

Tutorial

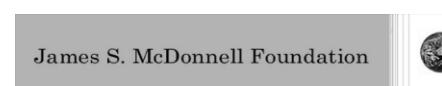
Resting state fMRI as a means to assess the consciousness after severe brain injury

1st Summer School
Interdisciplinary Research on Brain Network Dynamics

June 24 2019, Terzolas ITALY

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The problem

Patients cannot express themselves



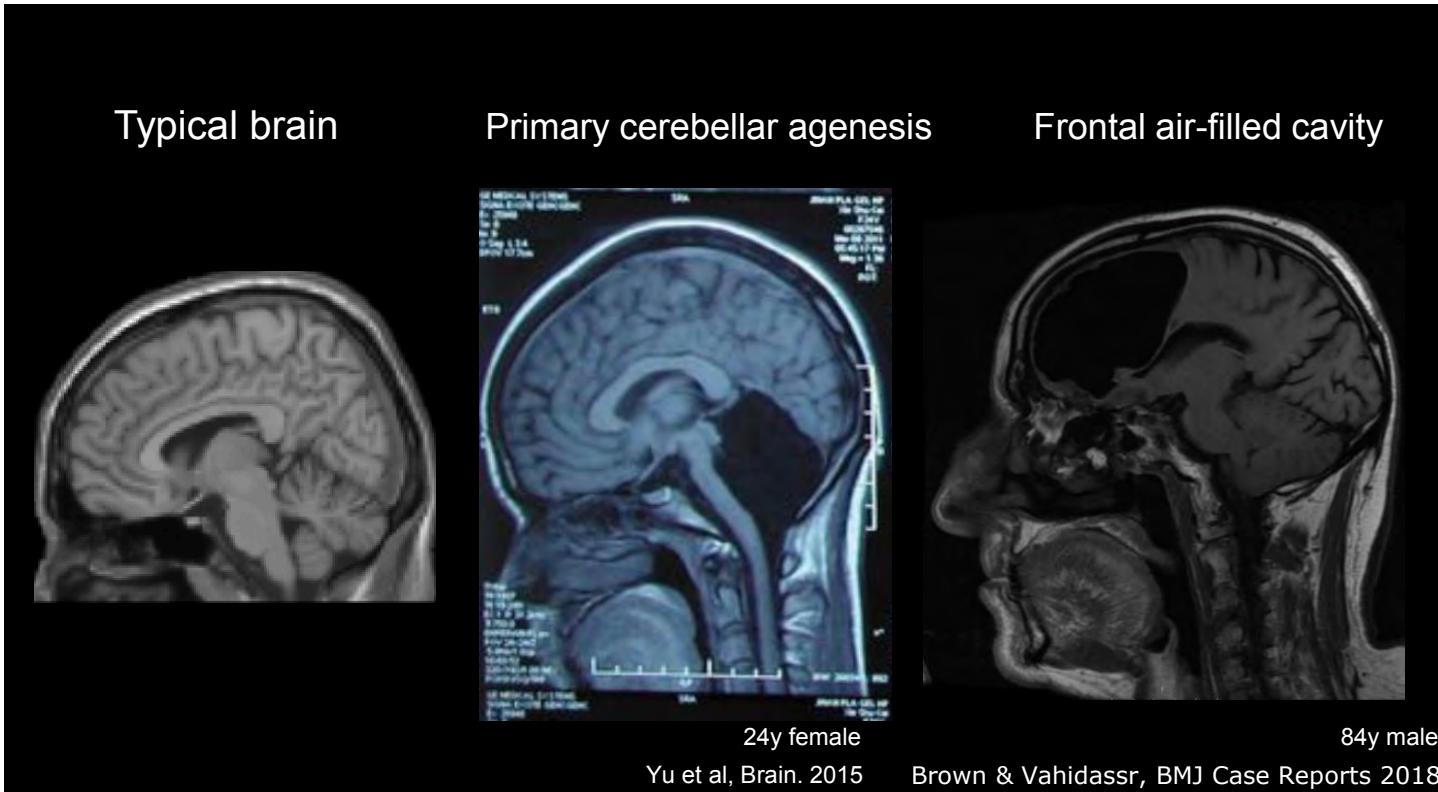
Hable con ella 2002, Pedro Almodóvar

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



How can we be conscious? (1)

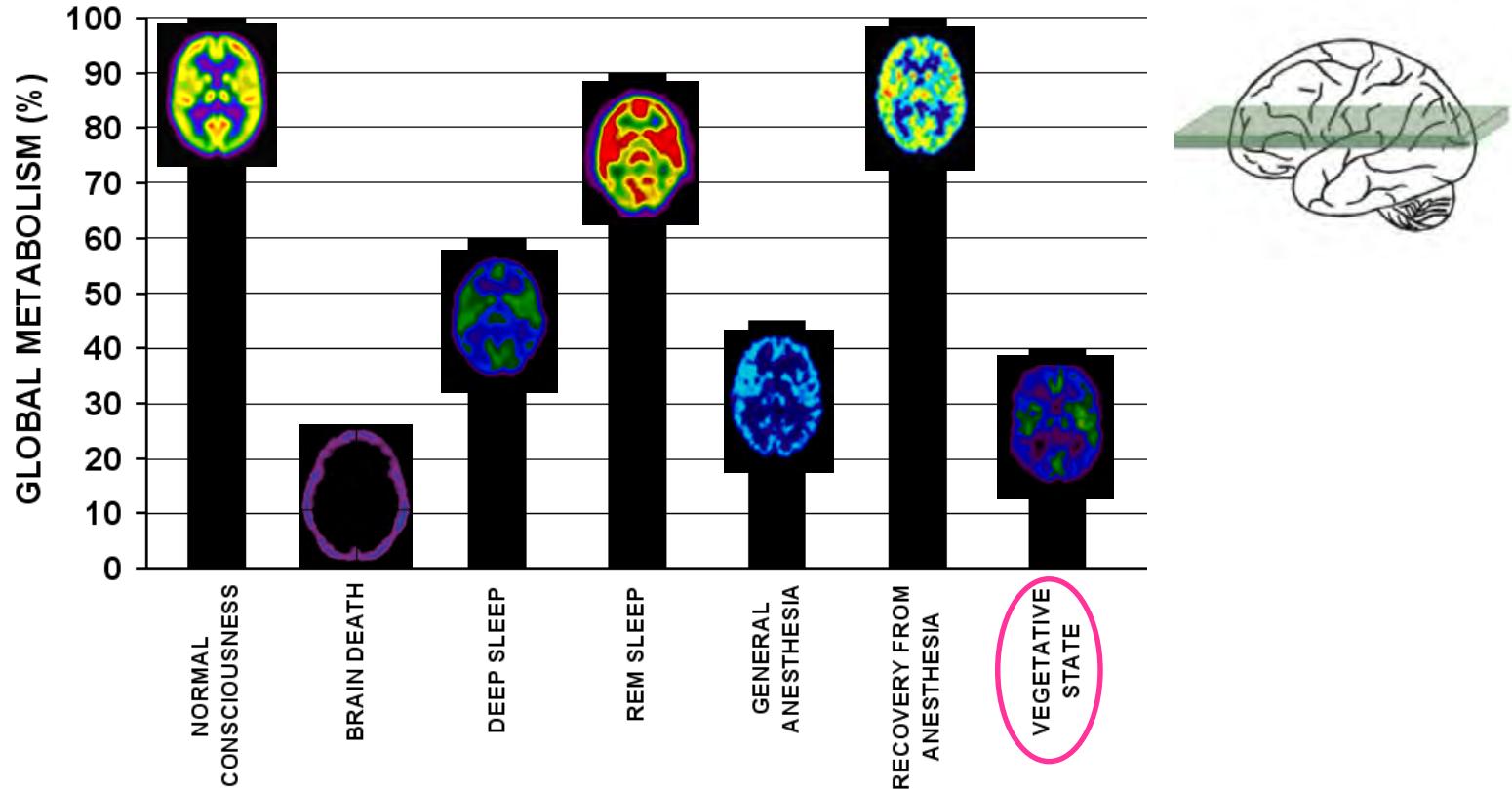
We need a brain (all of it?)





How can we be conscious? (2)

We need a functional brain





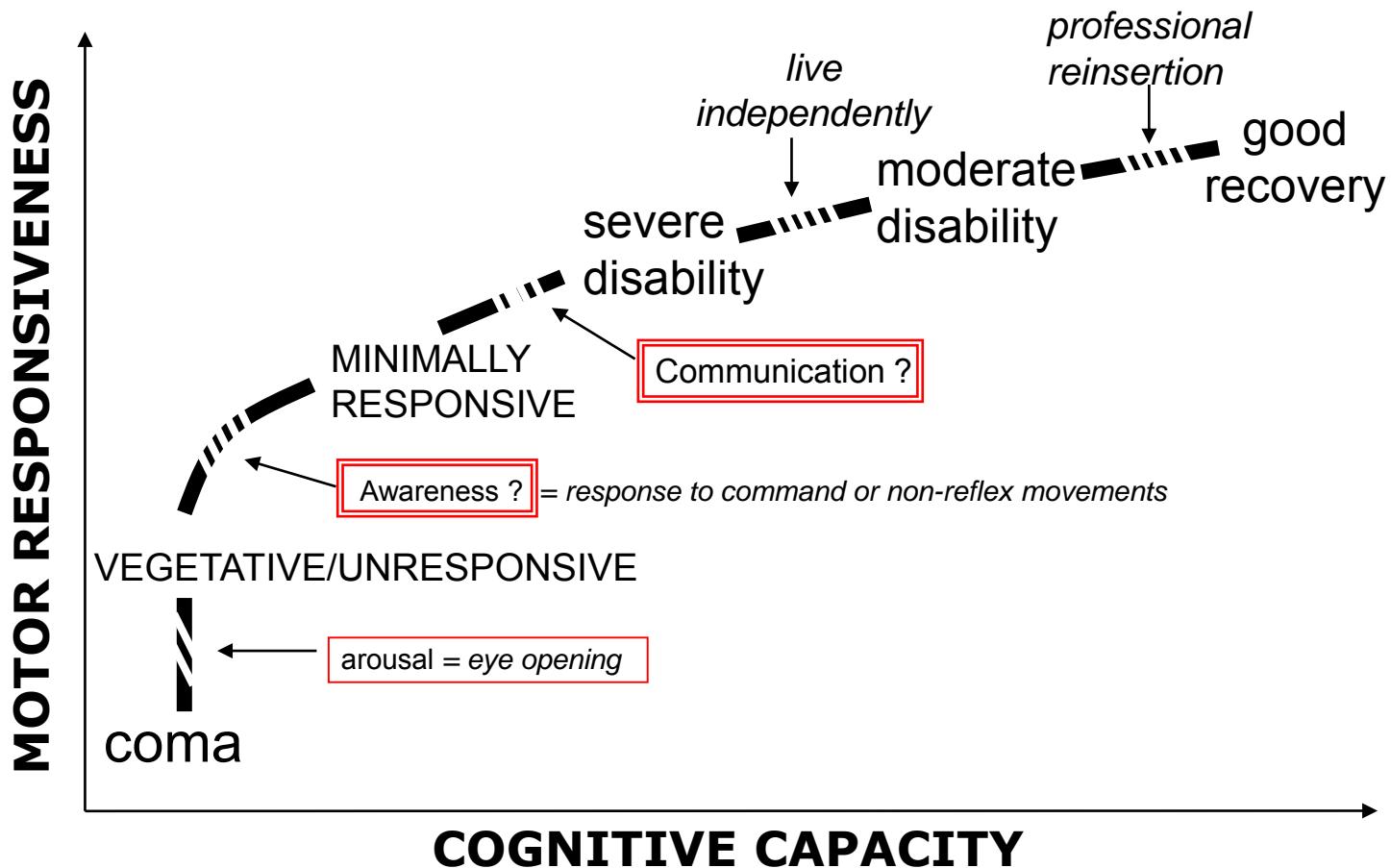
Is she conscious?



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

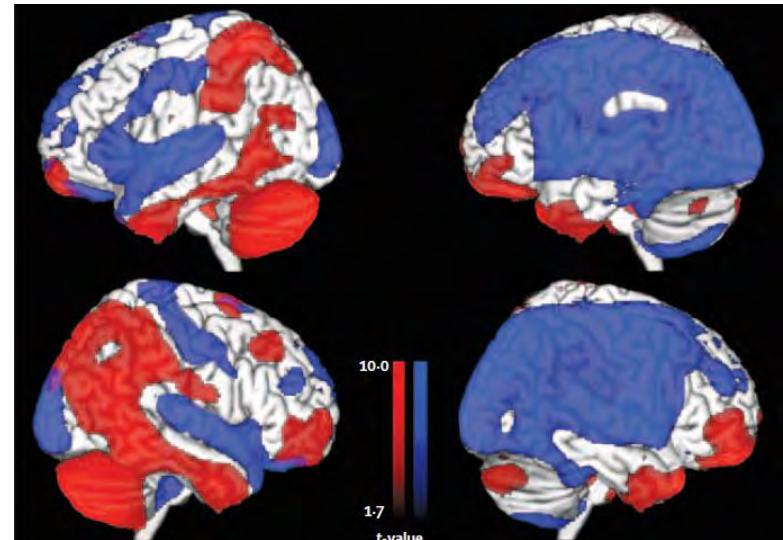
Schnakers et al, *Ann Neurol* 2006; *BMC Neurol* 2009

Neuroimaging

Coma Recovery Scale-Revised results			
	UWS	MCS	Total
Clinical consensus diagnosis			
¹⁸ F-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

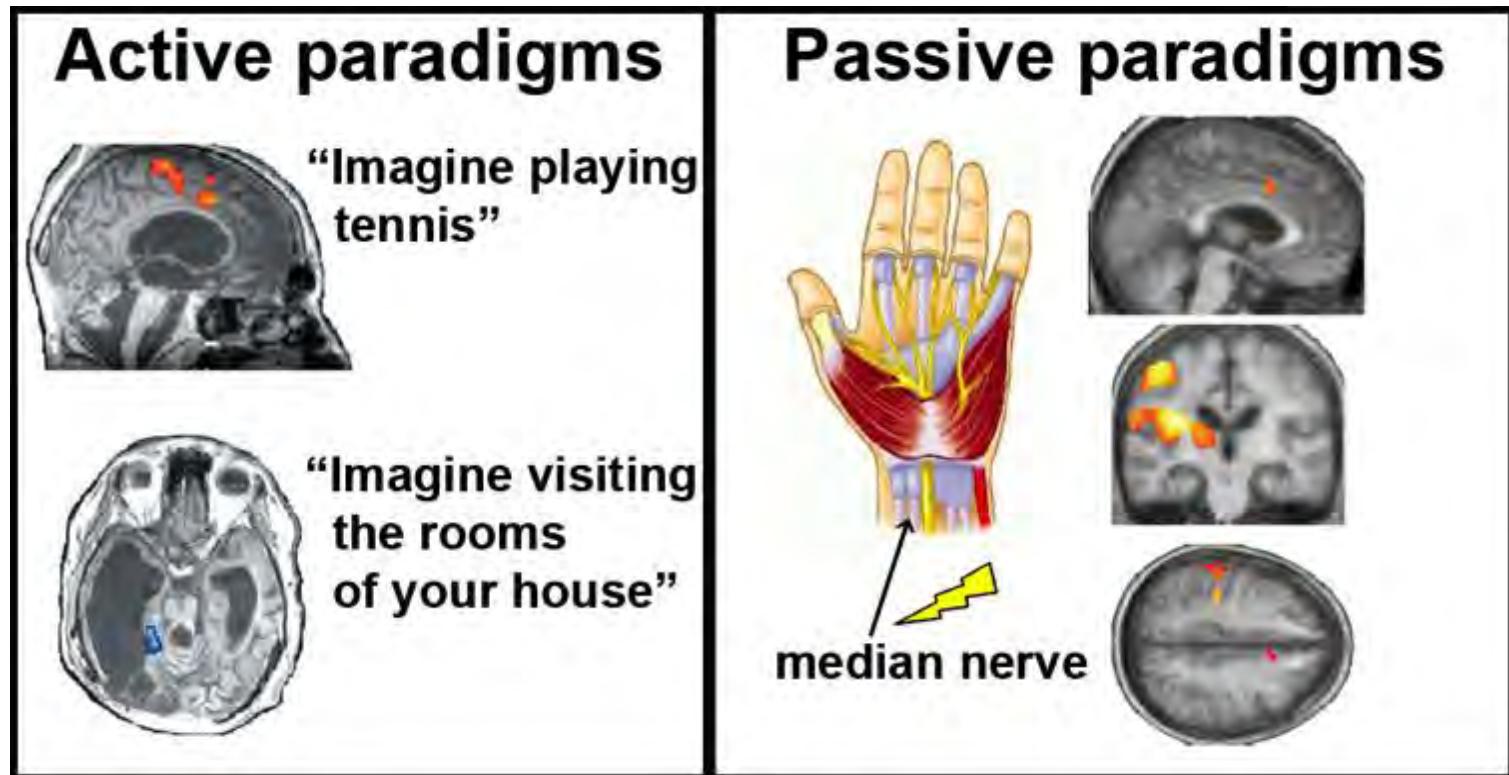


Neuroimaging paradigms

Owen et al, Science 2006

Monti & Vanhaudenhuyse et al, NEJM 2010

Boly et al, Lancet Neurol 2008

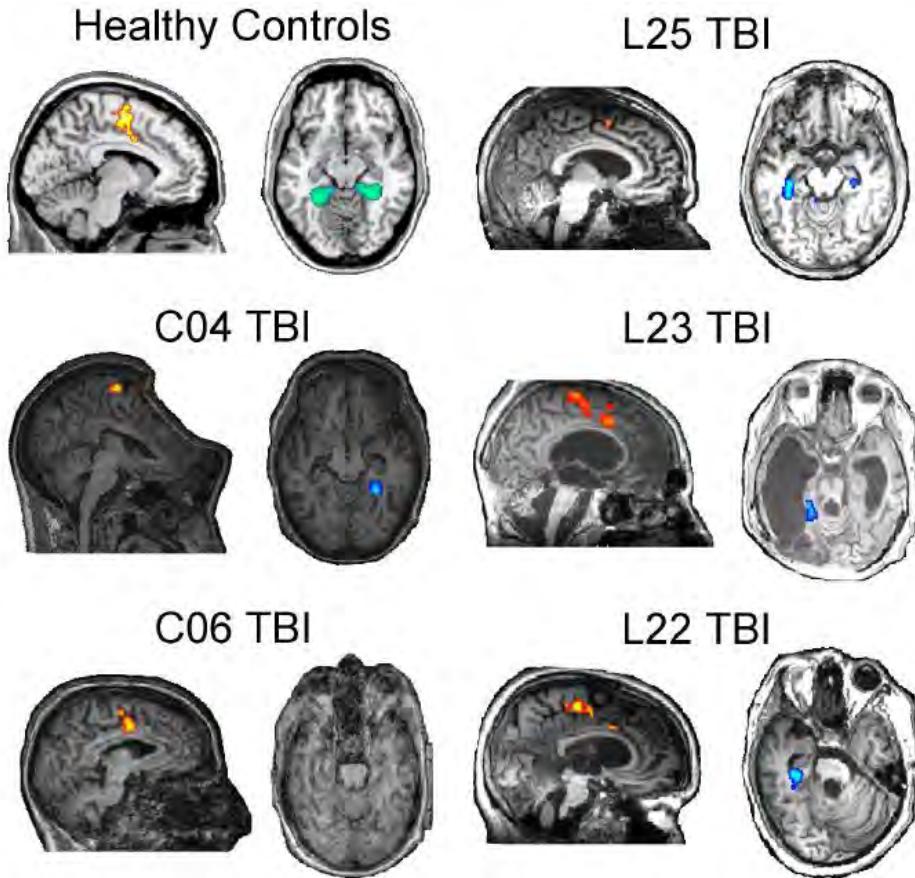


Heine, Di Perri, Soddu, Laureys, Demertzi
In: *Clinical Neurophysiology in Disorders of Consciousness*, Springer-Verlag 2015

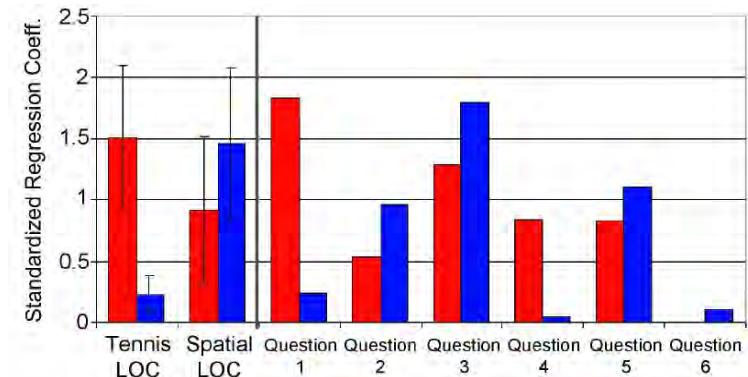
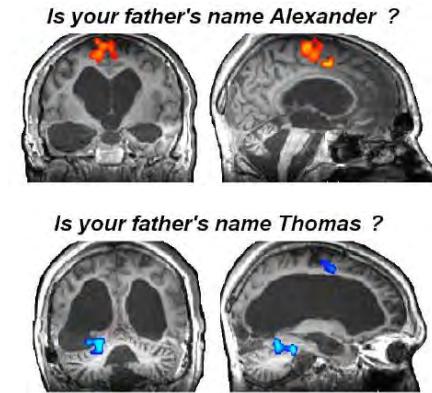
Demertzi & Laureys, In: *I know what you are thinking: brain imaging and mental privacy*, Oxford University Press 2012



Neuroimaging to find “hidden minds”

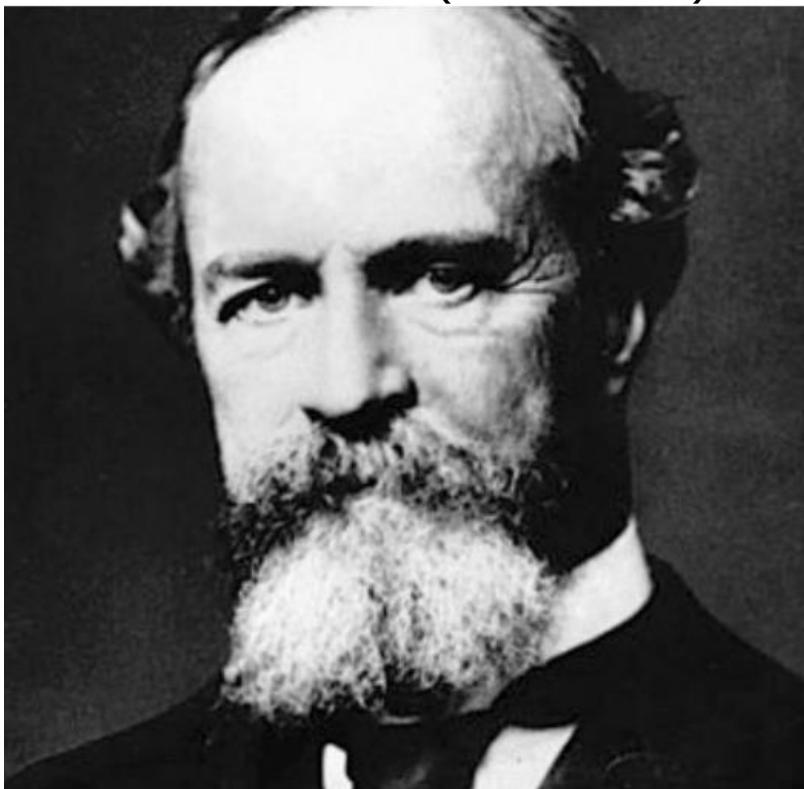


Imagine **Tennis** to answer 'YES'
Imagine **Navigating** to answer 'NO'

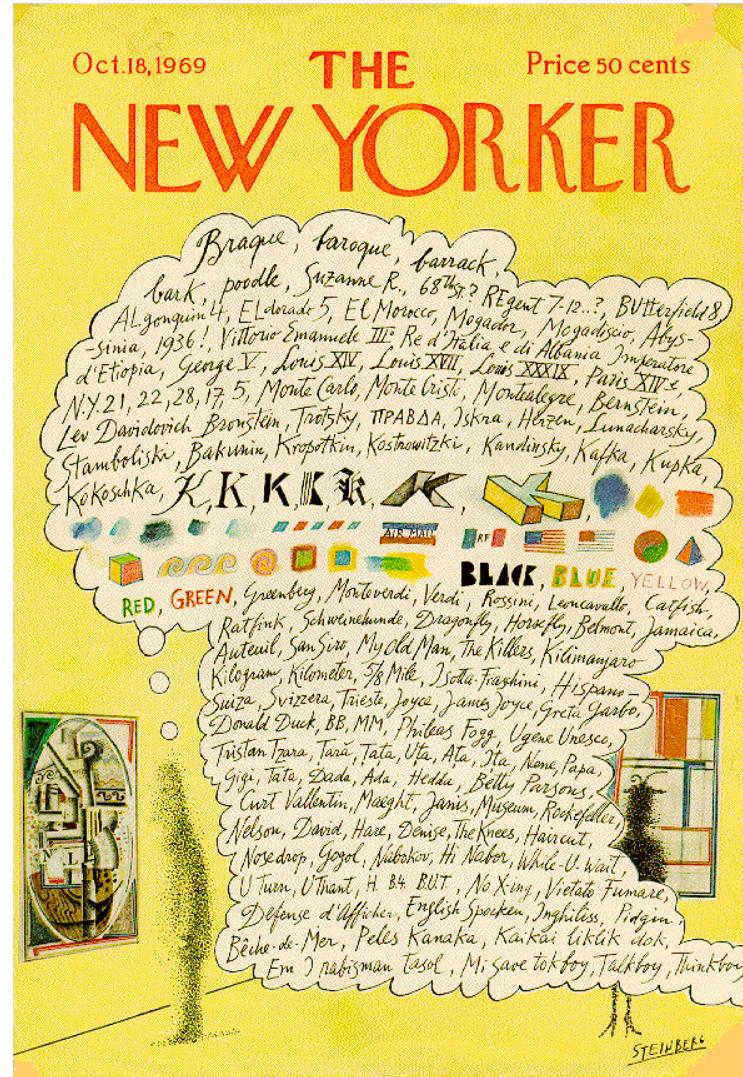


The stream of consciousness

William James (1842-1910)



The stream of thought (Chapter IX)
The principles of psychology 1890





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?



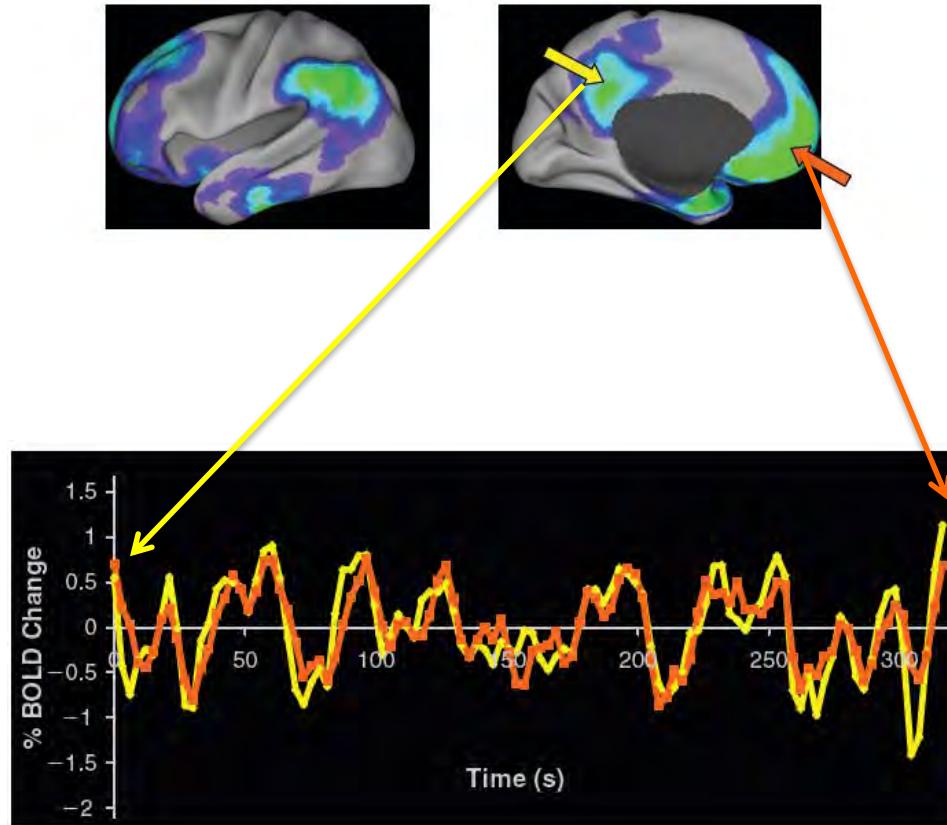
Cognitive psychology: Mental chronometry
(measures the time required to complete specific mental operations isolated by the careful selection of task and control states

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



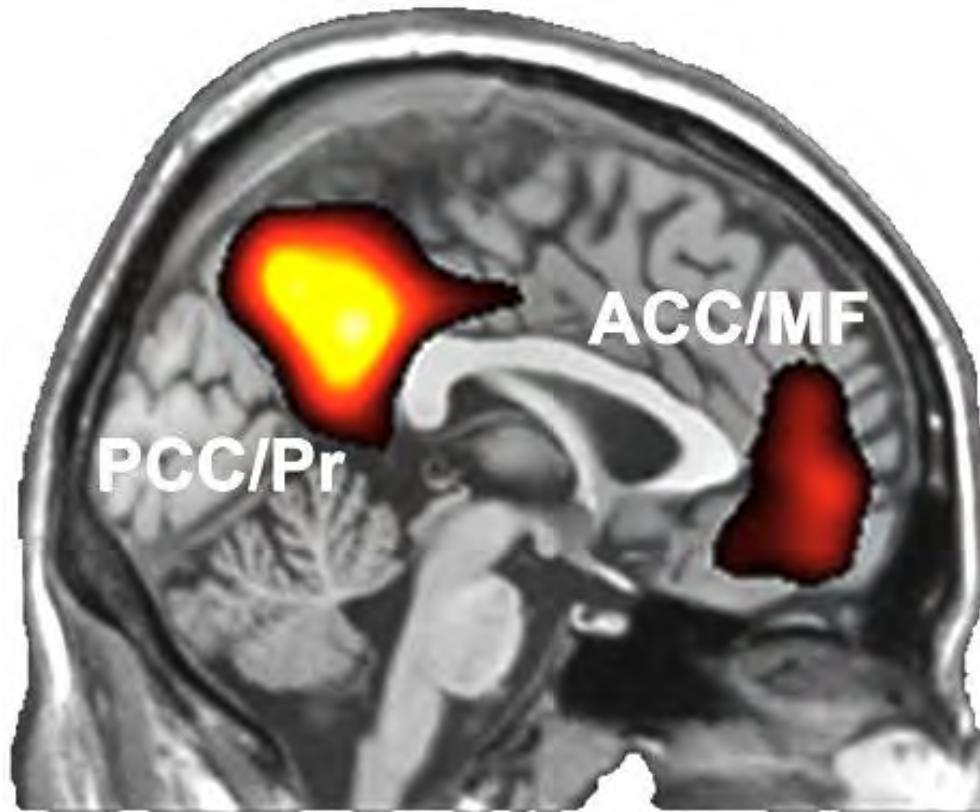
Task deactivations

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





The brain's default mode at rest



Demertzi & Whitfield-Gabrieli, in: Neurology of Consciousness 2nd ed. 2015

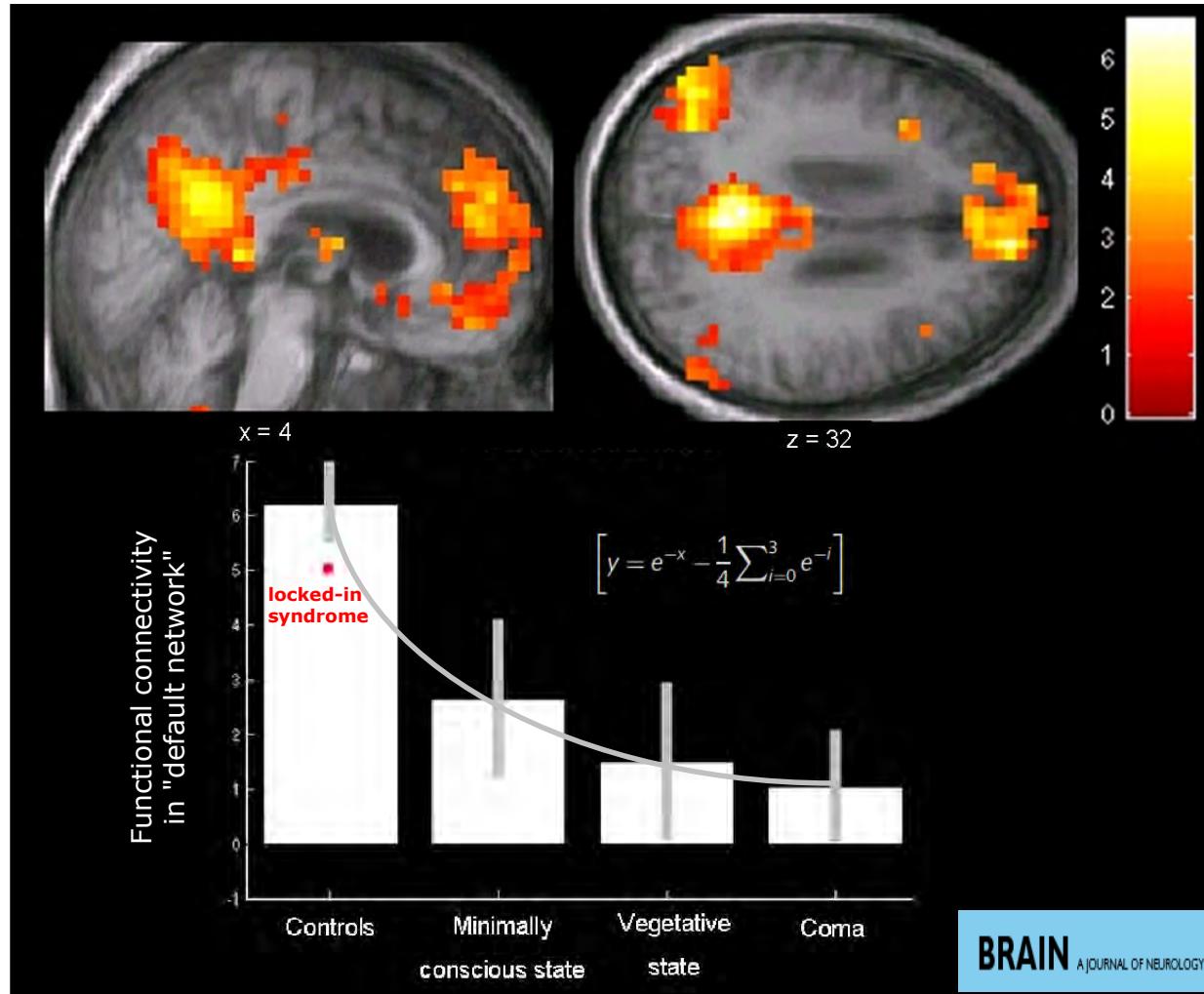
Demertzi, Soddu, Laureys, Curr Opin Neurobiology 2013

Demertzi et al, Front Hum Neurosci 2013

Raichle et al, PNAS 2001



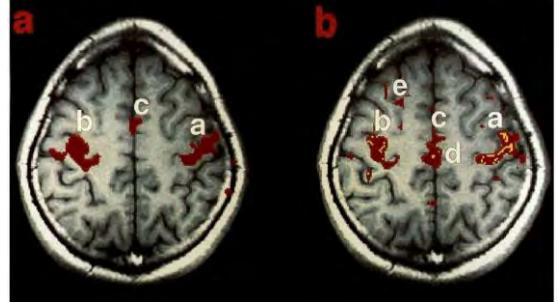
Default mode network in DOC



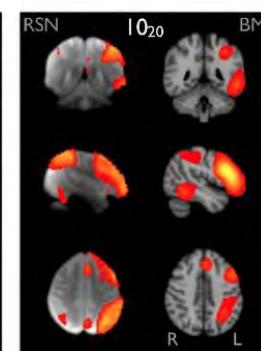
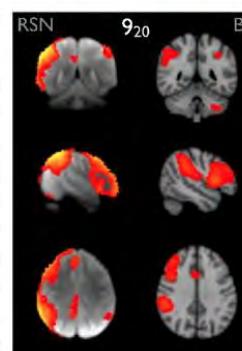
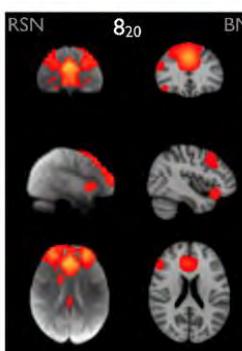
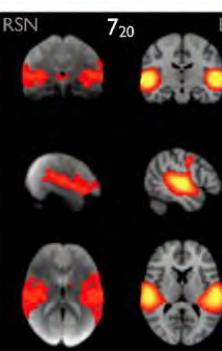
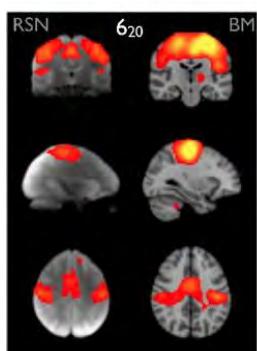
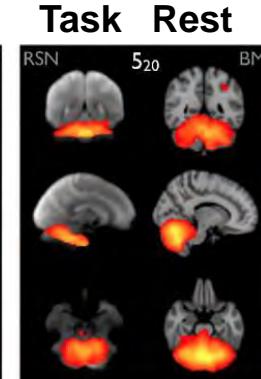
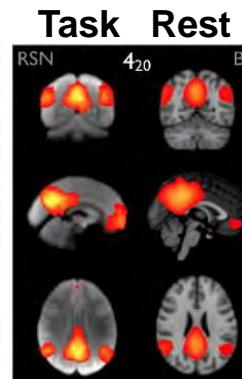
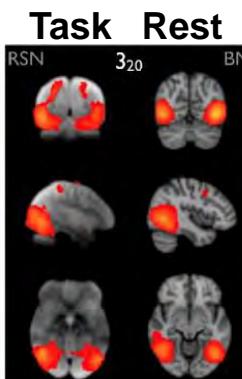
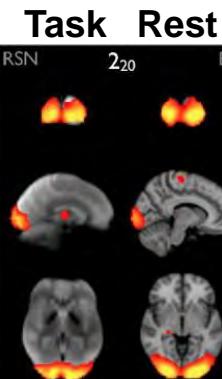
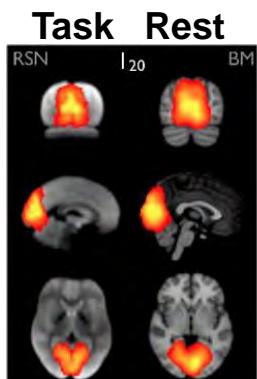


Intrinsic Connectivity Networks

Task



Rest

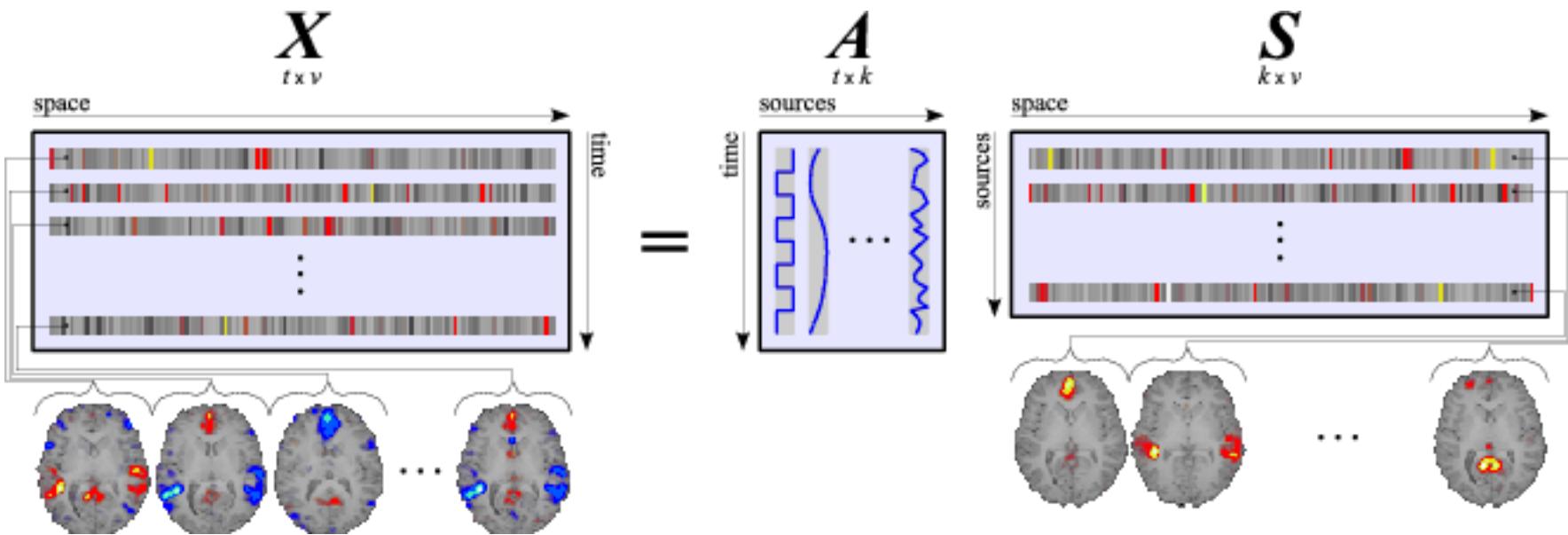


Smith et al, PNAS 2009

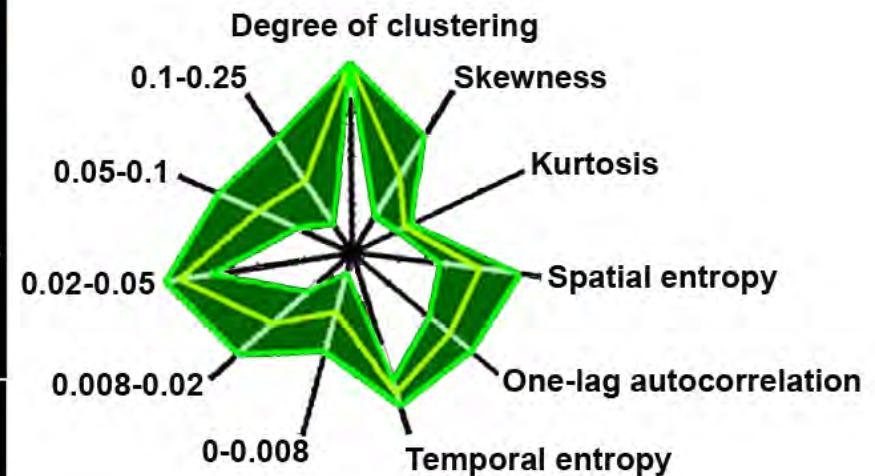
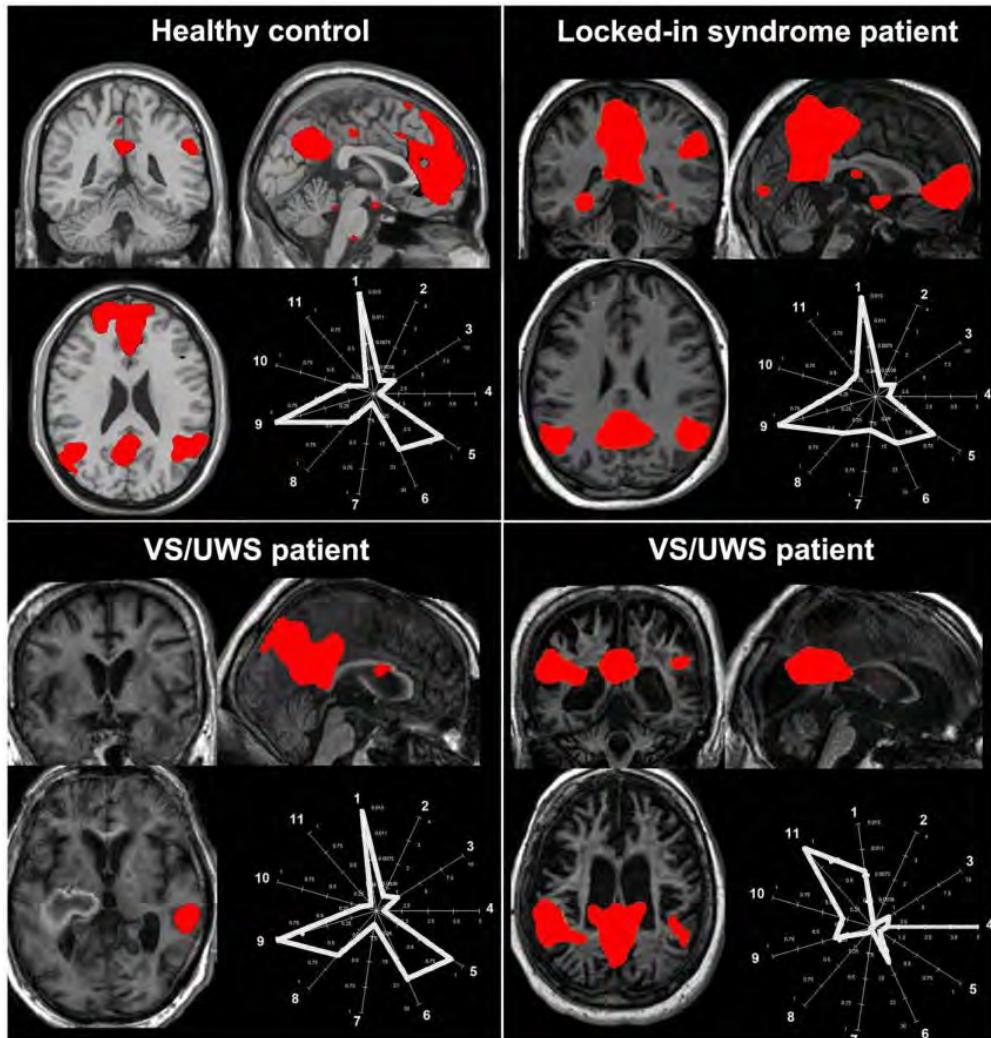
Biswal et al., Magn. Reson. Med. 19



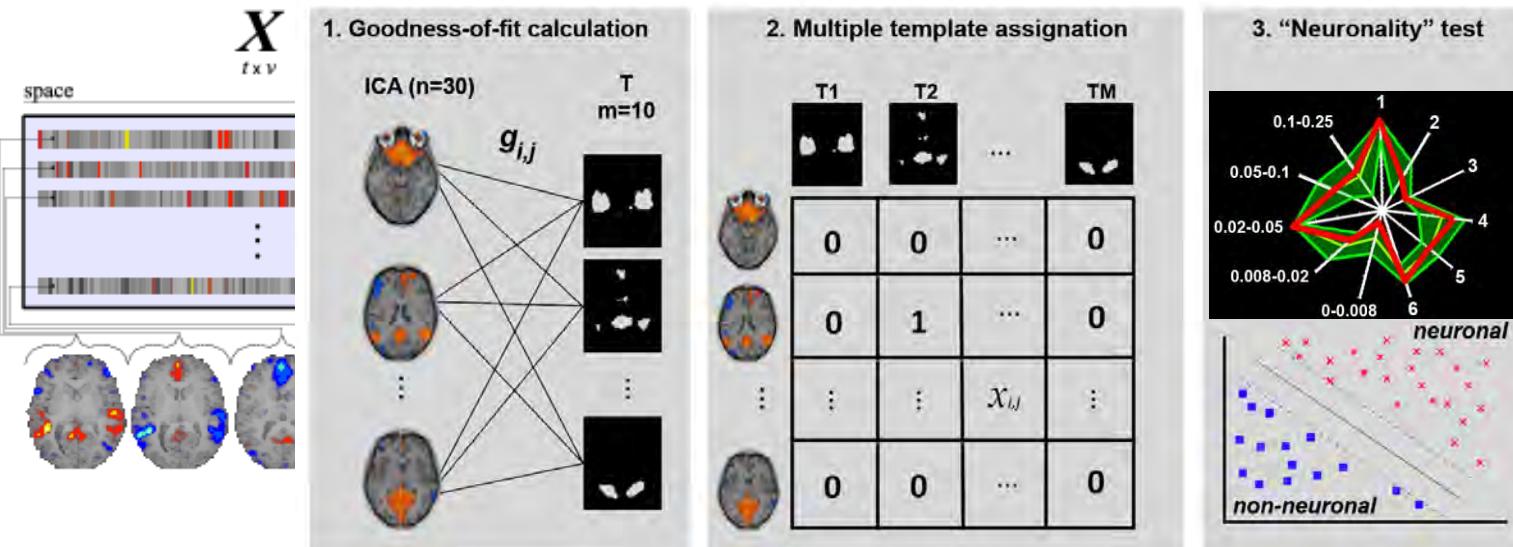
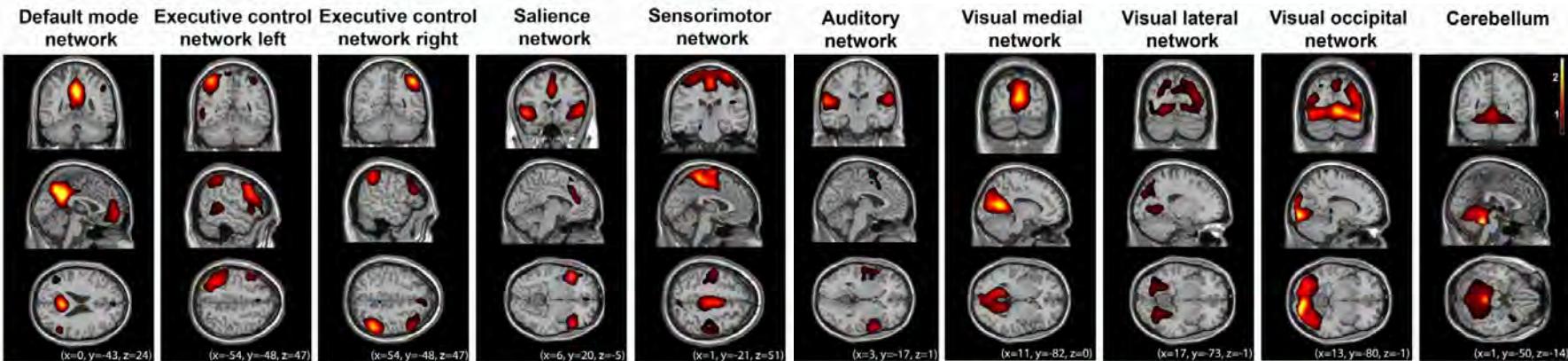
Independent component analysis (ICA)



A challenge...

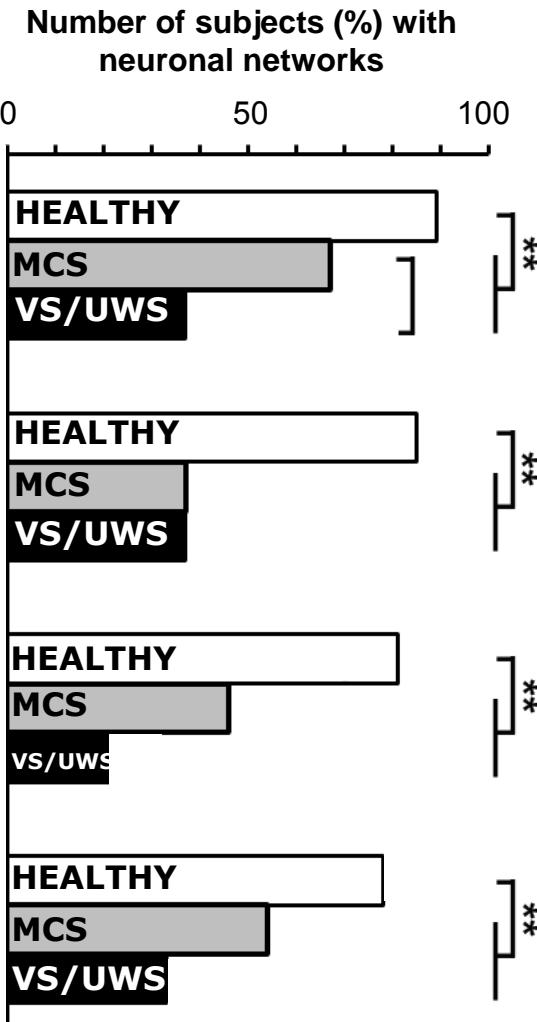
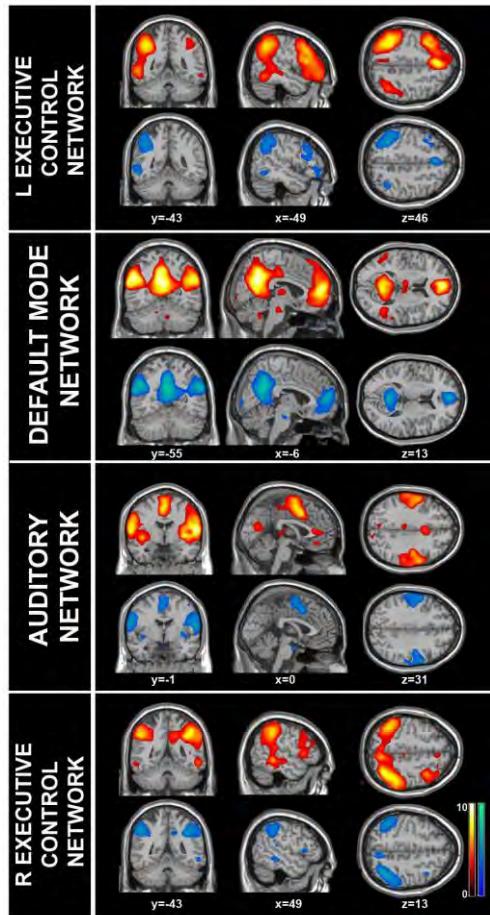


Systems-level intrinsic connectivity





Fewer “neuronal” networks in DOC

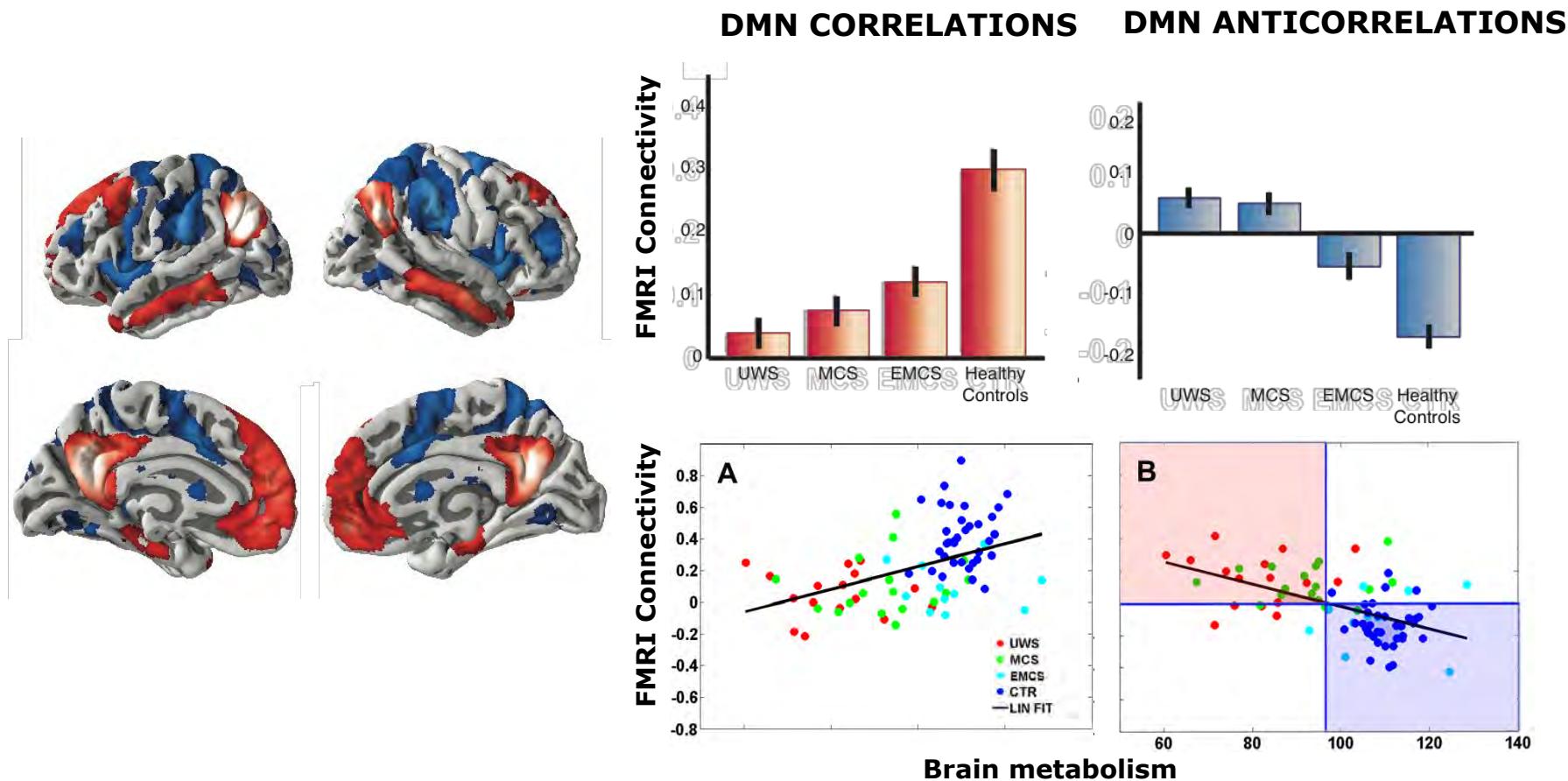


Single-patient classification

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

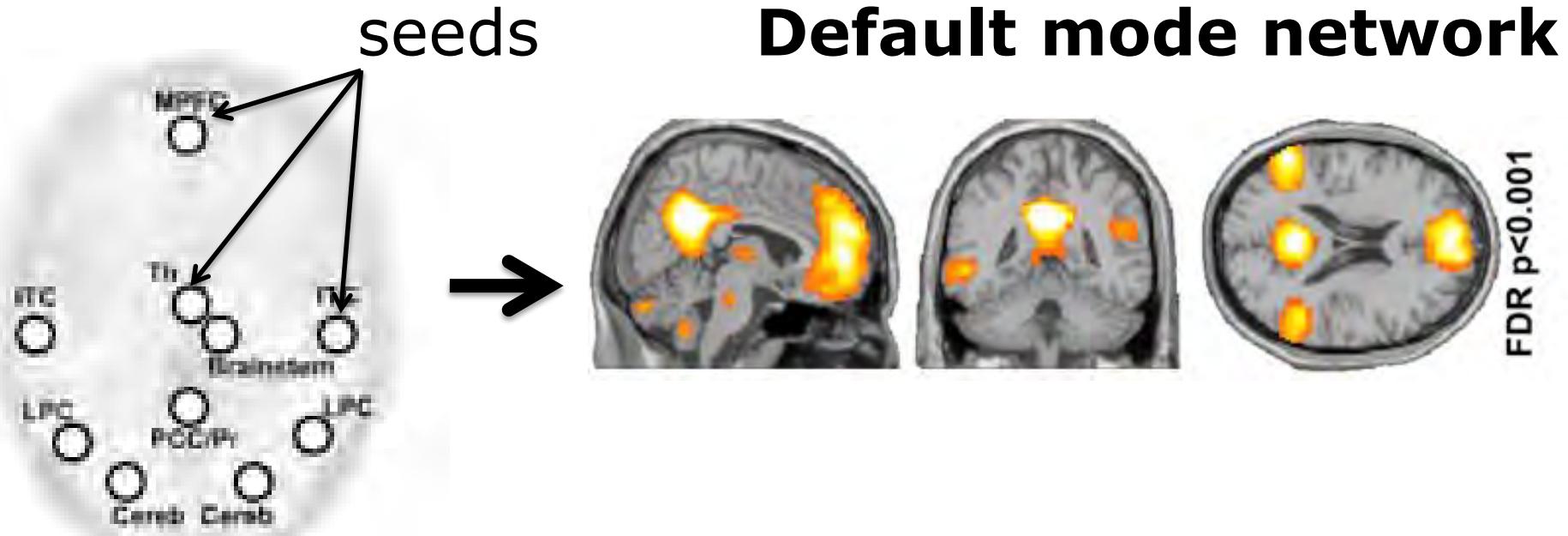


Effect of pathology

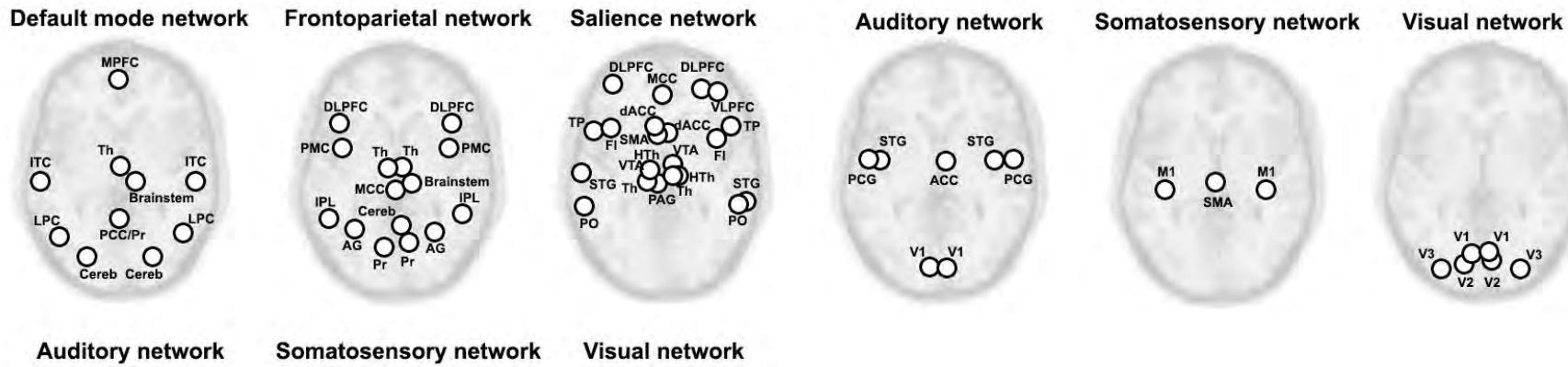




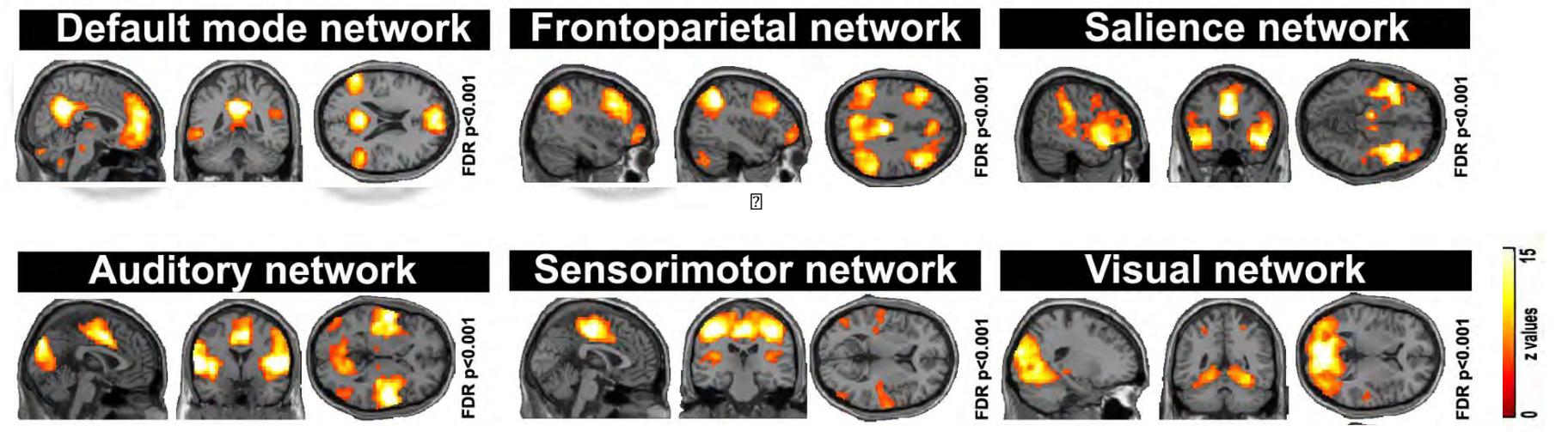
Seed-based functional connectivity



Seed-based functional connectivity

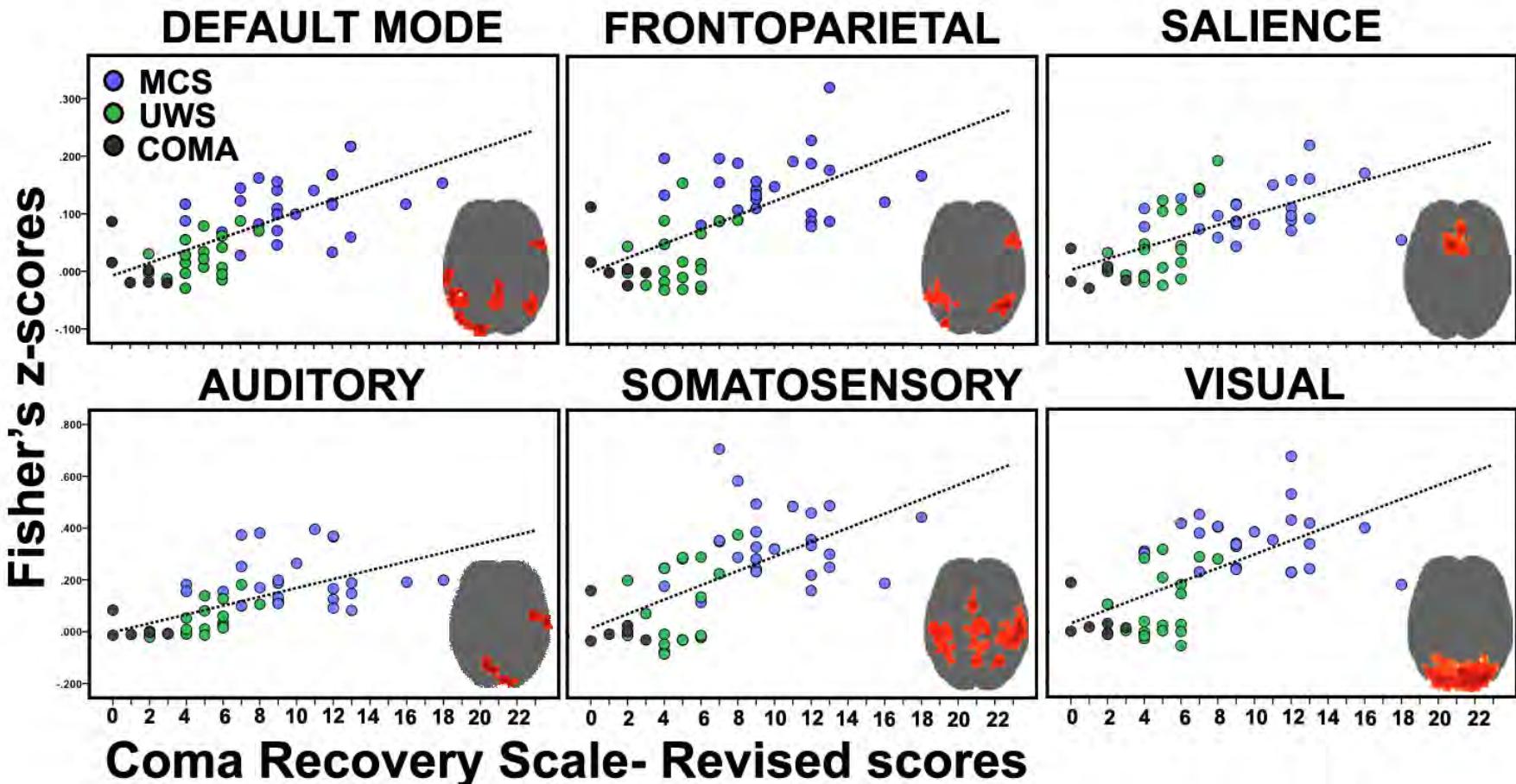


?





Connectivity reflects C state

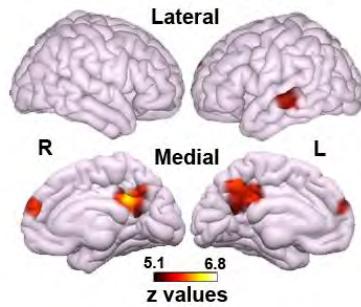




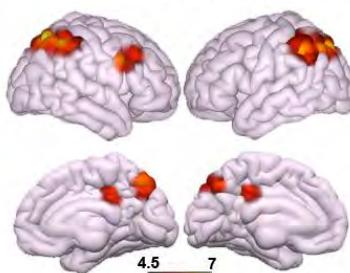
Which network discriminates best?

MCS > VS/UWS

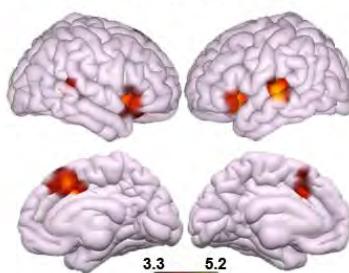
DEFAULT MODE



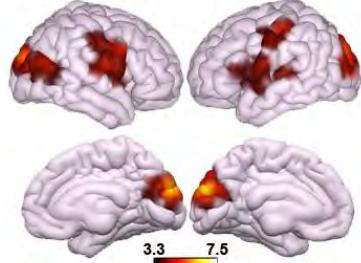
FRONTOPARIETAL



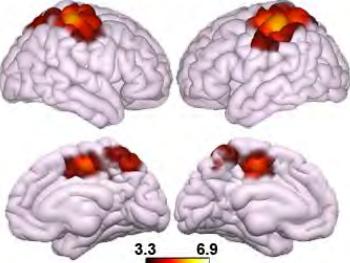
SALIENCE



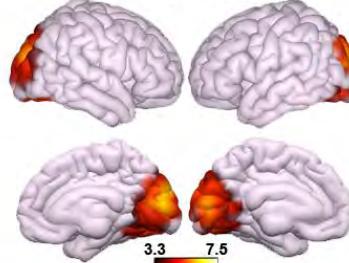
AUDITORY



SENSORIMOTOR



VISUAL



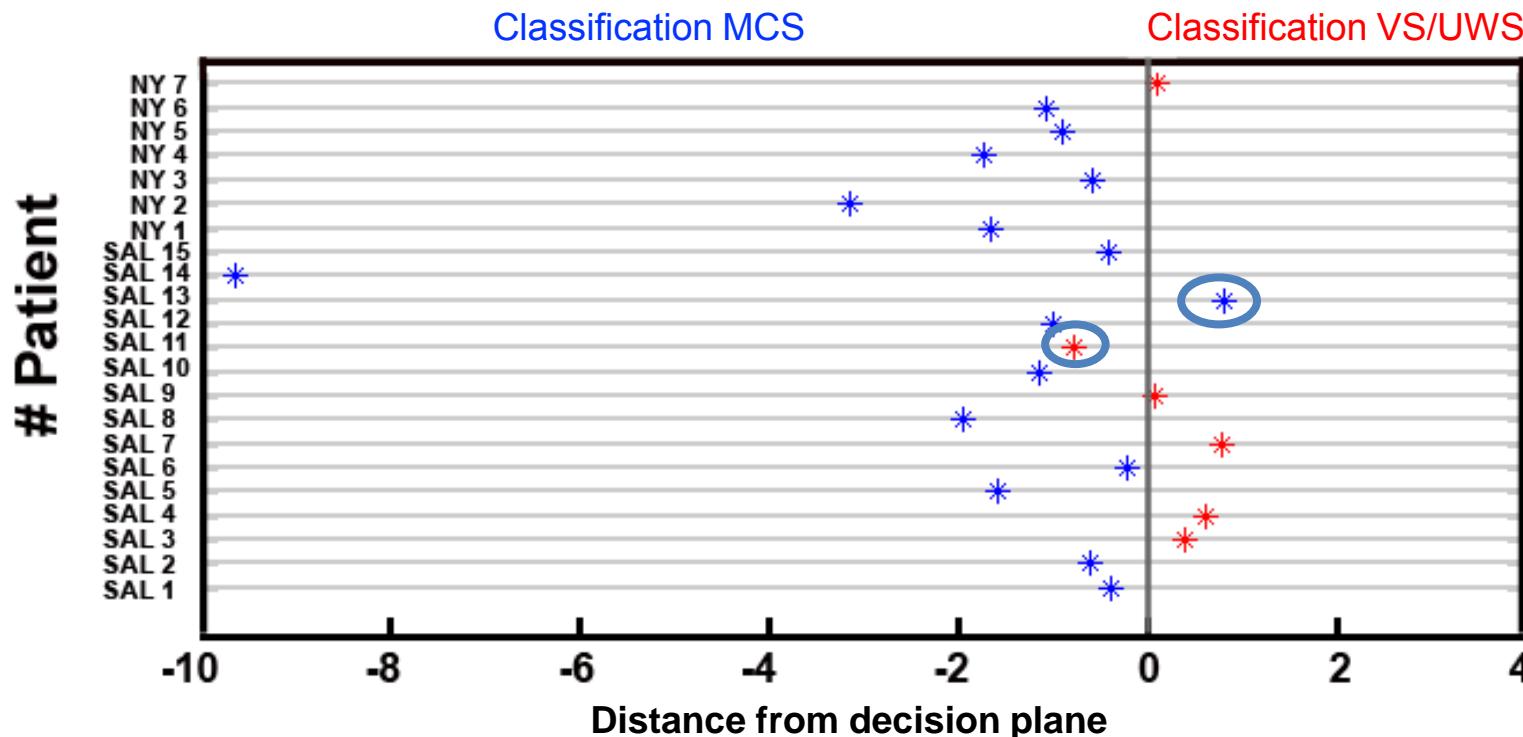
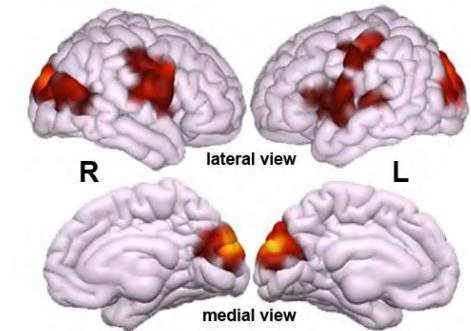
FWE $p < 0.05$ (cluster-level)

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



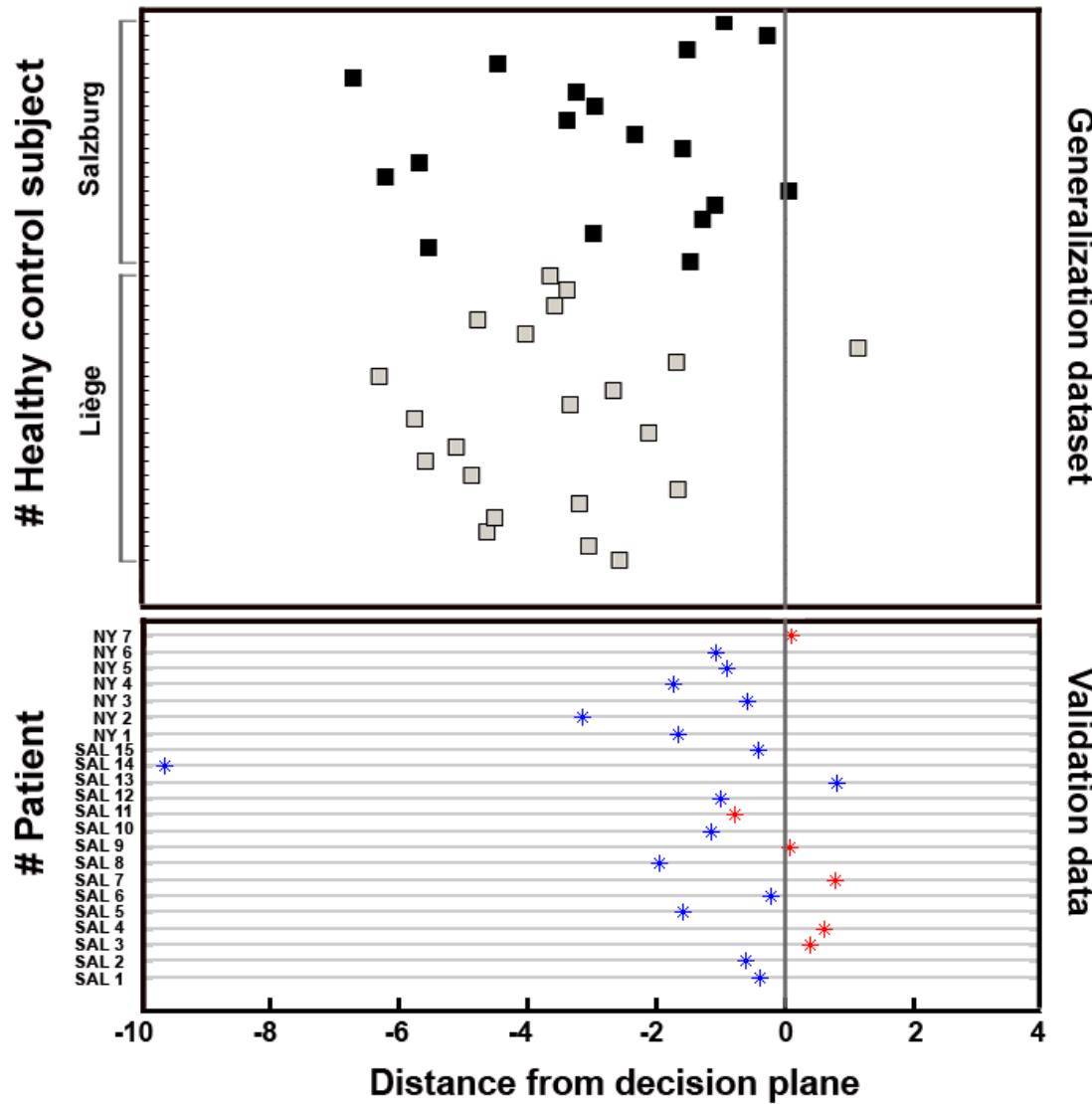
Crossmodal connectivity classifies DOC

- 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**

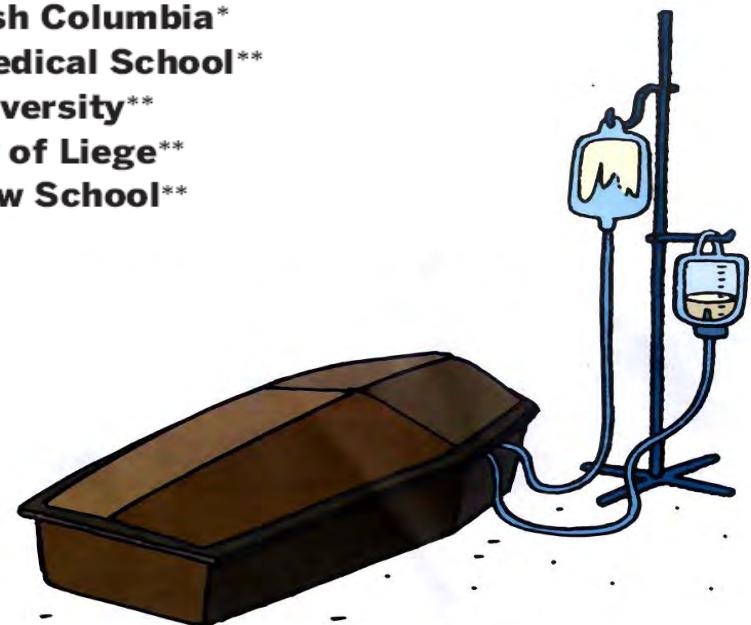
Joy Hirsch, Columbia University**

Steven Laureys, University of Liege**

Emily Murphy, Stanford Law School**

*Co-lead authors.

**Equal authors in alphabetical order.



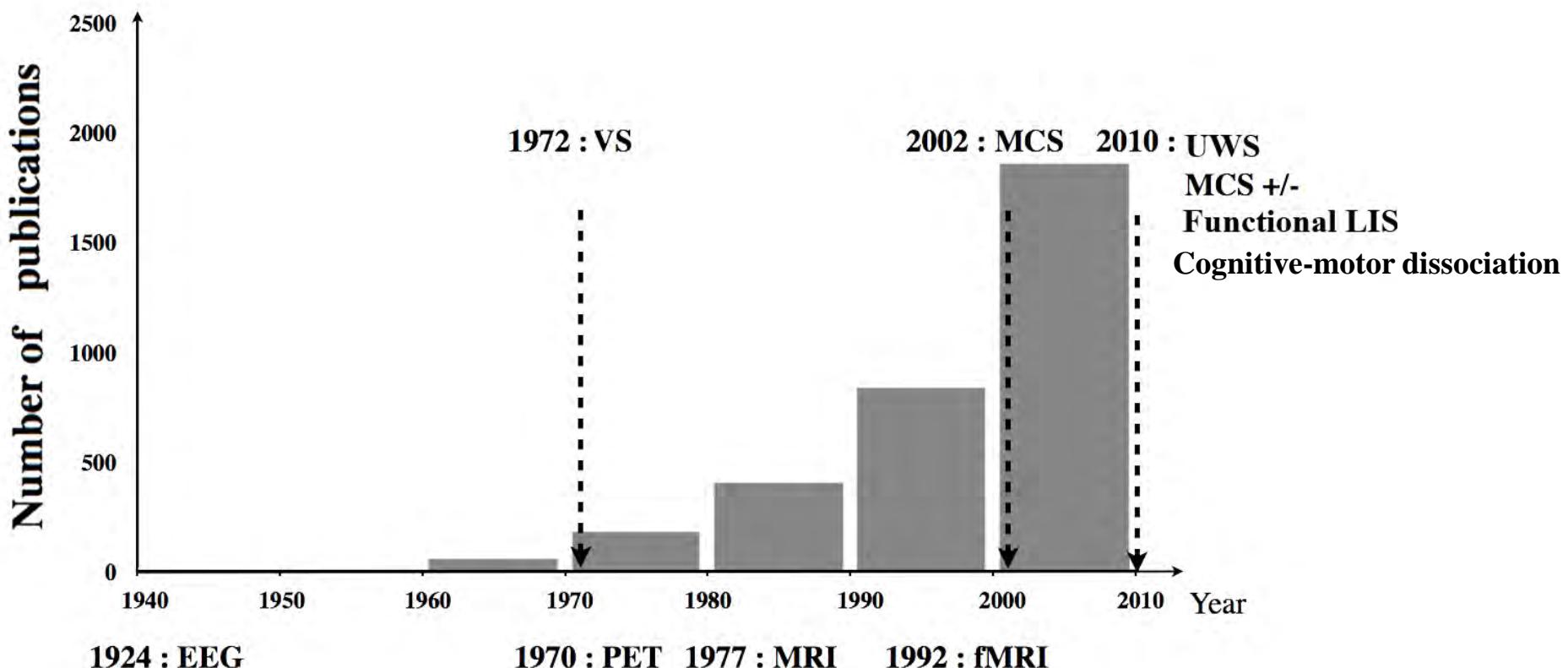


Balancing costs-benefits

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

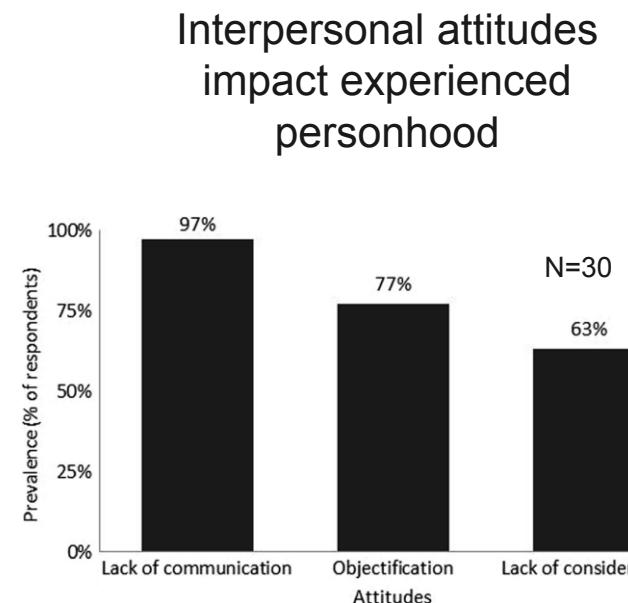
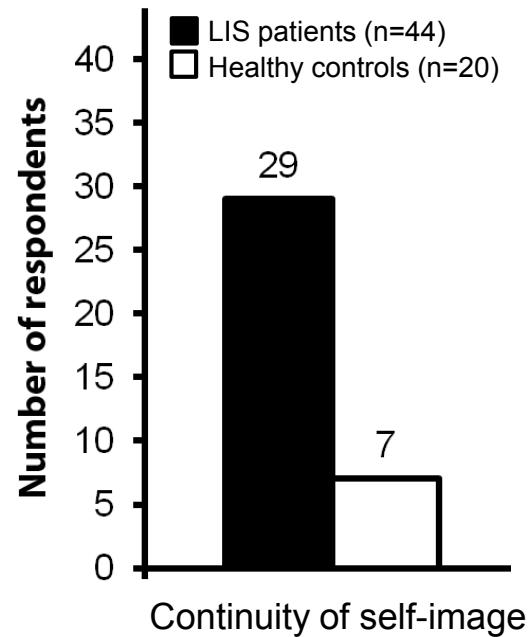
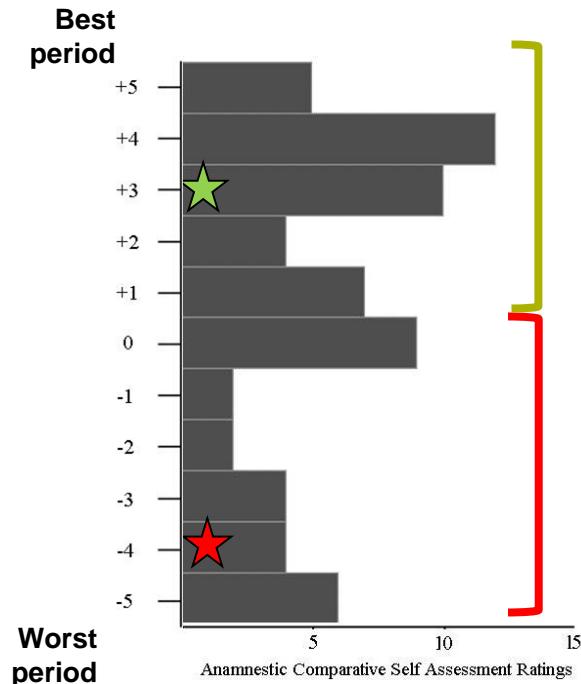


Benefit for science





Benefit for patients?



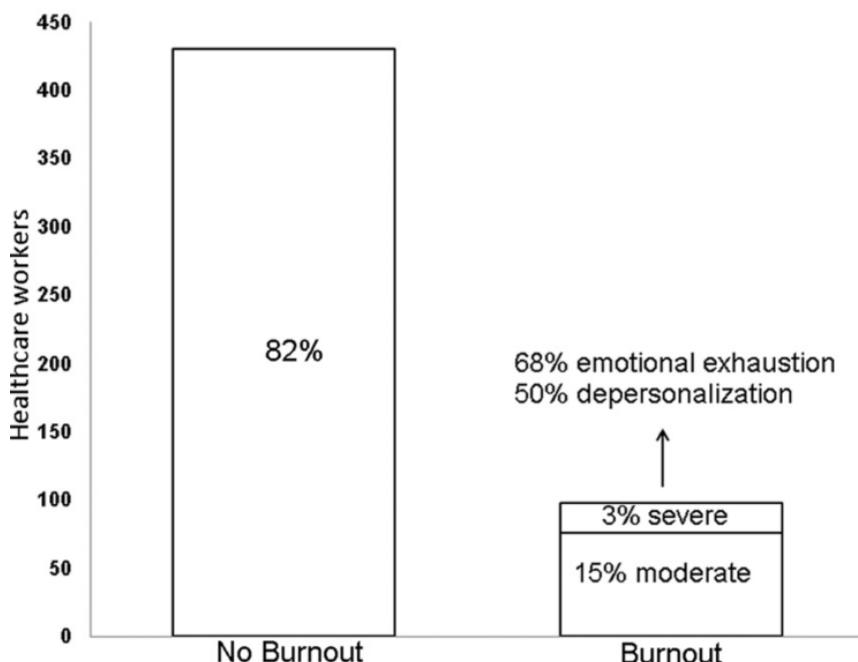
Bruno et al, *Br Med J Open* 2011

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

Nizzi, Blandin, Demertzi *NeuroEthics* 2018



Benefit for caregivers?



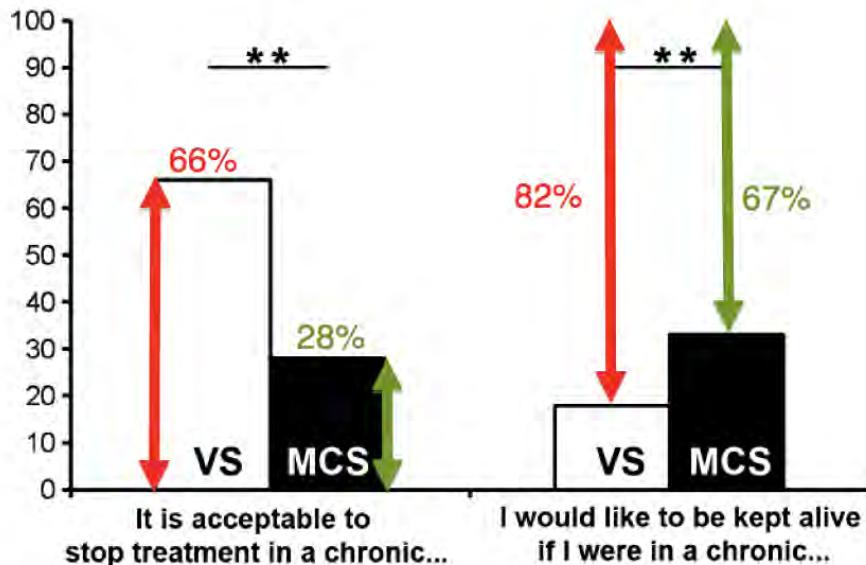
n=523

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%

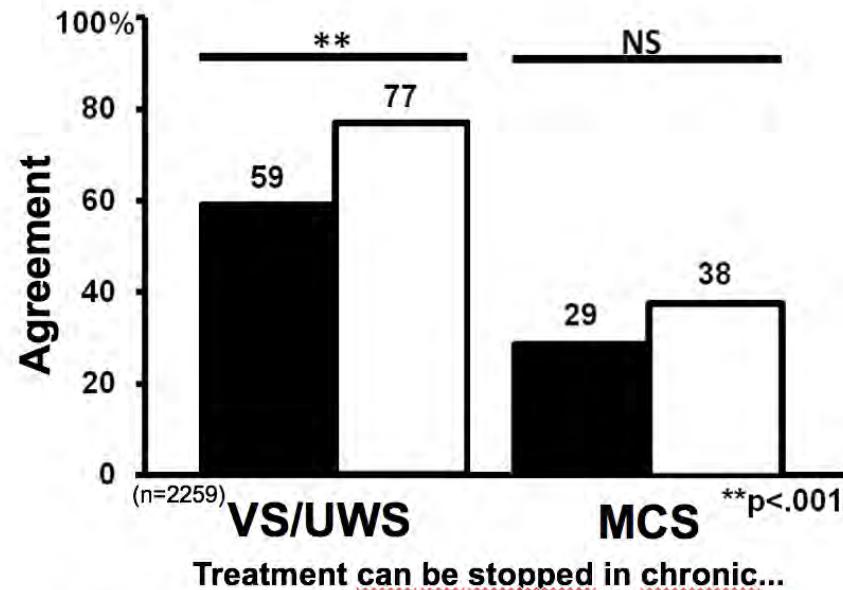
Consciousness has a moral significance

2,475 medical professionals



Demertzi et al, *J Neurol* 2011

■ Feel pain
□ Do not feel pain



Demertzi & Racine et al, *Neuroethics* 2012



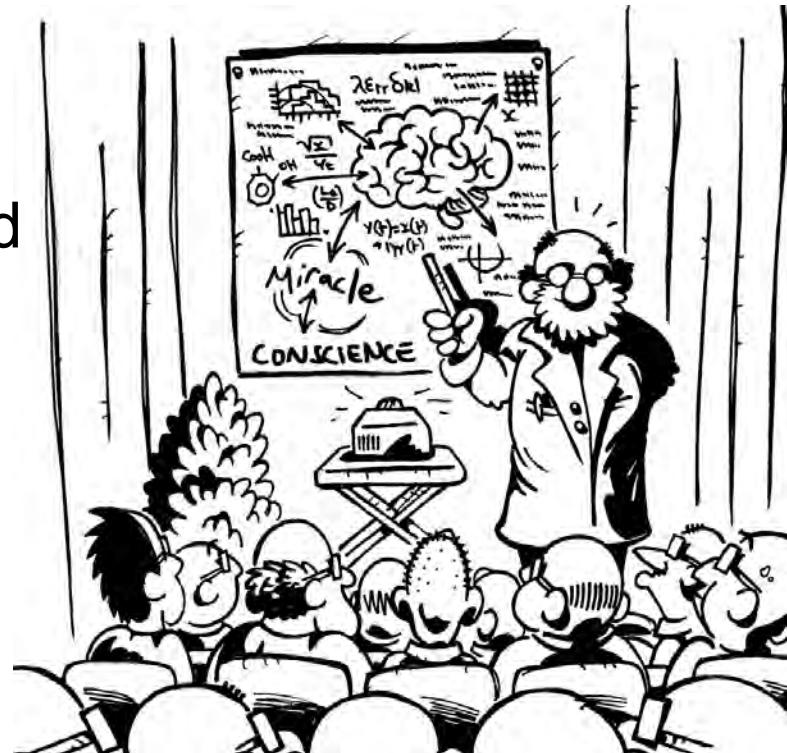
Neuro-ethical considerations

- 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

 **fnrs**
FREEDOM TO RESEARCH

 **LIÈGE université**
GIGA
Consciousness

 **esa**
European Space Agency

 **ICM**
Brain & Spine Institute

 **Human Brain Project**

James S. McDonnell Foundation