



Connectivity analysis

Resting state fMRI after severe brain injury



Université
de Liège

James S. McDonnell Foundation



CHERCHER, TROUVER, GUÉRIR, POUR VOUS & AVEC VOUS.



UNAM

4 April 2017

Querétaro, Mexico

Athena Demertzi, PhD

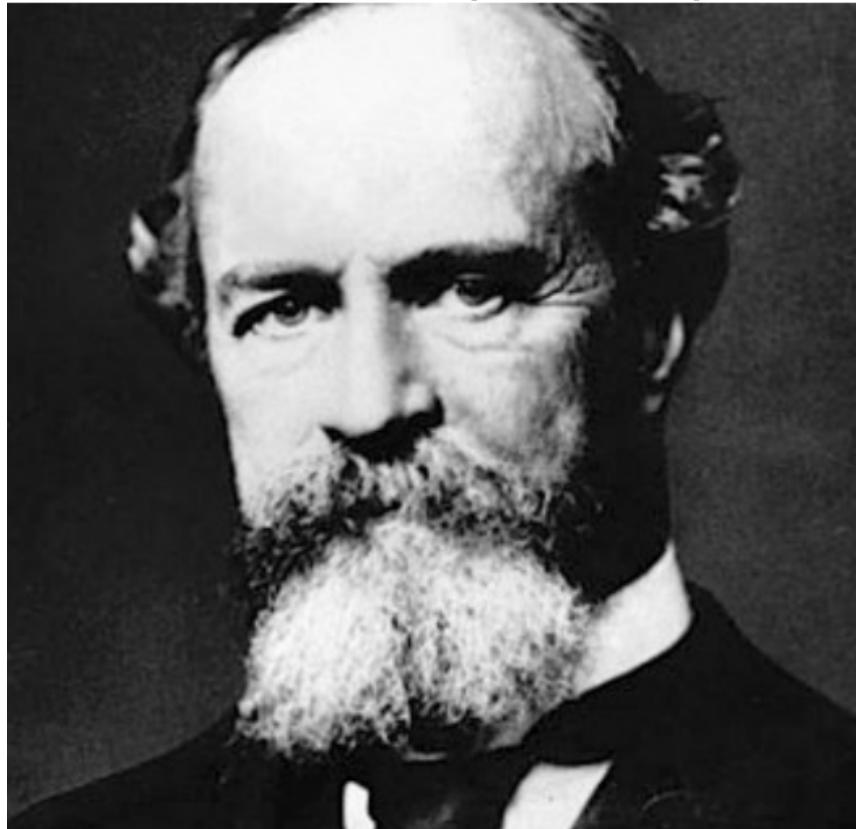
Institut du Cerveau et de la Moelle épinière – ICM
Hôpital Pitié-Salpêtrière, Paris, France

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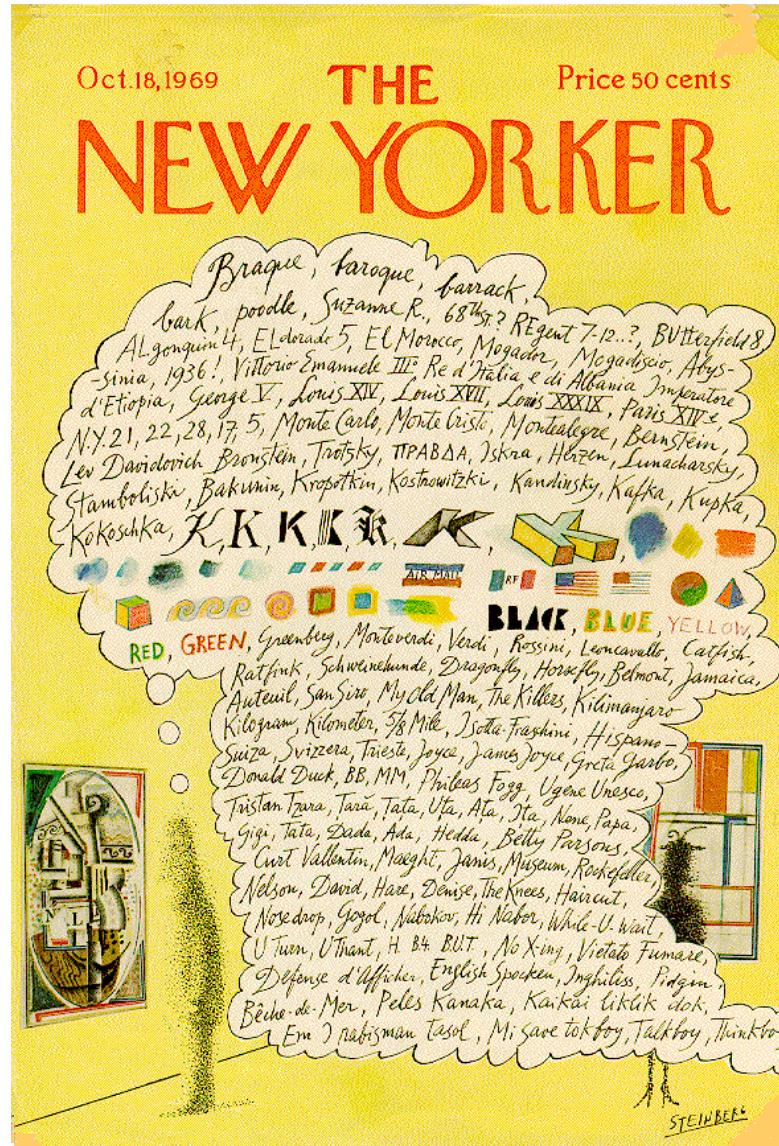
Coma Science Group
GIGA Research & Neurology Department
University & University Hospital of Liège, Belgium

The stream of consciousness

William James (1842-1910)



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



Some numbers...



- The human brain is approximately 2% of the weight of the body
- 80% of this energy consumption is used to support neuronal signalling → most of the energy consumed is used for functional activities
- Stimulus and performance-evoked changes in brain energy consumption are surprisingly small (typically <5%)



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

A control state?

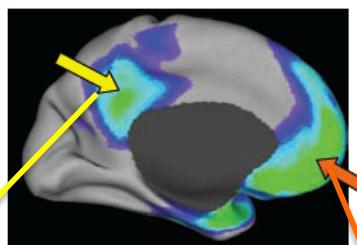
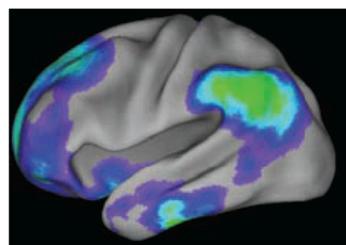


Cognitive psychology: Mental chronometry
(measures the time required to complete specific
mental operations isolated by the careful selection
of task and control states.

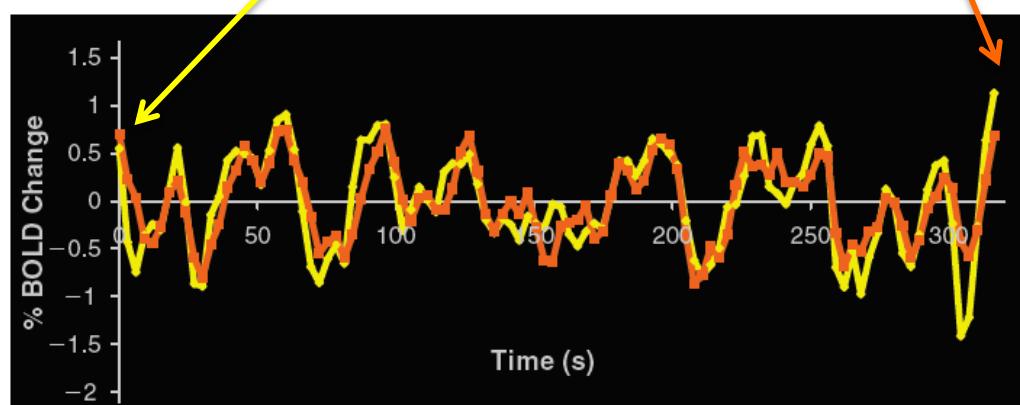


fMRI: Subtracting functional images acquired in a
task state from ones acquired in a control state

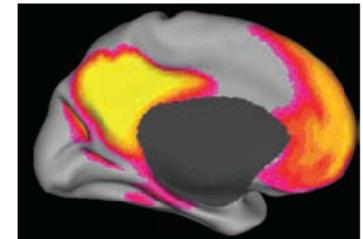
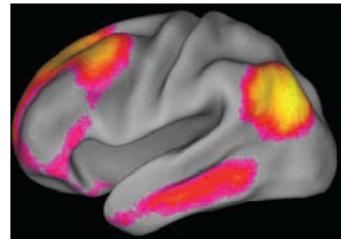
Default brain function



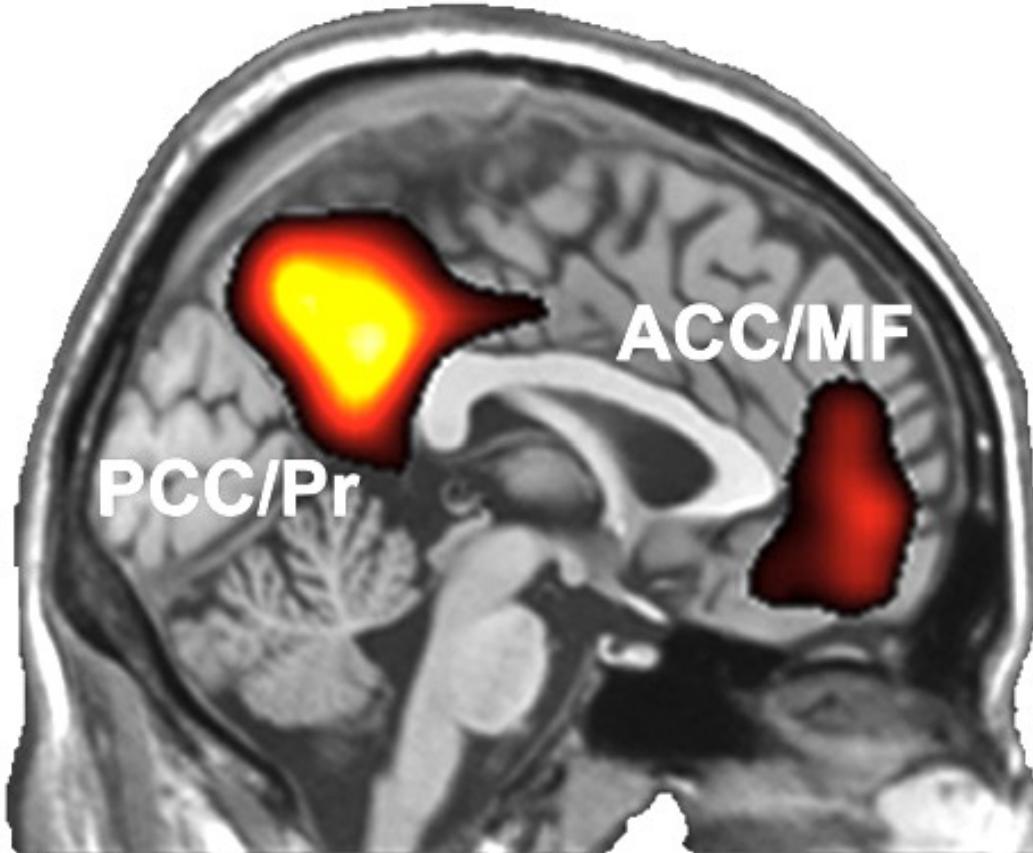
Task performance - Rest (fixation/eyes closed)
→ **Deactivations**



“Activations” during rest



The brain's default mode at rest



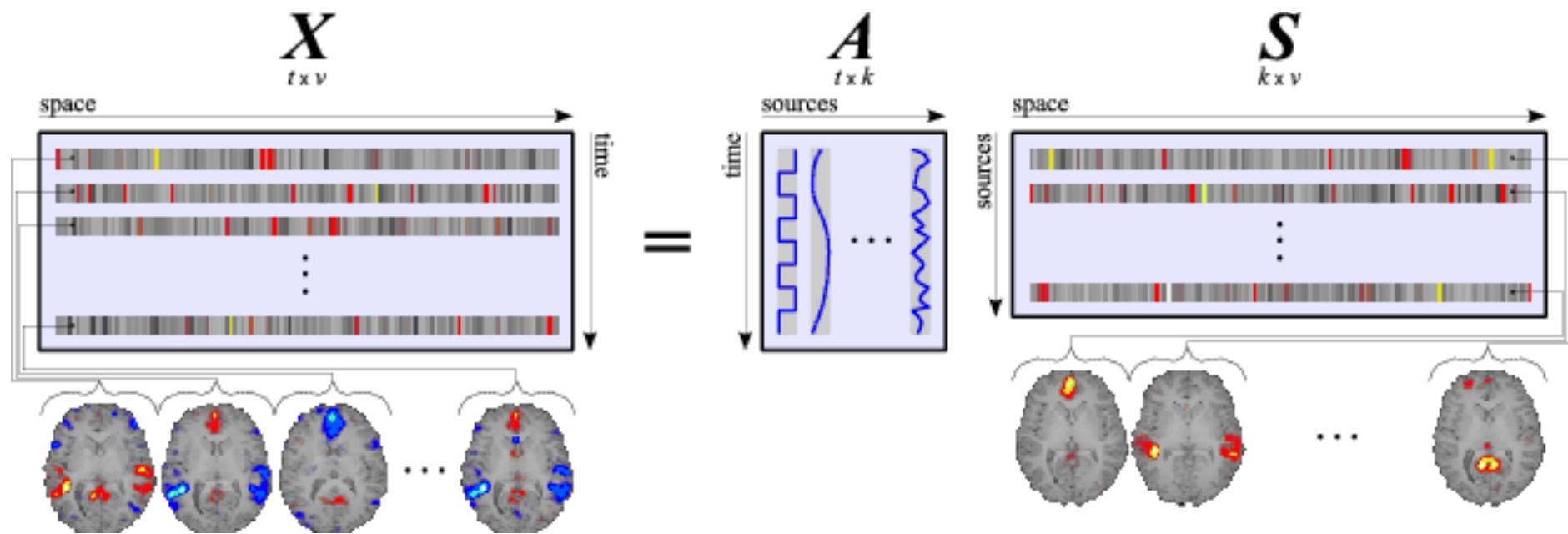
Demertzi & Whitfield-Gabrieli, in: *Neurology of Consciousness* 2nd ed. 2015

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

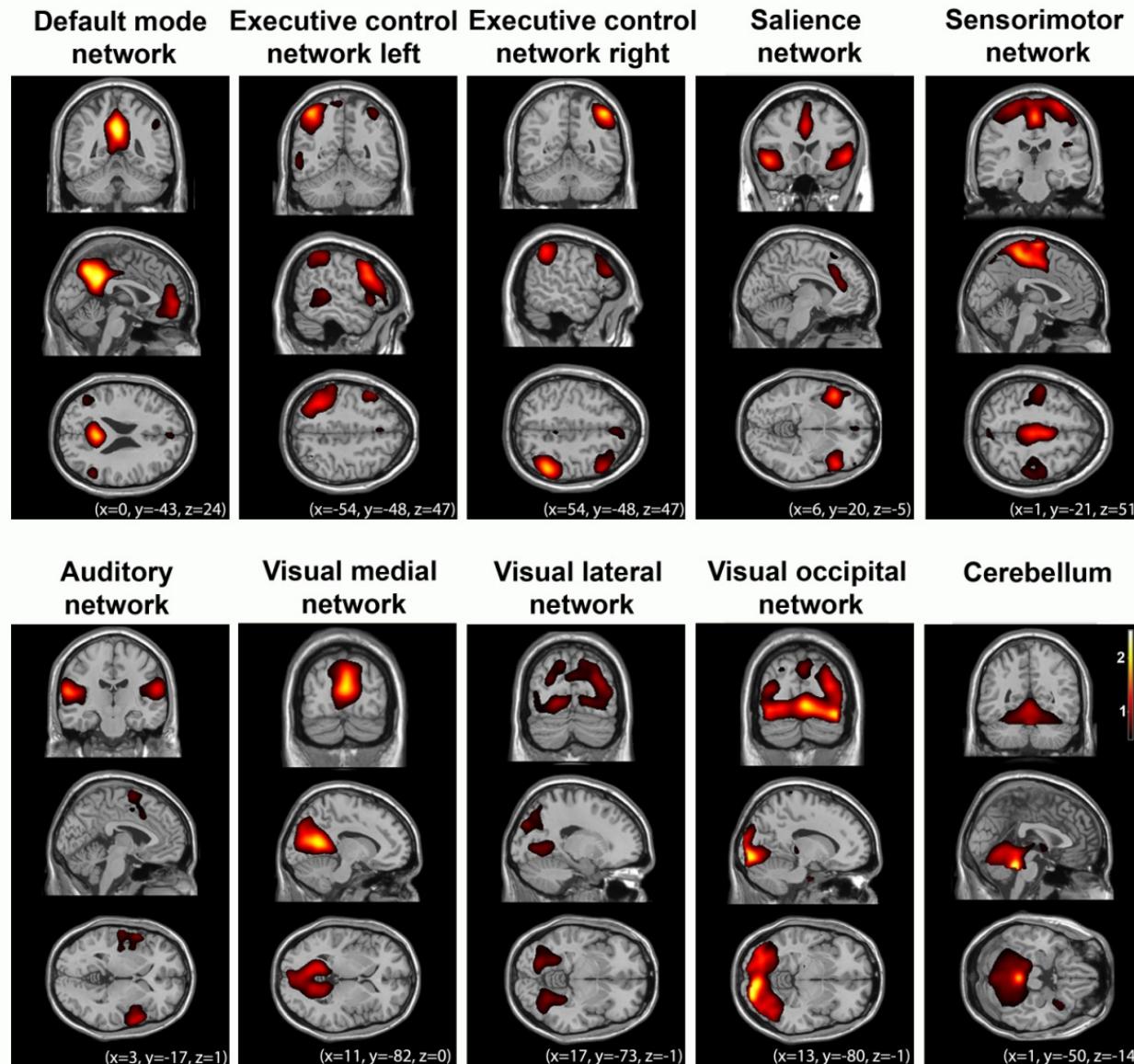
Demertzi et al, *Front Hum Neurosci* 2013

Raichle et al, *PNAS* 2001

Independent component analysis (ICA)



Intrinsic Connectivity Networks

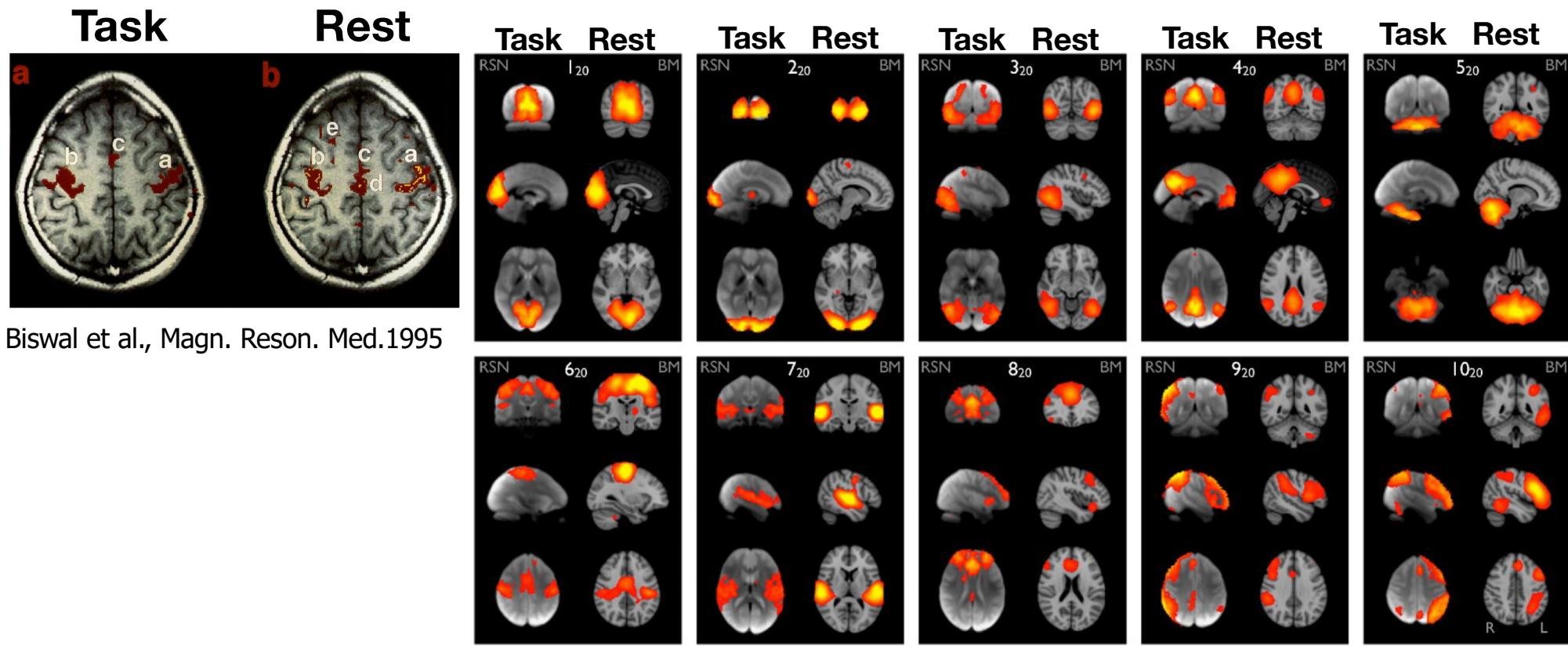


Heine et al, Frontiers in Psychology 2012

Smith et al, PNAS 2009

Beckmann et al, Phil. Trans. R. Soc. B 2005

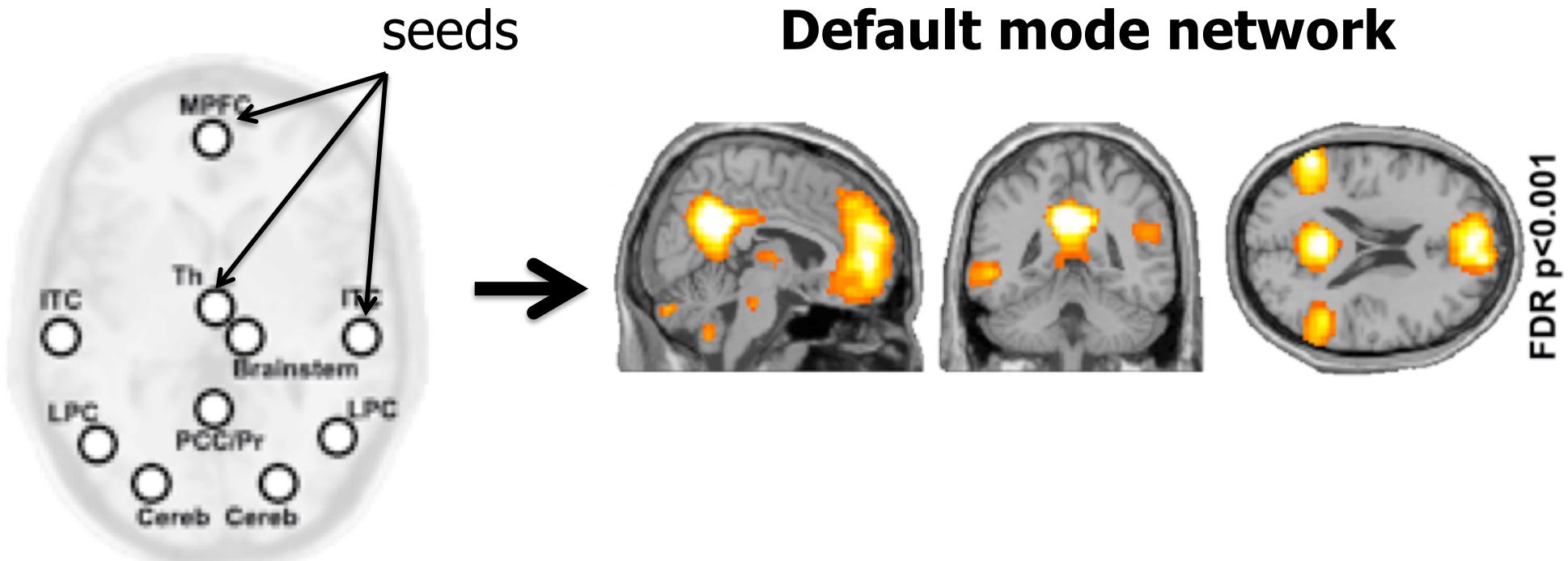
Intrinsic Connectivity Networks- Cognitive?



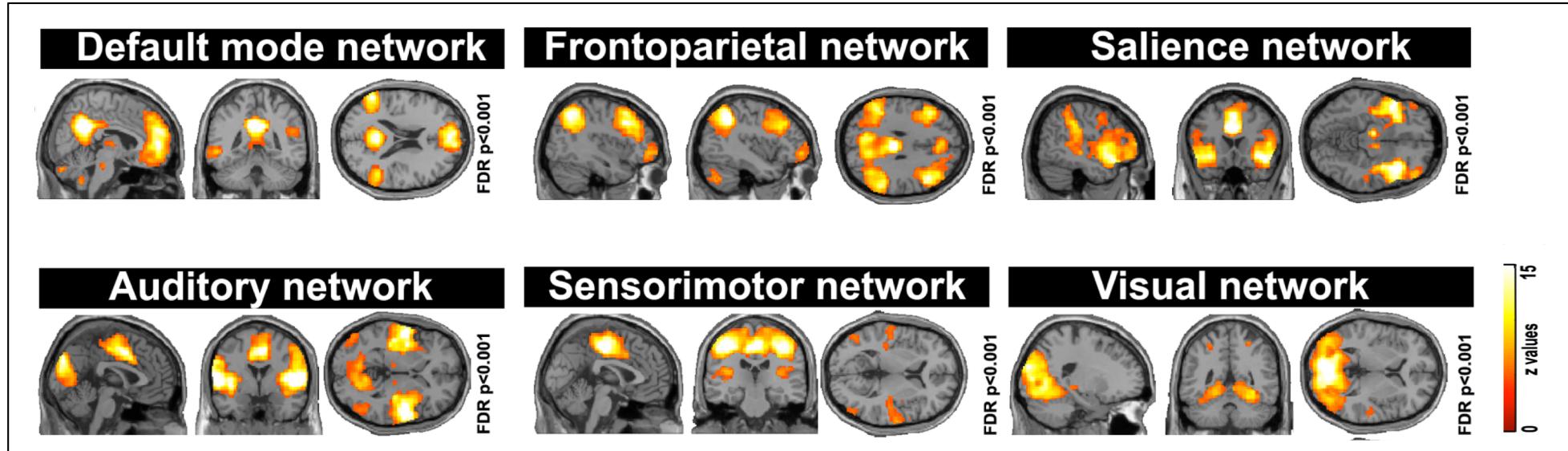
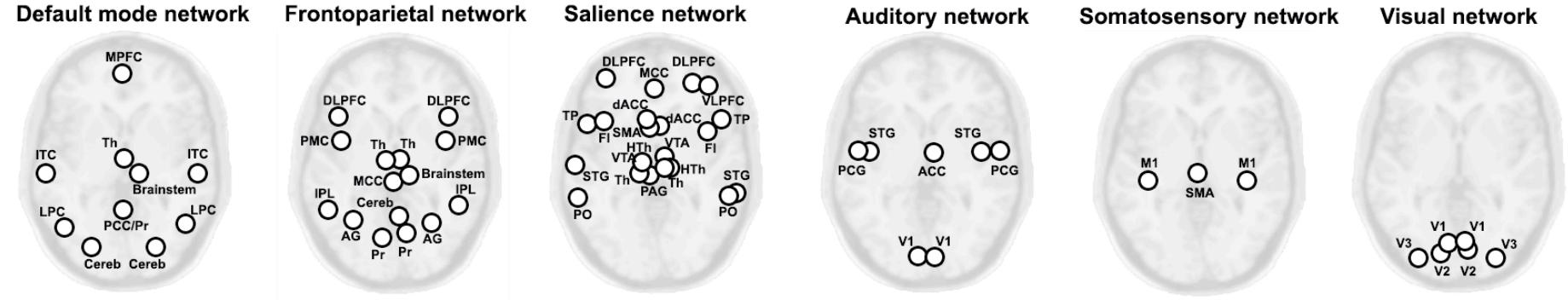
Biswal et al., Magn. Reson. Med. 1995

Smith et al., PNAS 2009

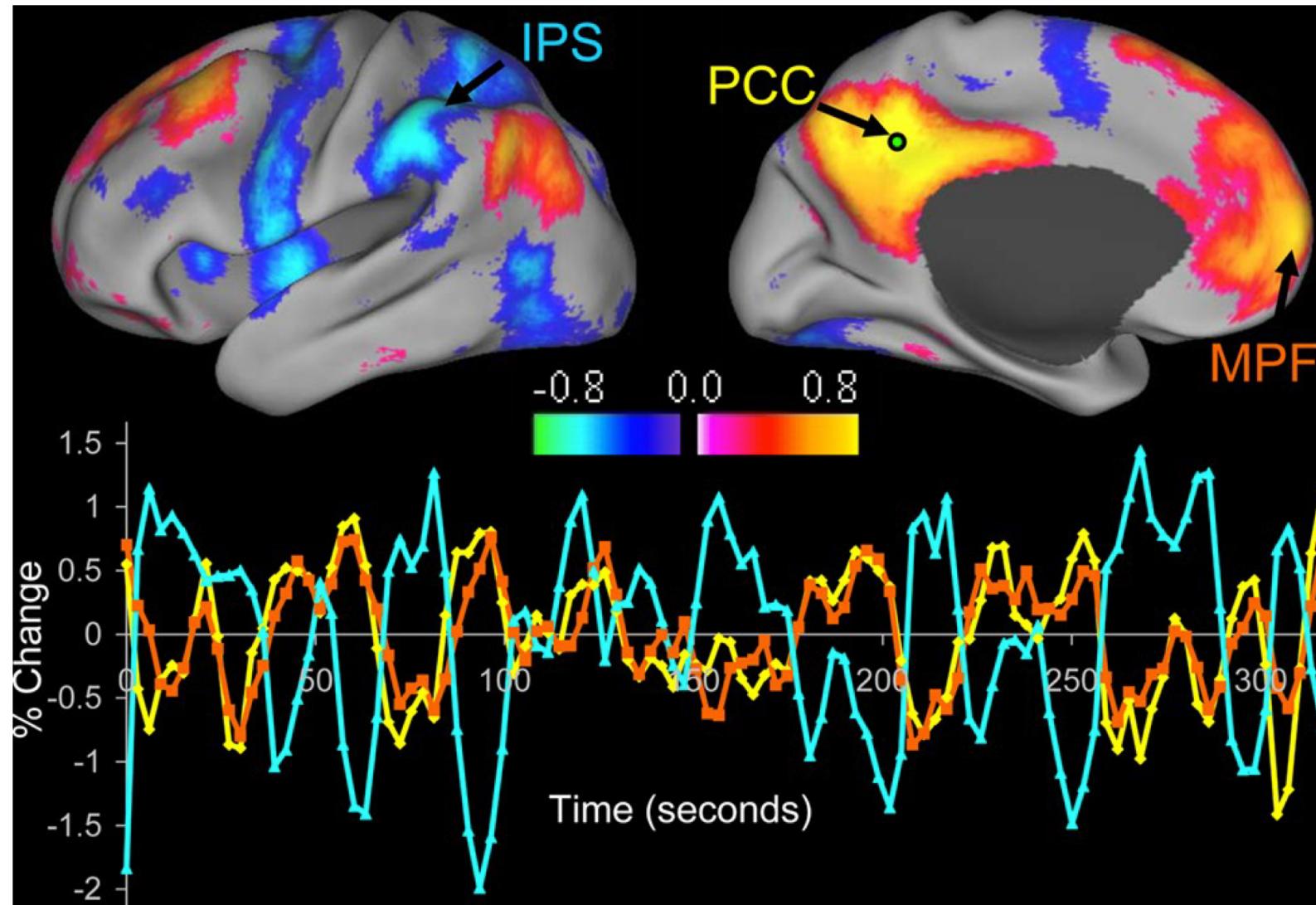
Seed-based region correlation



Seed-based region correlation

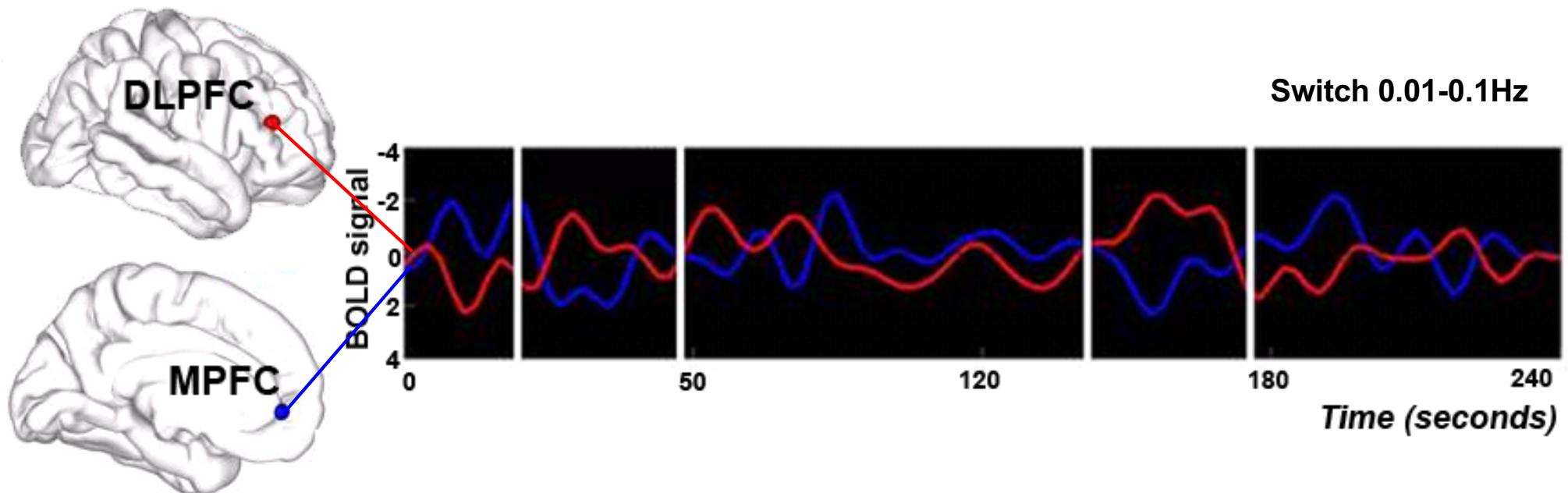


rsfMRI anticorrelations



rsfMRI anticorrelations

External awareness
or anticorrelated network



Internal awareness
or Default mode network

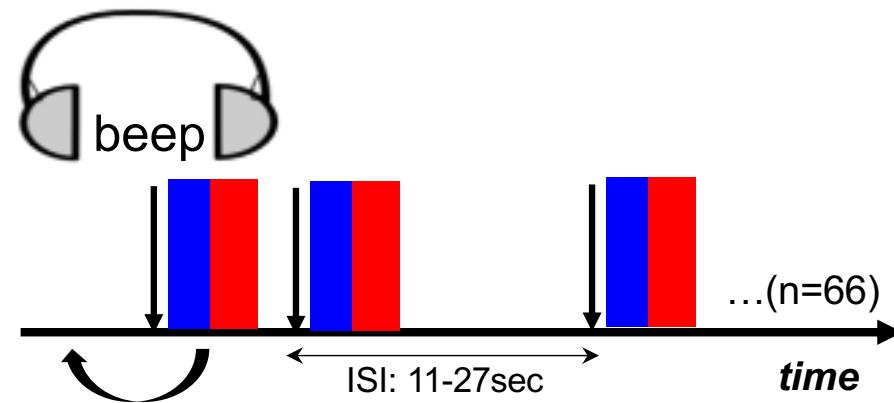
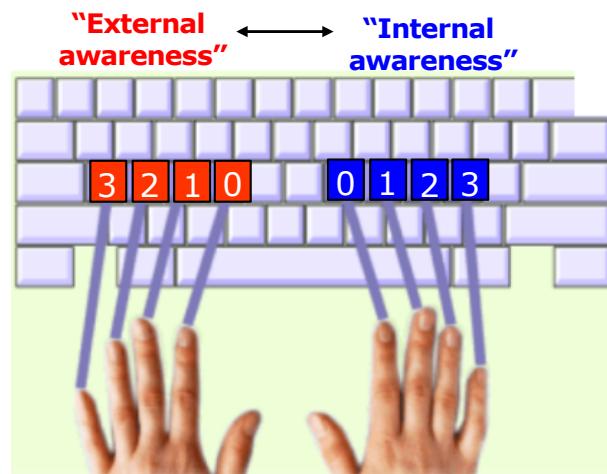
Demertzi & Whitfield-Gabrieli, in: *Neurology of Consciousness* 2nd ed. 2015

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

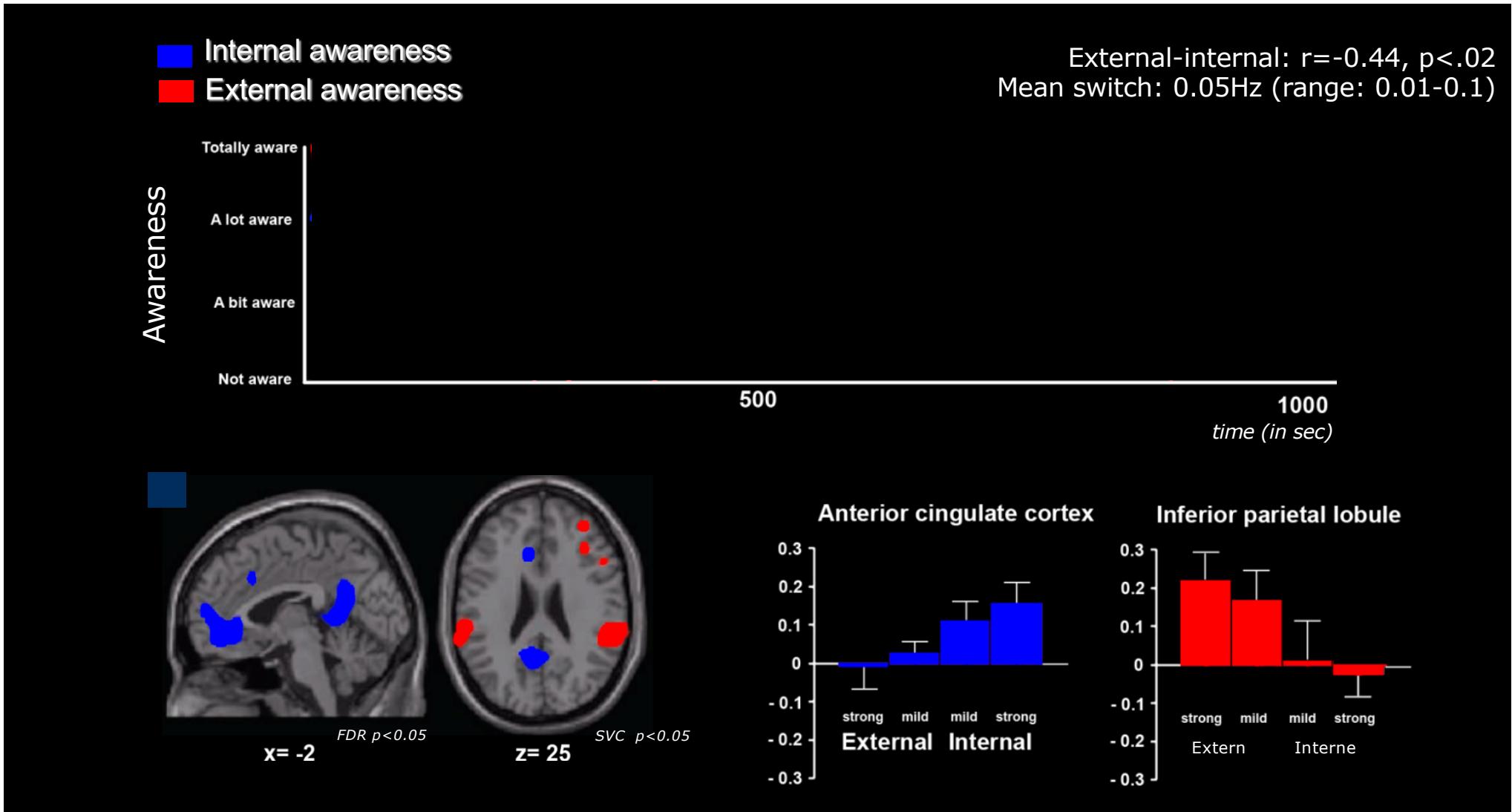
Demertzi et al, *Front Hum Neurosci* 2013

Laureys, *Scientific American* 2007

rsfMRI anticorrelations- Cognitive?

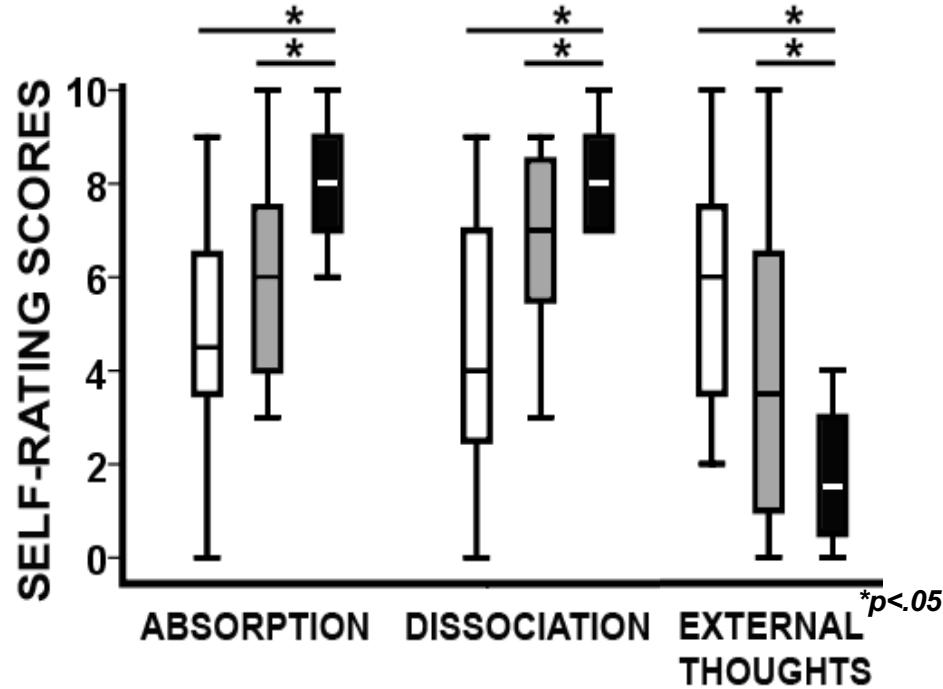


The cognitive counterpart of anticorrelations



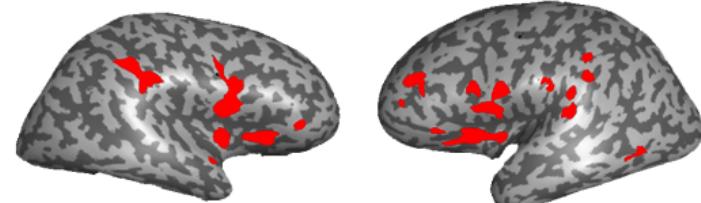
Anticorrelated connectivity is modified in hypnosis

- Normal consciousness
- Autobiographical mental imagery
- Hypnosis

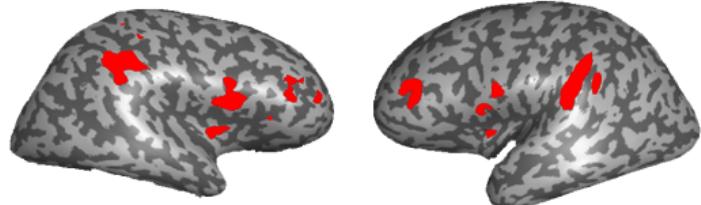


EXTRINSIC SYSTEM

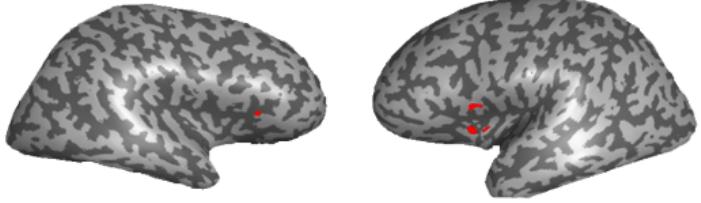
Normal consciousness



Autobiographical mental imagery

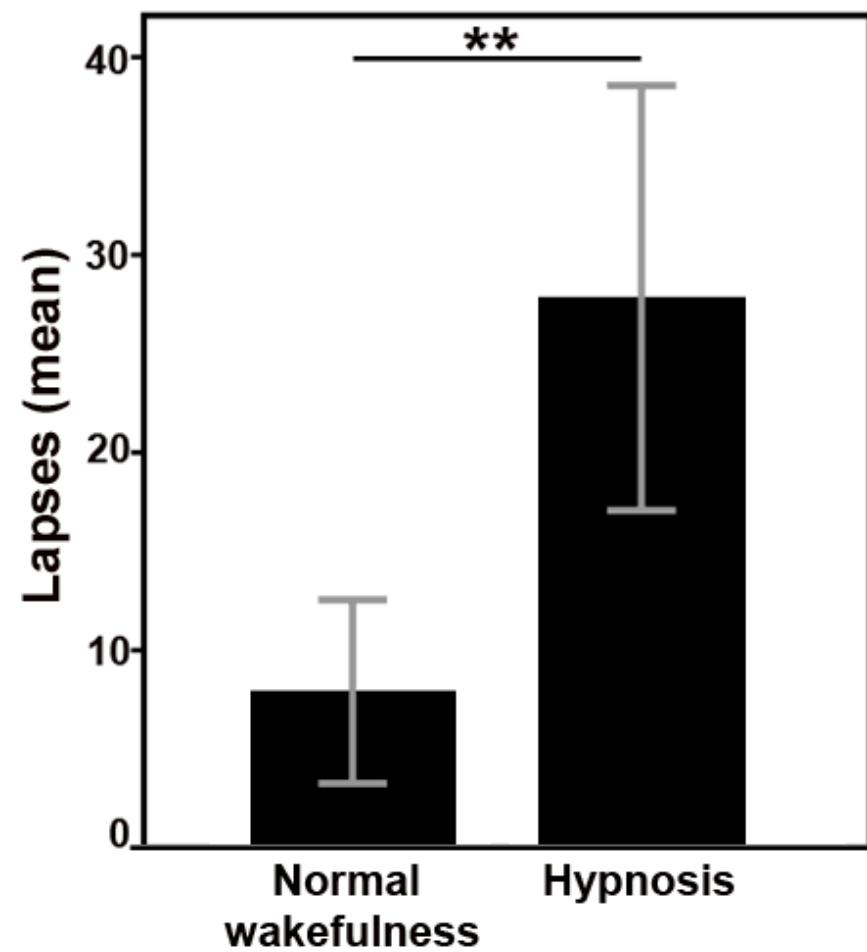
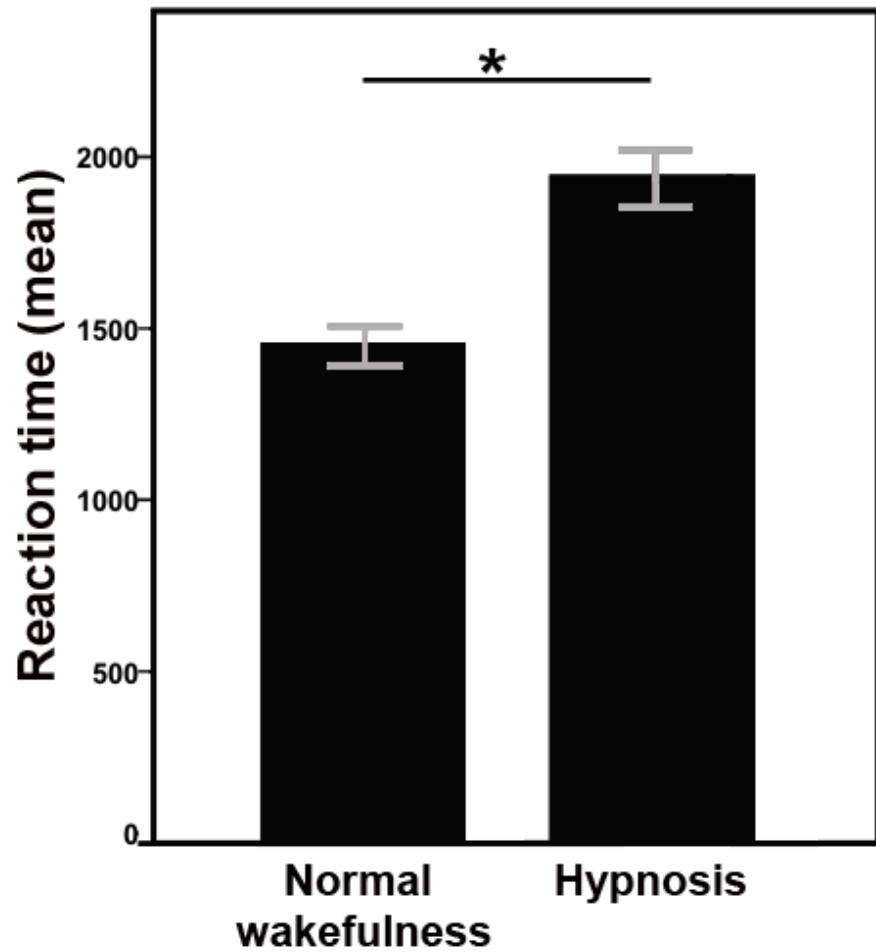


Hypnosis

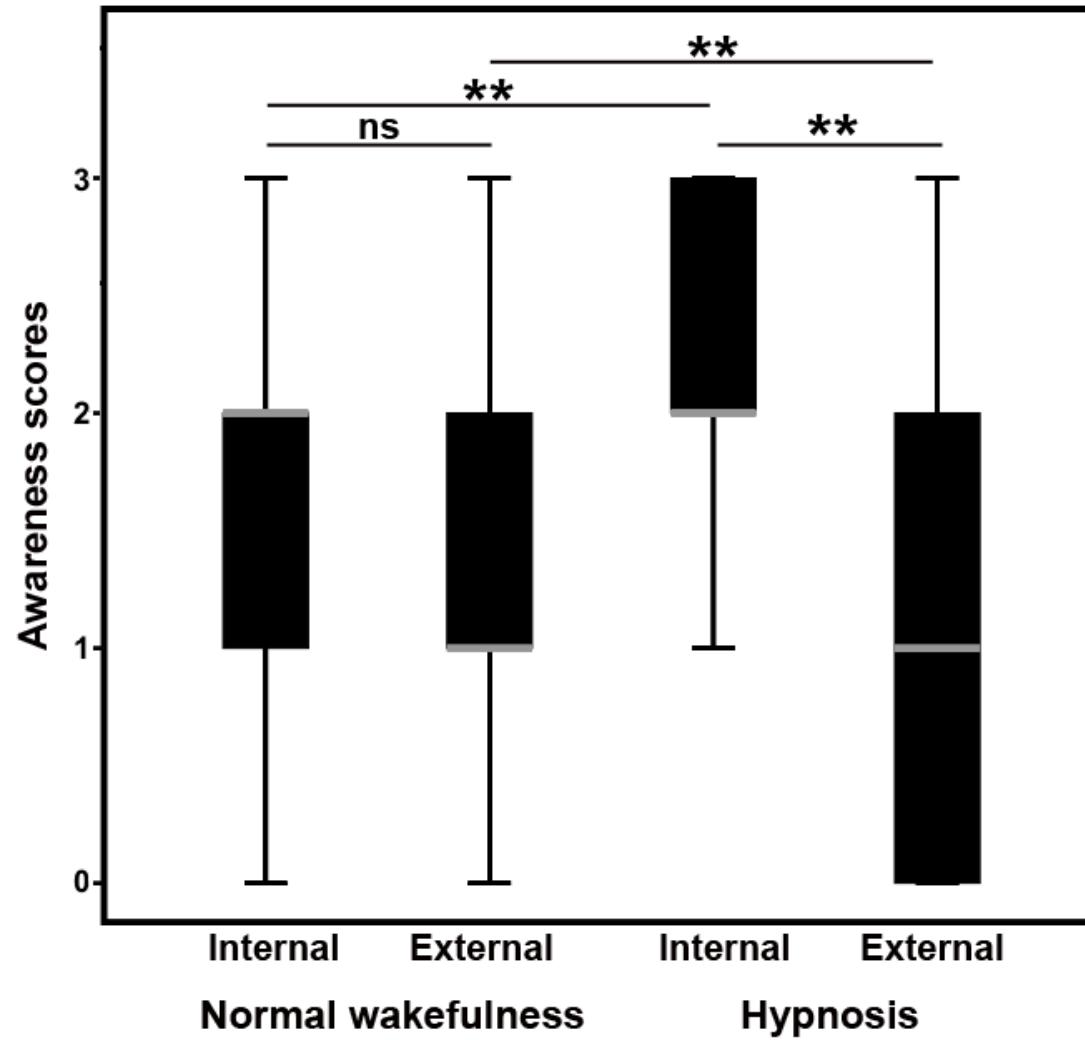


$p < 0.05$ corrected for multiple comparisons

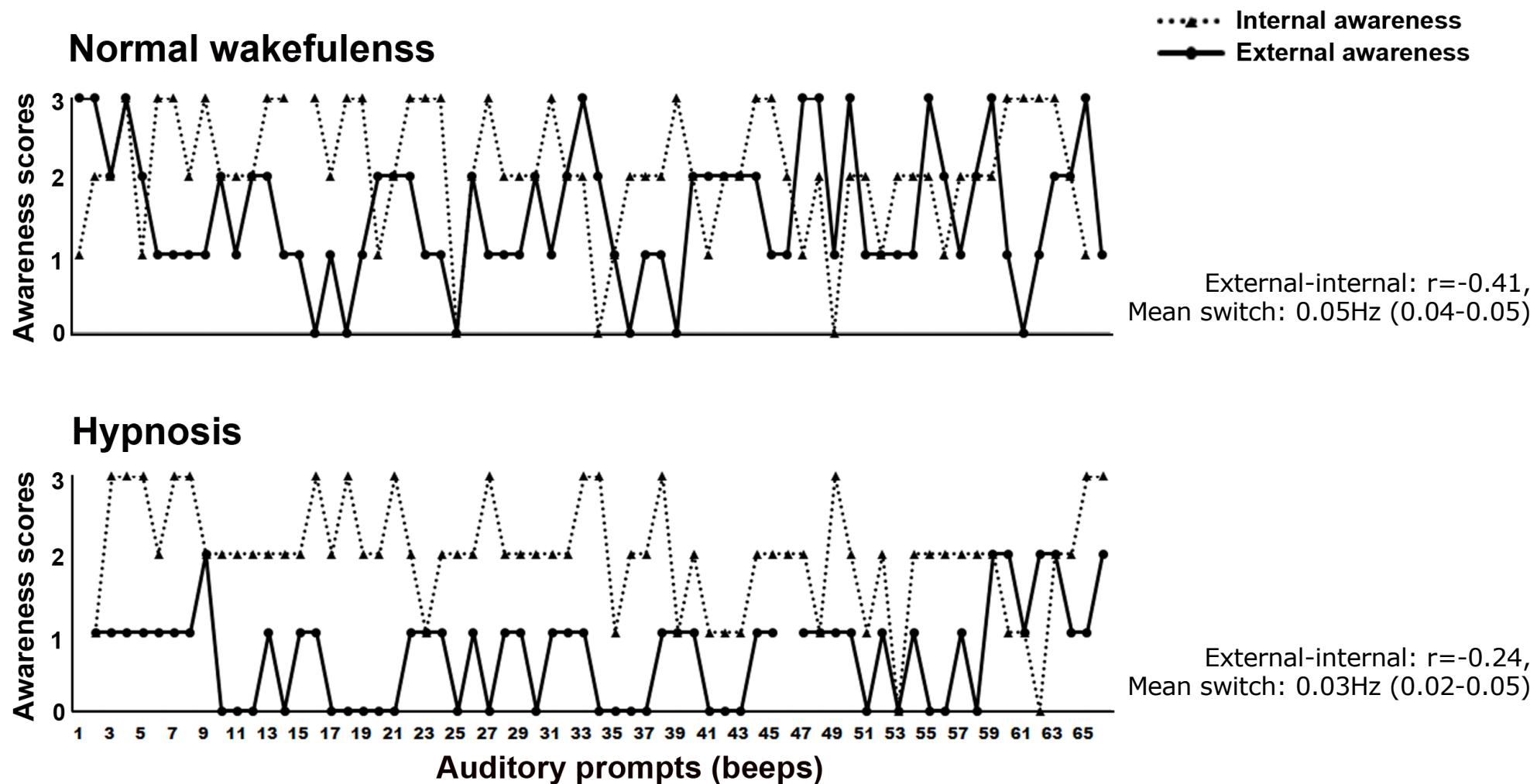
Behavior is modified in hypnosis



Awareness is modified in hypnosis



Awareness is modified in hypnosis





Consciousness

CHERCHER, TROUVER, GUÉRIR, POUR VOUS & AVEC VOUS.



Consciousness



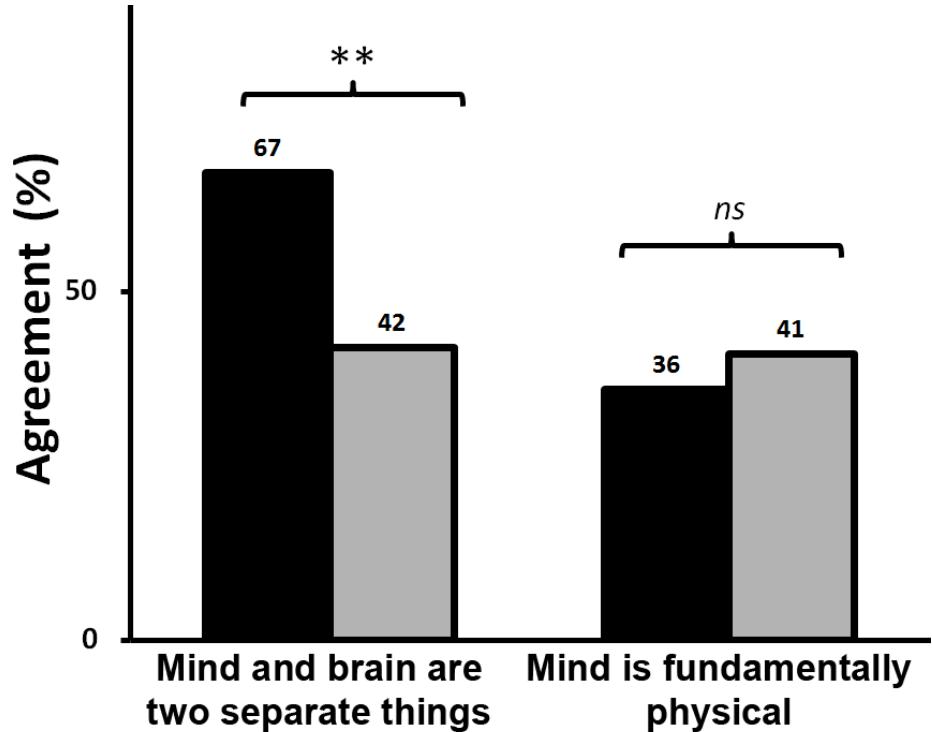
Functionalism

Materialism

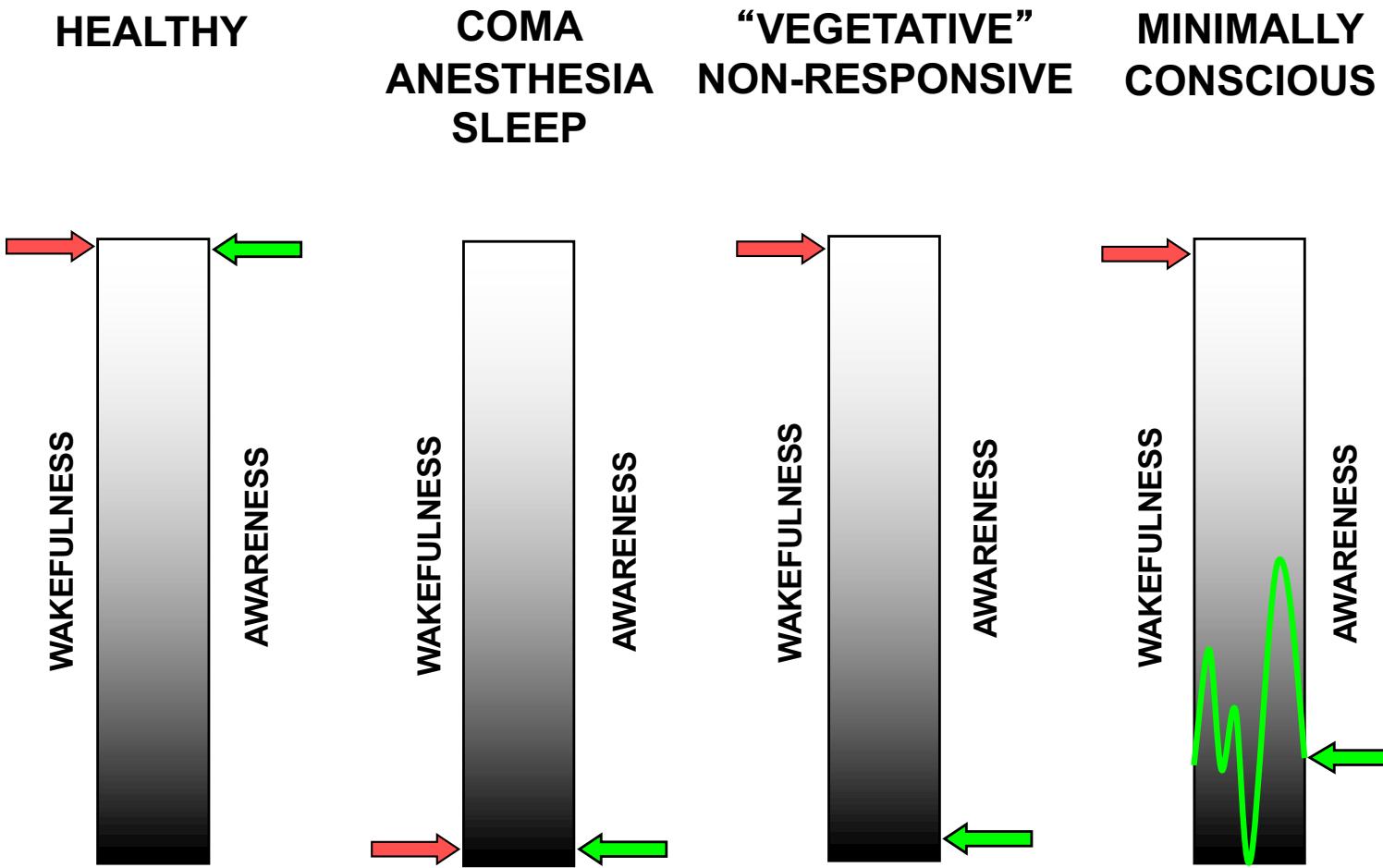
Dualism



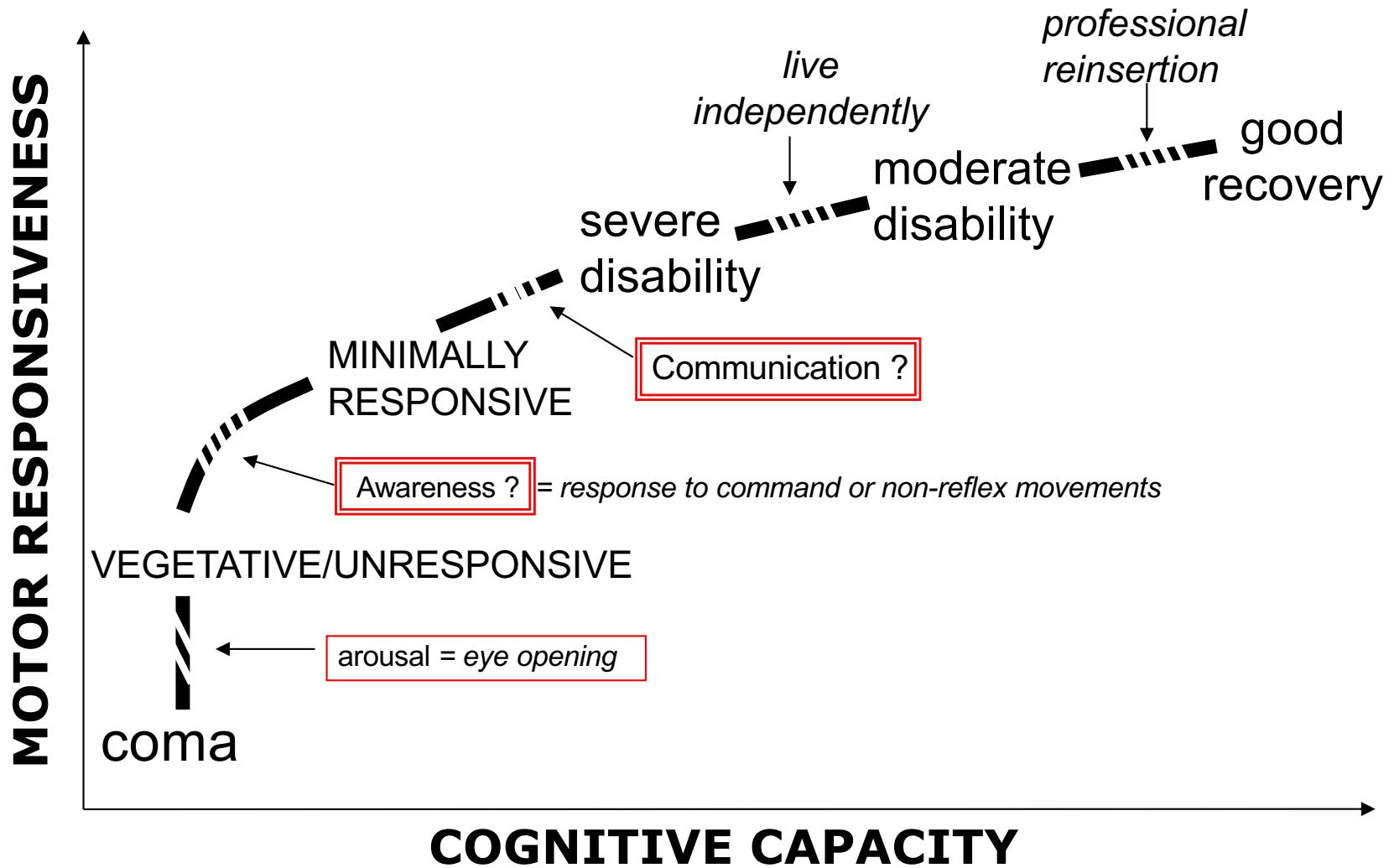
■ Edinburgh survey (n=250)
□ Liège survey (n=1858)



A clinical definition of consciousness



Behavioral evaluation of patients



Behavioral diagnosis: 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

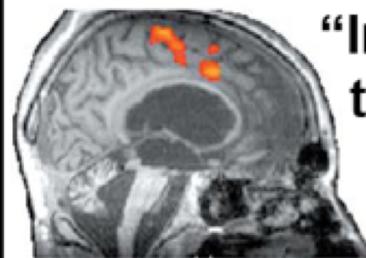
PET Neuroimaging

Coma Recovery Scale-Revised results		
	UWS	MCS
Clinical consensus diagnosis		
¹⁸F-FDG PET		
VS/UWS	24 (21%)	5 (4%)
MCS	12 (11%)	71 (63%)
Total	36 (32%)	76 (68%)
		112 (100%)
UWS=unresponsive wakefulness syndrome. MCS=minimally conscious state.		
Table 2: Diagnostic results by modality		

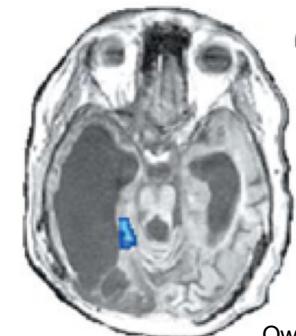
Stender & Gosseries et al, Lancet 2014

Detecting awareness with fMRI

Active paradigms



“Imagine playing tennis”



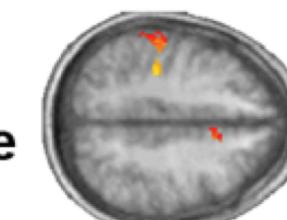
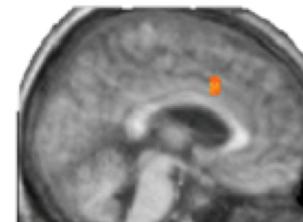
“Imagine visiting the rooms of your house”

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

Passive paradigms



median nerve

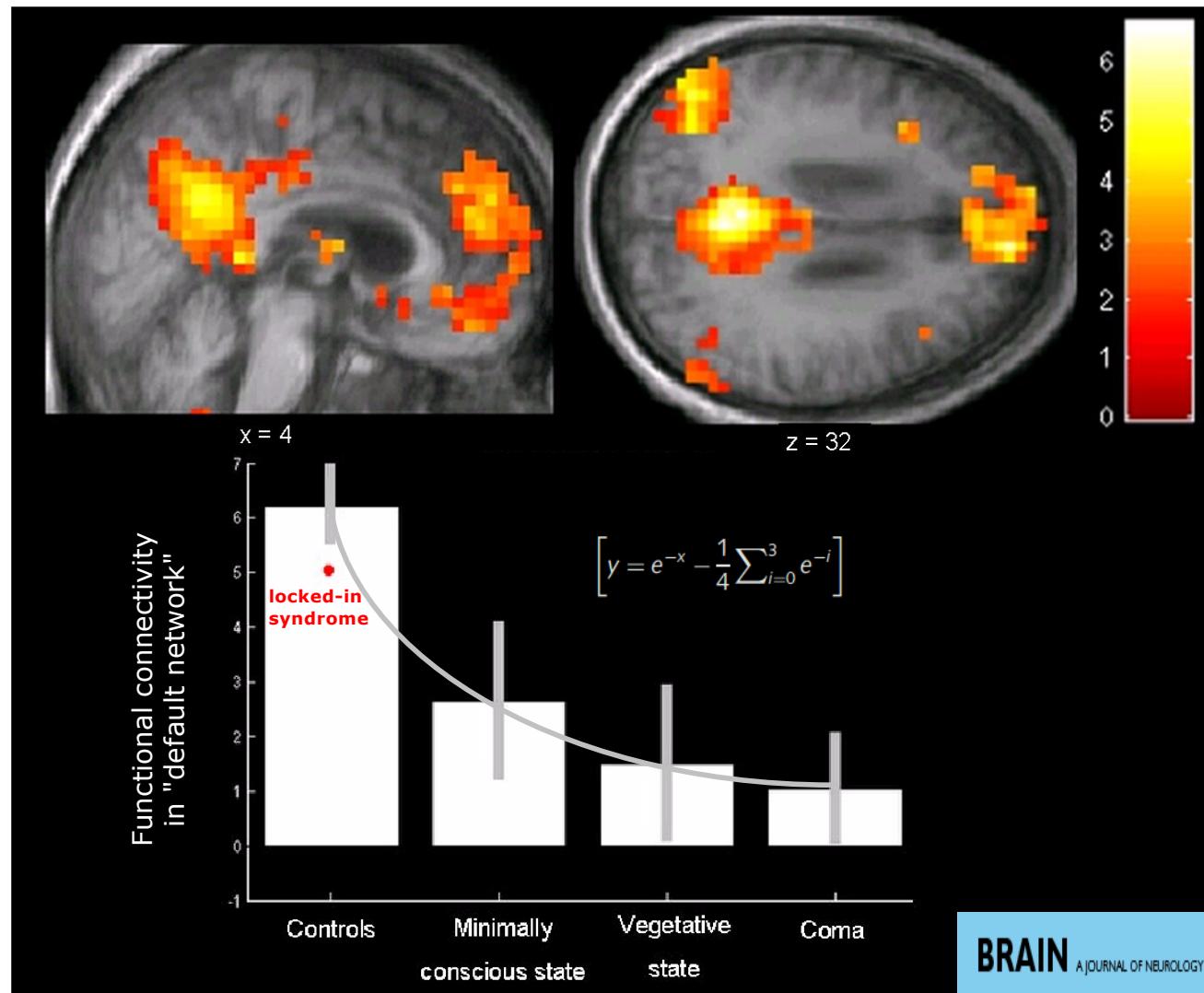


Boly et al, Lancet Neurol 2008

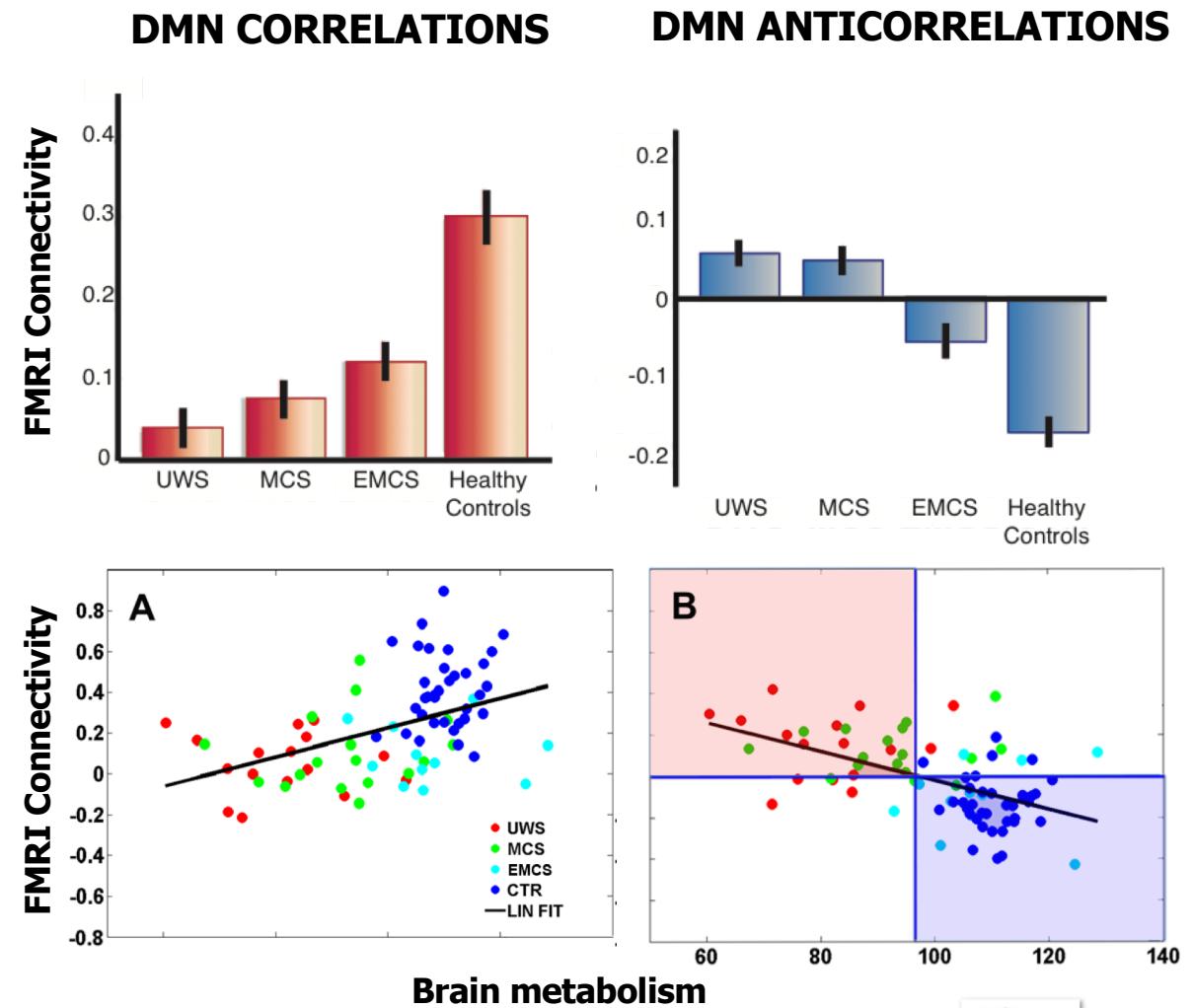
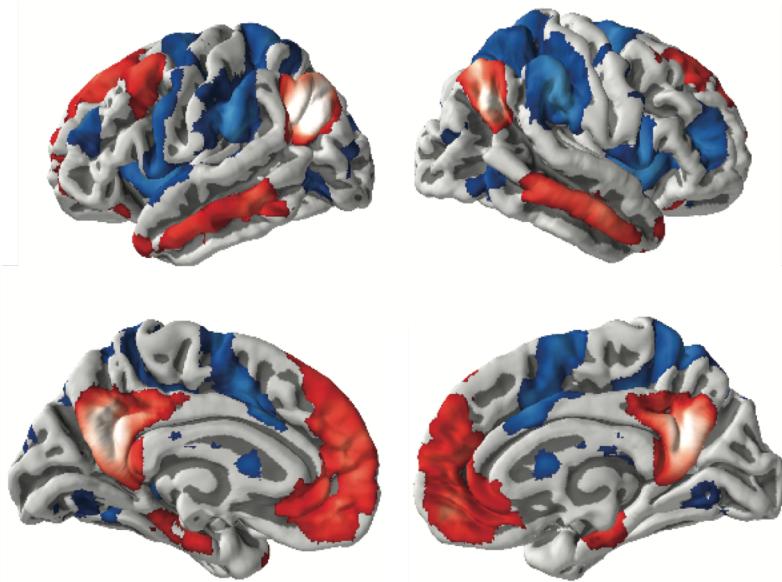
Heine, Di Perri, Soddu, Laureys, Demertzi
In: *Clinical Neurophysiology in Disorders of Consciousness*, Springer-Verlag 2015

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

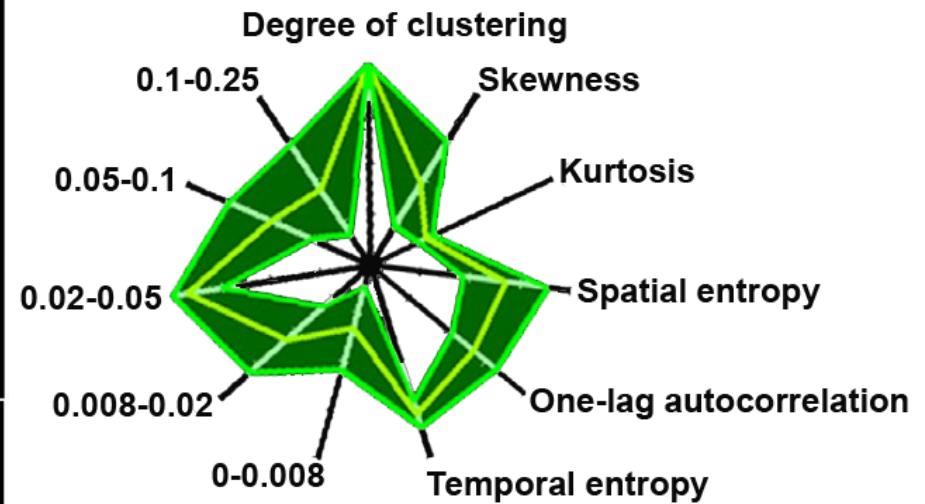
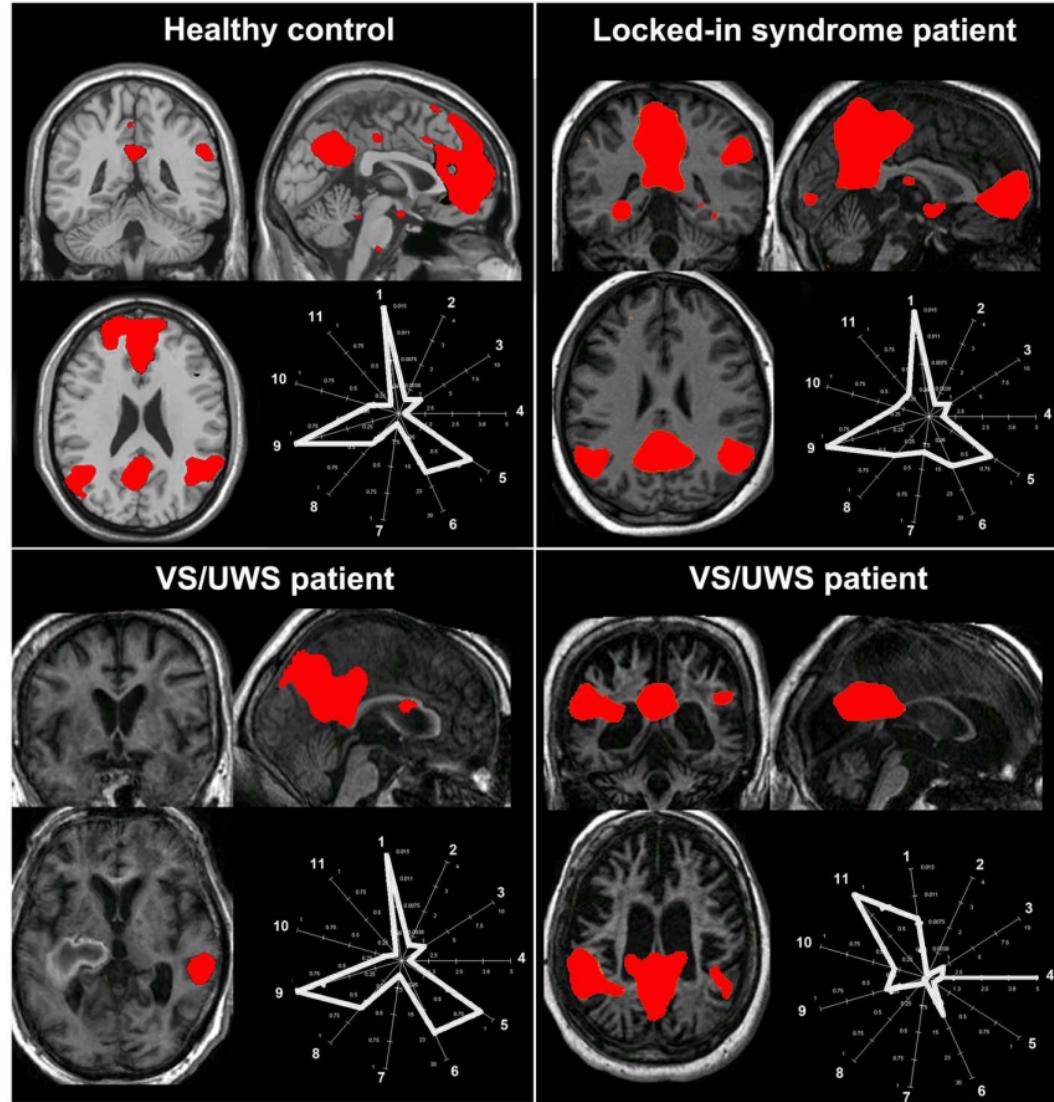
Default mode network in DOC



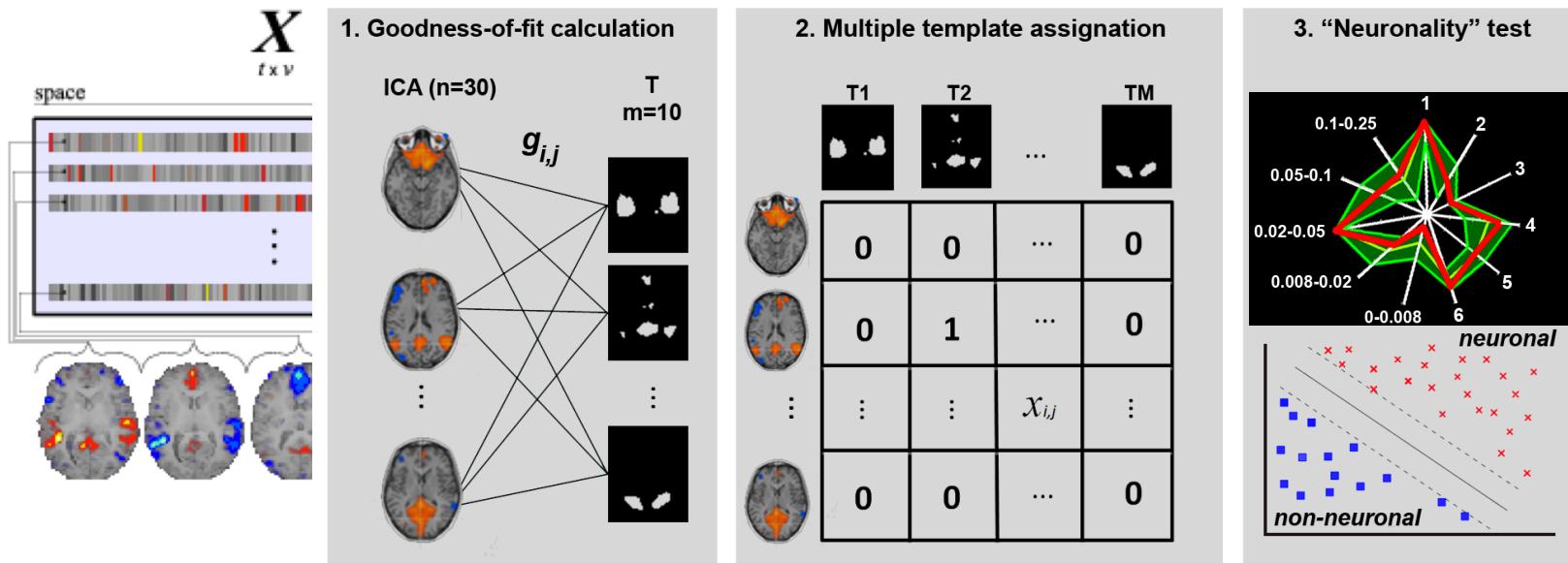
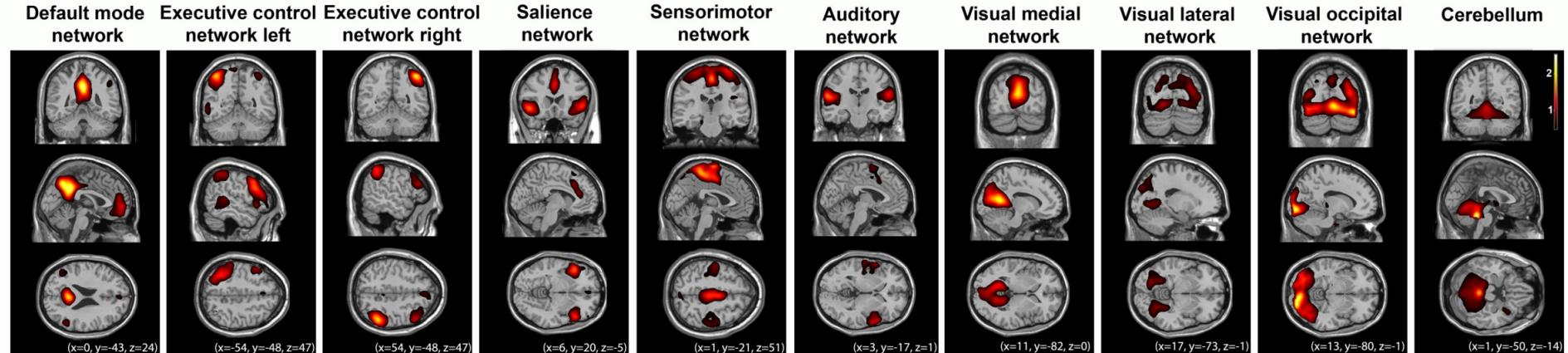
Anticorrelated activity is absent in DOC



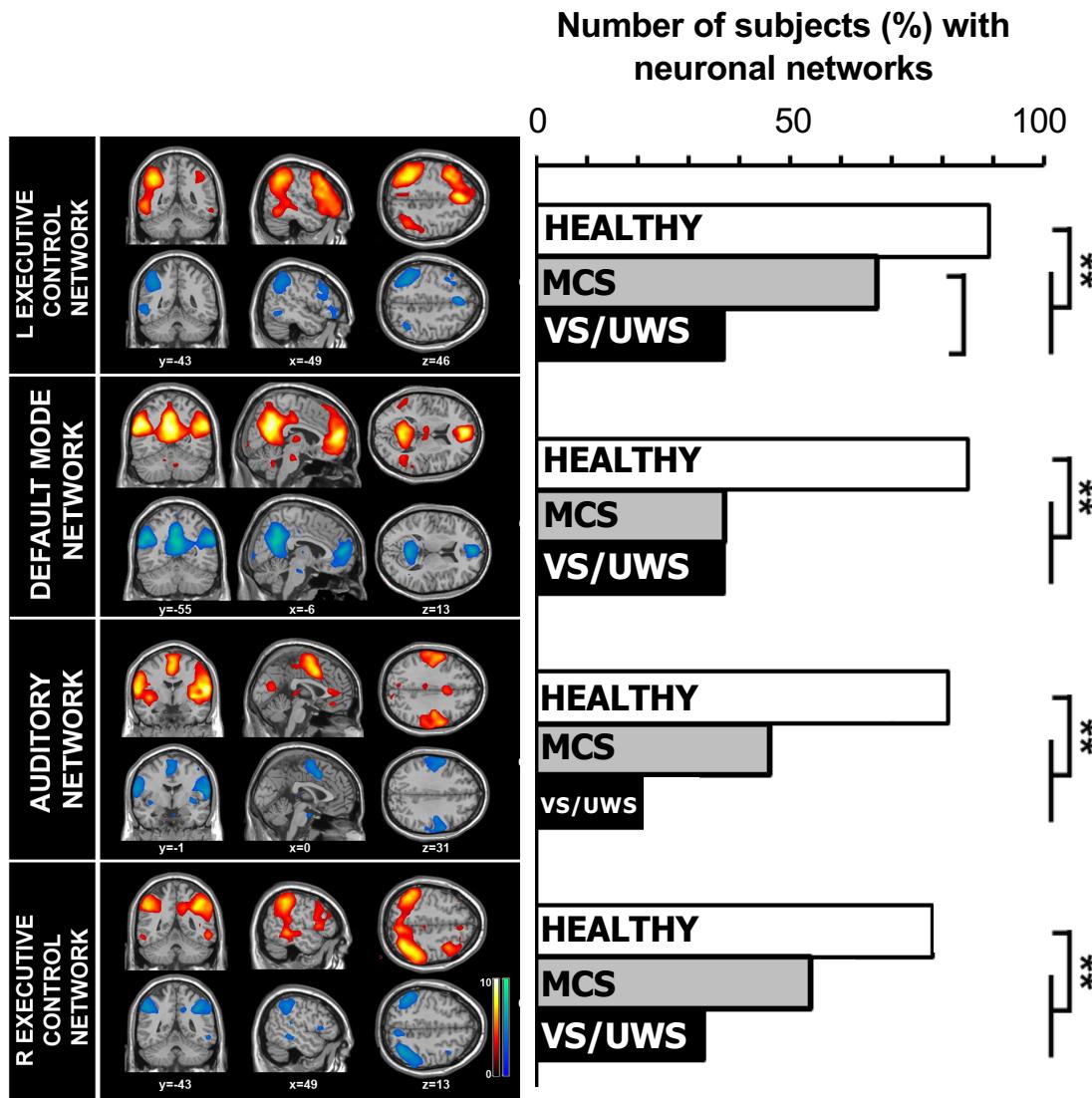
A challenge...



Systems-level intrinsic connectivity



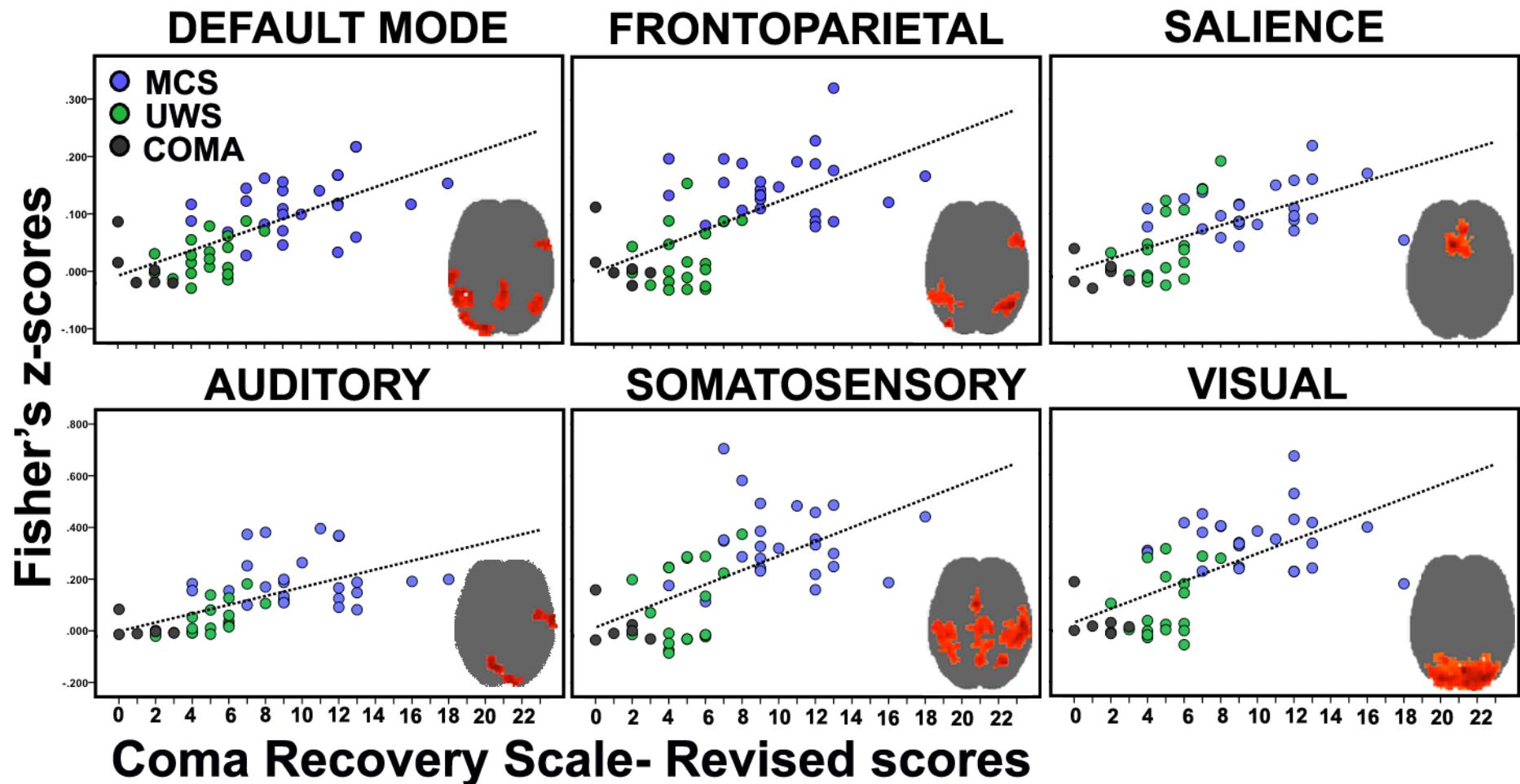
ICA: Fewer “neuronal” networks in DOC



Single-patient classification

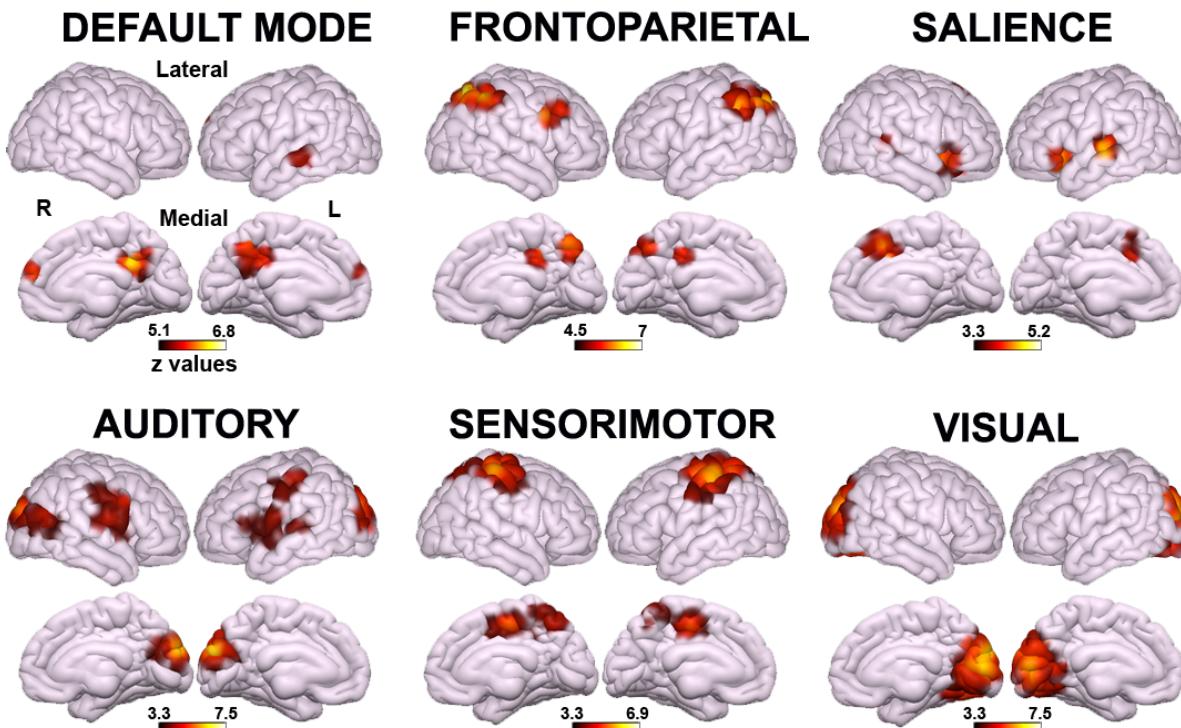
Performance measures	Accuracy	TPR healthy	TPR patients	Selected RSNs
Healthy vs. all patients				
Neuronal	85.3	.82	.87	Auditory, DMN

Seed-based: Connectivity reflects C state



Which network discriminates best?

MCS > VS/UWS

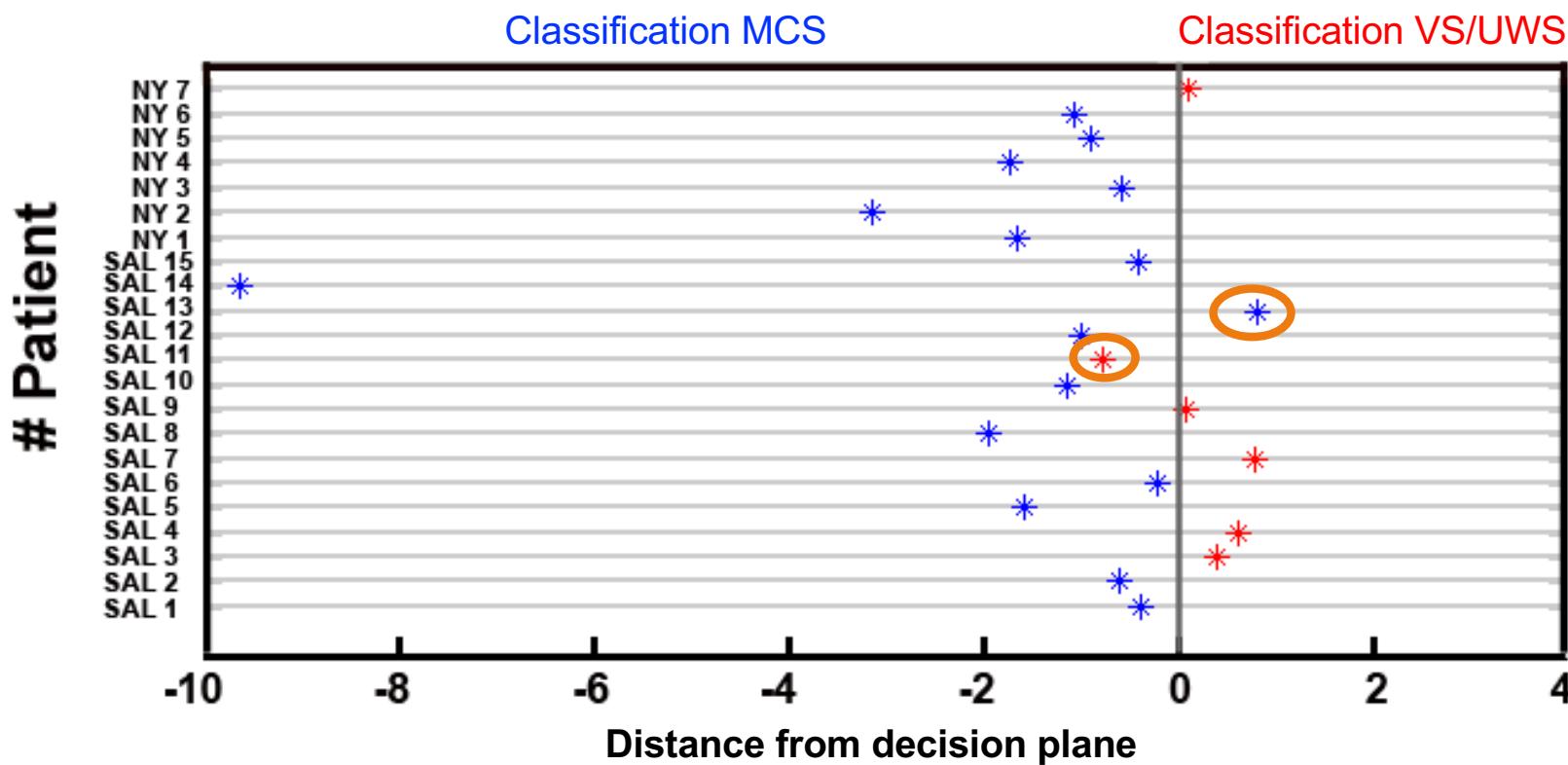
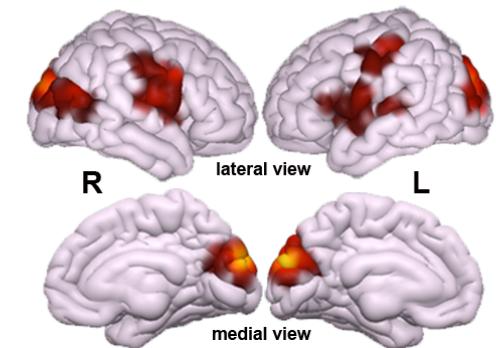


FWE $p < 0.05$ (cluster-level)

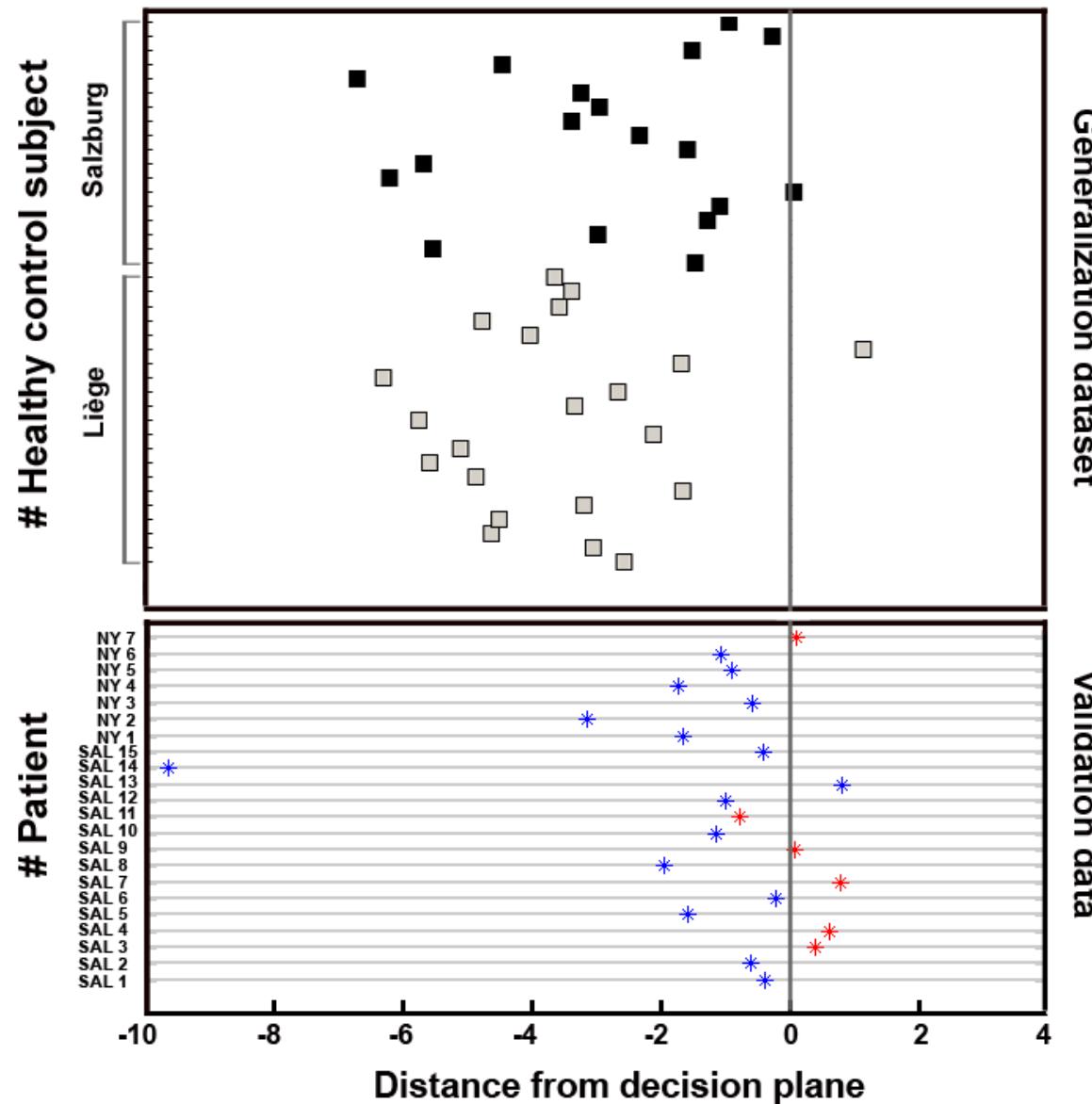
Network	Feature selection criterion (t-test)			Single-feature classification		
	t value	Rank	p value	TP MCS	TN VS/UWS	Accuracy
Auditory	8.32	1	<.001	25	18	43/45
Visual	7.79	2	<.001	23	15	38/45
Default mode	6.95	3	<.001	23	15	38/45
Frontoparietal	6.82	4	<.001	23	15	38/45
Salience	6.21	5	<.001	24	15	39/45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

Crossmodal connectivity classifies independently assessed patients

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



Classifier generalizes to healthy





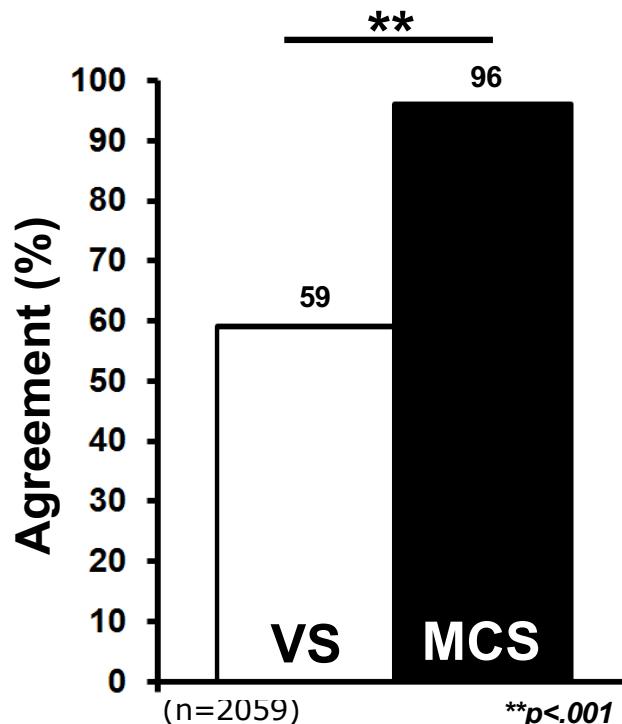
Ethical significance

CHERCHER, TROUVER, GUÉRIR, POUR VOUS & AVEC VOUS.



Attitudes towards pain

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

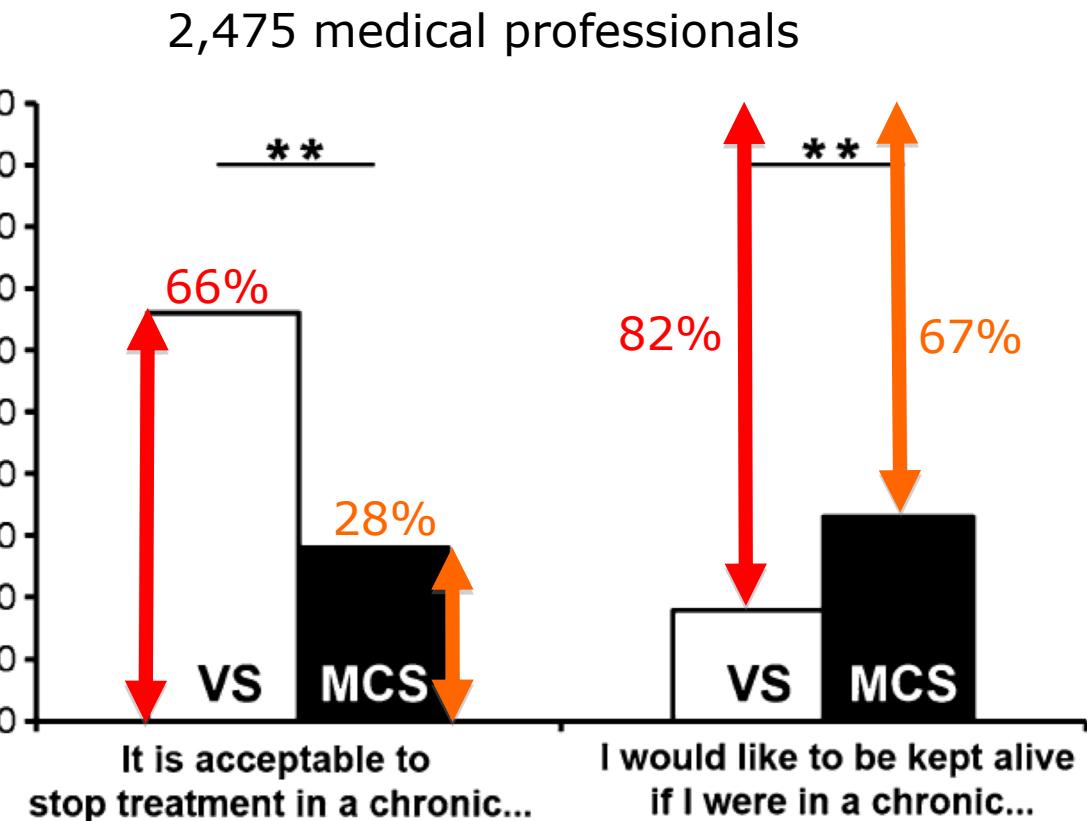


Question Predictors	Odds Ratio	95% Confidence Interval	p value
Do you think VS patients feel pain?			
Age	1.01	1.00 - 1.02	.050
Women	1.25	.99 - 1.58	.060
Northern Europe	1.00		
Central Europe	.81	.58 - 1.14	.240
Southern Europe	1.10	.76 - 1.60	.600
Paramedical professionals	1.56	1.20 - 2.00	<.001
Religious respondents	1.37	1.10 - 1.70	.004
Do you think MCS patients feel pain?			
Women	2.38	1.33 - 4.26	.003
Religious respondents	1.83	1.05 - 3.18	.031

Predicted response: "agreement"

Attitudes towards end-of-life

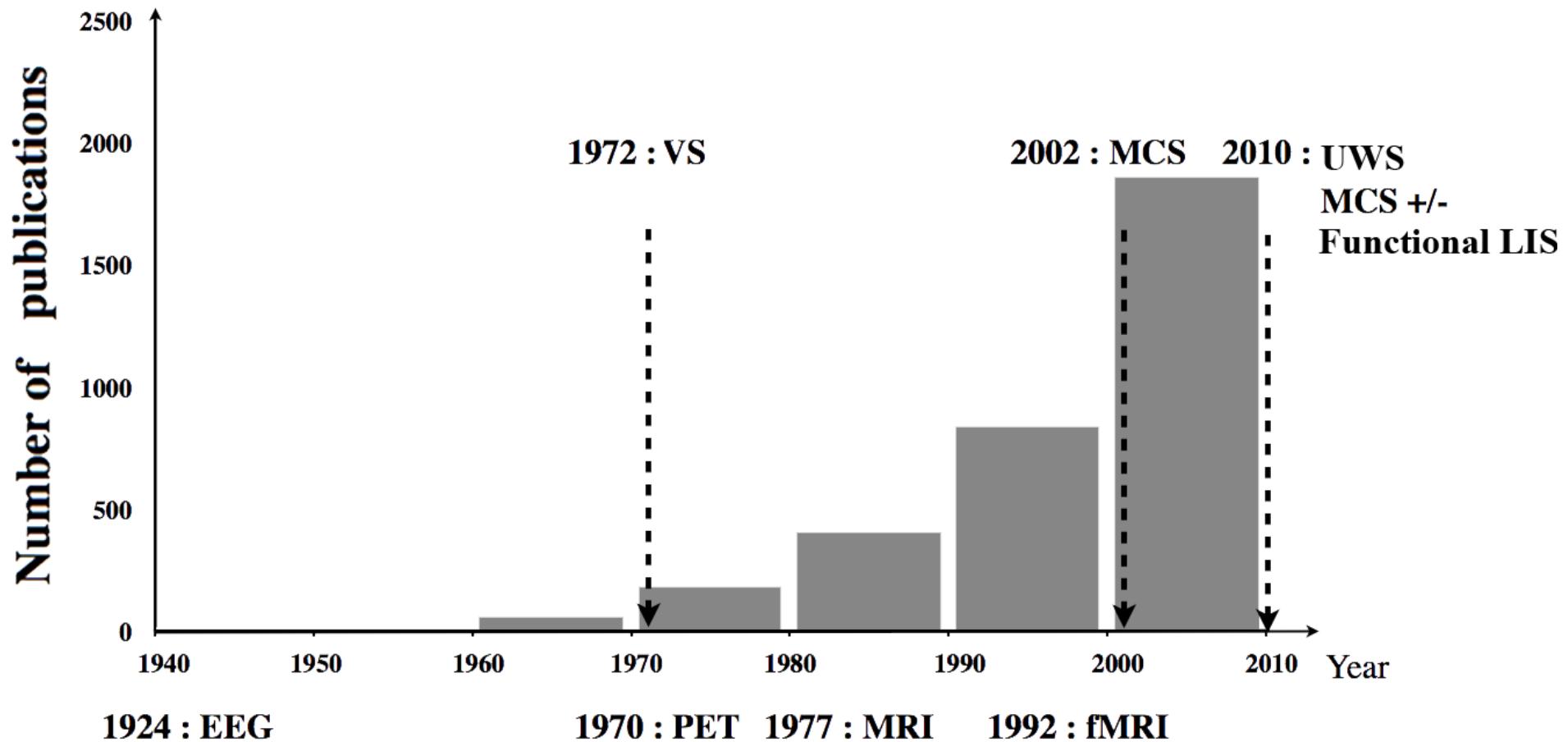
- VS worse than death for the patient: 55%
- VS worse than death for their families: 80%
- MCS worse than VS for the patient: 54%
- MCS worse than VS for their families: 42%



The ethics of technology-based assessment

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

New knowledge, new nosology



Neuro-ethical issues to consider

- The moral significance of Consciousness
 - ontological understanding: consciousness = personhood = moral agency
 - relational or contextual understanding: patients have value for others
- Legal challenges: responses to critical questions with NI
- Cognitive neuroscience is about brain/mind reading
 - to what degree do we neuroscientists have the right to interfere with a patient's intimacy, such as cognitive contents, in the absence of their consent?
 - in essence, where do we draw the limits of deciphering another person's cognitive content, like dreams, ongoing mentation etc? What is the additive value of it to a societal level?

Conclusions

- fMRI resting state connectivity carries information of cognitive function
- fMRI resting state connectivity can be used in the clinical setting
- fMRI resting state connectivity needs to generalize to unconscious conditions of diminished wakefulness
- NI studies have ethical consequences

Thank you!



Coma Science Group & PICNIC Lab

The departments of Neurology and Radiology in Liège and Paris

...and mostly patients and their families!

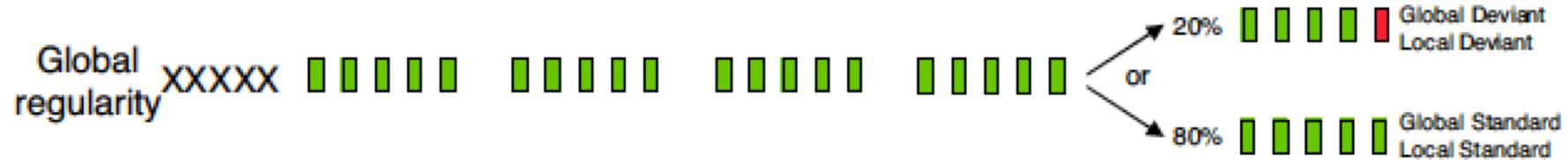


CHERCHER, TROUVER, GUÉRIR, POUR VOUS & AVEC VOUS.

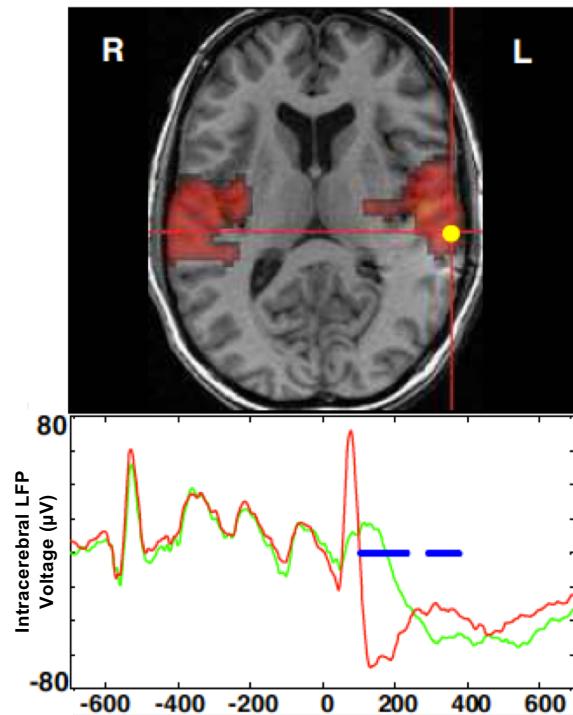
a.demertz@ulg.ac.be

Crossmodal interaction in consciousness

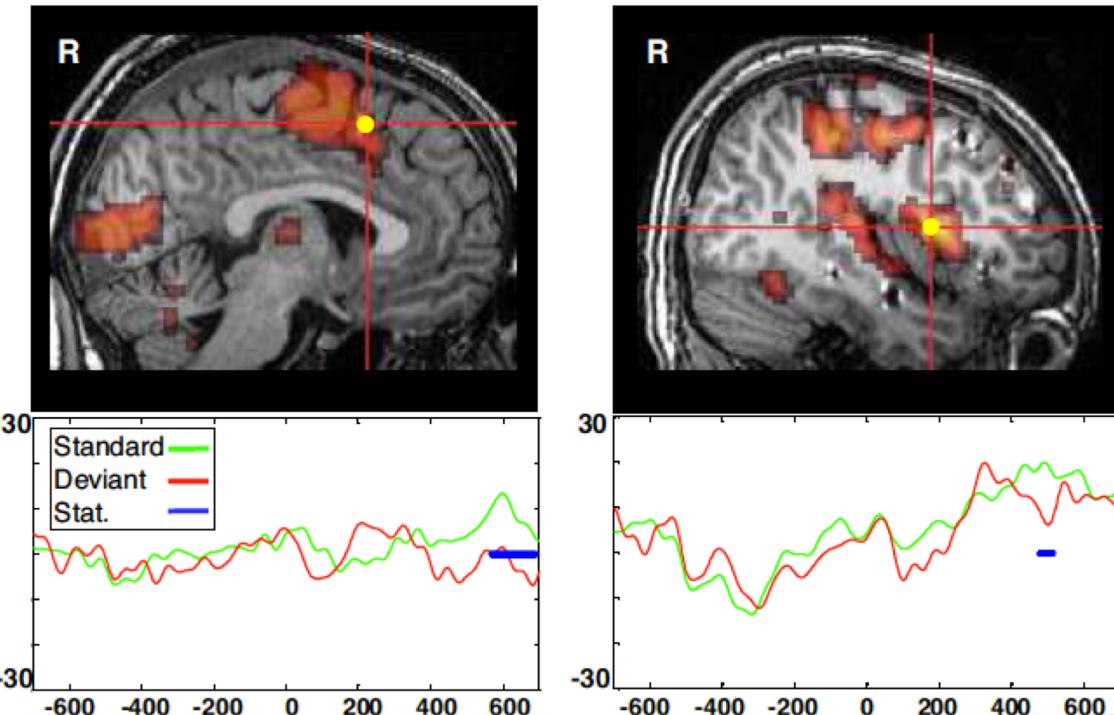
The local- global paradigm



Local effect



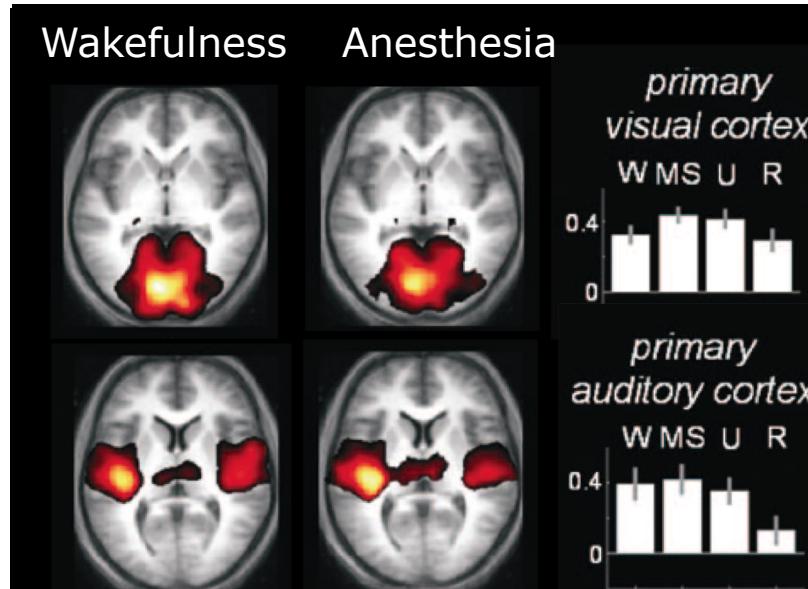
Global effect



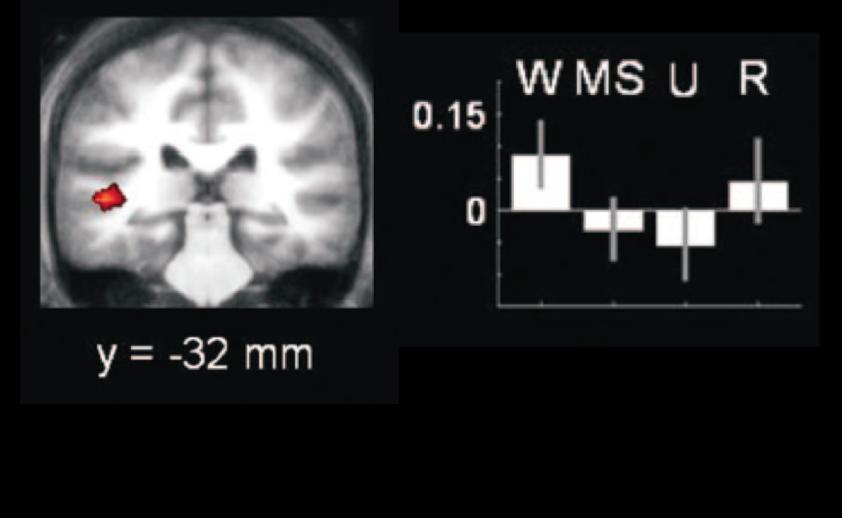
Crossmodal interaction in unconsciousness

Visual network

Auditory network

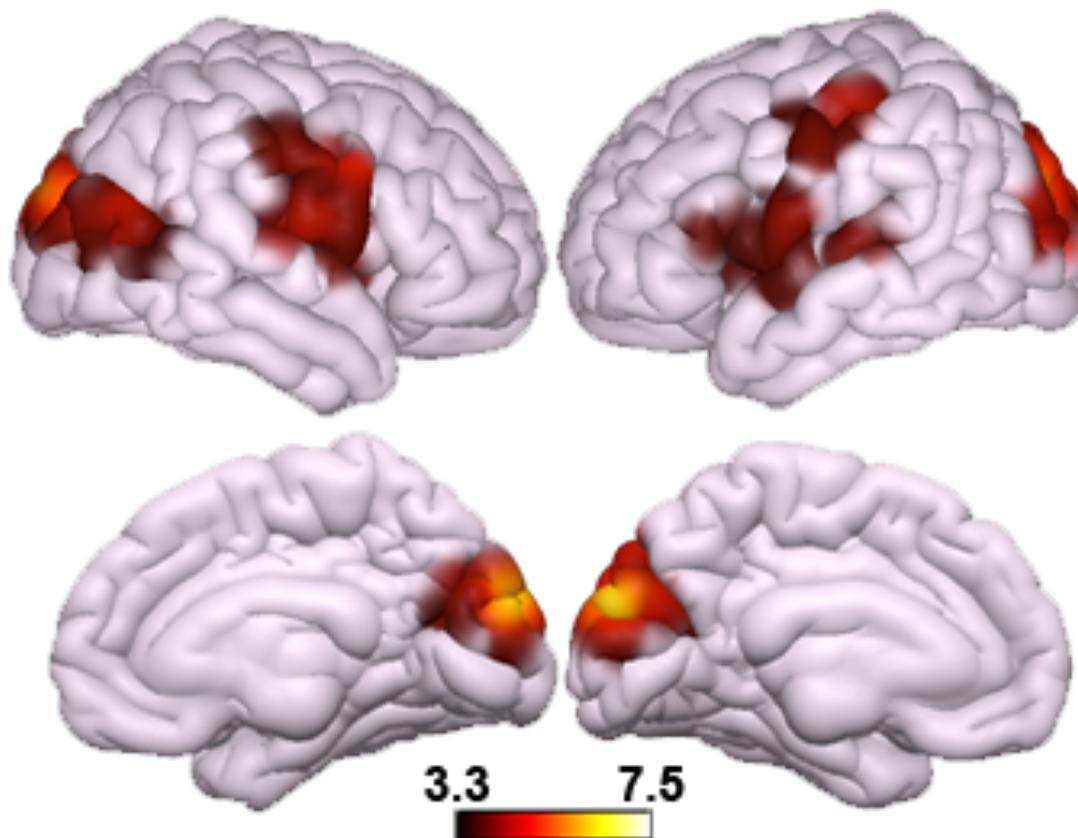


Cross-modal interaction

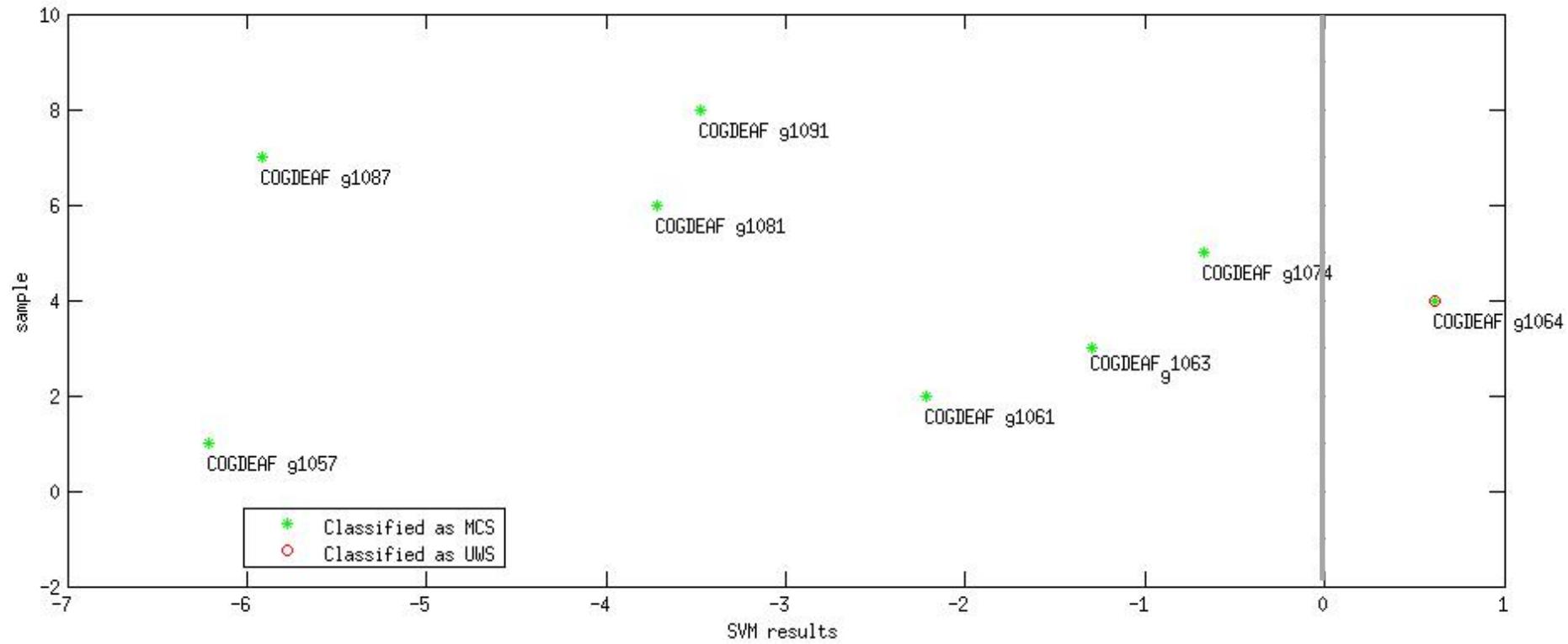




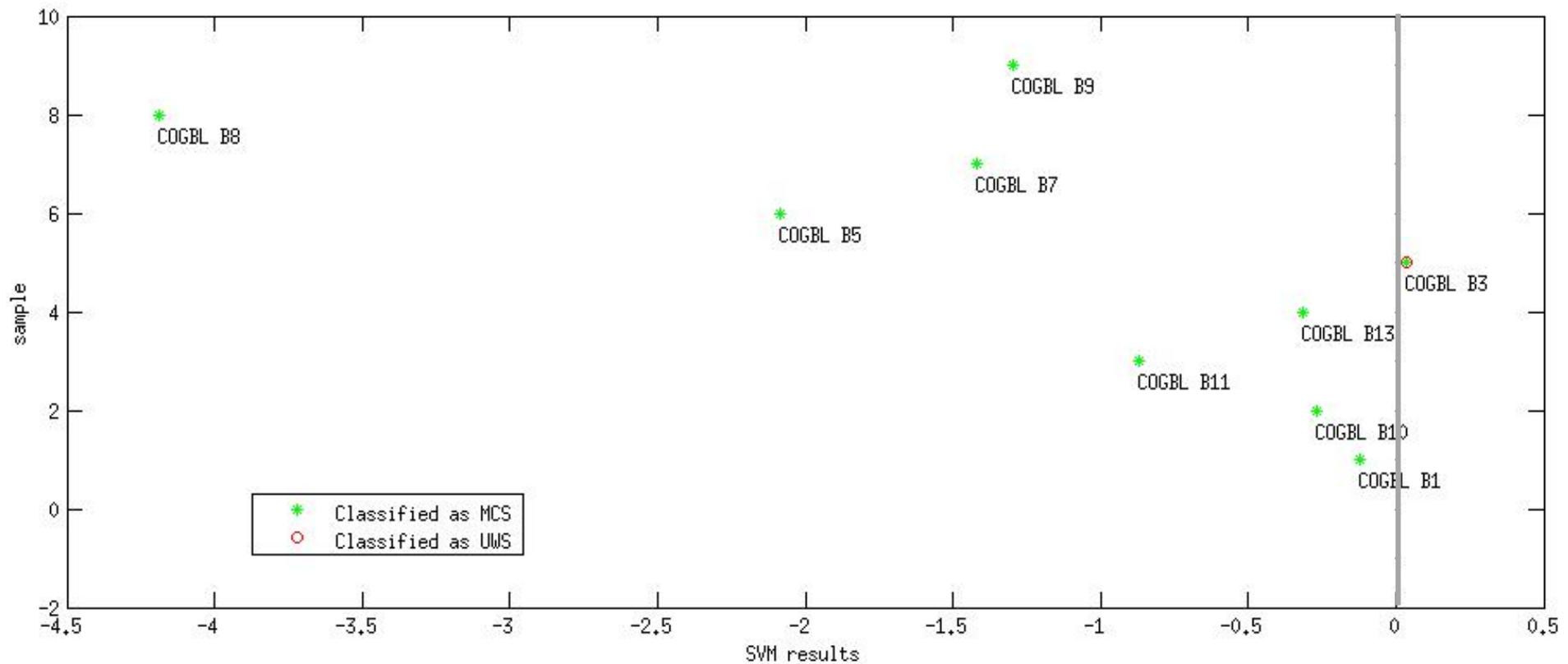
The “auditory” network



Validation in congenitally deaf



Validation in congenitally blind



Validation in propofol anesthesia

