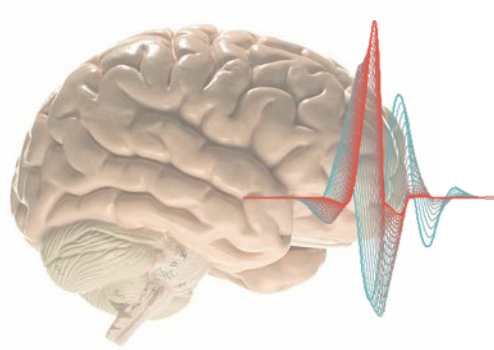

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The Big Neuroimaging Data Extraction:
How Advanced Signal Processing Can Unravel the Brain's Functional Organization

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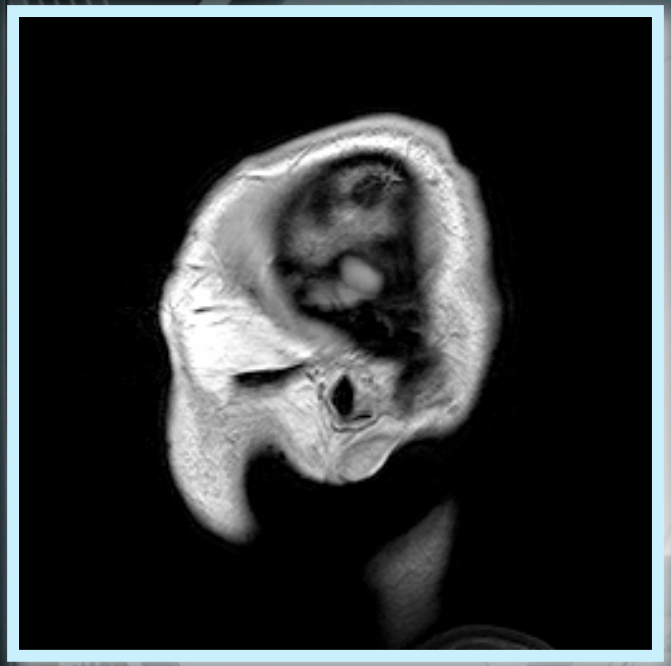
Washington DC / December 8, 2016 / IEEE GlobalSIP

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

Structural MRI



- Single 3D volume
  - 1x1x1 mm^3
  - takes couple of minutes

Functional MRI

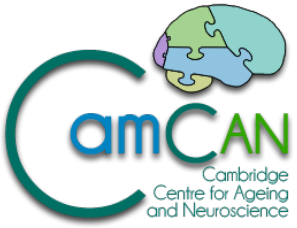
- Series of 3D volumes
  - 2x2x2 mm^3
  - 30-60 slices
  - every 1-3 sec
  - during 5-10 minutes

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

Big data in human MRI

- ... is a fact!

International Neuroimaging
Data-Sharing Initiative



Autism Brain Imaging
Data Exchange

Big data in human MRI

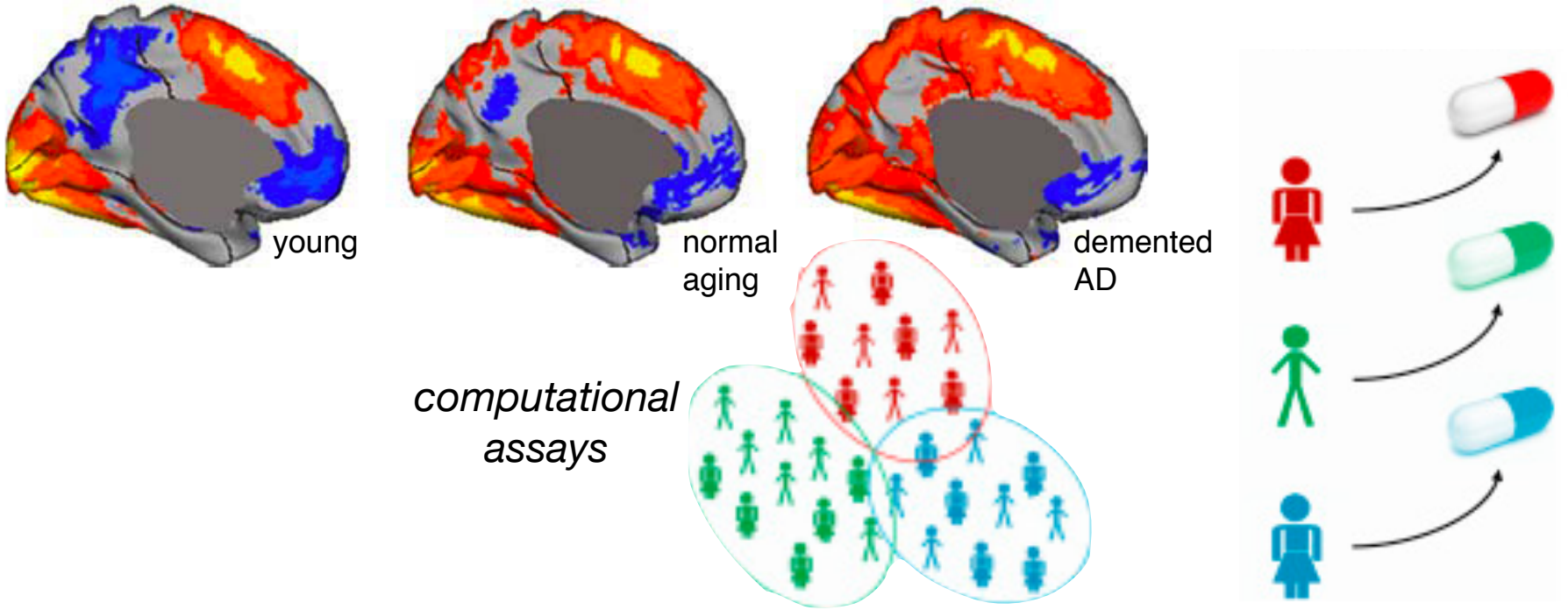
Resource	Sites	Subjects	Size	Population	sMRI	DWI	tfMRI	rfMRI
1000 func connectomes	35	1.355	~240GB	HC	x			x
ABIDE	20	1.112	~200GB	HC, ASD	x			x
ABIDE II NEW Jun 2016	17	1.144	~200GB	HC ASD	x			x
ADHD-200	8	776	~160GB	HC, ADHD	x			x
ADNI	59	758	~100GB	HC,MCI,AD	x			
ADNI 2	63	850	~800GB	HC,MCI,AD	x	x		x
BIRN	10	285	~30GB	HC, SZ	x			
Cam-CAN NEW Nov 2016	1	653	~1TB	HC	x	x	x	x
HCP	2	900	52TB	HC	x	x	x	x
Other INDI retrospective	8	568	~1TB	HC,EP,SZ,COC	x	x	x	x
Other INDI prospective	8	467	~500GB	HC	x	x		x
NKI-RS	1	921	1.2TB	HC	x	x	x	x
OASIS	2	566	70GB	HC,AD	x			
OpenfMRI	55	1.941	~2TB	HC,SZ	x	x	x	
ABCD Project	21	10.000		HC (9-10y)	x	x	x	x
UK Biobank		10.000		HC	x	x	x	x

- Open data of thousands of subjects!...

Adapted and updated from [Poldrack and Gorgolewski, Nature Neuroscience, 2014]

Big challenge is knowledge extraction

- Beyond normative models: human diversity
  - Discovery of how brain anatomy & function supports cognition, consciousness,...
  - Biomarker development for brain disease & disorder
    - Early & differential diagnosis, prognosis
    - Identification and stratification into subtypes

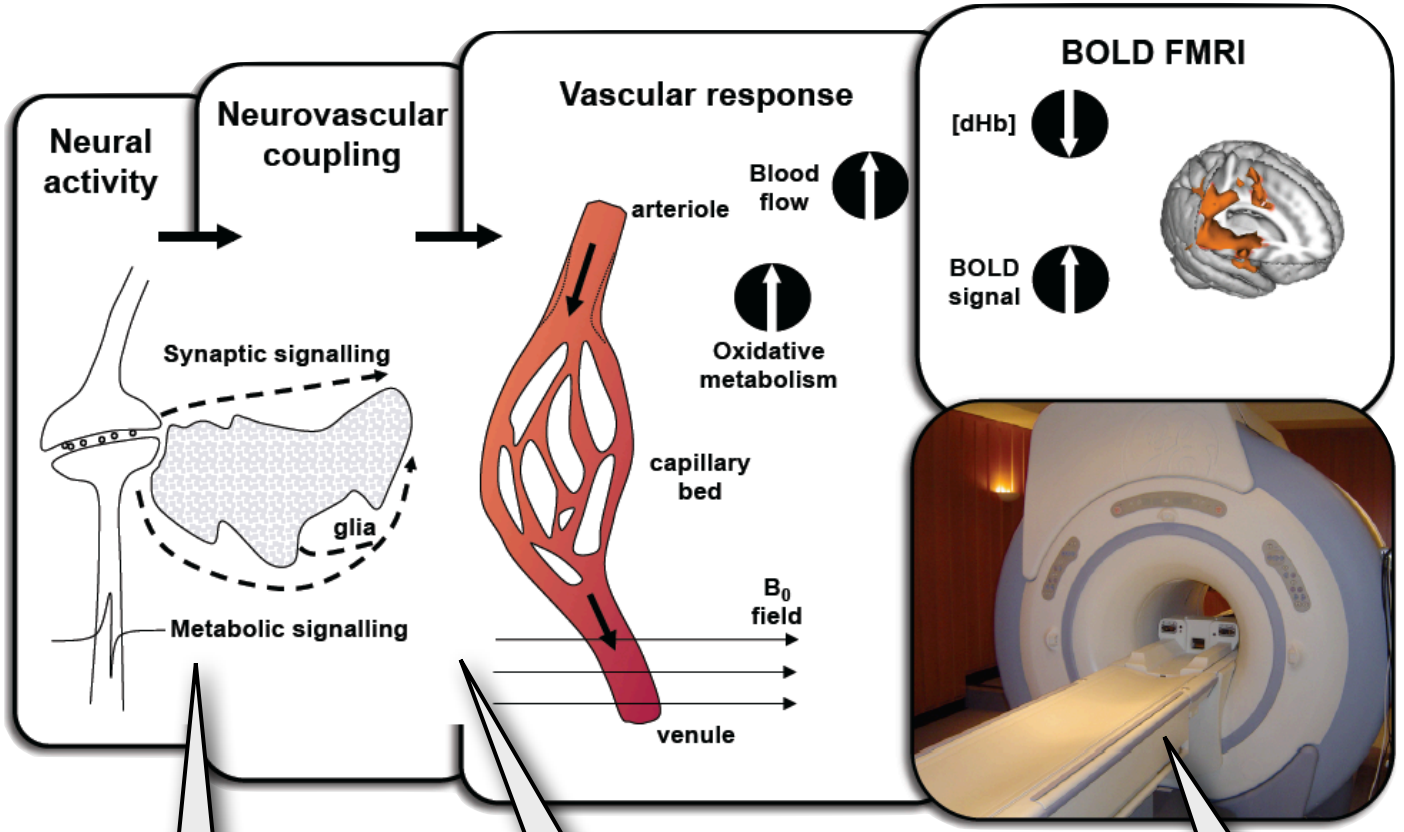


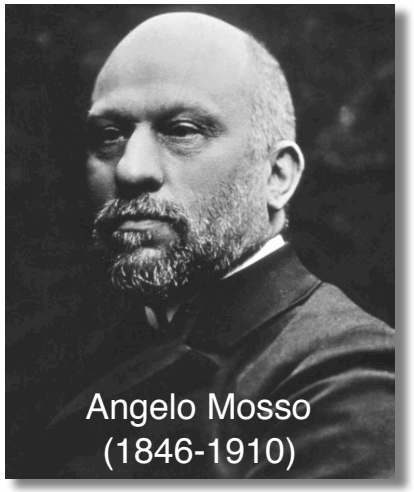
[Chen et al, 2009; Stephan et al, 2015; Lustig et al, 2003; Greicius, 2004]

Big challenge is knowledge extraction

- Beyond normative models: human diversity
  - Discovery of how brain anatomy & function supports cognition, consciousness,...
  - Biomarker development for brain disease & disorder
    - Early & differential diagnosis, prognosis
    - Identification and stratification into subtypes
- Functional MRI provides unique non-invasive window on the brain at work
  - Since 1991
  - 30’000 papers
    - 4’400 last year
  - “software that runs on the hardware” ~ dynamics!

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





Neurons are active: metabolic demand at synapses

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

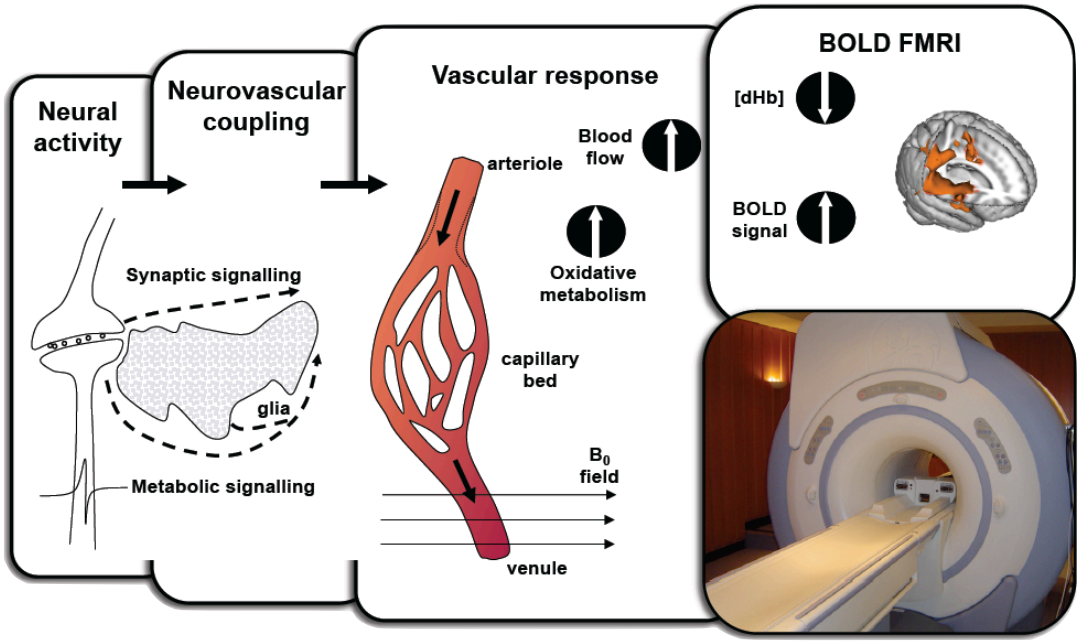
Oxygen is carried by hemoglobin in RBCs

Increase of ratio in oxygenated/deoxygenated hemoglobin

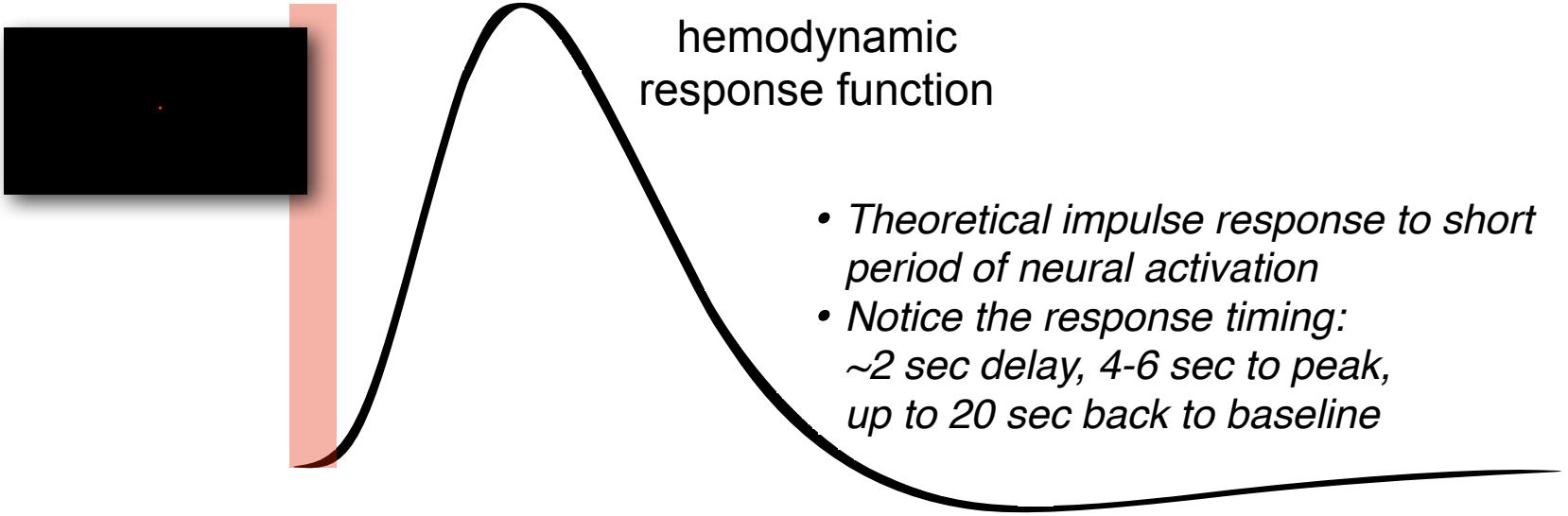
Deoxygenated Hb is paramagnetic and drives BOLD signal

[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

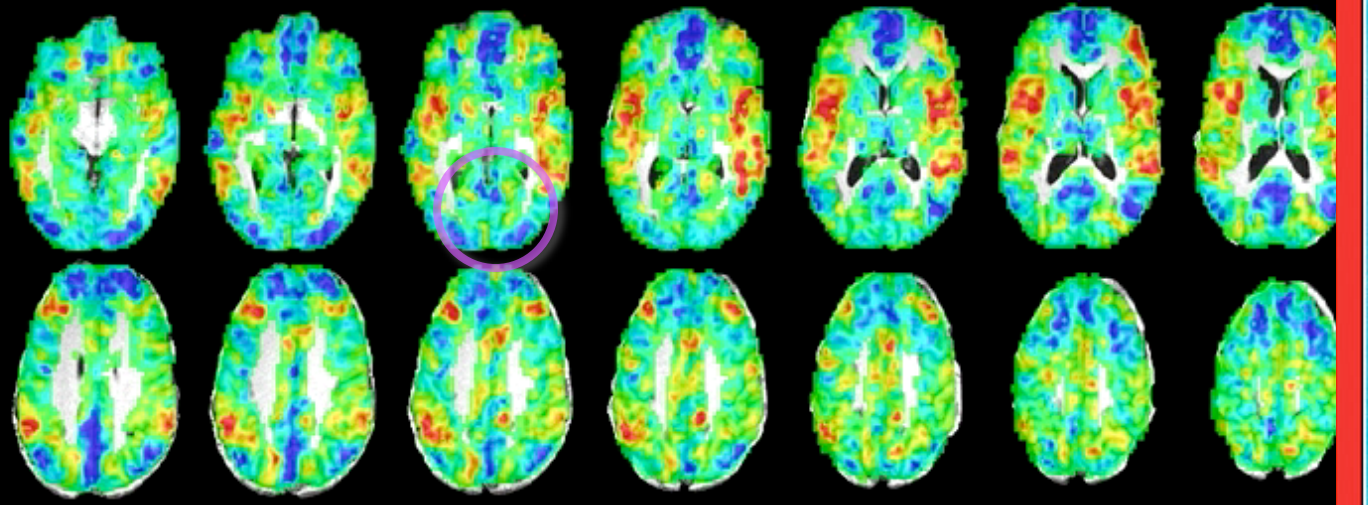


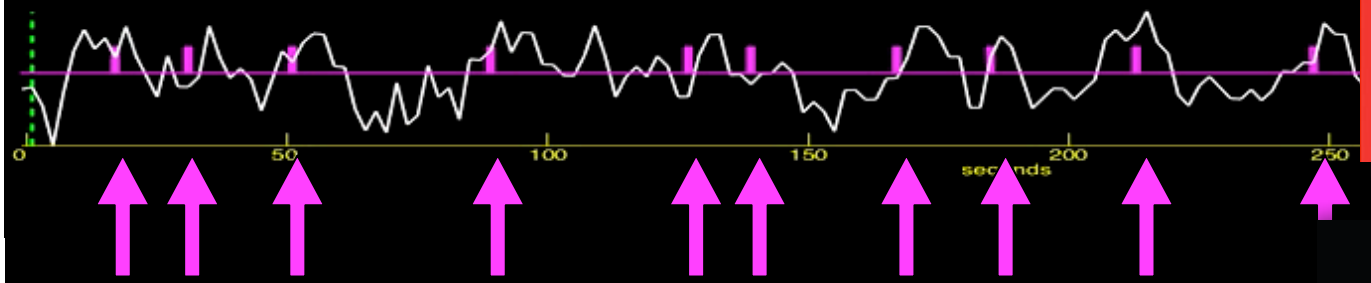
- *Theoretical impulse response to short period of neural activation*
- *Notice the response timing: ~2 sec delay, 4-6 sec to peak, up to 20 sec back to baseline*

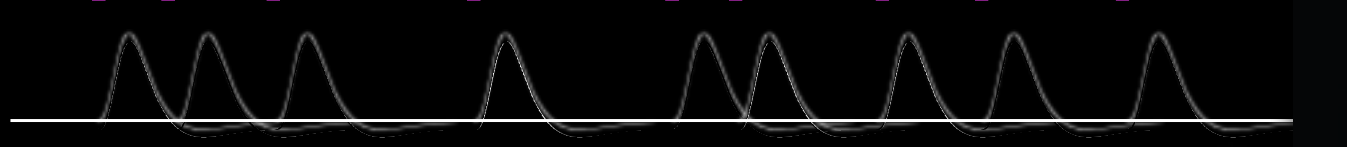
[Buxton et al 1997; Friston et al. 1998, 2000; Iannetti & Wise, 2007]

fMRI of evoked activity

min 0 max

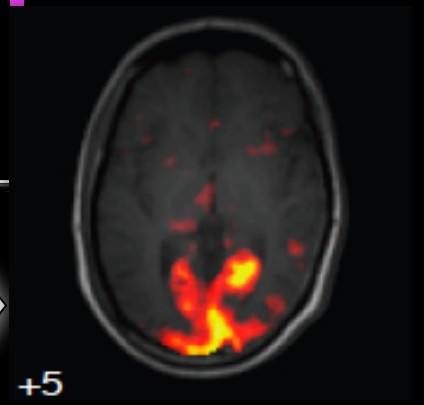


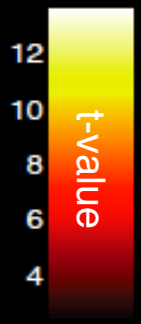




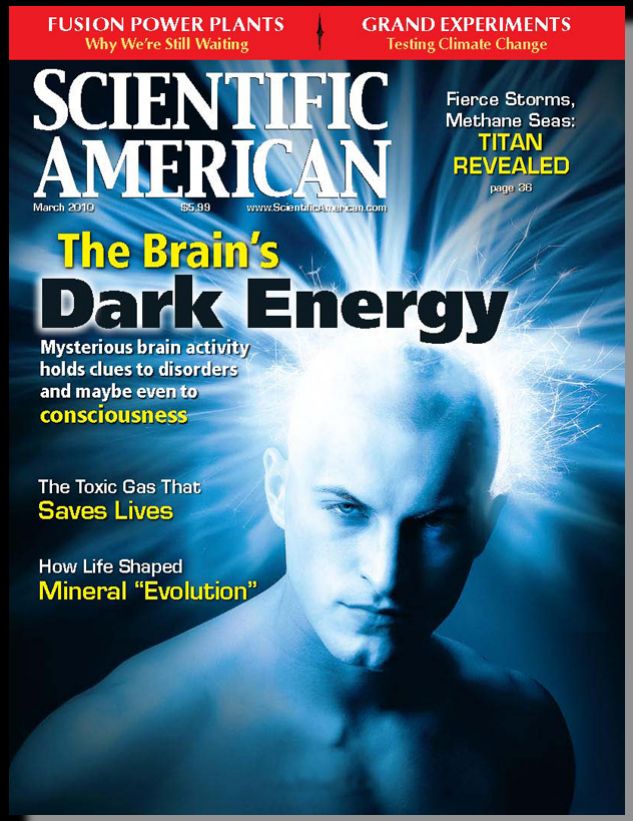
movie accelerated 4 times

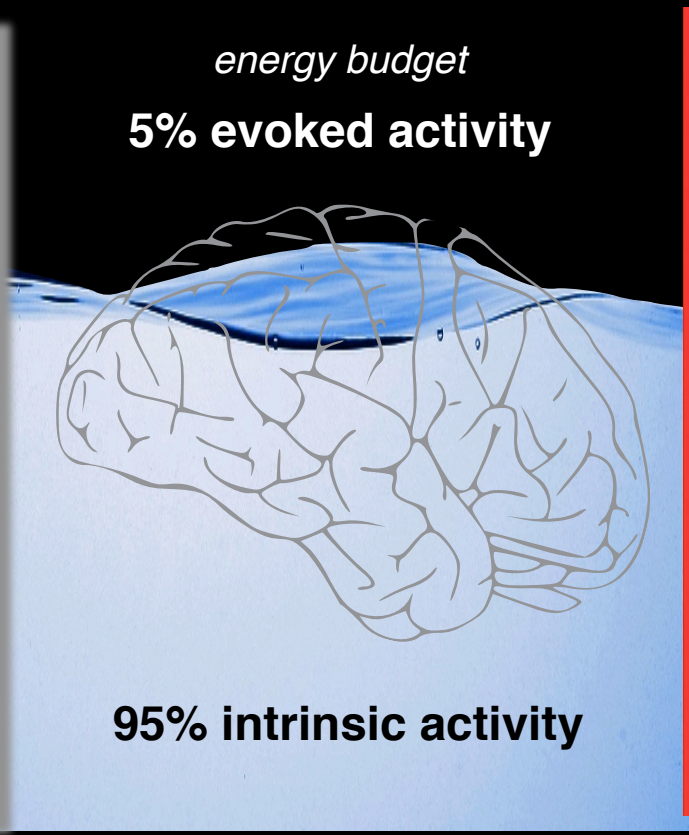
statistical processing





fMRI of evoked and intrinsic activity



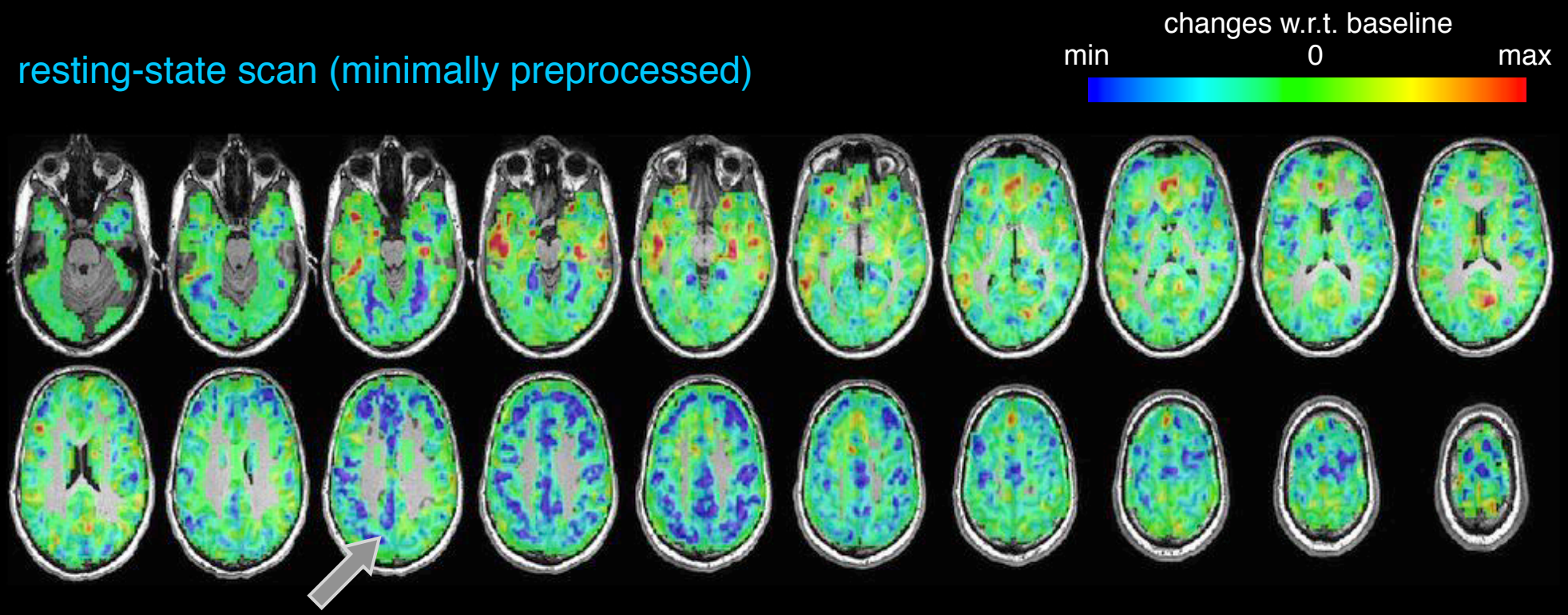


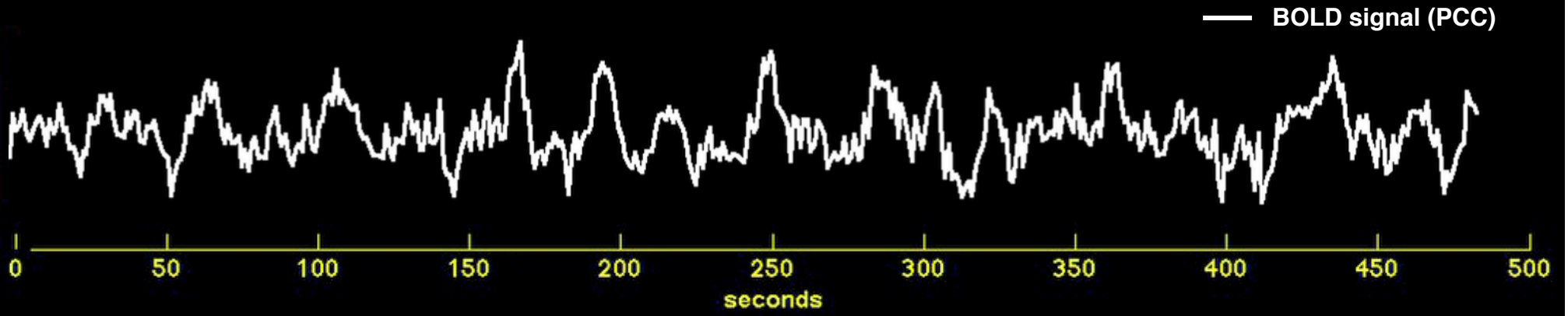
"the brain is active even in the absence of task, primarily driven by internal dynamics, with external events *modulating* rather than *determining* the activity of the system"

[Fox et al., 2006]

fMRI of spontaneous activity

resting-state scan (minimally preprocessed)

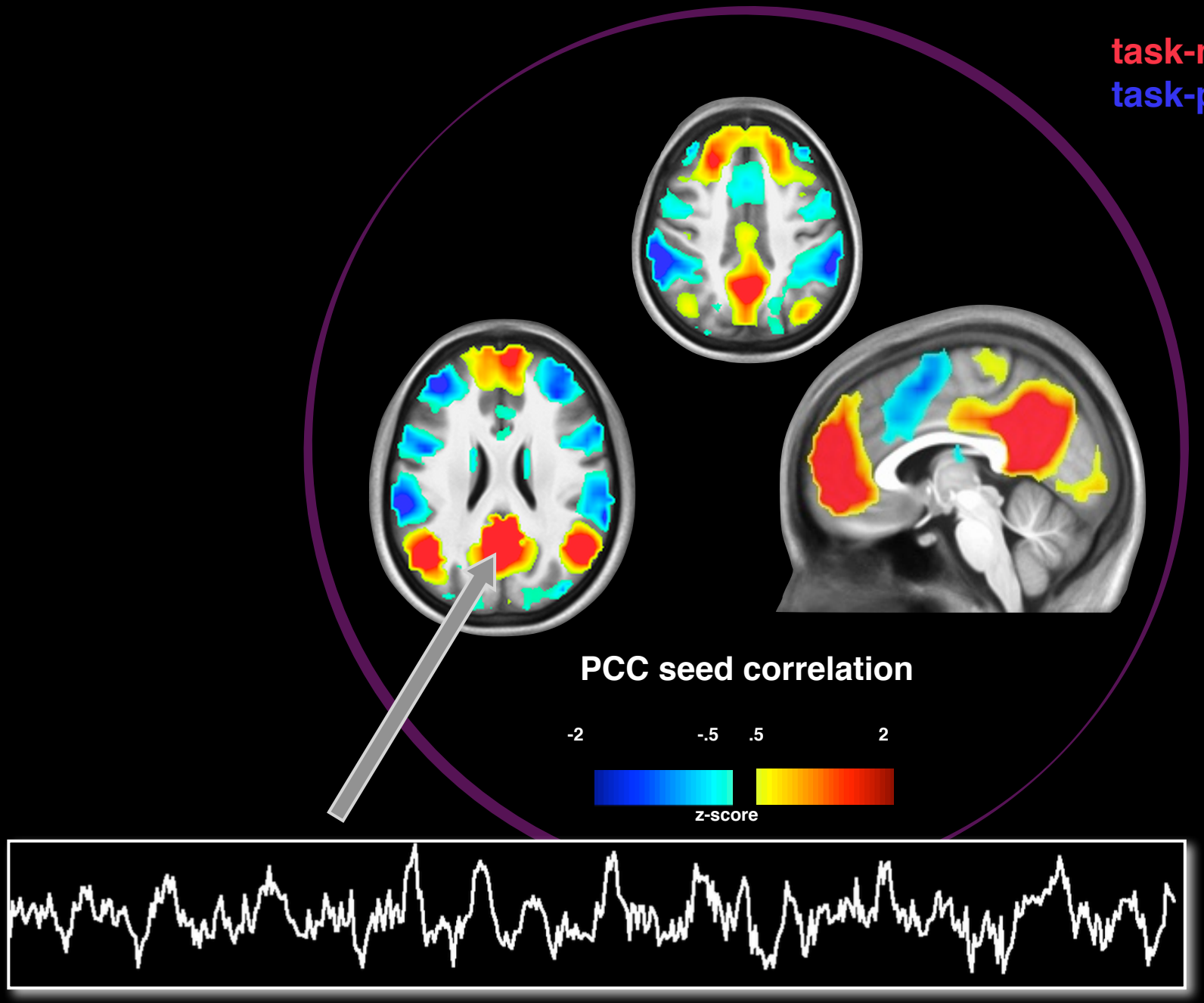




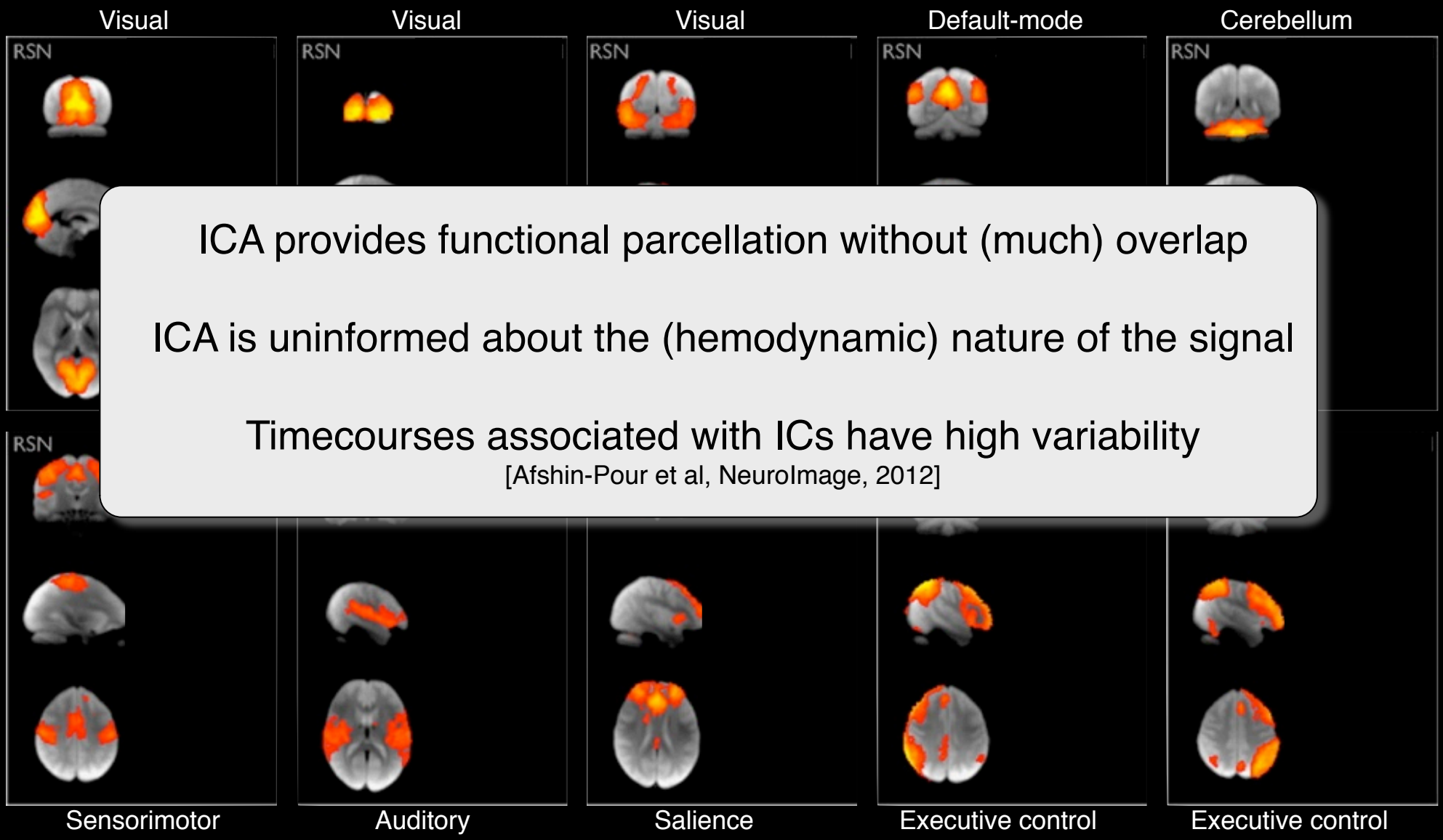
movie accelerated 4 times

minimal compliance!

PCC connectivity: task-positive and task-negative networks



Resting-state/intrinsic networks by (spatial) ICA



ICA provides functional parcellation without (much) overlap

ICA is uninformed about the (hemodynamic) nature of the signal

Timecourses associated with ICs have high variability

[Afshin-Pour et al, NeuroImage, 2012]

[Smith et al., 2009]

A case to account for spatial and temporal overlap

"The human association cortex consists of multiple, interdigitated large-scale networks, that, while partially overlapping, possess predominantly parallel organization.

...

Our (essential) correlational analyses will miss vital details of dynamics of network interactions."

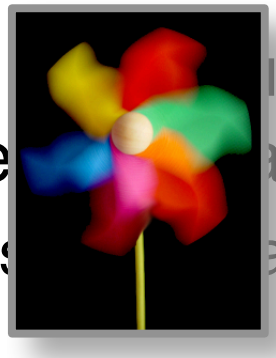
B.T. Thomas Yeo et al, NeuroImage, 2014

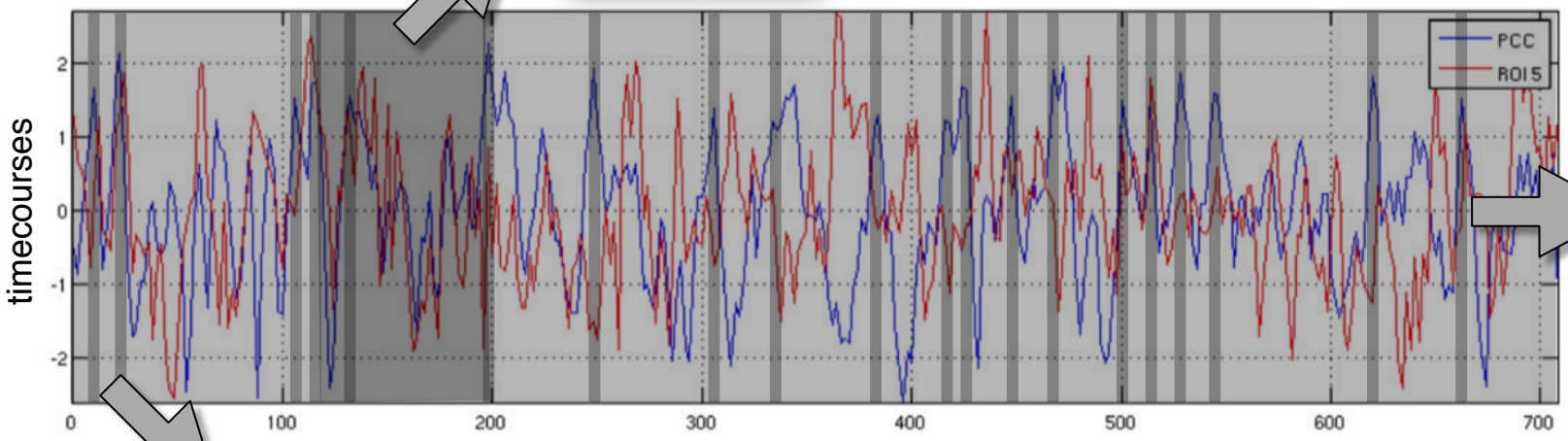
Towards capturing dynamics

- Correlational techniques establish a summary statistic over whole resting state scan
  - implicitly assume stationary behavior

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

[Chang and Glover, 2010; Allen et al, 2014; Leonardi et al, 2014]





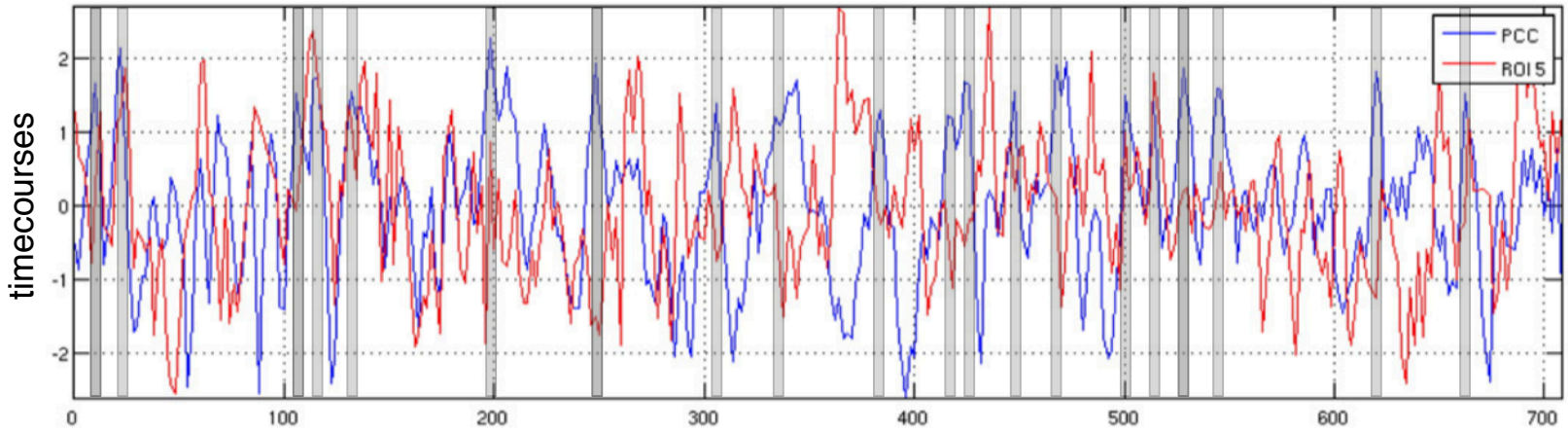
can we extract 'key points' that capture the important events?

[Tagliazucchi et al., 2012]

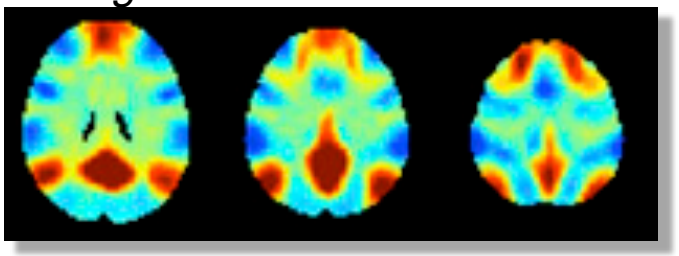
statistical dependencies characterize "average" behavior during resting state

Co-activation patterns

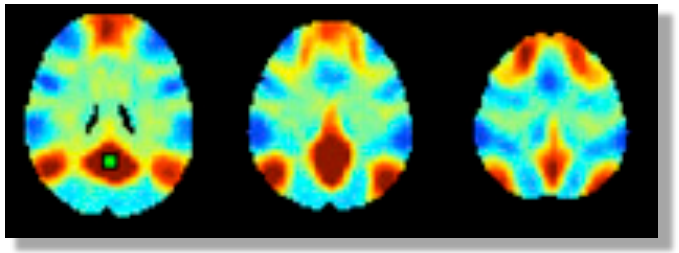
- Averaging of all spatial activity patterns leads to proxy for seed connectivity



average over all selected frames:



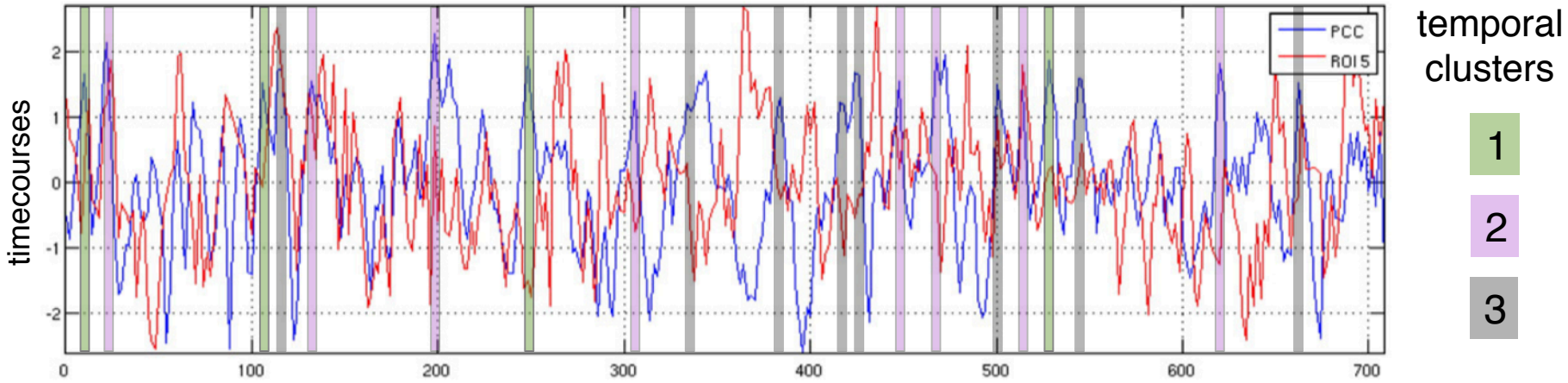
seed-based correlation:



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

Co-activation patterns

- Temporal clustering of selected frames for extreme values of a **seed region**

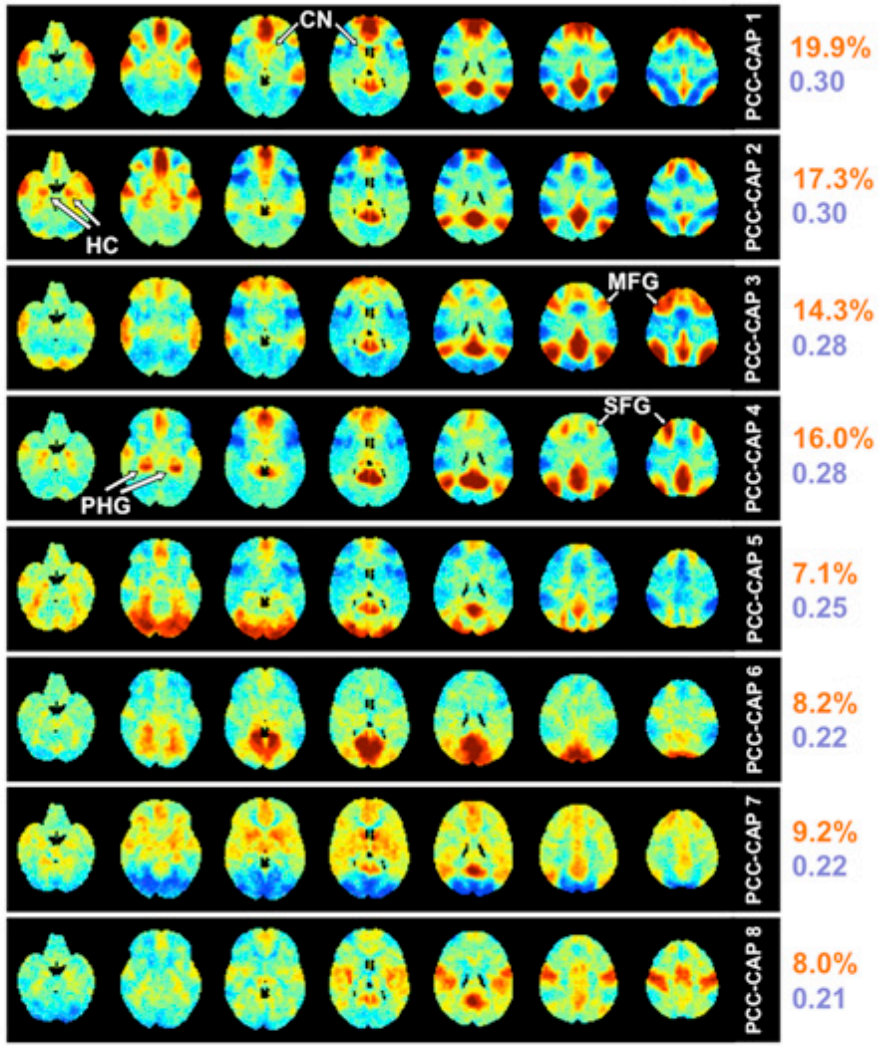


- Averaging of spatial activity patterns for each temporal cluster leads to “co-activation pattern” (CAP)

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

Co-activation patterns

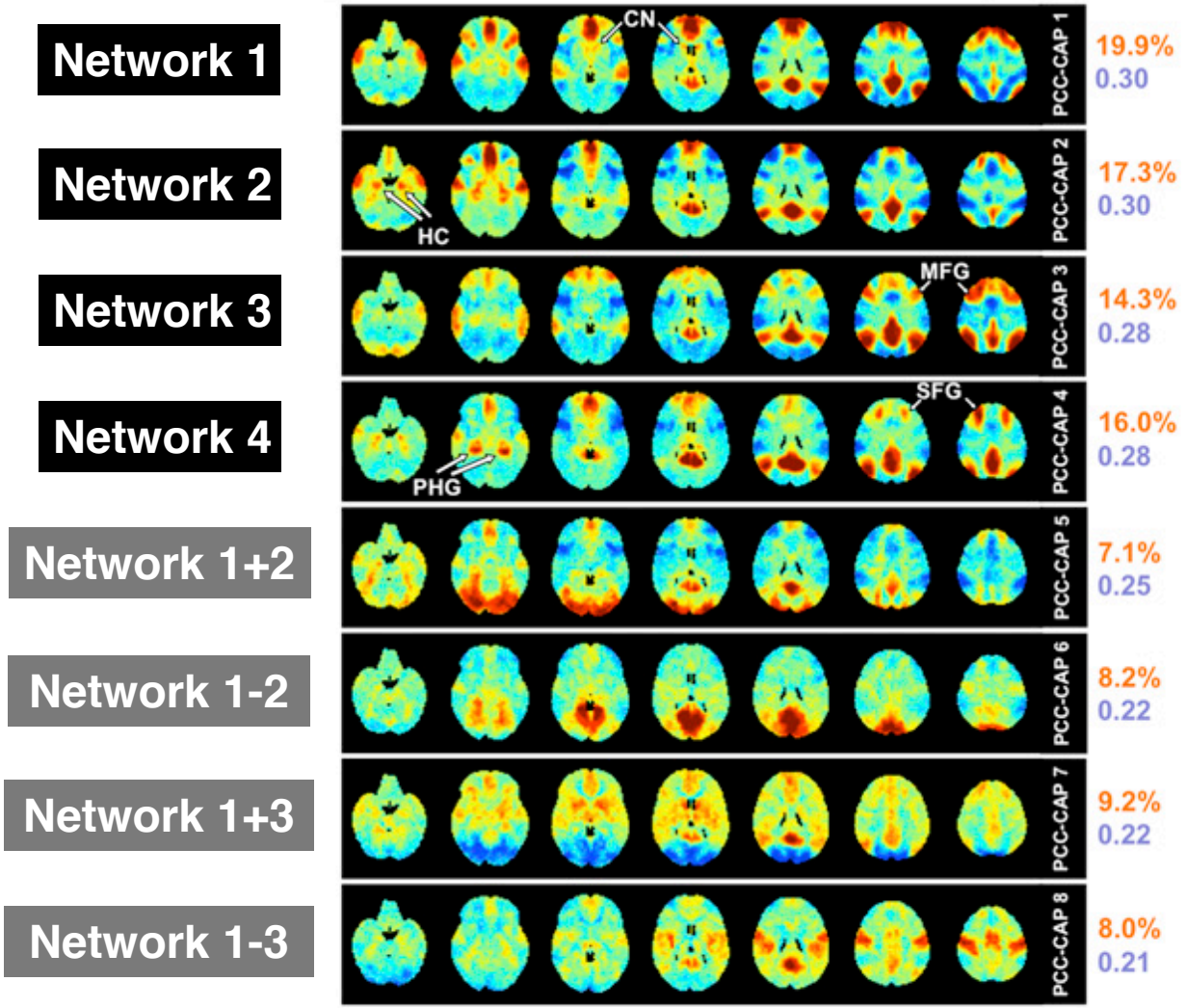
- Averaging of spatial activity patterns within temporal clusters lead to “co-activation patterns” (CAPs)



[Liu and Duyn, *PNAS*, 2013; Liu, Chang, Duyn, *Frontiers in Systems Neuroscience*, 2013]

Co-activation patterns

- Averaging of spatial activity patterns within temporal clusters lead to “co-activation patterns” (CAPs)
  - Does not disentangle temporal overlap!
  - Contaminated by non-seed related activity

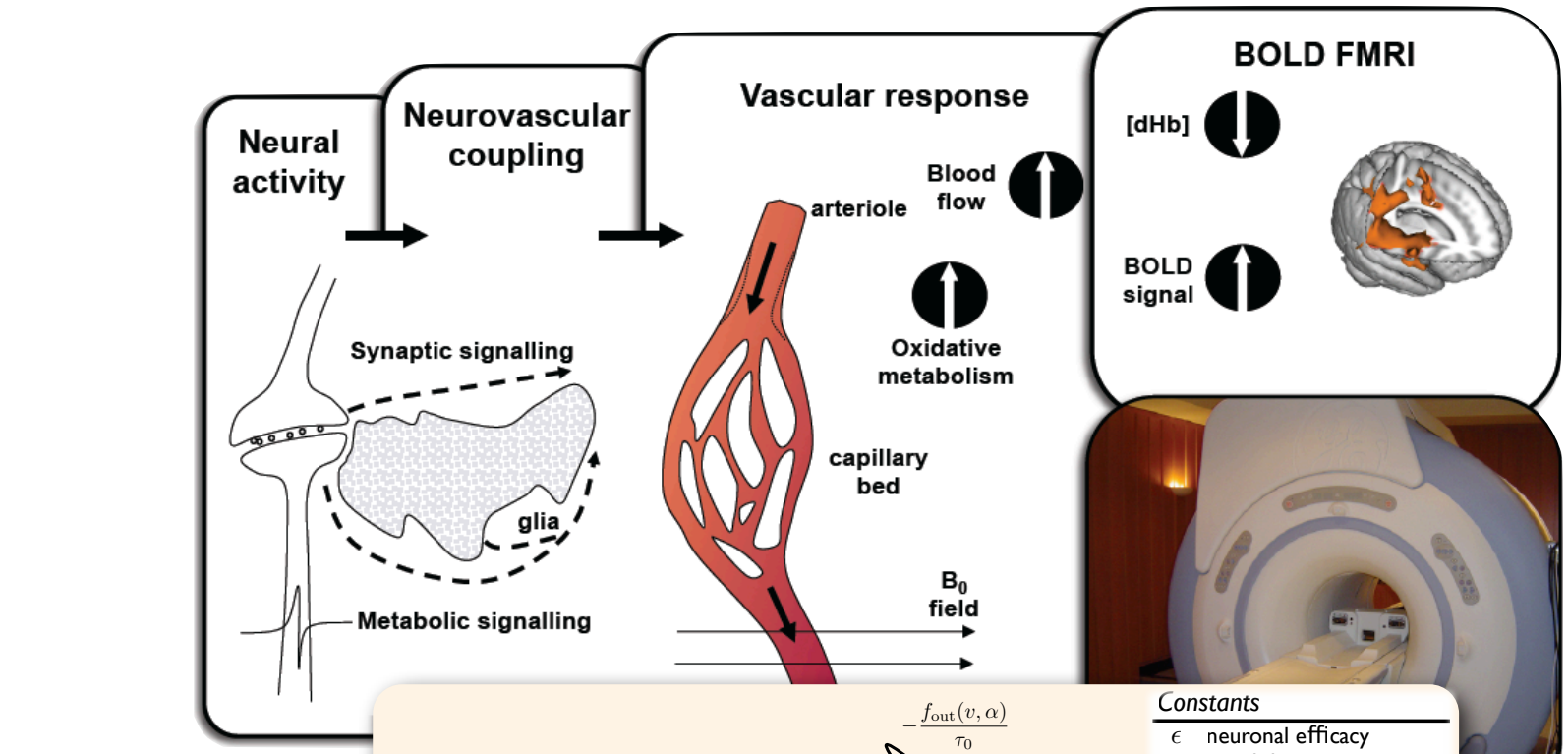


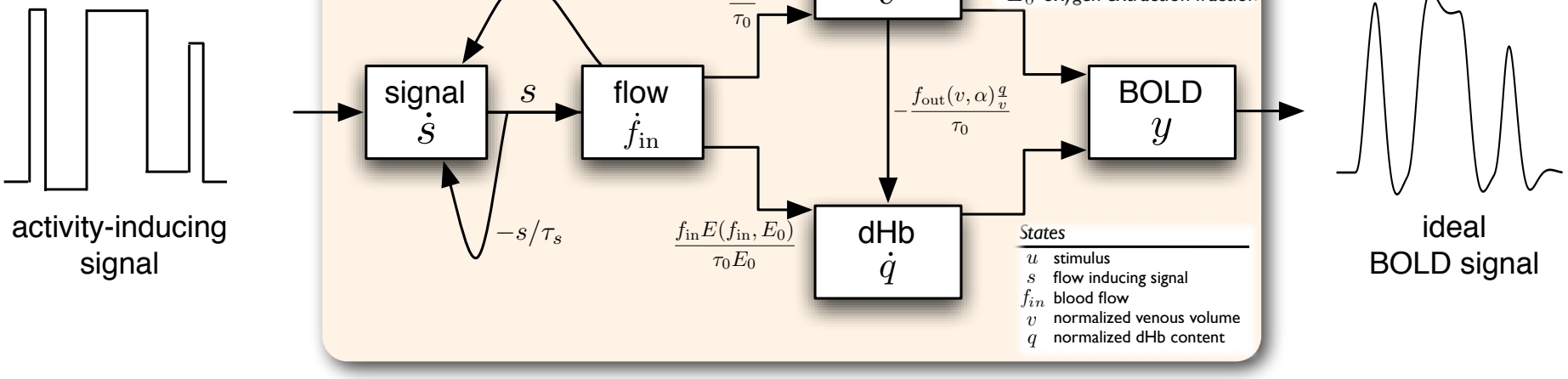
[Liu and Duyn, *PNAS*, 2013; Liu, Chang, Duyn, *Frontiers in Systems Neuroscience*, 2013]

Towards capturing dynamics

- For “sharper” dynamics, we propose a novel framework:
  - Incorporate knowledge about the hemodynamic system
    - Getting from activity-related to activity-inducing signal (*deconvolution*)
  - Assumption that underlying activity-inducing signal is of the “block type”
    - *Consists of moments of sustained activation and de-activation*
  - Avoid constraints on
    - Temporal overlap of components’ timecourses
    - Spatial overlap of components’ maps

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





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

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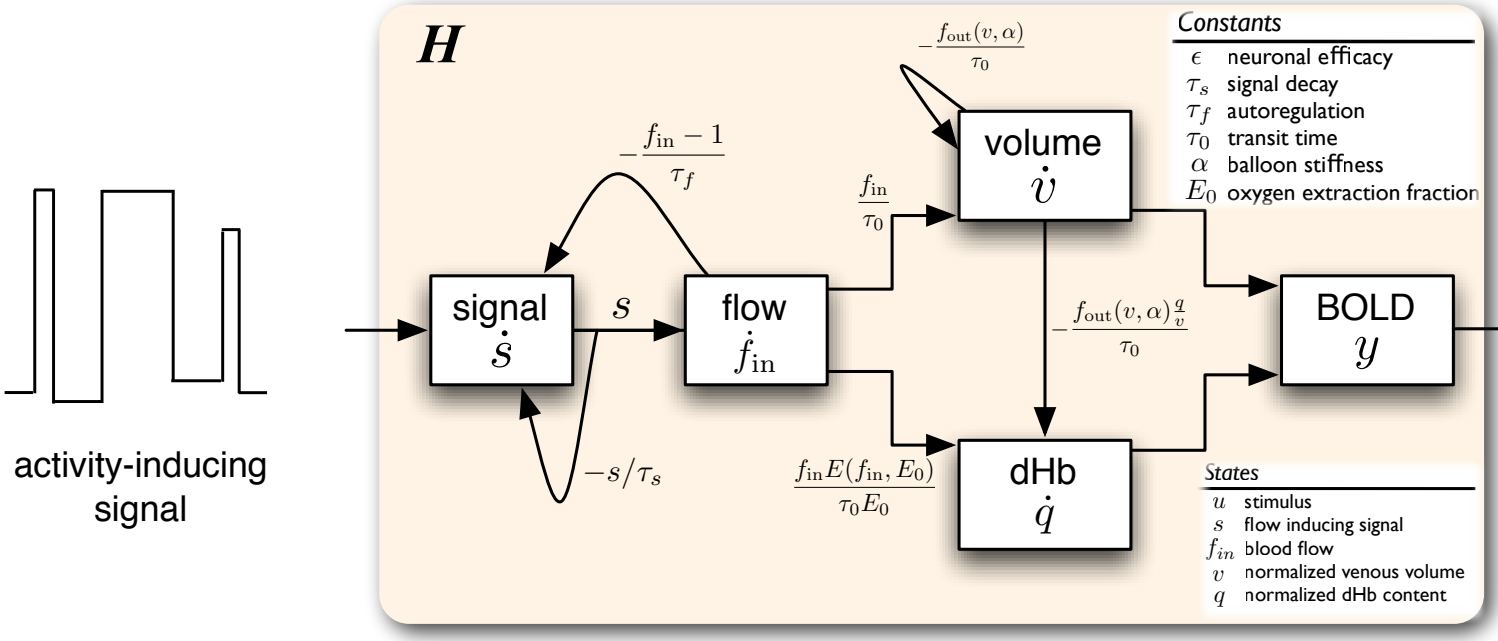


activity-inducing signal

ideal BOLD signal

noise

measured BOLD signal

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

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

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

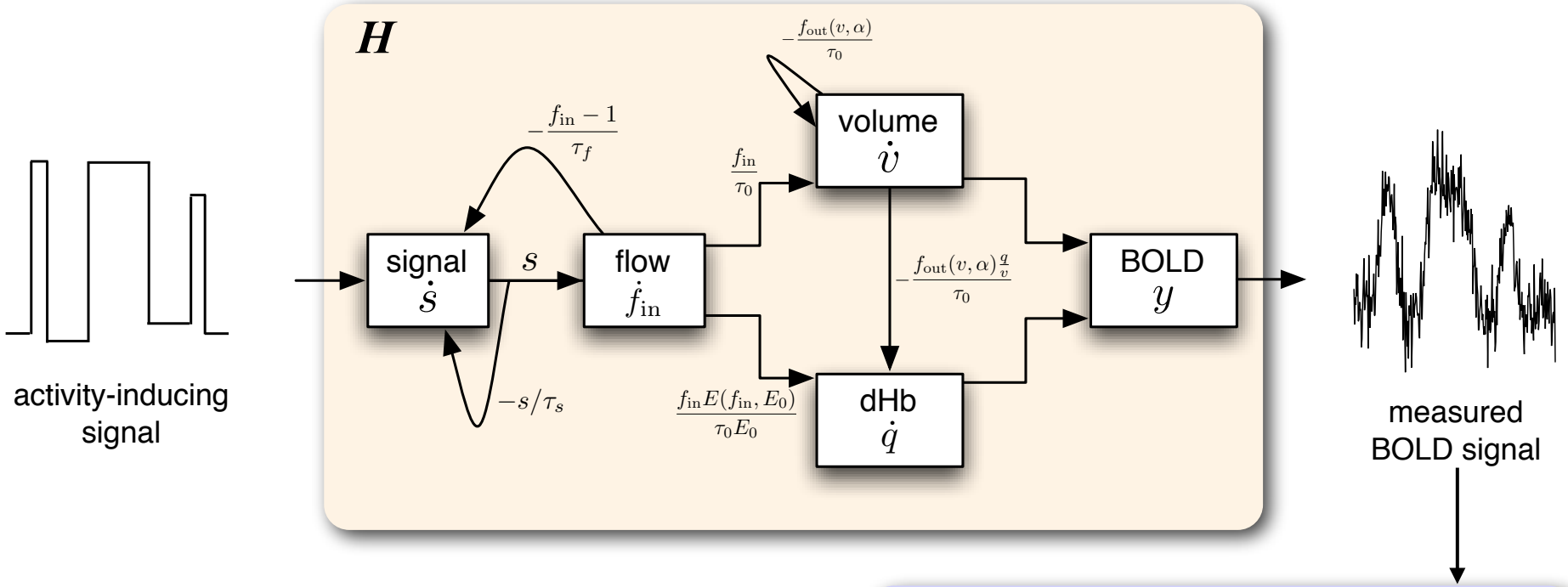
$$\vec{\gamma} = \left\{ \frac{(k_1 + k_2)(\frac{1-\alpha}{\alpha\tau_0} - \frac{c}{\alpha}) - (k_3 - k_2)\frac{1}{\tau_0}}{-(k_1 + k_2)c\tau_0 - k_3 + k_2} \right\}.$$

thou canst not recover what is lost

filtered signal

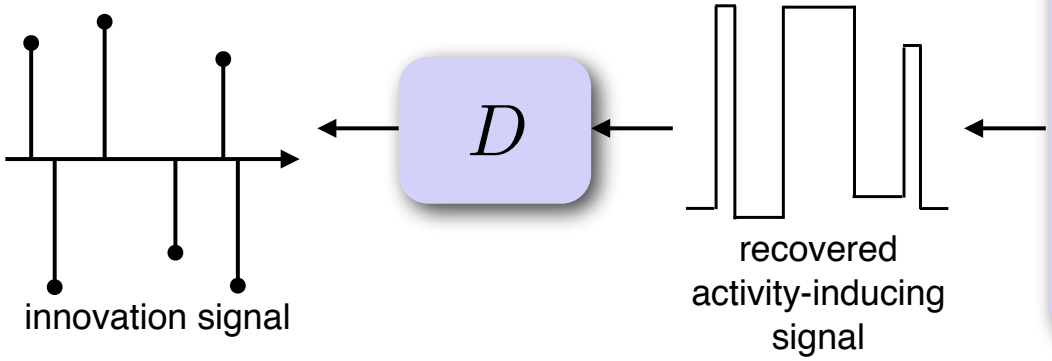
[Khalidov, VDV et al, *IEEE Transactions on SP*, 2011; Karahanoglu, VDV et al, *NeuroImage*, 2013]

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



- Total activation regularization:

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



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

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

BOLD is full of innovation

measured signal in posterior cingulate cortex (PCC)

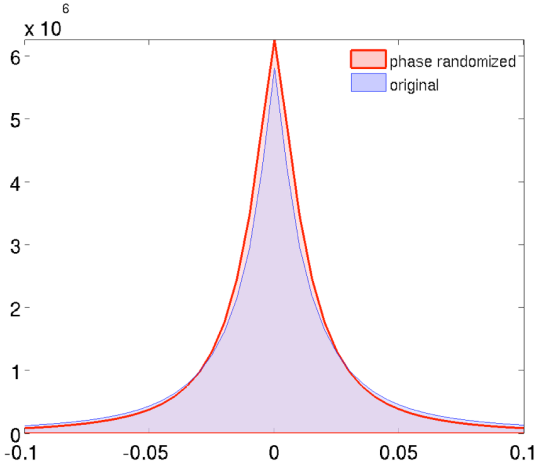
regularized deconvolution

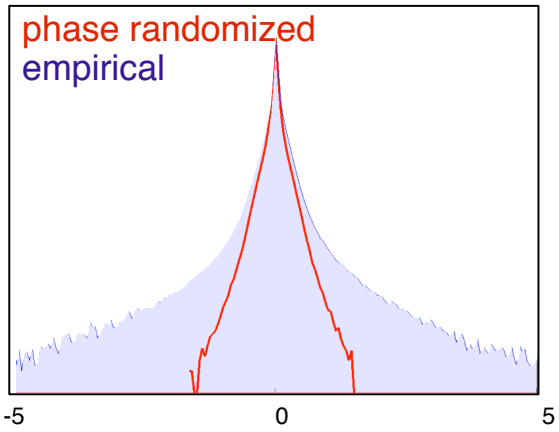
activity-inducing signal

derivative

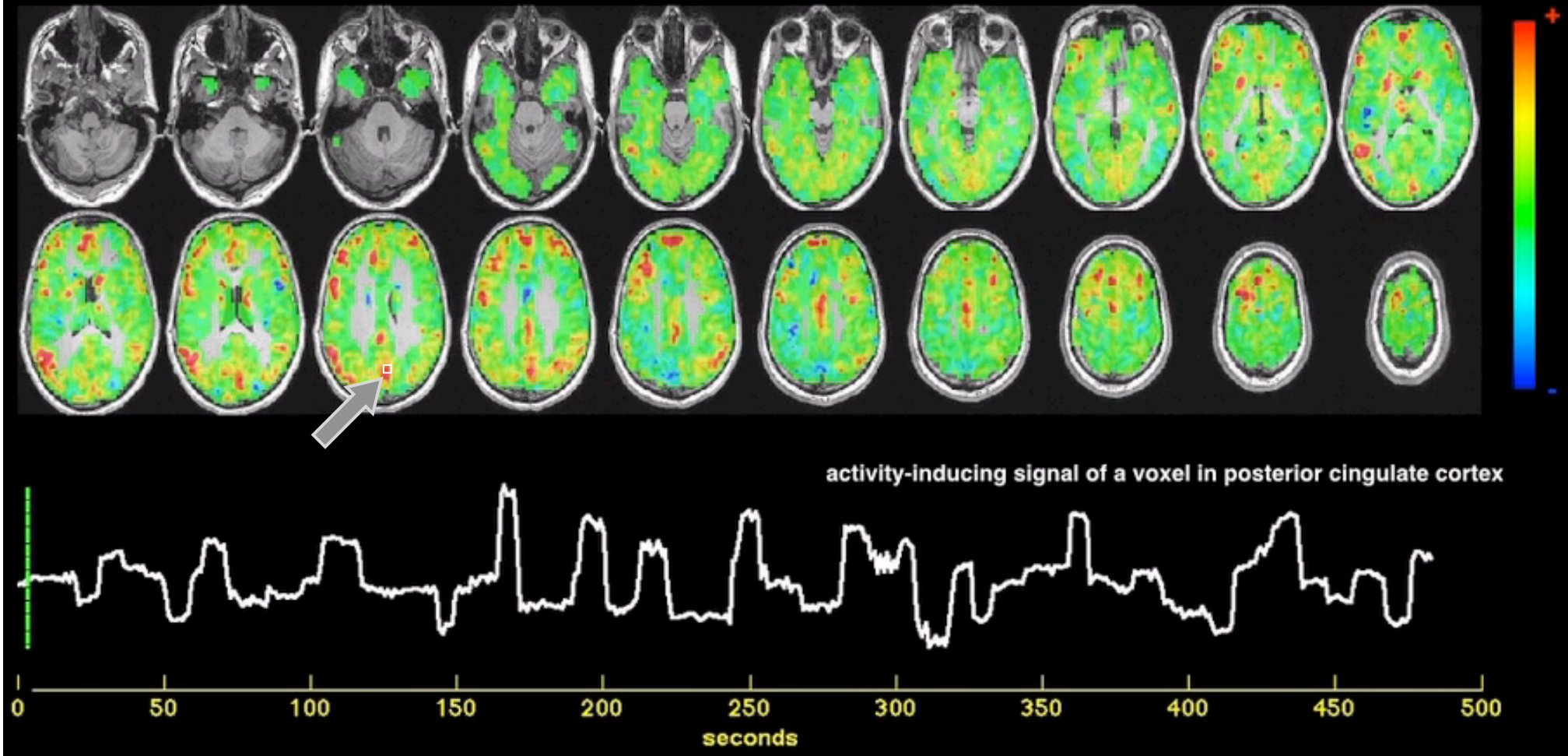
innovation signal

[Karahanoglu, VDV, et al, *NeuroImage*, 2013]



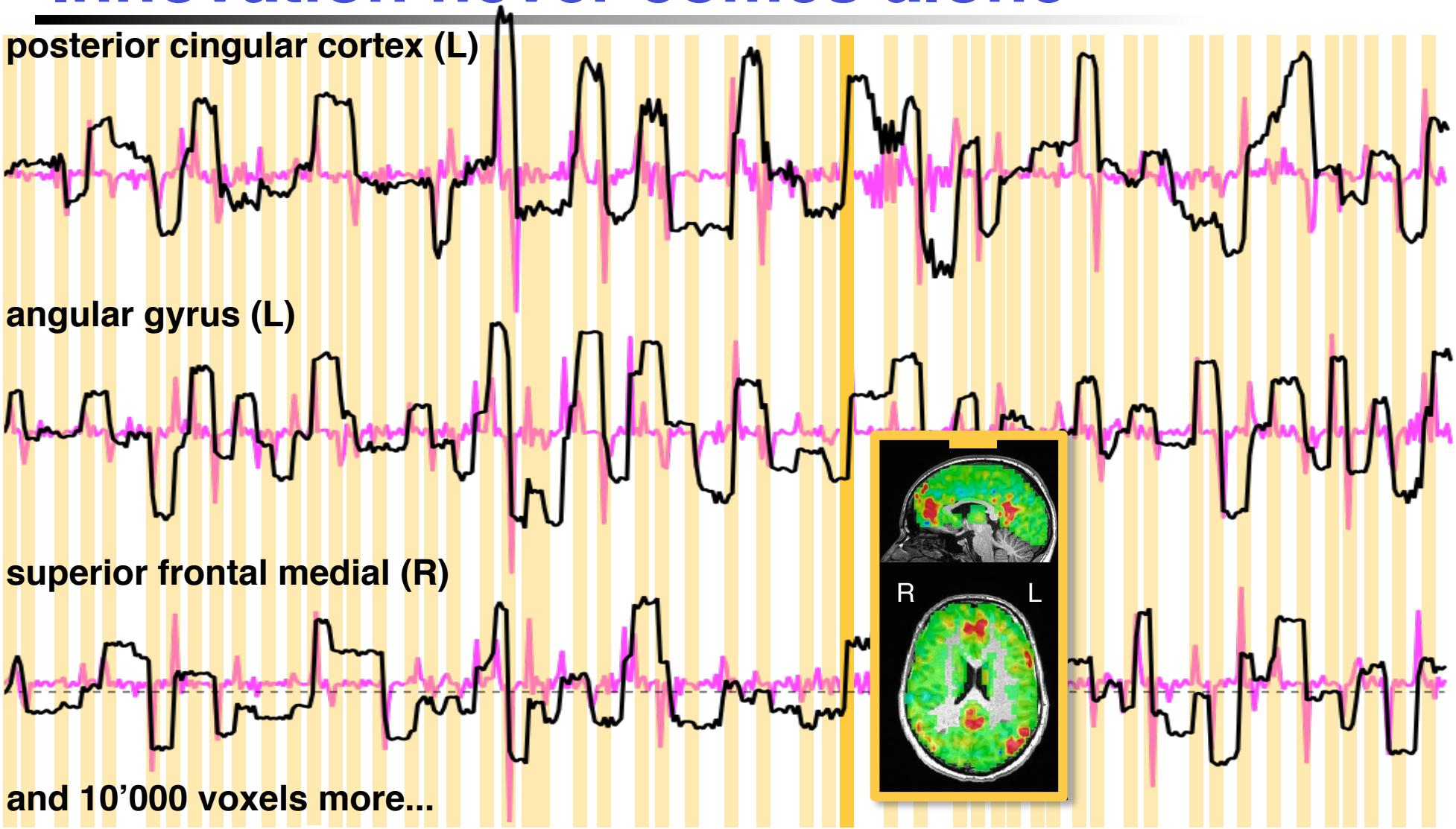


Activity-inducing view on resting-state fMRI



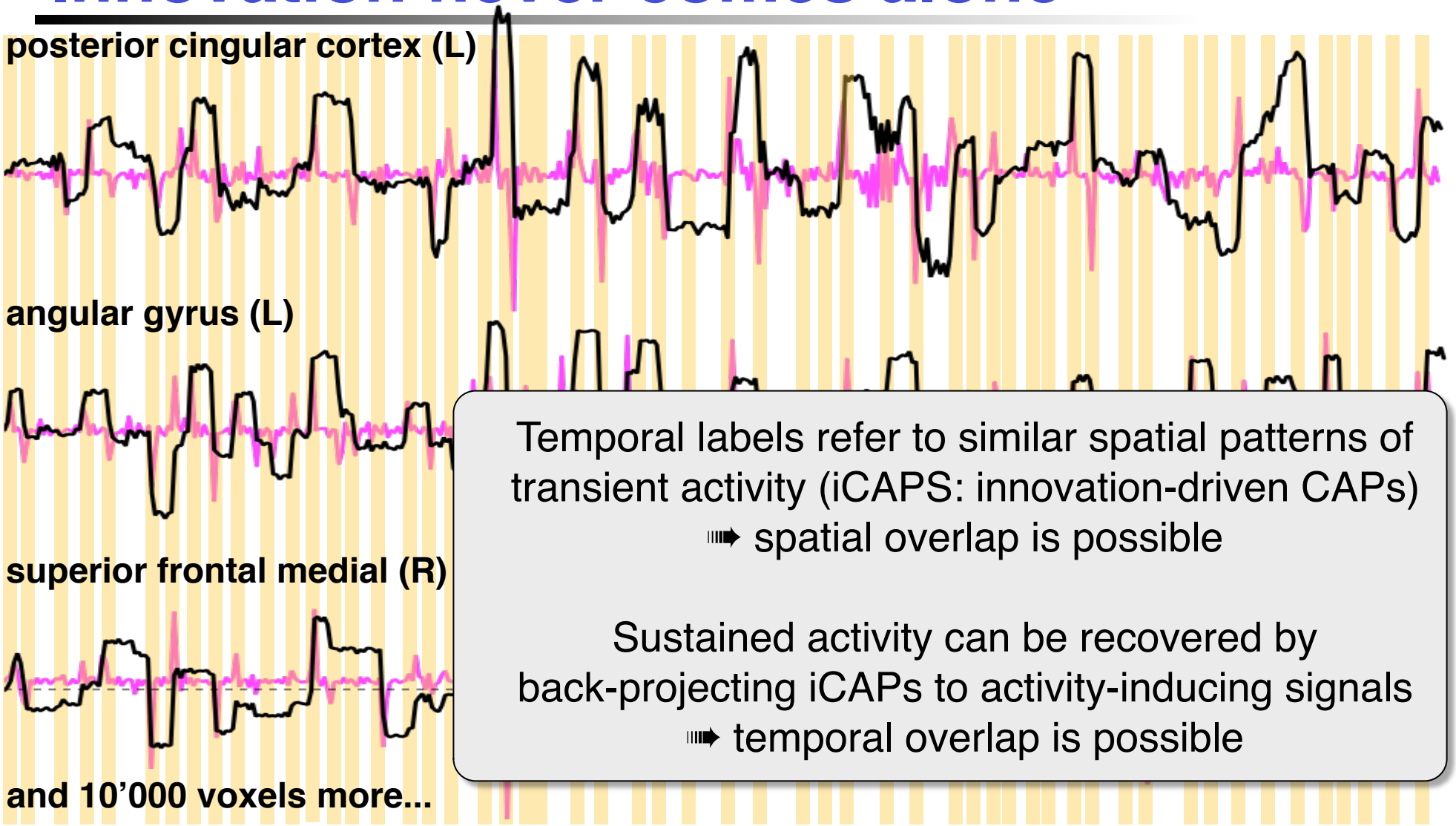
movie accelerated 4 times

Innovation never comes alone



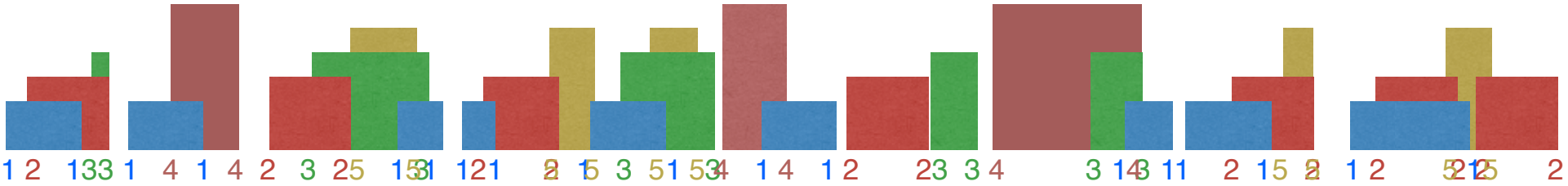
[Karahanoglu and VDV, *Nature Communications*, 2015]

Innovation never comes alone



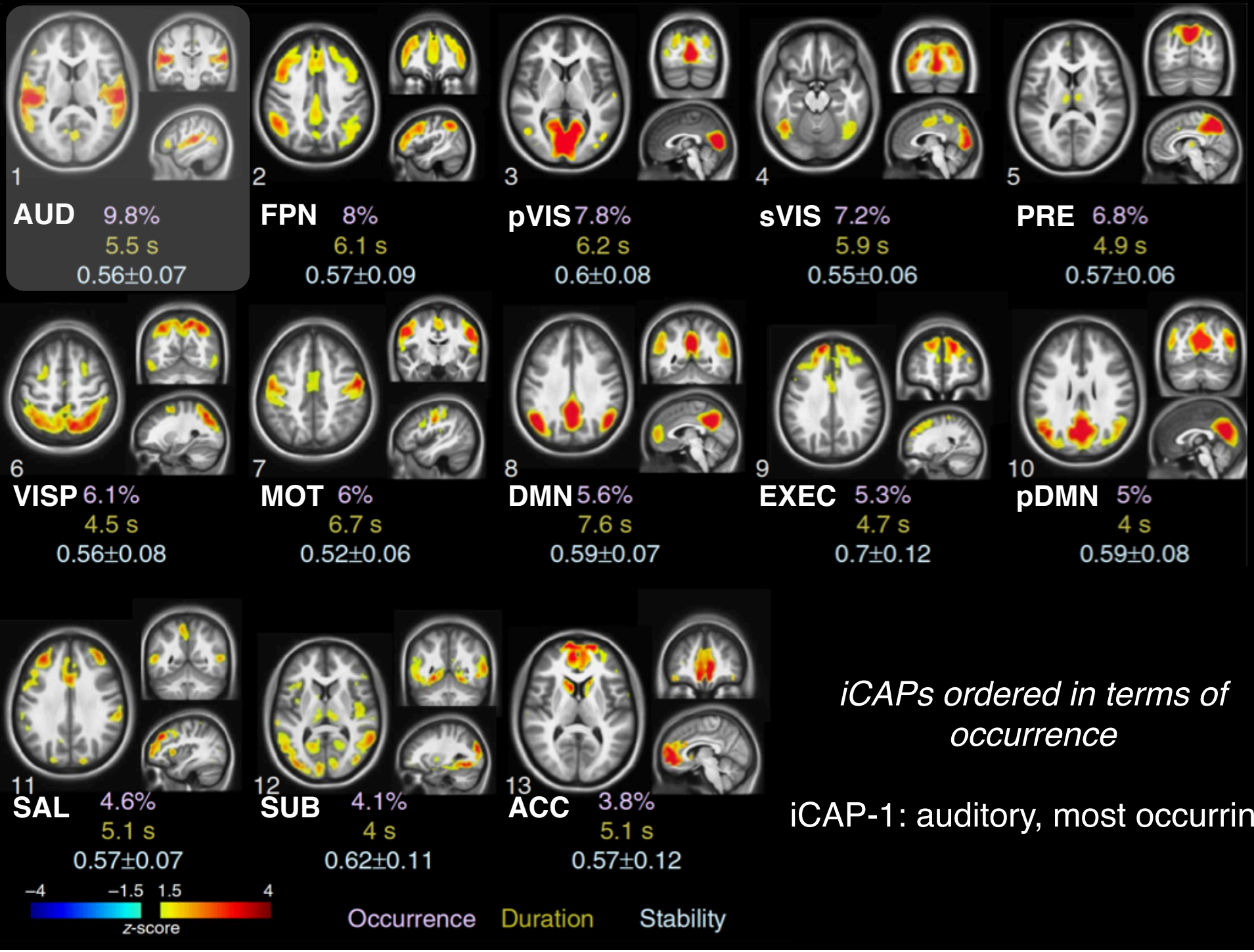
Temporal labels refer to similar spatial patterns of transient activity (iCAPS: innovation-driven CAPs)
➠ spatial overlap is possible

Sustained activity can be recovered by back-projecting iCAPs to activity-inducing signals
➠ temporal overlap is possible



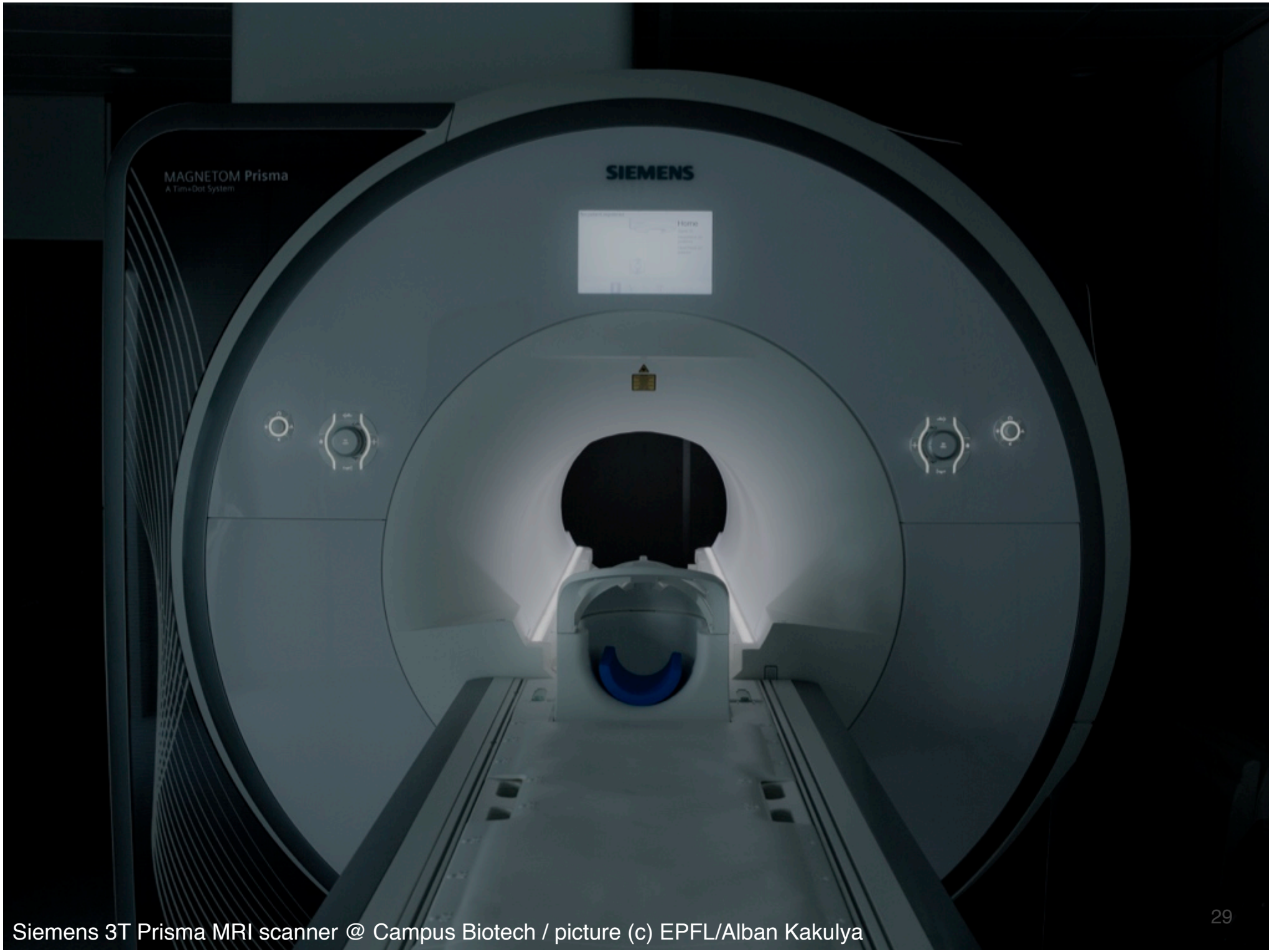
[Karahanoglu and VDV, *Nature Communications*, 2015]

iCAPS: innovation-driven co-activation patterns



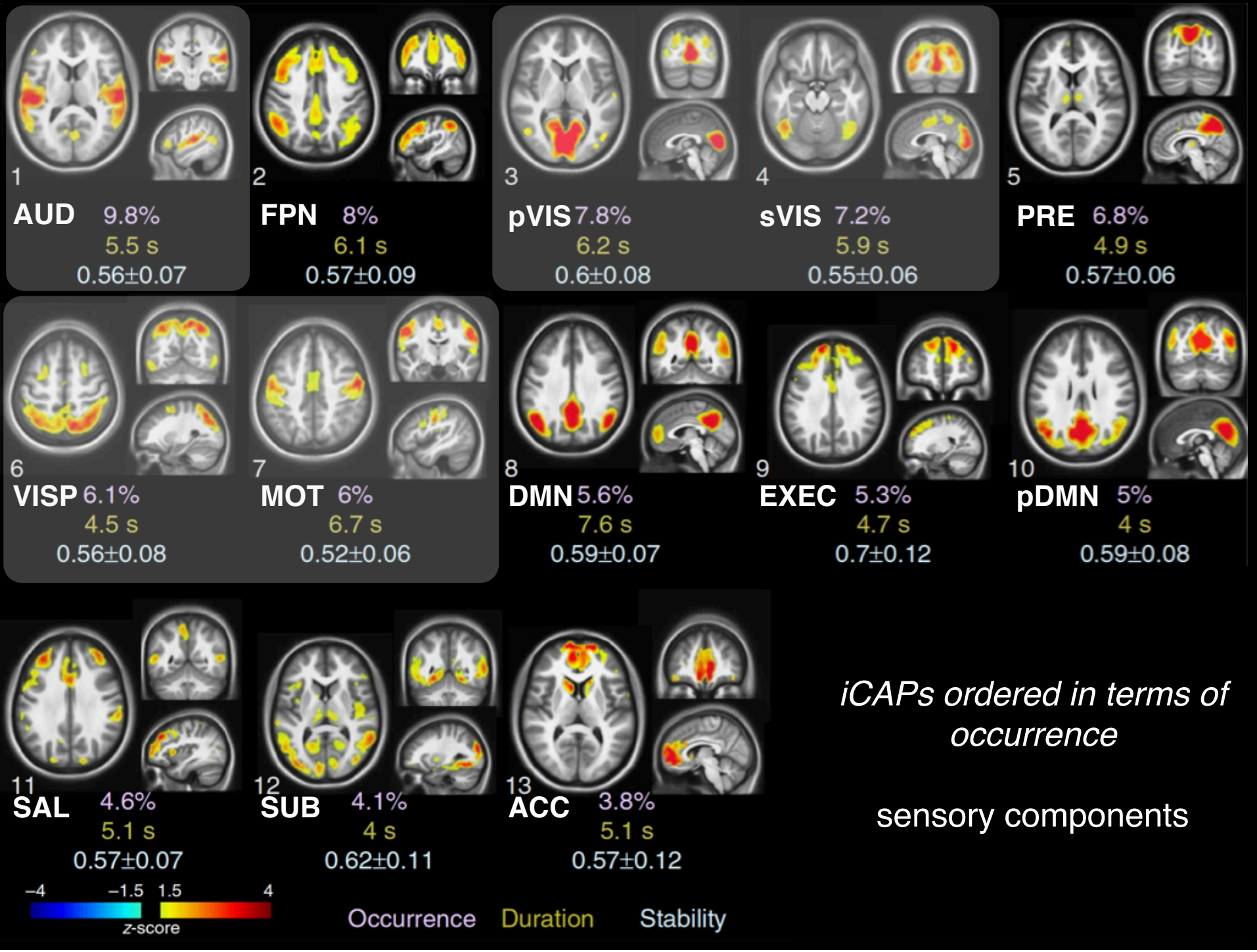
iCAPs ordered in terms of occurrence

iCAP-1: auditory, most occurring



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

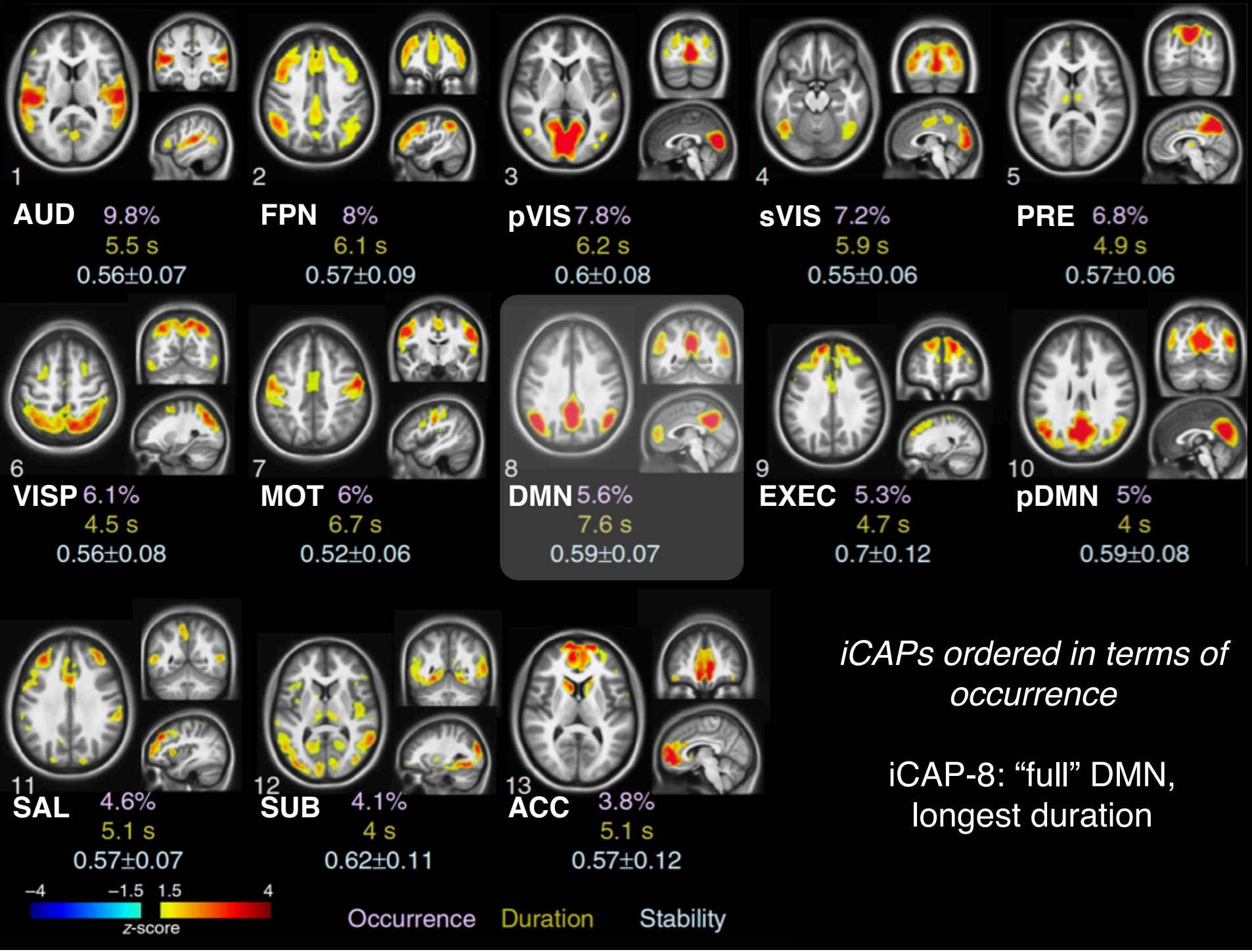
iCAPS: innovation-driven co-activation patterns



iCAPs ordered in terms of occurrence

sensory components

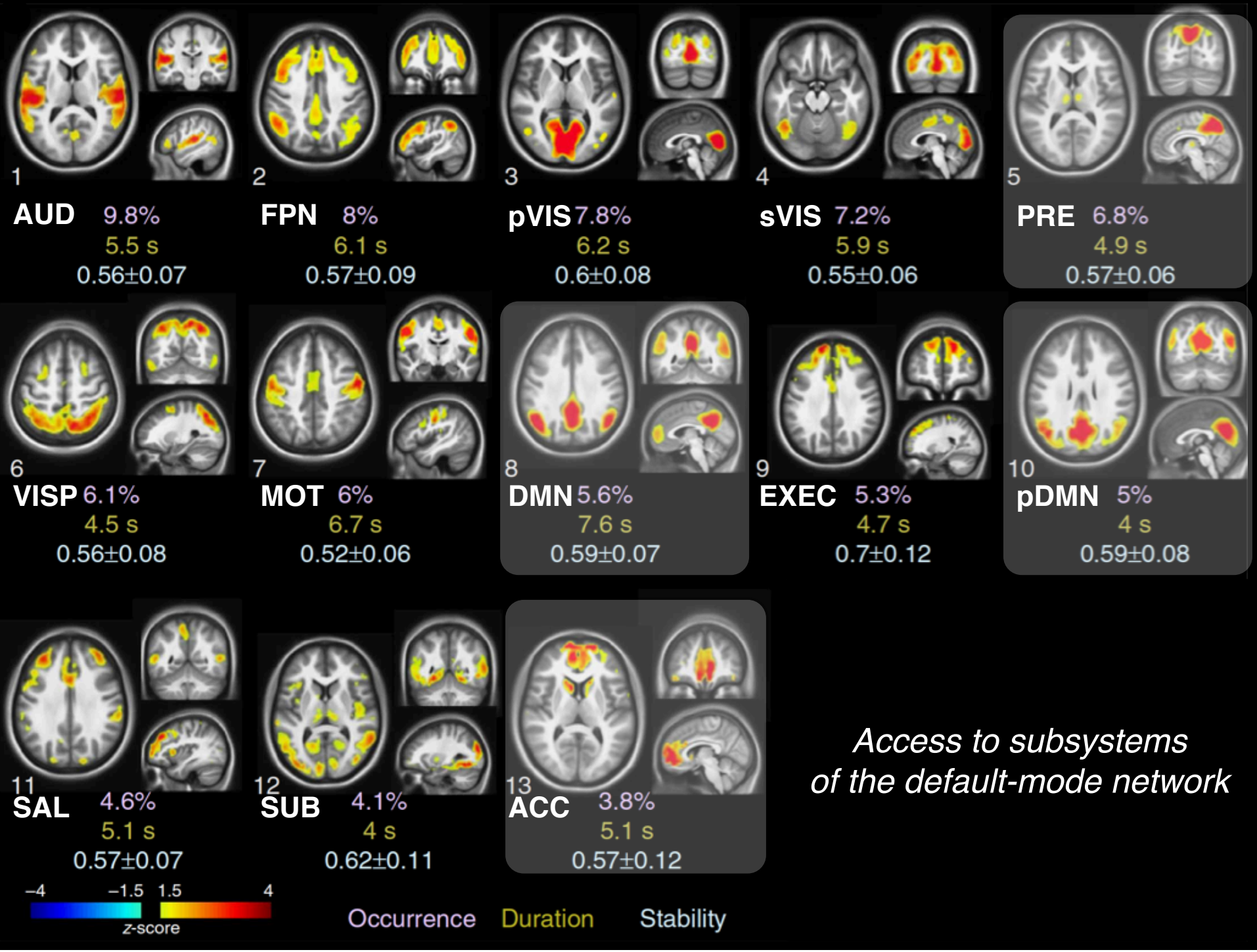
iCAPS: innovation-driven co-activation patterns



iCAPs ordered in terms of occurrence

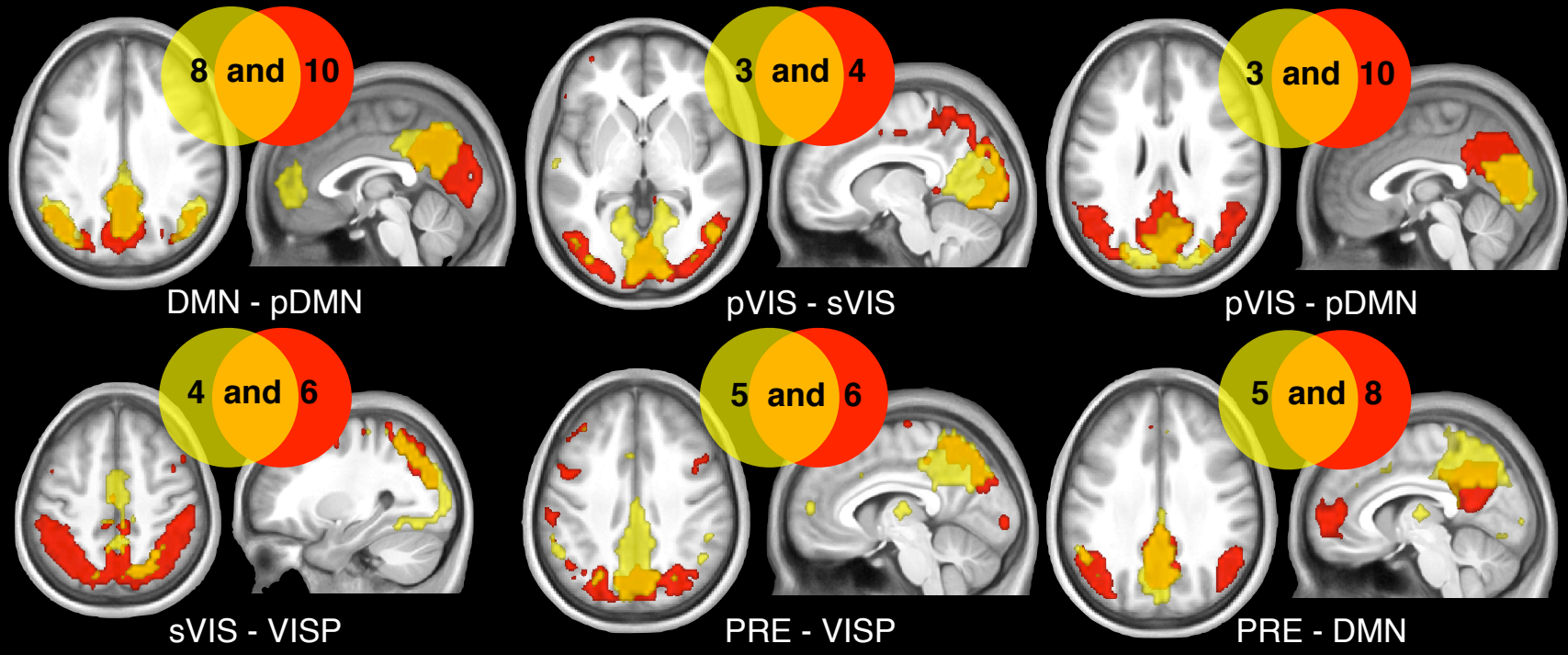
iCAP-8: “full” DMN, longest duration

iCAPS: innovation-driven co-activation patterns

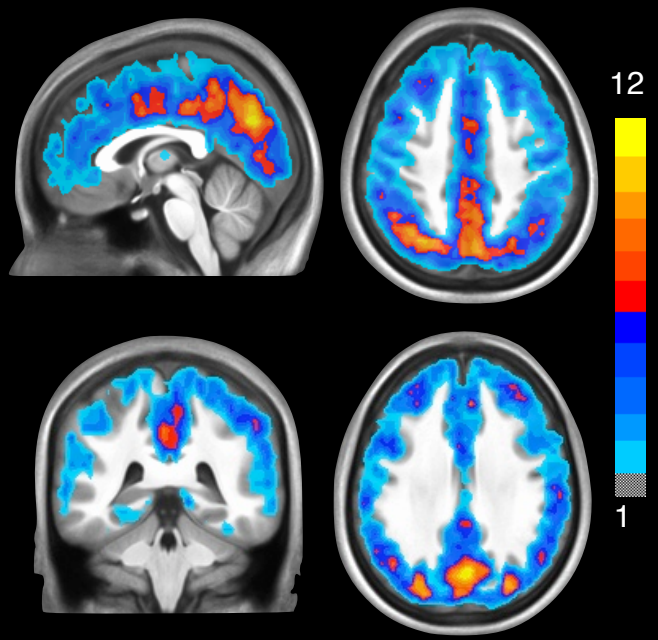


Access to subsystems of the default-mode network

Spatial overlap between iCAPs

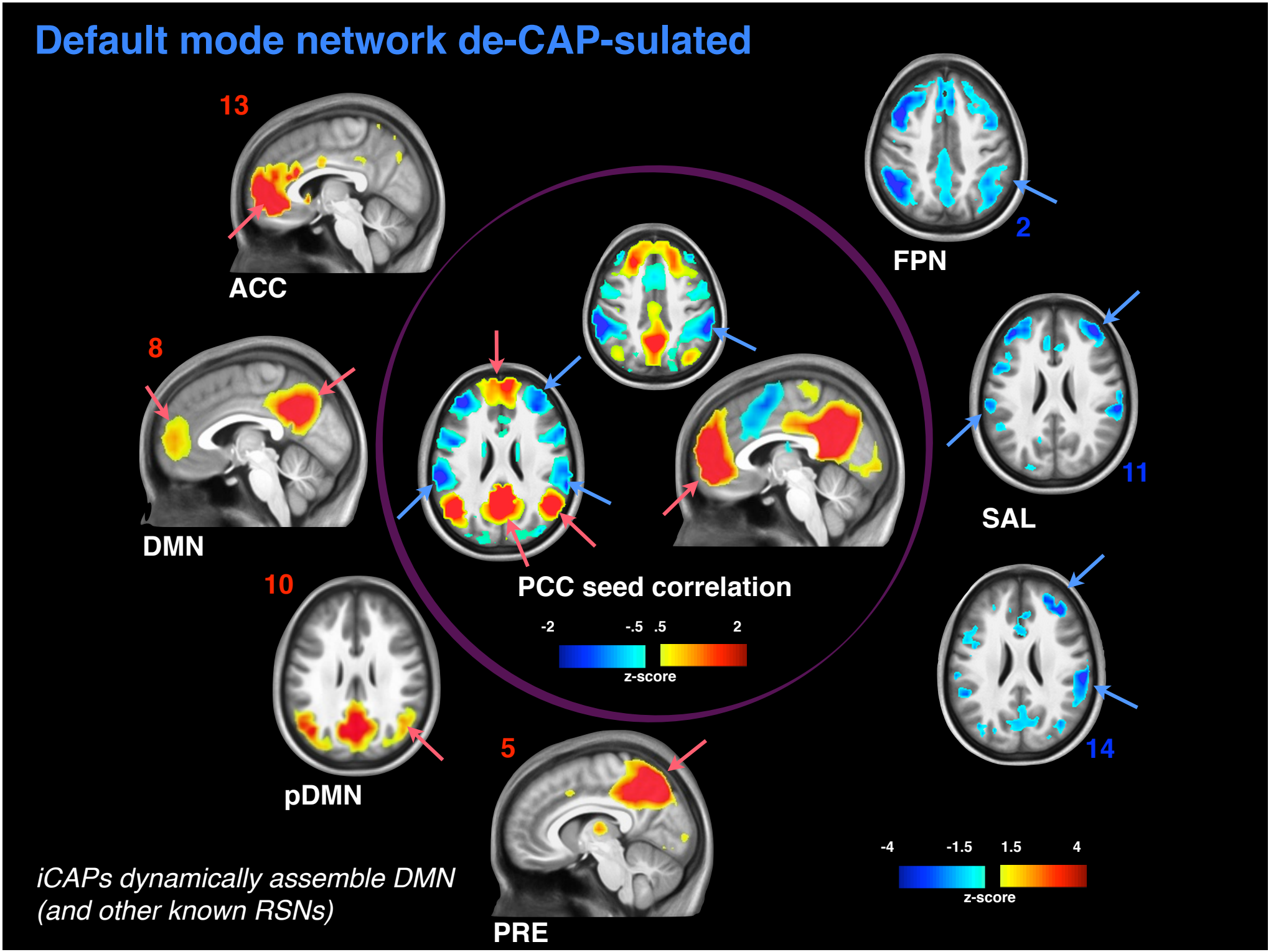


Hub regions of iCAPs



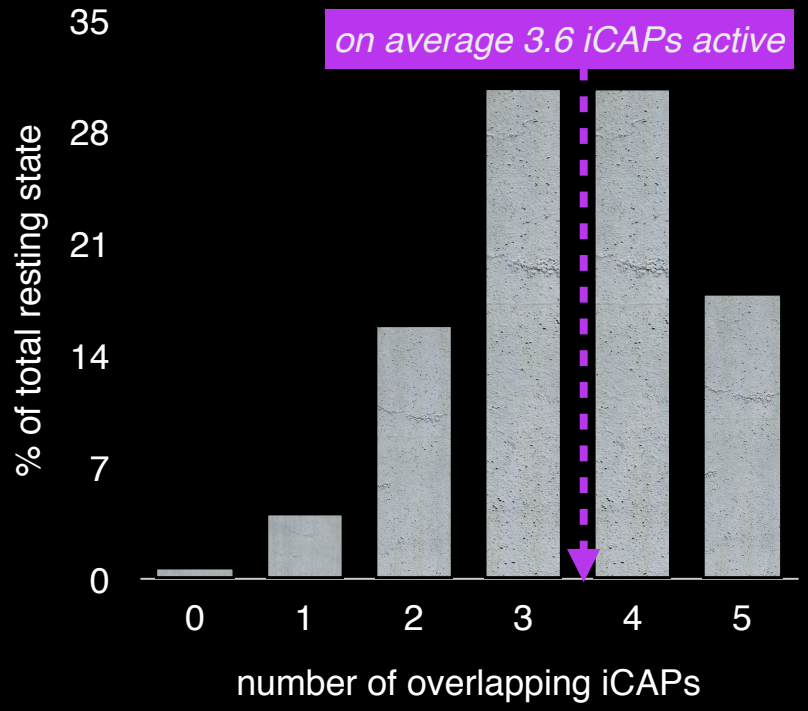
precuneus, dorsal PCC, superior parietal lobe,
mid cingulate cortex, middle occipital and angular gyrus

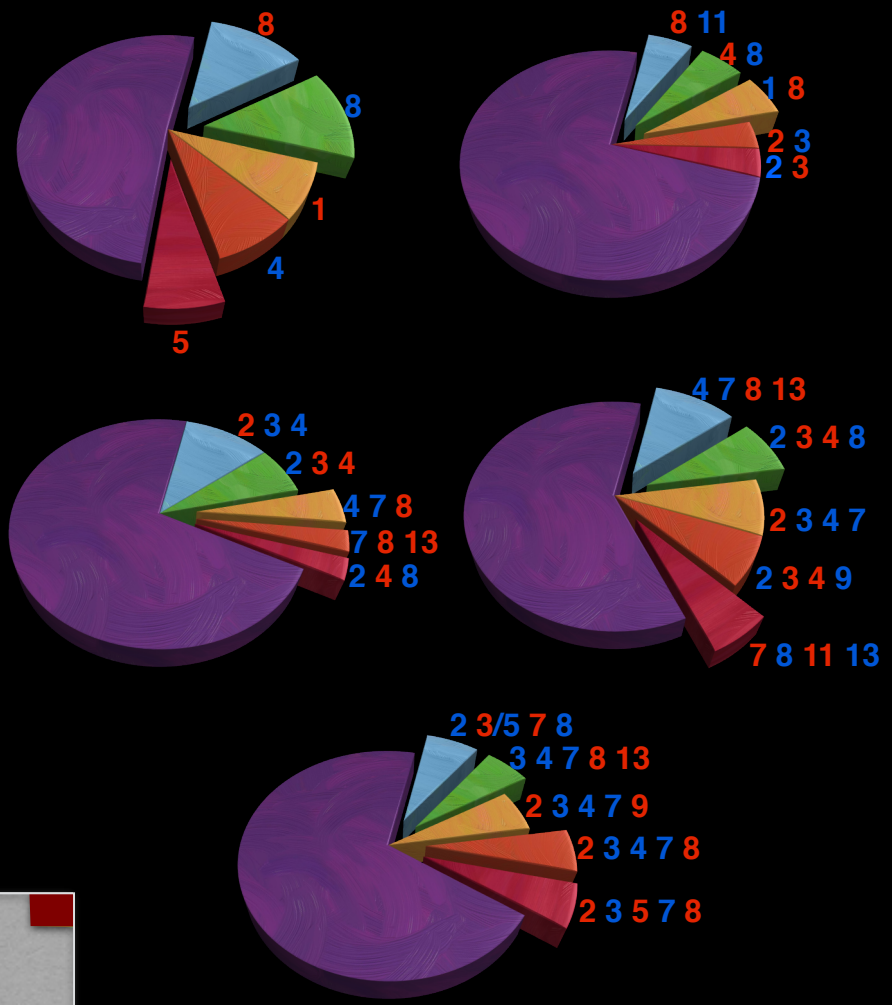
Default mode network de-CAP-sulated

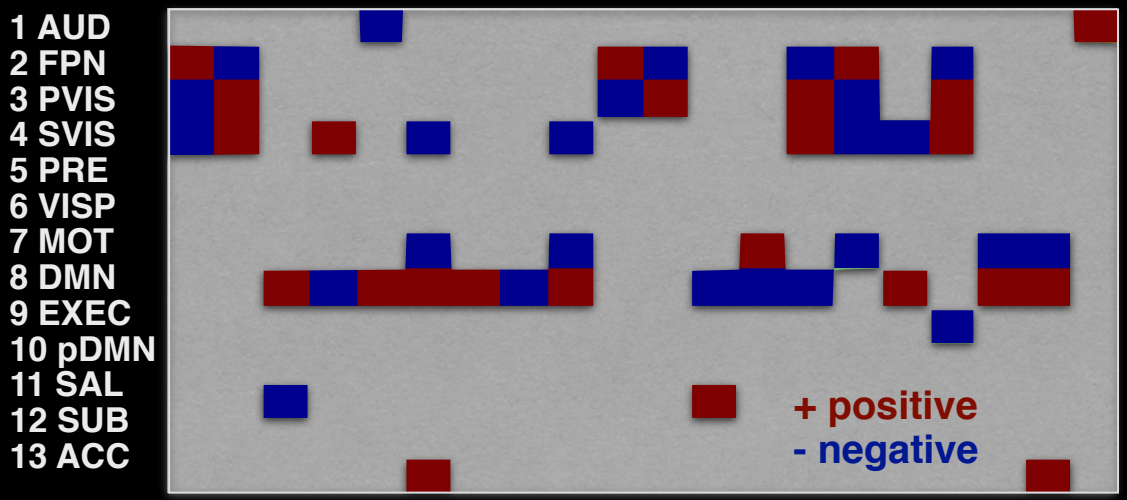


iCAPs dynamically assemble DMN (and other known RSNs)

Temporal overlap of iCAPs

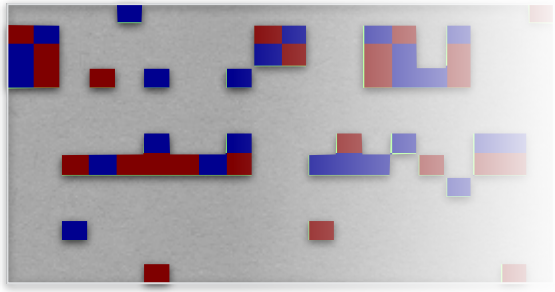






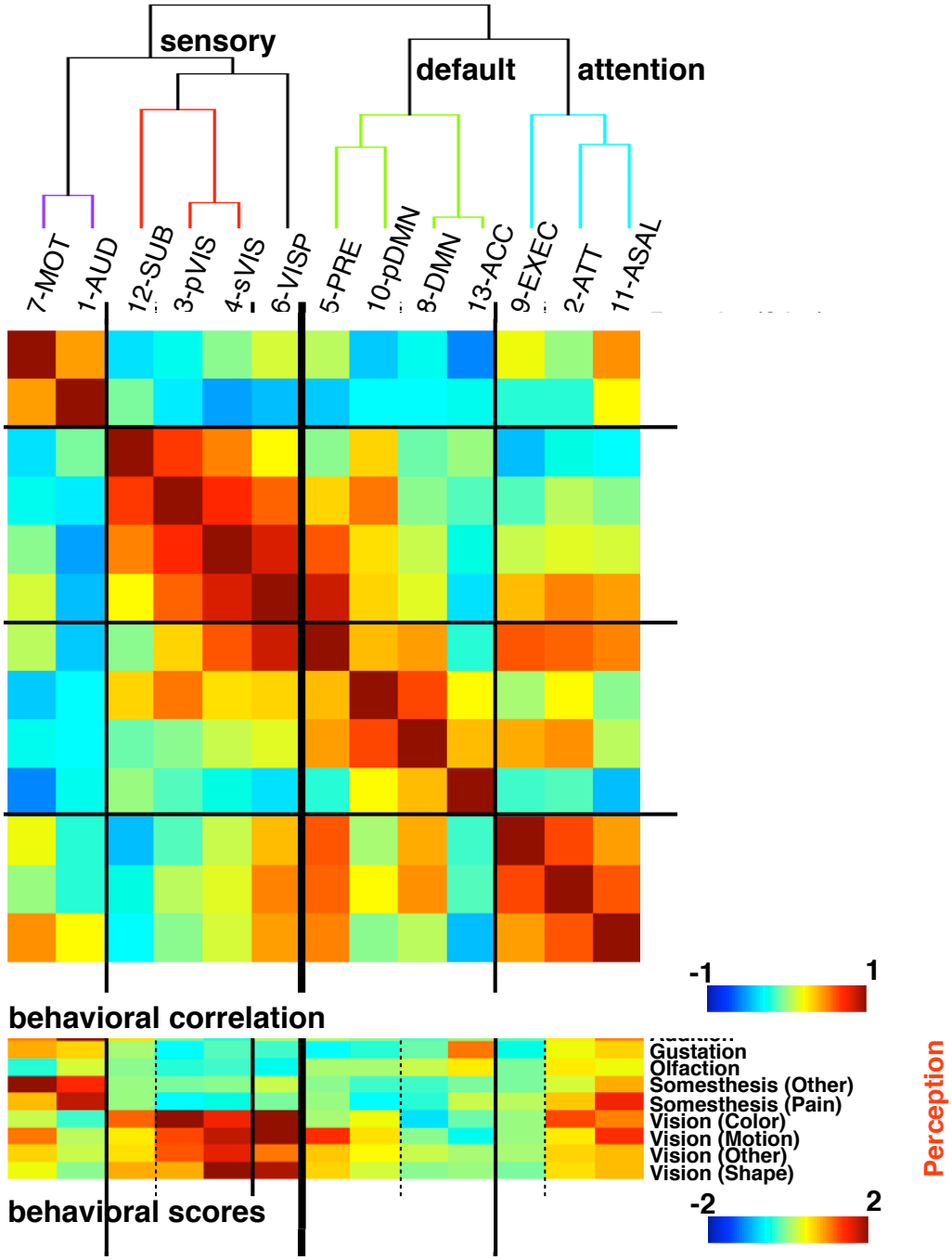
20 most frequent combinations

Relationship between iCAPs and behavior



2098 iCAPs combinations

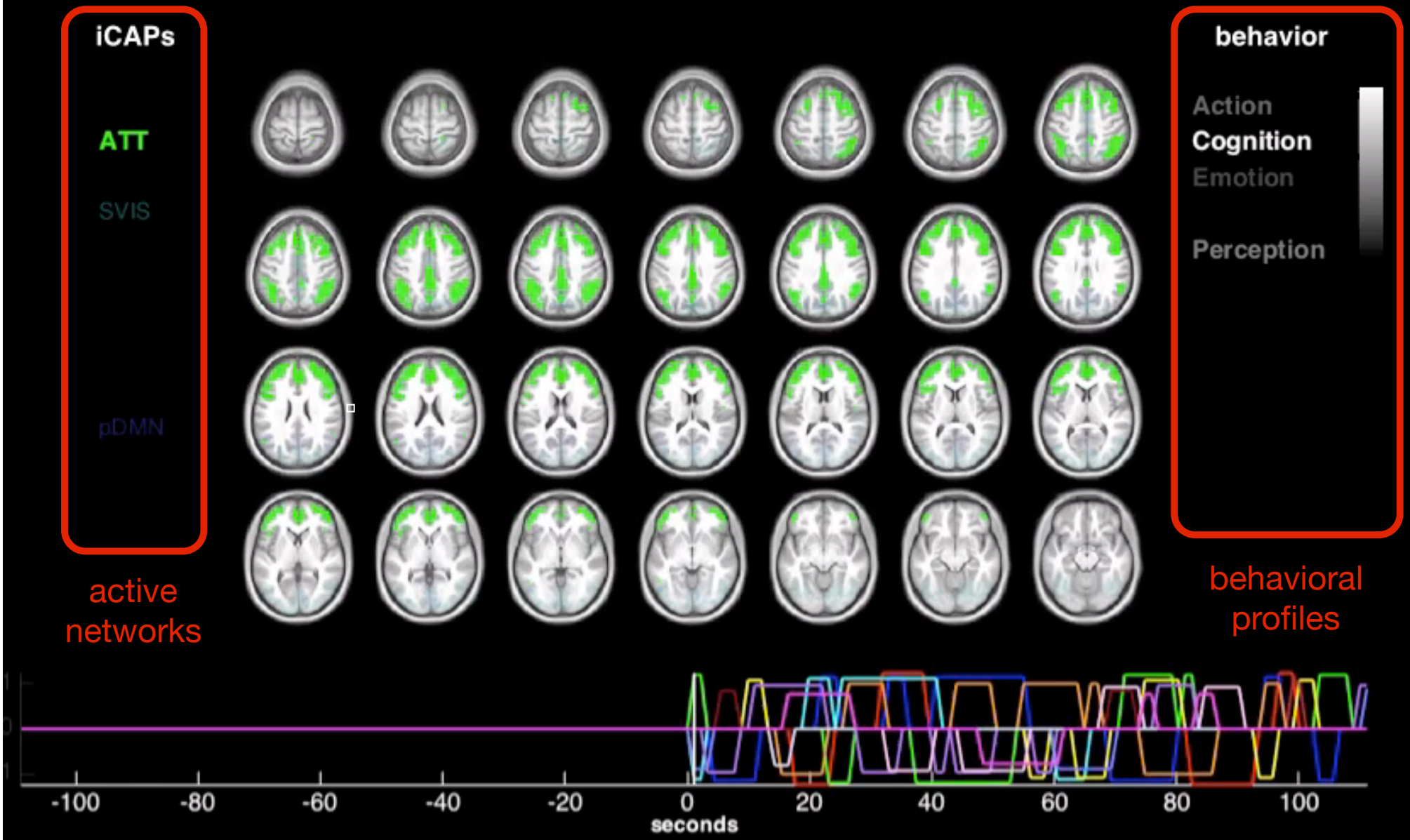
hierarchical clustering



- 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]

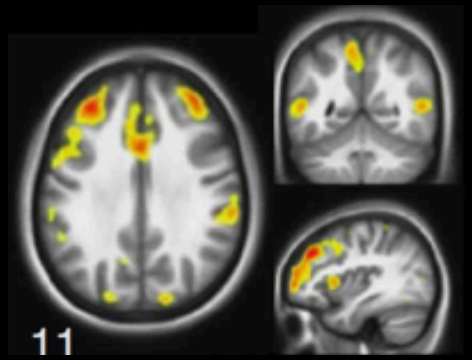
Deciphering moment-to-moment activity



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

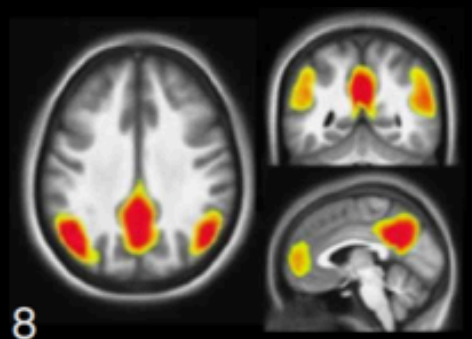
Time to rethink our models?

Salience network



psychomotor activity
goal-directed action
sensory & limbic processing

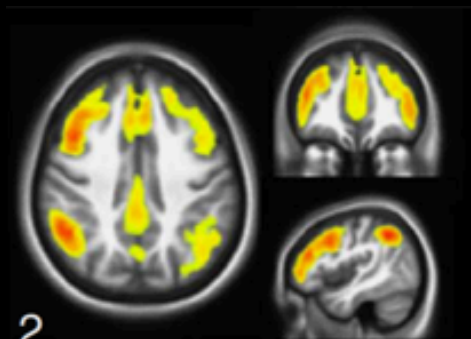
Default mode network



self-referential mental activity

anticorrelation

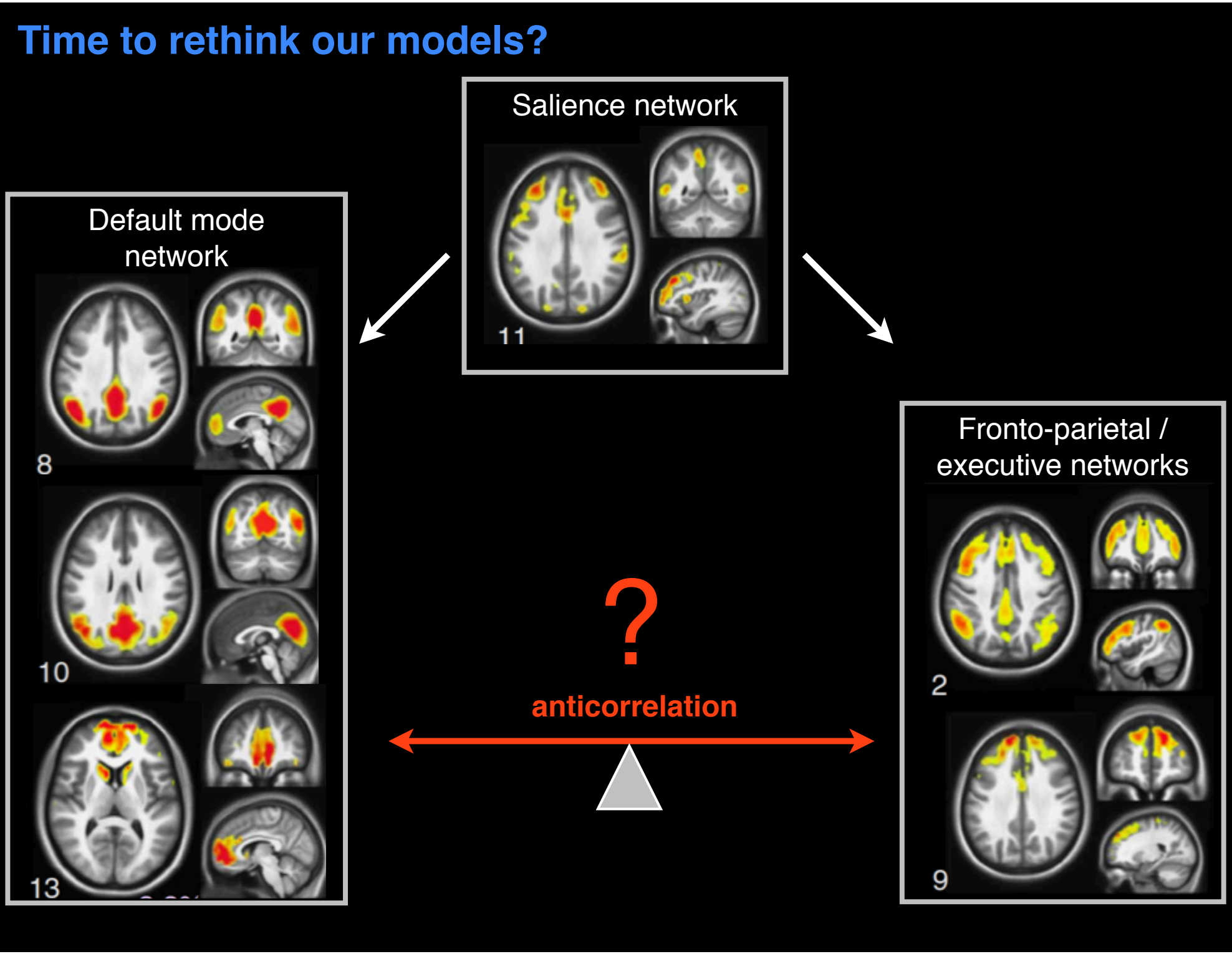
Fronto-parietal / executive networks



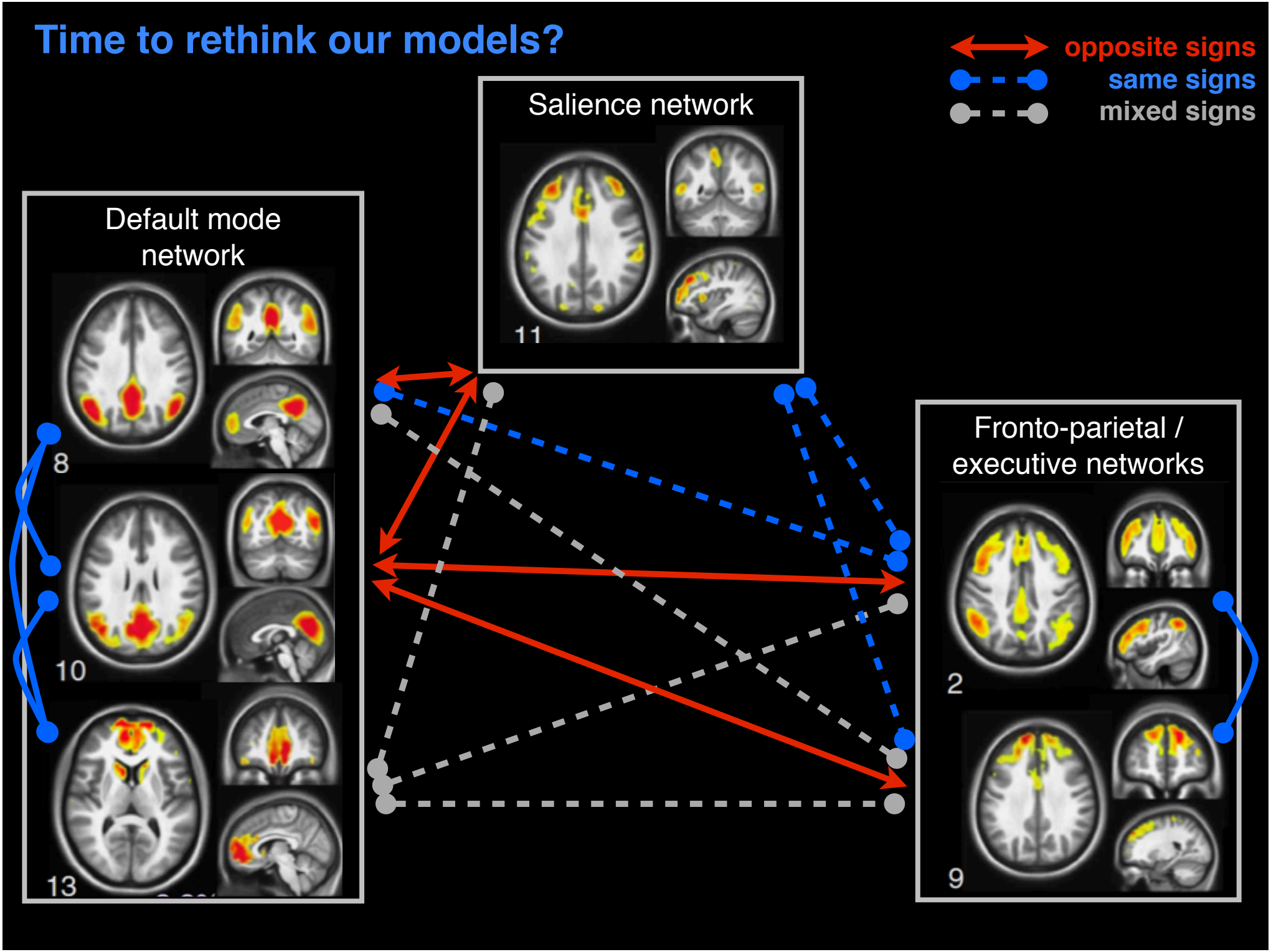
cognition, attention

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

Time to rethink our models?

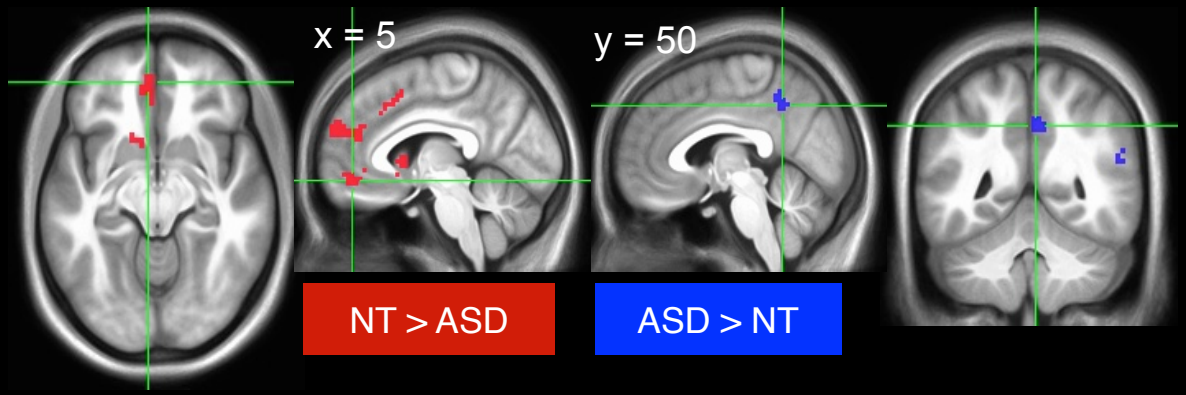


Time to rethink our models?



Preliminary results in ASD (51 ASD / 36 NT)

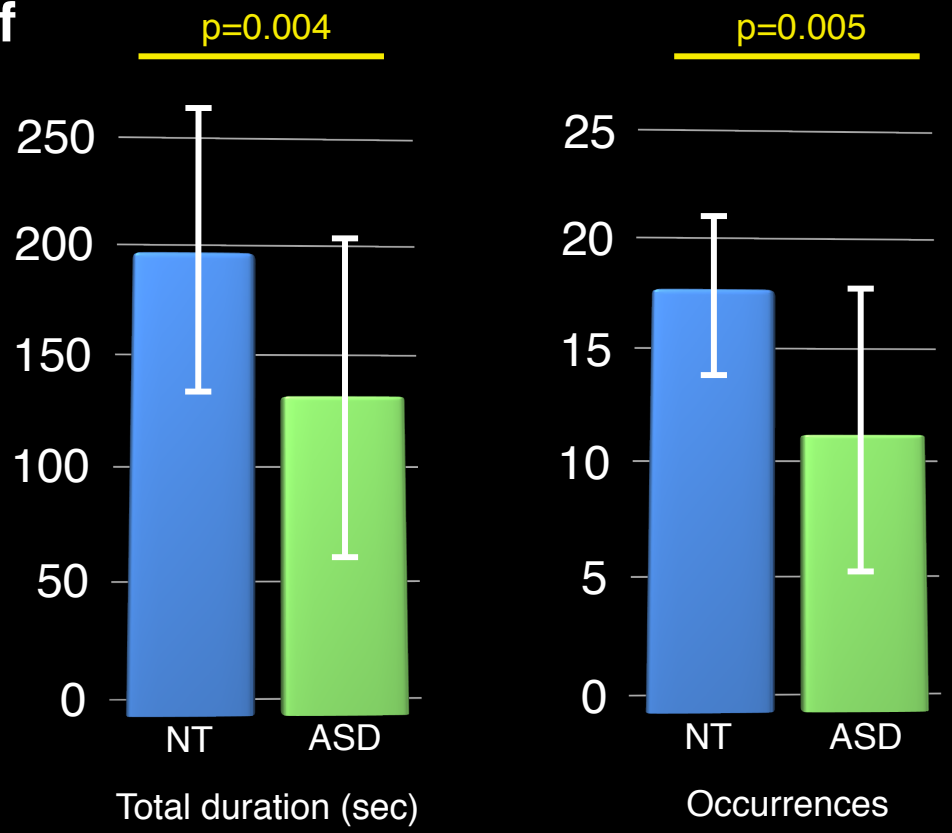
Spatial differences in DMN subsystem



- decreased activation in ventromedial prefrontal cortex
- increased activation in precuneus

Differences in temporal dynamics of DMN subsystem

- reduced total duration
- reduced occurrence
- suggests reduced self-referential processing during rest
- future examination of relationship with ASD core features

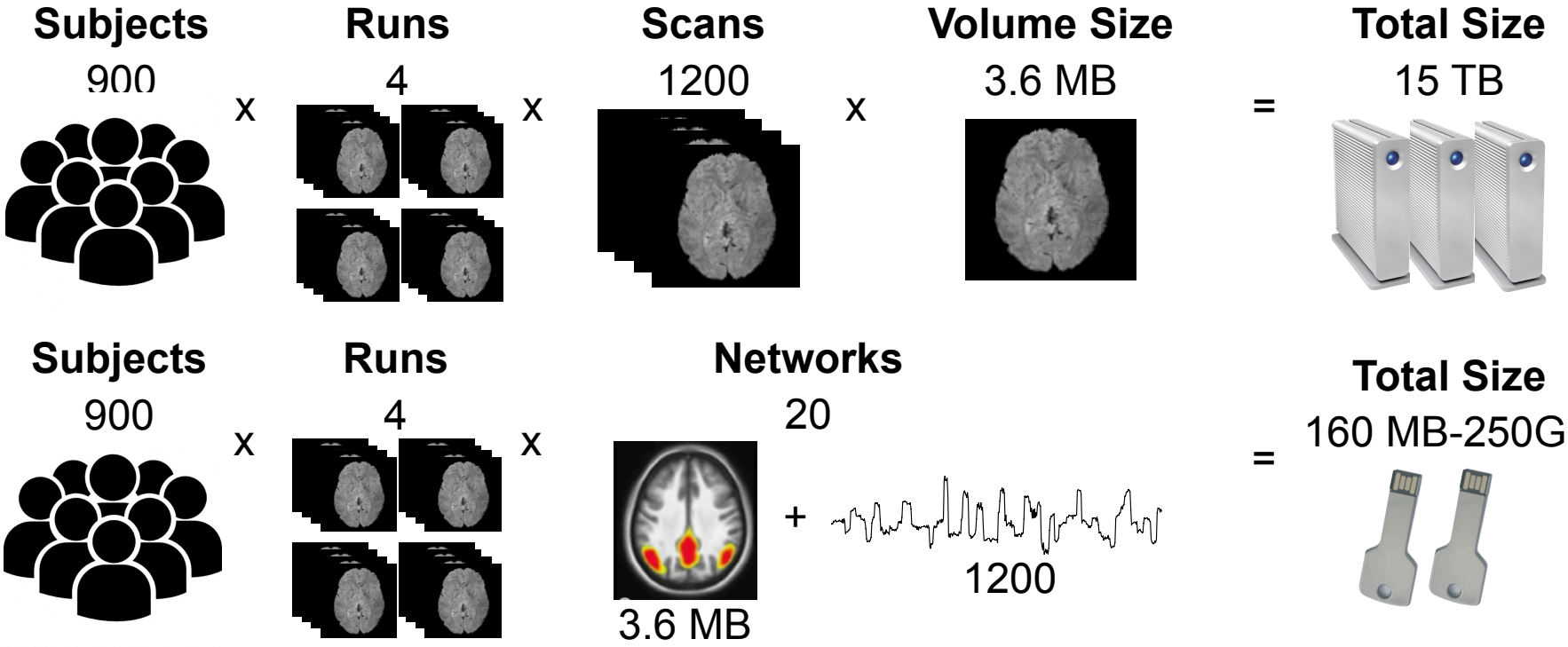


fondation bertarelli

collaboration with
Manoach and Van der Kouwe Labs

Big data extraction = reduction

- Resting-state fMRI data from HCP



- Still, this only provides an alternative view on the data and requires additional computational methods & models!
  - Characterize dynamics by temporal modeling
  - Combine with machine learning
  - System-level mechanistic models of brain processes

Conclusion & outlook

- Emergence of “big data” MRI offers unprecedented opportunities for brain science
  - Feature extraction (data representation) is crucial to obtain relevant and interpretable results
  - Interplay between hypothesis-driven and exploratory research
- Dynamics of resting-state fMRI
  - Is *not* about oscillations, but about *transients*! (=“broadband feature”)
    - ... note transient has a “deterministic” 1/f spectrum!
  - Clear transient behavior is recovered
  - Massive spatial and temporal overlap
  - Patterns of co-activation build up a (low-rank) approximation of functional connectivity measures

MIP:lab @ Campus Biotech

http://miplab.epfl.ch

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FNSNF Swiss National Science Foundation

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Brain & Behavior Research Foundation Awarding NARSAD Grants

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