

Connectivity analysis

Resting state fMRI after severe brain injury

UNAM

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James S. McDonnell Foundation



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



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?

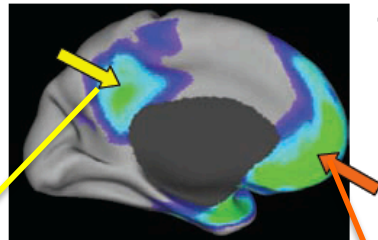
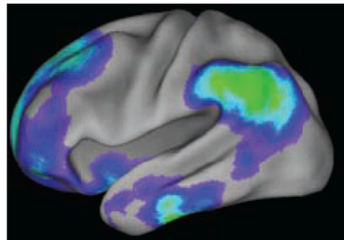


Cognitive psychology: Mental chronometry (measures the time required to complete specific mental operations isolated by the careful selection of task and control states.

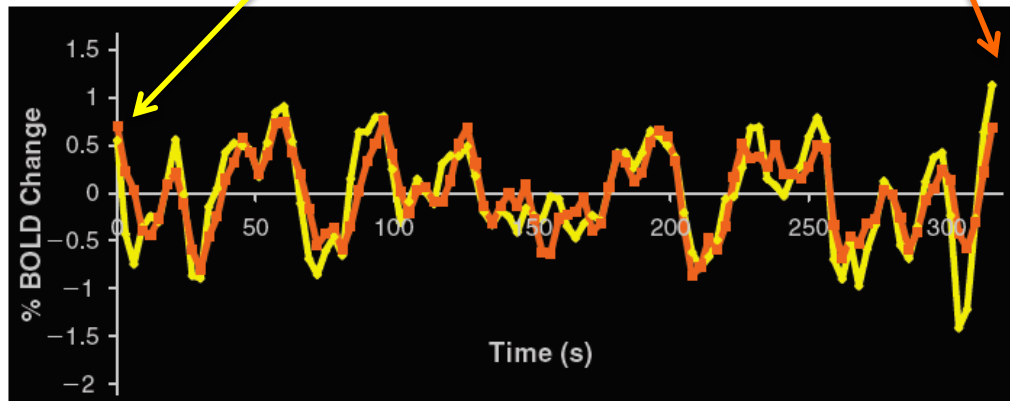


fMRI: Subtracting functional images acquired in a task state from ones acquired in a control state

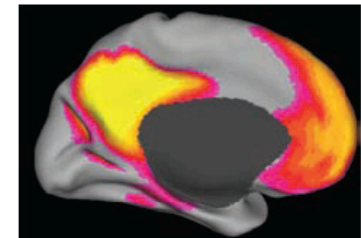
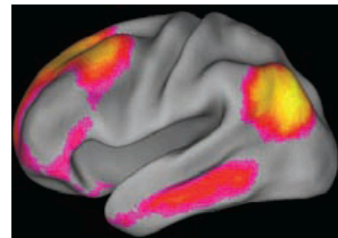
Default brain function



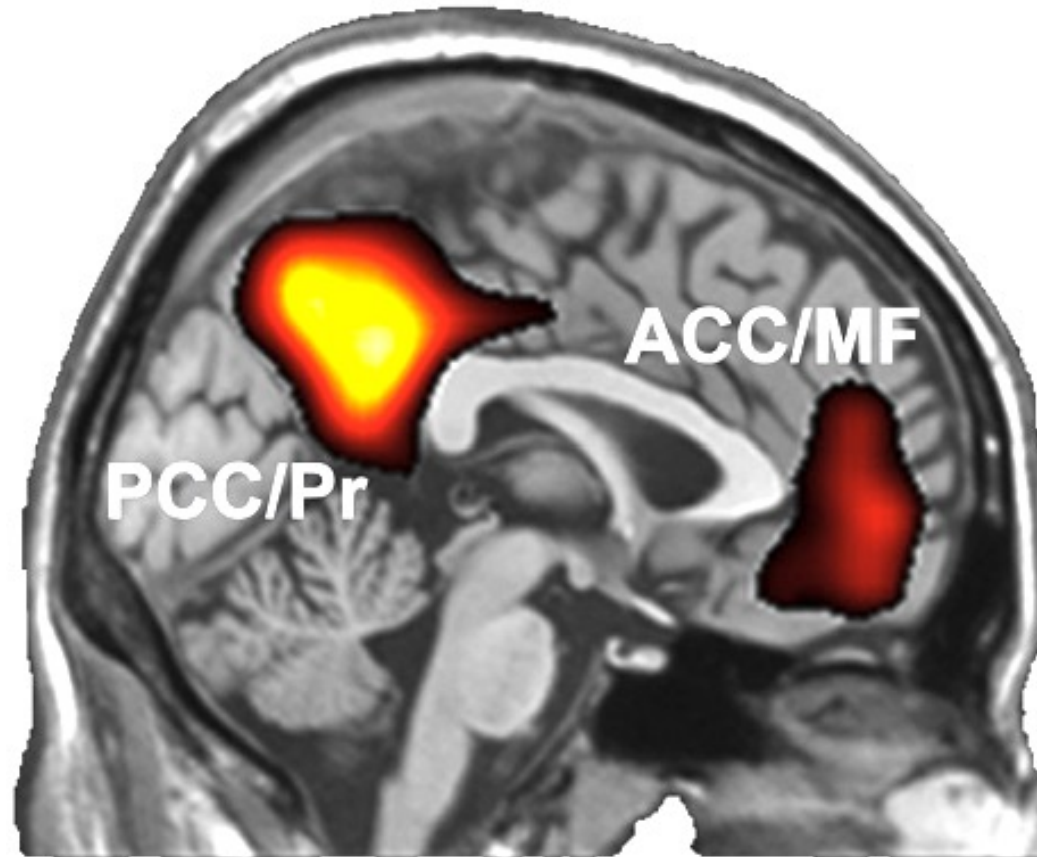
Task performance - Rest (fixation/eyes closed)
→ **Deactivations**



“Activations” during rest

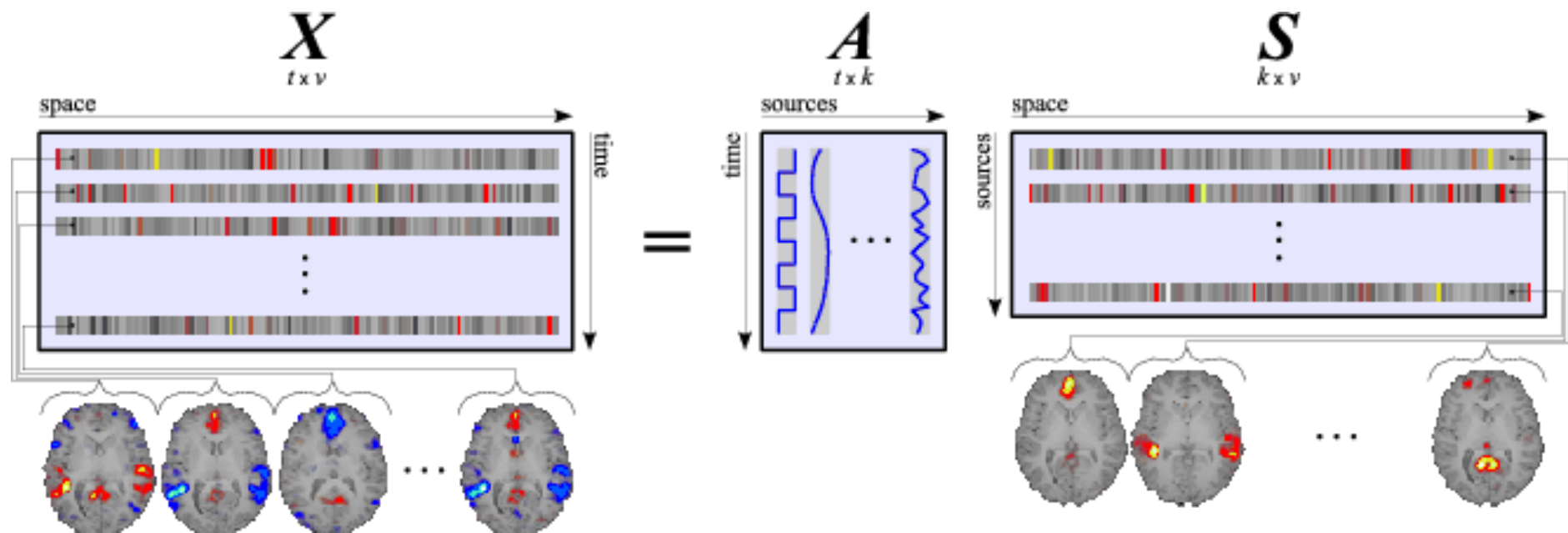


The brain's default mode at rest

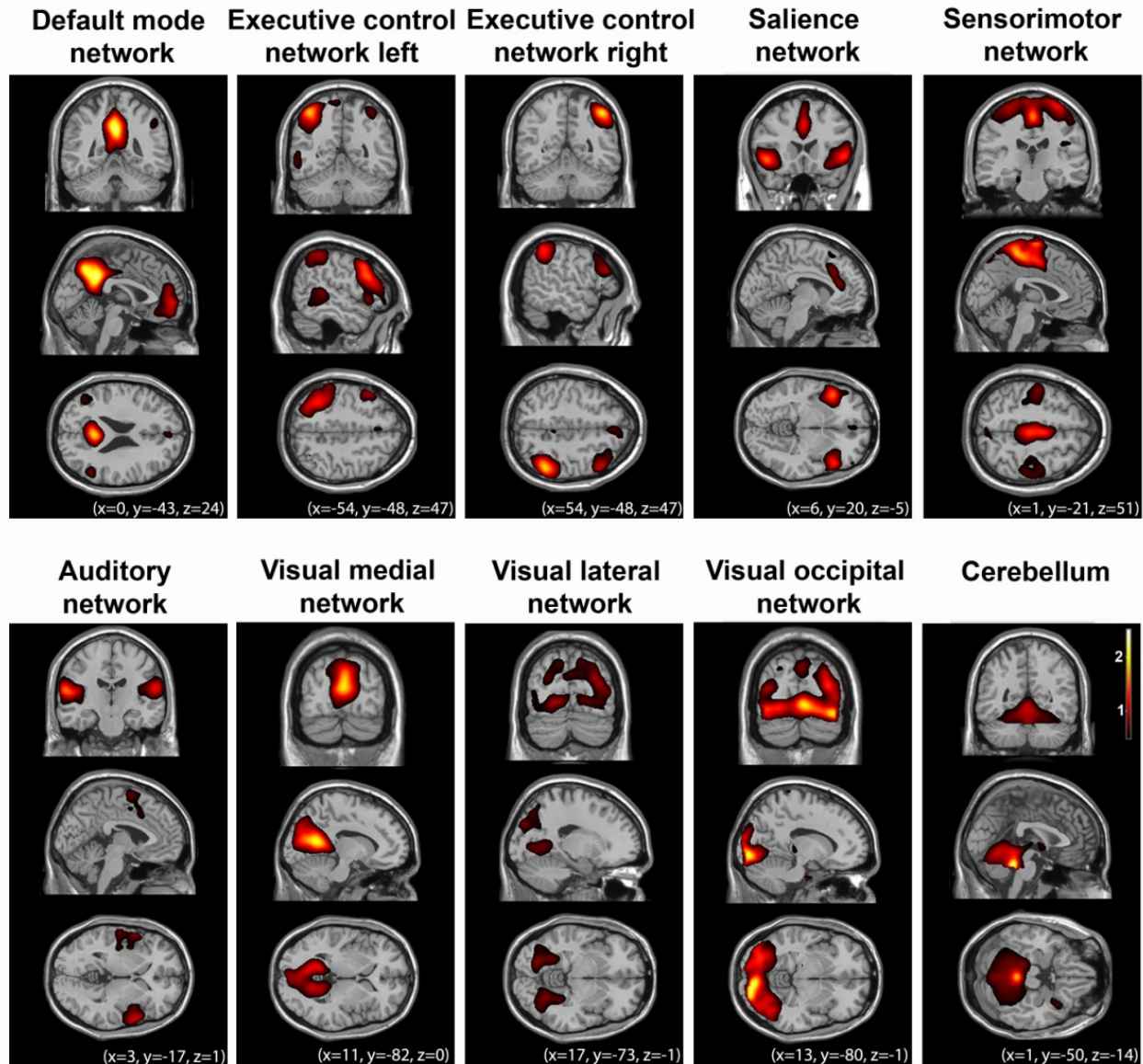


Demertzi & Whitfield-Gabrieli, in: Neurology of Consciousness 2nd ed. 2015
Demertzi, Soddu, Laureys, Curr Opin Neurobiology 2013
Demertzi et al, Front Hum Neurosci 2013
Raichle et al, PNAS 2001

Independent component analysis (ICA)



Intrinsic Connectivity Networks

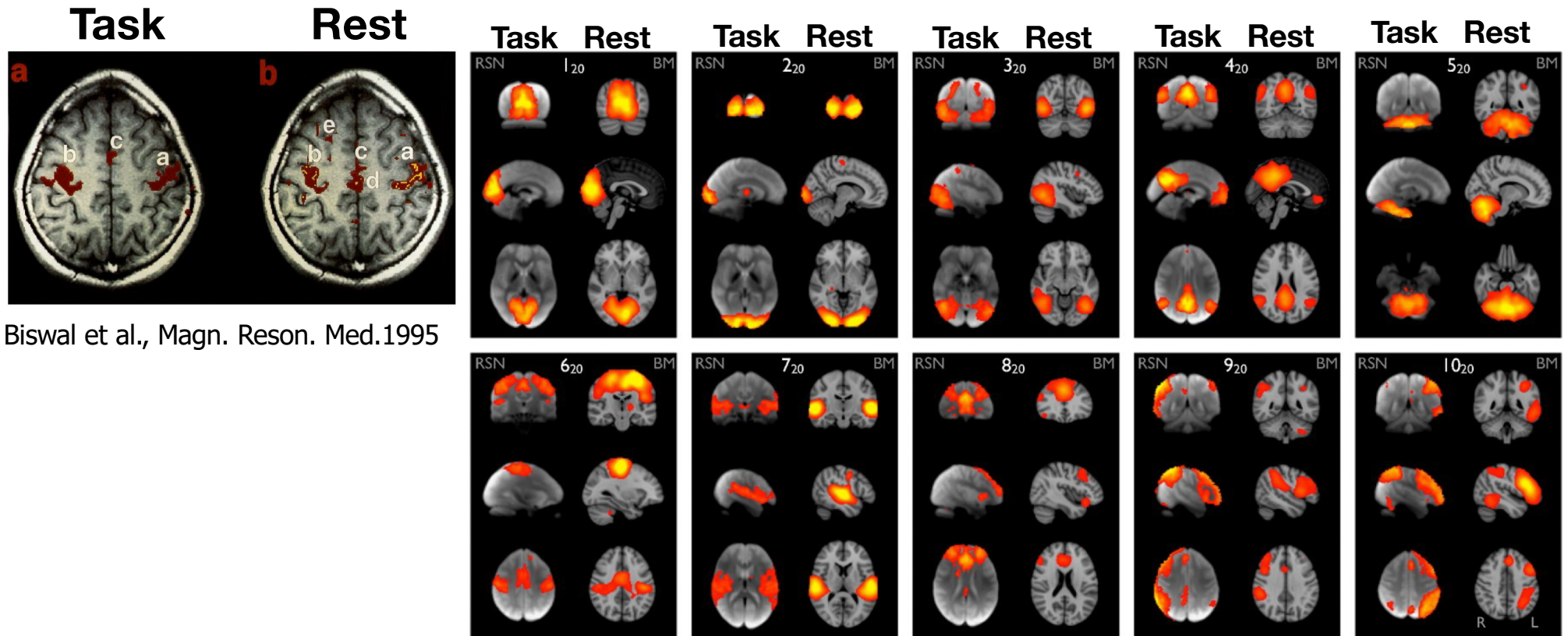


Heine et al, Frontiers in Psychology 2012

Smith et al, PNAS 2009

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

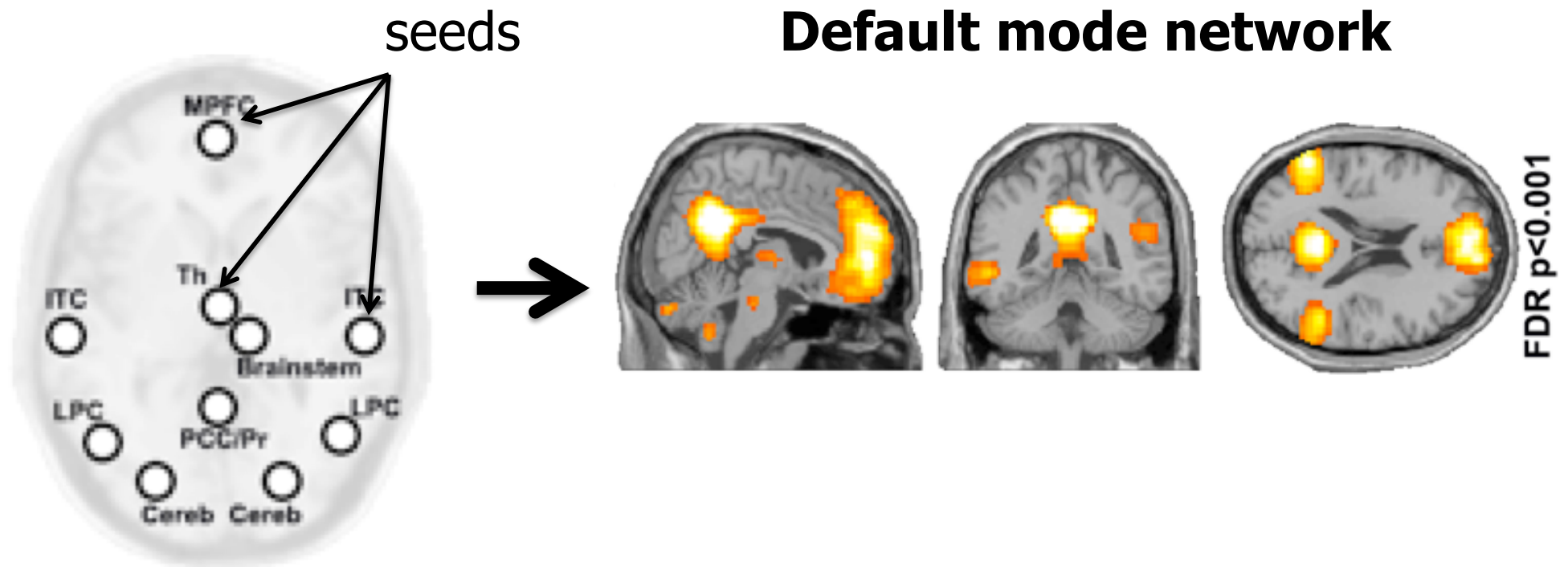
Intrinsic Connectivity Networks- Cognitive?



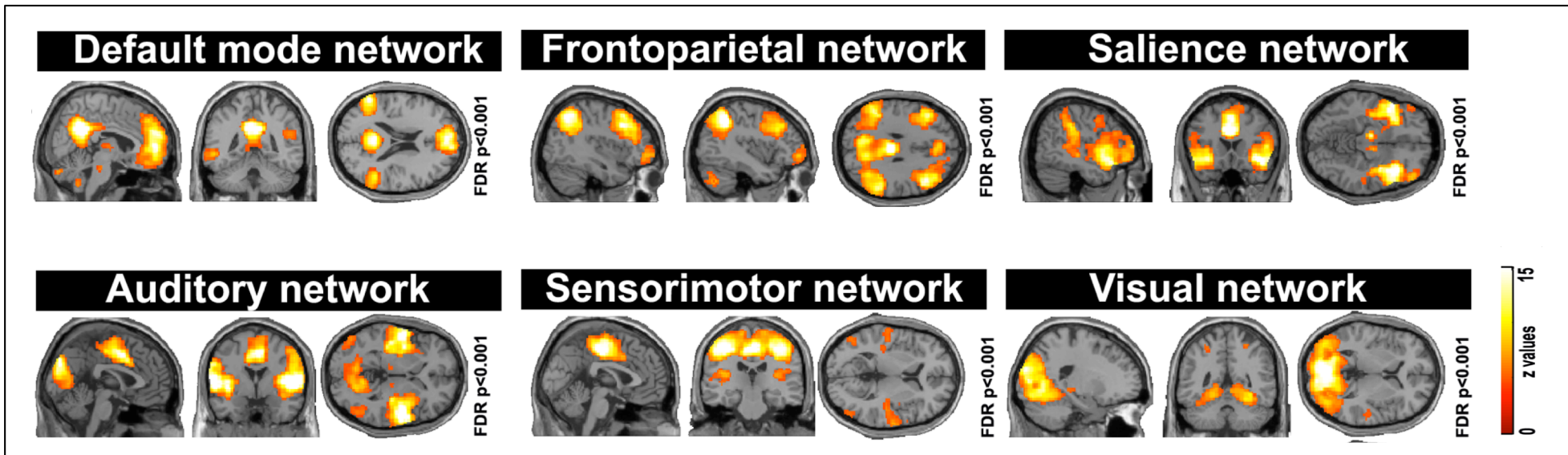
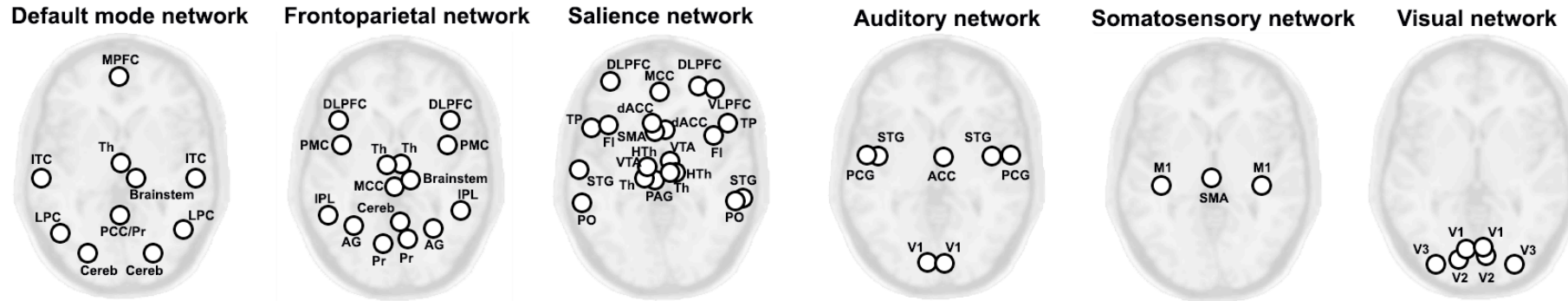
Biswal et al., Magn. Reson. Med. 1995

Smith et al, PNAS 2009

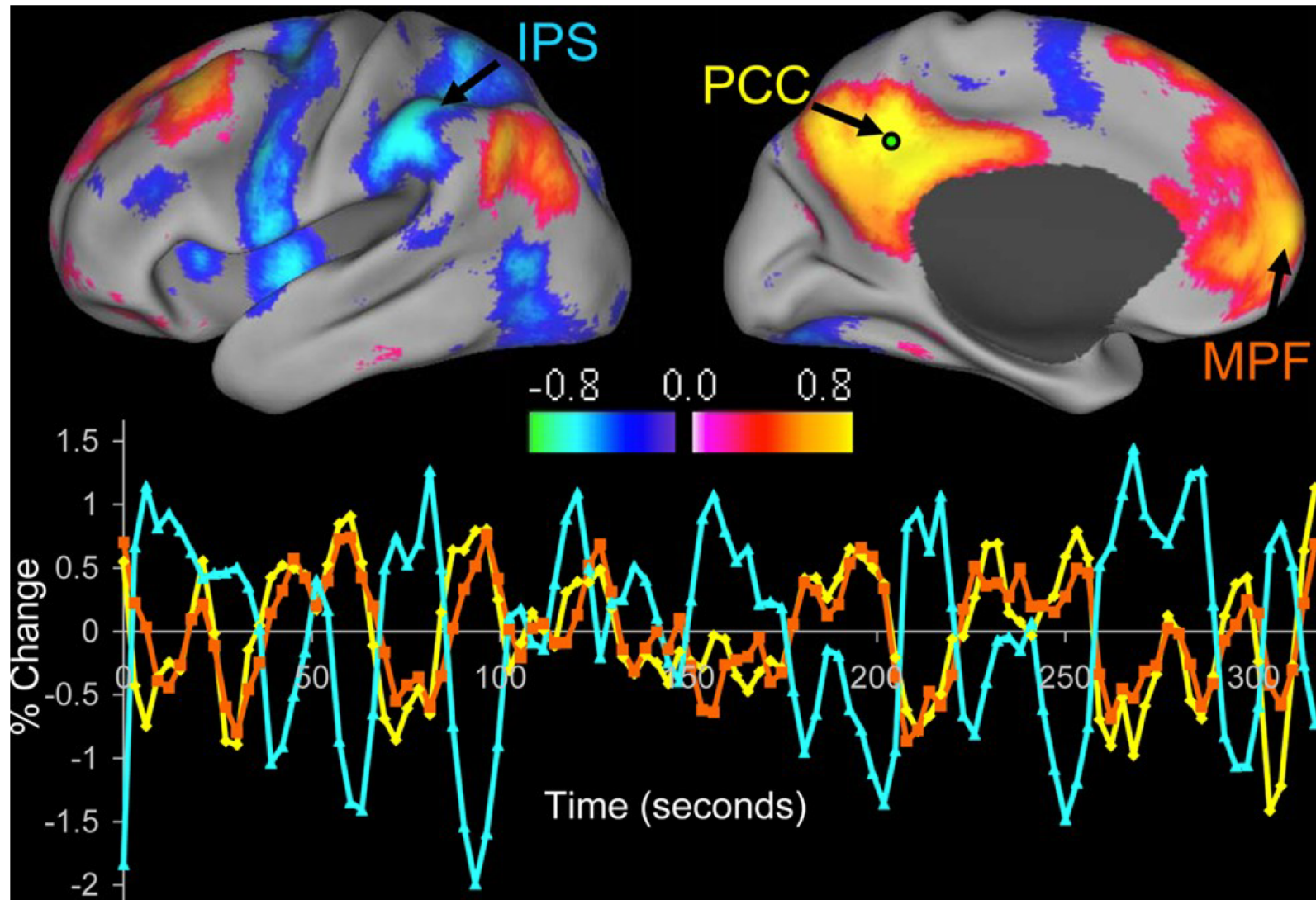
Seed-based region correlation



Seed-based region correlation

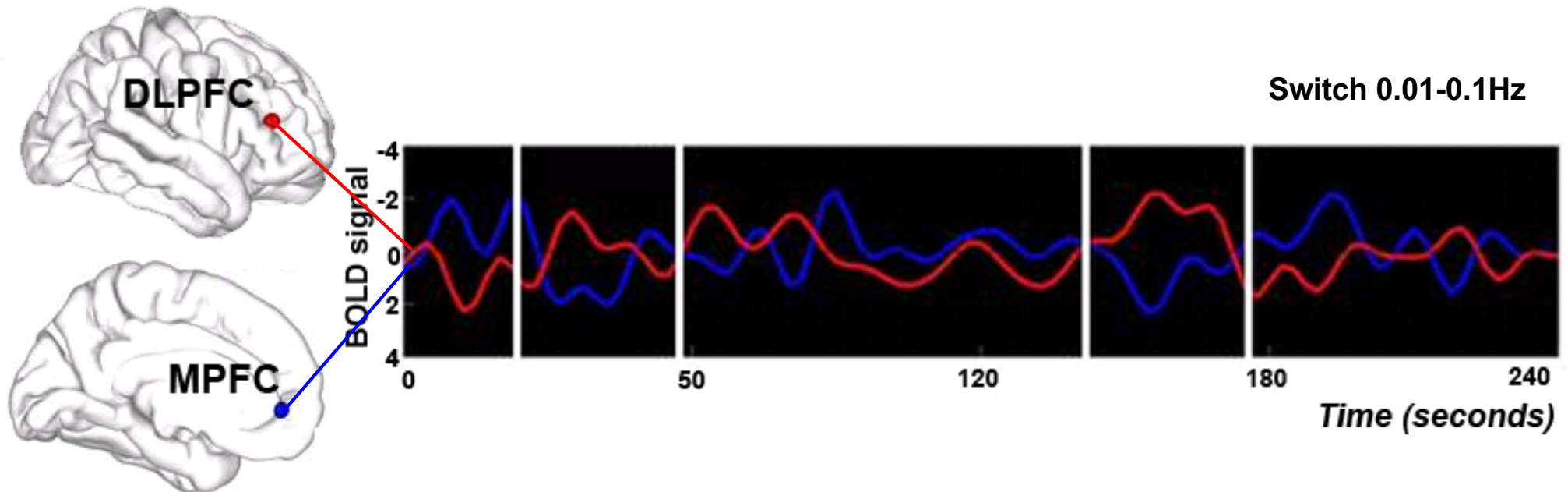


rsfMRI anticorrelations



rsfMRI anticorrelations

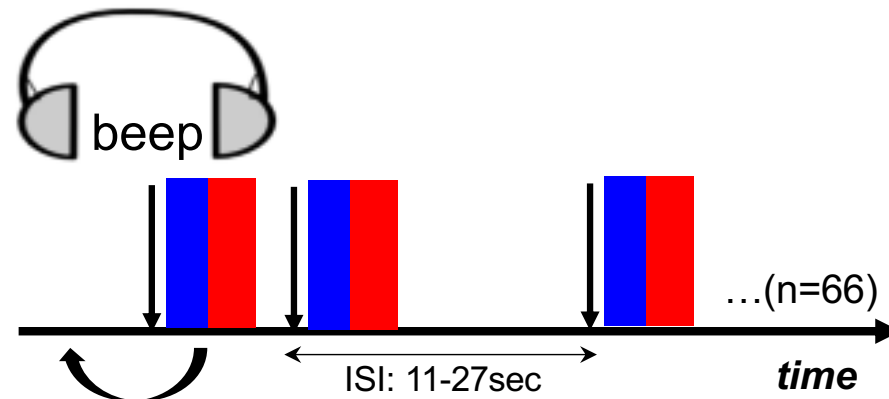
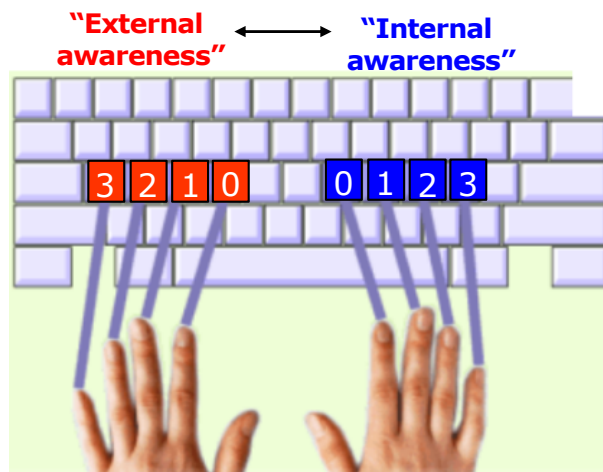
External awareness
or anticorrelated network



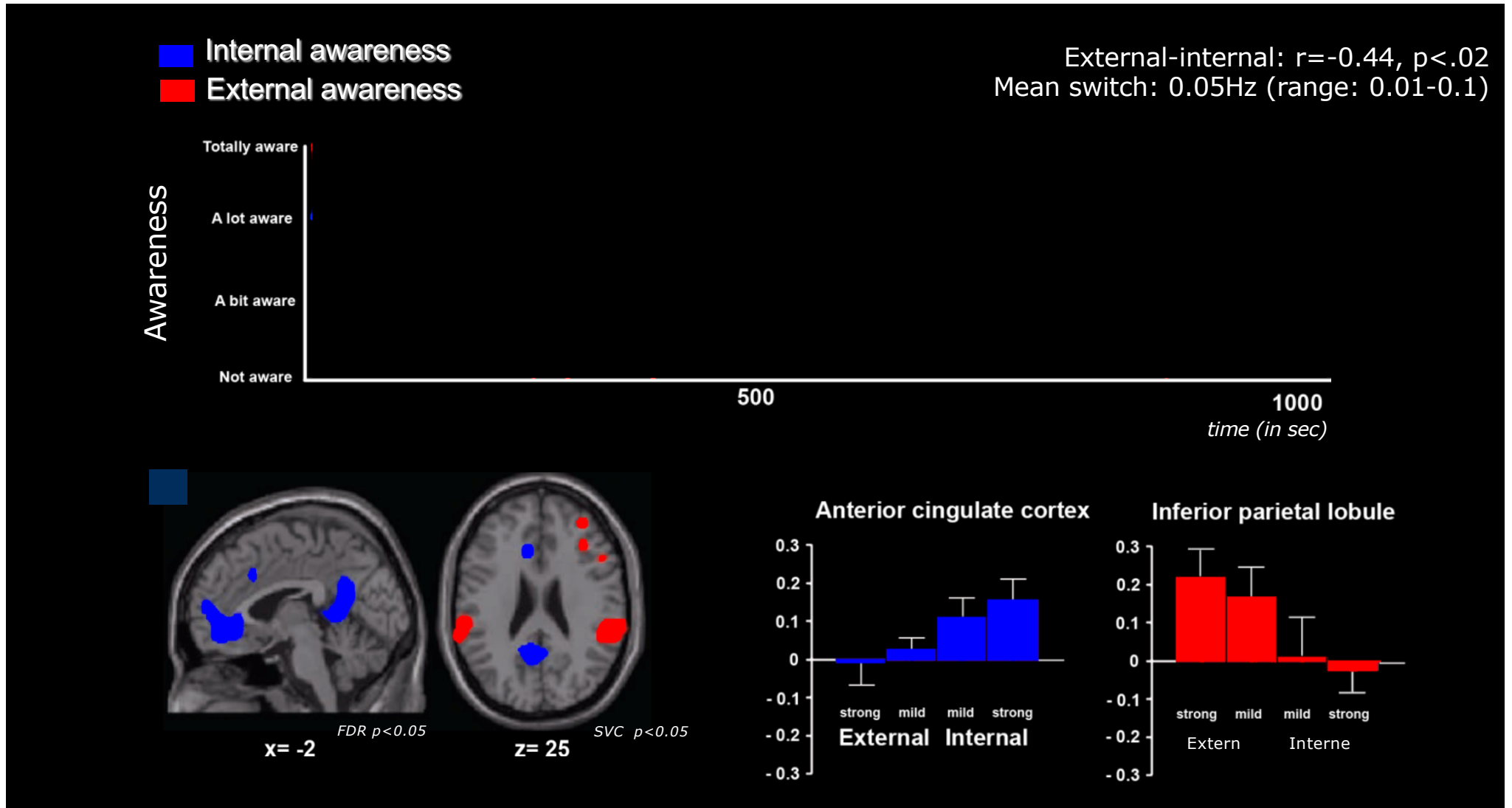
Internal awareness
or Default mode network

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?

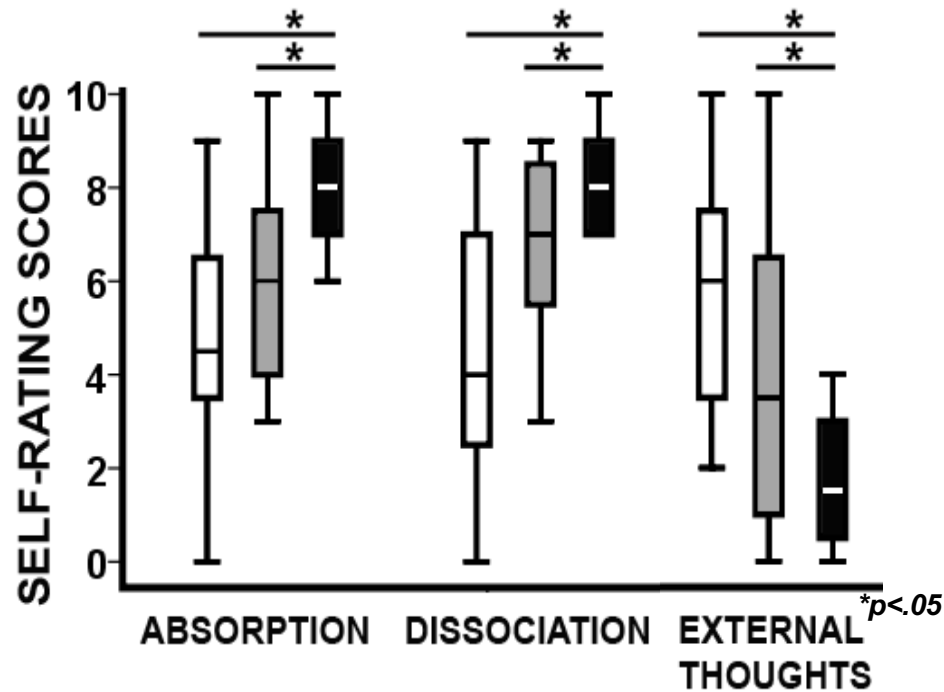


The cognitive counterpart of anticorrelations



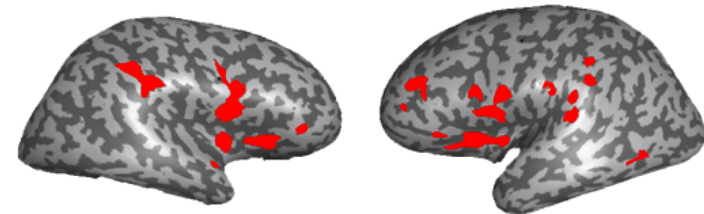
Anticorrelated connectivity is modified in hypnosis

- Normal consciousness
- Autobiographical mental imagery
- Hypnosis

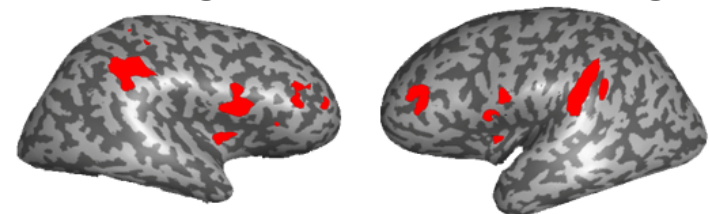


EXTRINSIC SYSTEM

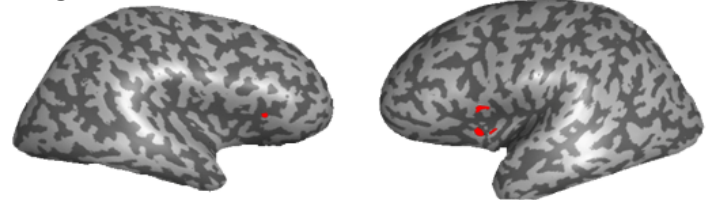
Normal consciousness



Autobiographical mental imagery

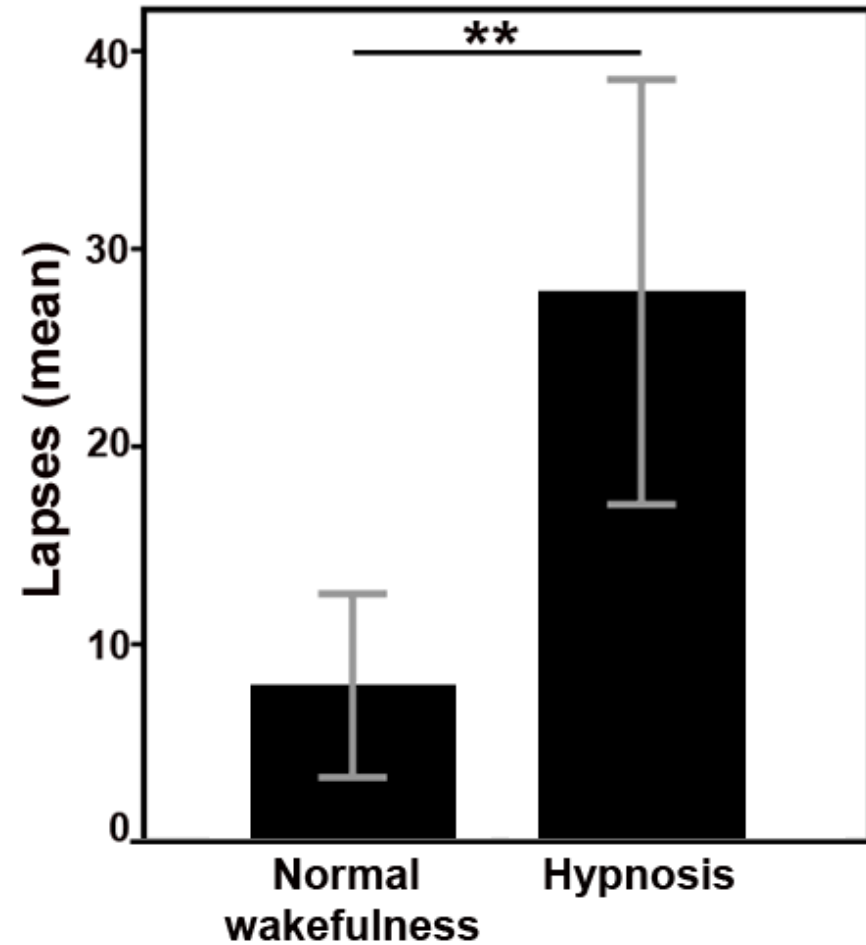
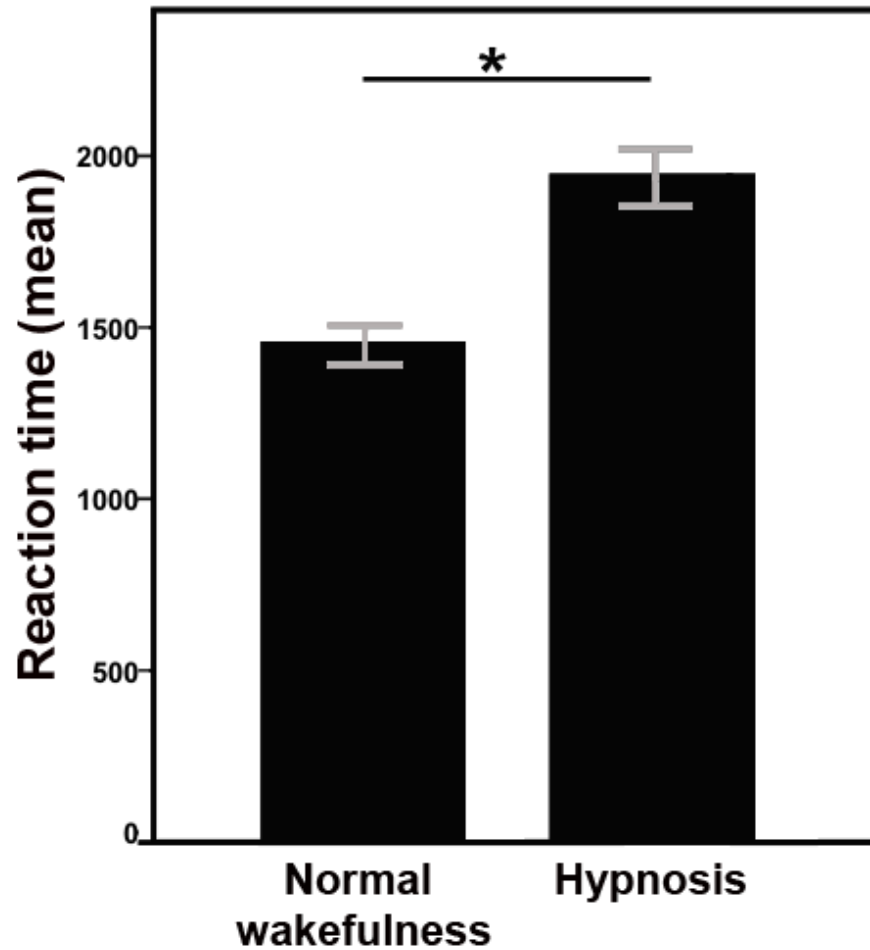


Hypnosis

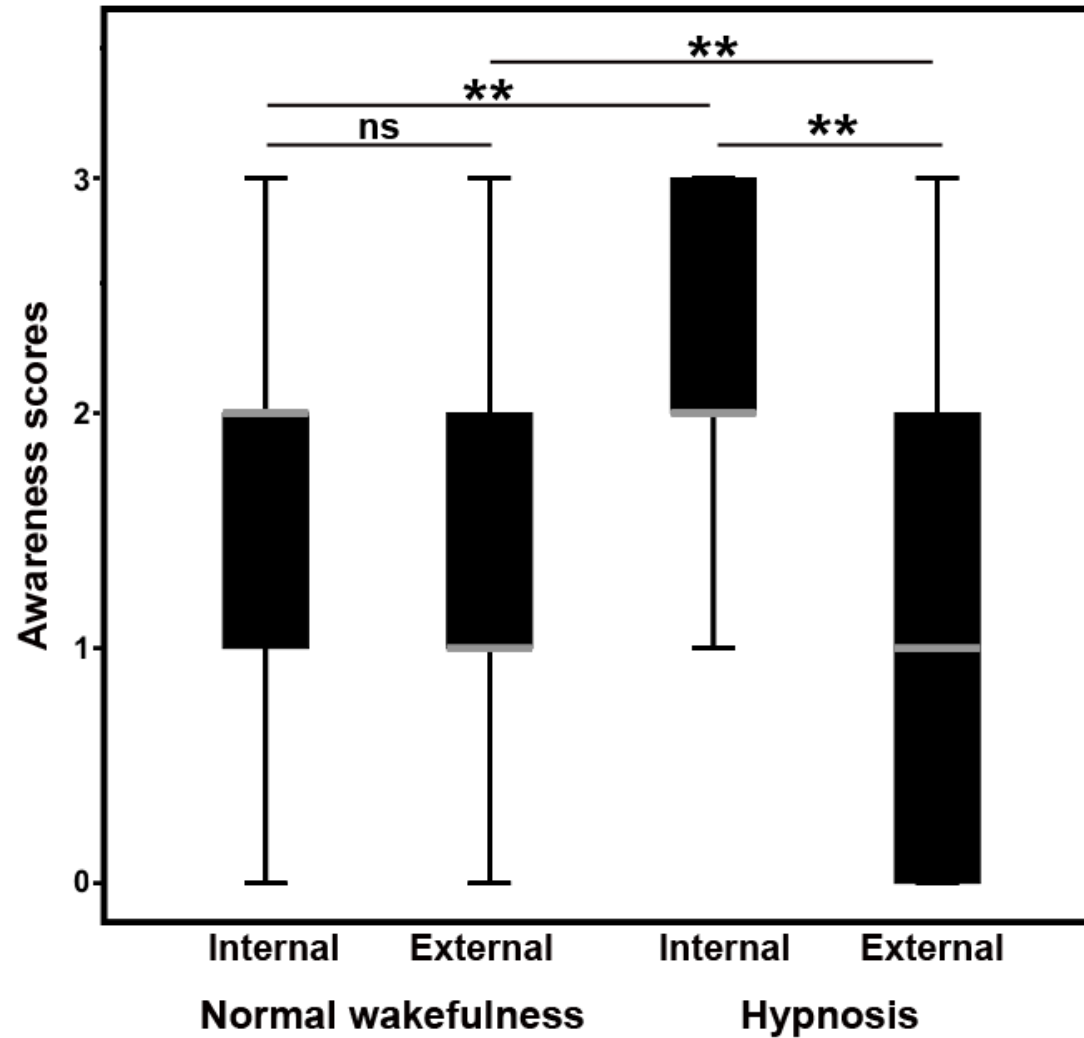


$p < 0.05$ corrected for multiple comparisons

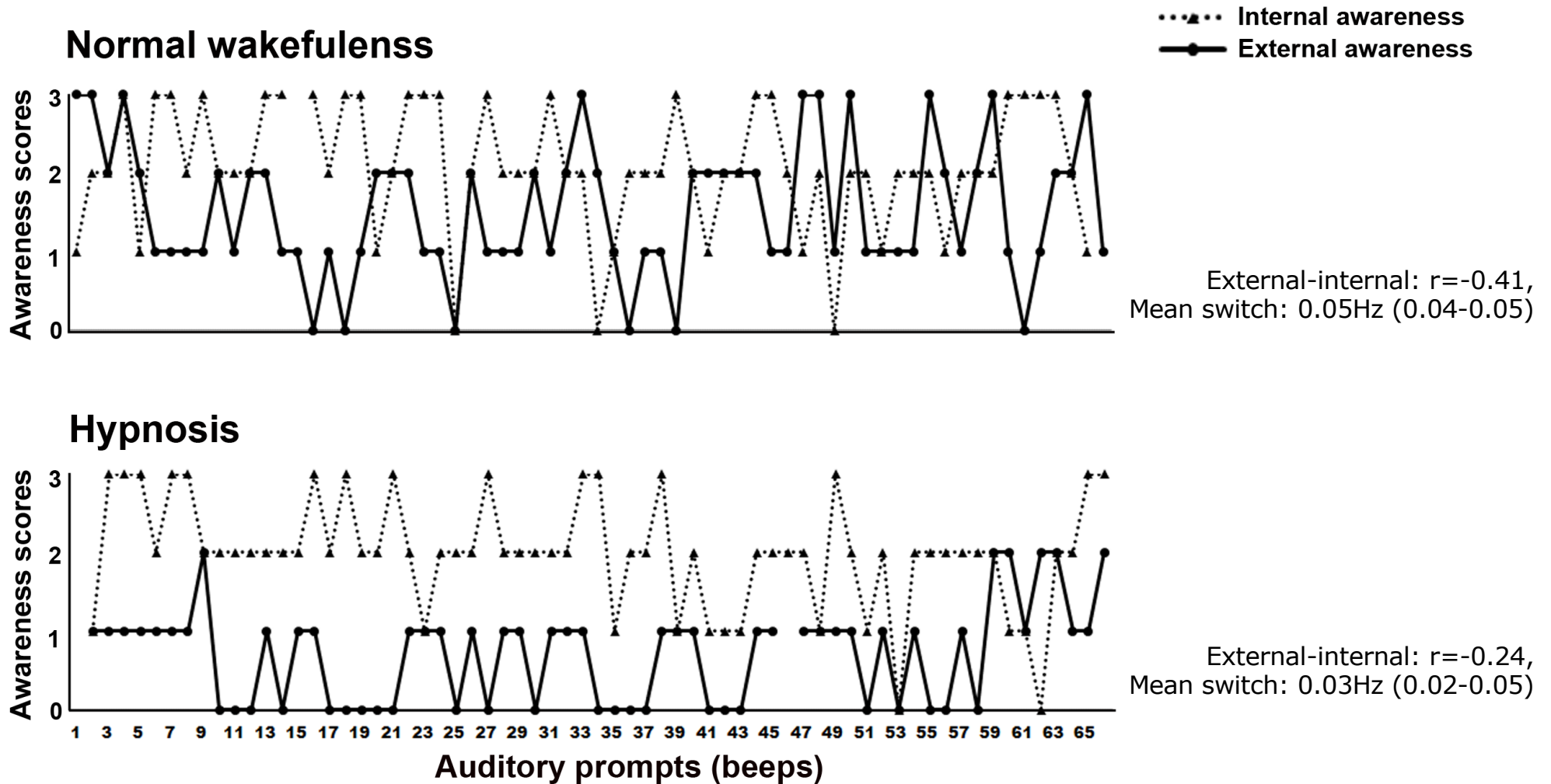
Behavior is modified in hypnosis



Awareness is modified in hypnosis



Awareness is modified in hypnosis



Consciousness

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



Consciousness



Functionalism

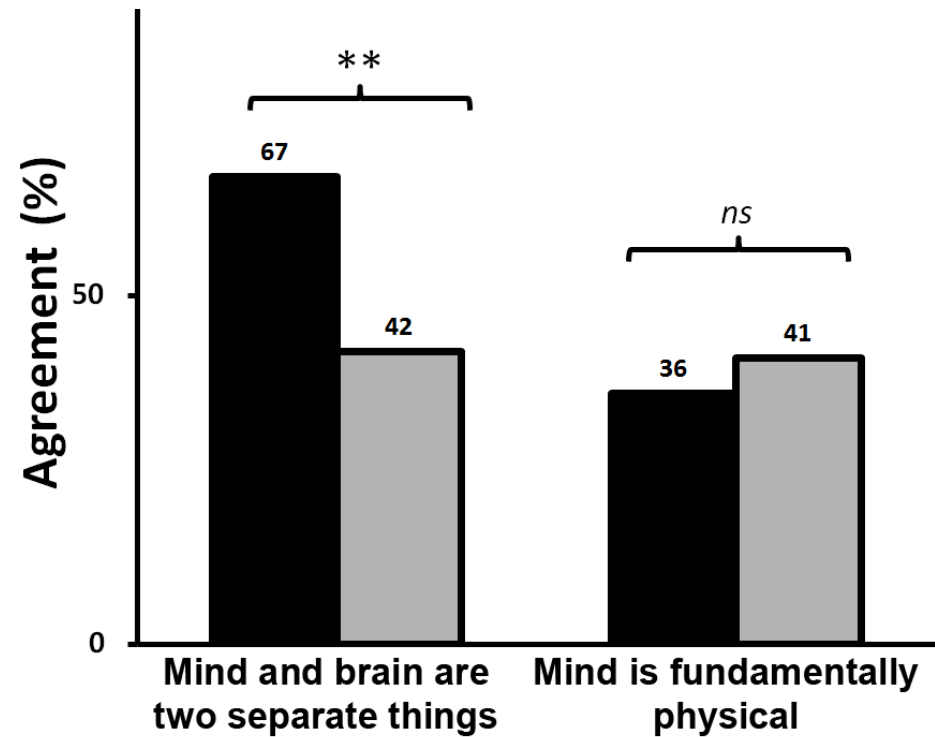
Materialism

Dualism

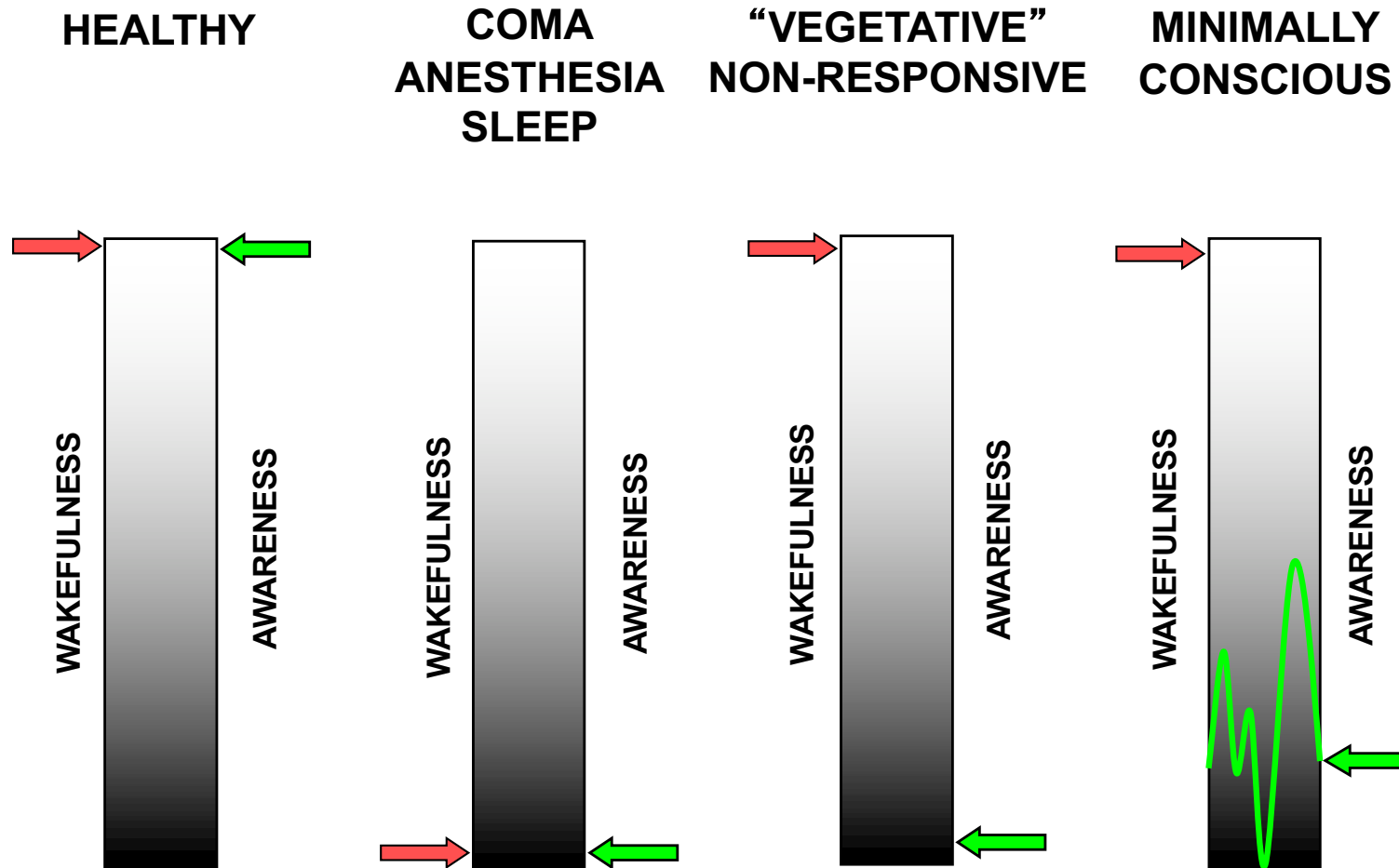


■ Edinburgh survey (n=250)

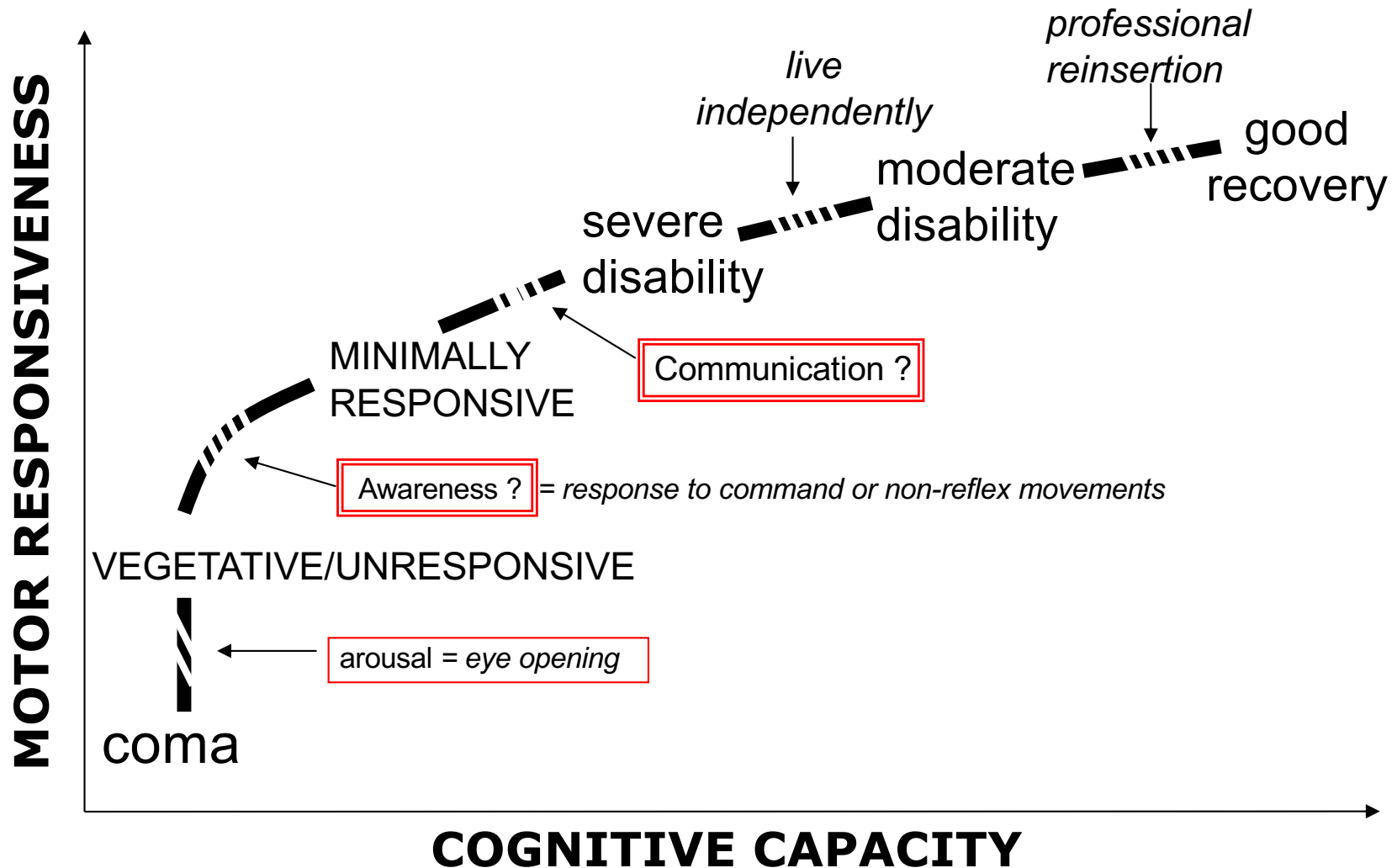
▣ Liège survey (n=1858)



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

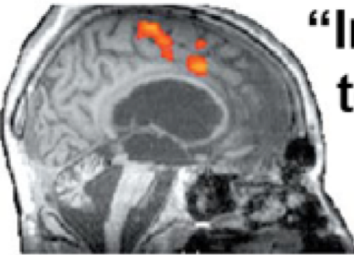


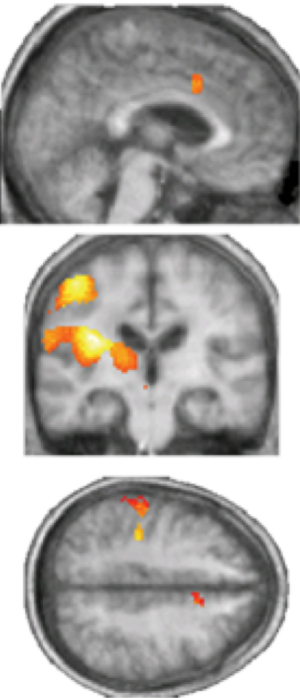
	Coma Recovery Scale-Revised results		
	UWS	MCS	Total
Clinical consensus diagnosis			
¹⁸F-FDG PET			
VS/UWS	24 (21%)	5 (4%)	29 (26%)
MCS	12 (11%)	71 (63%)	83 (74%)
Total	36 (32%)	76 (68%)	112 (100%)

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

Table 2: Diagnostic results by modality

Stender & Gosseries et al, Lancet 2014

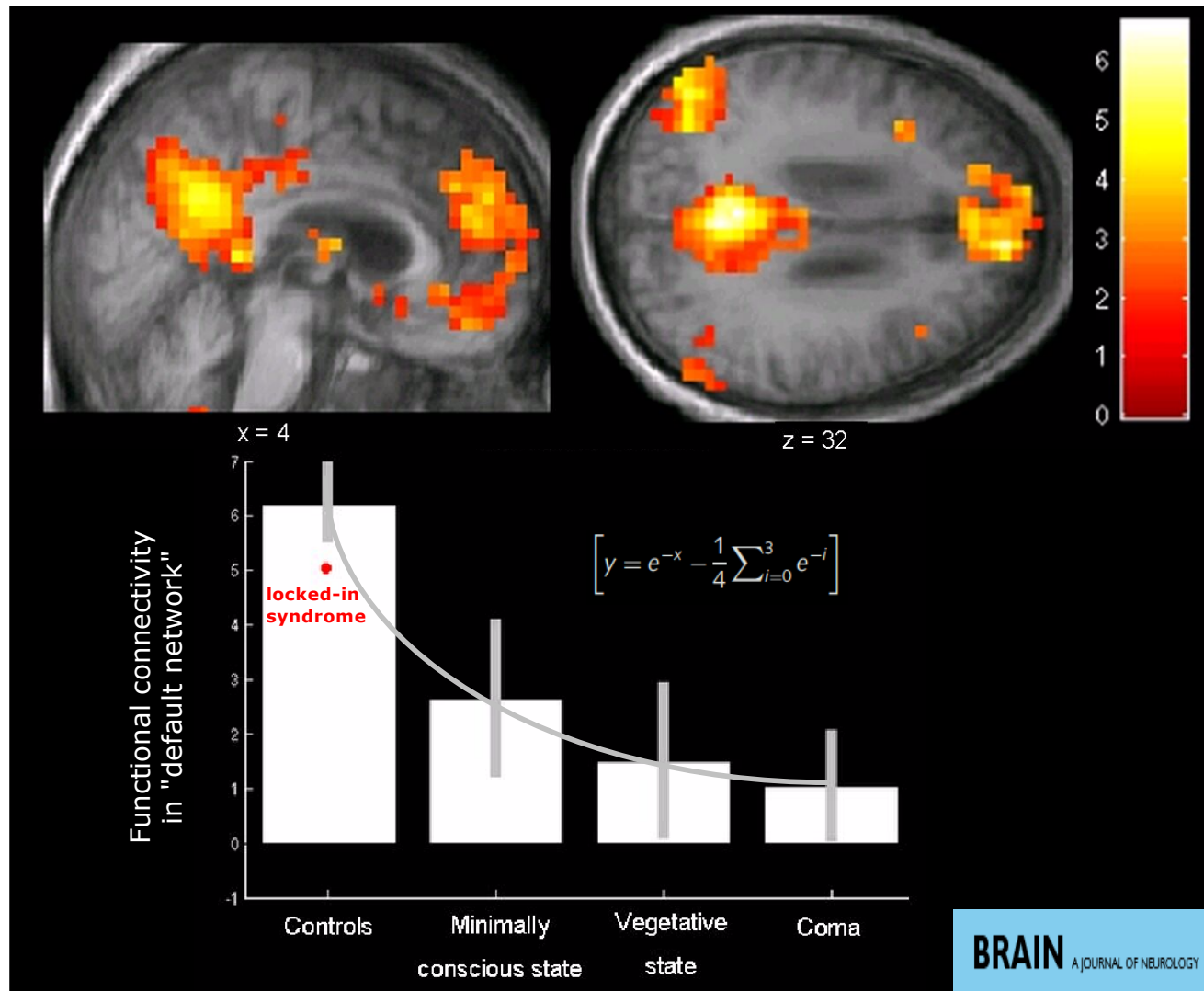
Detecting awareness with fMRI

Active paradigms	Passive paradigms
 <p data-bbox="600 544 1025 655">“Imagine playing tennis”</p>  <p data-bbox="600 884 1025 1059">“Imagine visiting the rooms of your house”</p> <p data-bbox="562 1187 1025 1235">Owen et al, Science 2006 Monti & Vanhaudenhuyse et al, NEJM 2010</p>	 <p data-bbox="1106 1098 1451 1145">median nerve</p>  <p data-bbox="1585 1214 1899 1235">Boly et al, Lancet Neurol 2008</p>

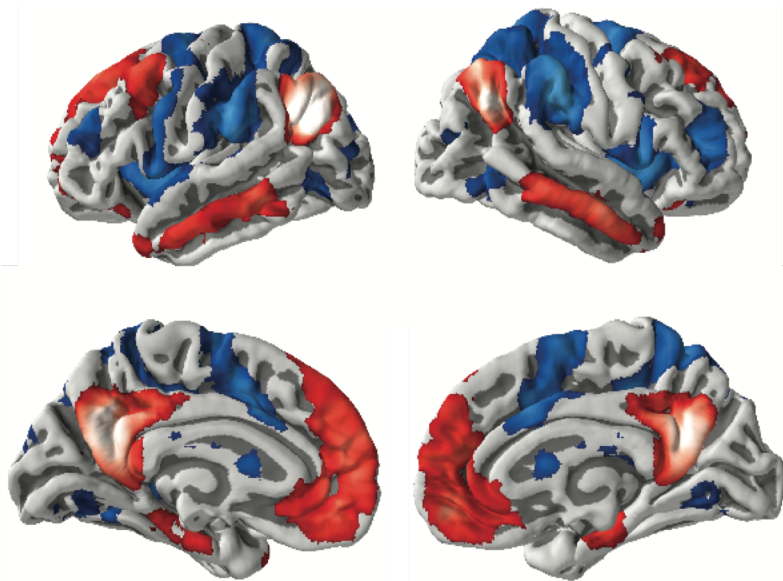
Heine, Di Perri, Soddu, Laureys, Demertzi
In: *Clinical Neurophysiology in Disorders of Consciousness*, Springer-Verlag 2015

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

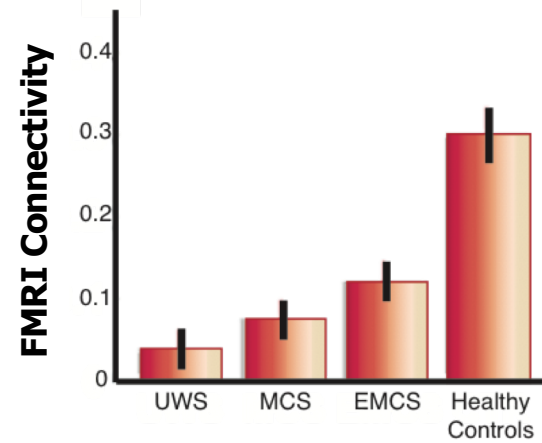
Default mode network in DOC



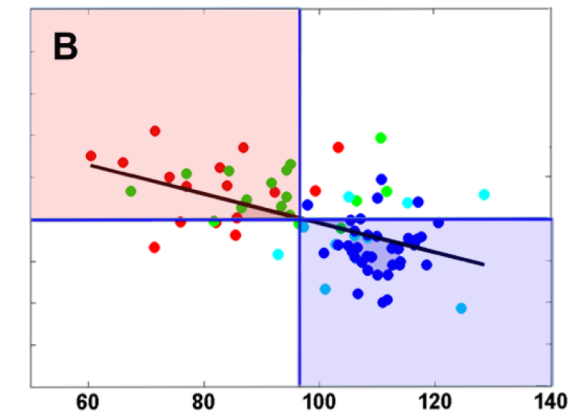
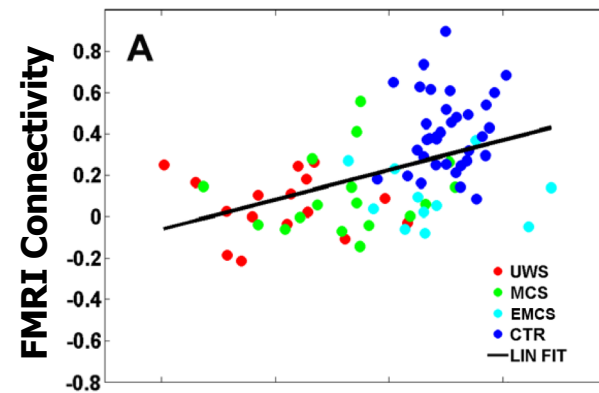
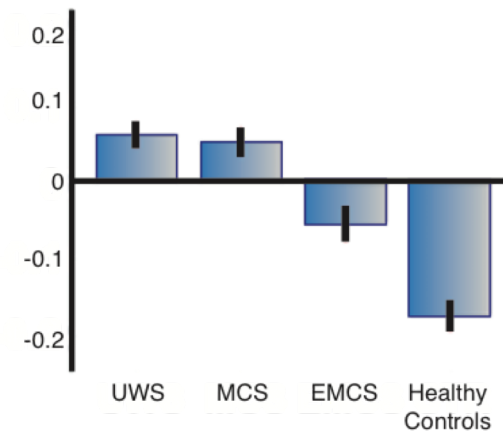
Anticorrelated activity is absent in DOC



DMN CORRELATIONS

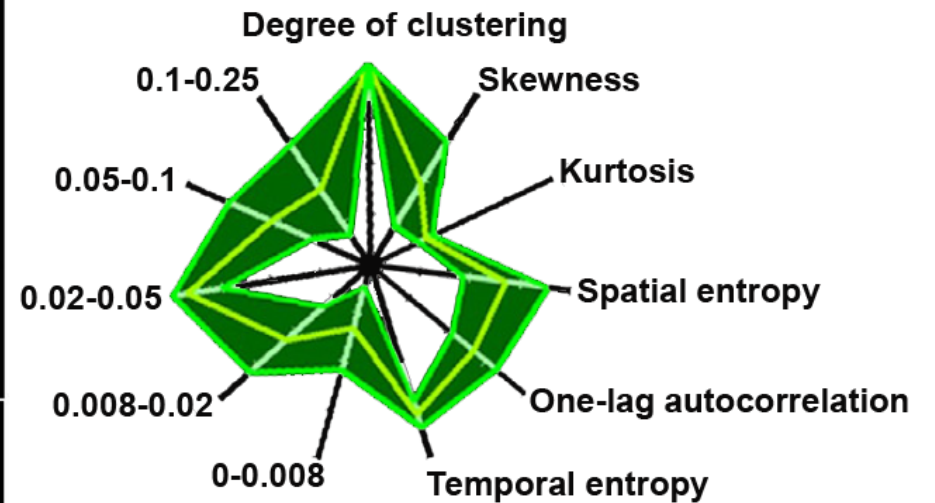
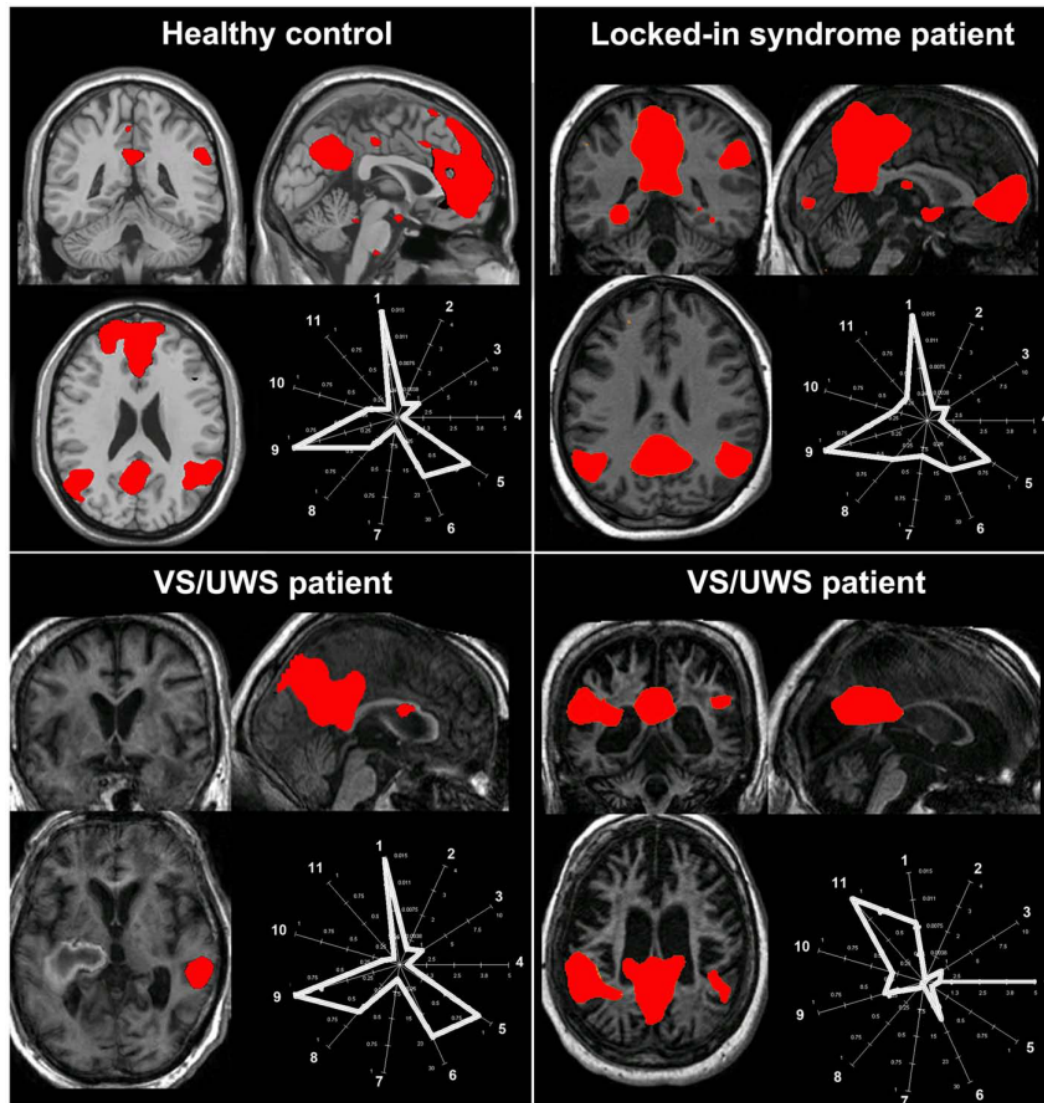


DMN ANTICORRELATIONS

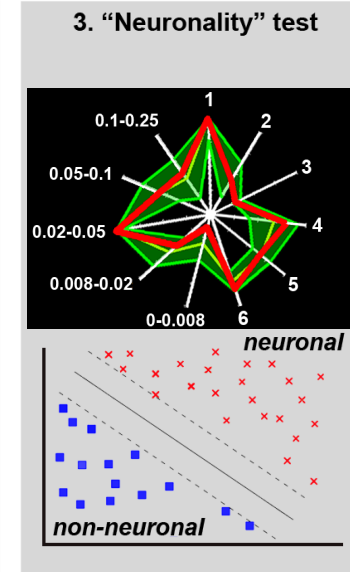
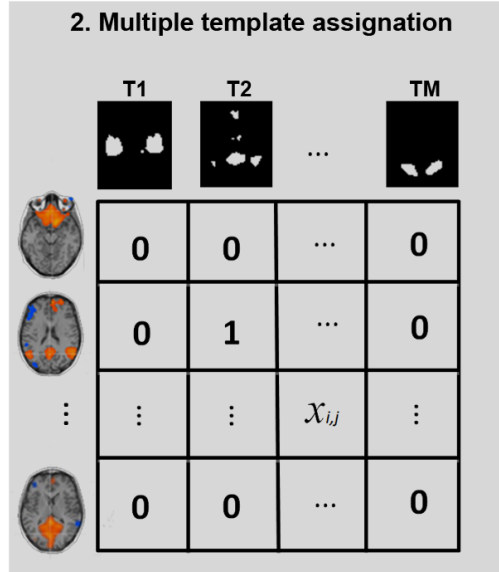
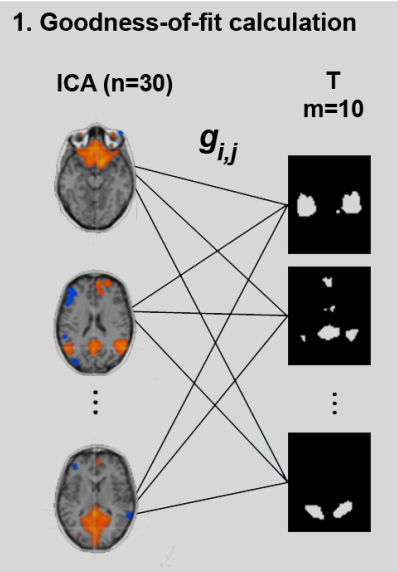
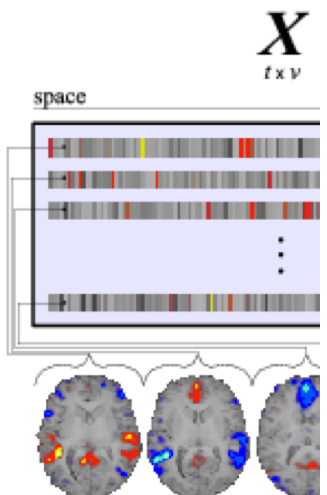
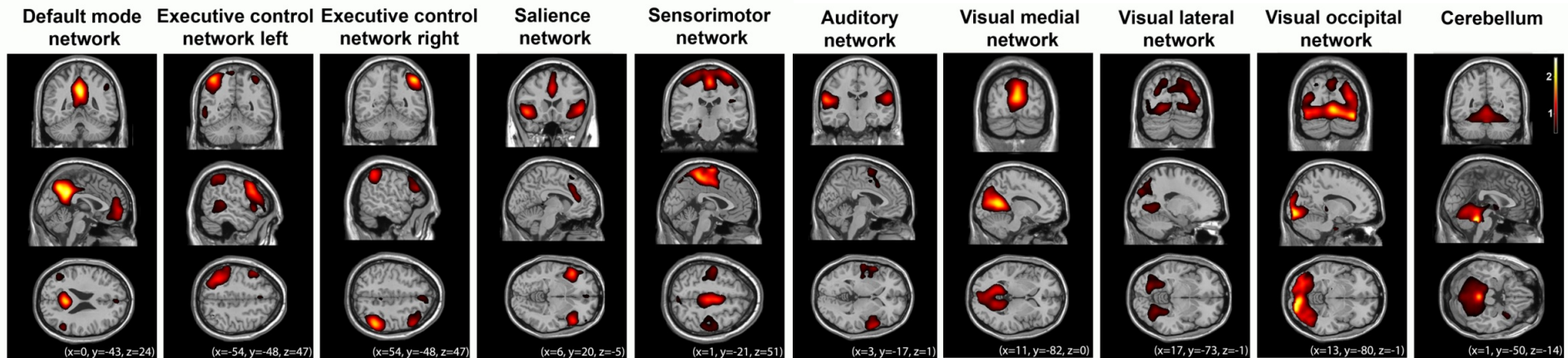


Brain metabolism

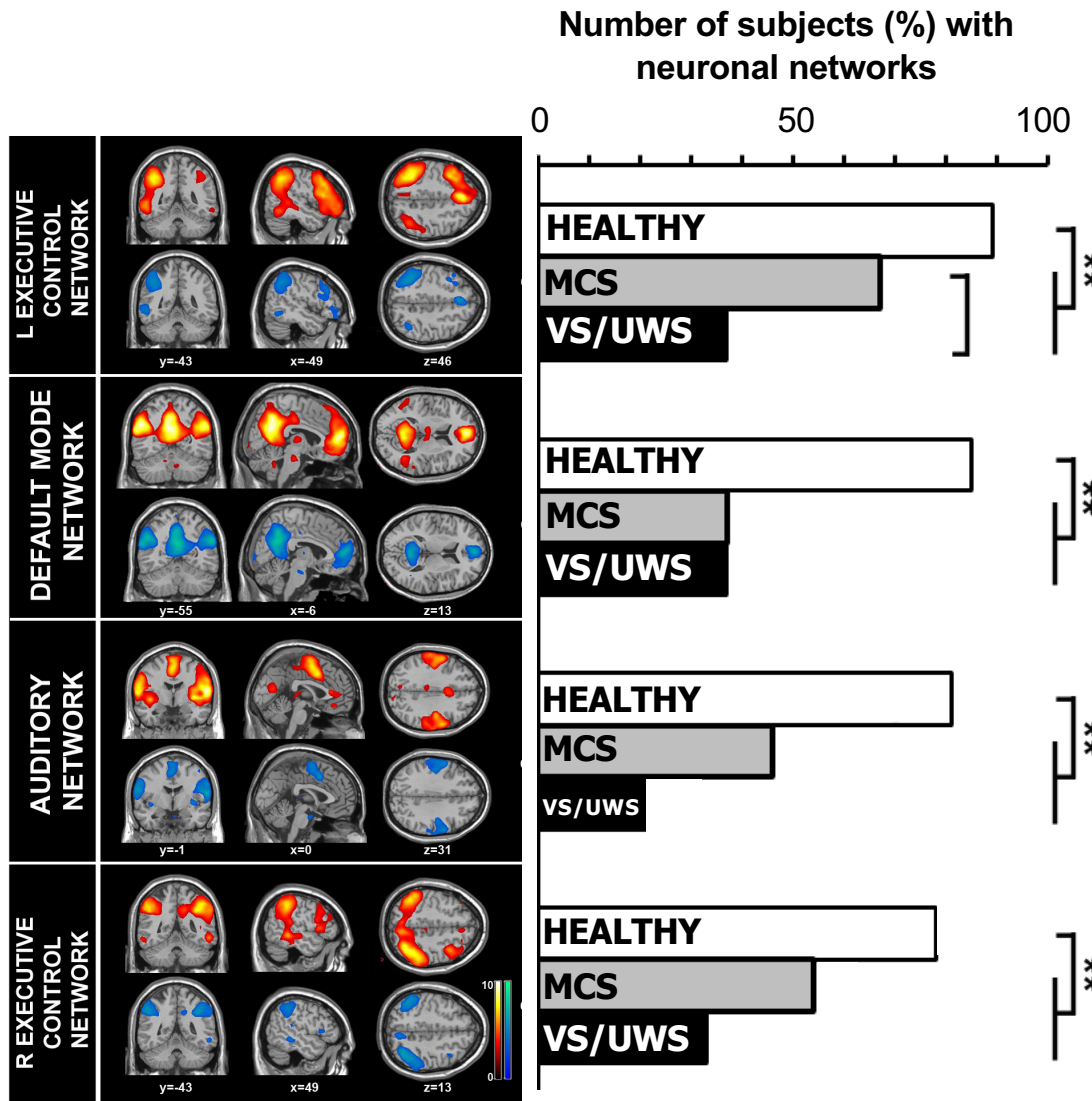
A challenge...



Systems-level intrinsic connectivity



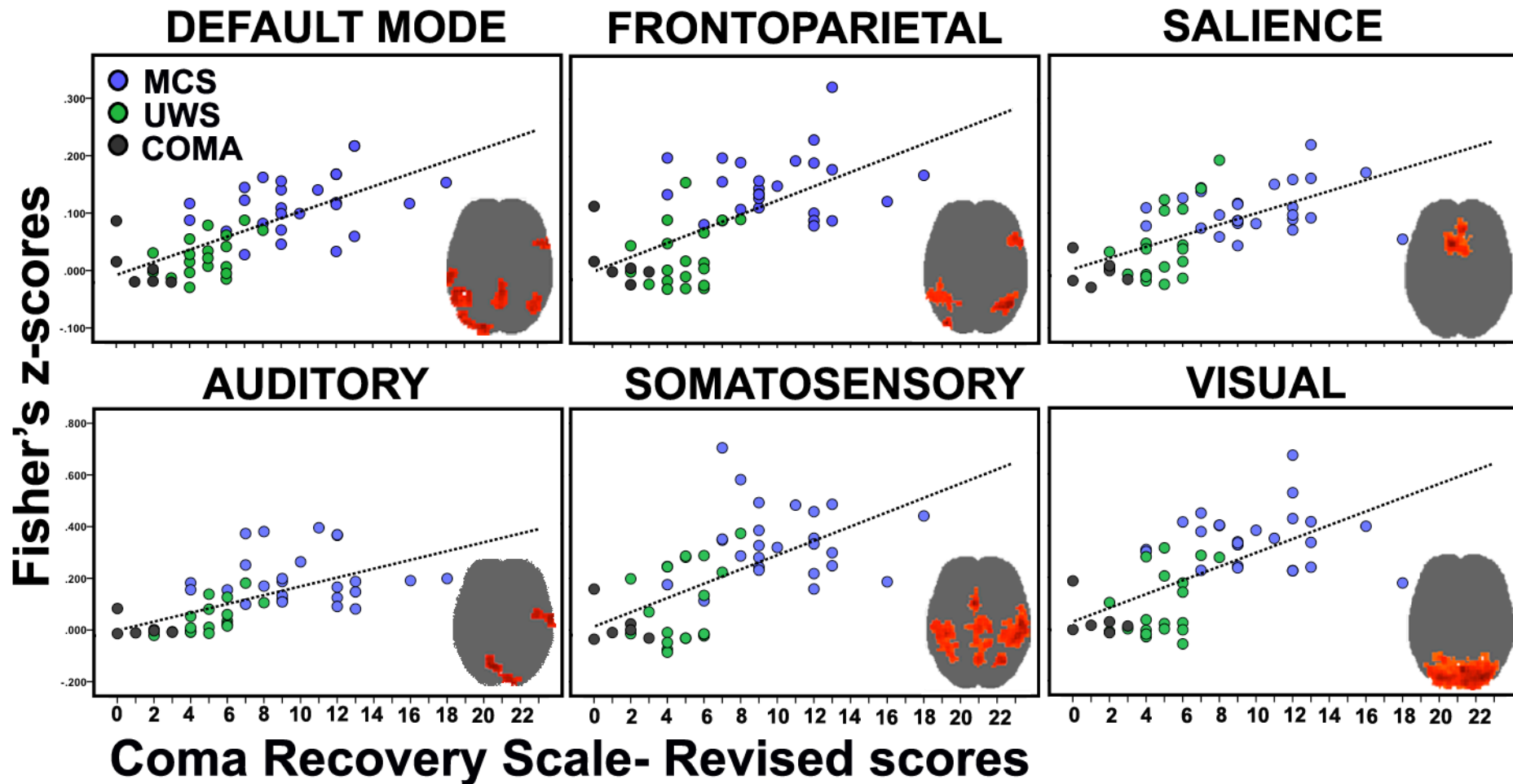
ICA: Fewer "neuronal" networks in DOC



Single-patient classification

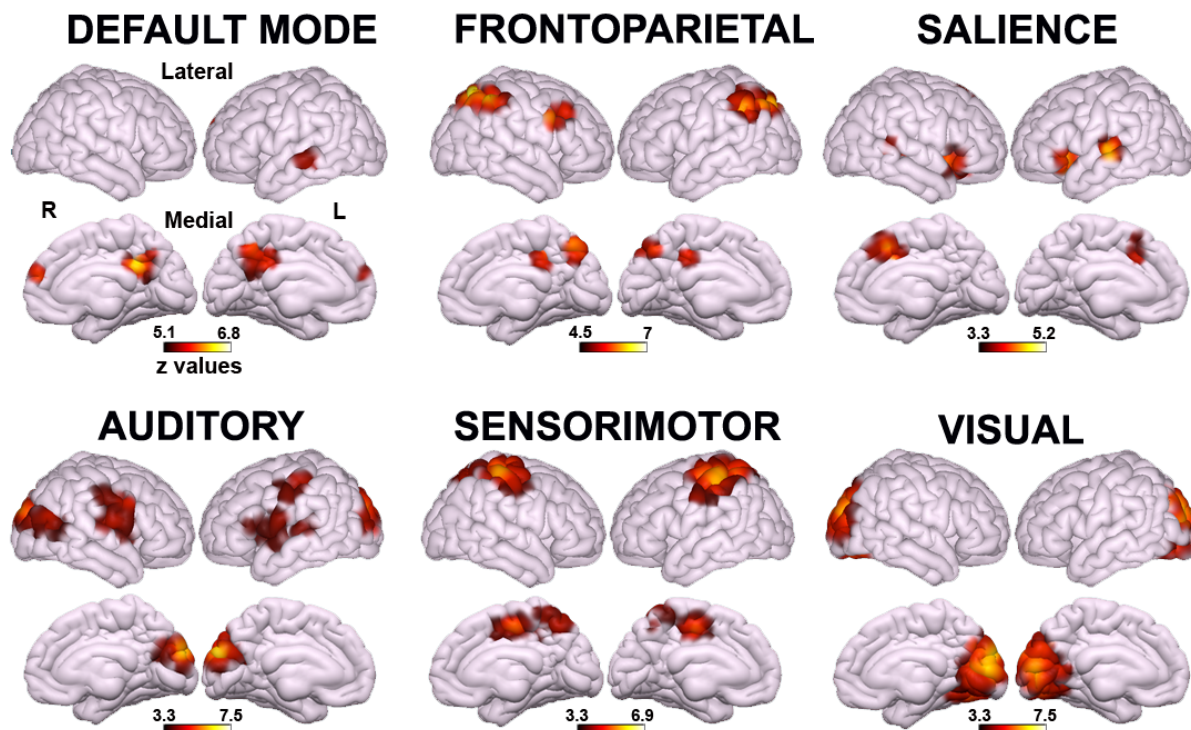
Performance measures	Accuracy	TPR healthy	TPR patients	Selected RSNs
	Healthy vs. all patients			
Neuronal	85.3	.82	.87	Auditory, DMN

Seed-based: Connectivity reflects C state



Which network discriminates best?

MCS > VS/UWS



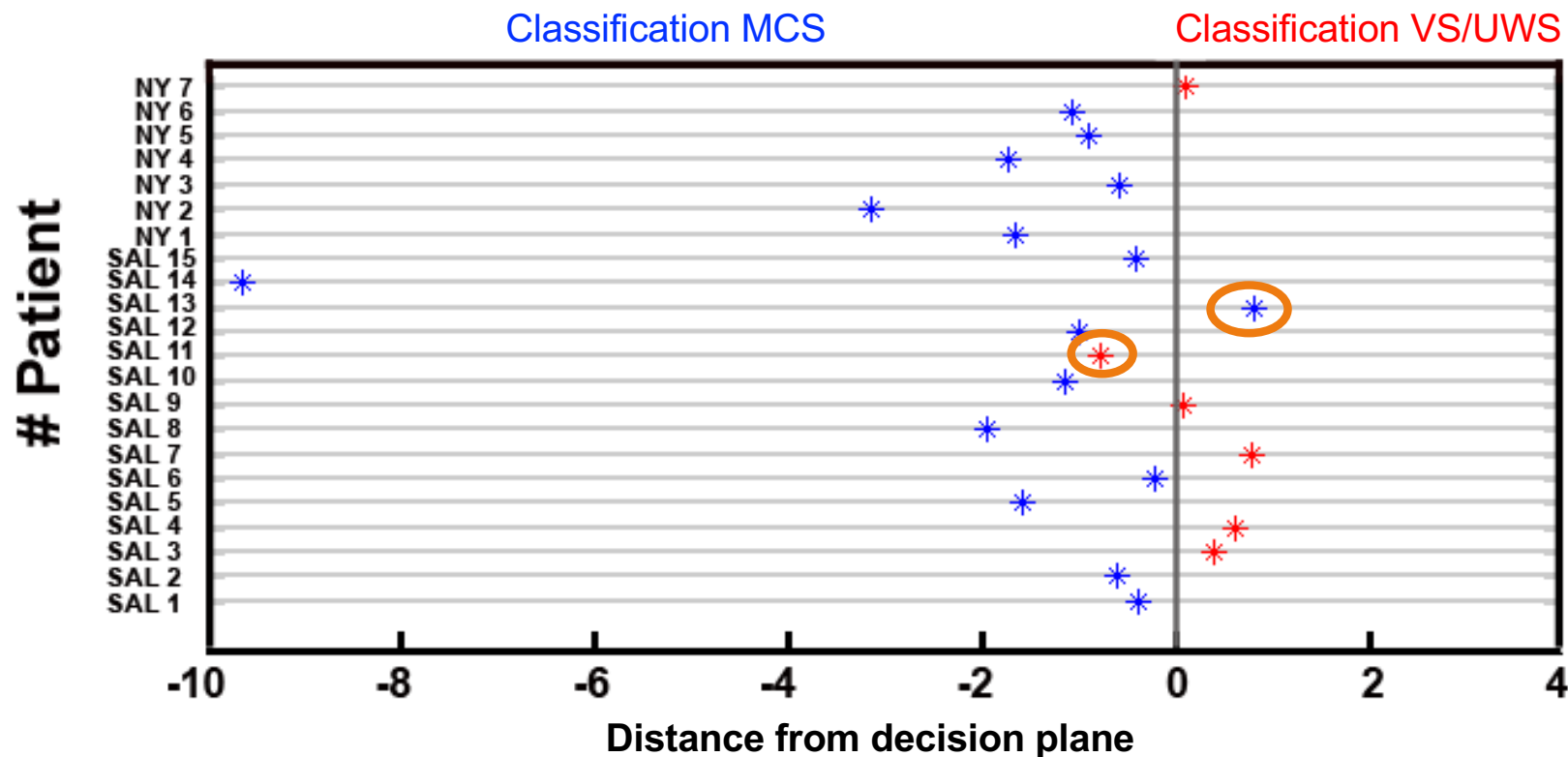
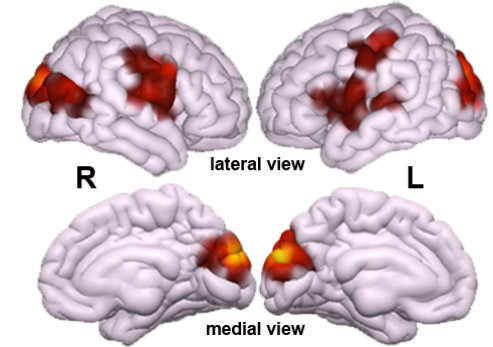
FWE $p < 0.05$ (cluster-level)

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

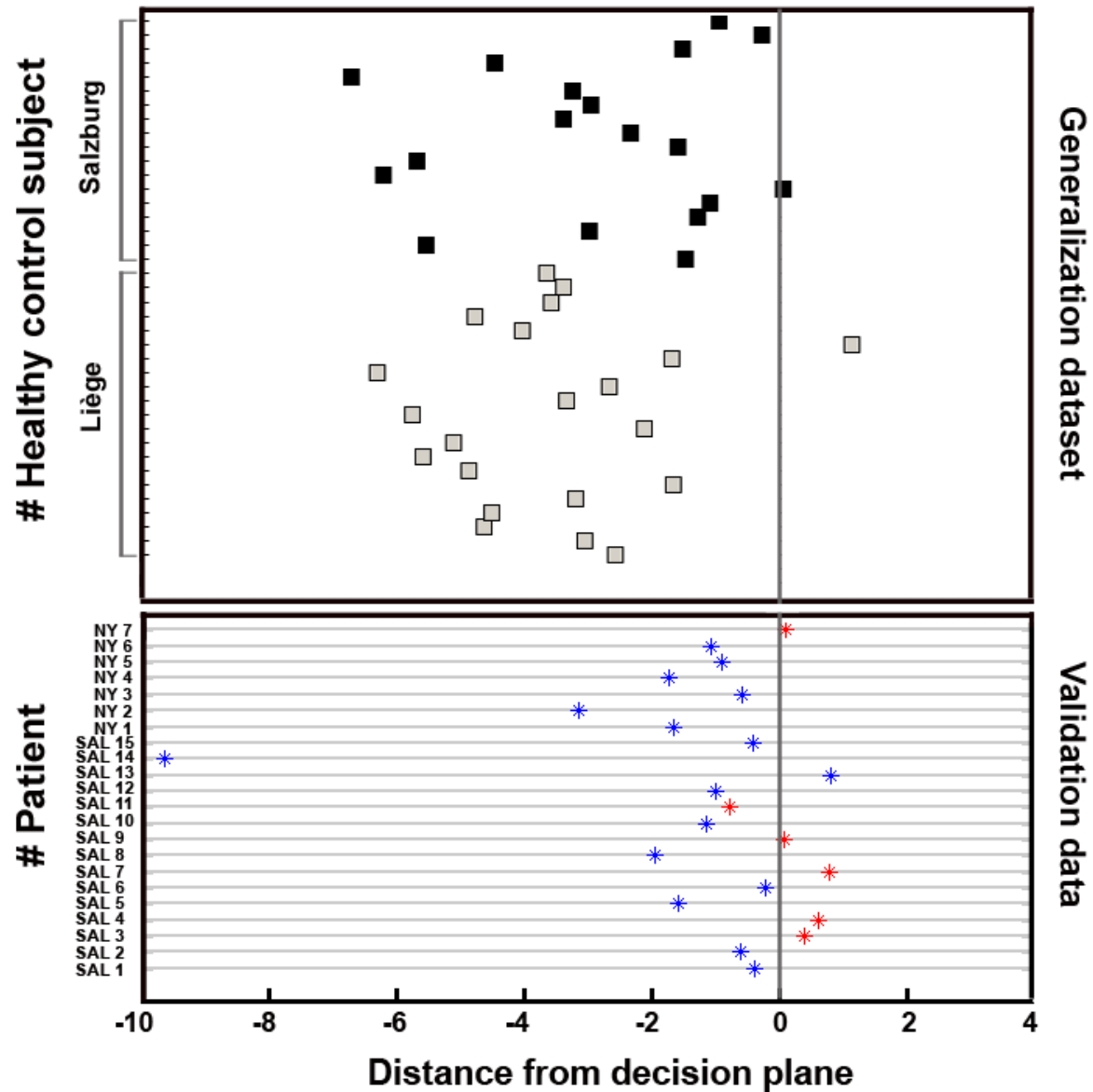
Crossmodal connectivity classifies independently assessed patients



- 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



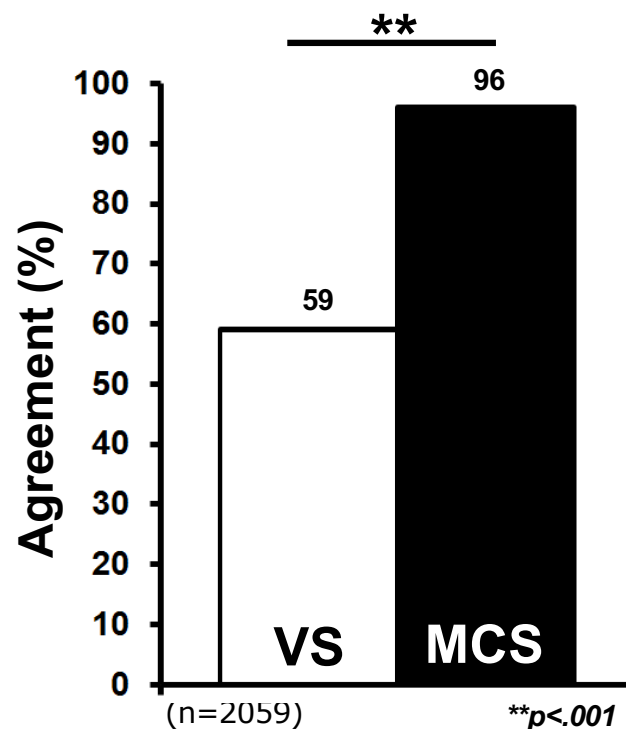
Ethical significance

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

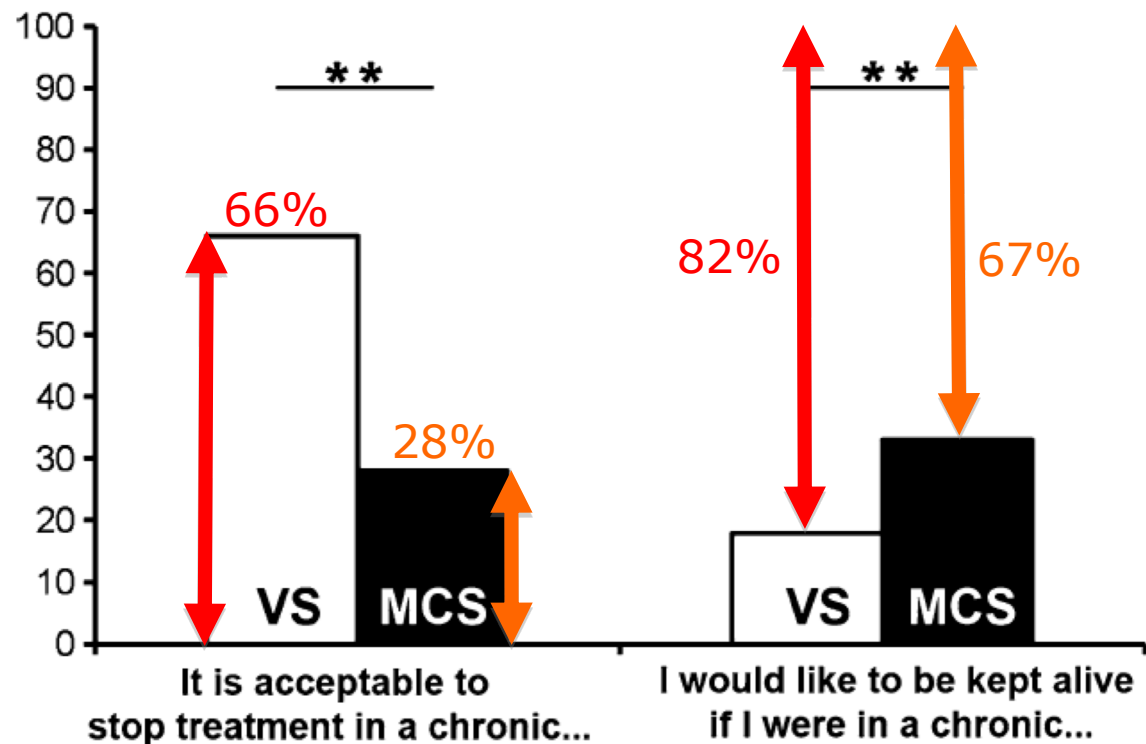
Predicted response: "agreement"

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%



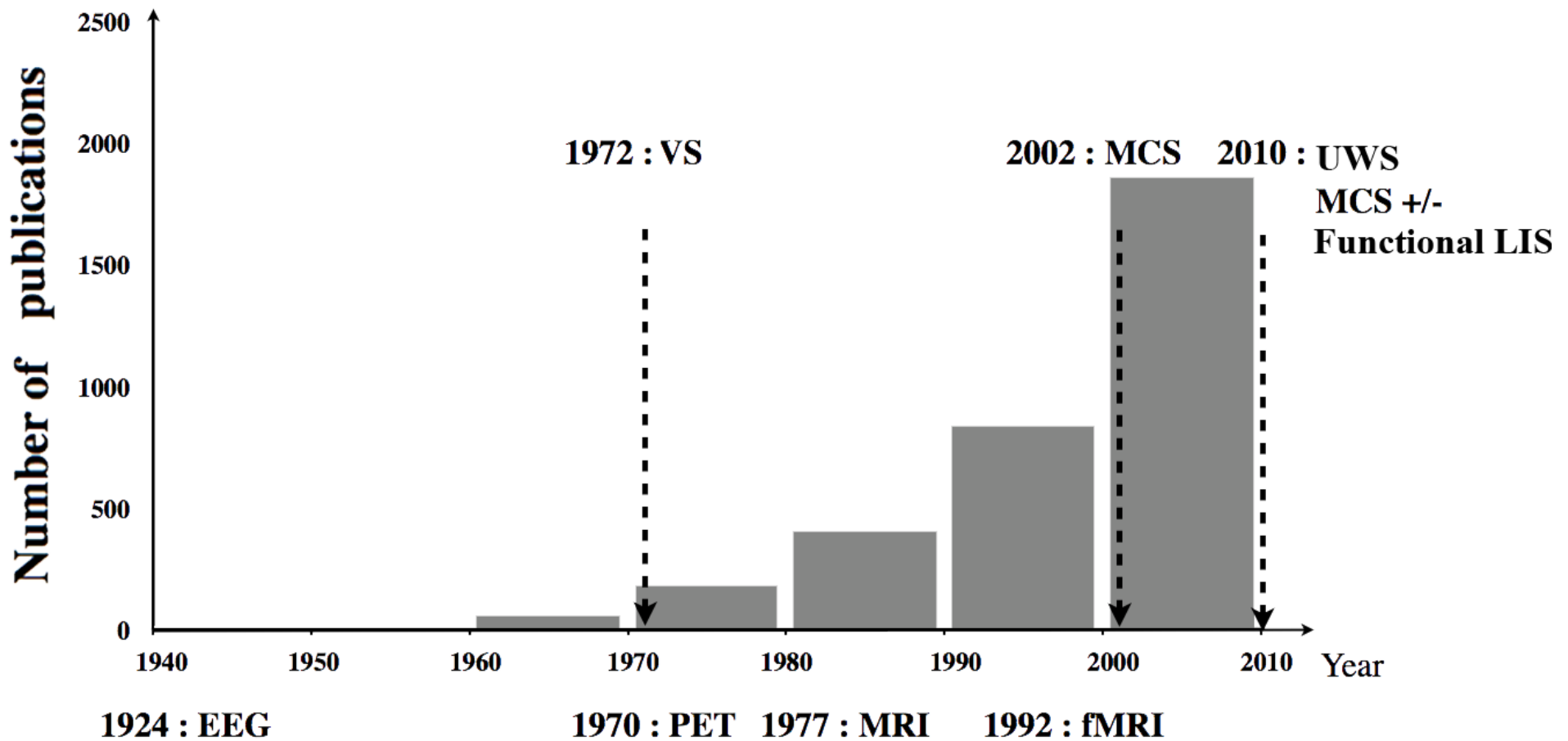
2,475 medical professionals



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!



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



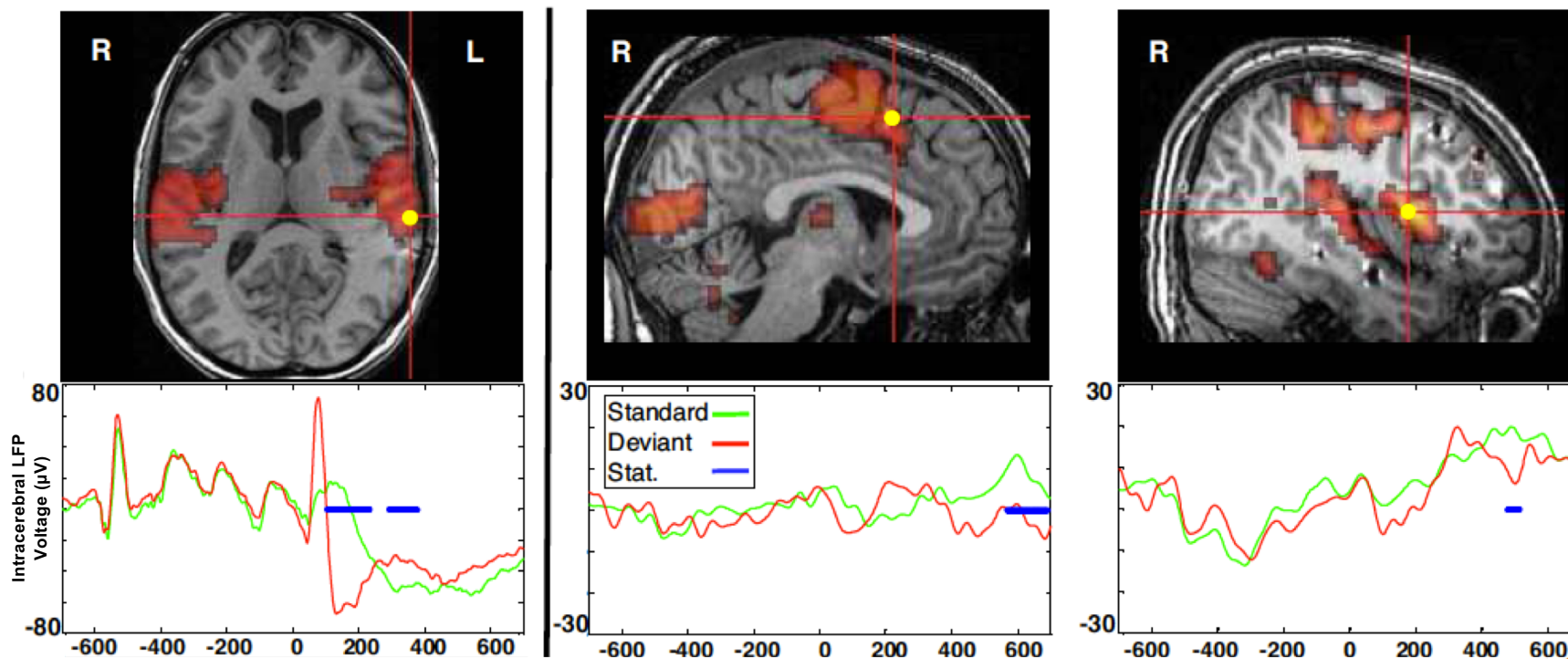
Crossmodal interaction in consciousness

The local-global paradigm

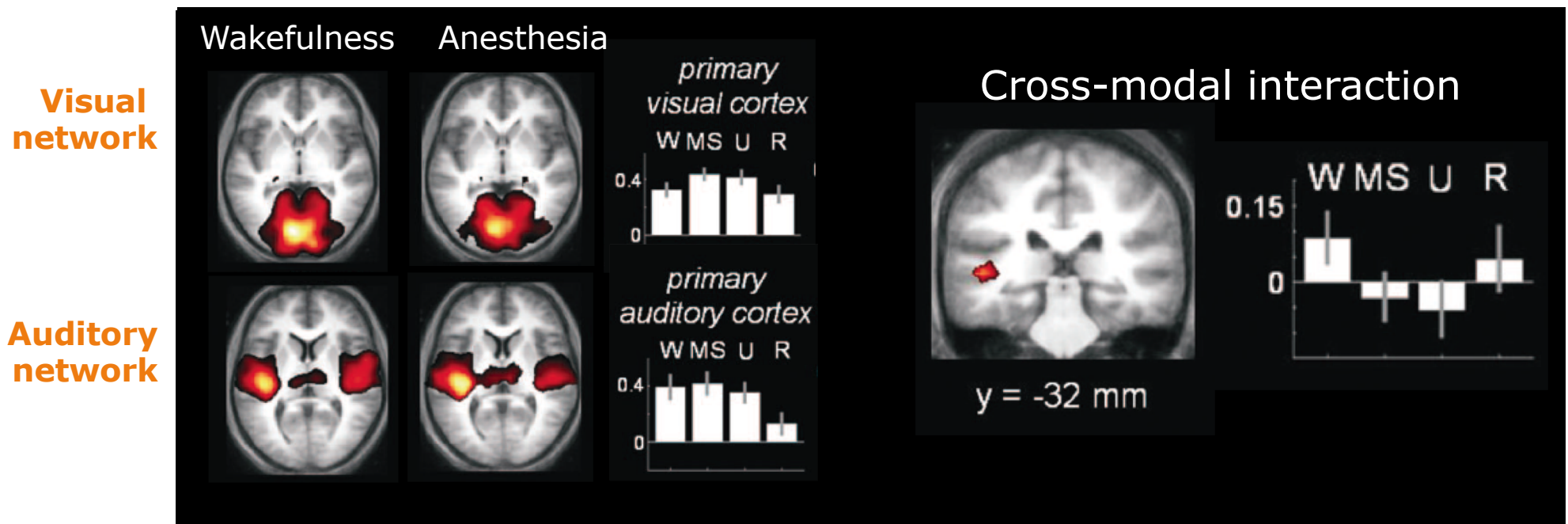


Local effect

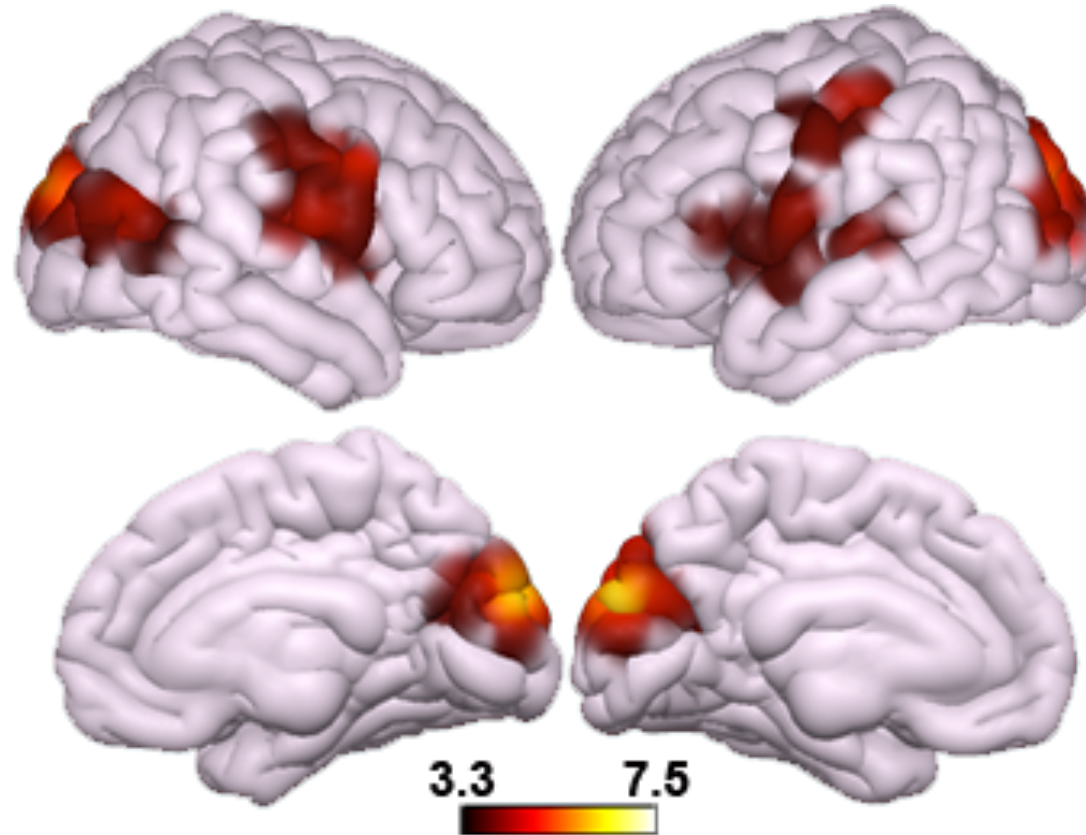
Global effect



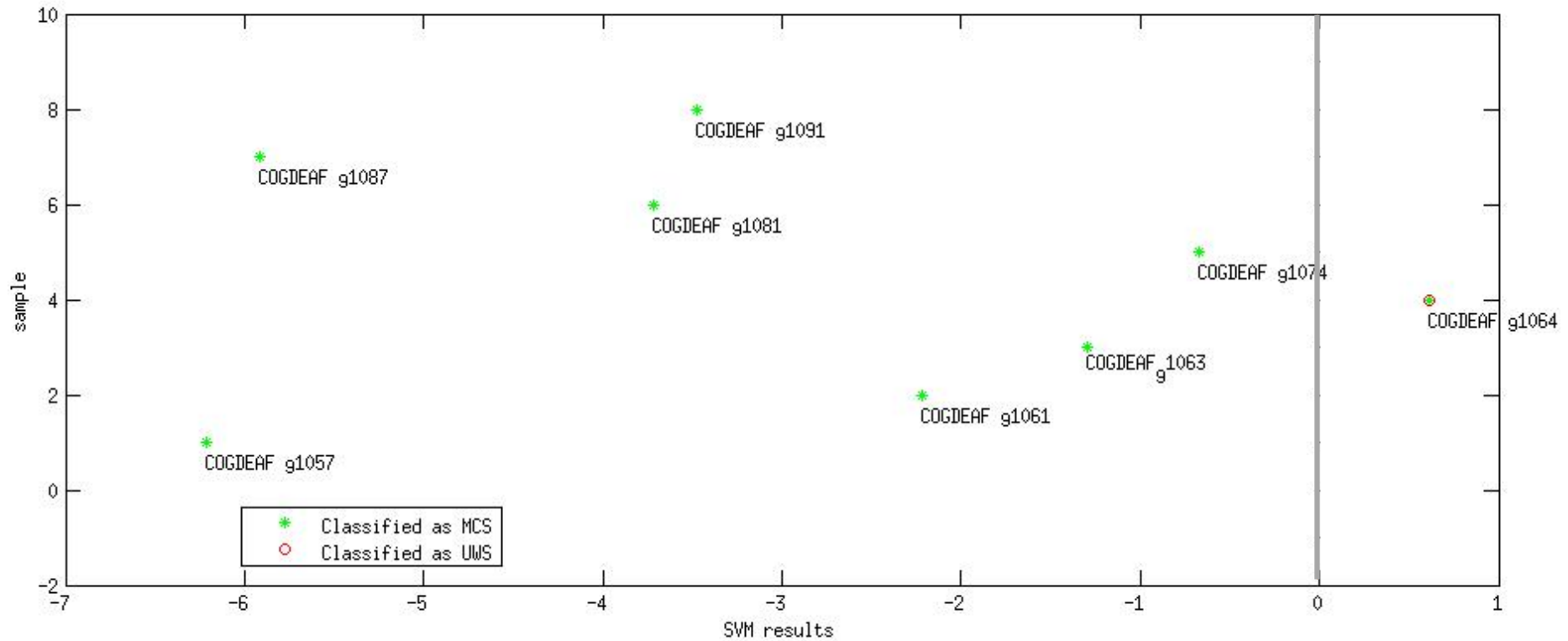
Crossmodal interaction in unconsciousness



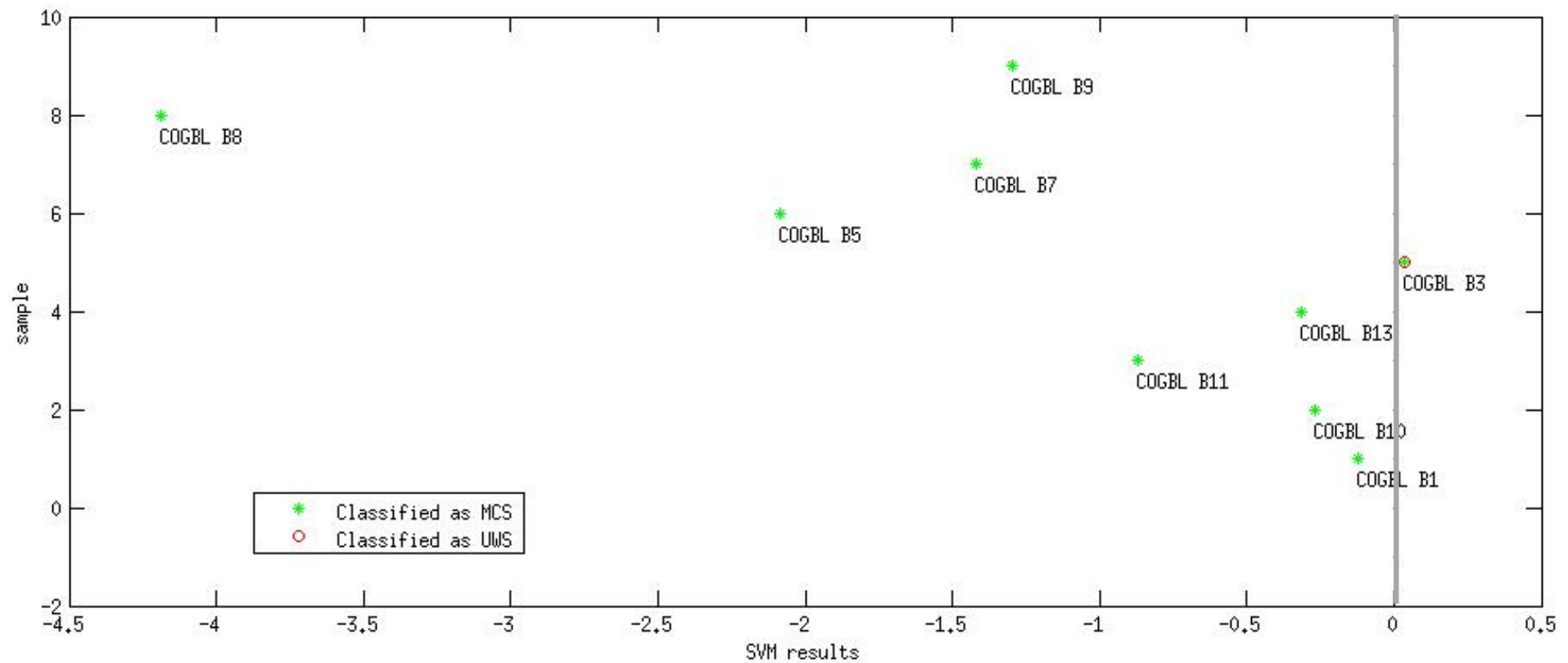
The “auditory” network



Validation in congenitally deaf



Validation in congenitally blind



Validation in propofol anesthesia

