# Assessing consciousness in the absence of communication

**1st Sleep Science Winter School**
**Wengen, Switzerland**
**2 March 2018**


**Athena Demertzi, PhD**
Coma Science Group
GIGA Research & Neurology Department
University & University Hospital of Liège
Belgium
&
Institut du Cerveau et de la Moelle épinière – ICM
Hôpital Pitié-Salpêtrière, Paris
France



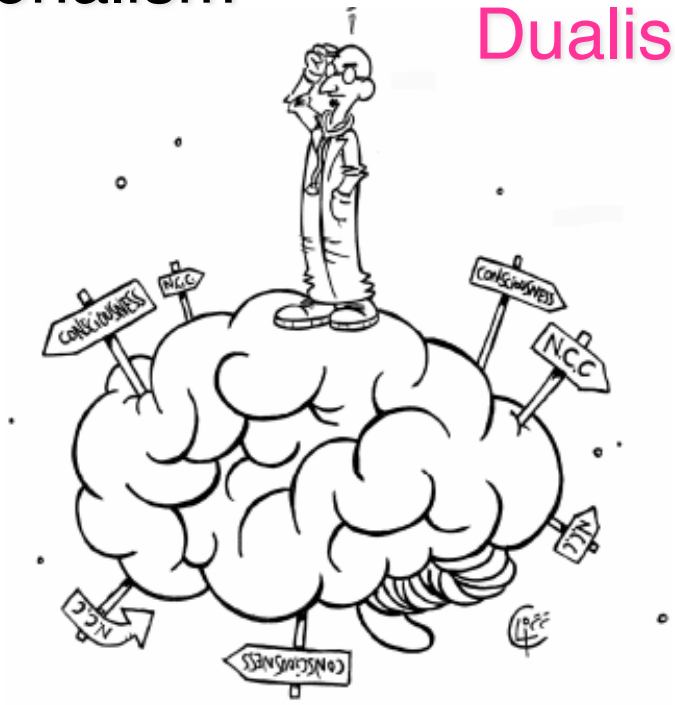
James S. McDonnell Foundation
Human Brain Project
European Space Agency

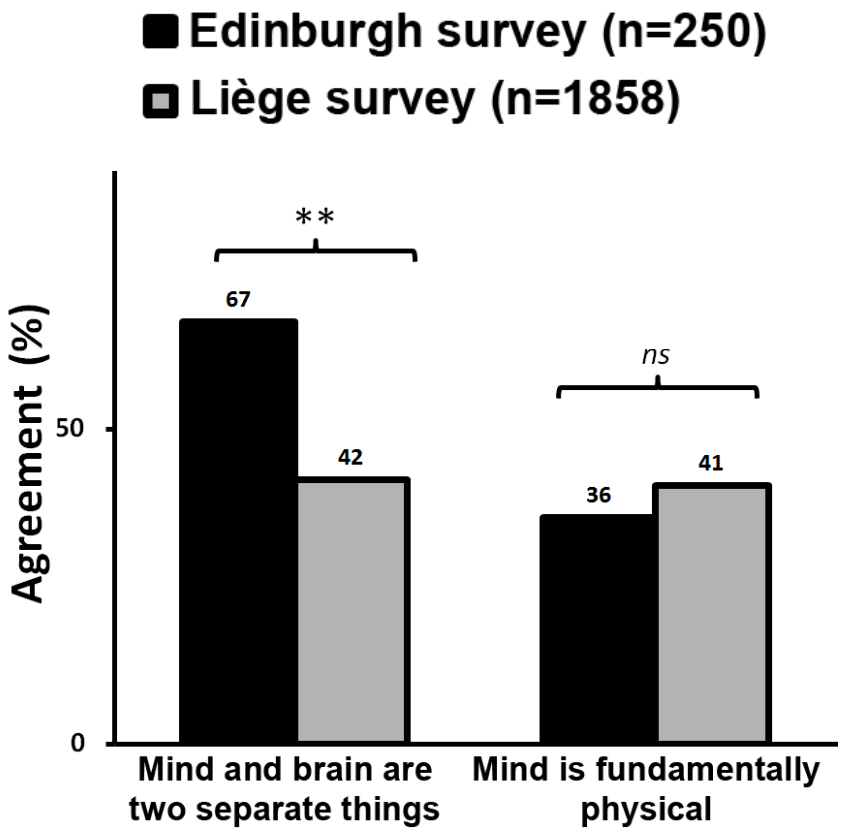
# What is Consciousness?

Functionalism

Materialism

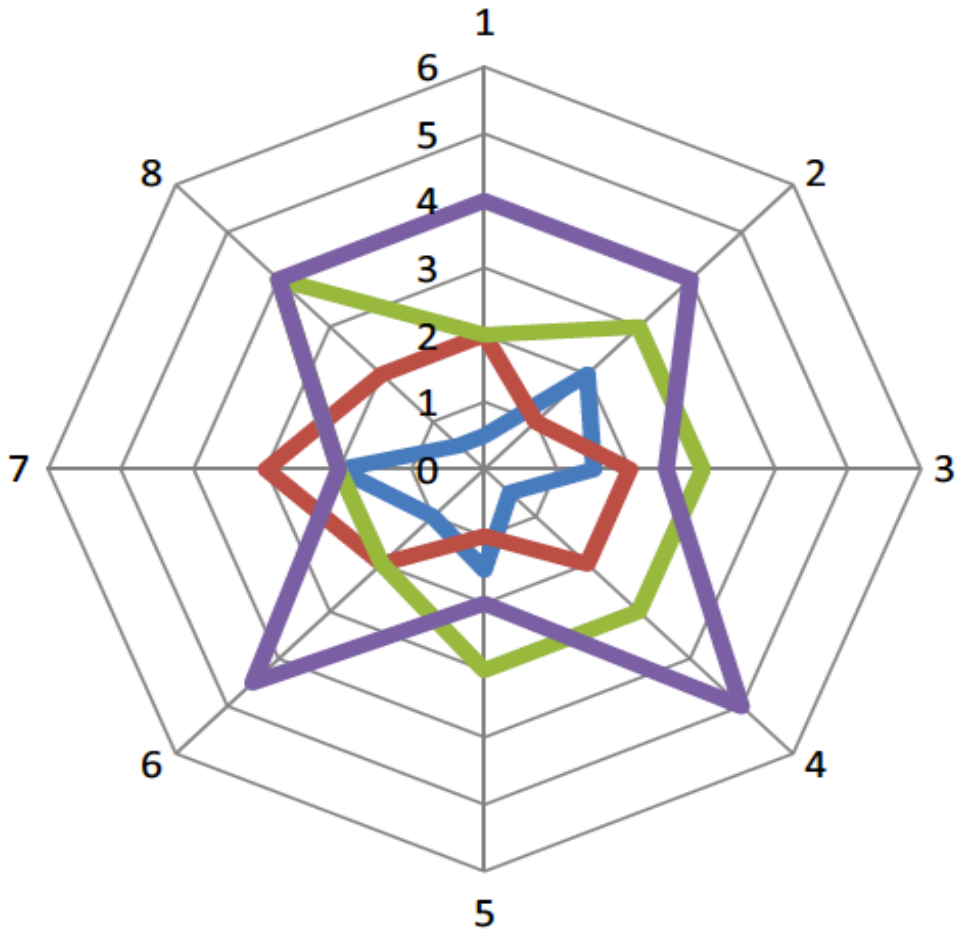
Dualism



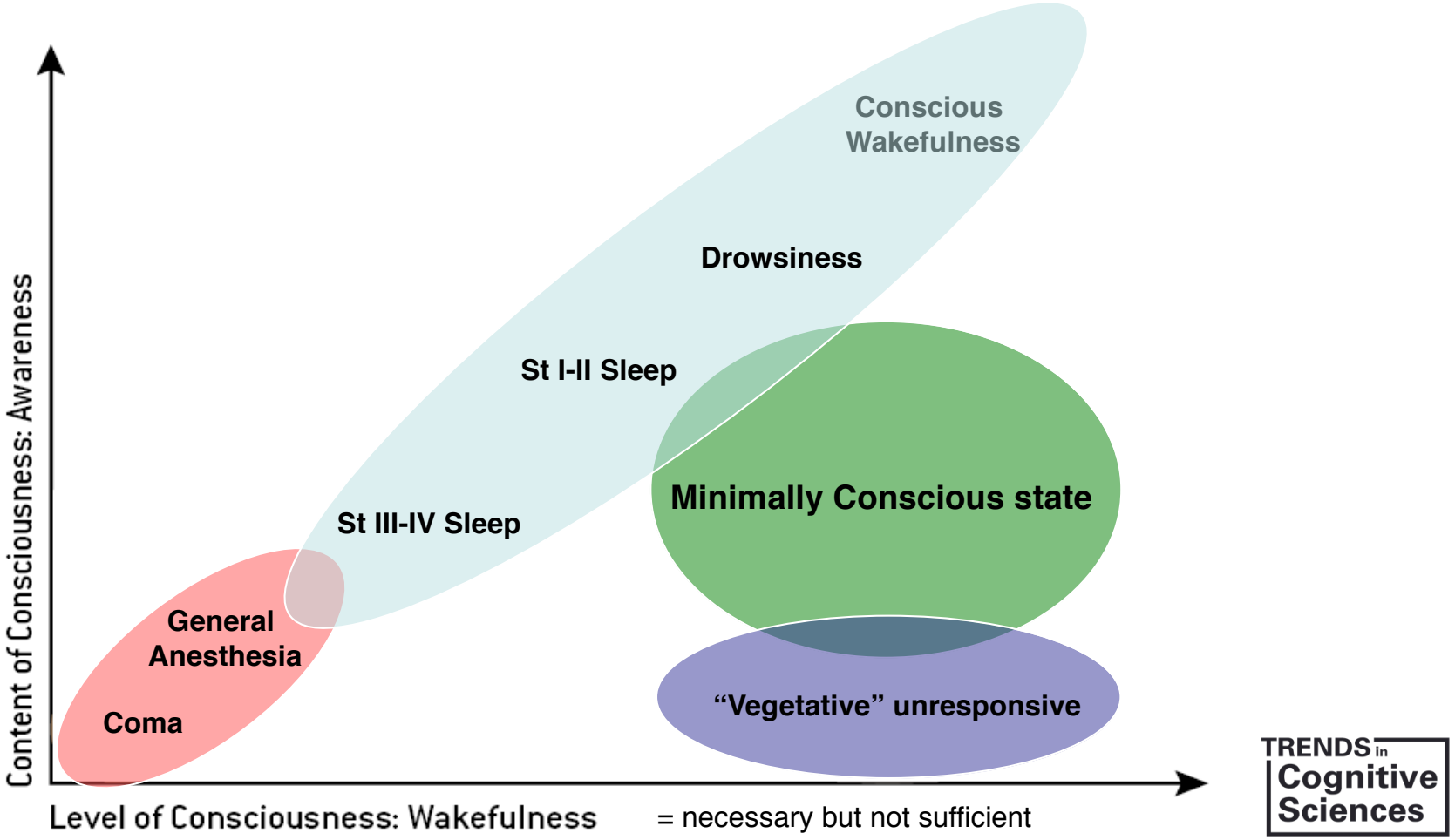

Demertzi et al, *Annals of the New York Academy of Sciences* 2009

# Defining Consciousness




Bayne, Hohwy, Owen. *Trends Cogn Sci* 2016

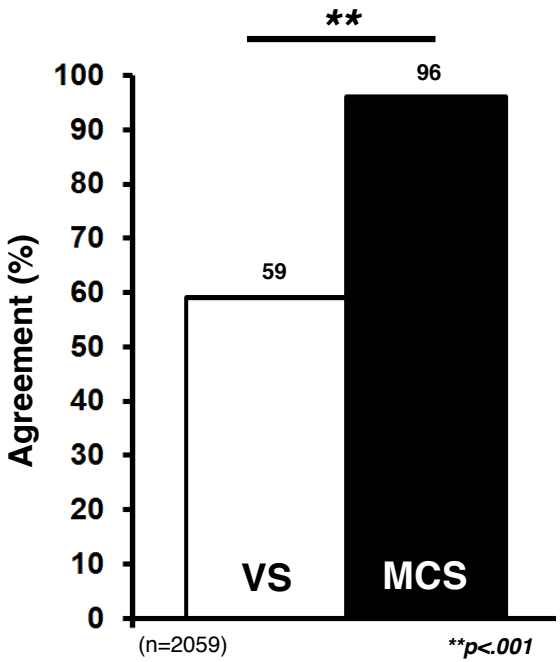
# A clinical definition




Laureys. *Trends Cogn Sci* 2005; Laureys et al, *Nat Clin Med* 2008
Demertzi, Boly, Laureys. *Encyclopedia of Consciousness* 2009

# Do they feel pain?

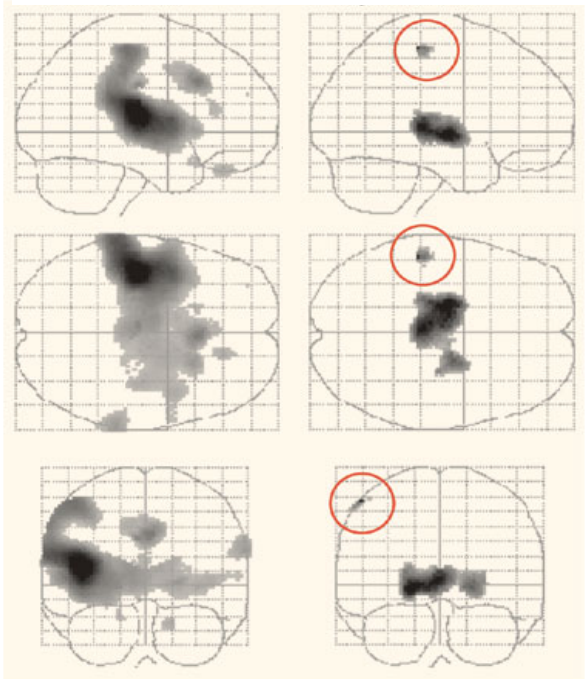

**Do you think patients in a ... can feel pain?**




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

**Unresponsive wakefulness syndrome**

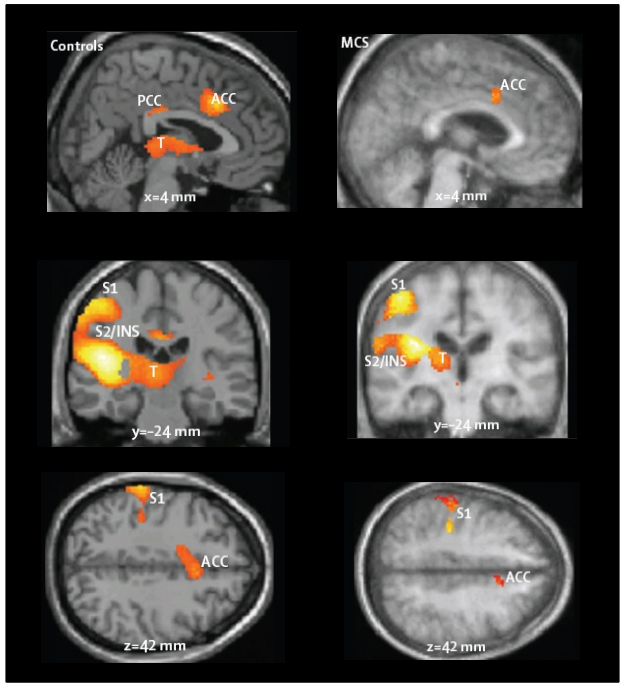
Healthy controls UWS patients



Laureys et al., *Neuroimage* 2002

**Minimally conscious state**

Healthy controls MCS patients



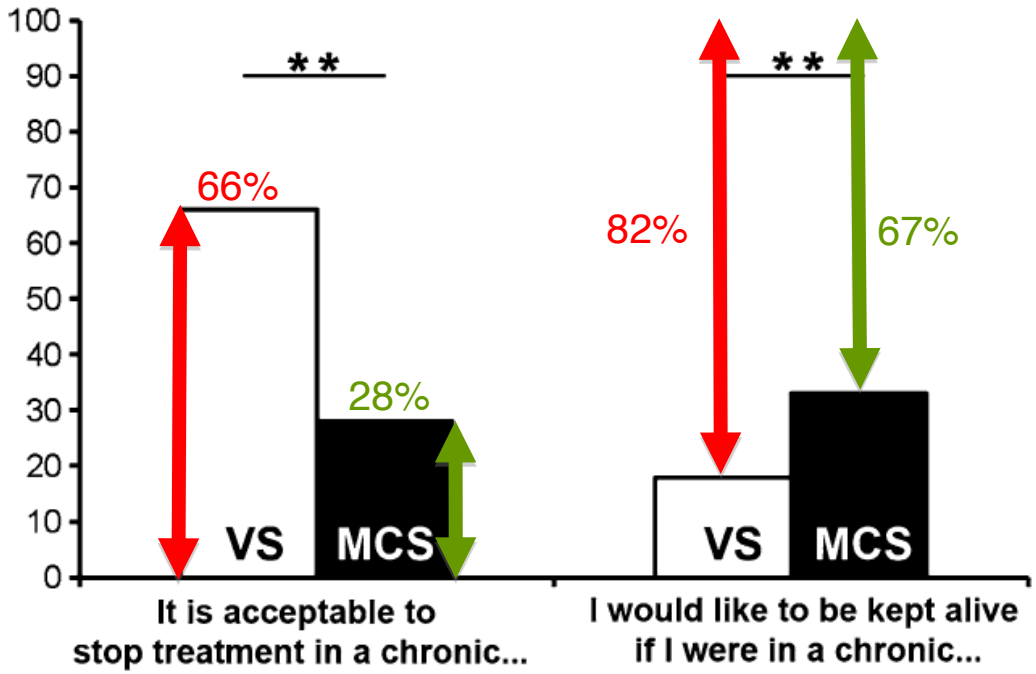

Boly et al, *Lancet Neurol* 2008

# End-of-life?

- VS worse than death for the patient: 55%
- VS worse than death for their families: 80%

- MCS worse than VS for the patient: 54%
- MCS worse than VS for their families: 42%

2,475 medical professionals

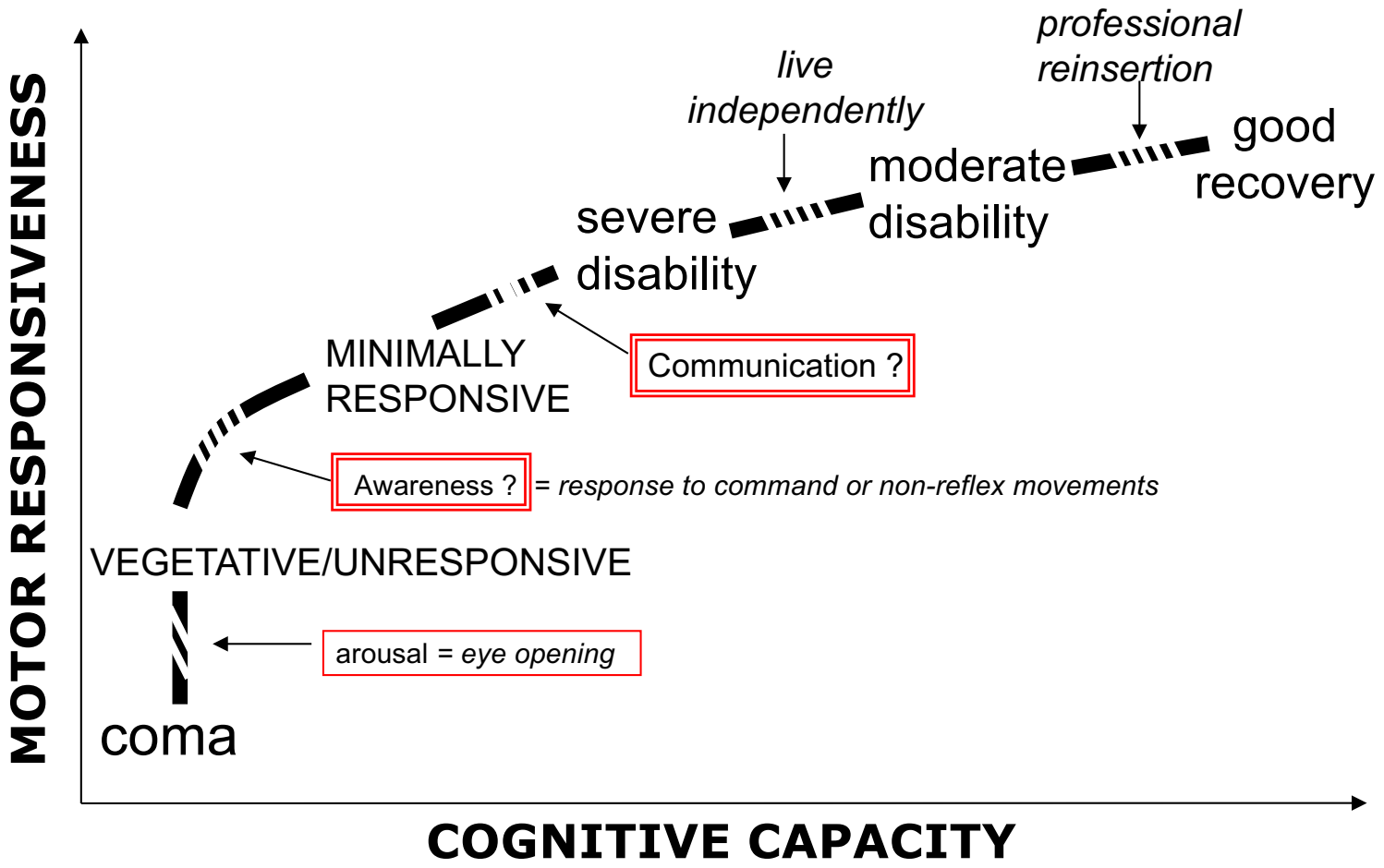




Demertzi et al, *J Neurol* 2011

# Behaviour

Terry Schiavo °1963,
vegetative 1990, † 2005 USA

# Behavioural signs of C




Laureys et al, *Curr Opin Neurol* 2005

# Gold standard?

## Standardized assessment

n=103 post-comatose patients

45 Clinical diagnosis of VS
18 Coma Recovery Scale MCS

40% misdiagnosed

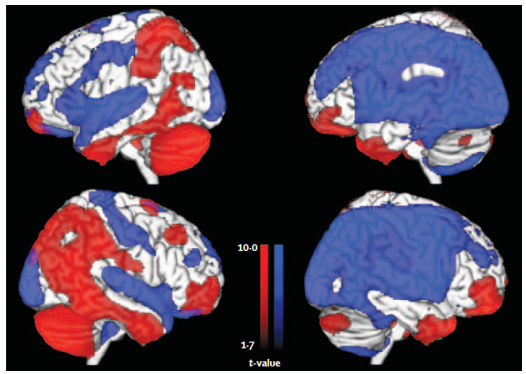
Schnakers et al, *Ann Neurol* 2006; *BMC Neurol* 2009

## PET 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**

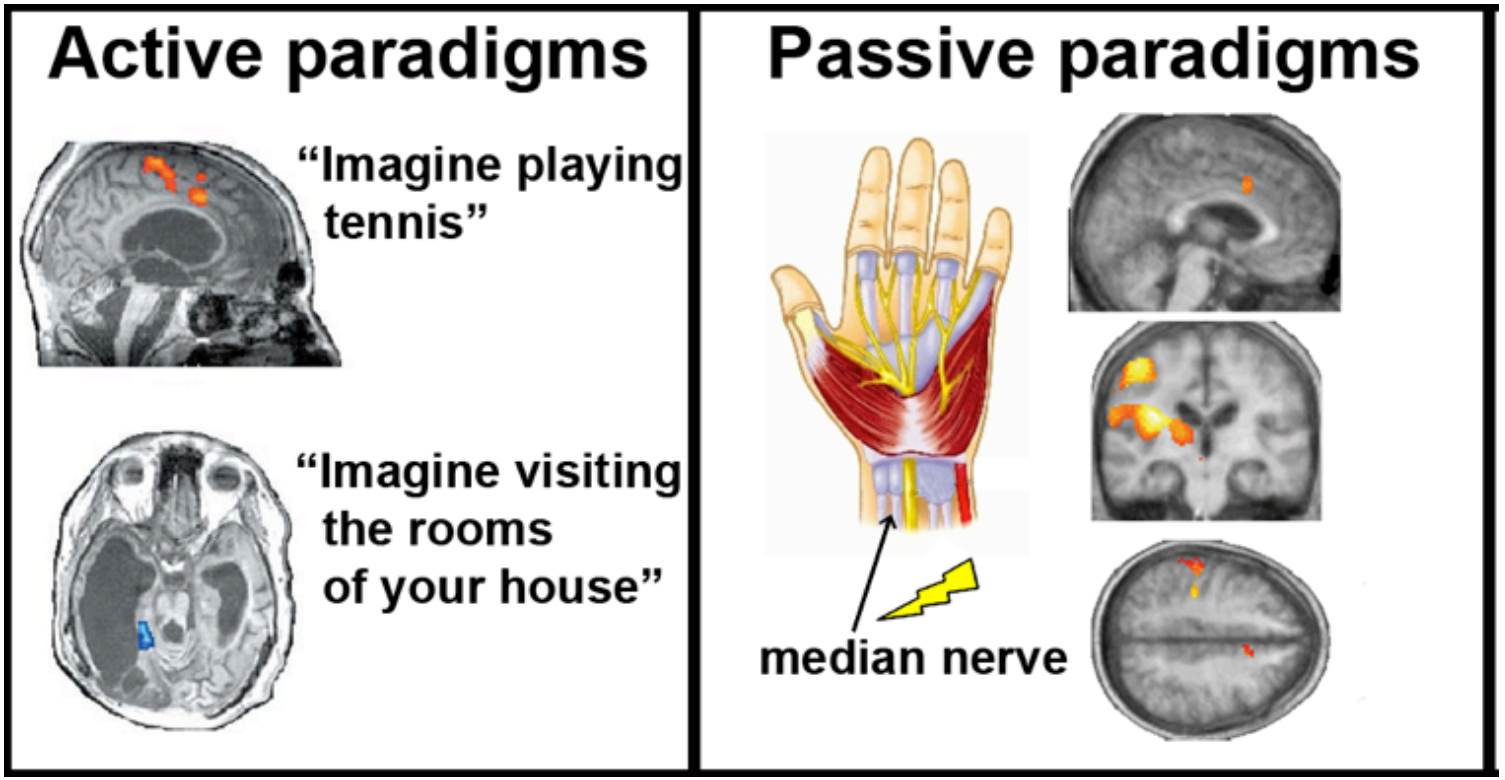



Stender & Gosseries et al, *Lancet* 2014

# Neuroimaging paradigms

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

Boly et al, Lancet Neurol 2008

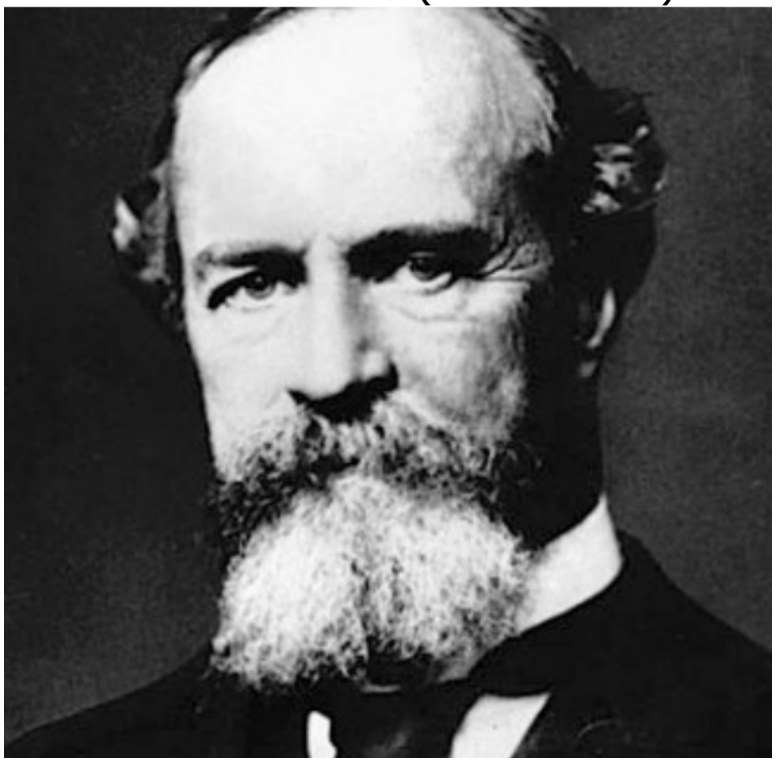



Heine, Di Perri, Soddu, Laureys, Demertzi
In: *Clinical Neurophysiology in Disorders of Consciousness,* Springer-Verlag 2015

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

# The mind at rest

William James (1842-1910)



The stream of thought (Chapter IX)

The principles of psychology 1890

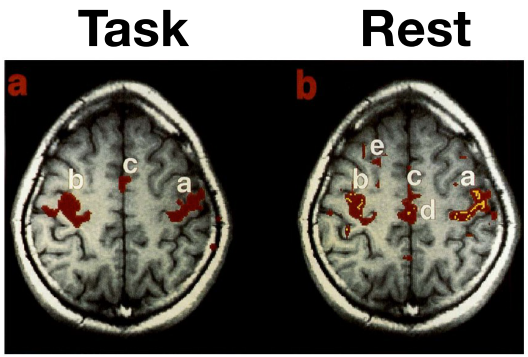
# Some numbers

- The human brain is approximately 2% of the weight of the body
- 80% of this energy consumption is used to support neuronal signaling
- Stimulus and performance-evoked changes in brain energy consumption <5%

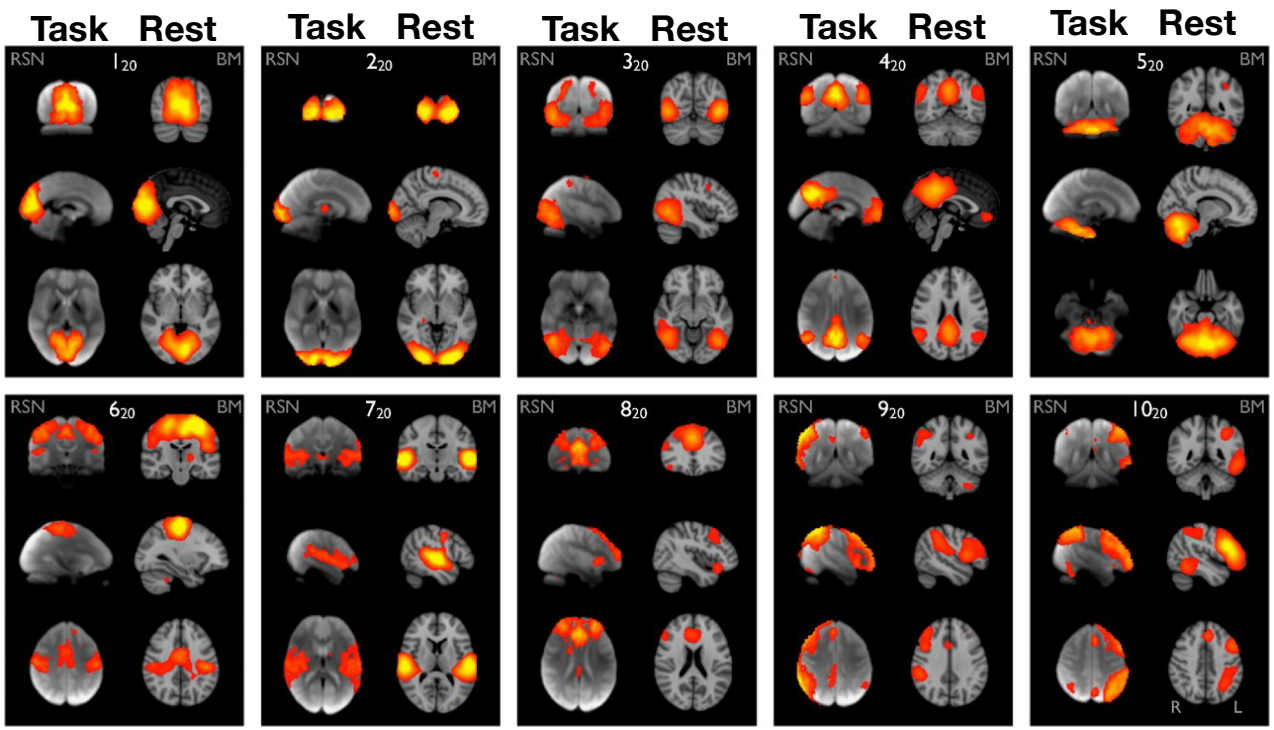
*While conscious awareness is energetically inexpensive, it is dependent upon a very complex, dynamically organized, non-conscious state of the brain that is achieved at great expense*

Raichle & Snyder. Intrinsic Brain Activity and Consciousness.
In: Laureys S, Tononi G, editors. The Neurology of Consciousness. Oxford: Elsevier Academic Press; 2009. p. 81-48

# Intrinsic functional organization

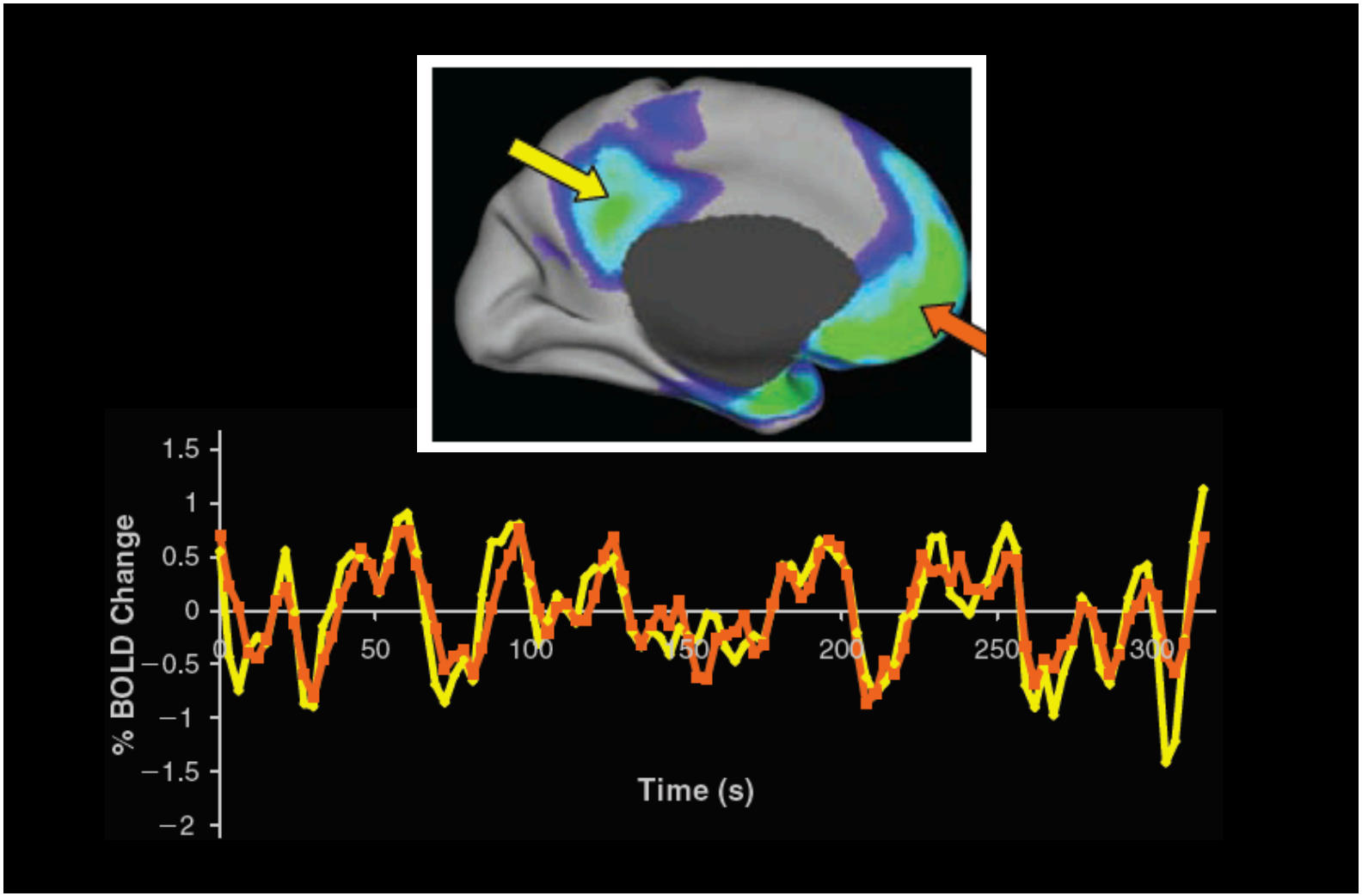



Biswal et al., *Magn. Reson. Med.*1995



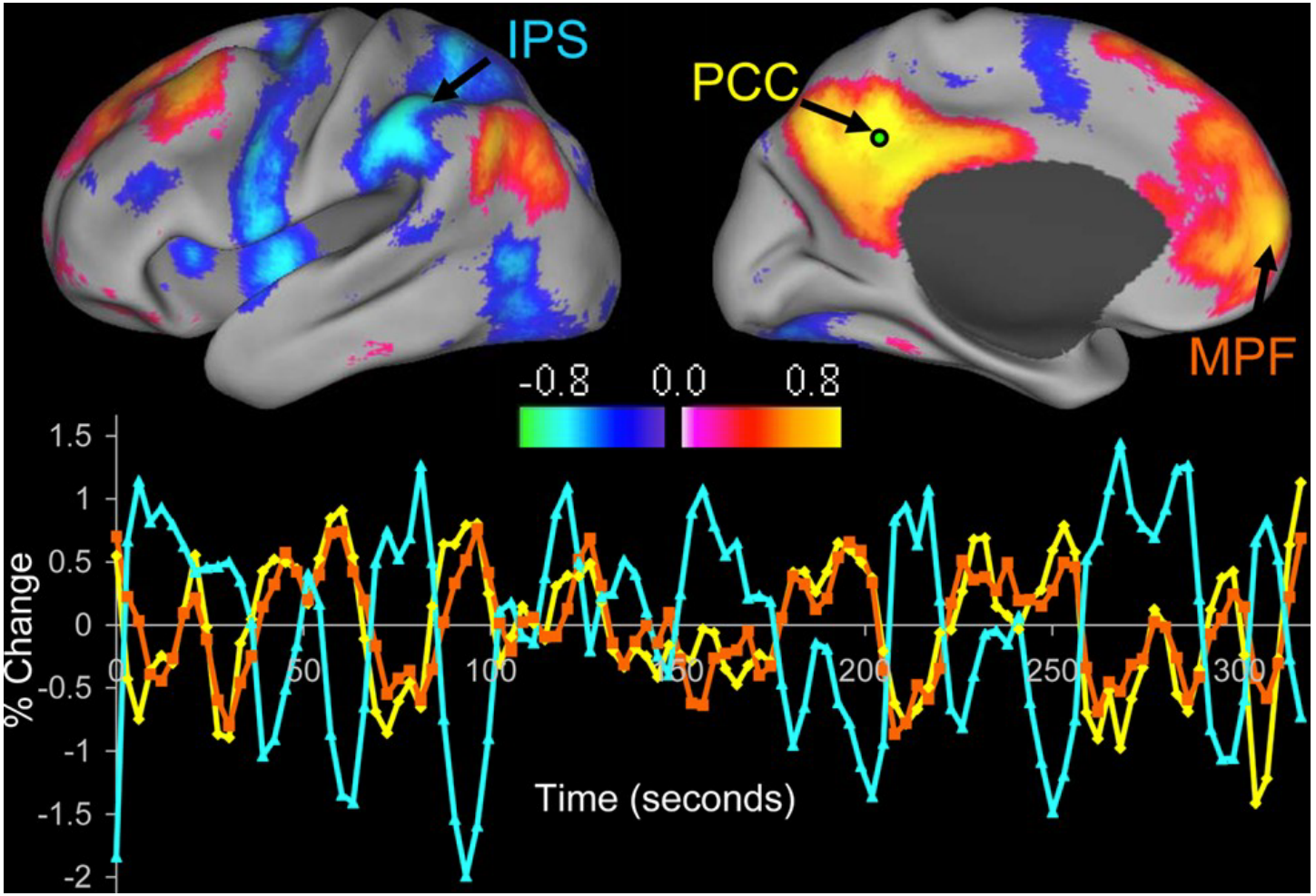

Smith et al, *PNAS* 2009

# Default mode network (DMN)




Raichle & Snyder. Intrinsic Brain Activity and Consciousness.
In: Laureys S, Tononi G, editors. The Neurology of Consciousness. Oxford: Elsevier Academic Press; 2009. p. 81-48

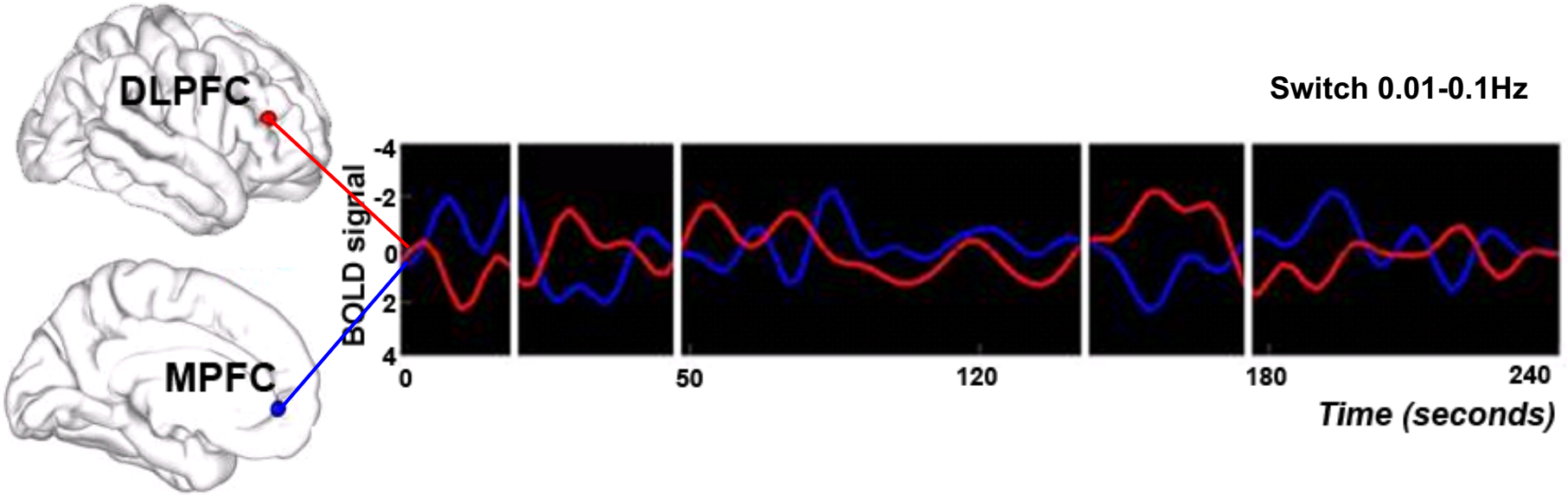
# DMN anticorrelations




Fox et al, *Proc N Acad Sci* 2005

# DMN anticorrelations

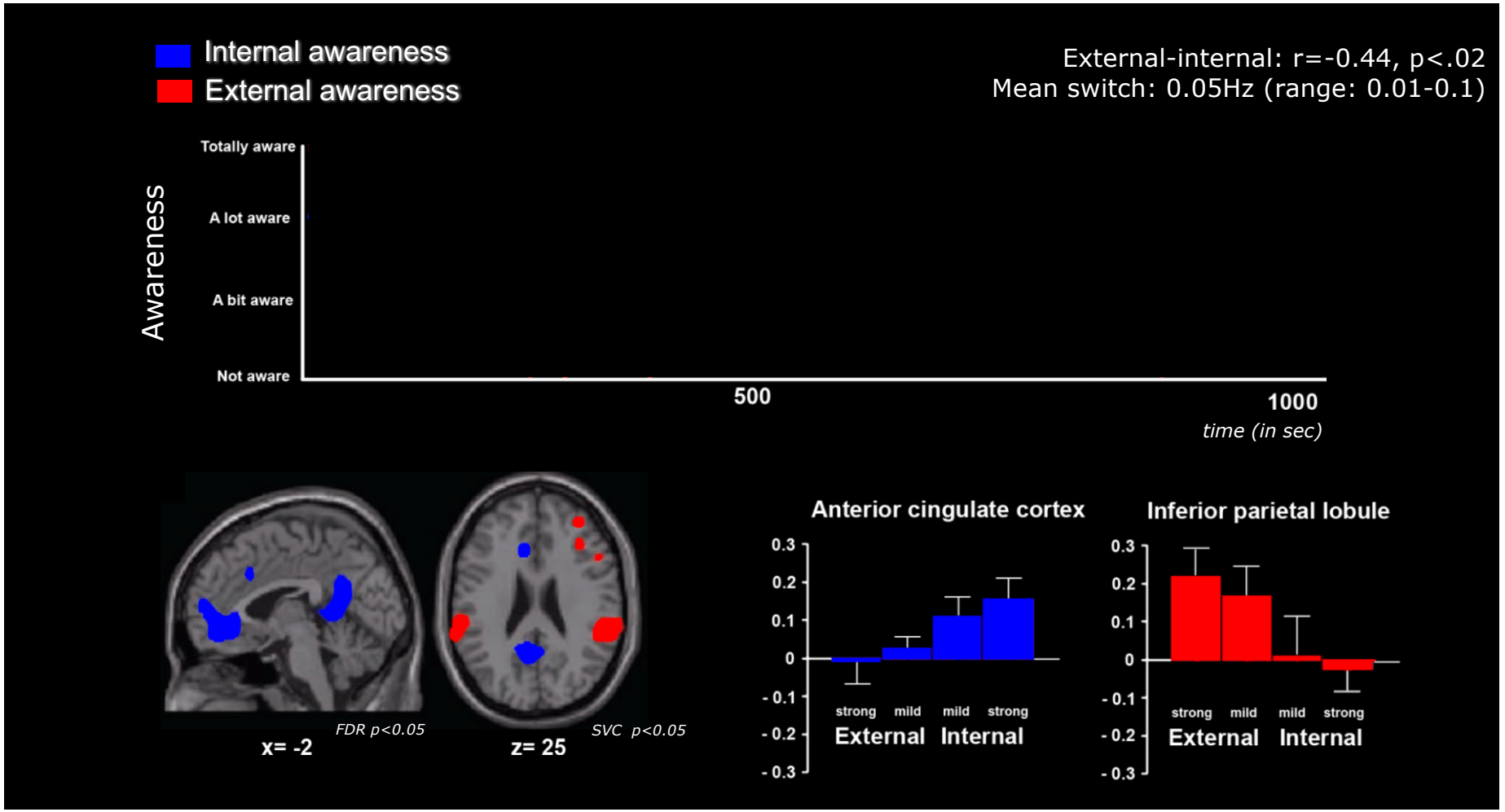
**External awareness**
***or* anticorrelated network**




**Internal awareness**
***or* Default mode network**

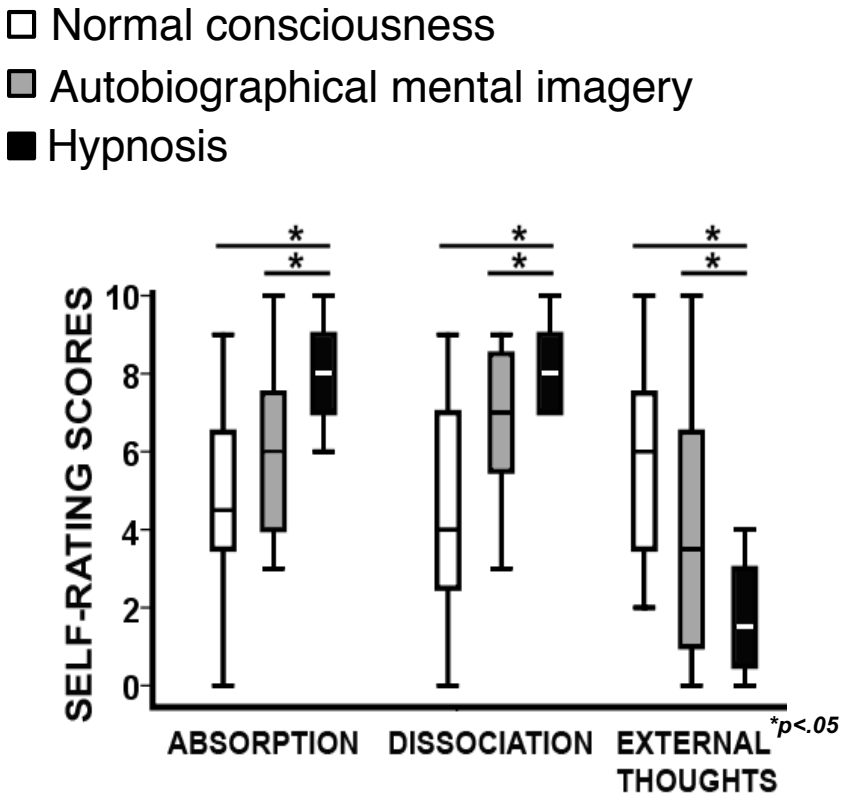
Demertzi & Whitfield-Gabrieli. in: *Neurology of Consciousness* 2nd ed. *2015*
Demertzi et al, *Front Hum Neurosci* 2013
Demertzi, Soddu, Laureys. *Curr Opin Neurobiology* 2013

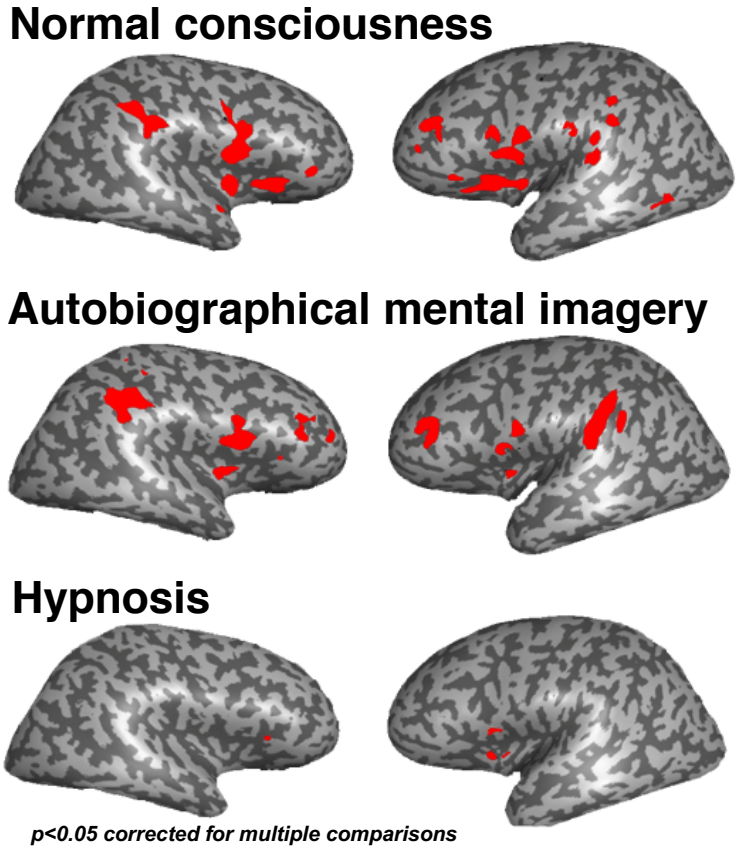
# Cognitive-behavioral relevance




Vanhaudenhuyse*, Demertzi* et al, *J Cogn Neurosci* 2011

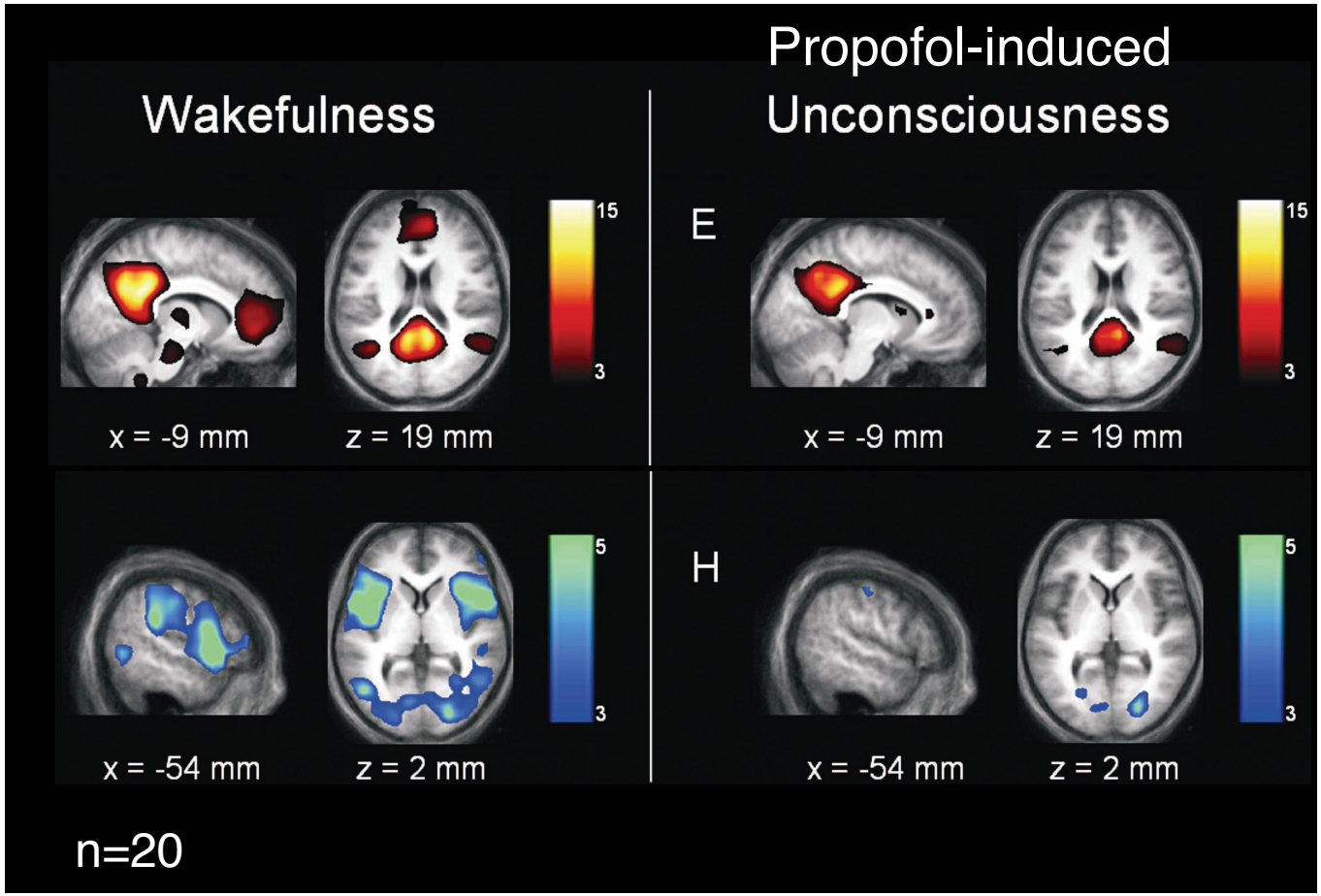
# Effect of awareness




Demertzi, Soddu, Faymonville et al, *Prog Brain Res* 2011
Demertzi, Vanhaudenhuyse, Noirhomme, Faymonville, Laureys, *J Physiol Paris* 2015

# Effect of arousal




Boveroux et al, *Anesthesiology* 2010

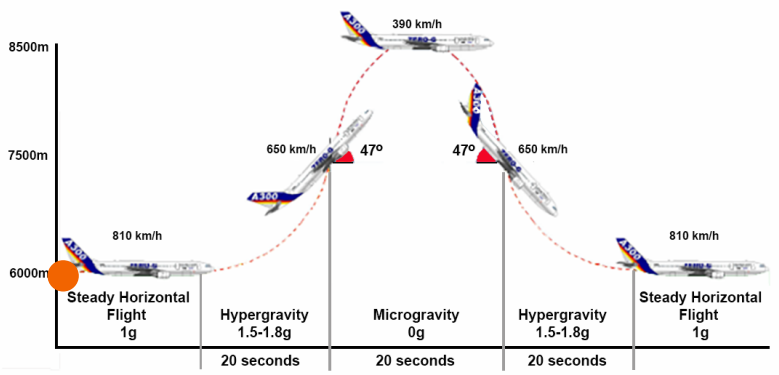
# Effect of environment

SCIENTIFIC REPORTS
www.nature.com/scientificreports/

## Parabolic flight

NOVESPACE

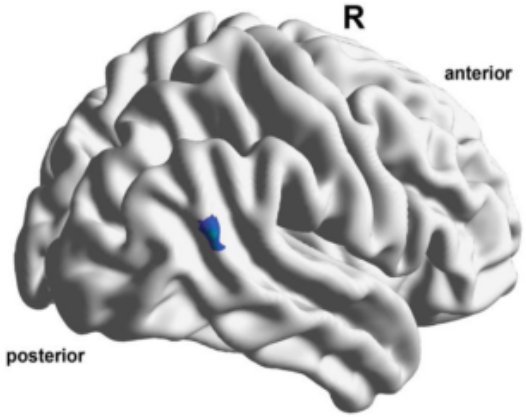
esa
European Space Agency

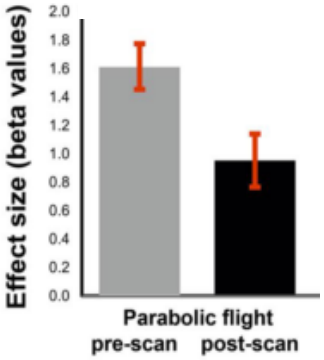


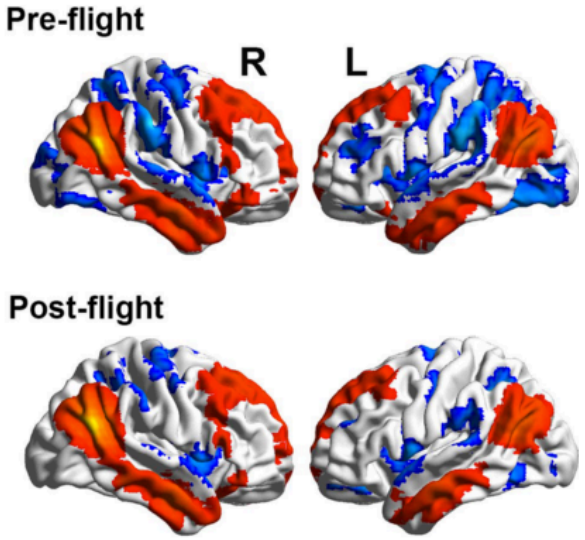

Parabolic flight trajectory

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

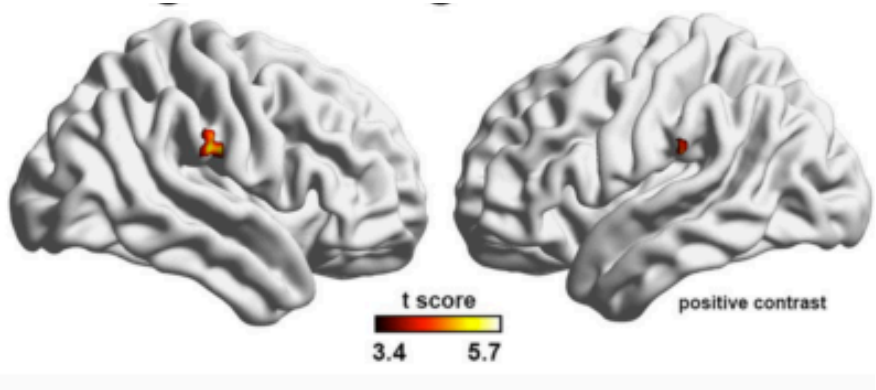
# Effect of environment

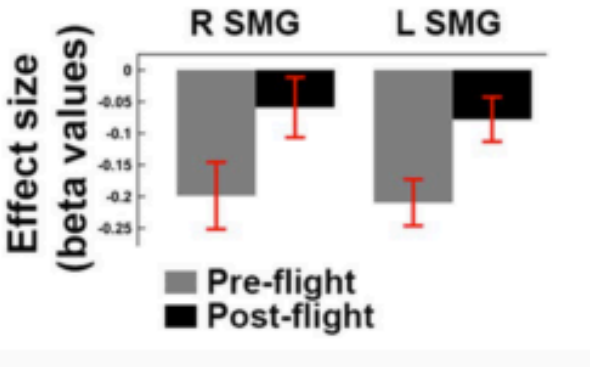


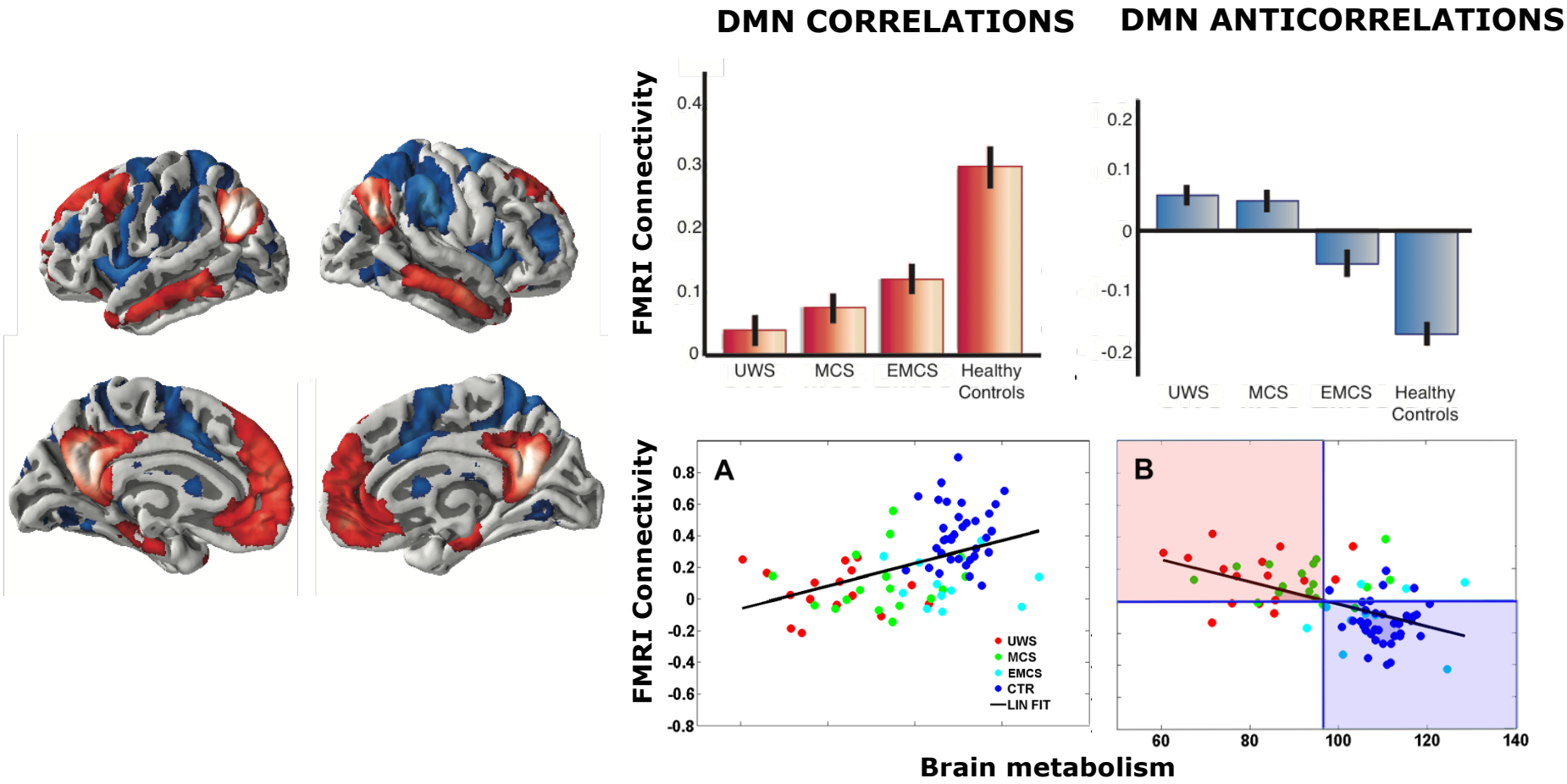

**Post – Pre flight**



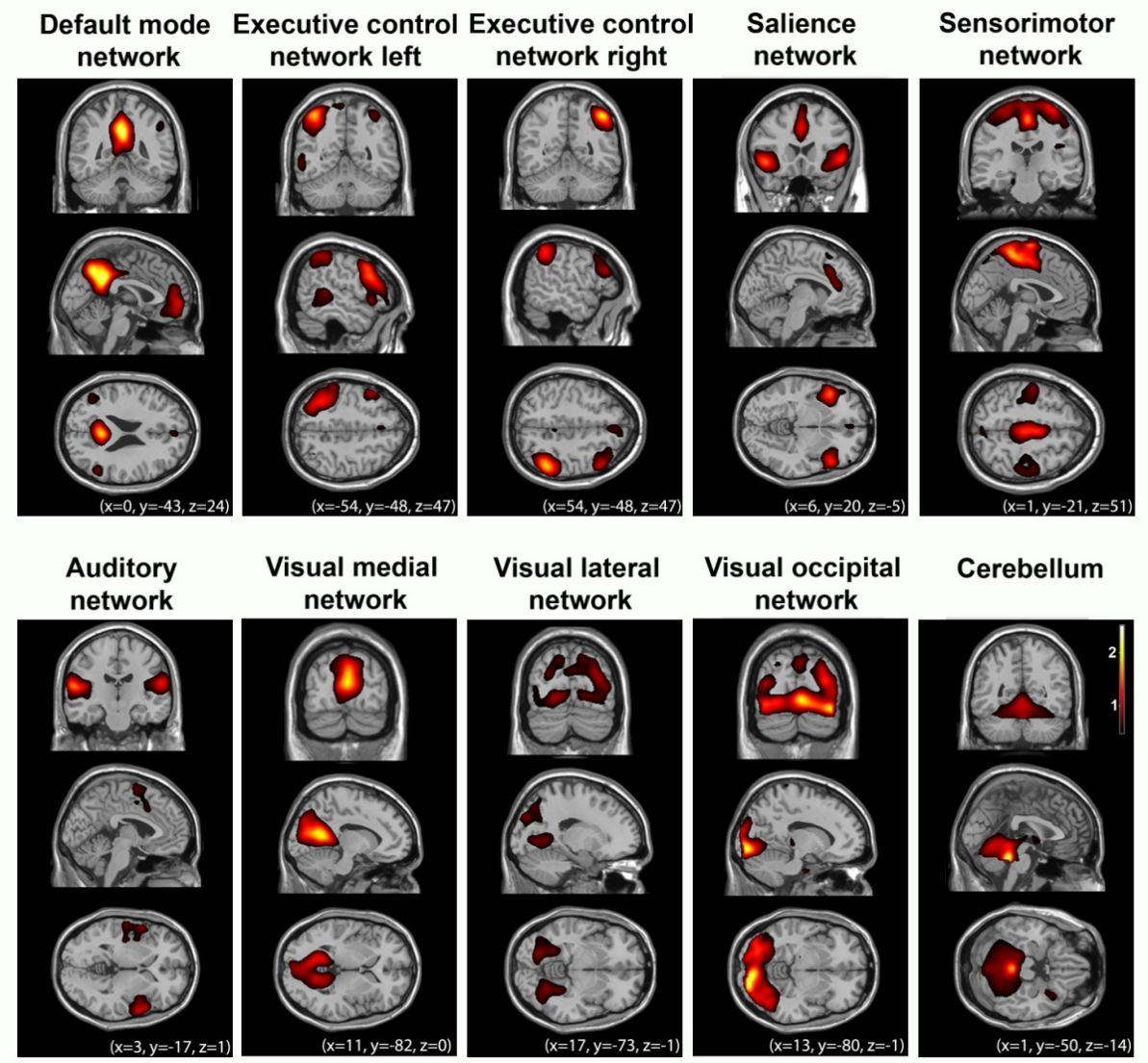

Van Ombergen … and Demertzi, *Sci Reports* 2017

# Effect of pathology



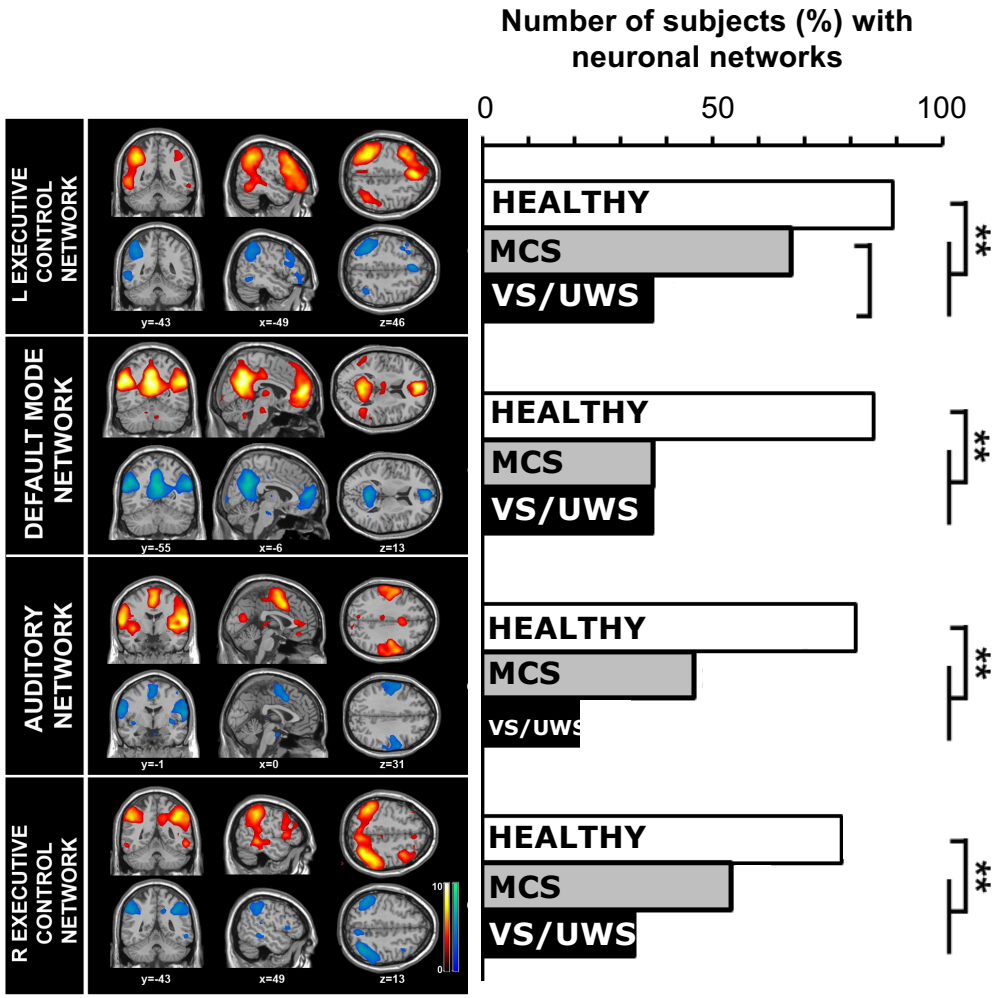

Di Perri, …, Demertzi*, Laureys*, Soddu*, *Lancet Neurol* 2017
Vanhaudenhuyse et al, *Brain* 2010

# Systems-level organization




Heine, … & Demertzi, *Front Psychol* 2012

# Networks are disrupted in low consciousness states



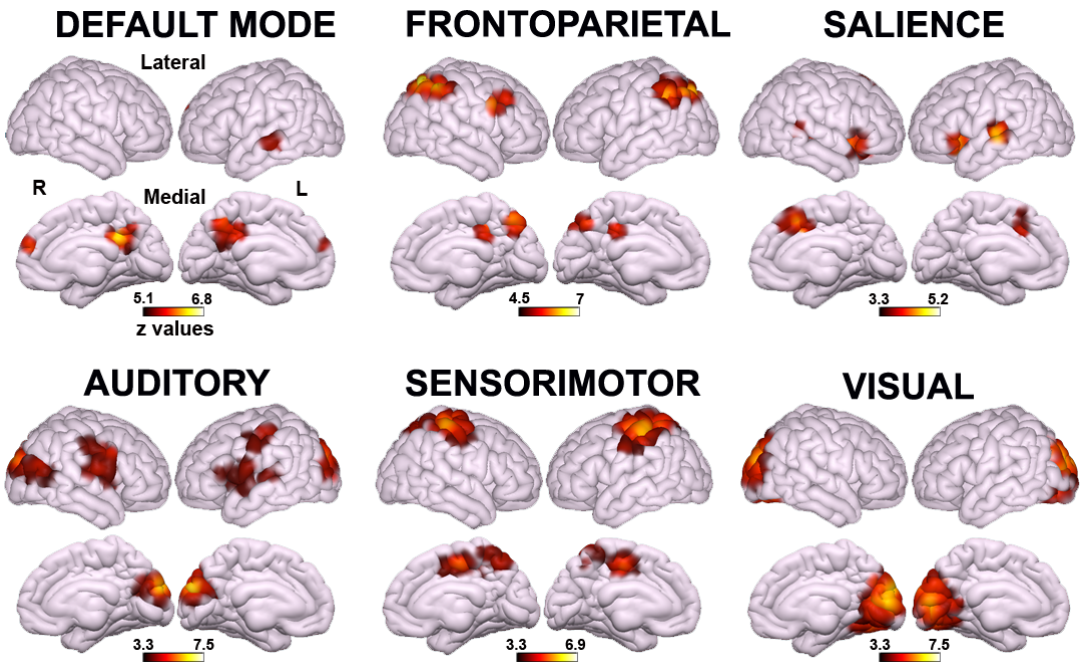

## Single-patient classification

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

Demertzi & Gómez et al, *Cortex* 2014

# Which network discriminates best?

## MCS> VS/UWS



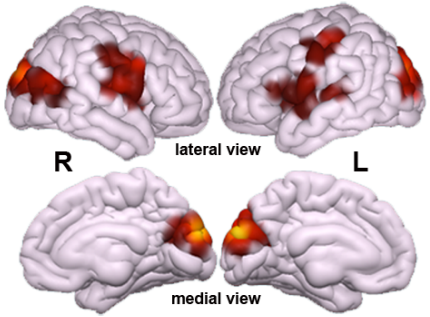

| | Feature selection criterion (t-test) | | | Single-feature classification | | |
|---|---|---|---|---|---|---|
| **Network** | **t value** | **Rank** | **p value** | **TP MCS** | **TN VS/UWS** | **Accuracy** |
| Auditory | 8.32 | 1 | <.001 | 25 | 18 | 43/45 |
| Visual | 7.79 | 2 | <.001 | 23 | 15 | 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 |

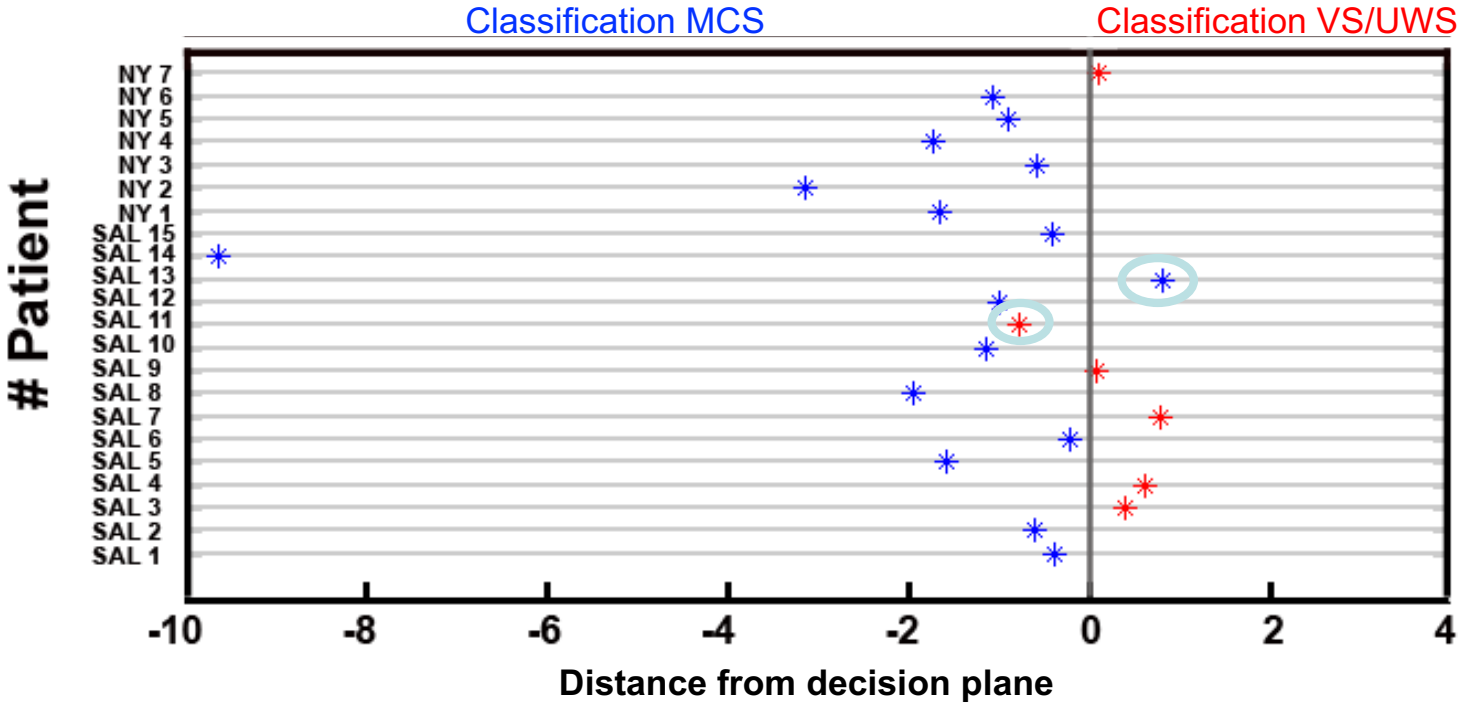
*FWE p<0.05 (cluster-level)*

Demertzi & Antonopoulos et al, *Brain* 2015

# Single-patient classification

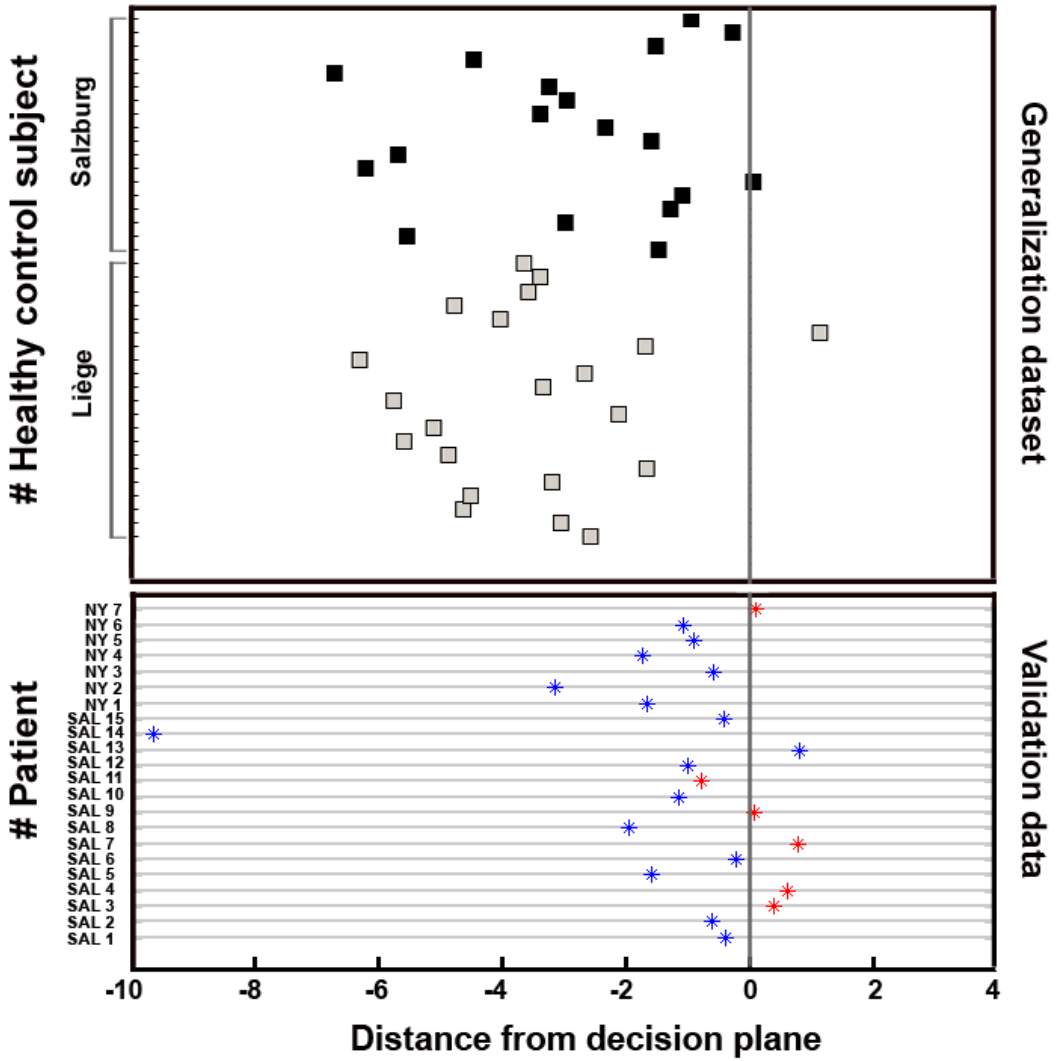
- Training set: 45 DOC (26 MCS, 19 VS/UWS)
  - 14 trauma, 28 non-trauma, 3 mixed
  - 34 patients assessed >1m post-insult
- Test set: **16 MCS**, **6 VS/UWS** ($M_{age}$: 43y, 15 non-trauma; all chronic), from 2 different centers




Demertzi & Antonopoulos et al, *Brain* 2015

# Sanity check: generalization on healthy

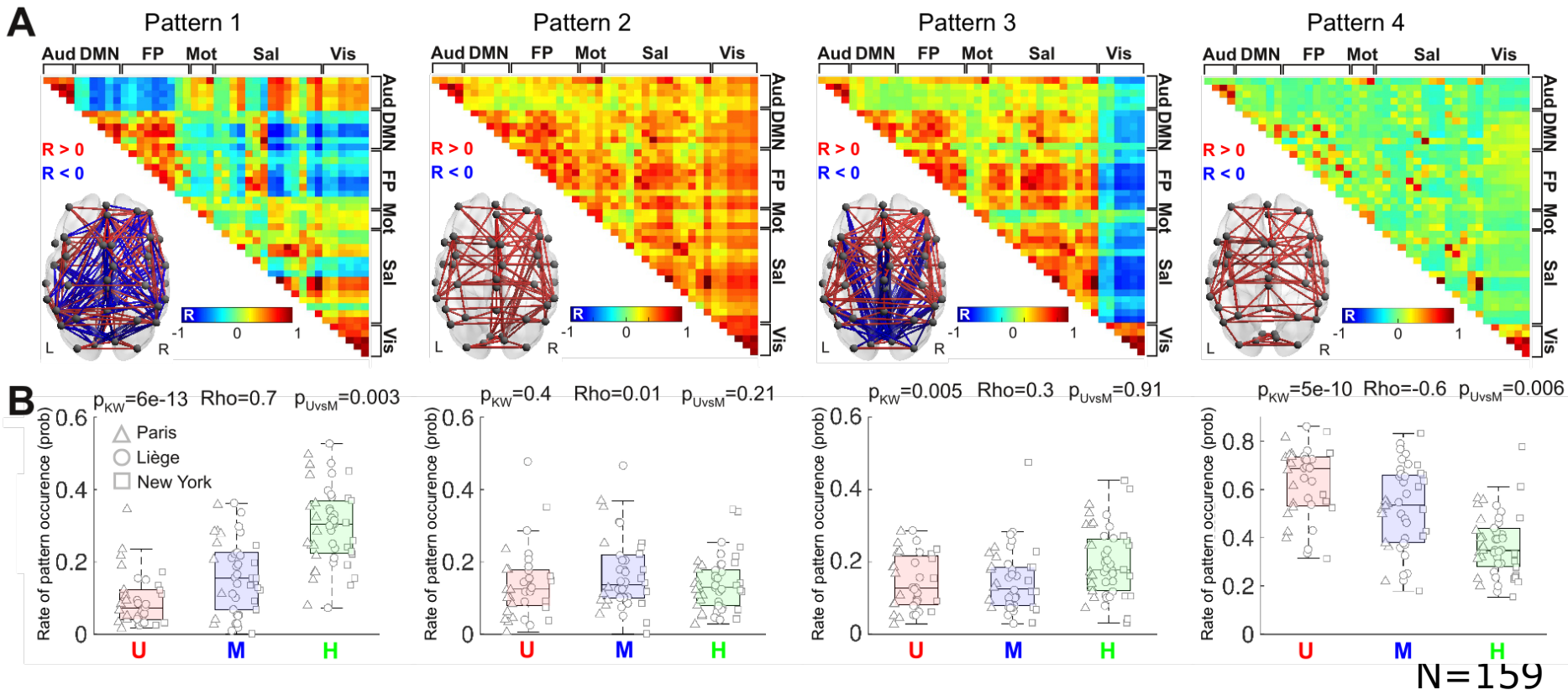



Demertzi & Antonopoulos et al, *Brain* 2015

# Consciousness is supported by cortical dynamics

James S. McDonnell Foundation

Grant Type: Collaborative Activity Award, Phase I & II (2008-2017)




Demertzi*, Tagliazucchi*, Dehaene, Deco, Barttfeld, Raimondo, Rohaut, Schiff, Owen, Laureys, Naccache, Sitt. *in prep*

# Conclusions

fMRI resting state connectivity

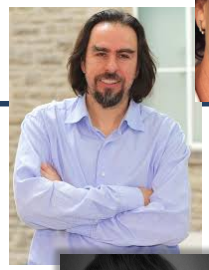
- carries information about cognitive function
- can be used in the clinical setting
- needs clinical translation
- illuminates the dynamic structure of consciousness

Need of a framework for applying techniques balancing:

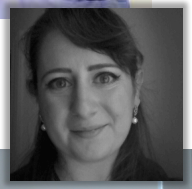
- availability
- sensitivity
- specificity

Demertzi, Sitt, Sarasso, Pinxten *Neurosci Consciousness* 2017












**Coma Science Group & PICNIC Lab**

The deparments of Neurology and Radiology in Liège and Paris

**...and mostly patients and their families!**

a.demertzi@uliege.be

James S. McDonnell Foundation

Human Brain Project

European Space Agency

Institut national de la santé et de la recherche médicale

Université de Liège

# Analysis pipeline

**EPI acquisition**

**Preprocessing**

Slice-time correction
Realignment
Segmentation
Normalization
Smoothing
Motion outliers (ART)
aCompCor
Regressing out realignment parameters and ART outliers
Bandpass filtering [0.008-0.09Hz]

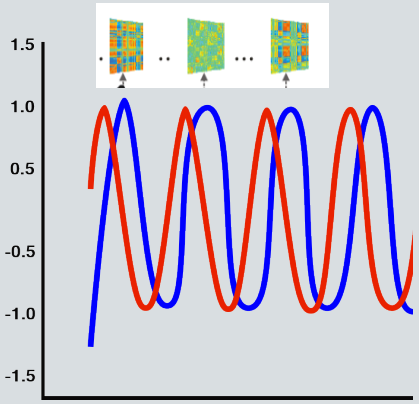
**Brain parcellation**

(Sphere ROIs)


**ROI timeseries extraction**

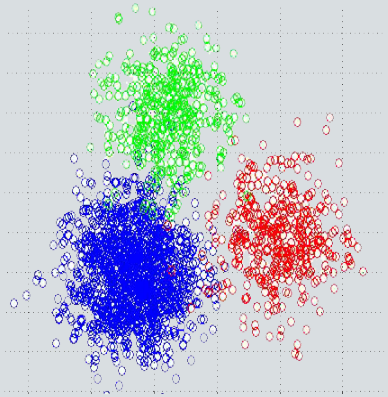
**Phase analysis**

(Hilbert transform)



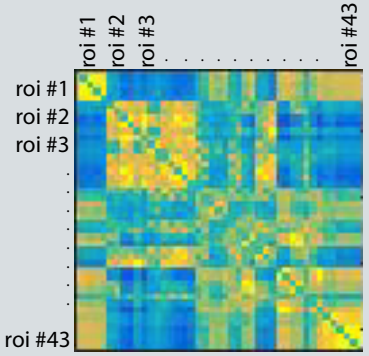

**Unsupervised clustering**

(k-means)



**State identification**

(cluster centroids)



# Study cohort (N=159)

## Main dataset

awake

| | VS/UWS | MCS | CTR |
|---|---|---|---|
| LIEGE | 17 | 23 | 21 |
| PARIS | 13 | 9 | 15 |
| NY | 6 | 10 | 11 |
| Total | 36 | 42 | 47 |

**n = 125**

## Validation datasets

sedated

| LIEGE | |
|---|---|
| EMCS | 3 |
| MCS | 14 |
| UWS | 6 |

**n = 23**

CMD

| ONTARIO | |
|---|---|
| VS/UWS- | 6 |
| VS/UWS+ | 5 |

**n = 11**

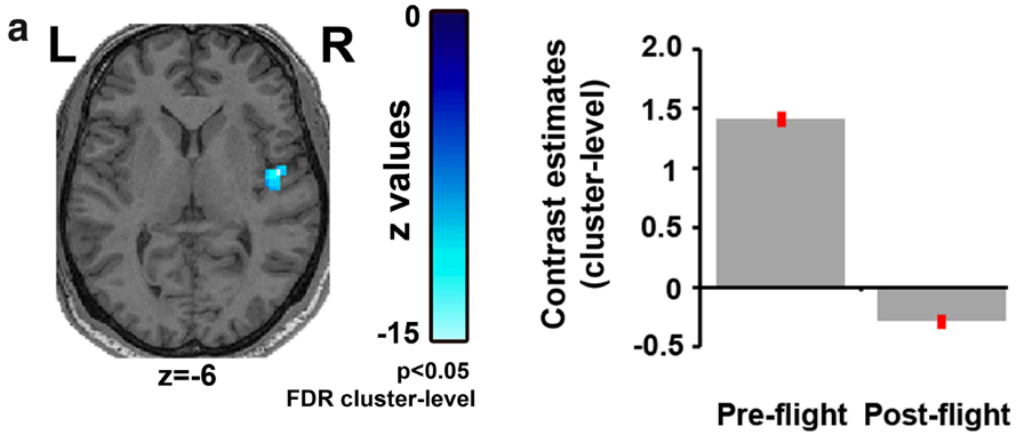
James S. McDonnell Foundation

Grant Type: Collaborative Activity Award, Phase I & II (2008-2017)

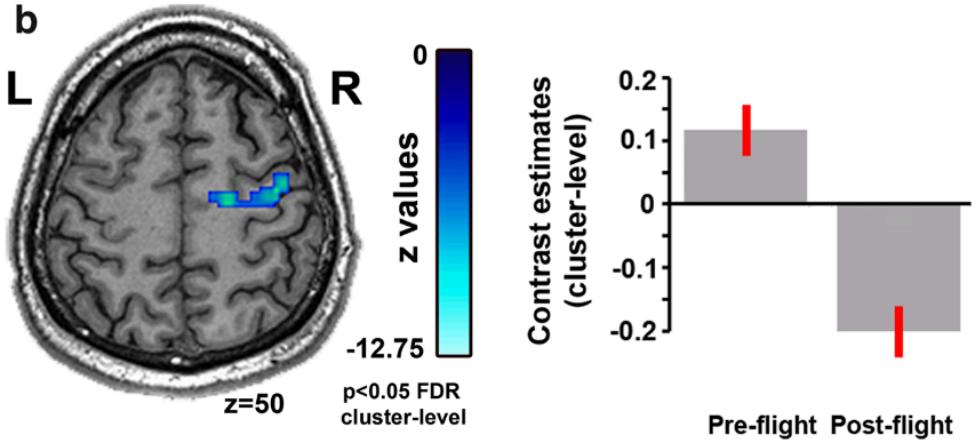
44-year-old male cosmonaut
First long-duration mission (169 days) to the ISS in 2014
fMRI protocol pre-flight: 30 days, post-flight: 9 days after Earth re-entry

European Space Agency

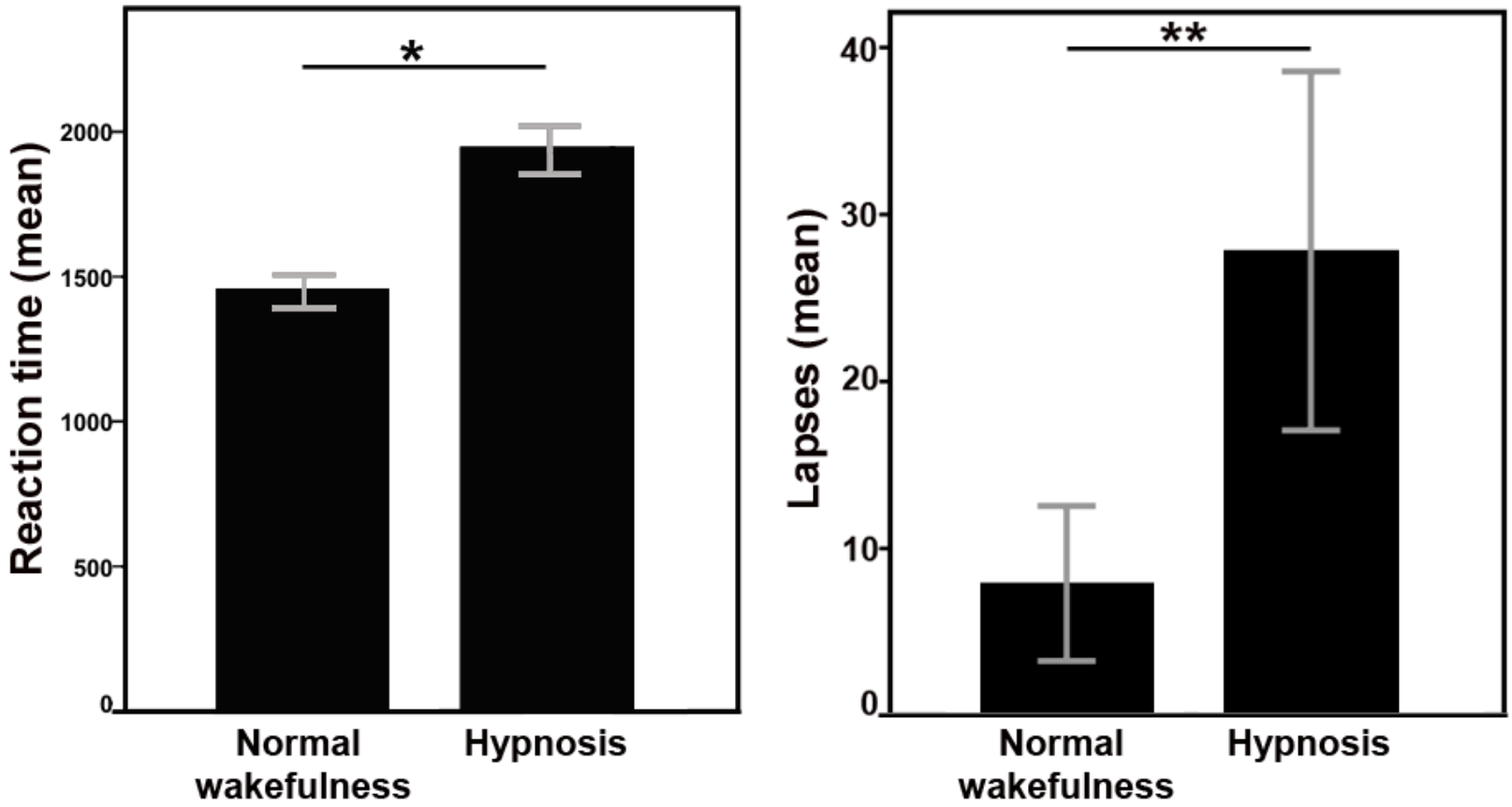
## Hypothesis-free

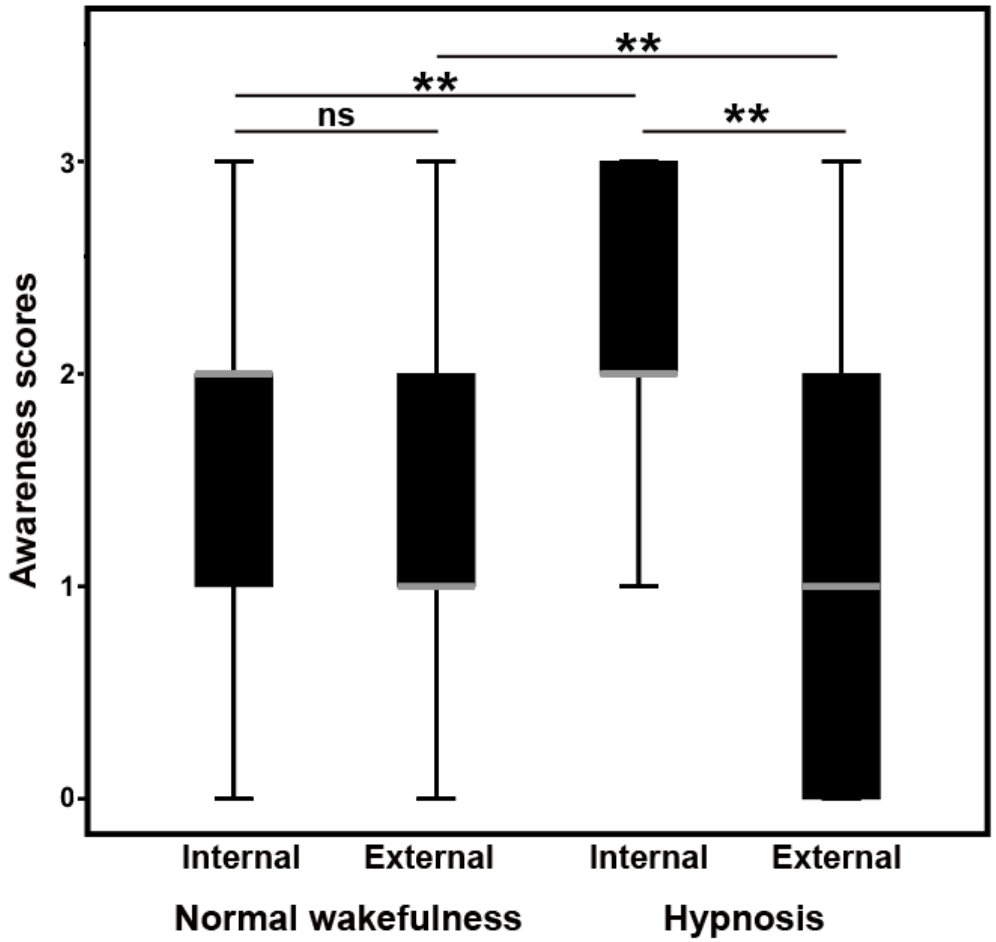



## Hypothesis-driven



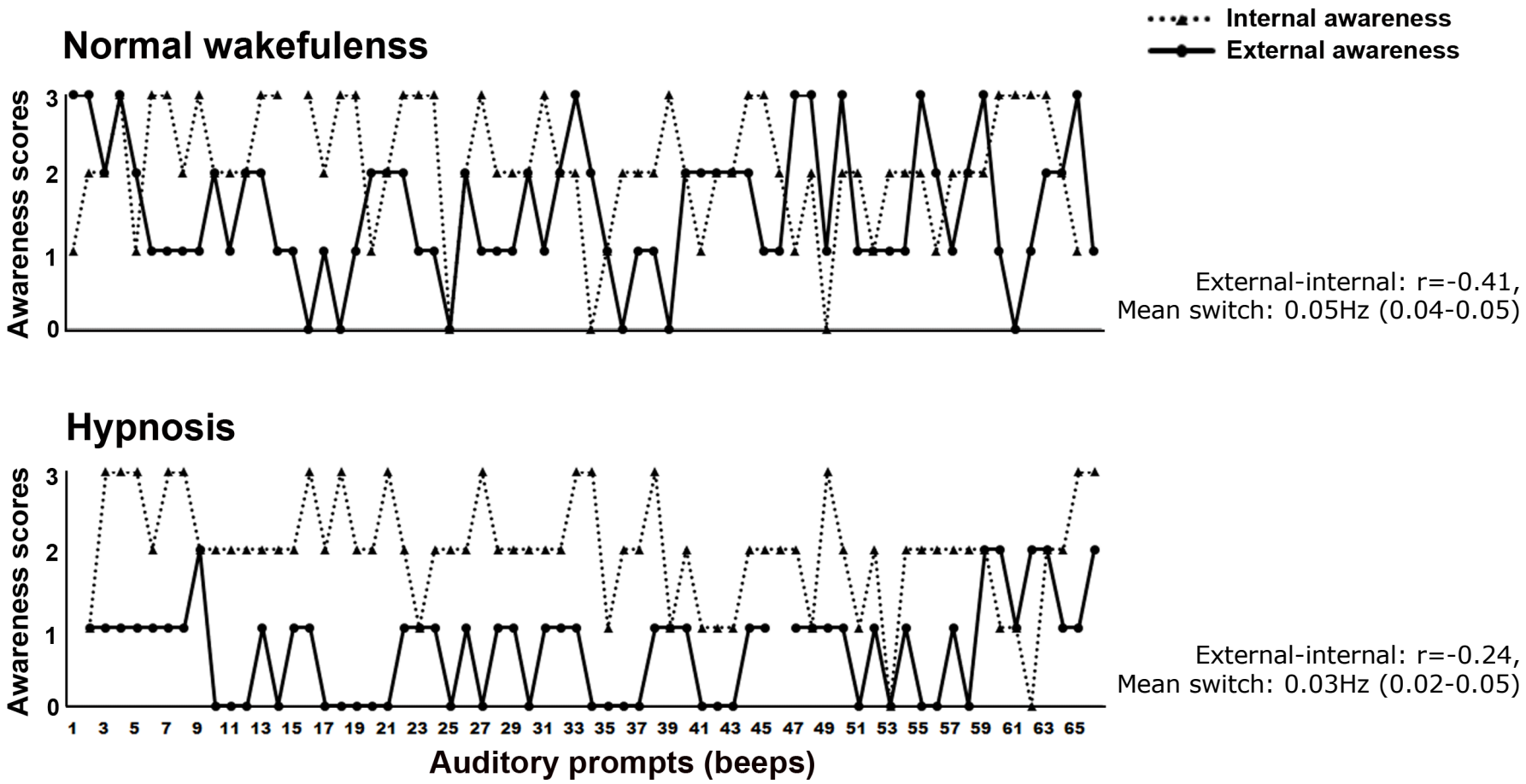

Demertzi & Van Ombergen et al, Brain Structure and Function 2015


*
Reaction time (mean)
2000
1500
1000
500
0
Normal wakefulness
Hypnosis
**
Lapses (mean)
40
30
20
10
0
Normal wakefulness
Hypnosis




Demertzi, Vanhaudenhuyse, Noirhomme, Faymonville, Laureys, J Physiol Paris 2015

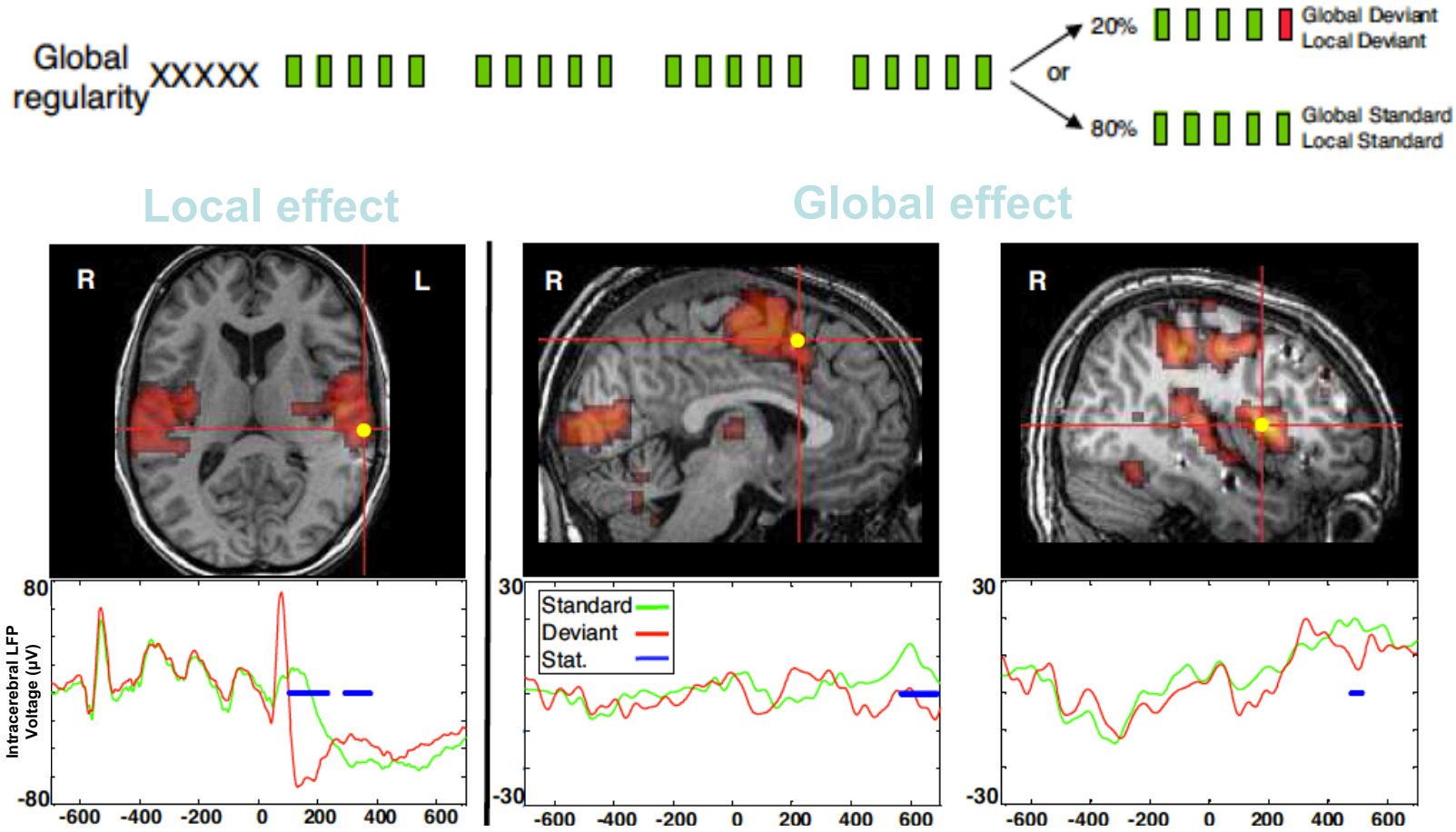
# Awareness is modified in hypnosis



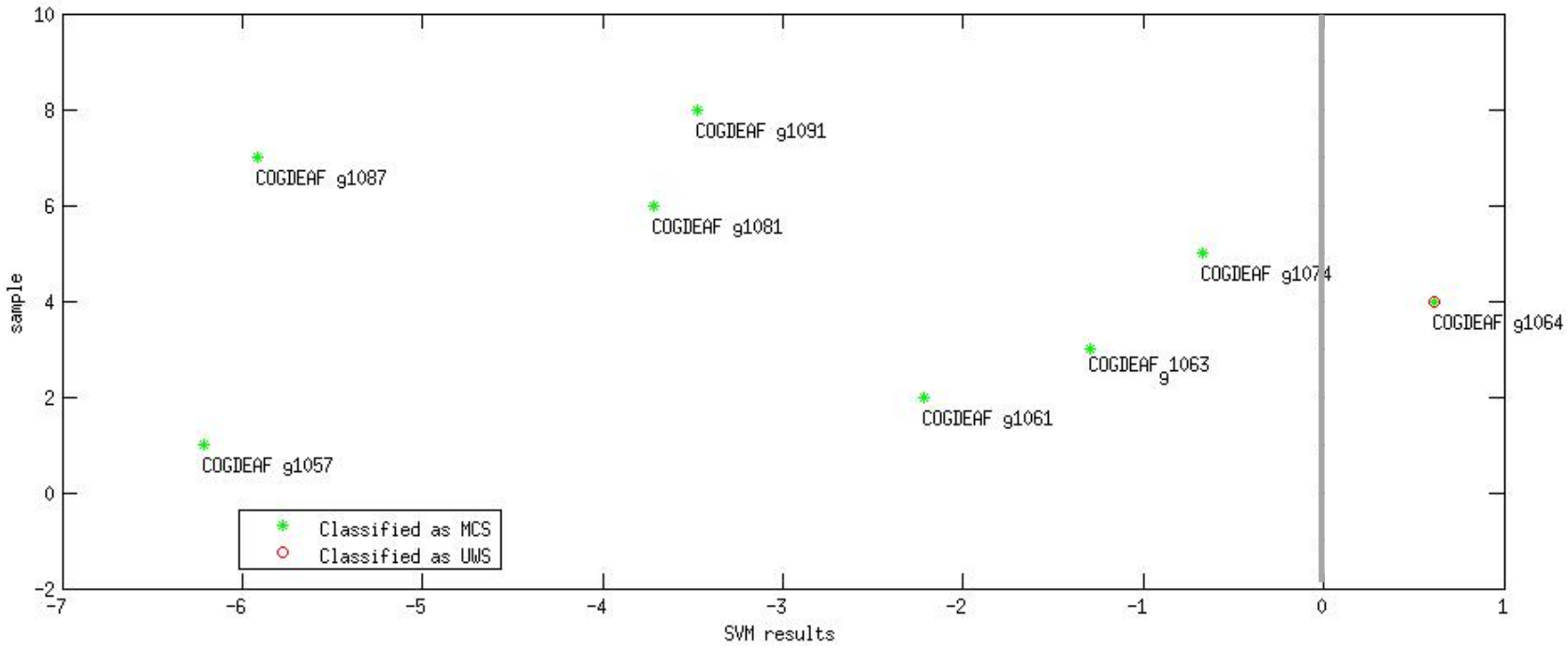

Demertzi, Vanhaudenhuyse, Noirhomme, Faymonville, Laureys, J Physiol Paris 2015

# Crossmodal interaction in consciousness

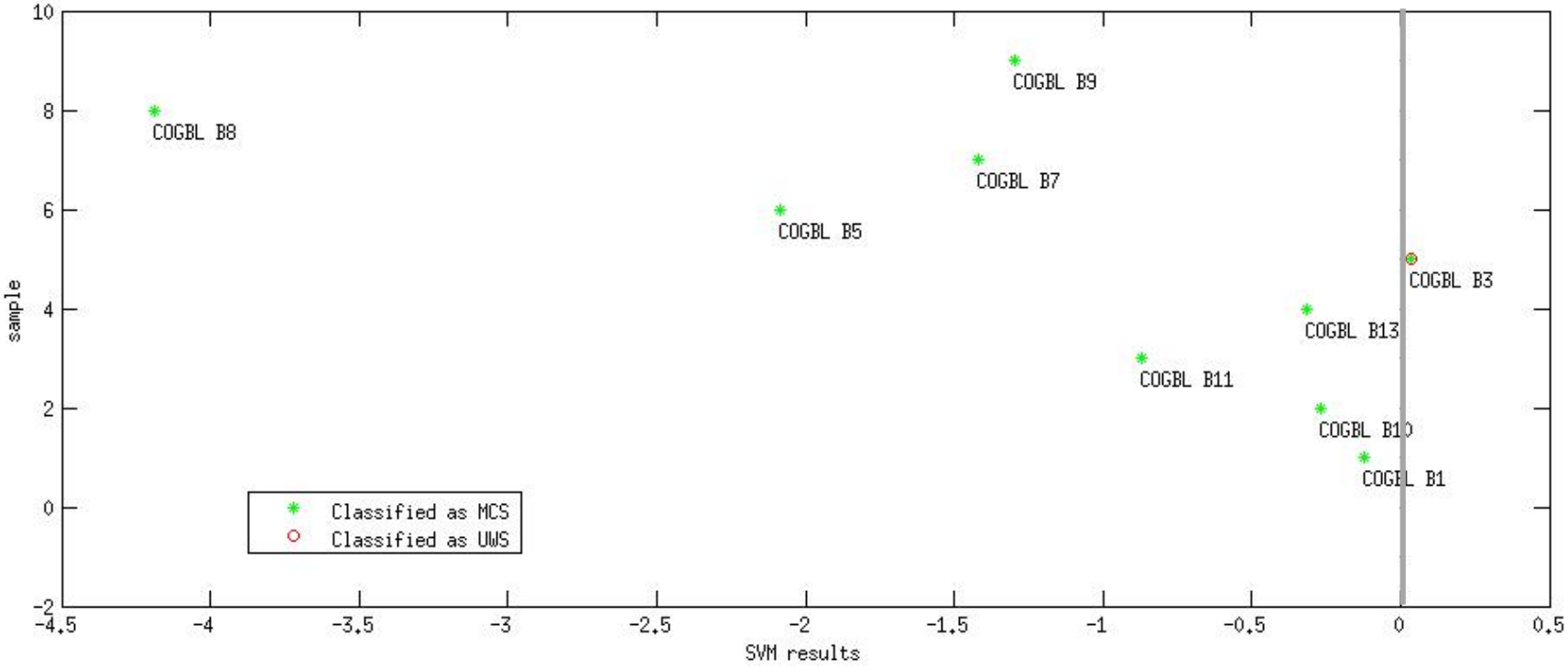
## The local- global paradigm



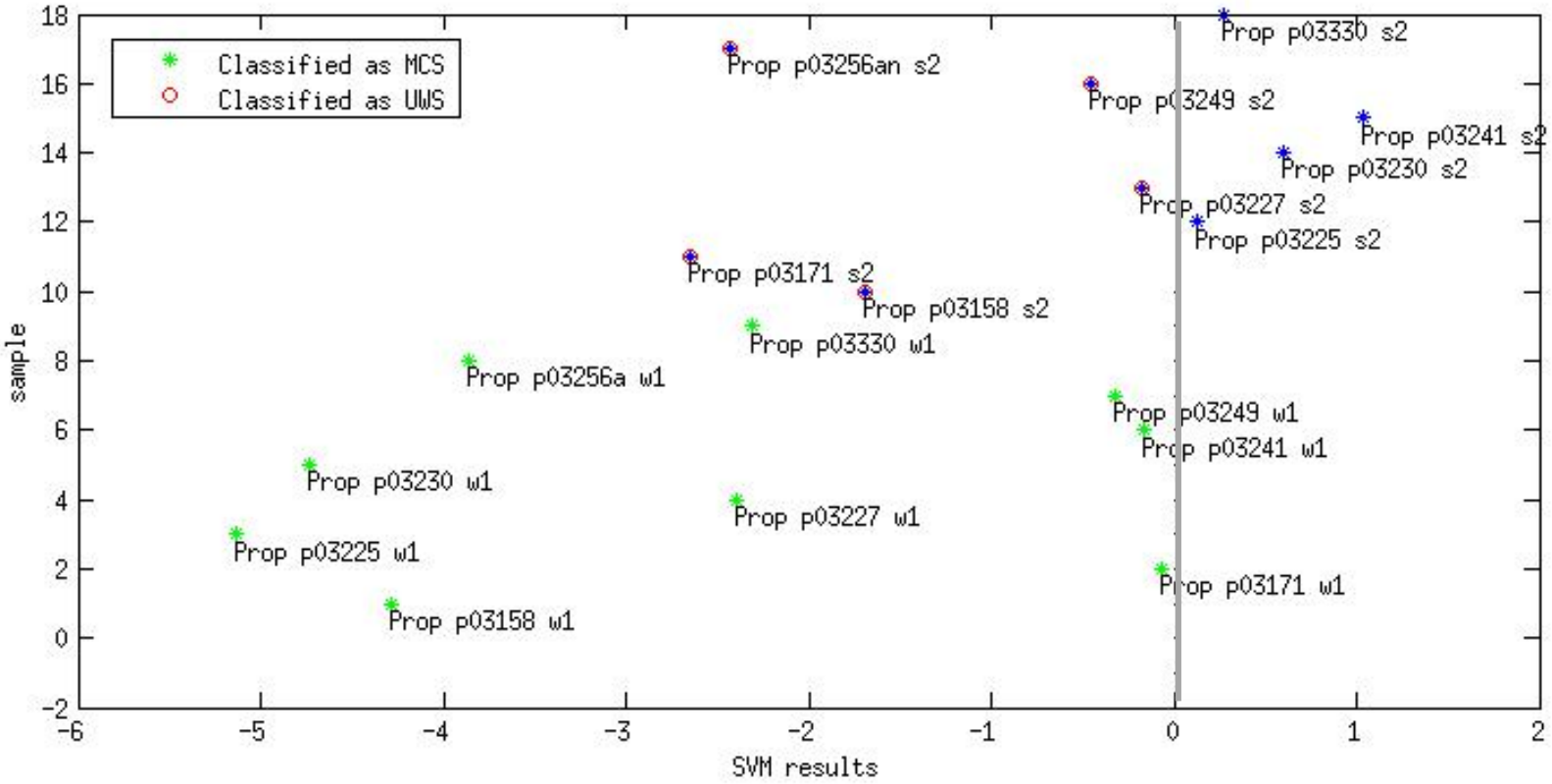
# Validation in congenitally deaf



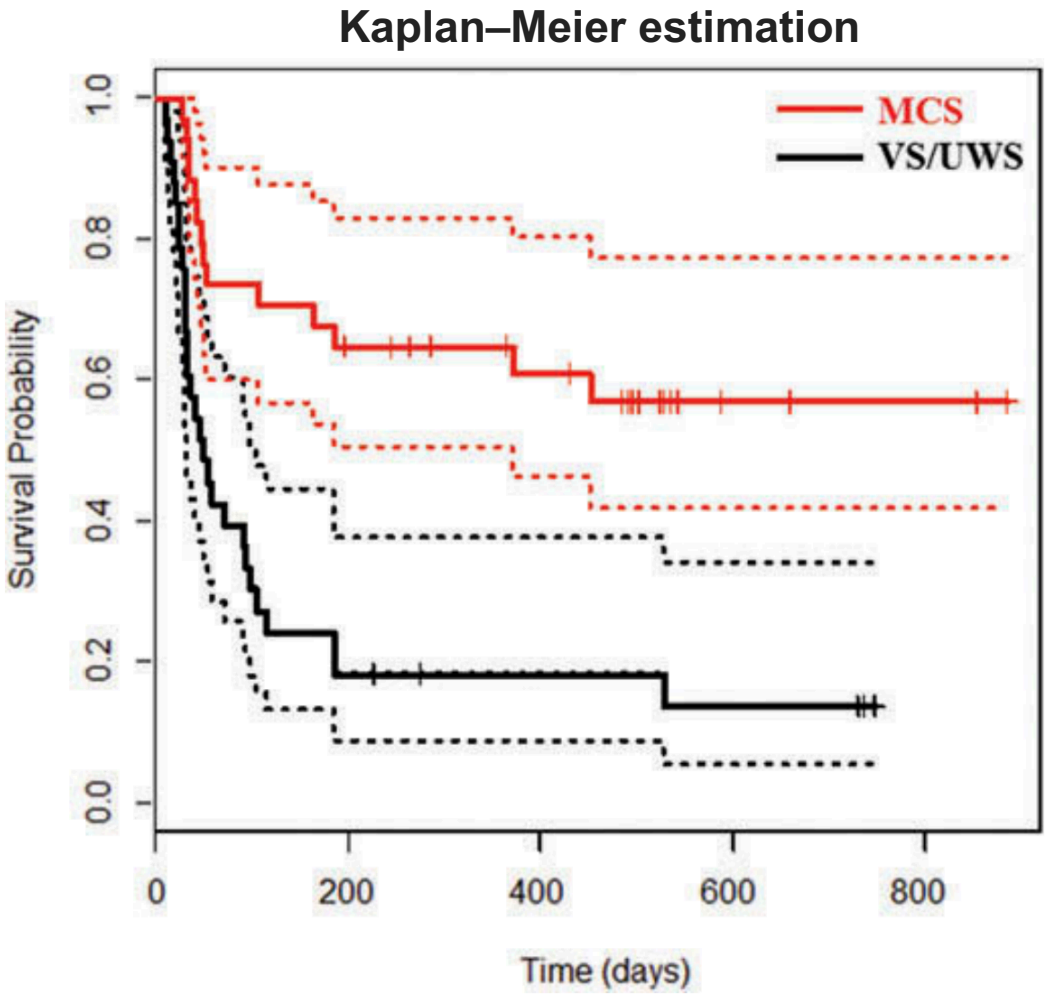
# Validation in congenitally blind



# Validation in propofol anesthesia



# Clinical evolution




n=67

Faugeras, Rohaut, Valente, Sitt, Demeret, Bolgerta, Weiss , Grinea , Marois, Quirins, Demertzi, Raimondo, Galanaud, Haberm, Engemann, Puybasse, Naccache, *Brain Inj* in press

# Why does it matter?

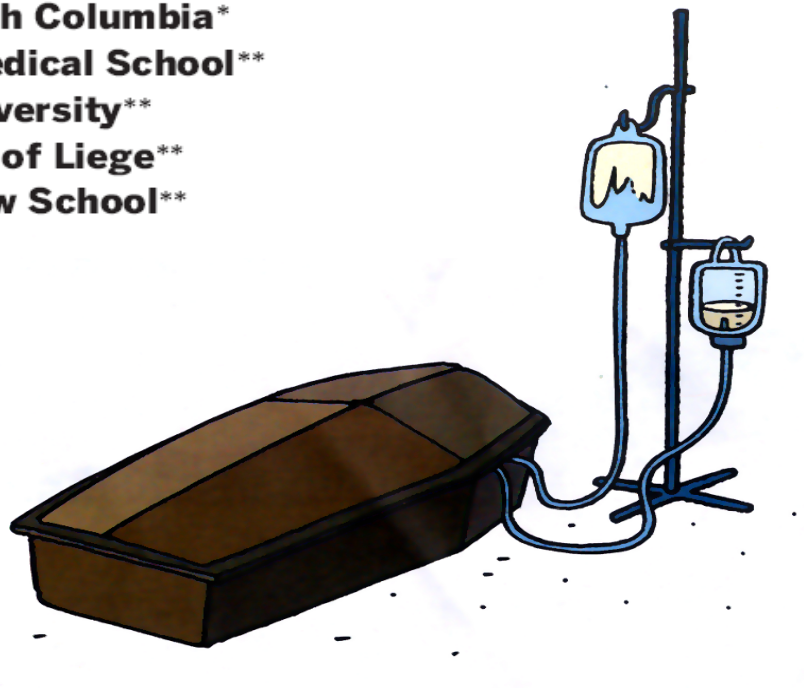
*The American Journal of Bioethics*, 8(9): 3–12, 2008

**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.

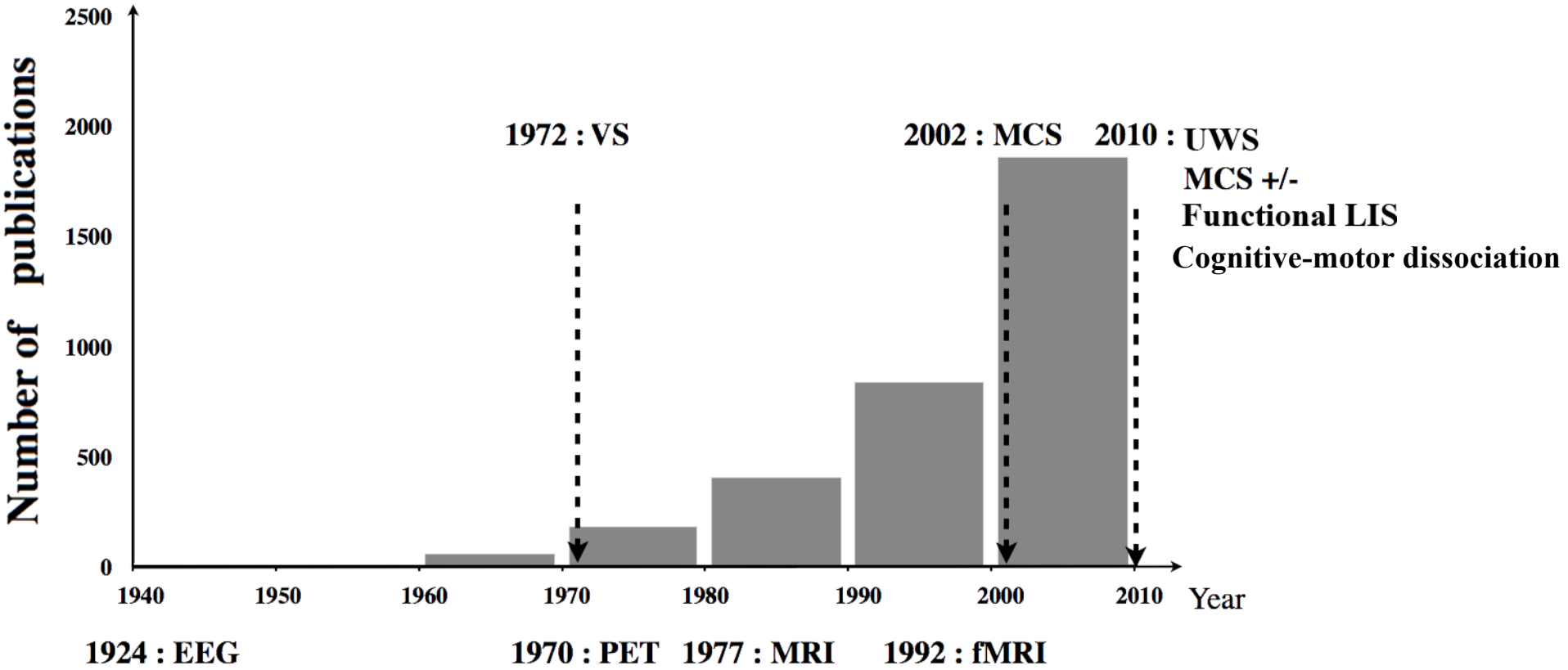


# Balancing costs-benefits

| 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 |

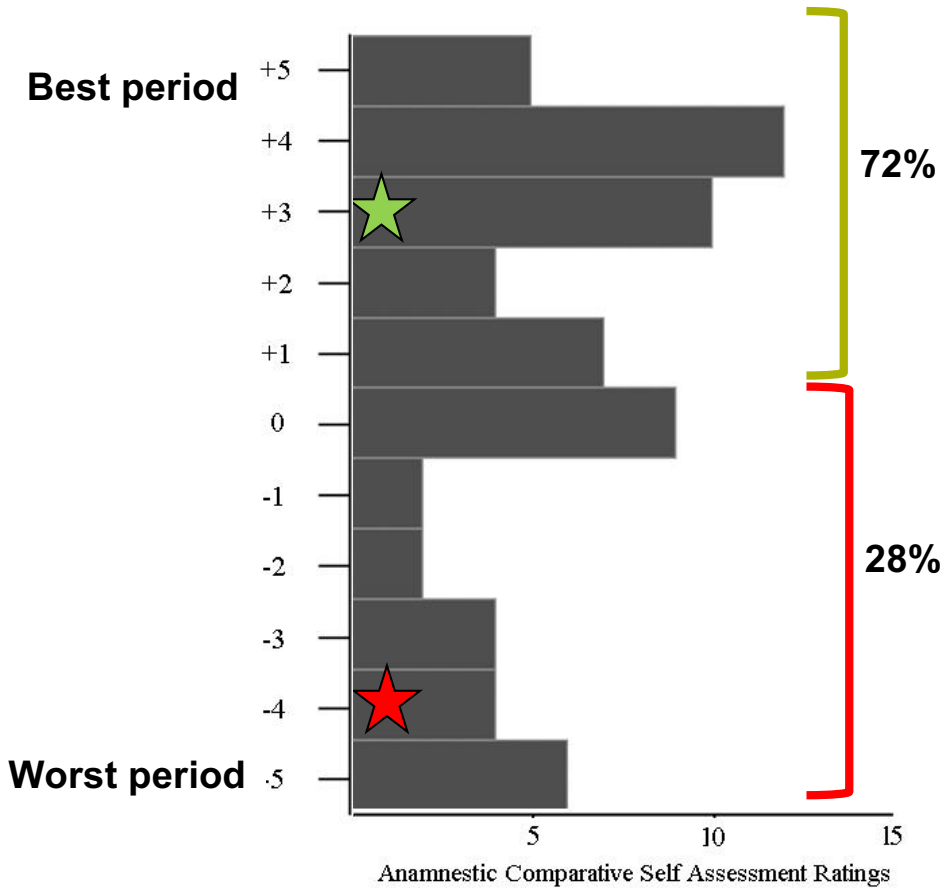
Jox, Bernat, Laureys, Racine, *Lancet Neurology* 2012

# Benefit for science

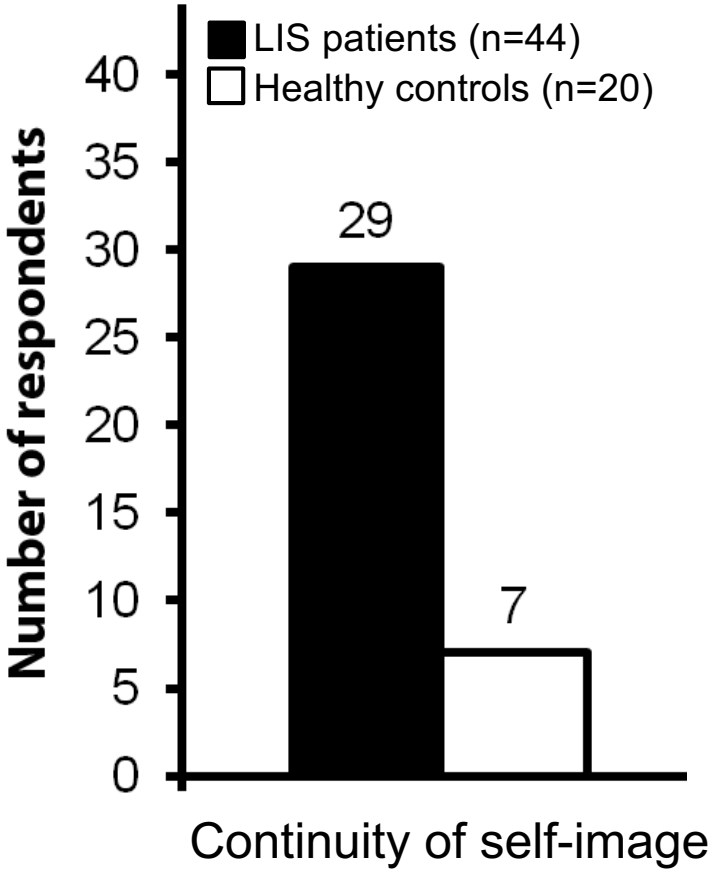



Gantner, et al, *Fut Neurol* 2013

# Benefit for patients?




Bruno et al, *Br Med J Open* 2011




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

# Benefit for caregivers?

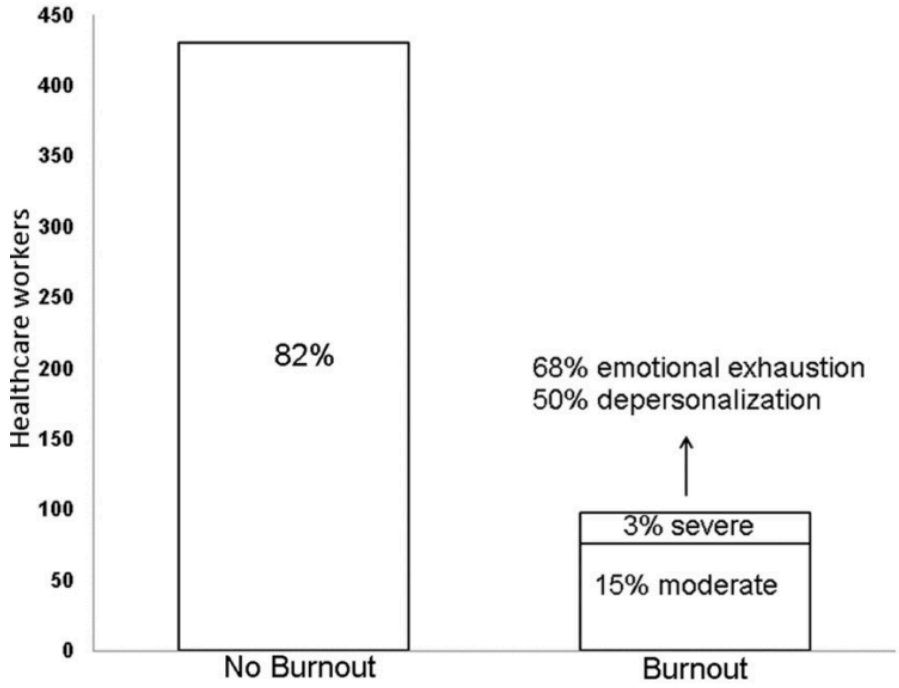


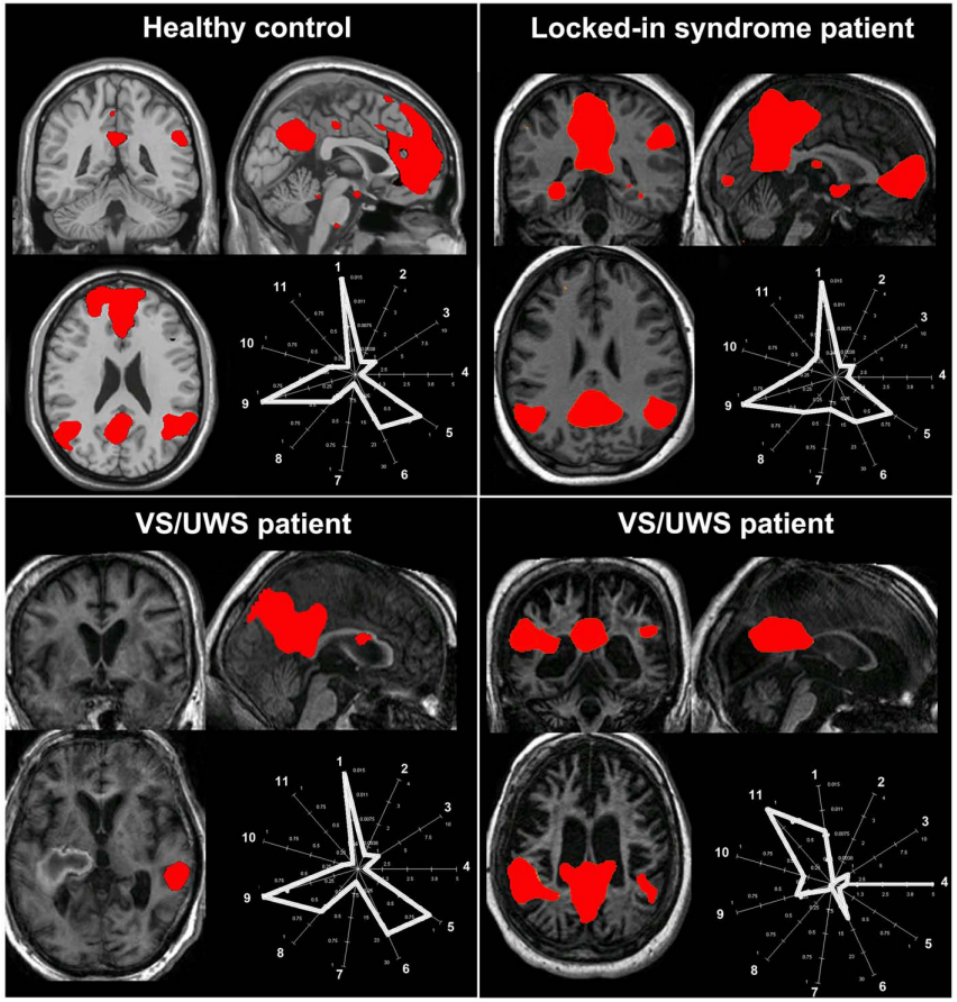

Table III. Percentage of healthcare workers presenting a burnout.

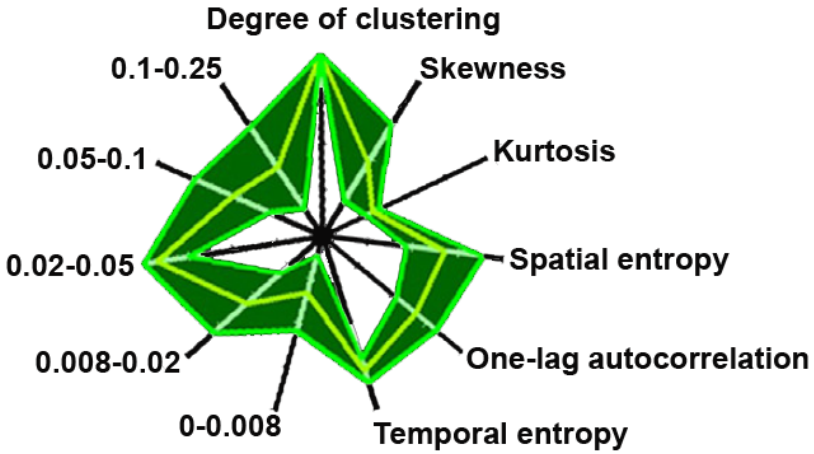
| Profession | Burnout |
|---|---|
| Physician | 8% |
| Nurse | 24% |
| Nursing assistant | 23% |
| Physio-/speech-/ergo-therapist | 8% |
| Psychologist/social worker | 10% |

n=523

Gosseries, Demertzi et al, Br Inj 2012

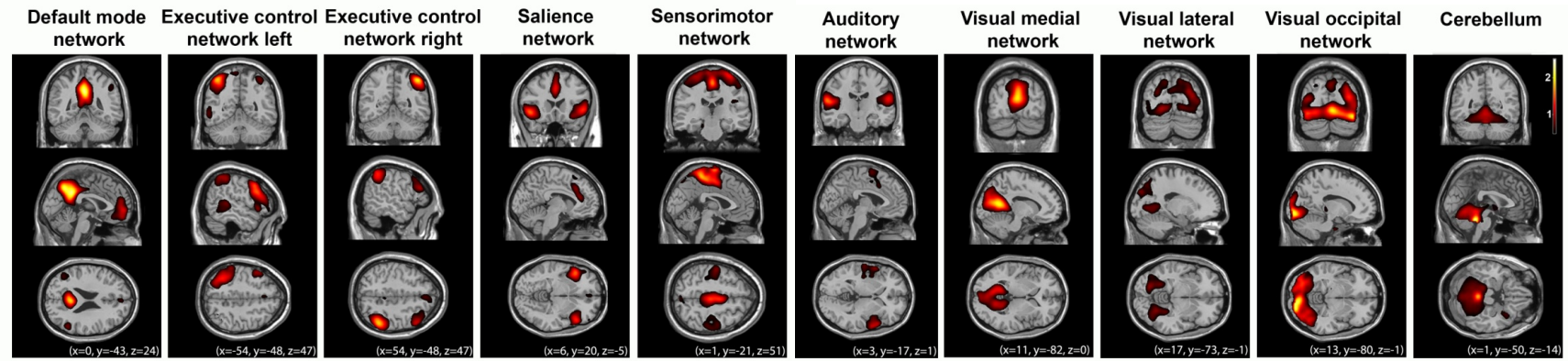
# Methodological challenges

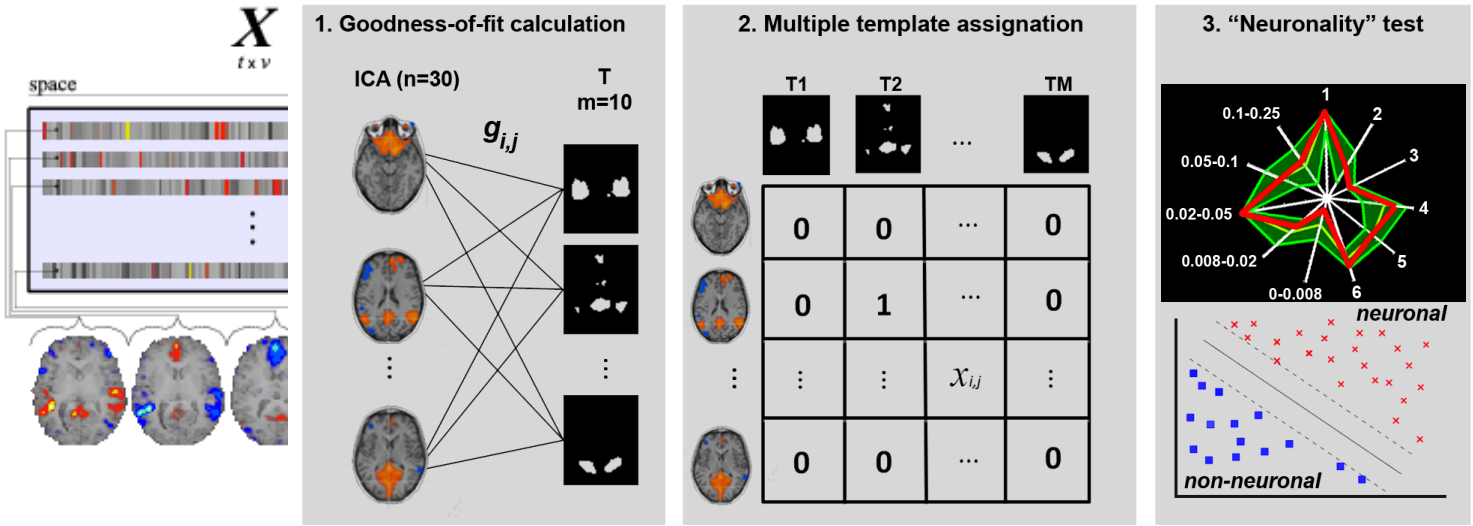



Heine, … & Demertzi, *Front Psychol* 2012

# How?




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