



Tracking consciousness in minimal behavioural responsiveness

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GIGA Research Institute & Neurology Department
University & University Hospital of Liège
Belgium



Patients cannot express themselves



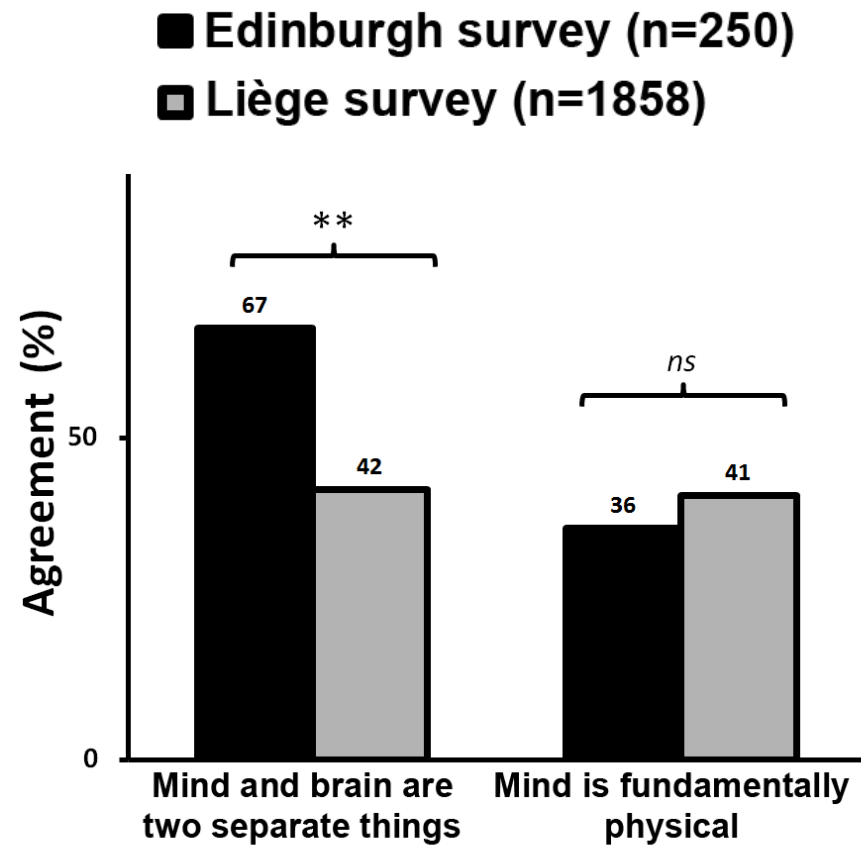
Hable con ella 2002, Pedro Almodóvar

What is Consciousness?

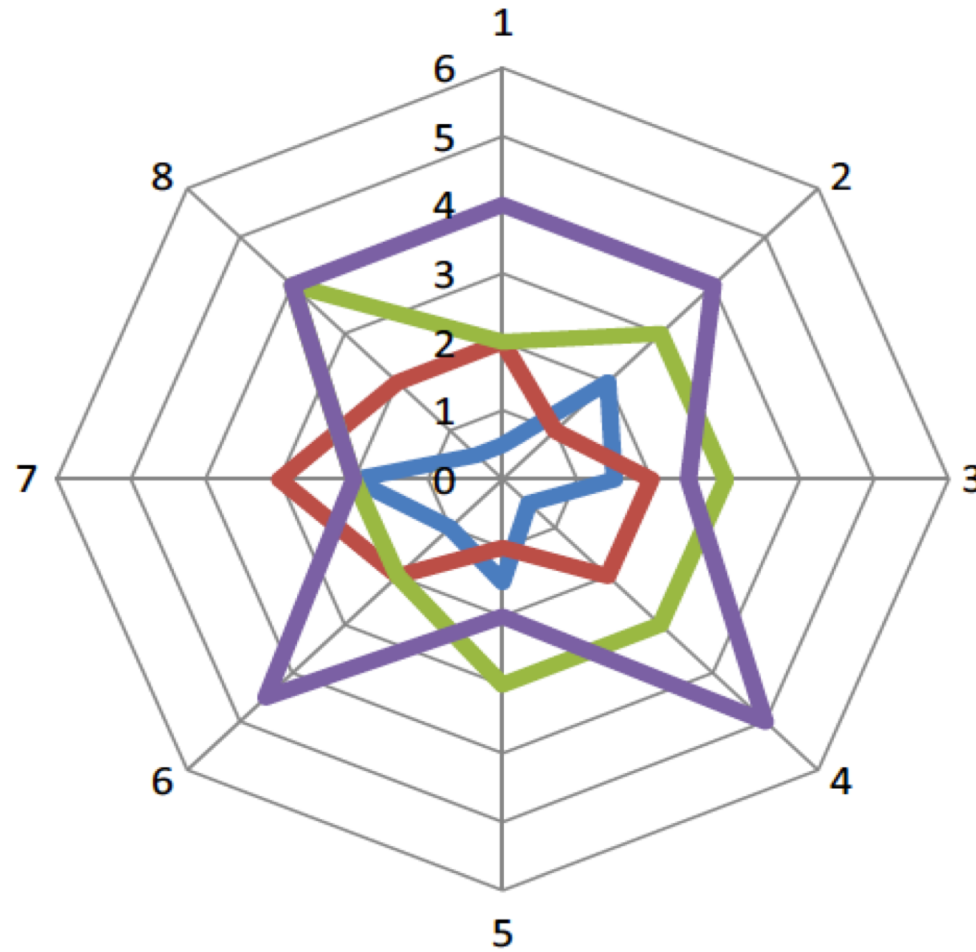


Materialism

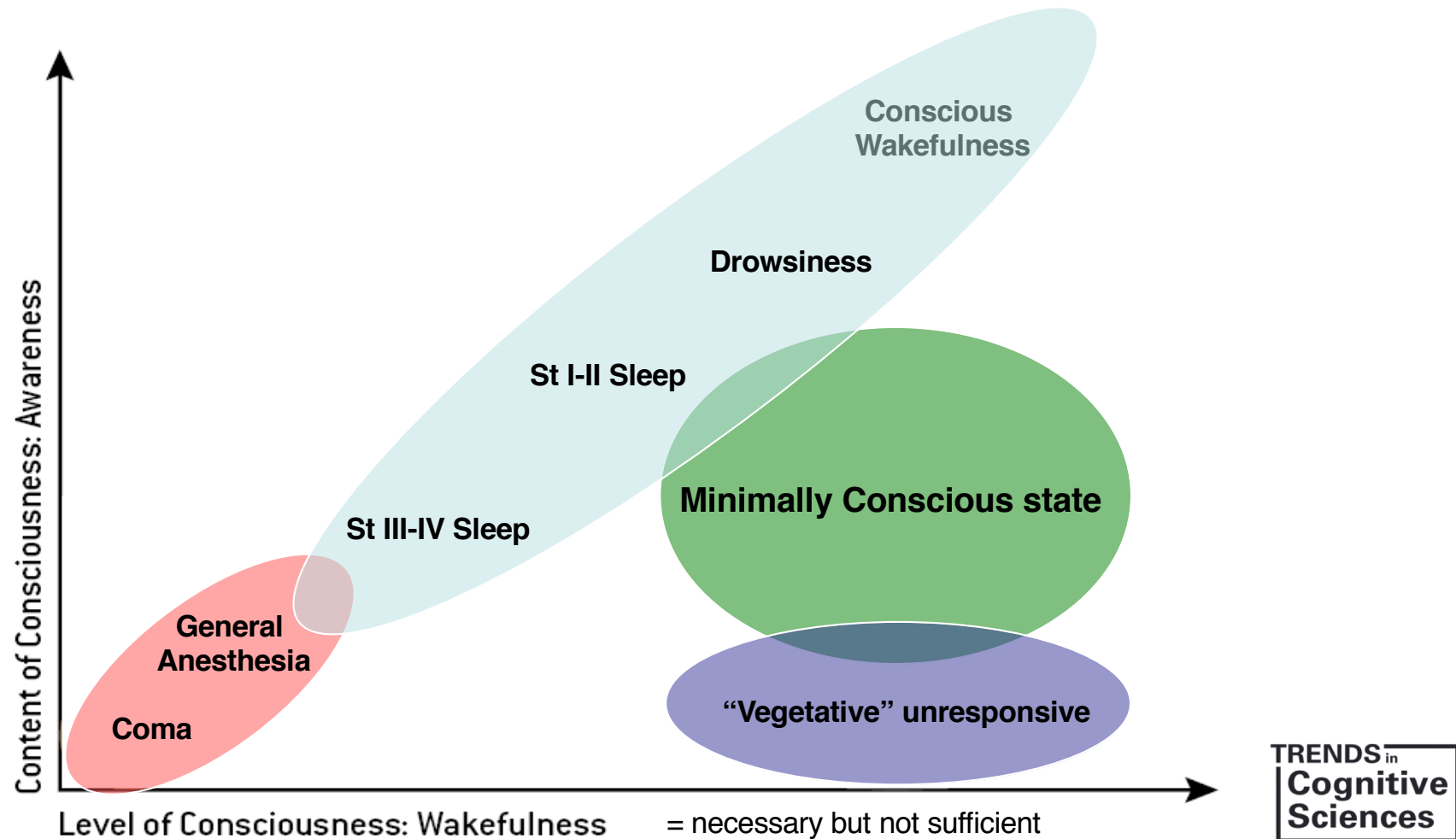
Functionalism



Defining Consciousness



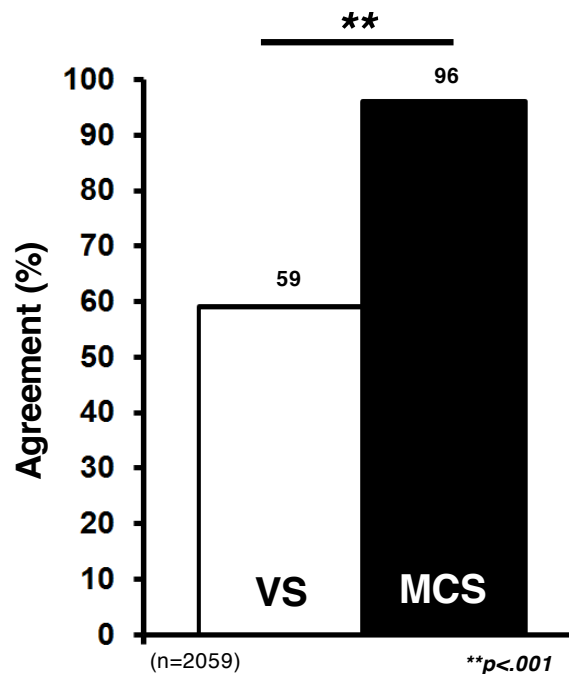
A clinical definition



Do they feel pain?



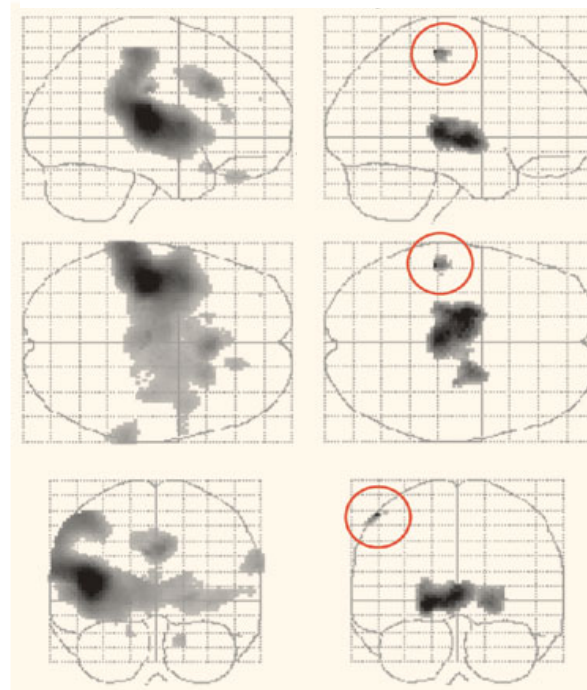
Do you think patients in a ...
can feel pain?



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

Unresponsive wakefulness syndrome

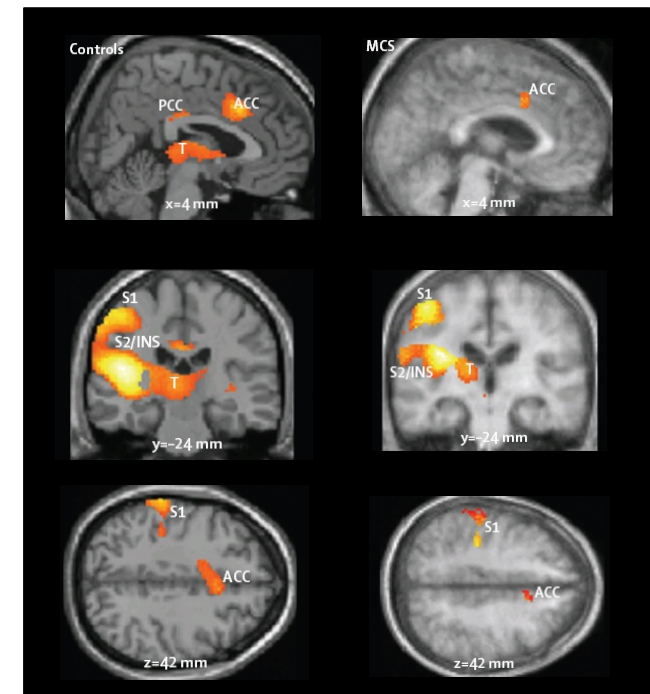
Healthy controls UWS patients



Laureys et al., *Neuroimage* 2002

Minimally conscious state

Healthy controls MCS patients



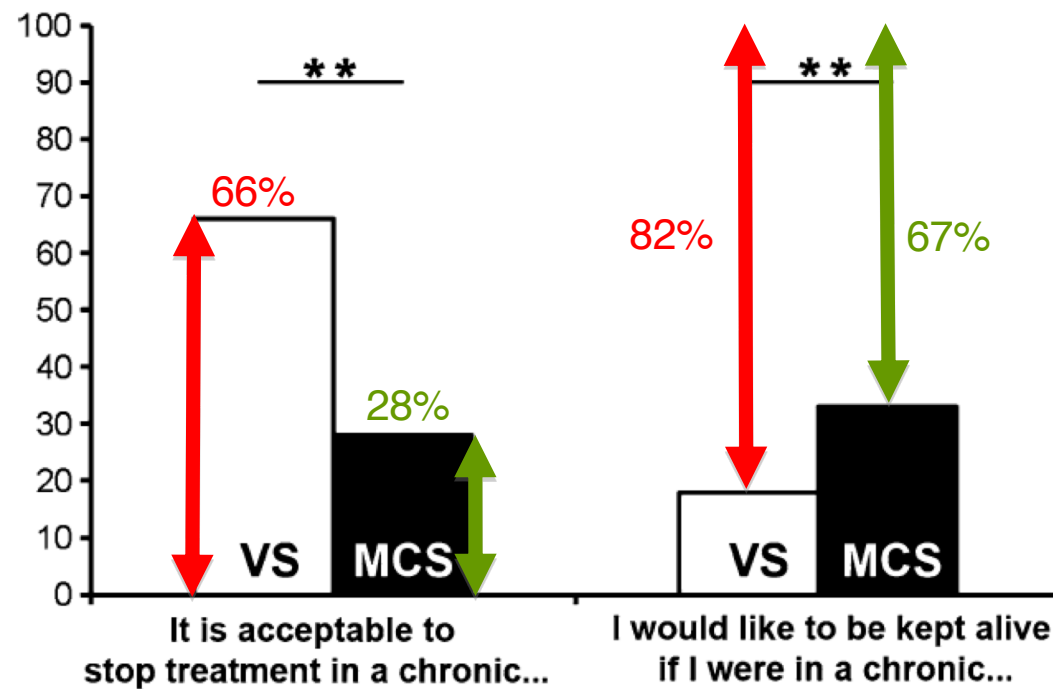
Boly et al, *Lancet Neurol* 2008

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

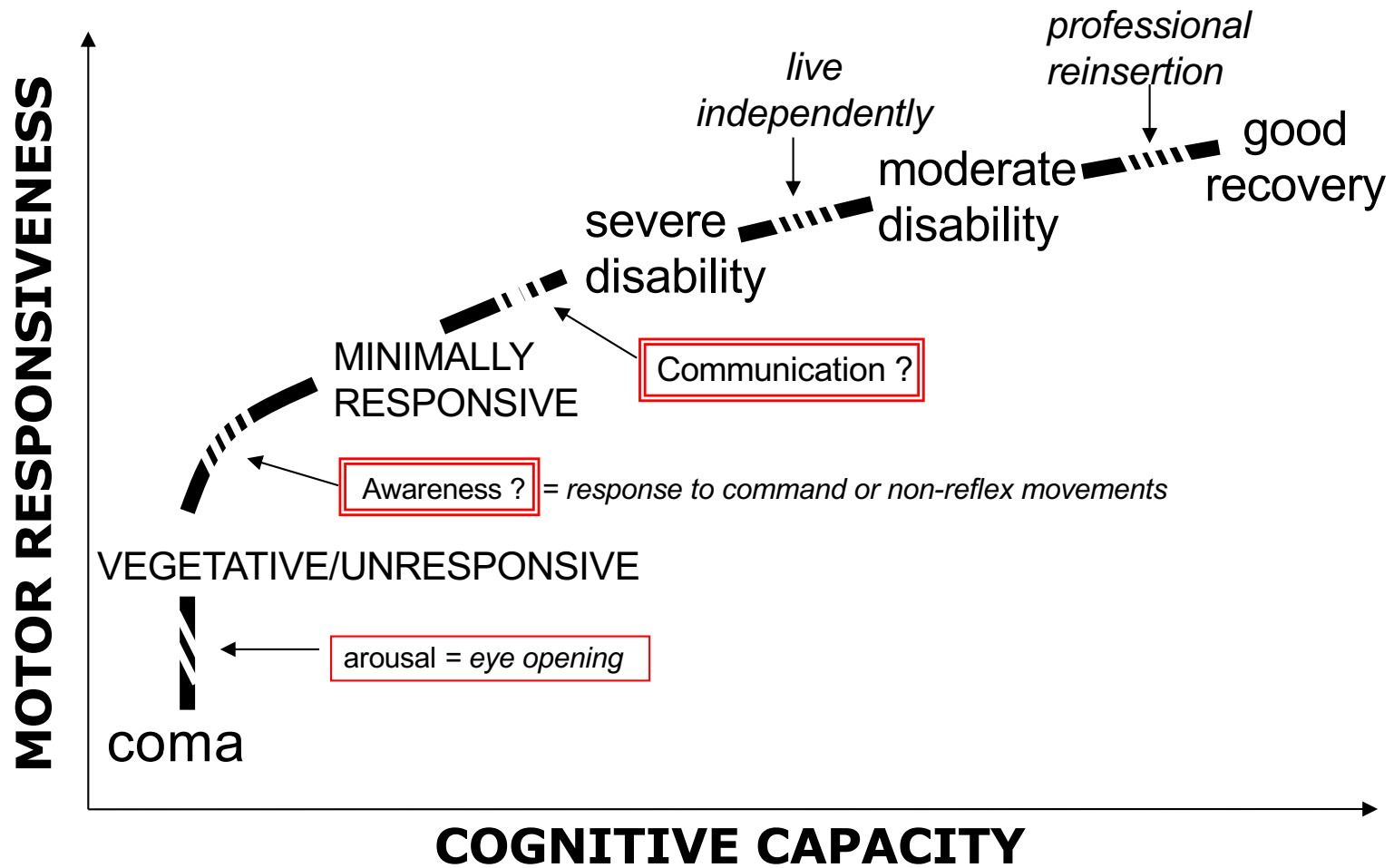


Behaviour



Terry Schiavo °1963,
vegetative 1990, † 2005 USA

Behavioural signs of C



Gold standard?



Standardized assessment

n=103 post-comatose patients

45 Clinical diagnosis of VS
18 Coma Recovery Scale MCS

↳ 40% misdiagnosed

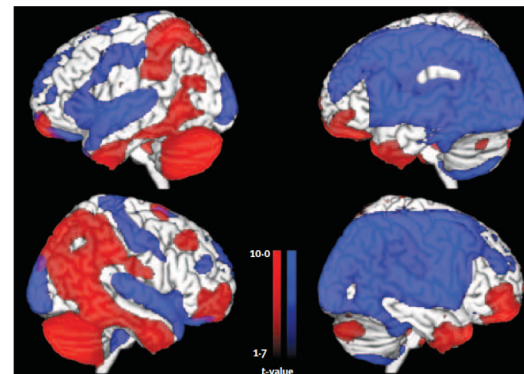
Schnakers et al, *Ann Neurol* 2006; *BMC Neurol* 2009

PET Neuroimaging

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

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

Table 2: Diagnostic results by modality

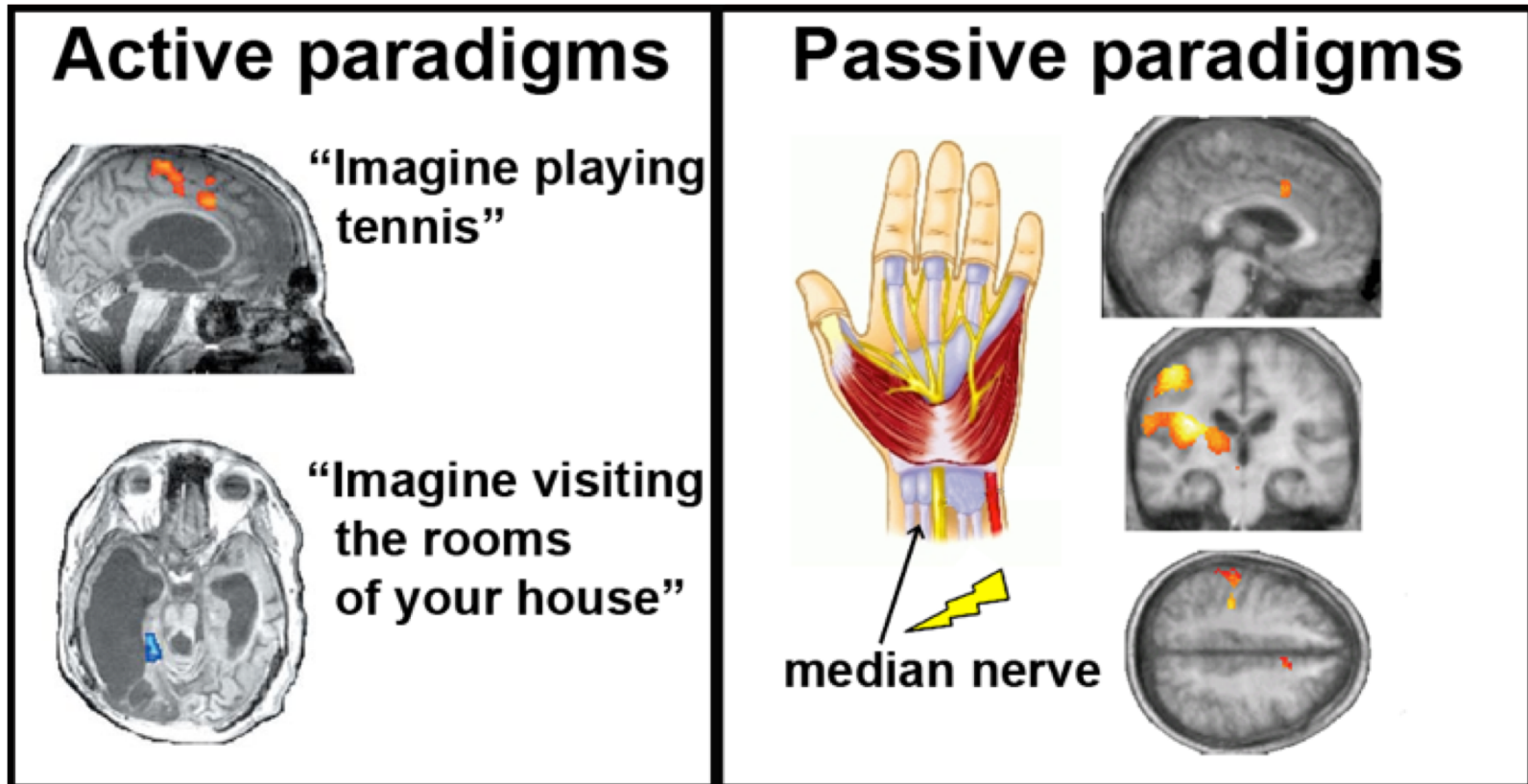


Stender & Gosseries et al, *Lancet* 2014

Neuroimaging paradigms

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

Boly et al, Lancet Neurol 2008



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

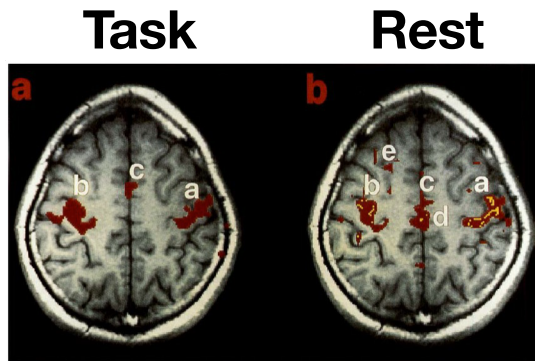


- The human brain is approximately 2% of the weight of the body
- 80% of this energy consumption is used to support neuronal signaling
- Stimulus and performance-evoked changes in brain energy consumption <5%

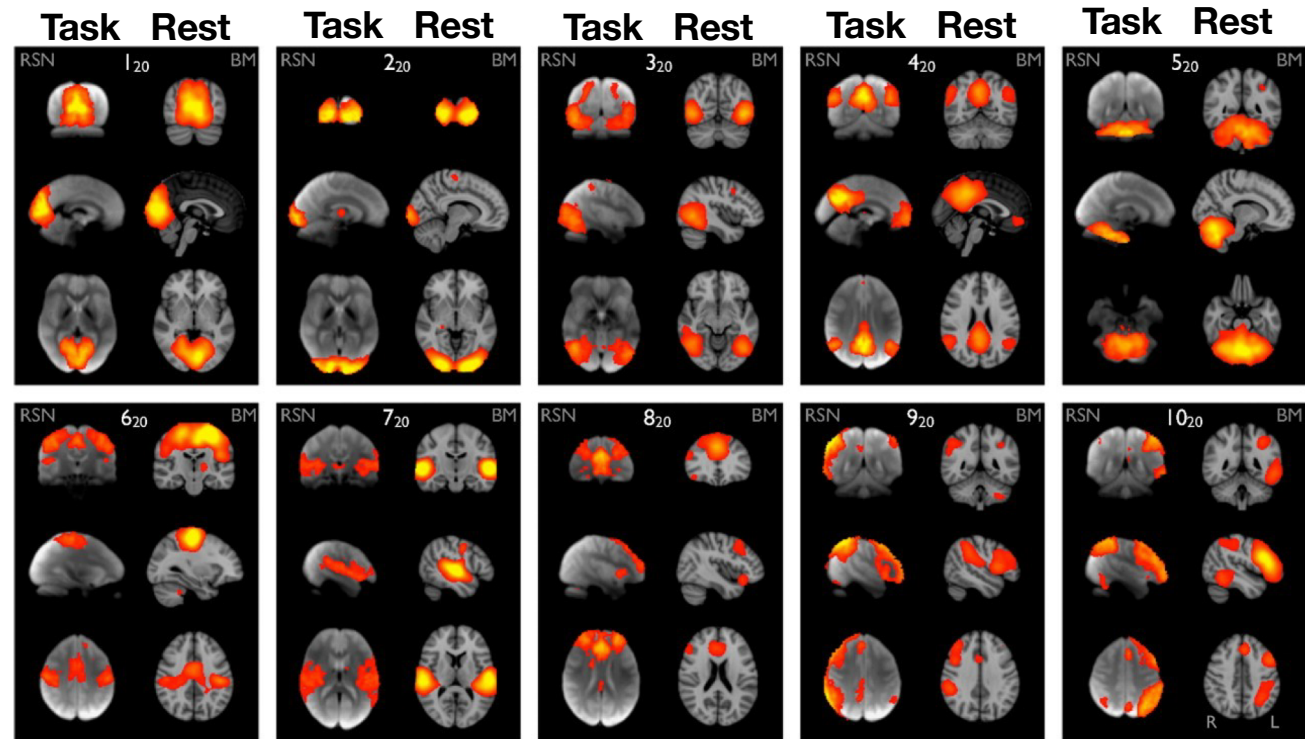


While conscious awareness is energetically inexpensive, it is dependent upon a very complex, dynamically organized, non-conscious state of the brain that is achieved at great expense

Intrinsic functional organization

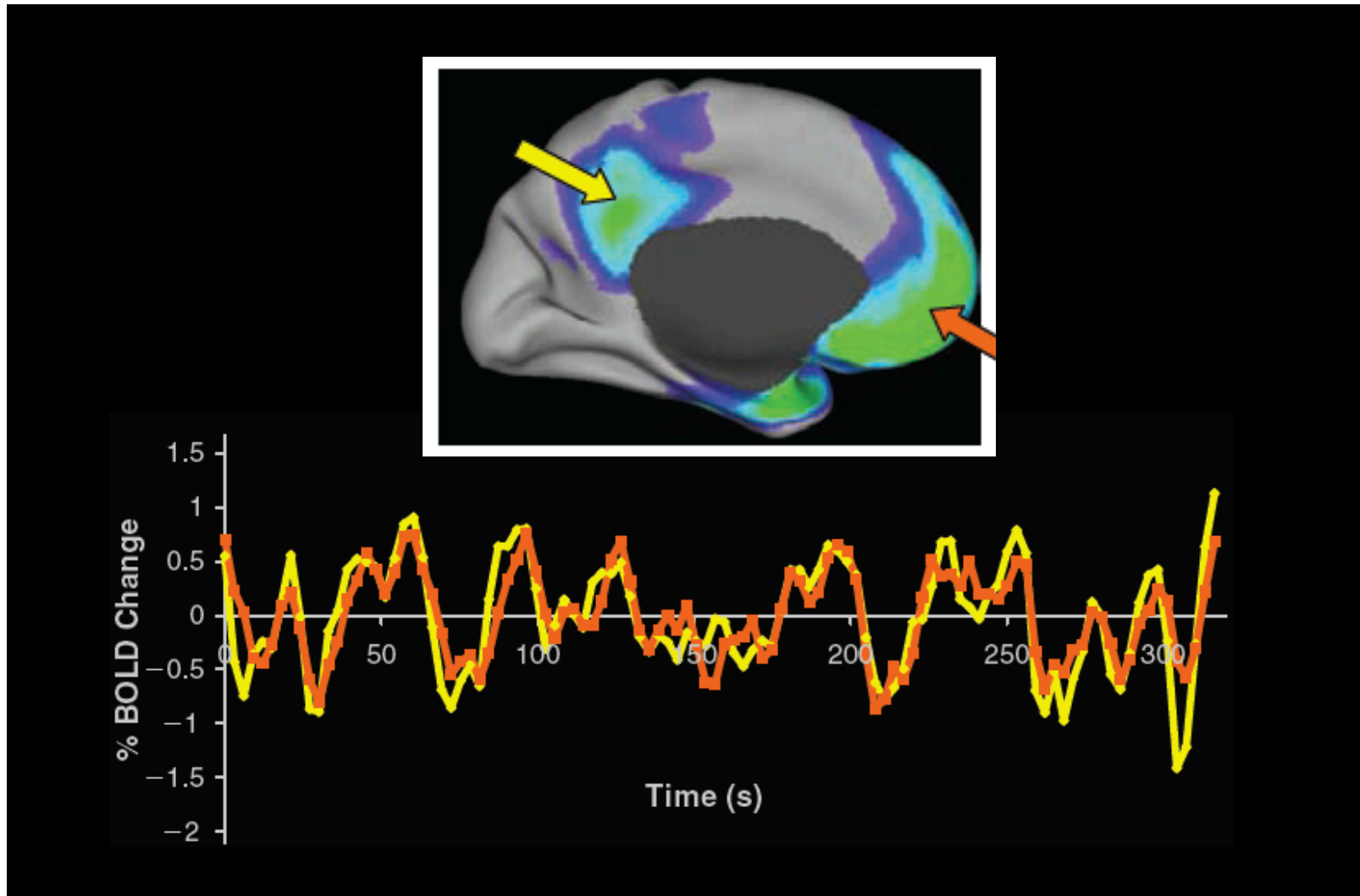


Biswal et al., *Magn. Reson. Med.* 1995



Smith et al, *PNAS* 2009

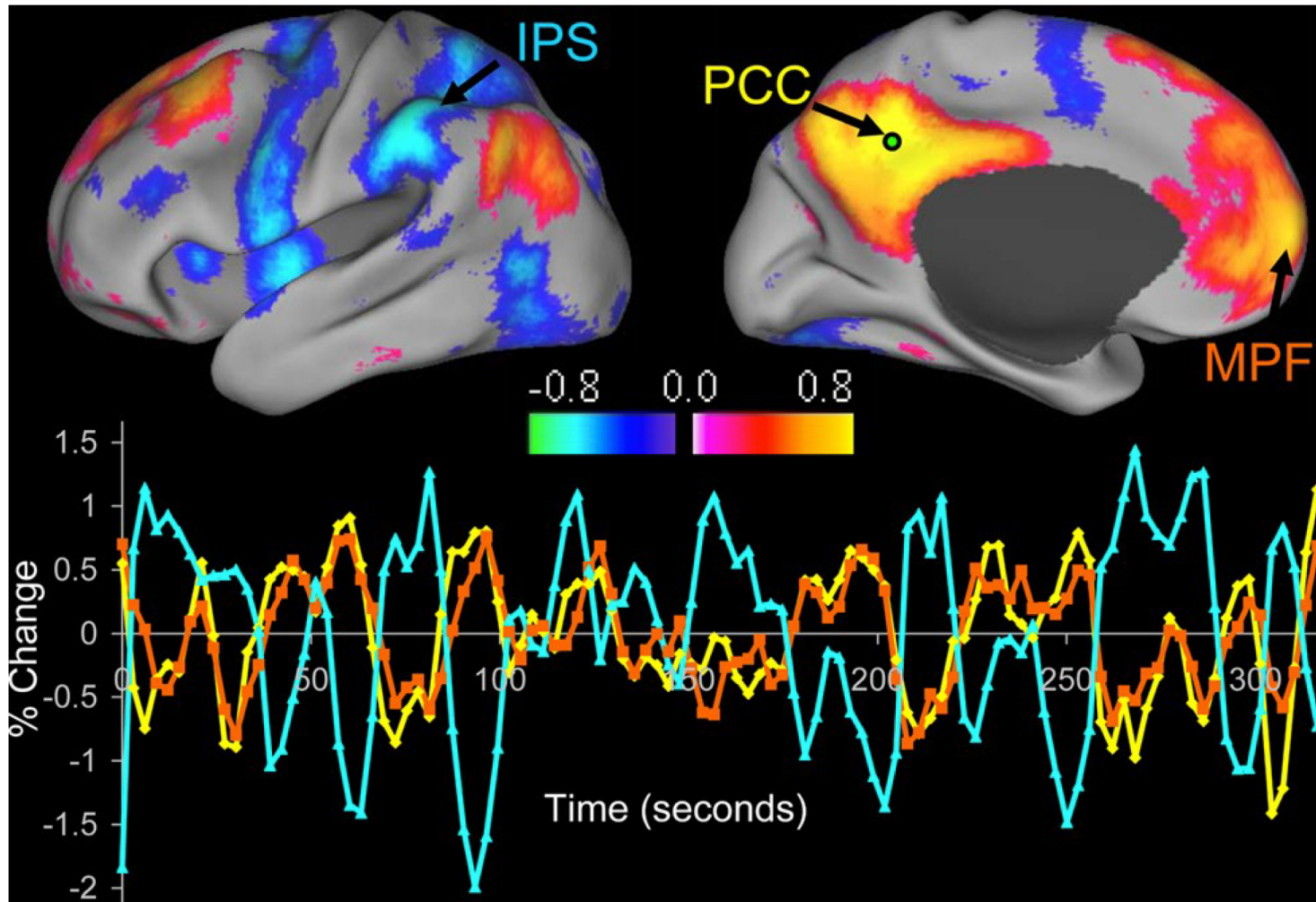
Default mode network (DMN)



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

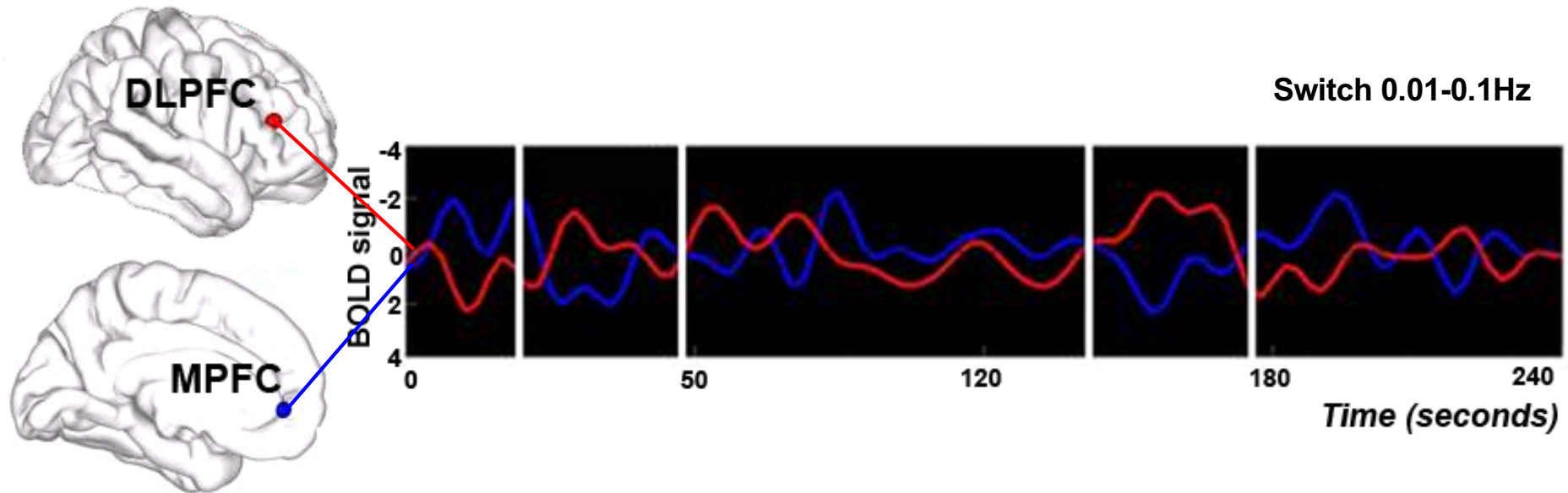
DMN anticorrelations



DMN anticorrelations



External awareness
or anticorrelated network



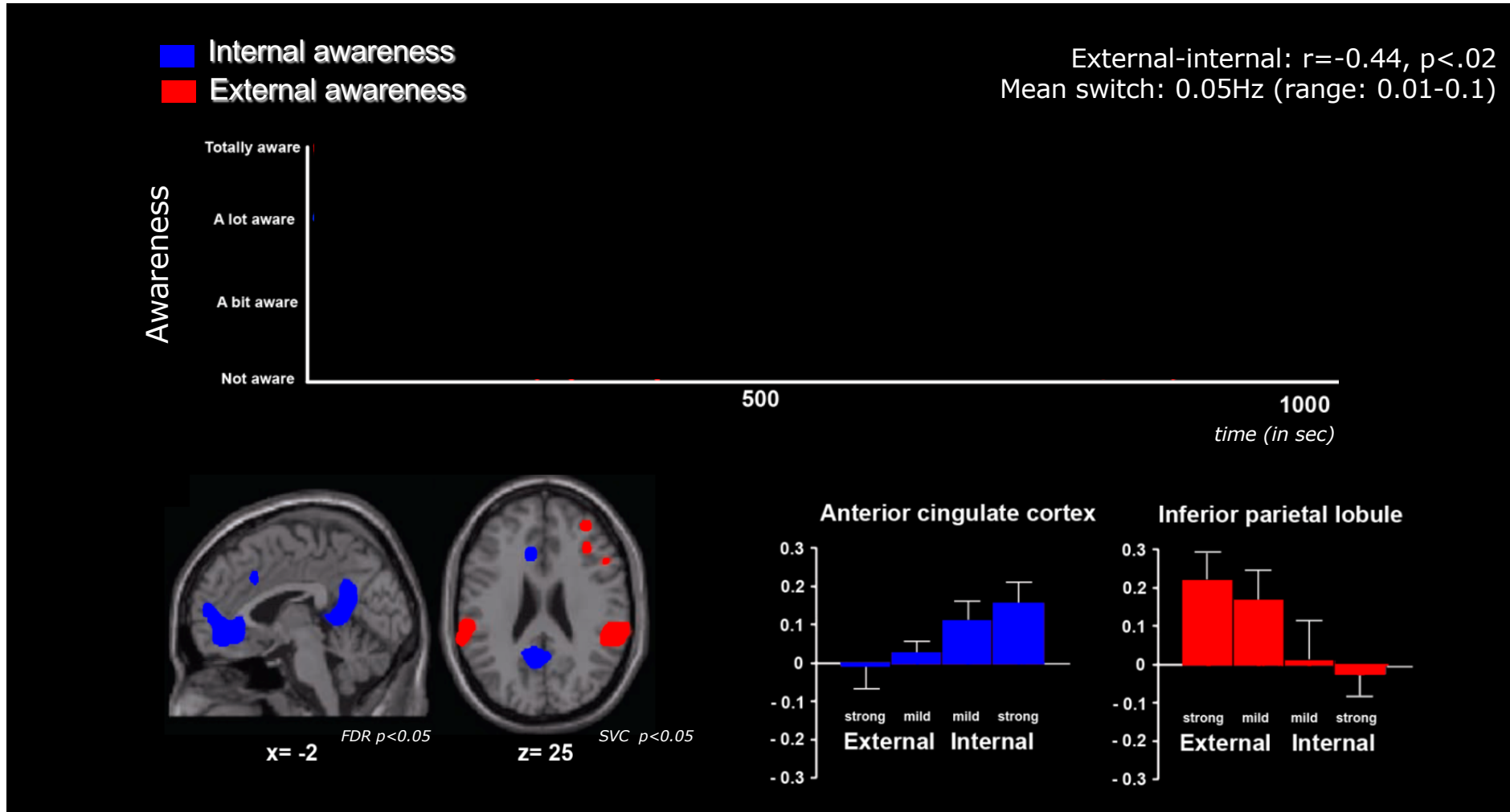
Internal awareness
or Default mode network

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

Demertzi et al, *Front Hum Neurosci* 2013

Demertzi, Soddu, Laureys. *Curr Opin Neurobiology* 2013

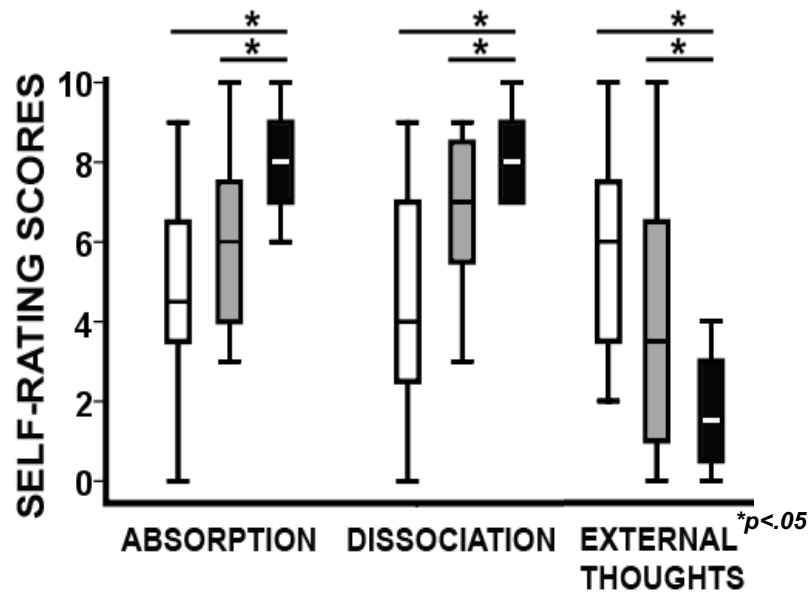
Cognitive-behavioral relevance



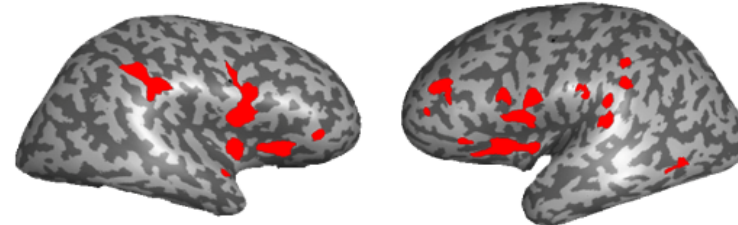
Effect of awareness



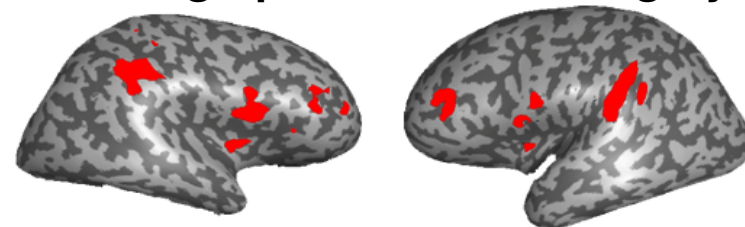
- Normal consciousness
- Autobiographical mental imagery
- Hypnosis



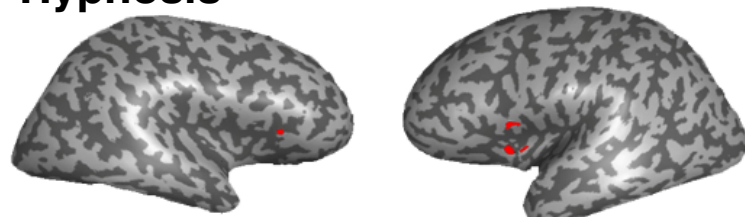
Normal consciousness



Autobiographical mental imagery

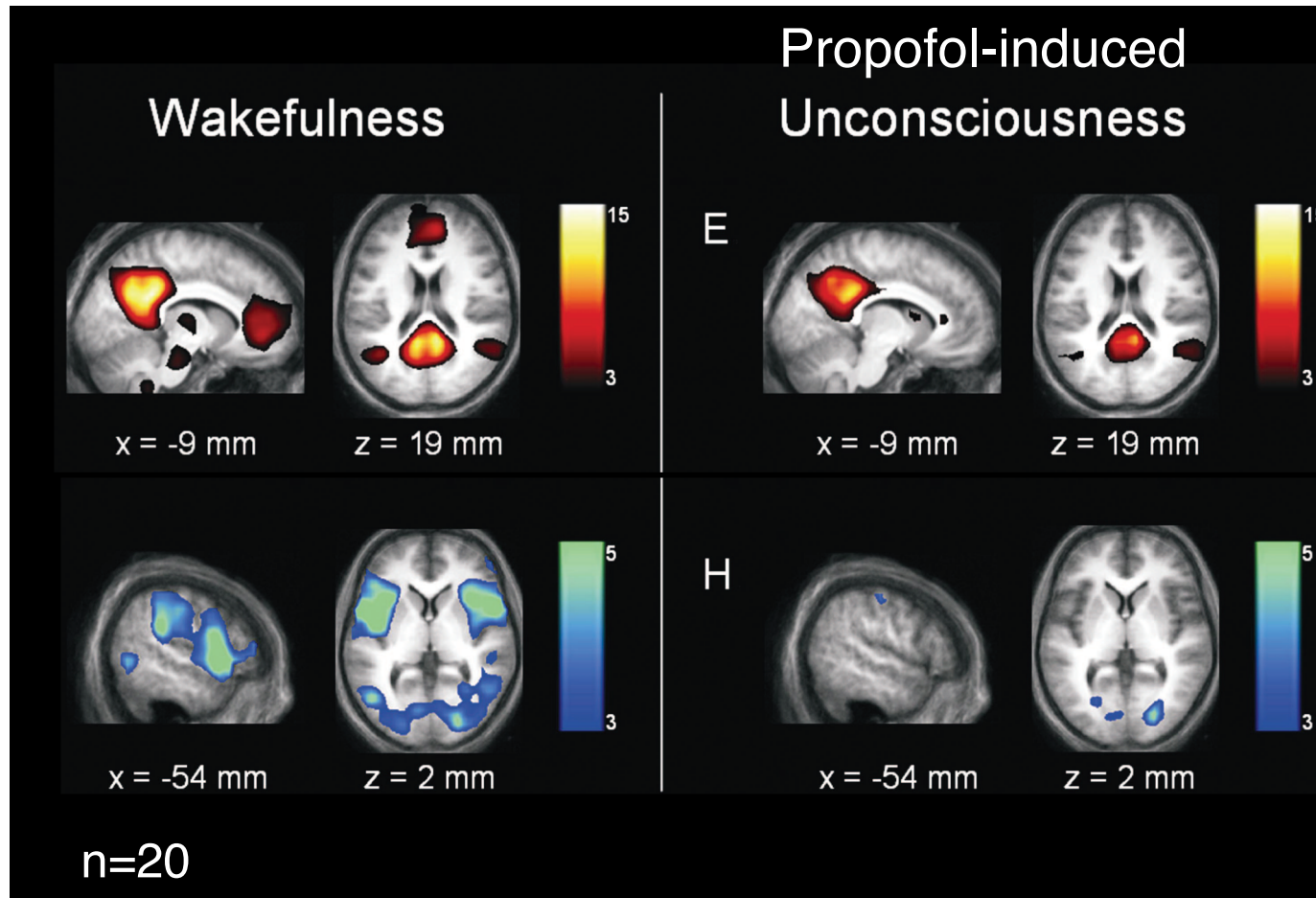


Hypnosis



p<0.05 corrected for multiple comparisons

Effect of arousal



Effect of environment



SCIENTIFIC REPORTS

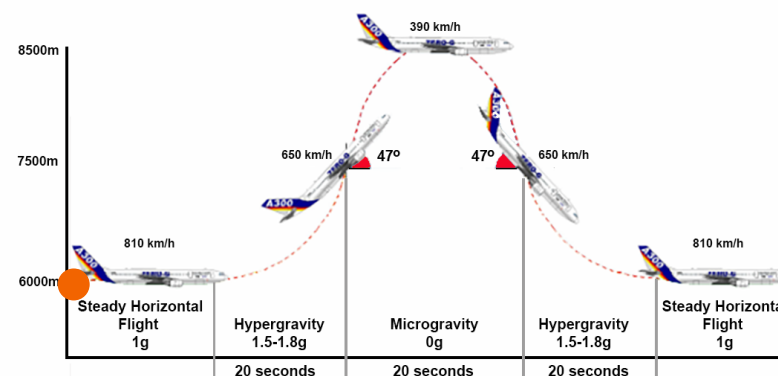
www.nature.com/scientificreports/



Parabolic flight



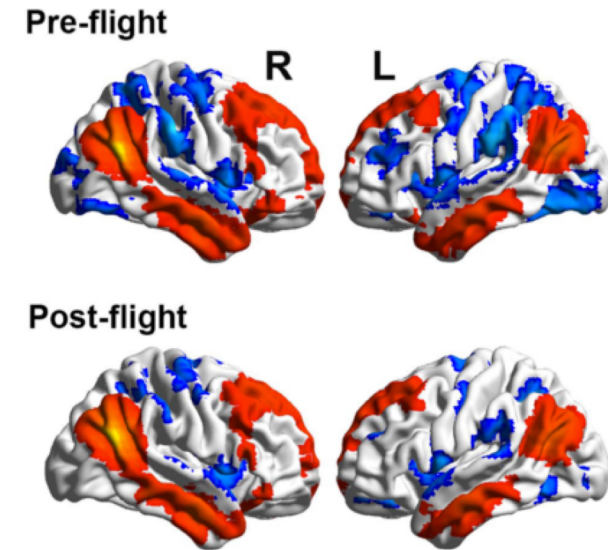
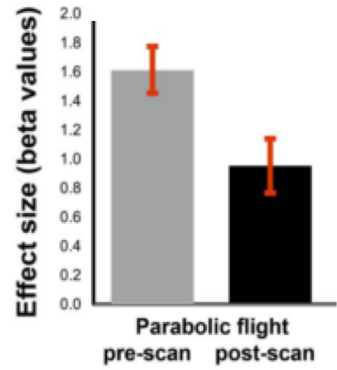
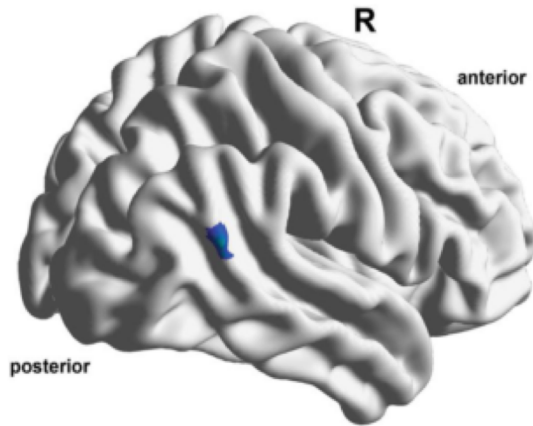
European Space Agency



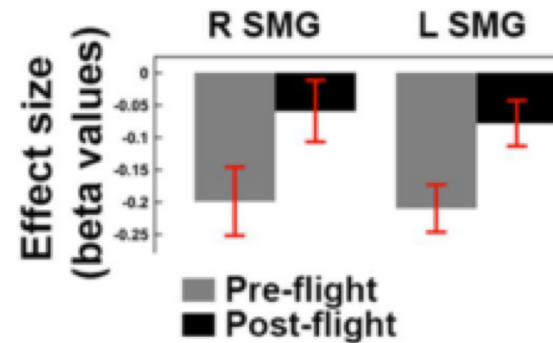
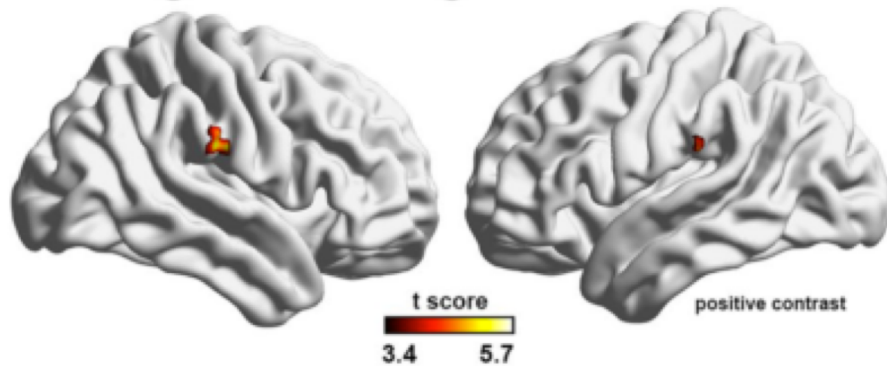
Parabolic flight trajectory

Angelique Van Ombergen¹, Floris L. Wuyts¹, Ben Jeurissen², Jan Sijbers², Floris Vanhevel³, Steven Jillings¹, Paul M. Parizel³, Stefan Sunaert⁴, Paul H. Van de Heyning¹, Vincent Dousset⁵, Steven Laureys⁶ & Athena Demertzi^{6,7}

Effect of environment



Post – Pre flight

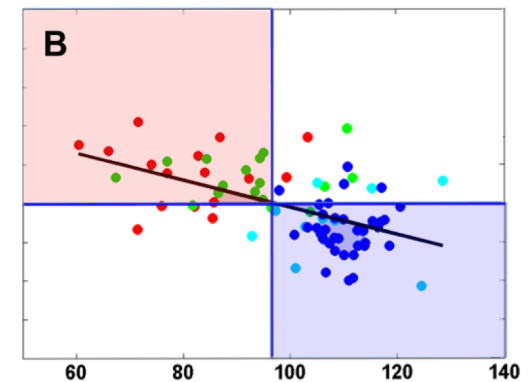
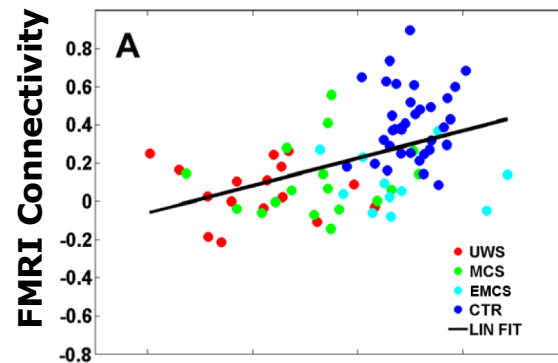
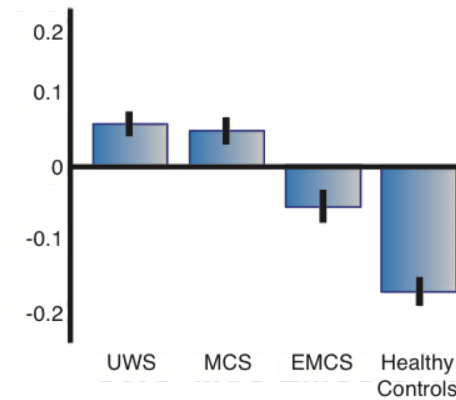
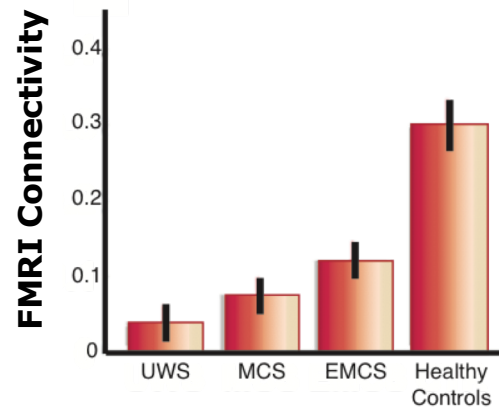
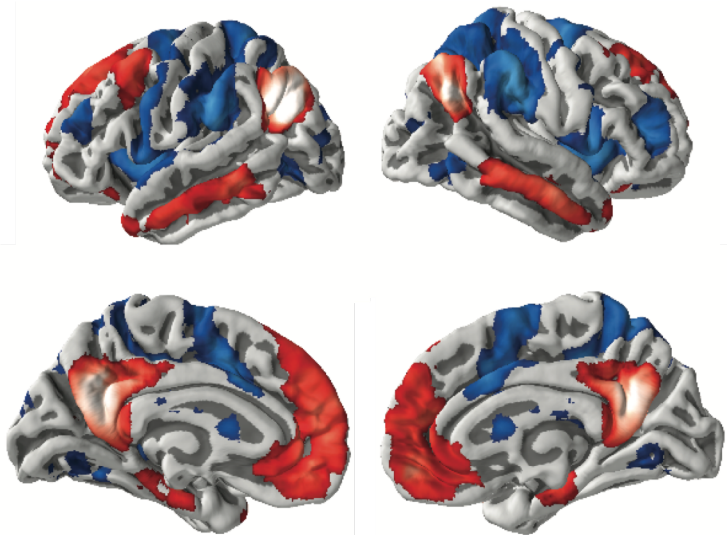


Effect of pathology



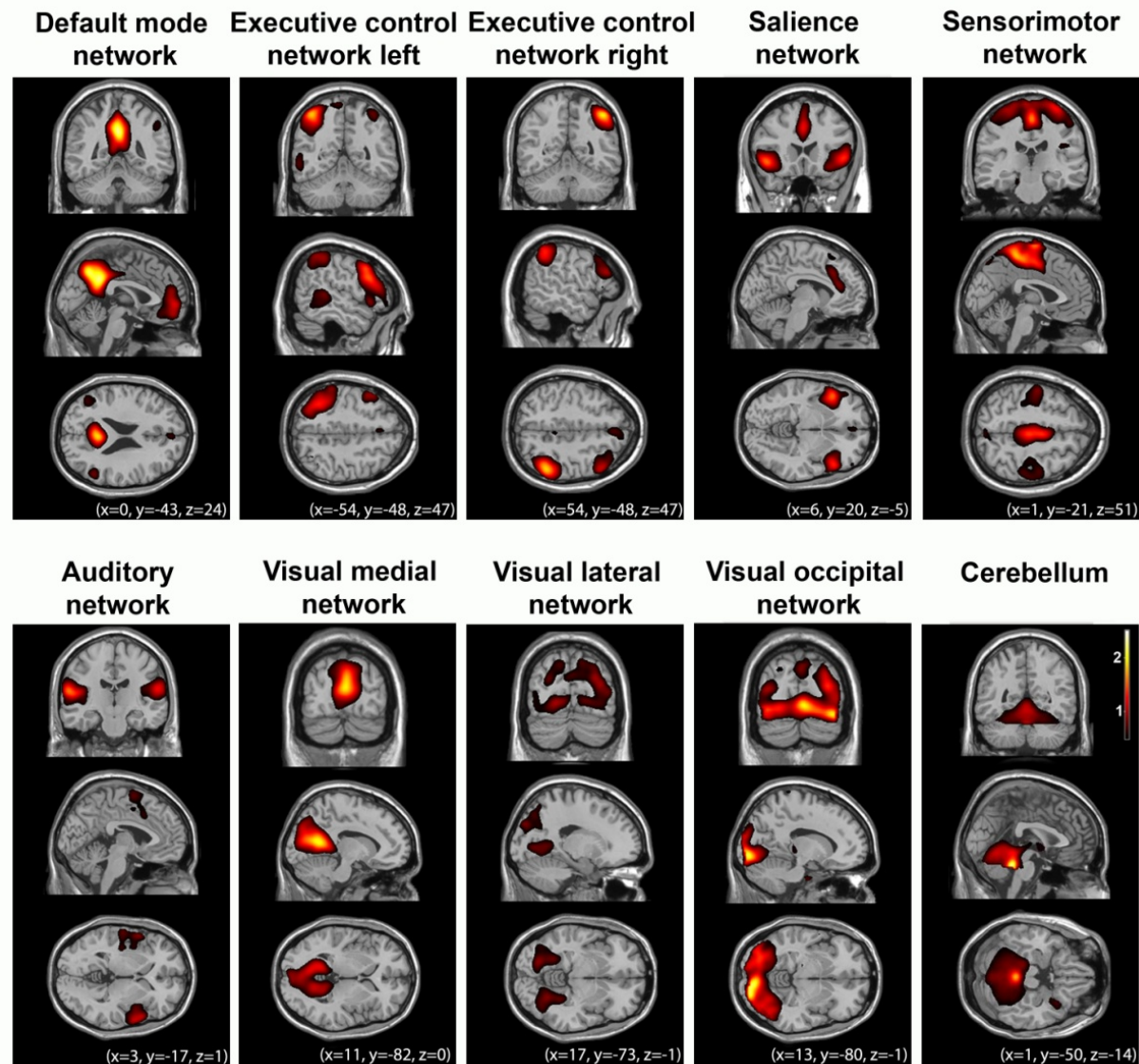
DMN CORRELATIONS

DMN ANTICORRELATIONS

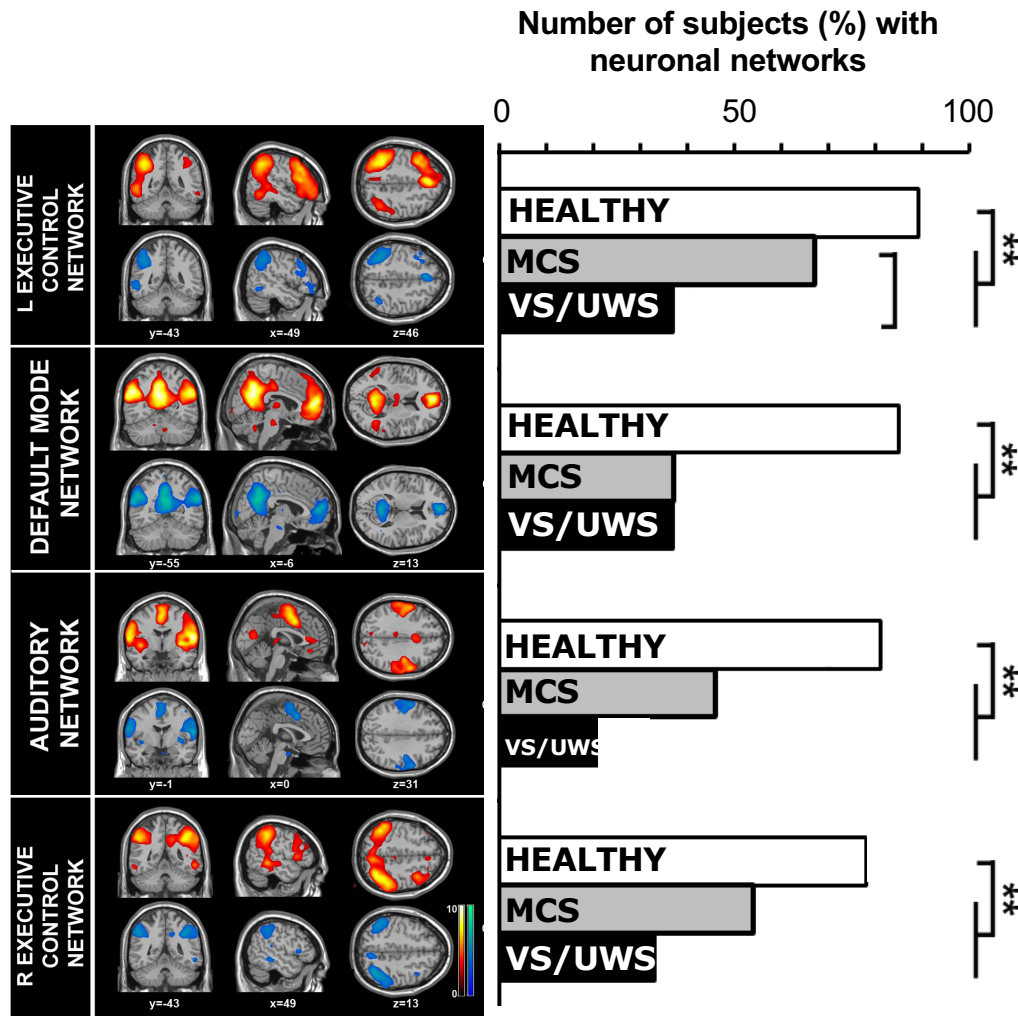


Brain metabolism

Systems-level organization



Networks are disrupted in low consciousness states



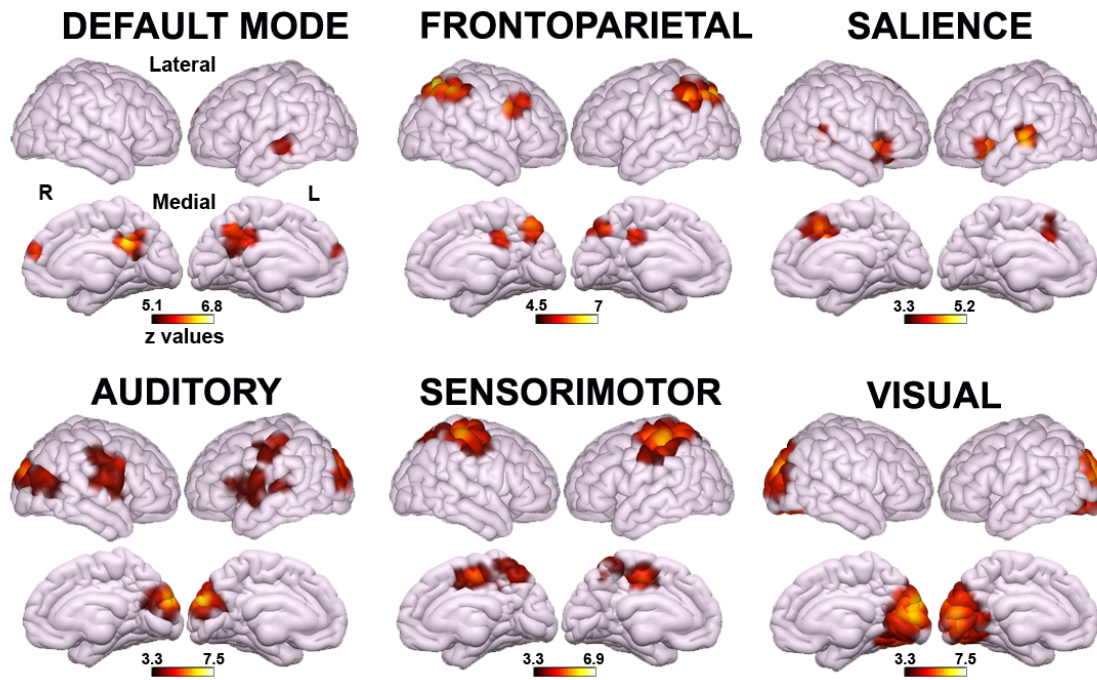
Single-patient classification

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

Which network discriminates best?



MCS > VS/UWS



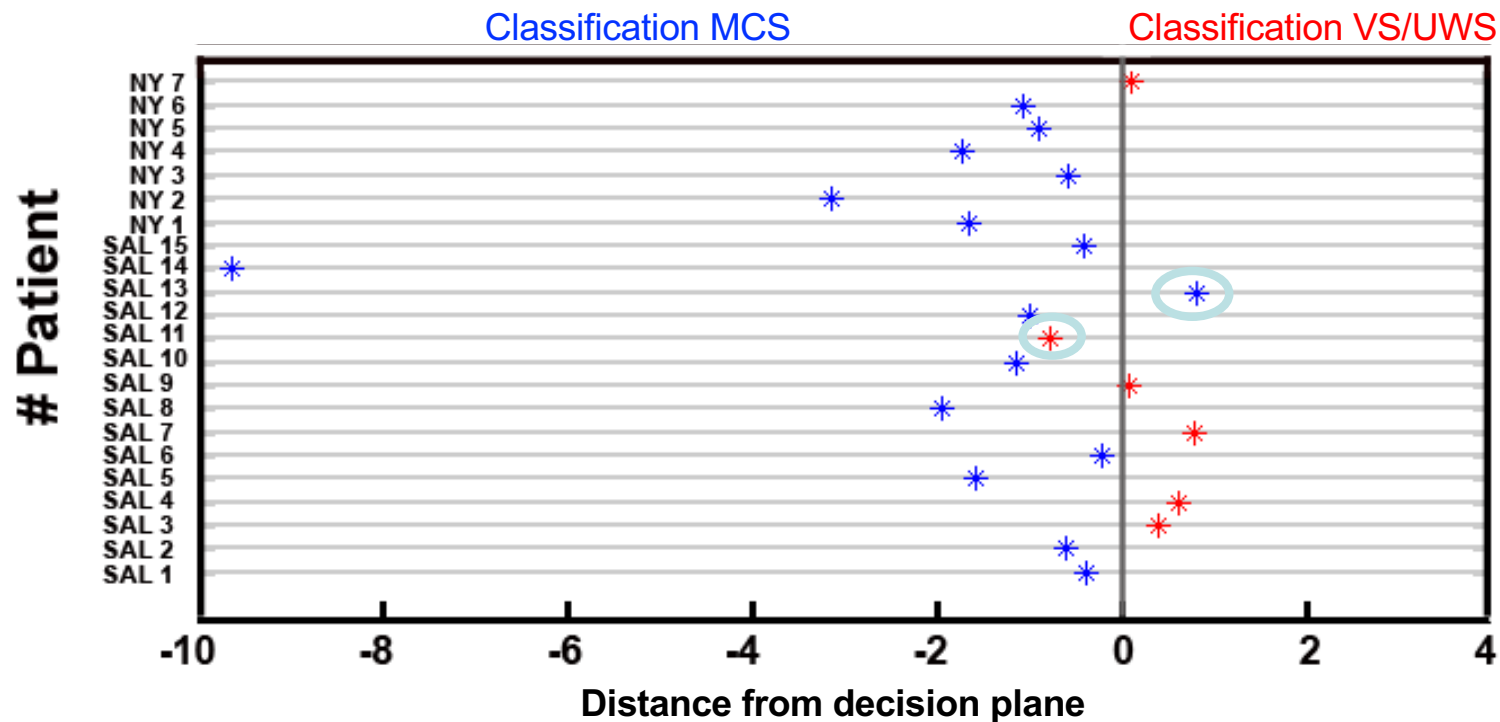
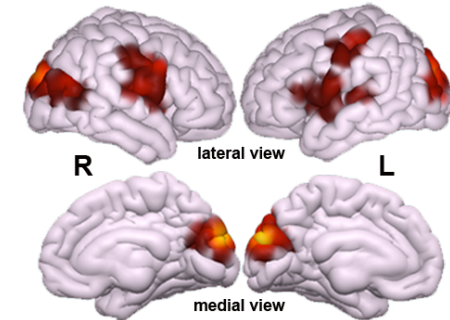
FWE $p < 0.05$ (cluster-level)

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

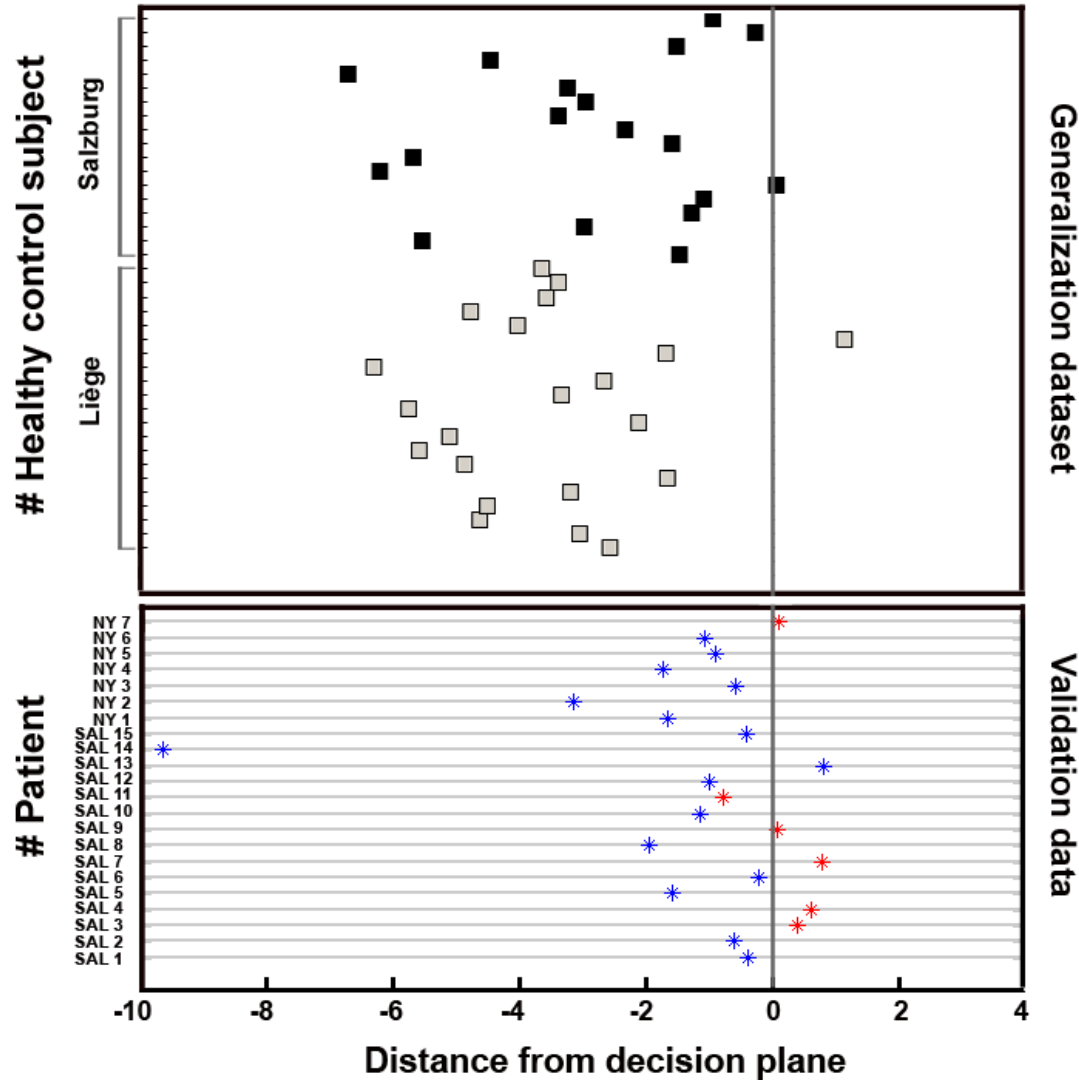
Single-patient classification



- 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



Sanity check: generalization on healthy



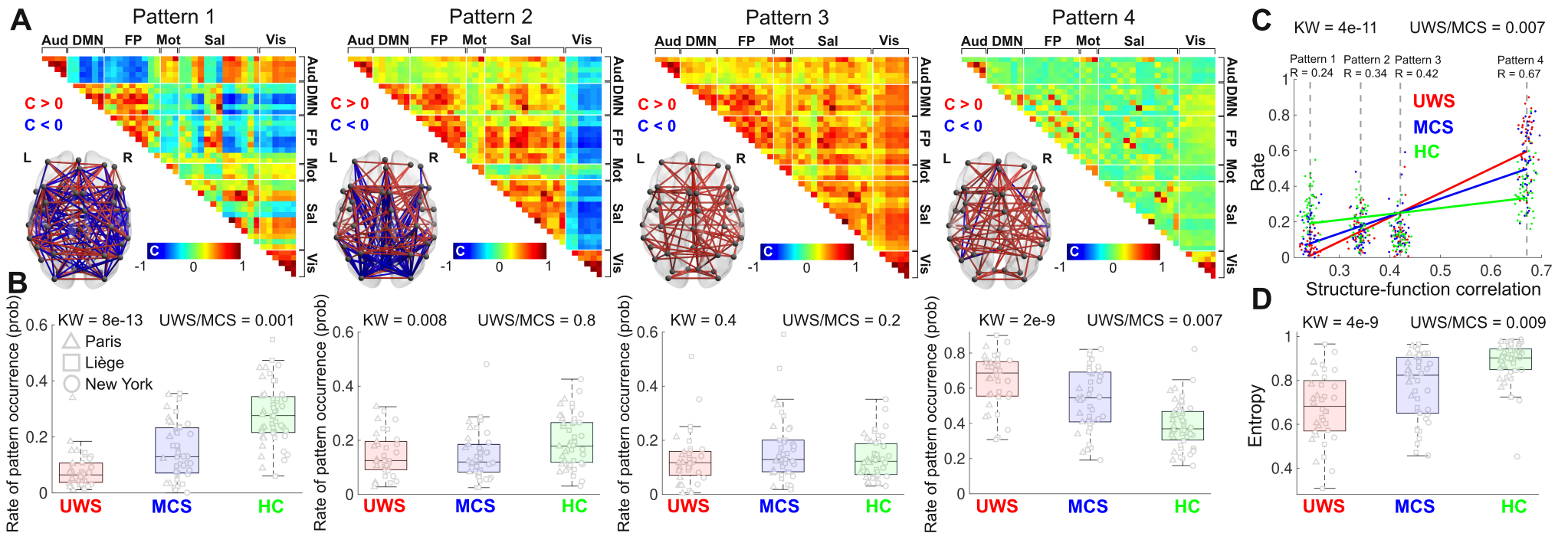
Consciousness is supported by cortical dynamics



James S. McDonnell Foundation 

N = 159

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



Demertzi*, Tagliazucchi*, Dehaene, Deco, ... Schiff, Owen, Laureys, Naccache, Sitt. *under review*



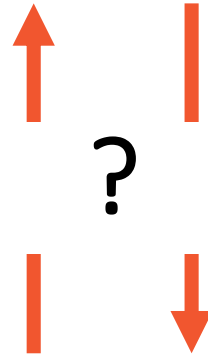
Patients cannot express *themselves*



Hable con ella 2002, Pedro Almodóvar



SELF



CONSCIOUSNESS

WHICH SELF IN UNCONSCIOUSNESS?



social

COMMON VIEW: no self

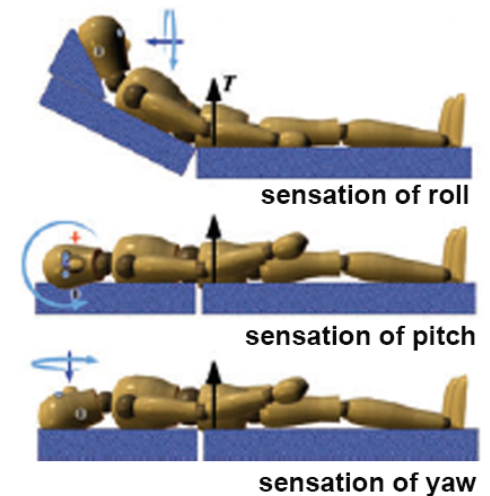
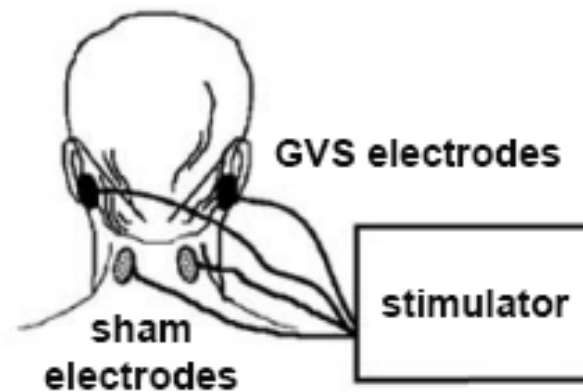
HYPOTHESIS: yes self

MODEL: Embodiment

narrative

HOW: Probe balance

minimal



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
-
- Consciousness:
 - needs to be inferred: framework for used technologies?
(Demertzi, Sitt, Sarasso, Pinxten, *Neurosci Consciousness* 2017)
 - carries a moral significance
 - is not out there to capture
 - a matter of social consensus? (Nizzi, Blandin, Demertzi, *NeuroEthics* 2018)

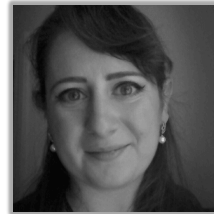


Consciousness concerns us all

Thank you for your attention!

a.demertzi@uliege.be

 ADemertzi



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]

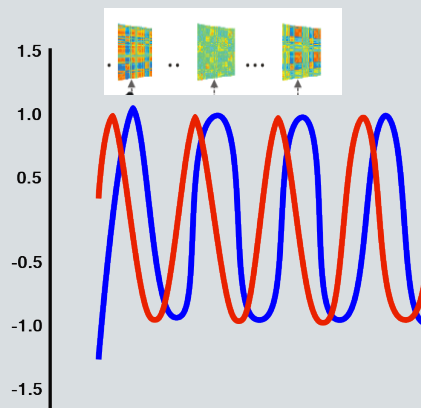
Brain parcellation

(Sphere ROIs)

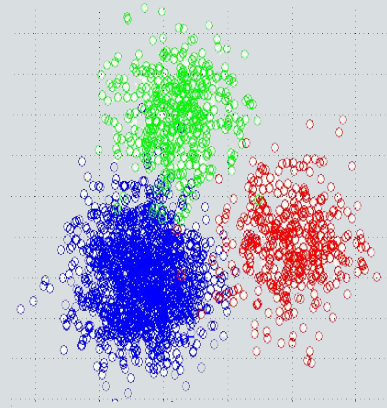


ROI timeseries extraction

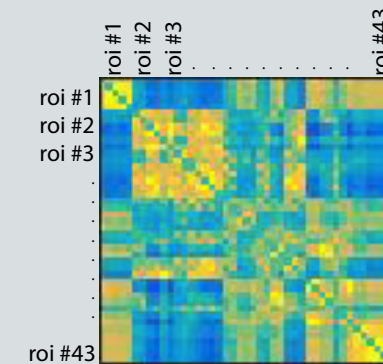
Phase analysis (Hilbert transform)



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



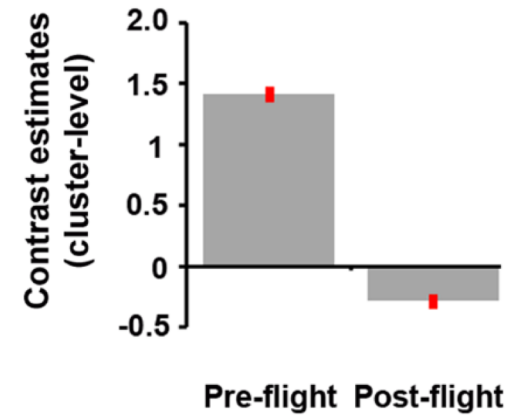
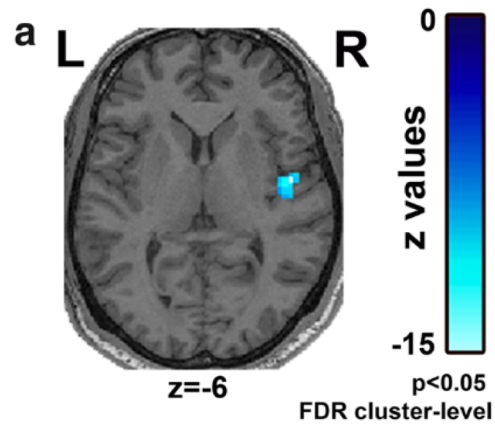
Grant Type: Collaborative Activity Award, Phase I & II (2008-2017)



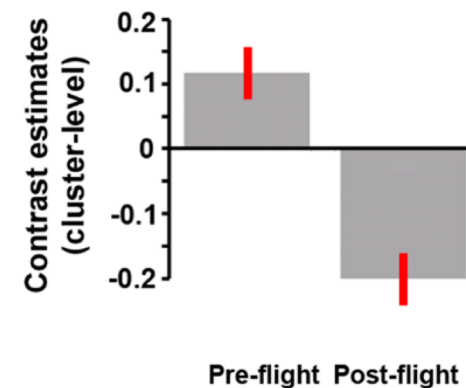
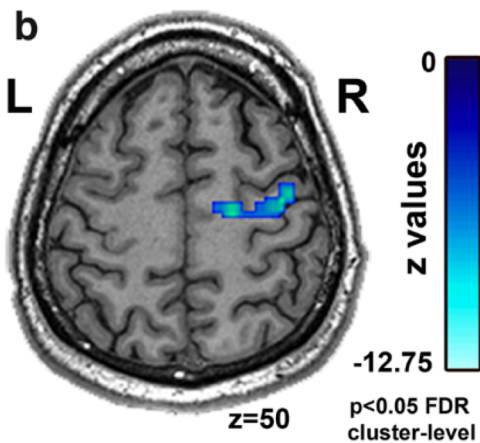


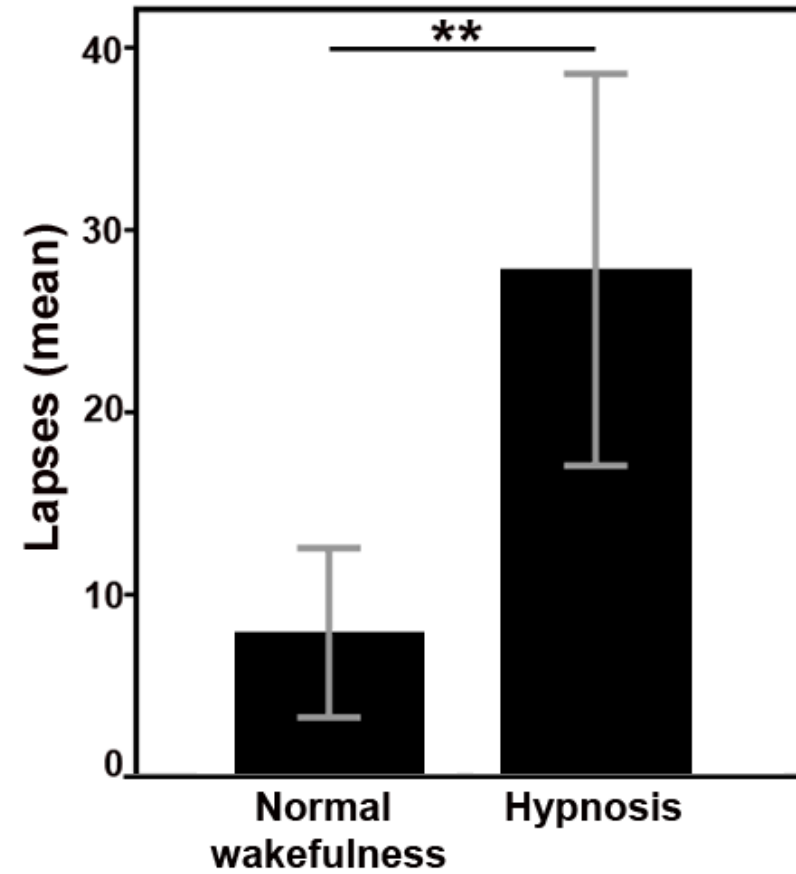
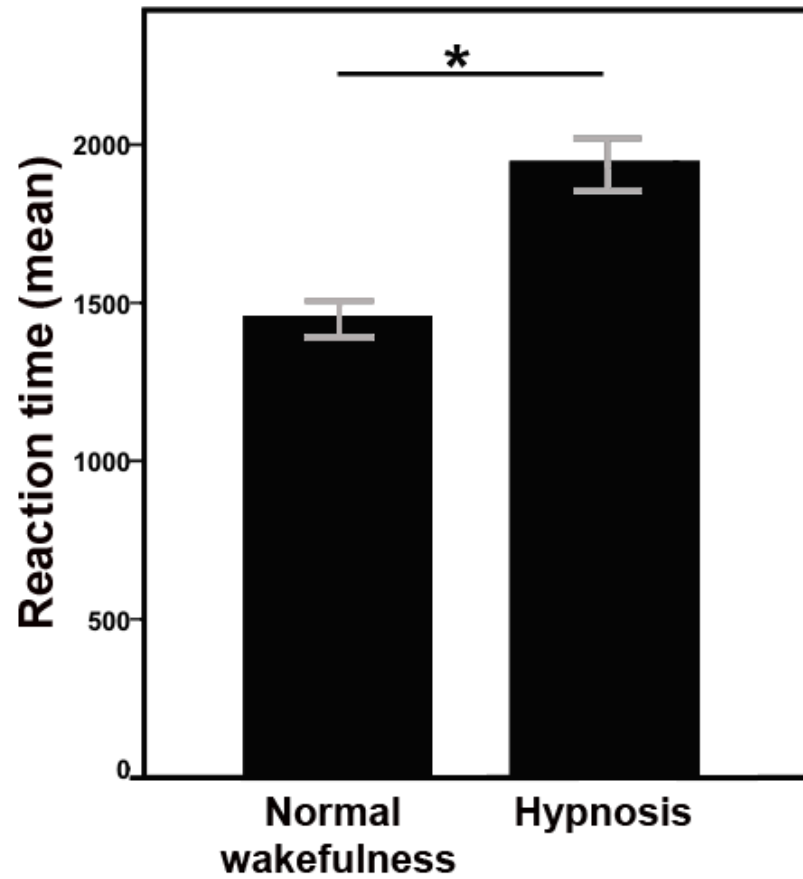
44-year-old male cosmonaut
First long-duration mission (169 days) to the ISS in 2014
fMRI protocol pre-flight: 30 days, post-flight: 9 days after Earth re-entry

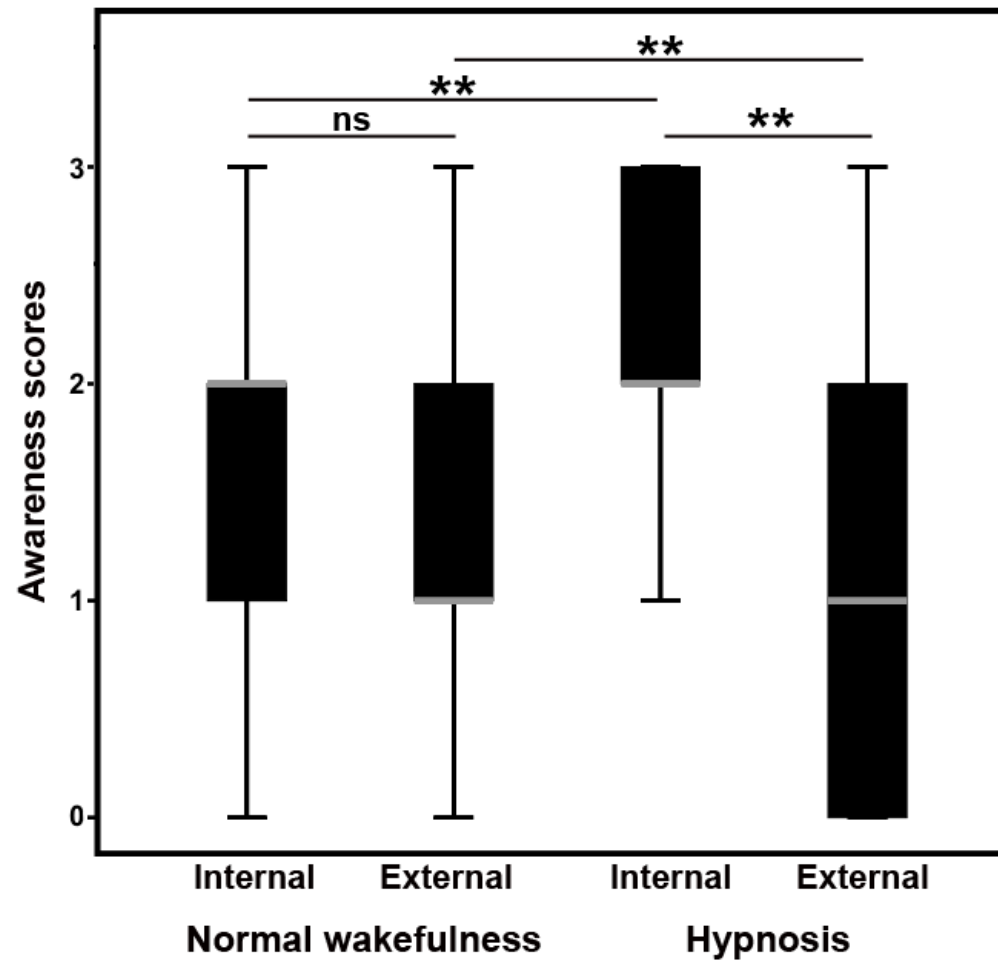
Hypothesis-free



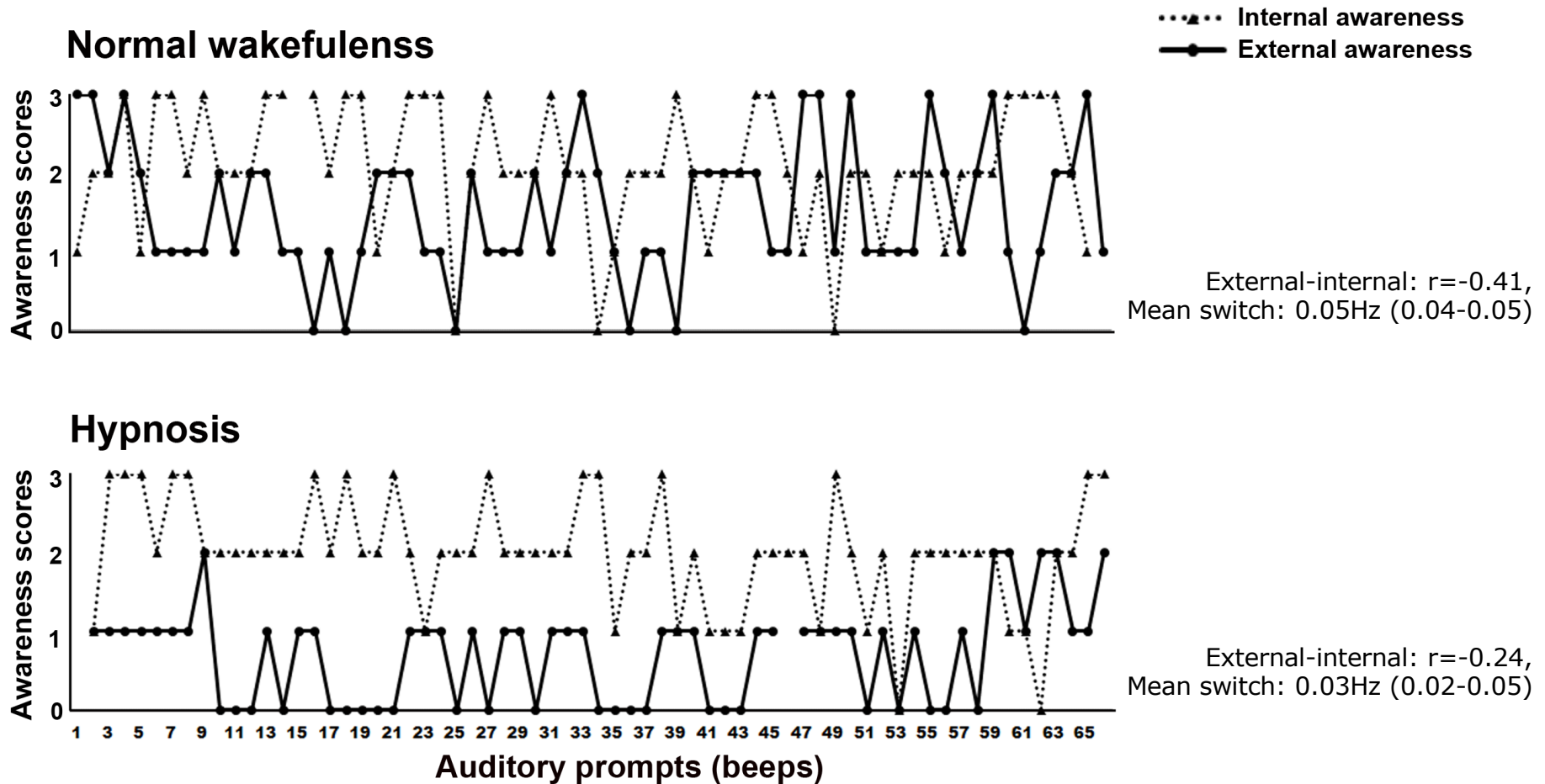
Hypothesis-driven







Awareness is modified in hypnosis

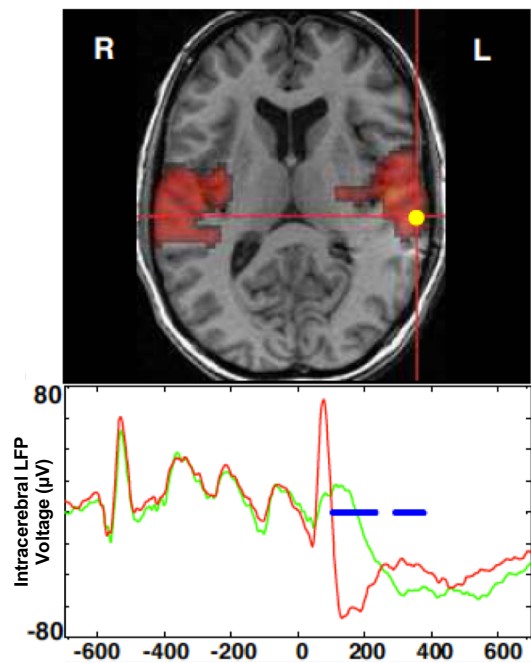


Crossmodal interaction in consciousness

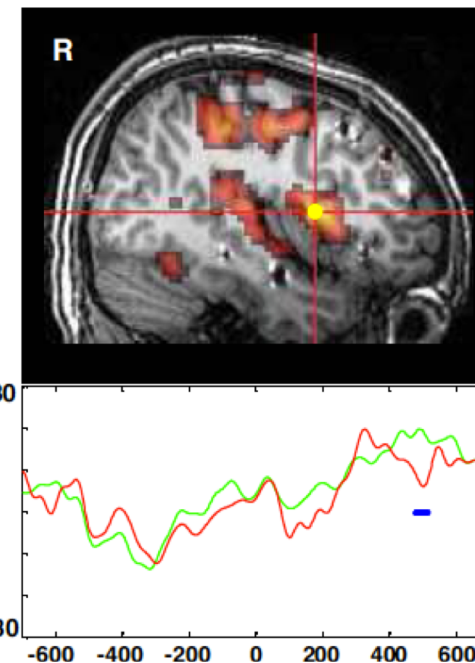
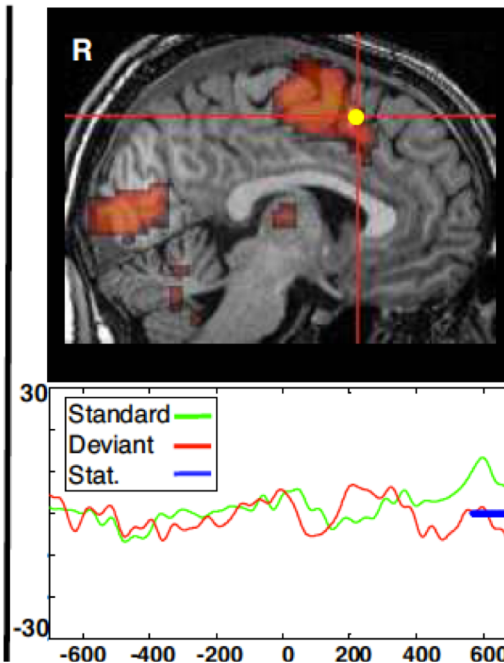
The local- global paradigm



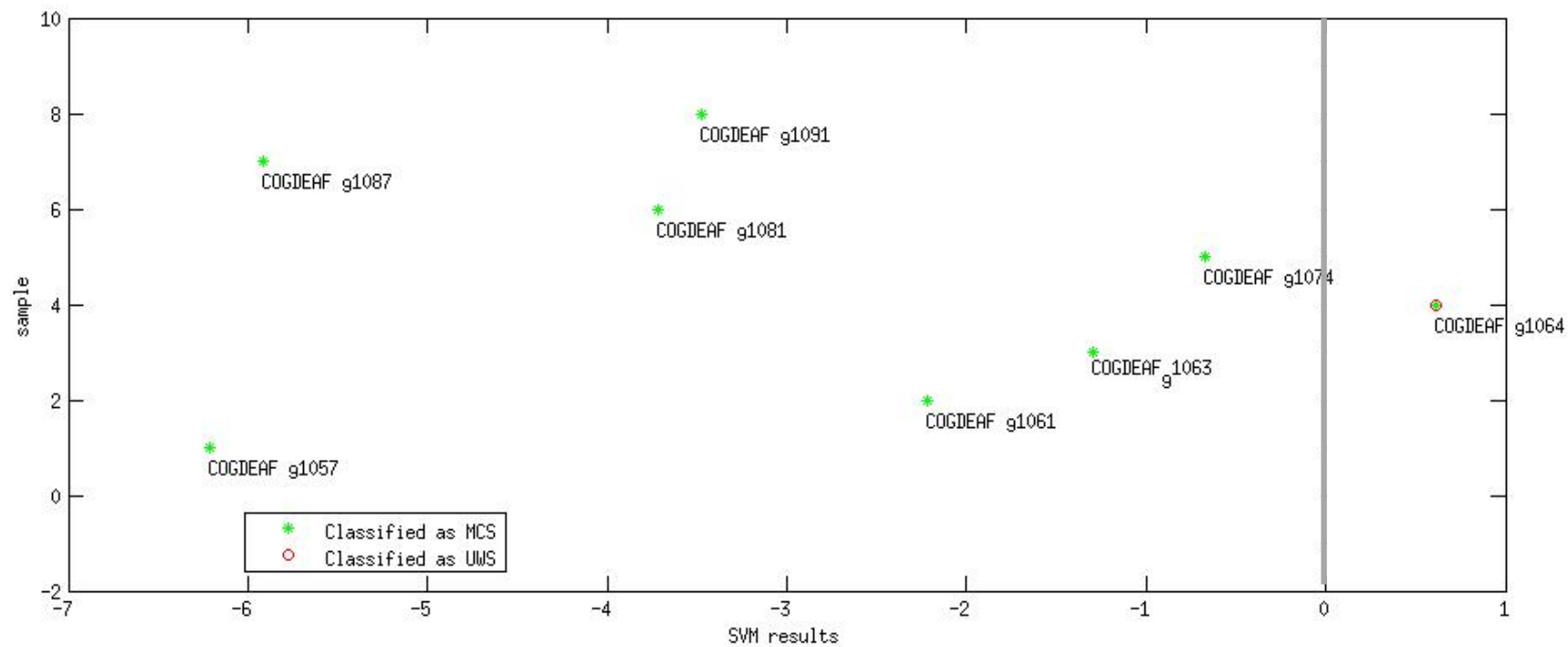
Local effect



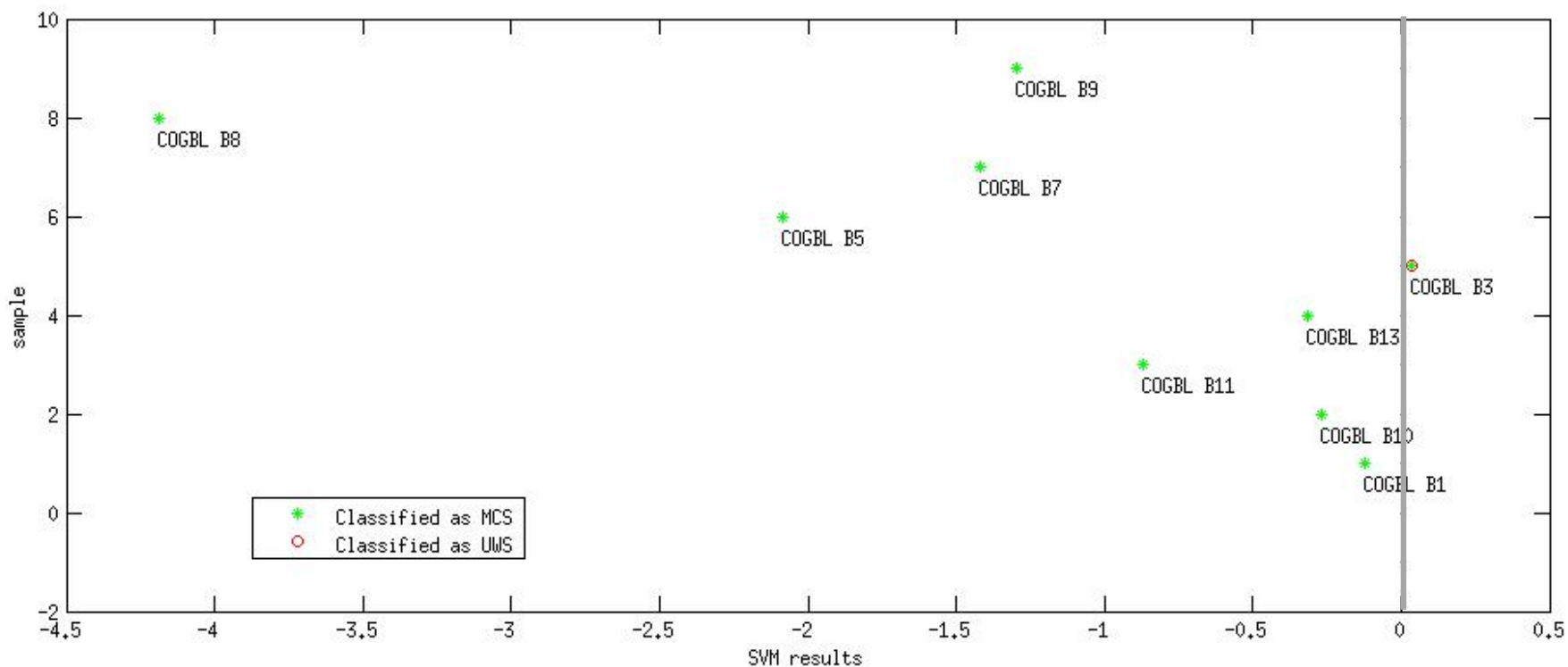
Global effect



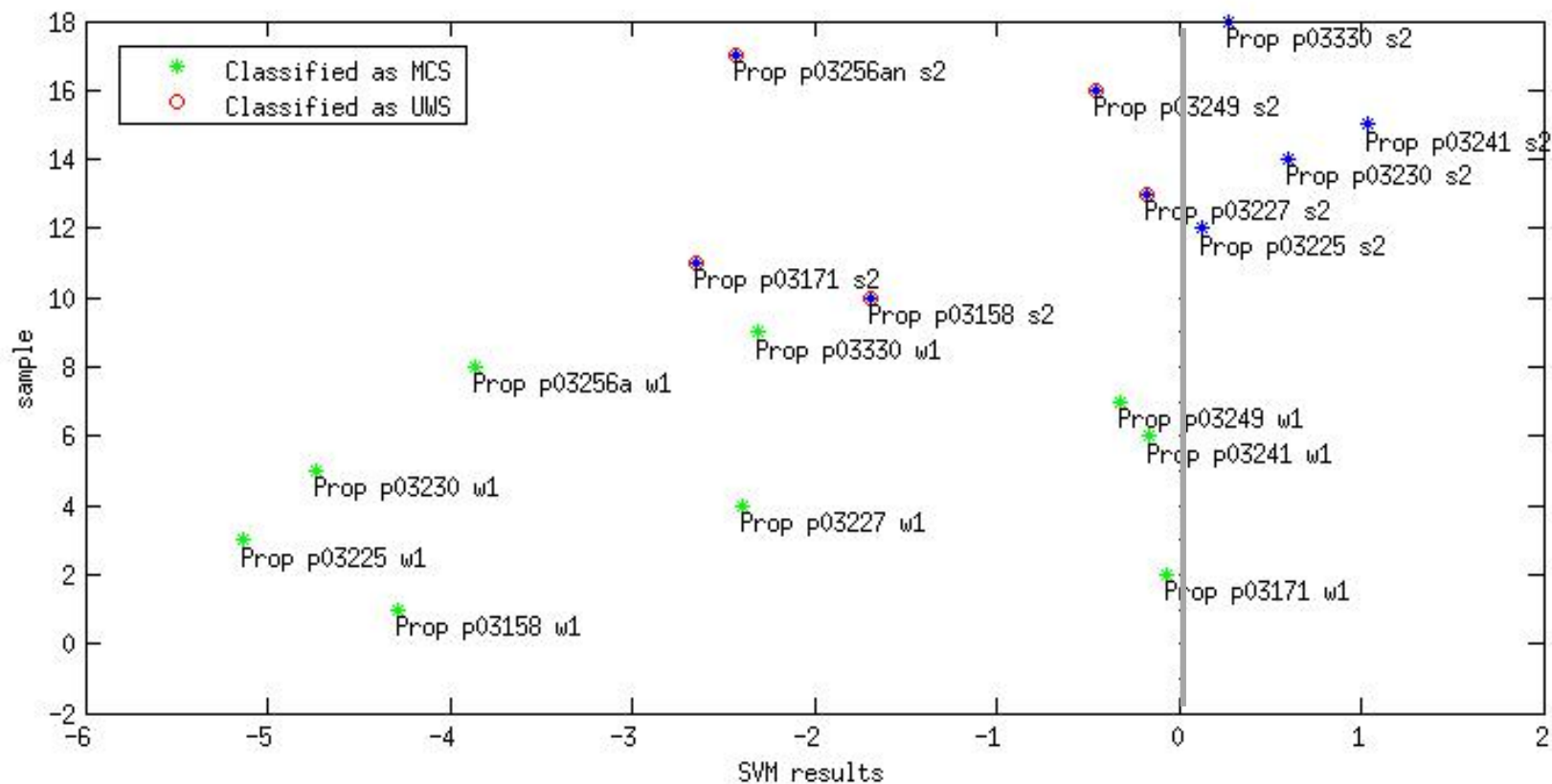
Validation in congenitally deaf



Validation in congenitally blind



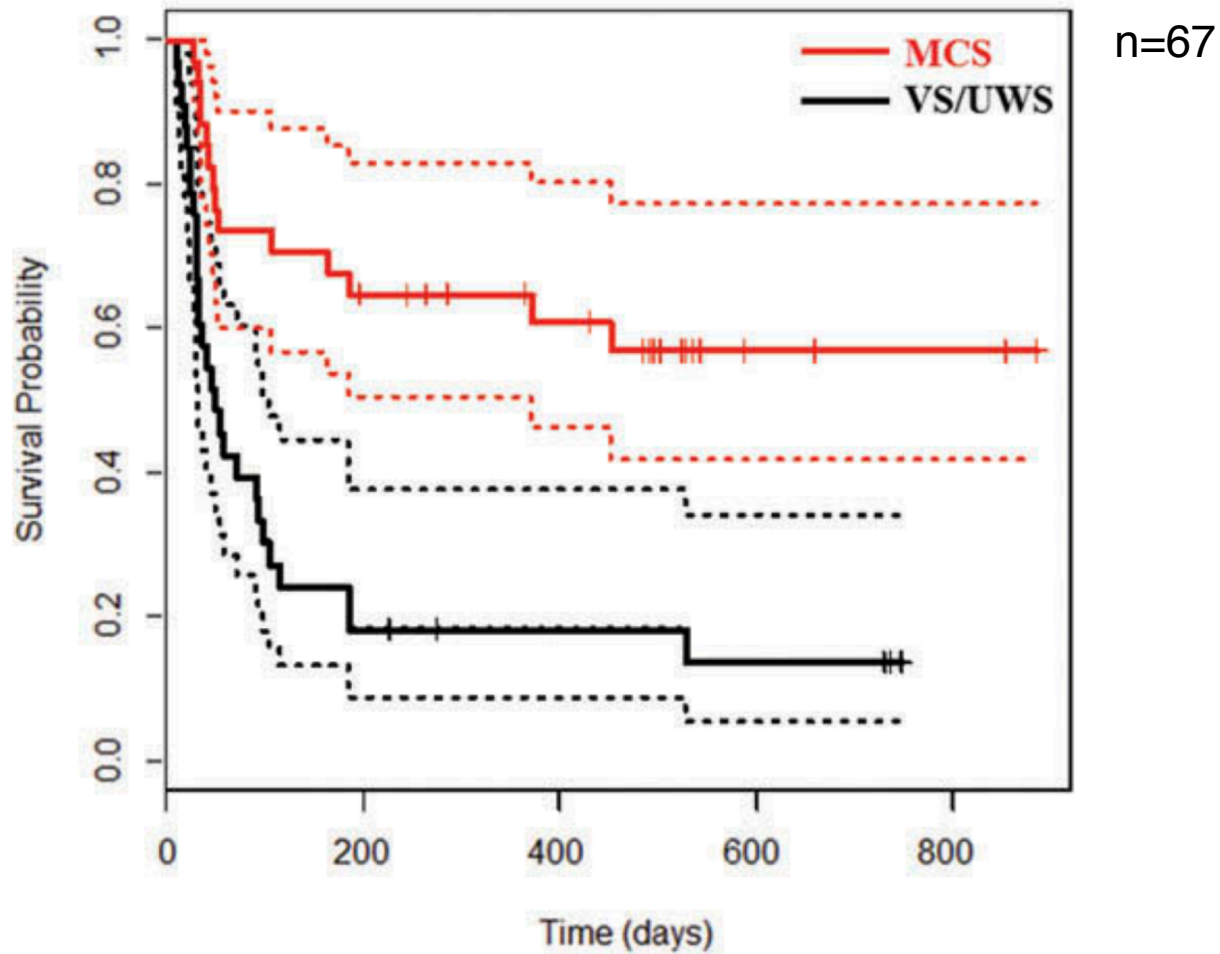
Validation in propofol anesthesia



Clinical evolution



Kaplan–Meier estimation



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**

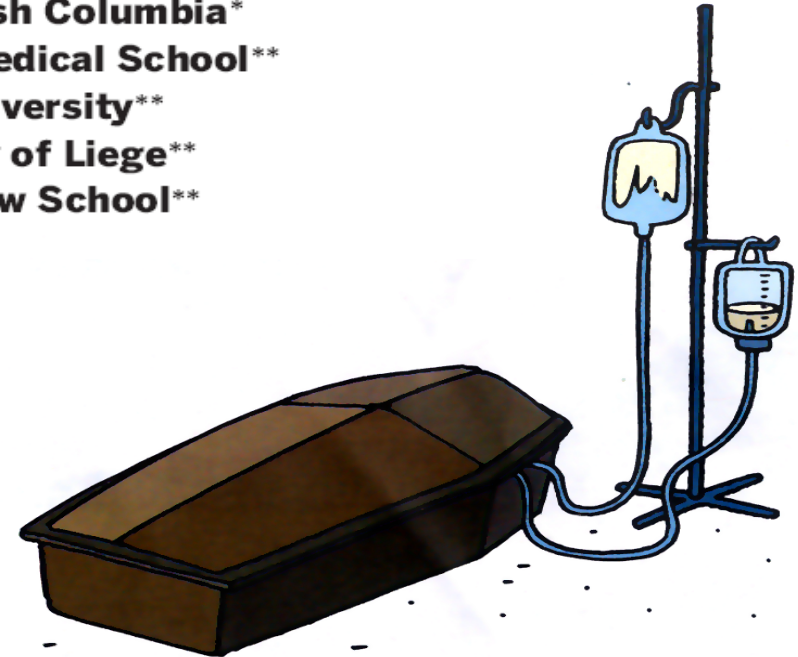
Joy Hirsch, Columbia University**

Steven Laureys, University of Liege**

Emily Murphy, Stanford Law School**

*Co-lead authors.

**Equal authors in alphabetical order.

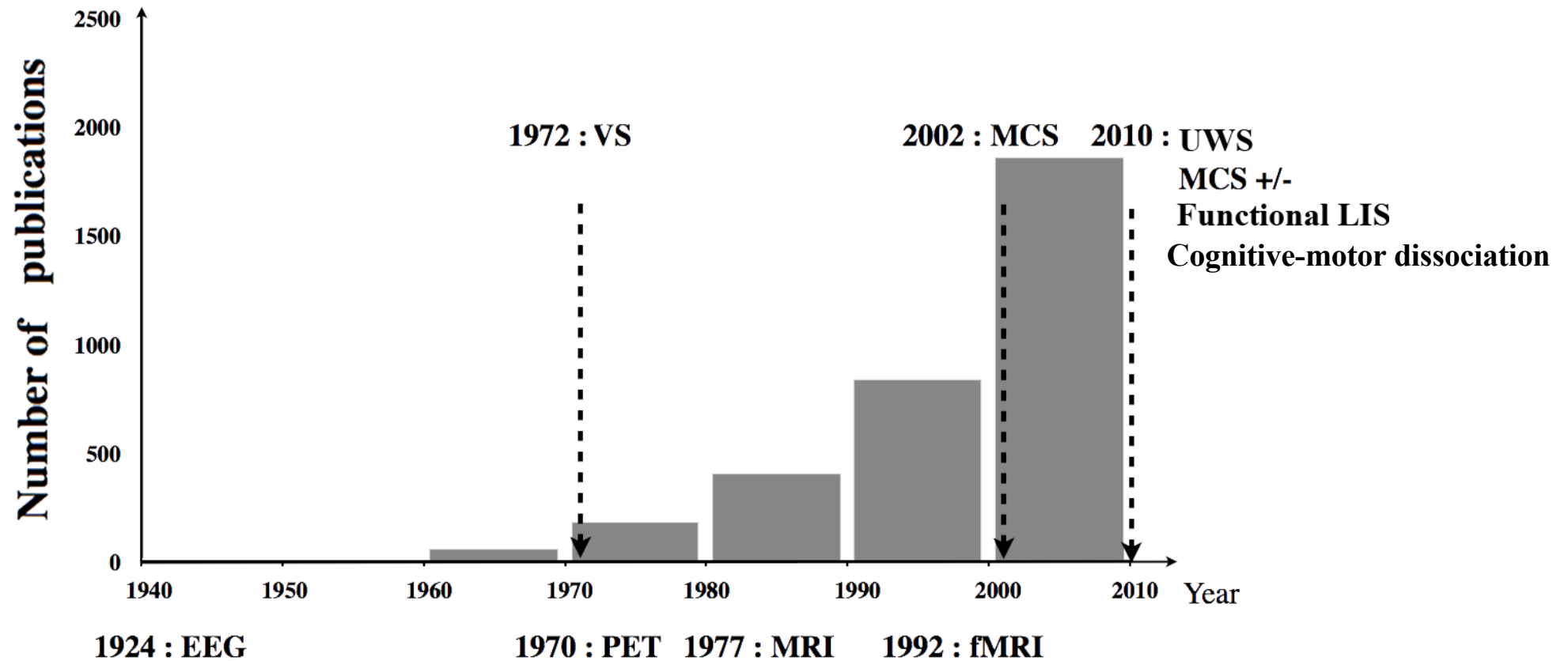


Balancing costs-benefits

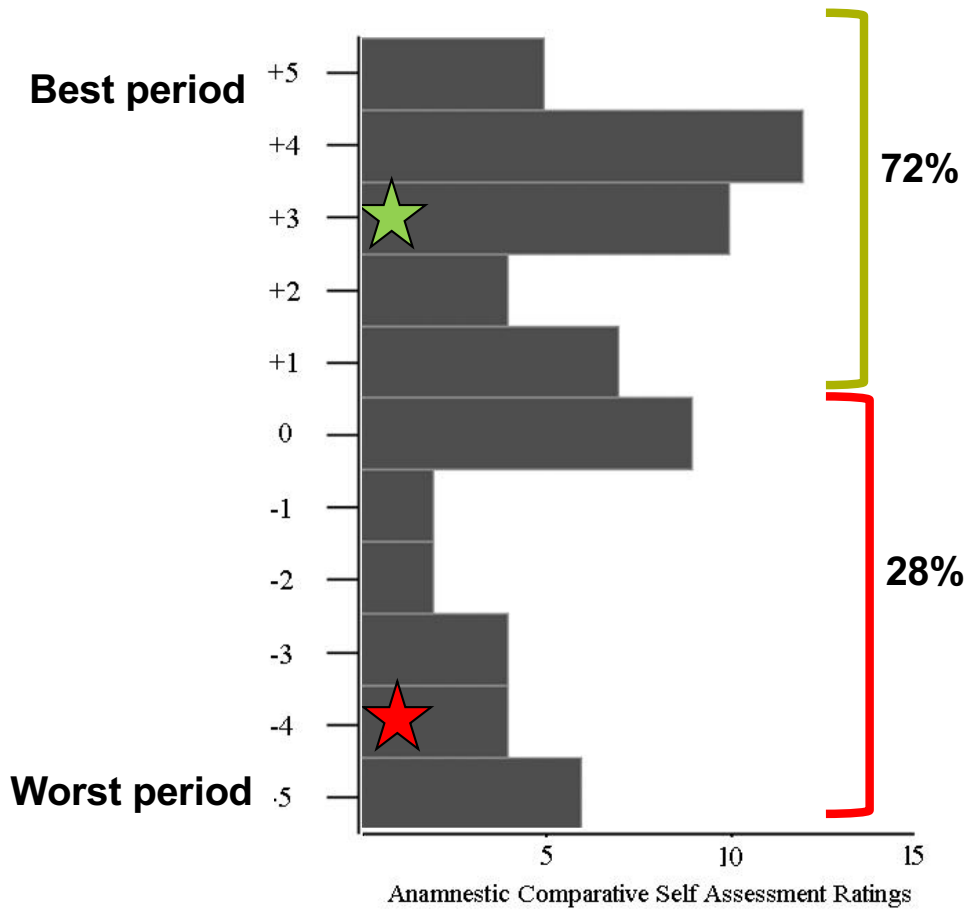


Results of Tests	Beneficial Effects	Harmful Effects
- brain activity than neurological examination	Relatives: decisions to limit life-sustaining treatment	Relatives: may lose hope, purpose, and meaning in life
+ brain activity than neurological examination	Clinical management: may be intensified by the 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

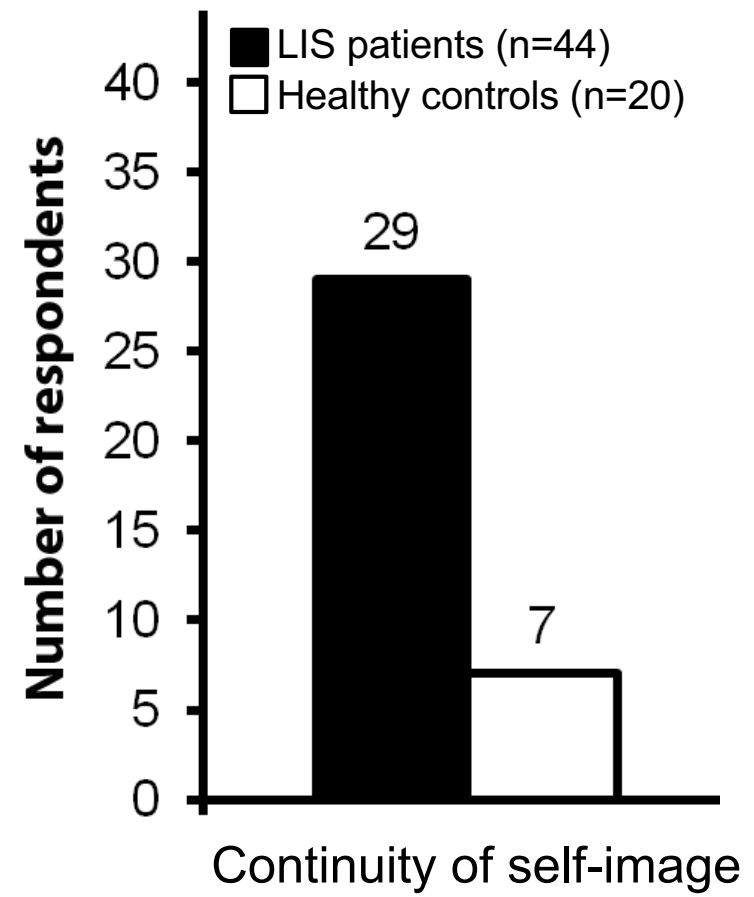
Benefit for science



Benefit for patients?



Bruno et al, *Br Med J Open* 2011



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

Benefit for caregivers?

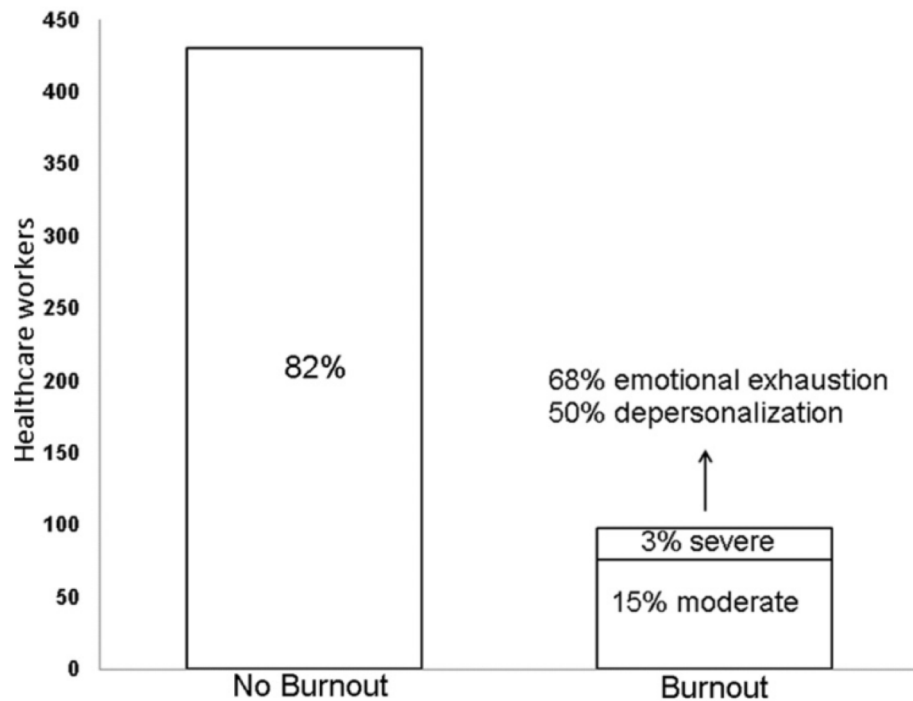
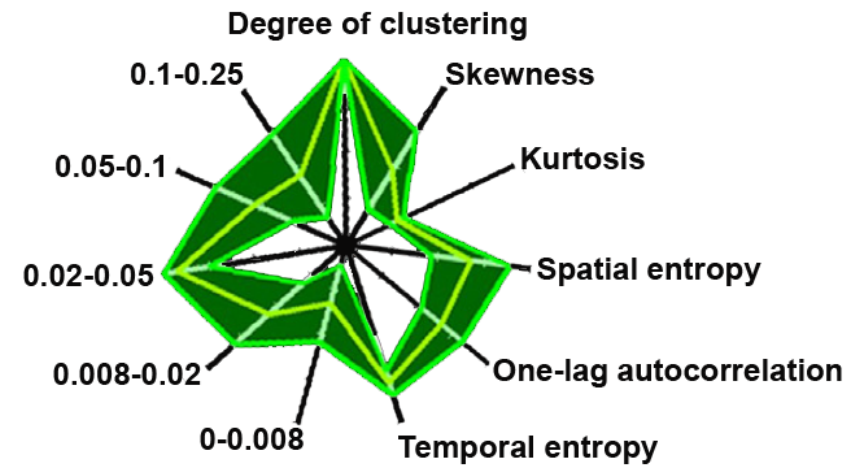
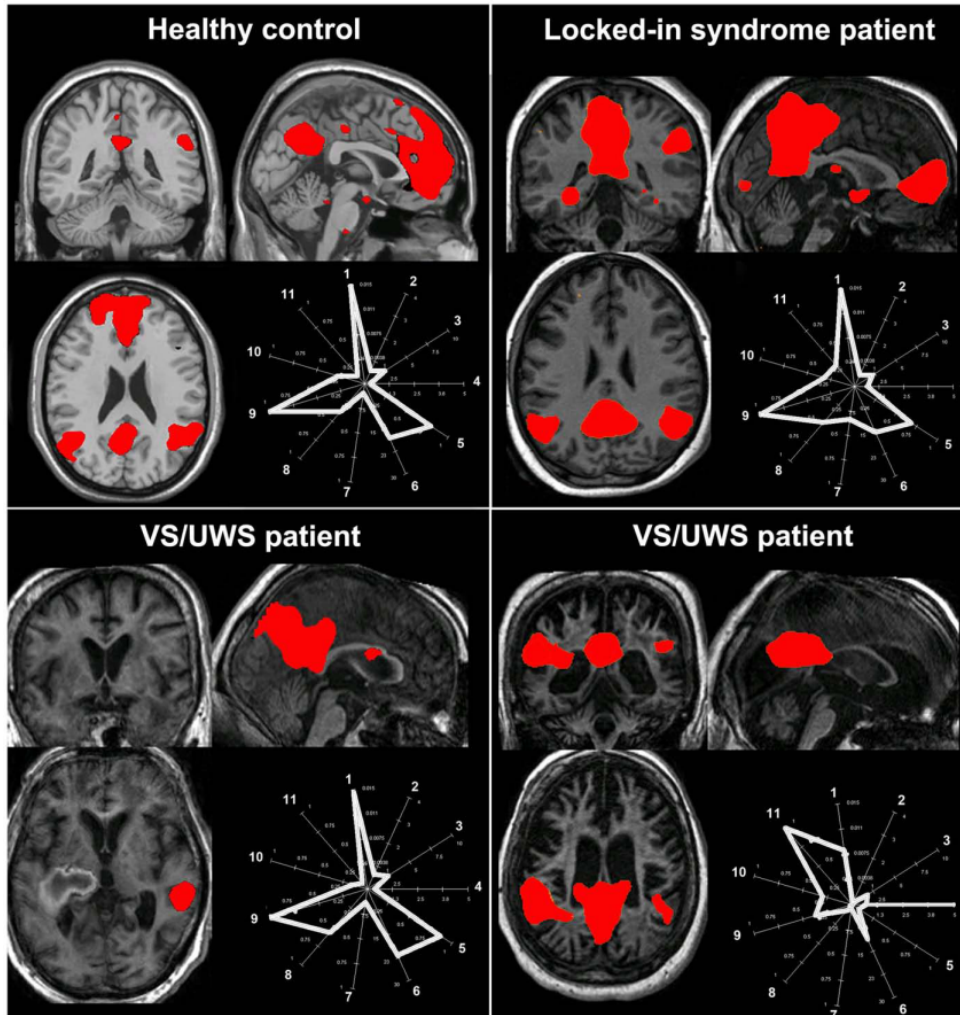


Table III. Percentage of healthcare workers presenting a burnout.

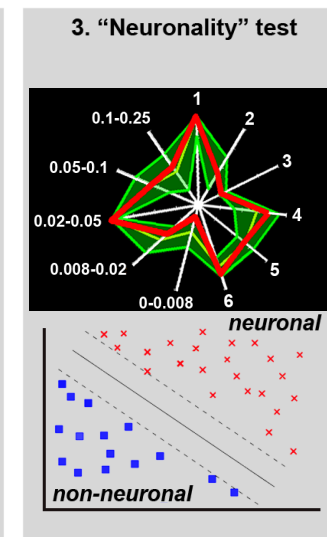
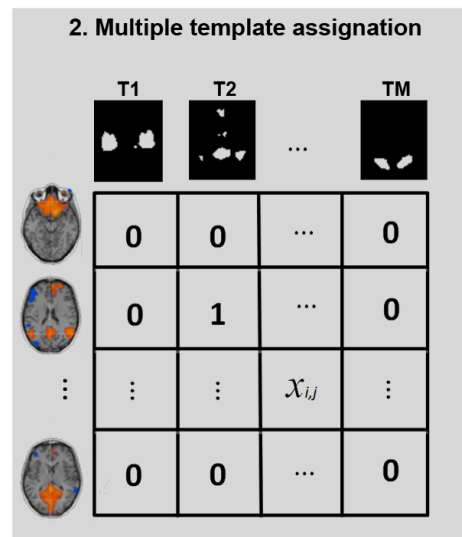
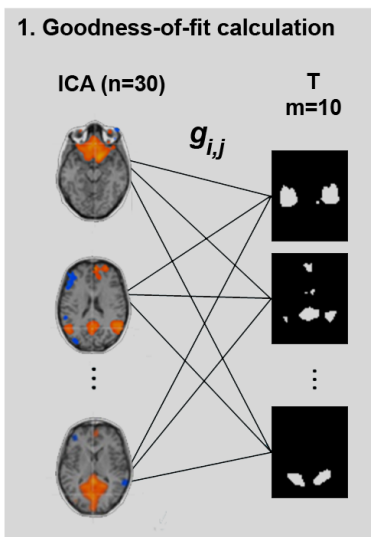
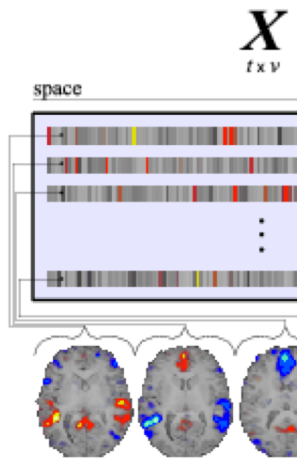
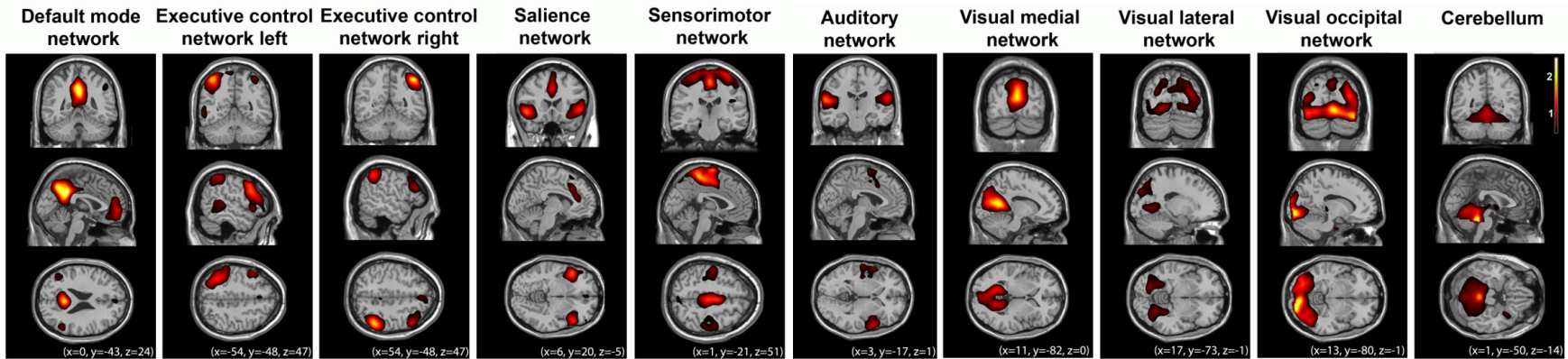
Profession	Burnout
Physician	8%
Nurse	24%
Nursing assistant	23%
Physio-/speech-/ergo-therapist	8%
Psychologist/social worker	10%

n=523

Methodological challenges



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