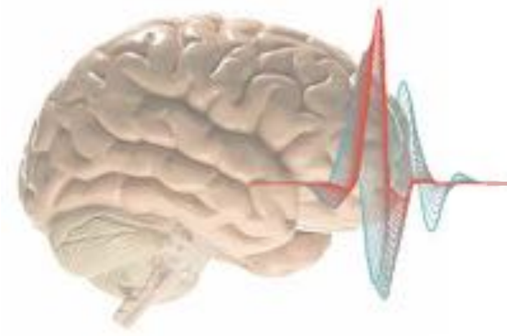

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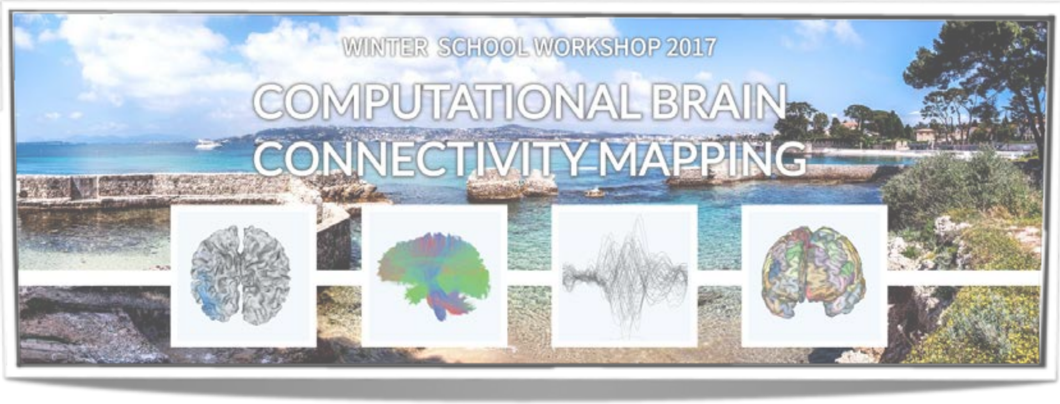

Functional connectivity models: from blobs to (dynamic) networks

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Juan-les-Pins / November 22, 2017

Overview

- The rise of (functional) MRI
- Activation mapping
  - Task-evoked activity
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  - General Linear Model (GLM)
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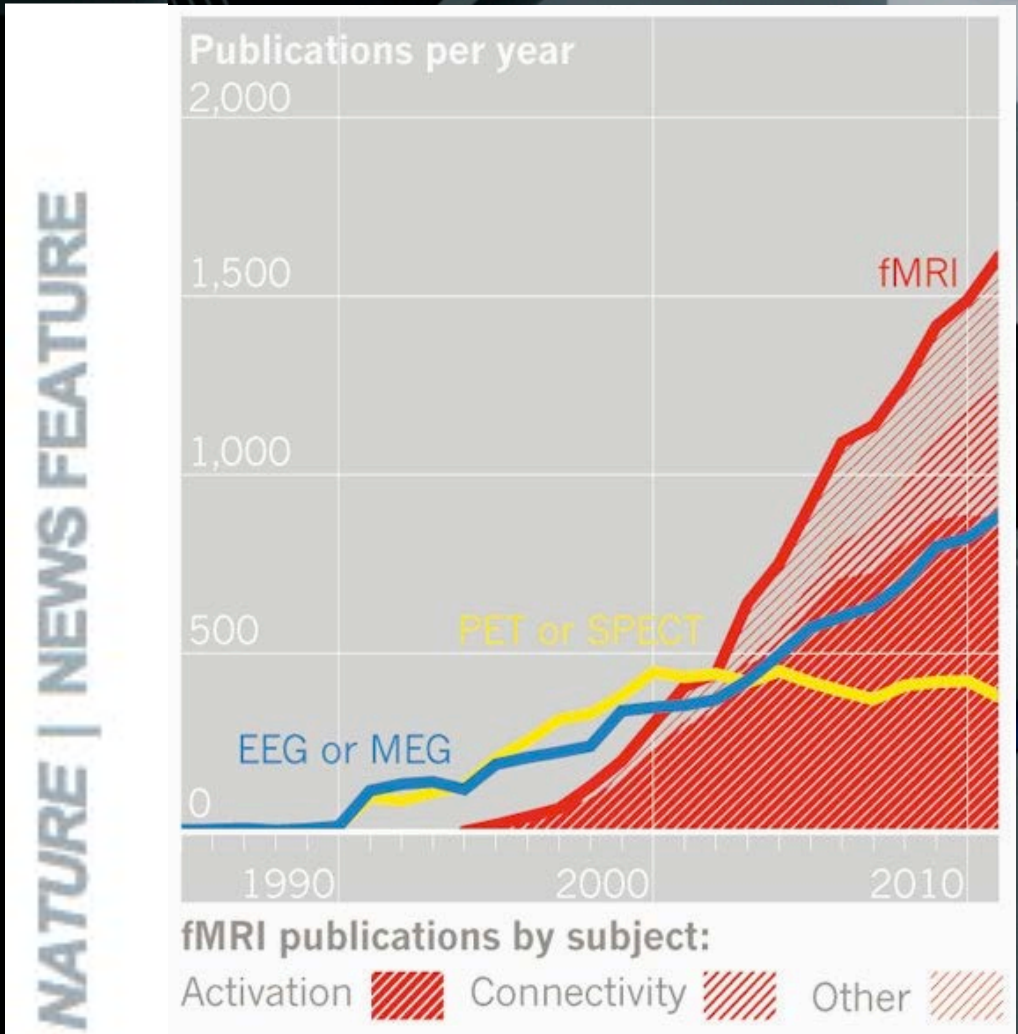
“the quest for an understanding of the functional organization of the [...] human brain, using techniques to assess changes in brain circulation, [a search that has occupied] mankind for more than a century”

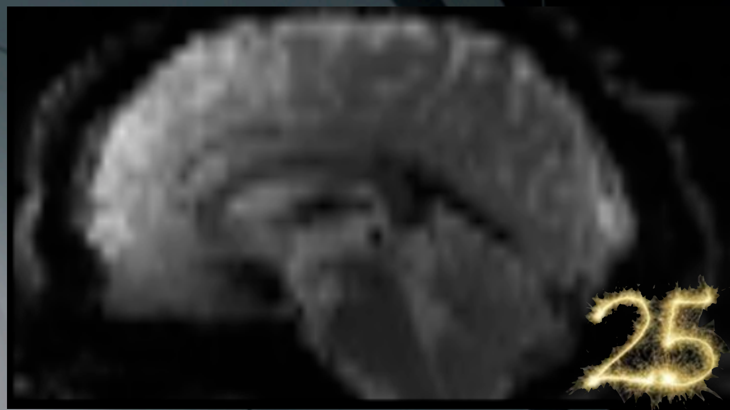
Marcus Raichle, 1998

Magnetic resonance imaging (MRI)

- Widely deployed in hospitals and research centers
- Endogenous contrast mechanism
- Non-invasive imaging tool to study human brain anatomy and function

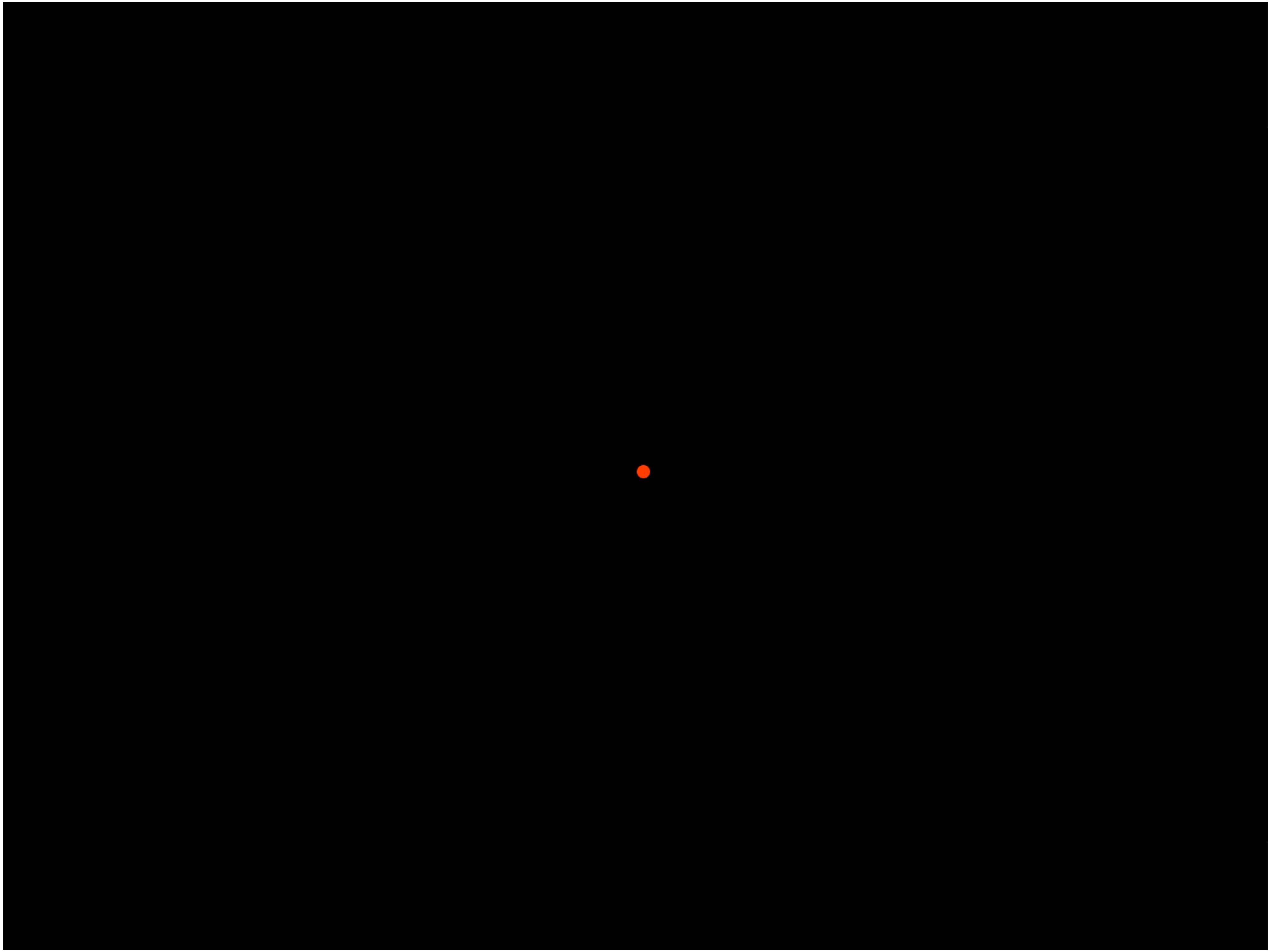


Functional MRI

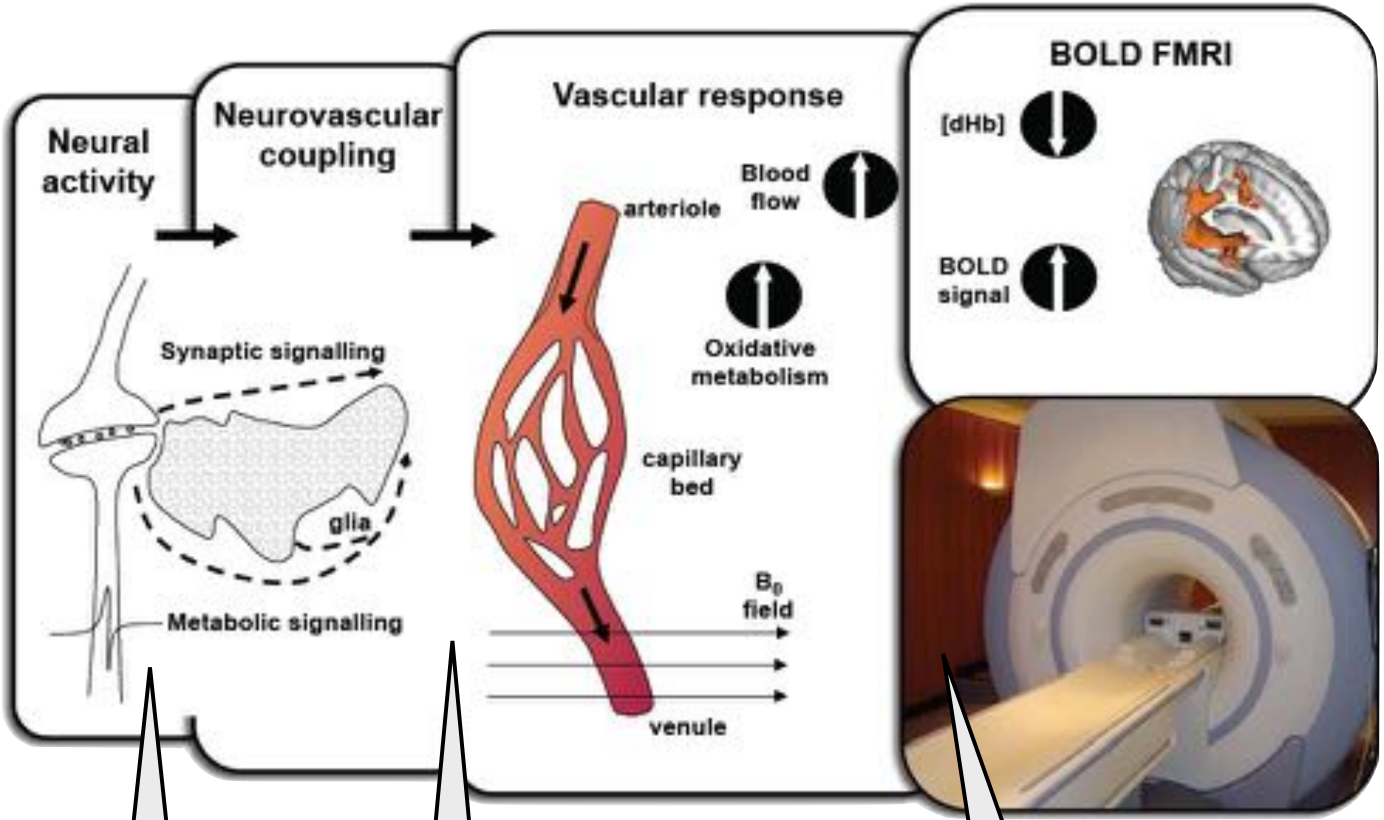


- Series of 3D volumes
  - 3x3x3 mm^3
  - 20-30 slices
  - every 2-4 sec
  - during 5-10 minutes

Siemens 3T Prisma MRI scanner @ Campus Biotech / picture (c) EPFL/Alban Kakulya



FMRI blood-oxygenation-level-dependent (BOLD) signals are slow proxy for neuronal activity



Neurons in the visual cortex are active (metabolic demand at synapses)

Neurovascular coupling: blood flow increases locally to bring in glucose and oxygen

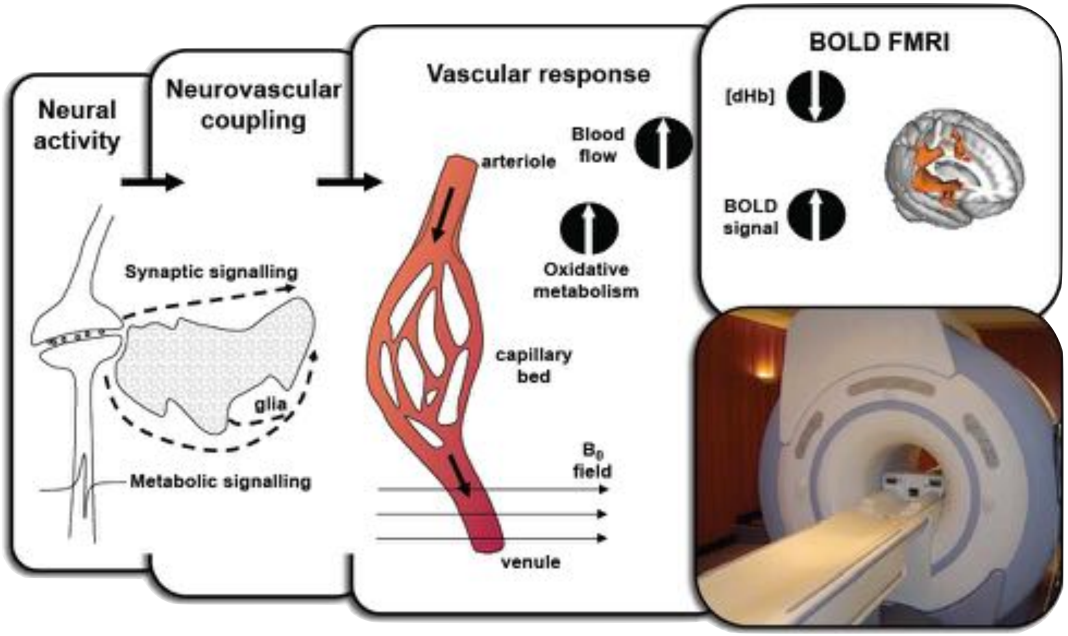
Oxygen is carried by hemoglobin in RBCs

Increase of ratio in oxygenated/deoxygenated hemoglobin

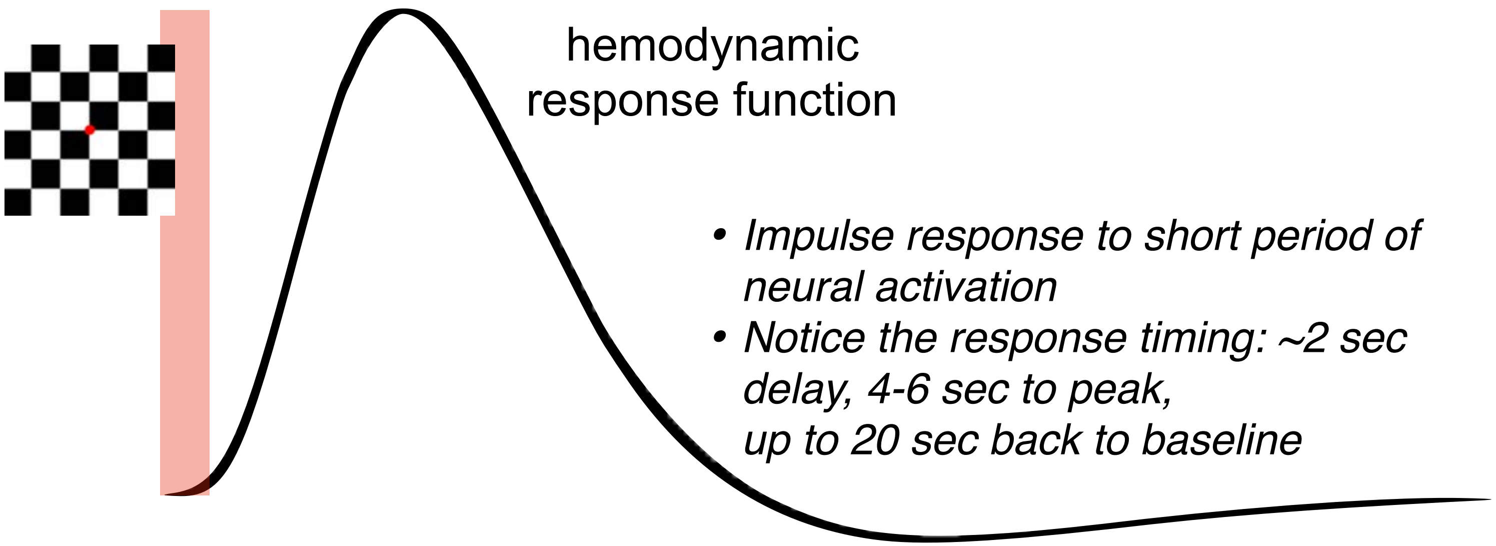
Deoxygenated Hb is paramagnetic and drives BOLD signal

[Buxton et al 1997; Friston et al. 1998, 2000; Iannetti & Wise, 2007]

FMRI blood-oxygenation-level-dependent (BOLD) signals are slow proxy for neuronal activity



20 sec

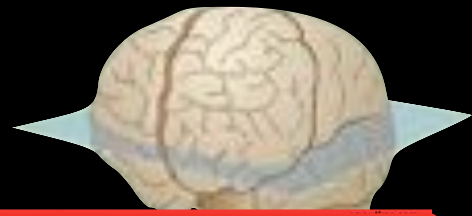


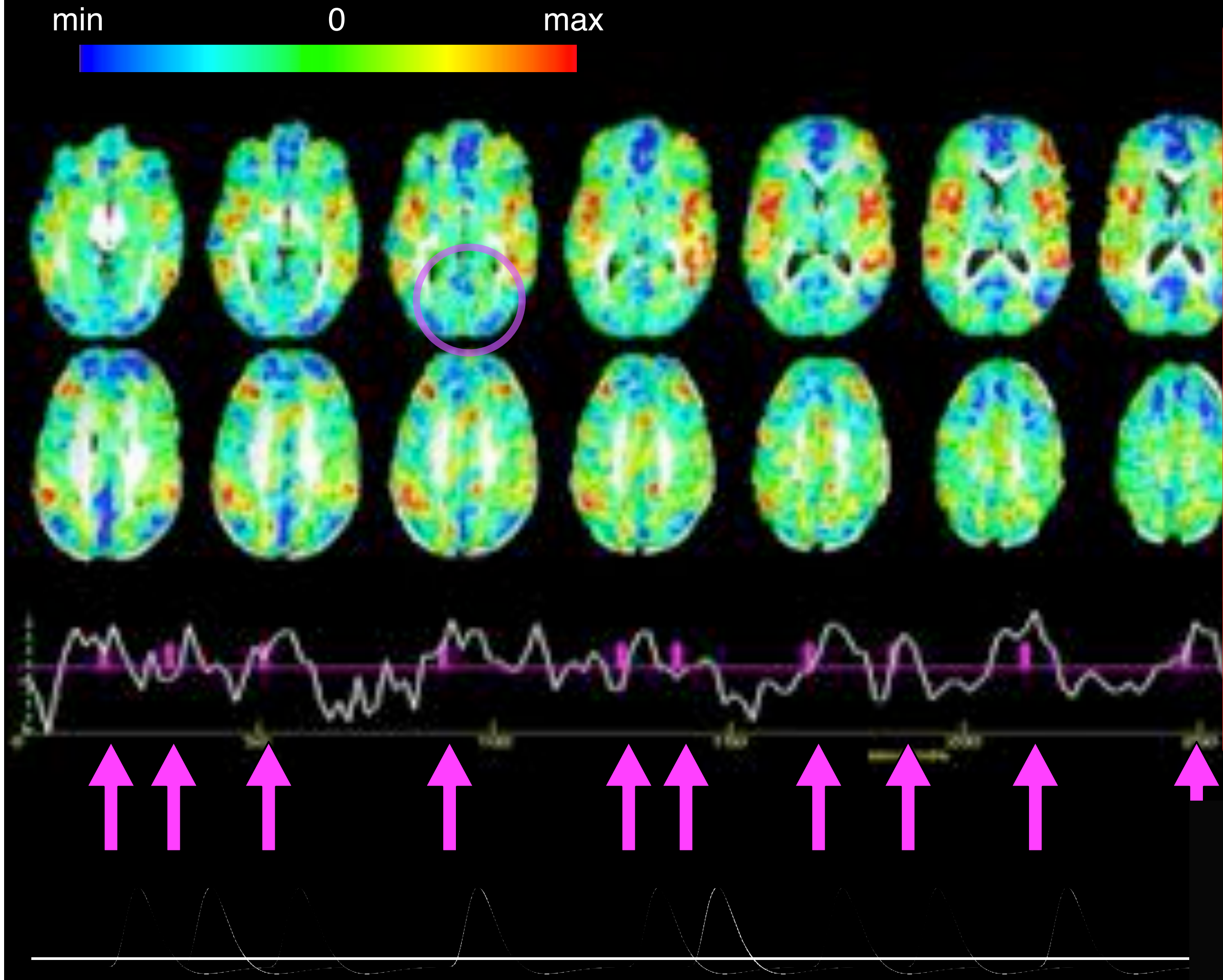
hemodynamic response function

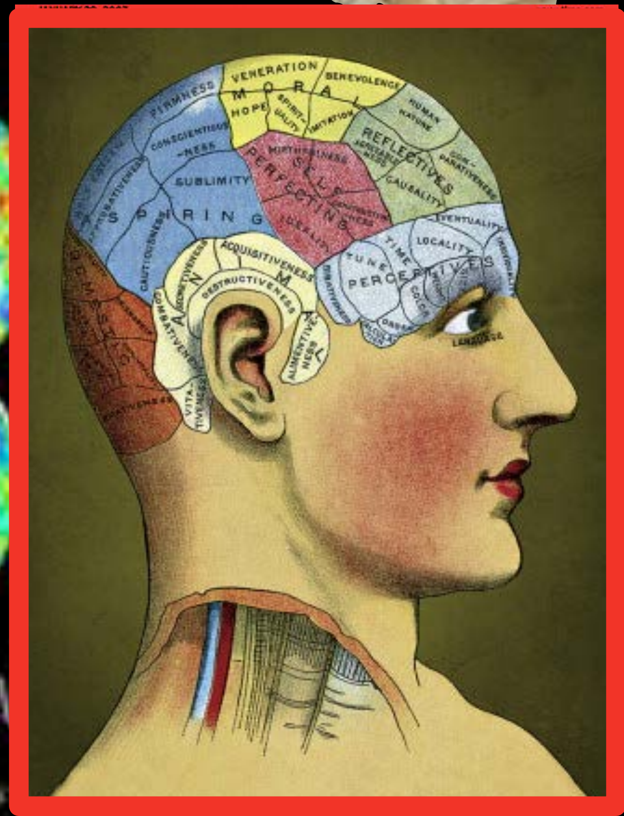
- *Impulse response to short period of neural activation*
- *Notice the response timing: ~2 sec delay, 4-6 sec to peak, up to 20 sec back to baseline*

[Buxton et al 1997; Friston et al. 1998, 2000; Iannetti & Wise, 2007]

fMRI of evoked activity

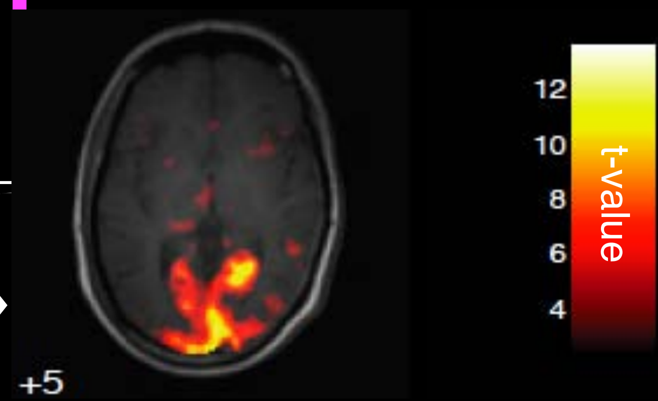




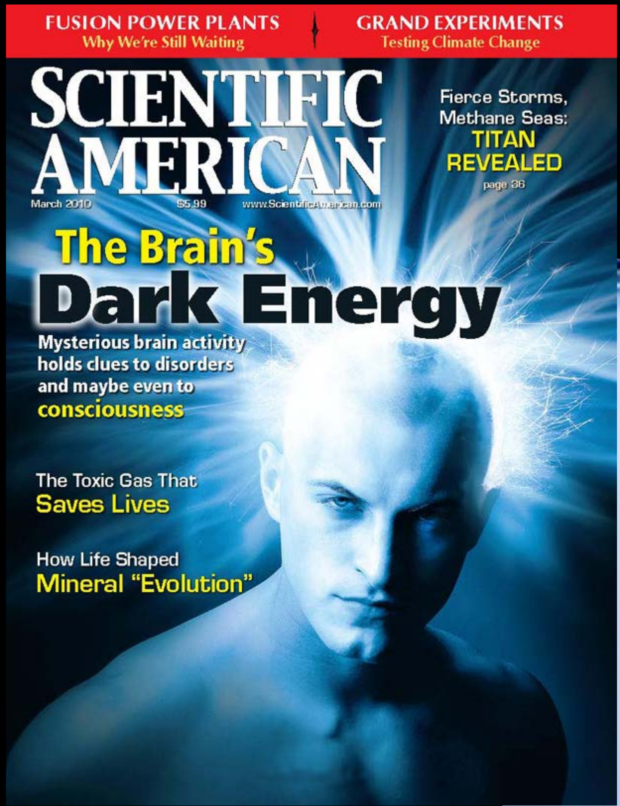


movie accelerated 4 times

GLM / statistical testing

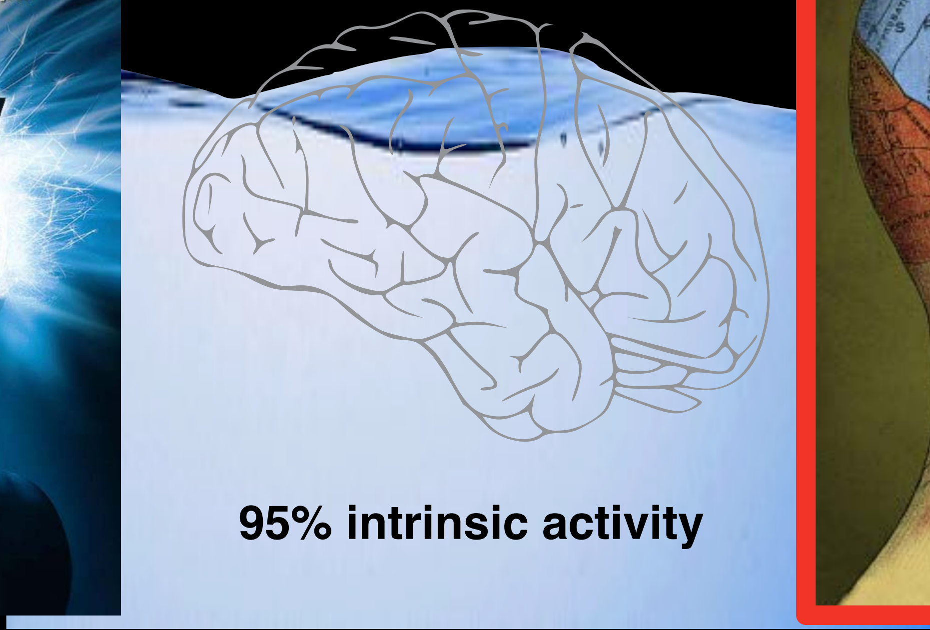


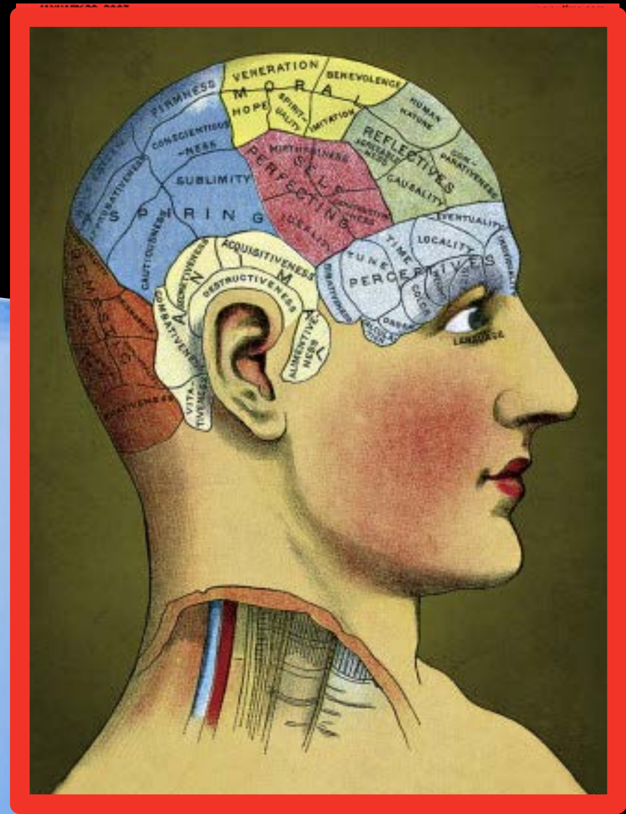
fMRI of evoked and intrinsic activity



energy budget

5% evoked activity



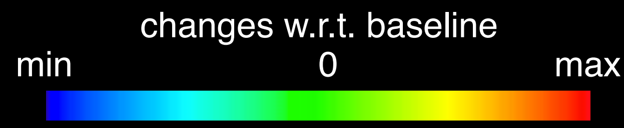


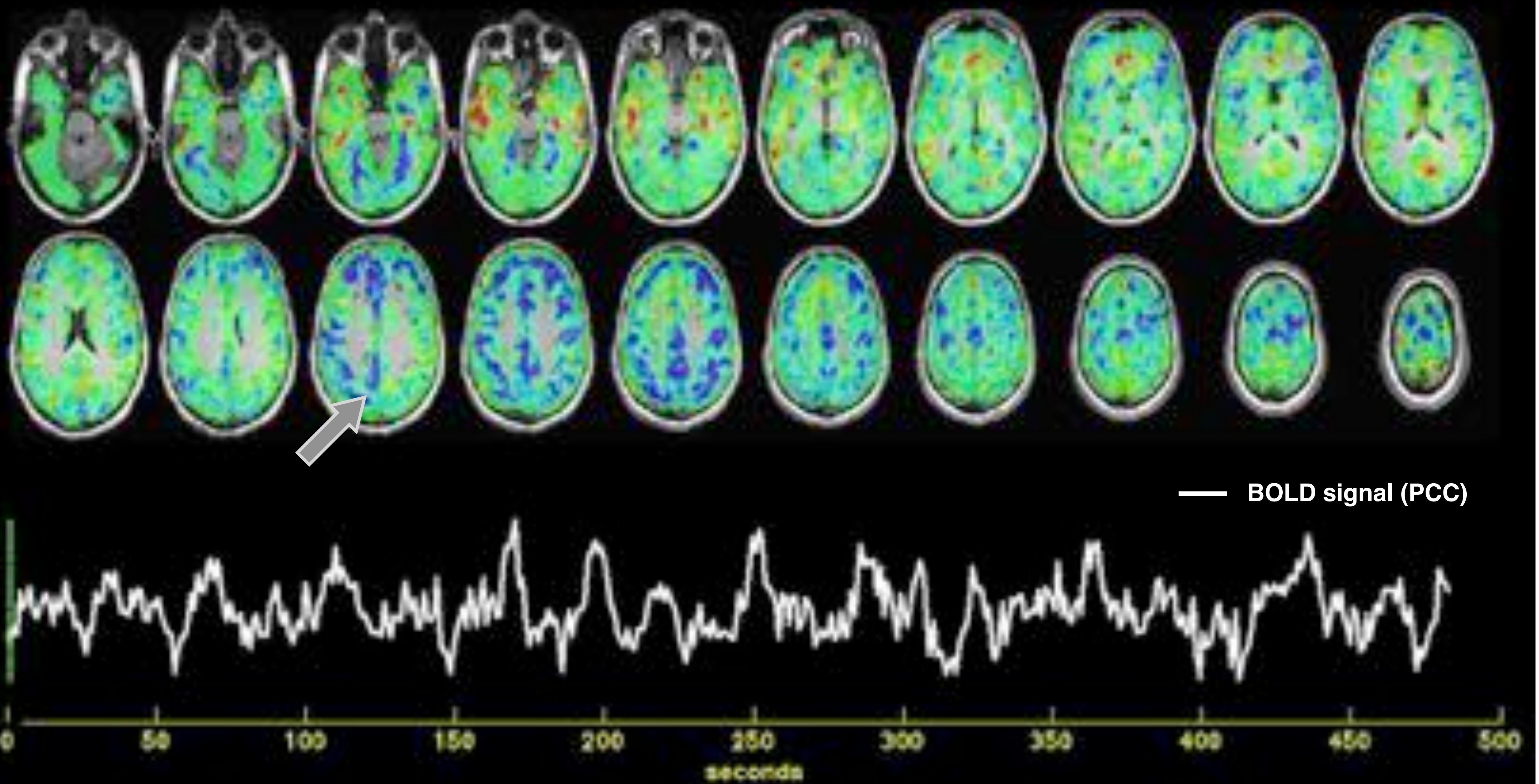
Condition of resting state:
Conscious and unconscious brain activity happen without premeditation or external stimulus

More profound change of viewpoint:
From brain processing stimuli/performing tasks to internal dynamics being modulated

fMRI of spontaneous activity

resting-state scan (minimally preprocessed)





movie accelerated 4 times

minimal compliance for patient studies!

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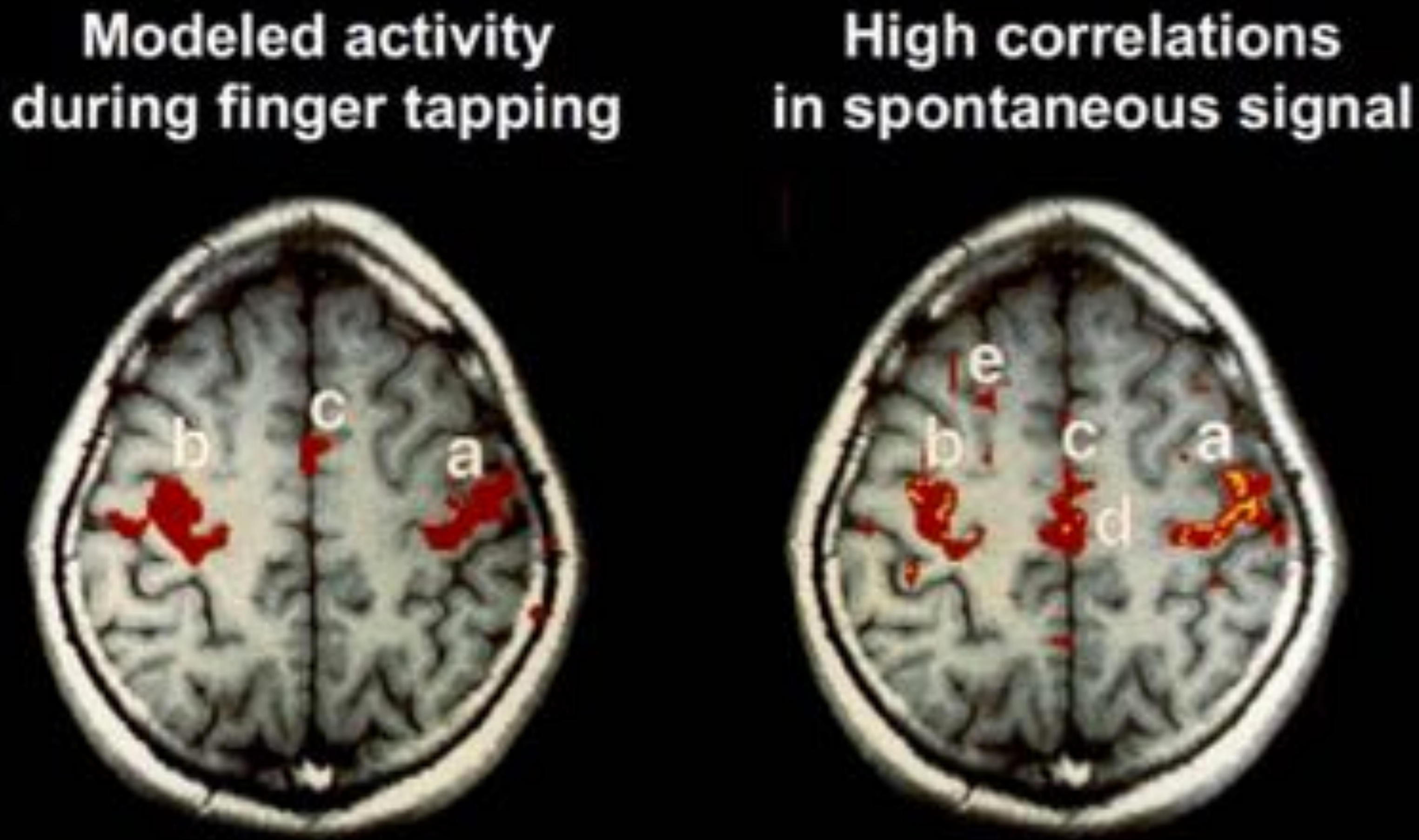
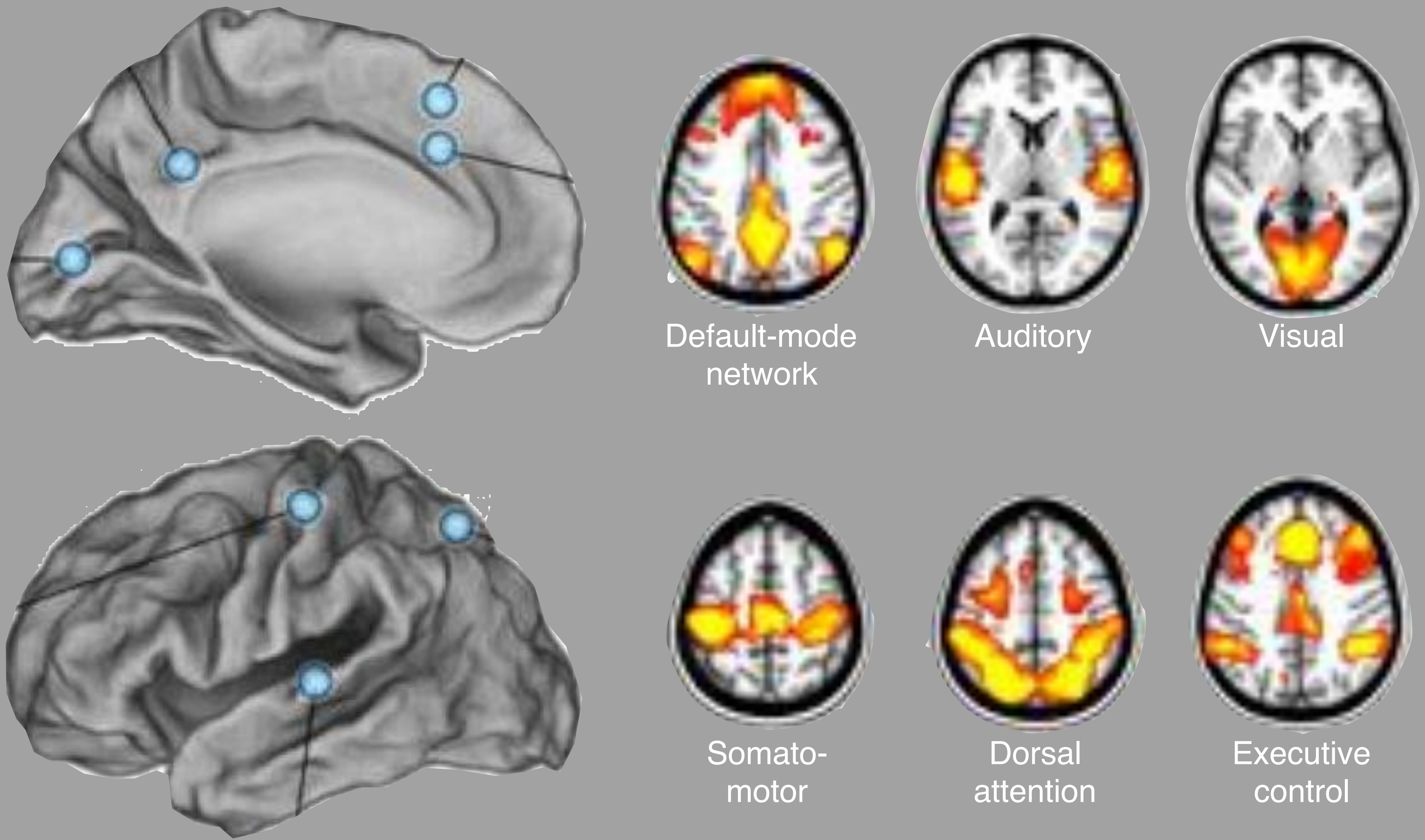


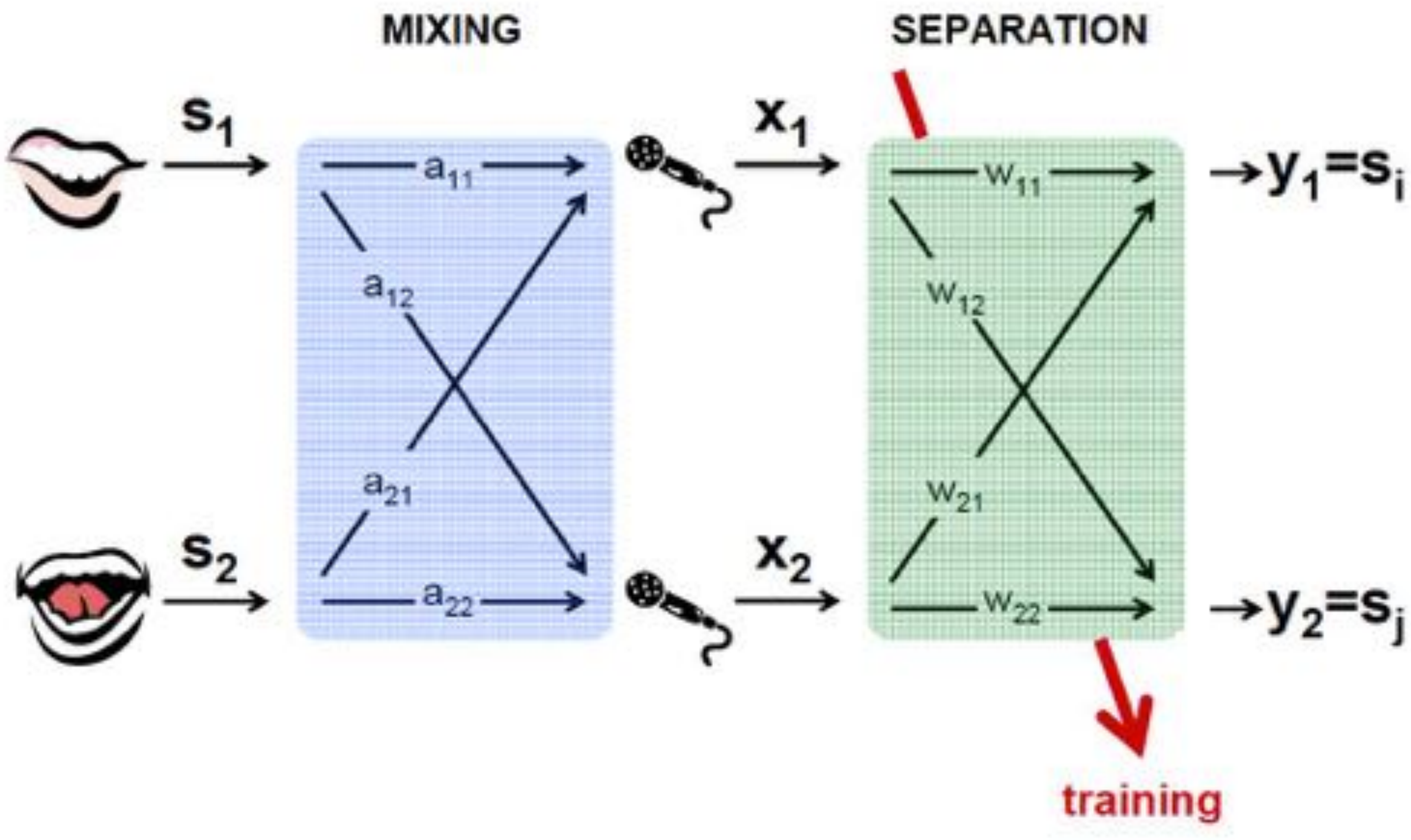
[Biswal et al., 1995]

Seed-based connectivity maps



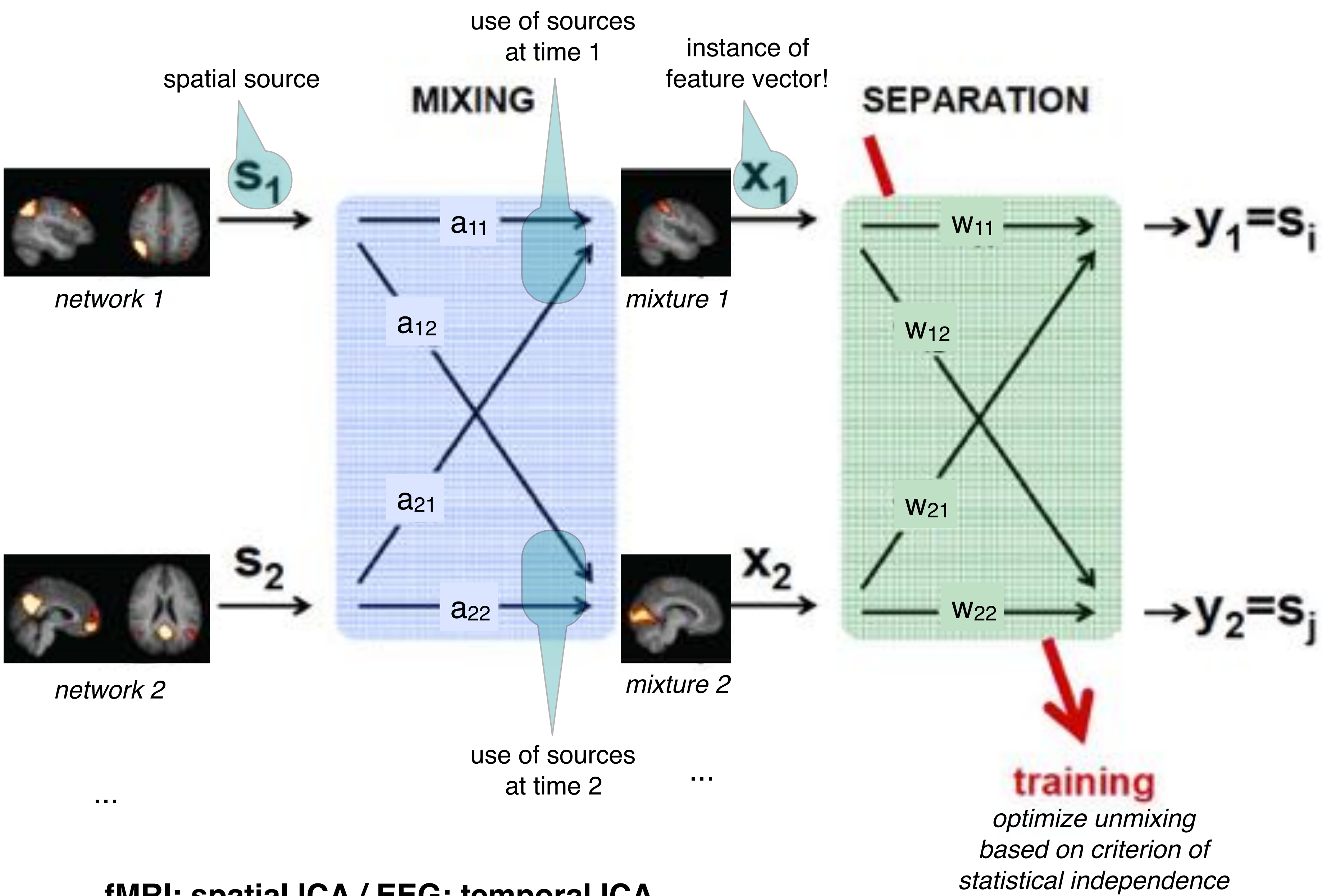
[Adapted from Raichle, TICS, 2010]

Cocktail problem: blind source separation



[Gutierrez-Osuna, Introduction to Pattern Analysis]

Mixing of spatial brain sources



fMRI: spatial ICA / EEG: temporal ICA

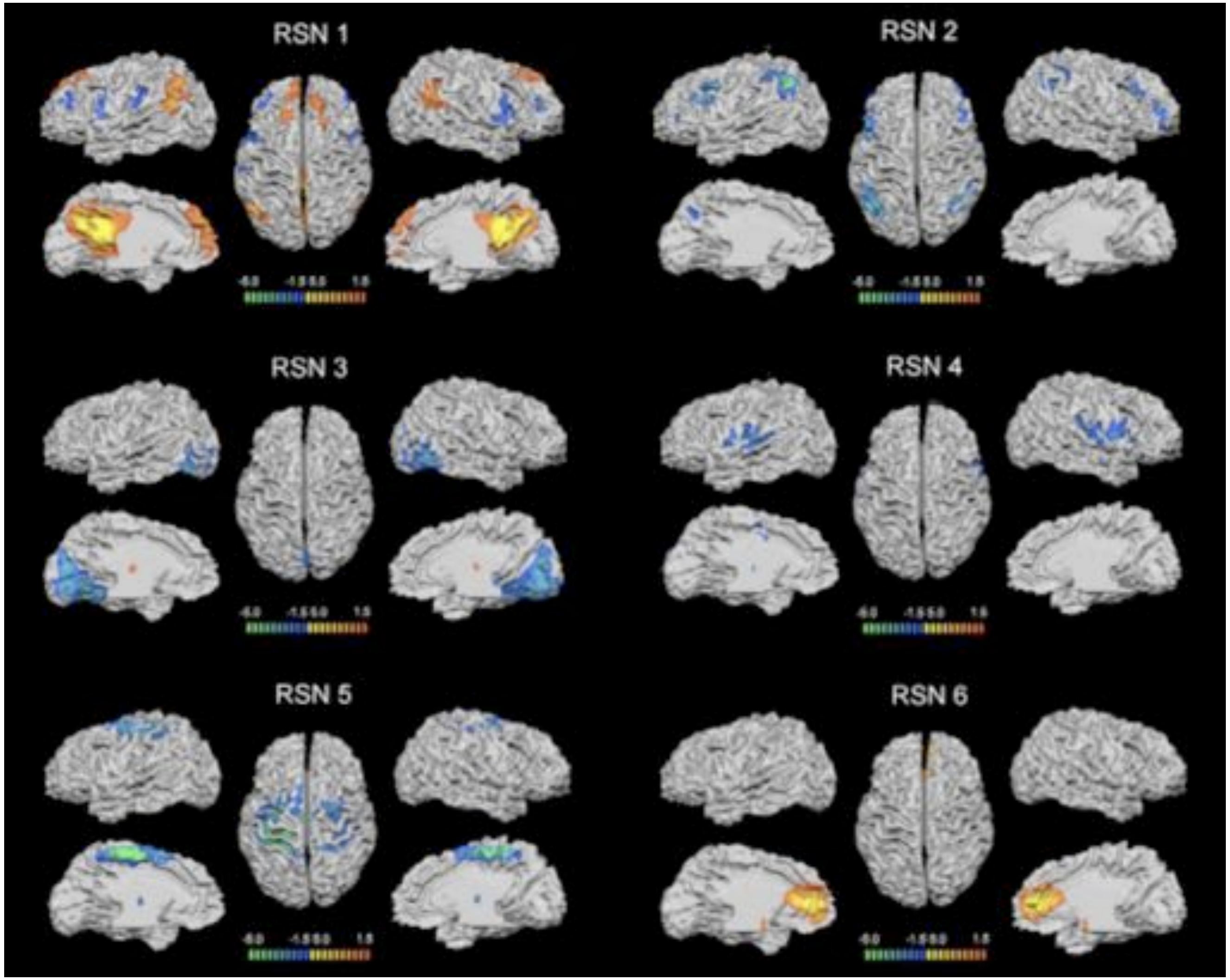
Unmixed spatial brain sources

- ICA reveals several large-scale brain networks (similar to task-evoked networks!)

Default-mode network

Visual network

Somatosensory network



Dorsal attention network

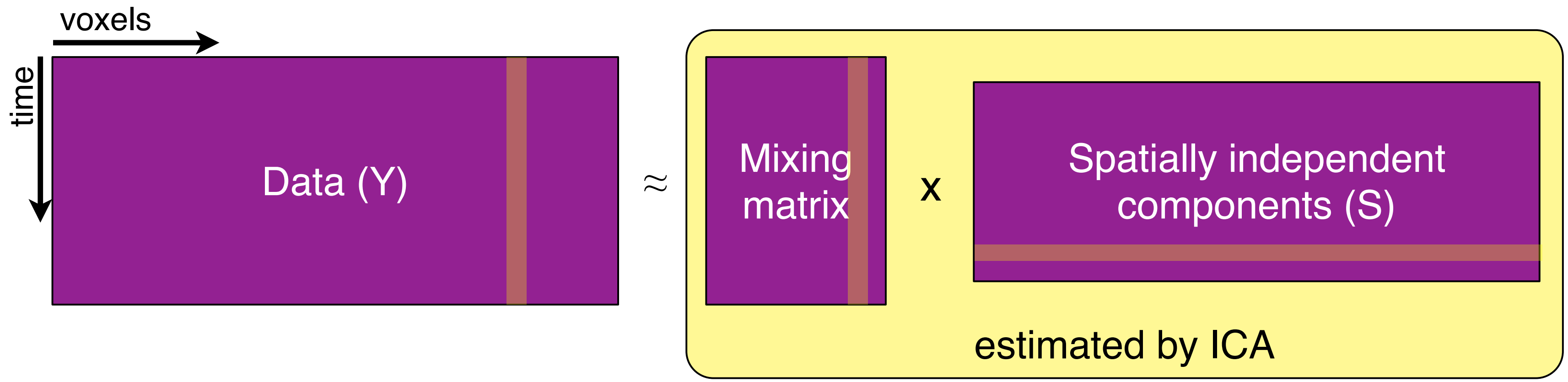
Auditory network

Executive control/ Saliency network

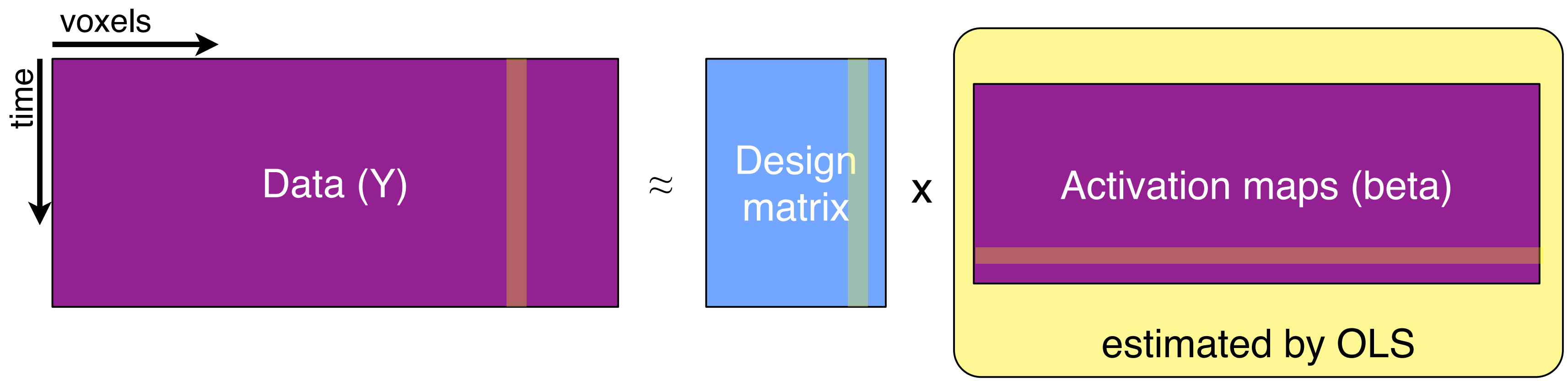
[Mantini et al, 2007]

Spatial ICA

- Unmixing of brain regions from fMRI data

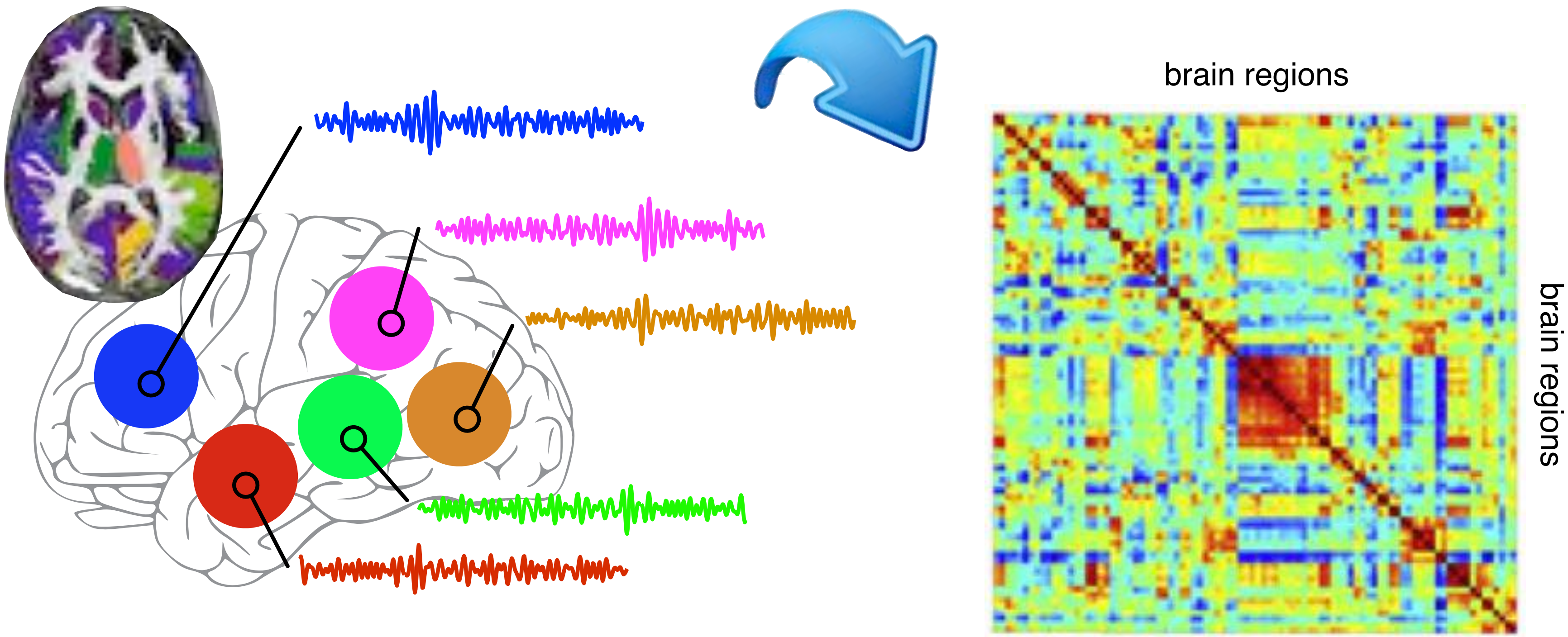


- Compare against the classical GLM



Graph analysis

- Parcellation into brain regions based on atlas
- Pairwise correlations between regionally-averaged timecourses of all brain regions



build connectivity matrix

[Richiardi et al, 2013]

Graph analysis

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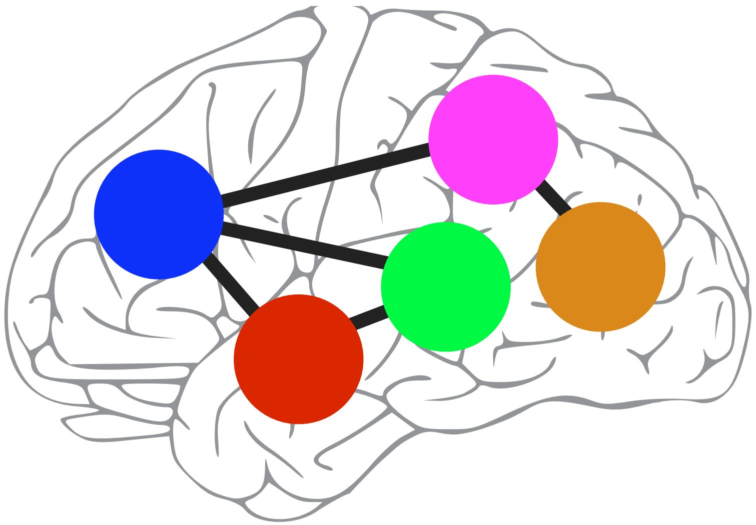
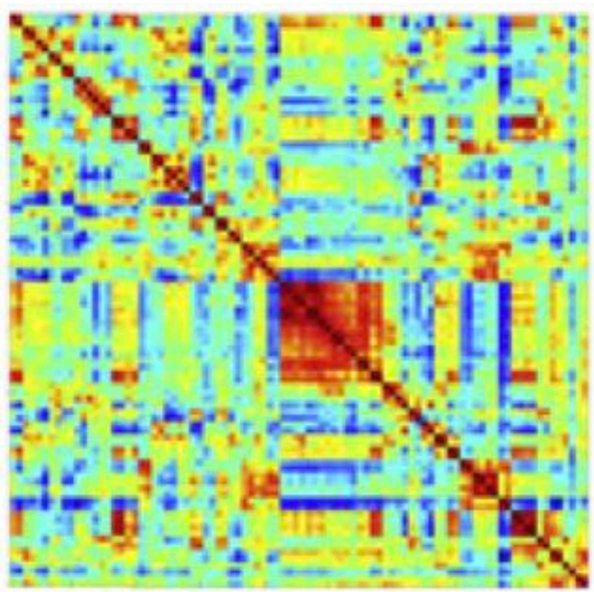
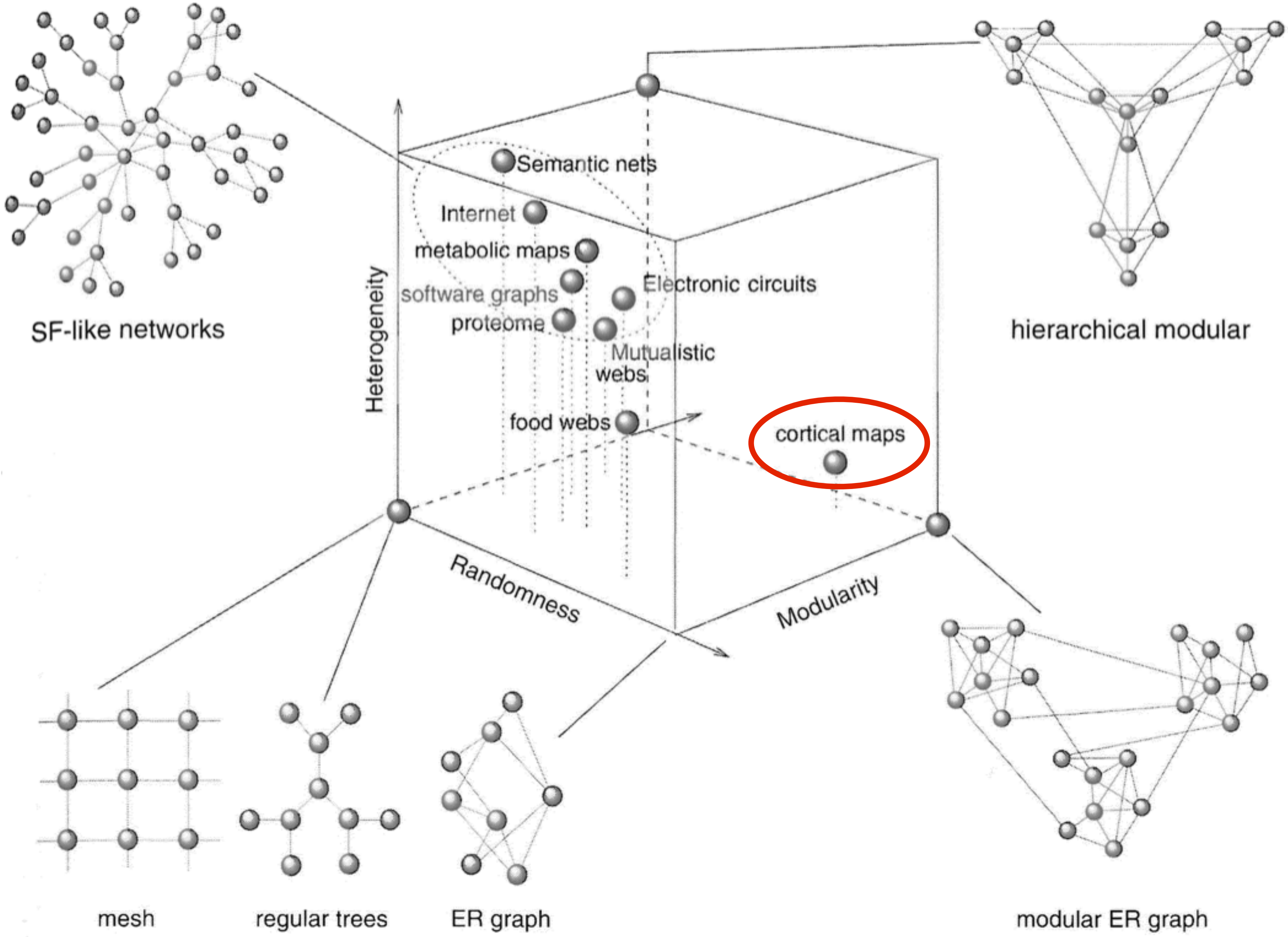
- Pairwise correlations between regionally-averaged timecourses of all brain regions





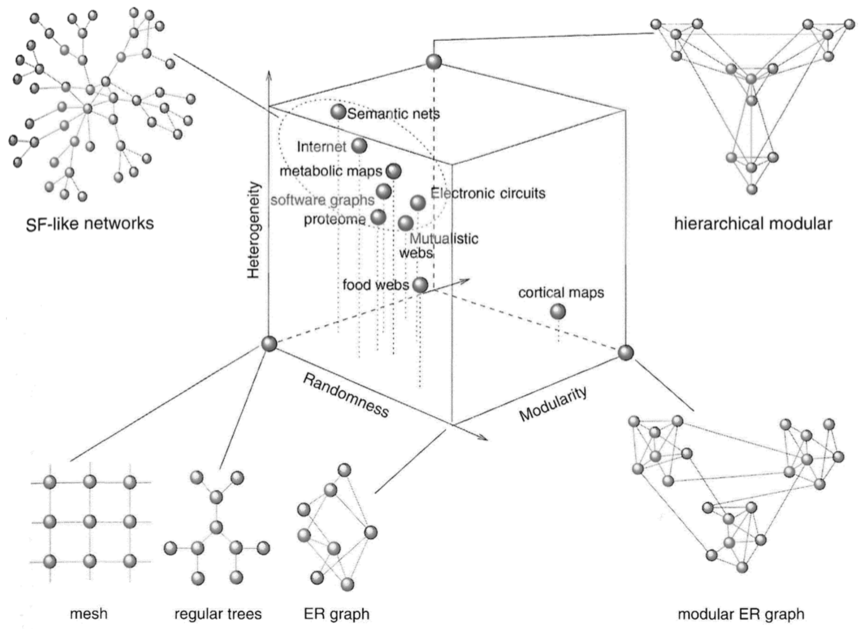
apply graph/network analysis

[Richiardi et al, 2013]



[Sole and Valverde, 2004]

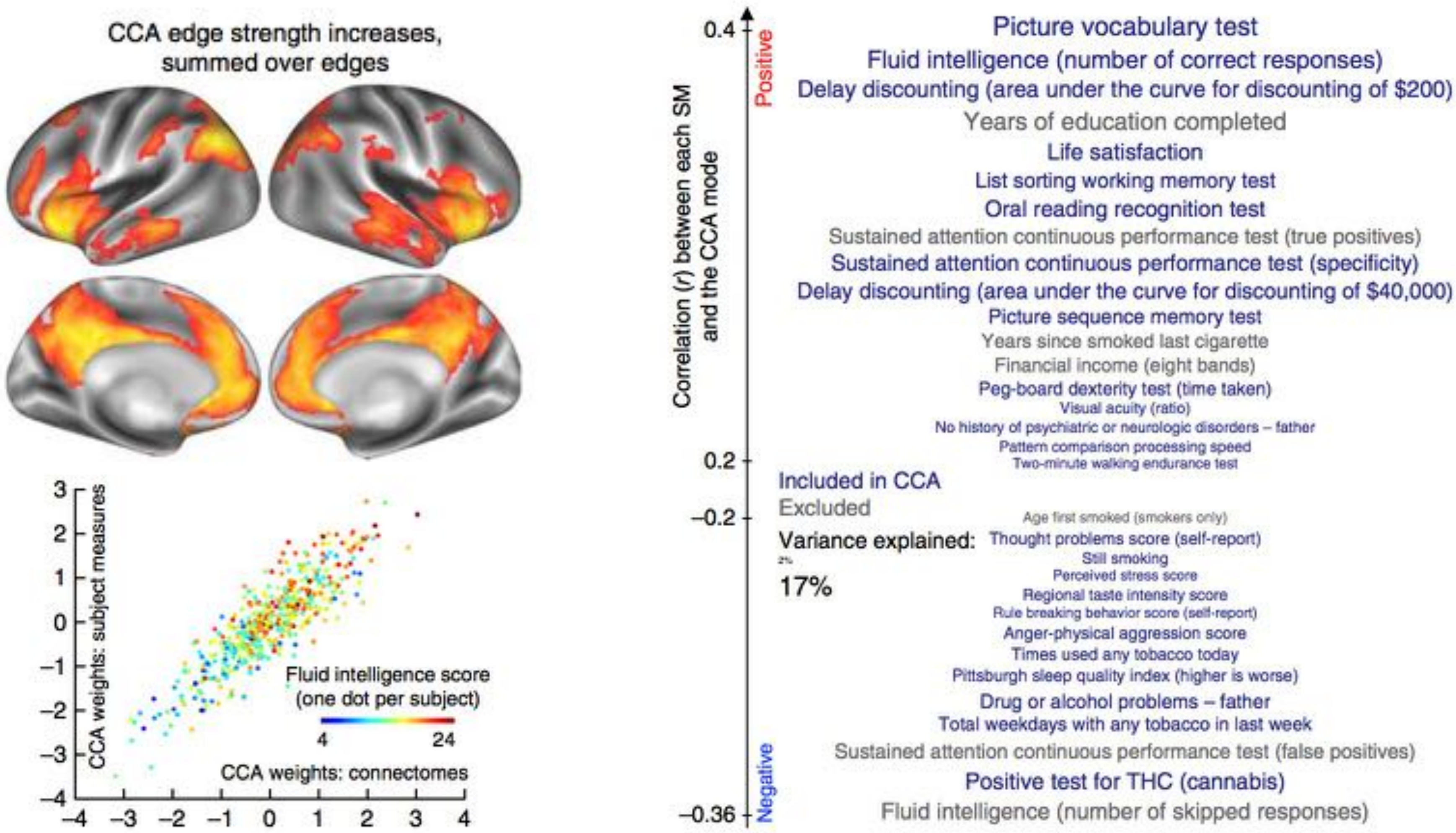
- Small-world
  - high clustering
    ~functional segregation
  - high efficiency
    ~functional integration
- Cost-efficient
  - high efficiency for
    low connection cost
- Hubby
  - fat-tailed degree distributions
  - hierarchical,
    but still resilient to attacks and errors
- Modular
  - more dense connections to nodes in
    module than to nodes in
    other modules



[Bullmore and Sporns, 2009; Bassett et al, 2010]

Show me your rest, and I tell your success

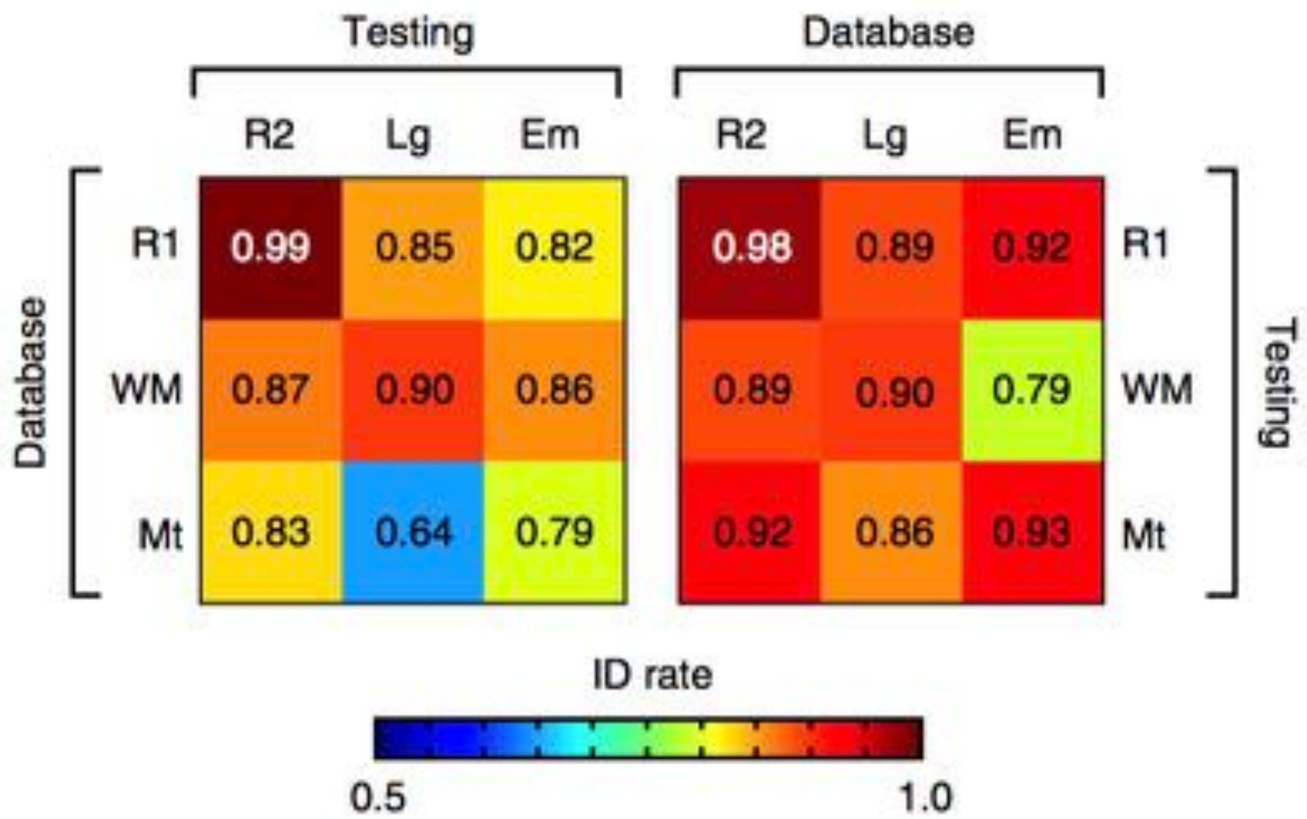
- Linking resting-state functional connectomes (280!) to life style/demographics/psychometric measures



[Smith et al., Nature Neuroscience, 2015]

Show me your rest, and I tell who you are

- Functional connectome serves as fingerprint to identify individuals
  - 126 individuals, across resting state & task sessions



R1: rest 1, R2: rest 2, WM: working memory,
Mt: motor task, Lg: language, Em: emotion

[Finn et al., Nature Neuroscience, 2015]

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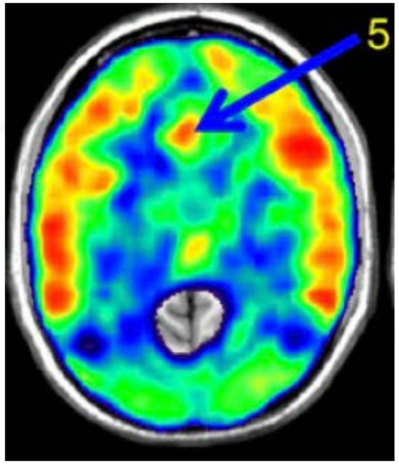
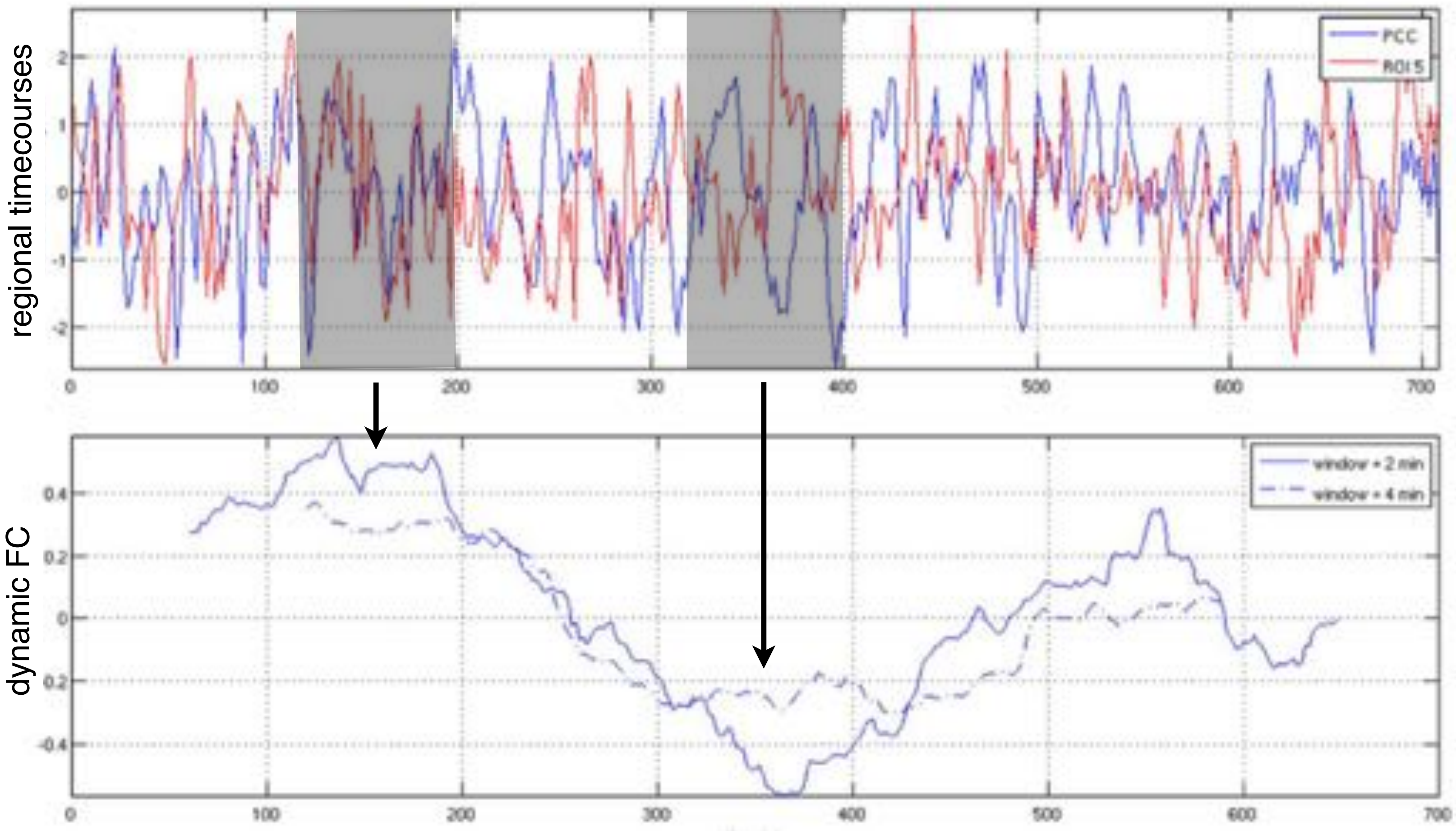
Dynamic functional connectivity



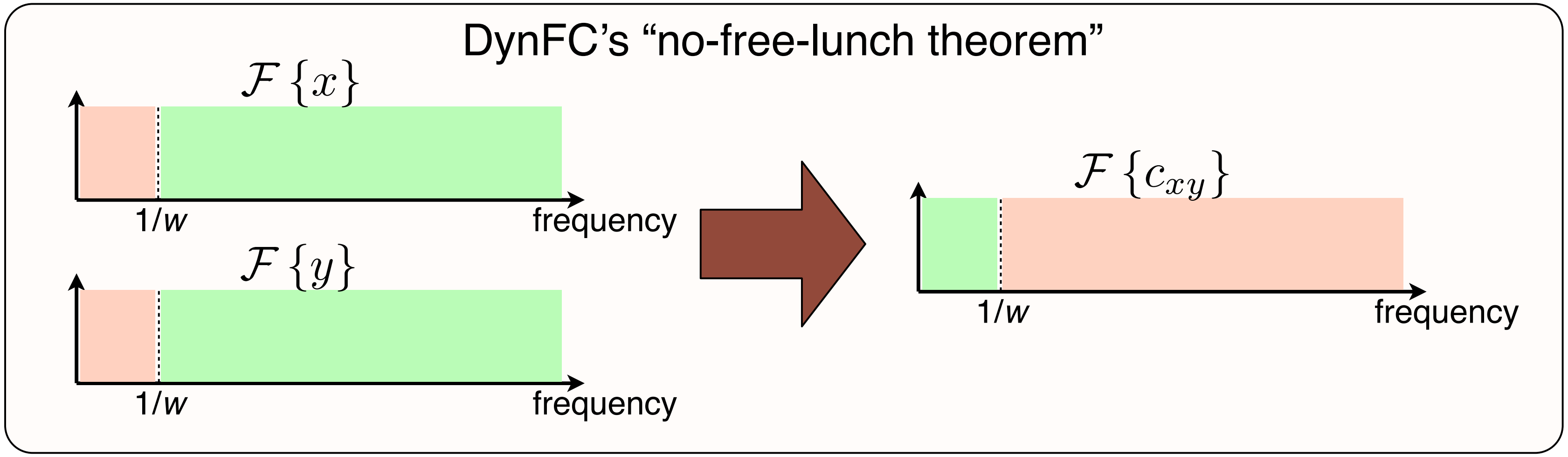
- Extract network dynamics by sliding-window pairwise correlations



[Chang and Glover, 2010]

Dynamic functional connectivity

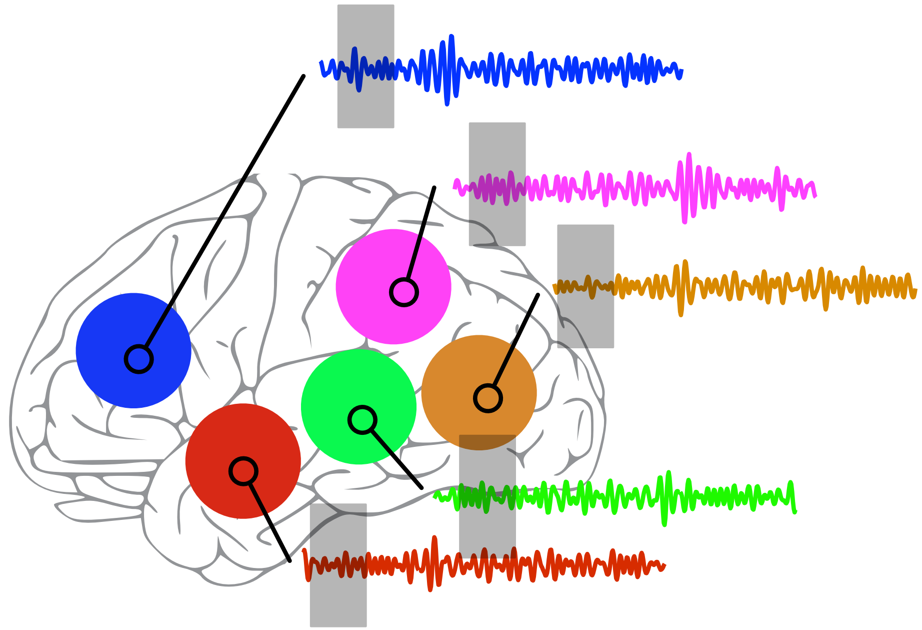
- Proper preprocessing of timecourses is required
  - To avoid aliasing artefact: high-pass filtering of input timecourses with reciprocal of window length *w*



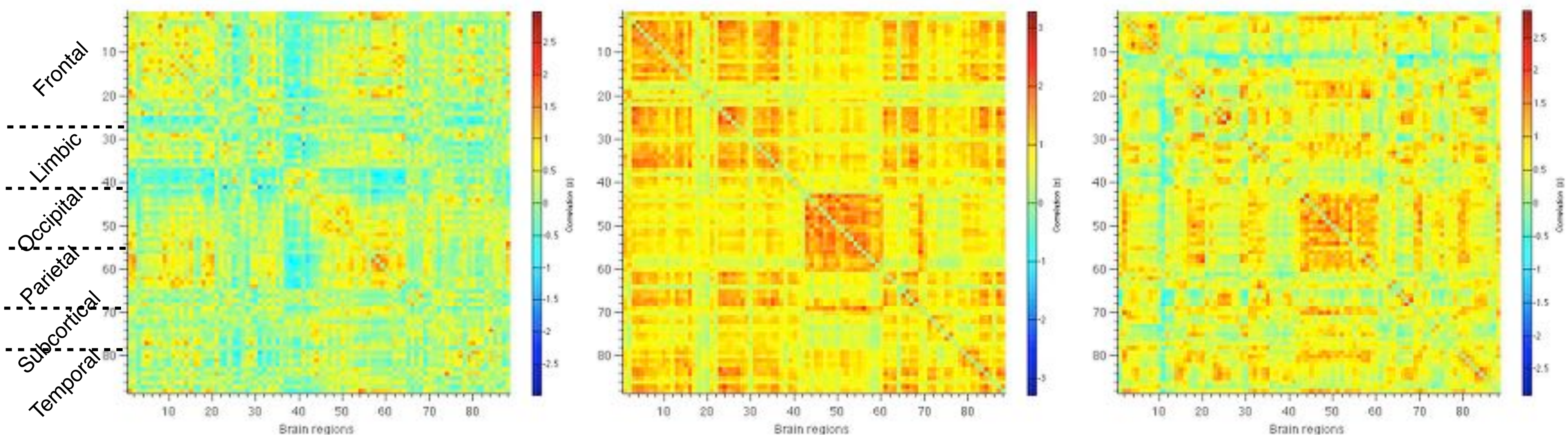
[Leonardi, VDV, *NeuroImage*, 2015]

Dynamic functional connectivity

- Sliding window correlation*
  - Window length is 30 TRs, step of 2 TRs, TR=1.1sec



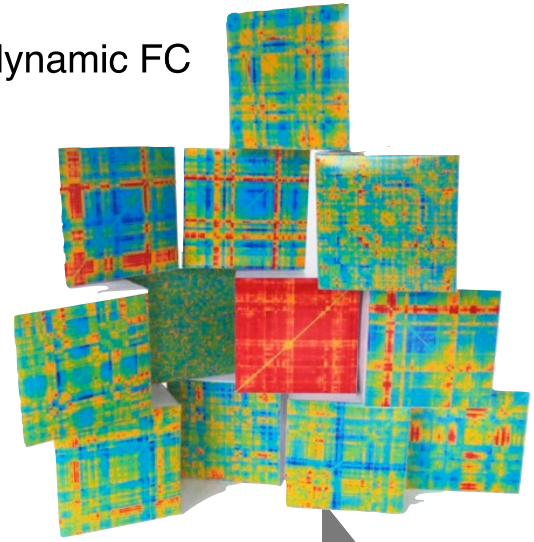
- Three healthy subjects:

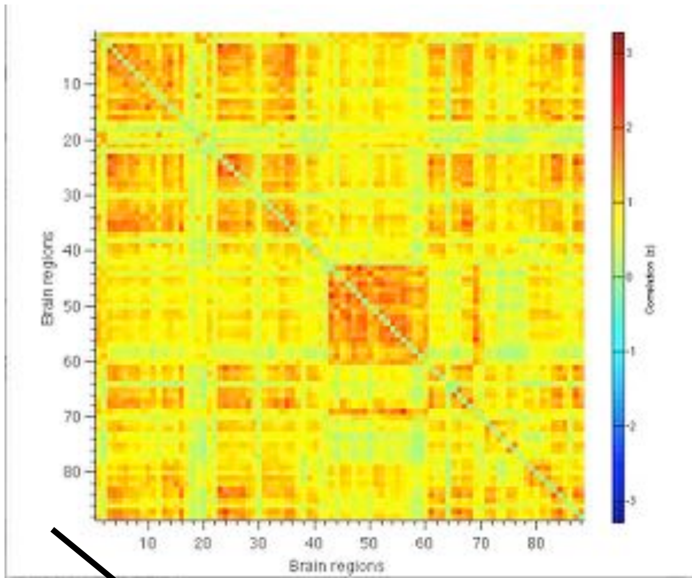


[Allen et al, 2014; Leonardi, VDV et al, 2013; Leonardi, VDV, 2014; Leonardi et al, 2014]

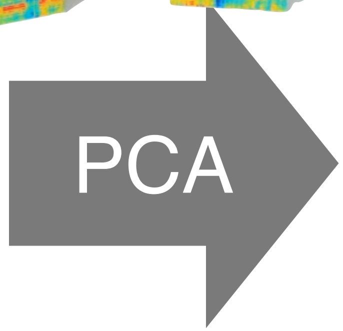
Eigenconnectivities

"Lego" of dynamic FC

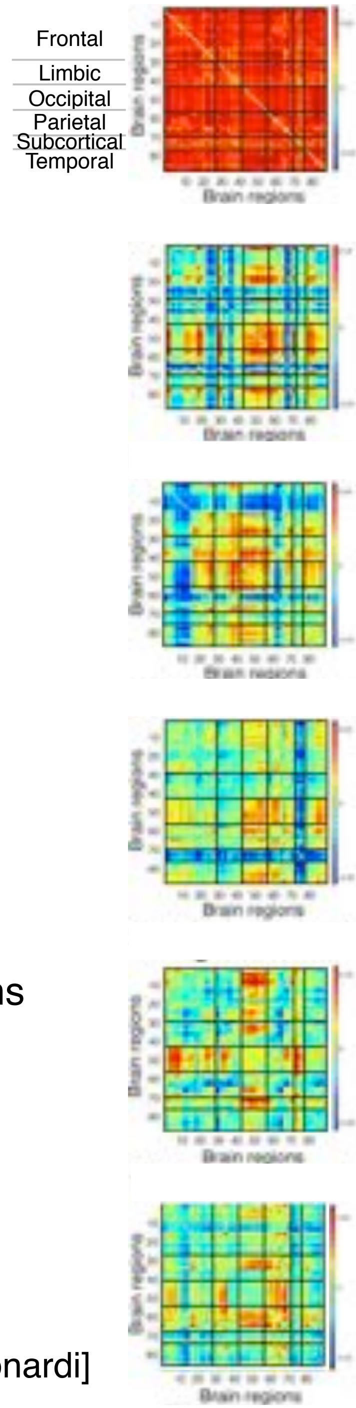


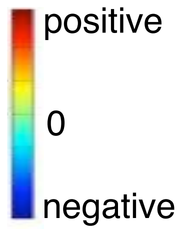


time x subjects



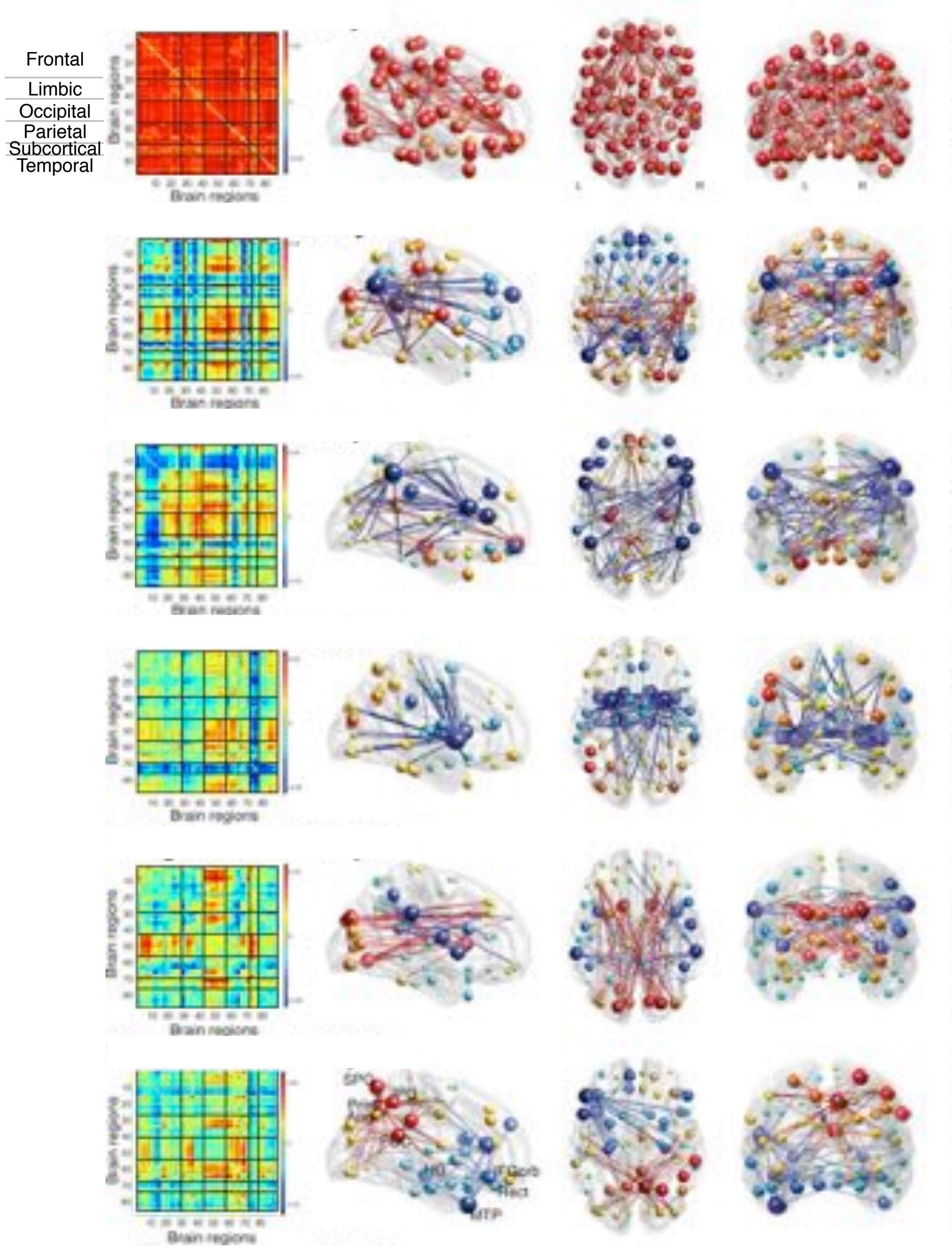
- average dynamic FC is subtracted out (i.e., driven by fluctuations of FC only!)
- optimized for explained variance
- orthogonality constraint





[Leonardi, VDV, *NeuroImage*, 2013; Leonardi, VDV, *HBM*, 2014; image by M. Leonardi]

Eigenconnectivities



global fluctuations in FC

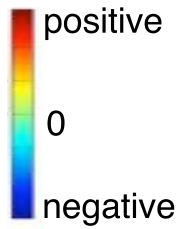
cingulate gyri, medial frontal gyri,
precuneus (default-mode network)
primary sensory in red

inferior and middle frontal gyri, inferior parietal
(fronto-parietal)

subcortical

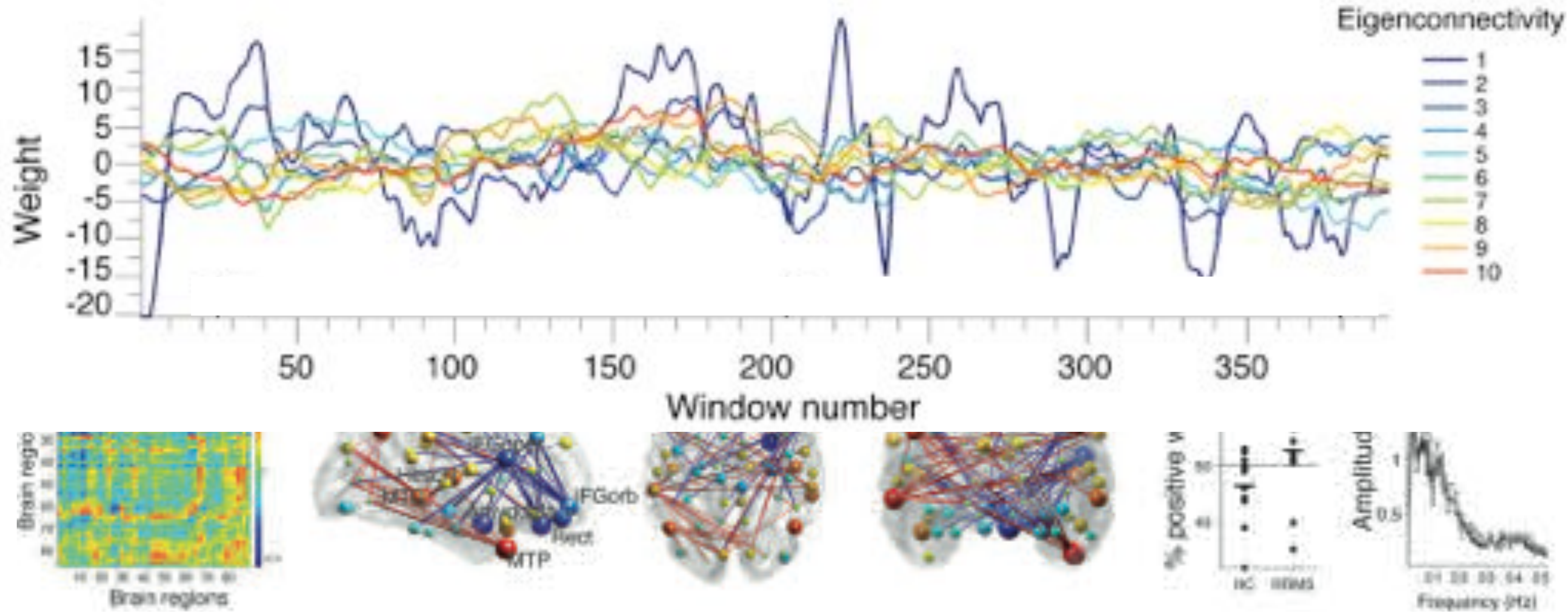
visual

posterior DMN
temporal and inferior frontal



Altered dynamics in multiple sclerosis

- Temporal contributions of eigenconnectivities is altered in minimally-disabled relapse-remitting multiple sclerosis patients ($F_{(10,19)}=2.6$, $p=0.005$)

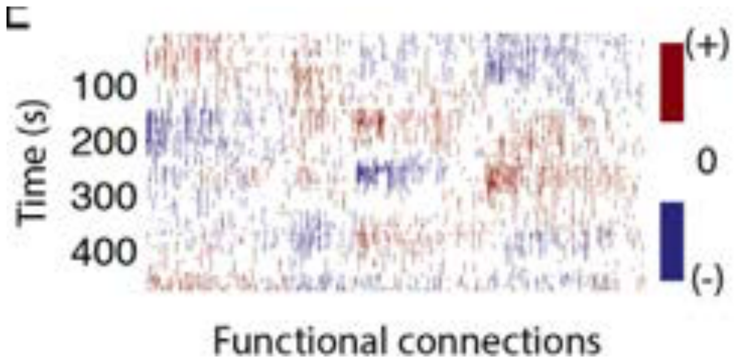


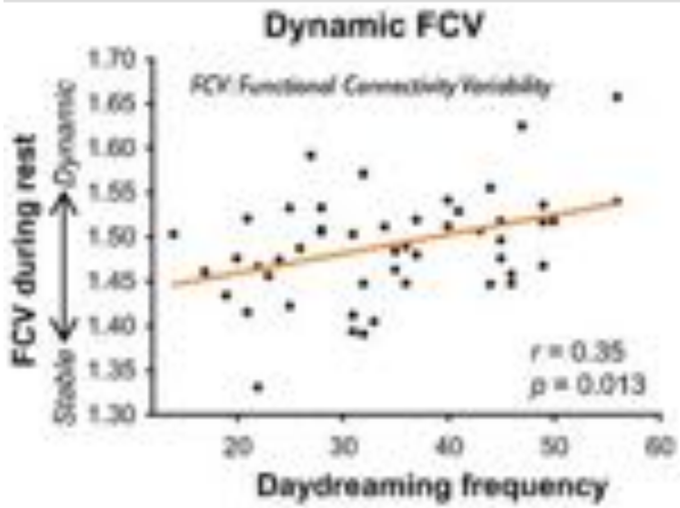
- Schizophrenia, autism, temporal lobe epilepsy, ...

[Leonardi, ..., VDV, *NeuroImage*, 2013] [Damaraju et al. 2014, Ma et al. 2014, Yu et al. 2015, Rashid et al. 2014]

Origin and relevance of dynamic FC

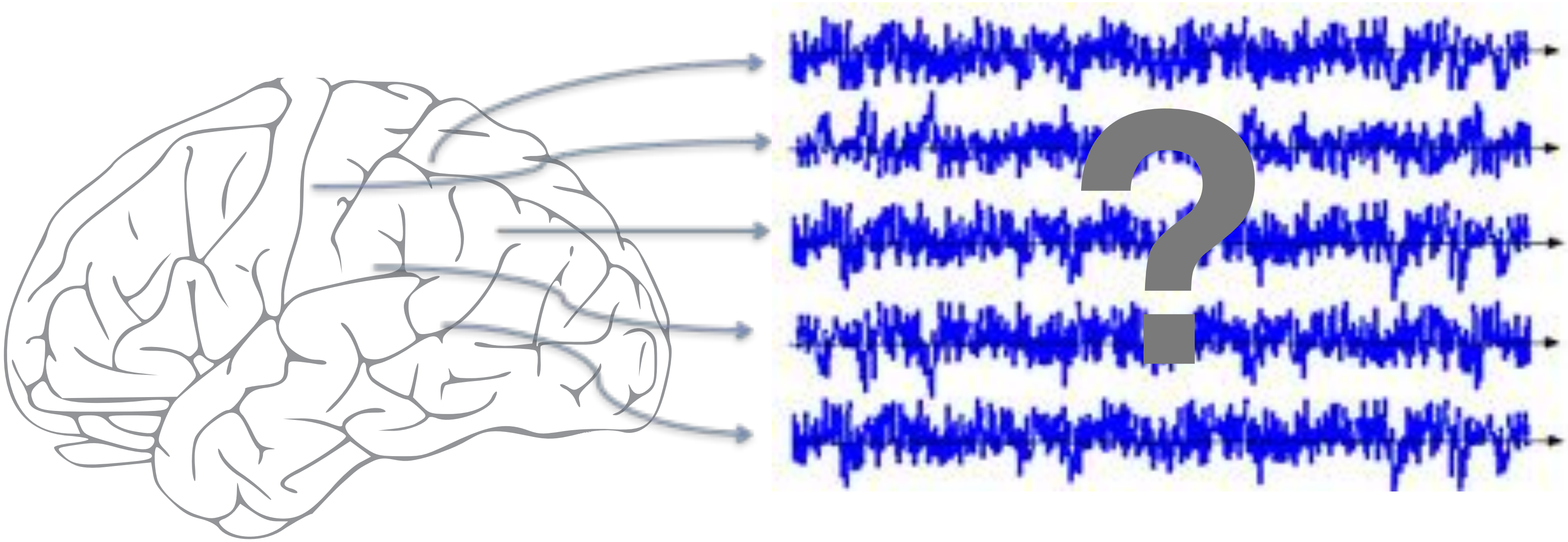
- Parts of dynFC **survive** rigorous statistical testing: non-parametric randomization
  - Betzel et al, 2016; Zalesky, 2014; Keilholz et al, 2013; Huang, et al, ArXiv
- DynFC correlates with **electrical** activity
  - Thompson et al, 2013; Tagliazucchi et al, 2013; Chang et al, 2013
- DynFC varies along **demographic** variables: age, gender
  - Hutchison, Morton, 2015; Yaesoubi et al, 2015
- DynFC is modulated by changes in **arousal**: anesthesia, caffeine
  - Rack-Gomer and Liu, 2012; Barttfeld et al, 2015; Tagliazucchi et al, 2014
- DynFC correlates with **cognition**: daydreaming, cognitive flexibility
  - Kucyi, Davis, 2013; Yang et al, 2014; Cheng et al, 2016





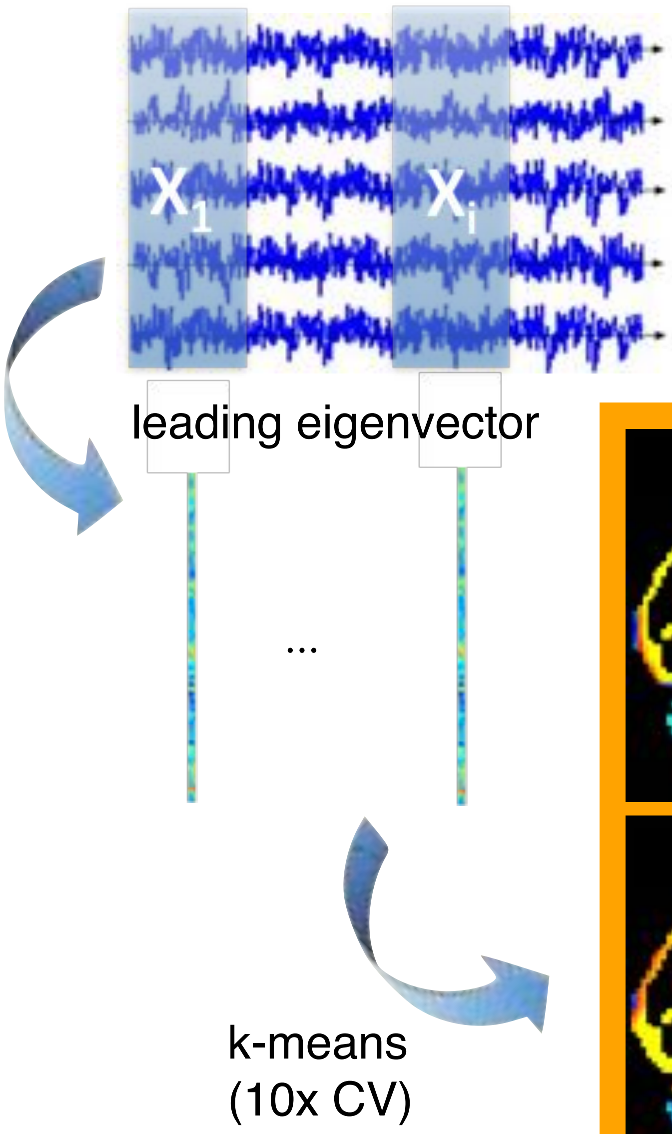
Spatially resolved dynamic FC

- Voxel-wise (dynamic) connectome
  - 10^5 timecourses
  - Connectivity matrix is huge!
  - Sliding-window approach... %@U$)!
- But matrix is low-rank!
  - Rank is at most #timepoints << 10^5

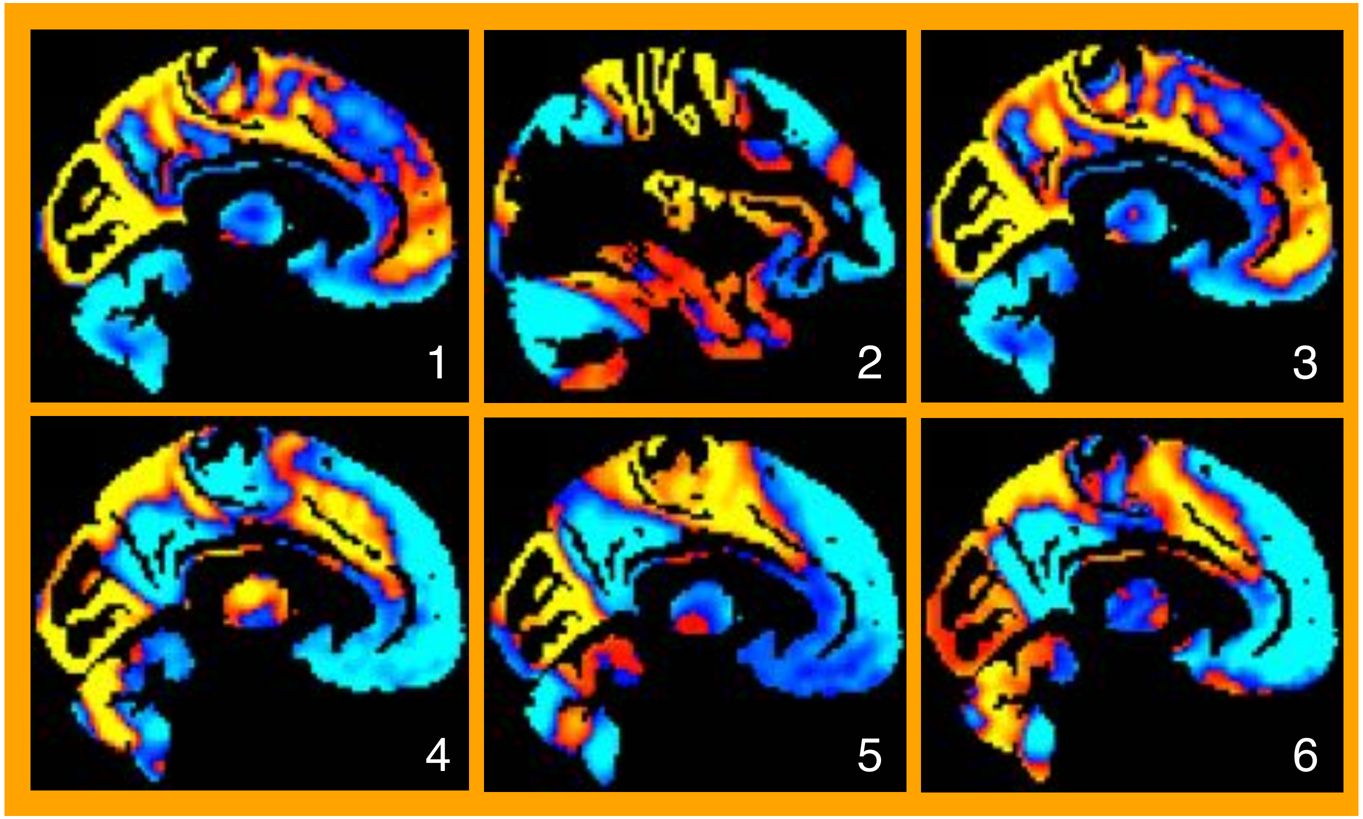


[Preti, VDV, *Scientific Reports*, 2017]

Representative dominant patterns

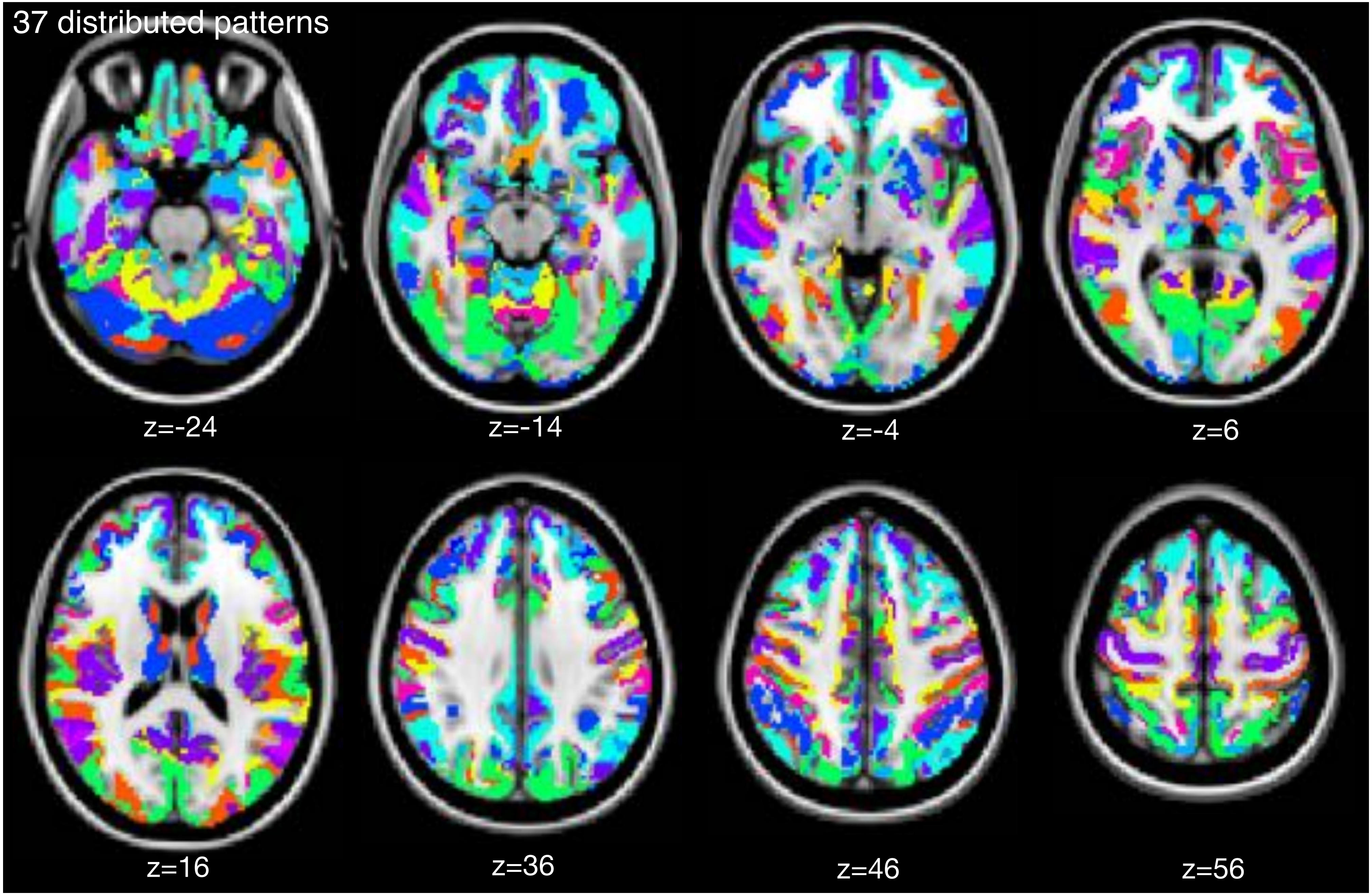


- Interplay between major networks
  - RDP5: full DMN vs sensorimotor
  - RDP4,6: segregation of DMN in dorsal/ventral parts



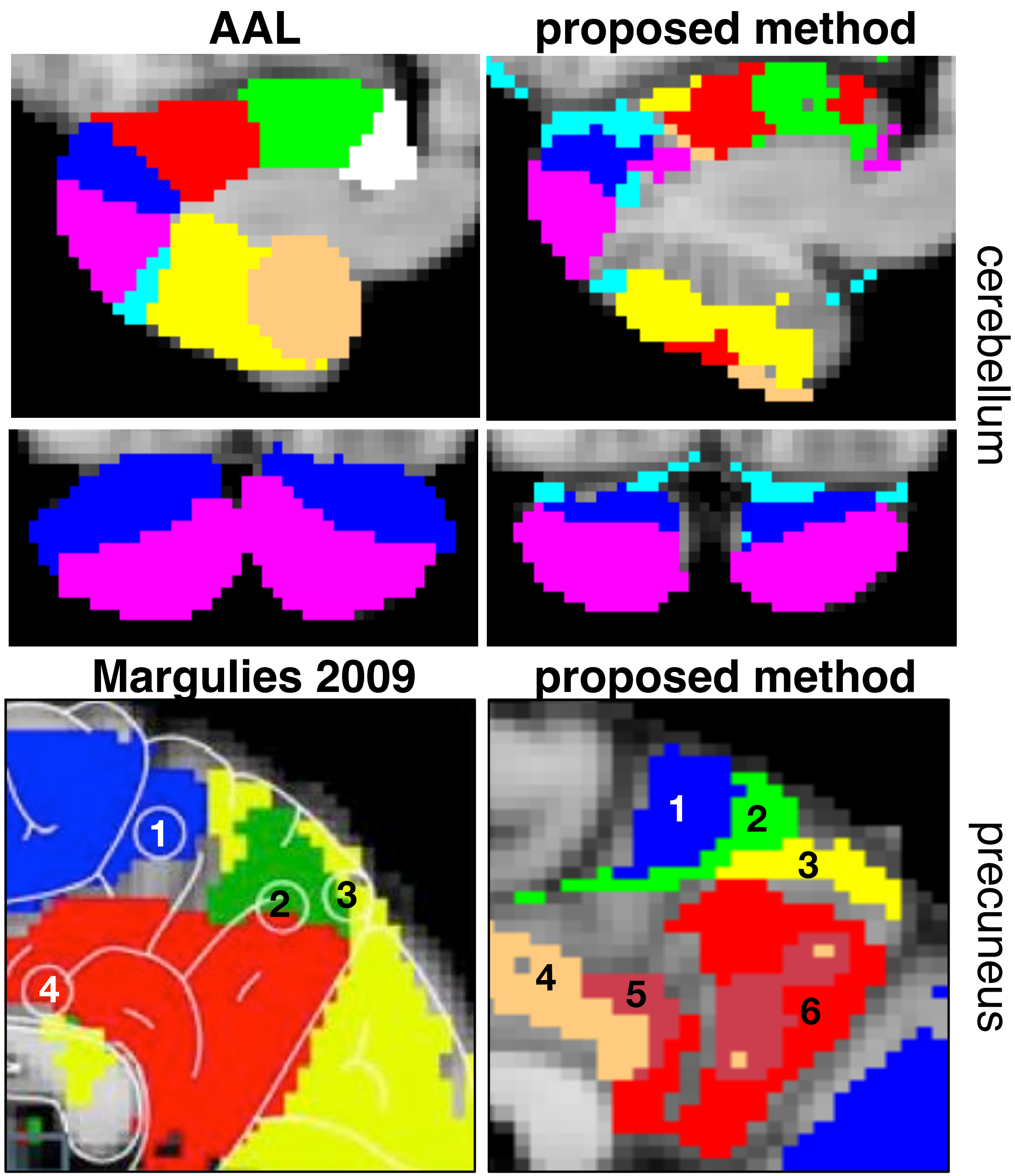
[Preti, VDV, *Scientific Reports*, 2017]

Dynamic FC voxel-wise parcellation



Dynamic FC voxel-wise parcellation

- Split into contiguous regions
  - Leads to 449 parcels
- Fluctuations of dynamic FC are meaningful in terms of long-range and short-range interactions
- Extensions
  - Higher rank
  - Clustering
  - ...



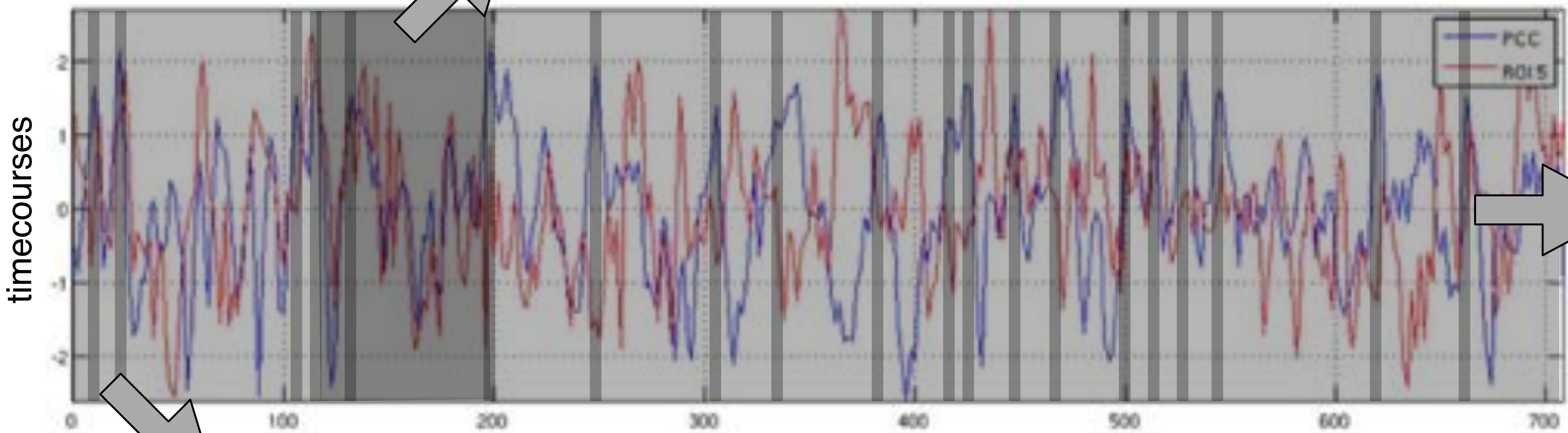
[Preti, VDV, Scientific Reports, 2017]

available online at https://neurovault.org/collections/3091/

Better capturing of dynamics

windowed correlation is temporally restricted, but suffers from low SNR and potential aliasing

[Chang and Glover, 2010; Leonardi, VDV, 2013, 2014]

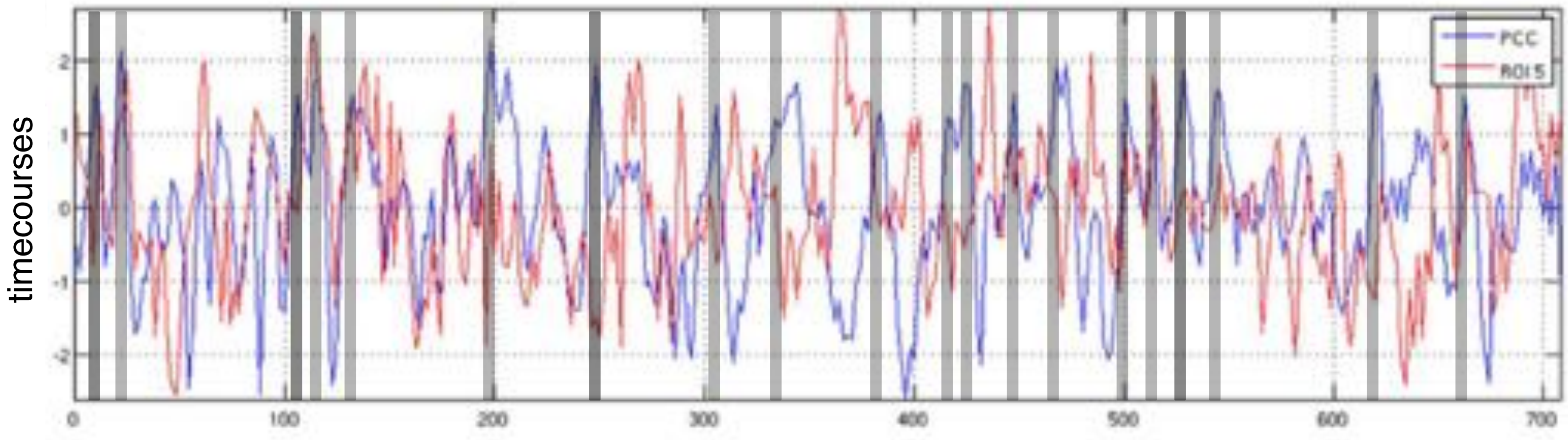


statistical dependencies characterize “average” behavior during resting state

can we extract ‘key points’ that capture the important events?

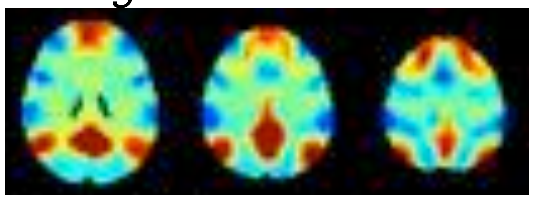
Co-activation patterns (CAPs)

- Selection of timepoints with extreme values of seed region (point process model)

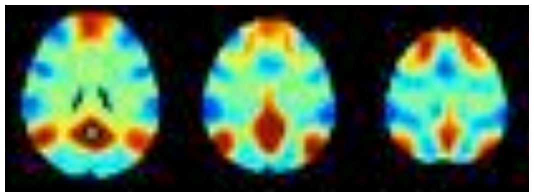


- Averaging is proxy of seed connectivity:

average over all selected frames:



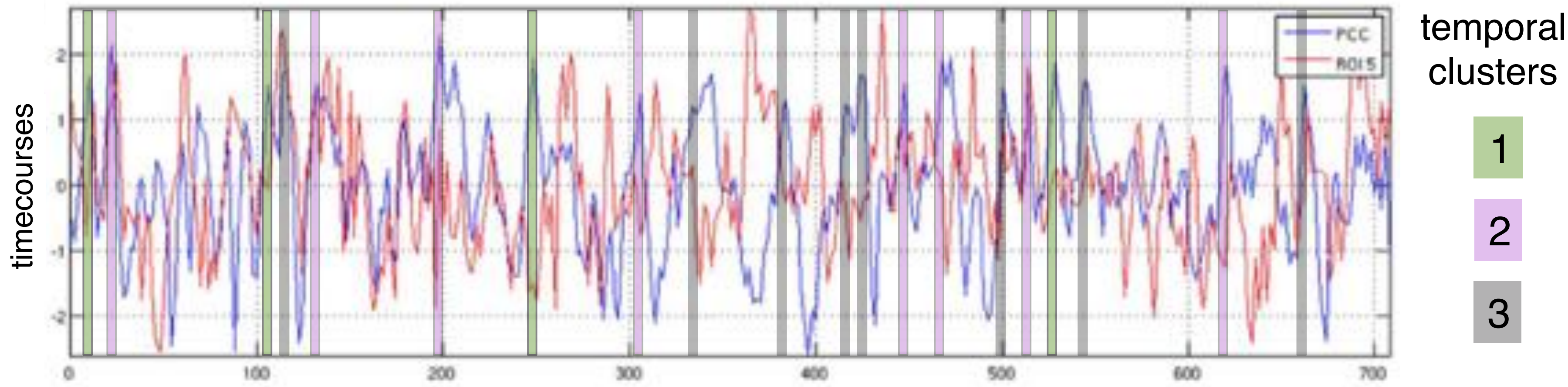
seed-based correlation:



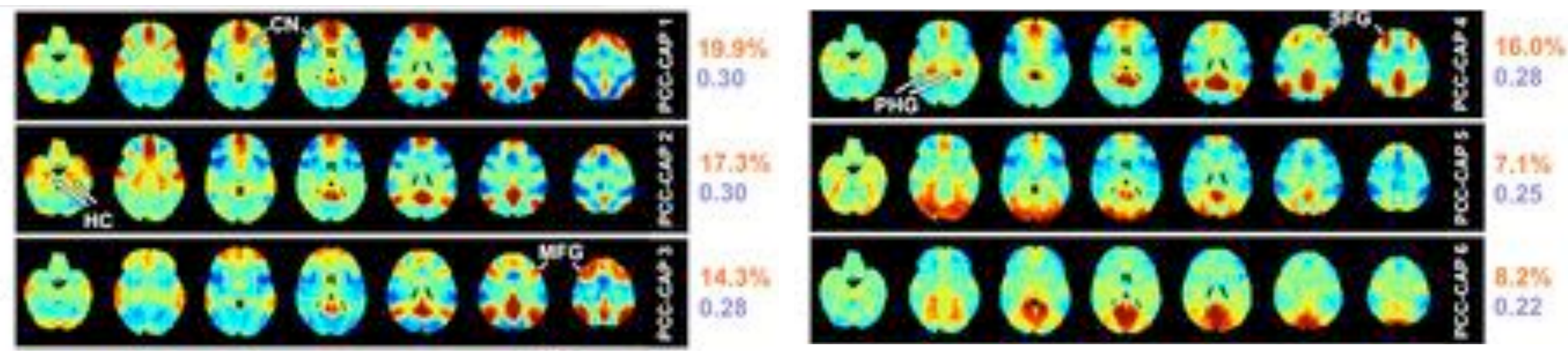
[Tagliazucchi et al., 2012; Liu and Duyn, *PNAS*, 2013]

Co-activation patterns (CAPs)

- Temporal clustering of selected frames



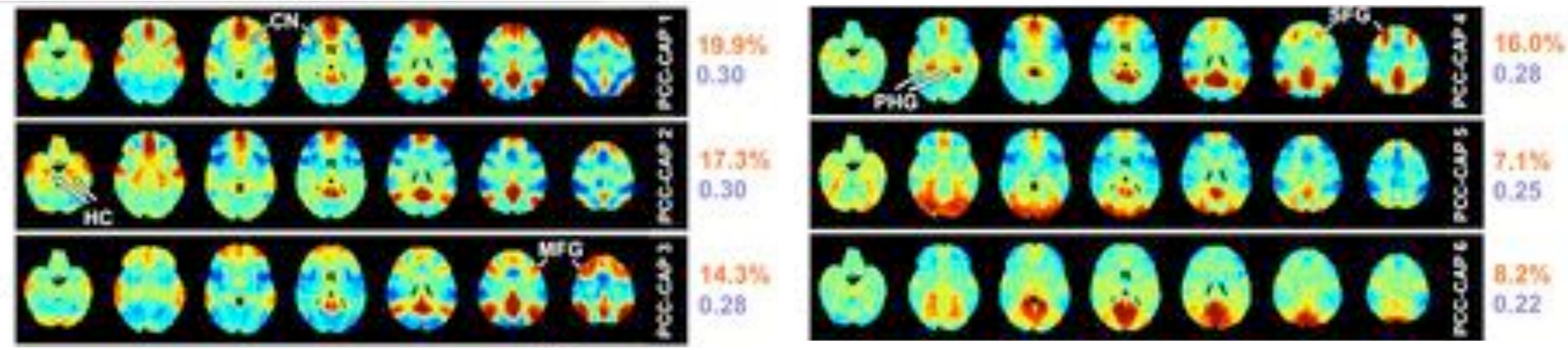
- Averaging of spatial activity patterns for each temporal cluster leads to “co-activation patterns” (CAPs)



[Tagliazucchi et al., 2012; Liu and Duyn, *PNAS*, 2013]

Co-activation patterns (CAPs)

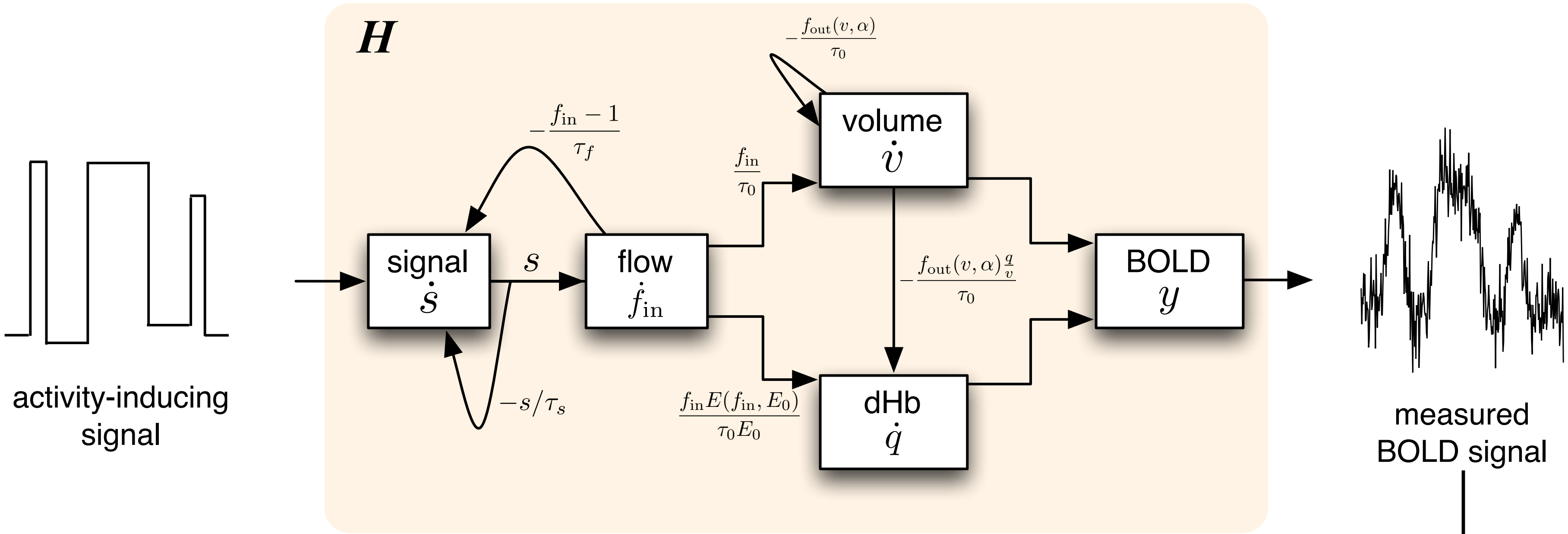
- Averaging of spatial activity patterns for each temporal cluster leads to "co-activation patterns" (CAPs)



- Temporal clustering allows CAPs to have spatial overlap, but it does not disentangle temporal overlap:
  - #CAPs suffers from combinatorial explosion:
    - N "fundamental" networks that can temporally overlap K at a time would lead to $\sim N^K$ CAPs
  - CAPs can be contaminated by non-seed related activity

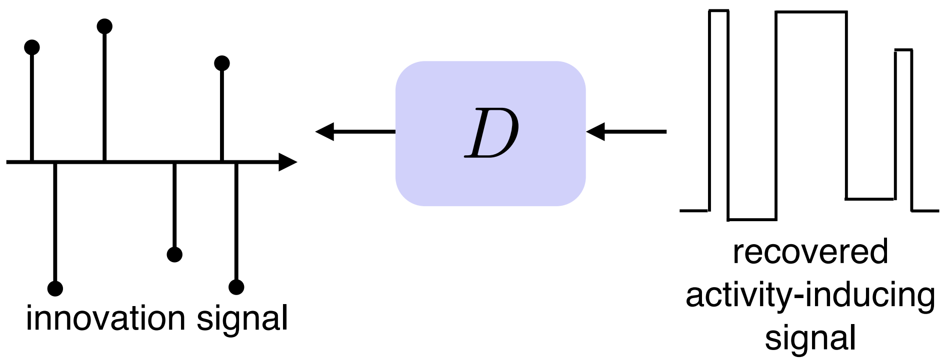
[Tagliazucchi et al., 2012; Liu and Duyn, *PNAS*, 2013]

Total activation regularized deconvolution of fMRI BOLD timeseries



- Total activation regularization:

$$\tilde{\boldsymbol{x}} = \arg\min_{\mathbf{x}} \underbrace{\frac{1}{2}\,||\boldsymbol{y}-\boldsymbol{x}||_2^2}_{\text{data fitness}} + \lambda \underbrace{\left|\left|DH^{-1}\{\boldsymbol{x}\}\right|\right|_1}_{\text{regularization}}$$



H*^-1^** ***First-order Volterra kernel

$$H^{-1} = \frac{\prod_{i=1}^{4}(D-\alpha_i I)}{D-\gamma I}$$

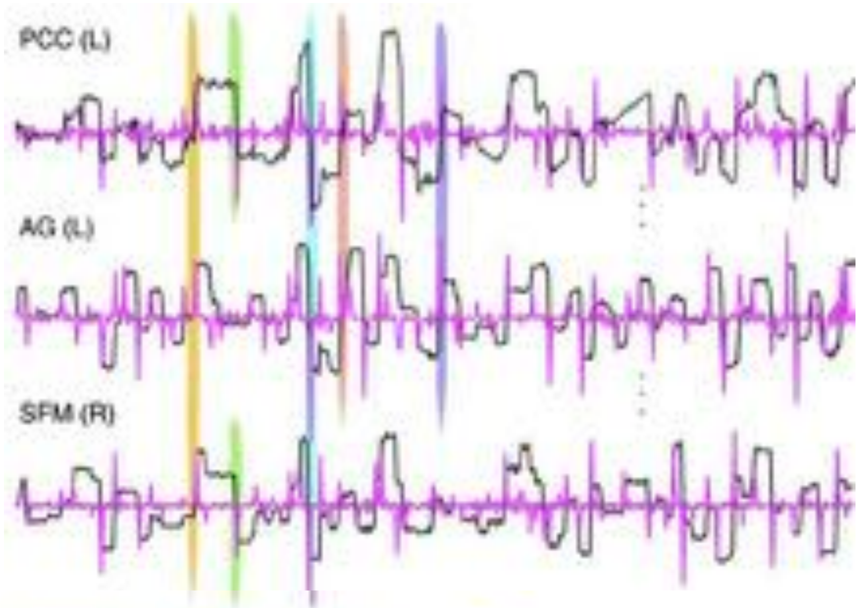
$$\vec{\boldsymbol{\alpha}} = \left\{-\frac{1}{\tau_0}, -\frac{1}{\alpha\tau_0}, -\frac{1}{2\tau_s}\left(1 \pm j\sqrt{\frac{4\tau_s^2}{\tau_f}-1}\right)\right\},$$

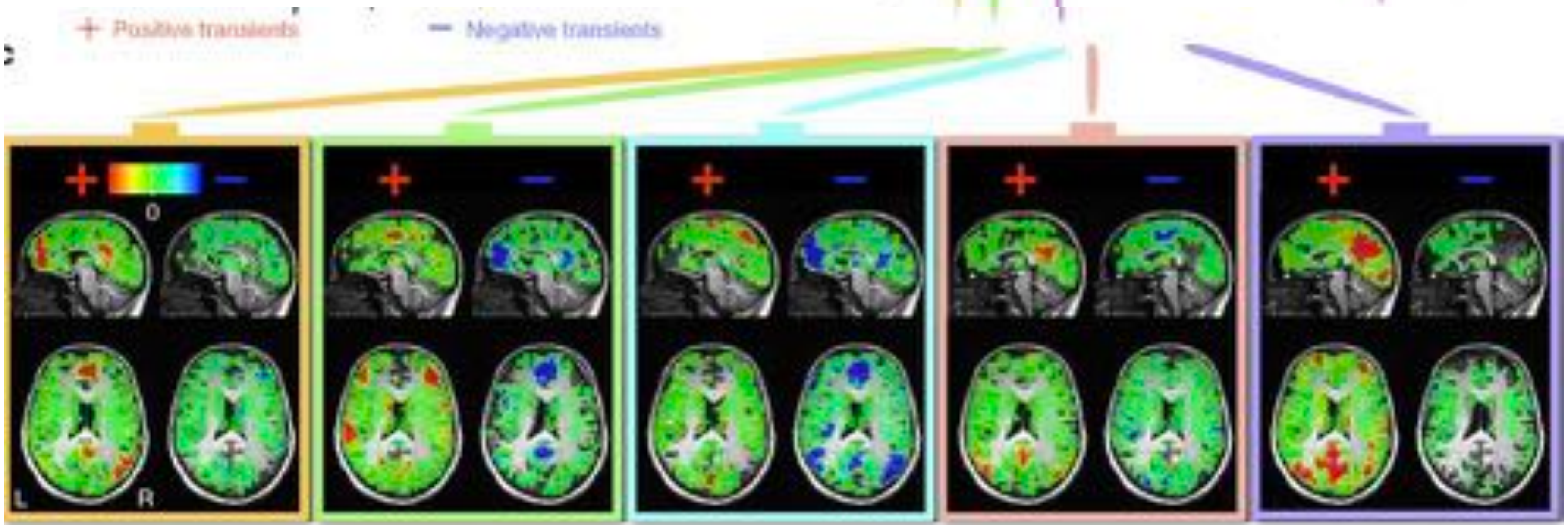
$$\vec{\boldsymbol{\gamma}} = \left\{\frac{(k_1+k_2)\left(\frac{1-\alpha}{\alpha\tau_0}-\frac{c}{\alpha}\right)-(k_3-k_2)\frac{1}{\tau_0}}{-(k_1+k_2)c\tau_0-k_3+k_2}\right\}.$$

[Khalidov, VDV et al, *IEEE Transactions on SP*, 2011; Karahanoglu, VDV et al, *NeuroImage*, 2013]

Innovation-driven co-activation patterns

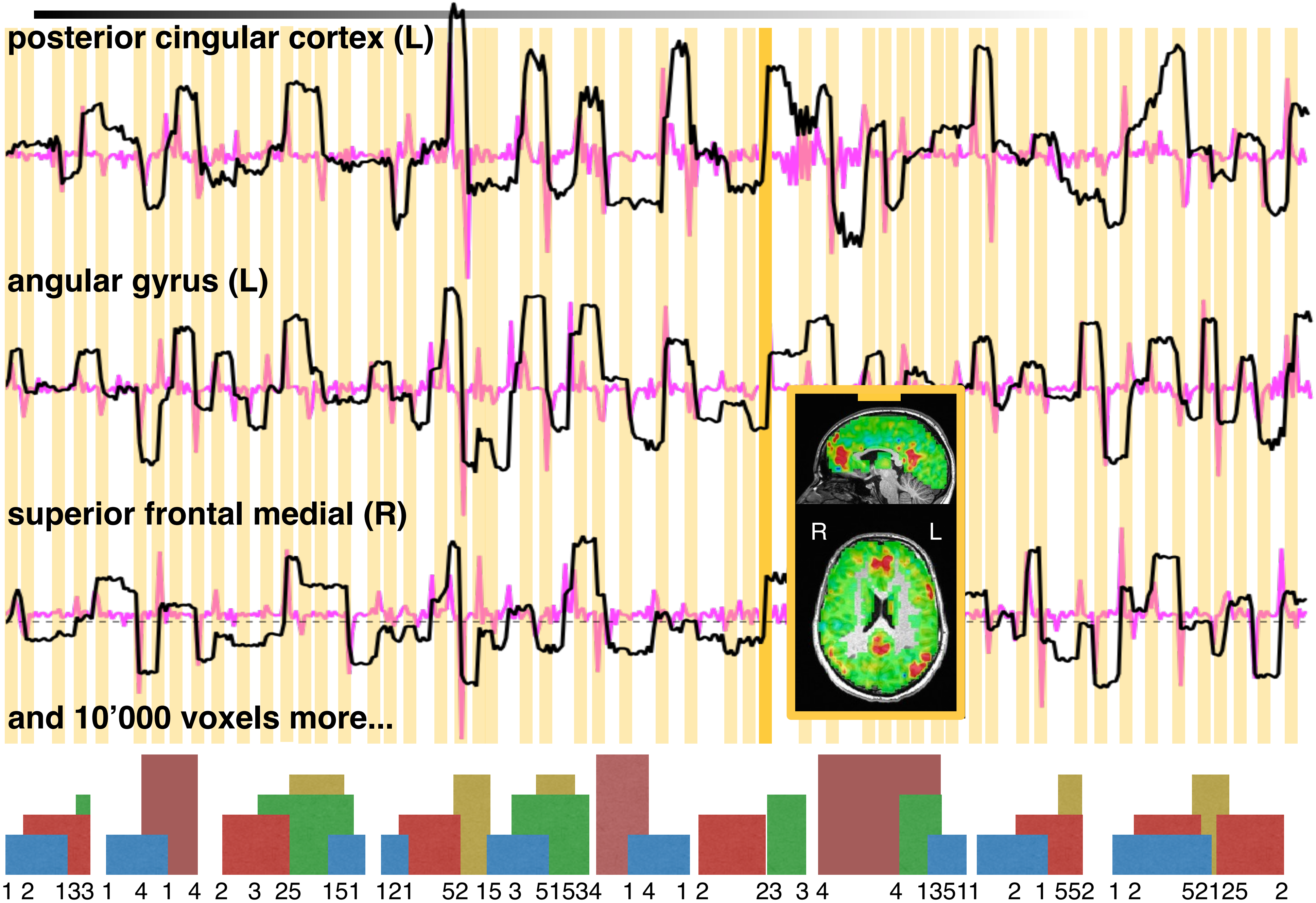
- After total-activation deconvolution, innovation signals are obtained
- *Transients* rather than BOLD enter into the clustering





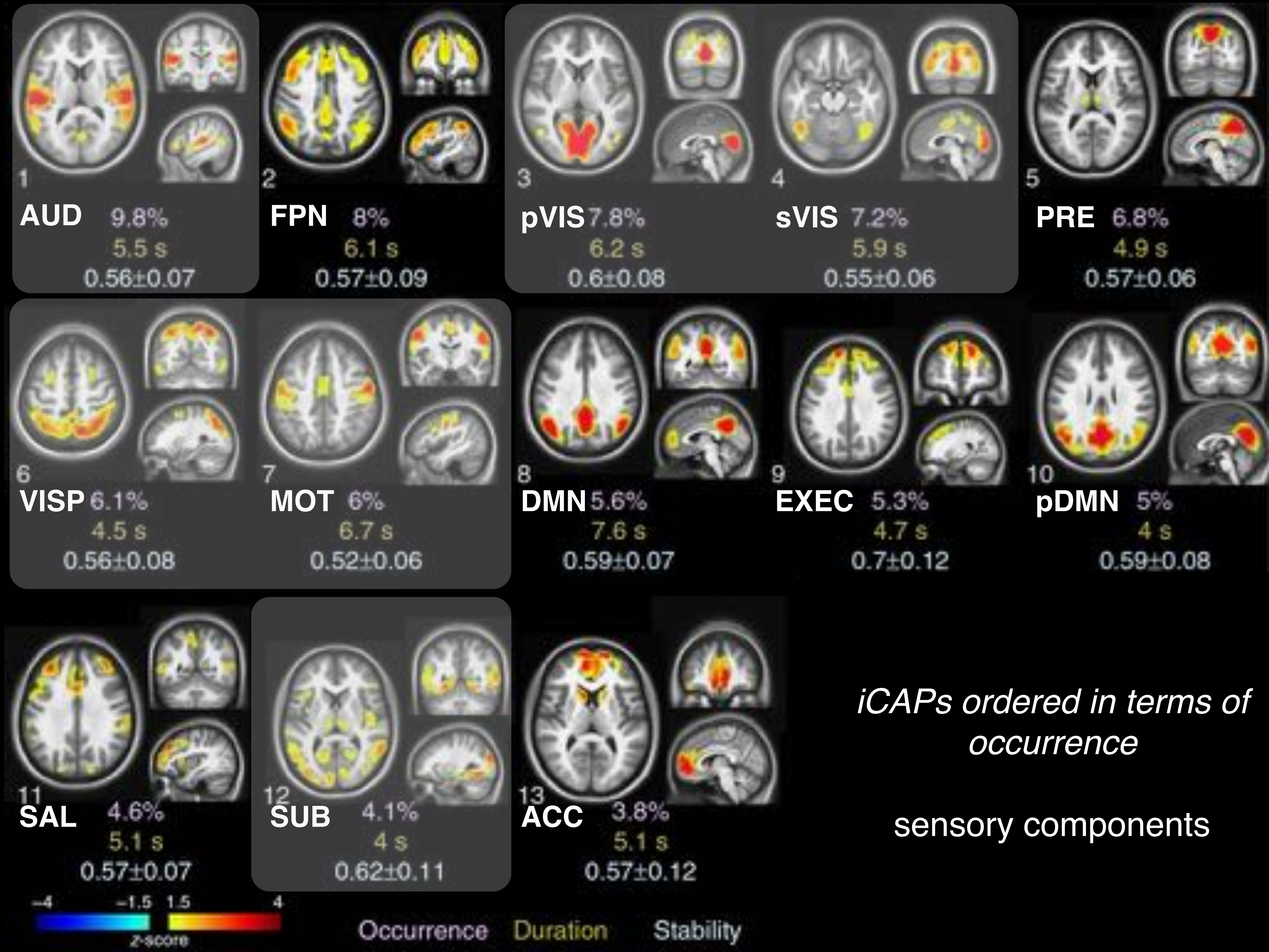
[Karahanoglu, VDV, *Nature Communications*, 2015; *Current Opinion in Biomedical Engineering*, 2017]

Innovation never comes alone



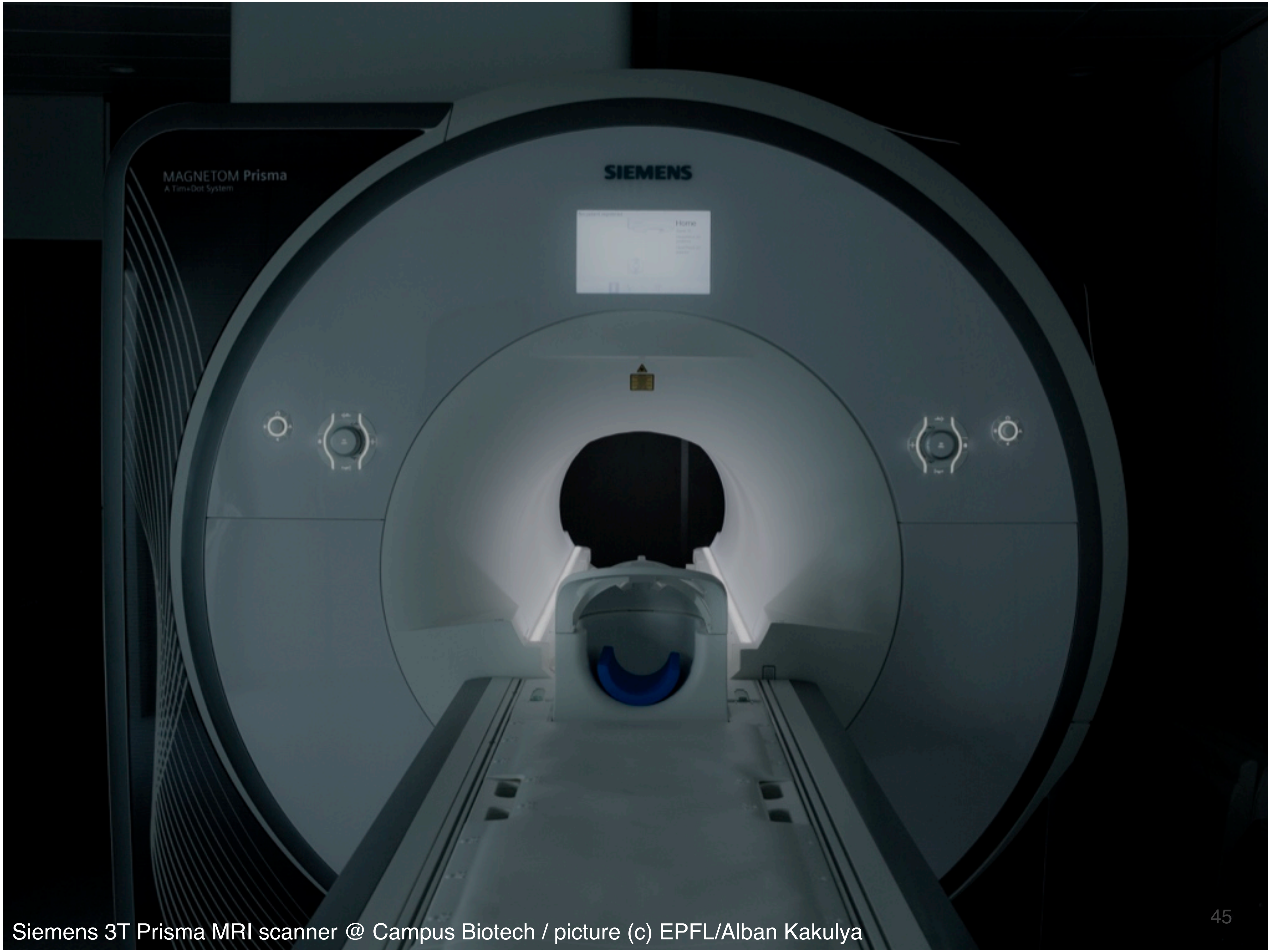
[Karahanoglu and VDV, *Nature Communications*, 2015]

Brain's repertoire of functional networks



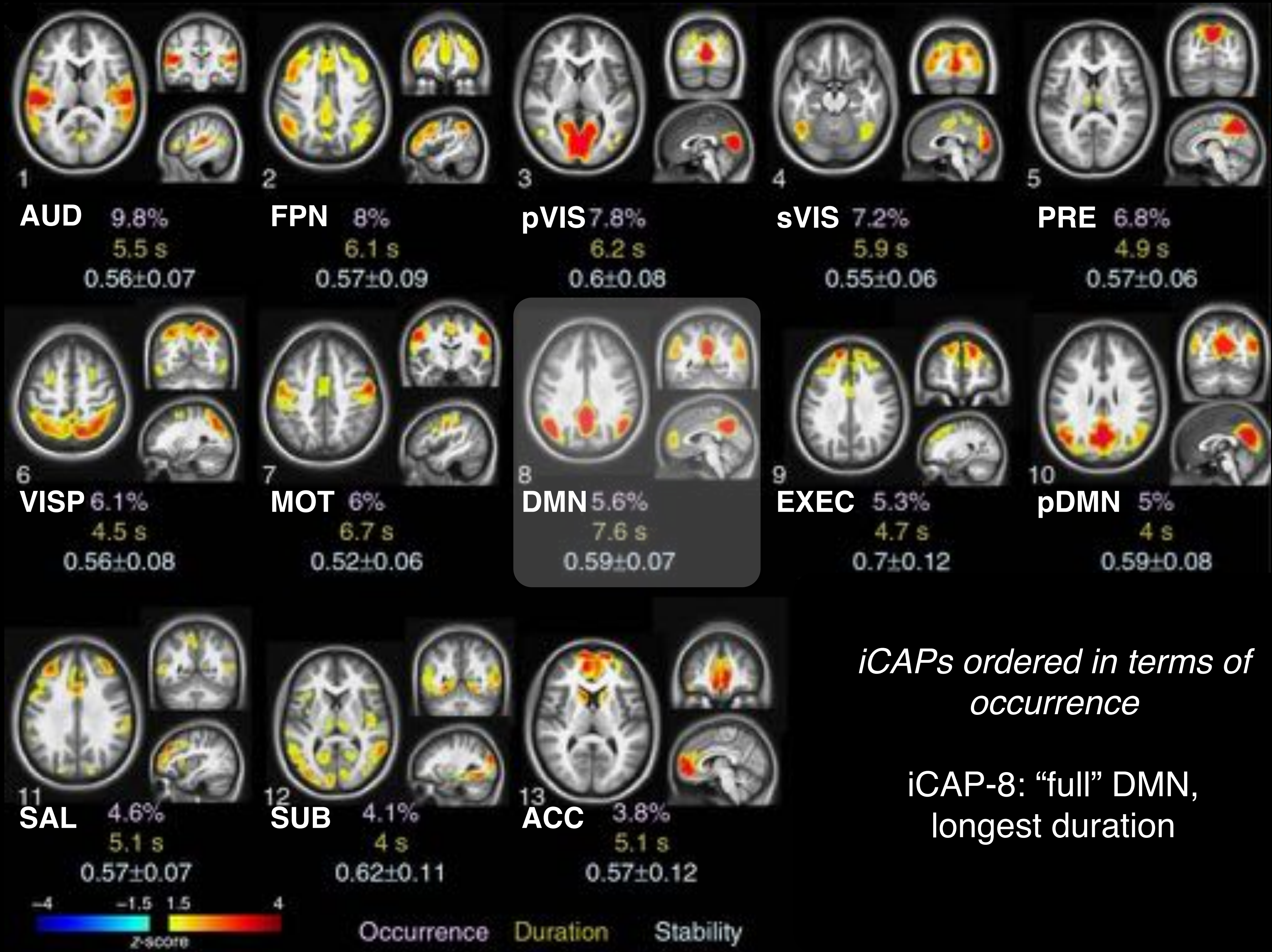
iCAPs ordered in terms of occurrence

sensory components



Siemens 3T Prisma MRI scanner @ Campus Biotech / picture (c) EPFL/Alban Kakulya

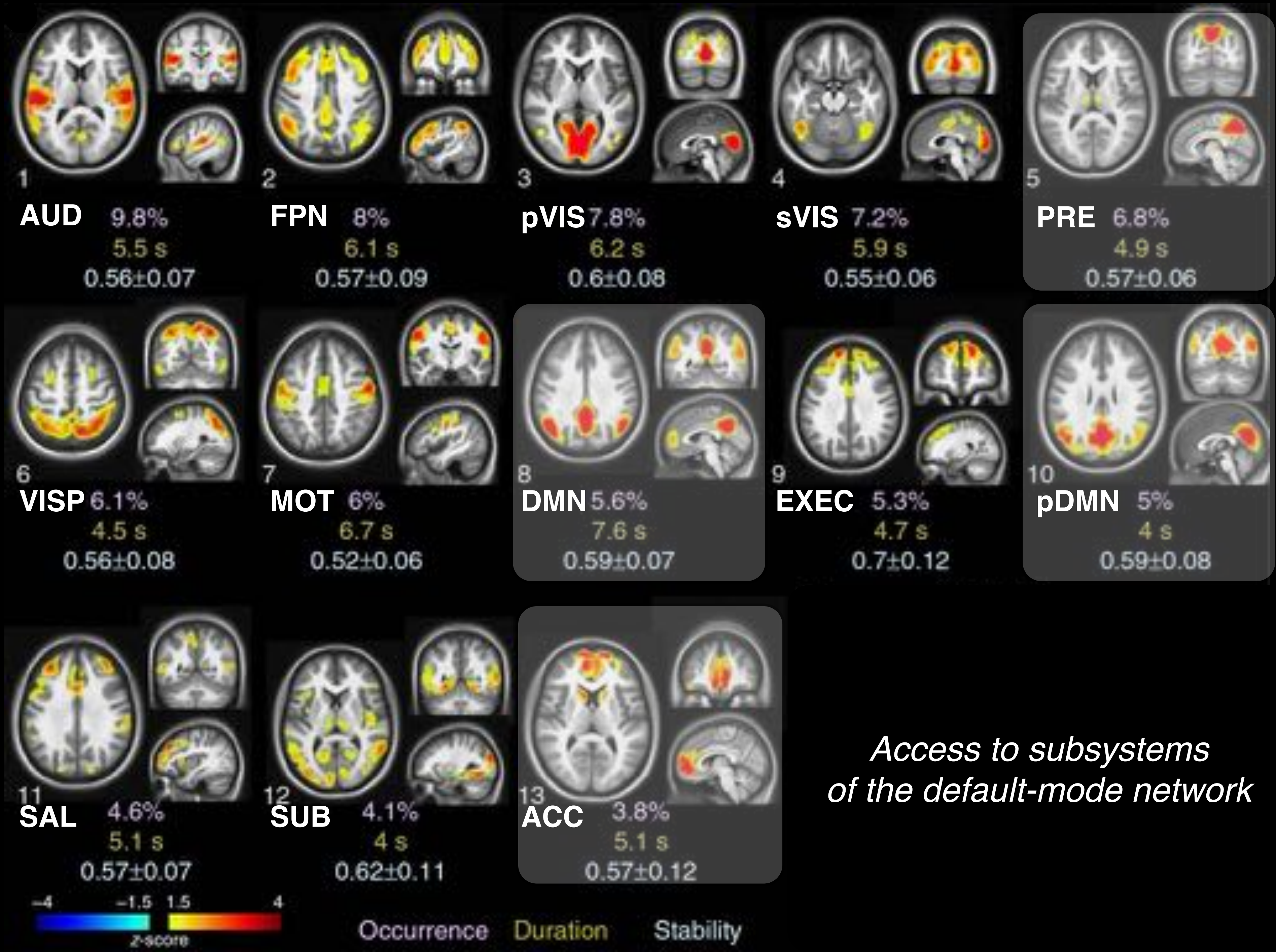
Brain's repertoire of functional networks



iCAPs ordered in terms of occurrence

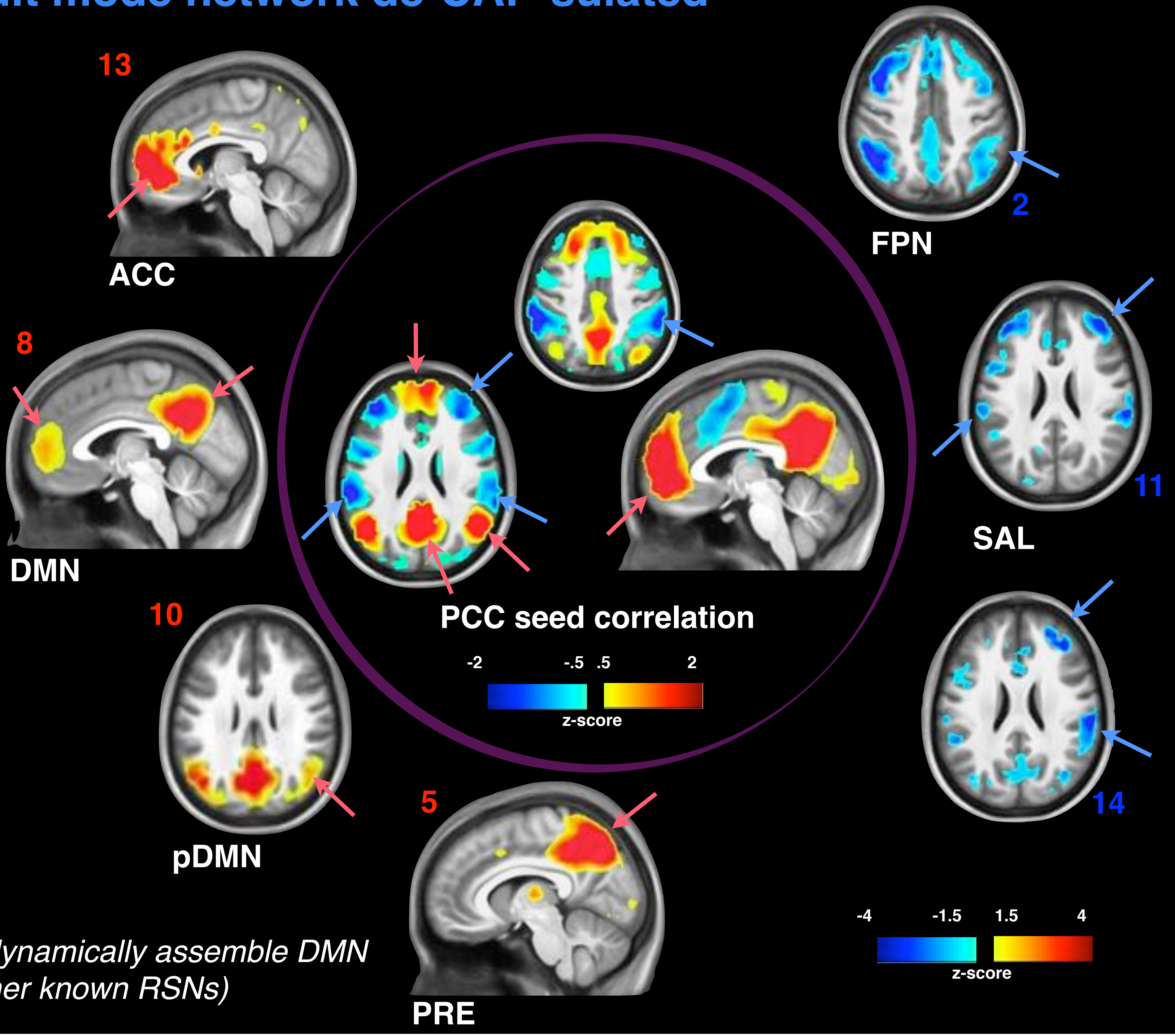
iCAP-8: "full" DMN, longest duration

Brain's repertoire of functional networks



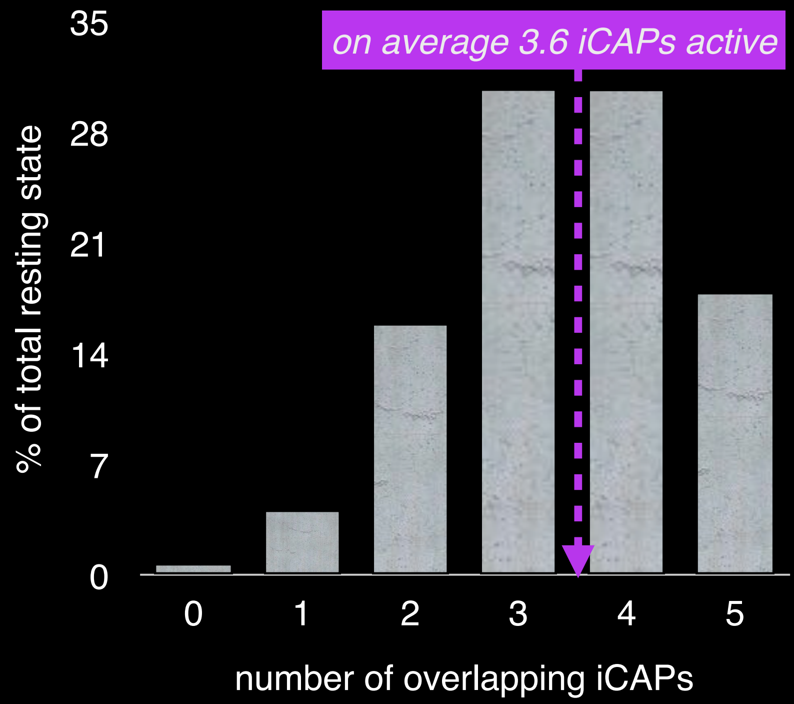
Access to subsystems of the default-mode network

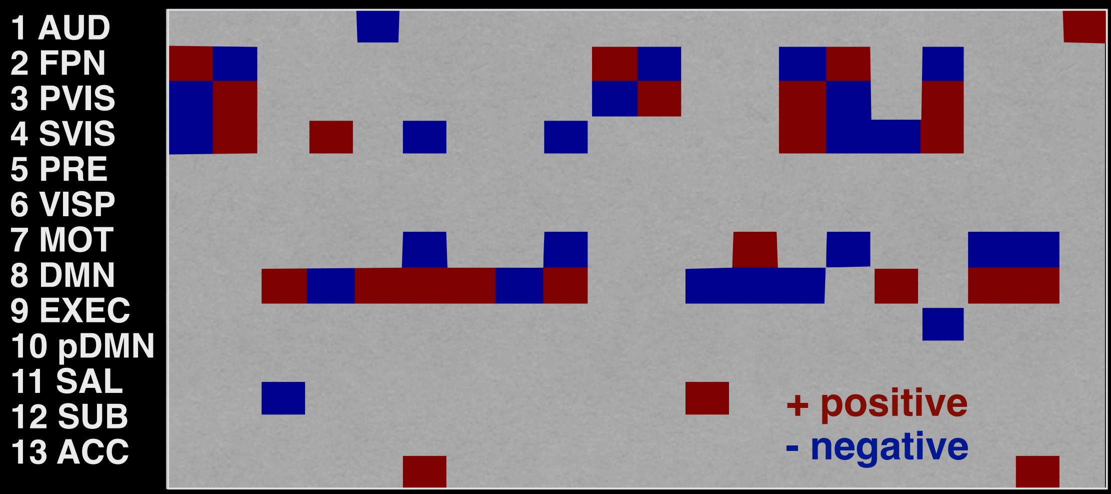
Default mode network de-CAP-sulated



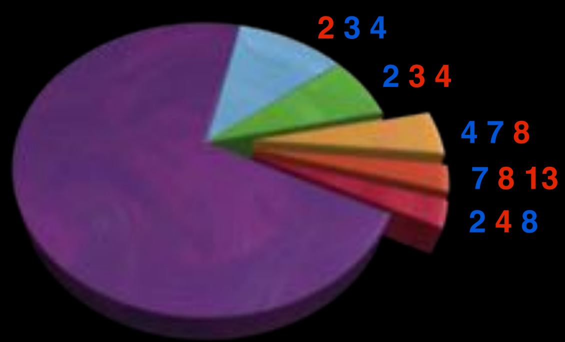
iCAPs dynamically assemble DMN (and other known RSNs)

Temporal overlap of iCAPs

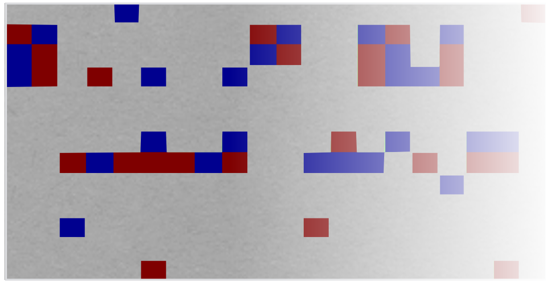




20 most frequent combinations

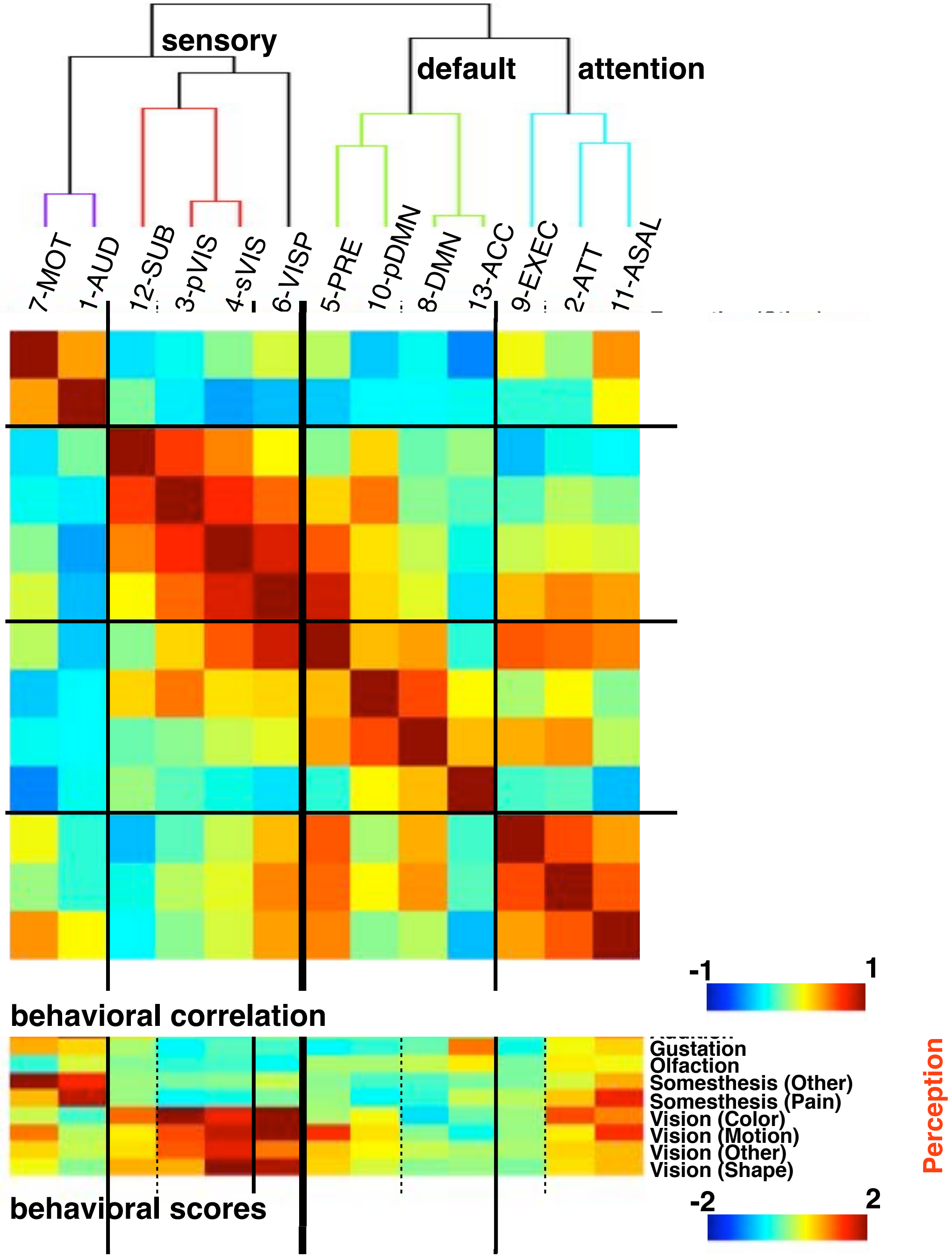


Relationship between iCAPs and behavior



2098 iCAPs combinations

hierarchical clustering

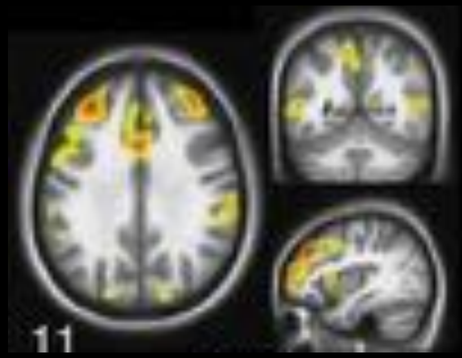


- Highest level of hierarchy: sensory / DMN / attention
- Behavioral profiles can be determined (BrainMap)
- ... and form consistent groupings as driven by iCAPs' combinations

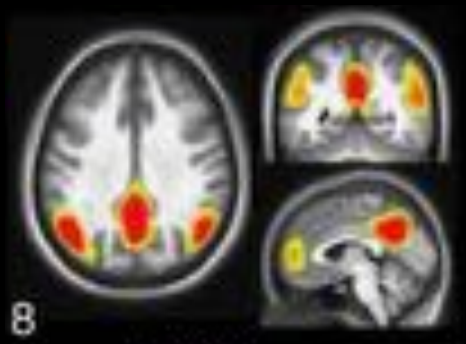
BrainMap:
[Lancaster et al, Frontiers Neuroinformatics, 2012]

Time to rethink our models?

Salience network

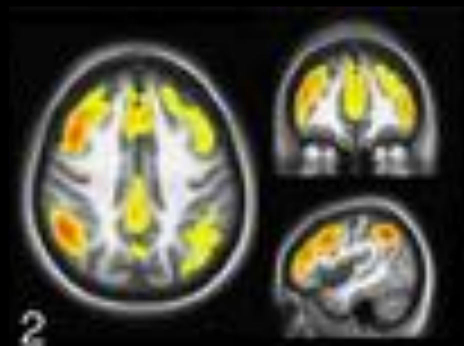


Default mode network



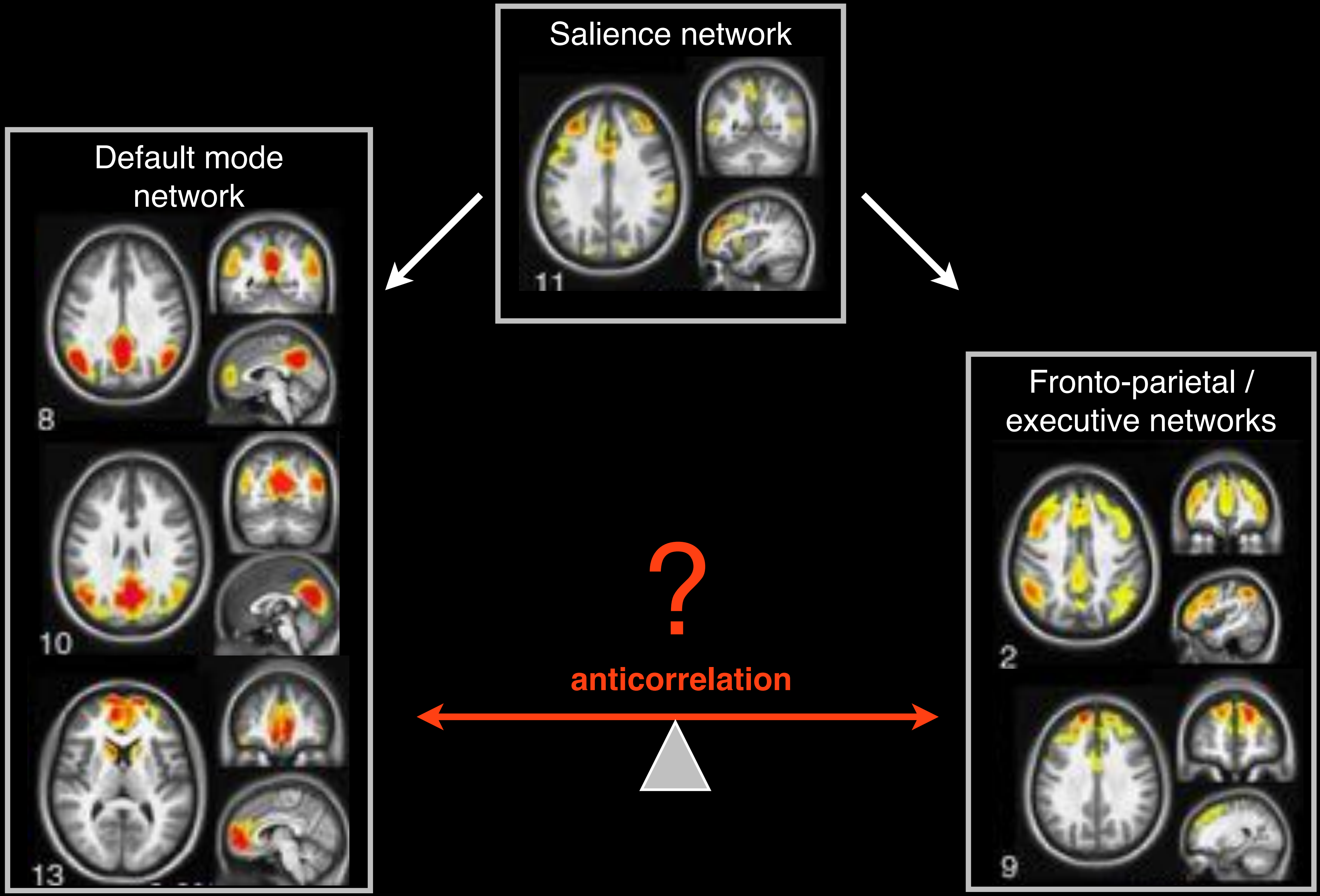
anticorrelation

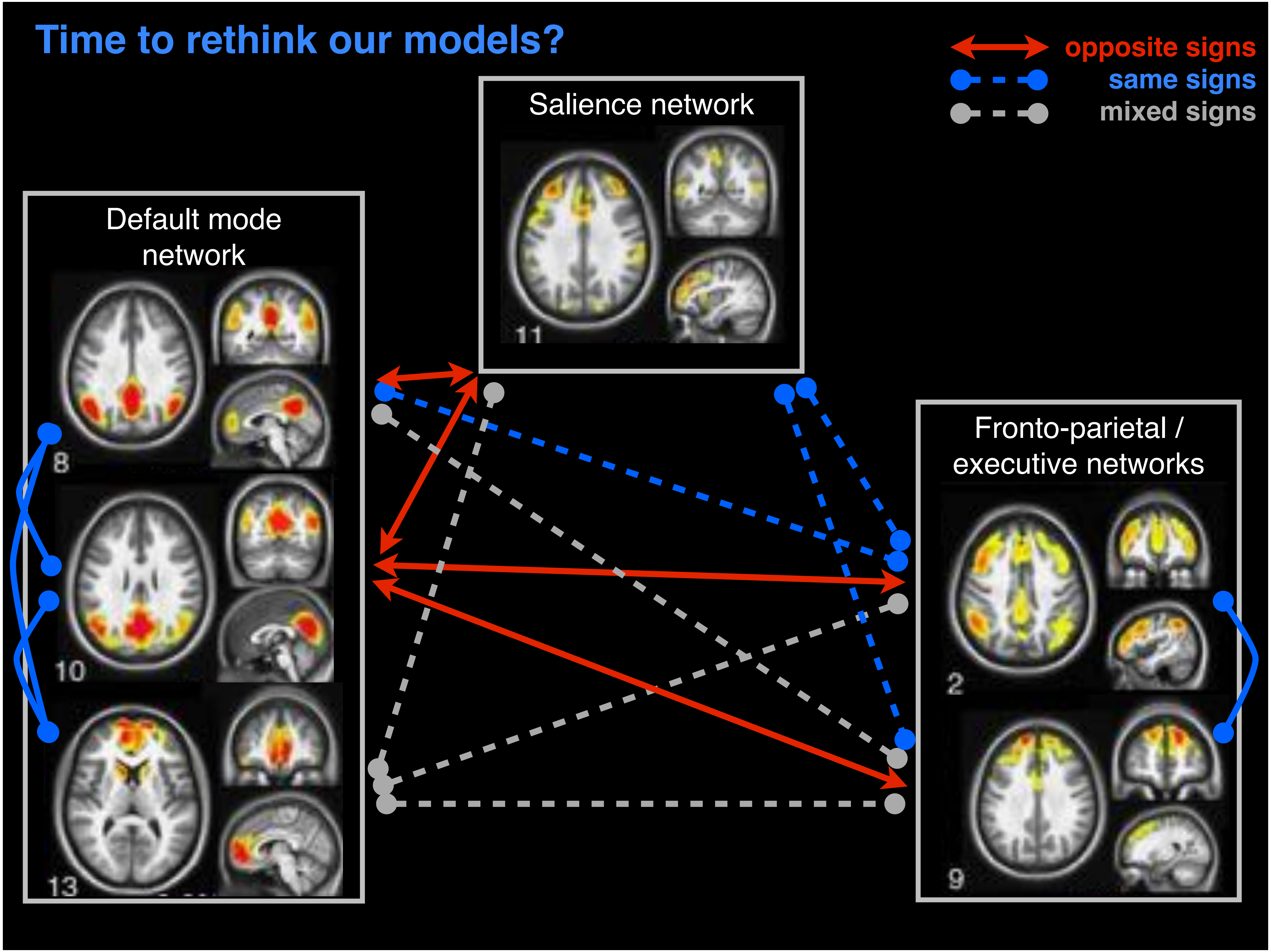
Fronto-parietal / executive networks



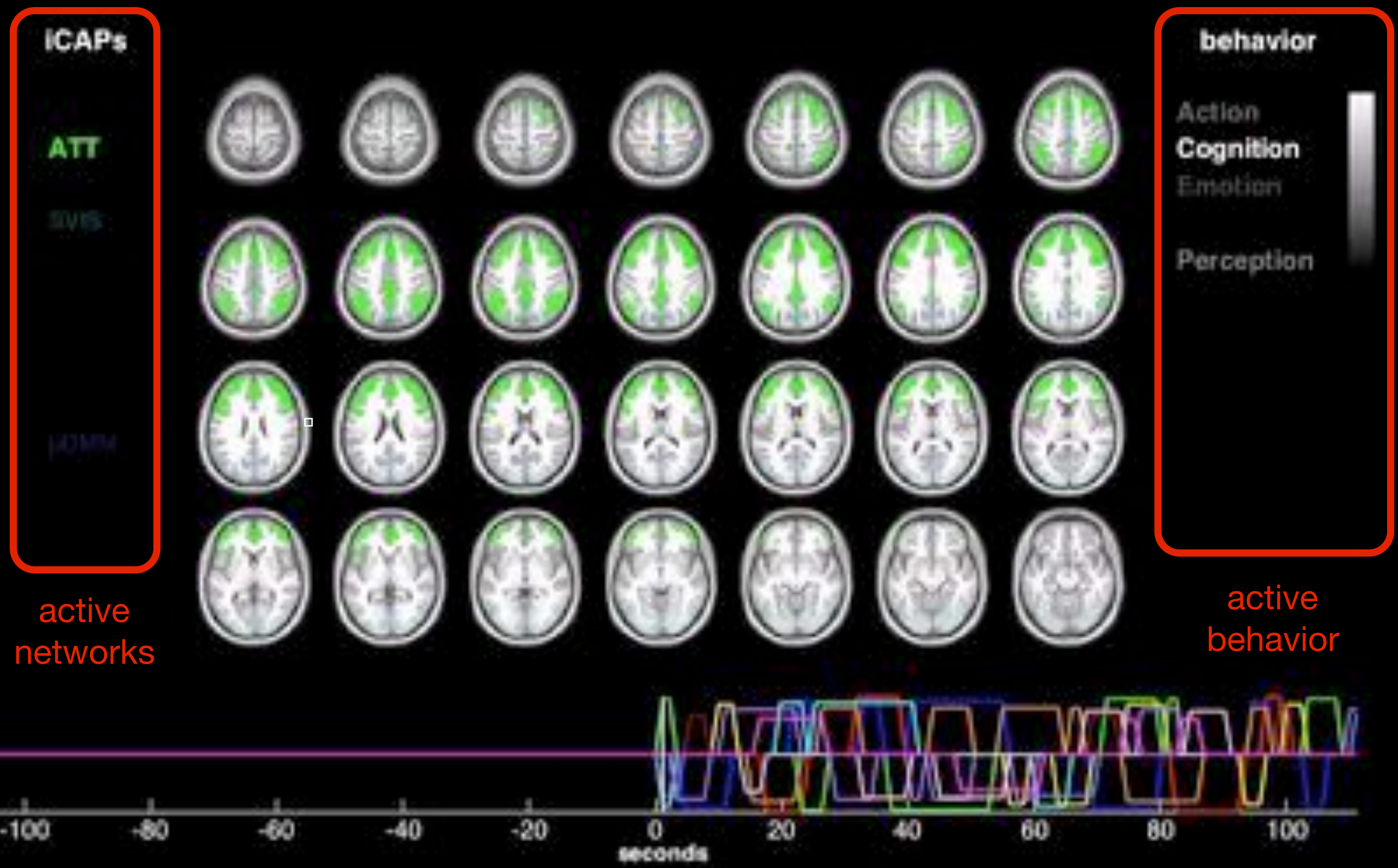
[Menon, Uddin, *Brain Struct Func*, 2010; Menon, *TICS*, 2011; Nekovarova et al, *Frontiers*, 2014]

Time to rethink our models?




Time to rethink our models?
opposite signs
same signs
mixed signs
Salience network
11
Default mode
network
8
10
13
Fronto-parietal /
executive networks
2
9

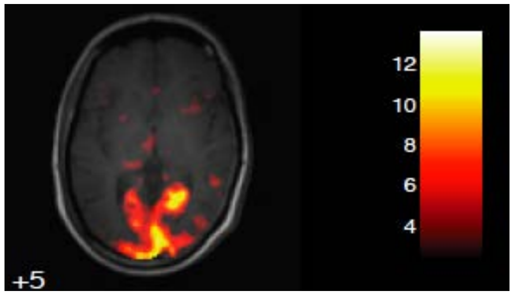
Unraveling crosstalk of ongoing spontaneous activity



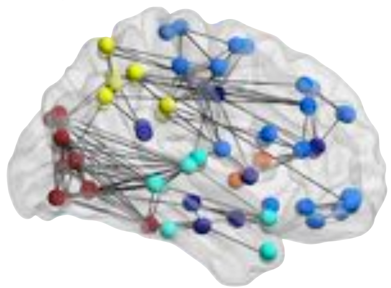
[Karahanoglu and VDV, *Nature Communications*, 2015]

Summary

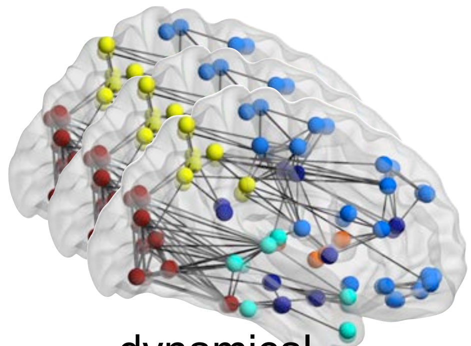
	activation mapping	functional connectivity mapping	dynamic functional connectivity mapping
objective	activation mapping	functional connectivity mapping	dynamic functional connectivity mapping
assumptions	experimental paradigm baseline is constant	baseline is fluctuating co-fluctuations are stable ("stationary")	co-fluctuations are unstable ("non-stationary")
methods	GLM	BSS (ICA,...), seed connectivity, graph analysis	sliding-window FC, point process analysis, CAPs, iCAPs,...
outcome	activation maps	networks	dynamical networks



activation maps



networks



dynamical networks

Take home message

- Seeing the brain in action, at any *moment*, and *systems* level
  - *Multidisciplinary* endeavor where *computational* approaches are essential
  - Understand how it all fits together
- Perspectives
  - Tracking of brain states
    - Naturalistic stimuli and tasks
    - Neurofeedback
    - Graph signal processing: connect function (signal) with structure (graph)
  - Towards new models and markers of brain (dys)function
    - Benefit from “big MRI data” in health and disease

Two recent review papers

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The dynamic functional connectome: State-of-the-art and perspectives

CrossMark

Maria Giulia Preti[a,b,*,1], Thomas AW Bolton[a,b,1], Dimitri Van De Ville[a,b]

[a] *Institute of Bioengineering, Center for Neuroprosthetics, Ecole Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland*
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Biomedical Engineering

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Dynamics of large-scale fMRI networks: Deconstruct brain activity to build better models of brain function

Fikret Işık Karahanoğlu[a,b] and Dimitri Van De Ville[c,d]

MIP:lab @ Campus Biotech

http://miplab.epfl.ch

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