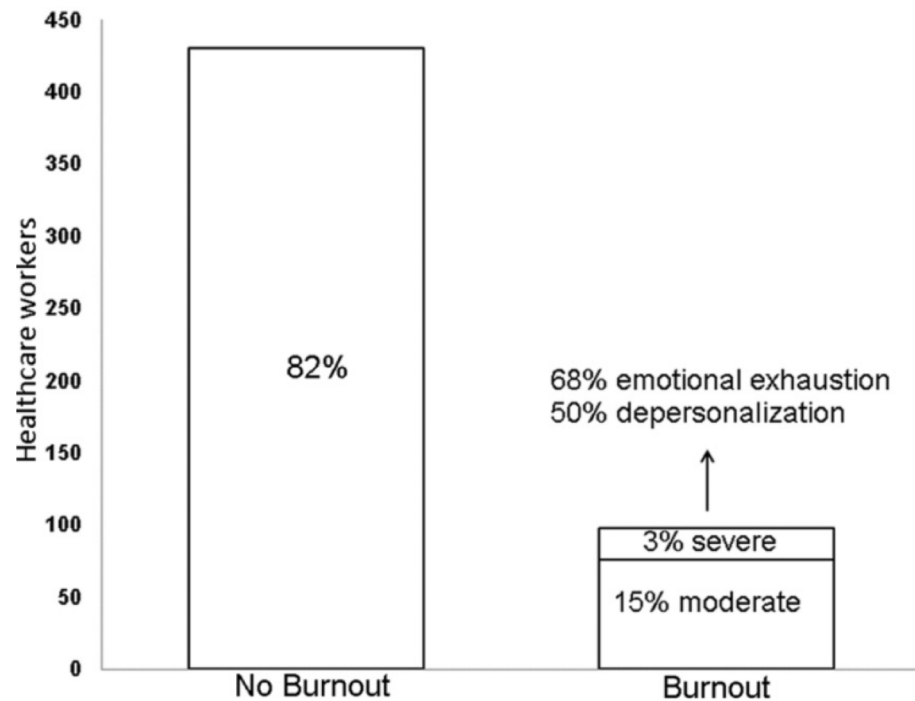


Table III. Percentage of healthcare workers presenting a burnout.

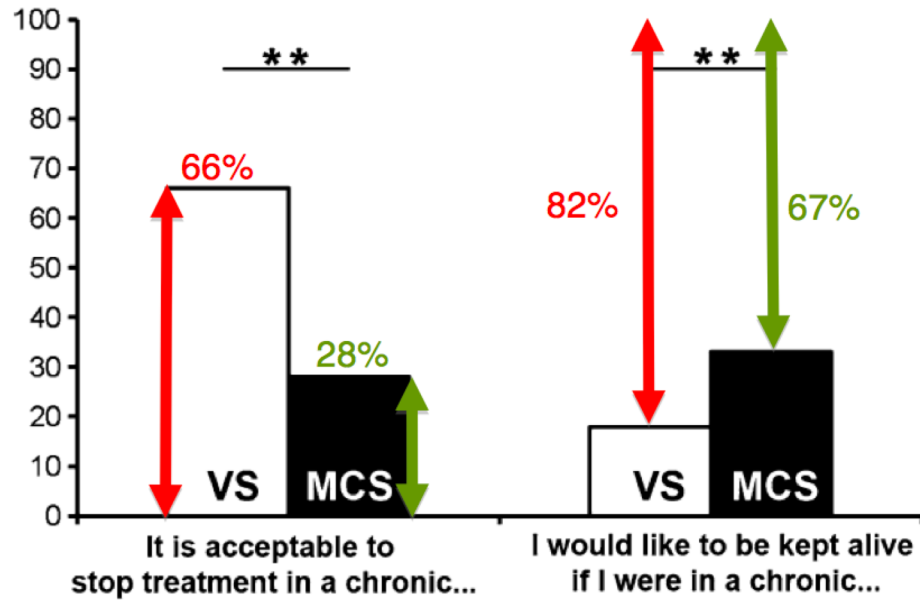
Profession	Burnout
Physician	8%
Nurse	24%
Nursing assistant	23%
Physio-/speech-/ergo-therapist	8%
Psychologist/social worker	10%

n=523



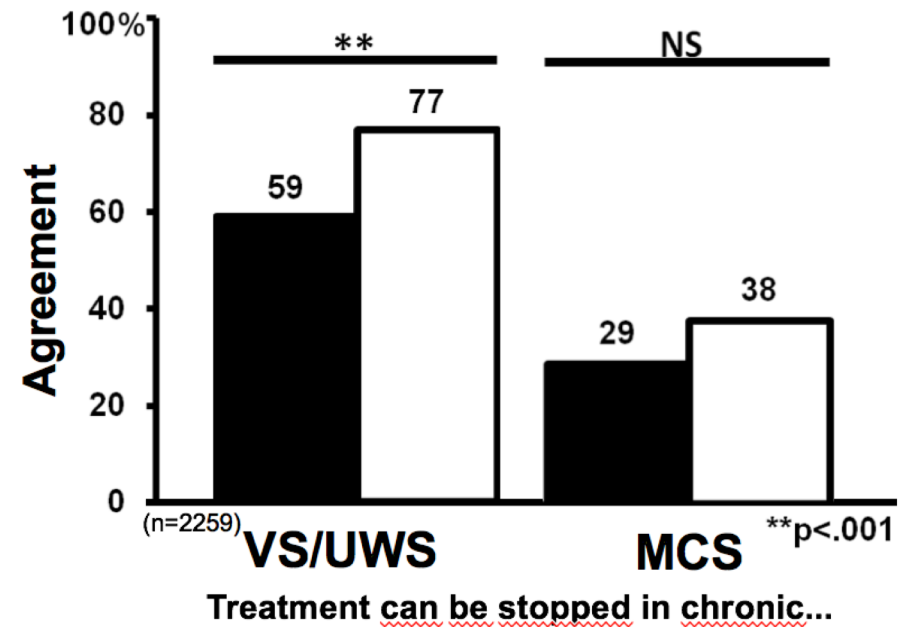
Consciousness has a moral significance

2,475 medical professionals



Demertzi et al, *J Neurol* 2011

■ Feel pain
□ Do not feel pain



Demertzi & Racine et al, *Neuroethics* 2012



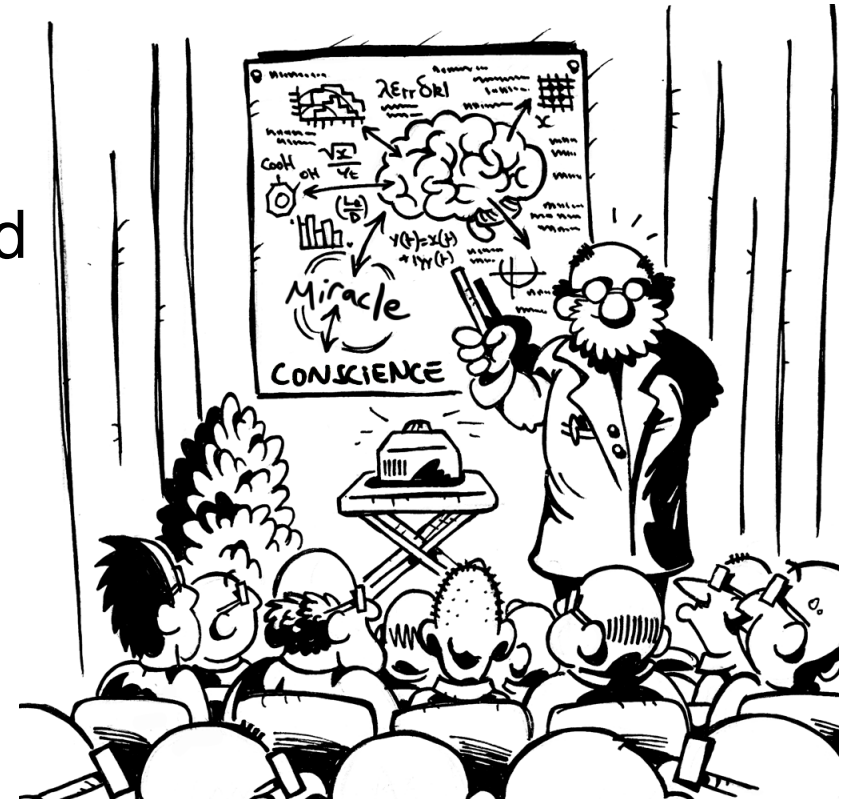
Neuro-ethical considerations

- The moral significance of Consciousness
 - ontological understanding: consciousness = personhood = moral agency
 - relational or contextual understanding: patients have value for others
- Legal challenges: responses to critical questions with NI
- Cognitive neuroscience is about brain/mind reading
 - to what degree do we neuroscientists have the right to interfere with a patient's intimacy, such as cognitive contents, in the absence of their consent?
 - in essence, where do we draw the limits of deciphering another person's cognitive content, like dreams, ongoing mentation etc? What is the additive value of it to a societal level?



Conclusions

- fMRI rs fc connectivity carries information about cognition
- fMRI rs fc connectivity can be used in the clinical setting
- fMRI rs fc connectivity needs to generalize to unconscious conditions
- NI studies have ethical consequences



Un si brillant cerveau – Editions Odile Jacob, 2015



Thank you

Coma Science Group & PICNIC Lab

The departments of Neurology and Radiology in Liège & Paris

...and mostly patients and their families!



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 ADemertzi



James S. McDonnell Foundation

