

# Quantifying conscious states by means of self-initiated brain activity

**Zangwill Club**  
**University of Cambridge, UK**

November 1 2019

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# The problem

## Patients cannot express themselves



Hable con ella 2002, Pedro Almodóvar



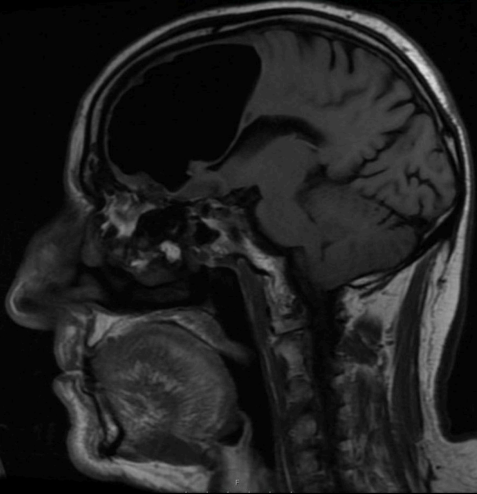


How can we evidence C in the absence of communication?  
What is the minimum information we need?



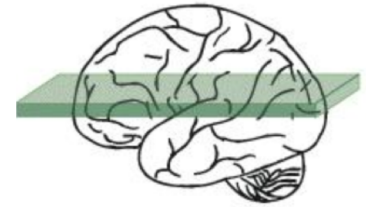
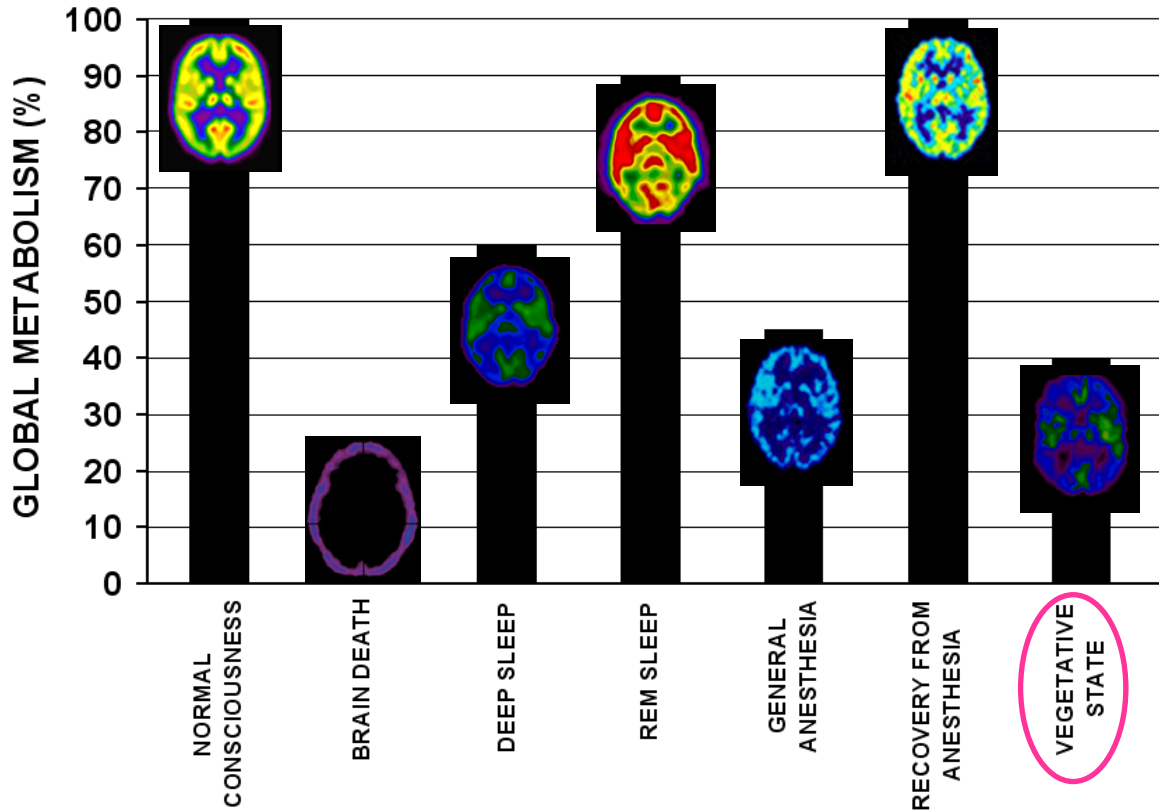
# How can we be conscious? (1)

We need a brain (all of it?)

Typical brain	Primary cerebellar agenesis	Frontal air-filled cavity
		
	24y female	84y male
	Yu et al, Brain. 2015	Brown & Vahidassr, BMJ Case Reports 2018

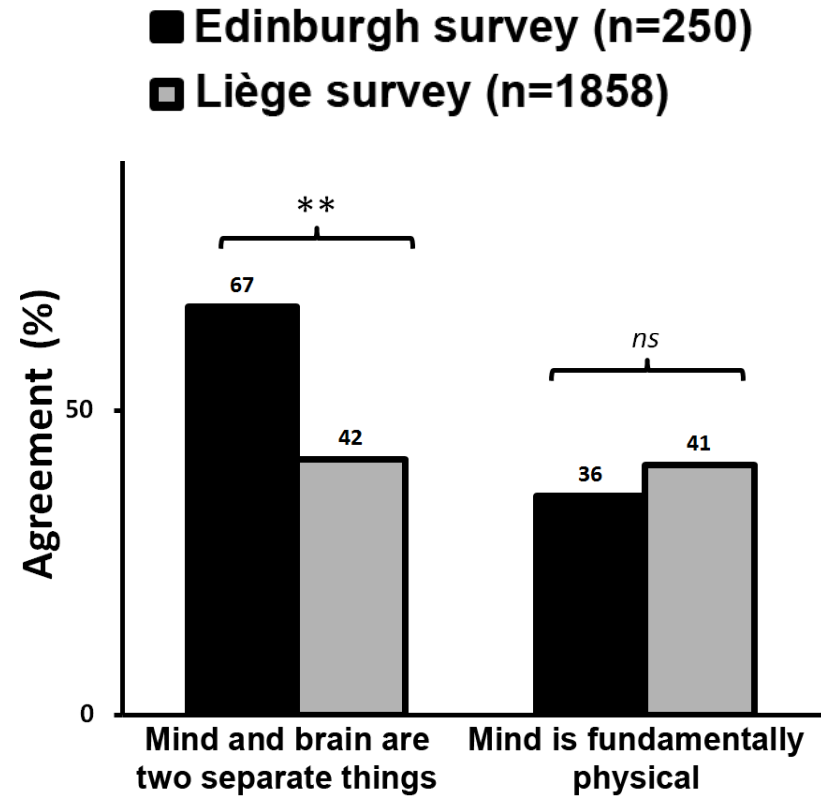
# How can we be conscious? (2)

We need a functional brain



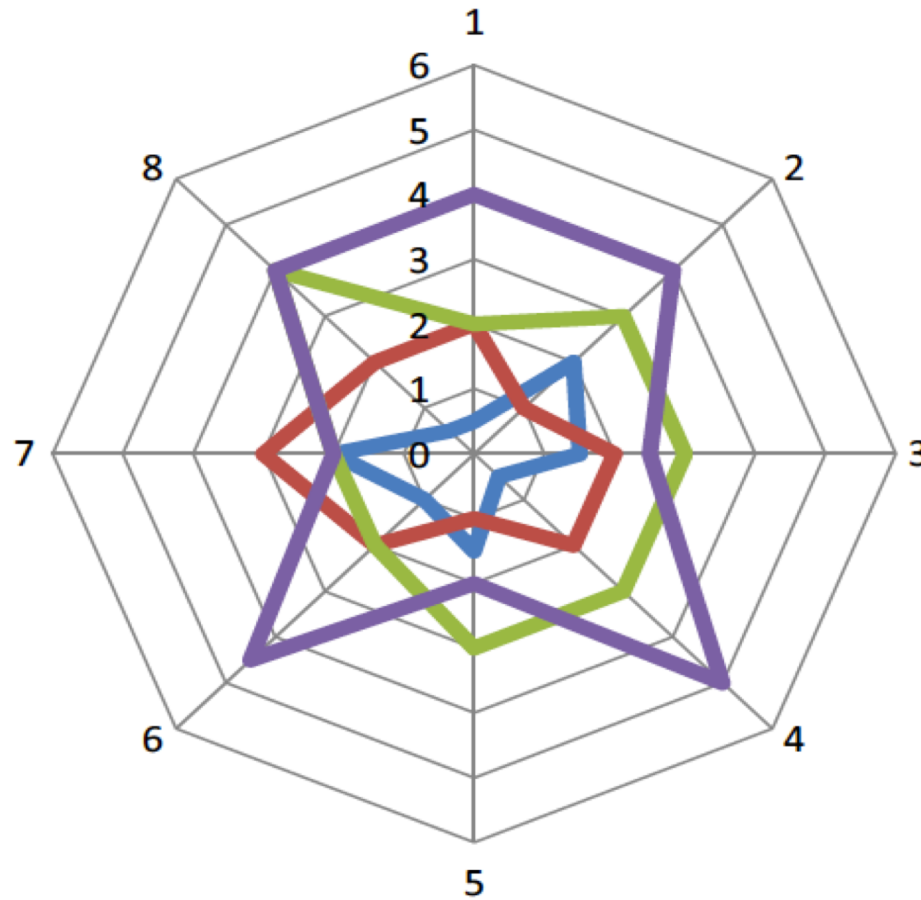
# What is Consciousness?

Functionalism  
Materialism  
Dualism



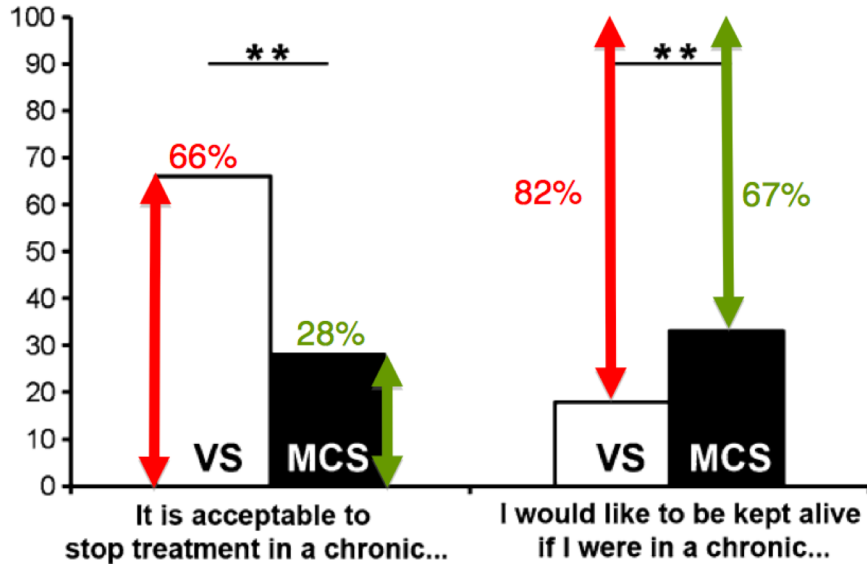


# Defining Consciousness



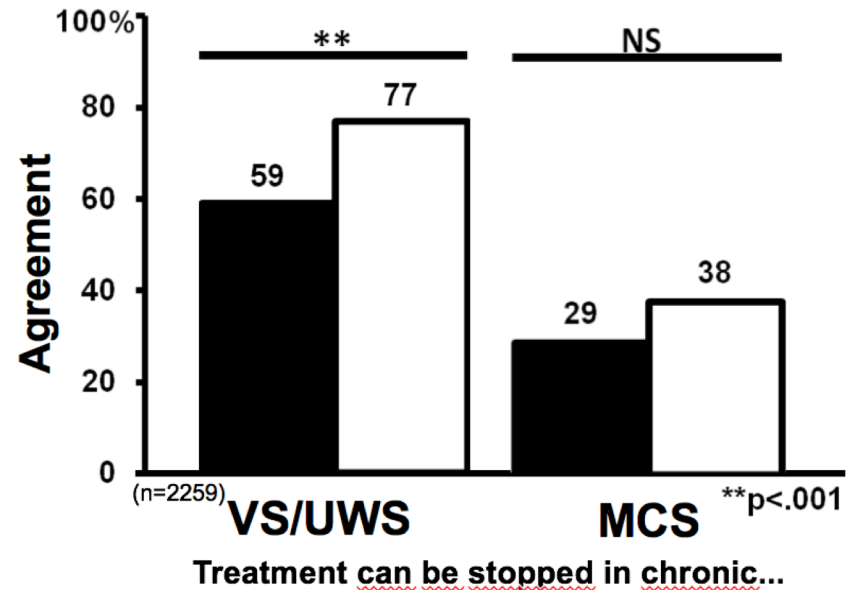
# A moral imperative

2,475 medical professionals



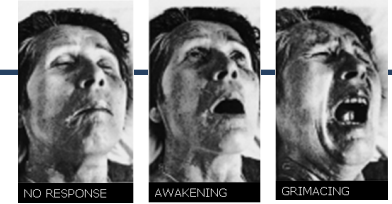
Demertzi et al, *J Neurol* 2011

■ Feel pain  
□ Do not feel pain

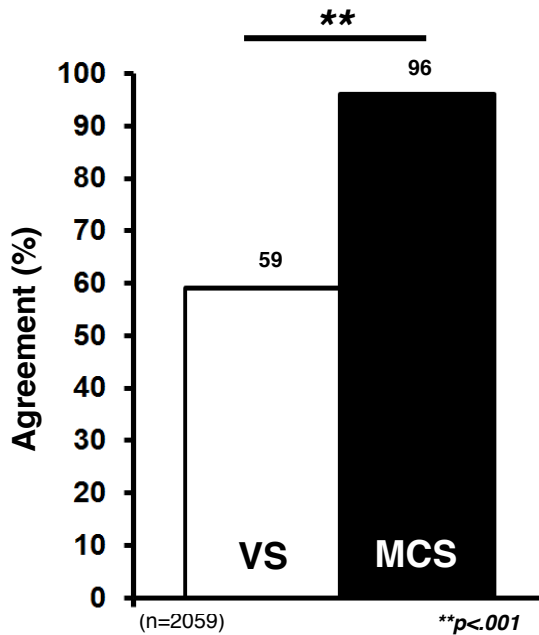


Demertzi & Racine et al, *Neuroethics* 2012

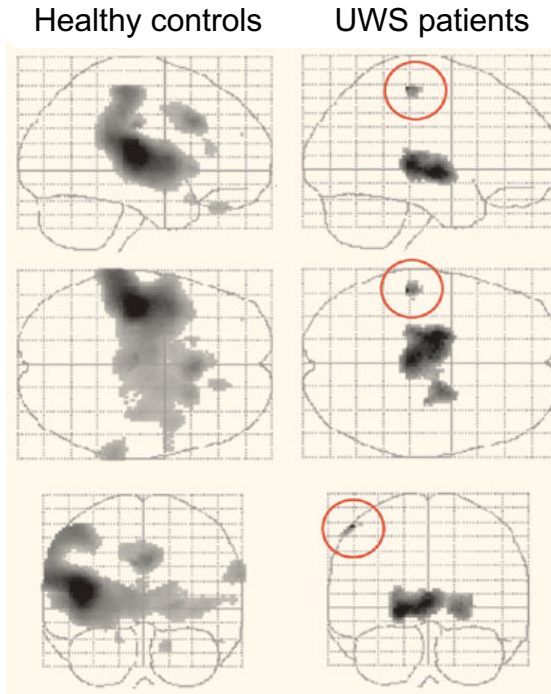
# Do they feel pain?



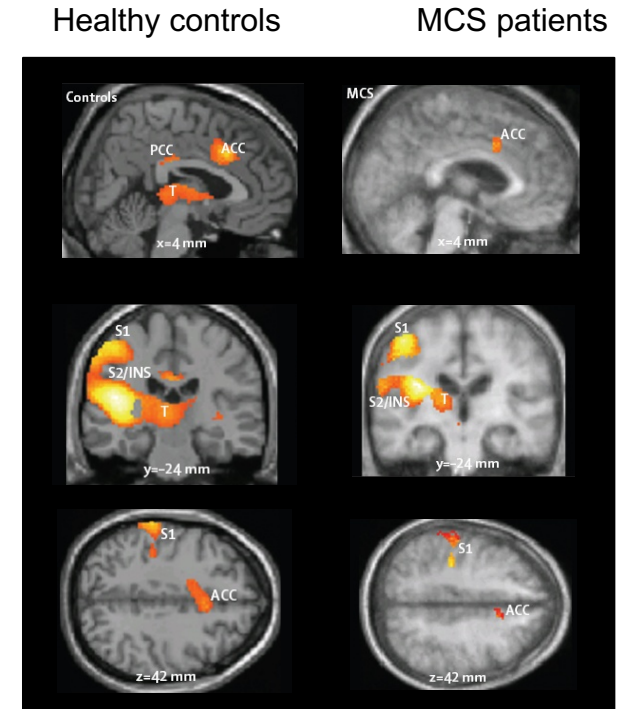
Do you think patients in a ...  
can feel pain?



Unresponsive wakefulness syndrome



Minimally conscious state



Demertzi et al, *Prog Brain Res* 2009  
Demertzi & Racine et al, *Neuroethics* 2012

Laureys et al., *Neuroimage* 2002

Boly et al, *Lancet Neurol* 2008



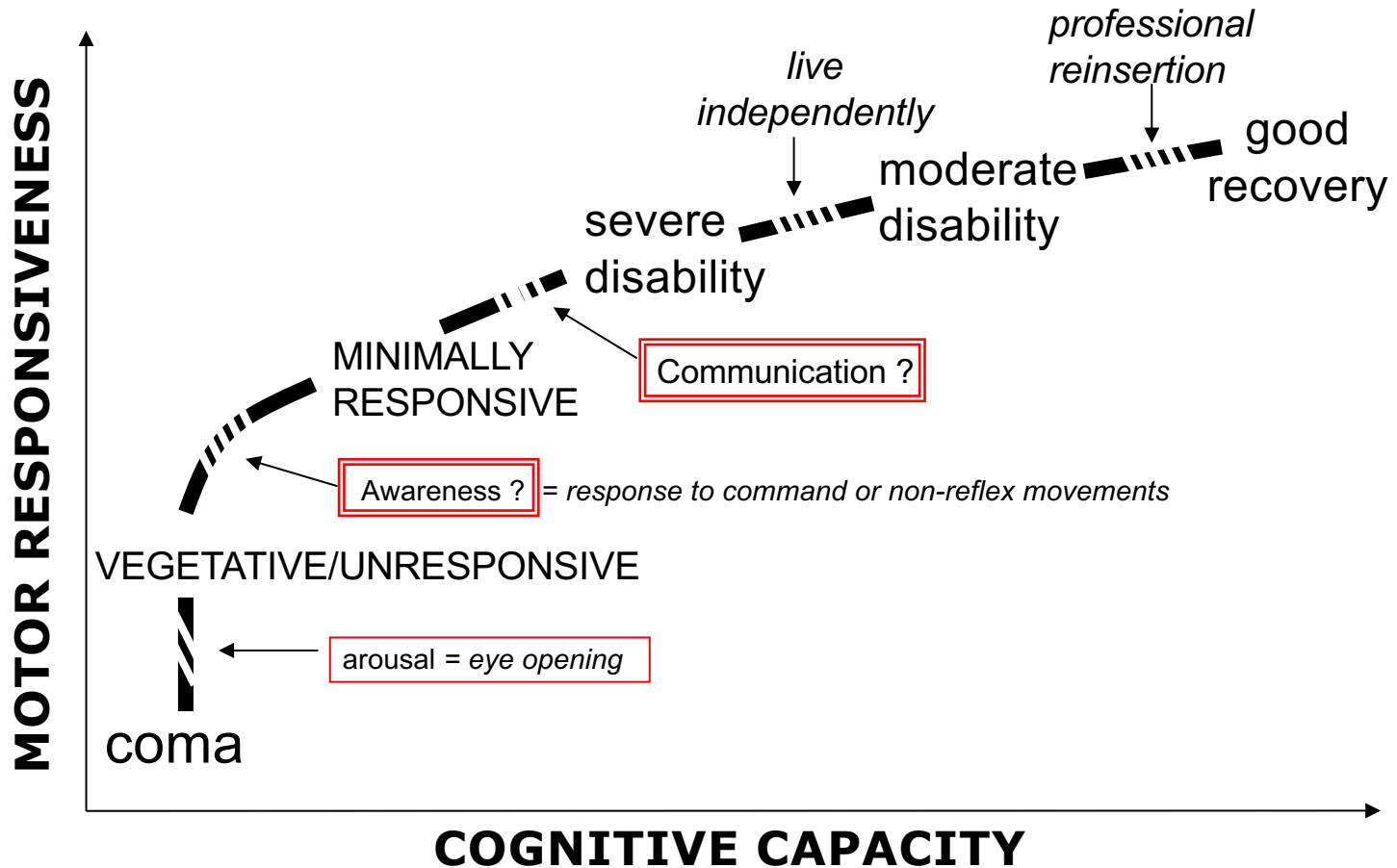


# Behaviour



Terry Schiavo °1963,  
vegetative 1990, † 2005 USA

# Behavioural signs





# We cannot always trust behavior

## Standardized assessment

n=103 post-comatose patients  
 45 Clinical diagnosis of VS  
 18 Coma Recovery Scale MCS



40% misdiagnosed

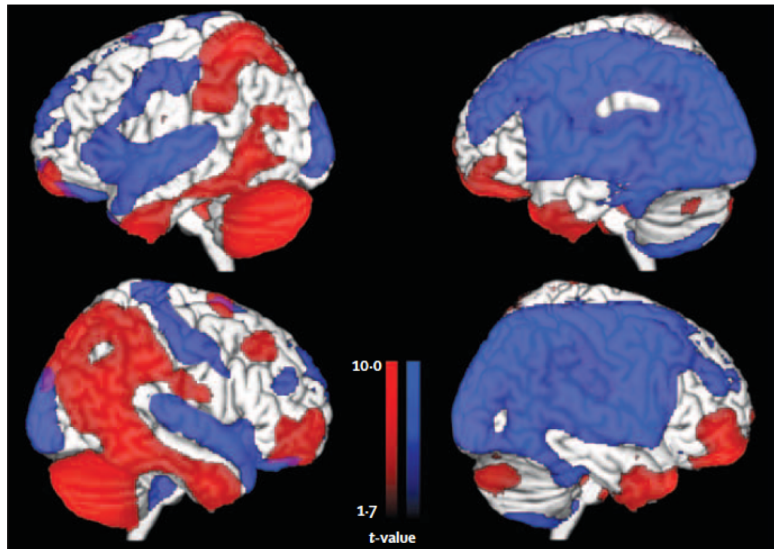
Schnakers et al, *Ann Neurol* 2006; *BMC Neurol* 2009

## Neuroimaging

Coma Recovery Scale-Revised results			
	UWS	MCS	Total
<b>Clinical consensus diagnosis</b>			
<b><sup>18</sup>F-FDG PET</b>			
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**

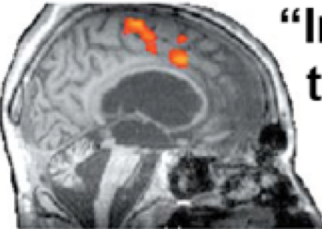

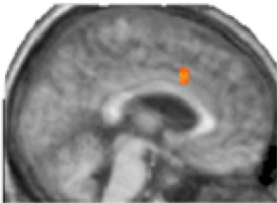

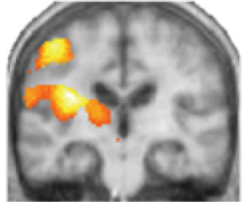
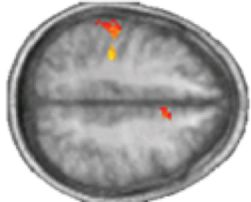


Stender & Gosseries et al, *Lancet* 2014

# 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="504 505 900 608">“Imagine playing tennis”</p>	 <p data-bbox="981 999 1290 1042">median nerve</p> 
 <p data-bbox="504 811 900 971">“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



# Some numbers...

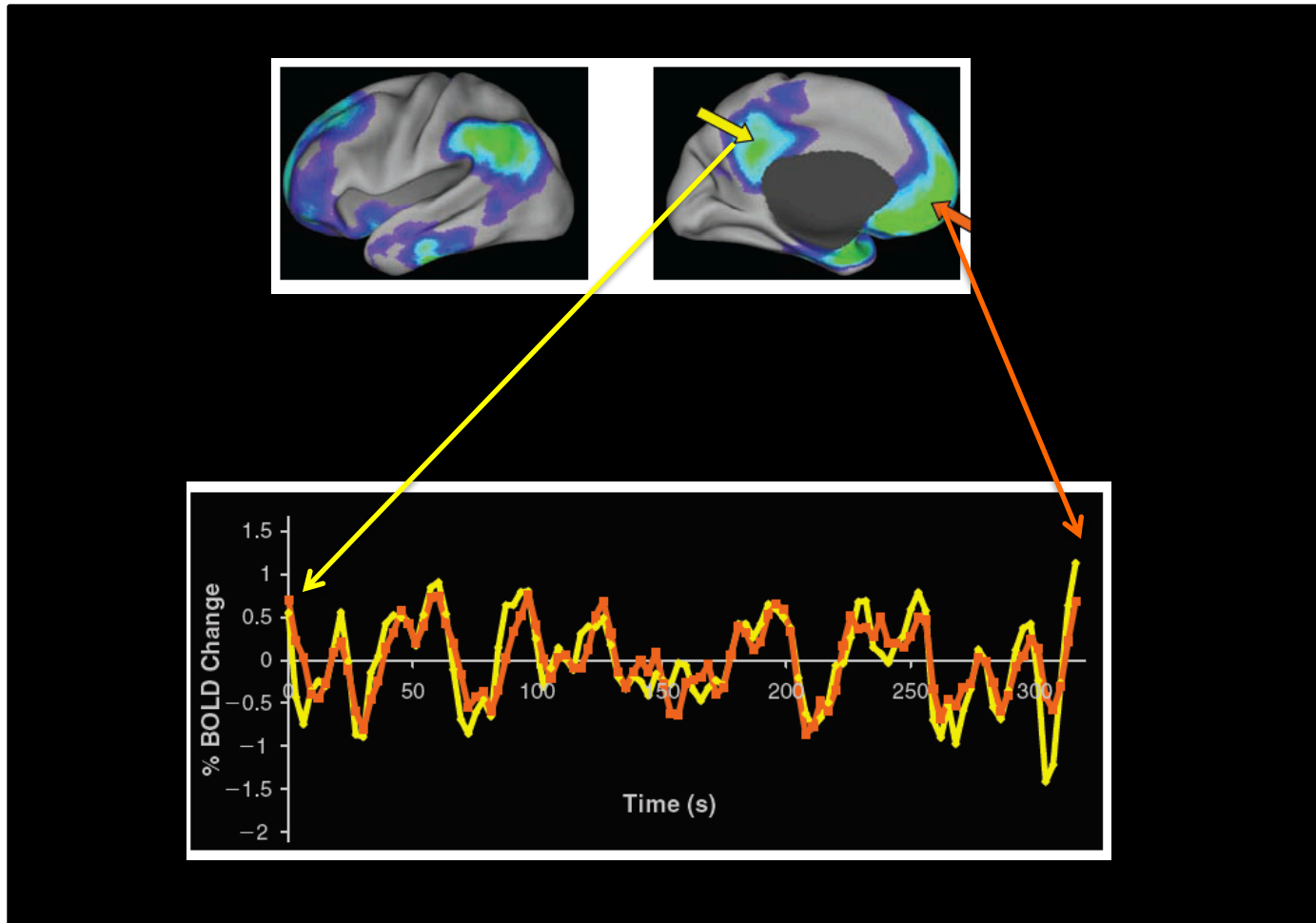
- The human brain is approximately 2% of body's weight
- 80% of this energy for neuronal signalling  
→ most of consumed energy used for function
- Stimulus & performance-evoked changes in brain energy consumption are surprisingly small (typically <5%)



*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*

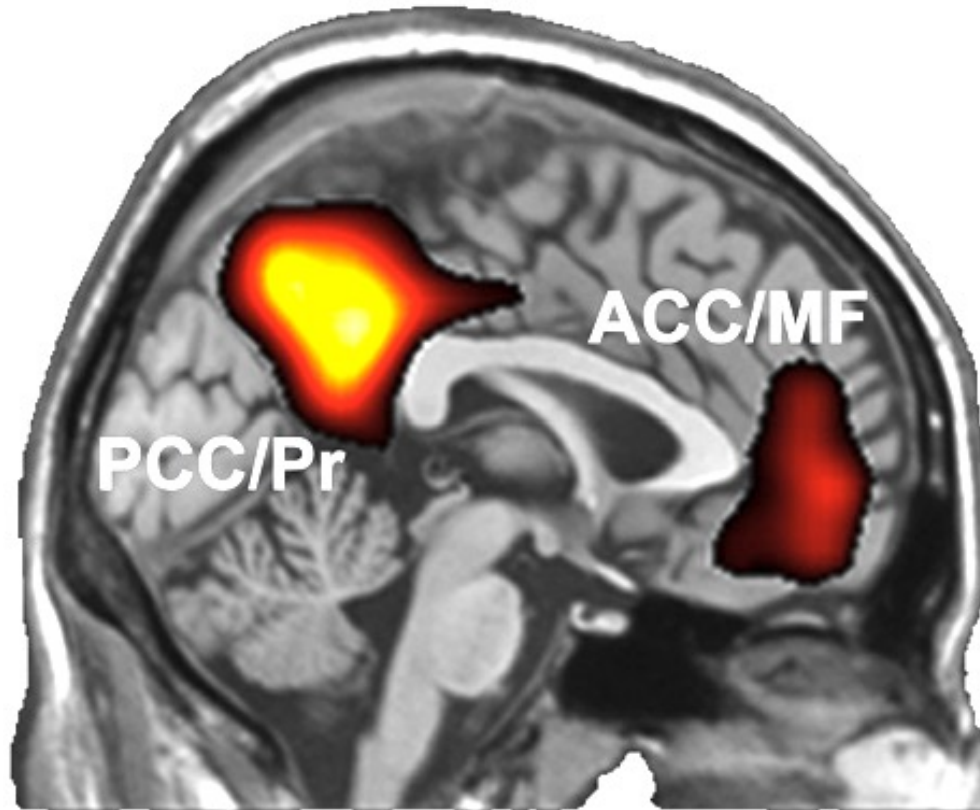
# Task deactivations

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





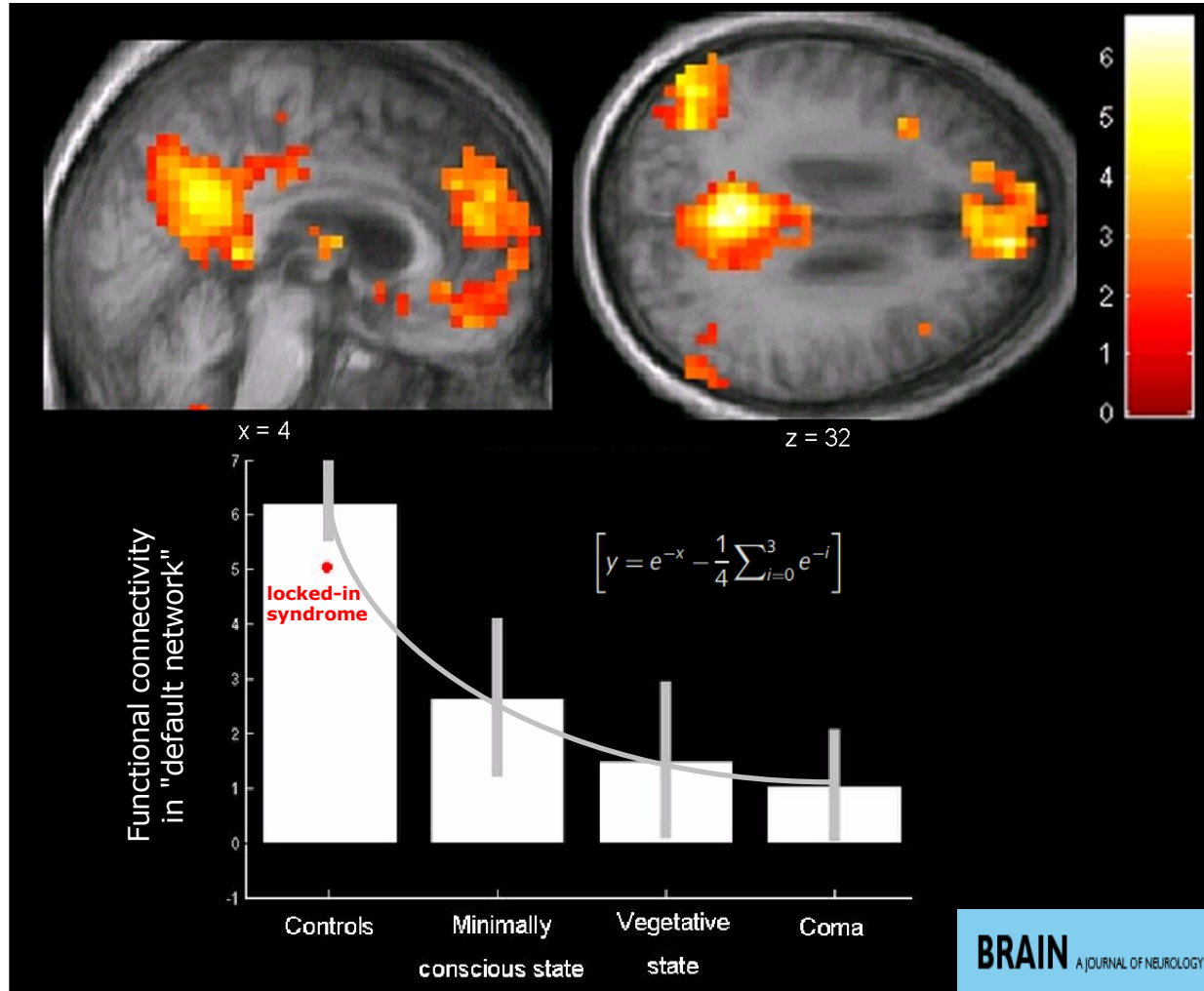
# The brain's default mode at rest



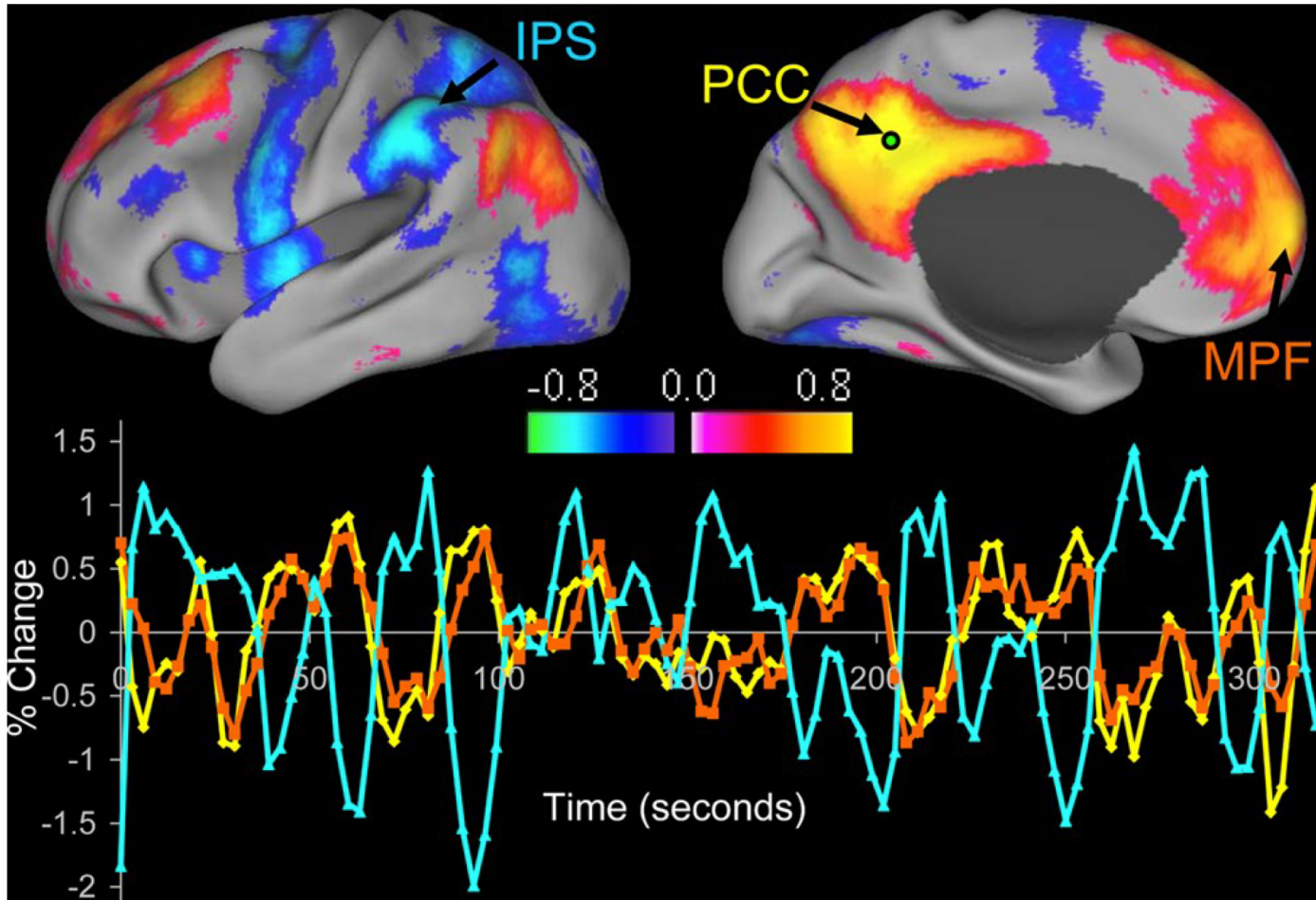
Demertzi & Whitfield-Gabrieli, in: *Neurology of Consciousness* 2<sup>nd</sup> ed. 2015  
Demertzi, Soddu, Laureys, *Curr Opin Neurobiology* 2013  
Demertzi et al, *Front Hum Neurosci* 2013  
Raichle et al, *PNAS* 2001



# Default mode network in DOC

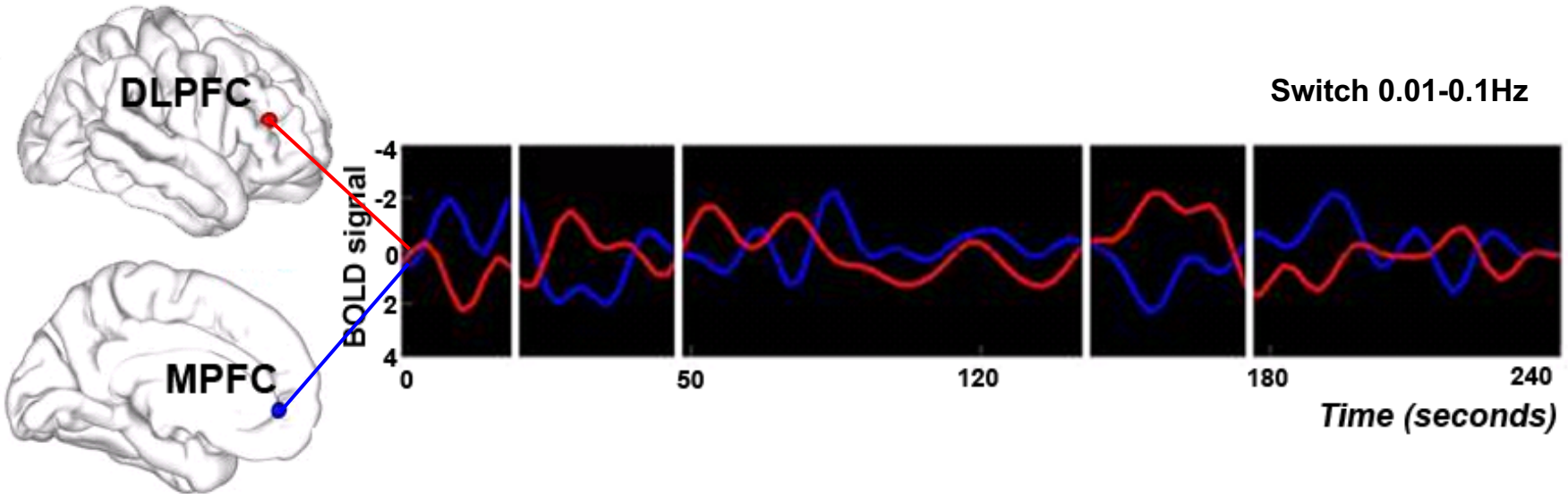


# DMN anticorrelations



# DMN anticorrelations

**External awareness  
or anticorrelated network**

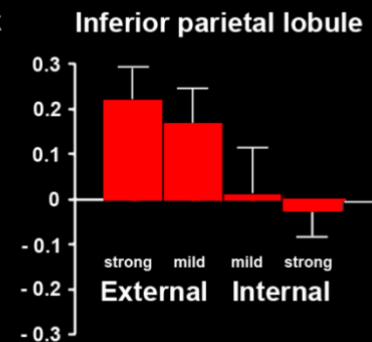
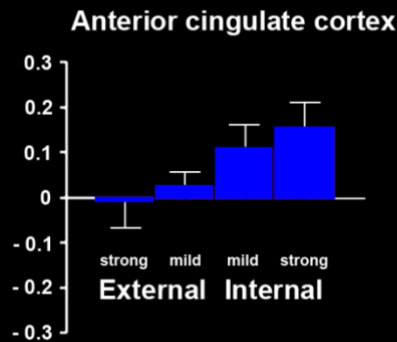
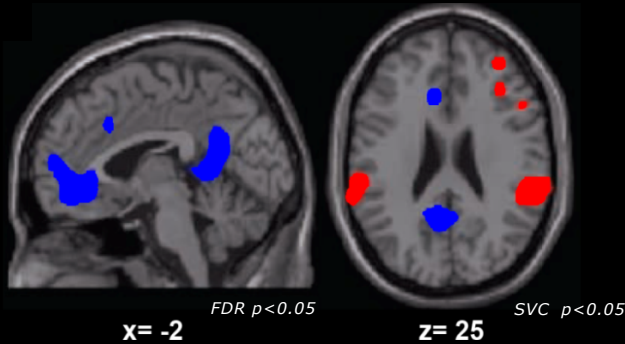
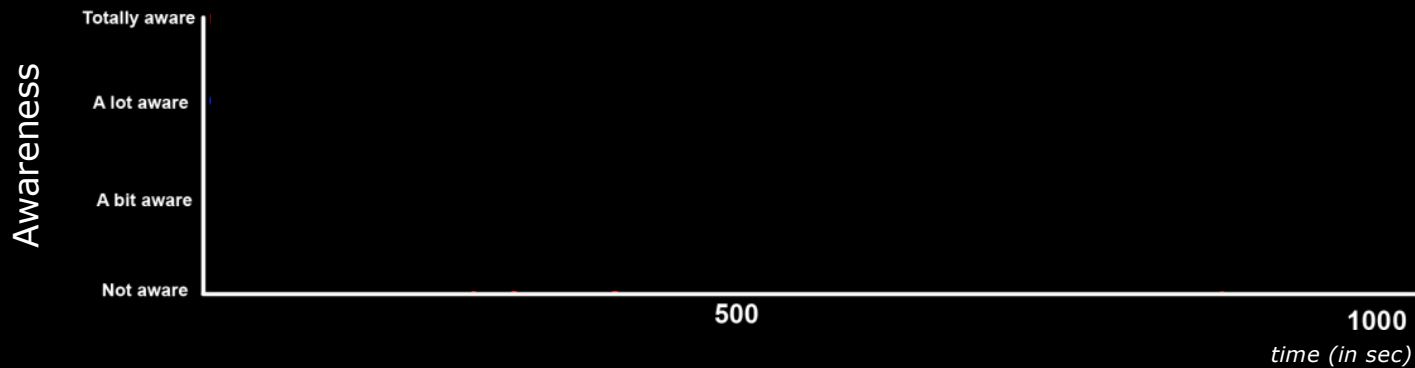


**Internal awareness  
or Default mode network**

# Cognitive-behavioral relevance

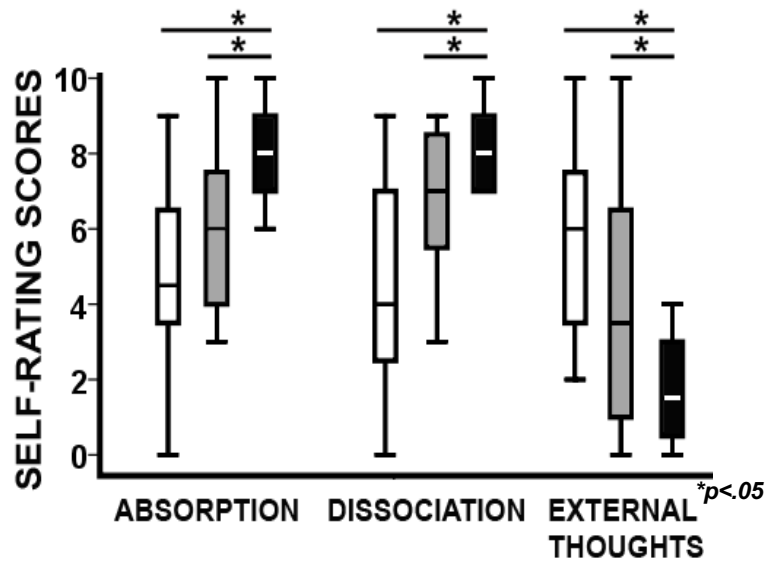
■ Internal awareness  
■ External awareness

External-internal:  $r = -0.44$ ,  $p < .02$   
 Mean switch: 0.05Hz (range: 0.01-0.1)

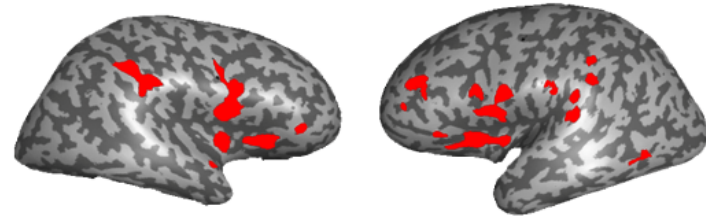


# Effect of awareness

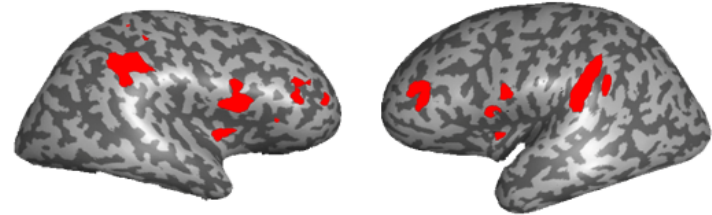
- Normal consciousness
- Autobiographical mental imagery
- Hypnosis



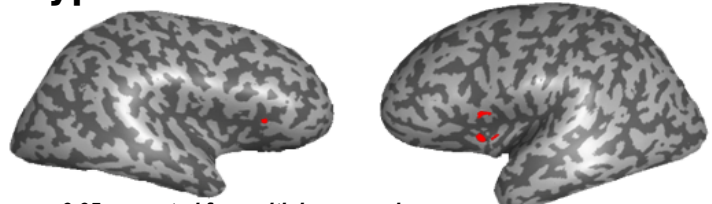
## Normal consciousness



## Autobiographical mental imagery

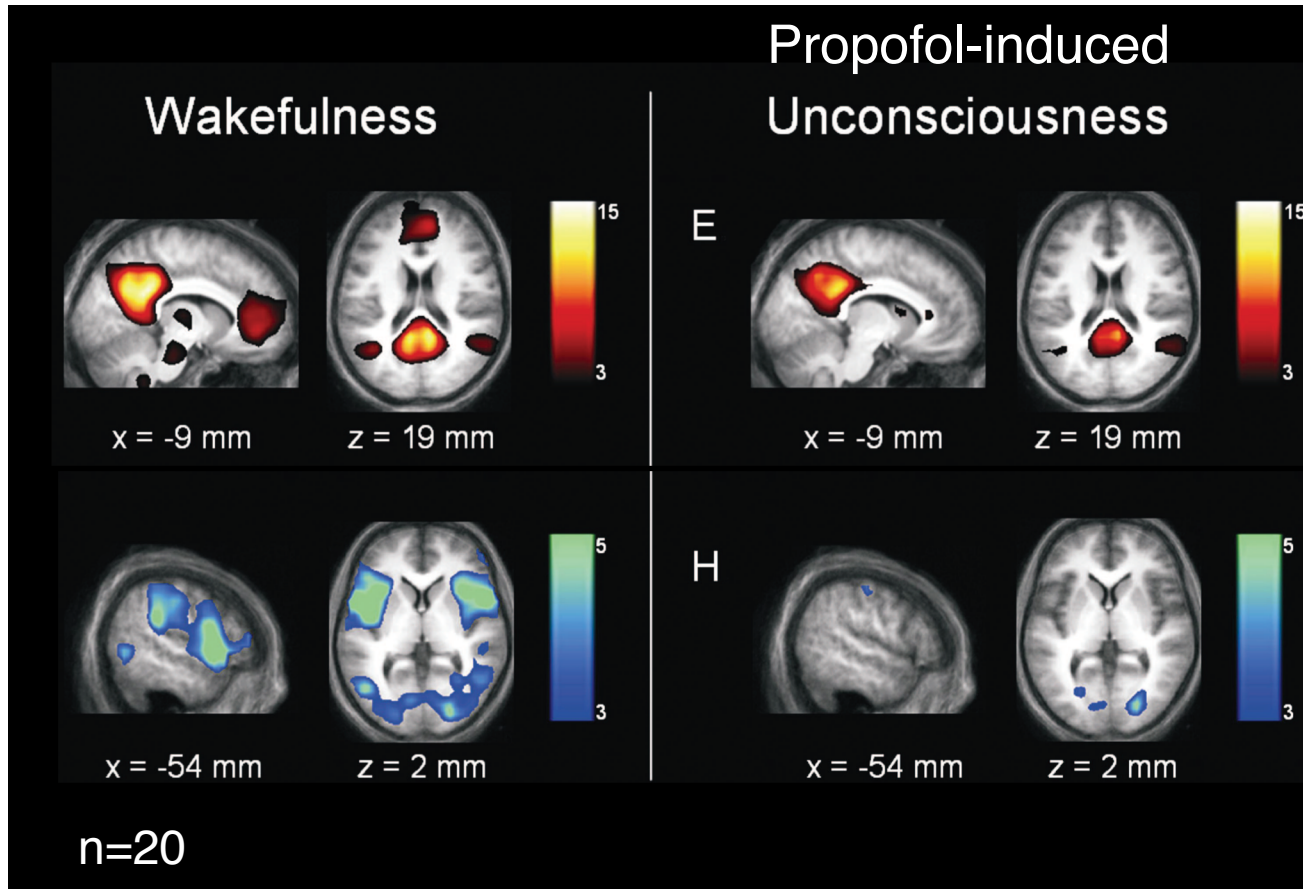


## Hypnosis



*p < 0.05 corrected for multiple comparisons*

# Effect of arousal



# Effect of environment

SCIENTIFIC REPORTS

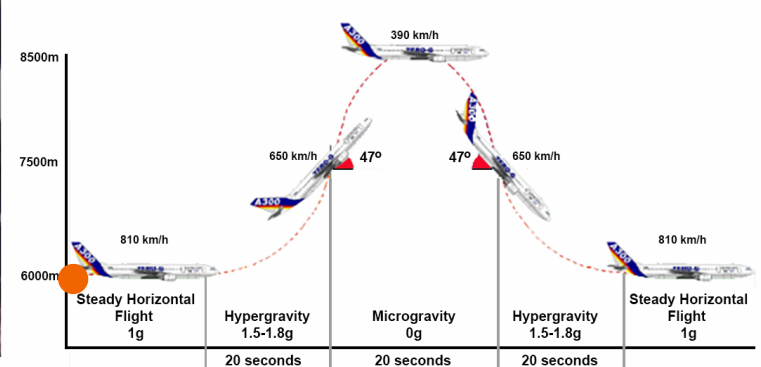
[www.nature.com/scientificreports/](http://www.nature.com/scientificreports/)



## Parabolic flight



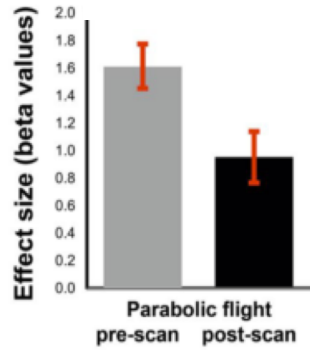
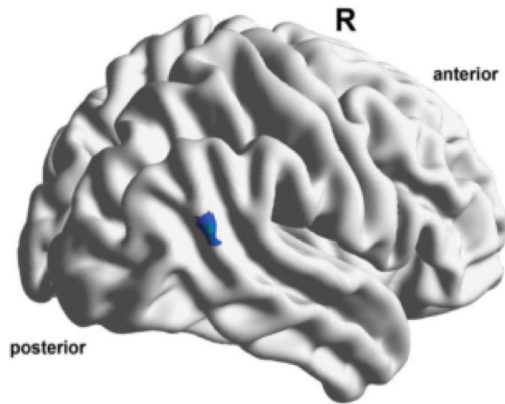
European Space Agency



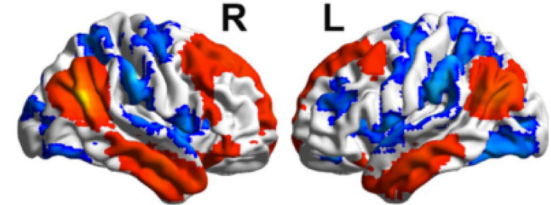
Parabolic flight trajectory

Angelique Van Ombergen<sup>1</sup>, Floris L. Wuyts<sup>1</sup>, Ben Jeurissen<sup>2</sup>, Jan Sijbers<sup>2</sup>, Floris Vanhevel<sup>3</sup>, Steven Jillings<sup>1</sup>, Paul M. Parizel<sup>3</sup>, Stefan Sunaert<sup>4</sup>, Paul H. Van de Heyning<sup>1</sup>, Vincent Dousset<sup>5</sup>, Steven Laureys<sup>6</sup> & Athena Demertzi<sup>6,7</sup>

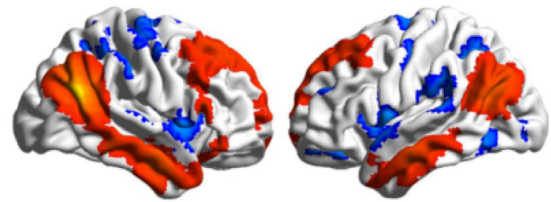
# Effect of environment



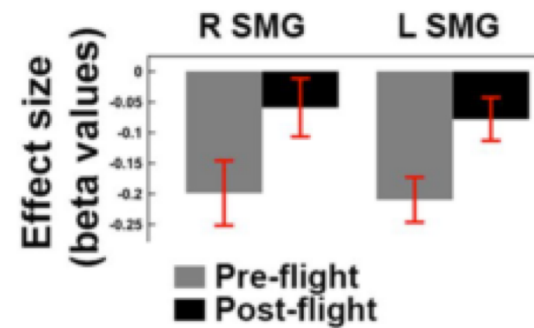
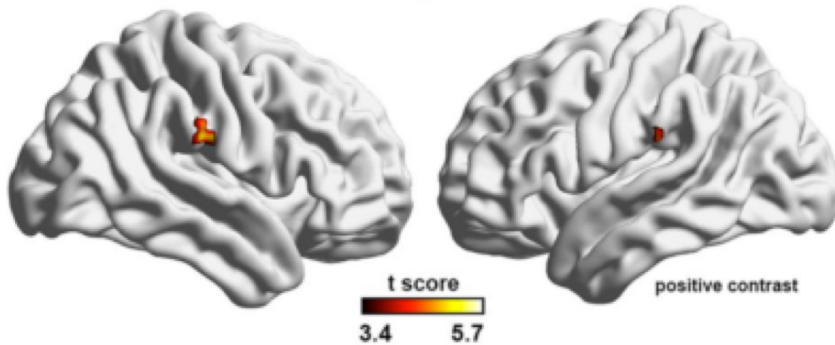
Pre-flight



Post-flight



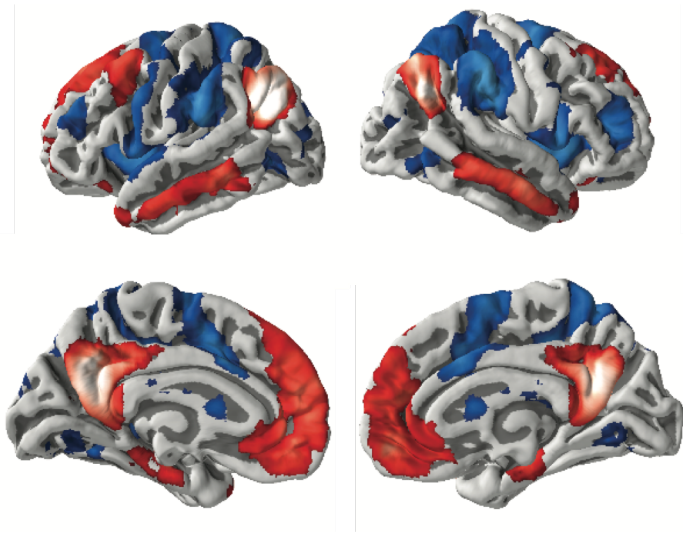
**Post – Pre flight**



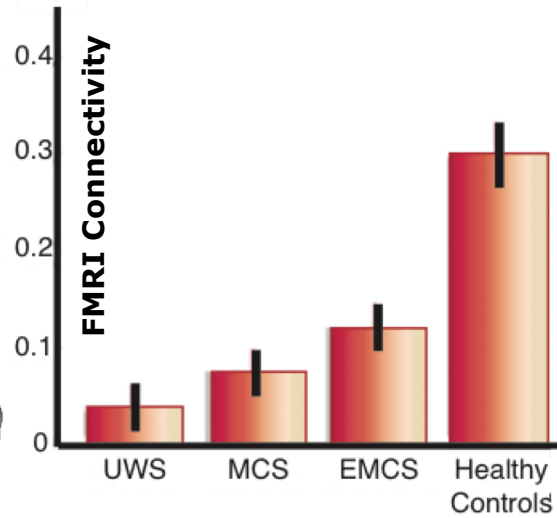




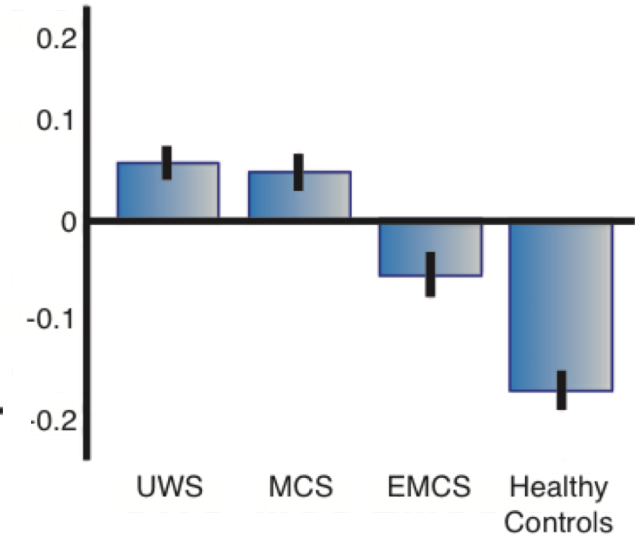
# Effect of pathology



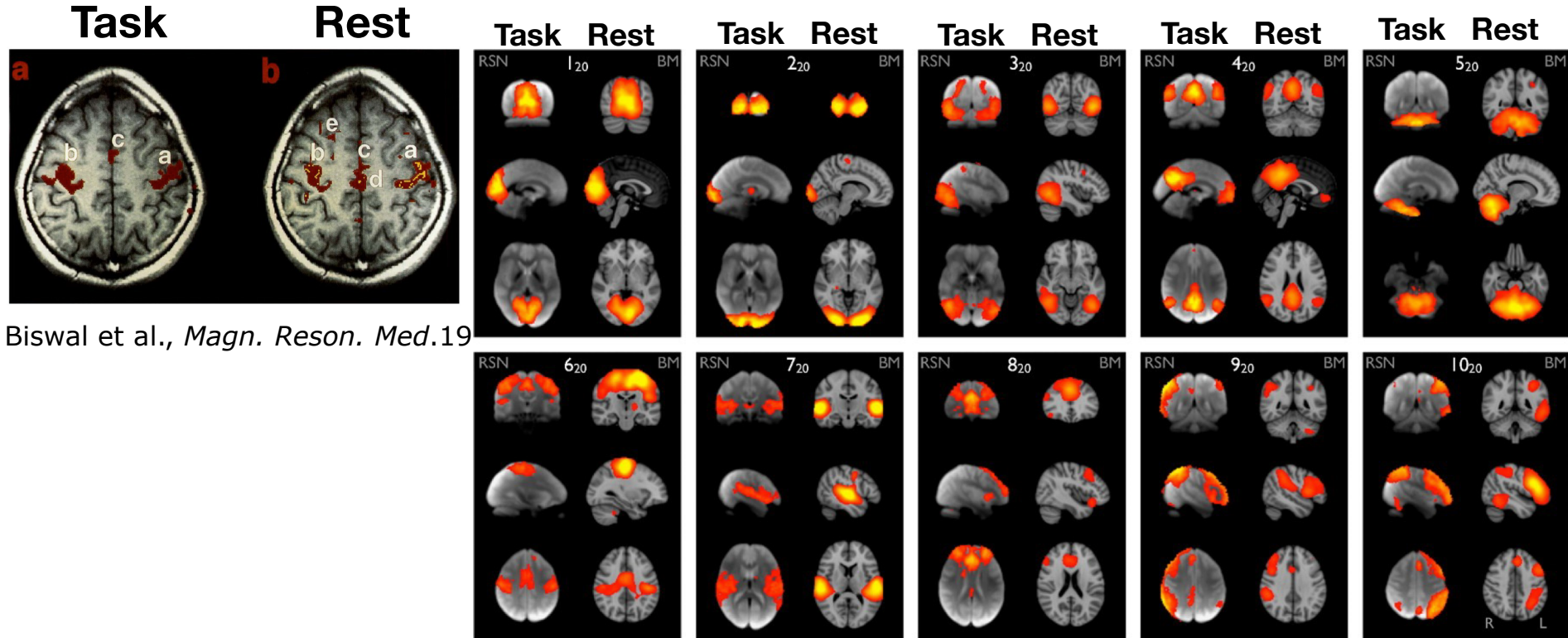
**DMN CORRELATIONS**



**DMN ANTICORRELATIONS**



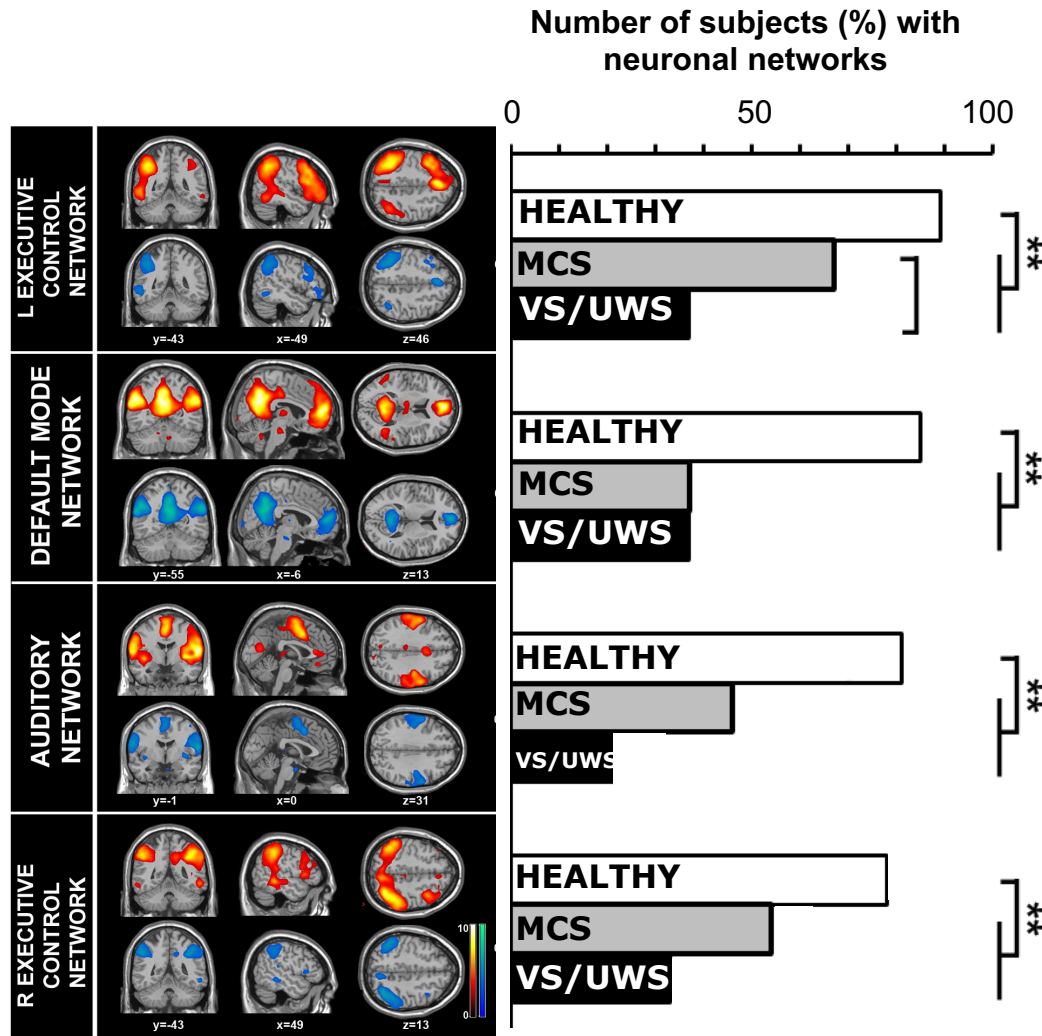
# Intrinsic Connectivity Networks



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

Smith et al, *PNAS* 2009

# Long-range system connectivity disrupted

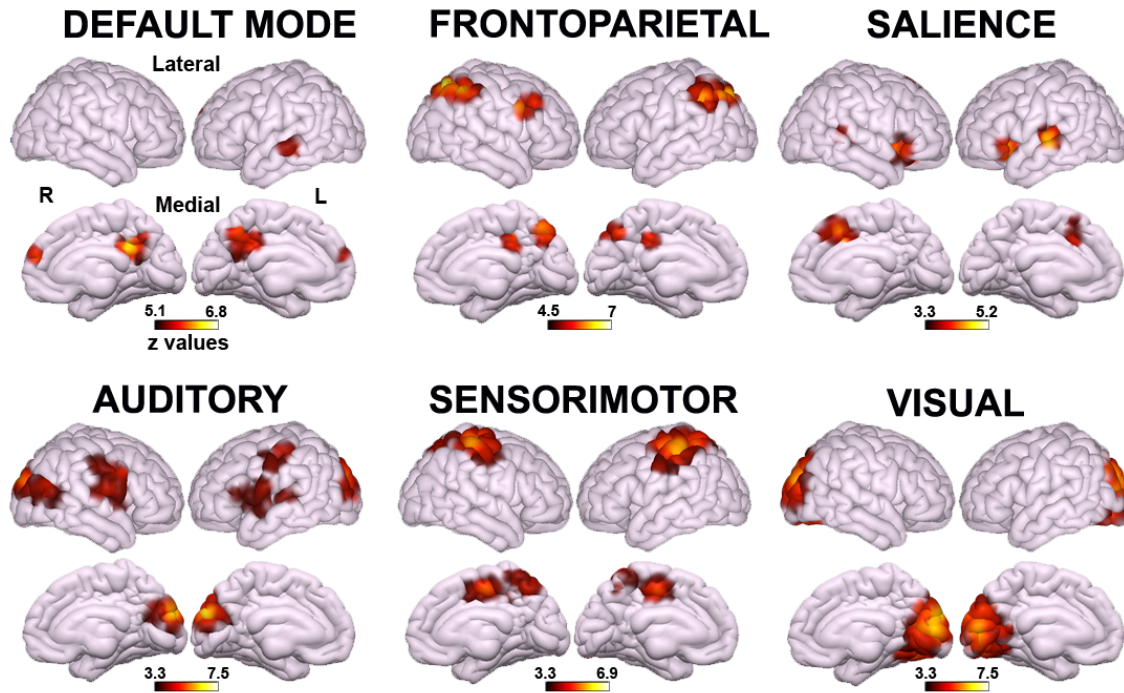


## Single-patient classification

Performance measures	Accuracy	TPR healthy	TPR patients	Selected RSNS
	<b>Healthy vs. all patients</b>			
Neuronal	85.3	.82	.87	Auditory, DMN

# Which network discriminates best?

## MCS > VS/UWS

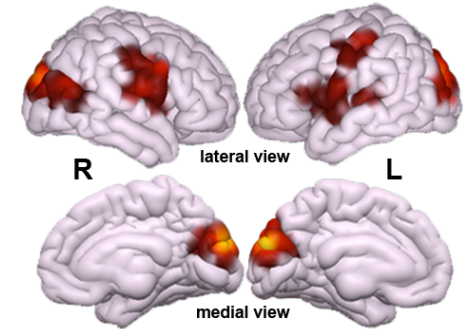


FWE  $p < 0.05$  (cluster-level)

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

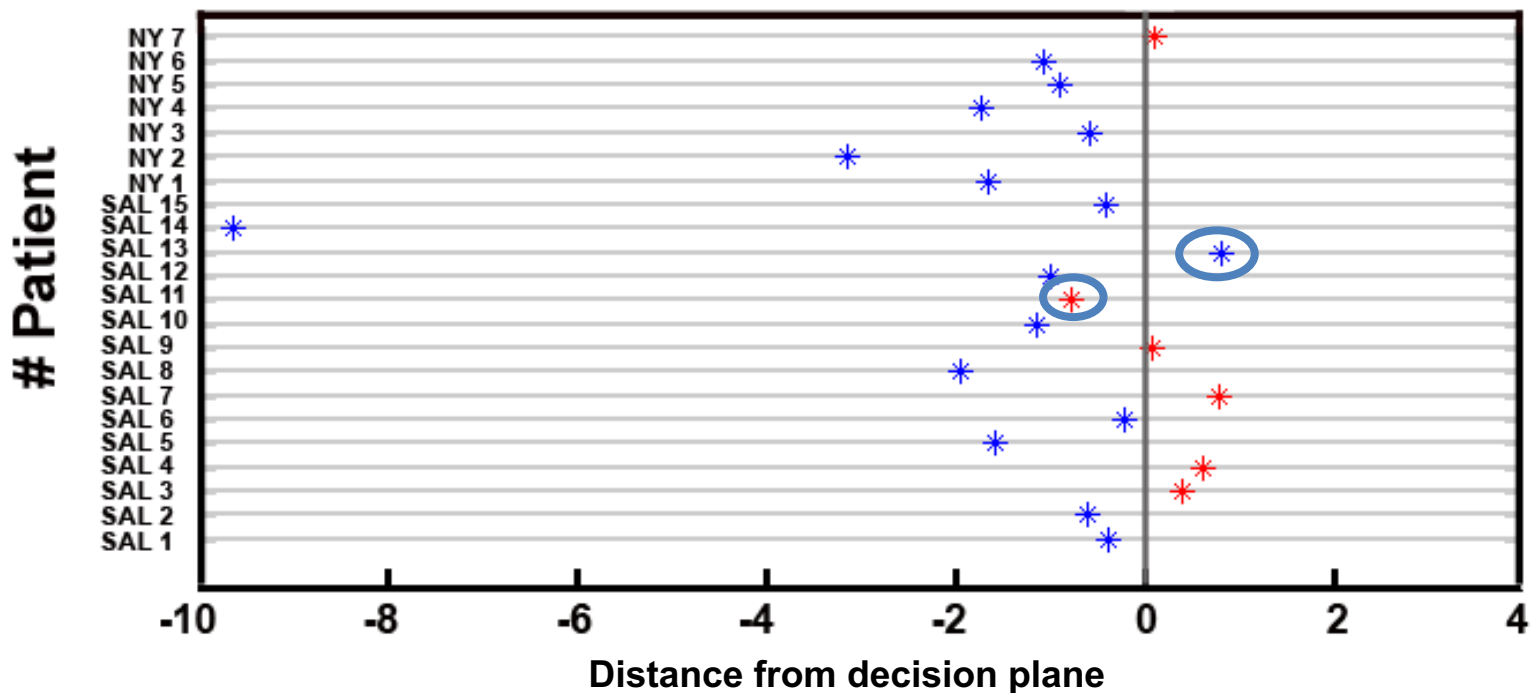
# Crossmodal connectivity classifies DOC

- 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



Classification MCS

Classification VS/UWS



# Stationary connectivity

## RS stationary connectivity :

- is linked to behavior and task performance (*Laird et al., J Cogn Neurosci 2011*)
- reflects physiological & pathological unconsciousness (*Heine et al, Front Psychol 2012*)
- permits single-patient automatic diagnosis (*Demertzi & Antonopoulos et al, Brain 2015*)

**But**

it remains unclear to what extent it provides a  
representative estimate of cognition

(*Peterson et al, Neurolmage Clin 2015*)



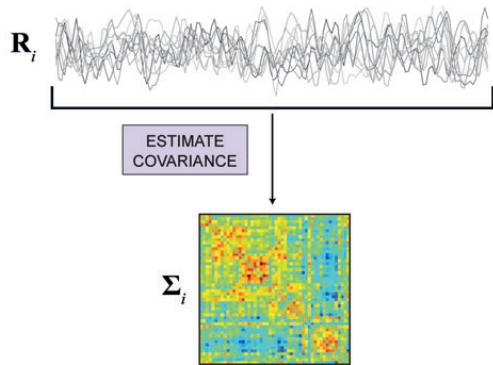
Ongoing interactions among distinct brain regions

(*Hutchison et al, Neurolmage 2013*)

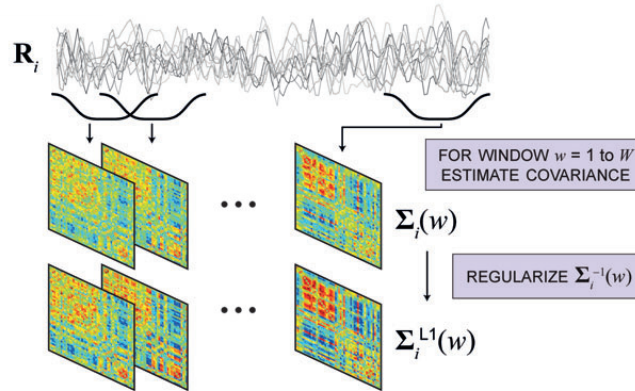


# From stationarity to dynamics

## Stationary fc



## Time-varying fc



## Dynamic

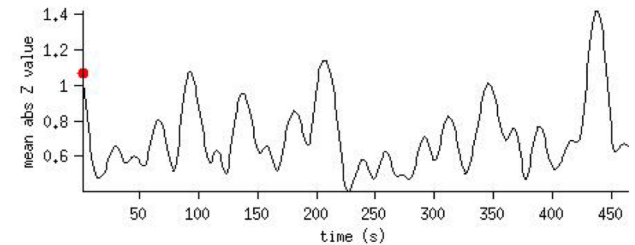
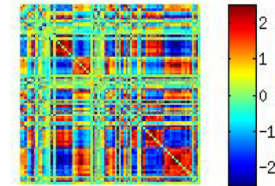
$$x_t = A \cdot x_{t-1} + \epsilon_t$$



# Brain dynamics and cognition

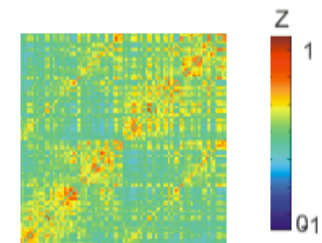
## Typical wakefulness: significance for performance, emotion and cognition

(Alavash et al, *Neuroimage*, 2016; Shine et al *Neuron*, 2016; Friston *Neuroimage*, 1997; Thompson et al, *Hum Brain Mapp*, 2013)



## Unconsciousness: rigid spatiotemporal organization, less metastable dynamics

- **sleep** (Tagliazucchi et al, *PNAS* 2013; Wang et al, *PNAS* 2016; Wilson et al., *Neuroimage* 2015; Chow et al, *PNAS* 2013)
- **anesthesia**
  - **in humans** (Tagliazucchi et al, *J. R. Soc. Interface* 2016; Kafashan et al, *Front Neural Circuits*, 2016; Amico et al, *PLoS One* 2014)
  - **in animals** (Barttfeld et al, *PNAS* 2014); Grandjean et al, *Neuroimage* 2017; Liang et al, *Neuroimage* 2015).



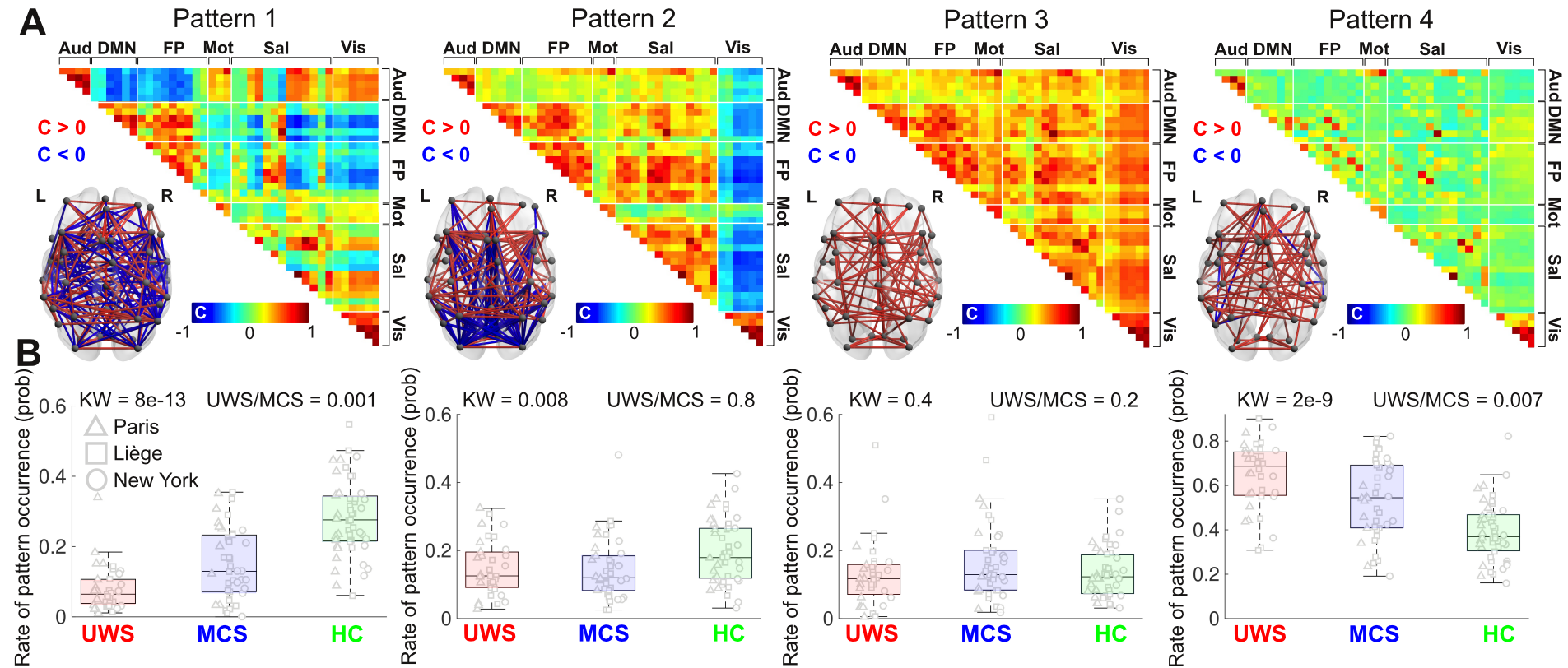
Barttfeld\*, Ulbrig\*, Sitt\*, et al, *PNAS* 2015



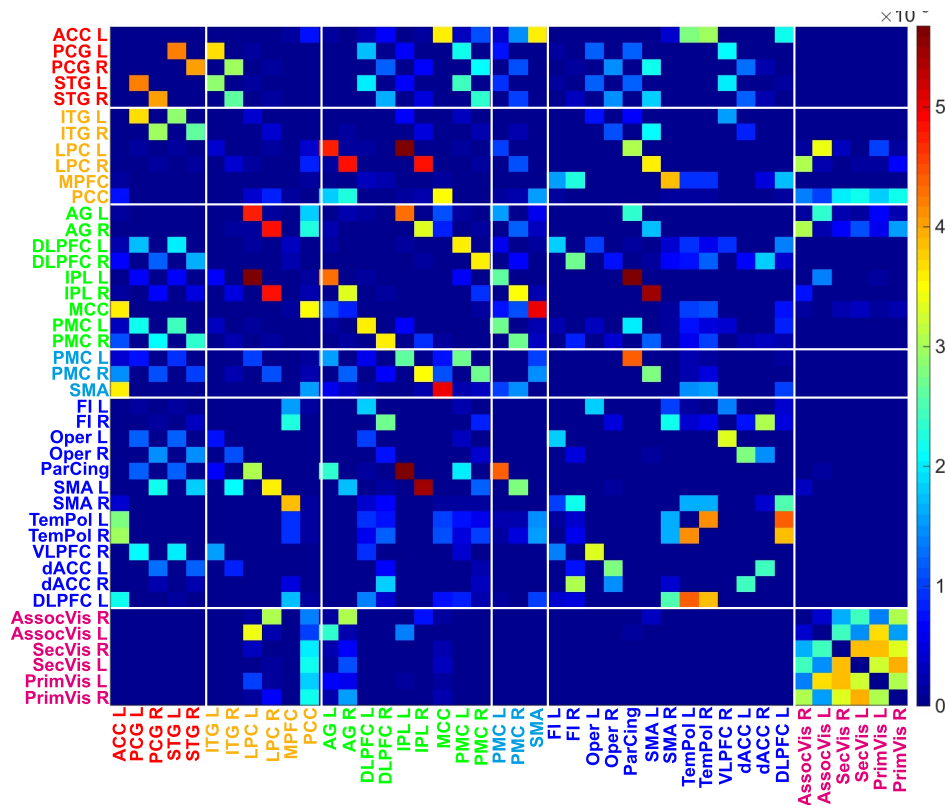
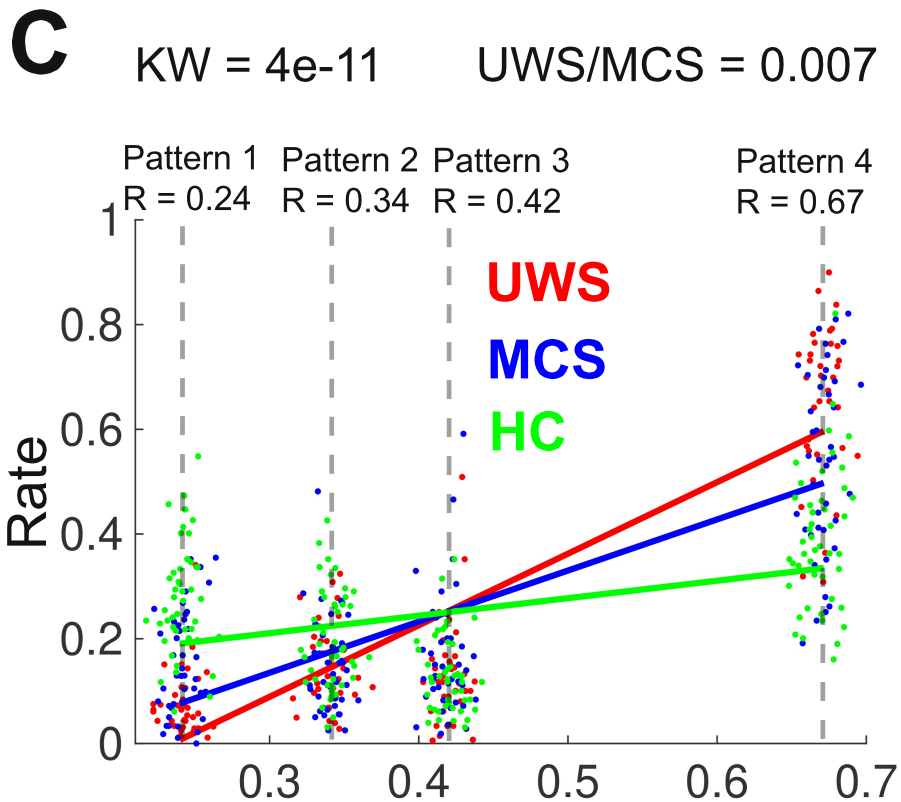
The brain cannot map the complexity of the internal and external world  
(Dehaene et al, *Trends Cog Sci*, 2006; Tononi et al, *Nat Rev Neurosci*. 2016)



# Patterns of recurrent coordinated activity



# Structure-function correlation



# More chances to transition if in higher conscious state

## Markov Process

- *stochastic process that has no memory*
- *selection of next state depends only on current state, and not on prior states*
- *process is fully defined by a set of transition probabilities  $\pi_{ij}$*   
 $\pi_{ij}$  = probability of selecting state  $j$  next, given that presently in state  $i$ .  
 Transition-probability matrix  $\Pi$  collects all  $\pi_{ij}$

## Transition-Probability Matrix

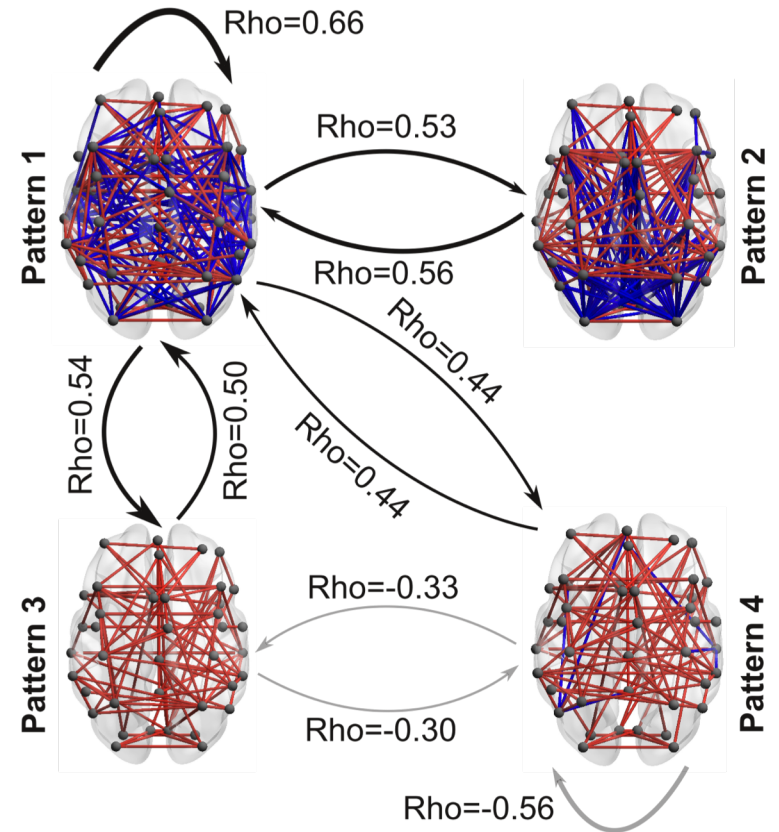
### Example

- *system with three states*

$$\Pi \equiv \begin{pmatrix} \pi_{11} & \pi_{12} & \pi_{13} \\ \pi_{21} & \pi_{22} & \pi_{23} \\ \pi_{31} & \pi_{32} & \pi_{33} \end{pmatrix} = \begin{pmatrix} 0.1 & 0.5 & 0.4 \\ 0.9 & 0.1 & 0.0 \\ 0.3 & 0.3 & 0.4 \end{pmatrix}$$

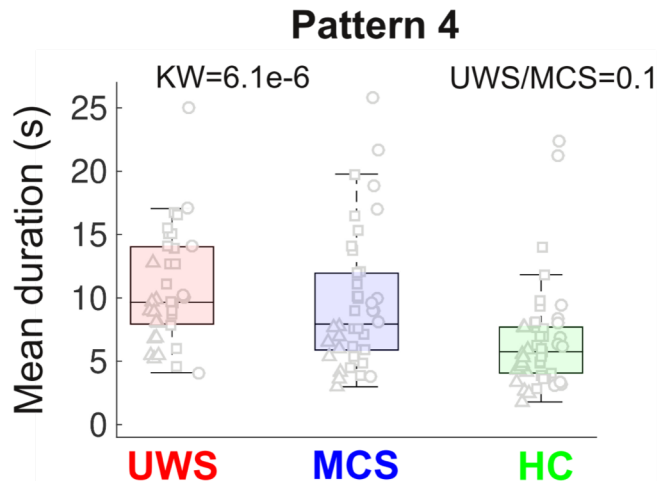
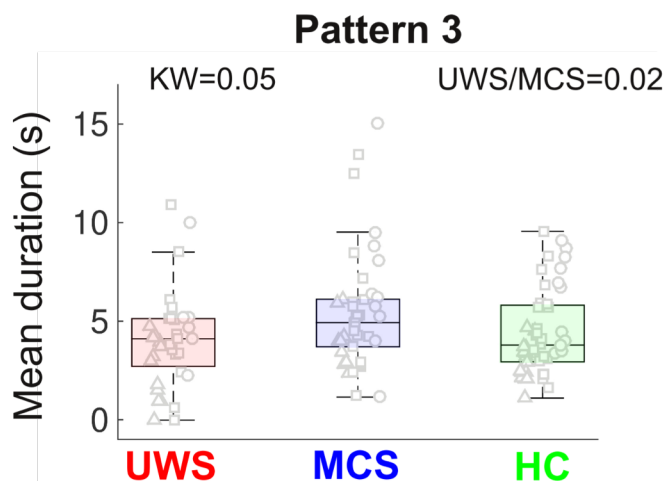
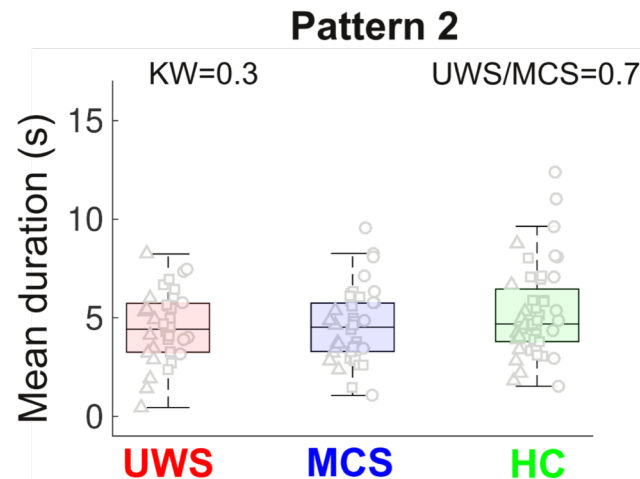
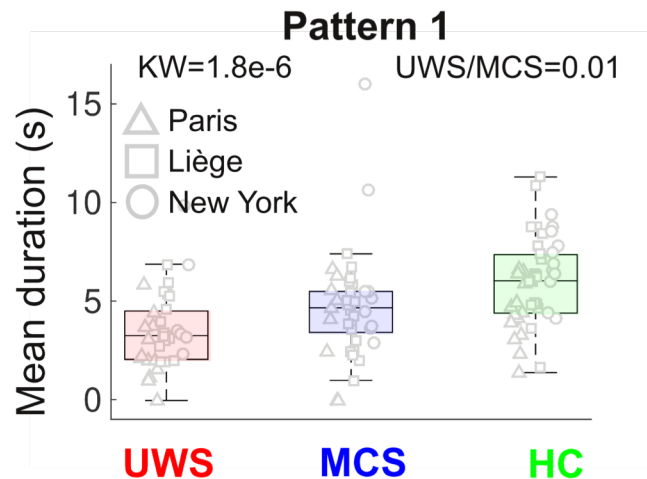
If in state 1, will stay in state 1 with probability 0.1  
 If in state 1, will move to state 3 with probability 0.4  
 Never go to state 3 from state 2

## Consciousness-level dependent



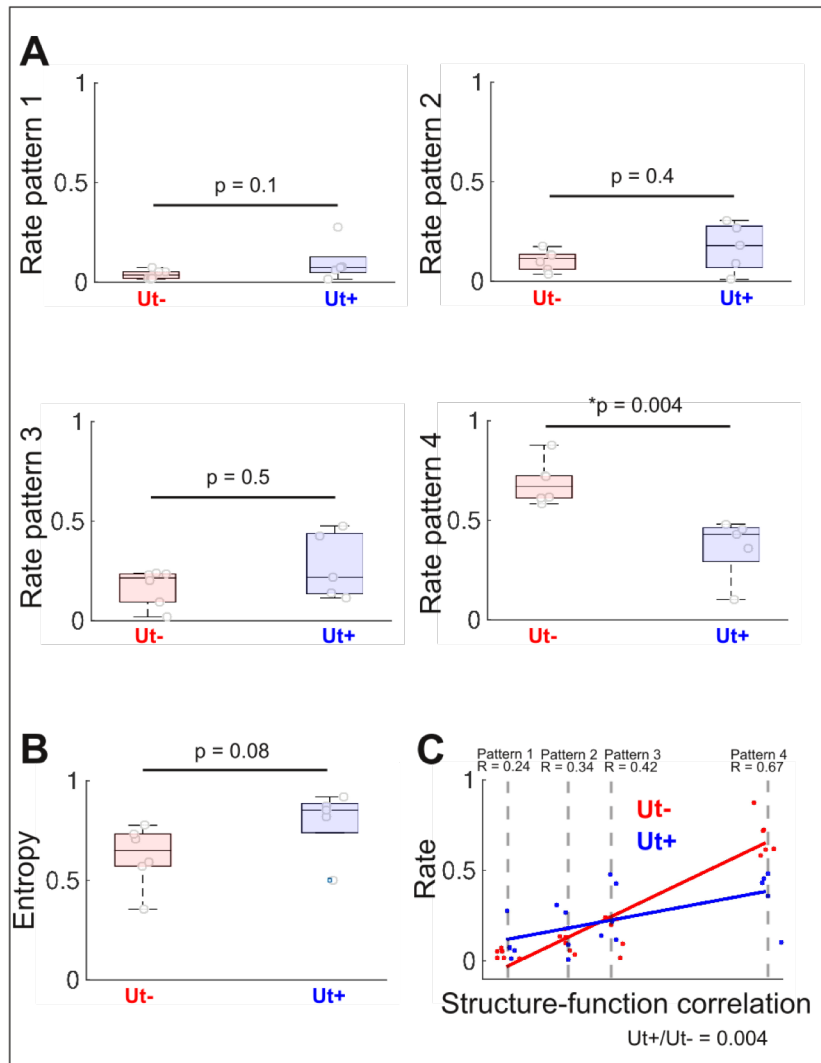
# Exploration is longer for complex patterns

## B. Duration of pattern occupation

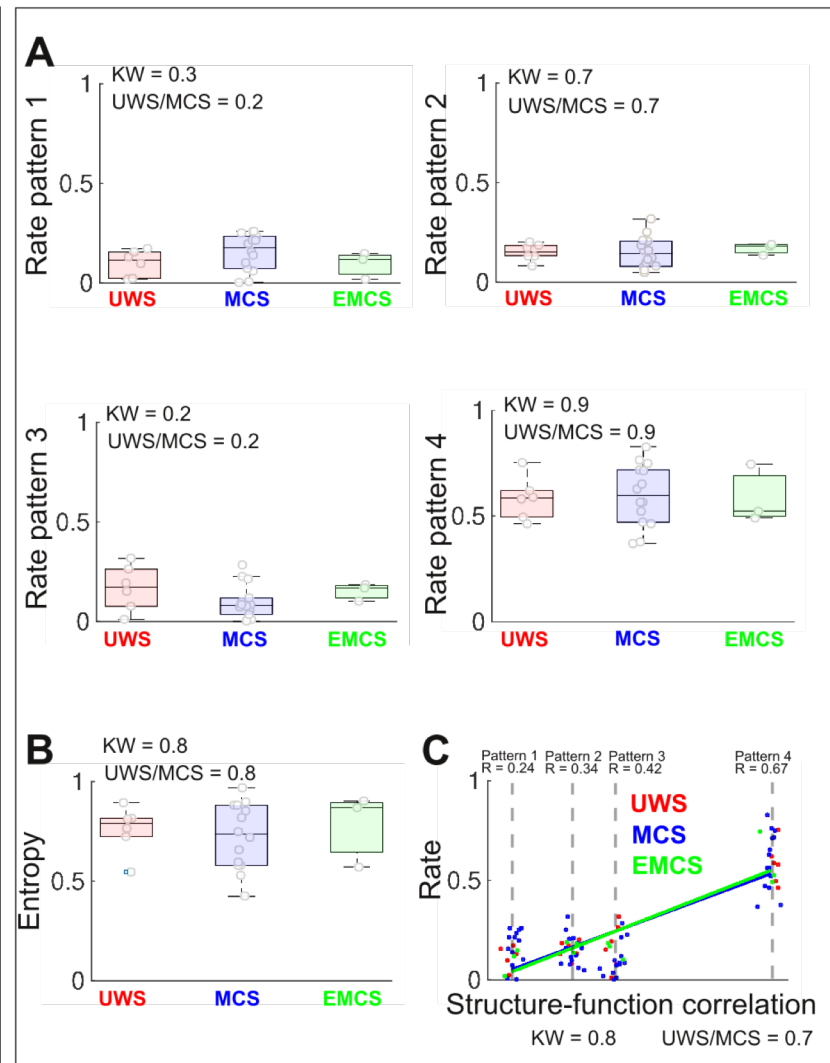


# Do we measure consciousness?

## Pattern prediction in cognitive-motor dissociation



## Pattern prediction in anesthesia





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

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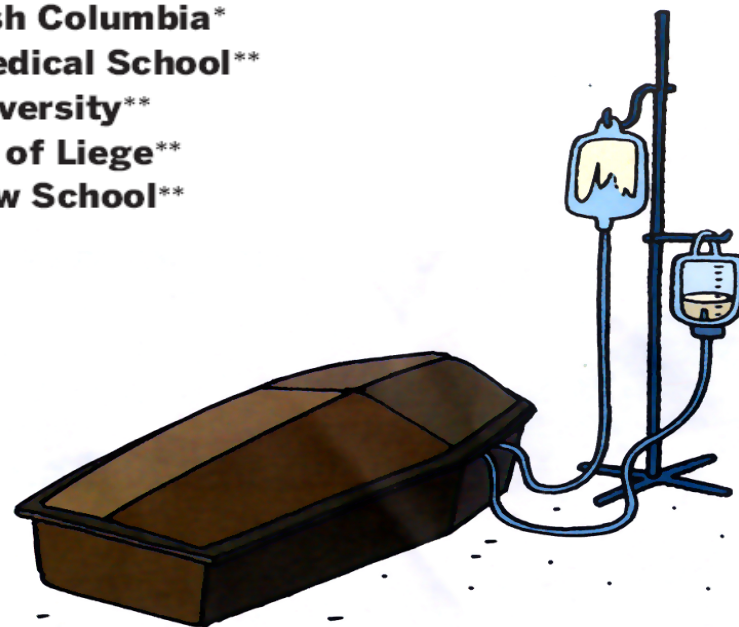
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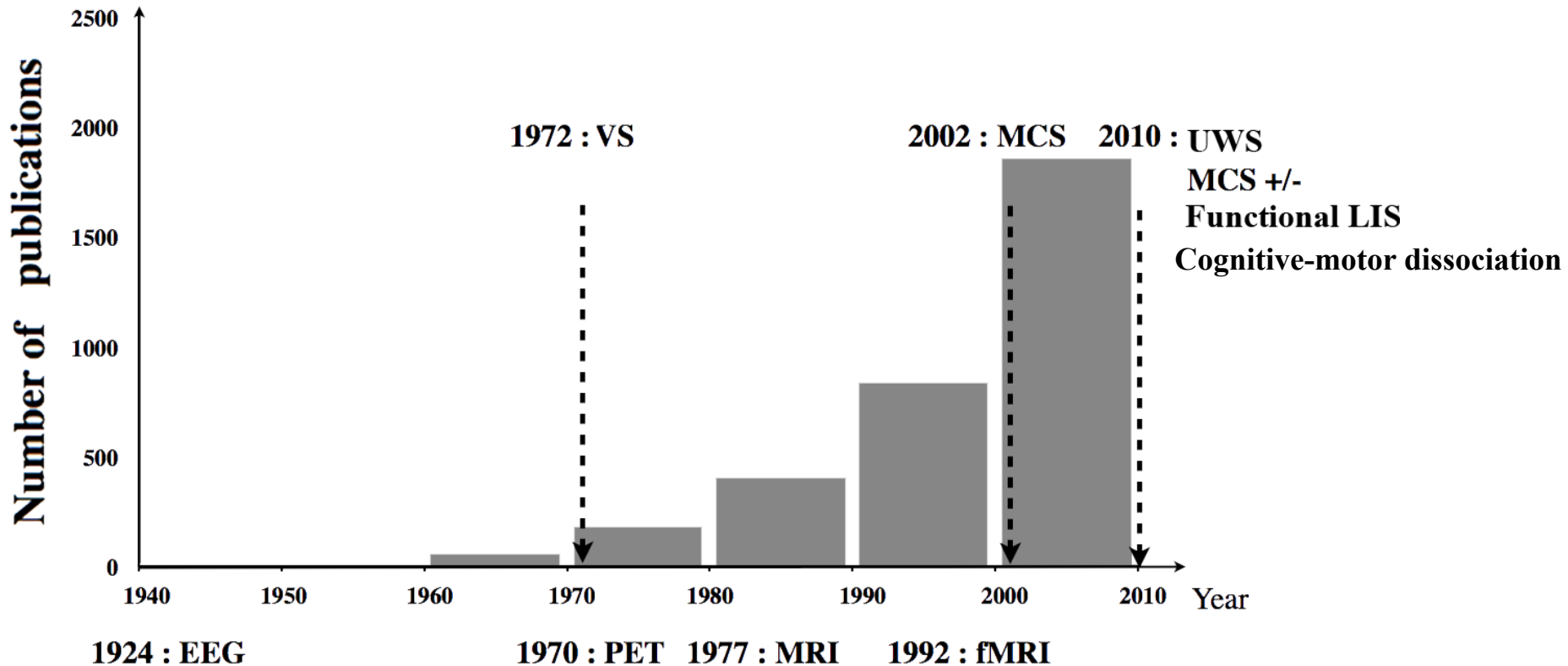
# Balancing costs-benefits

<b>Results of Tests</b>	<b>Beneficial Effects</b>	<b>Harmful Effects</b>
- 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



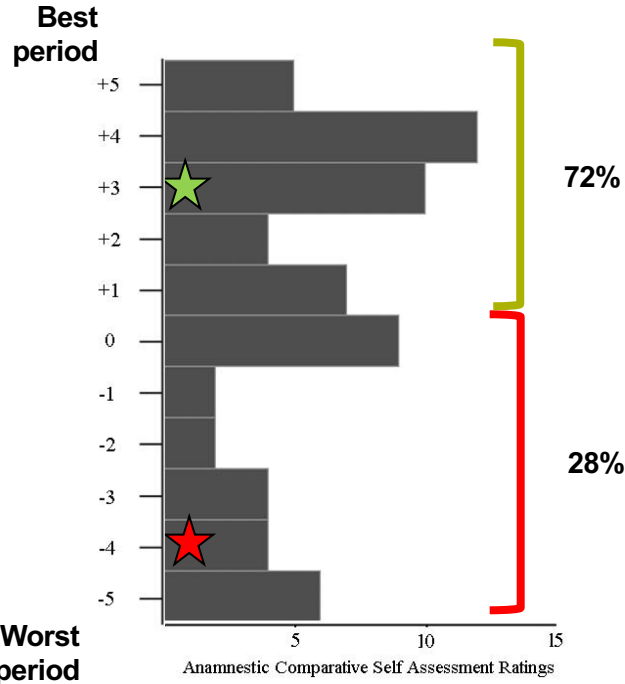


# Benefit for science

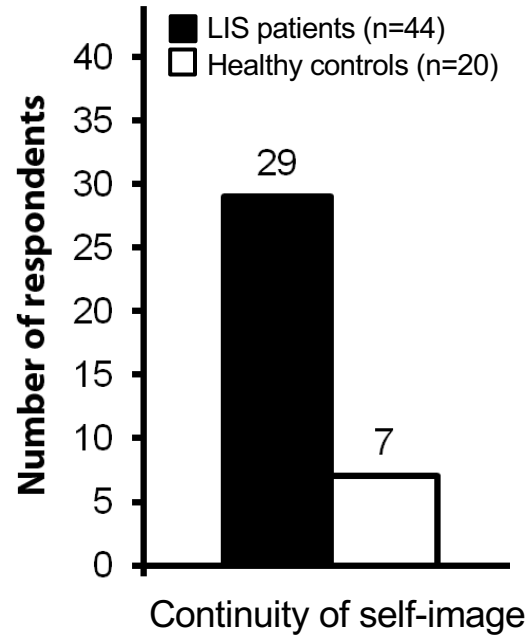




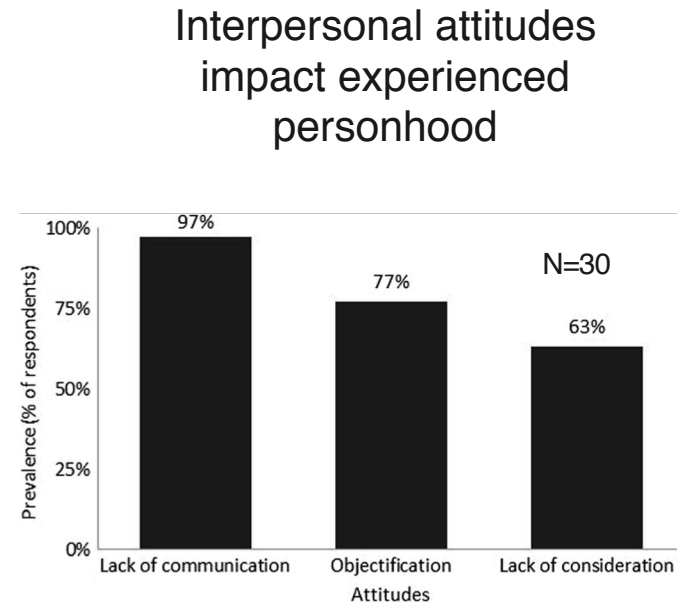
# Benefit for patients?



Bruno et al, *Br Med J Open* 2011



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



Nizzi, Blandin, Demertzi *NeuroEthics* 2018



# Benefit for caregivers?

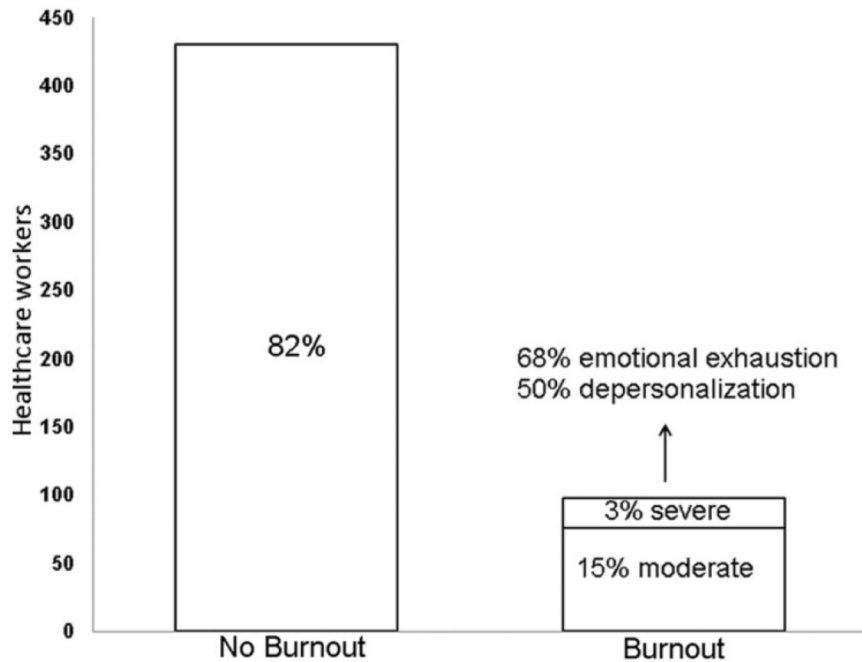


Table III. Percentage of healthcare workers presenting a burnout.

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

n=523



# 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

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## **Consciousness needs a brain which:**

- is intrinsically organized
- shows complexity
- shows dynamic flexibility

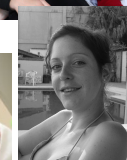
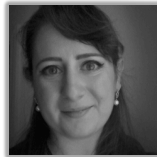
## **Consciousness as a collective consensus**

## **Consciousness ....**

# Many thanks to Coma Science Group & PICNIC Lab

The departments of Neurology and Radiology in Liège & Paris

...and mostly  
patients and their families!



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James S. McDonnell Foundation

