Donders Institute
for Brain, Cognition and Behaviour

Brain Reading (MKI43)

Lecture 6: Connectivity Analysis

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Distributed Representations Group
Donders Centre for Cognition

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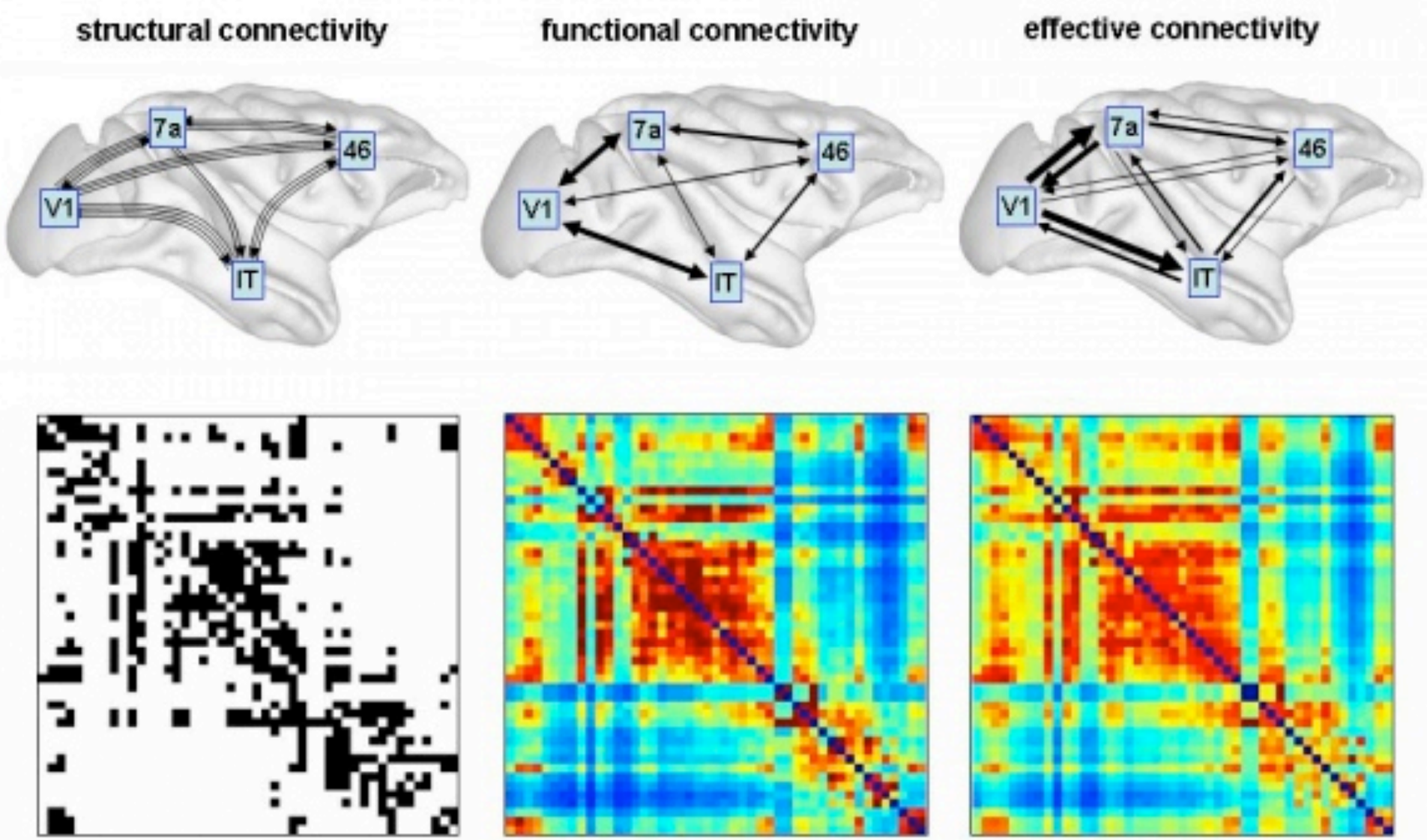
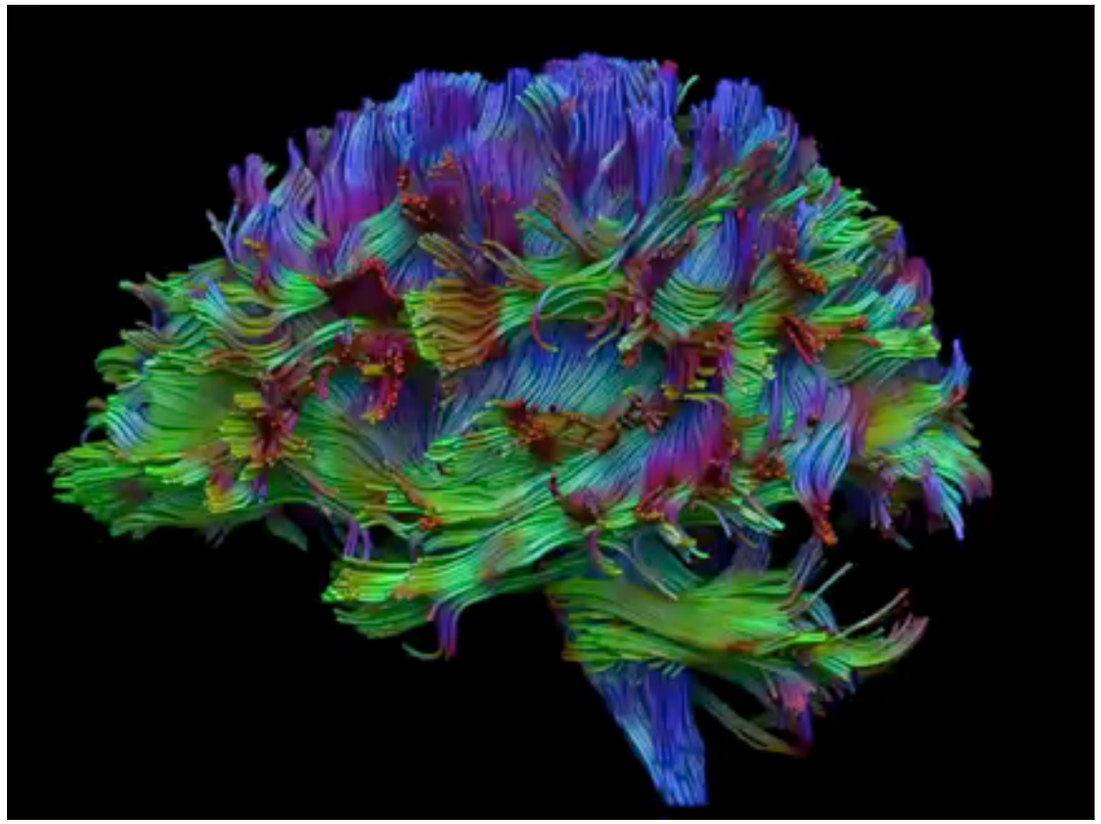
Multivariate analyses of regional interactions



Structural connectivity



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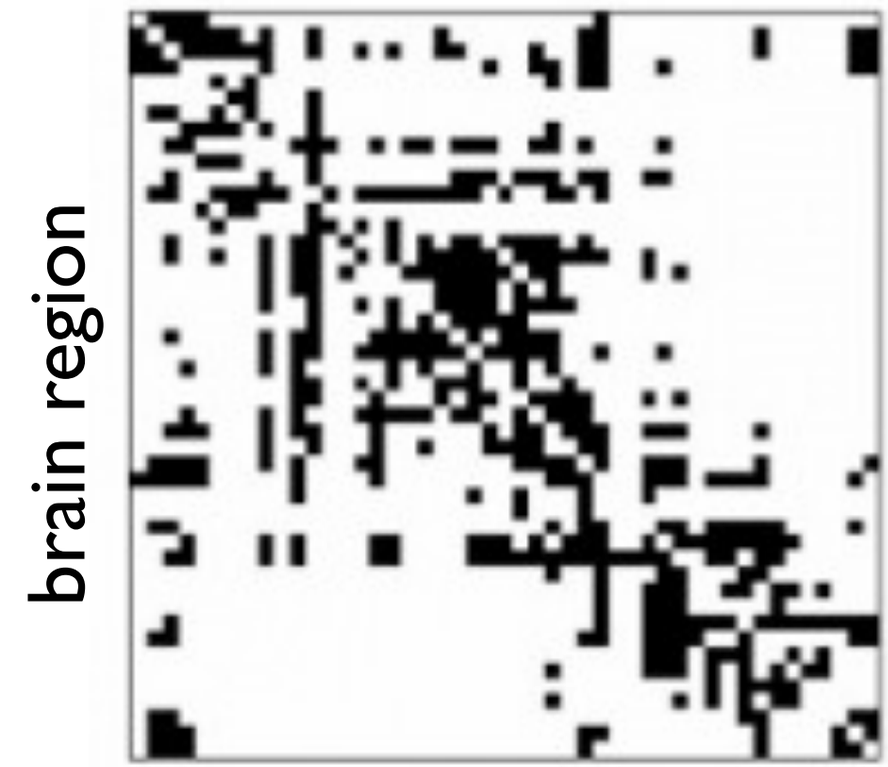
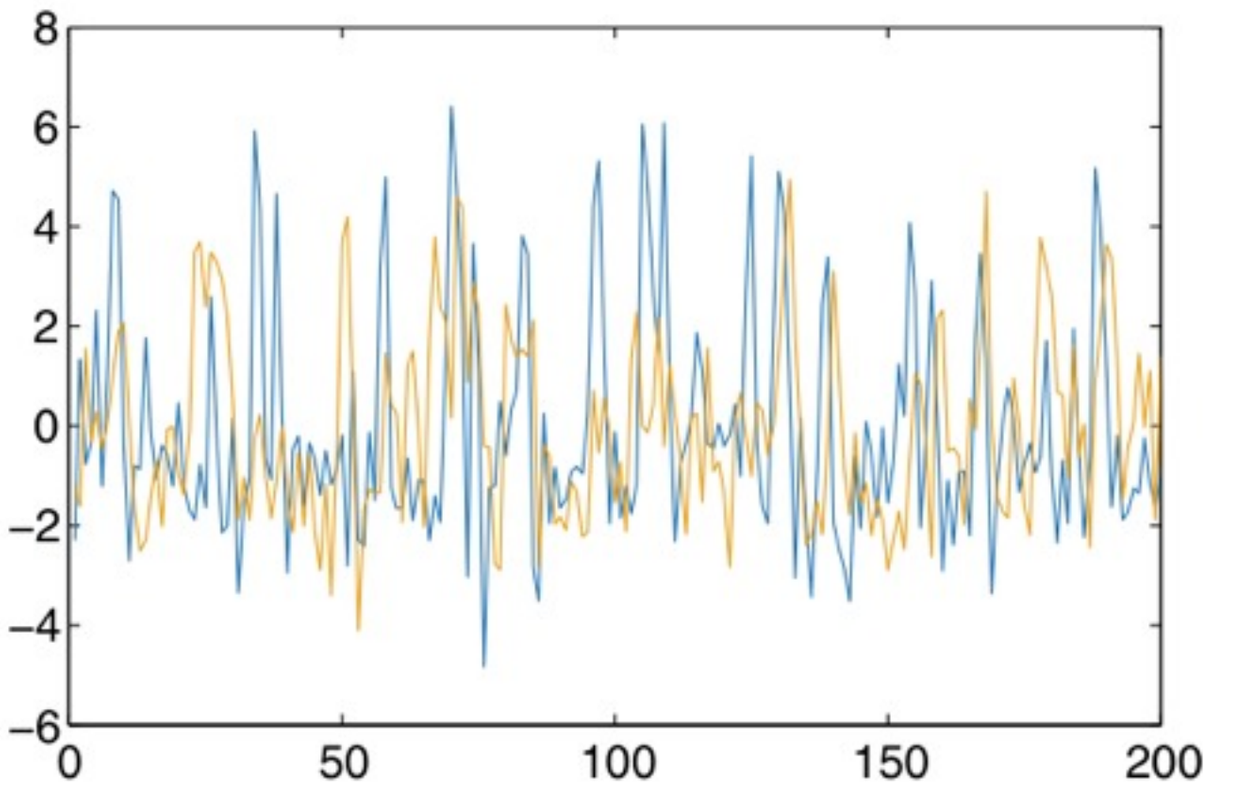


- how do we obtain tracts?
- which brain regions to choose?
- how do we deal with noise?
- how do we interpret this data?

topic of next lecture...

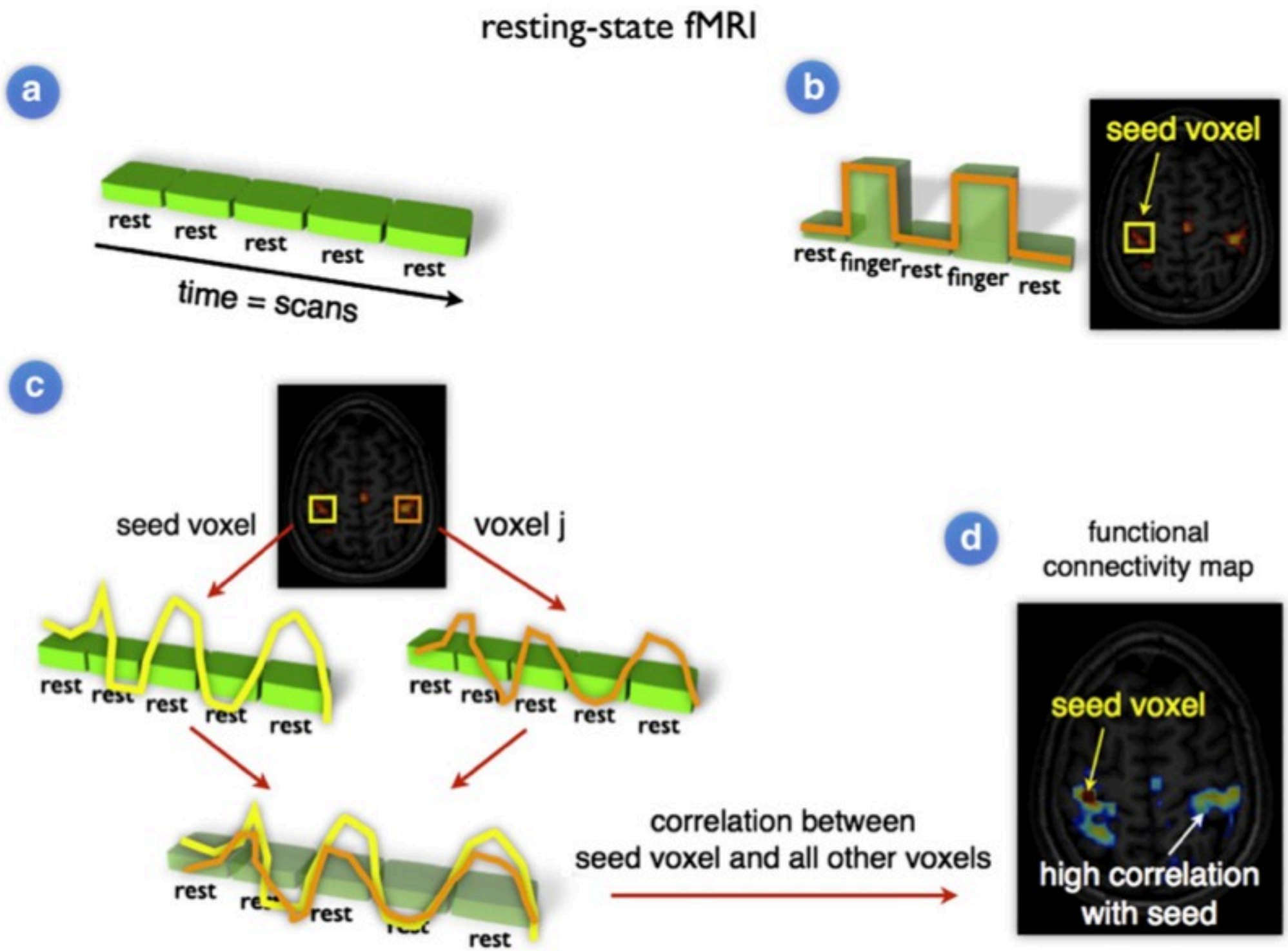
How do we determine if two brain regions are functionally connected?

Temporal correlation between neurophysiological events:



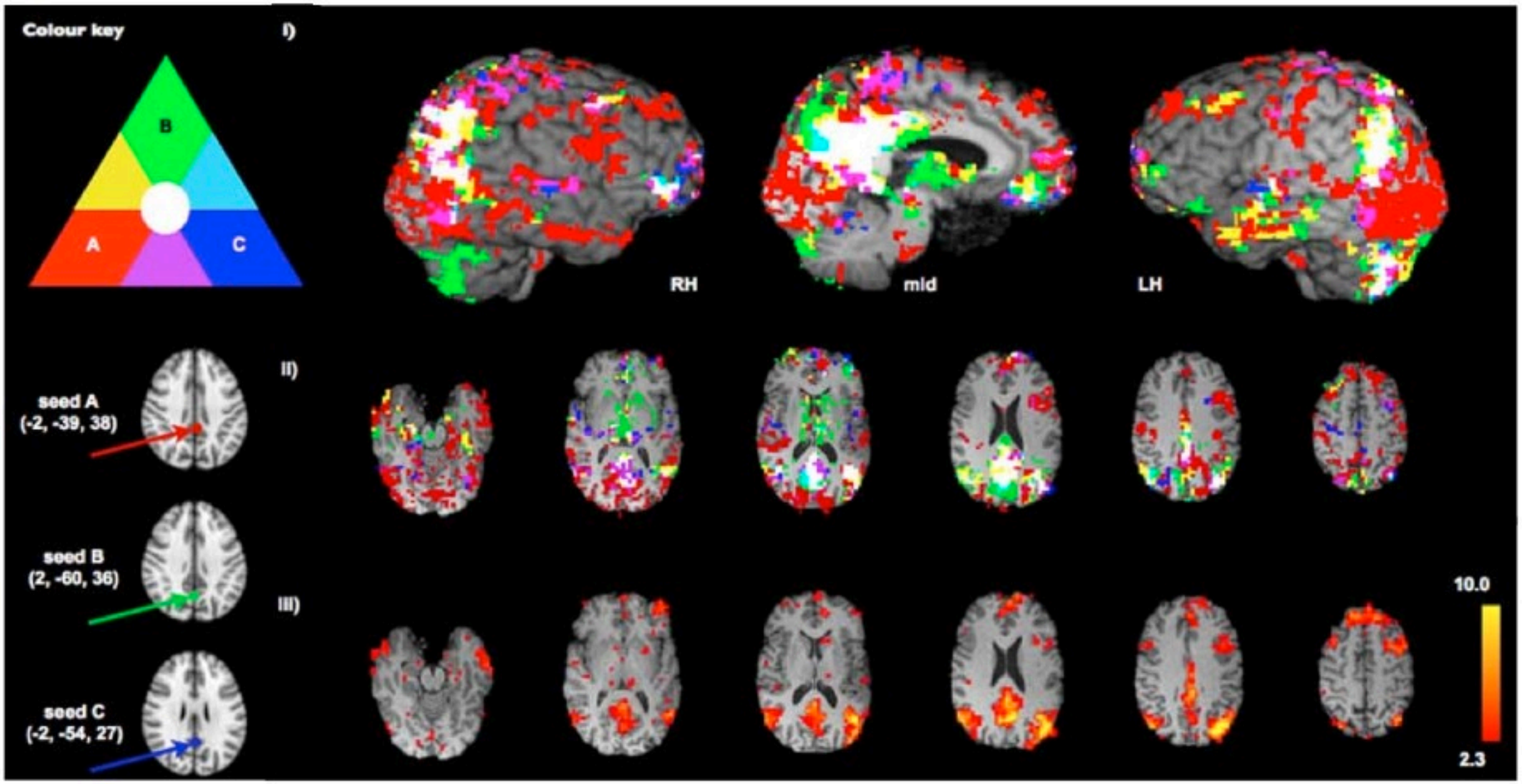
BOLD FMRI timeseries (sampled every 3s)

Functional connectivity 1: seed-based analysis



van den Heuvel MP, Pol HEH. Exploring the brain network: A review on resting-state fMRI functional connectivity. Eur Neuropsychopharm. 2010;20(8):519–34.

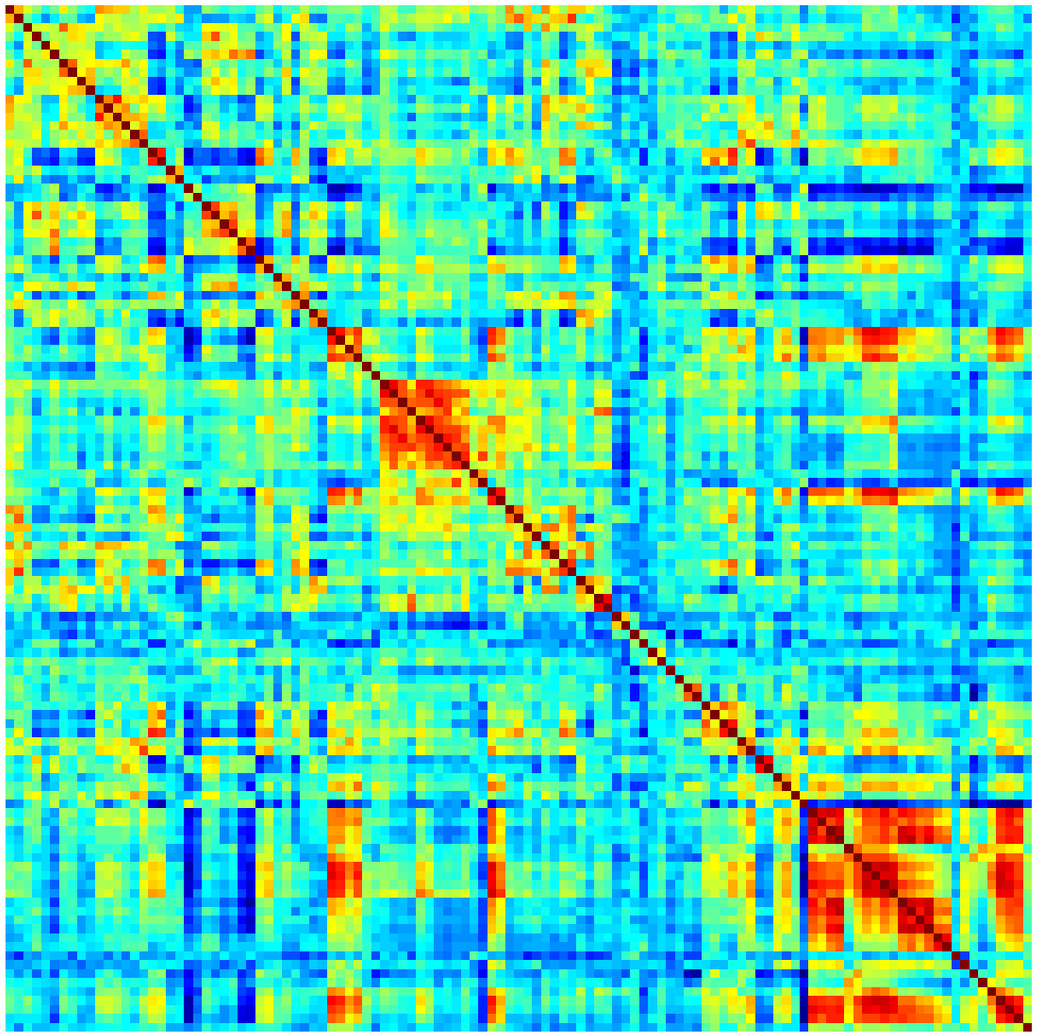
Functional connectivity 1: seed-selection bias



- potentially ignoring secondary effect and/ or nuisance effects
- analysis becomes conditional on the specific seed location
- need to define *consistent* way of defining seed within and across subjects

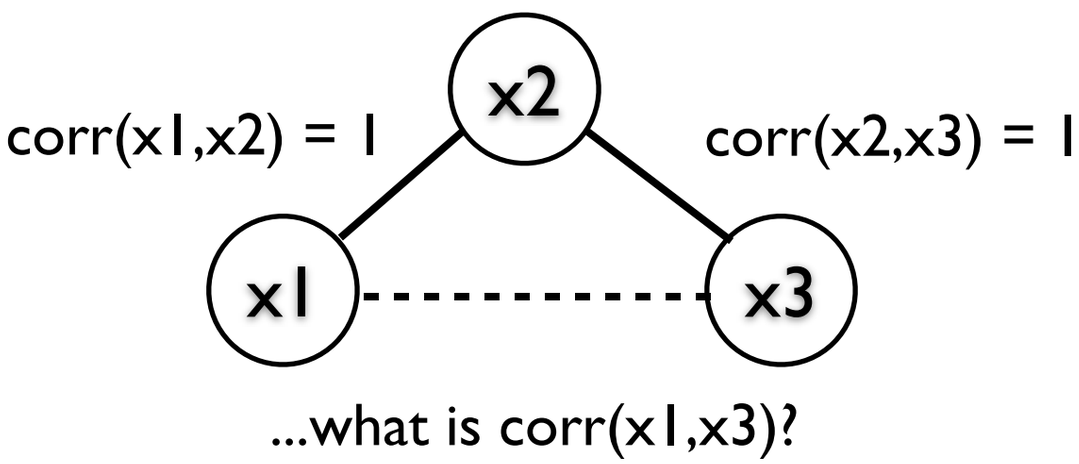
Cole et al (2010)
Front Syst Neurosci

Ignore seed selection; look at full correlation/covariance pattern



How do we determine if two brain regions are functionally connected?

Compute correlation?



correlation $\phi_{XY} = E[(X - E[X])(Y - E[Y])]/(\sigma_X \sigma_Y)$

covariance $\gamma_{XY} = E[(X - E[X])\,(Y - E[Y])]$

- Correlation and covariance capture polysynaptic activity

Functional connectivity 2: correlation structure

Suppose the N x K data matrix **Y** follows a multivariate Gaussian distribution with mean zero and empirical covariance matrix:

$$\hat{\boldsymbol{\Sigma}} = \frac{1}{N-1}\boldsymbol{Y}^T\boldsymbol{Y}$$

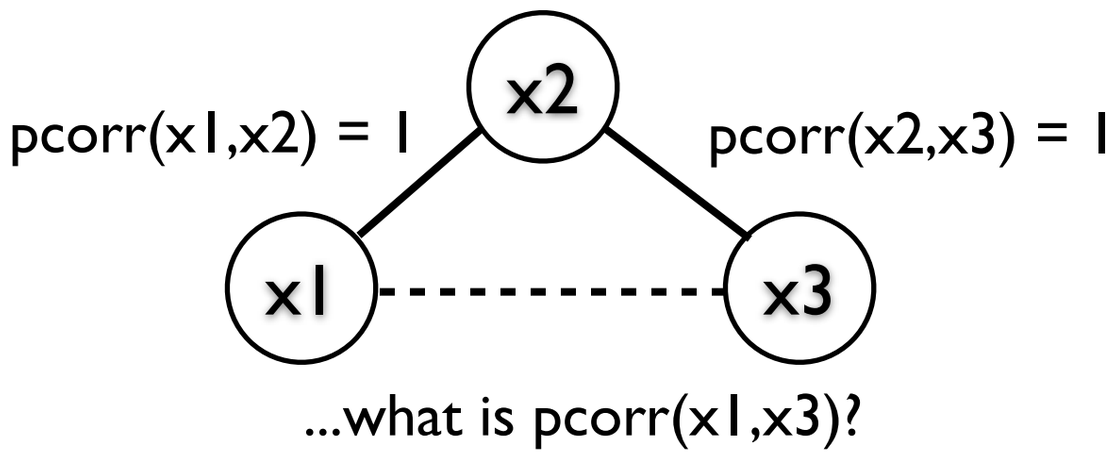
Let $\boldsymbol{Q} = \hat{\boldsymbol{\Sigma}}^{-1}$ denote the precision matrix.

Then:

$$P(\mathbf{y} \mid \mathbf{Q}) = (2\pi)^{-K/2}|\mathbf{Q}|^{1/2}\exp\left\{-\frac{1}{2}\mathbf{y}^\top\mathbf{Q}\mathbf{y}\right\}$$

Define partial correlation

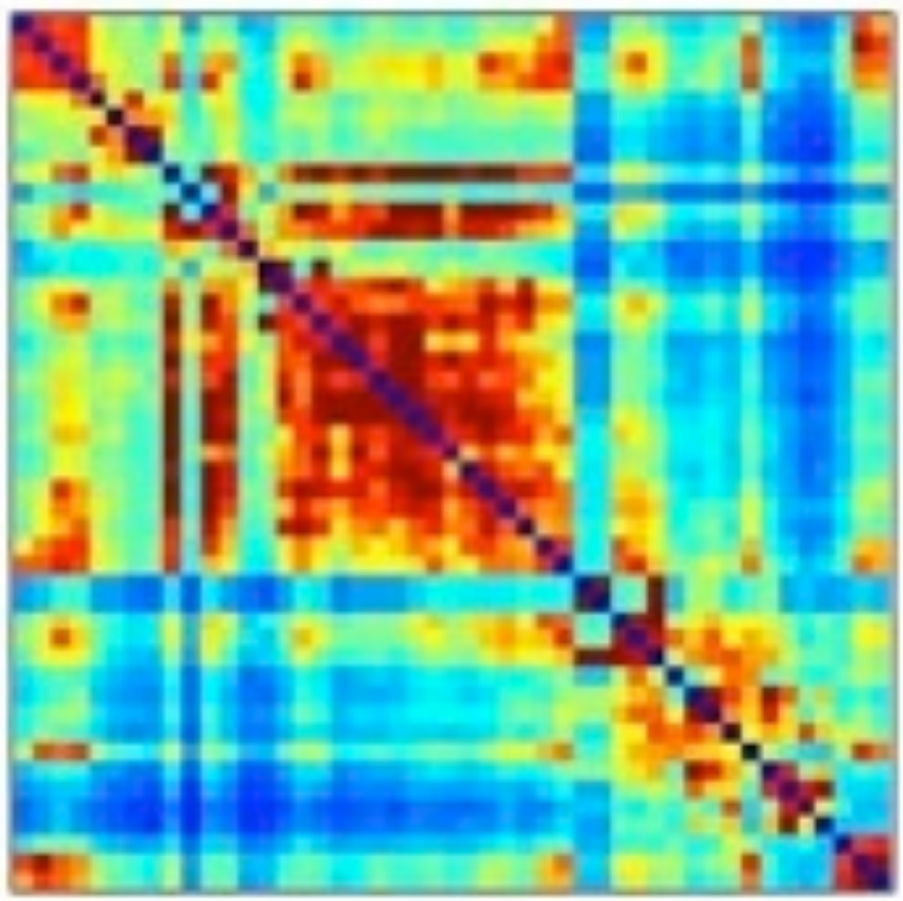
$$\Pi_{ij} = -\frac{Q_{ij}}{\sqrt{Q_{ii}Q_{jj}}} = \mathrm{corr}(Y_i, Y_j \mid \mathbf{Y}_{\setminus i,j})$$

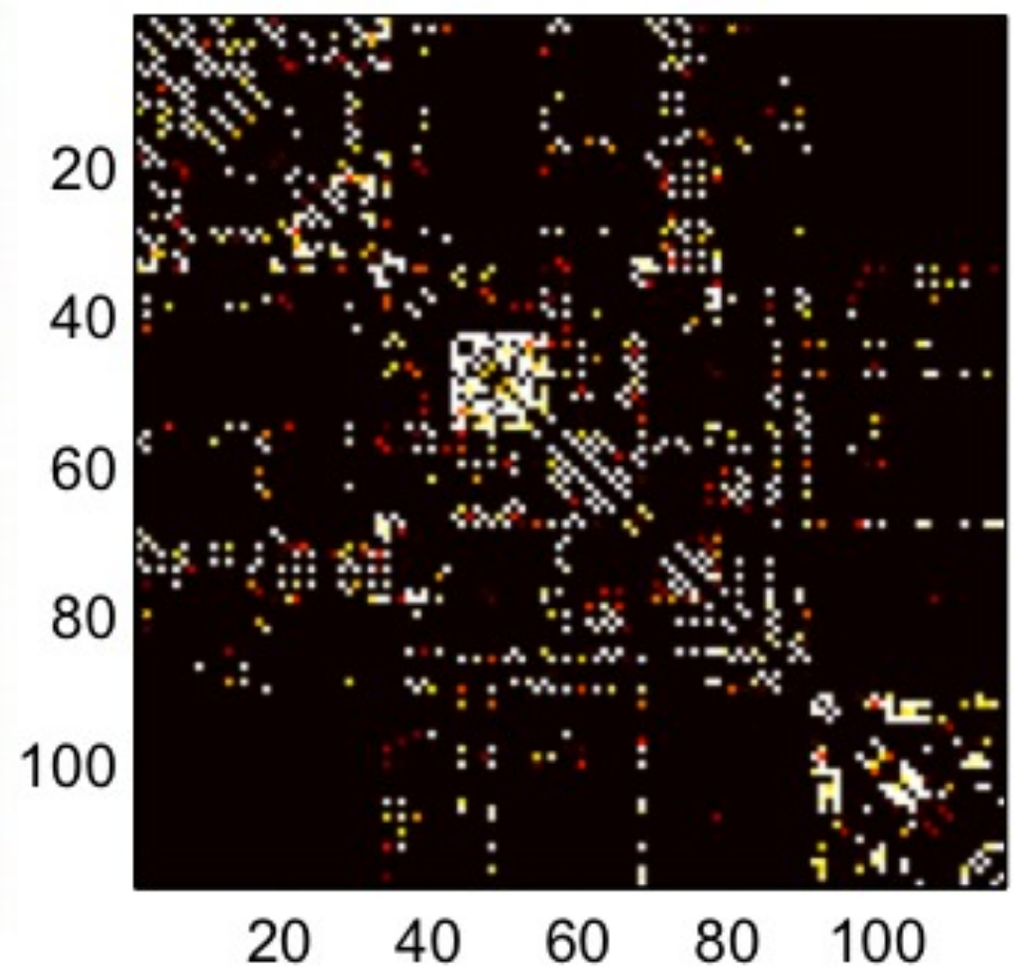


- Partial correlation captures monosynaptic activity
- Zero partial correlation shows up as zeros in Q
- The sparsity pattern of Q gives the underlying structural connectivity!

Monosynaptic via polysynaptic functional connectivity

- covariance matrix/correlation matrix: polysynaptic
- precision matrix: monosynaptic





Estimating the precision matrix

Maximum likelihood estimate:

$$\hat{\boldsymbol{Q}} = \arg\max_{\boldsymbol{Q}} \ell(\boldsymbol{Q})$$

with $\ell(\boldsymbol{Q}) = (N/2)\left(\log\det \boldsymbol{Q} - \mathrm{trace}(\boldsymbol{Q}\hat{\boldsymbol{\Sigma}})\right)$

However: we need to estimate Q (containing many parameters) using a small number of trials.

This makes

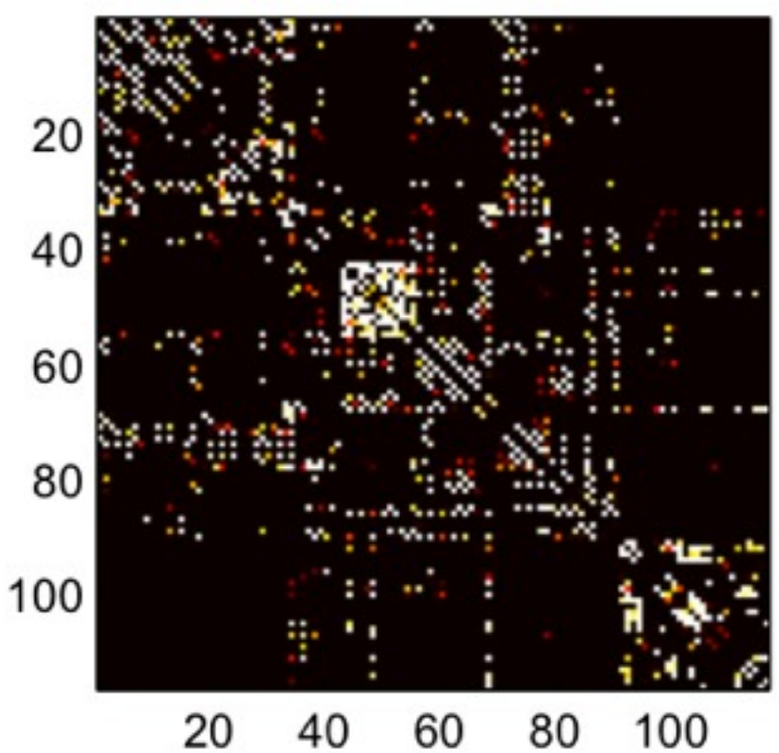
$$\hat{\boldsymbol{Q}} = \arg\max_{\boldsymbol{Q}} \ell(\boldsymbol{Q})$$

unstable.

Solution: use

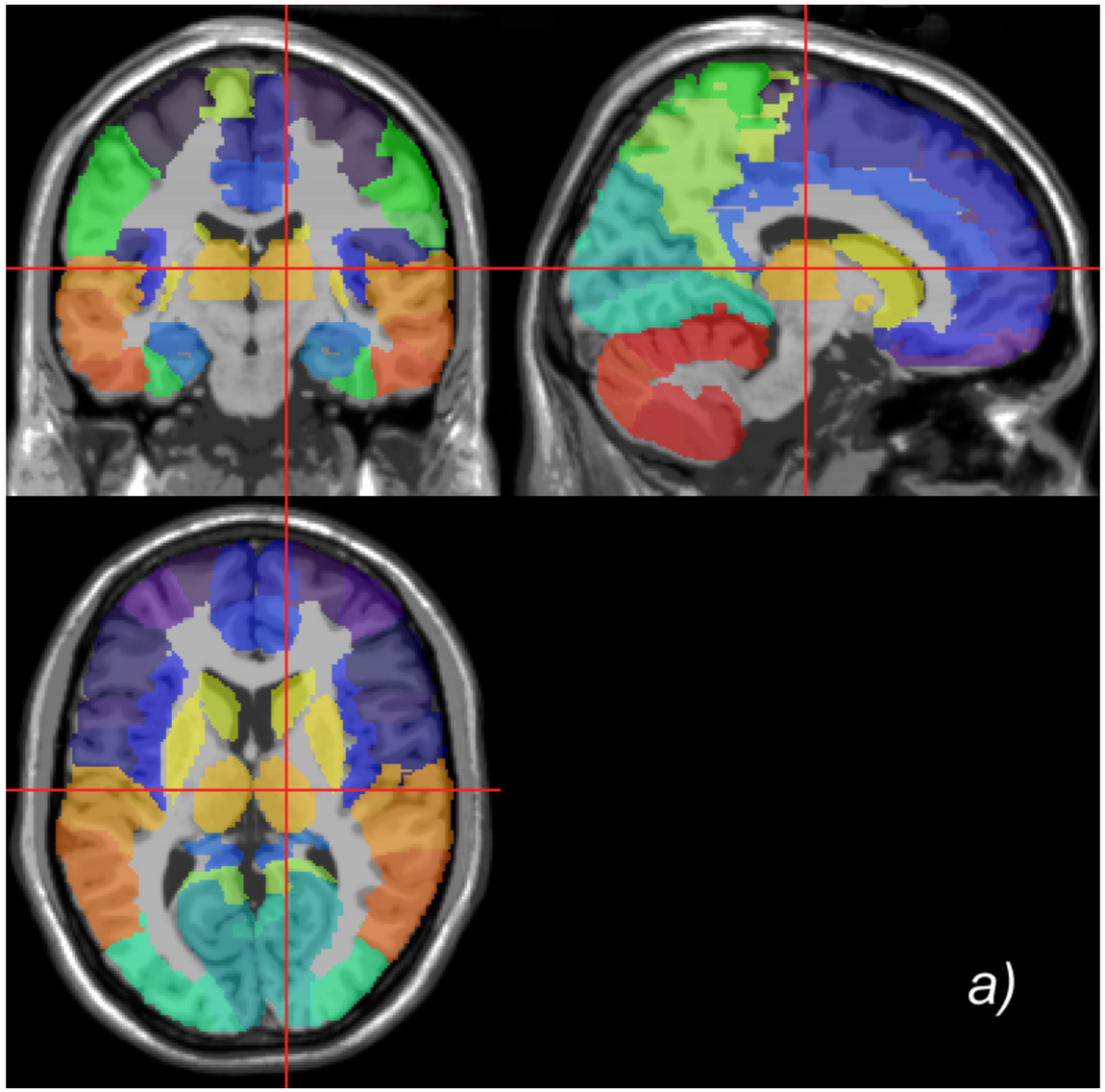
$$\hat{\boldsymbol{Q}} = \arg\max \left[\ell(\boldsymbol{Q}) - \lambda \sum_{i<j} |q_{ij}| \right]$$

Effect: the precision matrix contains just a few non-zero parameters



Friedman J, Hastie T, Tibshirani R. Sparse inverse covariance estimation with the graphical lasso. Biostatistics. 2008;9(3):432–41.

Parcellating the brain



- Define regions using a template: E.g. Automated Anatomical Labeling (AAL) atlas
- Each node is the center of mass of one parcel.
- We average all voxel time series belonging to a brain region
- What constitutes a good parcellation?

Connectivity-based parcellation

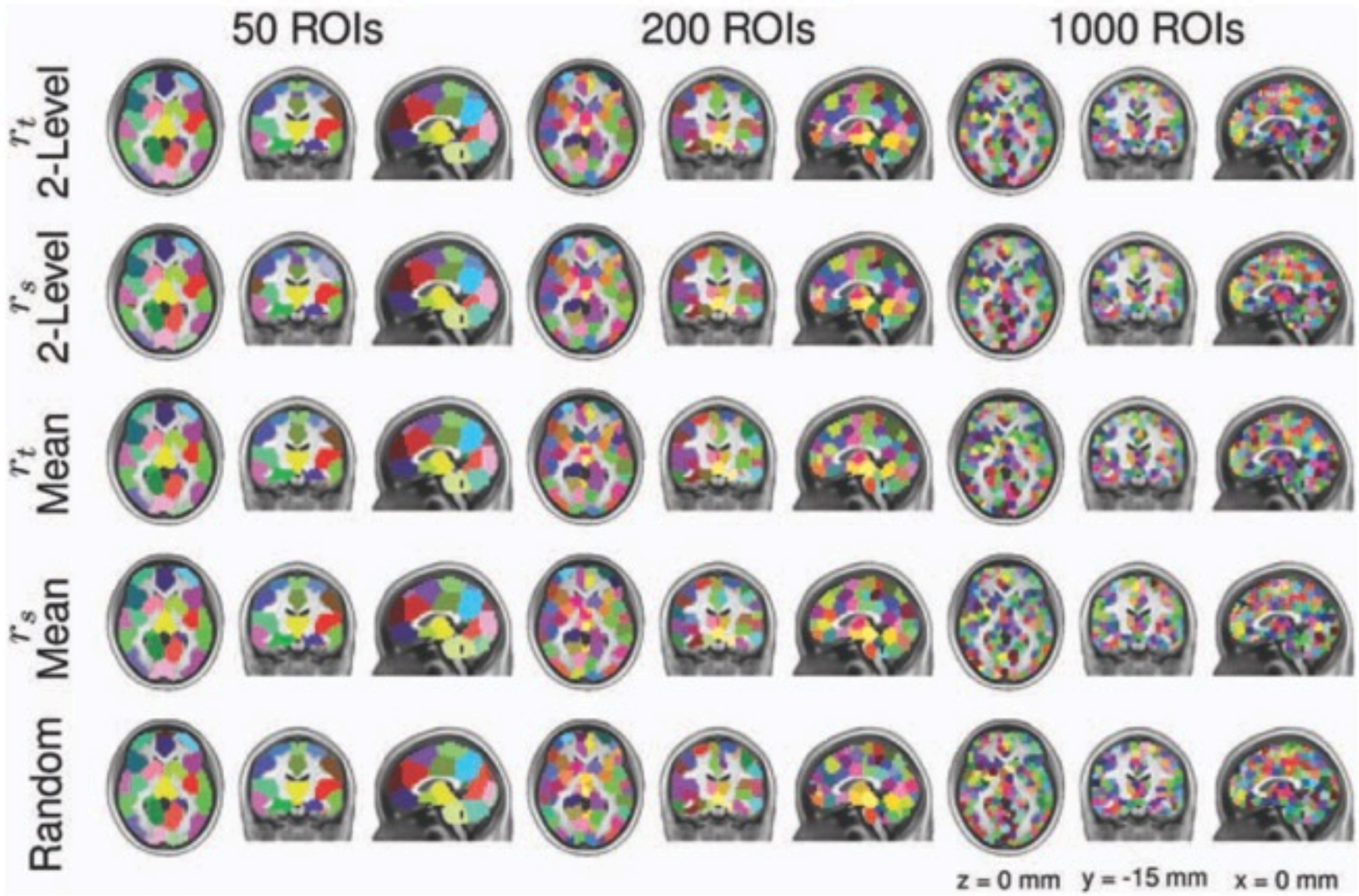


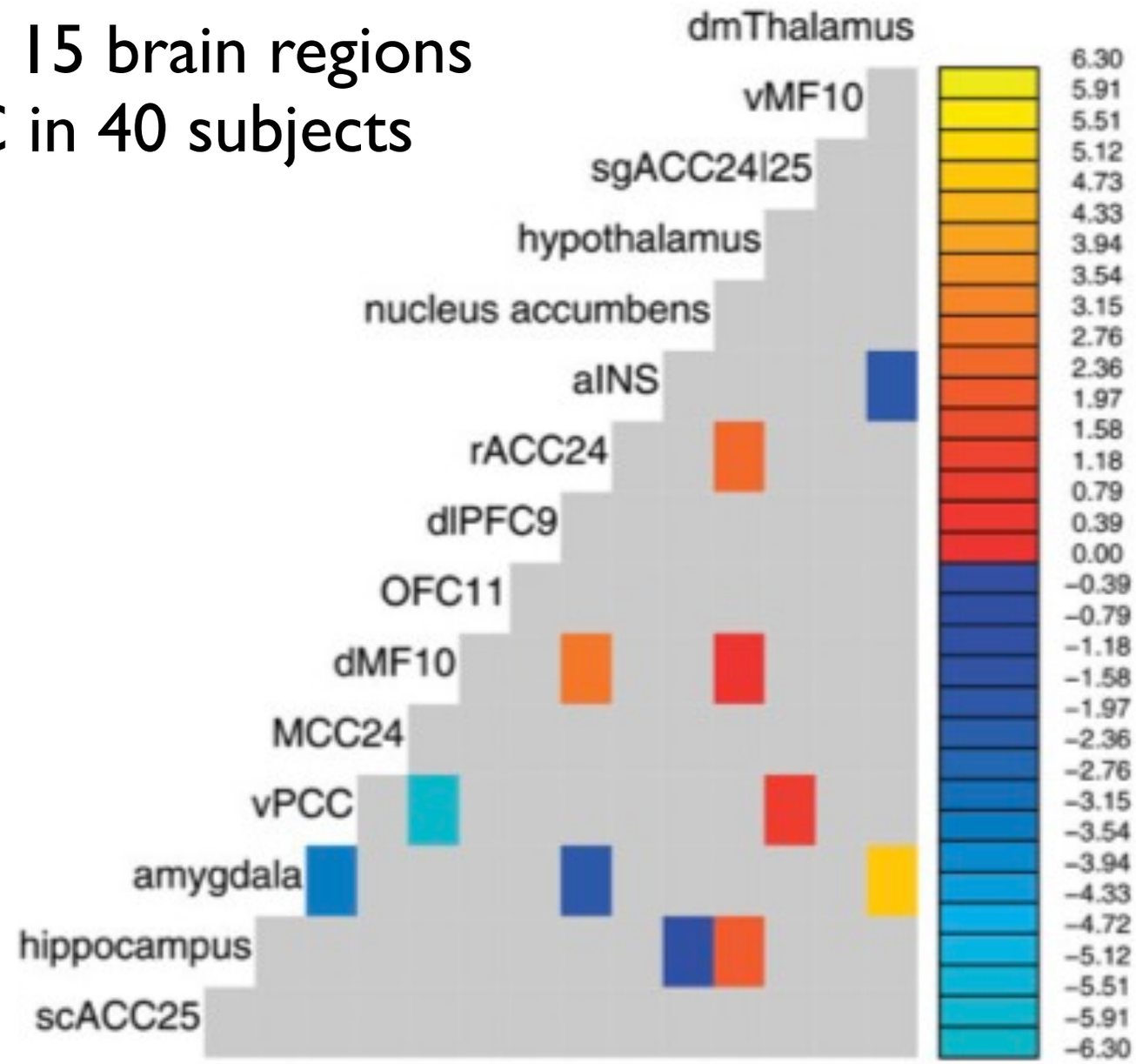
Figure 3.

Illustration of clustering results for the four combinations of functional parcellation methods and random parcellation containing 50, 200, or 1000 ROIs. Each parcellation is depicted as three orthogonal views. Color-coding is arbitrarily used to best emphasize ROI boundaries. ROI coloring was matched across parcellation results to emphasize similarities in ROI locations between methods.

Craddock RC, James GA, Holtzheimer PE, Hu XP, Mayberg HS. A whole brain fMRI atlas generated via spatially constrained spectral clustering. Hum Brain Mapp. 2012 Aug;33(8):1914–28.

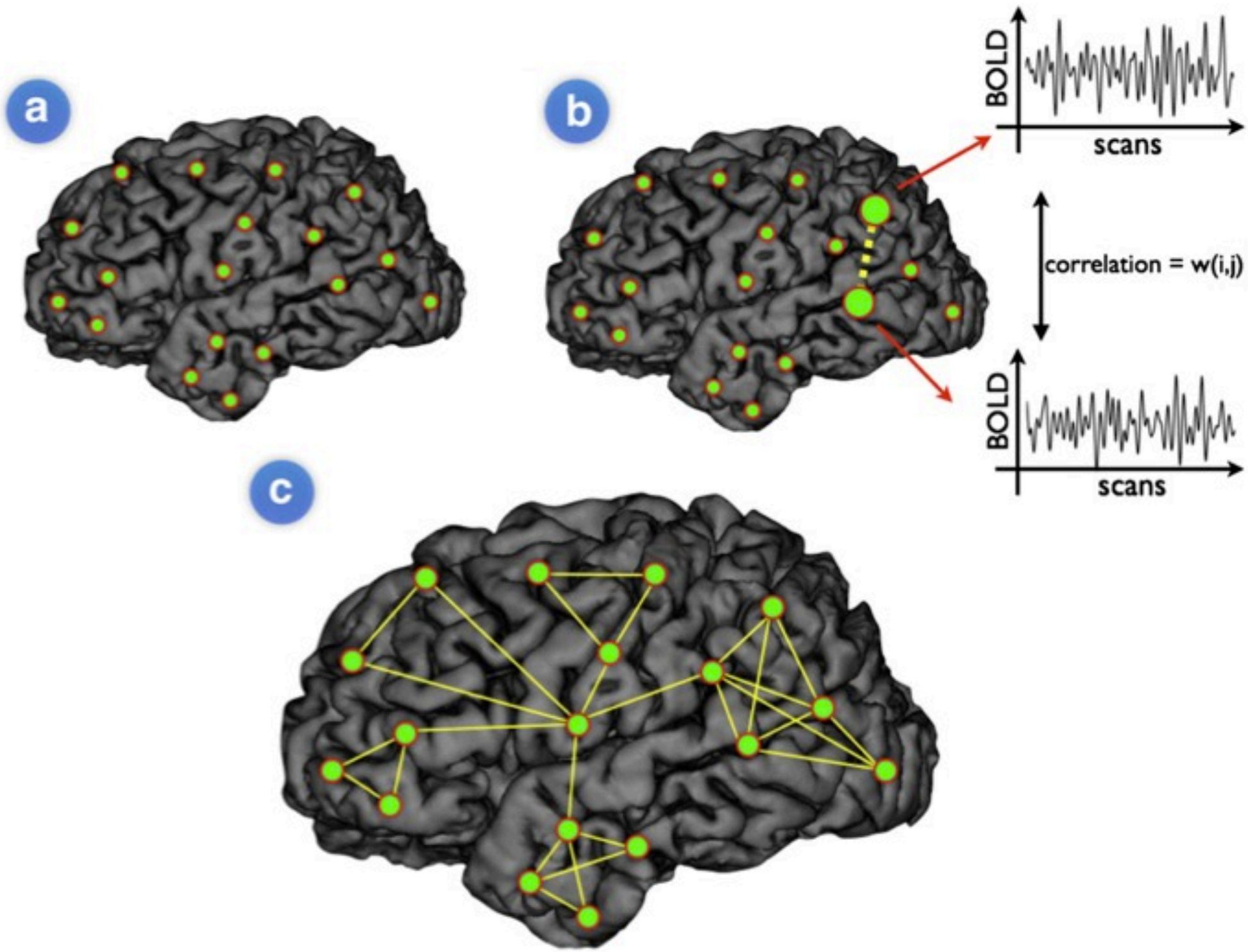
Connectivity-based decoding

- pairwise correlation of 15 brain regions
- predict MDD from HC in 40 subjects
- 95% accuracy reached



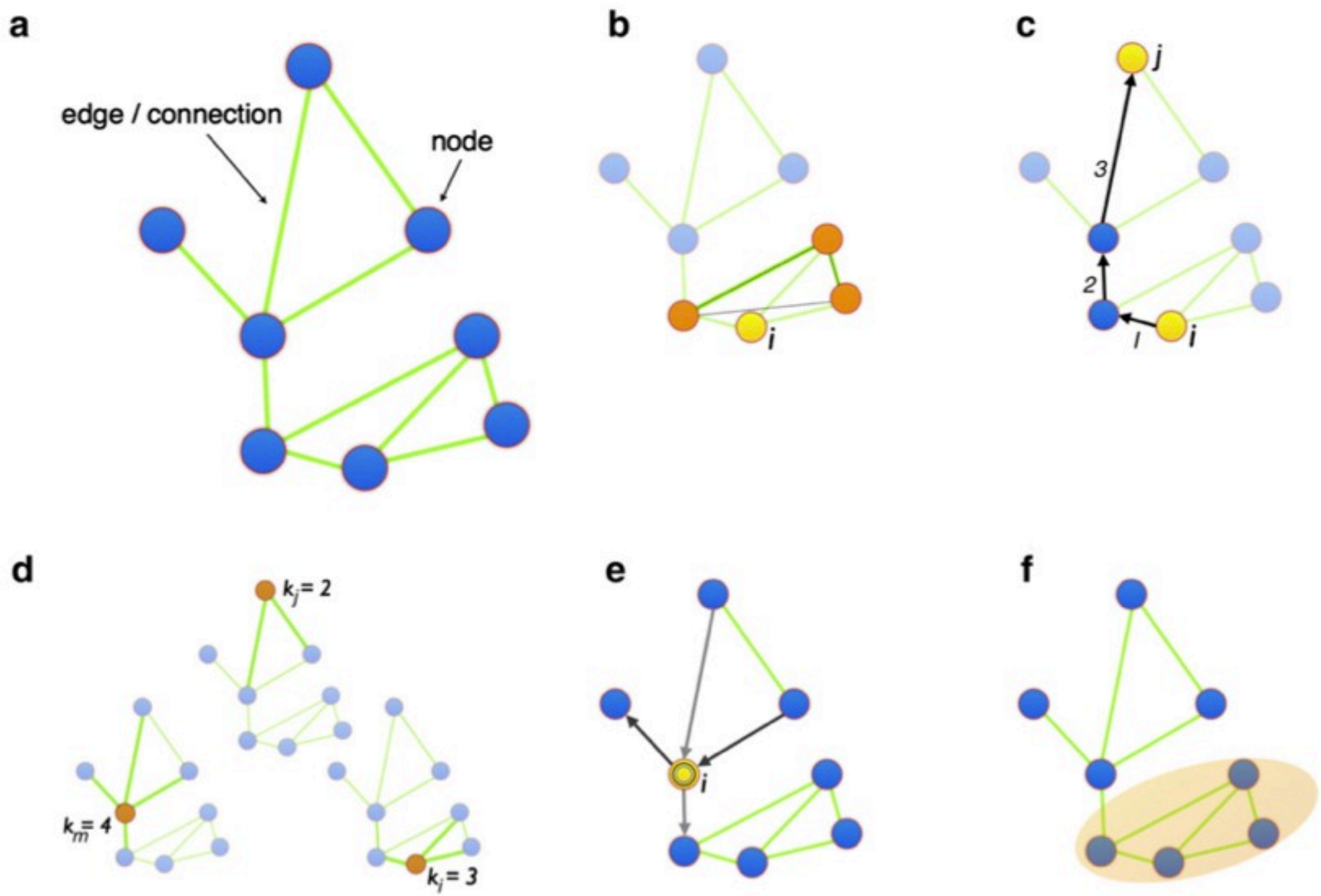
Craddock RC, Holtzheimer PE, Hu XP, Mayberg HS. Disease state prediction from resting state functional connectivity. Magn Reson Med. 2009;62(6):1619–28.

Graph-theoretical analysis of (functional) connectivity



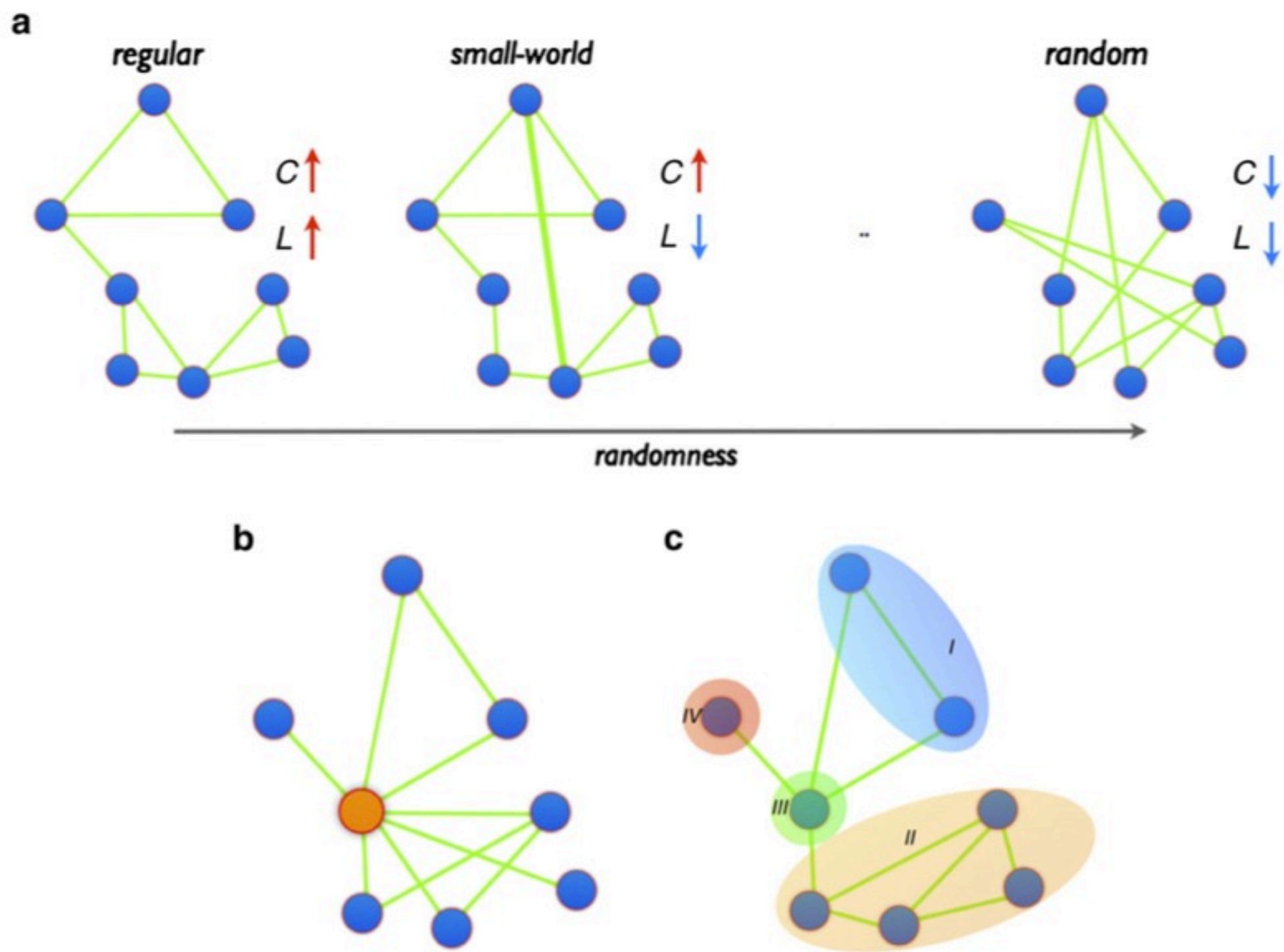
van den Heuvel MP, Pol HEH. Exploring the brain network: A review on resting-state fMRI functional connectivity. Eur Neuropsychopharm. 2010;20(8):519–34.

Graph-theoretical properties



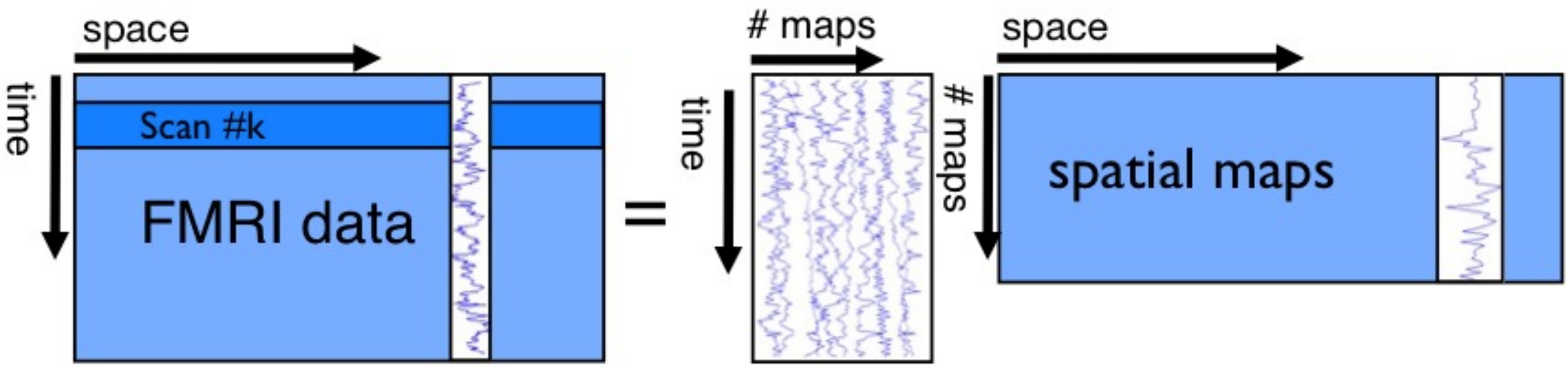
van den Heuvel MP, Pol HEH. Exploring the brain network: A review on resting-state fMRI functional connectivity. Eur Neuropsychopharm. 2010;20(8):519–34.

Small-worlds, hubs and modules



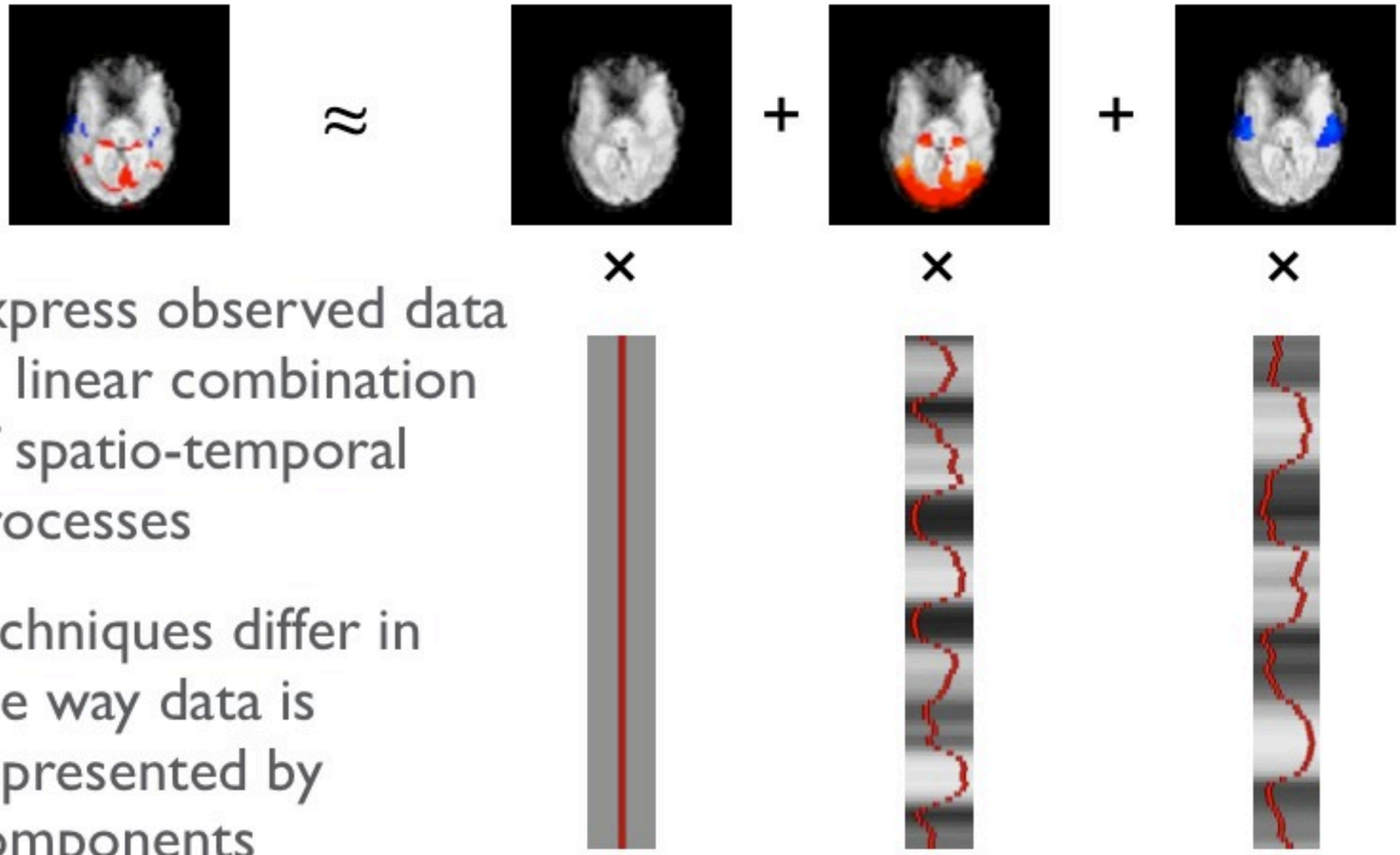
van den Heuvel MP, Pol HEH. Exploring the brain network: A review on resting-state fMRI functional connectivity. Eur Neuropsychopharm. 2010;20(8):519–34.

Find structured patterns in the data:



Data is represented as a 2D matrix and decomposed into components (modes, maps)

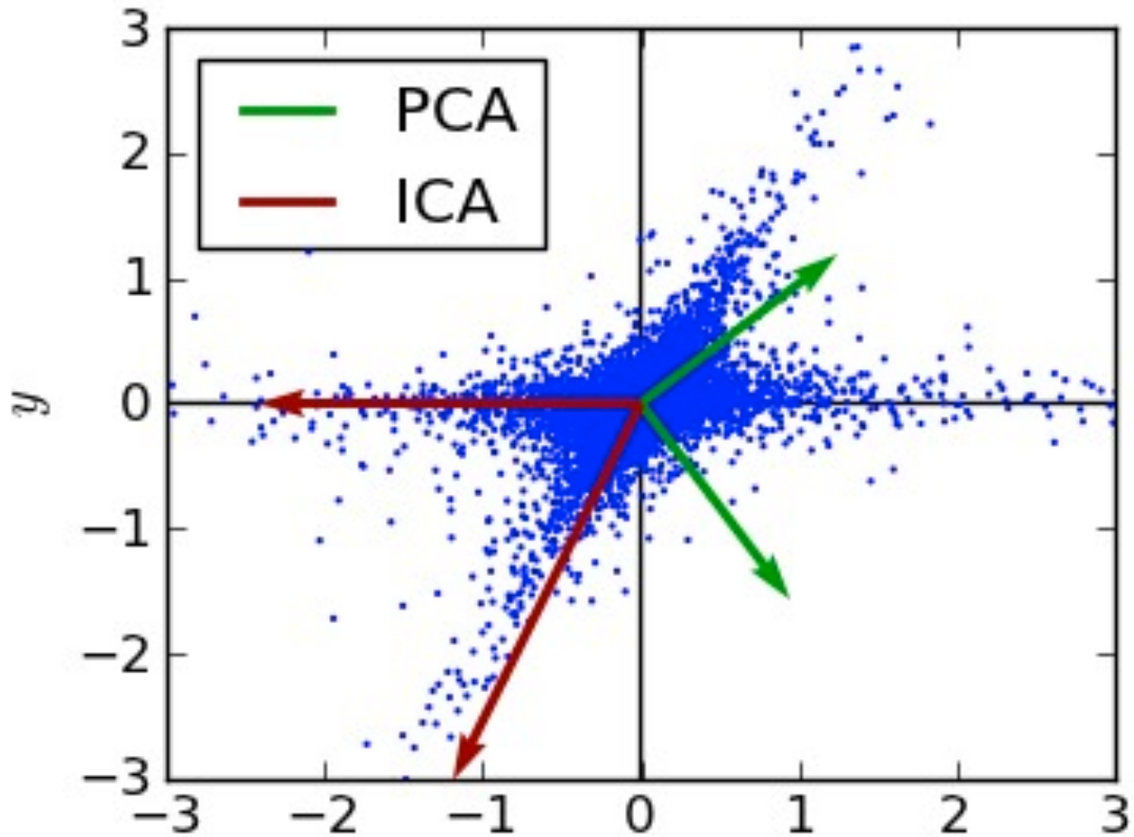
What are components?



- express observed data as linear combination of spatio-temporal processes
- techniques differ in the way data is represented by components

slide courtesy Christian Beckmann

PCA versus ICA

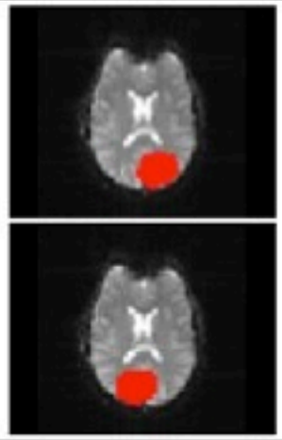


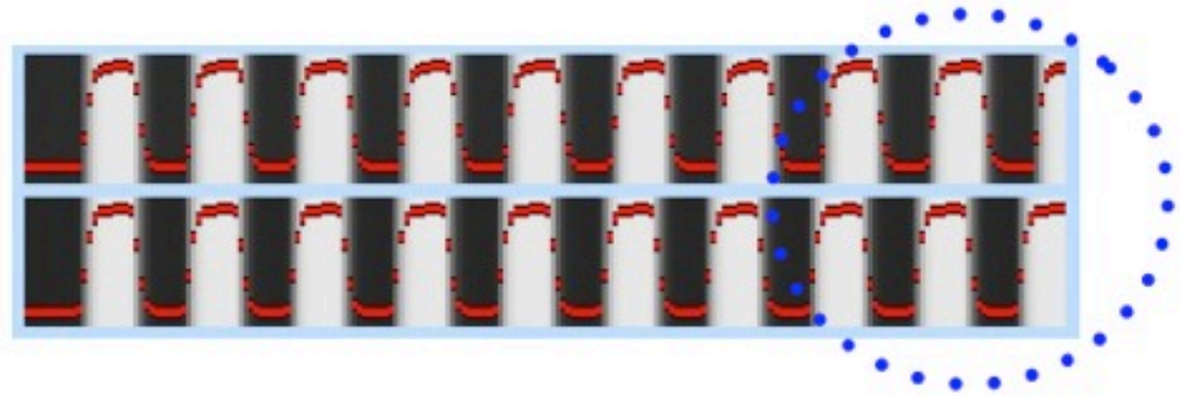
PCA: find directions of maximal variance
ICA: find directions that minimize statistical dependence

PCA versus ICA

Simulated Data

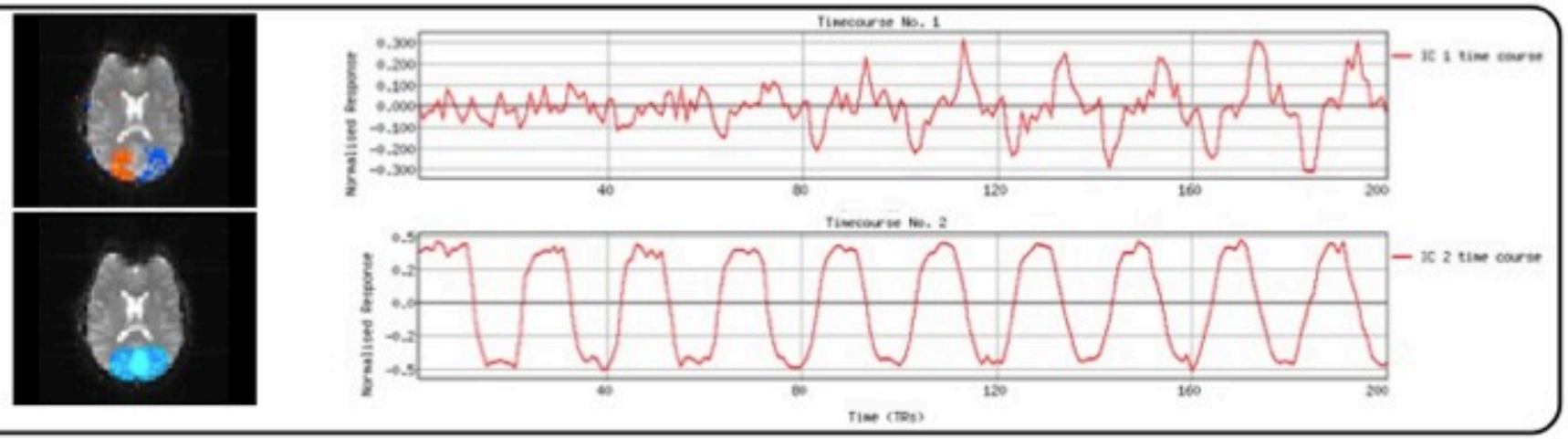
(2 components, slightly different timecourses)





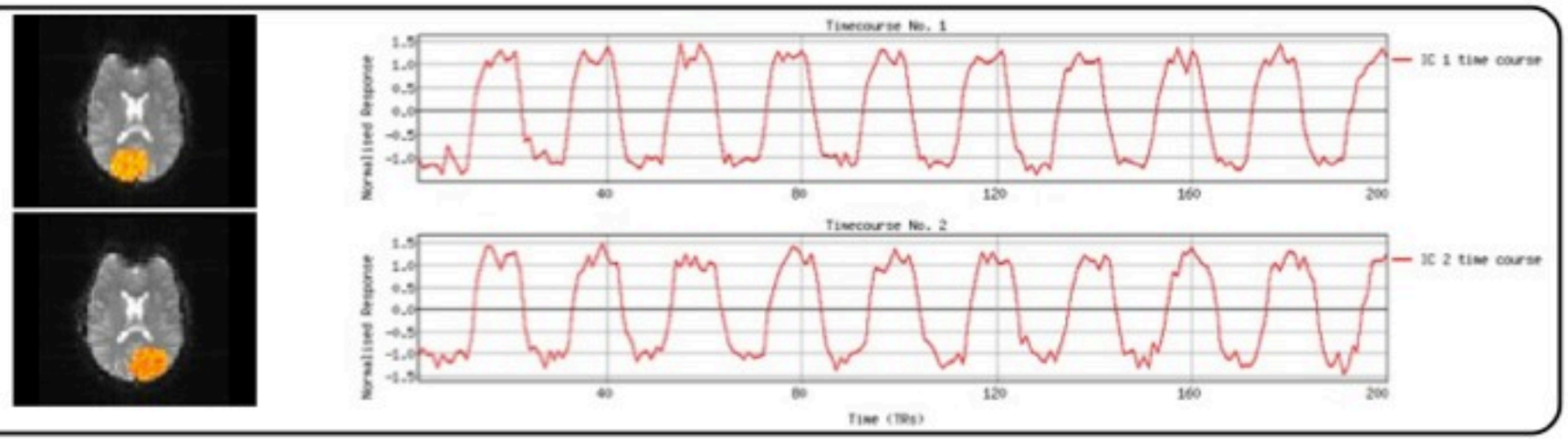
PCA

- Timecourses orthogonal
- Spatial maps and timecourses "wrong"



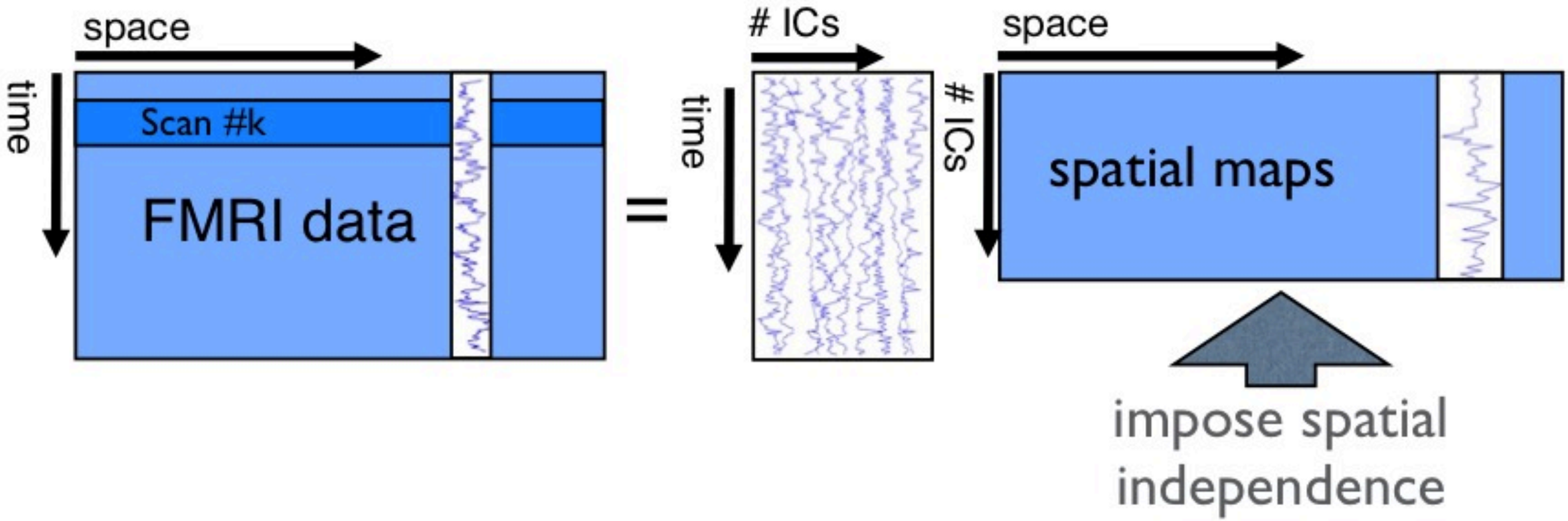
ICA

- Timecourses non-co-linear
- Spatial maps and timecourses "right"



slide courtesy Christian Beckmann

Spatial ICA

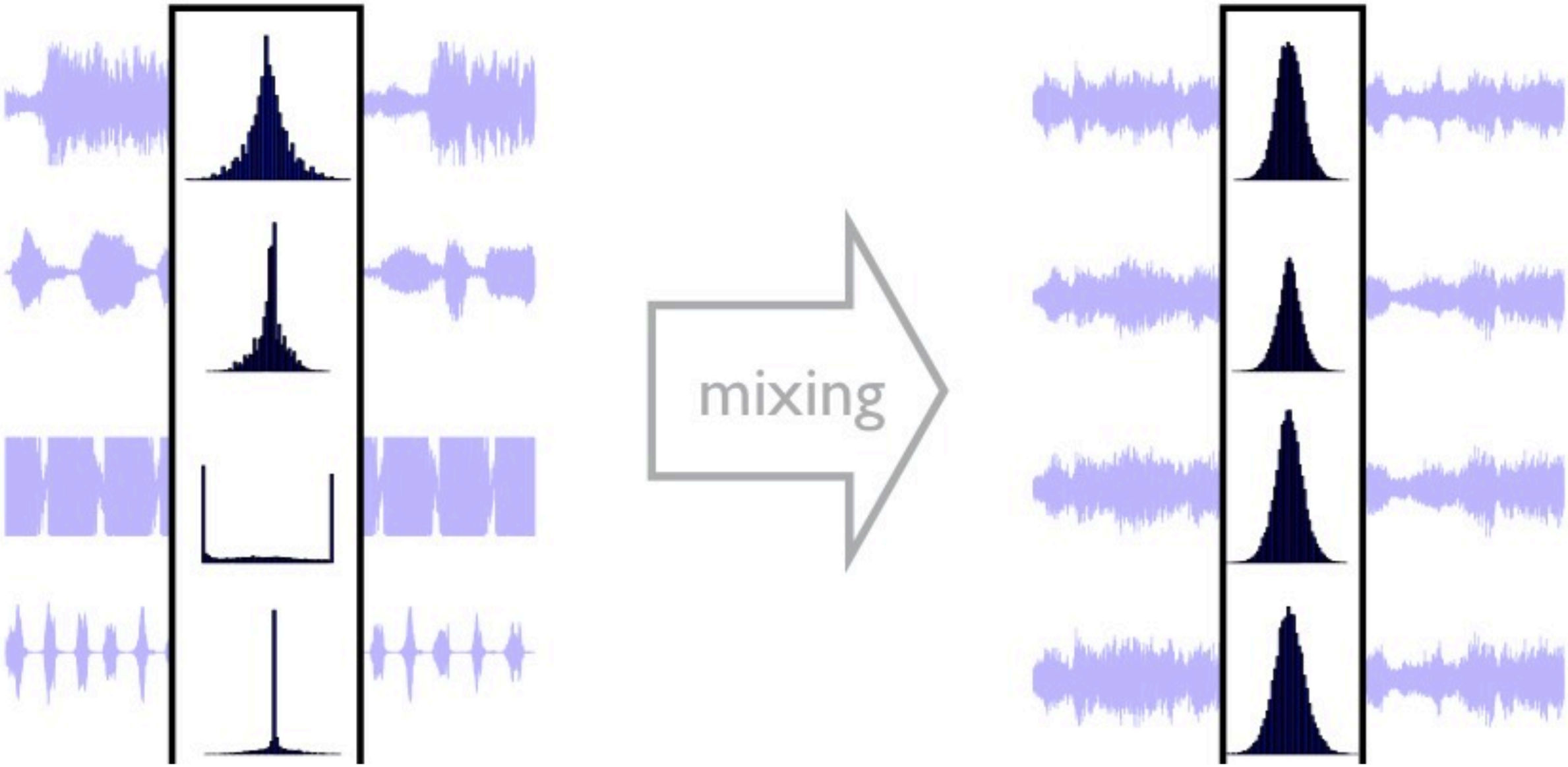


Statistical latent variable model: we observe linear mixtures of hidden sources in the presence of Gaussian noise:

$$Y = XB + E$$

McKeown et al.
HBM 1998

Non-Gaussianity



time series of ICs

Observed data

slide courtesy Christian Beckmann

Random mixing results in more Gaussian- shaped PDFs (Central Limit Theorem)

Conversely:
if mixing matrix produces *less* Gaussian- shaped PDFs this is unlikely to be a random result

➡ **measure non-Gaussianity**

Bell AJ, Sejnowski TJ. An information-maximization approach to blind separation and blind deconvolution. Neural Comput. MIT Press; 1995;7(6):1129–59.

slide courtesy Christian Beckmann

- need to find an *unmixing matrix* such that the dependency between estimated sources is minimised

  need (i) a *contrast (objective/cost) function* to drive the unmixing which measures statistical independence and (ii) an *optimisation technique*:

  - maximum entropy & gradient descent (Infomax)
  - kurtosis or cumulants & gradient descent (Jade)
  - neg-entropy & fixed point iteration (FastICA)

slide courtesy Christian Beckmann

"The fact that the body is lying down is no reason for supposing that the mind is at peace. Rest is far from restful"

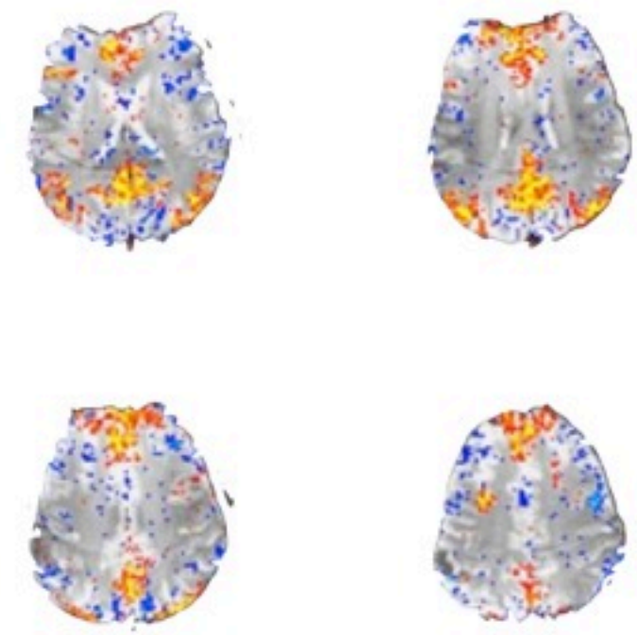
Seneca the younger, ~65A.D.

Poorly characterised experimental condition:

"a behavioural condition characterised by quiet repose usually with eyes closed but occasionally, in the experimental setting, with eyes open with or without visual fixation."

Raichle, M, Trends Cogn Sci 2010

Multiple spatial patterns of correlated temporal dynamics, resembling activation maps

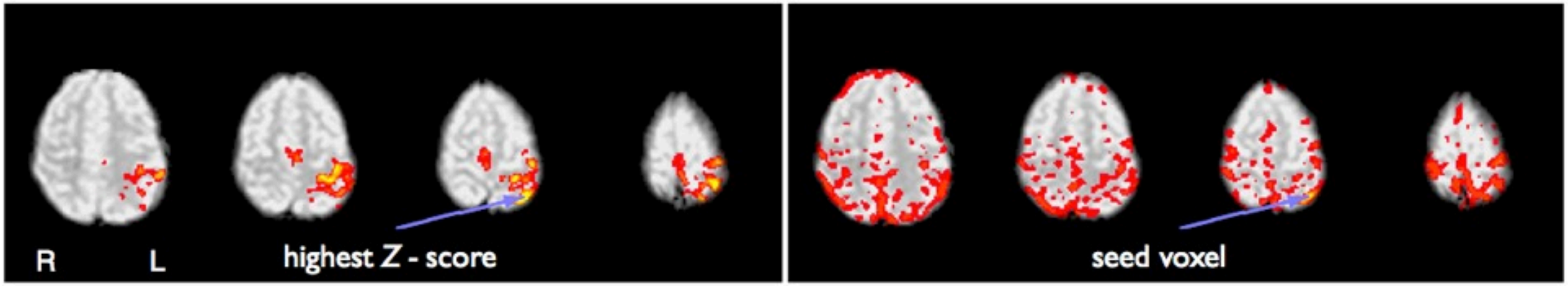


- can be found in FMRI data (BOLD & ASL) obtained at rest *and* in activation data
- characterised by (apparent) low frequency power spectra...
- seen when awake/sleep/anaesthesia, human/ animals

Two popular approaches for RSN analysis:
- Seed-based correlation (Biswal, Raichle/Fox)
- ICA-based analysis (Kiviniemi, Beckmann, Calhoun)

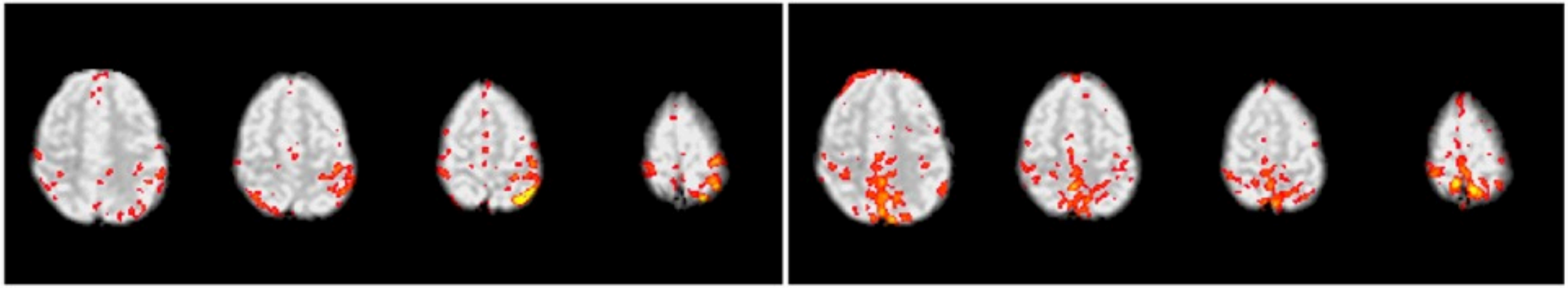
Comparison

Seed-based analysis



Activation maps from a finger tapping experiment

Correlation maps from a resting state experiment

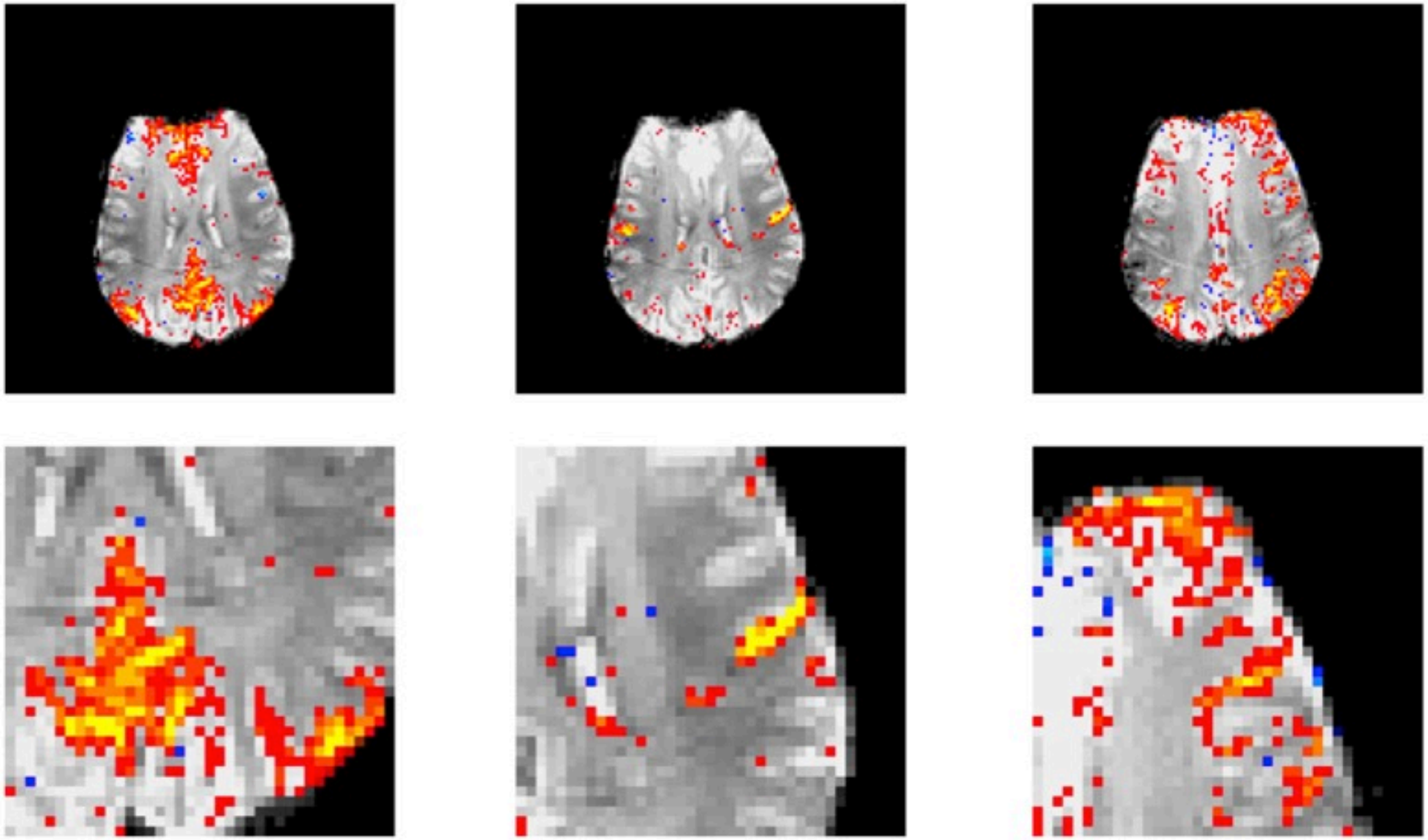


Spatial maps from an ICA decomposition

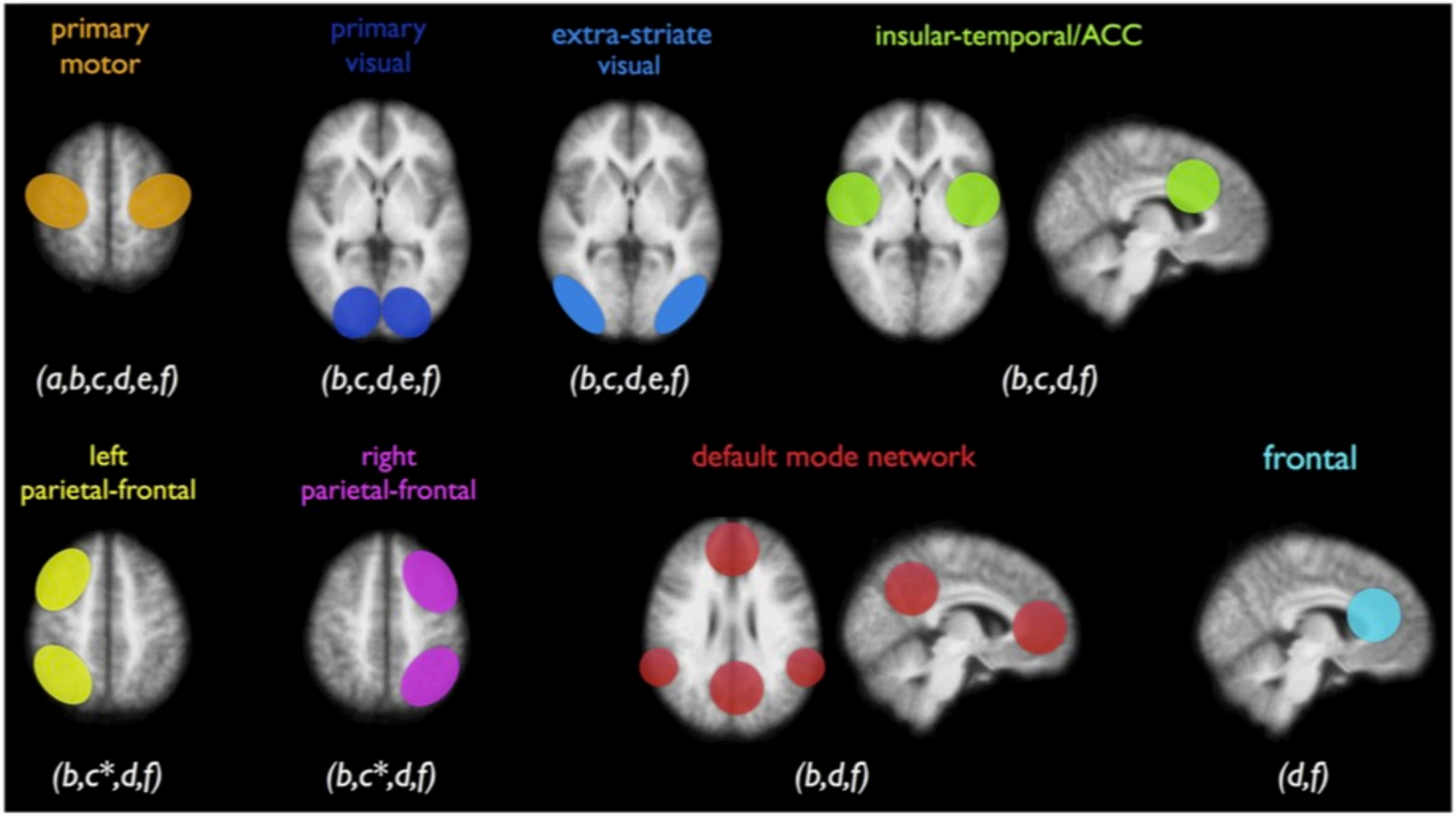
Biswal et al. (1995) MRM

Beckmann et al (2005) Philos Trans R Soc Lond, B, Biol Sci

- RSNs are grey-matter networks

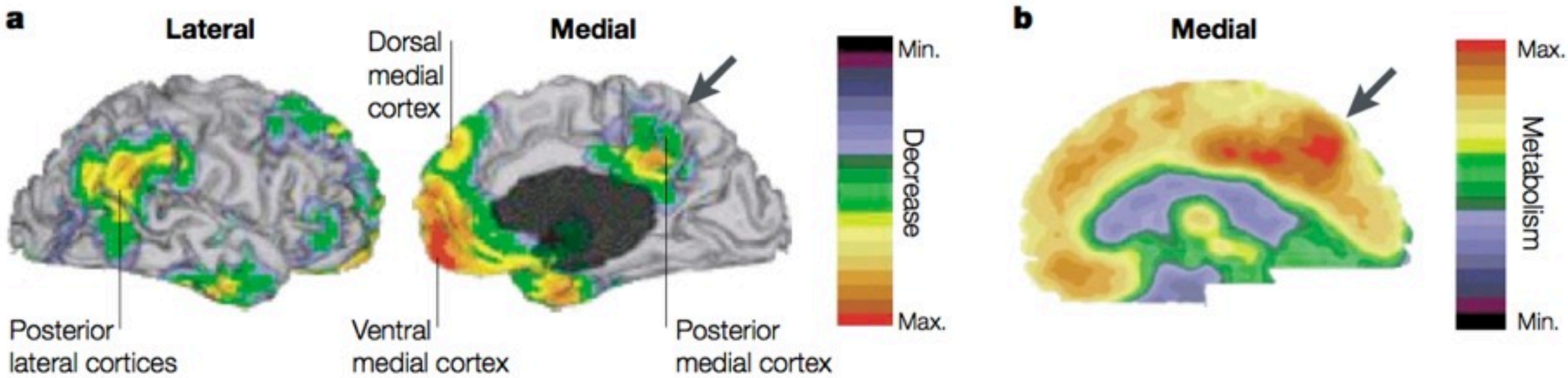


Spatial characteristics



van den Heuvel MP, Pol HEH. Exploring the brain network: A review on resting-state fMRI functional connectivity. Eur Neuropsychopharm. 2010;20(8):519–34.

The default-mode network



- Meta-analysis of 9 functional PET studies (N=132): consistent decreases during performance of attention demanding cognitive tasks
- Glucose metabolism in N=22 subjects under rest measured using FDG-PET

Shulman et al., J Cog Neurosci 1997

Gusnard et al., NRN 2001

Raichle et al., PNAS 2001

Development of resting-state networks

PNAS

Emergence of resting state networks in the preterm human brain

Valentina Doria[a], Christian F. Beckmann[b,c], Tomoki Arichi[a], Nazakat Merchant[a], Michela Groppo[a], Federico E. Turkheimer[b], Serena J. Counsell[a], Maria Murgasova[d], Paul Aljabar[d], Rita G. Nunes[a], David J. Larkman[a], Geraint Rees[e,f], and A. David Edwards[a,1]

[a]Institute of Clinical Sciences and [b]Centre for Neuroscience, Imperial College London, and Medical Research Council Clinical Sciences United Kingdom; [c]Functional Magnetic Resonance Imaging of the Brain Centre, University of Oxford, Oxford OX3 9DU, United King Processing Group, Department of Computing, Imperial College London, London SW7 2AZ, United Kingdom; [e]University College Lon Neuroscience, London WC1N 3AR, United Kingdom; and [f]Wellcome Trust Centre for Neuroimaging at UCL, London WC1N 3BG, U

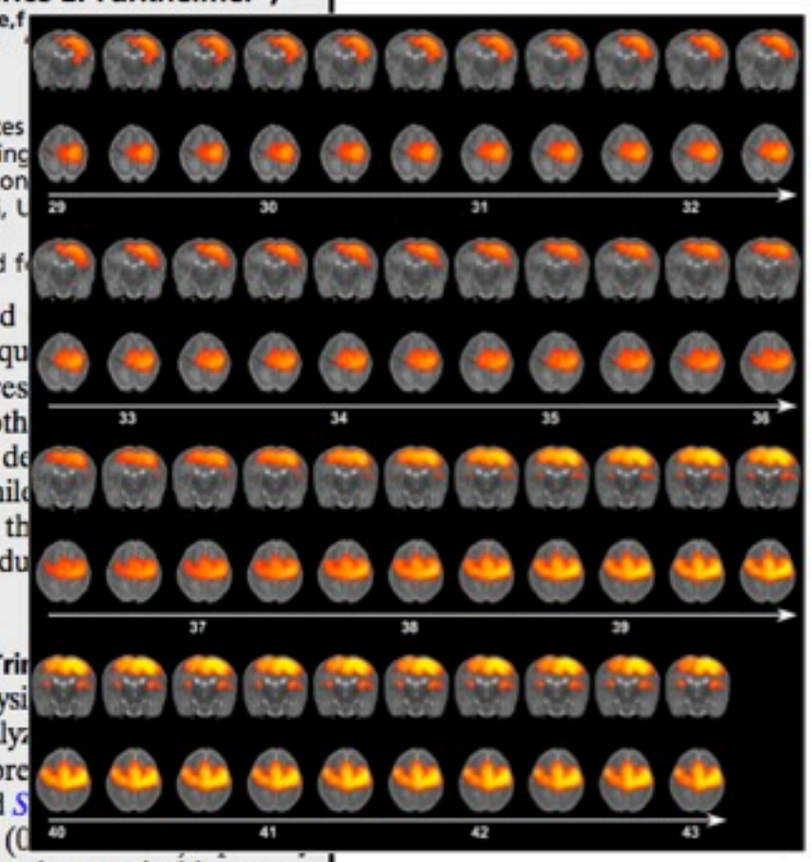
Edited by Marcus E. Raichle, The Washington University of St. Louis, St. Louis, MO, and approved September 28, 2010 (received f

The functions of the resting state networks (RSNs) revealed by functional MRI remain unclear, but it has seemed possible that networks emerge in parallel with the development of related cognitive functions. We tested the alternative hypothesis: that the full repertoire of resting state dynamics emerges during the period of rapid neural growth before the normal time of birth at term (around 40 wk of gestation). We used a series of independent analytical techniques to map in detail the development of different networks in 70 infants born between 29 and 43 wk of postmenstrual age (PMA). We characterized and charted the development of RSNs from recognizable but often fragmentary elements at 30 wk of PMA to full facsimiles of adult patterns at term. Visual, auditory, somatosensory, motor, default mode, frontoparietal, and executive control networks developed at different rates; however, by term, complete networks were present, several of which were integrated with thalamic activity. These results place the emergence of RSNs largely during the period of rapid neural growth in the third trimester of gestation, suggesting that they are formed before the acquisition of

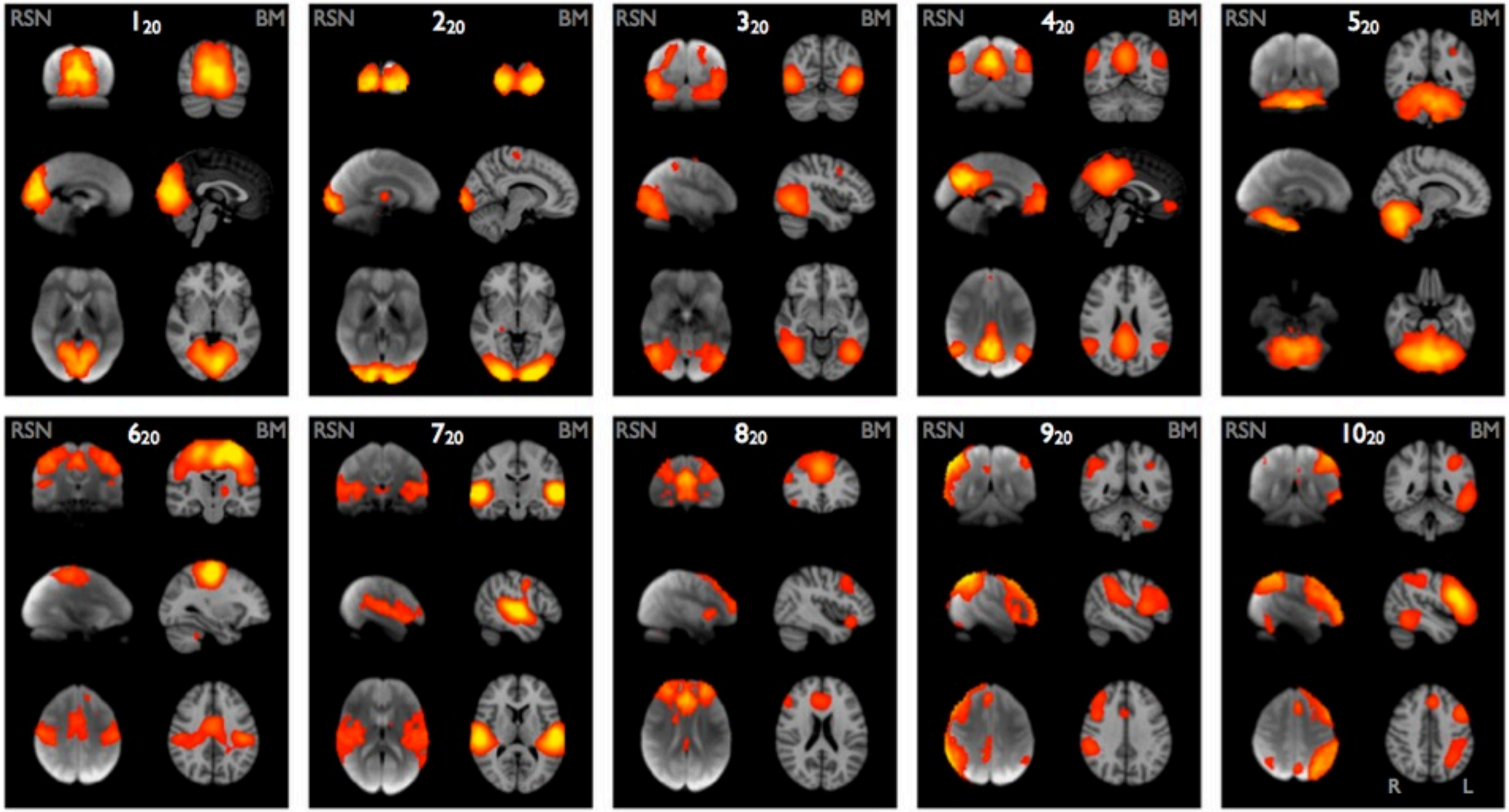
between 29 and 43 wk of PMA. We used
including improved registration and a uniqu
of the developing brain with consistent thres
data-driven exploratory analysis and hypoth
to show that synchronous BOLD activity de
tary RSNs in preterm infants into facsimile
term, including involvement of relevant th
quantify the growing network coherence du

Results

Identification of RSNs During the Third Tri
probabilistic independent component analysi
free detection of RSNs (Fig. 1). We analyz
from resting state fMRI in early preterm, pre
(full details are presented in *Methods* and *S*
ysis revealed correlated low-frequency (0
distributed BOLD signals that characterized recognizable neuro-
anatomical systems comparable to adult networks, including vi-

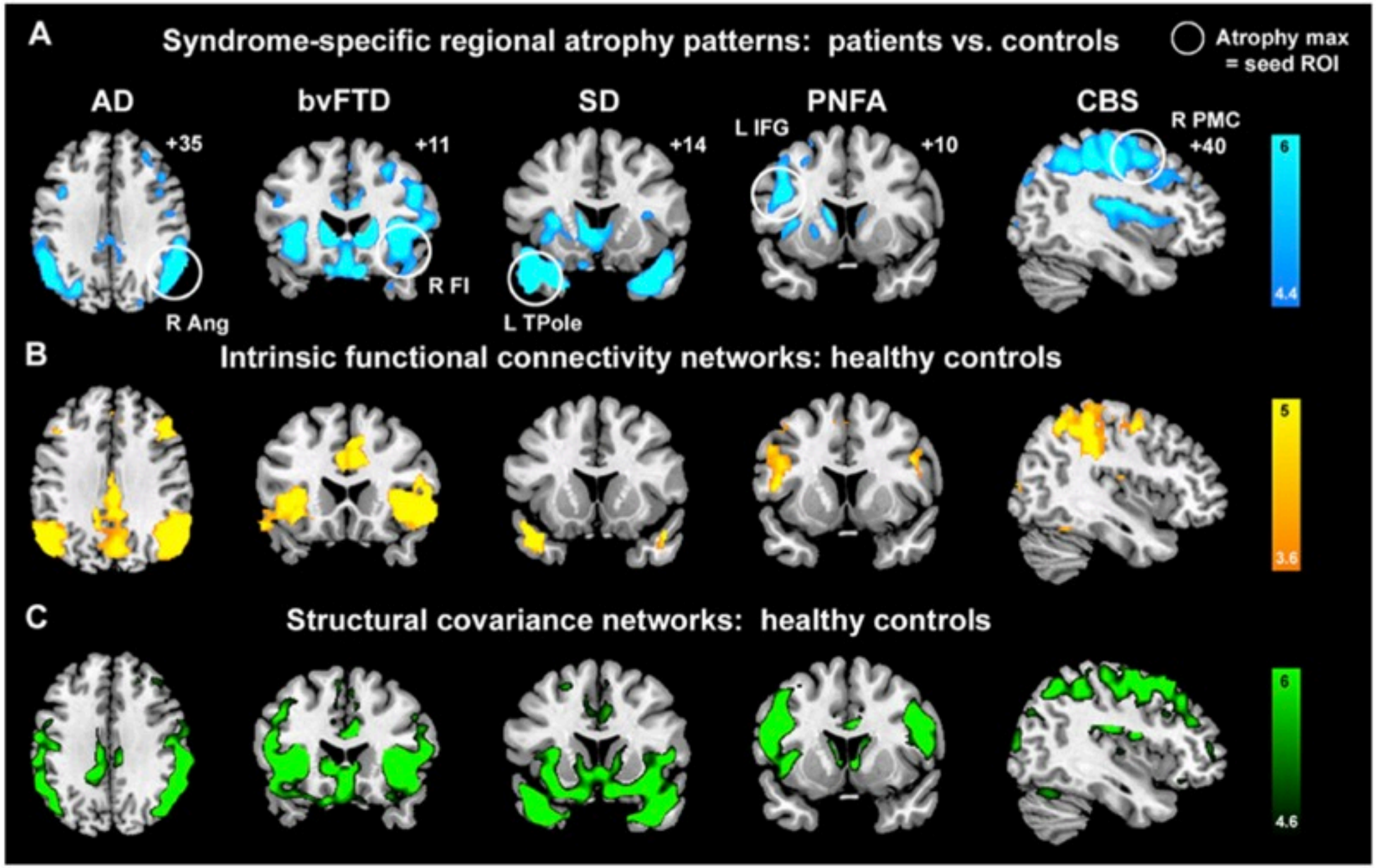


Correspondence between task and resting-state data



Smith SM, Fox PT, Miller KL, Glahn DC, Fox PM, Mackay CE, et al. Correspondence of the brain's functional architecture during activation and rest. PNAS

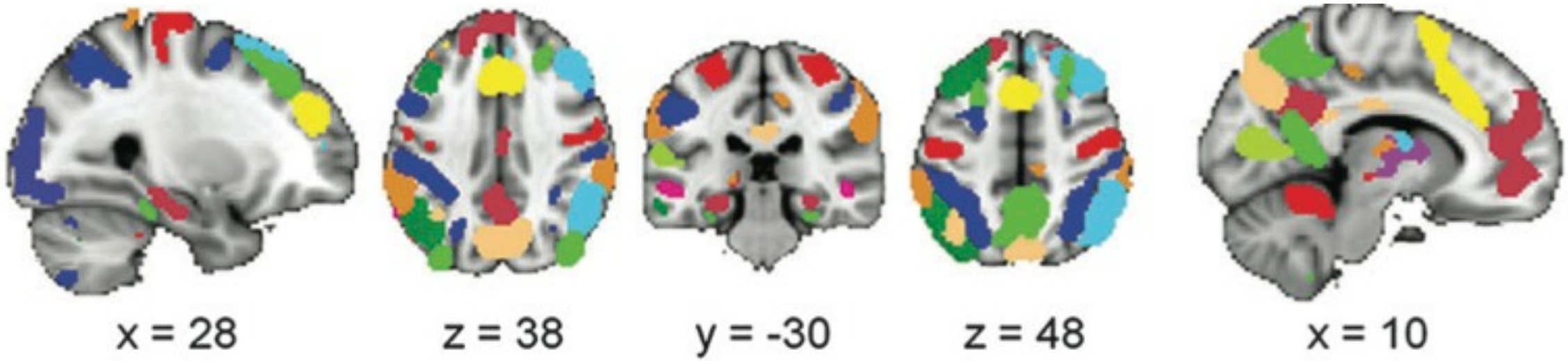
RSNs and neurodegeneration

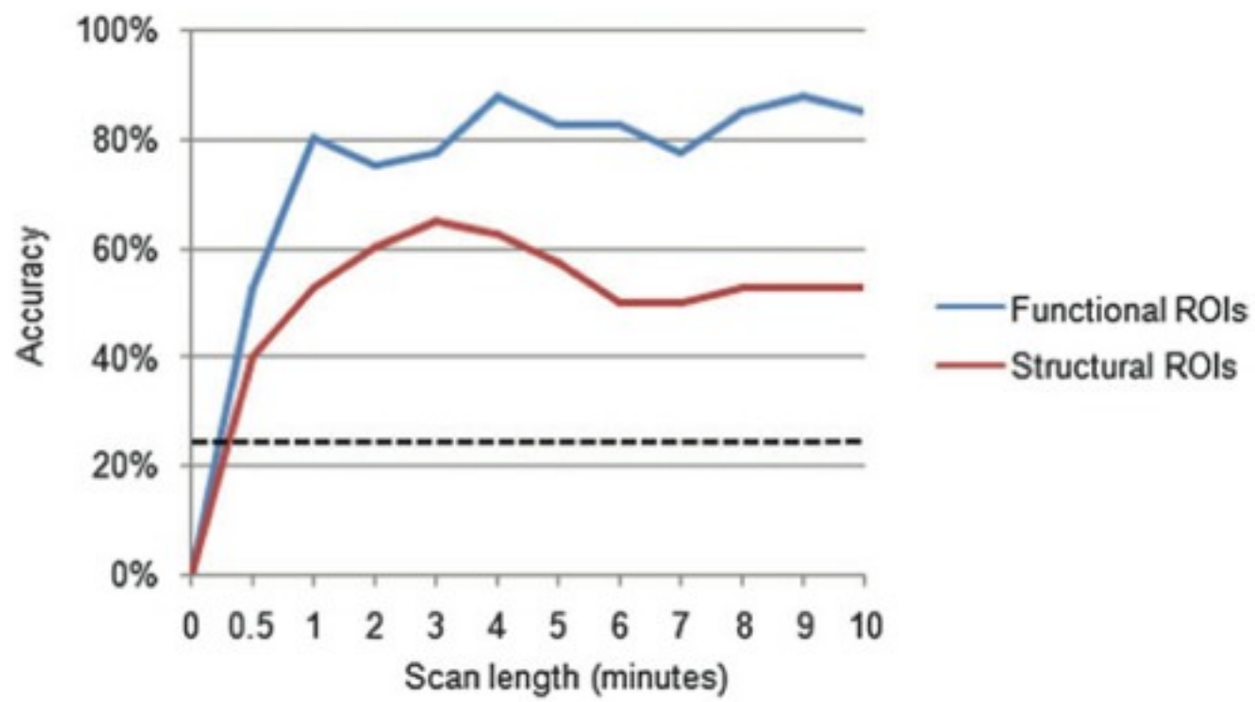


Neurodegenerative diseases target large-scale human brain networks

Seeley et al. (2009) Neuron

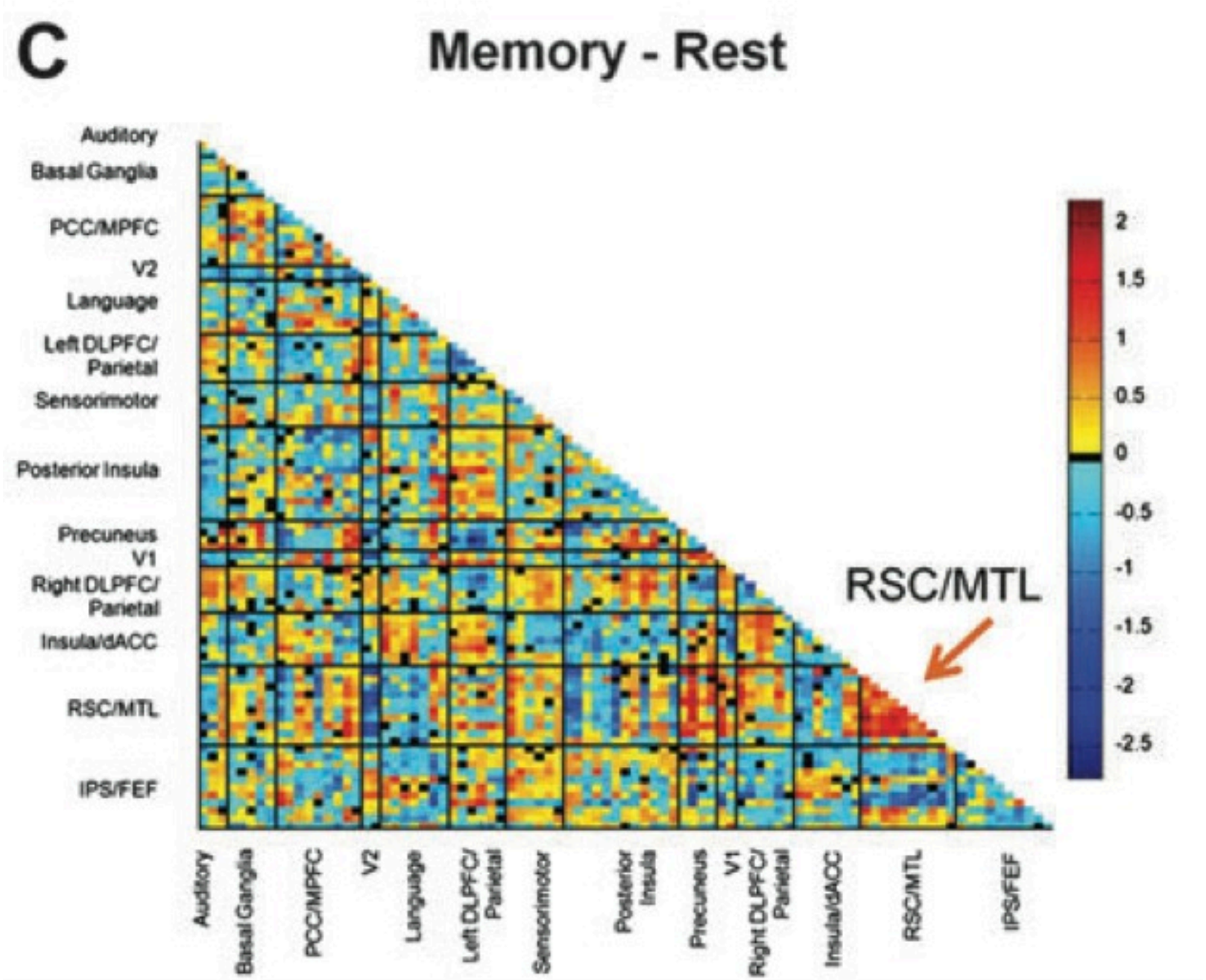
ICA based parcellation:





Shirer WR, Ryali S, Rykhlevskaia E, Menon V, Greicius MD. Decoding subject-driven cognitive states with whole-brain connectivity patterns. Cerebral Cortex. 2012;22(1):158–65.

Connectivity-based decoding



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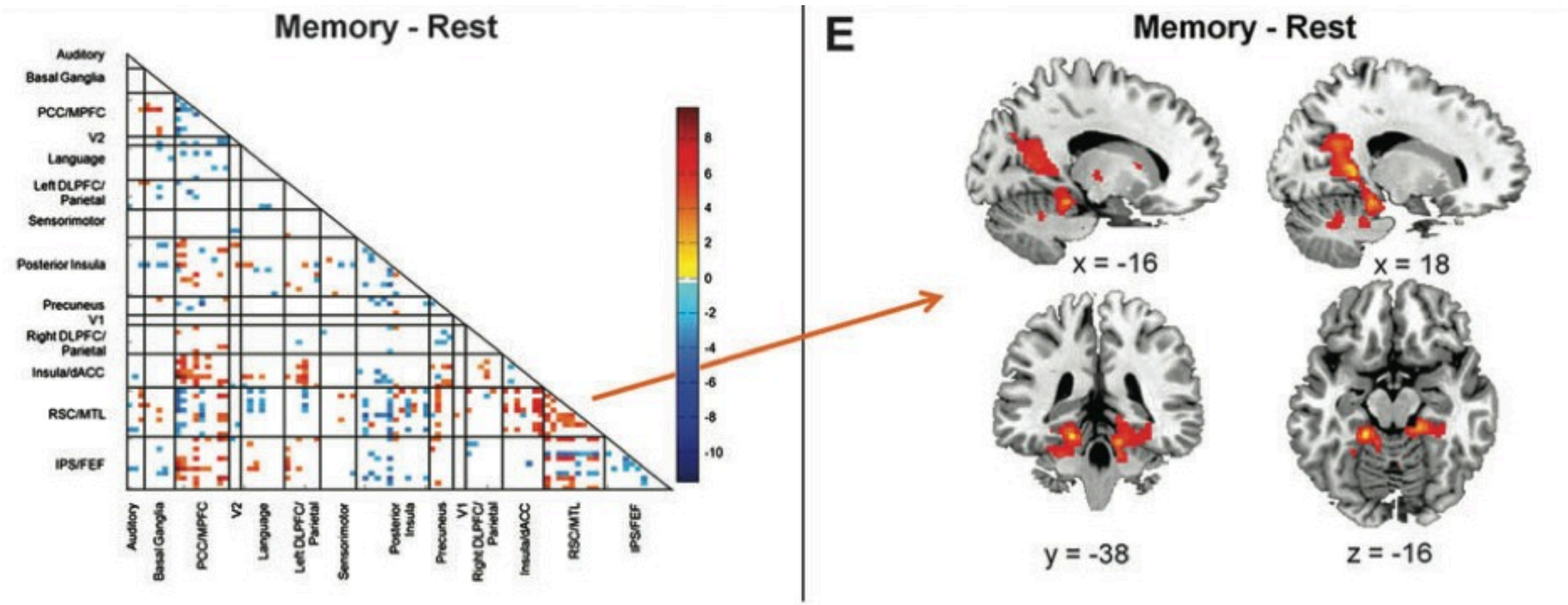

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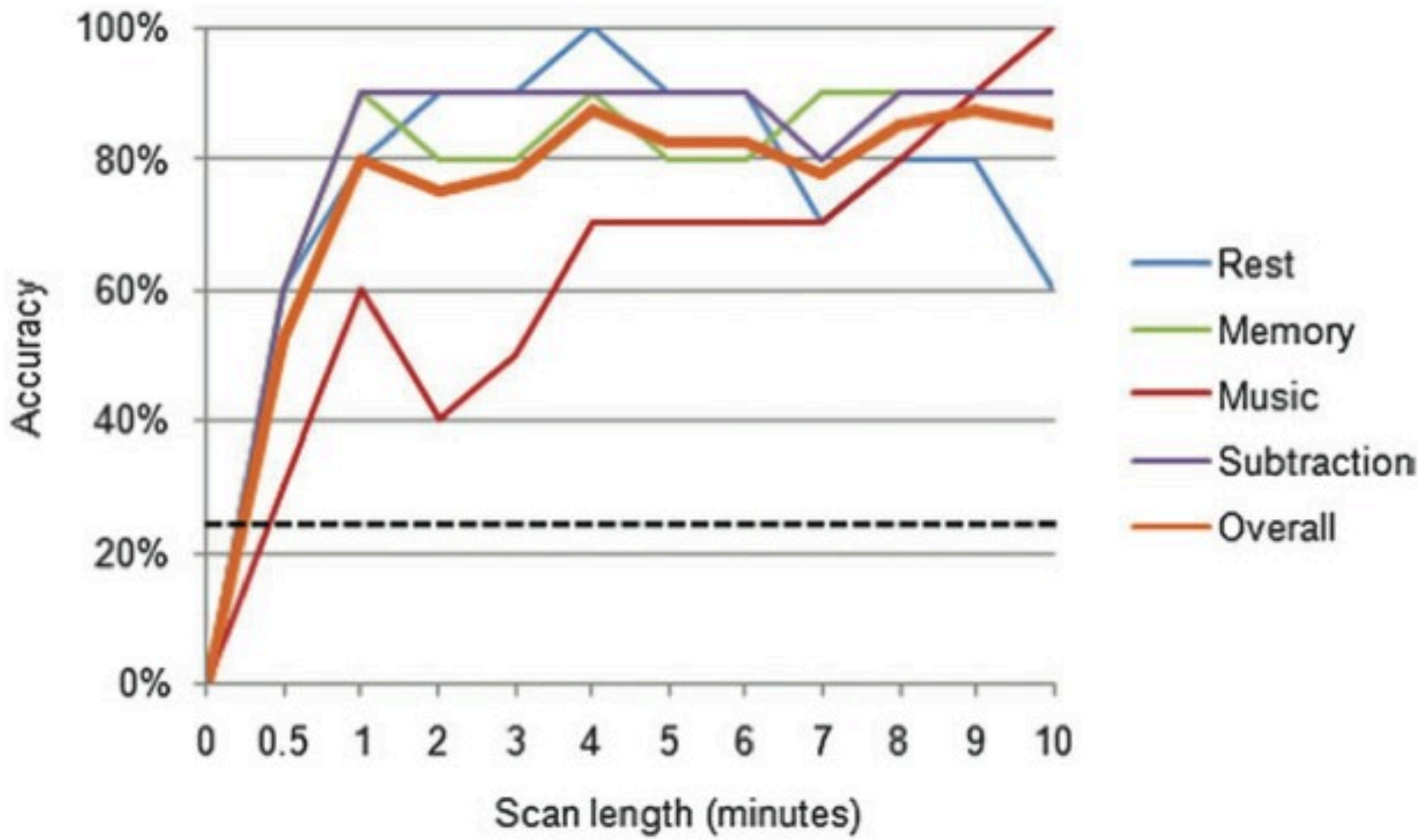
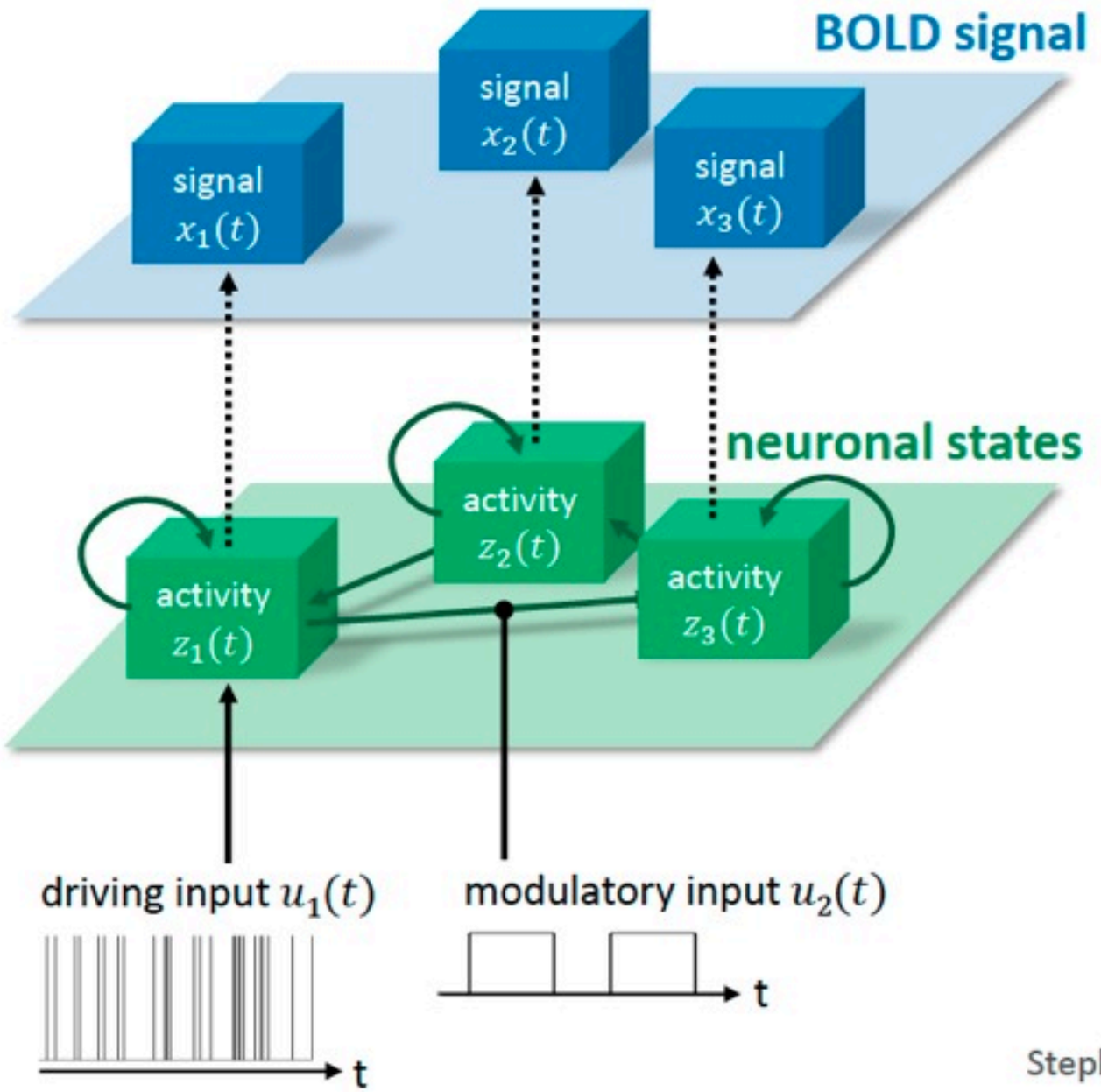
Connectivity-based decoding



Shirer WR, Ryali S, Rykhlevskaia E, Menon V, Greicius MD. Decoding subject-driven cognitive states with whole-brain connectivity patterns. Cerebral Cortex. 2012;22(1):158–65.

Effective connectivity: Dynamic causal modelling



haemodynamic forward model

$$x = g(z, \theta_h)$$

neural state equation

$$\dot{z} = \left(A + \sum u_j B^{(j)}\right) z + Cu$$

intrinsic connectivity

modulation of connectivity

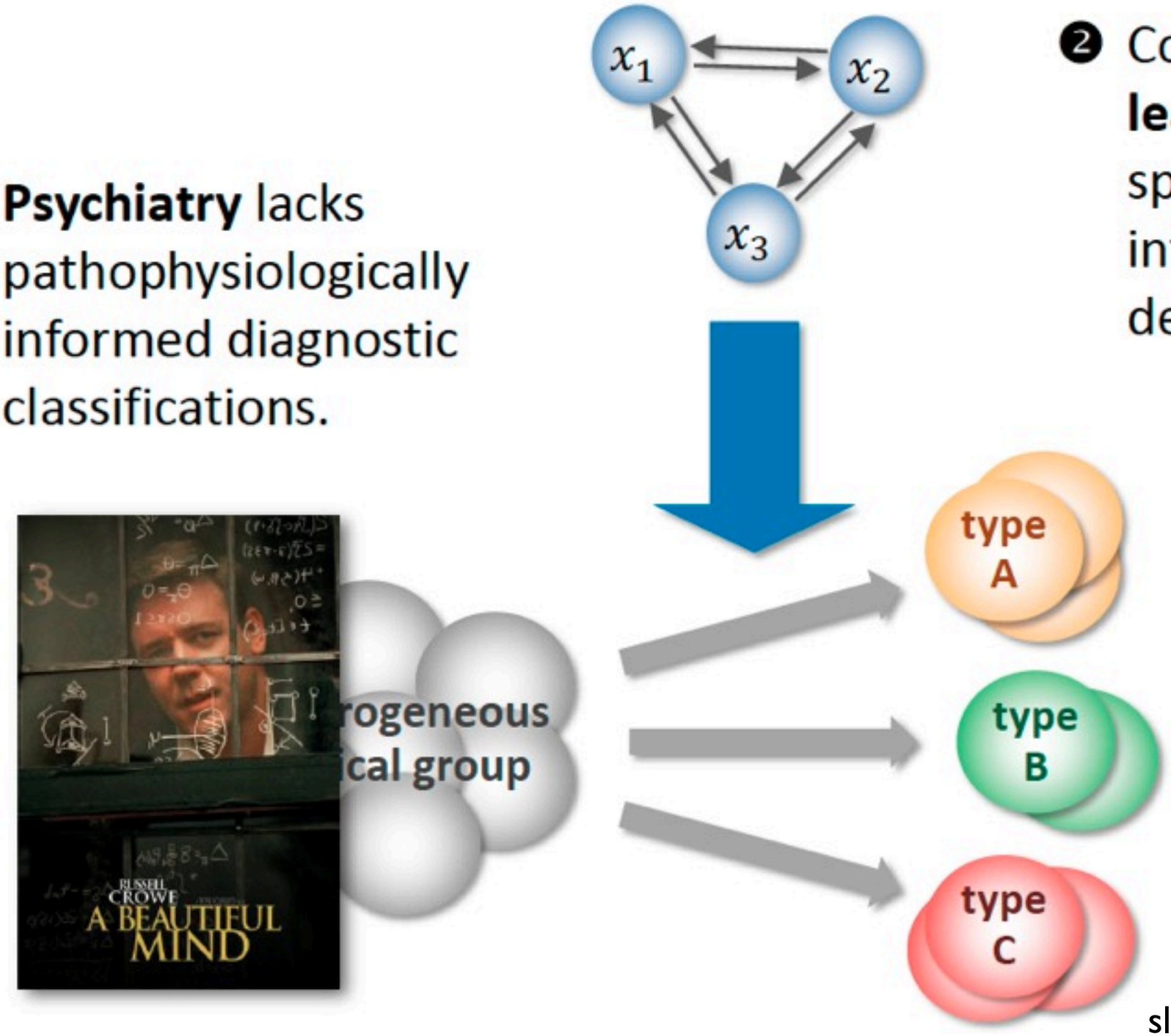
direct inputs

Friston, Harrison & Penny (2003) *NeuroImage*
Stephan & Friston (2007) *Handbook of Brain Connectivity*

slide courtesy Kai Brodersen

Model-based classification via a generative embedding

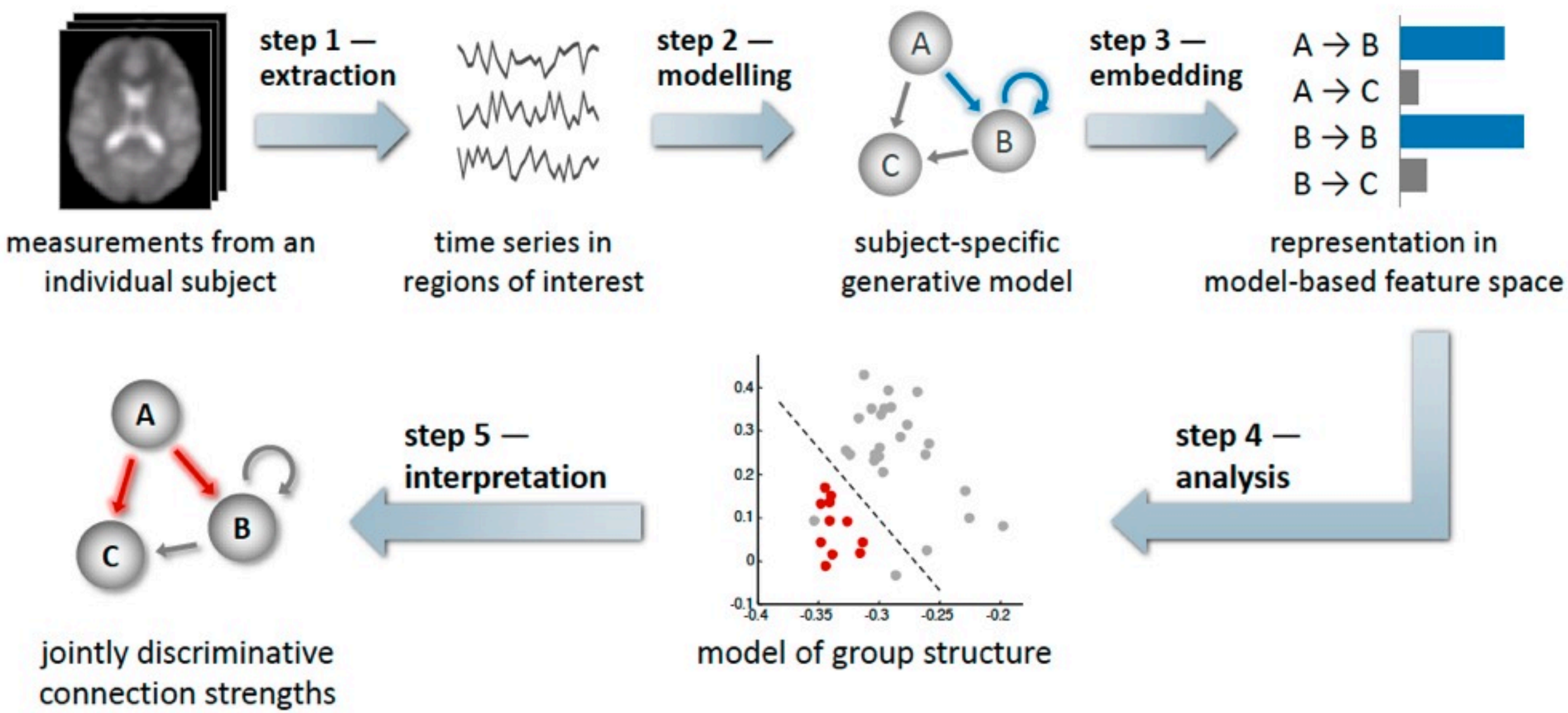
❶ **Psychiatry** lacks pathophysiologically informed diagnostic classifications.



❷ Could **machine learning** help dissect spectrum disorders into mechanistically defined subgroups?

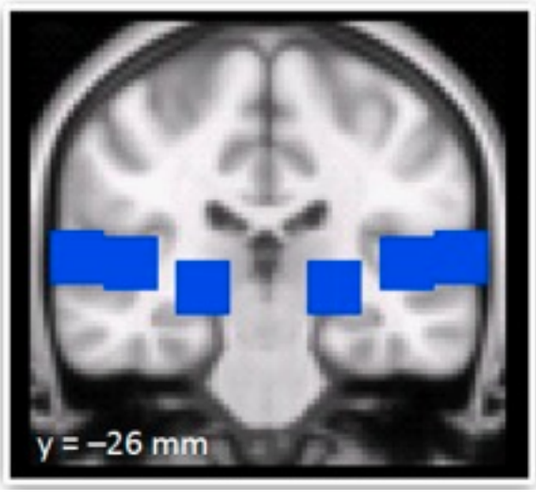
slide courtesy Kai Brodersen

Model-based classification

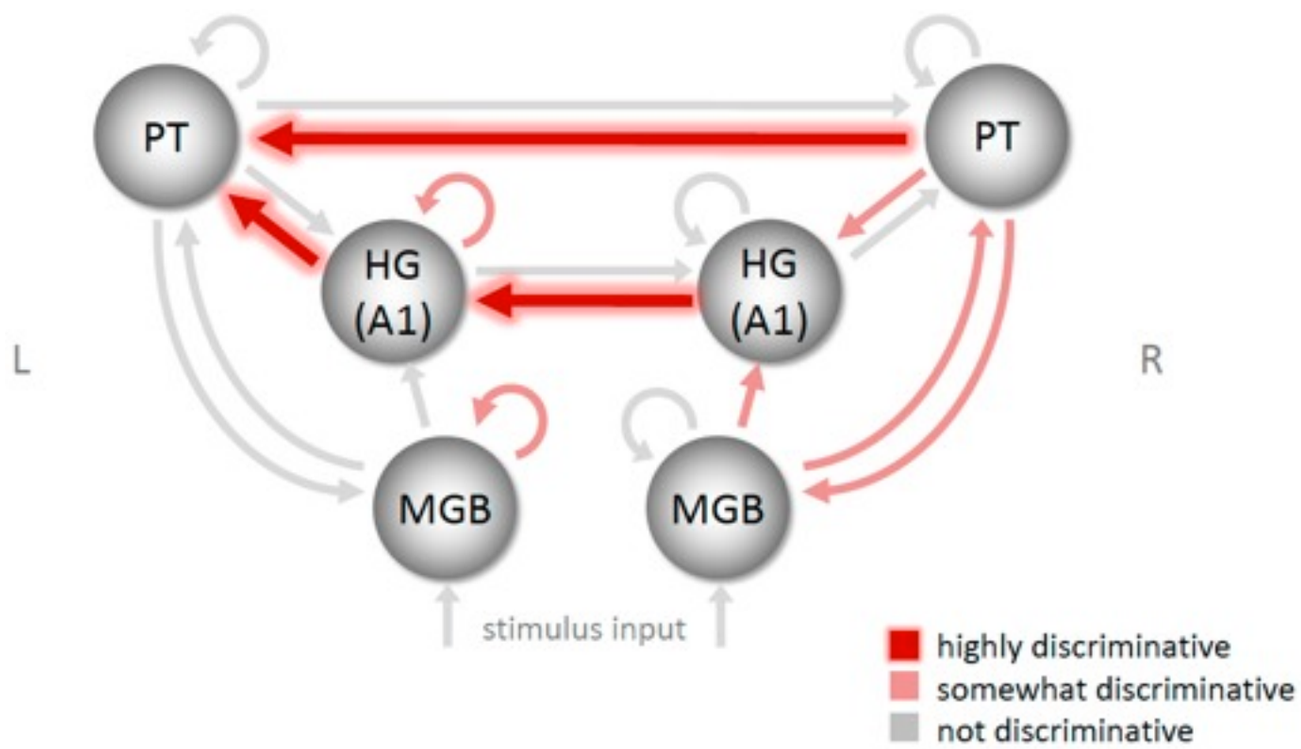


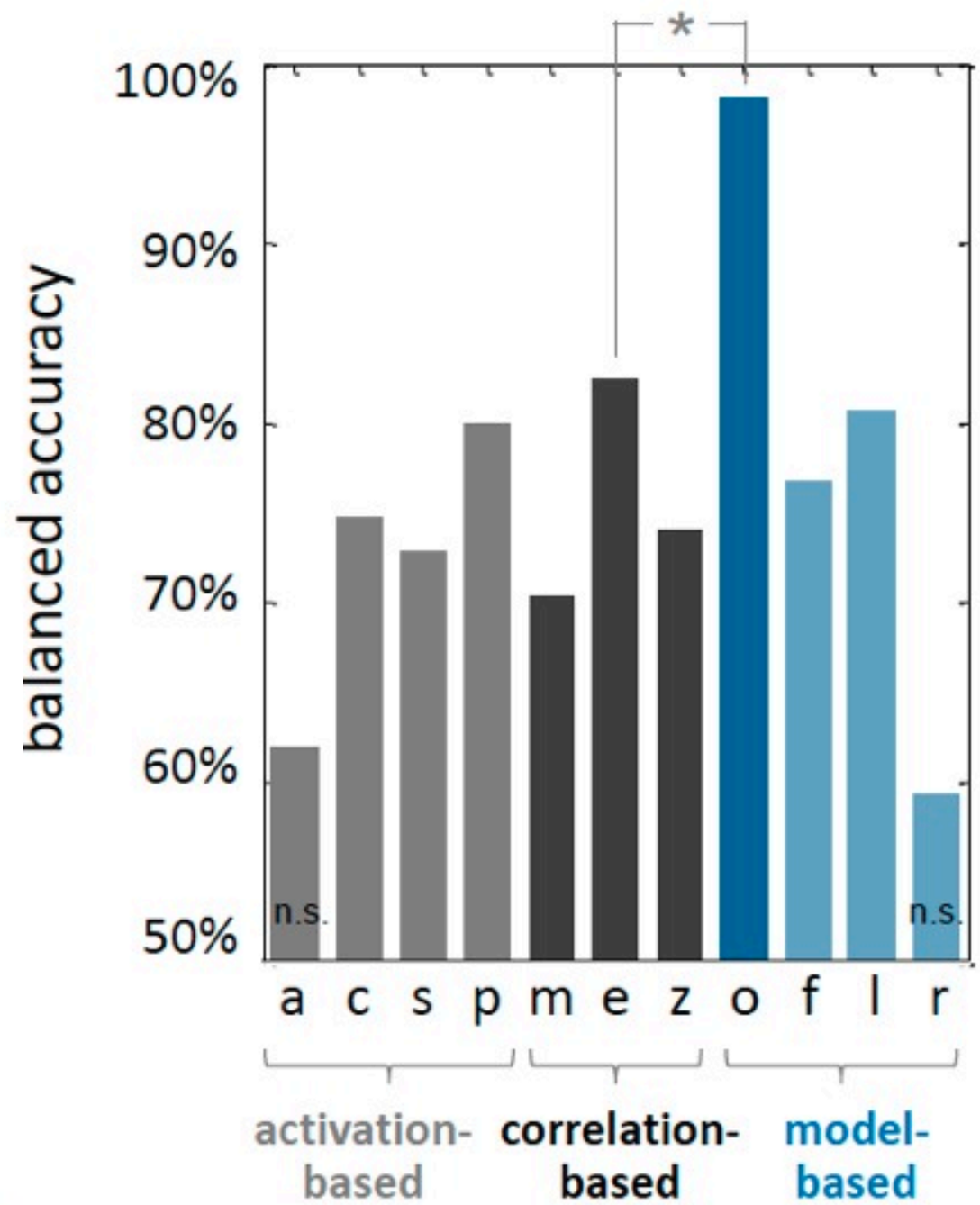
Brodersen KH, Schofield TM, Leff AP, Ong CS, Lomakina EI, Buhmann JM, et al. Generative Embedding for Model-Based Classification of fMRI Data. Sporns O, editor. PLoS Comput Biol. 2011 Jun 23;7(6):e1002079.

Predicting stroke patients versus healthy controls



anatomical regions of interest





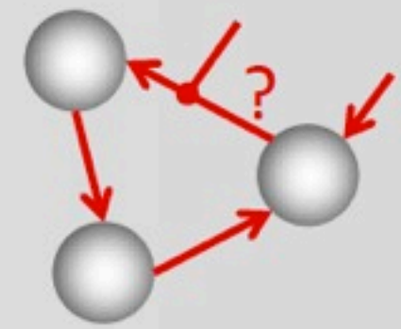
slide courtesy Kai Brodersen

Relevance of Bayesian model-based approaches

Question 1 – What do the data tell us about hidden processes in the brain?

⇨ compute the posterior

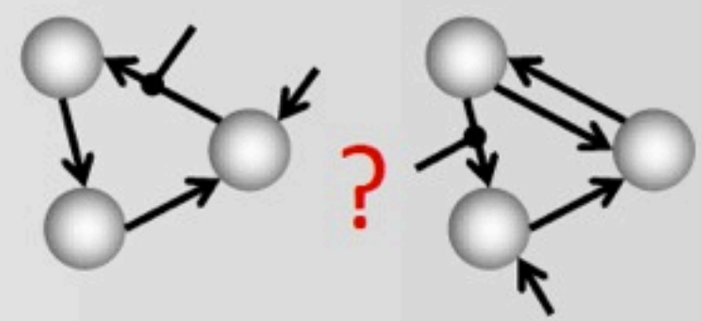
$$p(\theta|y,m) = \frac{p(y|\theta,m)p(\theta|m)}{p(y|m)}$$



Question 2 – Which model is best w.r.t. the observed fMRI data?

⇨ compute the model evidence

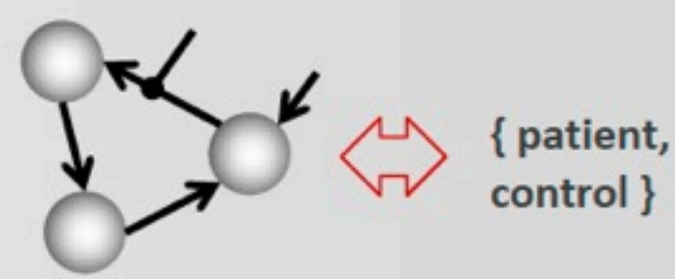
$$p(m|y) \propto p(y|m)p(m)$$
$$= \int p(y|\theta,m)p(\theta|m)d\theta$$



Question 3 – Which model is best w.r.t. an external criterion?

⇨ compute classification accuracy or clustering purity

$$p(h(y) = x|y)$$
$$= \iiint p(h(y) = x|y, y_{\text{train}}, x_{\text{train}})\, p(y)\, p(y_{\text{train}})\, p(x_{\text{train}})\; dy\, dy_{\text{train}}\, dx_{\text{train}}$$



slide courtesy Kai Brodersen

Required reading

- van den Heuvel MP, Pol HEH. Exploring the brain network: A review on resting-state fMRI functional connectivity. Eur Neuropsychopharm. 2010;20(8):519–34.

REVIEW

Exploring the brain network: A review on resting-state fMRI functional connectivity

Martijn P. van den Heuvel*, Hilleke E. Hulshoff Pol

Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, Neuroimaging Division, The Netherlands

Learning goals

- Structural, functional, effective connectivity
- Partial correlation
- ICA
- Resting state networks
- Connectivity-based decoding

Coming week

Practical

Finish assignments!

Essay

Decide on a topic; start early!

Lecture

Bayesian connectomics (8 January)

ENJOY YOU HOLIDAYS!