Measuring (un)conscious states: research, clinical applications & ethics

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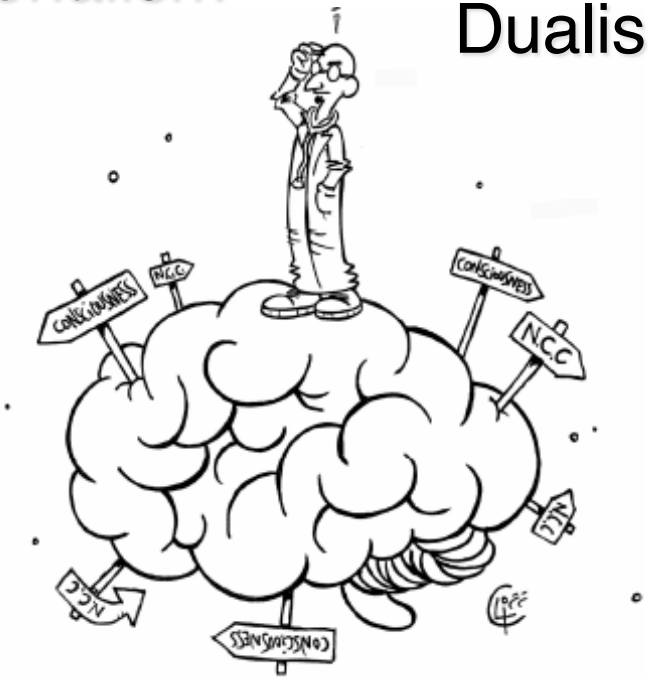
James S. McDonnell Foundation
Human Brain Project
European Space Agency

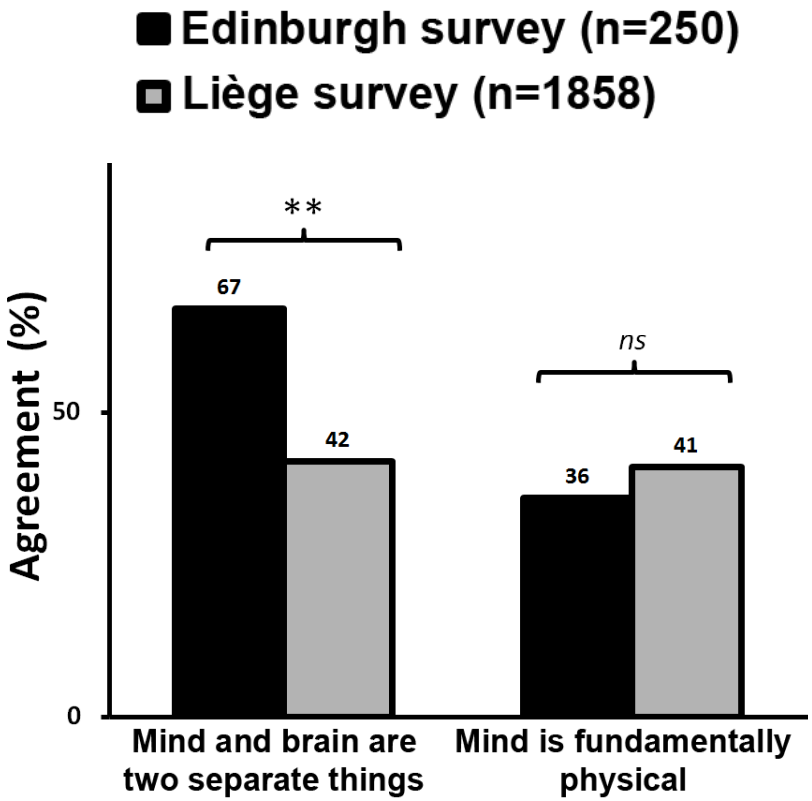
What is Consciousness?

Functionalism

Materialism

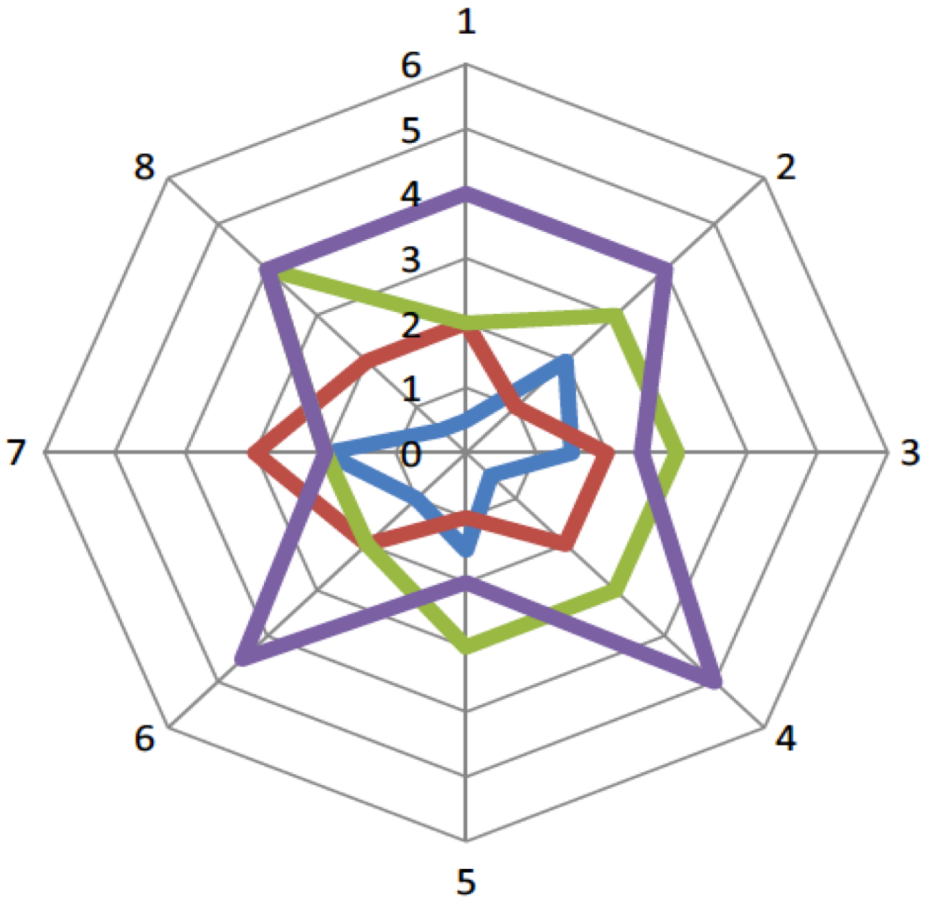
Dualism





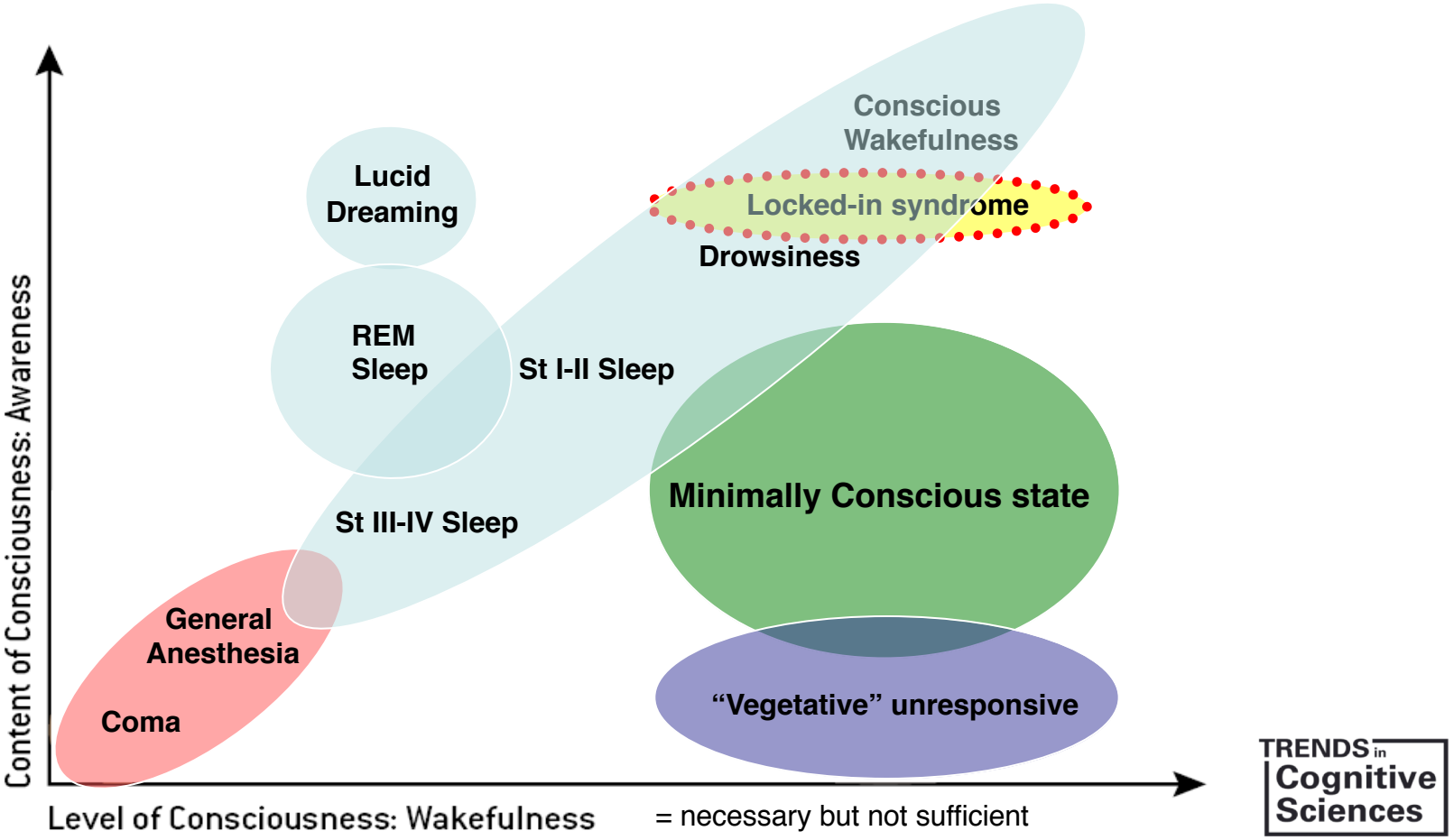
Demertzi et al, *Annals of the New York Academy of Sciences* 2009

Defining Consciousness



Bayne, Hohwy, Owen *Trends Cogn Sci* 2016

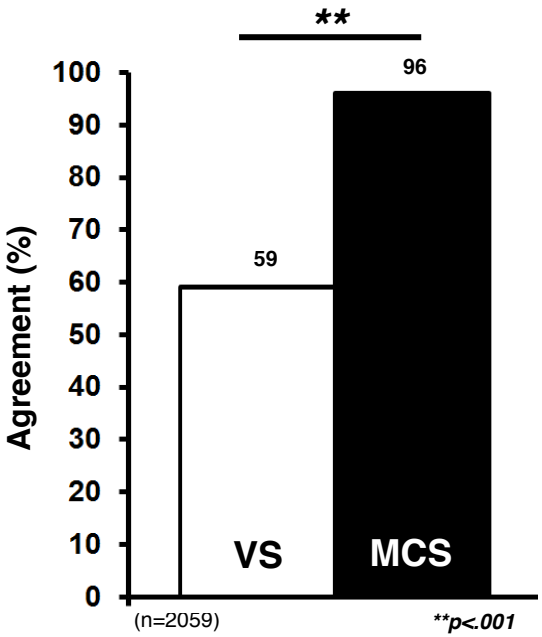
A clinical definition



Laureys, *Trends Cogn Sci* 2005
Laureys et al, *Nat Clin Med* 2008

Do they feel pain?

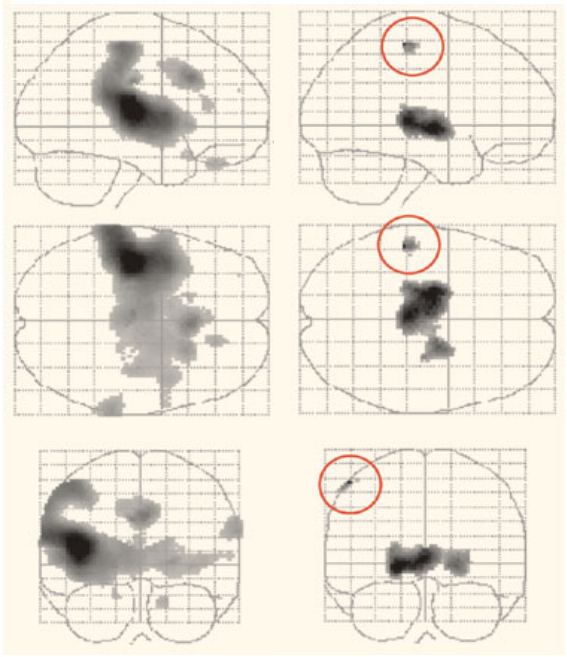
Do you think patients in a ... can feel pain?



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

Unresponsive wakefulness syndrome

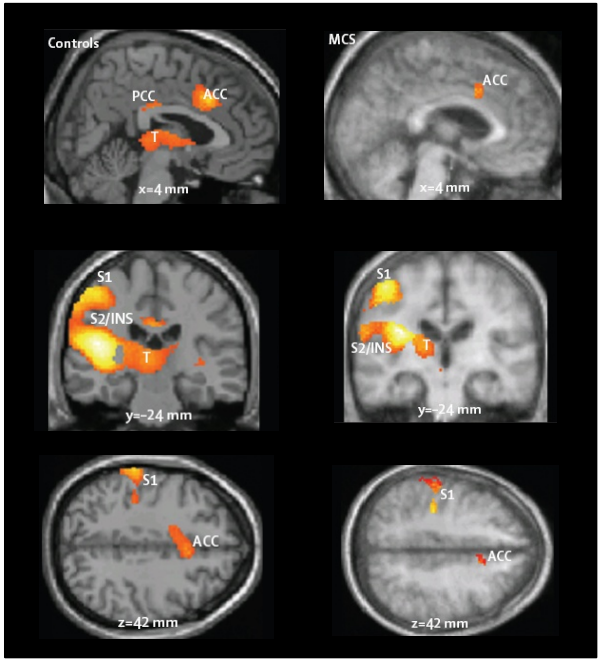
Healthy controls UWS patients



Laureys et al., *Neuroimage* 2002

Minimally conscious state

Healthy controls MCS patients



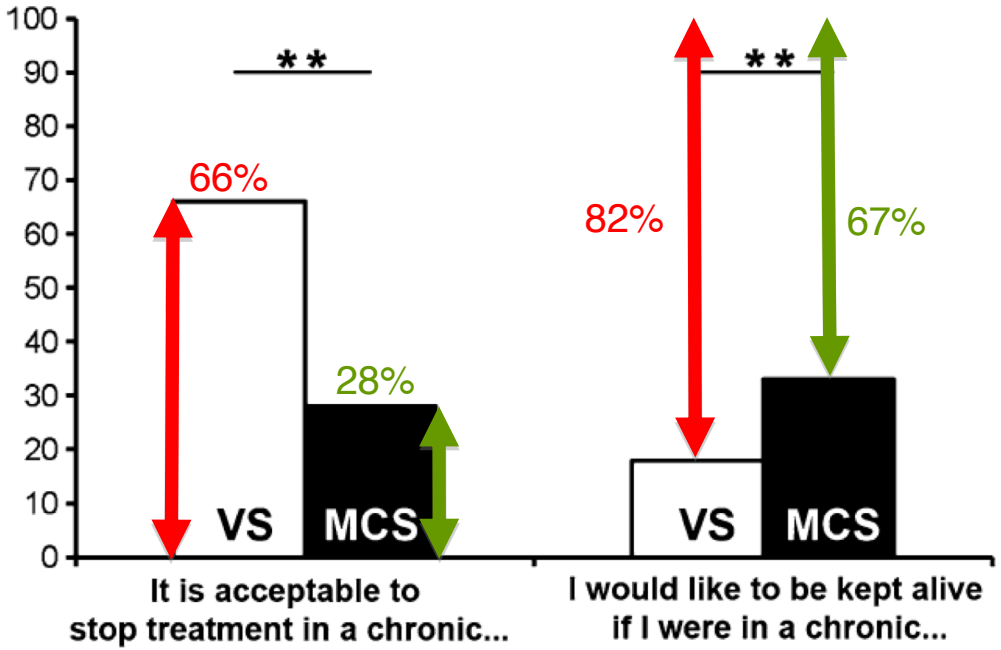
Boly et al, *Lancet Neurol* 2008

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

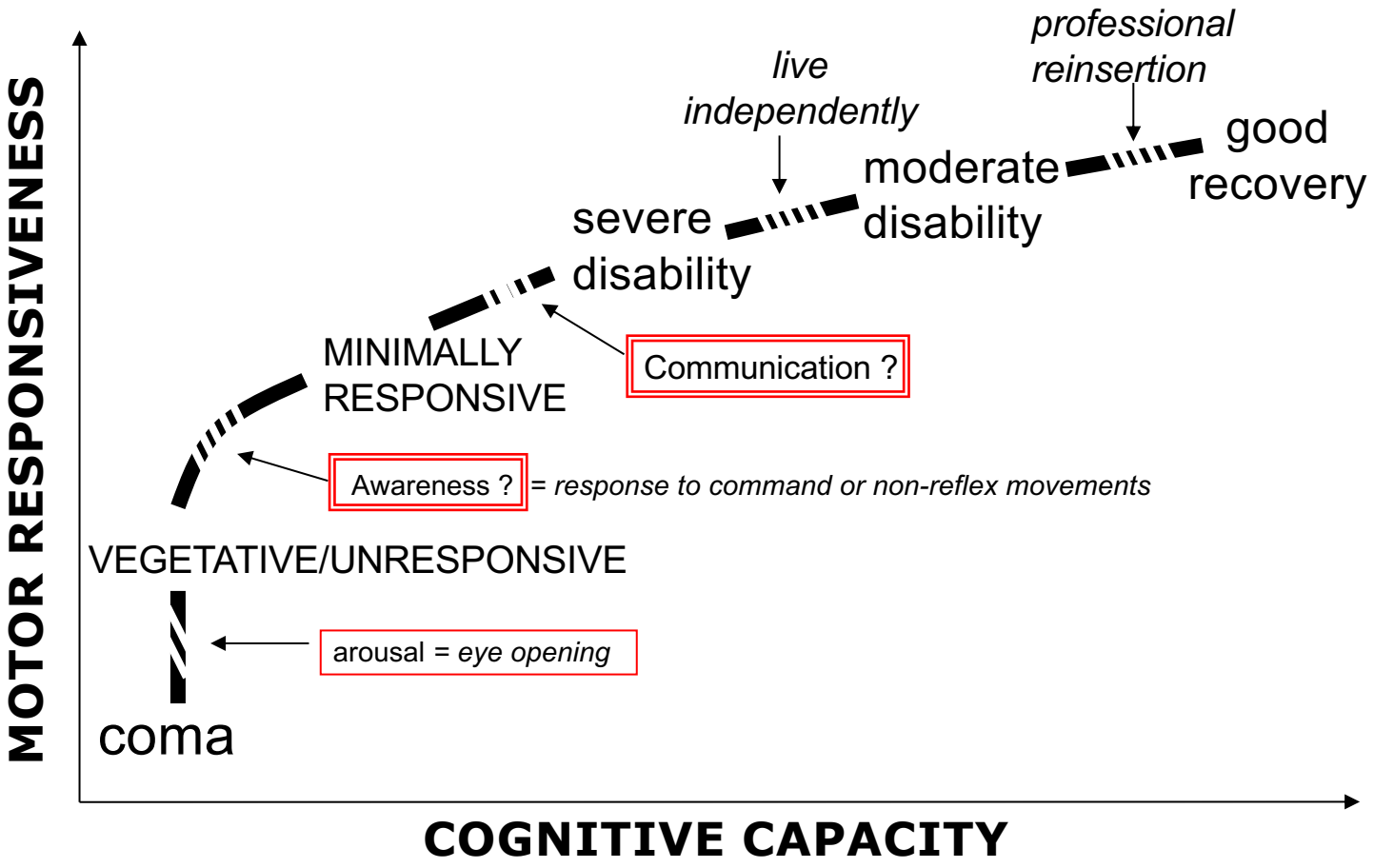


Demertzi et al, *J Neurol* 2011

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

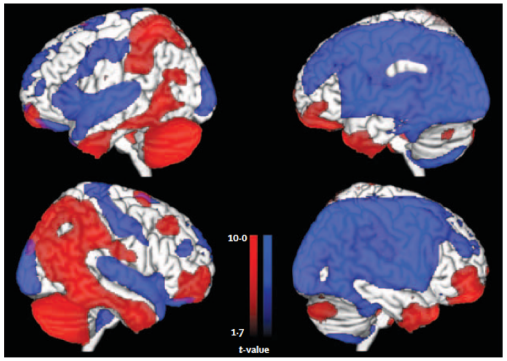
Schnakers et al, *Ann Neurol* 2006; *BMC Neurol* 2009

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**

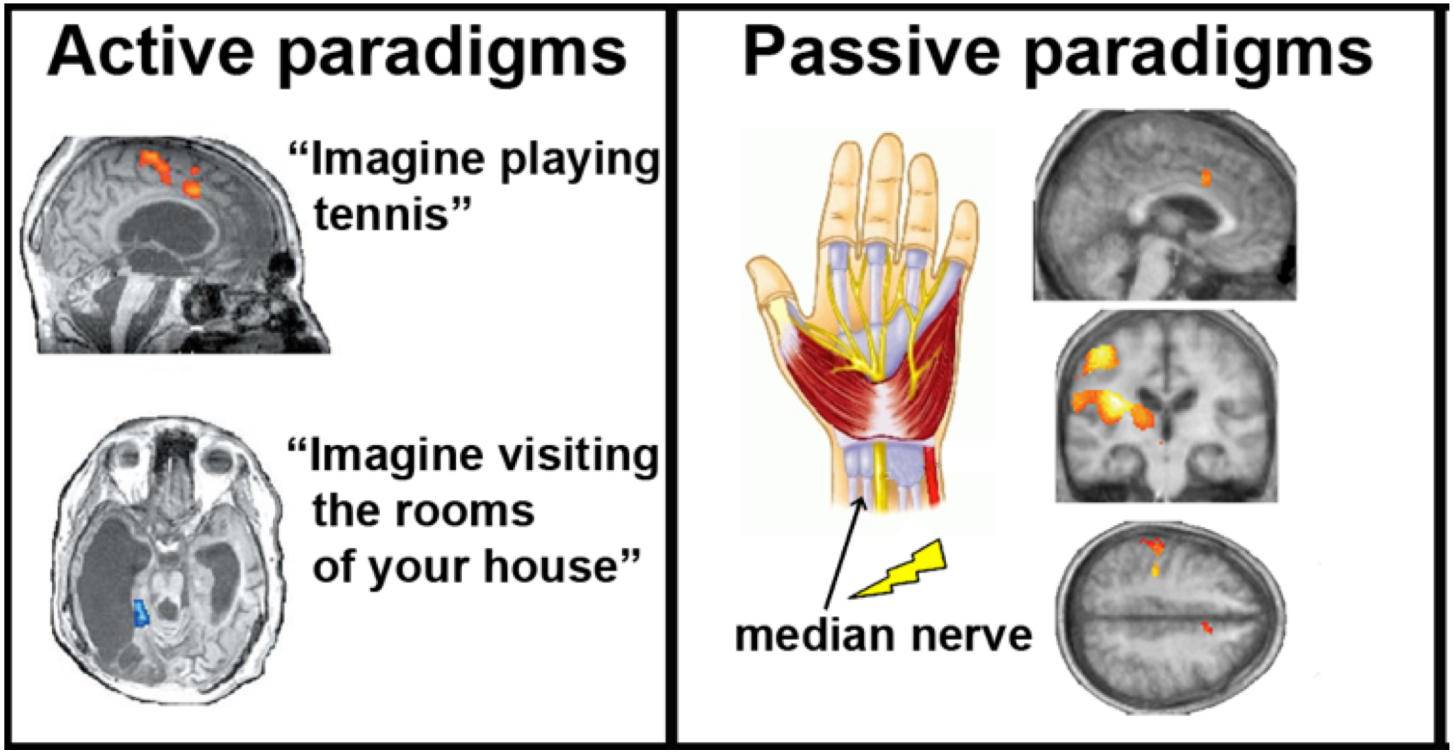


Stender & Gosseries et al, *Lancet* 2014

Neuroimaging paradigms

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

Boly et al, Lancet Neurol 2008

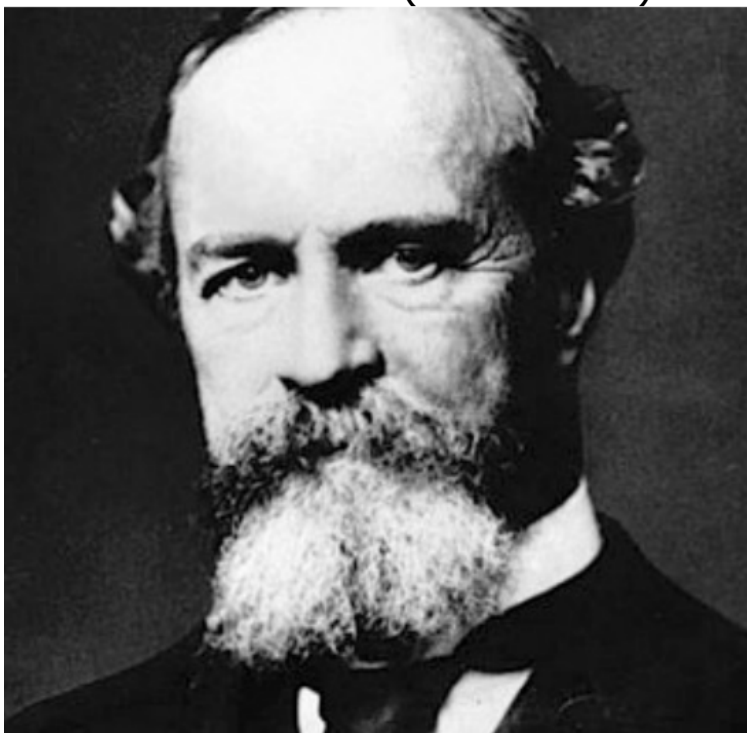


Heine, Di Perri, Soddu, Laureys, Demertzi
In: *Clinical Neurophysiology in Disorders of Consciousness,* Springer-Verlag 2015

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

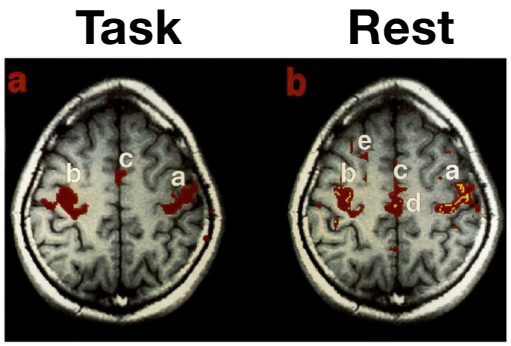
Some numbers

- 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%

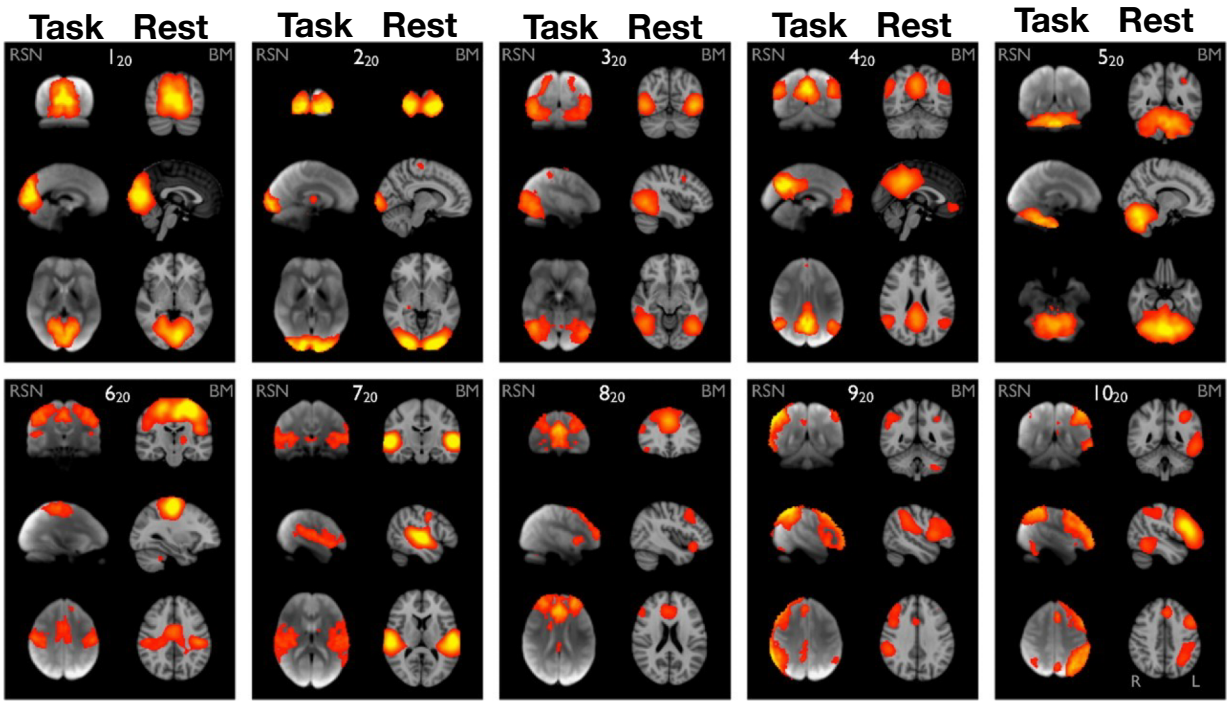
While conscious awareness is energetically inexpensive, it is dependent upon a very complex, dynamically organized, non-conscious state of the brain that is achieved at great expense

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 orgnization

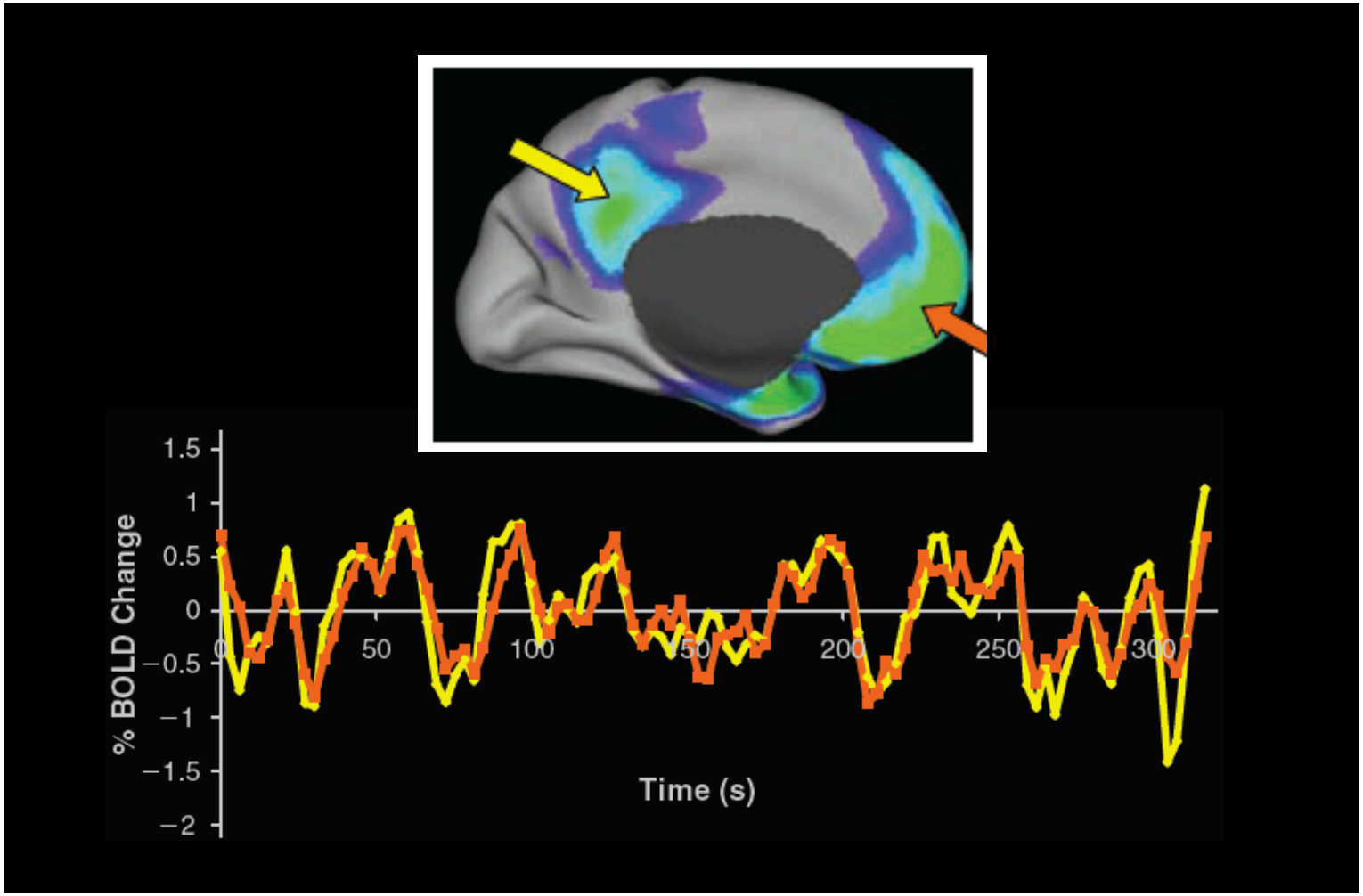


Biswal et al., *Magn. Reson. Med.*1995



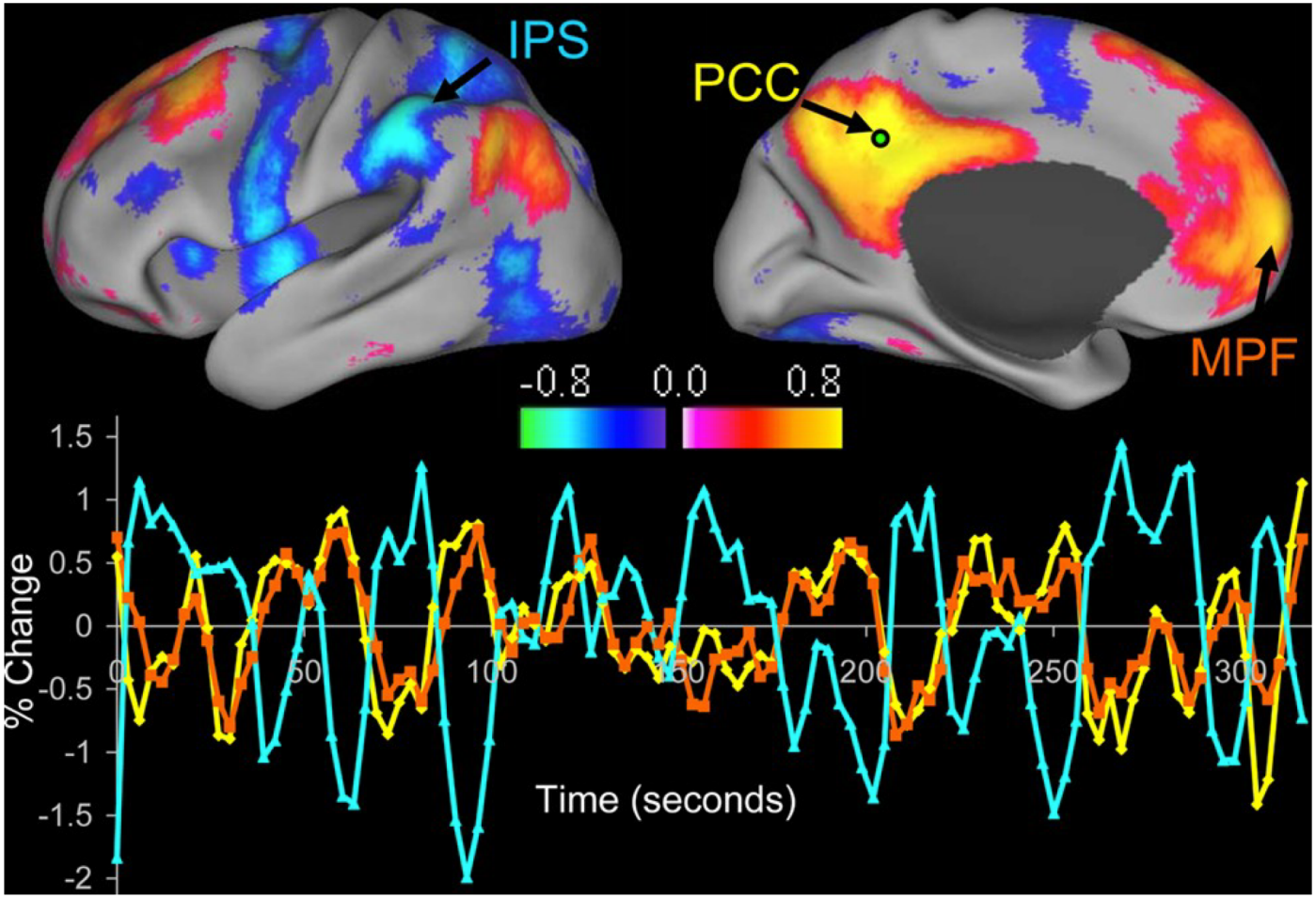
Smith et al, *PNAS* 2009

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

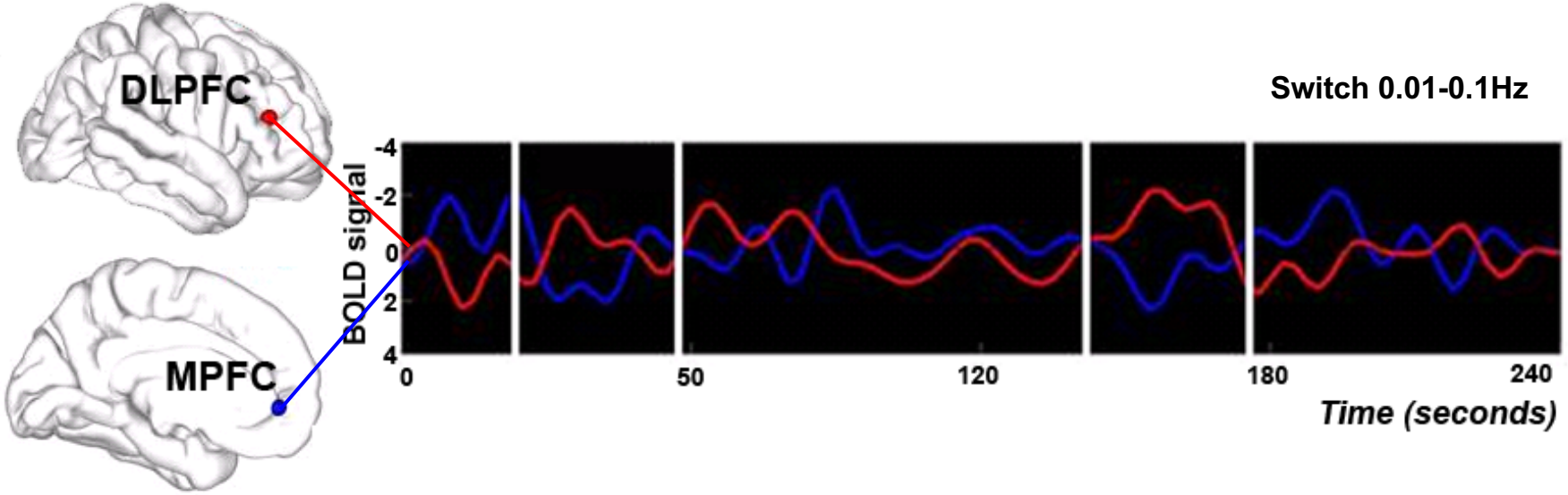
DMN anticorrelations



Fox et al, *Proc N Acad Sci* 2005

DMN anticorrelations

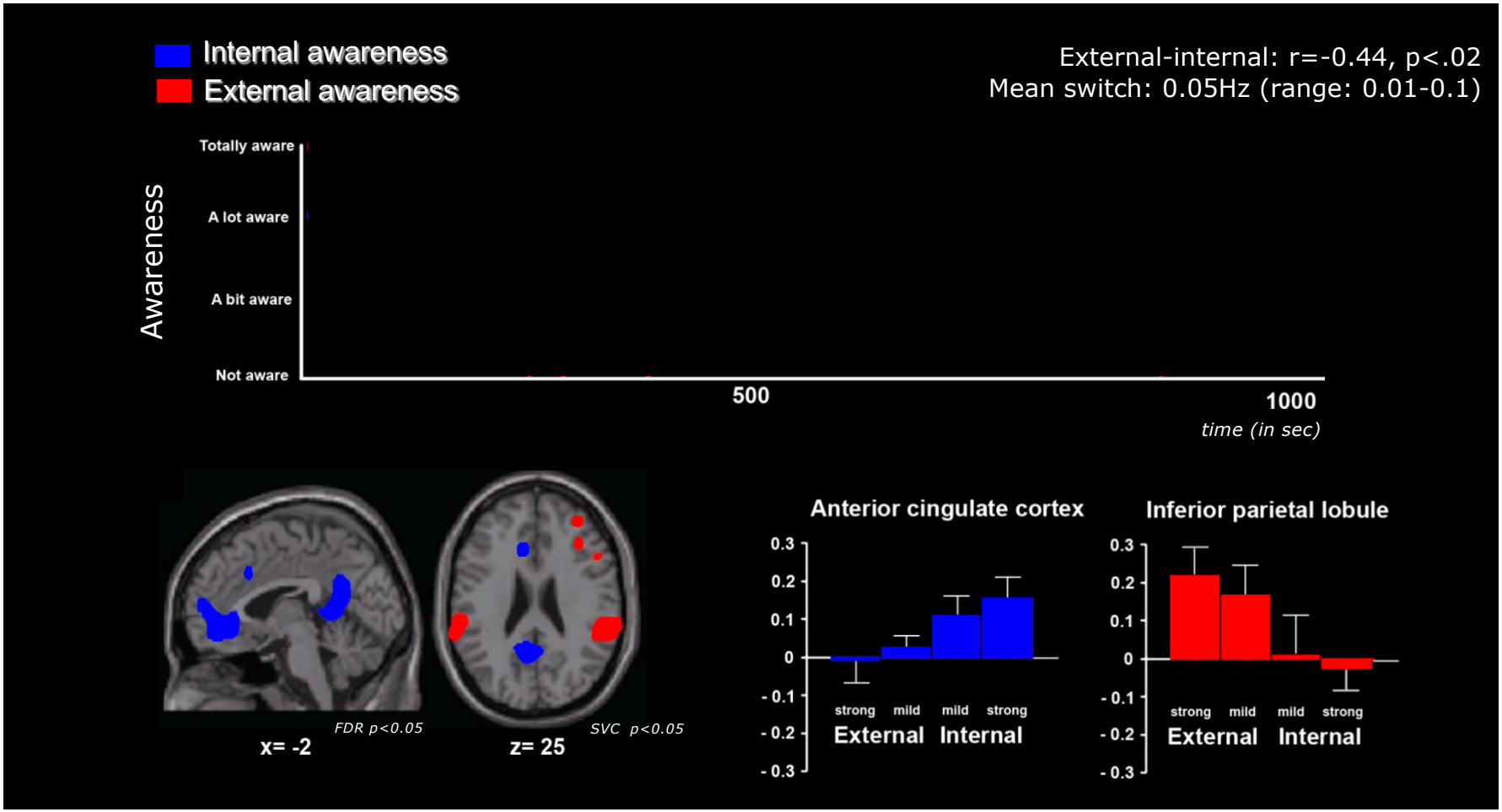
External awareness
***or* anticorrelated network**



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

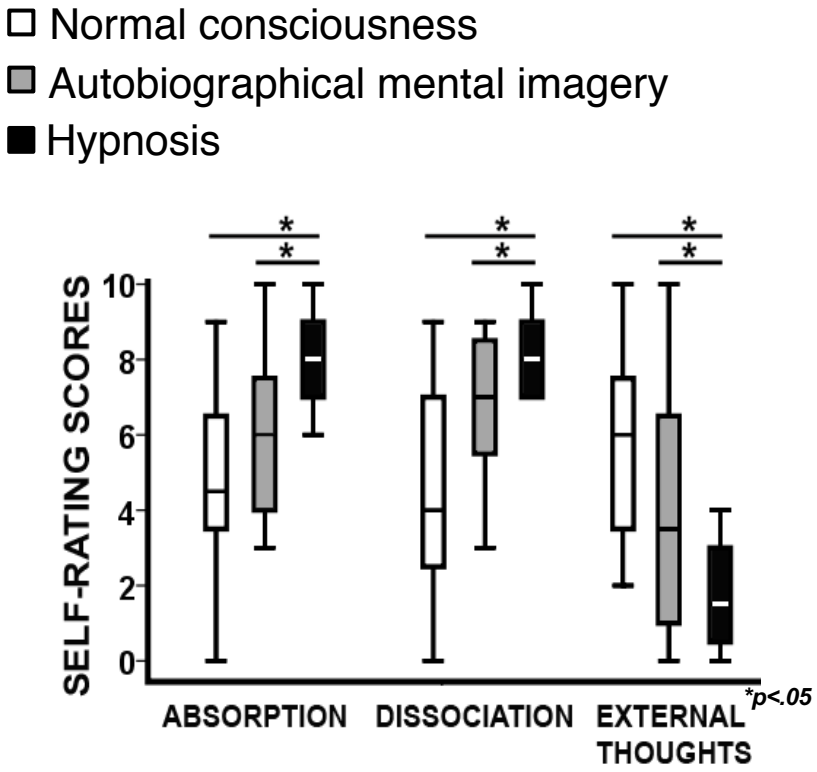
Demertzi & Whitfield-Gabrieli, in: *Neurology of Consciousness* 2nd ed. *2015*
Demertzi, Soddu, Laureys, *Curr Opin Neurobiology* 2013
Demertzi et al, *Front Hum Neurosci* 2013

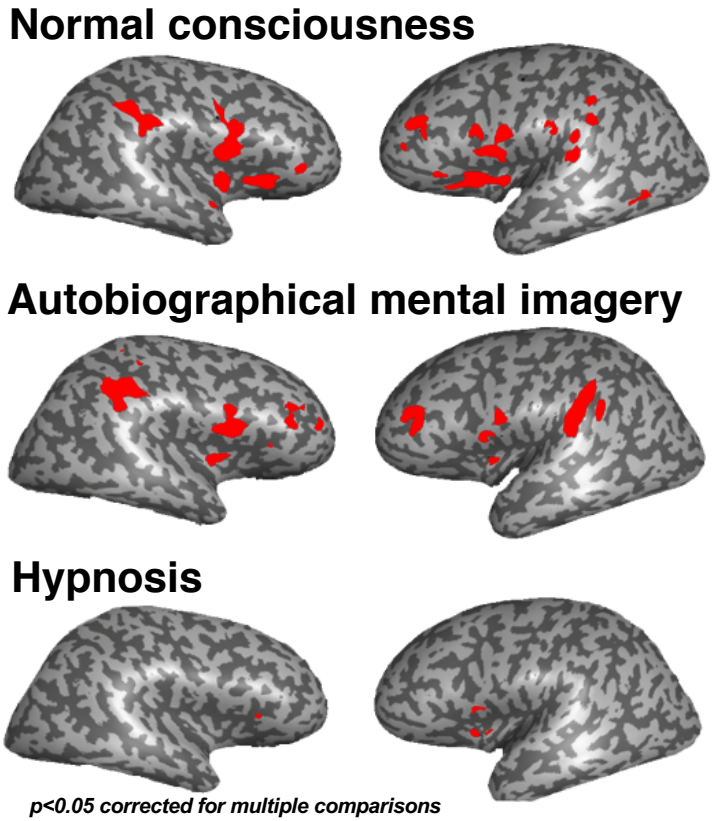
Cognitive-behavioral relevance



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

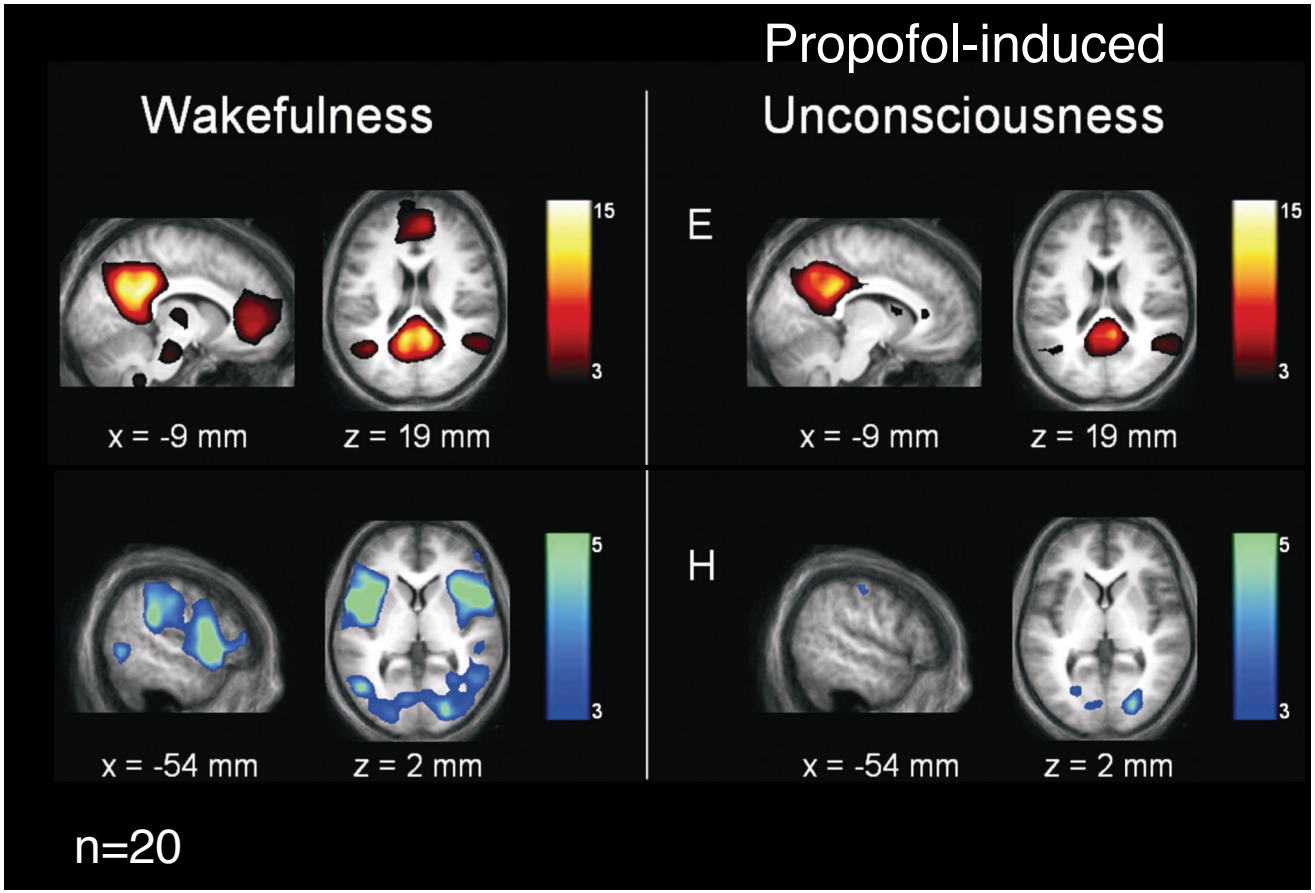
Effect of awareness





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

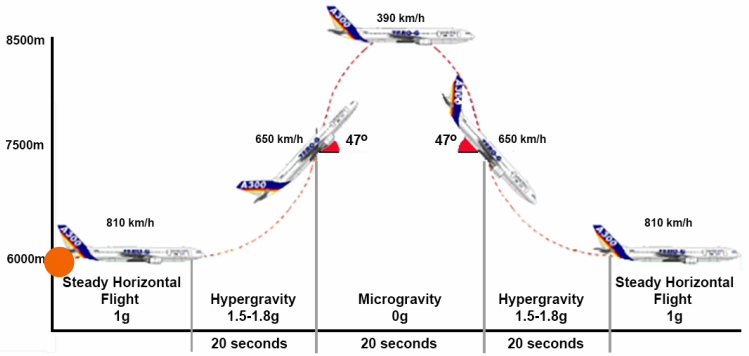
www.nature.com/scientificreports/

Parabolic flight

NOVESPACE

esa

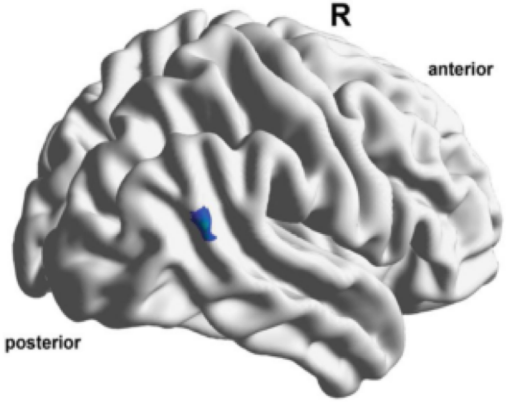
European Space Agency

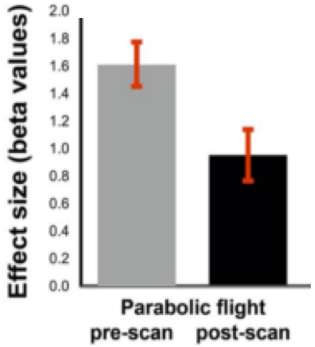


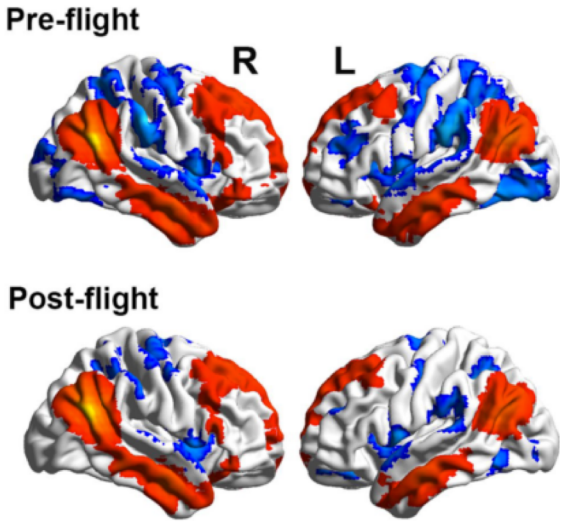
Parabolic flight trajectory

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]

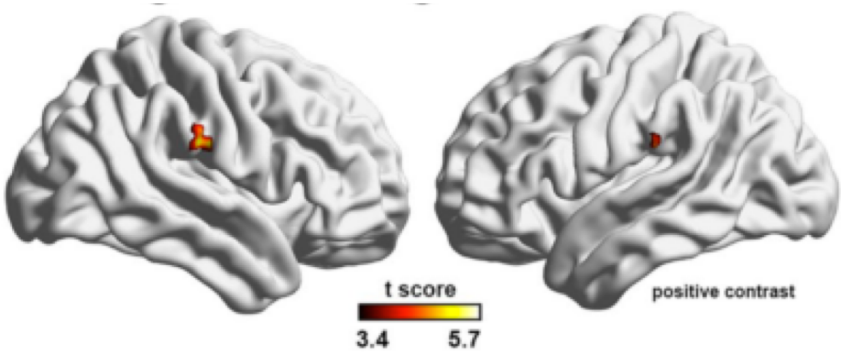
Effect of environment

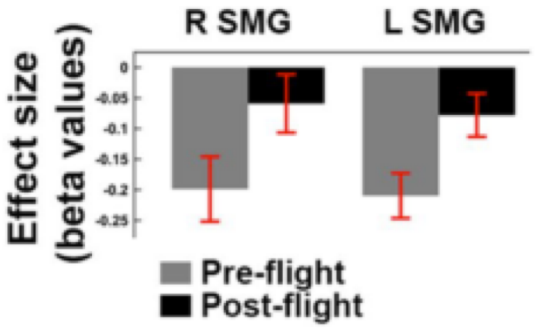






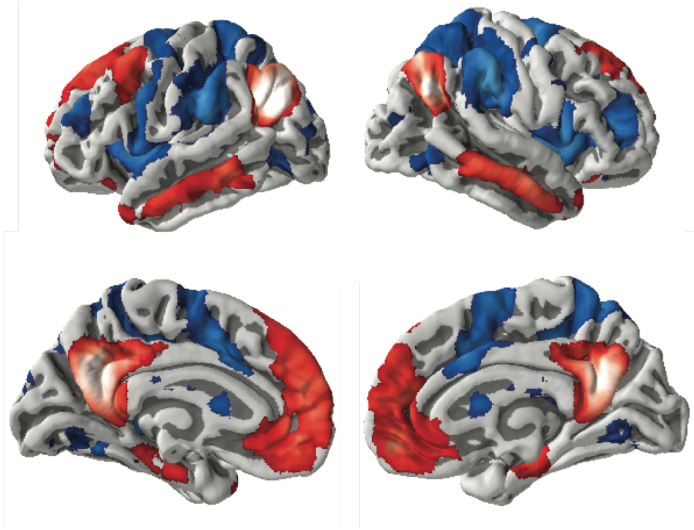
Post – Pre flight

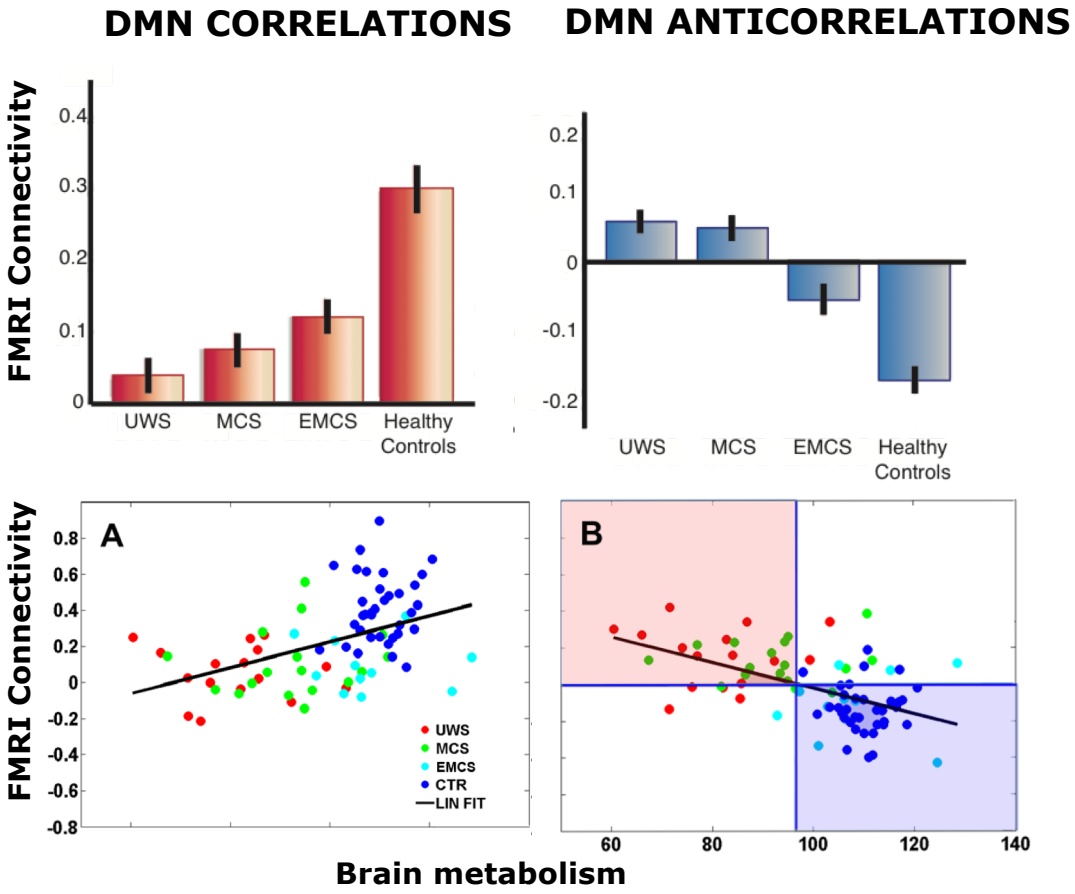




Van Ombergen … and Demertzi, *Sci Reports* 2017

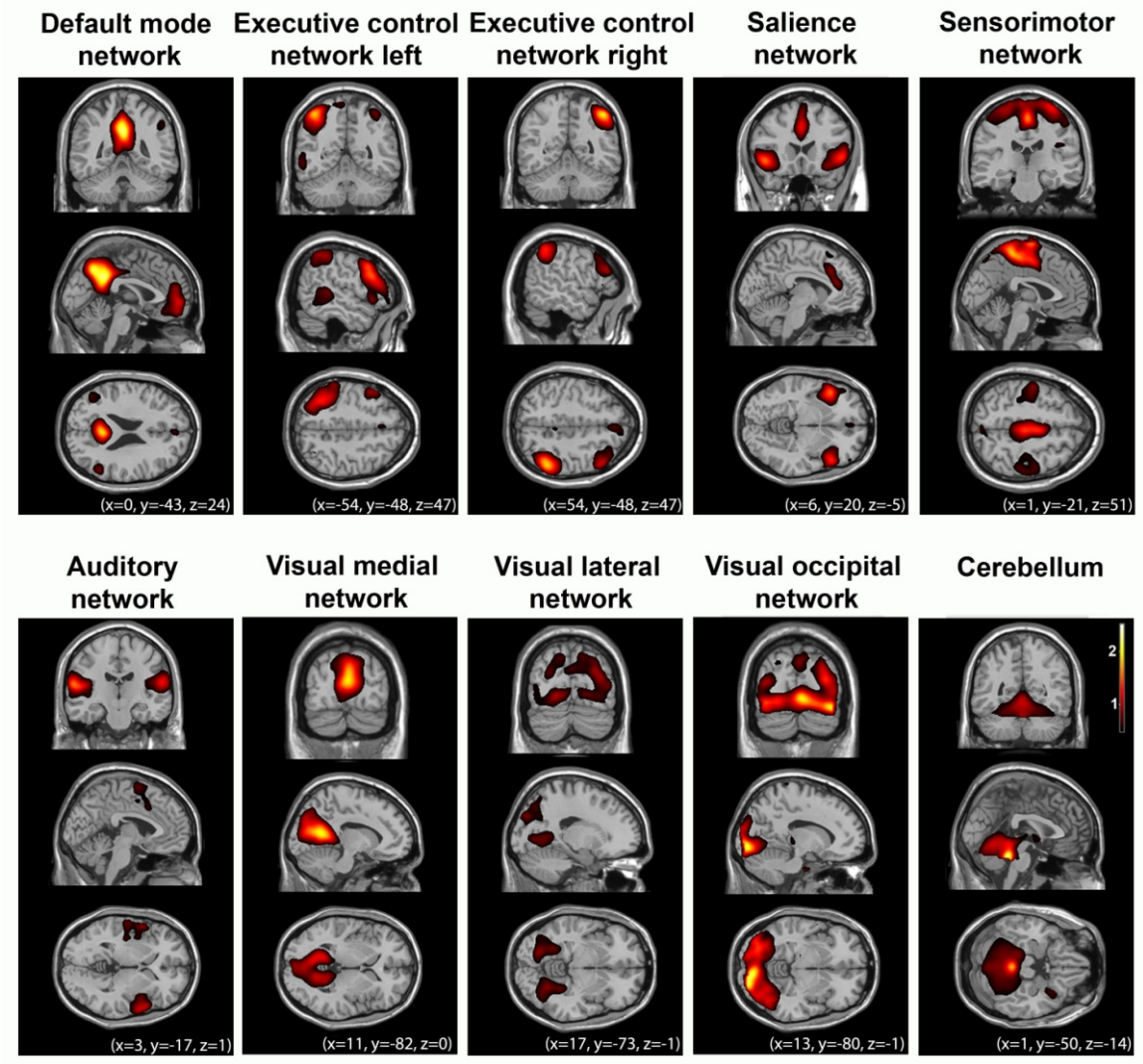
Effect of pathology





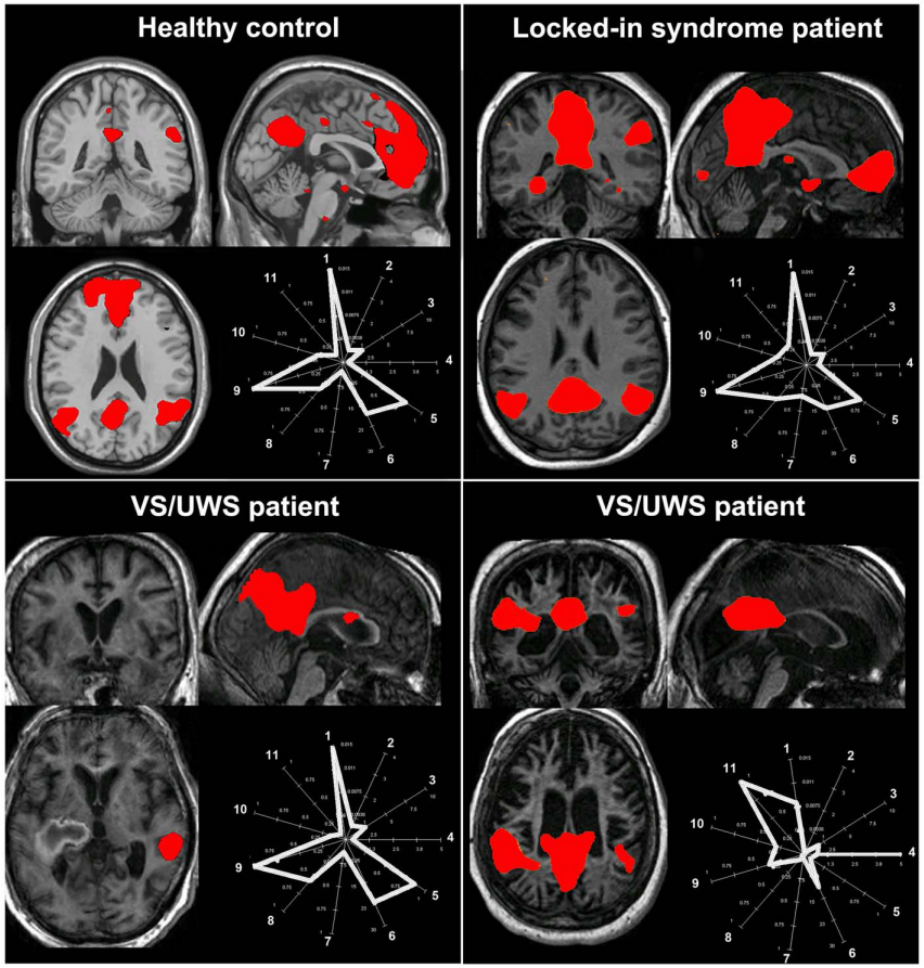
Di Perri, …, Demertzi*, Laureys*, Soddu*, *Lancet Neurol* 2017
Vanhaudenhuyse et al, *Brain* 2010

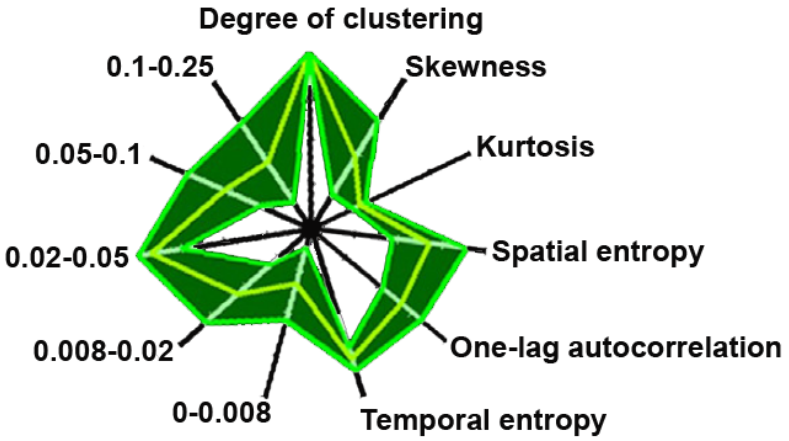
Systems-level organization



Heine, … & Demertzi, *Front Psychol* 2012

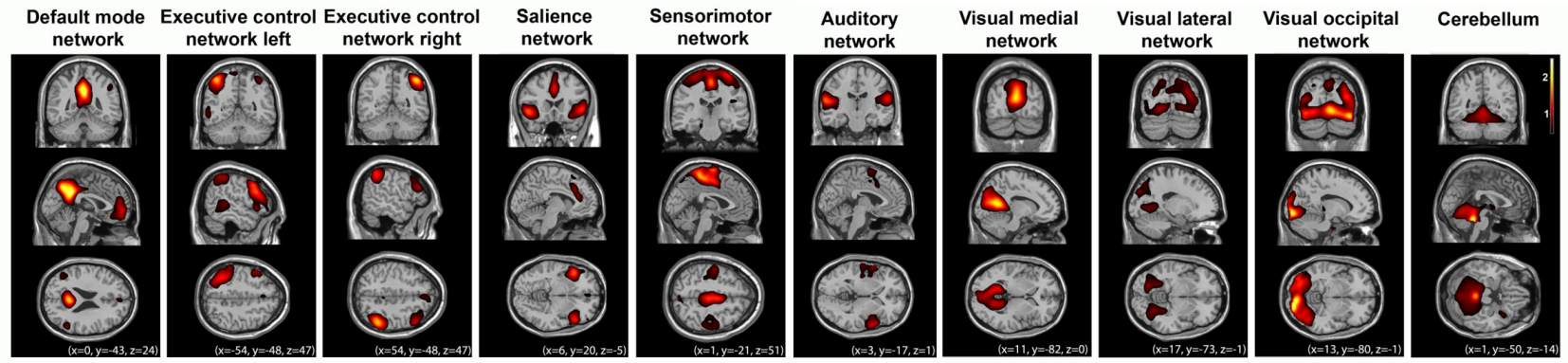
Methodological challenges

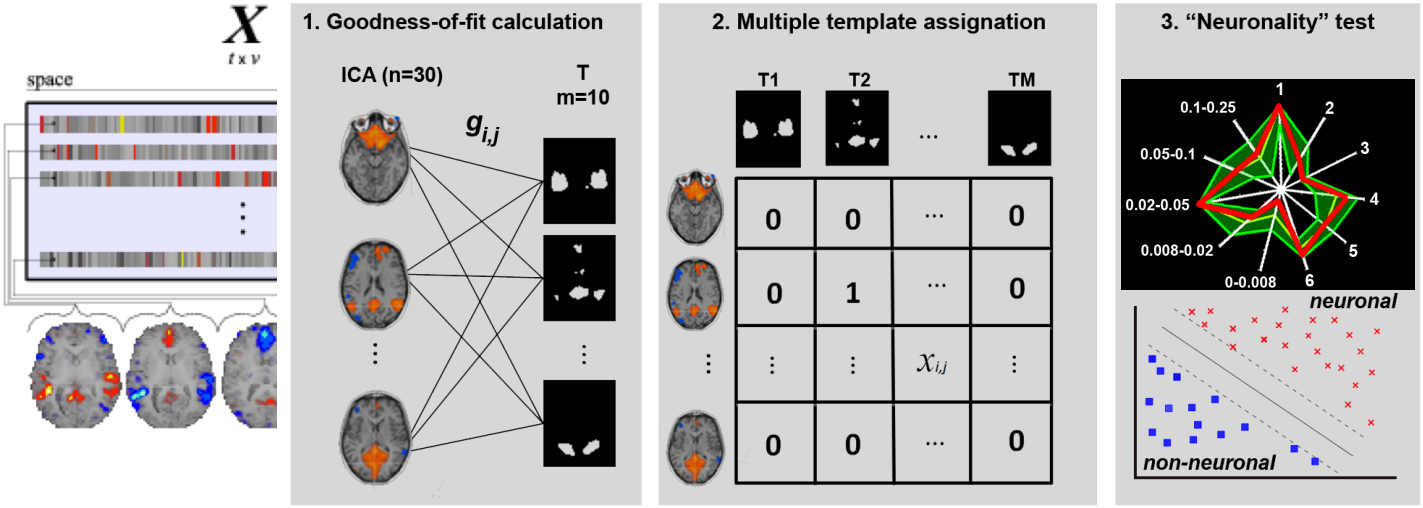




Heine, … & Demertzi, *Front Psychol* 2012

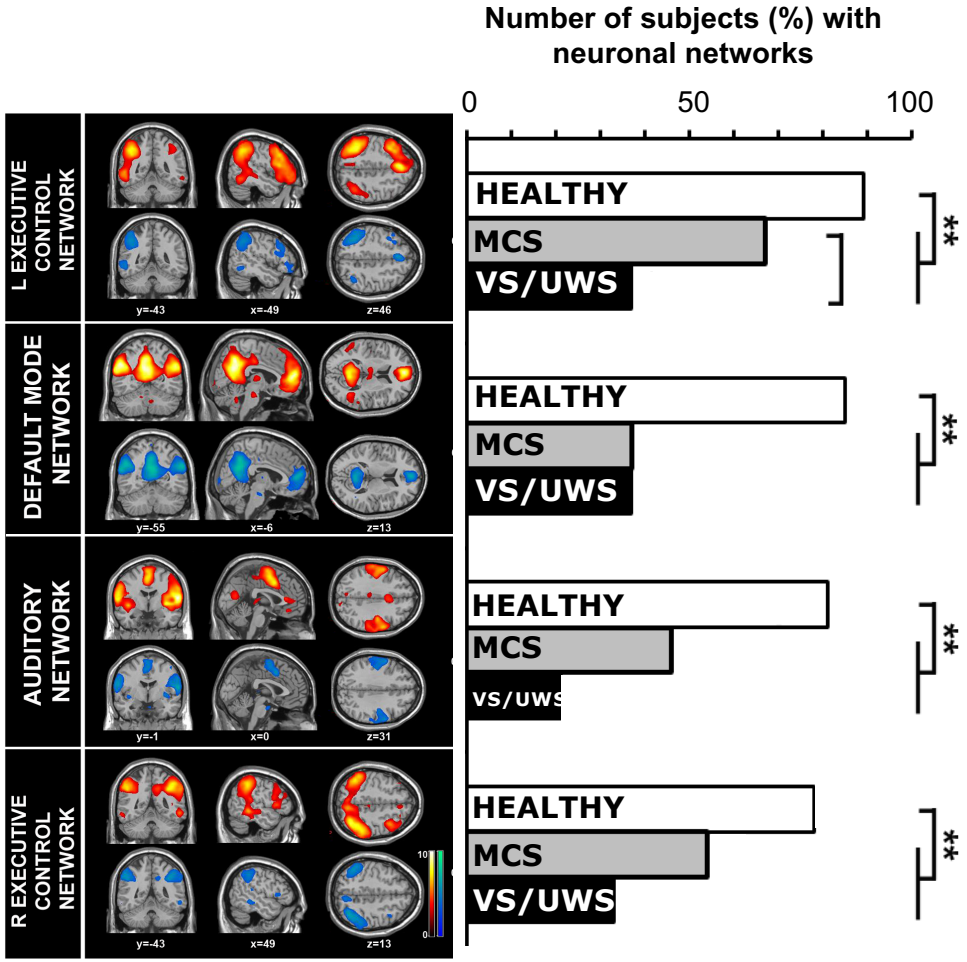
How?





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

Connecitivy decreases in low consciousness states

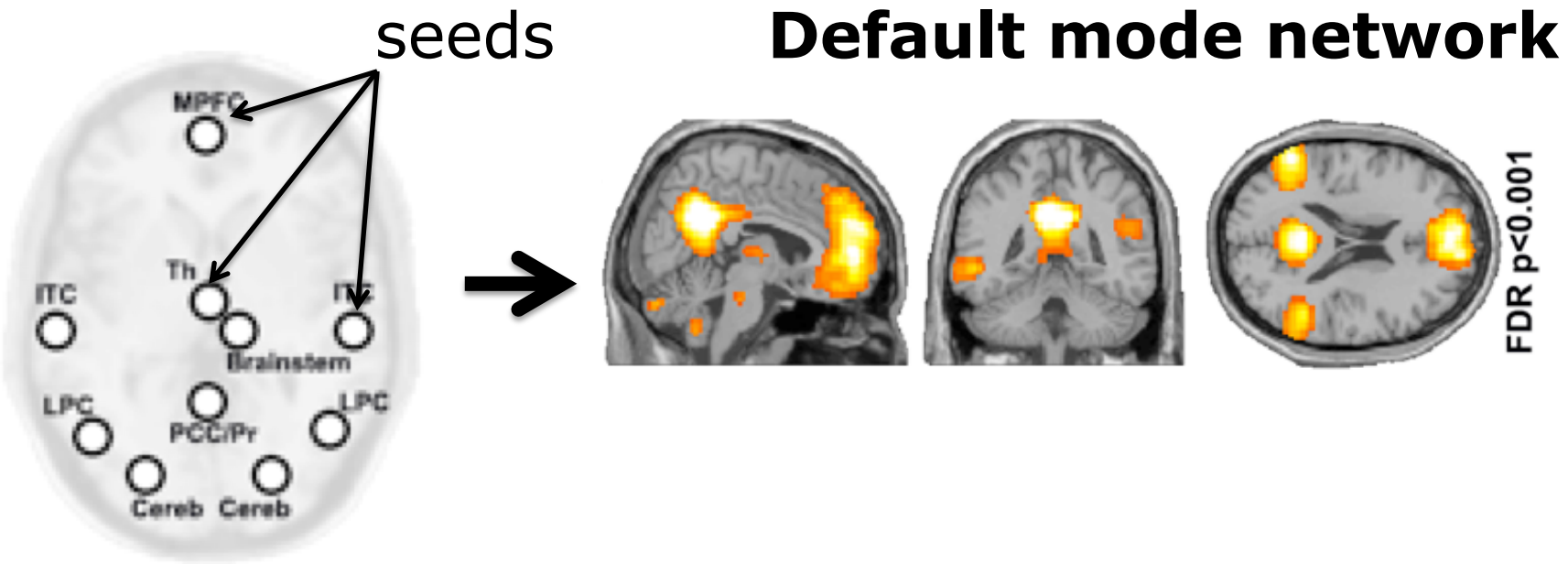


Single-patient classification

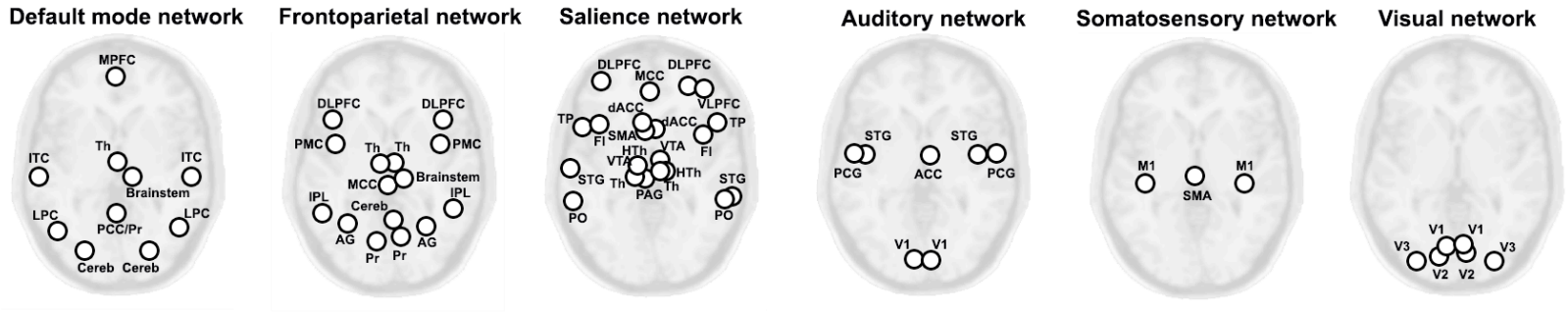
Performance measures	Accuracy	TPR healthy	TPR patients	Selected RSNs
	Healthy vs. all patients			
Neuronal	85.3	.82	.87	Auditory, DMN

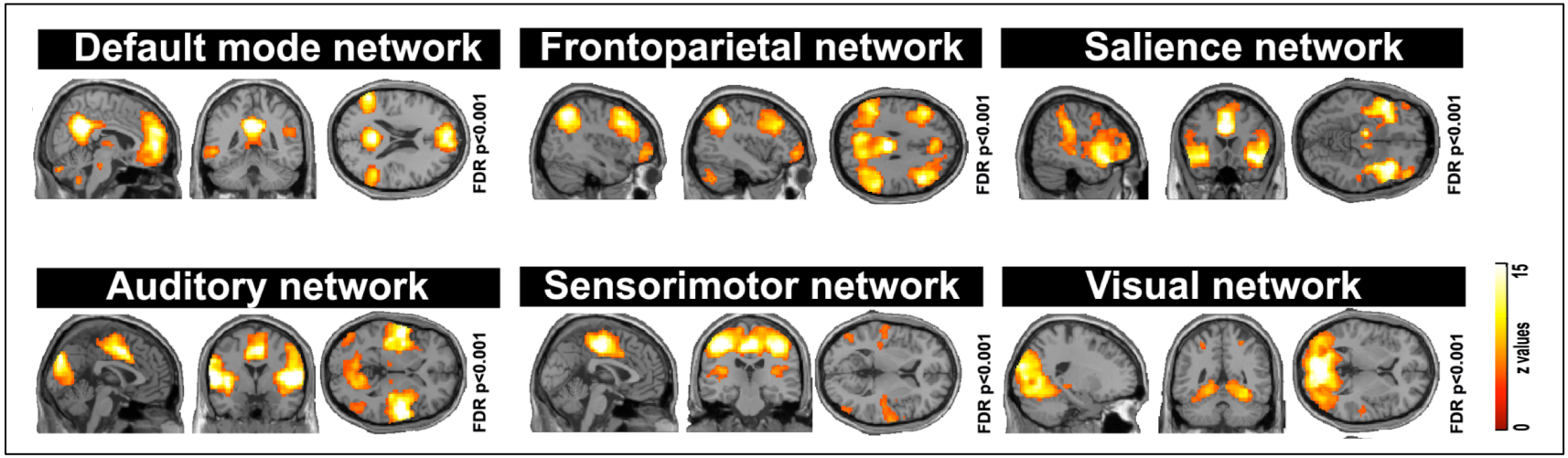
Demertzi & Gómez et al, *Cortex* 2014

Towards single-patient classification



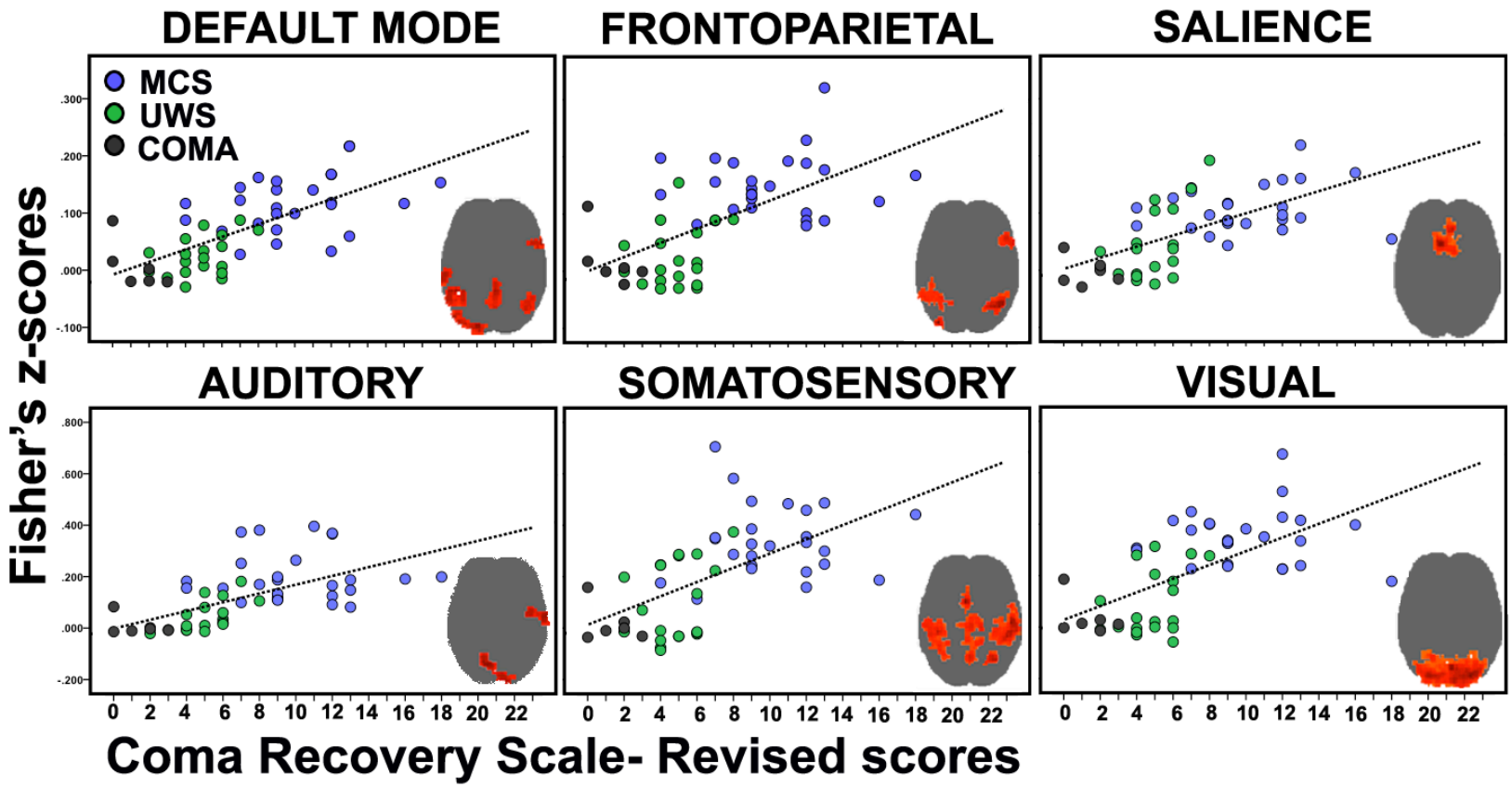
Intrinsic connectivity systems





Demertzi & Antonopoulos et al, *Brain* 2015

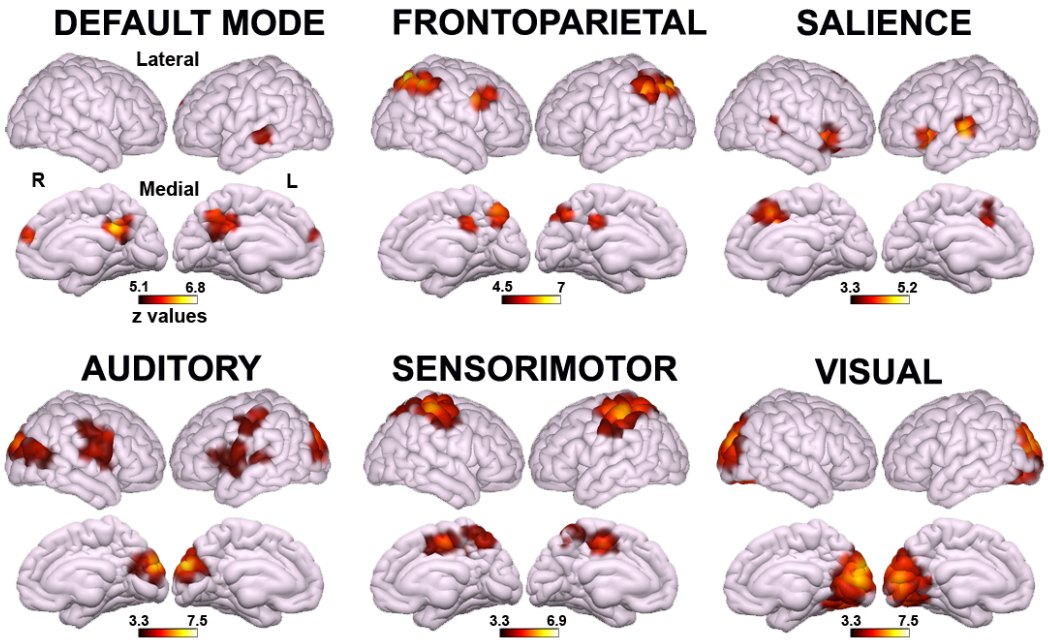
Connectivity correlates with conscious states



Demertzi & Antonopoulos et al, *Brain* 2015

Which network discriminates best?

MCS> VS/UWS



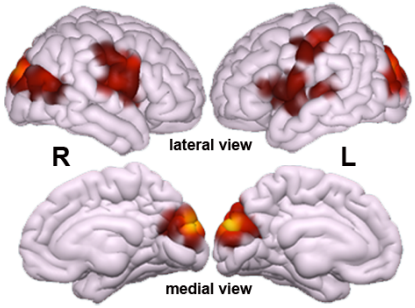
	Feature selection criterion (t-test)			Single-feature classification		
Network	**t value**	**Rank**	**p value**	**TP MCS**	**TN VS/UWS**	**Accuracy**
Auditory	8.32	1	<.001	25	18	43/45
Visual	7.79	2	<.001	23	15	38/45
Default mode	6.95	3	<.001	23	15	38/45
Frontoparietal	6.82	4	<.001	23	15	38/45
Salience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

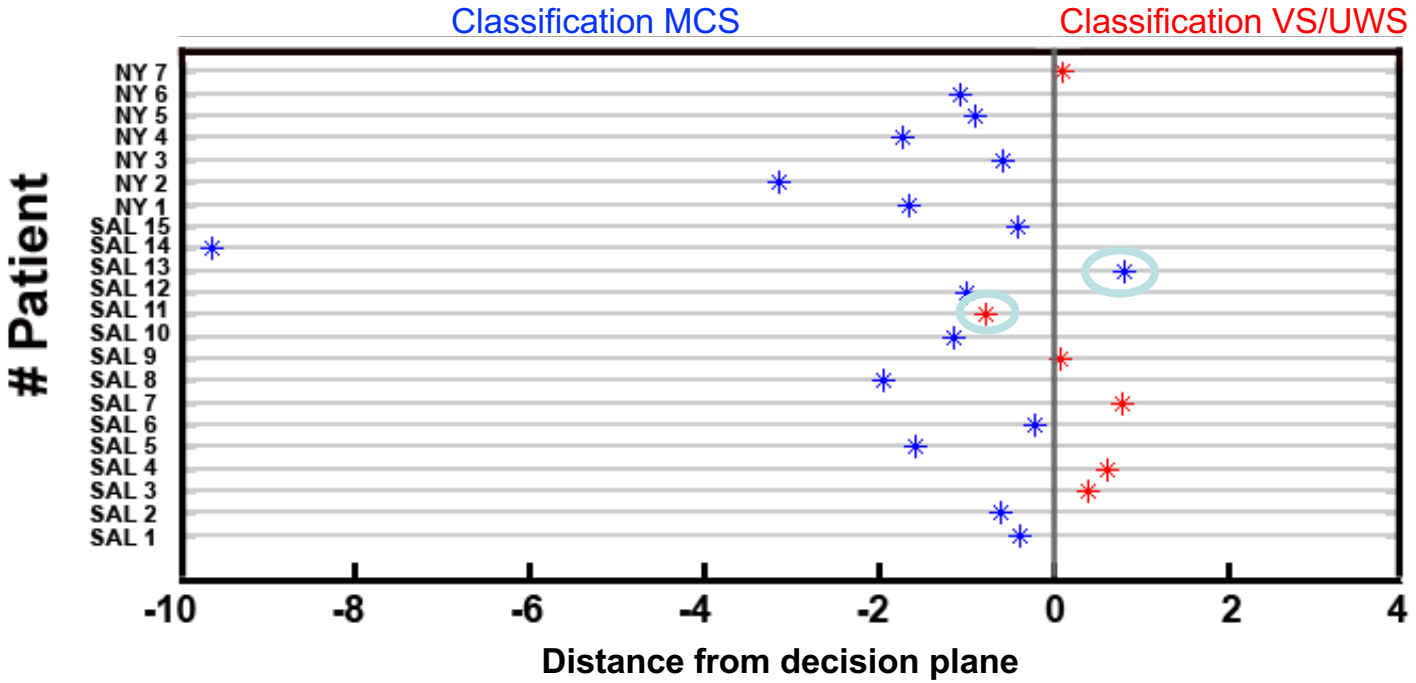
FWE p<0.05 (cluster-level)

Demertzi & Antonopoulos et al, *Brain* 2015

Single-patient classification

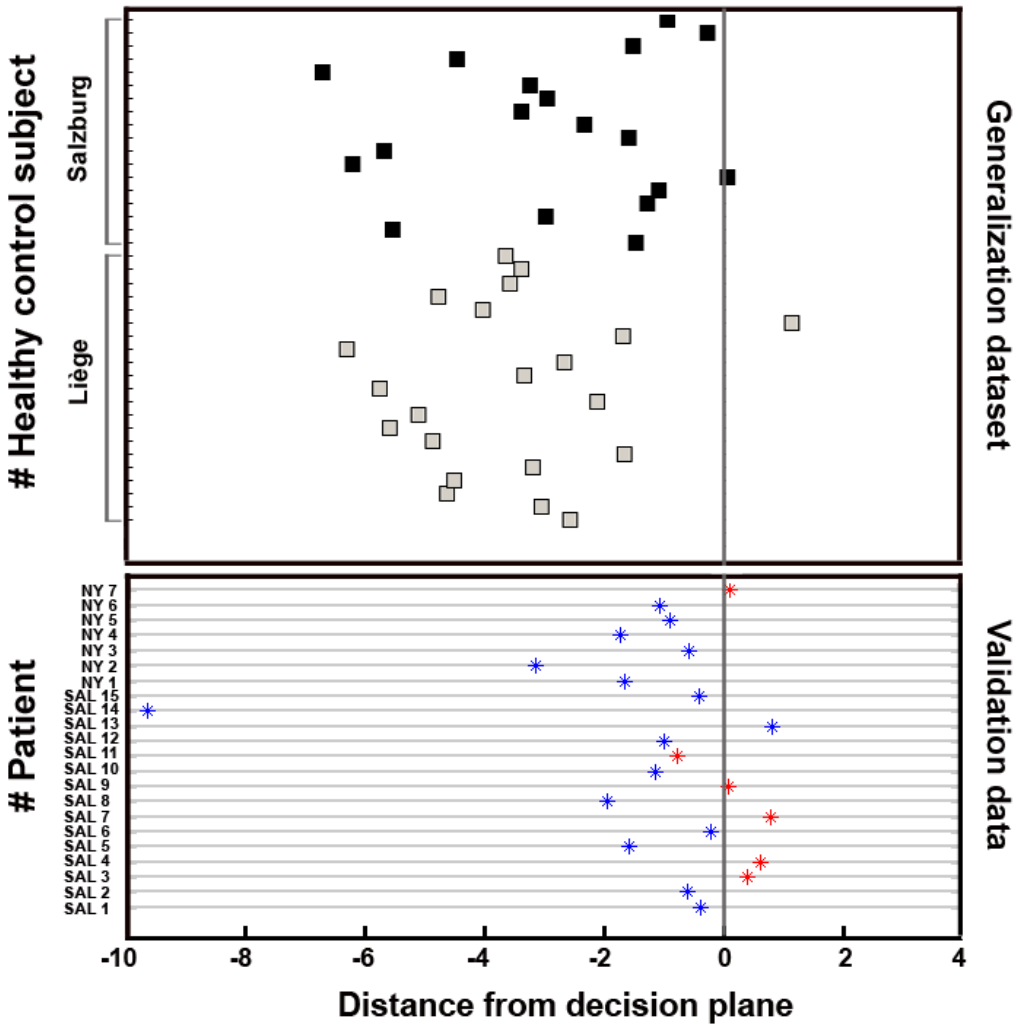
- Training set: 45 DOC (26 MCS, 19 VS/UWS)
  - 14 trauma, 28 non-trauma, 3 mixed
  - 34 patients assessed >1m post-insult
- Test set: **16 MCS**, **6 VS/UWS** (M_{age}: 43y, 15 non-trauma; all chronic), from 2 different centers





Demertzi & Antonopoulos et al, *Brain* 2015

Sanity check: generalization on healthy

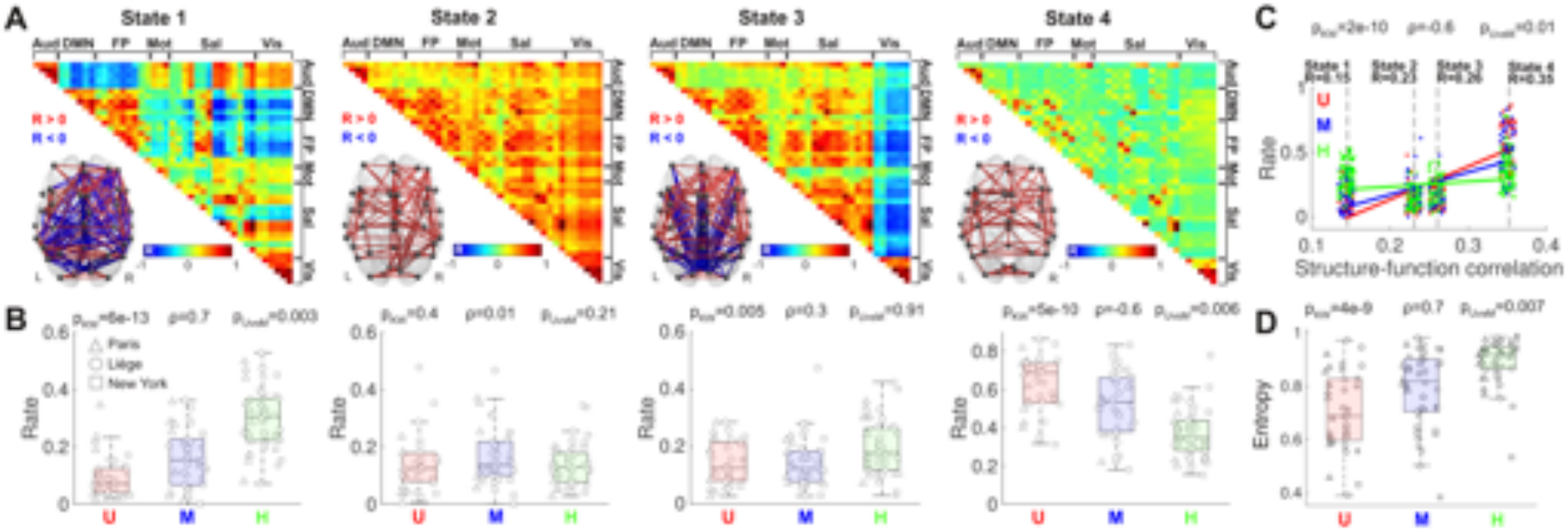


Demertzi & Antonopoulos et al, *Brain* 2015

Dynamic inter-regional coordination patterns predict consciousness states

James S. McDonnell Foundation

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



N=159

Demertzi, Tagliazucchi, … , Laureys, Schiff, Owen, Naccache, Sitt, in prep

Why does it matter?

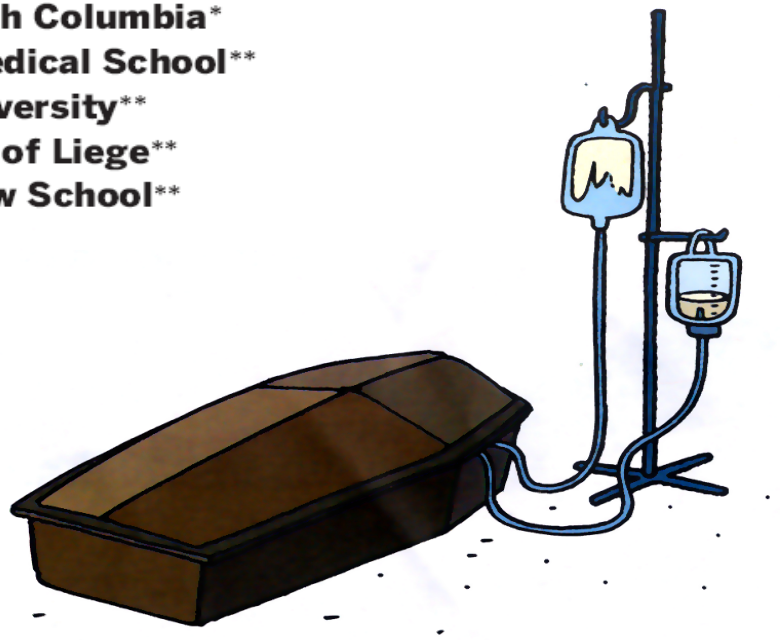
The American Journal of Bioethics, 8(9): 3–12, 2008

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.

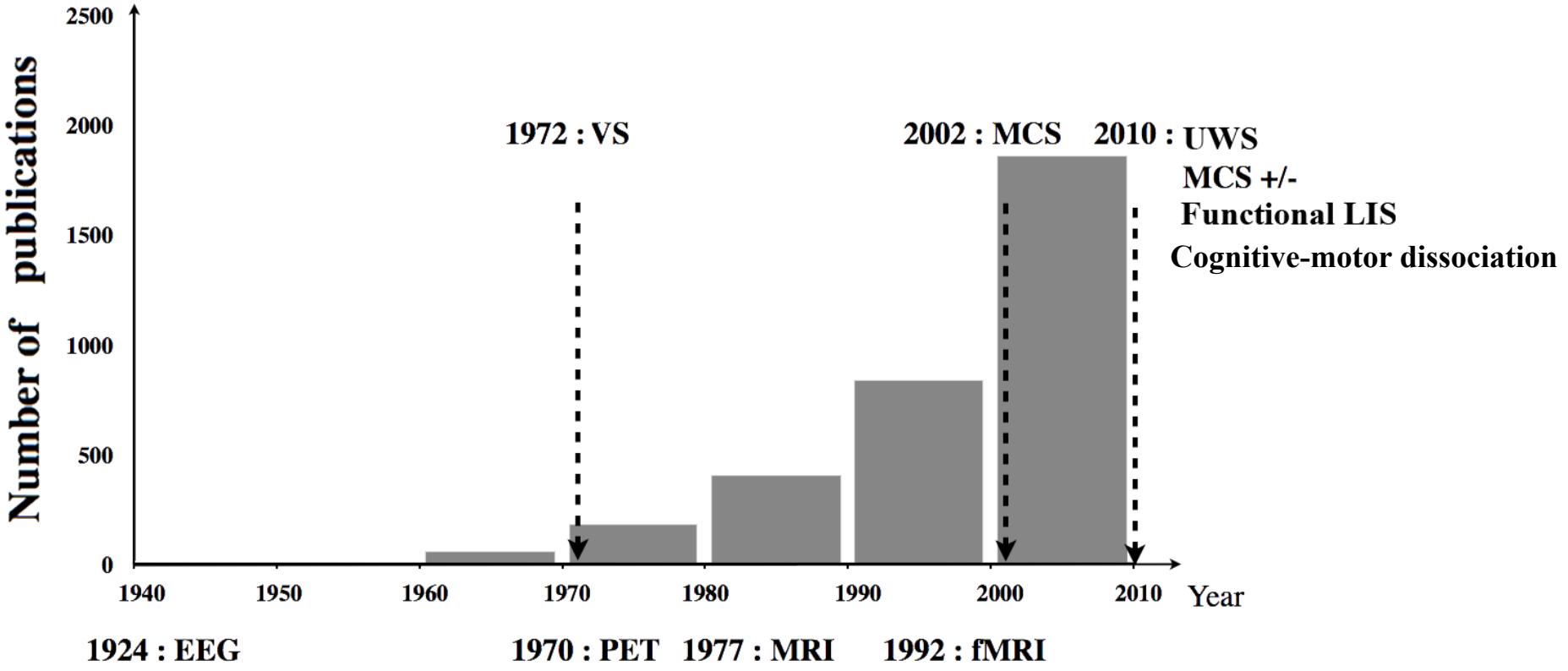


Balancing costs-benefits

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

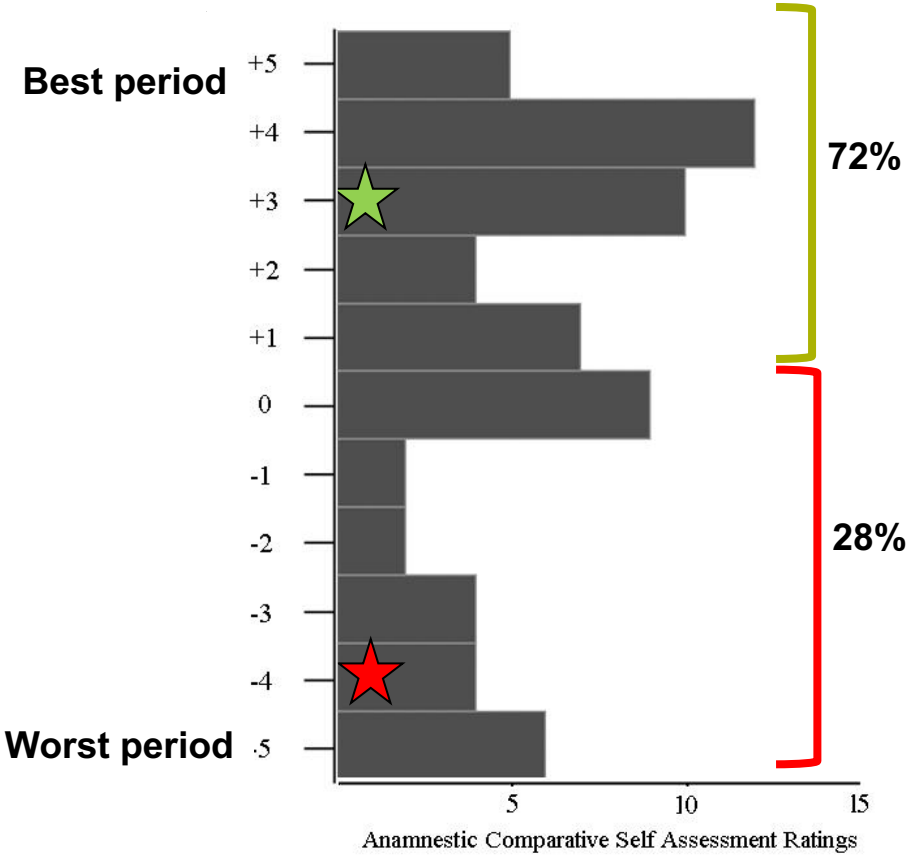
Jox, Bernat, Laureys, Racine, *Lancet Neurology* 2012

Benefit for science

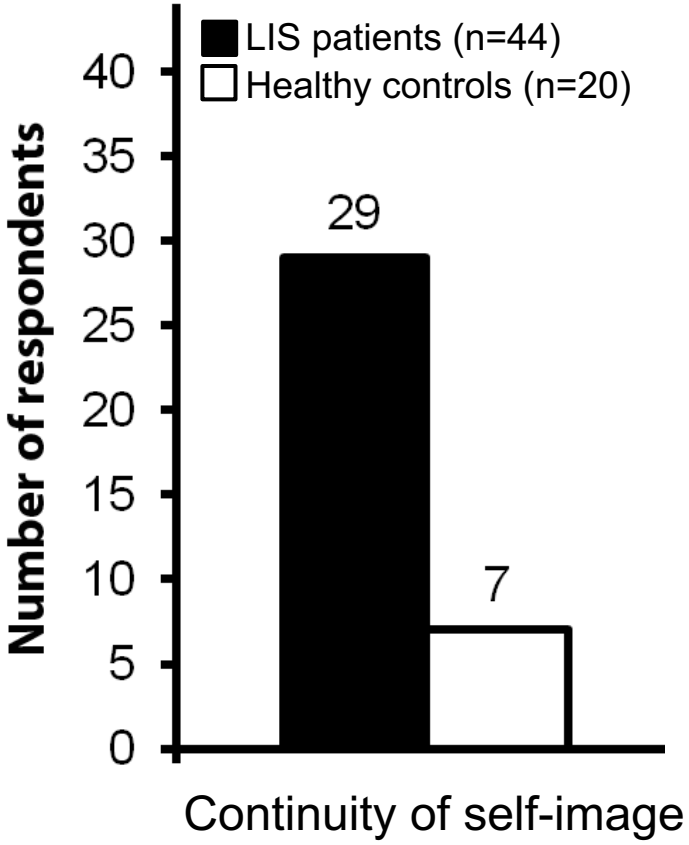


Gantner, et al, *Fut Neurol* 2013

Benefit for patients?



Bruno et al, *Br Med J Open* 2011



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

Benefit for caregivers?

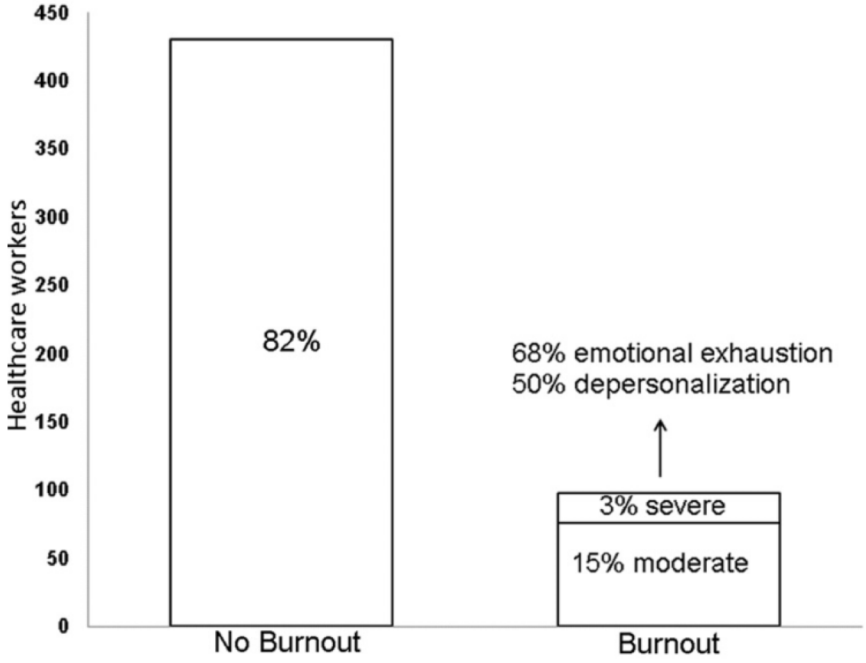


Table III. Percentage of healthcare workers presenting a burnout.

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

Benefit for families?

Conclusions

fMRI resting state connectivity

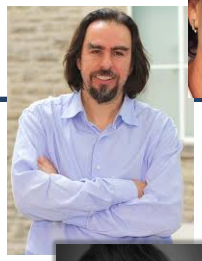
- carries information about cognitive function
- can be used in the clinical setting

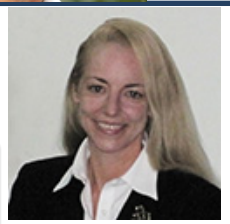
Need of a framework for applying techniques balancing:

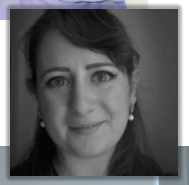
- availability
- sensitivity
- specificity

Ethical significance: what matters?

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]

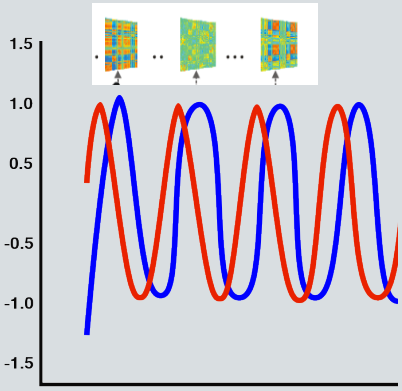
Brain parcellation

(Sphere ROIs)

ROI timeseries extraction

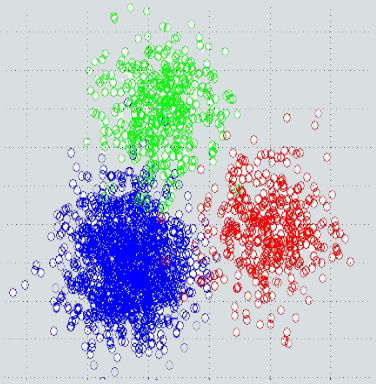
Phase analysis

(Hilbert transform)



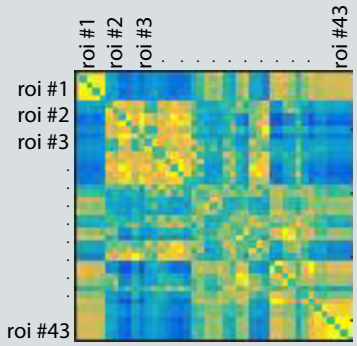
Unsupervised clustering

(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

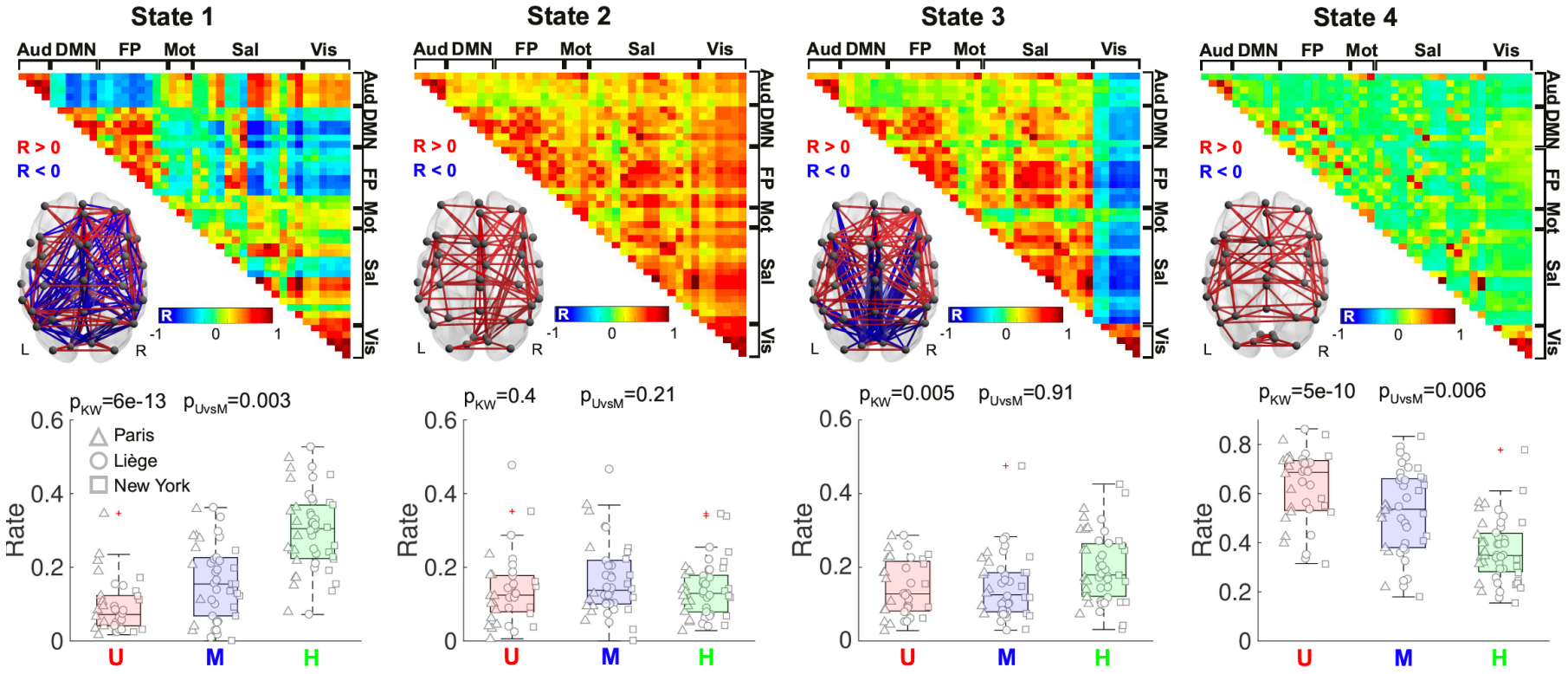
ONTARIO	
VS/UWS-	6
VS/UWS+	5

n = 11

James S. McDonnell Foundation

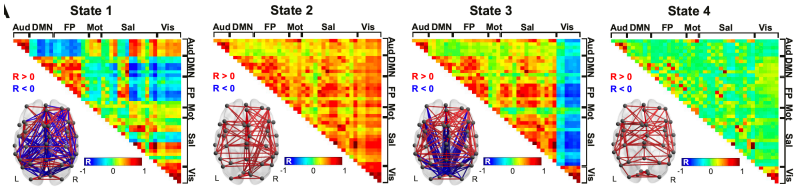
Grant Type: Collaborative Activity Award, Phase I & II (2008-2017)

Brain States (all sites)

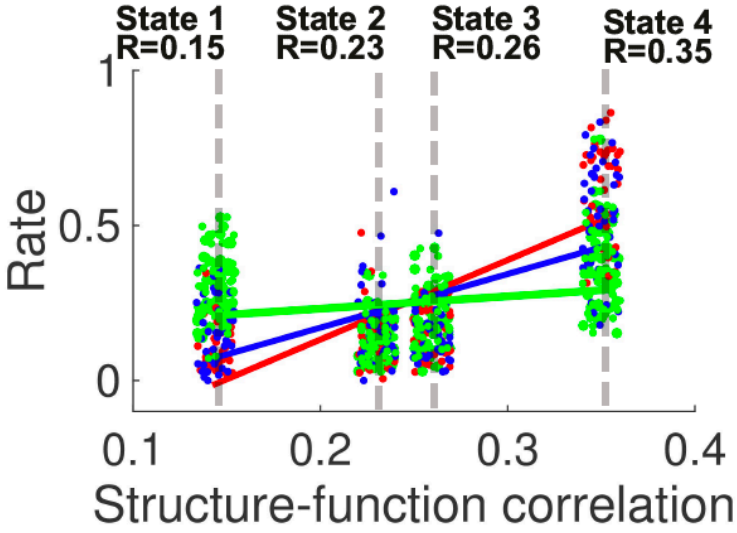


Demertzi, Tagliazucchi, … , Laureys, Schiff, Owen, Naccache, Sitt, in prep

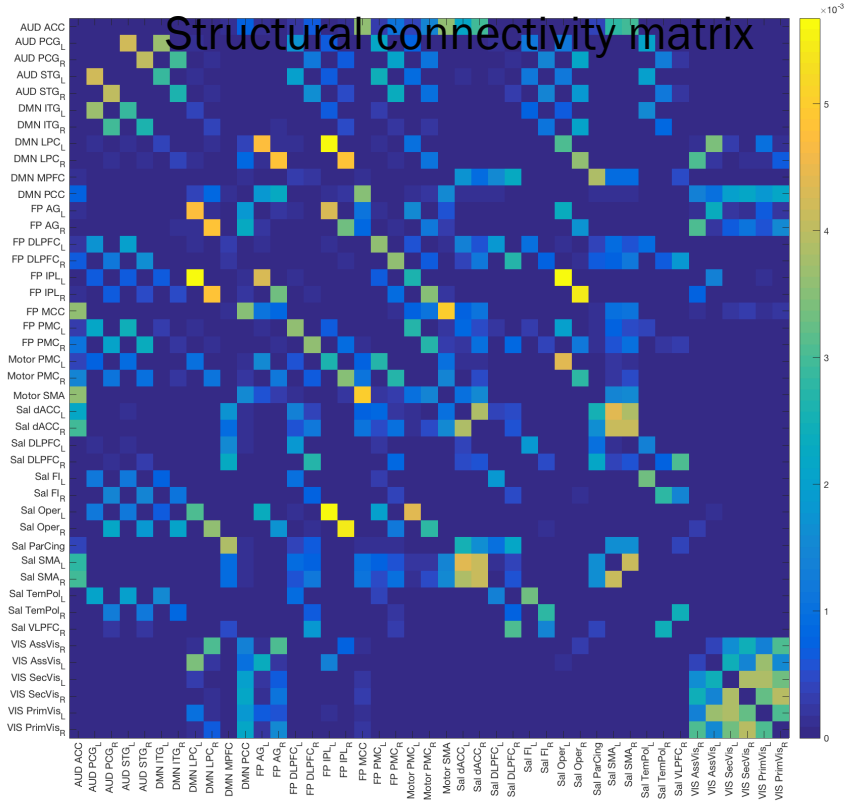
States sorted by similarity to anatomy



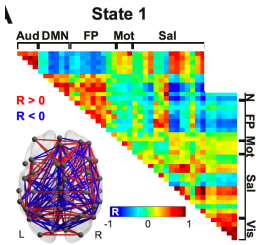
p_{KW}=2e-10 p_{UvsM}=0.01 ρ=-0.6

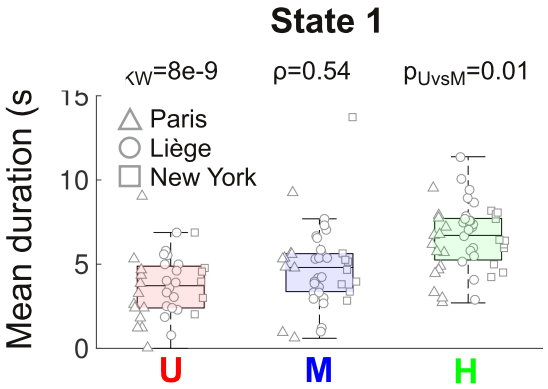


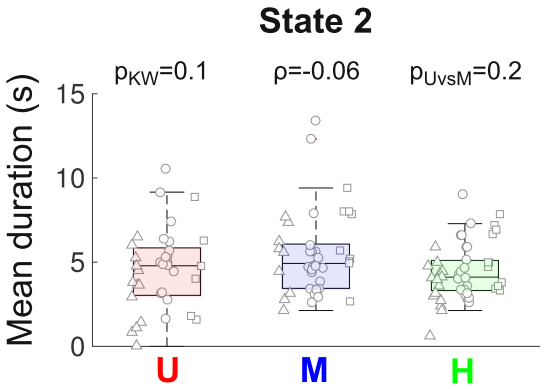
UWS
MCS
Healthy

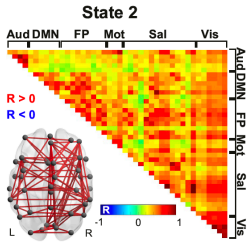


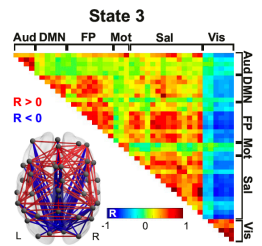
How long in each state?

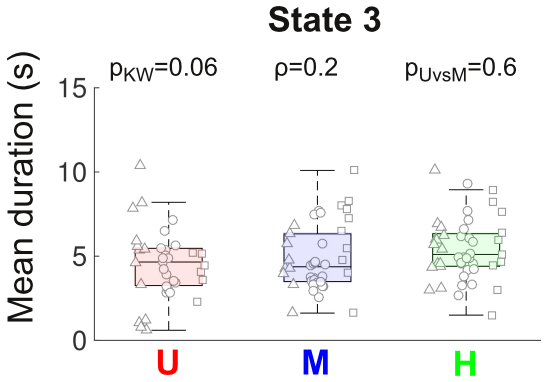


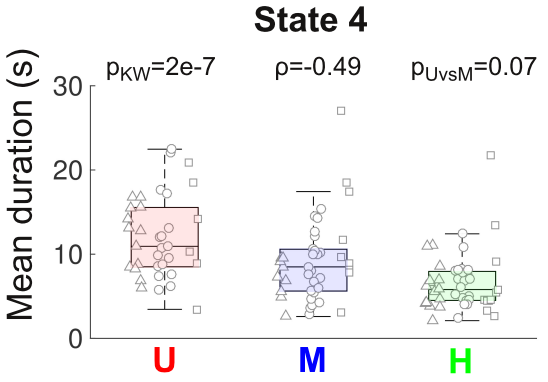


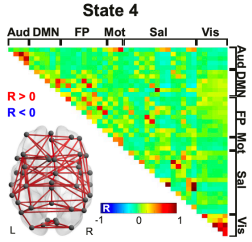






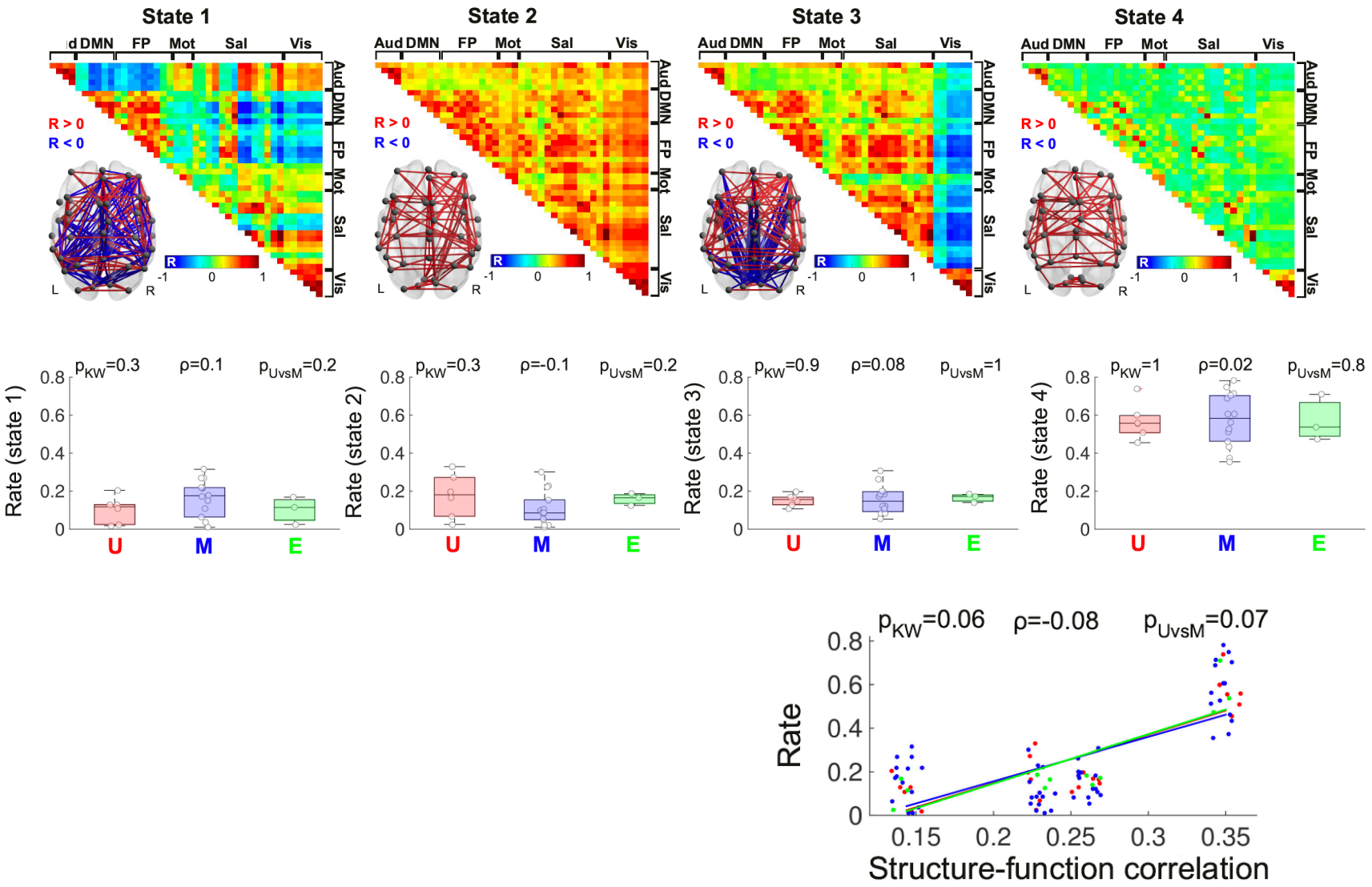






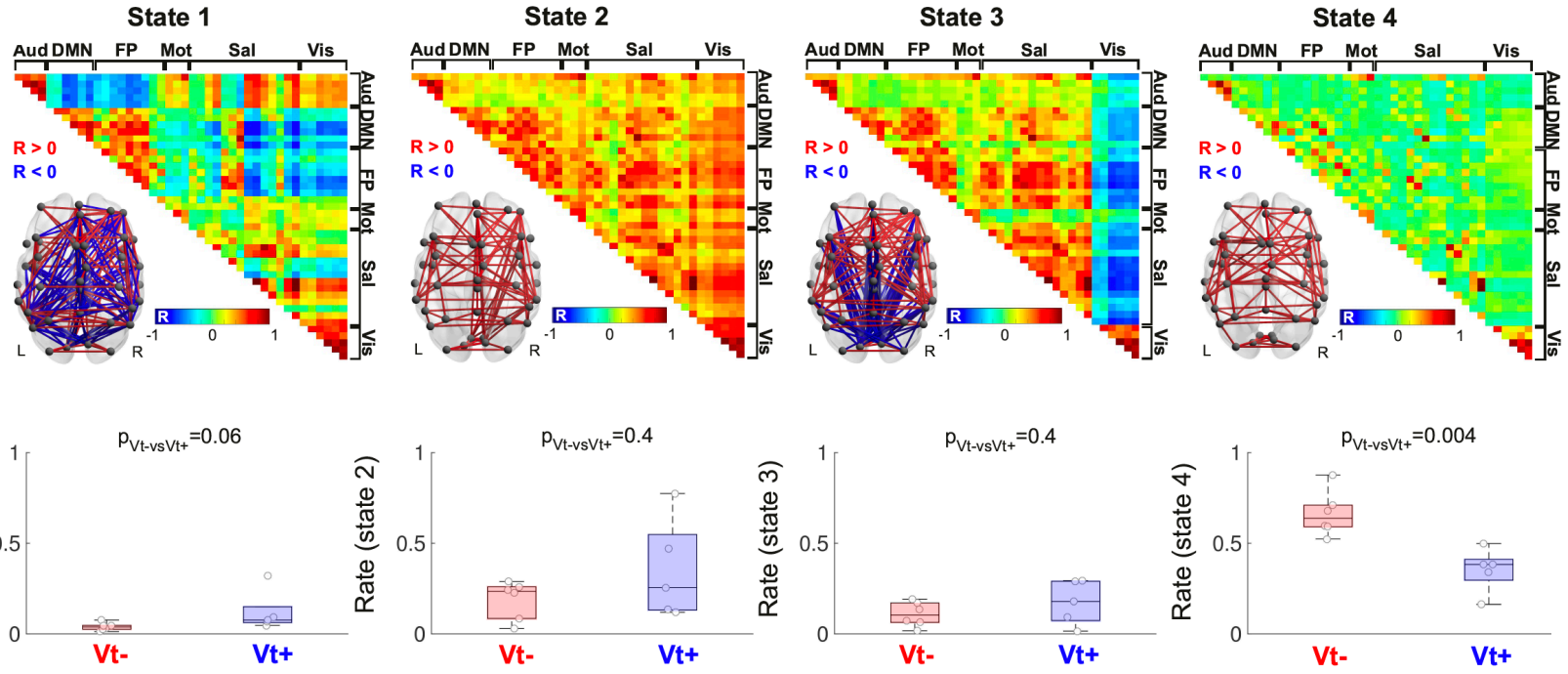
We measure consciousness?

Homogenous loss of consciousness after pharmacological manipulation



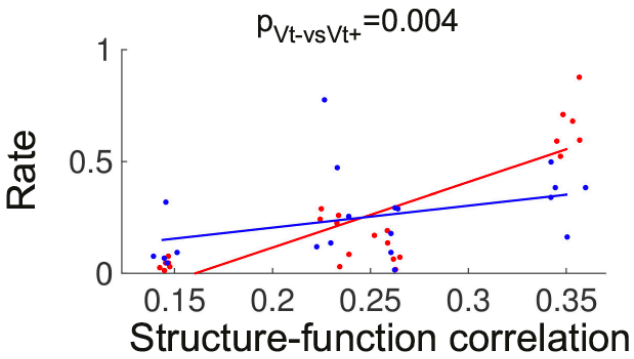
We measure consciousness?

Capturing covert awareness in cortex-motor dissociation



n Vt- = 6

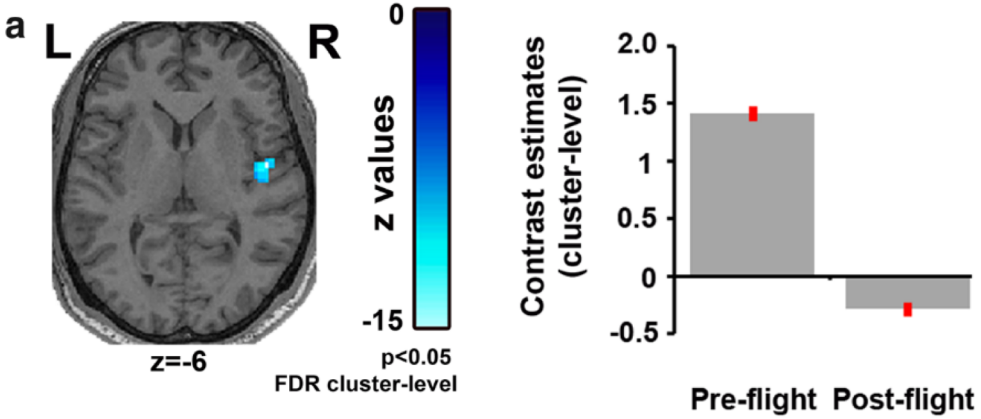
n Vt+= 5



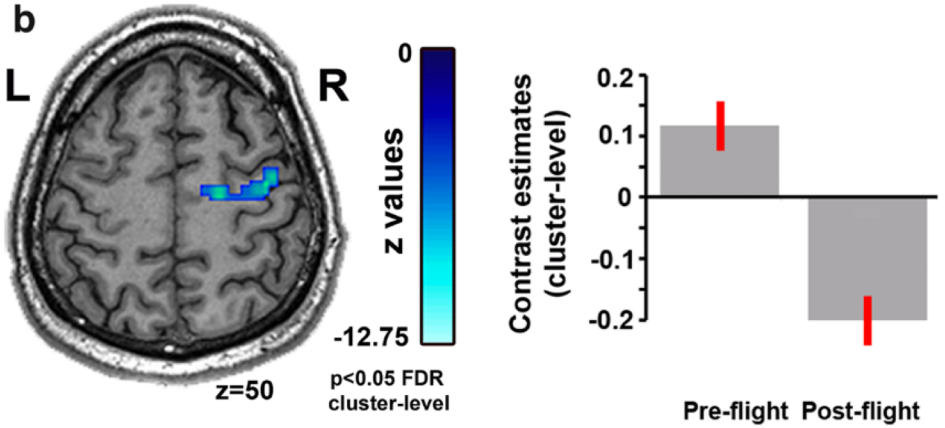
44-year-old male cosmonaut
First long-duration mission (169 days) to the ISS in 2014
fMRI protocol pre-flight: 30 days, post-flight: 9 days after Earth re-entry

European Space Agency

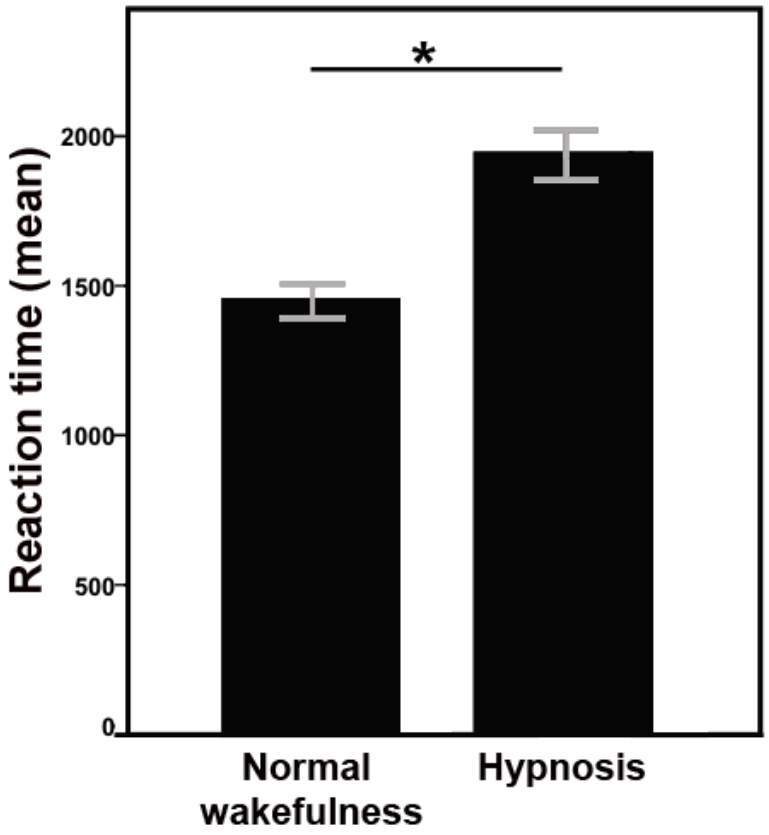
Hypothesis-free

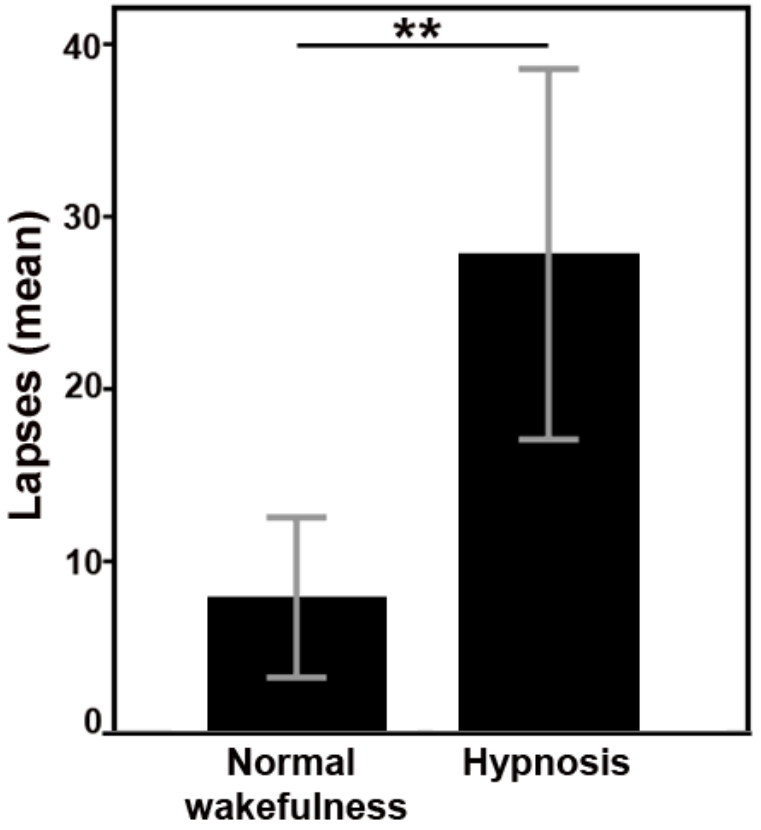


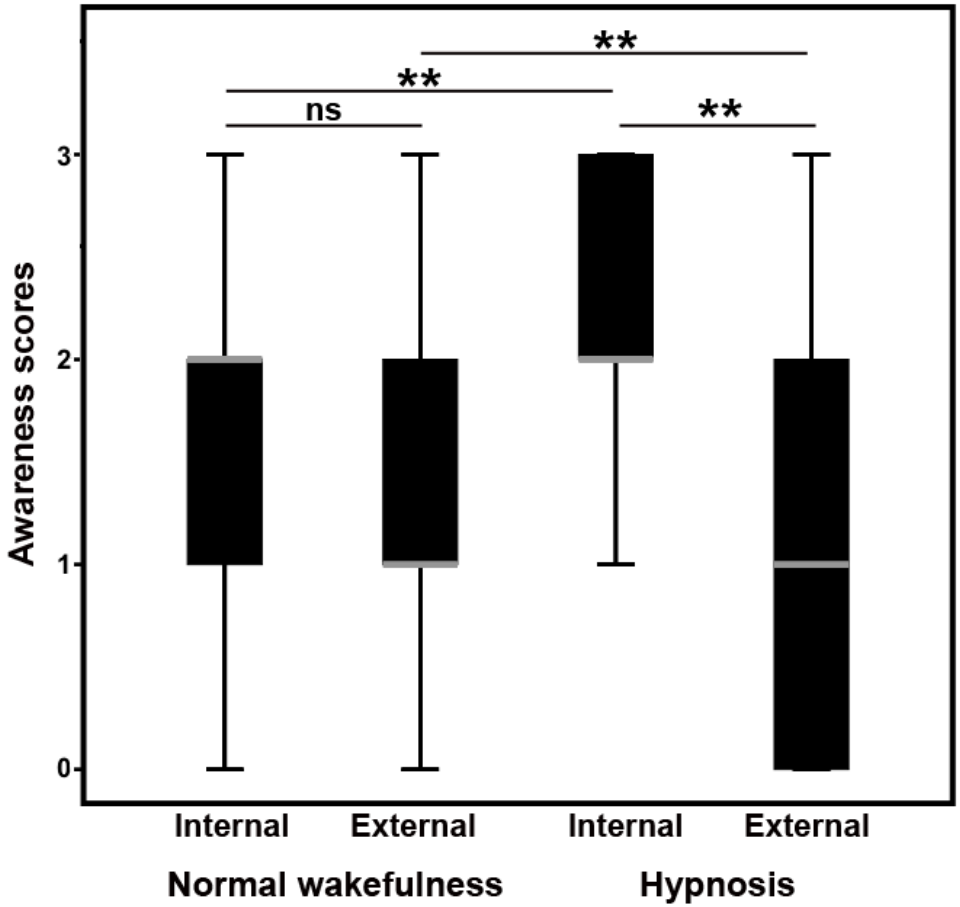
Hypothesis-driven



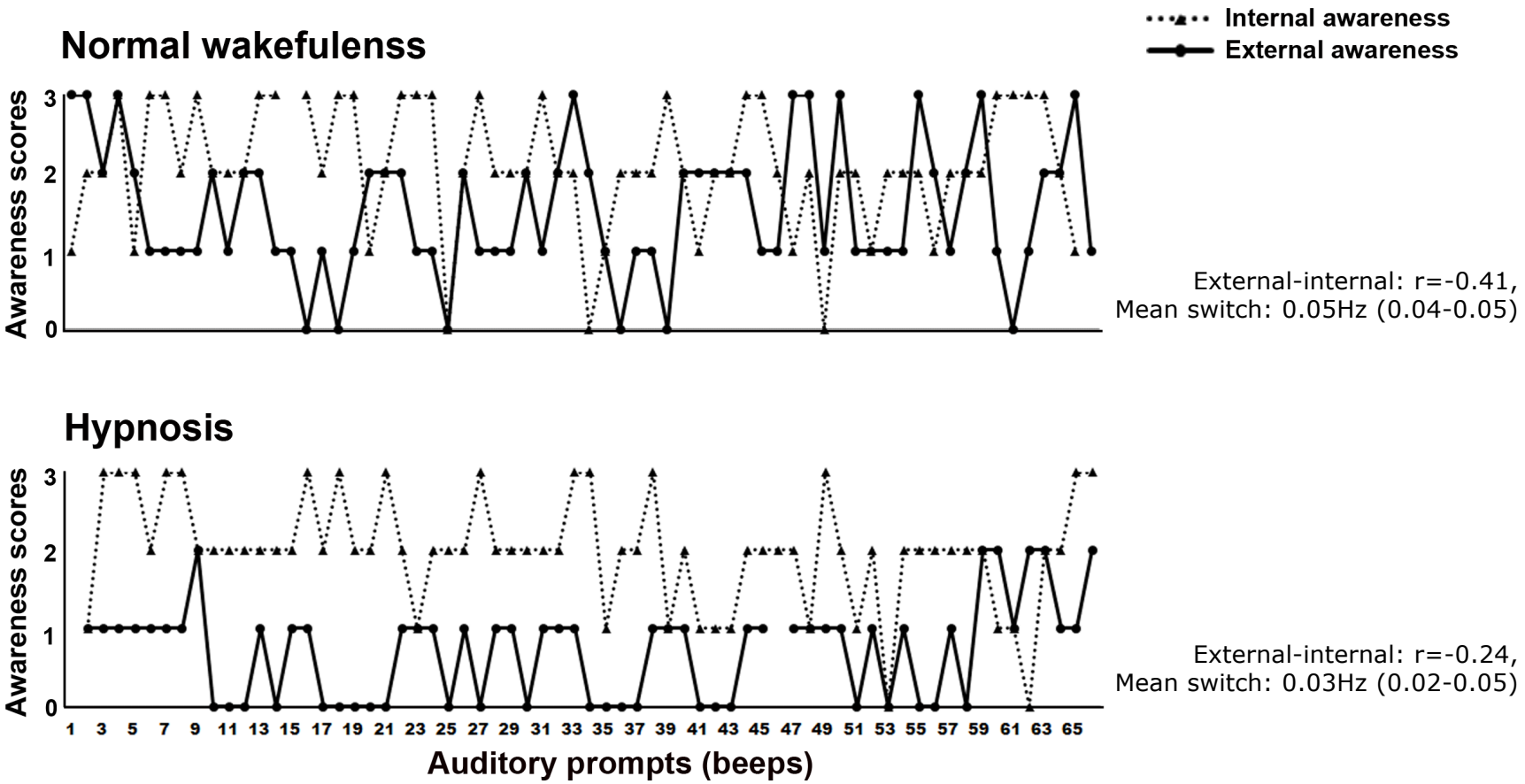
Demertzi & Van Ombergen et al, Brain Structure and Function 2015


*
Reaction time (mean)
2000
1500
1000
500
0
Normal wakefulness
Hypnosis


**
Lapses (mean)
40
30
20
10
0
Normal wakefulness
Hypnosis


**
**
ns
**
Awareness scores
3
2
1
0
Internal
External
Internal
External
Normal wakefulness
Hypnosis

Awareness is modified in hypnosis

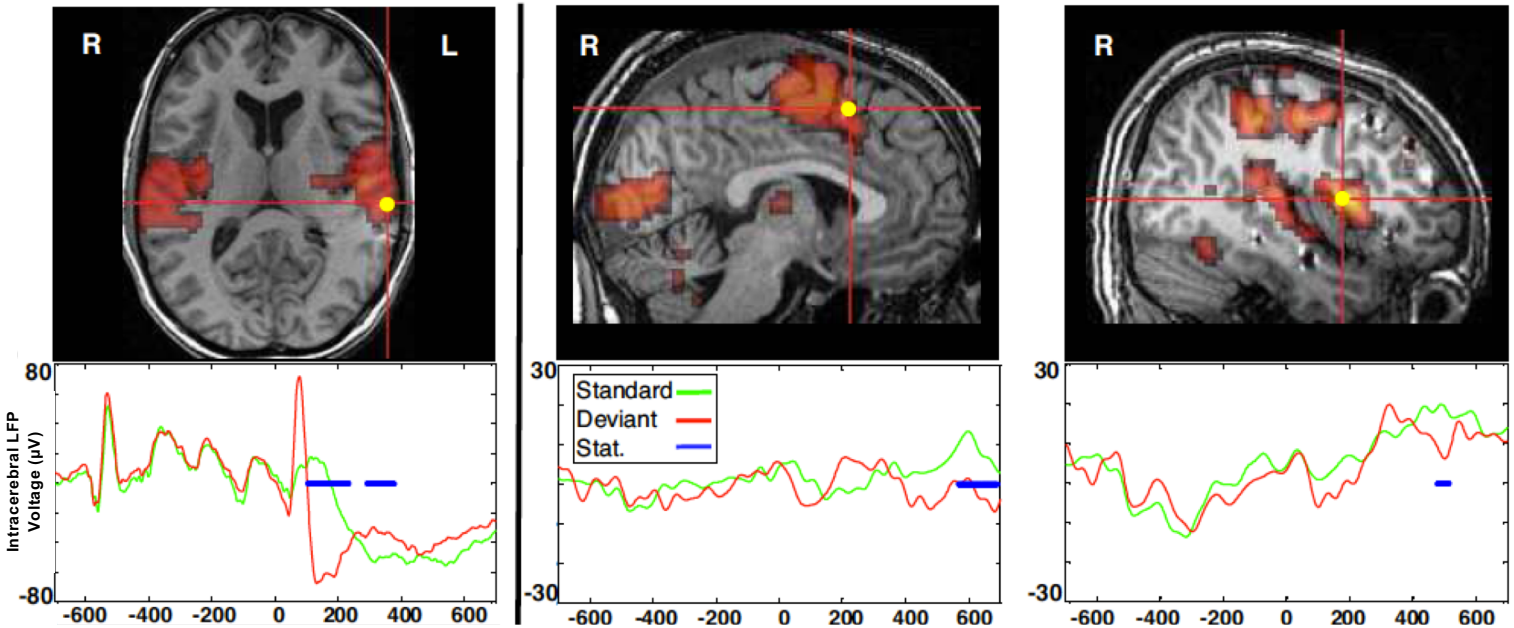


Crossmodal interaction in consciousness

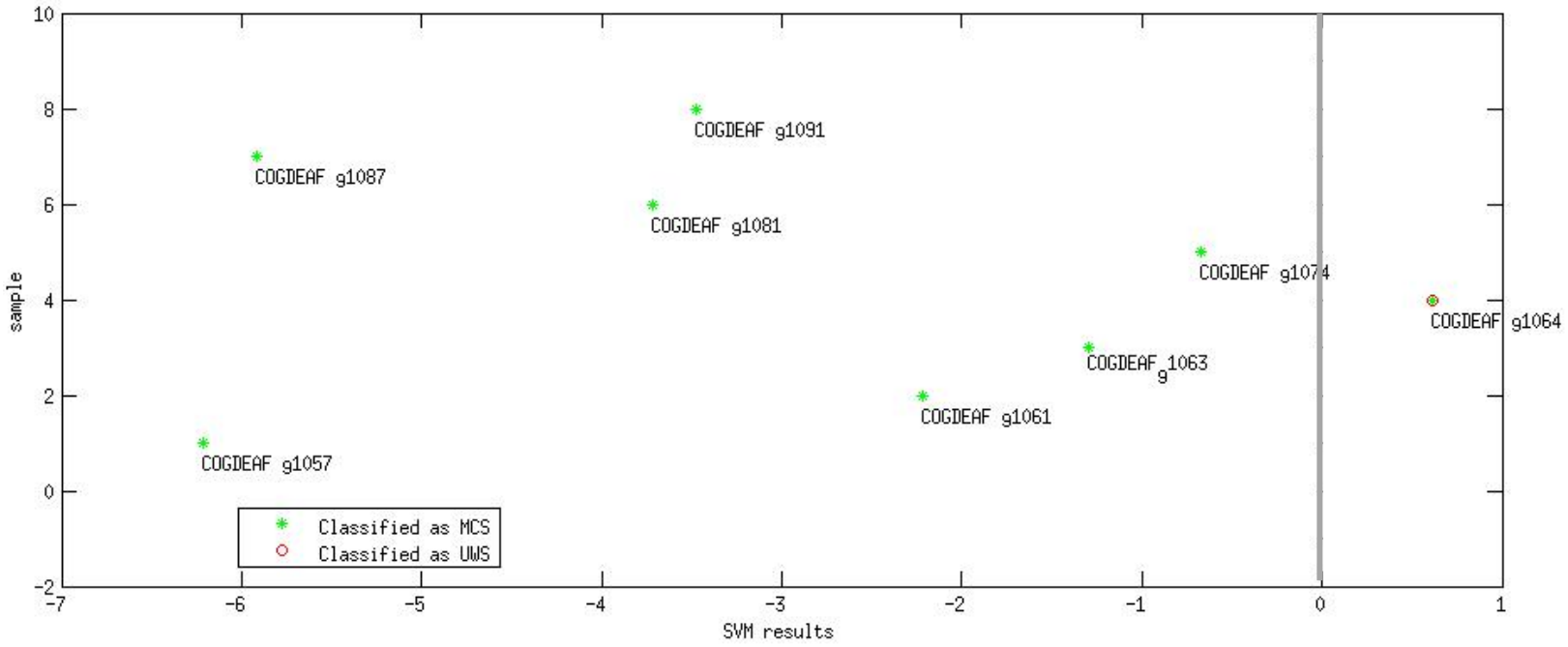
The local- global paradigm

Local effect

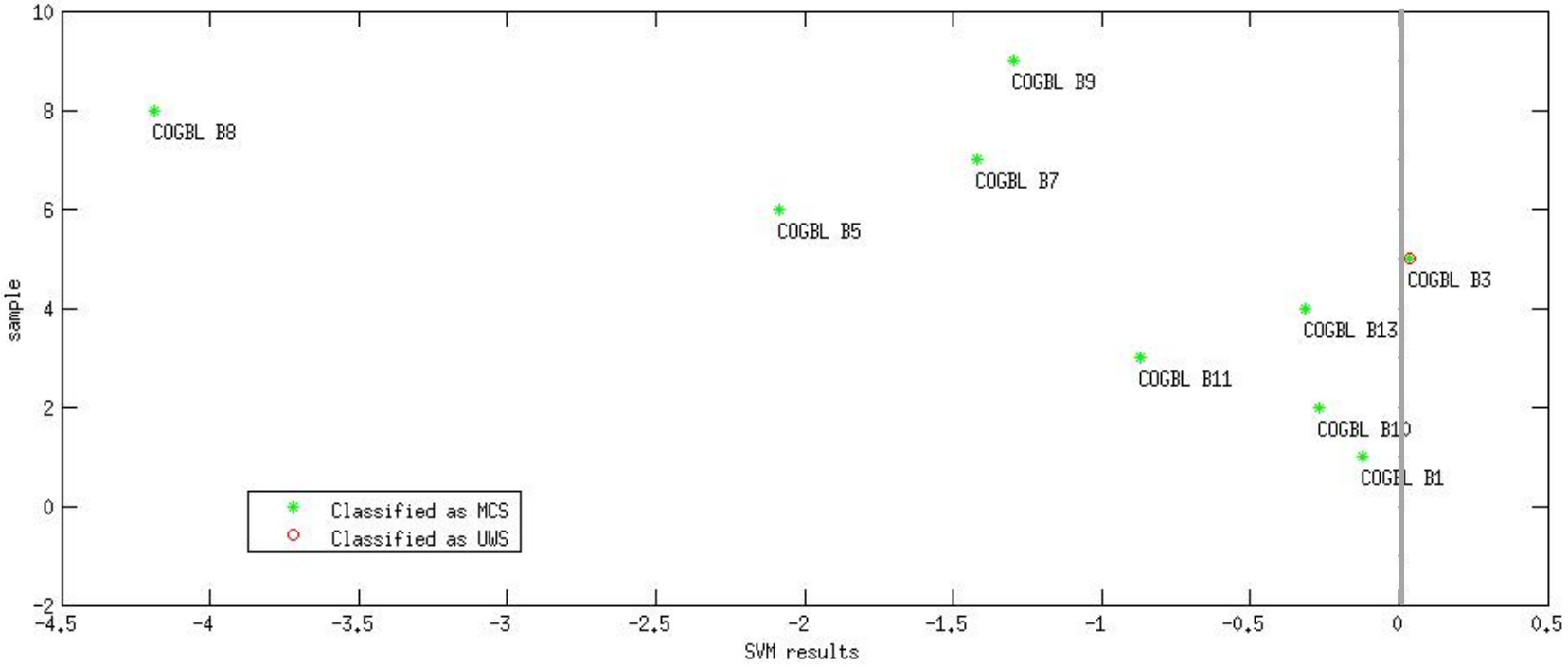
Global effect



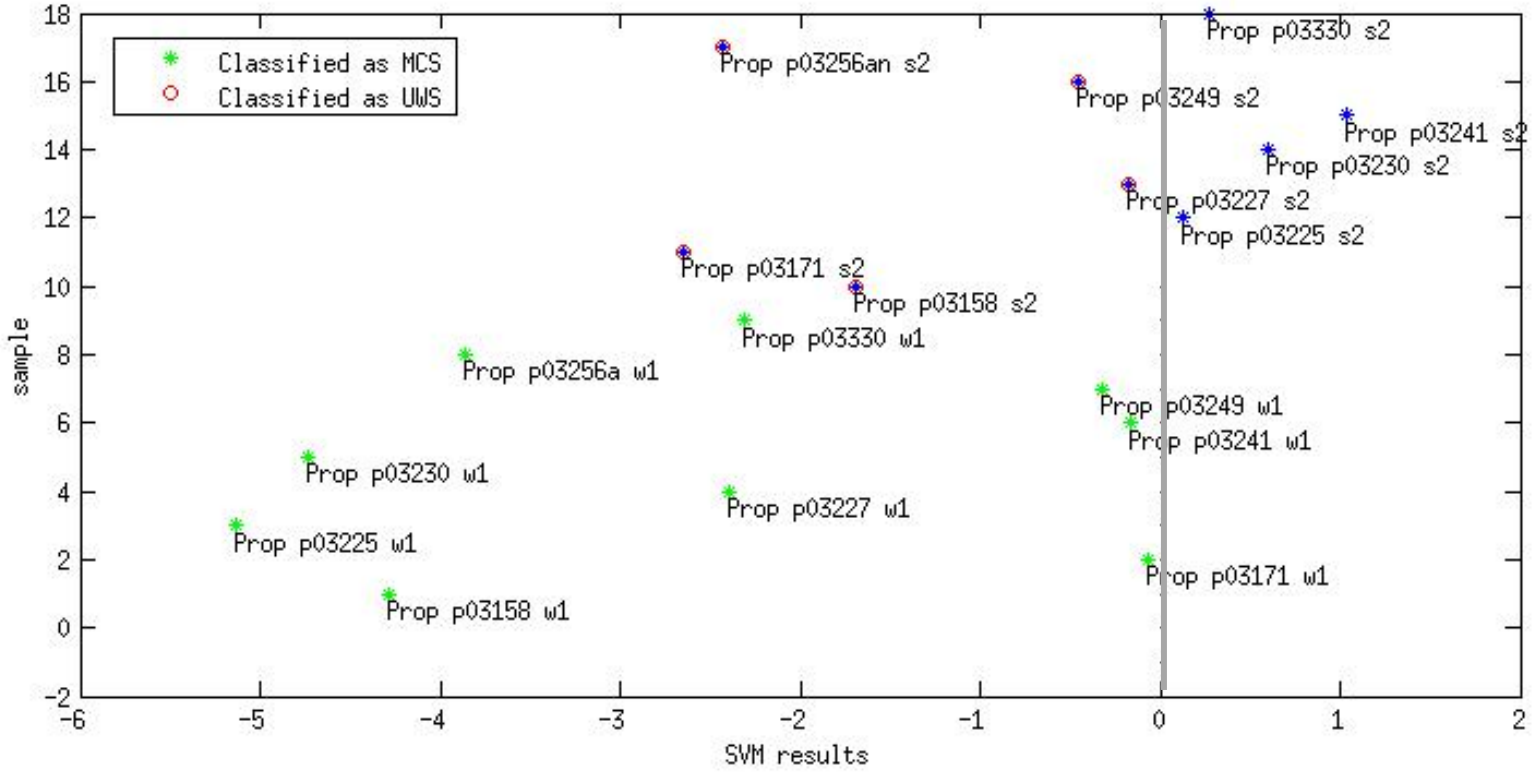
Validation in congenitally deaf



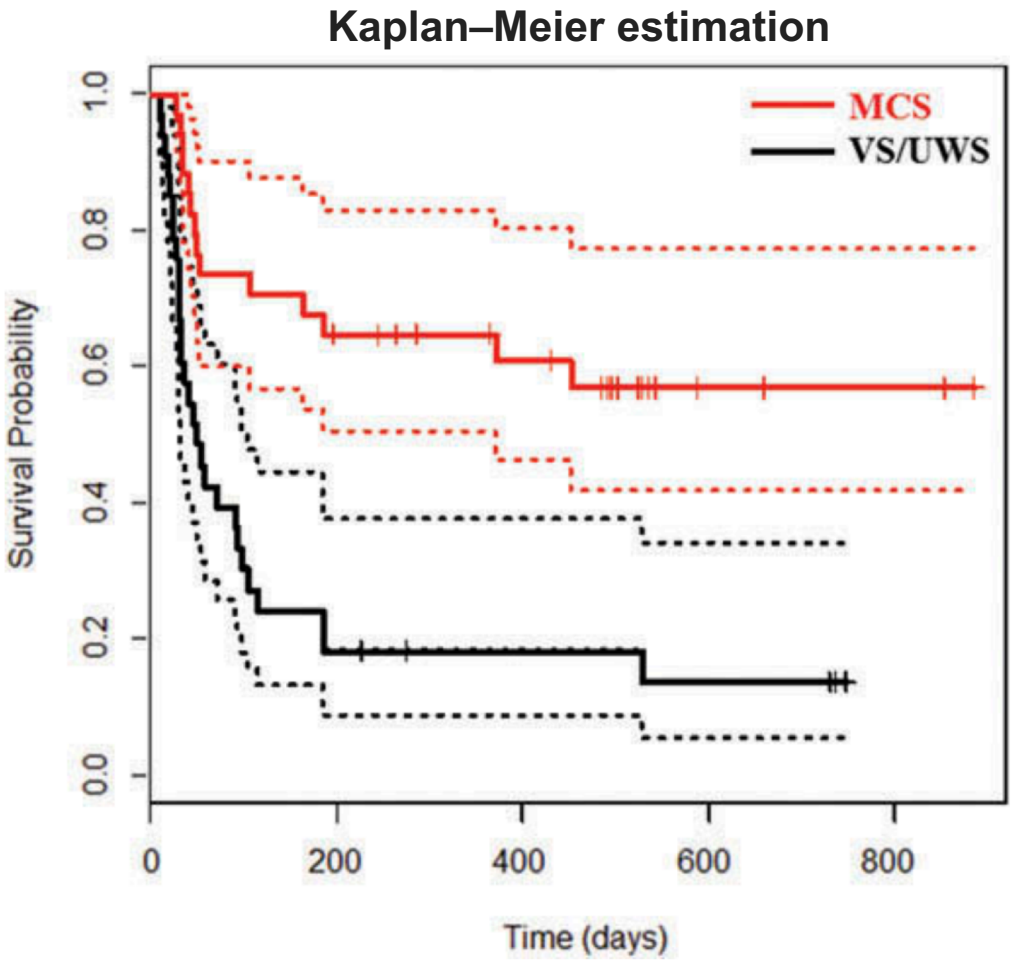
Validation in congenitally blind



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