Neural proxies to Consciousness and its Disorders

Implications for Resignation Syndrome

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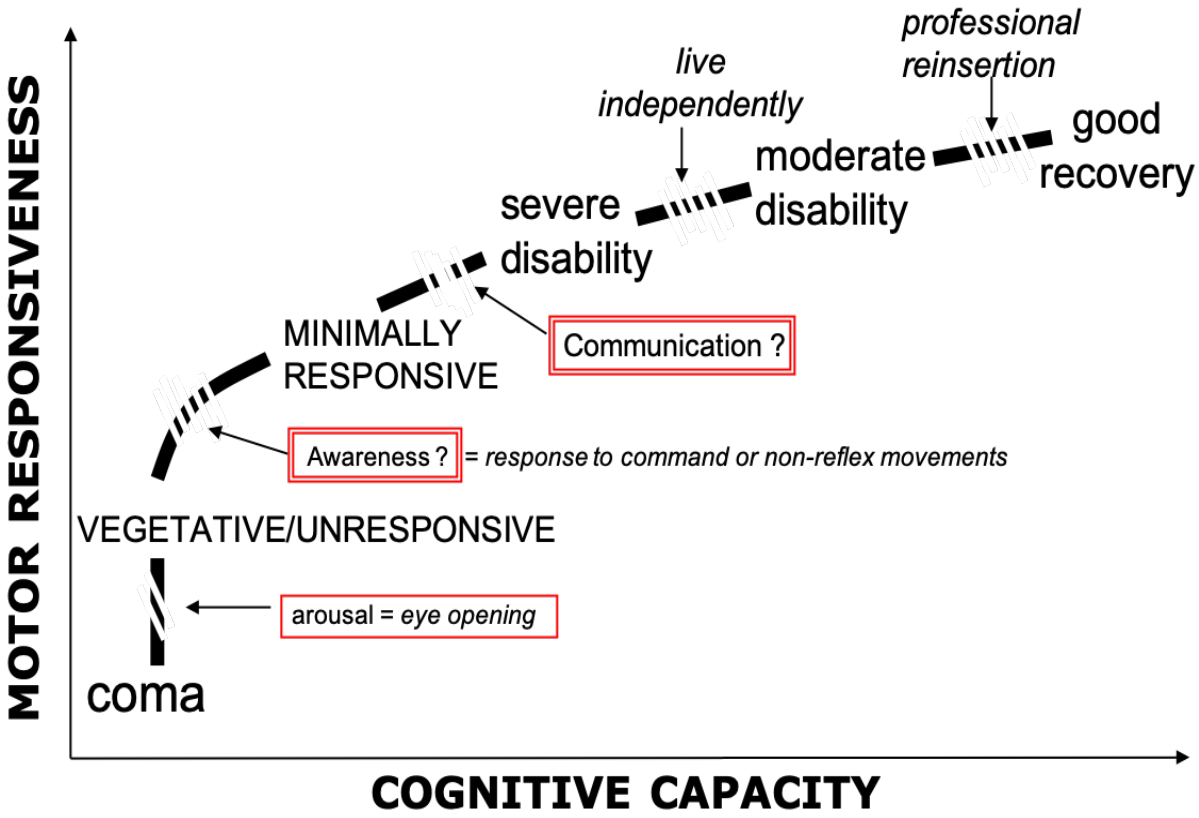
"Is Resignation Syndrome a Functional Neurological Disorder?"
Friday 4th November 2022
Wellcome Centre for Human Neuroimaging
London, UK

Consciousness inferred from behavior



Source: Google pictures (Credit: CC-BY-SA; M Appelman)

Laureys, Perrin, Brédart, *Consc Cogn* 2007

The ethical imperative of Consciousness

We cannot always trust behavior

n=103 post-comatose patients

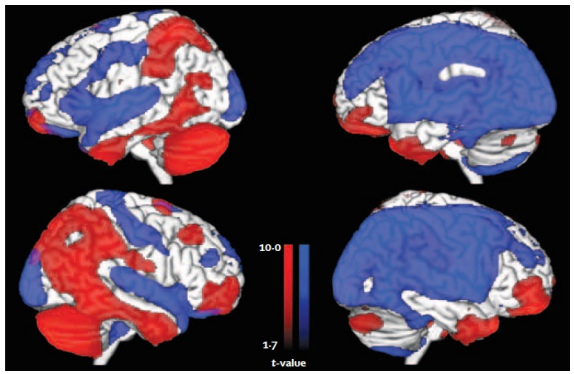
45 Clinical diagnosis of VS
18 Coma Recovery Scale MCS

⇩

40% misdiagnosis

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

Standardized assessment & 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%)

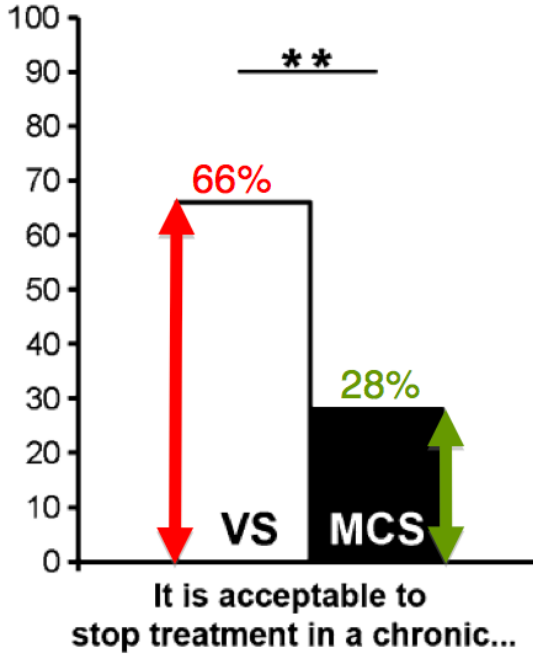
UWS=unresponsive wakefulness syndrome. MCS=minimally conscious state.

Table 2: Diagnostic results by modality

Stender & Gosseries et al, *Lancet 2*014

End-of-life support for "unconscious" patients

2,475 medical professionals



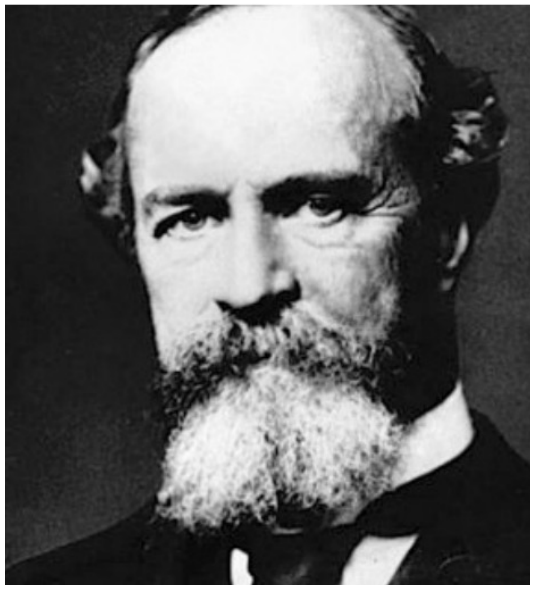
Demertzi et al, *Prog Brain Res* 2009
Demertzi et al, *J Neurol* 2011
Demertzi & Racine et al, *Neuroethics* 2012

The resting paradigm

Brain ~2% body's weight
Evoked changes <5%
80% for neuronal signaling

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

The stream of thought (Chapter IX)
The Principles of Psychology 1890



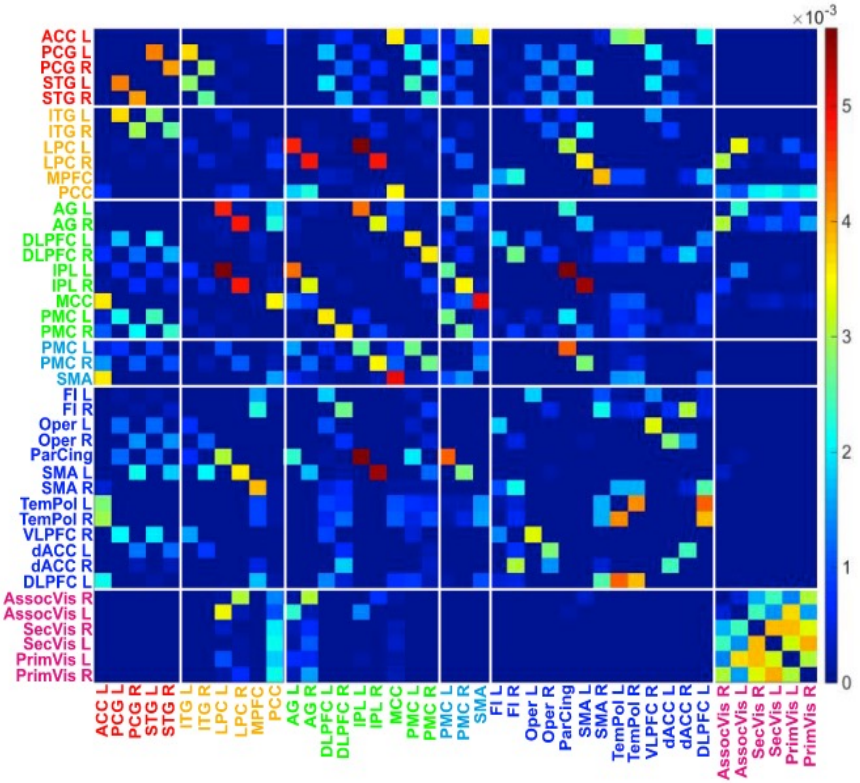
William James (1842-1910)

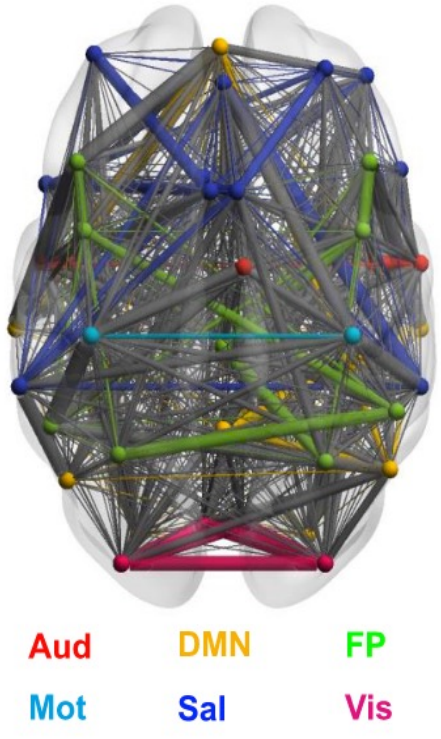
Raichle & Snyder, 2009 In: Laureys S, Tononi G *The Neurology of Consciousness*. Oxford: Elsevier Academic Press

The brain as a network

100 billion neurons, ~100 trillion synaptic connections

The Connectome





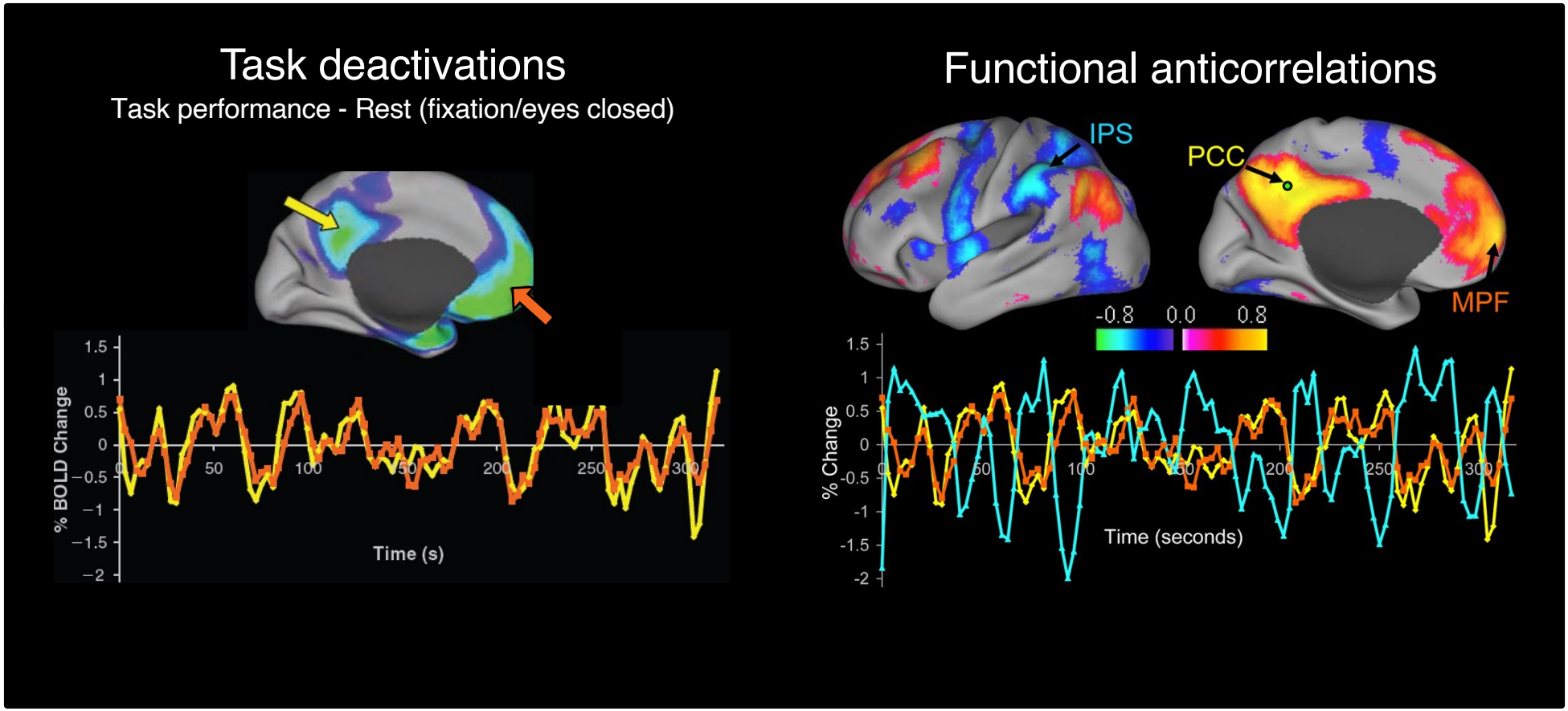
A matrix representing all possible pairwise anatomical connections between neural elements of the brain

Sporns, Tononi, & Koetter. *PLoS Comput. Biol.* 2005

Fornito, Zalesky, Bullmore. Ch 1: An Introduction to Brain Networks. *Fundamentals of Brain Network Analysis, Academic Press* 2016

Image from: Demertzi & Tagliazucchi, Dehaene, Deco, Barttfeld, Raimondo […], Schiff, Owen, Laureys, Naccache, Sitt. *Science Advances* 2019

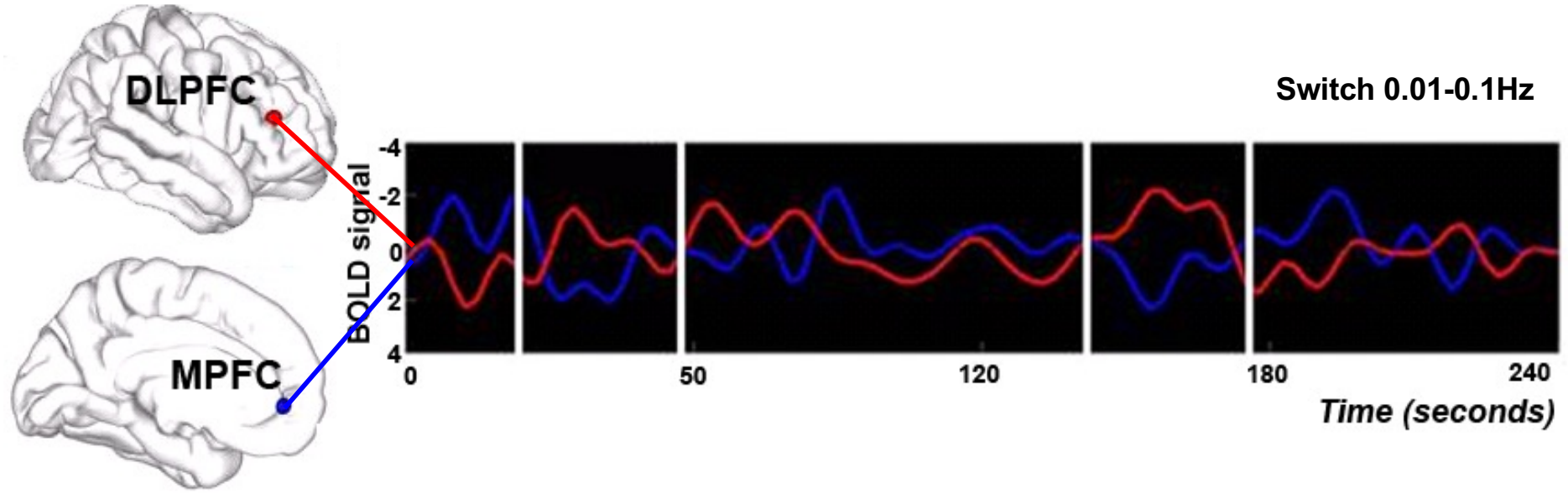
Default mode of brain function



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
Fox et al, *PNAS* 2005

Anticorrelations inform cognitive function?

External awareness
***or* anticorrelated network**

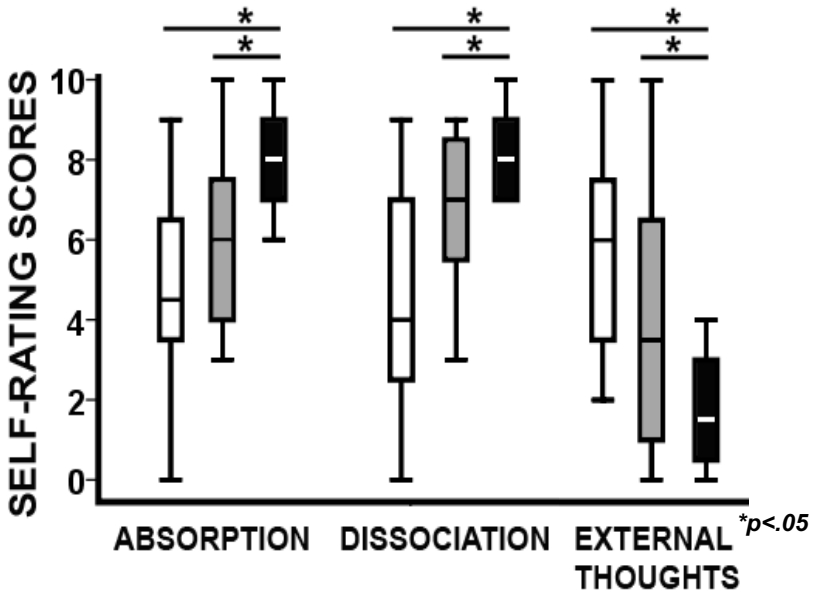


Internal awareness
***or* Default mode network**

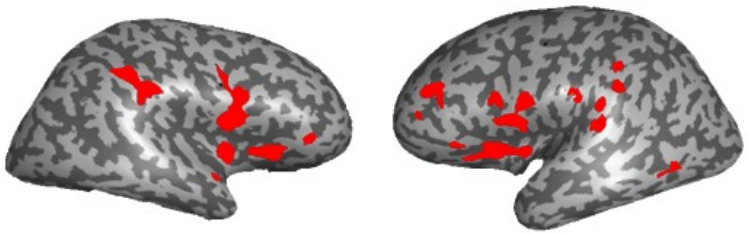
Vanhaudenhuyse*, Demertzi* et al, *J Cogn Neurosci* 2011
Demertzi, Soddu, Laureys, *Curr Opin Neurobiology* 2013
Demertzi & Whitfield-Gabrieli, in: *Neurology of Consciousness* 2nd ed. *2015*
Demertzi et al, *Front Hum Neurosci* 2013
Demertzi, Kucyi, Ponces-Alvarez, Keliris, Whitfield-Gabrieli, Deco. *Netw Neurosci* in press

Modified awareness reduces anticorrelations

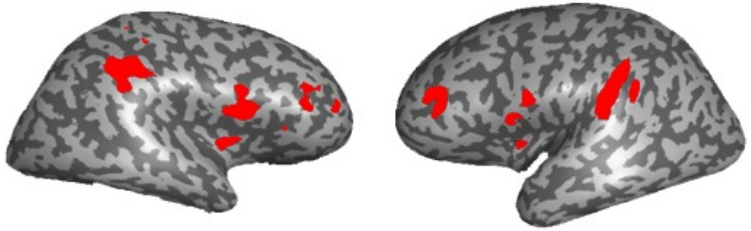
- Normal wakefulness
- Autobiographical mental imagery
- Hypnosis



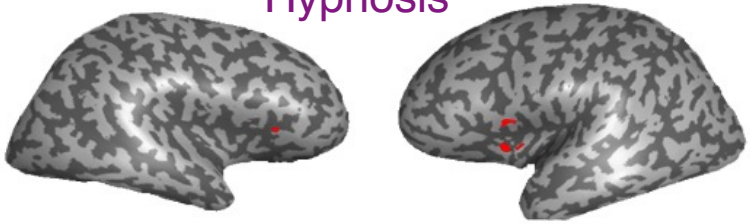
Normal wakefulness



Autobiographical mental imagery



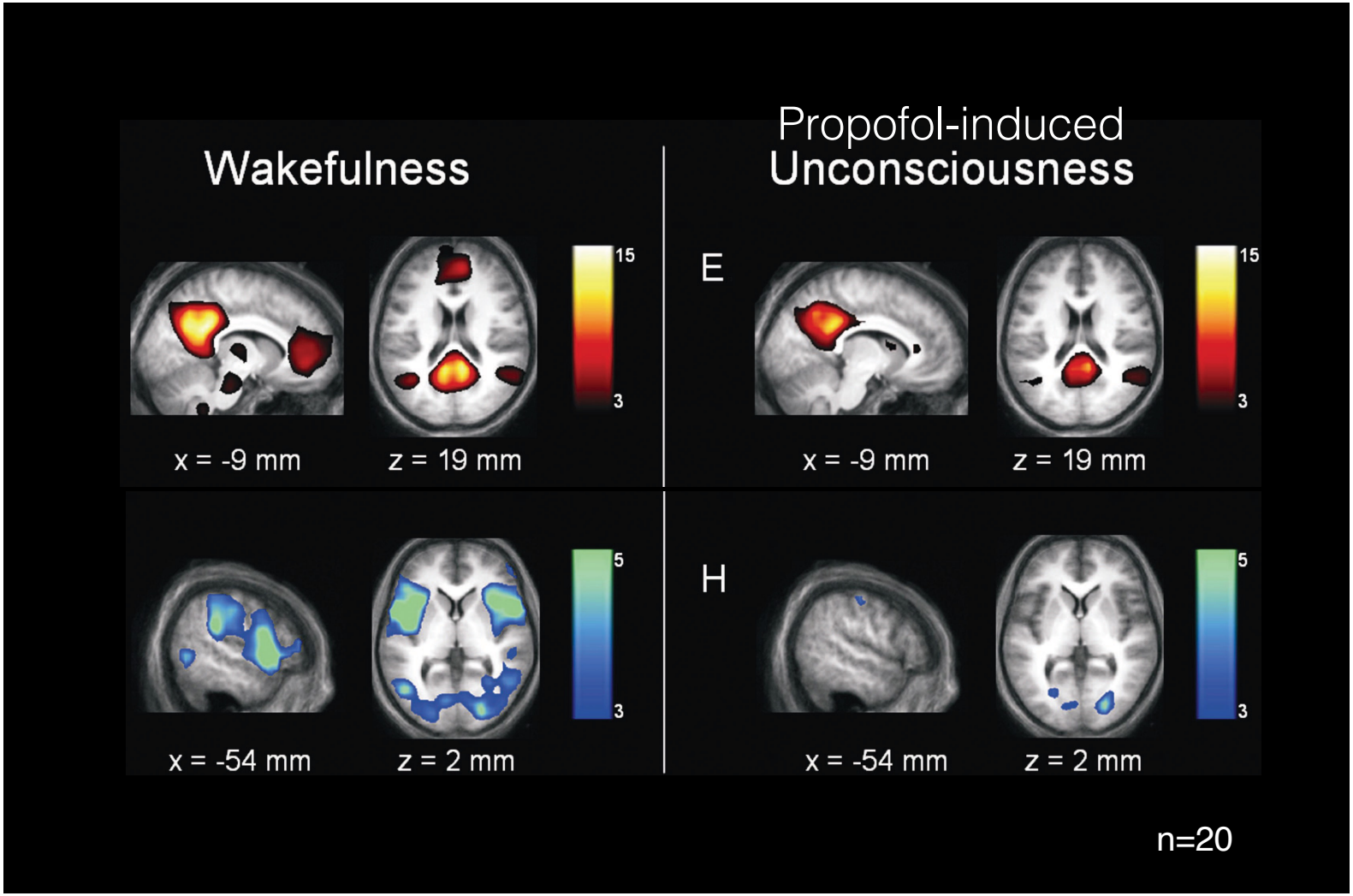
Hypnosis



p<0.05 corrected for multiple comparisons

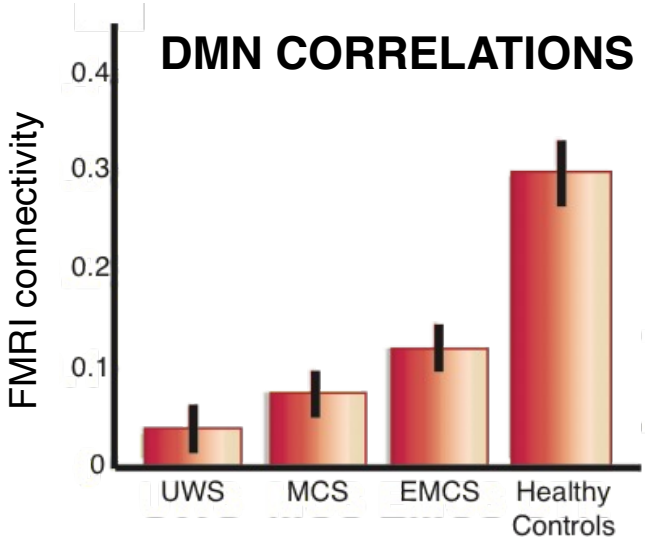
Demertzi, Soddu, Faymonville et al, *Prog Brain Res* 2011
Demertzi, Vanhaudenhuyse, Noirhomme, Faymonville, Laureys, *J Physiol Paris* 2015

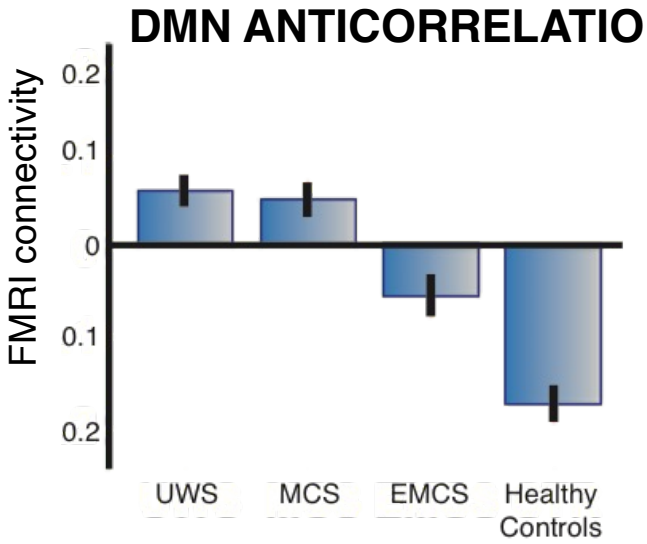
Modified arousal reduces anticorrelations

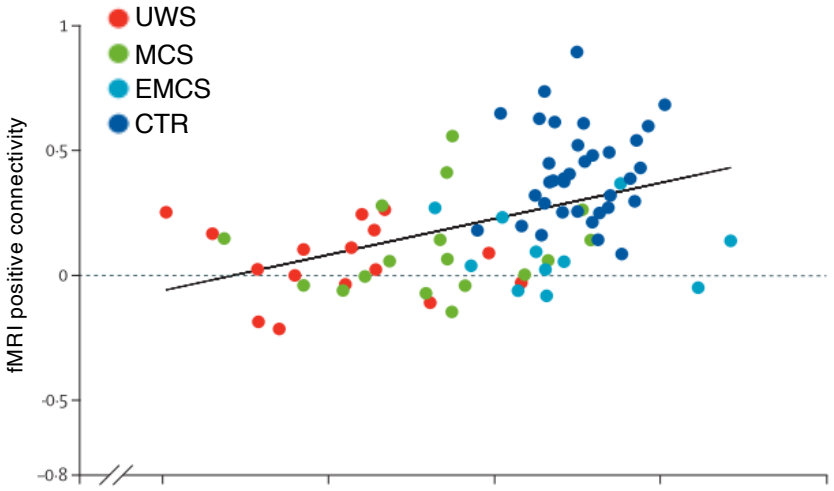


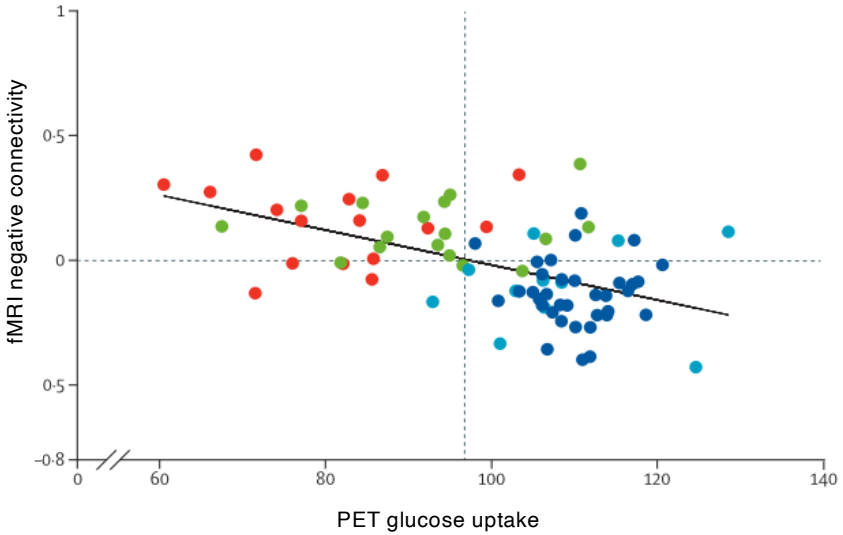
Boveroux et al, *Anesthesiology* 2010

No anticorrelations in DOC







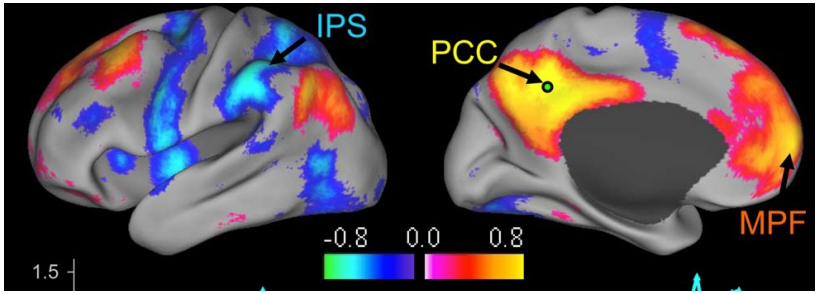


Di Perri, …, Demertzi*, Laureys*, Soddu*, *Lancet Neurol* 2016

Anticorrelations and Consciousness

Anticorrelations **reduce** in intensity or are undetectable in :

- unresponsive brain-damaged patients (Di Perri et al., 2016; Threlkeld et al., 2018)
- hypnosis (Demertzi et al., 2011)
- in deep anesthesia (Boveroux et al., 2010)
- after sleep deprivation (De Havas et al., 2012; Yeo et al., 2015)
- slow wave sleep and REM (Chow et al., 2013)
- deep sedation (Luppi et al., 2019)



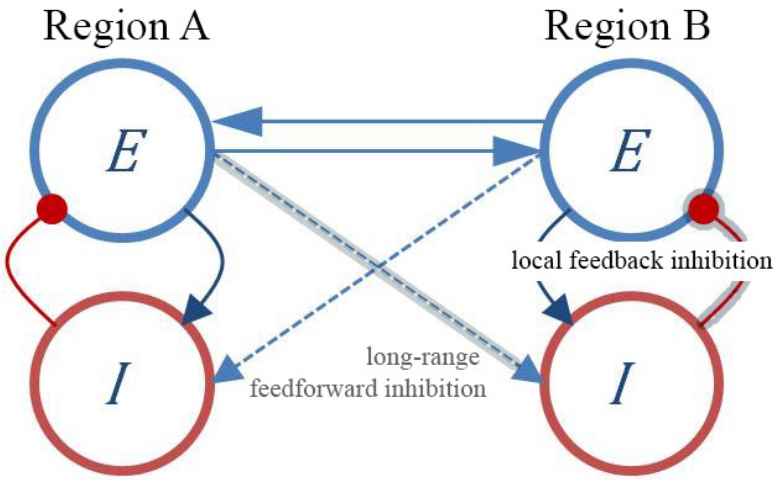
Anticorrelations **recover:**

- at post-anesthetic period (Nir et al., 2020)
- after emergence from a disorder of consciousness (Di Perri et al., 2016; Threlkeld et al., 2018).

Anticorrelations **contribute** to:

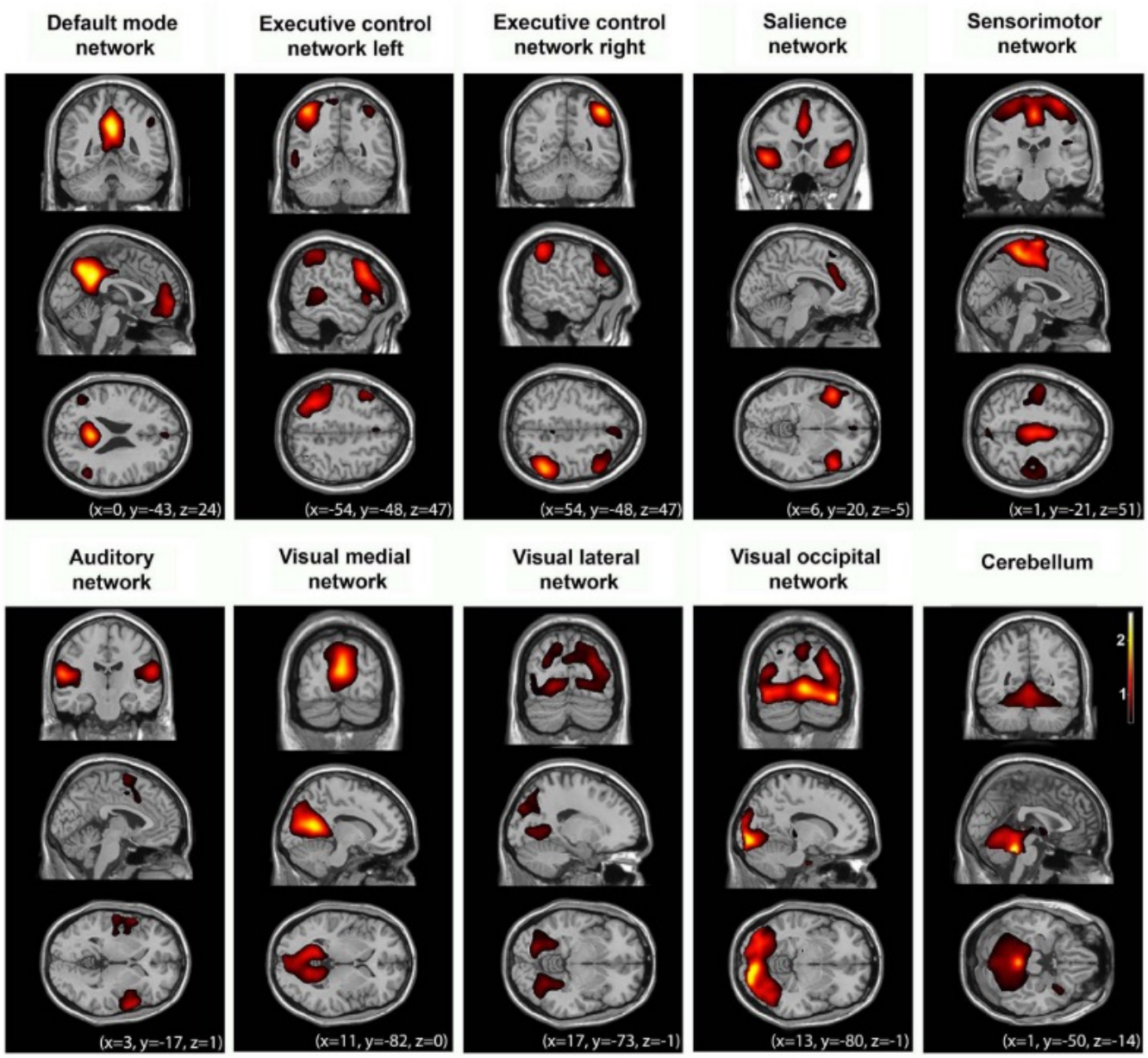
- cognitive function (Keller et al., 2015; Vanhaudenhuyse et al., 2011),
- greater intensity lead to better within-subject performance (Kucyi et al., 2017)
- between-subject performance (Spreng et al., 2010).
- life span
  - start weak in children, strengthen during adolescence, end up fully anticorrelated in young adulthood (Chai et al., 2014)
  - get selectively decreased during healthy aging (Keller et al., 2015)

neural inhibition



Demertzi, Kucyi, Ponce-Alvarez, Keliris, Whitfield-Gabrieli, Deco. *Network Neurosci* in press

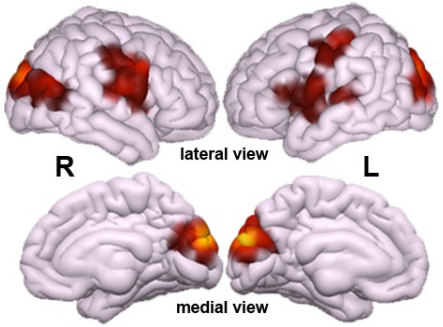
More networks during rest

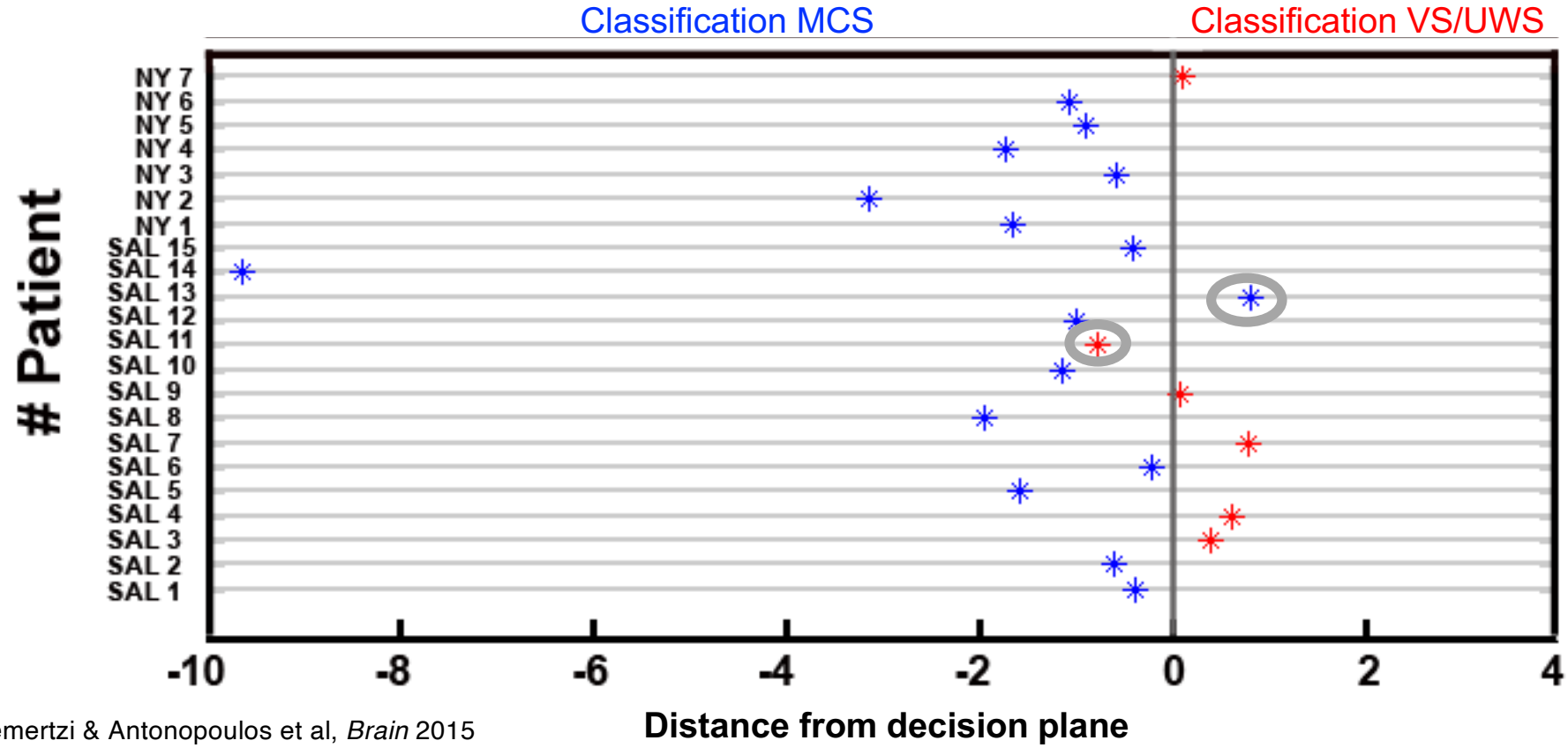


Biswal et al., *Magn Reson. Med* 1995
Smith et al, *PNAS* 2009
Heine et al, *Front Psych 2012*

Lower cross-modal interaction in UWS

- 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** (15 non-trauma; all chronic)
  - 2 different centers

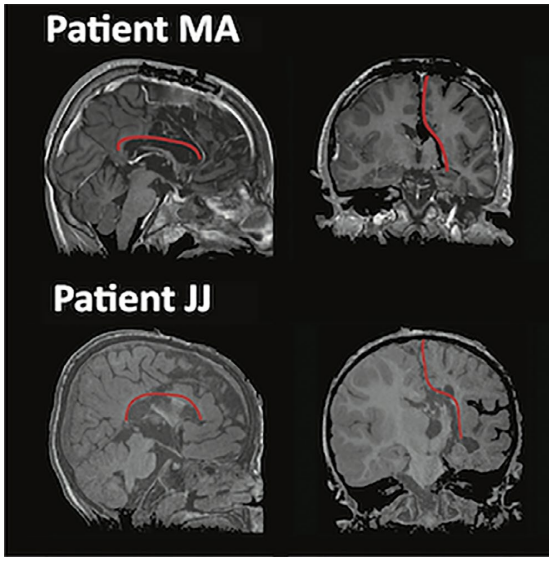




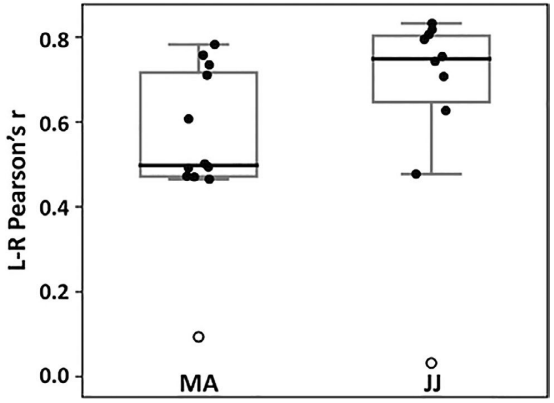
Demertzi & Antonopoulos et al, *Brain* 2015

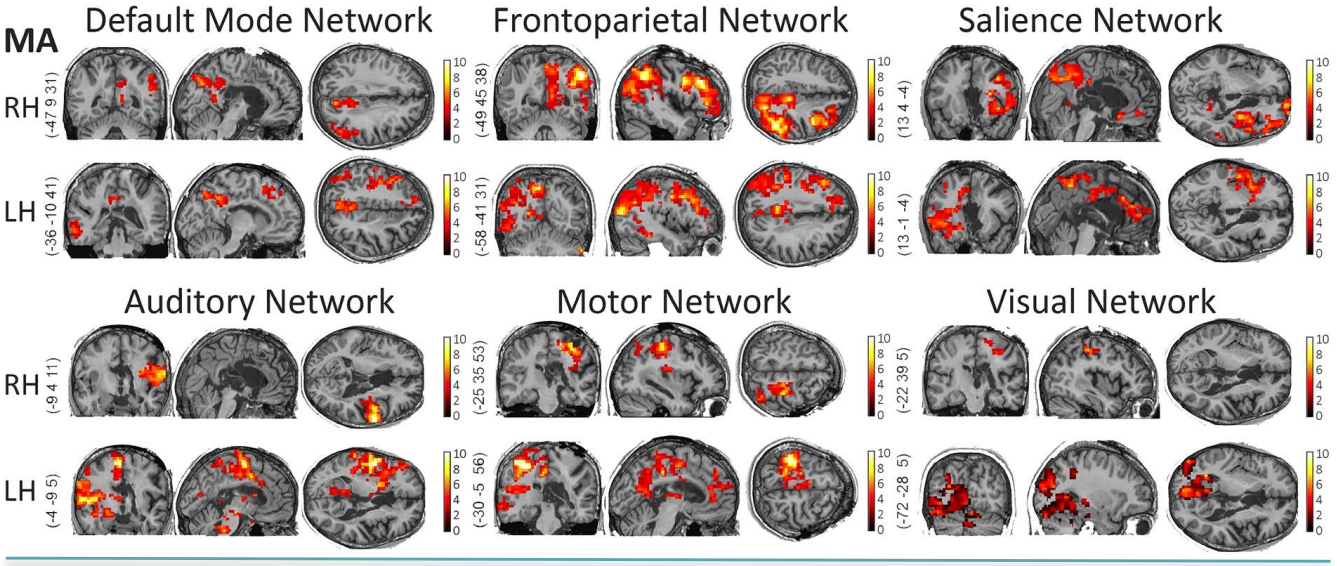
Lower cross-modal interaction in the isolated brain

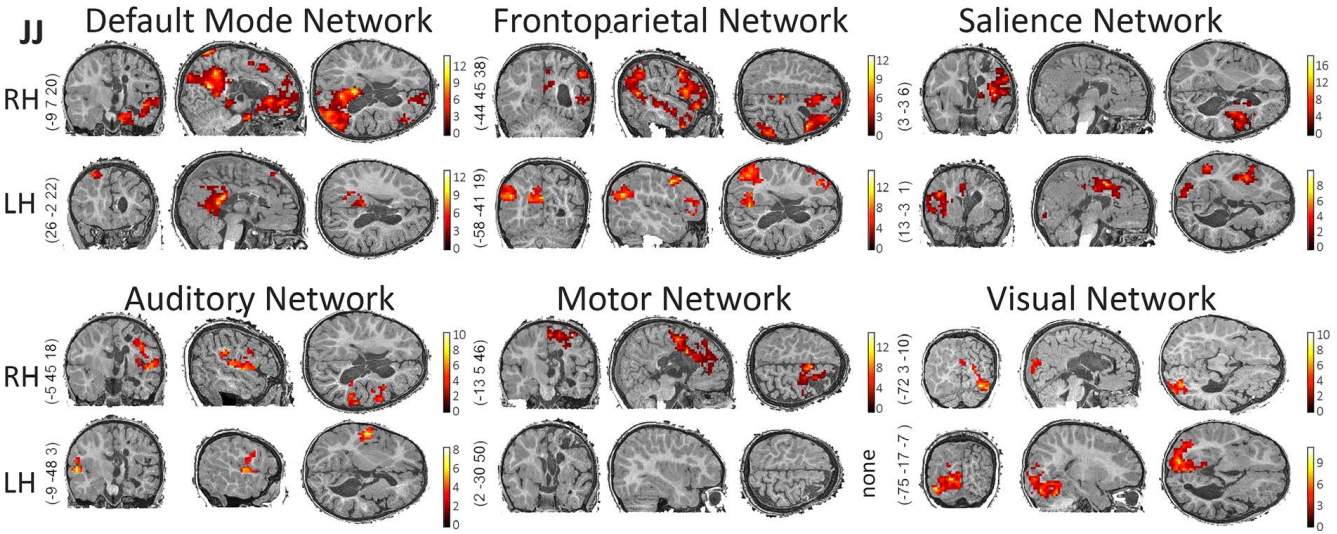
Complete hemispherotomy



Inter-hemispheric connectivity

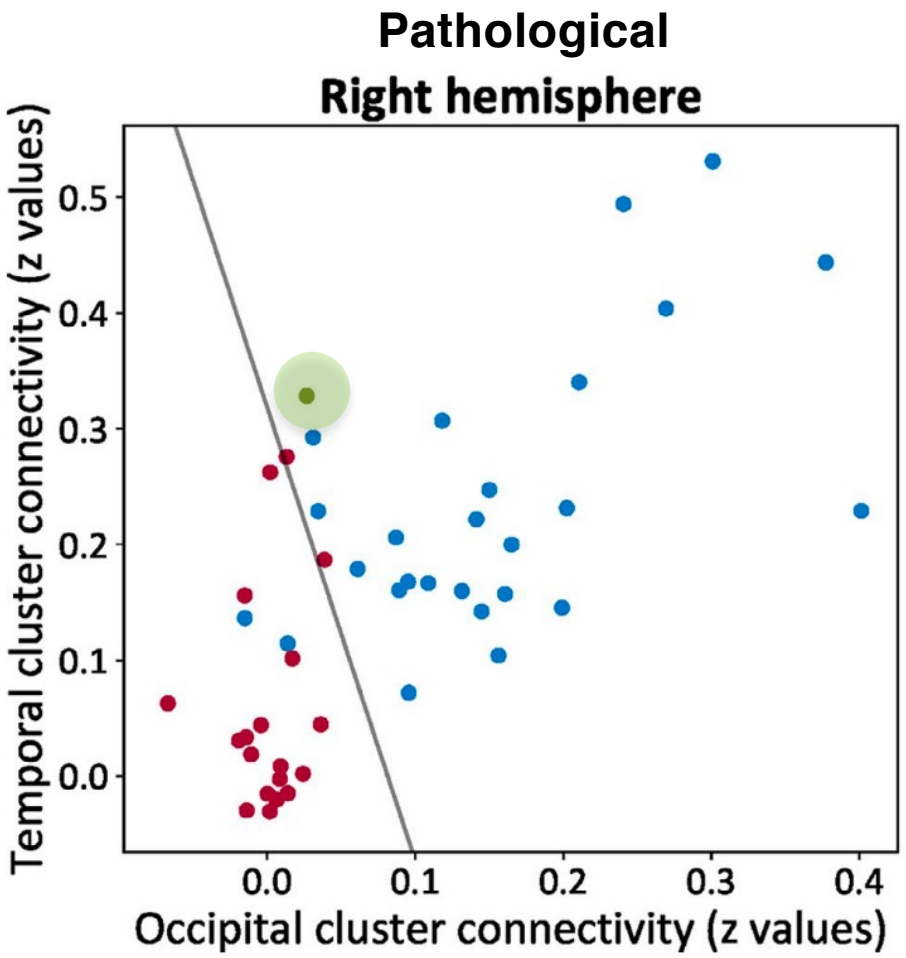


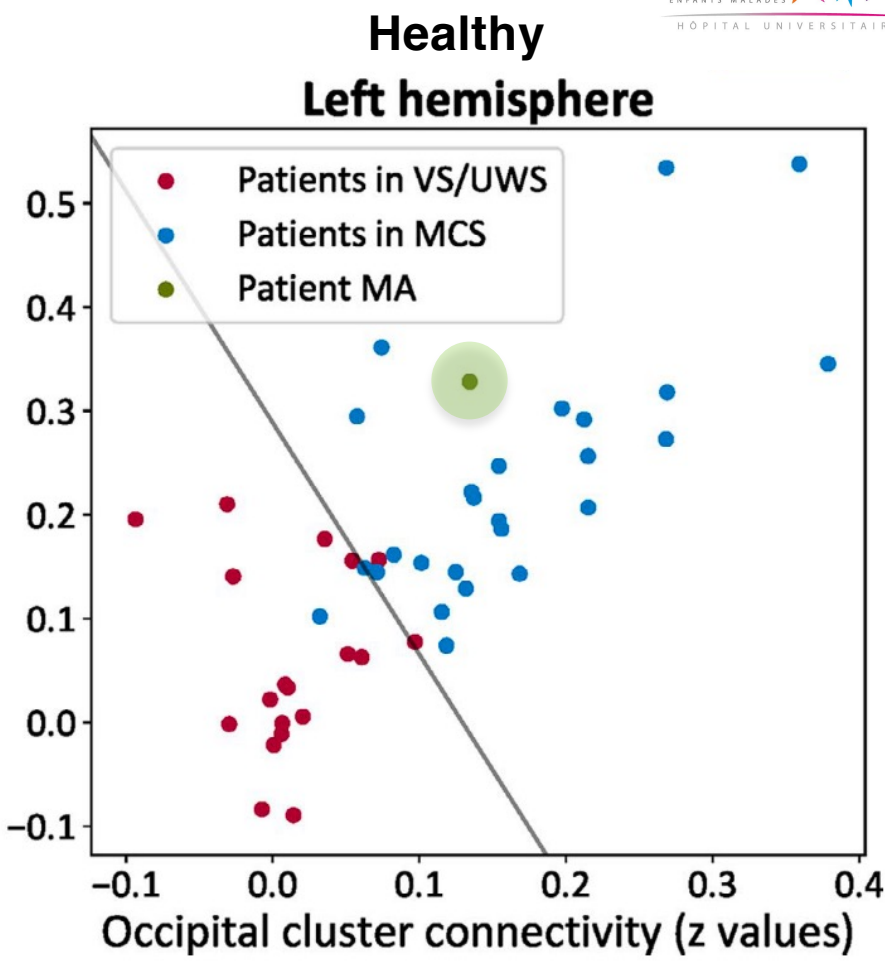




Blauwblomme & Demertzi et al, *Epilepsia Open* 2020

Lower cross-modal interaction in the isolated brain

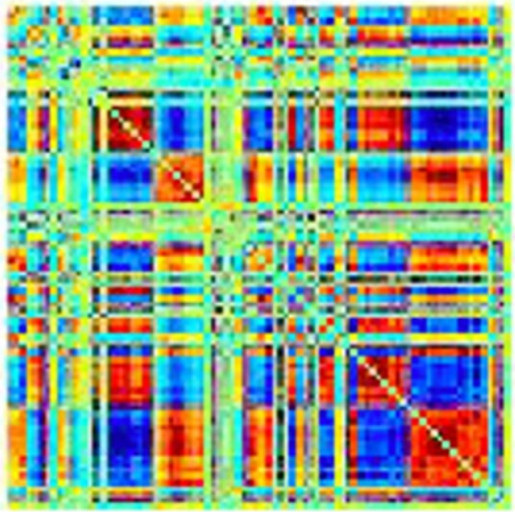




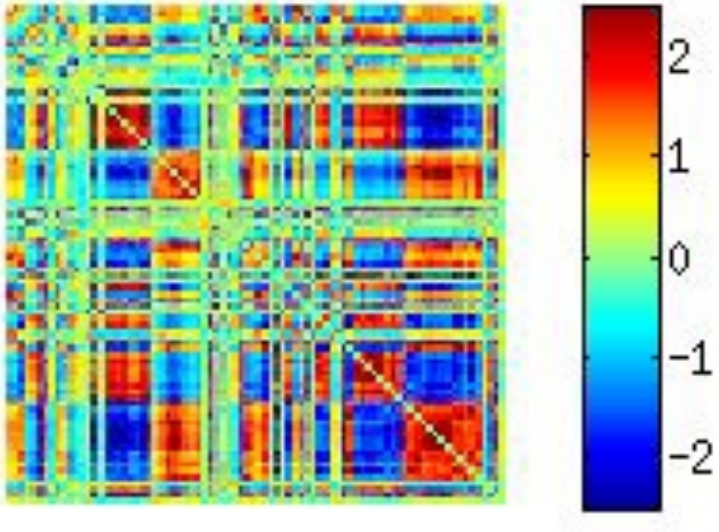
Blauwblomme & Demertzi et al, *Epilepsia Open* 2020

Brain dynamics and cognition

Averaged connectome



Time-varying connectome



Typical wakefulness

Performance, emotion and cognition

Alavash et al, *Neuroimage*, 2016; Shine et al *Neuron*, 2016; Friston *Neuroimage*, 1997; Thompson et al, *Hum Brain Mapp,* 2013

Unconsciousness

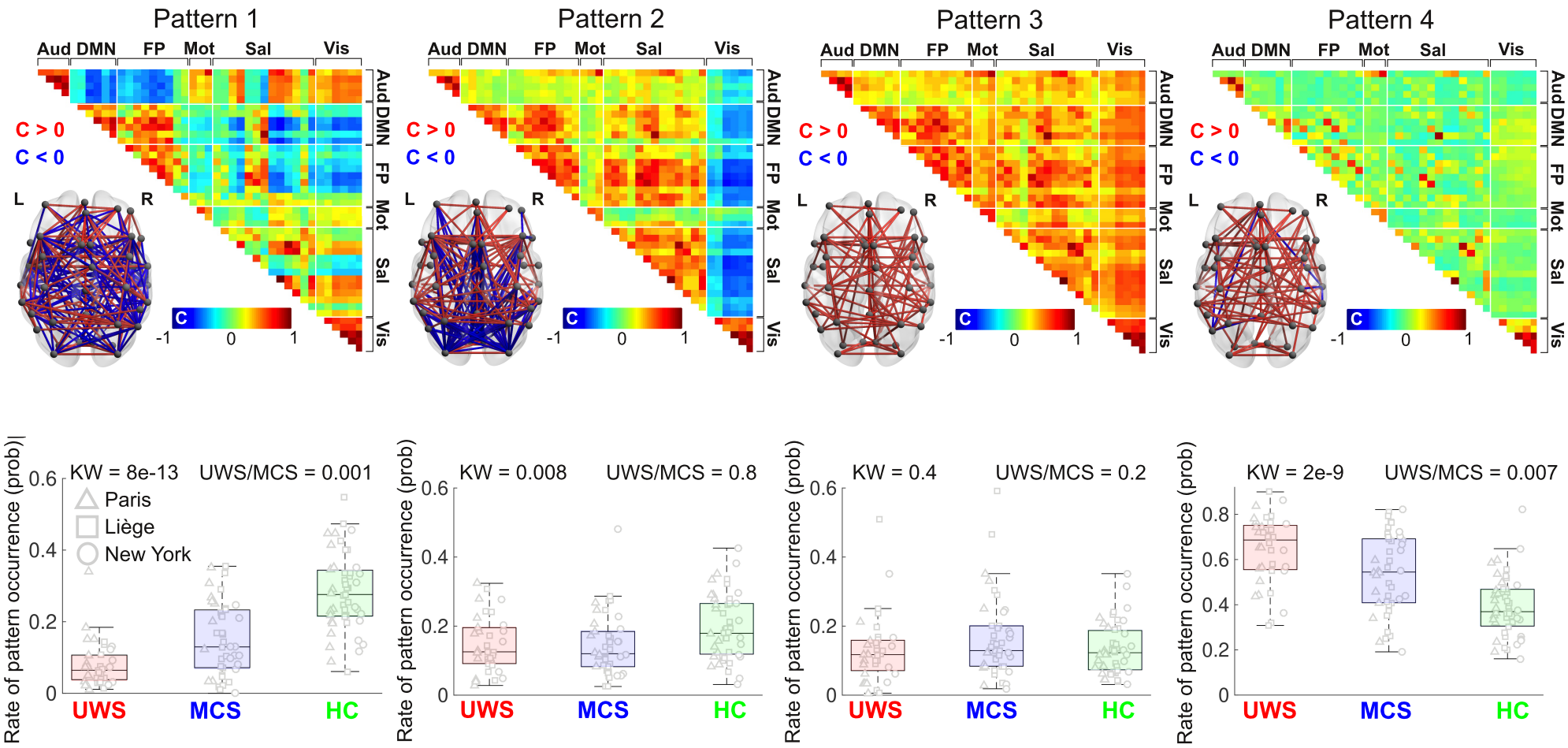
Rigid spatiotemporal organization, less metastable dynamics

- sleep (Tagliazucchi et al, *PNAS* 2013; Wang et al, *PNAS* 2016; Wilson et al., *Neuroimage* 2015; Chow et al, *PNAS* 2013)
- anesthesia
  - humans (Tagliazucchi et al, *J. R. Soc. Interface* 2016; Kafashan et al, *Front Neural Circuits*, 2016; Amico et al, *PLoS One* 2014)
  - animals (Barttfeld et al, *PNAS* 2014; Grandjean et al, *Neuroimage* 2017; Liang et al, *Neuroimage* 2015)

The brain cannot map the complexity of internal and external world

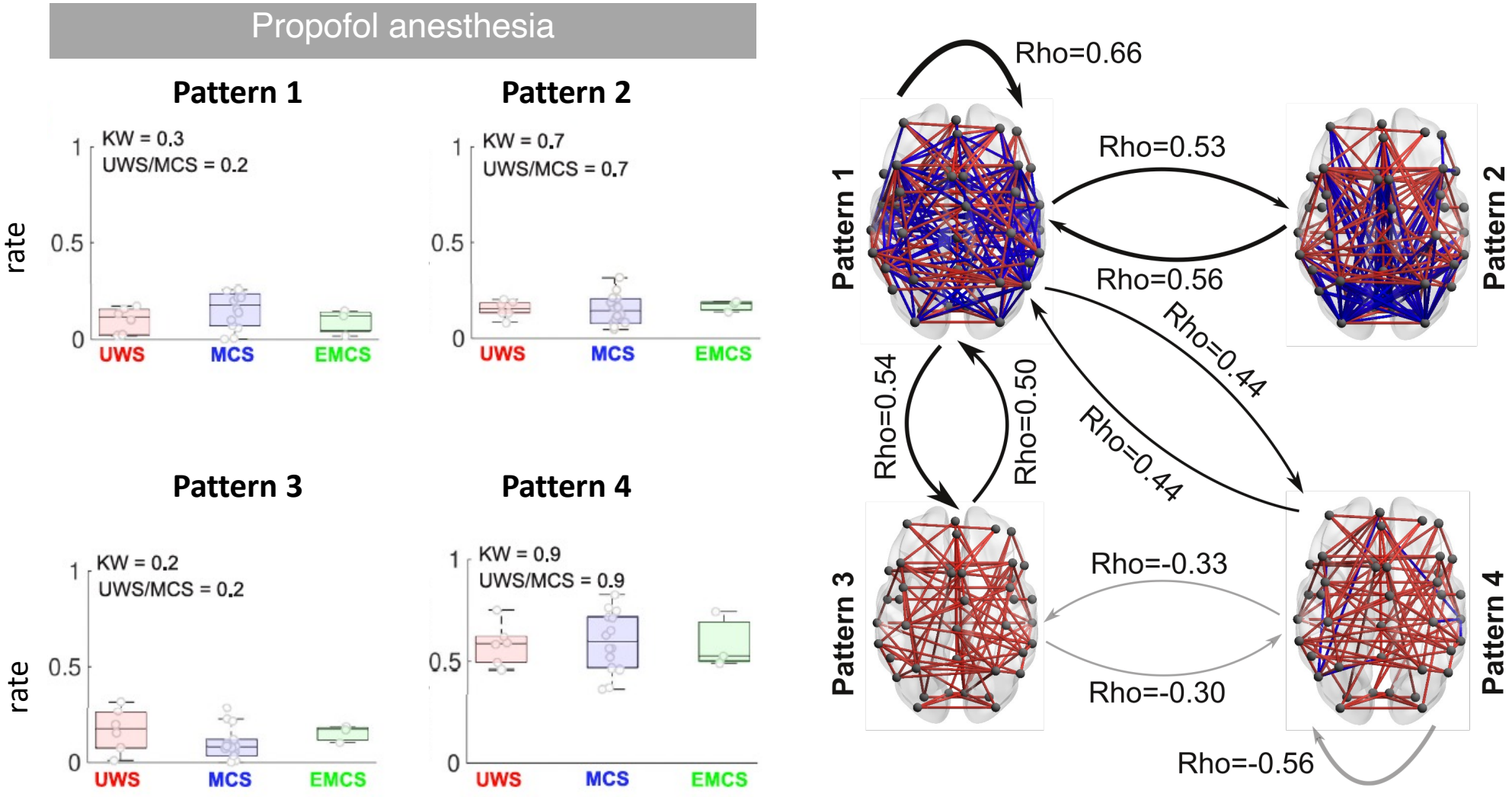
(Dehaene et al, *Trends Cog Sci, 2006;* Tononi et al, *Nat Rev Neurosci.* 2016)

Complex patterns in higher conscious states



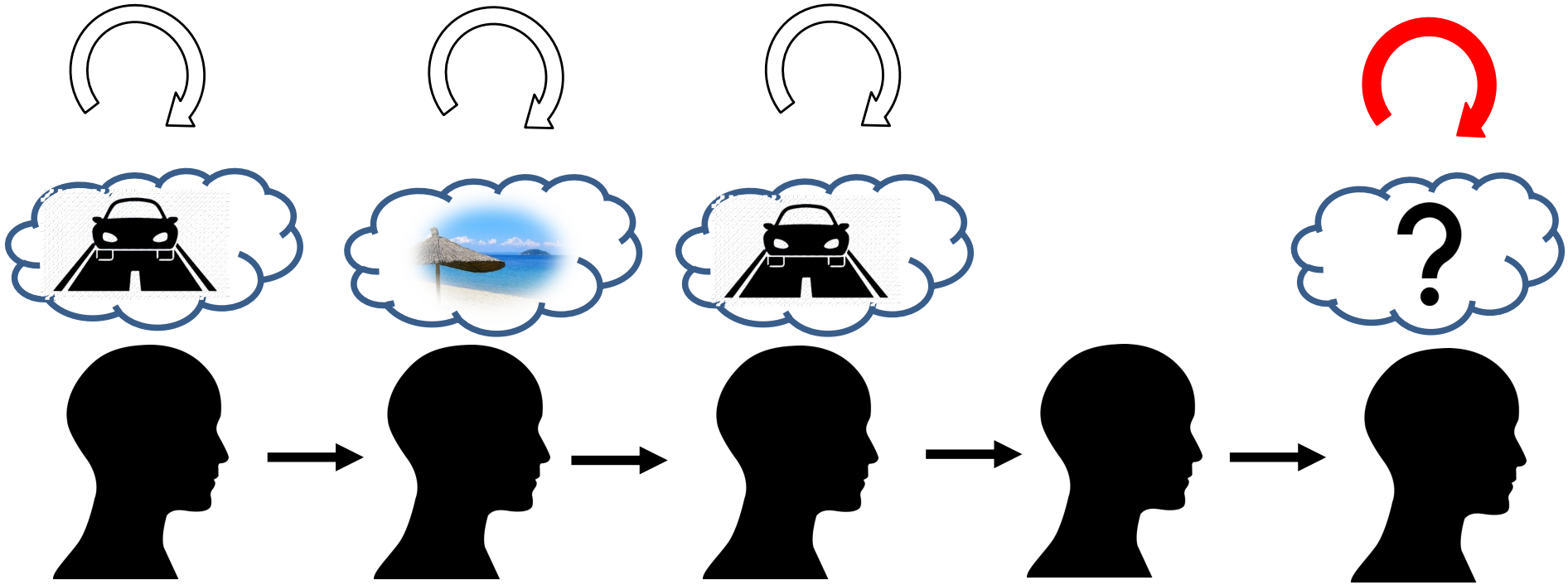
Demertzi & Tagliazucchi, Dehaene, Deco, Barttfeld, Raimondo, Martial, Fernández-Espejo, Rohaut, Voss, Schiff, Owen, Laureys, Naccache, Sitt. *Science Advances* 2019

More chances to transition when conscious



Demertzi & Tagliazucchi, Dehaene, Deco, Barttfeld, Raimondo, Martial, Fernández-Espejo, Rohaut, Voss, Schiff, Owen, Laureys, Naccache, Sitt. *Science Advances* 2019

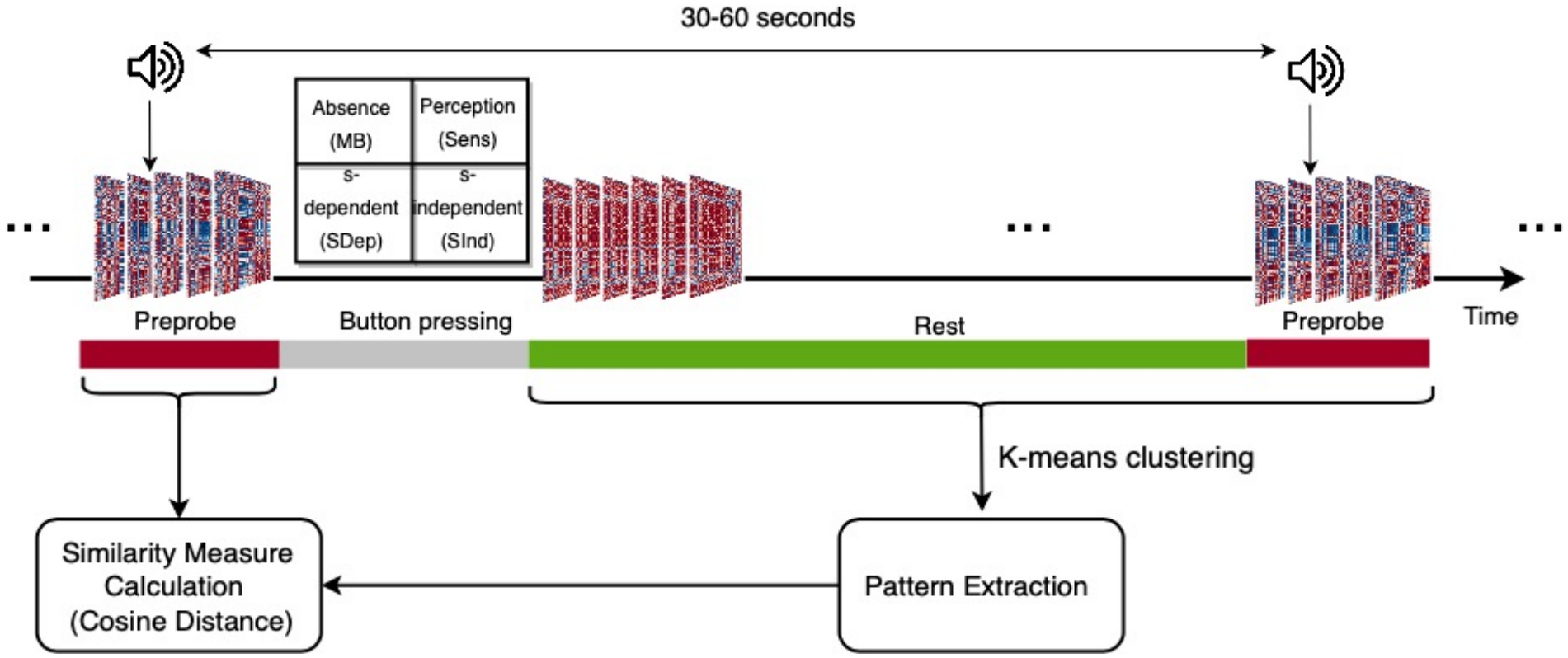
Mental states



Slide courtesy: Boulakis Paris

Christoff et al, *Nat Rev Neurosci* 2016

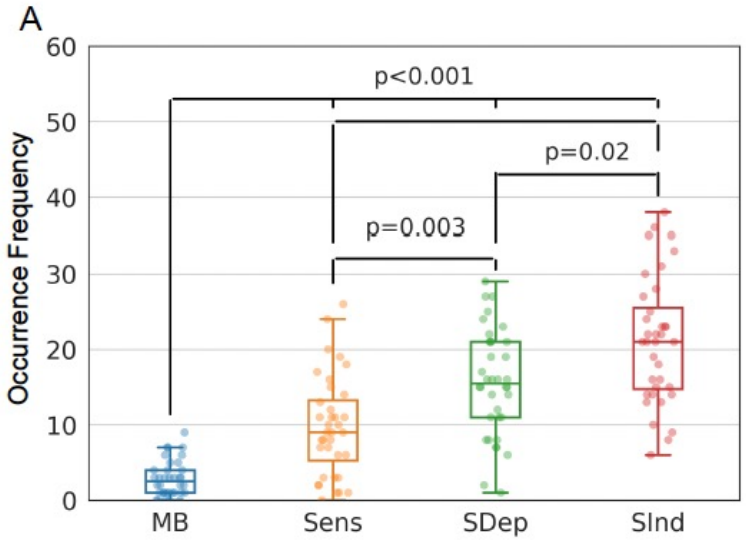
Experience-sampling



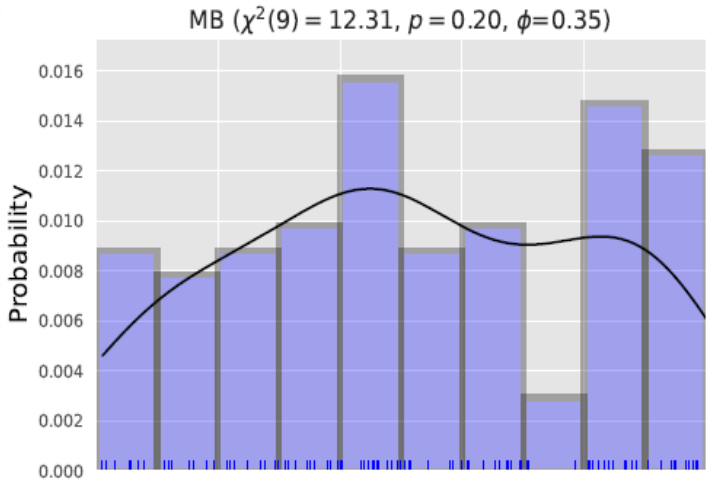
Mortaheb, Van Calster, Raimondo, Klados, Boulakis, Georgoulaa, Majerus, Van De Ville*, Demertzi*. *PNAS* 2022
Van Calster, D'Argembeau, Salmon, Peters, Majerus, *J Cogn Neurosci* 2017

Mind Blanking has a distinct behavioral profile

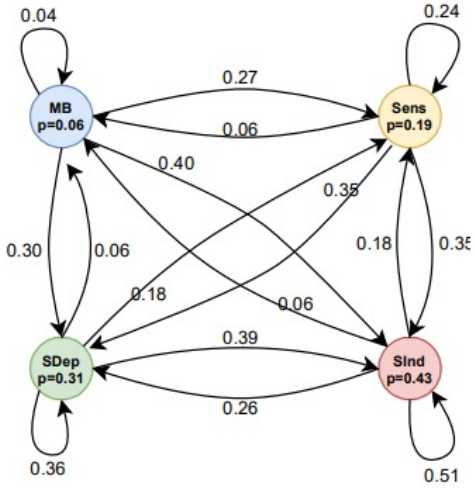
Less frequent



Equally probable across time

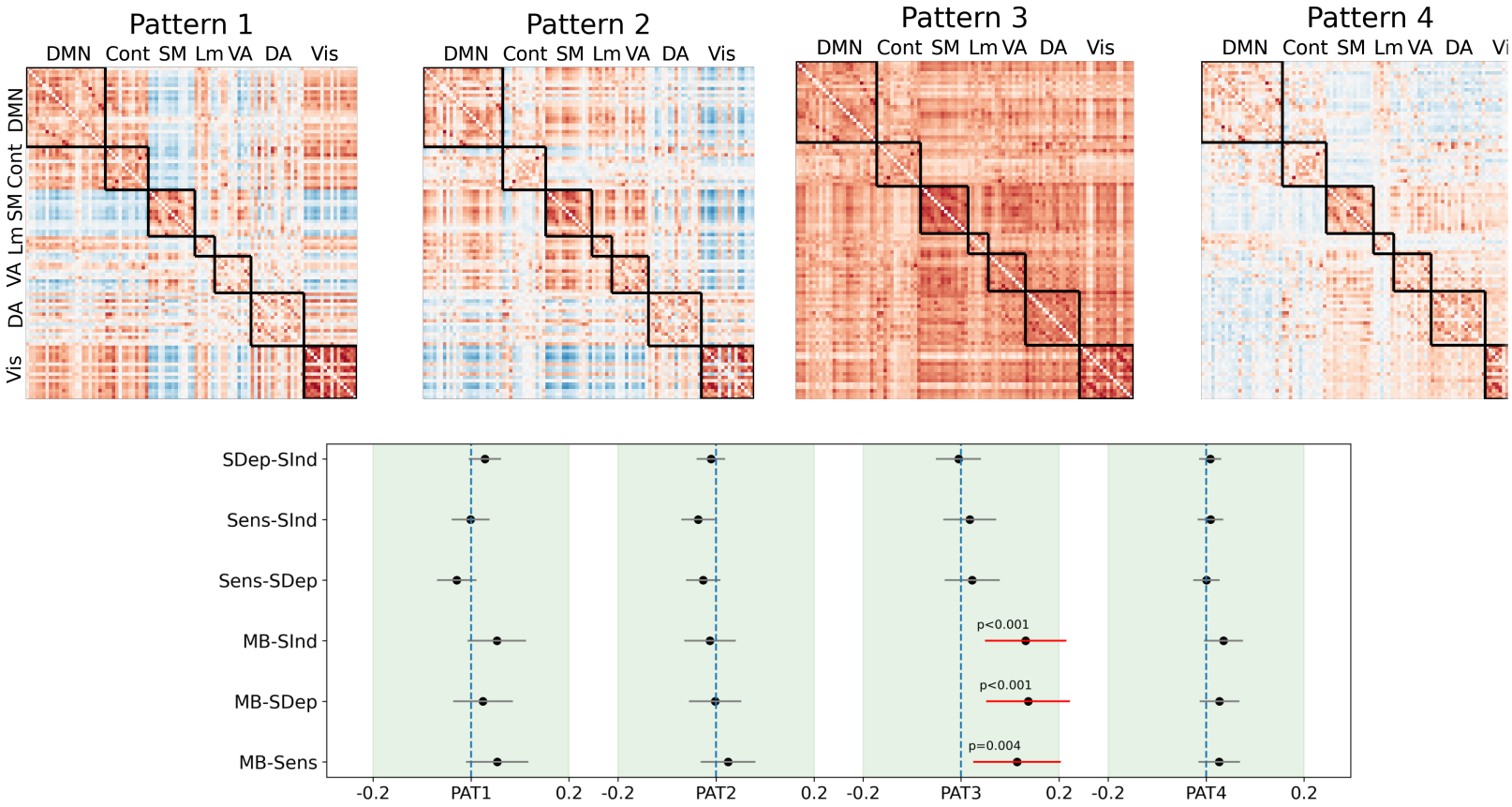


Transient relay



Mortaheb, Van Calster, Raimondo, Klados, Boulakis, Georgoulaa, Majerus, Van De Ville*, Demertzi*, *bioRxiv; under review, PNAS accepted (today!)*
Van Calster, D'Argembeau, Salmon, Peters, Majerus, *J Cogn Neurosci* 2017

MB is linked to a hyper-connected state

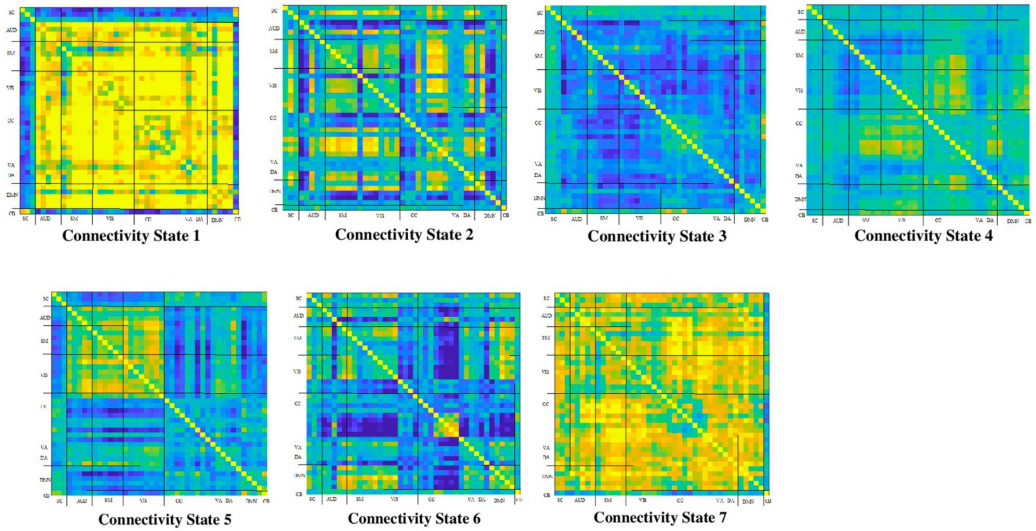


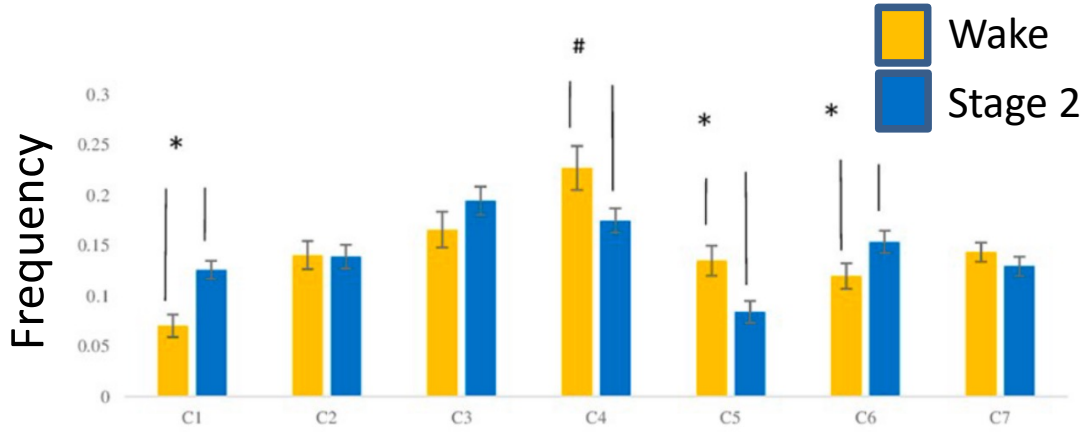
Mortaheb, Van Calster, Raimondo, Klados, Boulakis, Georgoulaa, Majerus, Van De Ville*, Demertzi*. *PNAS* 2022
Van Calster, D'Argembeau, Salmon, Peters, Majerus, *J Cogn Neurosci* 2017

Higher functional connectivity due to slow waves

NREM sleep

Humans

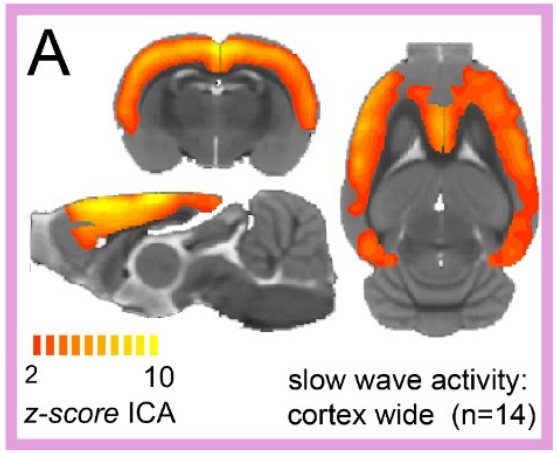


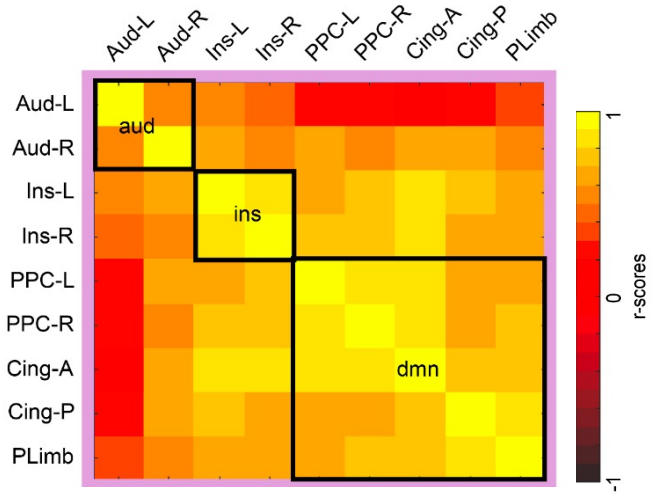


El-Baba et al, *PLOS One* 2019

Isoflurane anesthesia

Rats





Aedo-Jury et al, *eLife* 2019

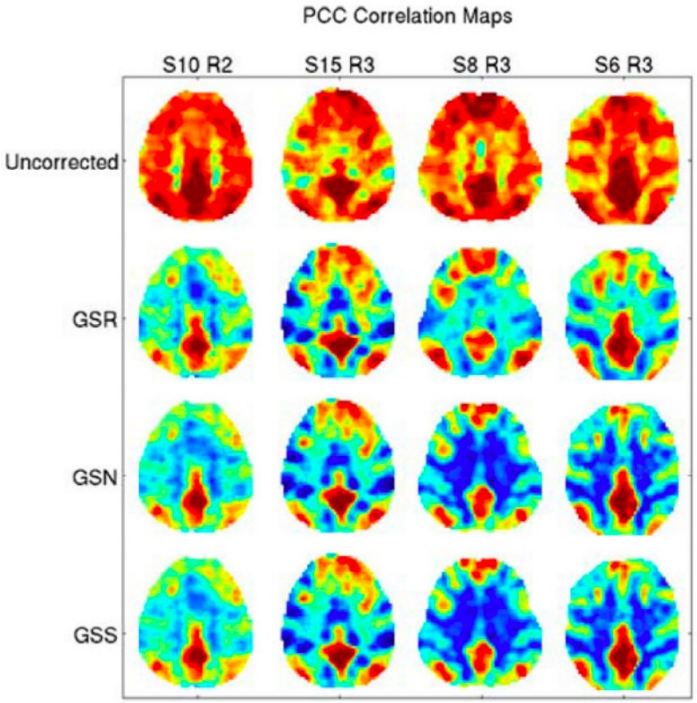
Lower cortical arousal in MB?

Global signal

Average voxel timeseries

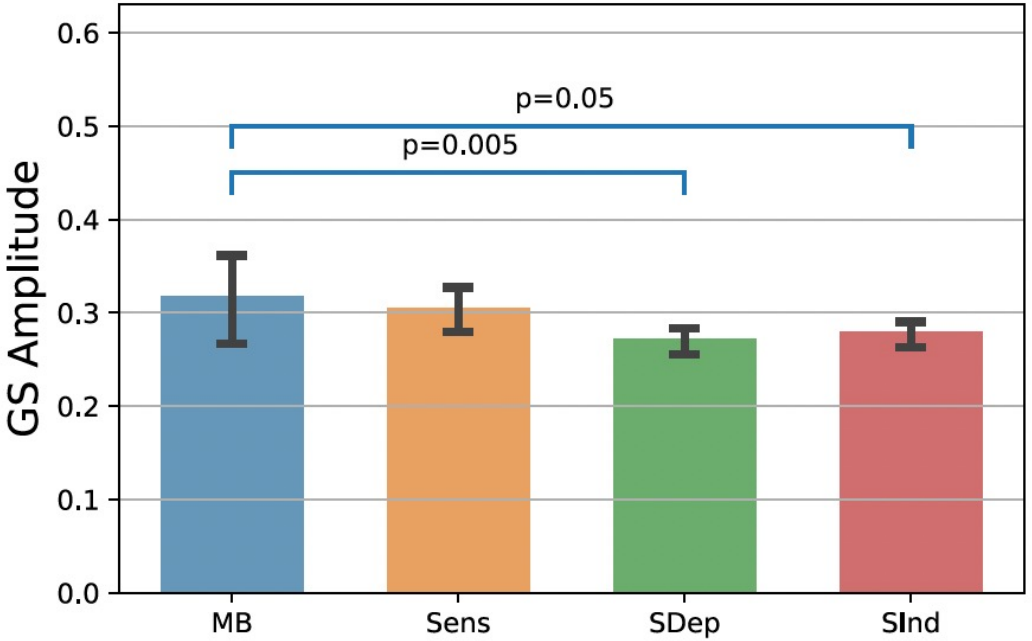
Zarahn, Aguirre, D'Esposito, NeuroImage 1997

("Global flow'' in PET, Friston et al., 1990)



Liu et al, *NeuroImage* 2017

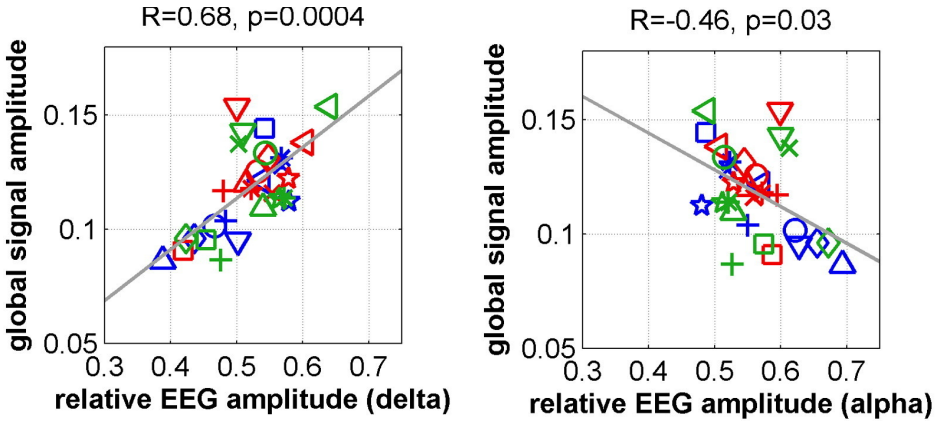
Higher Global Signal Amplitude
around MB reports



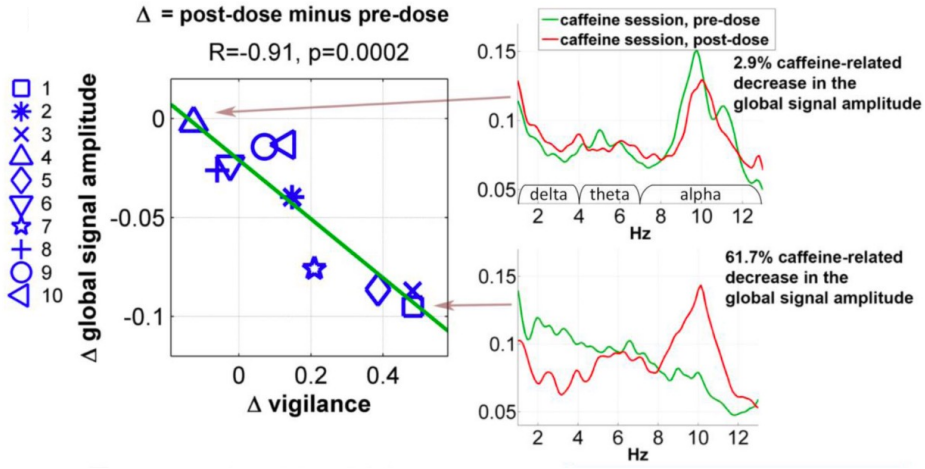
Mortaheb, et al, *PNAS 2022*

GS amplitude and Arousal

High GS amplitude is linked to low arousal

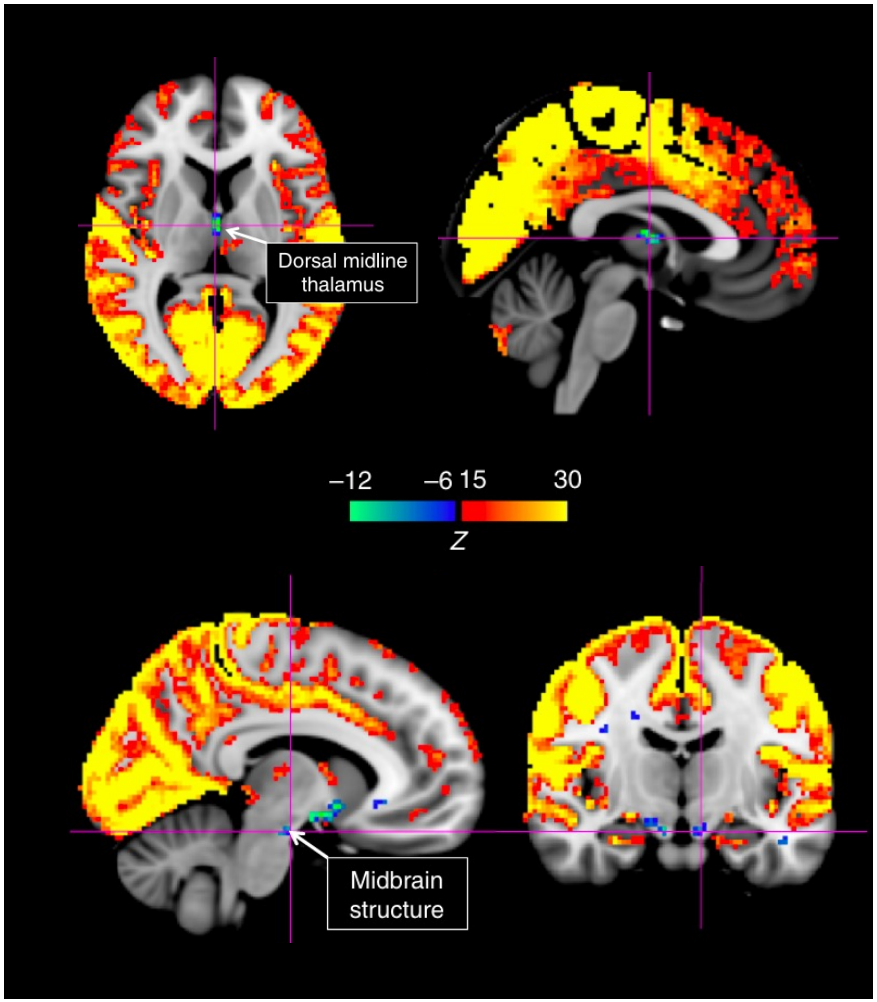


GS amplitude decreases with caffeine intake



Wong et al, *Neuroimage*, 2013

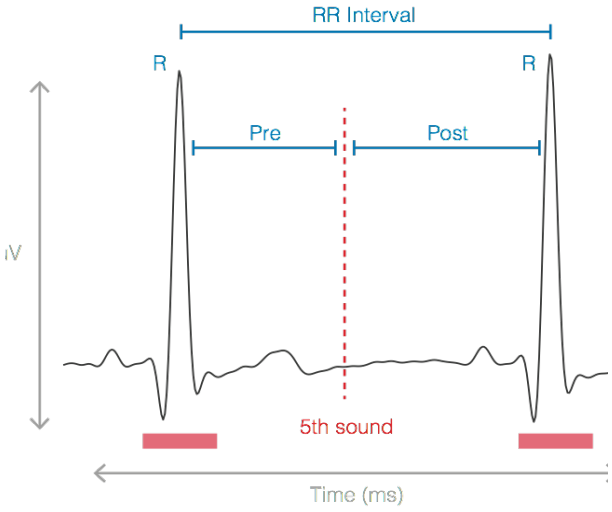
GS amplitude linked to signal decreases in subcortical structures of arousal



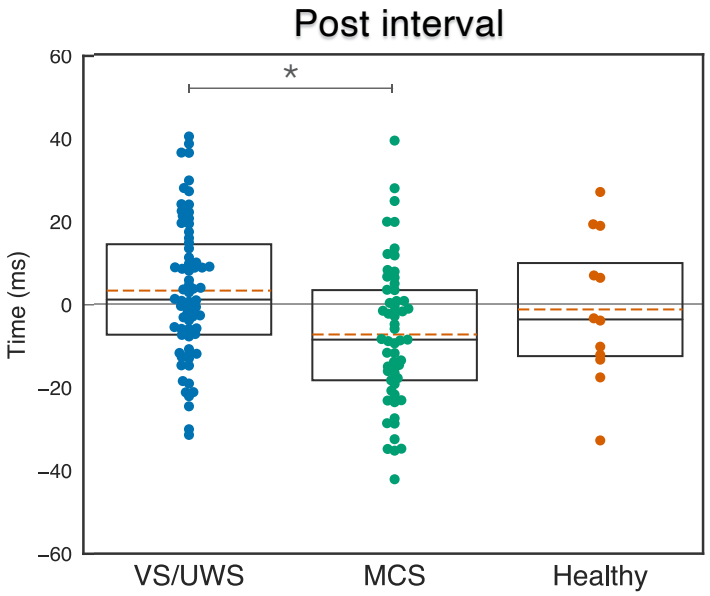
Liu et al, *Nat Commun* 2018

Cardiac reactions to oddballs in MCS

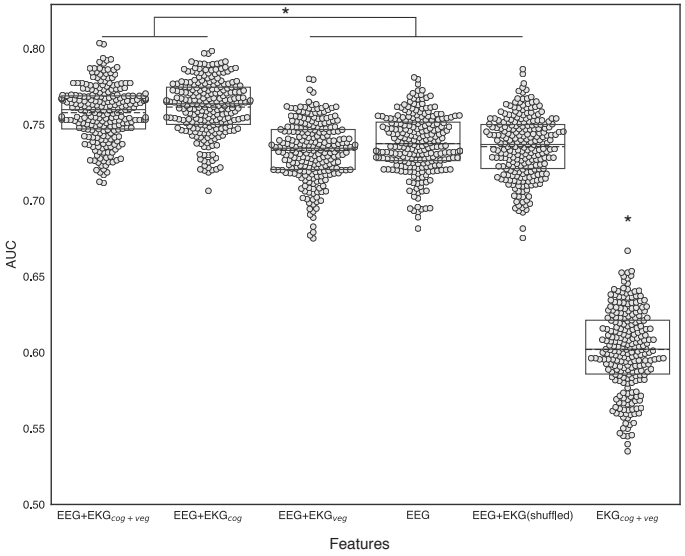
Auditory oddball paradigm



Cardiac cycle-phase acceleration only in MCS



Electrocardiographic markers carry independent information from EEG

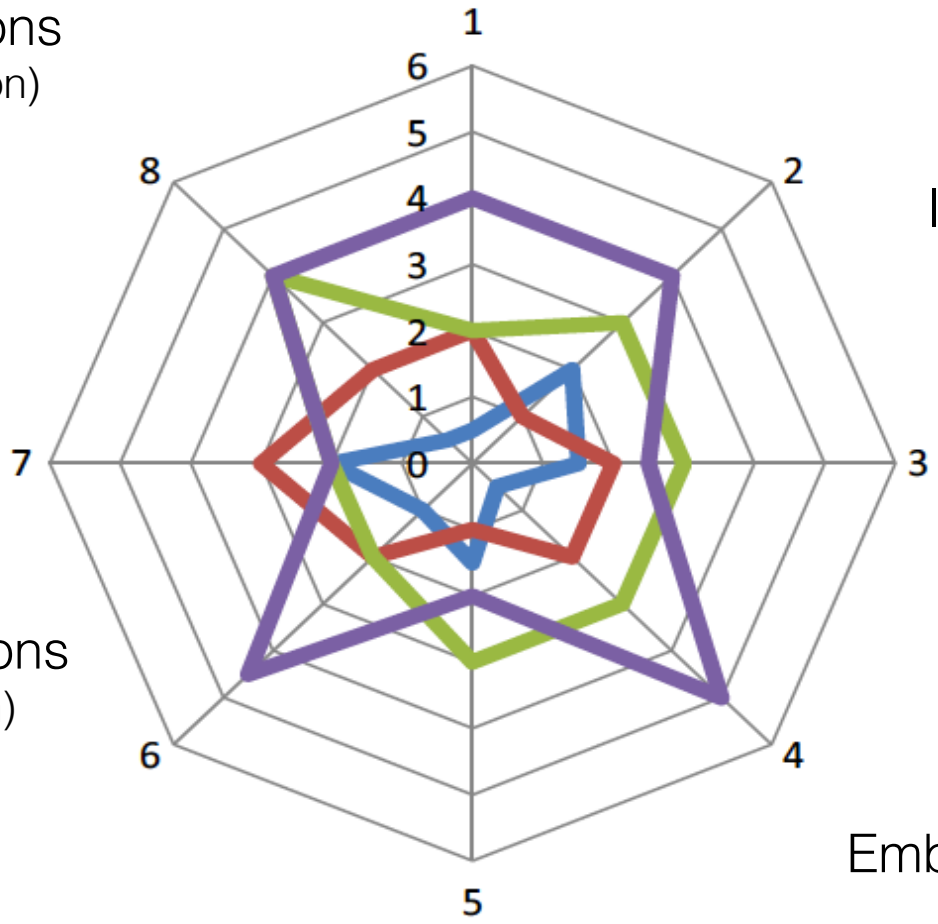


Annals of NEUROLOGY
An Official Journal of the American Neurological Association and the Child Neurology Society
ANA AMERICAN NEUROLOGICAL ASSOCIATION

Federico Raimondo [1,2,3,4] Benjamin Rohaut, MD, PhD [5,6]
Athena Demertzi, PhD [3,5] Melanie Valente,[3,5] Denis A. Engemann [3,5,7,8]
Moti Salti, PhD,[9] Diego Fernandez Slezak, PhD,[1,2]
Lionel Naccache, MD, PhD,[3,4,5,6,10] and Jacobo D. Sitt, MD, PhD [3,5]

Consciousness is multidimensional

Anticorrelations
(neural inhibition)



Inter-state dynamism
(metastability)

Cross-modal interactions
(multi-sensory integration)

Embodied responsiveness
(active inference)

Bayne, Hohwy, Owen *Trends Cogn Sci* 2016

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of collective consensus and concerns us all

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