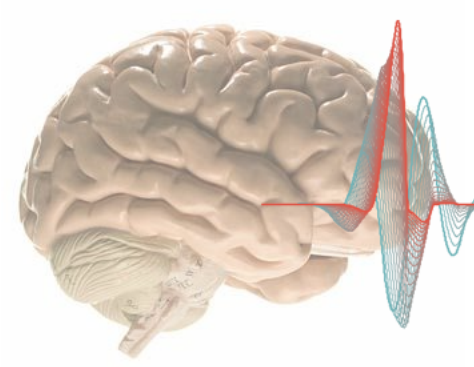


campus biotech

UNIVERSITÉ DE GENÈVE

ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

# The dynamic functional connectome:

## *state-of-the-art and methods*


**Dimitri Van De Ville**

Medical Image Processing Laboratory (MIP:lab)
Institute of Bioengineering/Center for Neuroprosthetics
Ecole polytechnique fédérale de Lausanne

Department of Radiology
Université de Genève

http://miplab.epfl.ch/

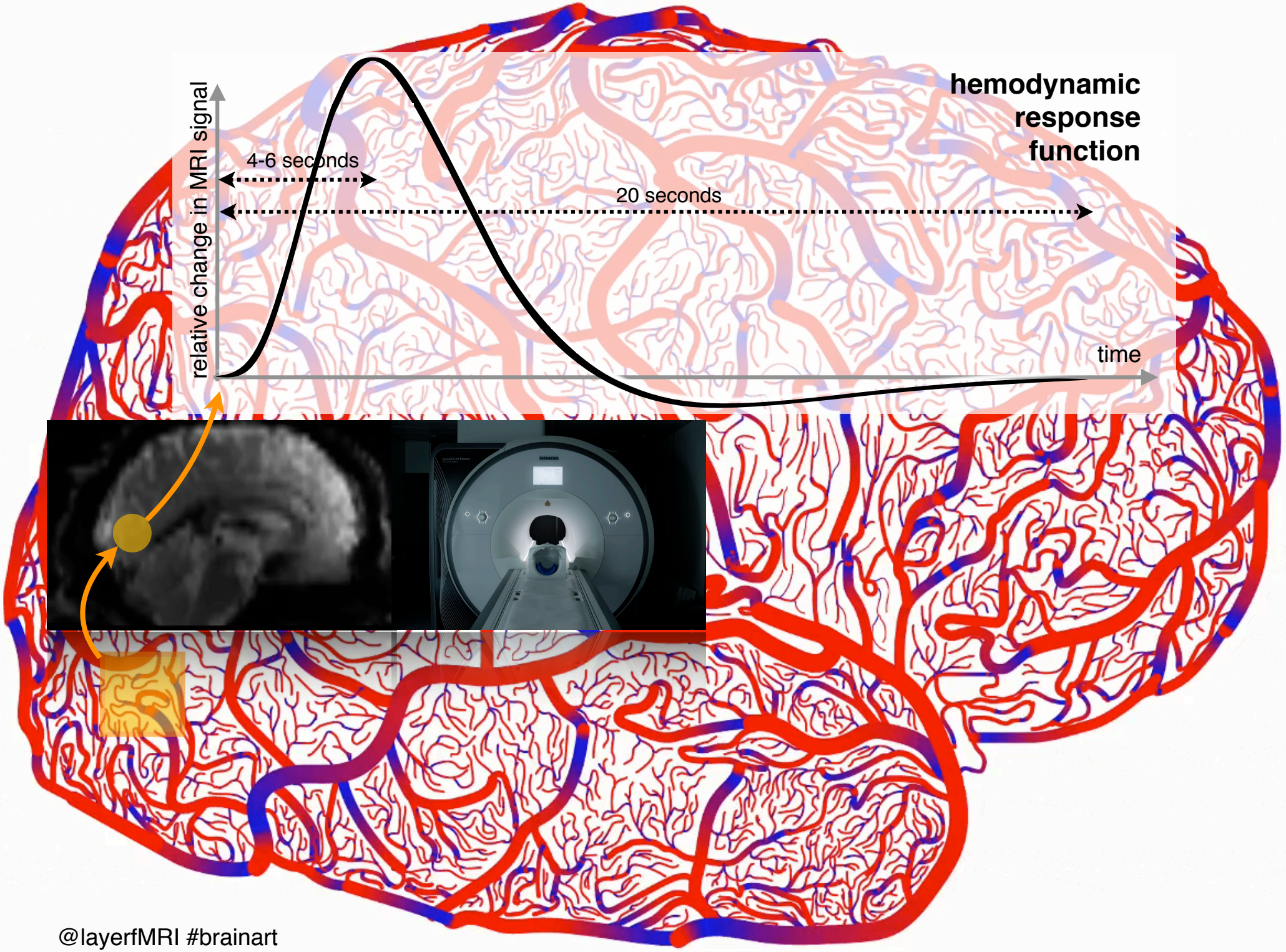
@dvdevill



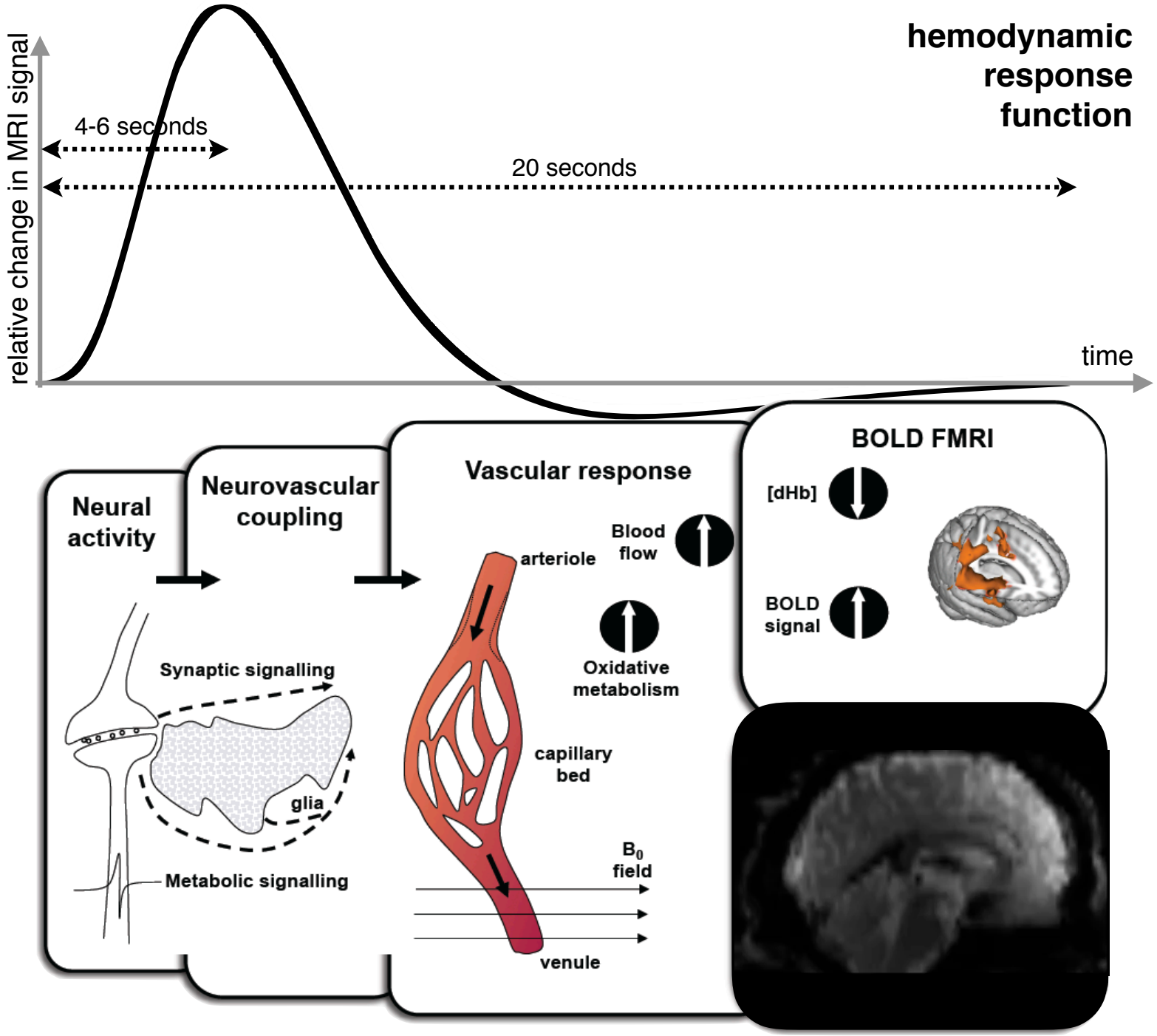
NEUROSCIENCE 2018

NOVEMBER 3–7
SAN DIEGO, CA

The Dynamic Brain: Signatures of Fast Functional Reconfiguration, Their Interpretability, and Clinical Value

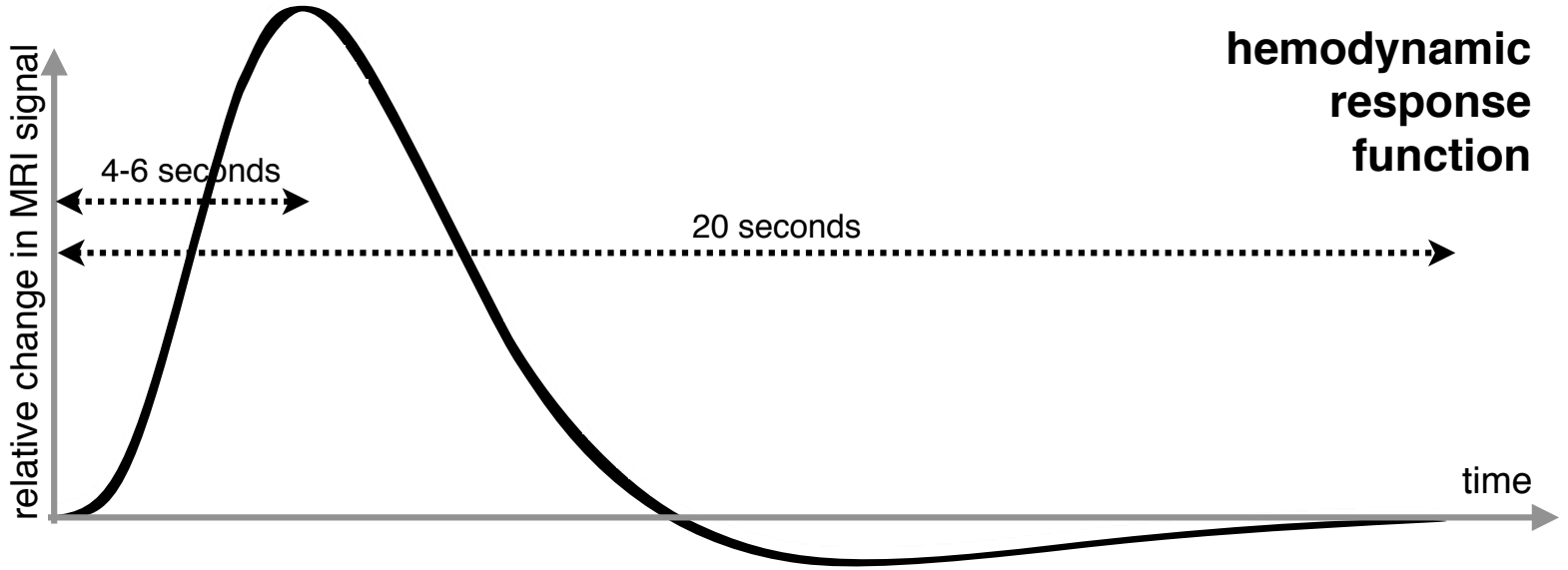

hemodynamic
response
function
relative change in MRI signal
4-6 seconds
20 seconds
time
@layerfMRI #brainart

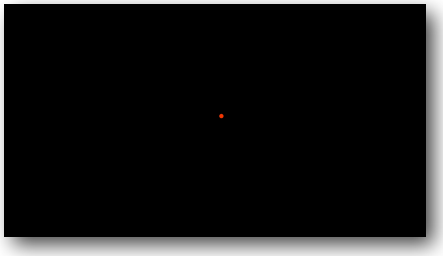
# FMRI blood-oxygenation-level-dependent (BOLD) signals are slow proxy for neuronal activity

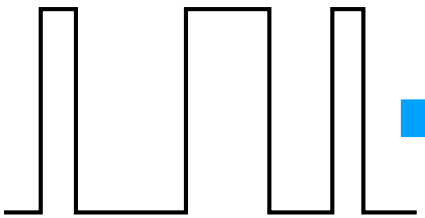



[Iannetti and Wise, *MRI*, 2007]

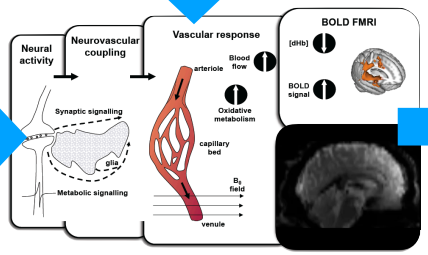
# Modeling the BOLD signal can be used to find evidence of induced brain activity



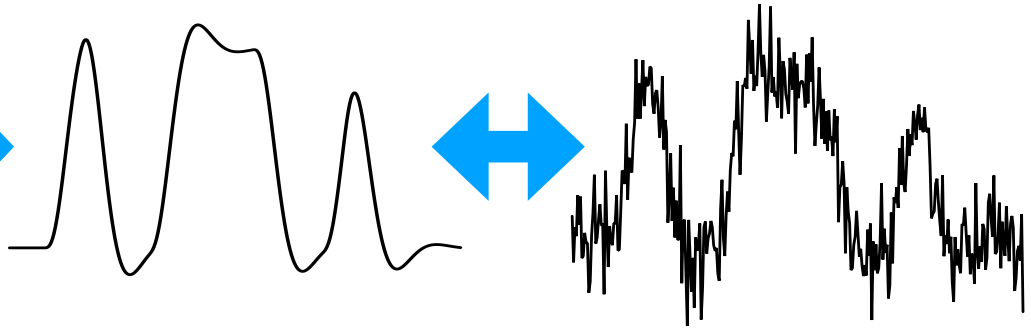


experimental paradigm




**statistical hypothesis testing**

- evidence against noise assumption
- non-modeled baseline is considered constant+noise

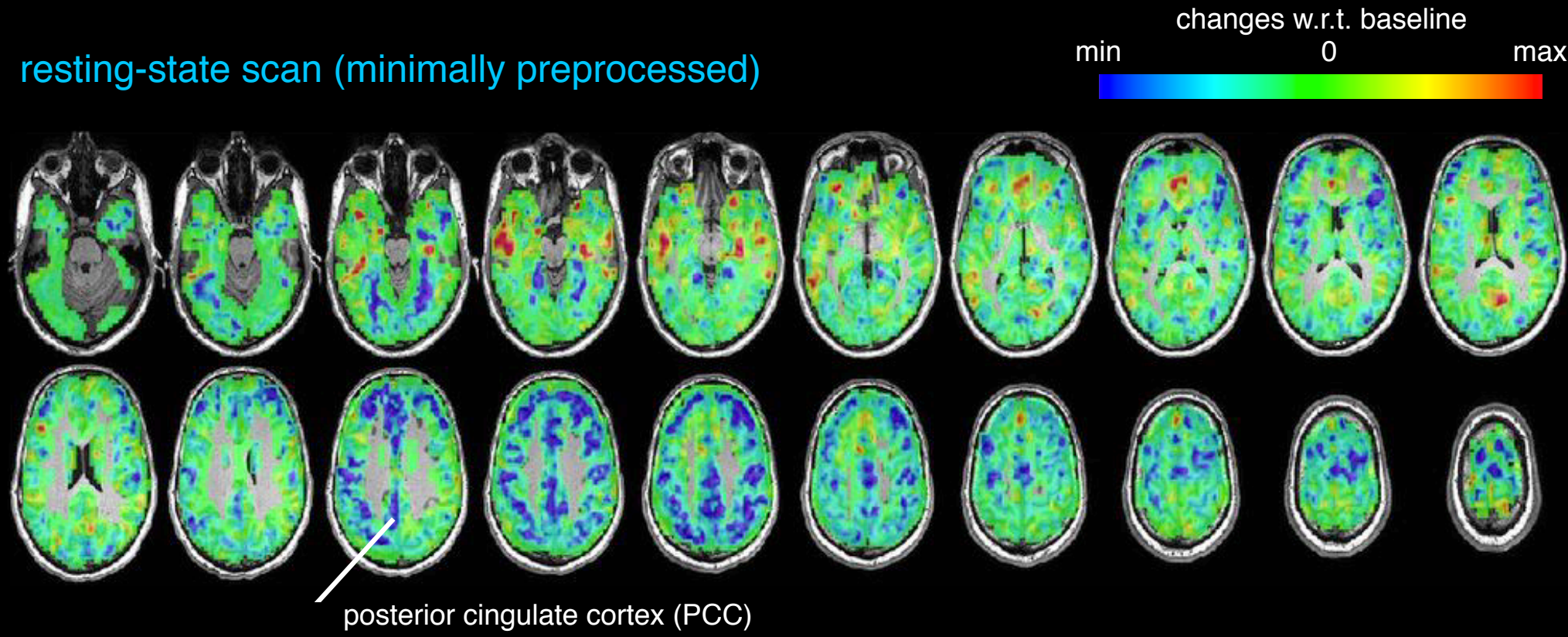


ideal BOLD signal

measured BOLD signal

# What is the baseline? *spontaneous activity*

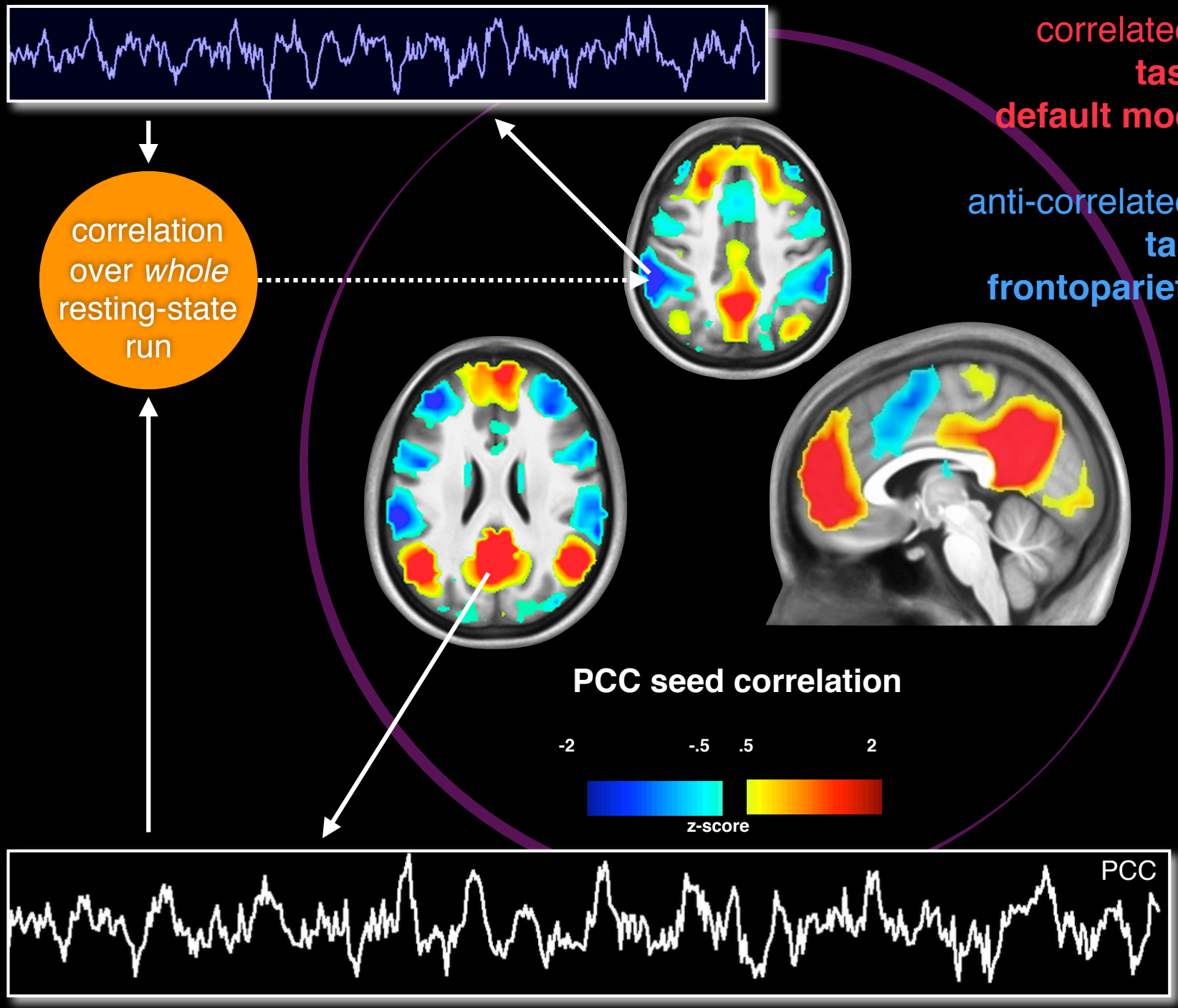
resting-state scan (minimally preprocessed)




8 minutes

*movie accelerated 4 times*

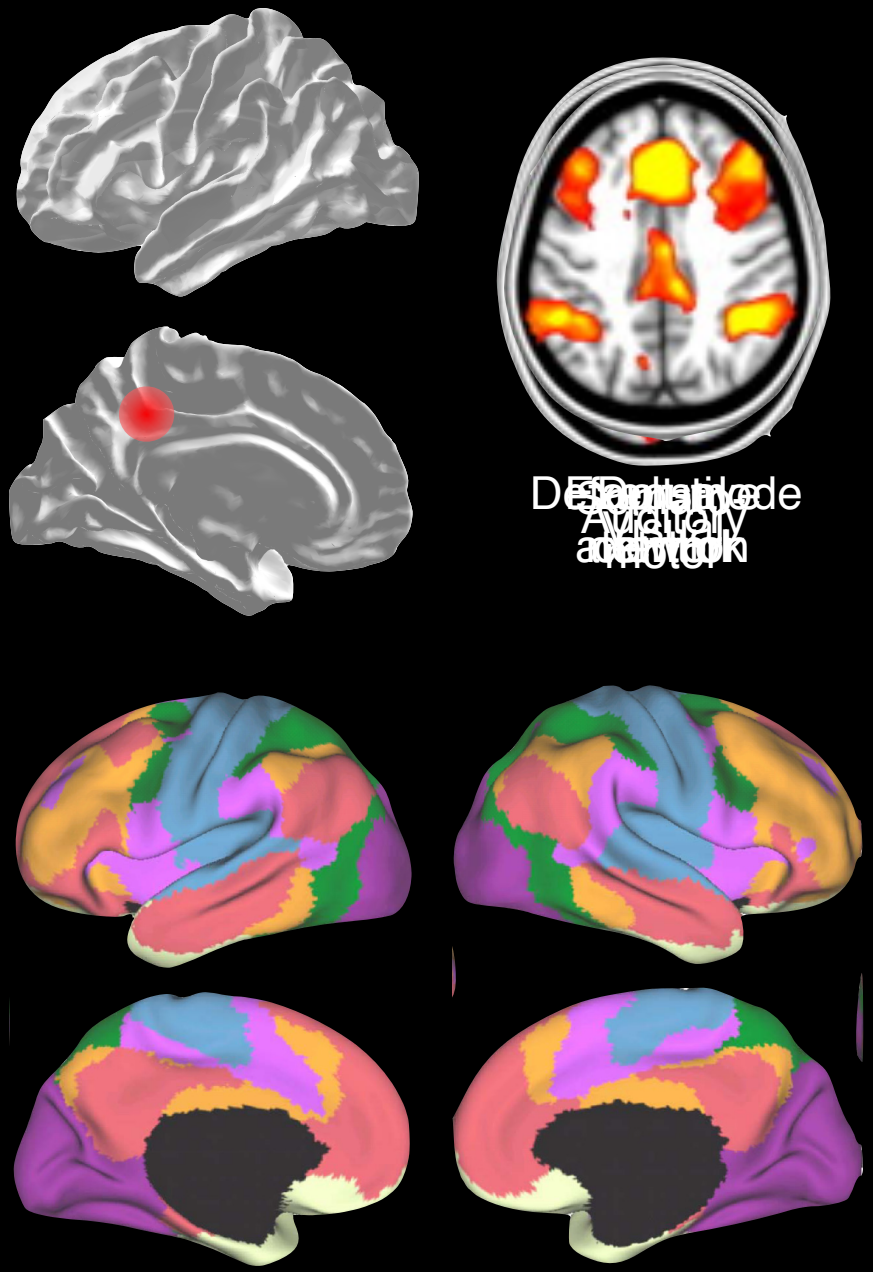
# Connectivity mapping: integration of the brain



# Connectivity mapping: functional networks

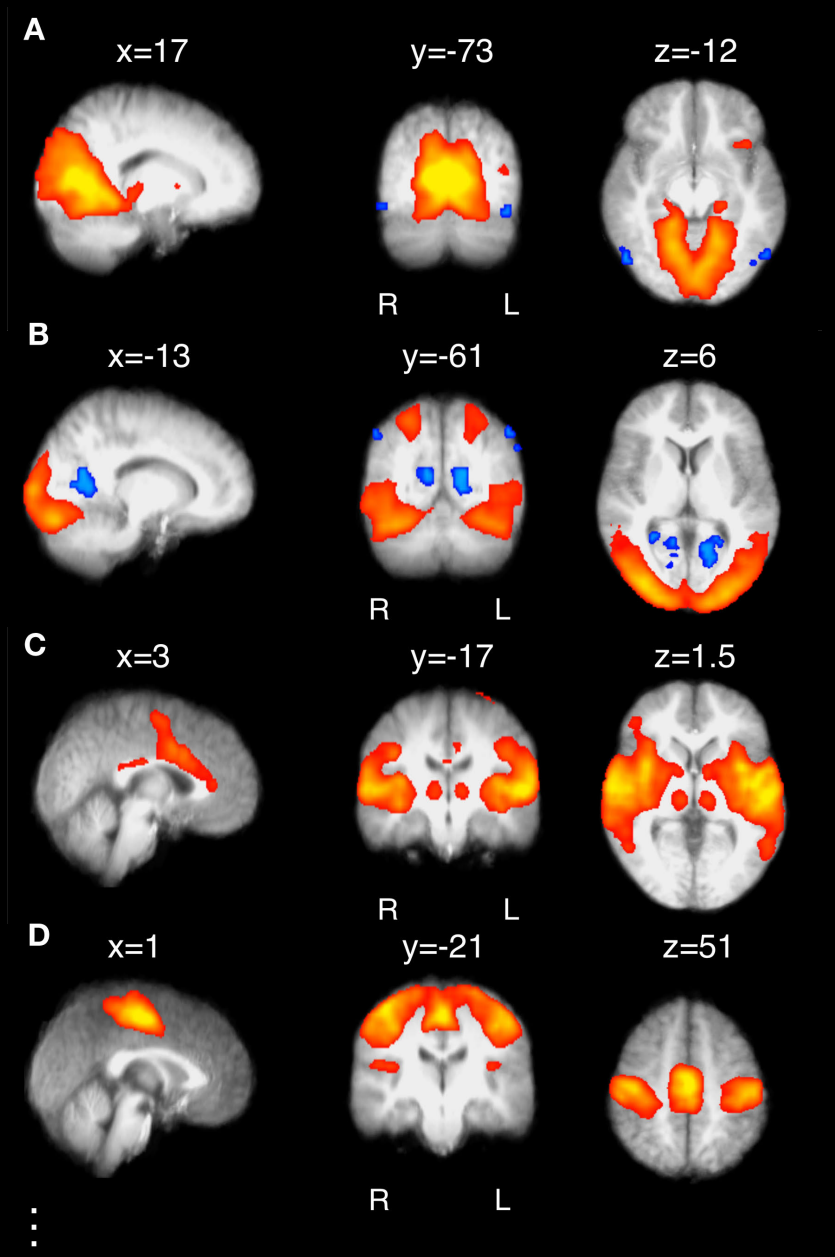
seed connectivity

clustering



[Adapted from Raichle, *TICS*, 2010;
Yeo et al, *J Neurophys.*, 2011]

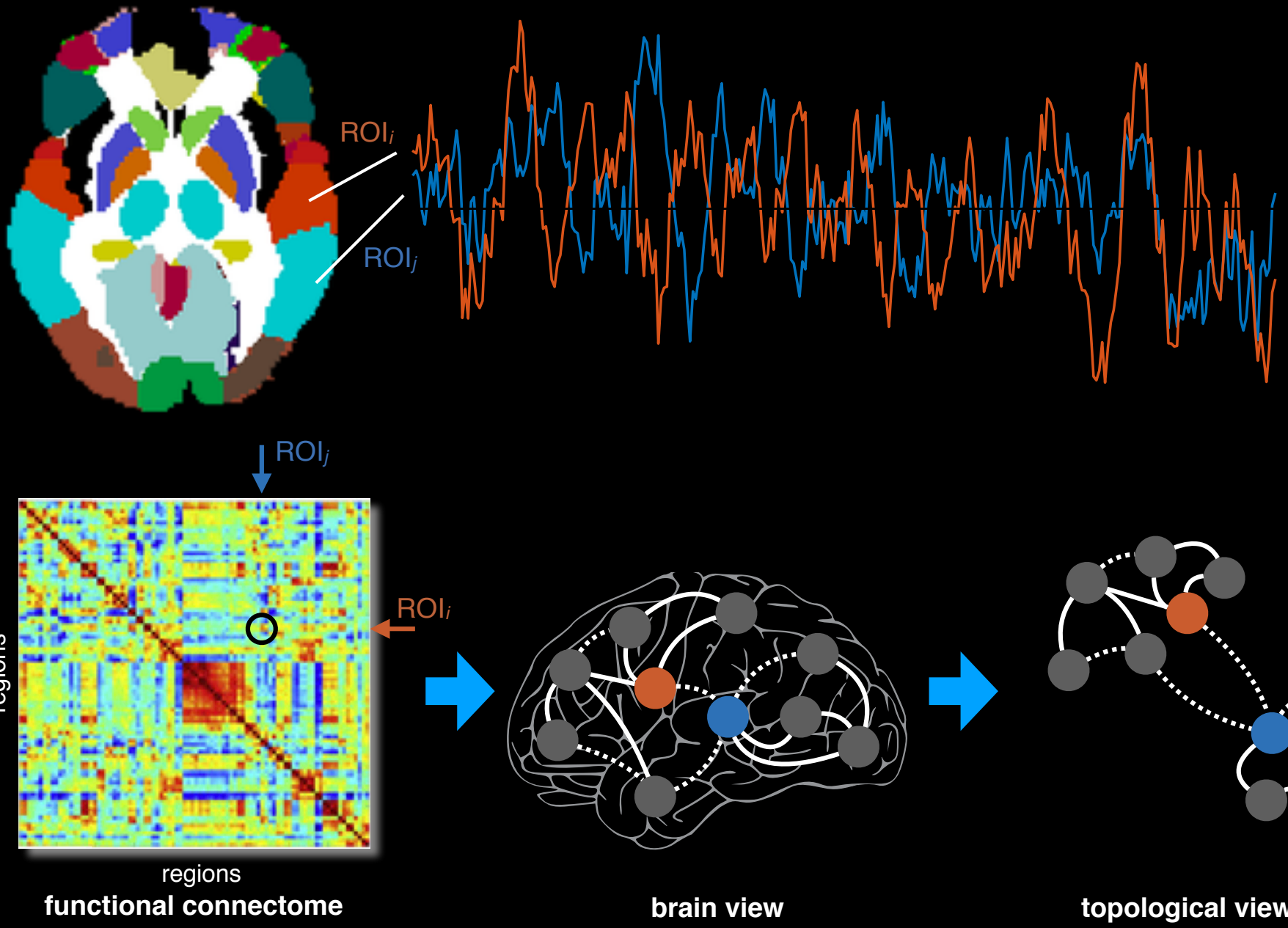
independent component analysis




[McKeown et al, 1998; Calhoun et al, 2001;
Beckmann et al. 2005]

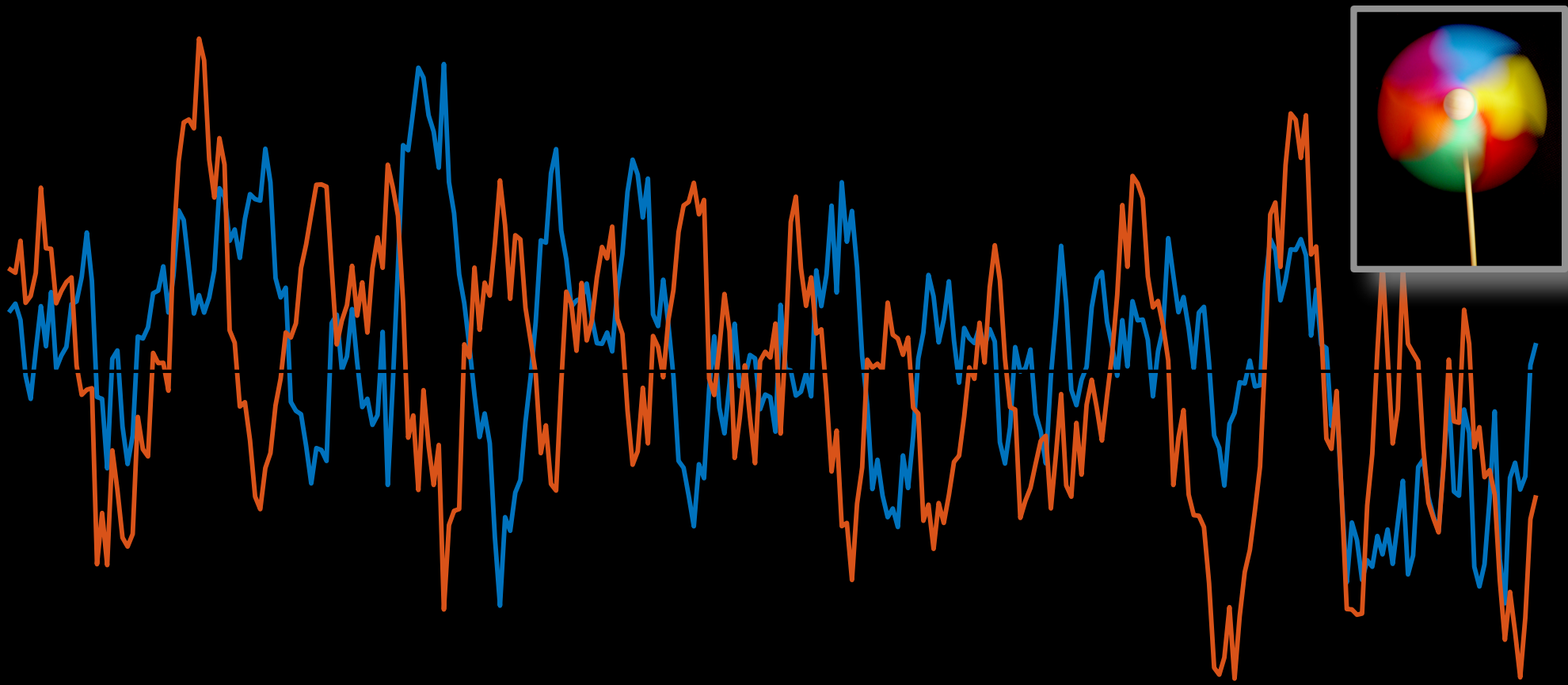
# Connectivity mapping: functional networks

graph models




[Bullmore and Sporns, *Nat Rev Neurosci*, 2009]

# Connectivity mapping: functional networks



- Functional connectivity (FC) establishes summary statistic over the whole (resting-state) run
  - Average behavior and insensitive to temporal order
- Need to acknowledge time-varying features of FC

# Dynamic functional connectome

- **Extracting** and representing time-resolved information from fMRI activity
  - *Correlational* measures (2nd order statistical measures)
    - Sliding-window functional connectivity
    - Connectivity *modes* versus *states* (i.e., latent space versus clustering)
    - Dynamic graphs
  - *Instantaneous* measures (1st order statistical measures)
    - Point process analysis; seed-based CAPs
    - Hemodynamic-informed transient activity (iCAPs)
- **Summarizing** time-resolved information
  - Observational summary statistics
    - Durations, dwell times, switchings, couplings, …
  - Temporal models
    - Generative models: autoregressive models, hidden Markov models
    - Information-theoretic approaches

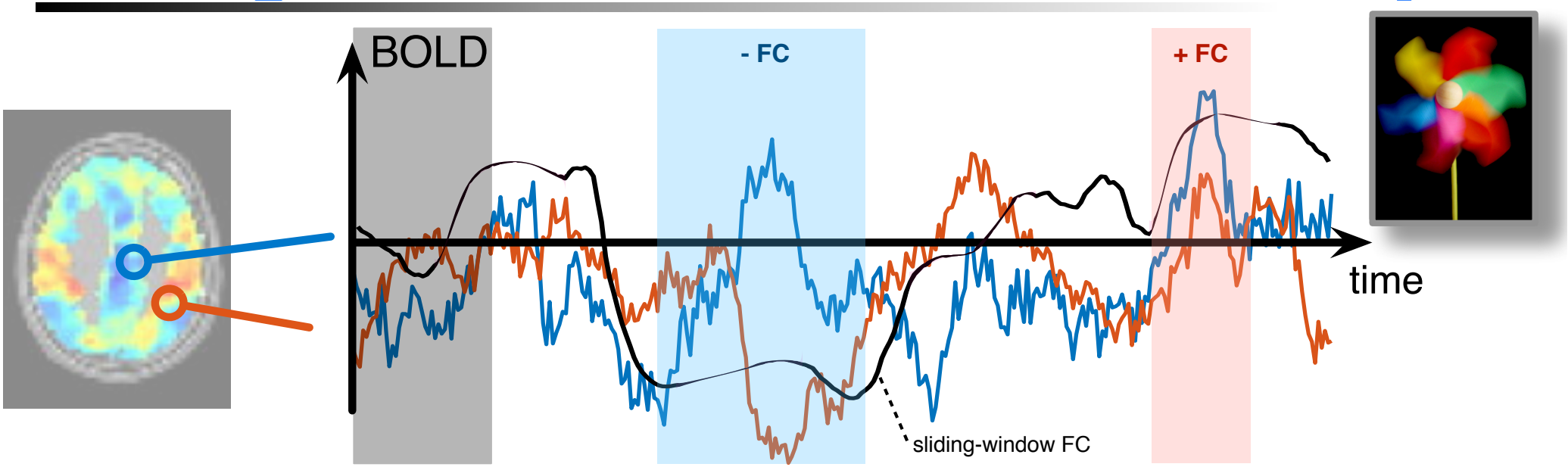
[Preti*, Bolton*, VDV, *Neuroimage*, 2017; Karahanoglu, VDV, *Current Op. Bioeng.*, 2017]

# Dynamic functional connectome

- **Extracting** and representing time-resolved information from fMRI activity
  - *Correlational* measures (2nd order statistical measures)
    - Sliding-window functional connectivity
    - Connectivity *modes* versus *states* (i.e., latent space versus clustering)
    - Dynamic graphs
  - *Instantaneous* measures (1st order statistical measures)
    - Point process analysis; seed-based CAPs
    - Hemodynamic-informed transient activity (iCAPs)
- **Summarizing** time-resolved information
  - Observational summary statistics
    - Durations, dwell times, switchings, couplings, …
  - Temporal models
    - Generative models: autoregressive models, hidden Markov models
    - Information-theoretic approaches

[Preti*, Bolton*, VDV, *Neuroimage*, 2017; Karahanoglu, VDV, *Current Op. Bioeng.*, 2017]

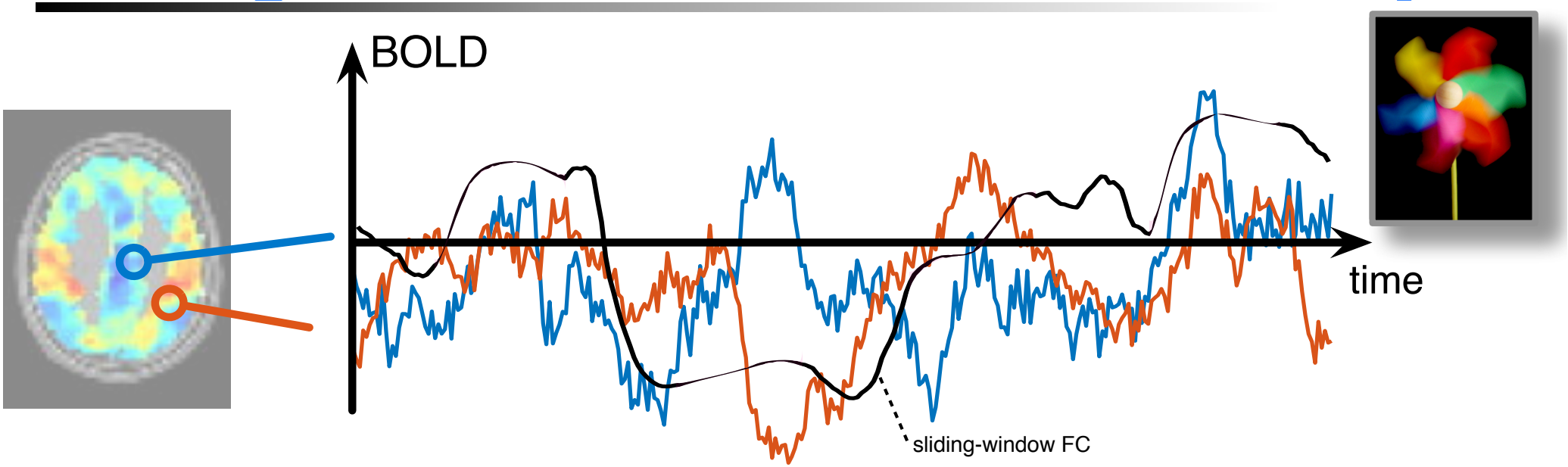
# Sliding-window functional connectivity

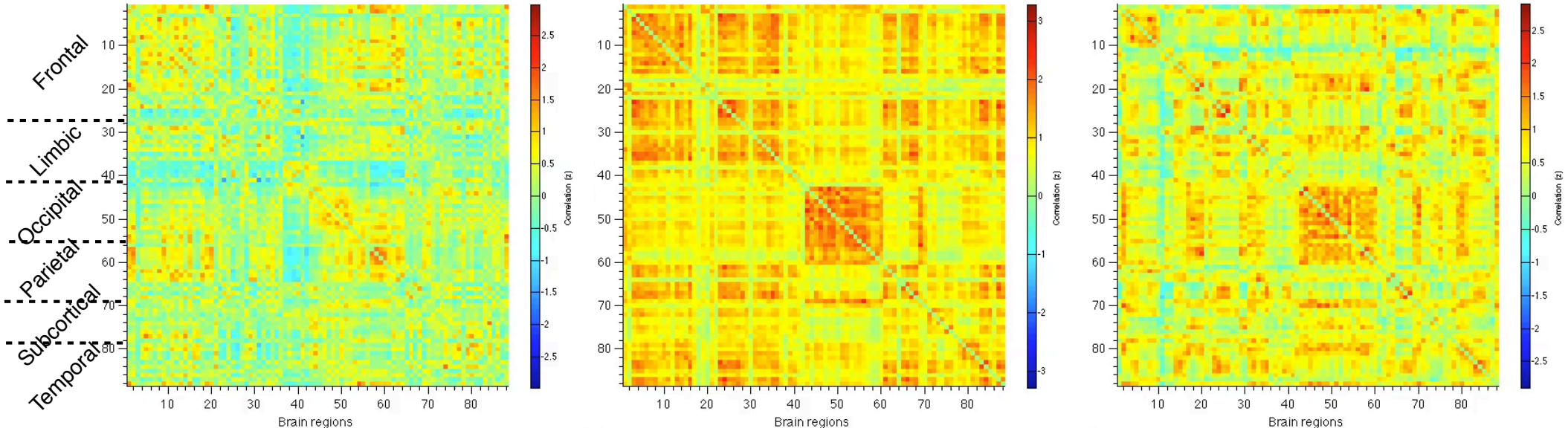



- Temporally windowed FC
  - Straightforward to implement
  - One FC value per window position
  - Trade-off for window length: shorter = access to faster dynamics
    - Suffers from lower SNR and thus lower statistical significance
    - Prone to aliasing without proper high-pass filtering
- Side-effect: large increase in number of extracted measures

[Chang and Glover, *NeuroImage*, 2010; Sakoglu et al, *MAGMA*, 2010; Leonardi, VDV, *NeuroImage*, 2014]

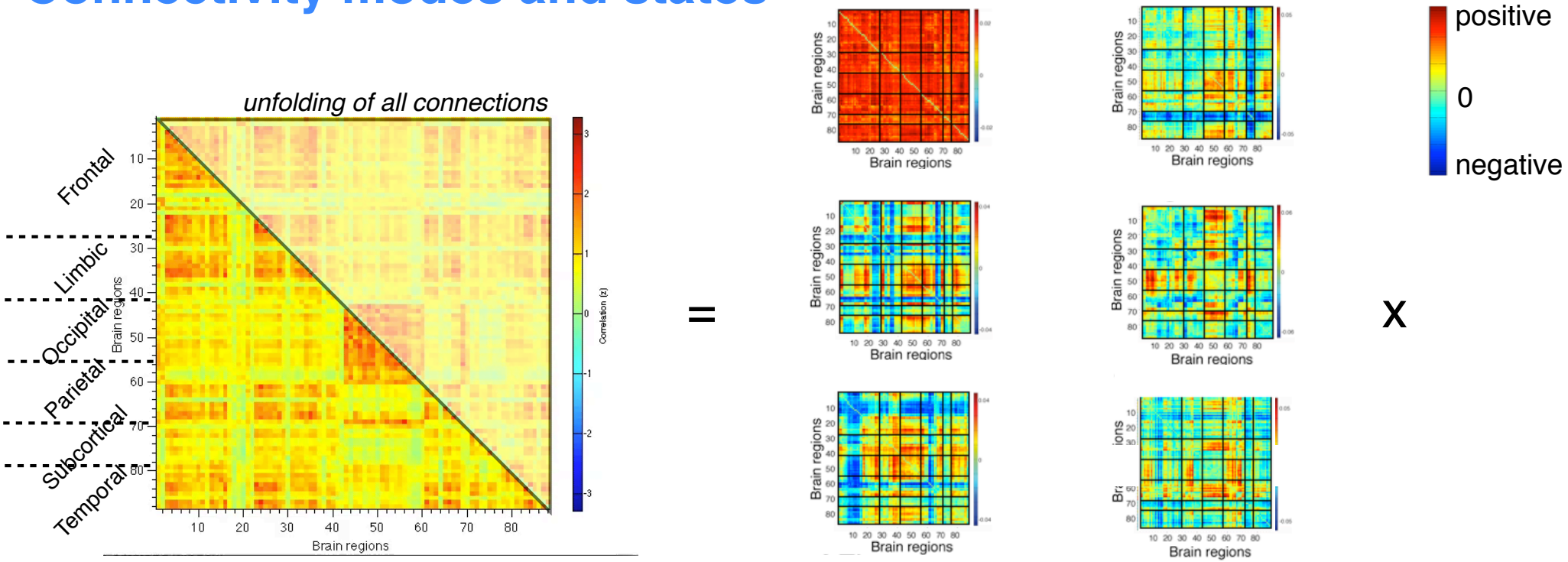
# Sliding-window functional connectivity

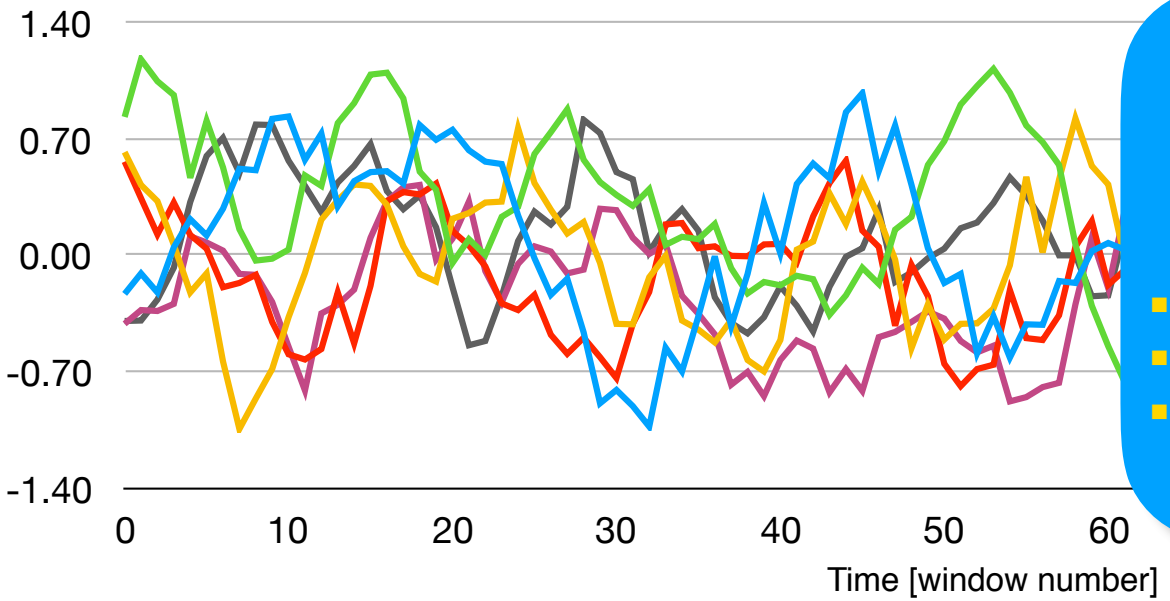



[Leonardi et al, *NeuroImage*, 2013; Hutchison et al, *HBM*, 2013; Allen et al, *Cerebral Cortex*,2014]

# Connectivity modes and states



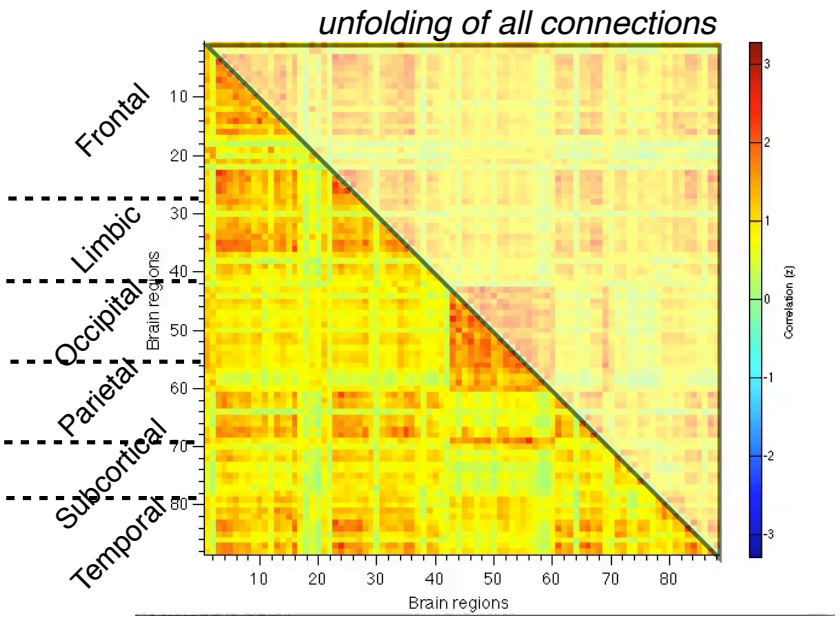




**Modes** by
singular value decomposition (SVD) /
principal component analysis (PCA)

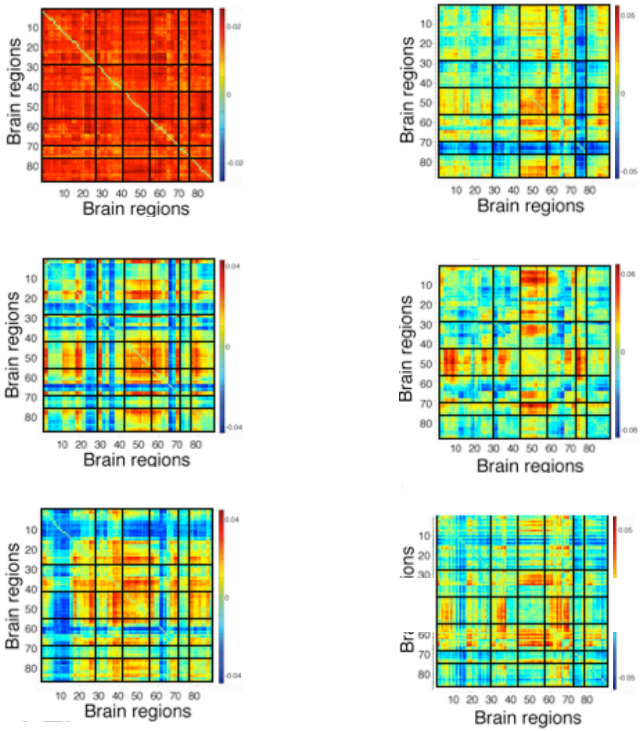
- optimized for explained variance
- orthogonality constraint
- average dynamic FC is subtracted out (i.e., driven by fluctuations of FC only)

[Leonardi et al, *NeuroImage*, 2013]

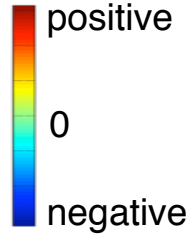
# Connectivity modes and states

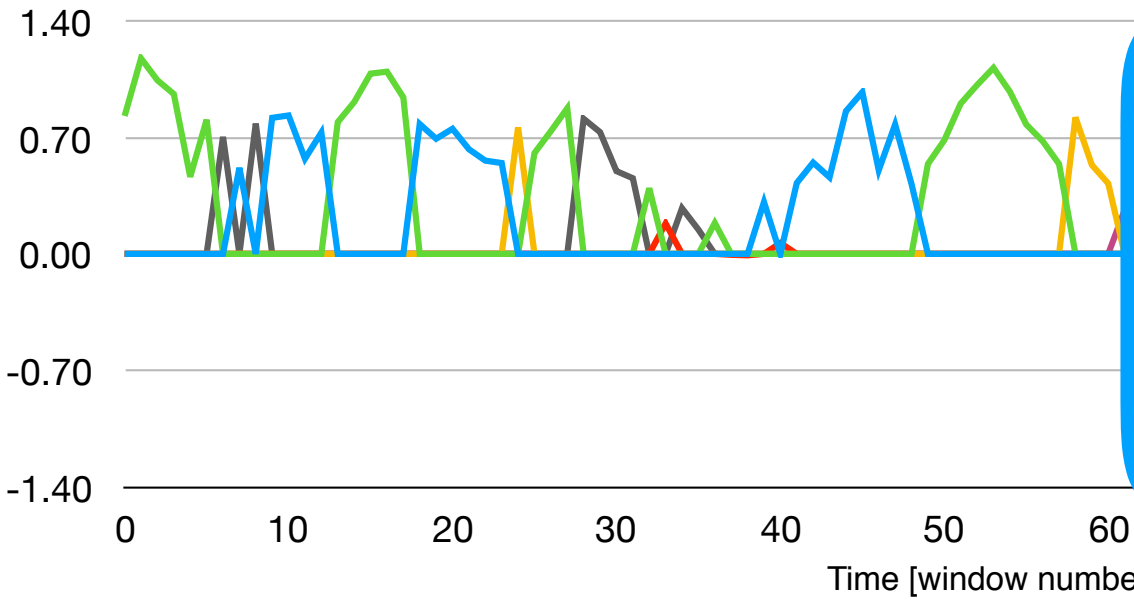



=




x



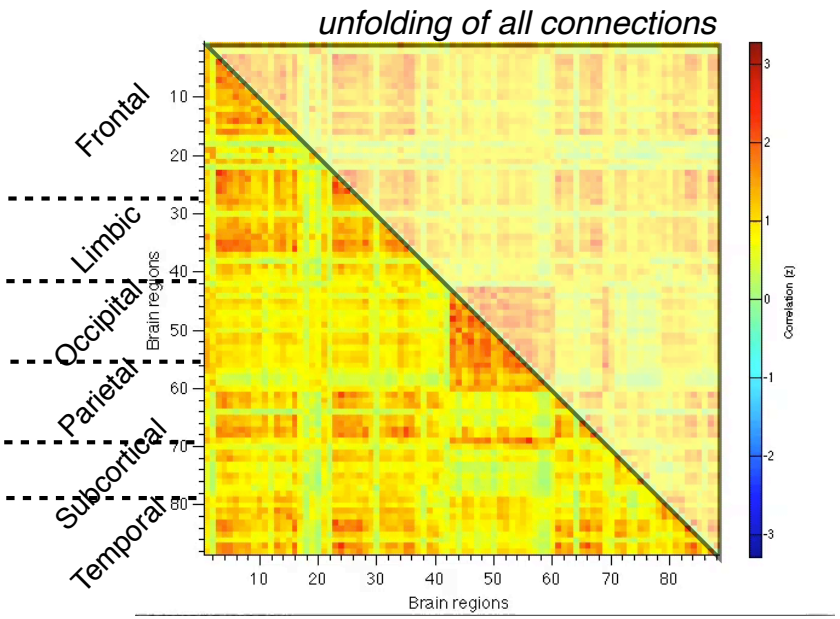




**States** by
k-means clustering and variants

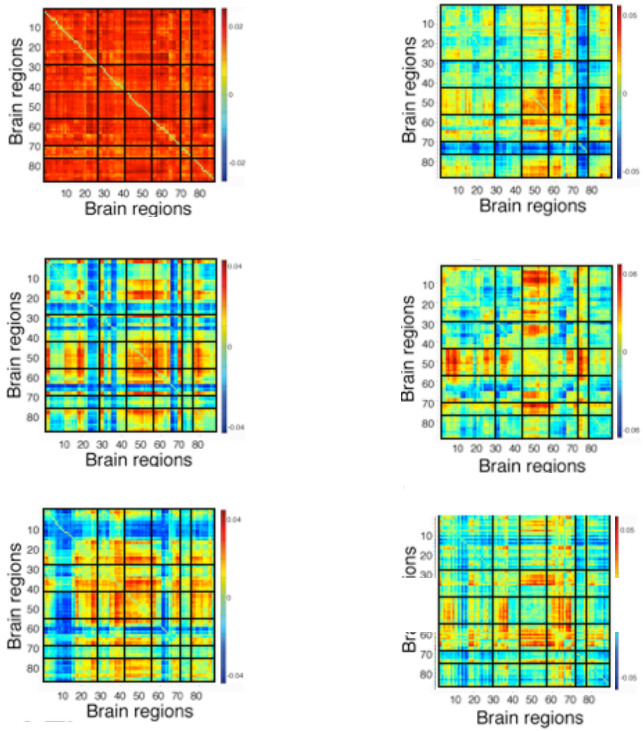
- winner takes it all strategy
- matching criterion is usually “shape” based (e.g., cosine distance)

[Allen et al, *Cerebral Cortex*, 2014]

# Connectivity modes and states




=

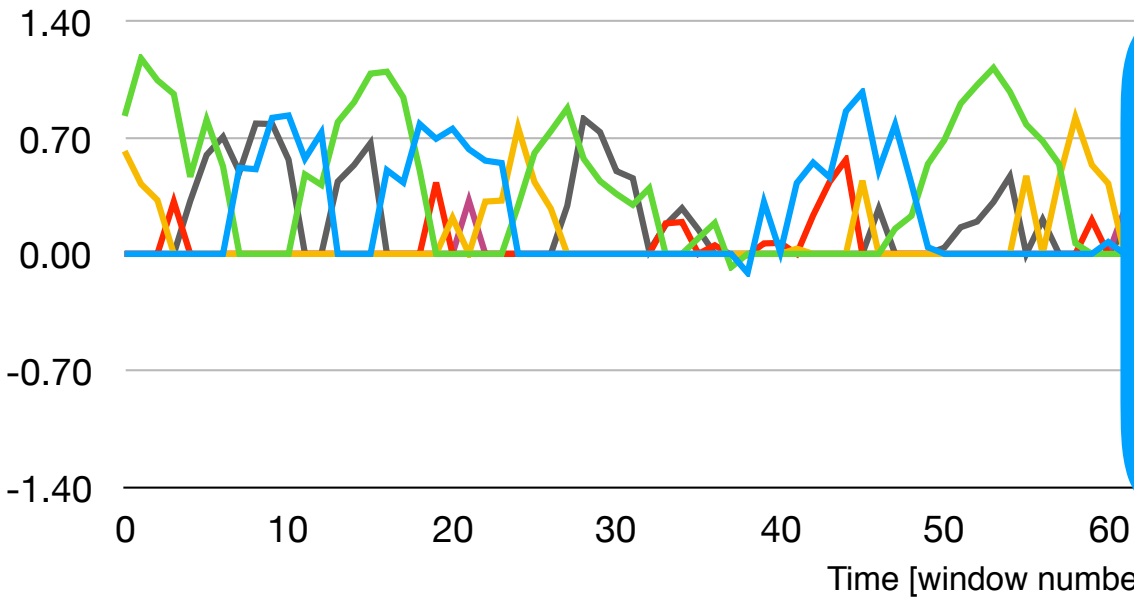



x

positive

0

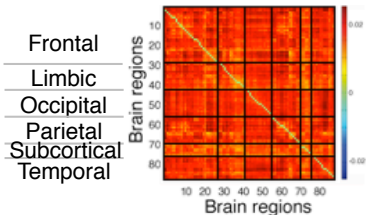
negative

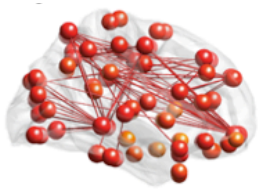


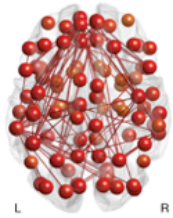

**Mixed mode-state** by dictionary learning (e.g., k-SVD)

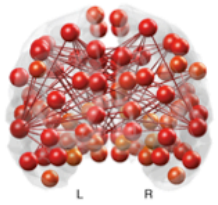
- few winners for each timepoints
- optimized for explained variance; other constraints can be added (non-neg.)
- explained variance increases by #flexibility (amount of superposition) and #states

[Leonardi et al, *HBM*, 2014; Miller et al, *PLoS One*, 2016; Grandjean et al, *NeuroImage*, 2017]

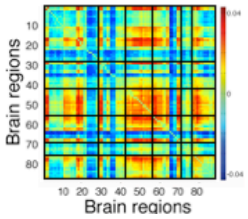


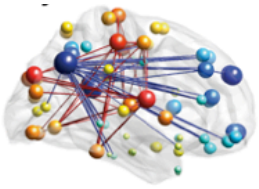



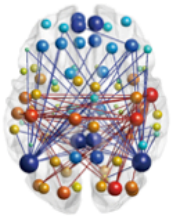


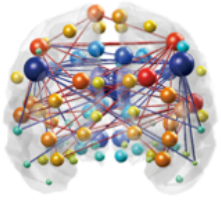




global fluctuations in FC (no GSR)

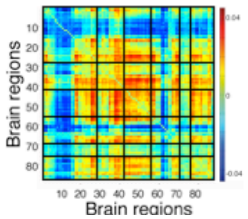


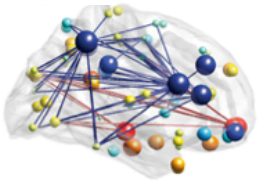



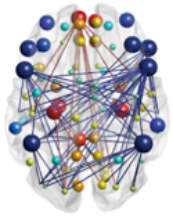


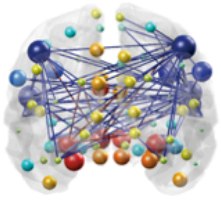


cingulate gyri, medial frontal gyri, precuneus (default-mode network)
primary sensory in red

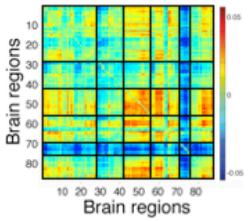


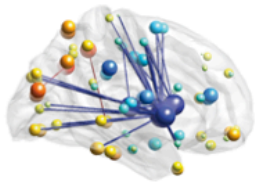



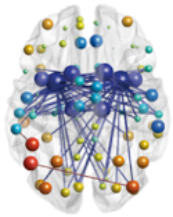


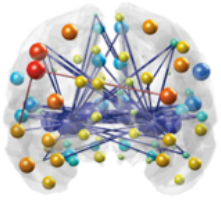


inferior and middle frontal gyri, inferior parietal
(fronto-parietal)

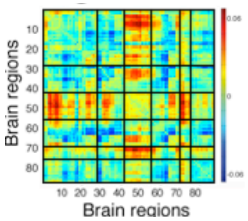


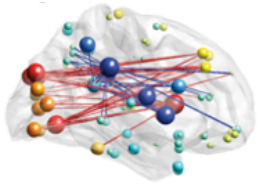



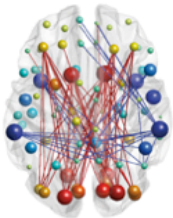


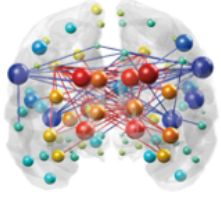


subcortical

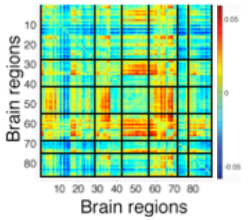


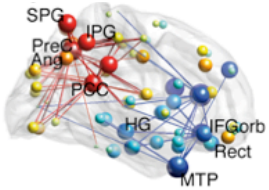



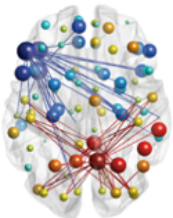


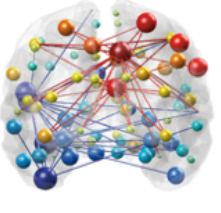


visual

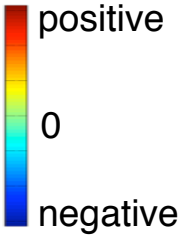


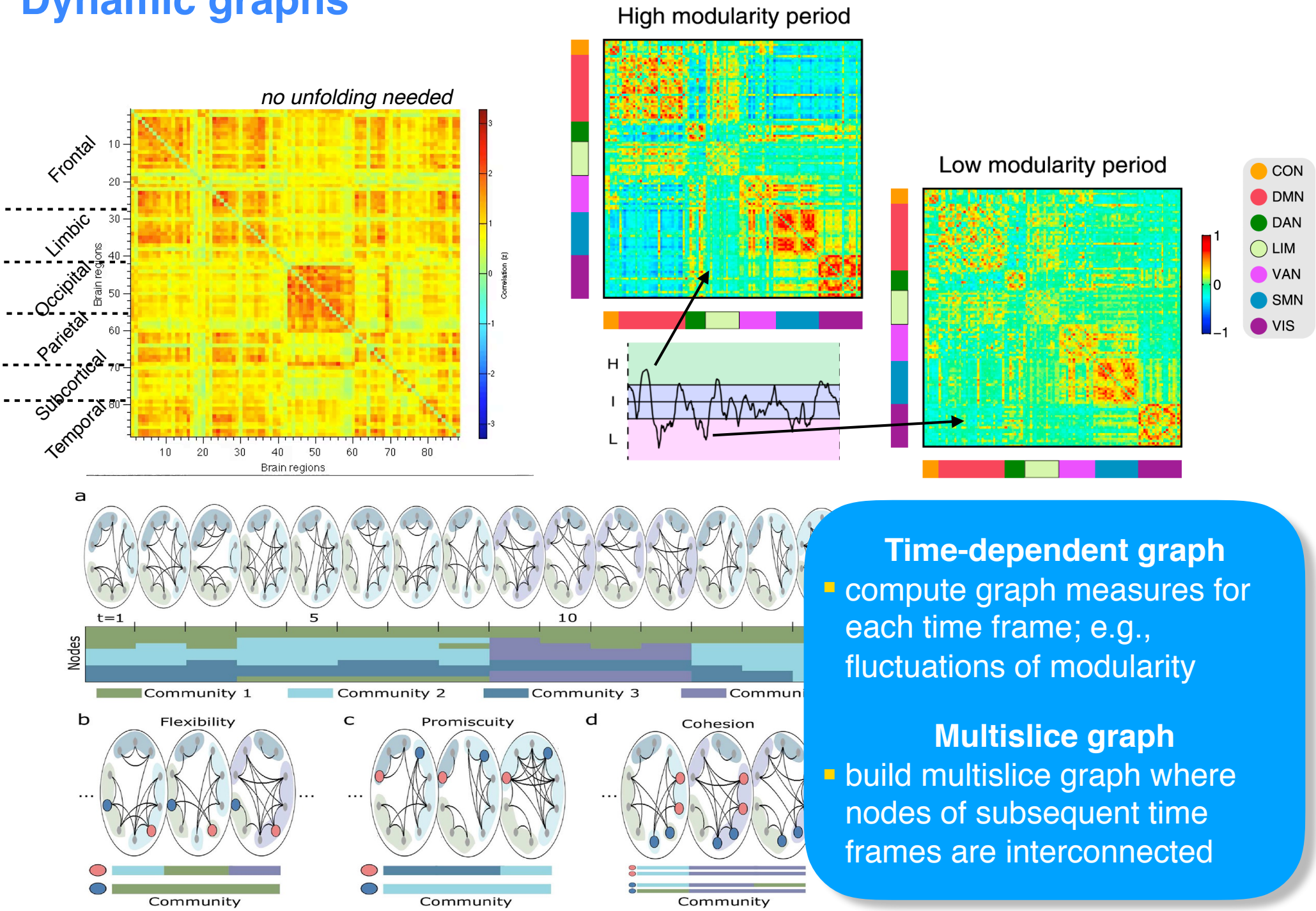


posterior DMN
temporal and inferior frontal




[Leonardi et al, *NeuroImage*, 2013]

# Dynamic graphs




**Time-dependent graph**

- compute graph measures for each time frame; e.g., fluctuations of modularity

**Multislice graph**

- build multislice graph where nodes of subsequent time frames are interconnected

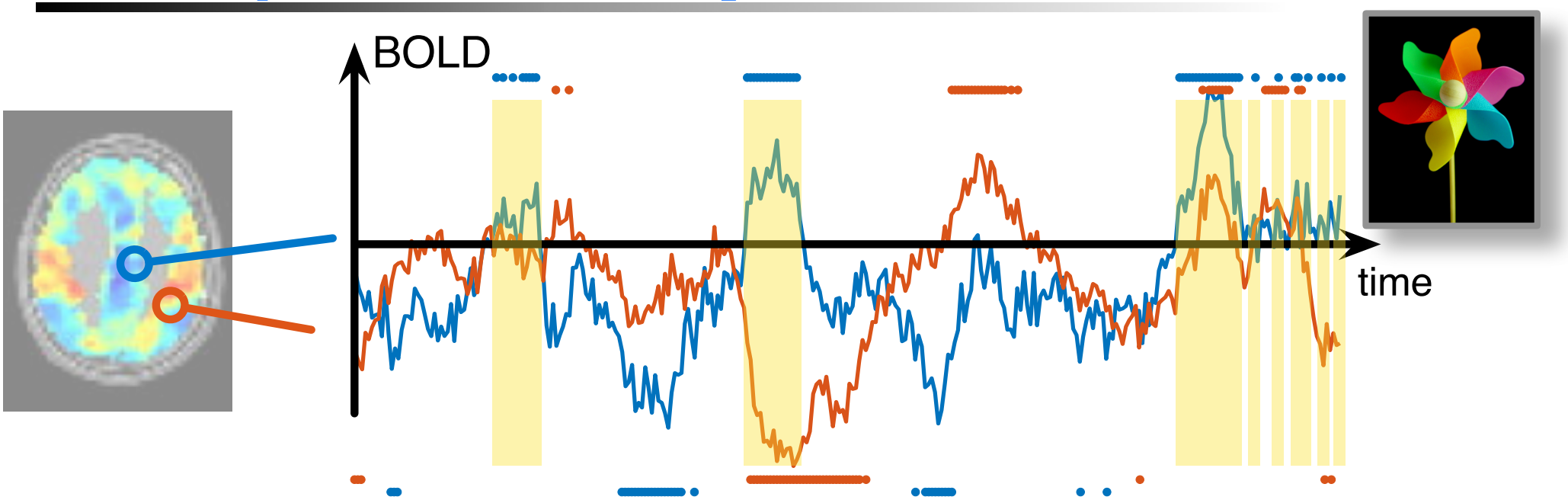
[Qu et al, *NeuroImage*, 2015; Fukushima et al, *NeuroImage*, 2018; Sizemore, Bassett, *NeuroImage*, 2018]

# Dynamic functional connectome

- **Extracting** and representing time-resolved information from fMRI activity
  - *Correlational* measures (2nd order statistical measures)
    - Sliding-window functional connectivity
    - Connectivity *modes* versus *states* (i.e., latent space versus clustering)
    - Dynamic graphs
  - *Instantaneous* measures (1st order statistical measures)
    - Point process analysis; seed-based CAPs
    - Hemodynamic-informed transient activity (iCAPs)
- **Summarizing** time-resolved information
  - Observational summary statistics
    - Durations, dwell times, switchings, couplings, …
  - Temporal models
    - Generative models: autoregressive models, hidden Markov models
    - Information-theoretic approaches

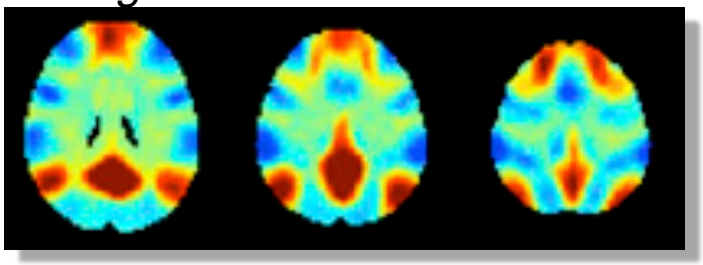
[Preti, Bolton, VDV, *Neuroimage*, 2017; Karahanoglu, VDV, *Current Op. Bioeng.*, 2017]

# Point process analysis

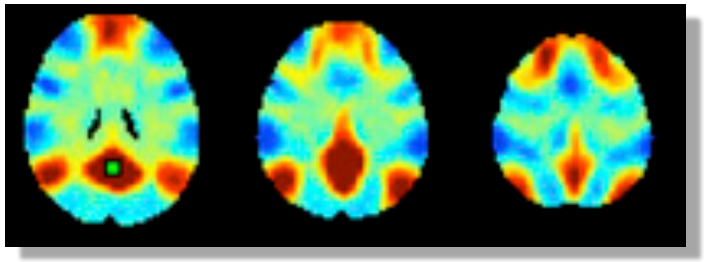



- Identifying data frames that correspond to “key events”
  - Exceeding threshold of activity timecourse of seed region
- Averaging of all selected frames leads to proxy for seed connectivity

*average over all selected frames:*

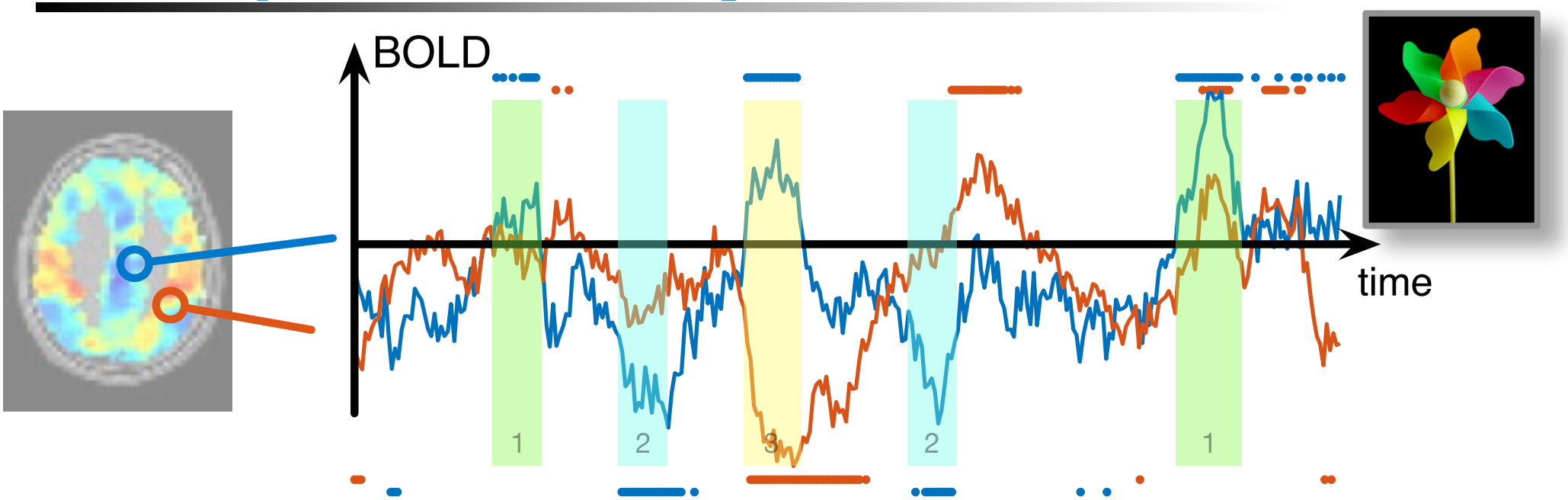


*seed-based correlation:*

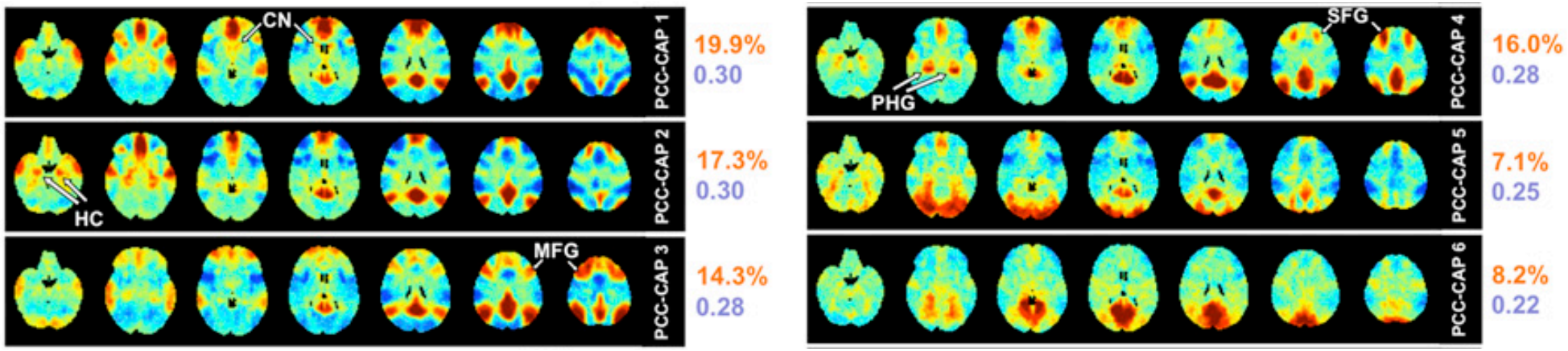


[Tagliazucchi et al, *Neurosci Lett*, 2011 and *Front Physio*, 2012; Liu and Duyn, *PNAS*, 2013]

# Point process analysis

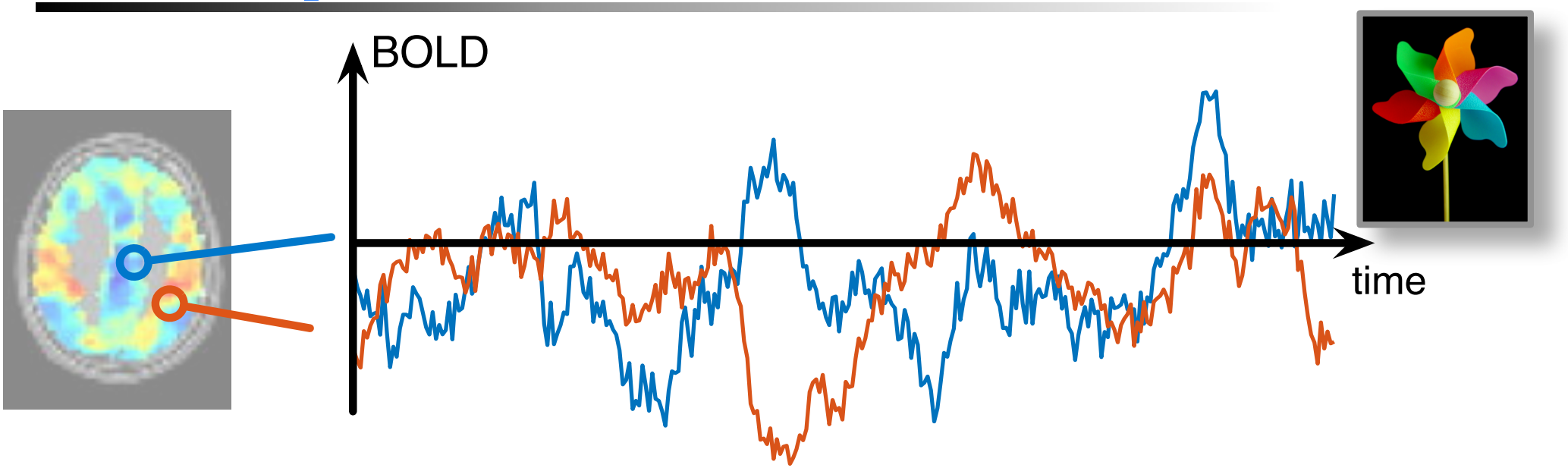



- Temporal clustering of selected frames
  - Spatial representatives are co-activation patterns (CAPs)



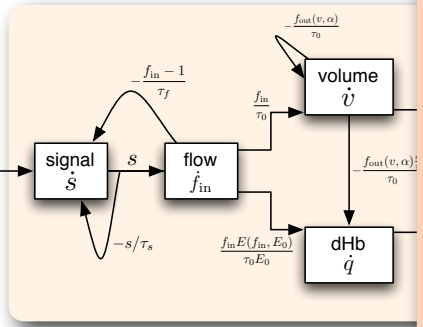

[Liu and Duyn, *PNAS*, 2013]

# Hemodynamic-informed transients




- Incorporate knowledge about hemodynamic response

activity-inducing signal




*States*

| | |
|---|---|
| $u$ | stimulus |
| $s$ | flow inducing signal |
| $f_{in}$ | blood flow |
| $v$ | normalized venous volume |
| $q$ | normalized dHb content |

***First-order Volterra kernel***

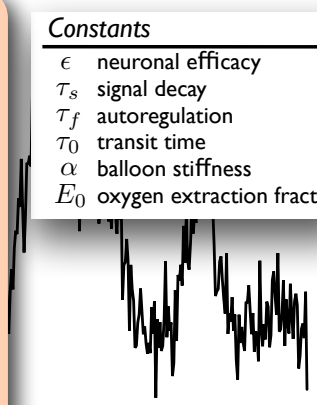
$$H = \frac{D - \gamma I}{\prod_{i=1}^{4}(D - \alpha_i I)}$$

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

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

*Constants*

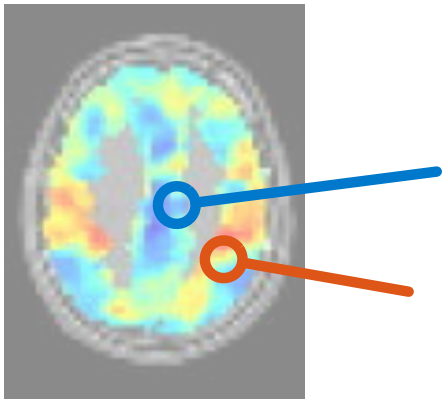
| | |
|---|---|
| $\epsilon$ | neuronal efficacy |
| $\tau_s$ | signal decay |
| $\tau_f$ | autoregulation |
| $\tau_0$ | transit time |
| $\alpha$ | balloon stiffness |
| $E_0$ | oxygen extraction fraction |

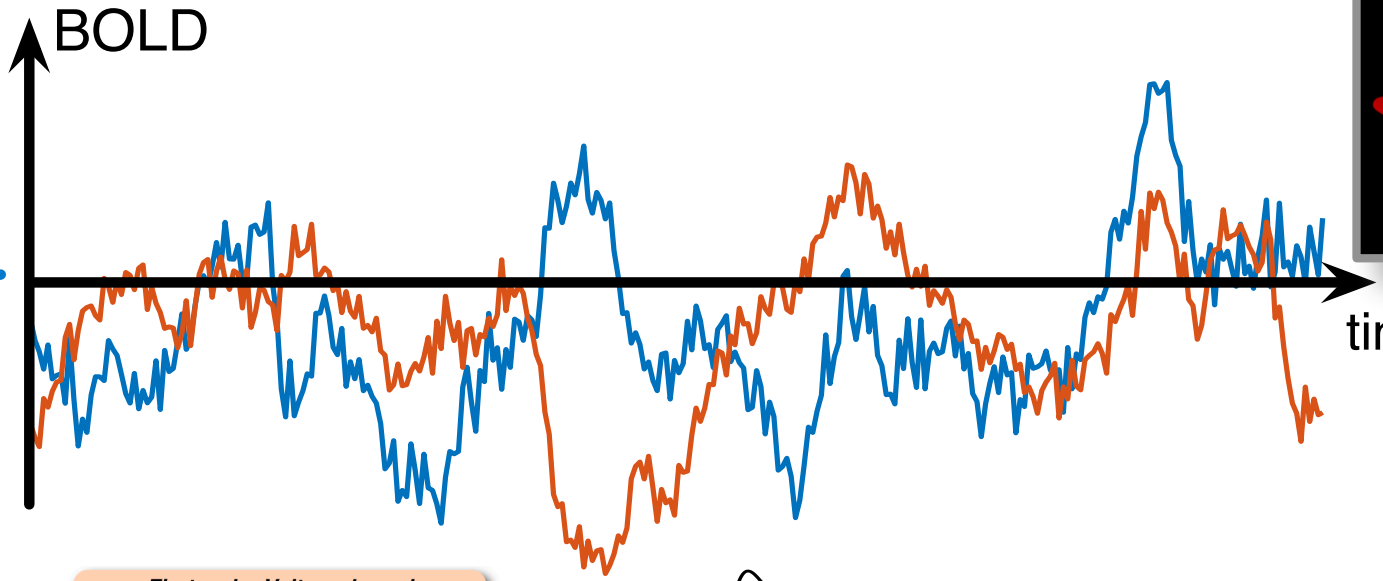


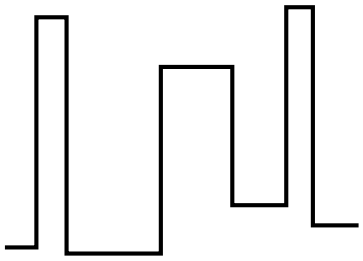
ed BOLD signal

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

# Hemodynamic-informed transients





activity-inducing signal

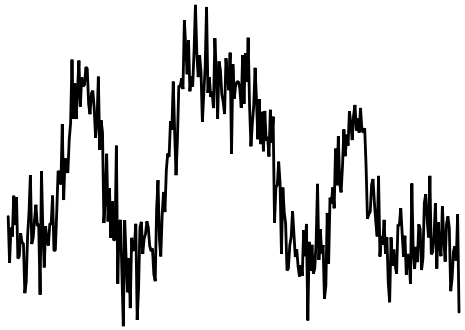
**First-order Volterra kernel**

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

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

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

ideal BOLD signal



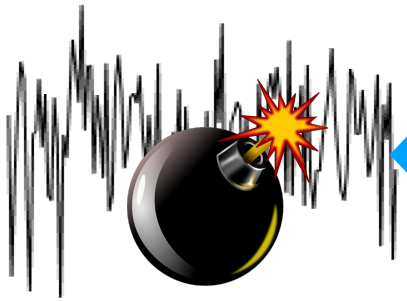
measured BOLD signal

**Inverse: linear differential operator**

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

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

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

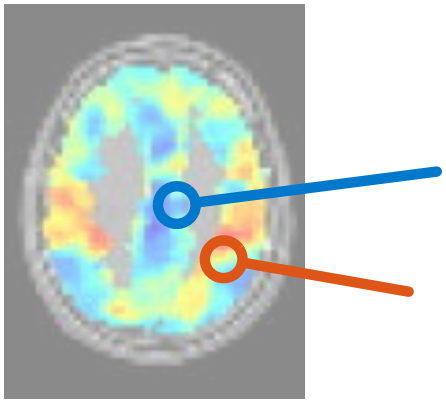


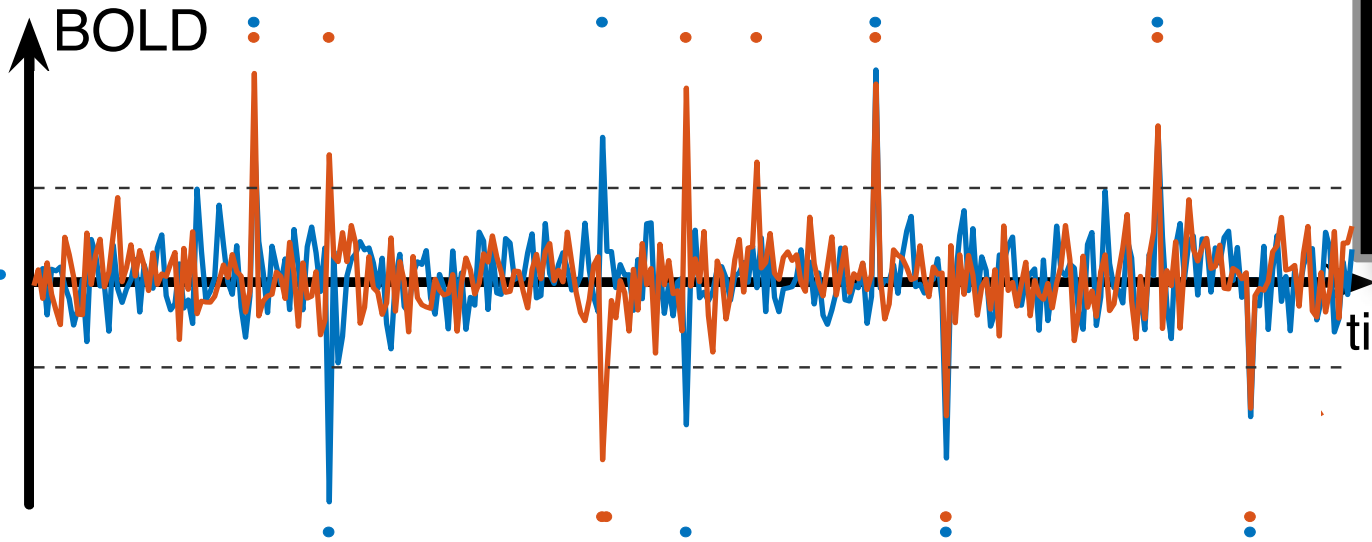
filtered signal

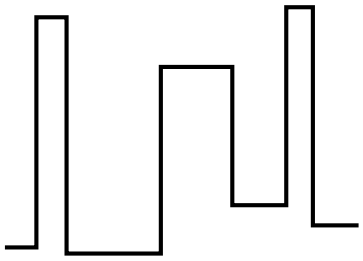
*thou canst not recover what is lost*

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

# Hemodynamic-informed transients





activity-inducing signal

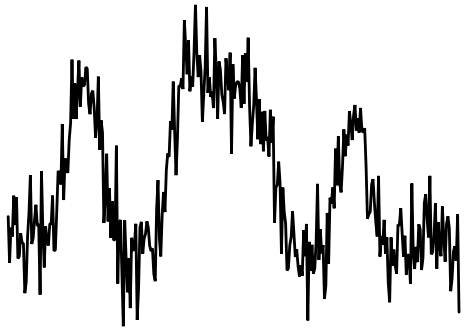
***First-order Volterra kernel***

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

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

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

ideal BOLD signal



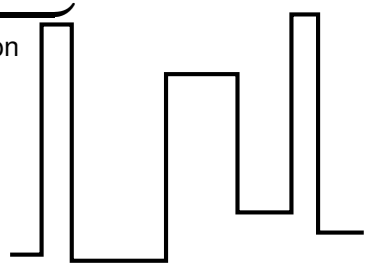
measured BOLD signal

***Inverse: linear differential operator***

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

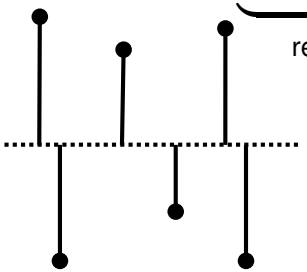
$$\vec{\alpha} = \left\{ -\frac{1}{\tau_0}, -\frac{1}{\alpha\tau_0}, -\frac{1}{2\tau_s}\left(1 \pm j\sqrt{\frac{4\tau_s^2}{\tau_f} - 1}\right) \right\},$$

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



recovered activity-inducing signal

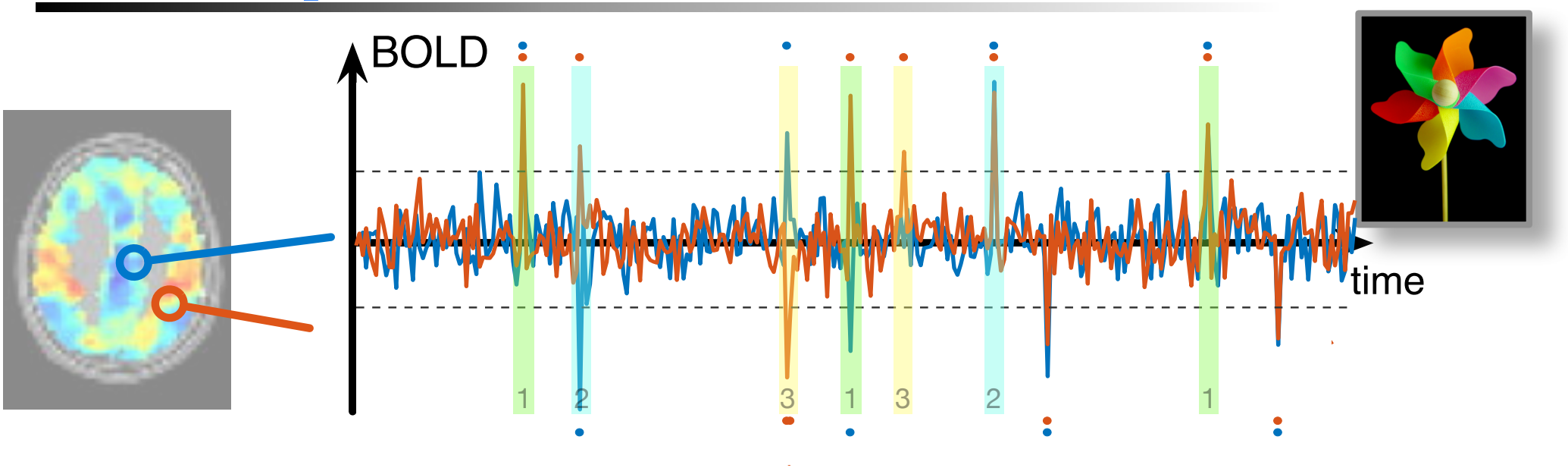
$$\underbrace{||DH^{-1}\{\boldsymbol{x}\}||_1}_{\text{regularization}}$$



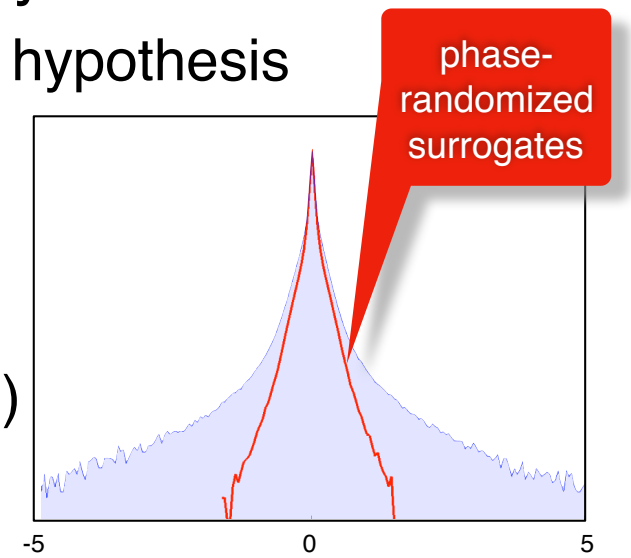
innovation signal

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

# Hemodynamic-informed transients

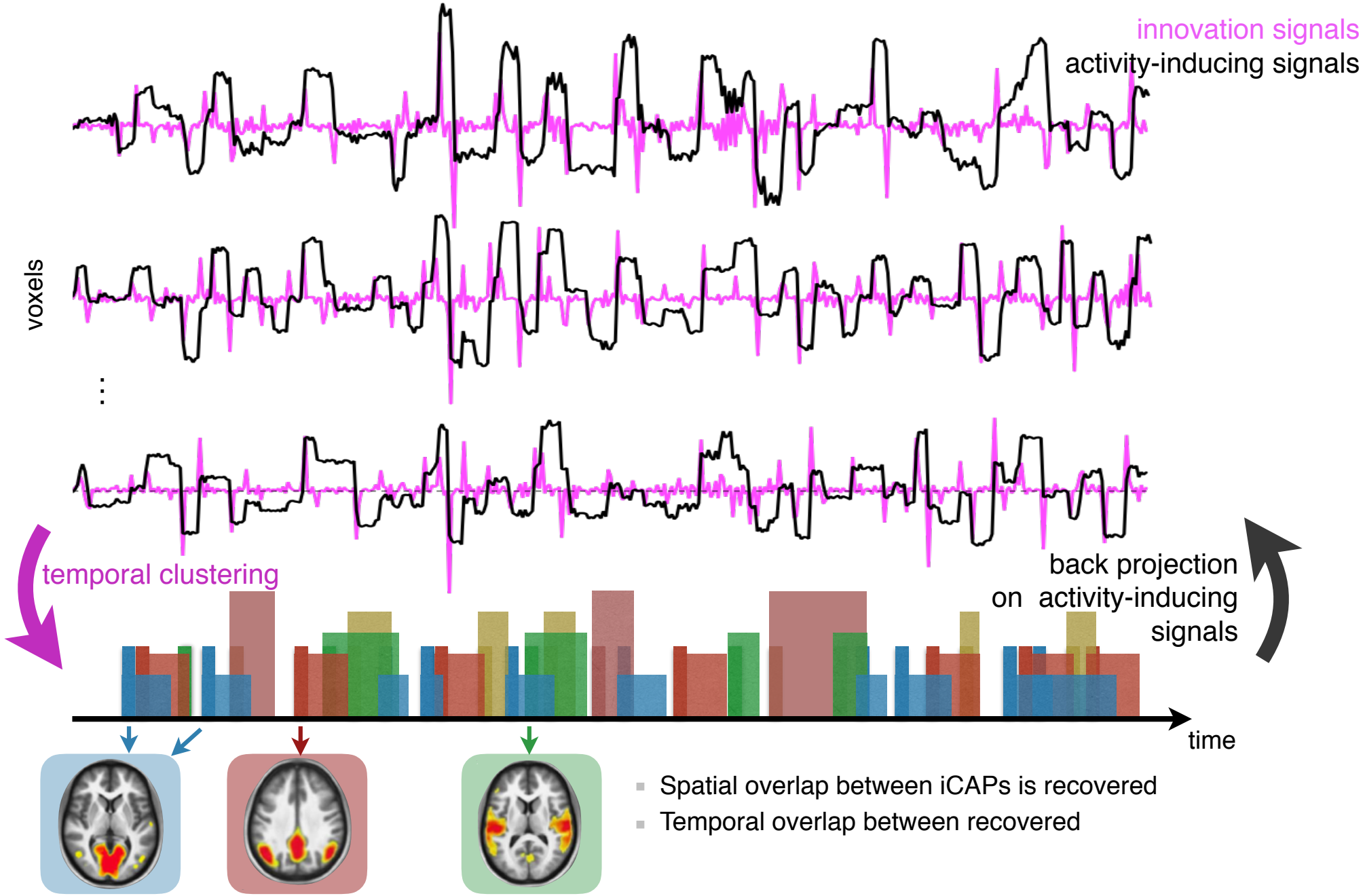



- Identifying data frames that correspond to “key transient events”
  - Amount of whole-brain innovation exceeds null hypothesis
- Temporal clustering of selected frames from innovation signals
  - Spatial representatives are innovation-driven co-activation patterns (iCAPs)




[Karahanoglu, VDV, *Nat Comm*, 2015]

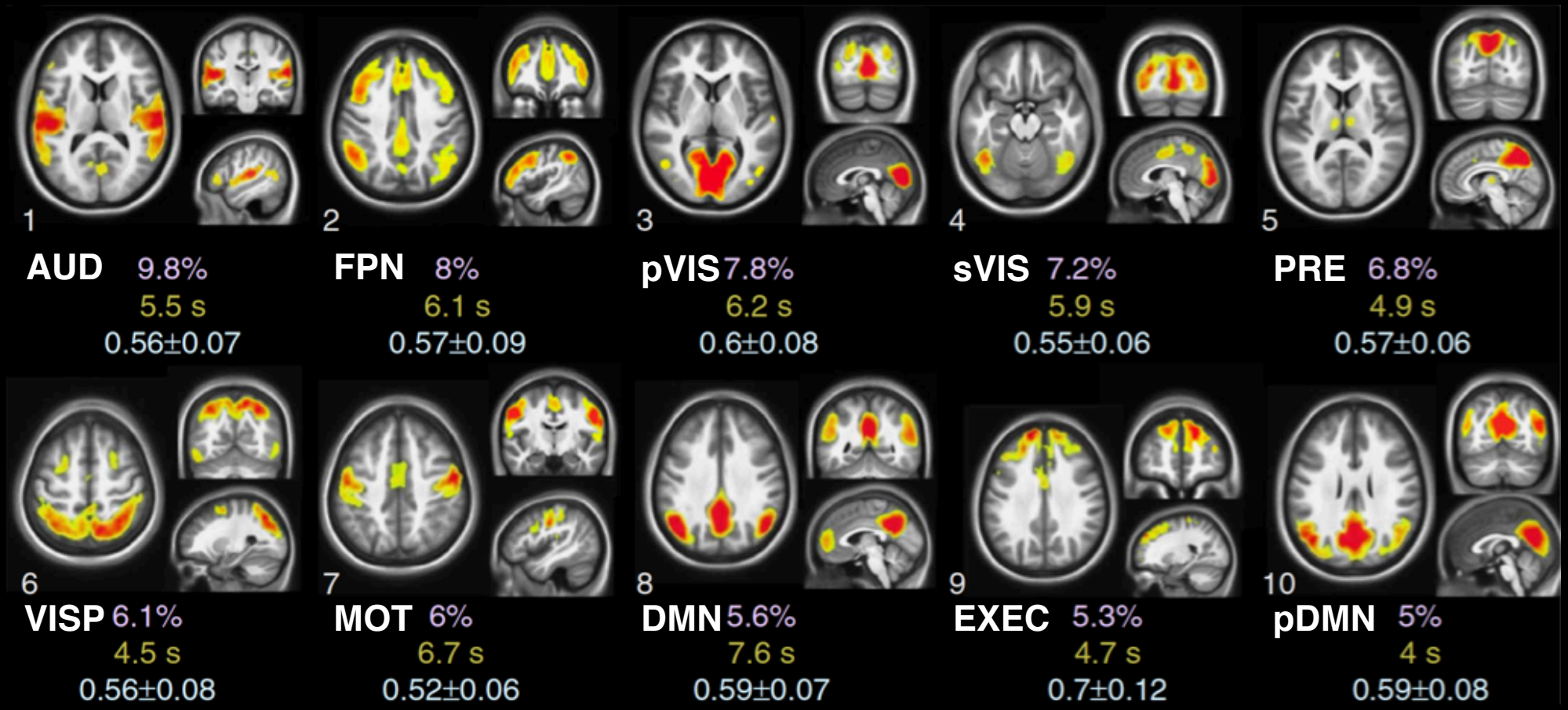
# Hemodynamic-informed transients



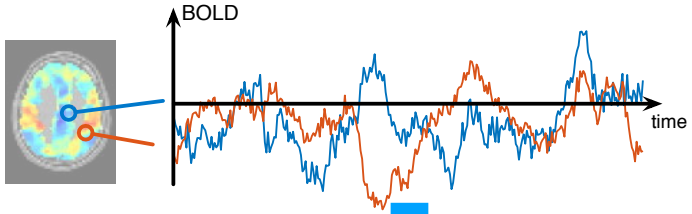

- Spatial overlap between iCAPs is recovered
- Temporal overlap between recovered

[Karahanoglu and VDV, *Nat Comm*, 2015; Zöller et al, *IEEE TMI*, in press]

# Repertoire of functional brain networks (iCAPs)

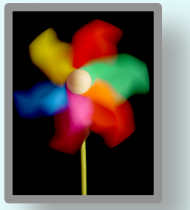


# Summarizing time-resolved information




## Correlational measures

connectivity modes or states



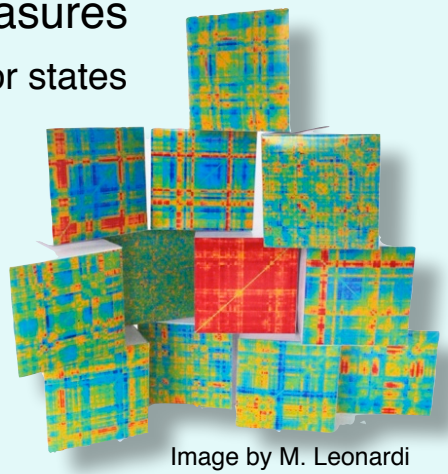
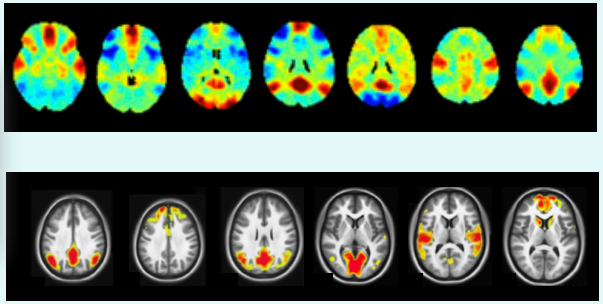


Image by M. Leonardi

## Instantaneous measures

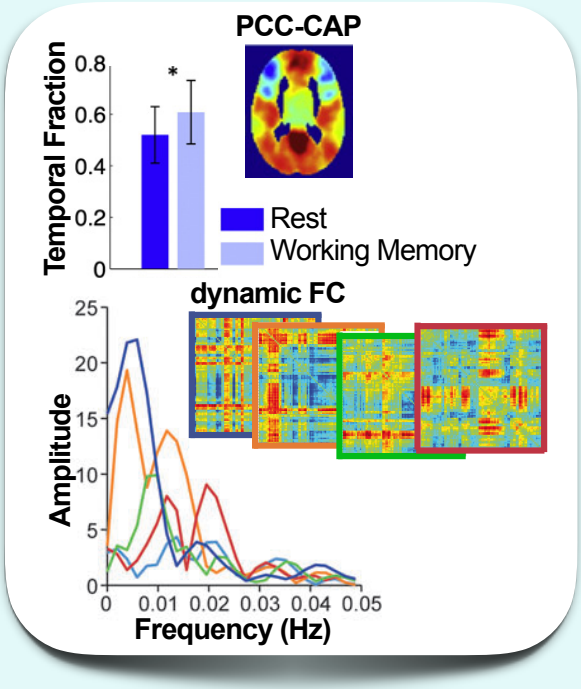
CAPs and iCAPs



[Karahanoglu, VDV, *Curr. Op. Bioengineering*, 2017]

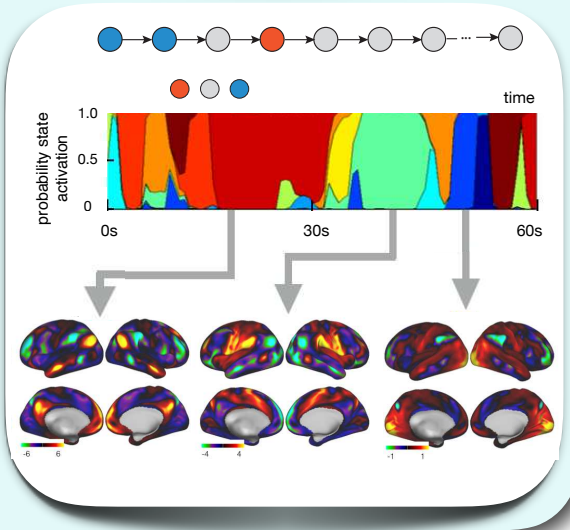
## Observational summary statistics

durations
fractions
dwell times
spectral analysis
switchings
couplings
graph measures
…



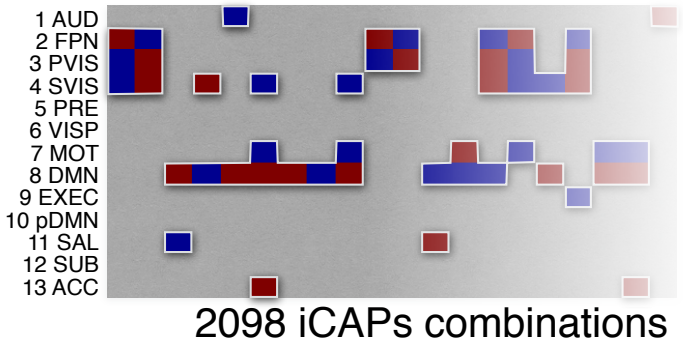

## Temporal models

autoregressive models
hidden Markov models
information-theoretic
deep neural networks
…

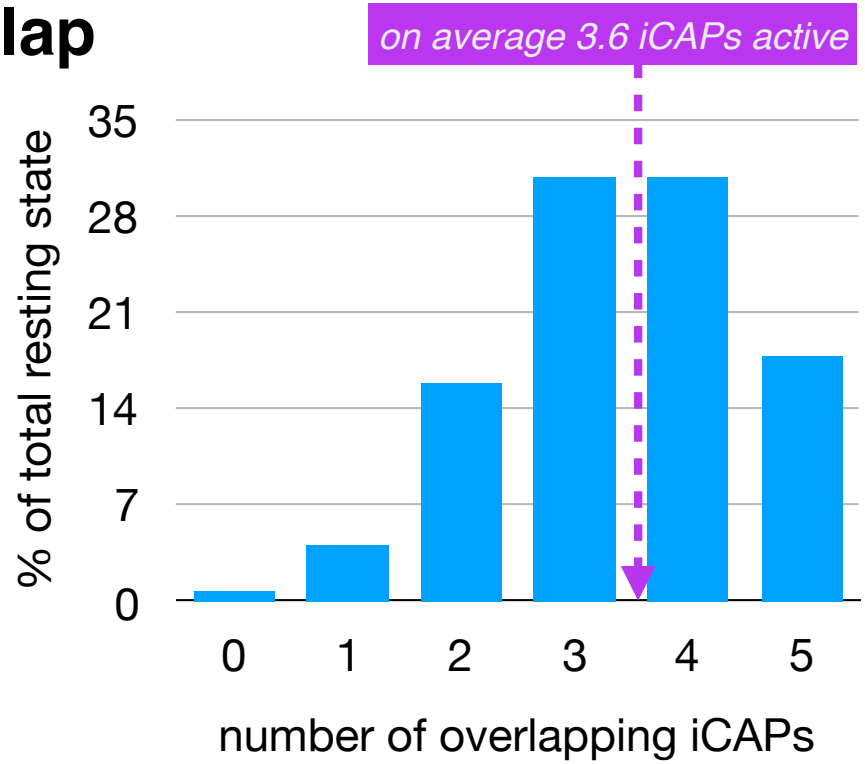



[Chen et al, 2015, 2017; Allen et al, 2014, Vidaurre et al. 2017; Bolton et al, 2018; Ashourvan et al, 2017; …]

# Meaning of iCAPs' temporal overlap



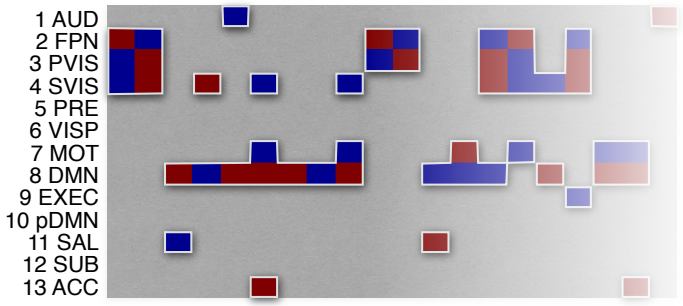

histogram




- Significant overlap at any point in time

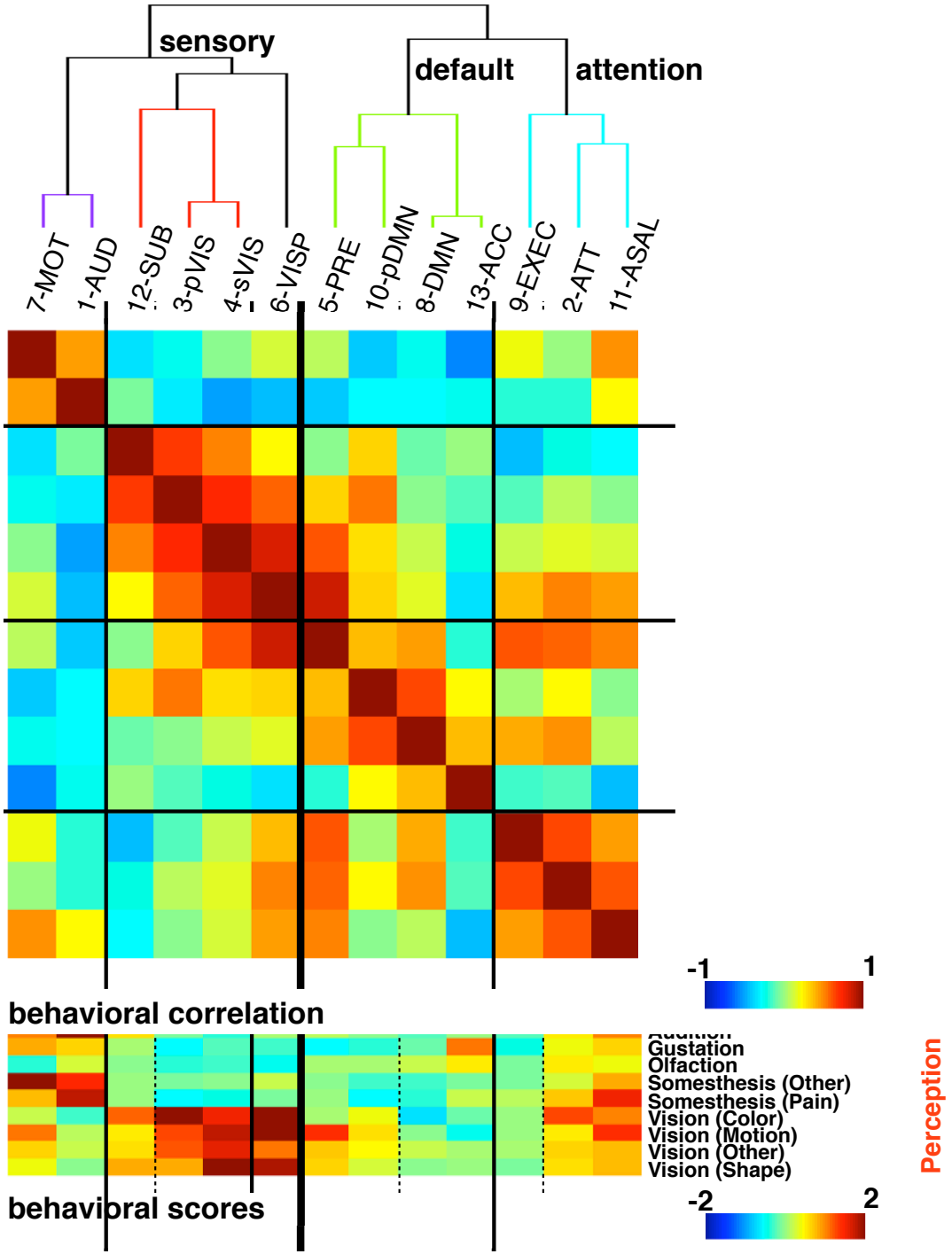
[Karahanoglu and VDV, *Nat Comm*, 2015]

# Meaning of iCAPs' temporal overlap




2098 iCAPs combinations

hierarchical clustering

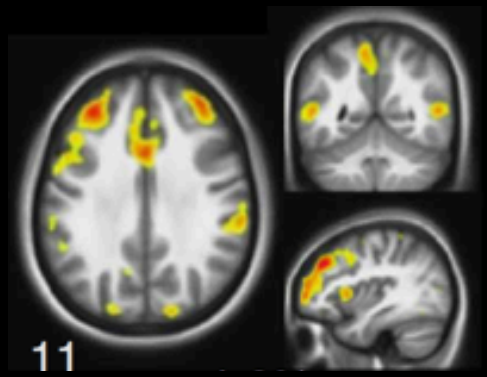



- Significant overlap at any point in time
- Highest level of hierarchy according to temporal overlap: sensory / default / attention
- Behavioral profiles of iCAPs' spatial maps form are consistent with the their "usage"

[Karahanoglu and VDV, *Nat Comm*, 2015; Lancaster et al, Frontiers Neuroinformatics, 2012]

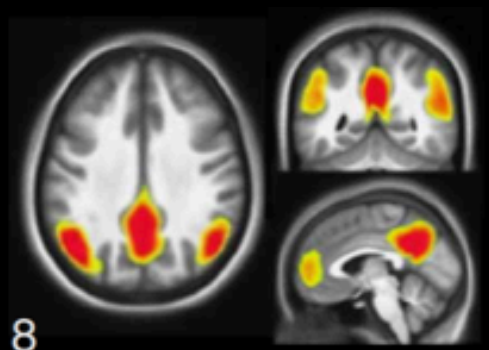
# Rethink models extrapolated from conventional FC

Salience network



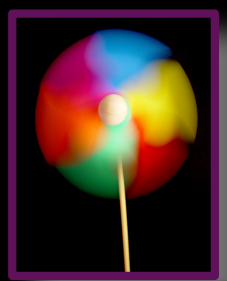

*psychomotor activity*
*goal-directed action*
*sensory & limbic processing*

Default mode network

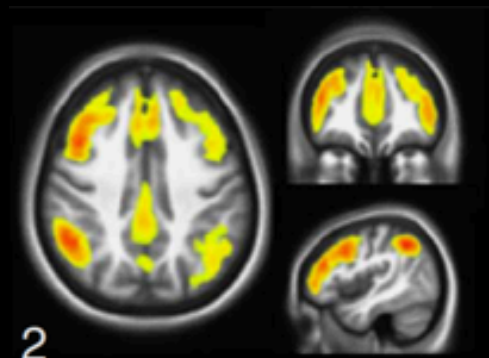



*self-referential mental activity*

**anticorrelation**



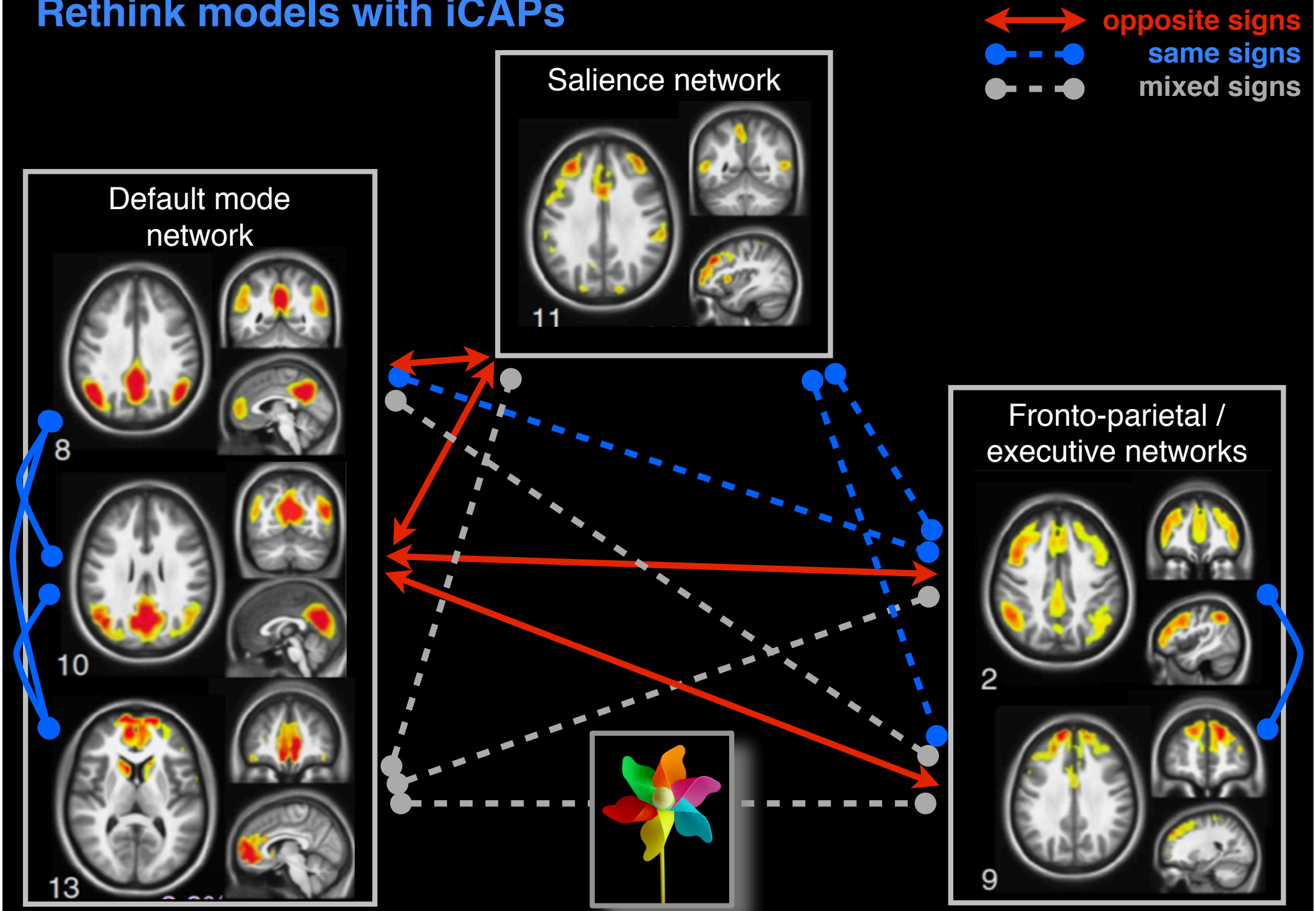
Fronto-parietal / executive networks




*cognition, attention*

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

# Rethink models with iCAPs

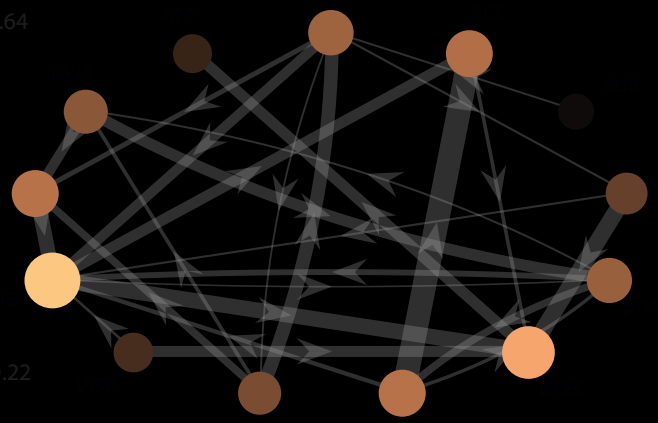


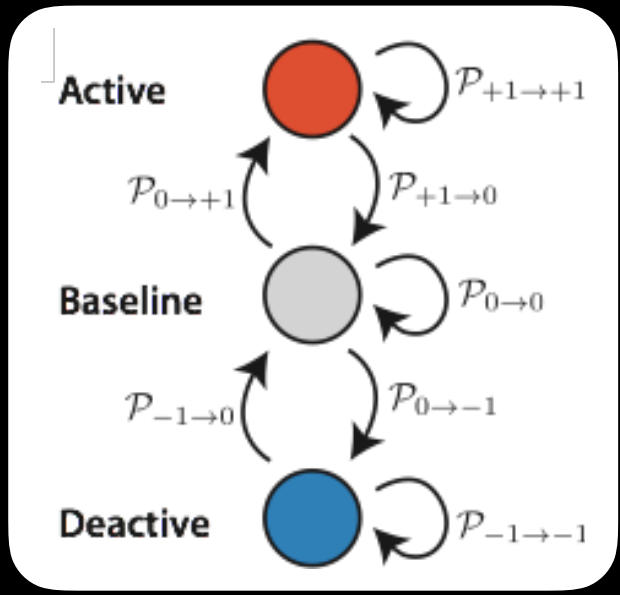

[Karahanoglu and VDV, *Nat Comm*, 2015]

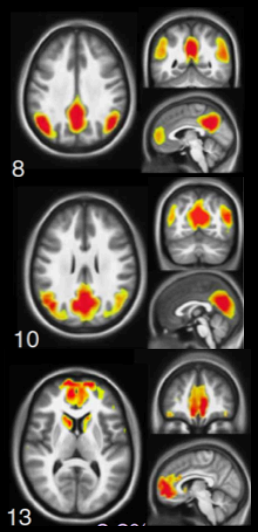
# Rethink models with iCAPs

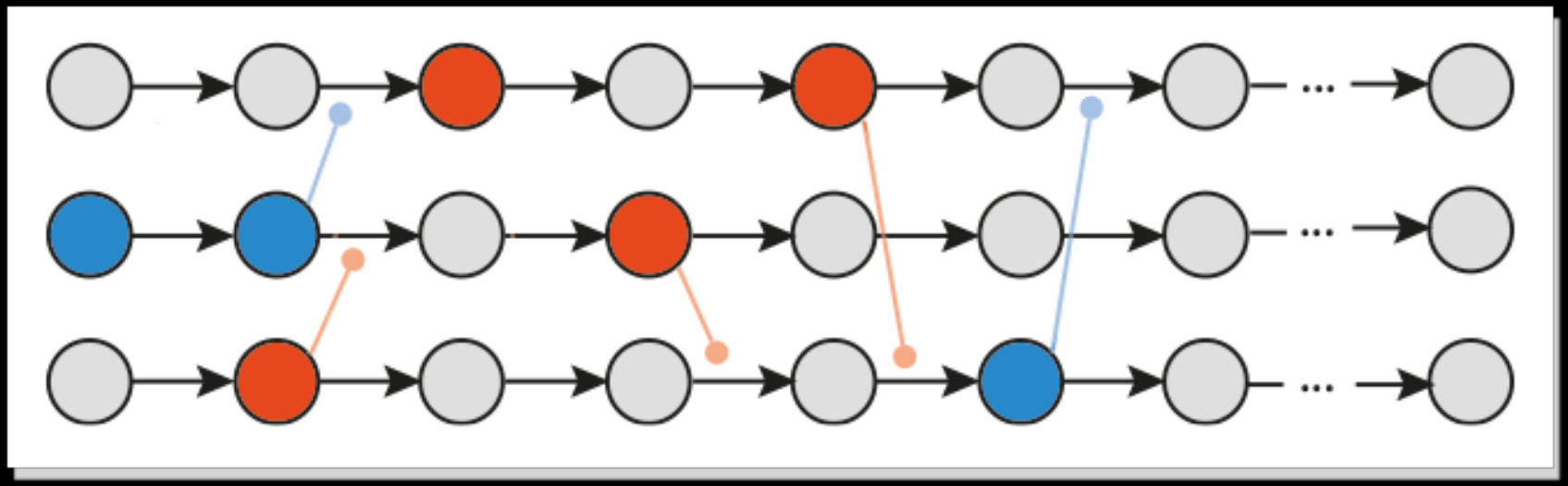
down-regulation
up-regulation

- Define states of each iCAP and model transition probabilities
- Model interactions by *sparsely coupled* hidden Markov models



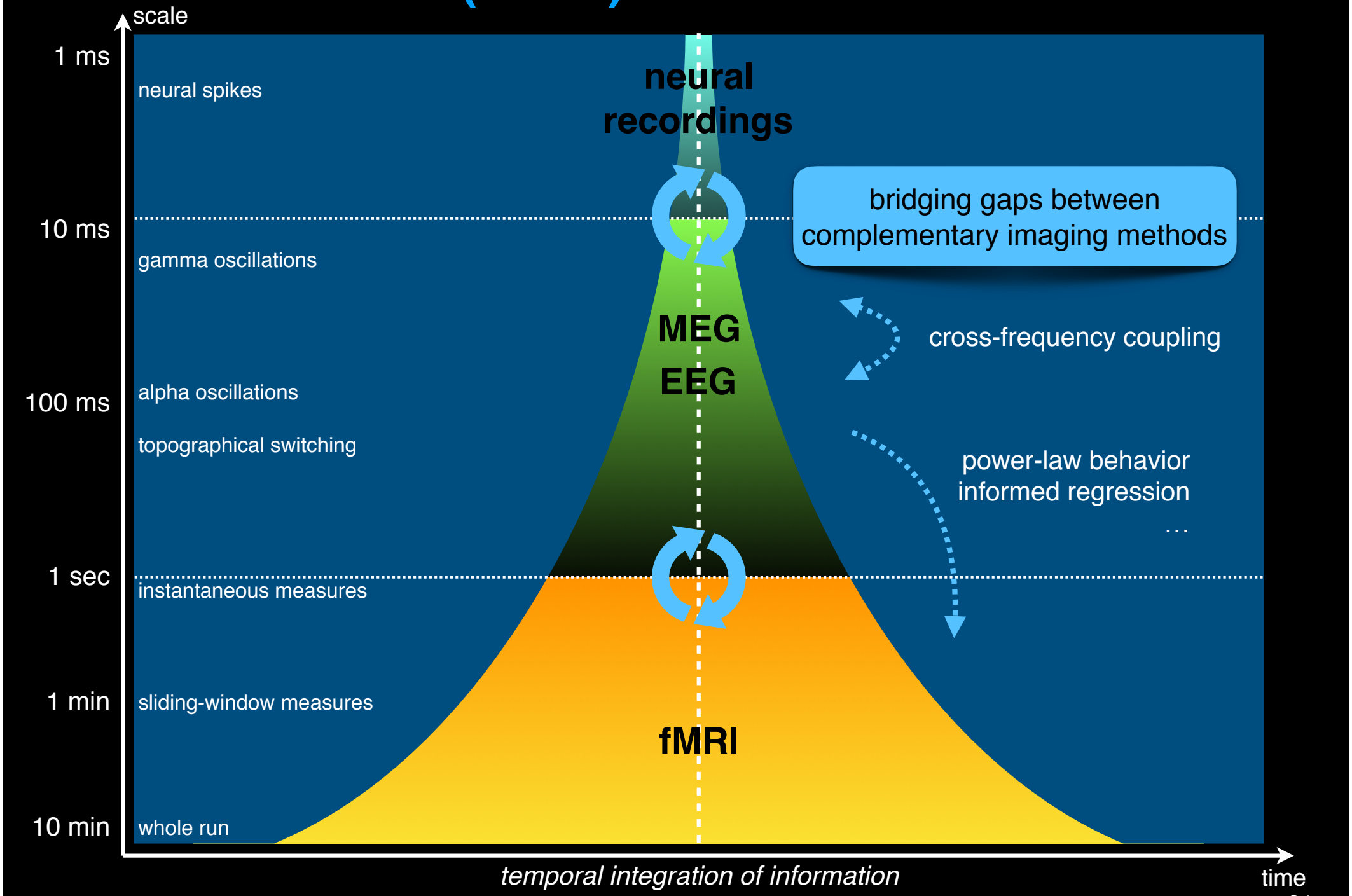


[Bolton et al, *IEEE TMI*, 2017; Vidaurre et al, *PNAS*, 2017]

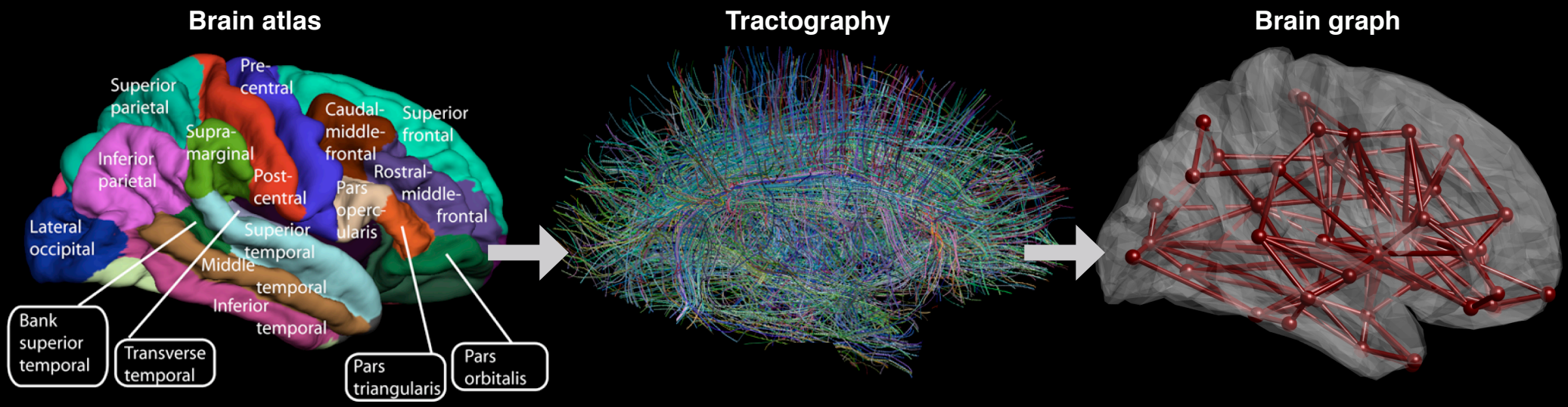
# It's all about time(scale)



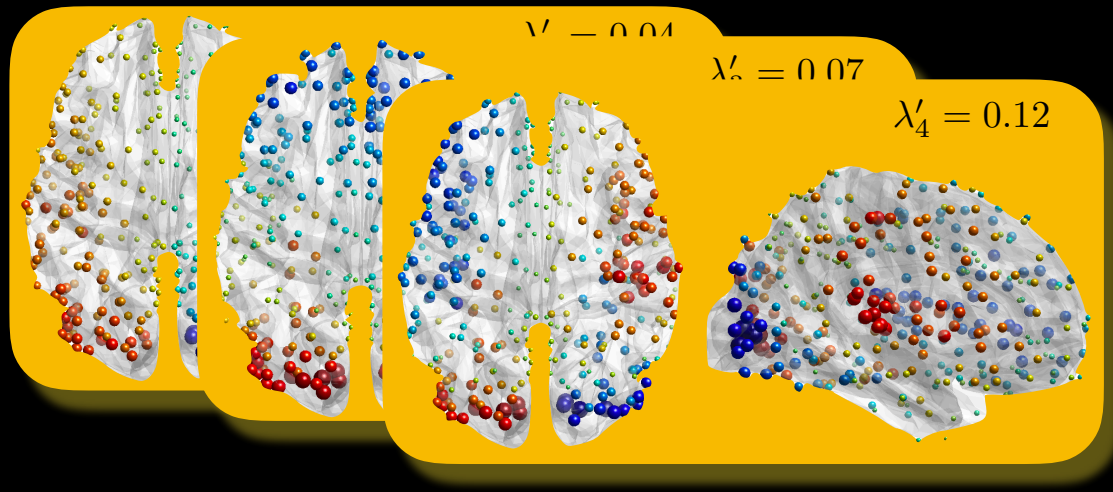



[Buzsaki et al, *Nat Rev Neurosci*, 2012; Britz et al, *NeuroImage*, 2010; VDV et al, *PNAS*, 2010; Chang et al, *NeuroImage*, 2013; Keilholz, *Brain Conn*, 2014]

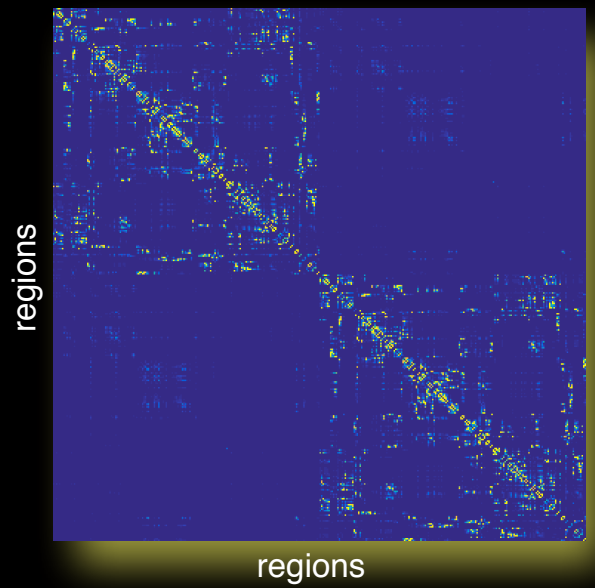
# Integration of function and structure




- How is function using underlying structure?
  - *simulation perspective*: The Virtual Brain
  - *graph signal processing perspective*: fMRI data constitute graph signals on structural backbone


**Structural connectome**




[Sporns et al, 2005; Hagmann et al, 2005; Deco, Jirsa, McIntosh, *TiN*, 2013; Atasoy et al, *Nat Comm*, 2016; Huang*, Bolton* et al, *Proceedings of the IEEE*, 2017]

# Take home messages

- fMRI captures **rich spatiotemporal structure** of brain activity
  - Dynamics are useful to study *resting state*, *naturalistic* conditions, and *task*
  - Minimal compliance of resting state for patient populations
- Time-resolved measures as **new tools for connectivity mapping**
  - Different measures reveal different features
    - Dynamic FC shows fragmentation of large-scale functional networks
    - iCAPs reveal extensive spatial and temporal overlap between (sub-)networks
  - Many other variations have been proposed
    - Dynamic connectivity regression [Cribben et al, NeuroImage, 2012]; Independent vector analysis [Ma et al, *NeuroImage*, 2014]; Multiplication of temporal derivatives [Shine et al, *NeuroImage*, 2015]; Dynamic connectivity detection [Xu and Lindquist, *Front Neurosci*, 2015]; Dynamic coherence analysis [Yaesoubi et al, *NeuroImage*, 2015];…
- Summarize into **(mechanistic) models of brain (dys)function**
  - How brain dynamics support coordinated cognition by linking perception, attention, goal-directed thought?
  - What are neural correlates of behavioral and clinical measures?
- Ongoing **challenges**
  - Multimodal imaging to access different timescales and underlying anatomy
  - Impact of neurostimulation and -modulation
  - Biomarkers: precision psychiatry,…

# MIP:lab @ Campus Biotech

http://miplab.epfl.ch

campus biotech

UNIVERSITÉ DE GENÈVE

ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE


FNSNF Swiss National Science Foundation

fondation bertarelli

BRAIN & BEHAVIOR RESEARCH FOUNDATION Awarding NARSAD Grants

HASLER STIFTUNG

Fondation Leenaards

# Key people (and their papers)

http://miplab.epfl.ch/media/SfN18-dynFC.pdf

### Nora Leonardi, PhD

- N. Leonardi, J. Richiardi, M. Gschwind, S. Simoni, J.-M. Annoni, M. Schluep, P. Vuilleumier, D. Van De Ville, “Principal Components of Functional Connectivity: A New Approach to Study Dynamic Brain Connectivity During Rest”, *NeuroImage*, 2013, 83, 937-950
- N. Leonardi, W. Shirer, M. Greicius, D. Van De Ville, “Disentangling Dynamic Networks: Separated and Joint Expressions of Functional Connectivity Patterns in Time”, *Human Brain Mapping*, 2014, 35, 5984-5995
- N. Leonardi, D. Van De Ville, “On Spurious and Real Fluctuations of Dynamic Functional Connectivity During Rest”, *NeuroImage*, 2015, 104, 430-436

### F. Isik Karahanoglu, PhD *(now at MGH, Boston)*

- F. I. Karahanoglu, D. Van De Ville, “Transient Brain Activity Disentangles fMRI Resting-State Dynamics in Terms of Spatially and Temporally Overlapping Networks”, *Nature Communications*, 2015, 6, 7751
- F. I. Karahanoglu, D. Van De Ville, ”Dynamics of Large-Scale fMRI Networks: Deconstruct Brain Activity to Build Better Models of Brain Function”, *Current Opinion in Biomedical Engineering*, 2017, 3, 28-36
- F. I. Karahanoglu, C. Caballero Gaudes, F. Lazeyras, D. Van De Ville, “Total Activation: FMRI Deconvolution through Spatio-Temporal Regularization”, *NeuroImage*, 2013, 73, 121-134

### M. Giulia Preti, PhD

- M. G. Preti*, T. Bolton*, D. Van De Ville, “The Dynamic Functional Connectome: State-of-the-Art and Perspectives”, *NeuroImage*, 2017, 160, 41-54
- M. G. Preti, D. Van De Ville, “Dynamics of Functional Connectivity at High Spatial Resolution Reveal Long-Range Interactions and Fine-Scale Organization”, *Scientific Reports*, 2017, 7, 12773
- J. Grandjean, M. G. Preti, T. Bolton, M. Buerge, E. Seifritz, C. R. Pryce, D. Van De Ville, M. Rudin, “Dynamic Reorganization of Intrinsic Functional Networks in the Mouse Brain”, *NeuroImage*, 2017, 152, 497-508

### Thomas Bolton

- T. Bolton, A. Tarun, V. Sterpenich, S. Schwartz, D. Van De Ville, “Interactions Between Large-Scale Functional Brain Networks Are Captured by Sparse Coupled HMMs”, *IEEE Transactions on Medical Imaging*, 2018, 37, 230-240
- W. Huang*, T. Bolton*, J. D. Medaglia, D. S. Bassett, A. Ribeiro, D. Van De Ville, “A Graph Signal Processing Perspective on Functional Brain Imaging”, *Proceedings of the IEEE*, 2018, 106, 868-885
- T. Bolton, D. Jochaut, A.-L. Giraud, D. Van De Ville, “Brain Dynamics in ASD During Movie-watching Show Idiosyncratic Functional Integration and Segregation”, *Human Brain Mapping*, 2018, 39, 2391-2404

### Daniela Zöller

- D. Zoeller, T. Bolton, F. I. Karahanoglu, M. Schaer, S. Eliez, D. Van De Ville, “Robust Recovery of Temporal Overlap Between Network Activity Using Transient-Informed Spatio-Temporal Regression”, *IEEE Transactions on Medical Imaging*, in press