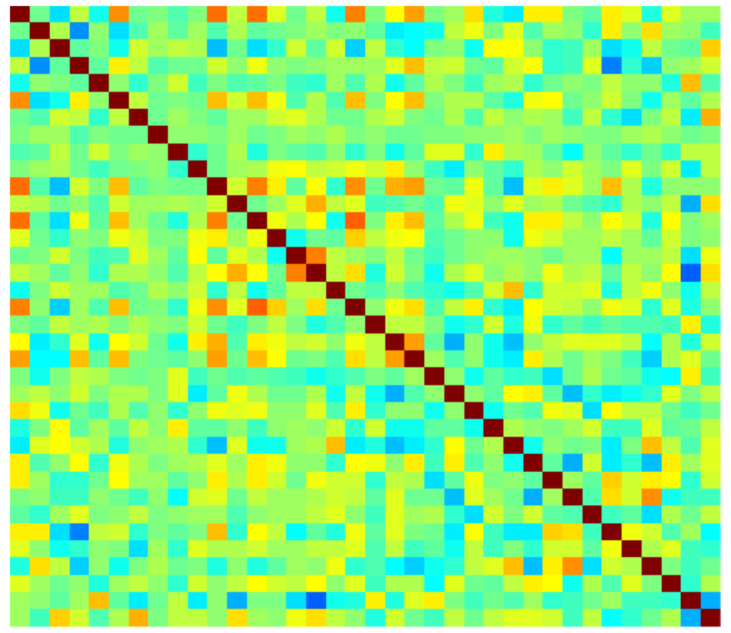
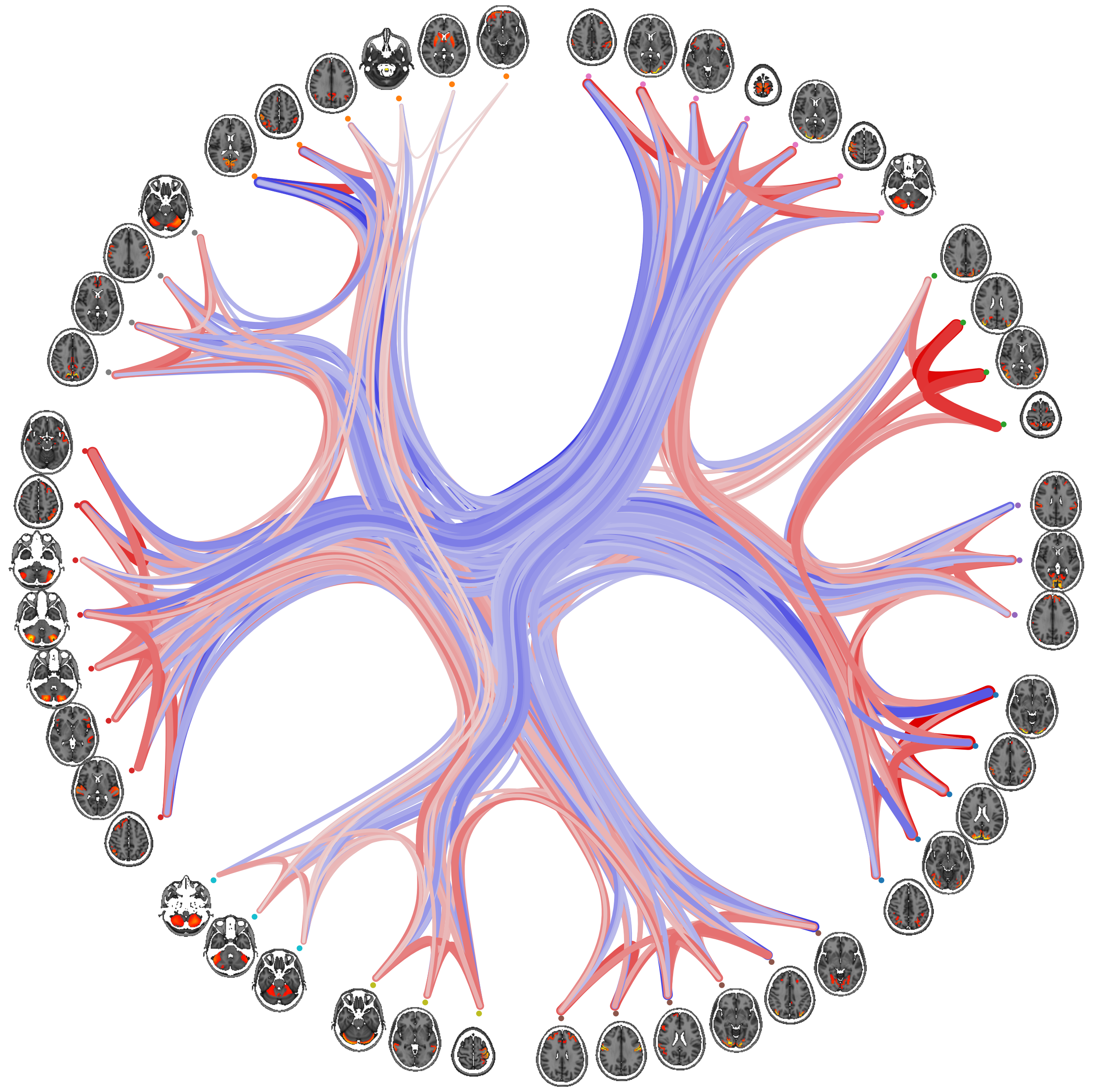
Network modelling analysis

- Resting state data characteristics
- Preprocessing
- Network modelling analysis
- Methods comparisons and considerations

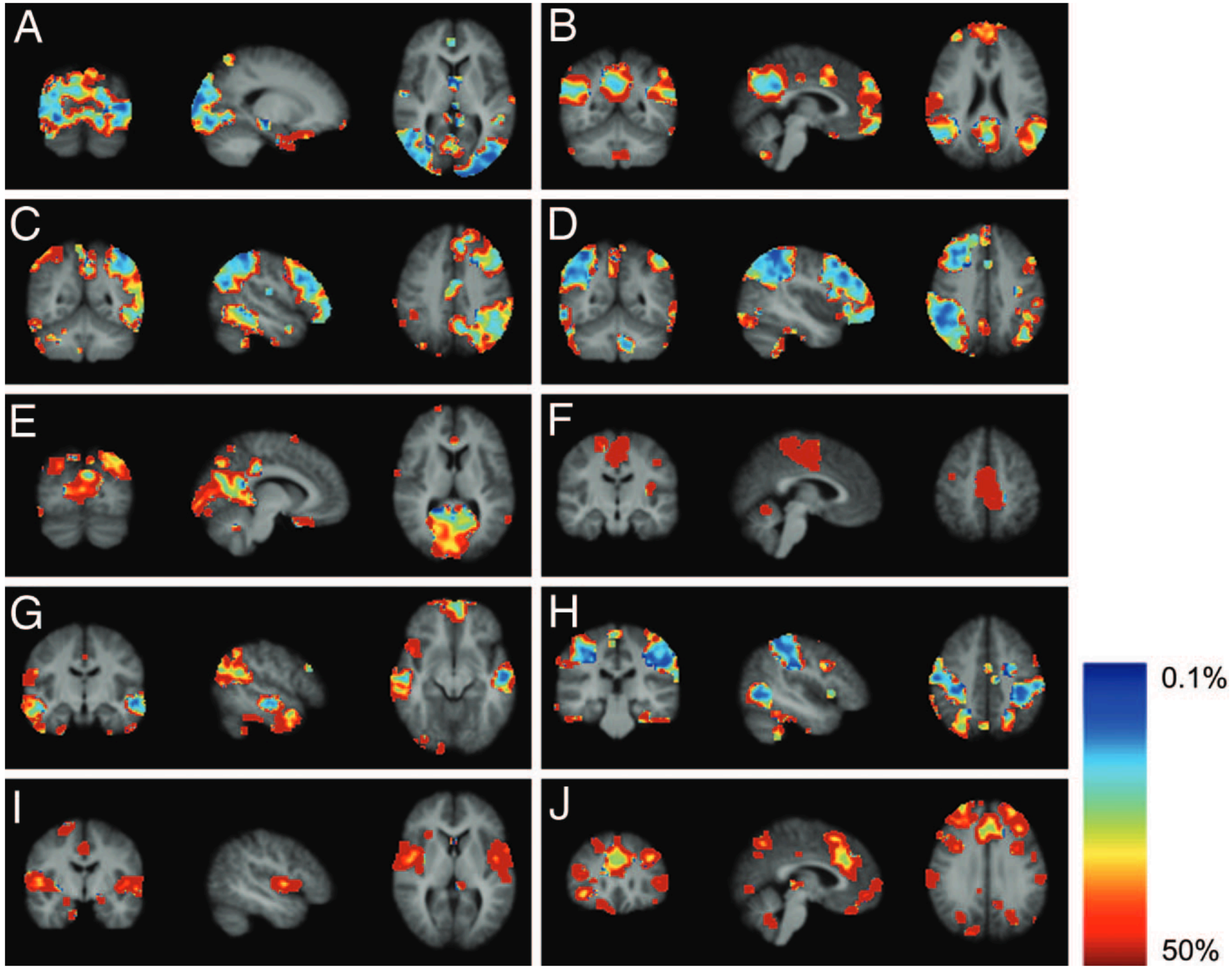




Data characteristics

Replicable networks

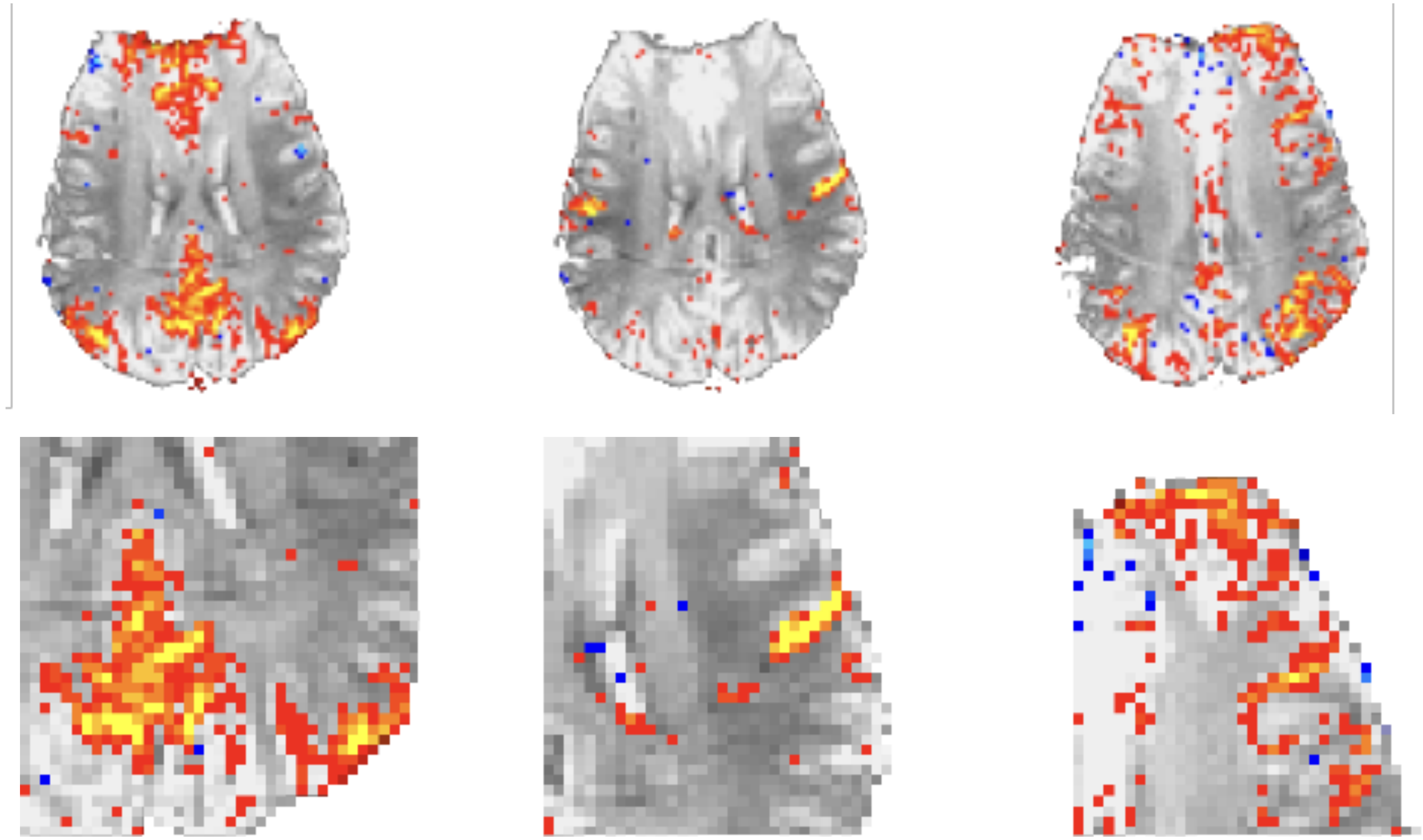
Large-scale inherent organisation is reproducibly found across studies and approaches



Damoiseaux et al (2006)

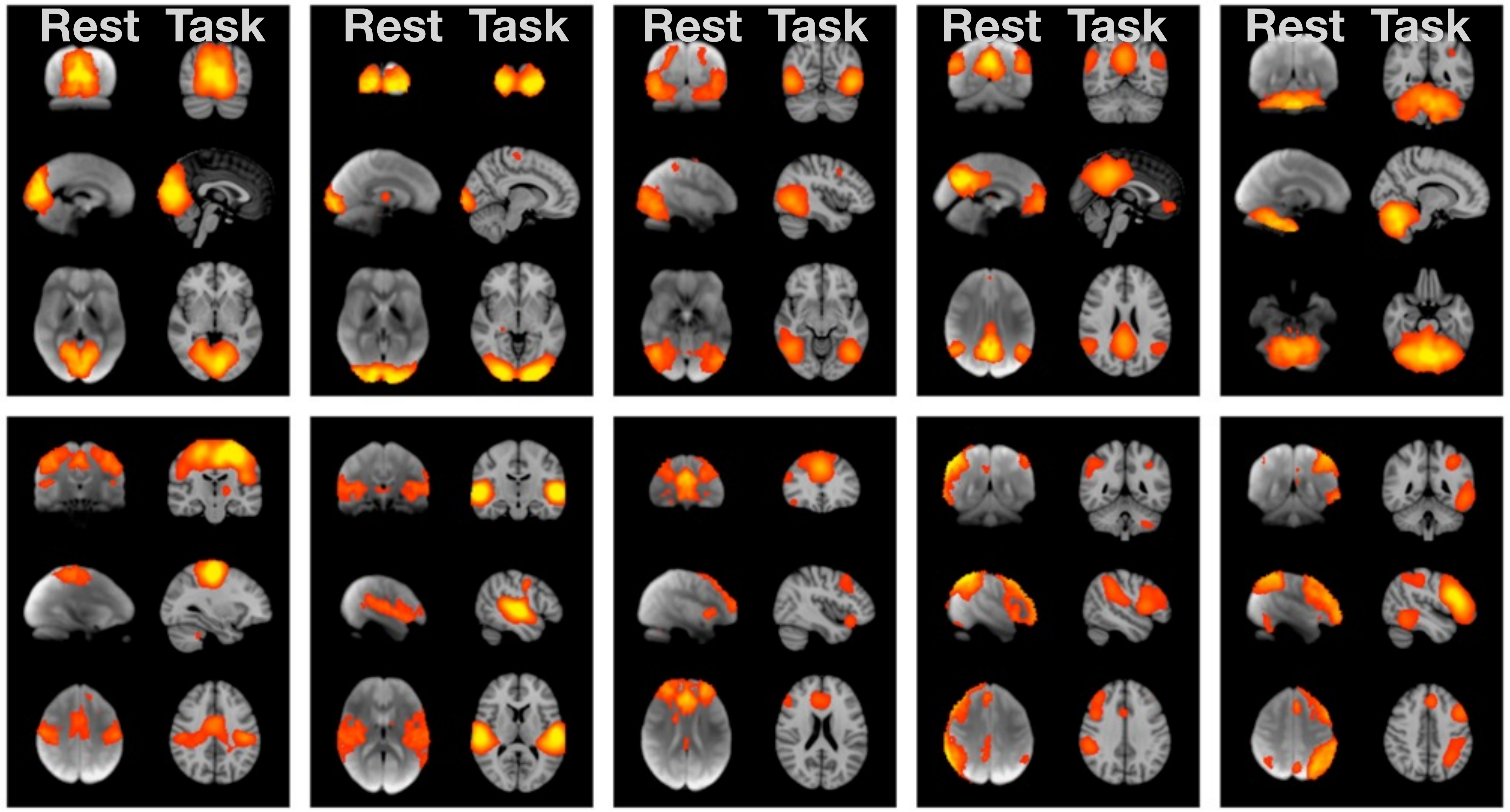
Grey matter networks

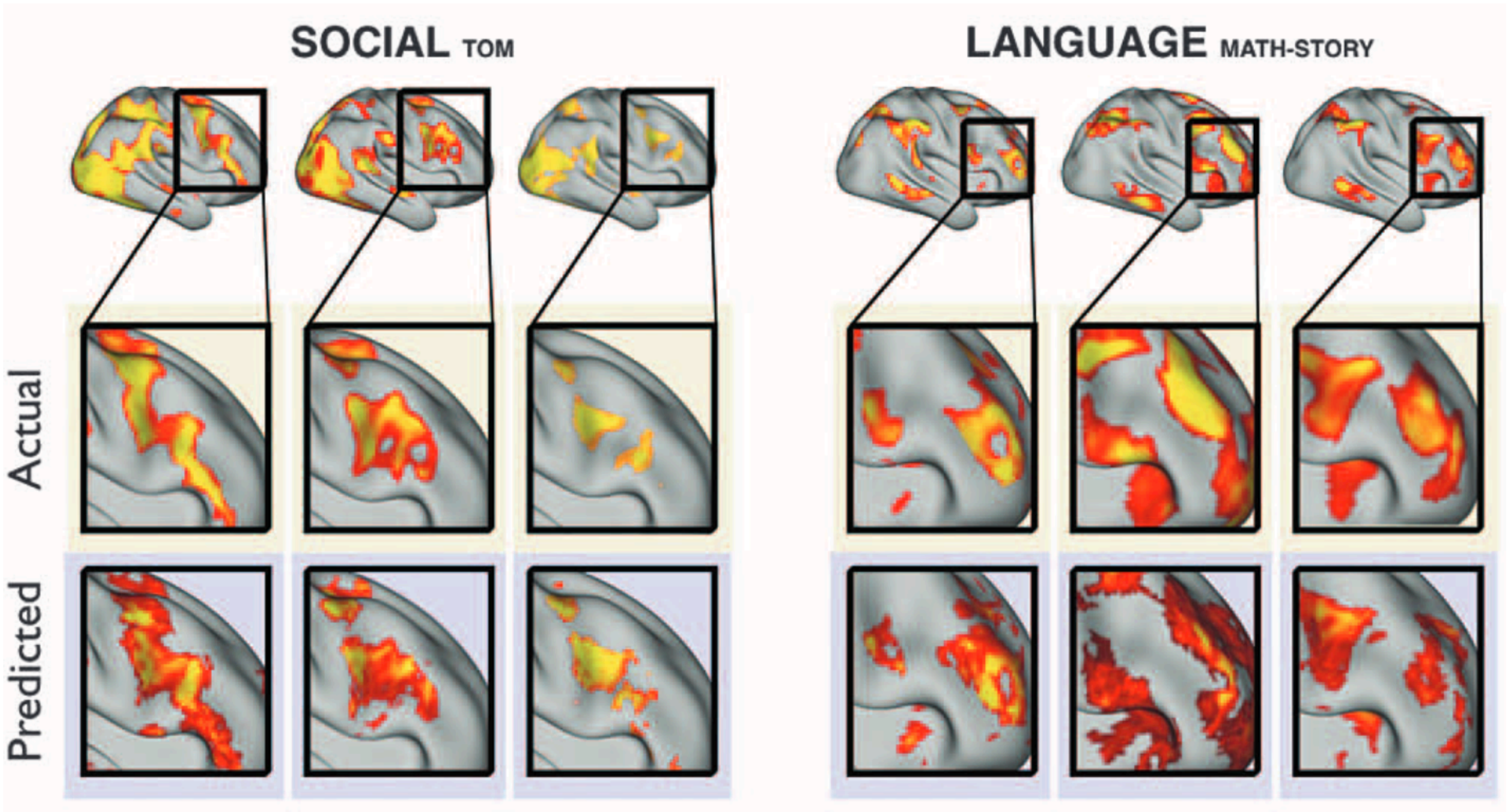
Resting state network structure is localised in grey matter



Relationship to task

Resting state networks are similar to task activation patterns at group and single subject level

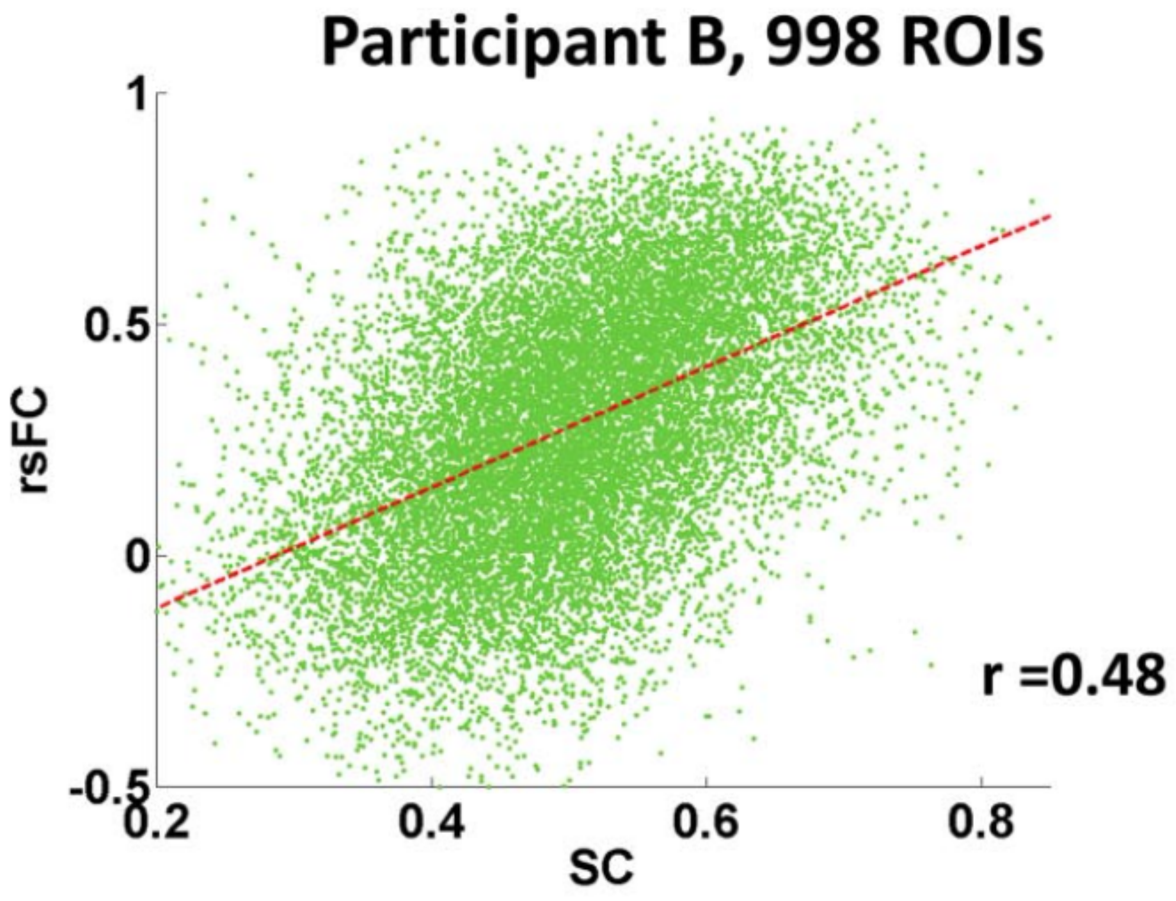


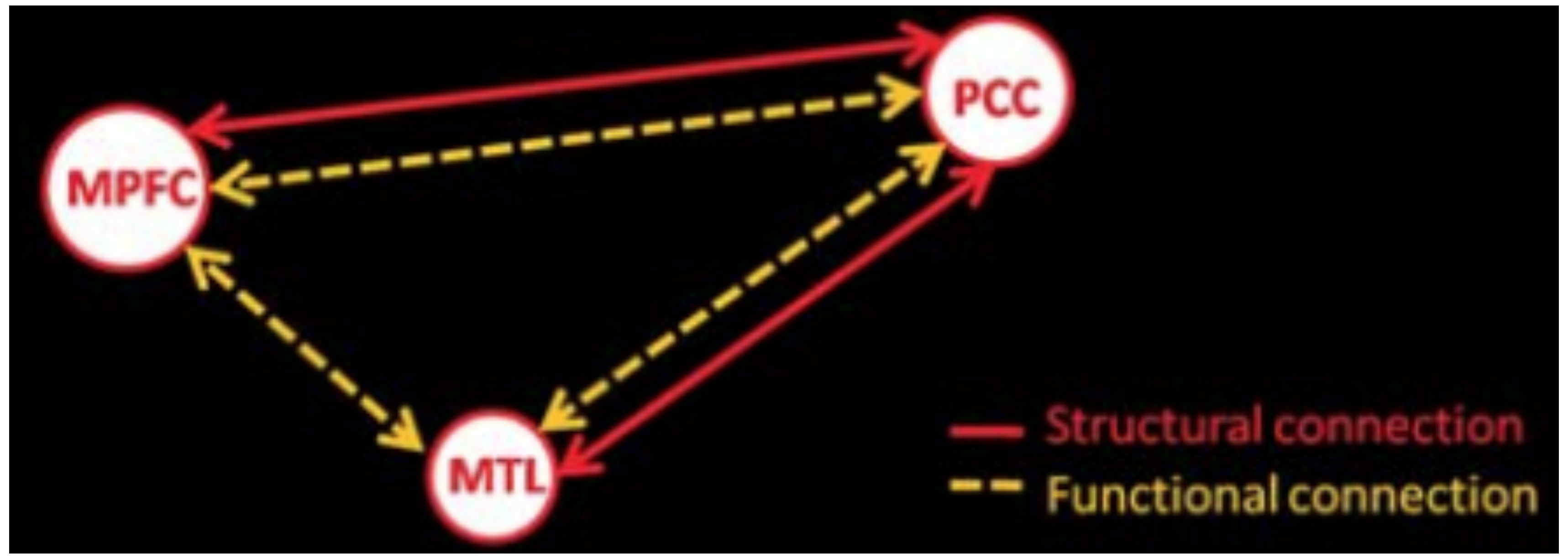


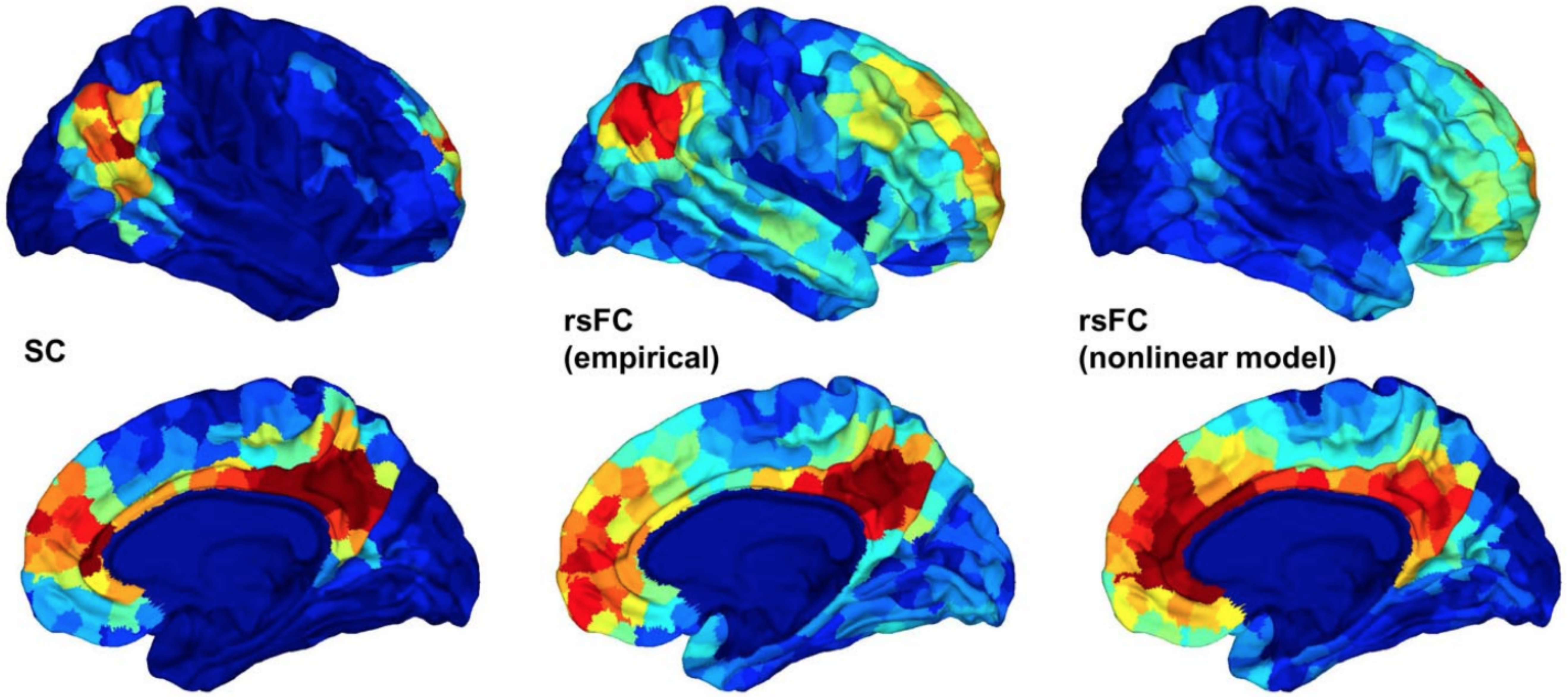
Smith et al (2009), Tavor et al (2016)

Functional vs structural connectivity

Functional connectivity is related to structural connectivity

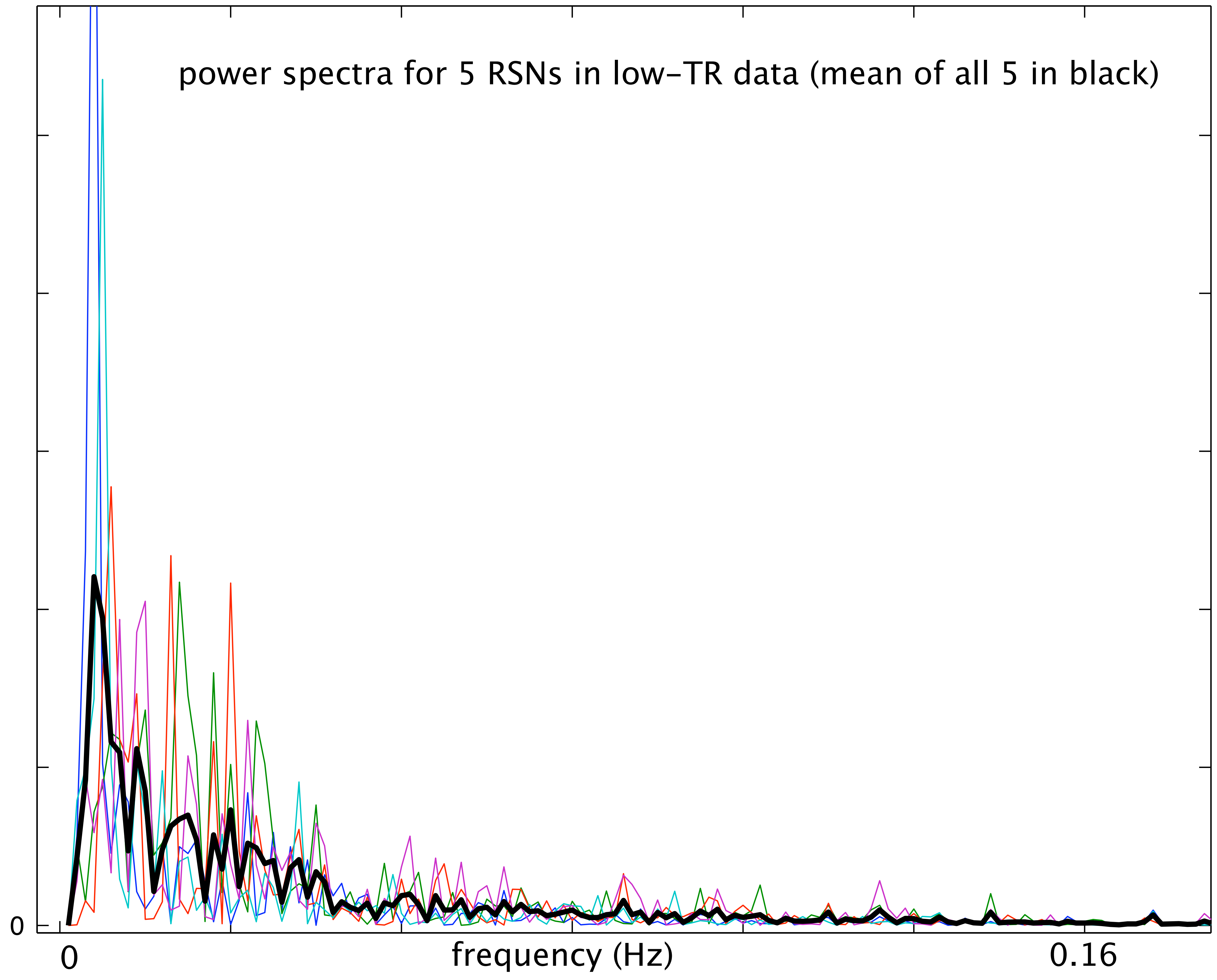


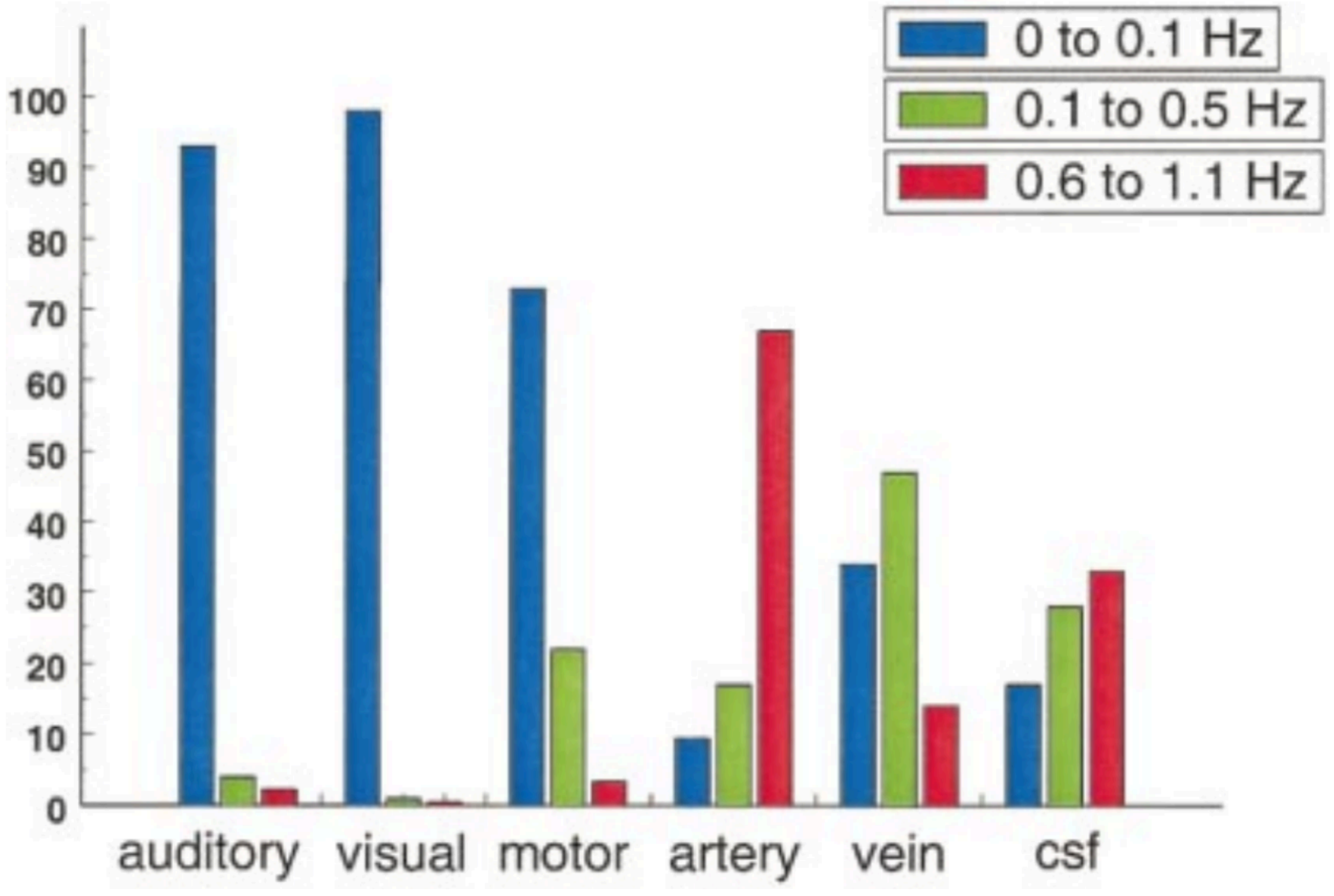




Honey et al (2009), Damoiseaux & Greicius (2009)

Low frequency fluctuations?

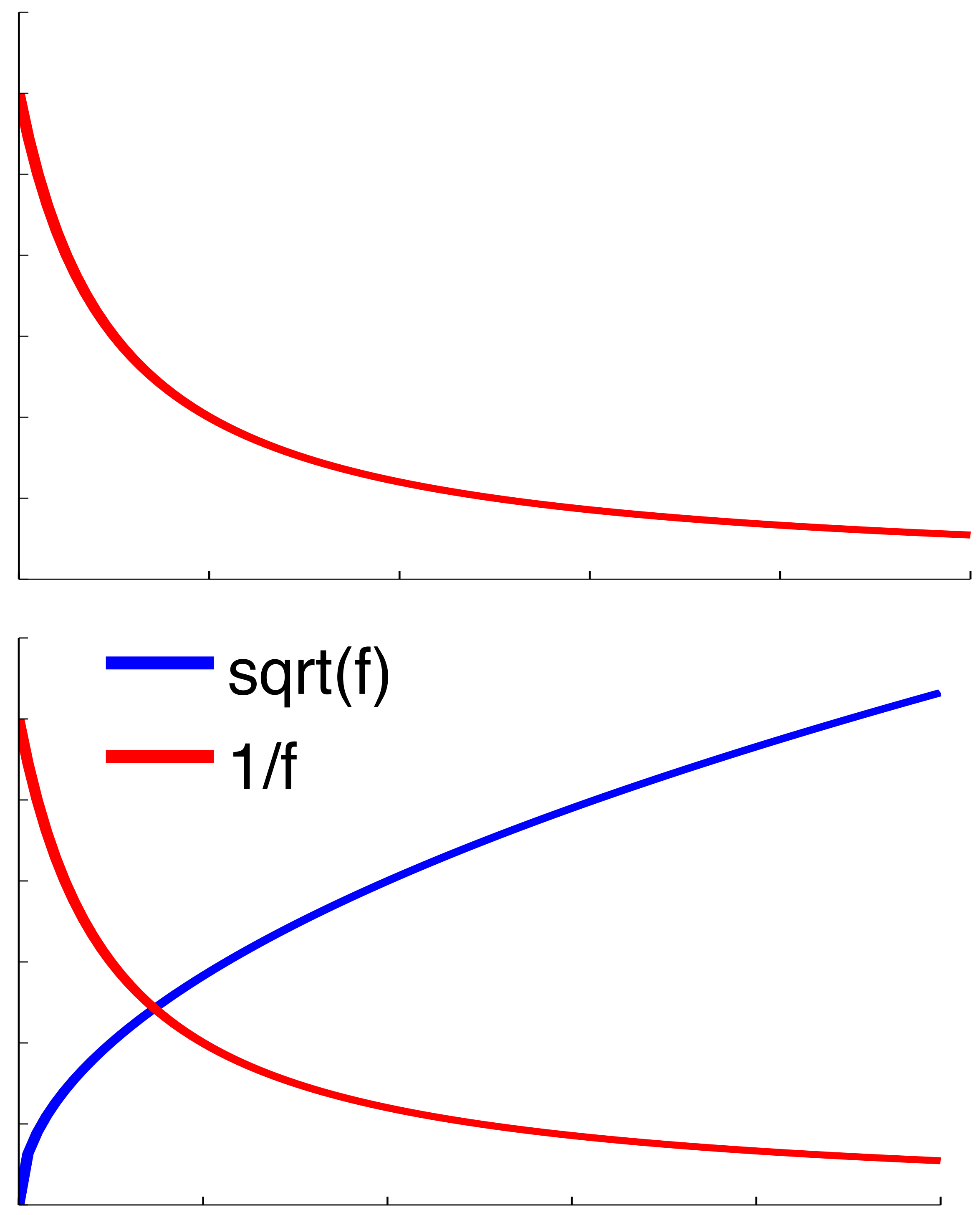




Cordes et al (2001)

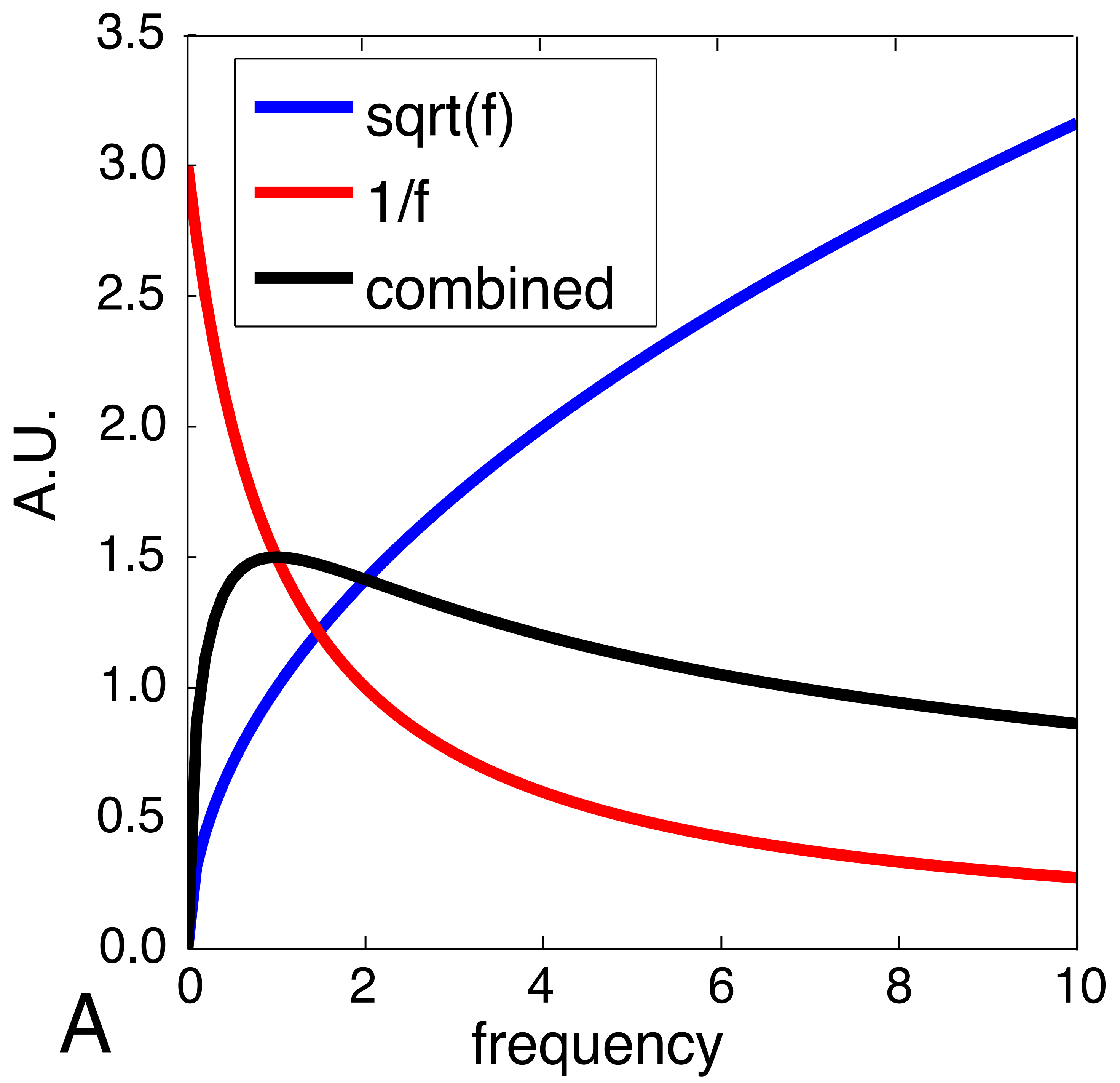
Low frequency fluctuations?

- BOLD decreases as 1/*f*
- Degrees of freedom increase as sqrt(*f*)



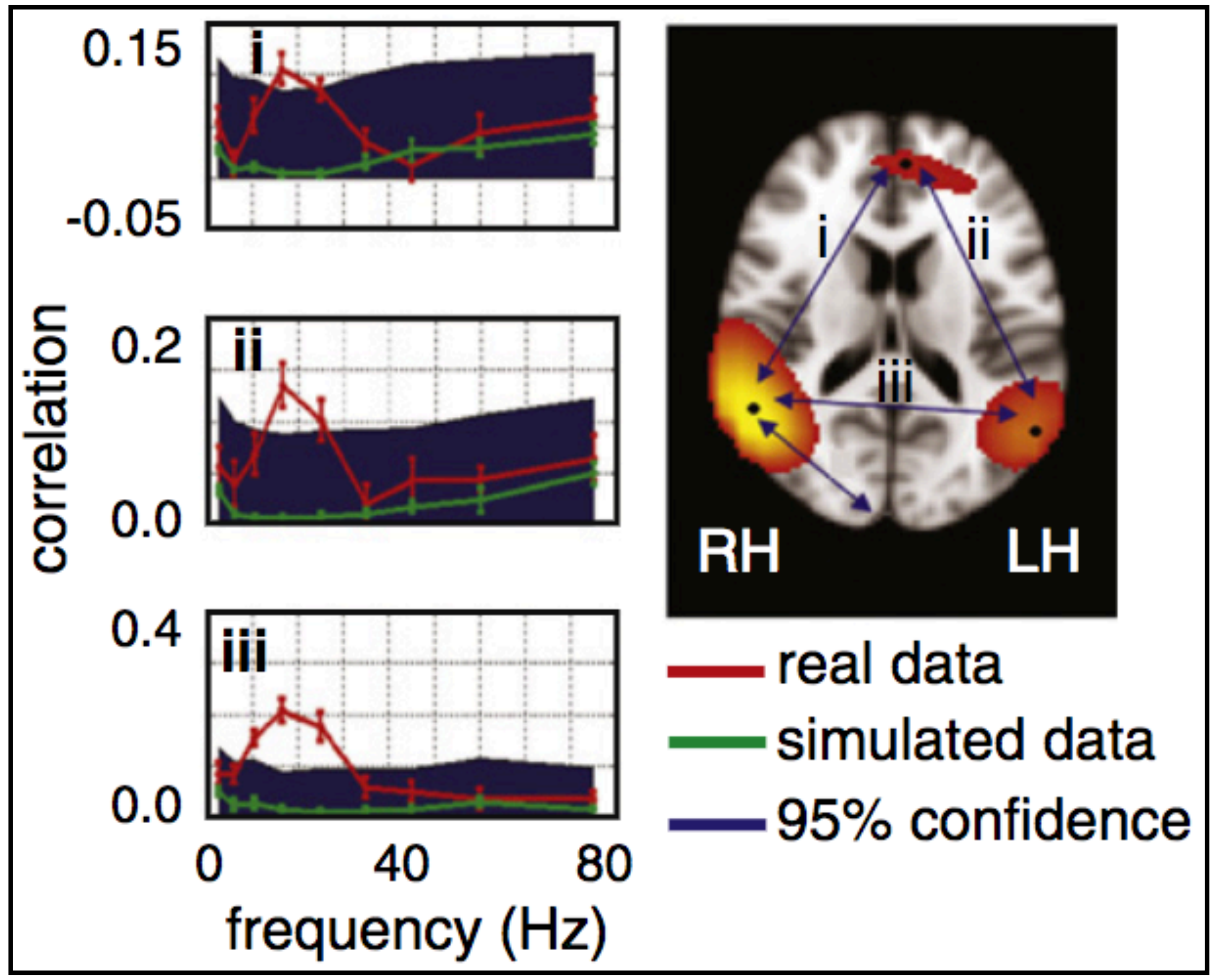
Low frequency fluctuations?

- BOLD decreases as 1/*f*
- Degrees of freedom increase as sqrt(*f*)
- Combined effect contributes to RSN estimation across frequency range!

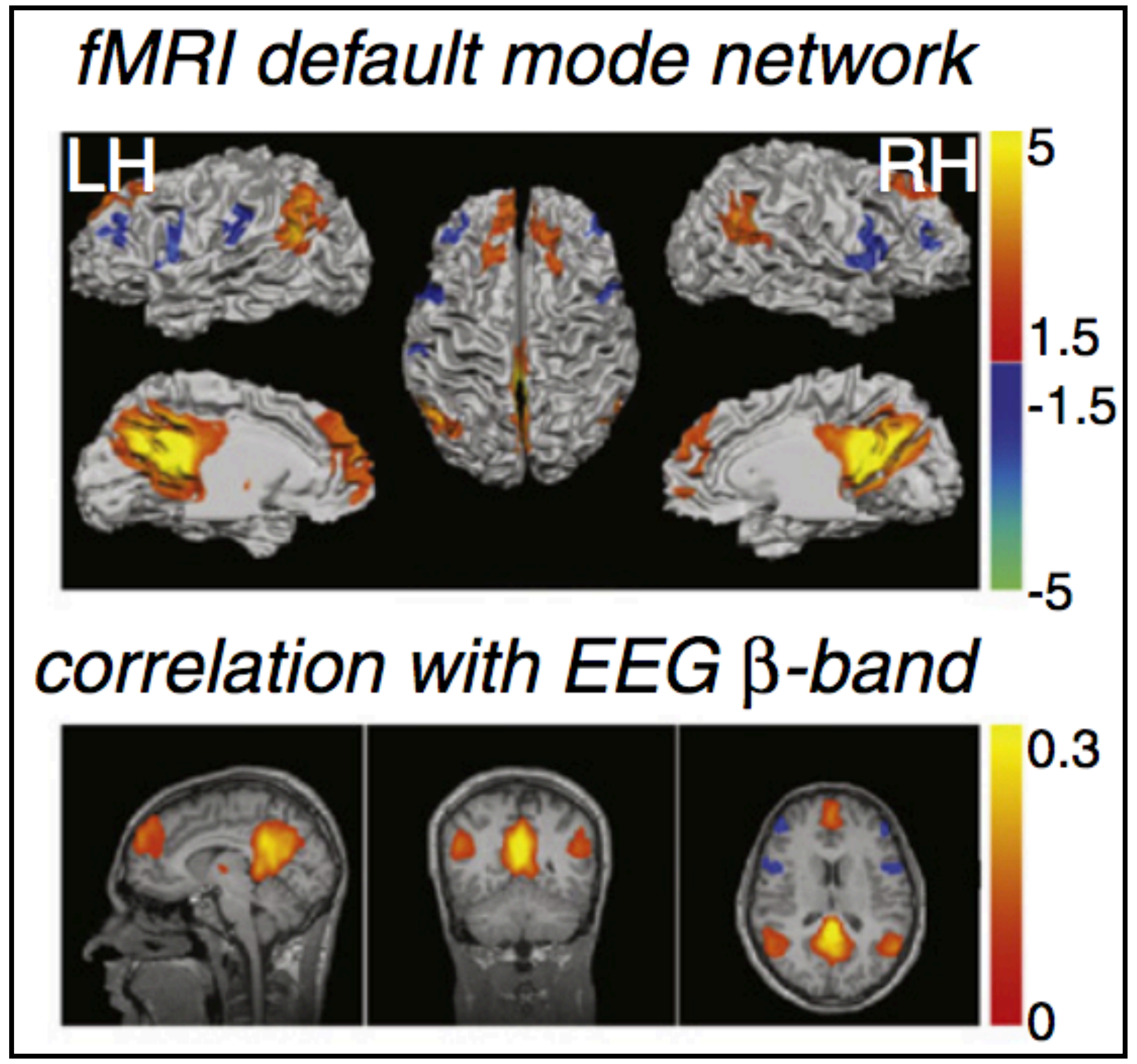


Electrophysiology of BOLD connectivity

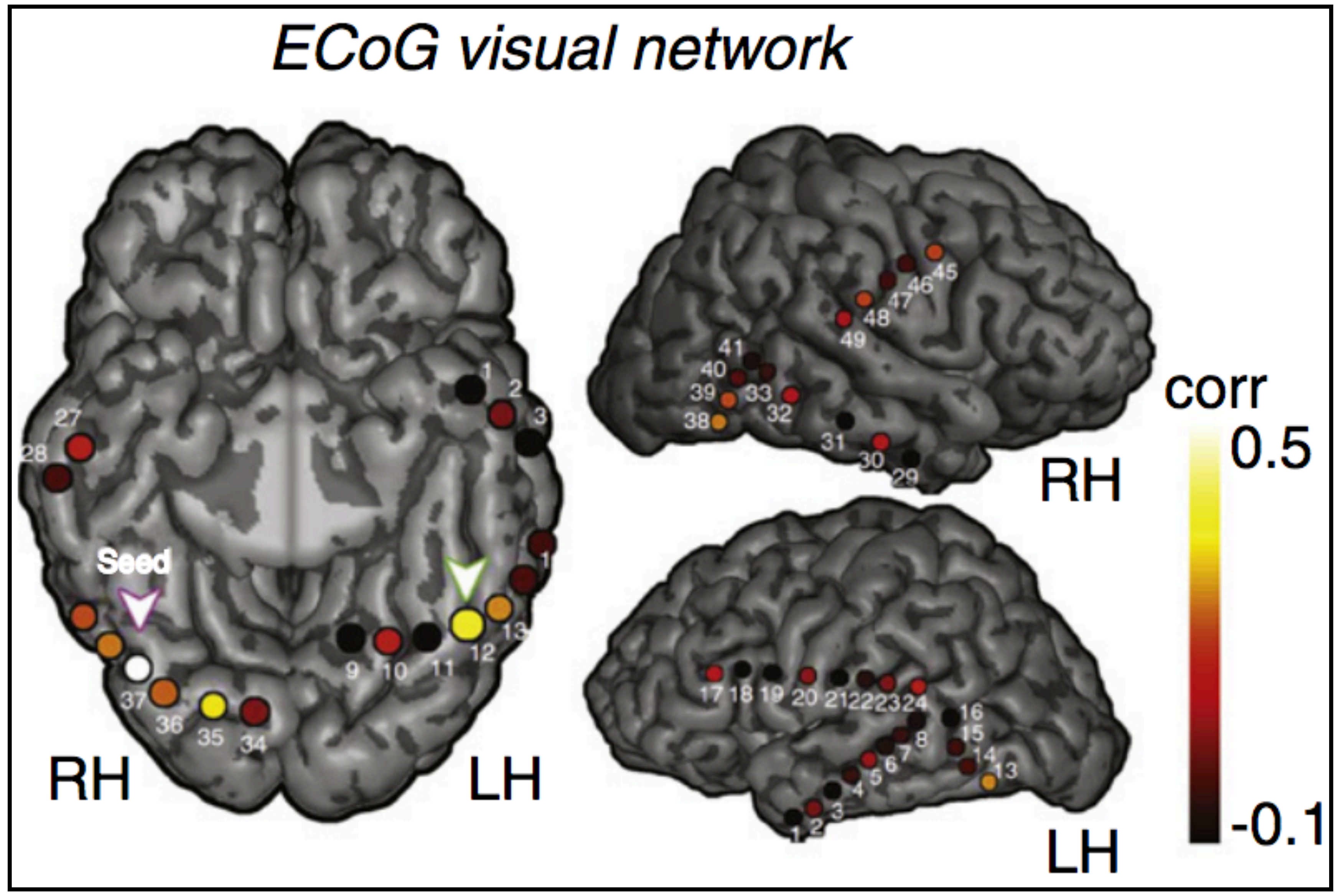
MEG



EEG



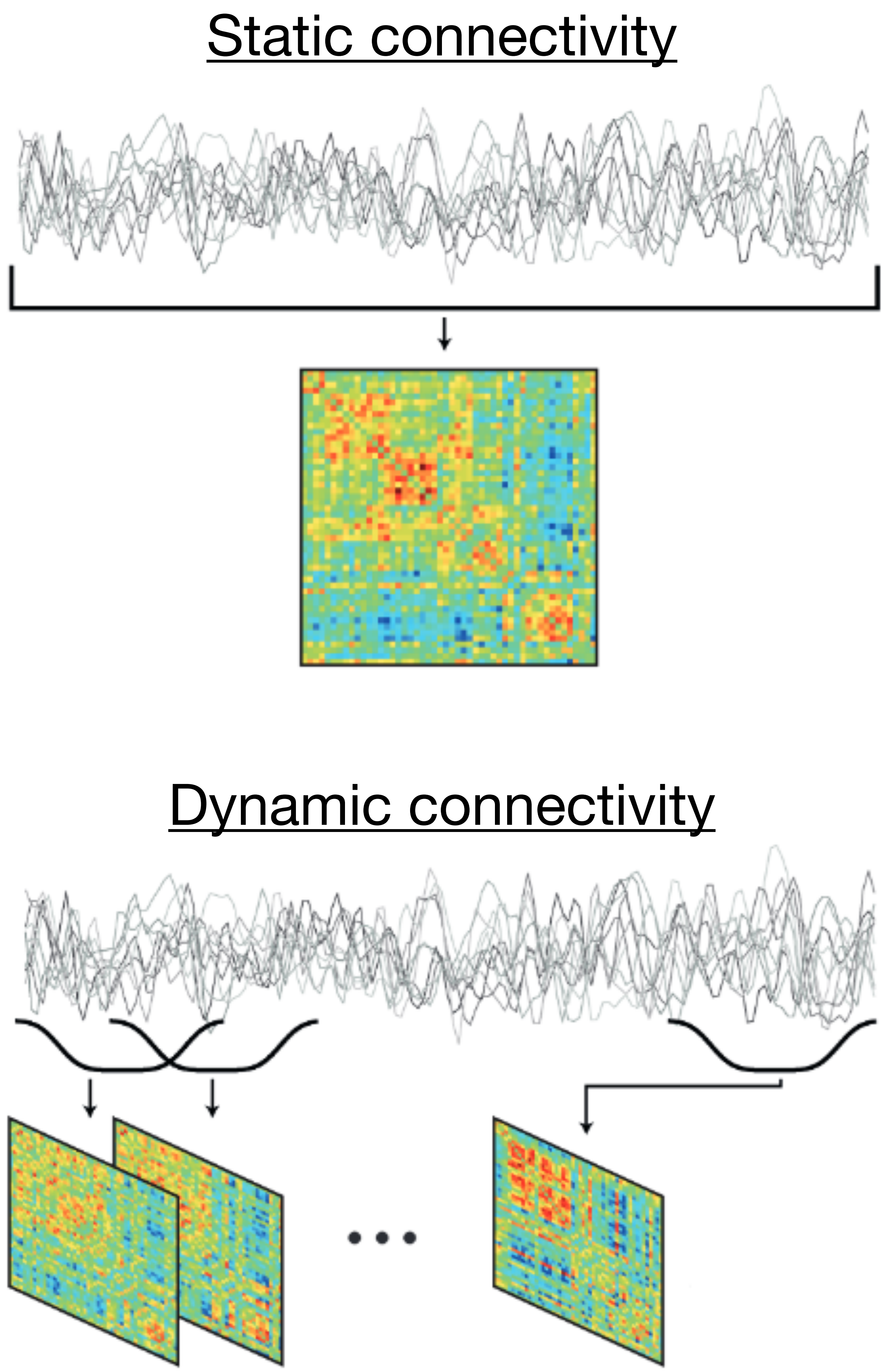
ECoG



Schölvinck et al (2013), Brookes et al (2011), Mantini et al (2007), Nir et al (2008)

Static versus dynamic connectivity

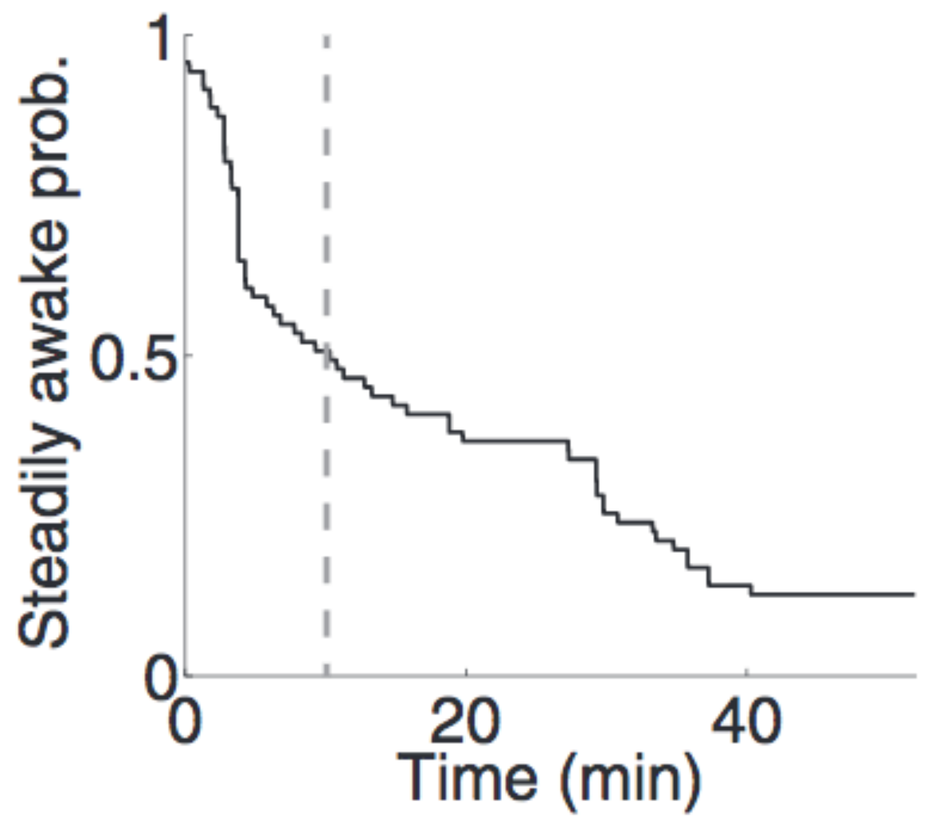
- Most connectivity measures are static (based on the full resting state scan)
- Dynamic connectivity is like to occur (changes over time)
- Static connectivity measures reflect average across dynamic states
- Dynamic connectivity measures are challenging (in terms of noise influences, significance testing)

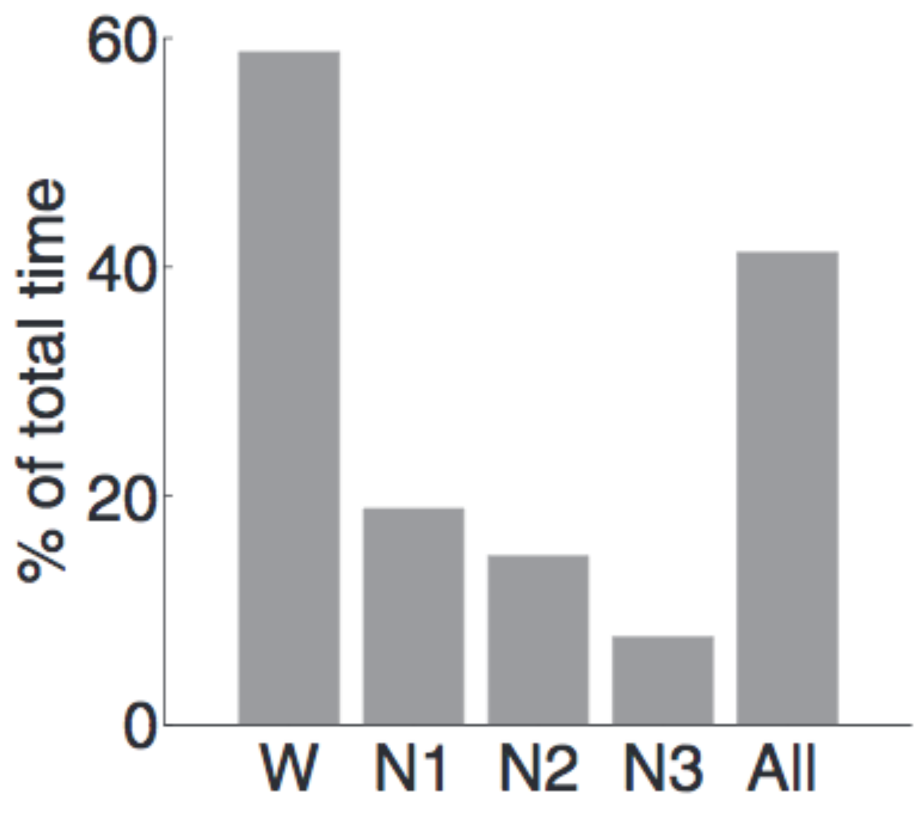


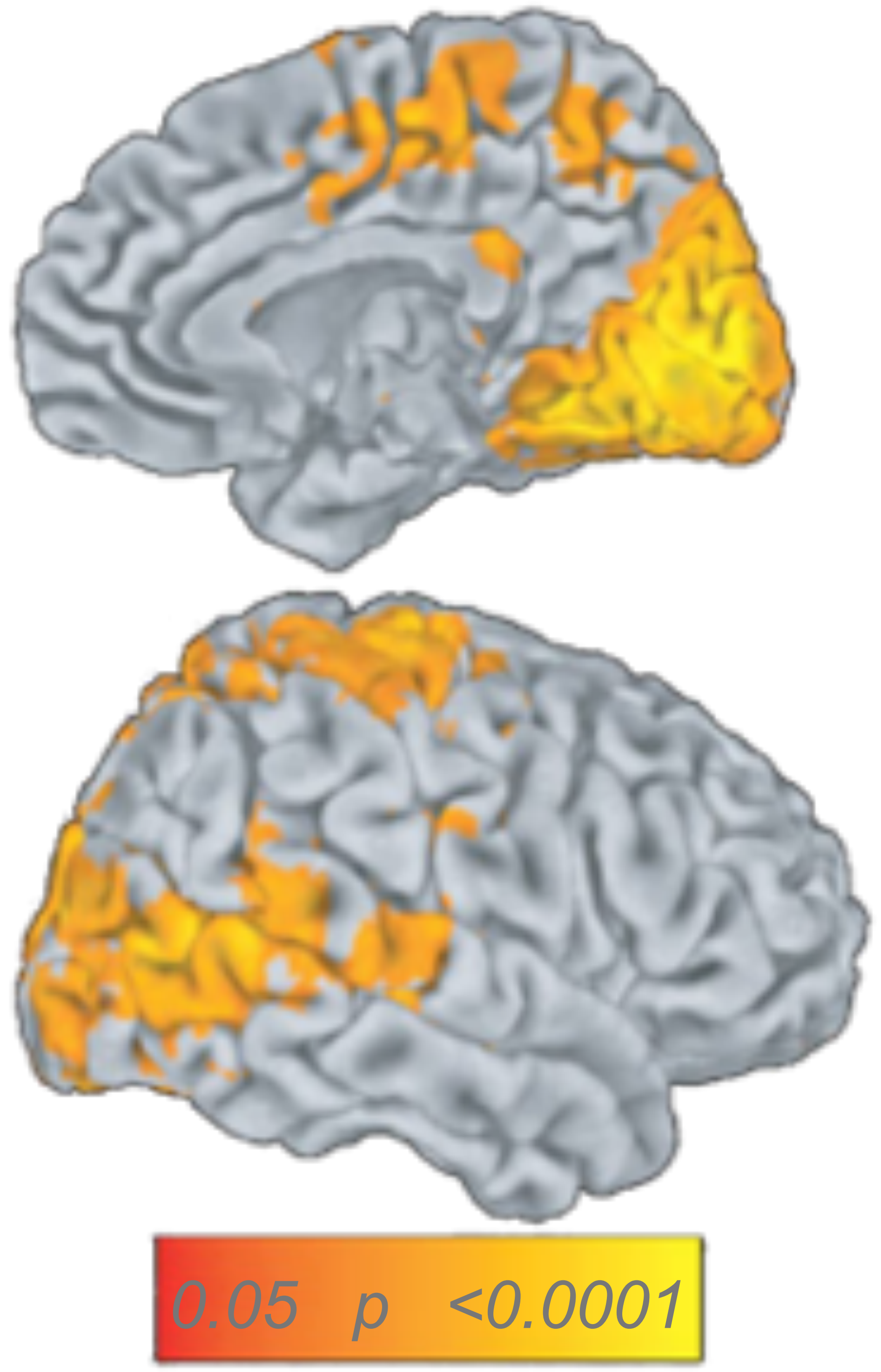
Allen et al (2012), Hutchison et al (2013)

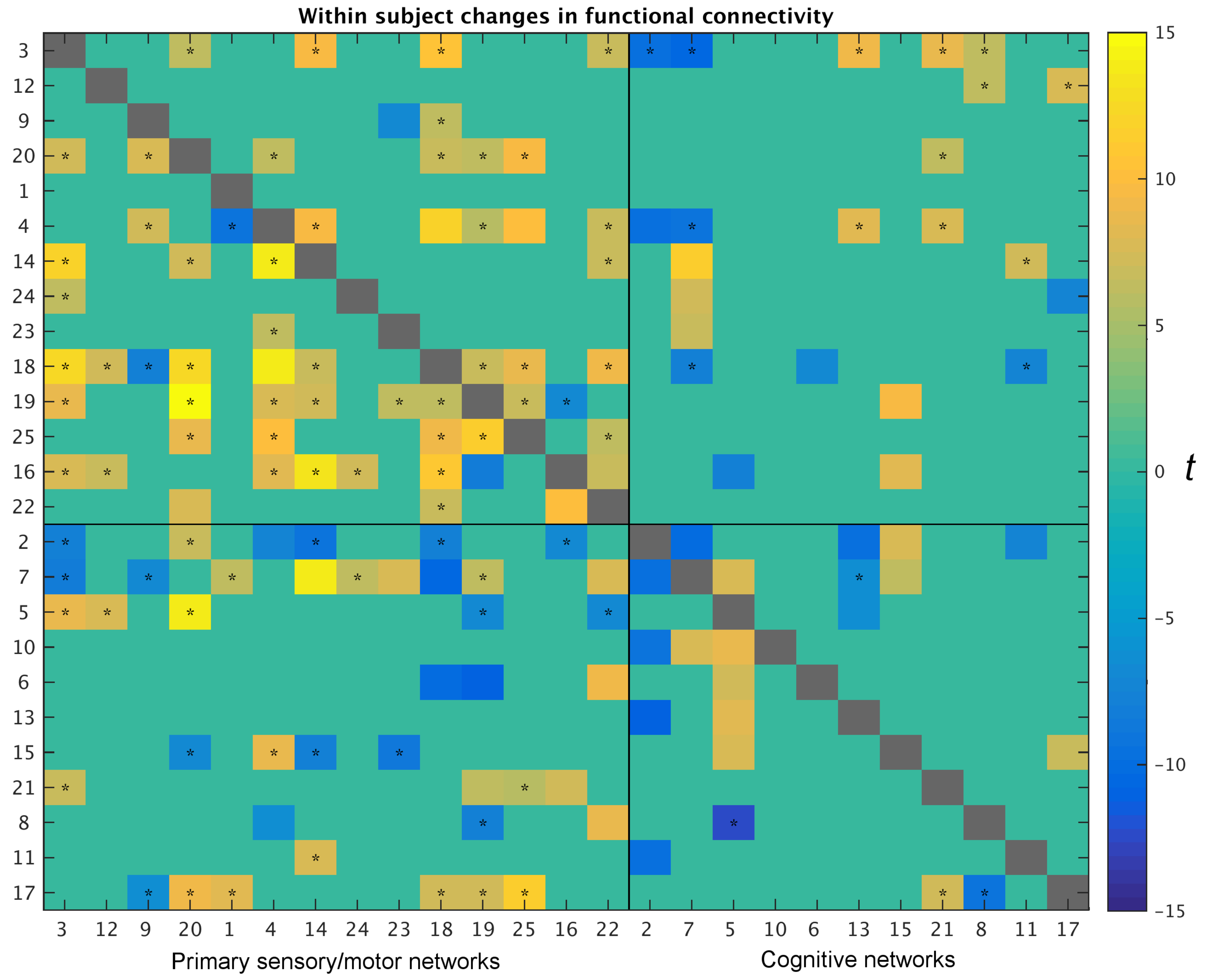
Arousal

- Subjects fall asleep
- Changes in BOLD amplitude
- Related changes in correlation









Tagliazucchi and Laufs (2014), Horovitz et al (2008), Bijsterbosch et al (2017)

Resting state big picture

Generic study blueprint

1. Data acquisition
2. Data preprocessing
3. Single-subject analysis
4. Group-level analysis
5. Statistical inference

ICA+dual regression

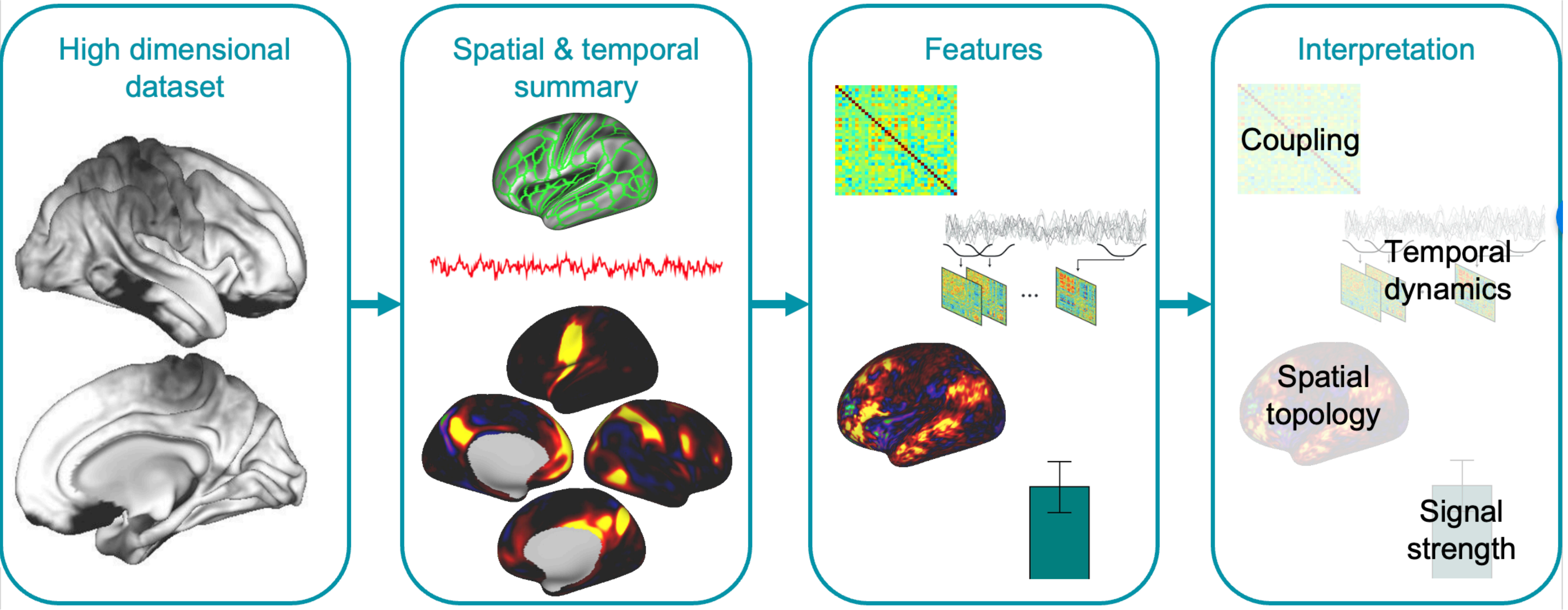
Connectome modeling

Seed-based correlation

Dynamic causal modeling

Why more than one tool?

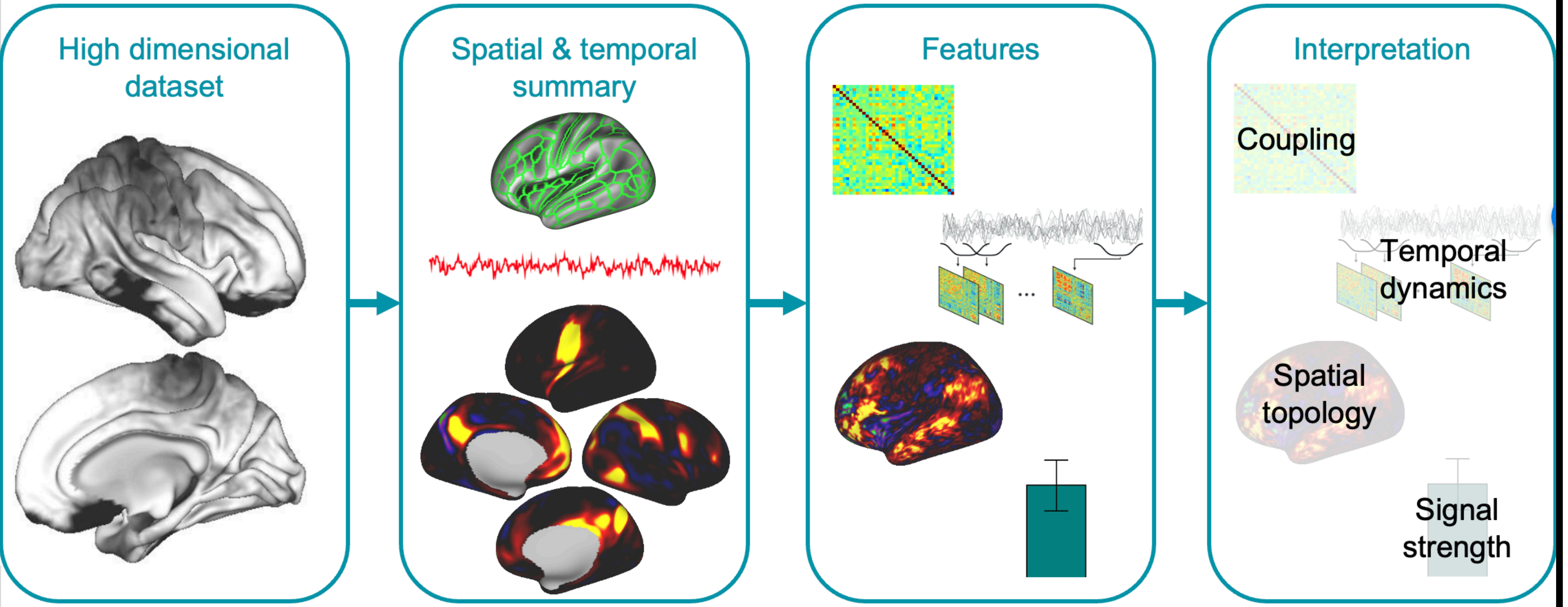
<u>"Brain representations"</u>



Bijsterbosch et al (2020)

Why more than one tool?

<u>“Brain representations”</u>



Bijsterbosch et al (2020)

Which tool to use?

What parts of the brain are interesting in your study?

What type of change do you expect (e.g., strength/ shape/ connection)?

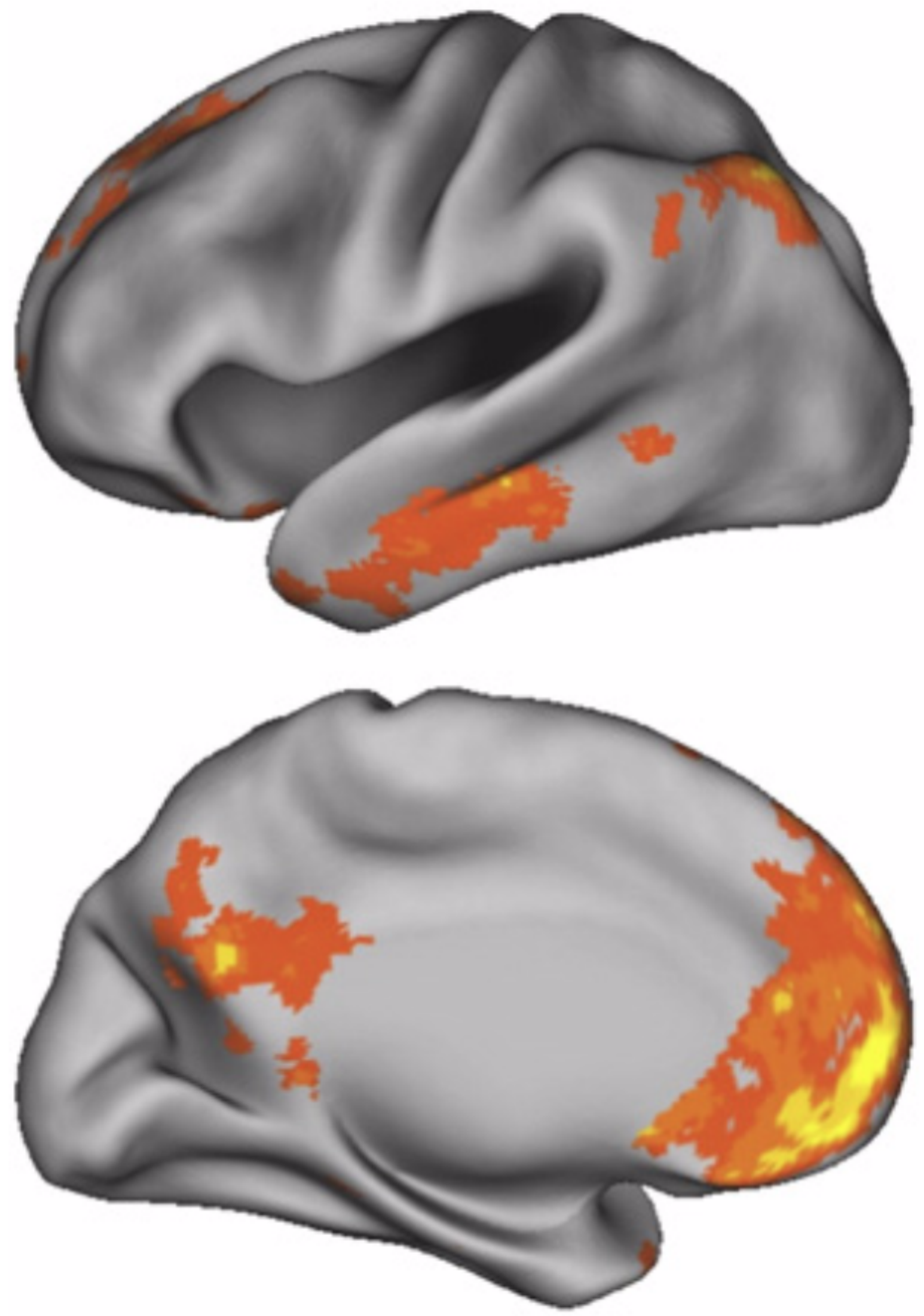
How much power do you have?

Preprocessing

Careful cleanup required

- Structured artefacts much more of a problem for rfMRI than task-fMRI
  - No model of expected activation
  - Instead based on correlating timeseries with each other

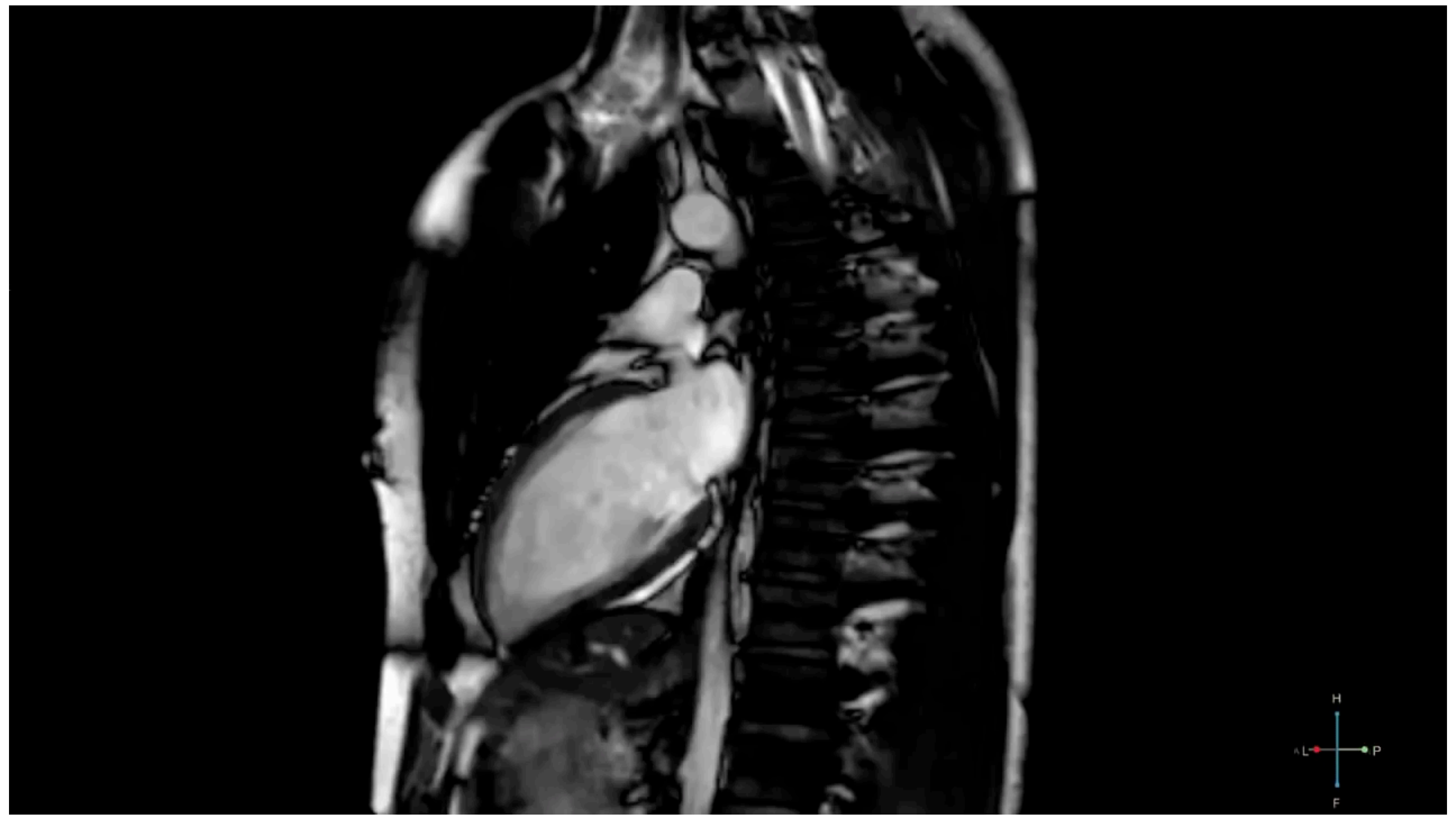
Low motion > high motion

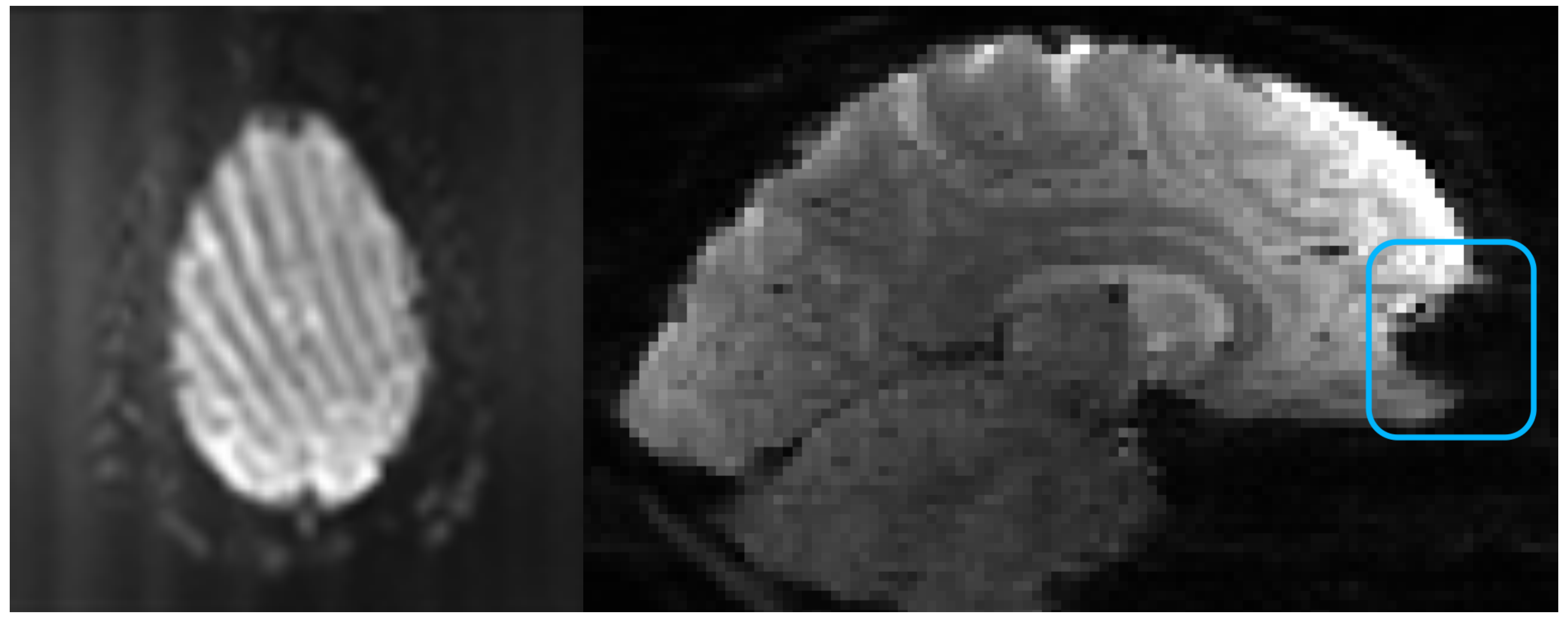


Van Dijk et al (2012)

Noise sources

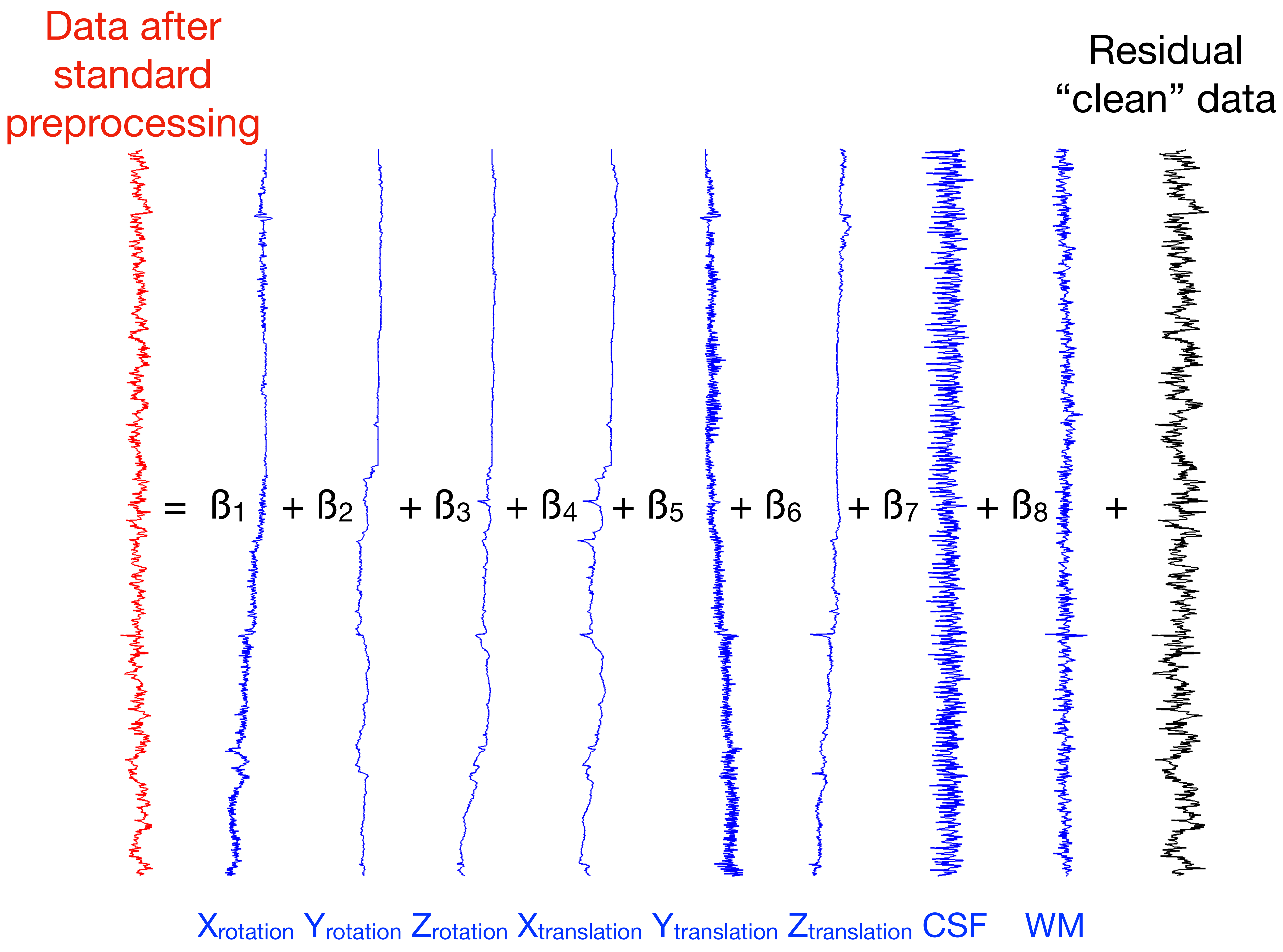
- Head motion
- Cardiac & breathing cycles
- Scanner artefacts





Regressing out noise

- Head motion parameters
- White-matter / CSF
- Use GLM to remove nuisance timeseries
- Perform analysis on residuals
- “CompCor” method (PCA-based)



Muschelli et al (2014)

Preprocessing overview

Conventional preprocessing steps

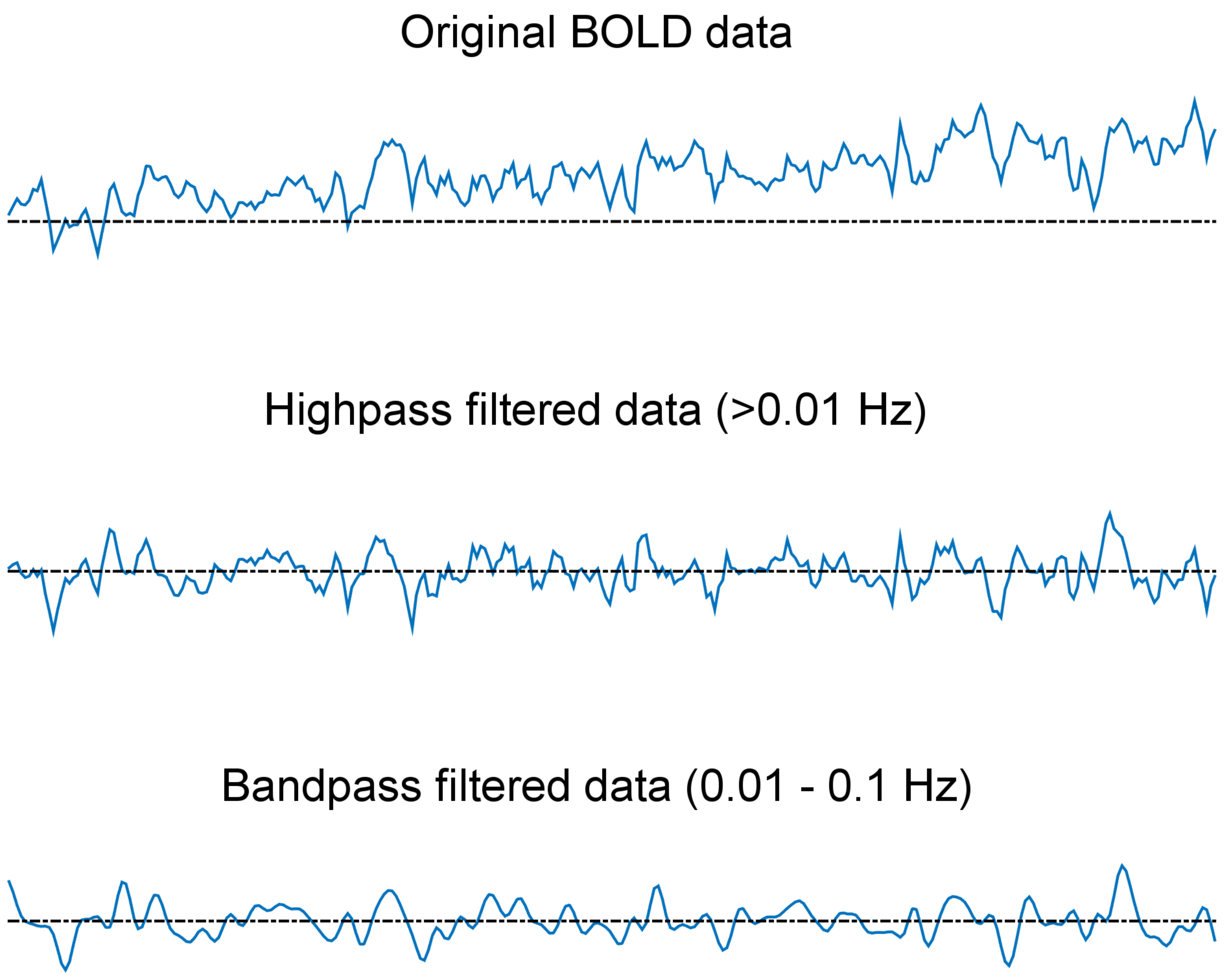
- Motion & distortion correction
- Slice timing correction
- High pass temporal filtering
- Spatial smoothing
- Registration

Noise reduction steps (use at least one of these)

- Nuisance regression
- Low pass temporal filtering
- Volume censoring
- Global signal regression
- ICA-based clean-up
- Physiological noise regression

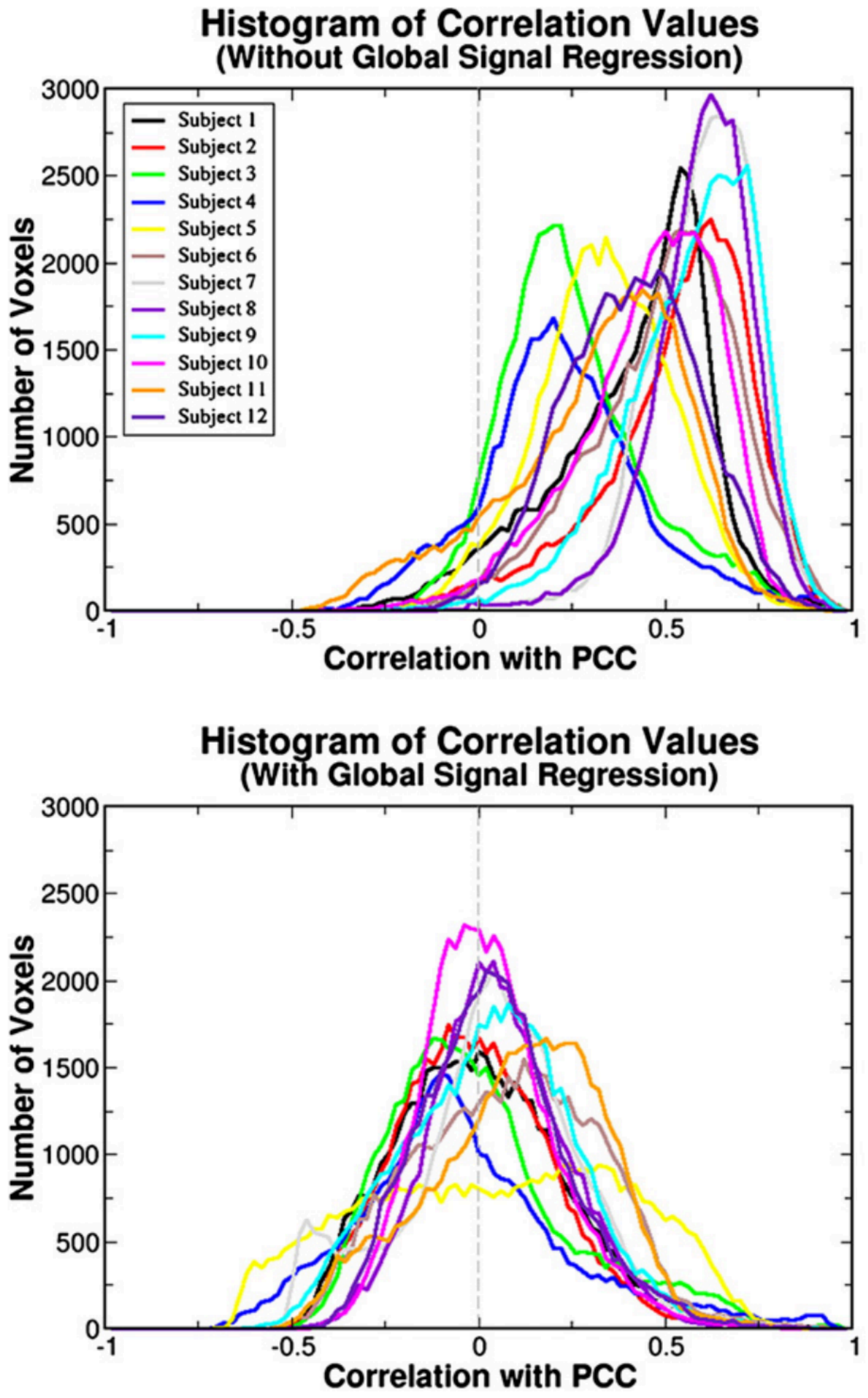
Lowpass temporal filtering

- E.g., common to remove frequencies > 0.1Hz
- May remove useful signal
- Not guaranteed to remove much artefact



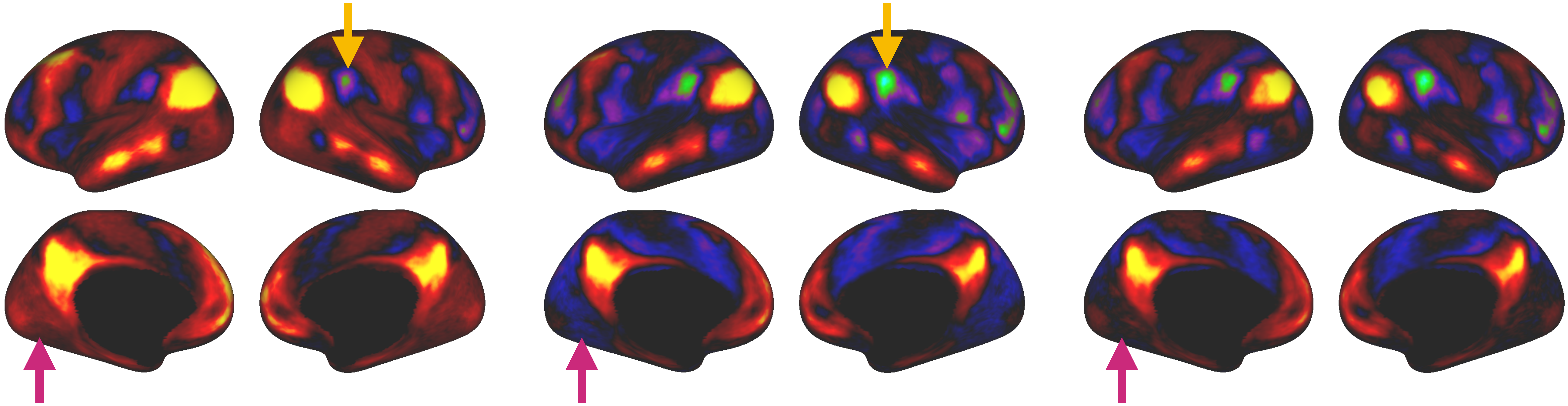
Global signal regression

- Regress out mean timeseries across all voxels (or all grey matter voxels)
- Shifts connectivity values to be zero mean
- Therefore, more negative correlations
- Not necessary if using partial correlation



Murphy et al (2009)

GSR effects & alternative



PCC correlation
spatial ICA cleanup

PCC correlation
spatial ICA cleanup + GSR

PCC correlation
spatial ICA cleanup + temporal ICA cleanup

Glasser et al (2018)

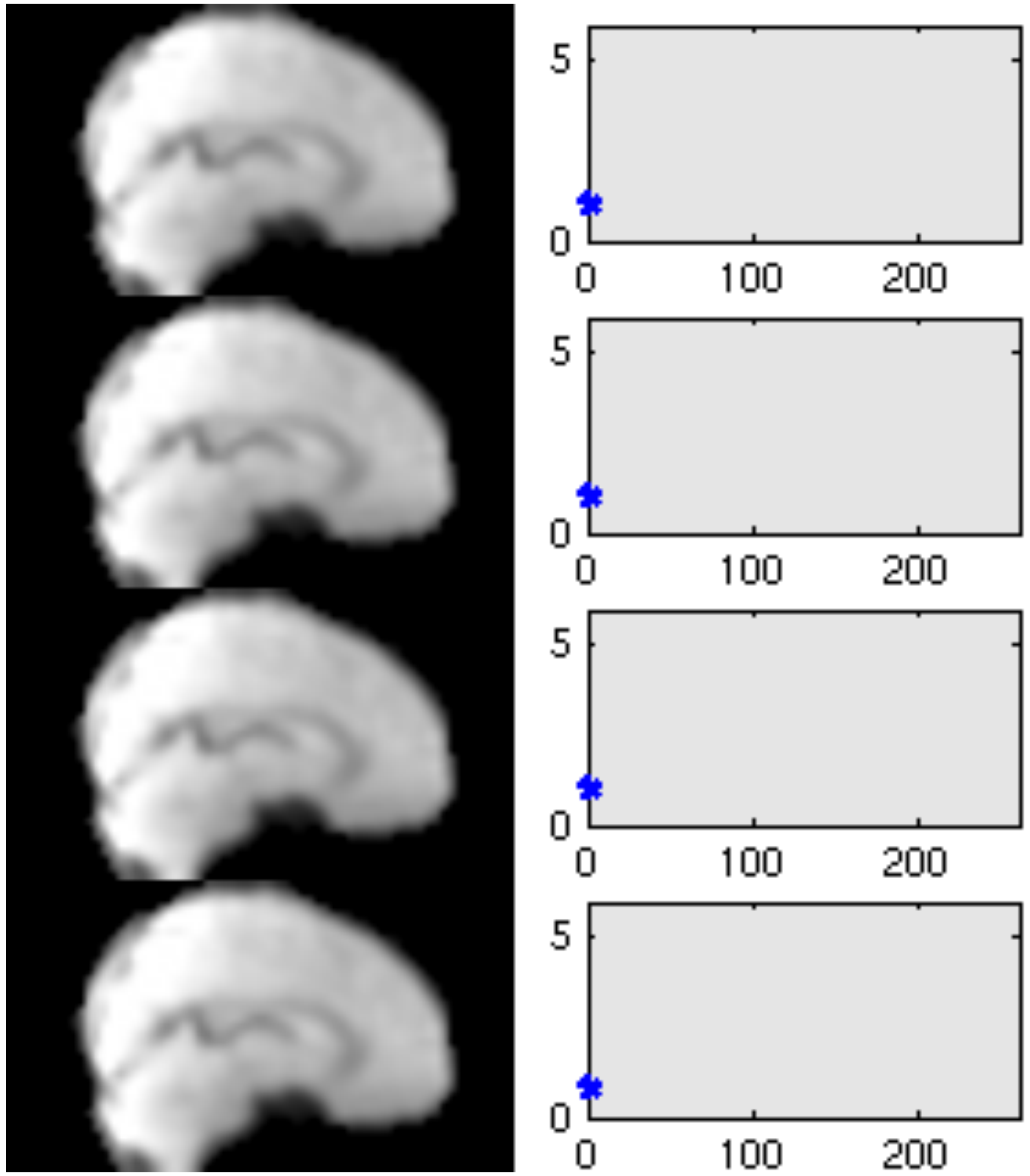
Clean-up comparison

no additional correction

24RP-regression

24RP + volume censoring

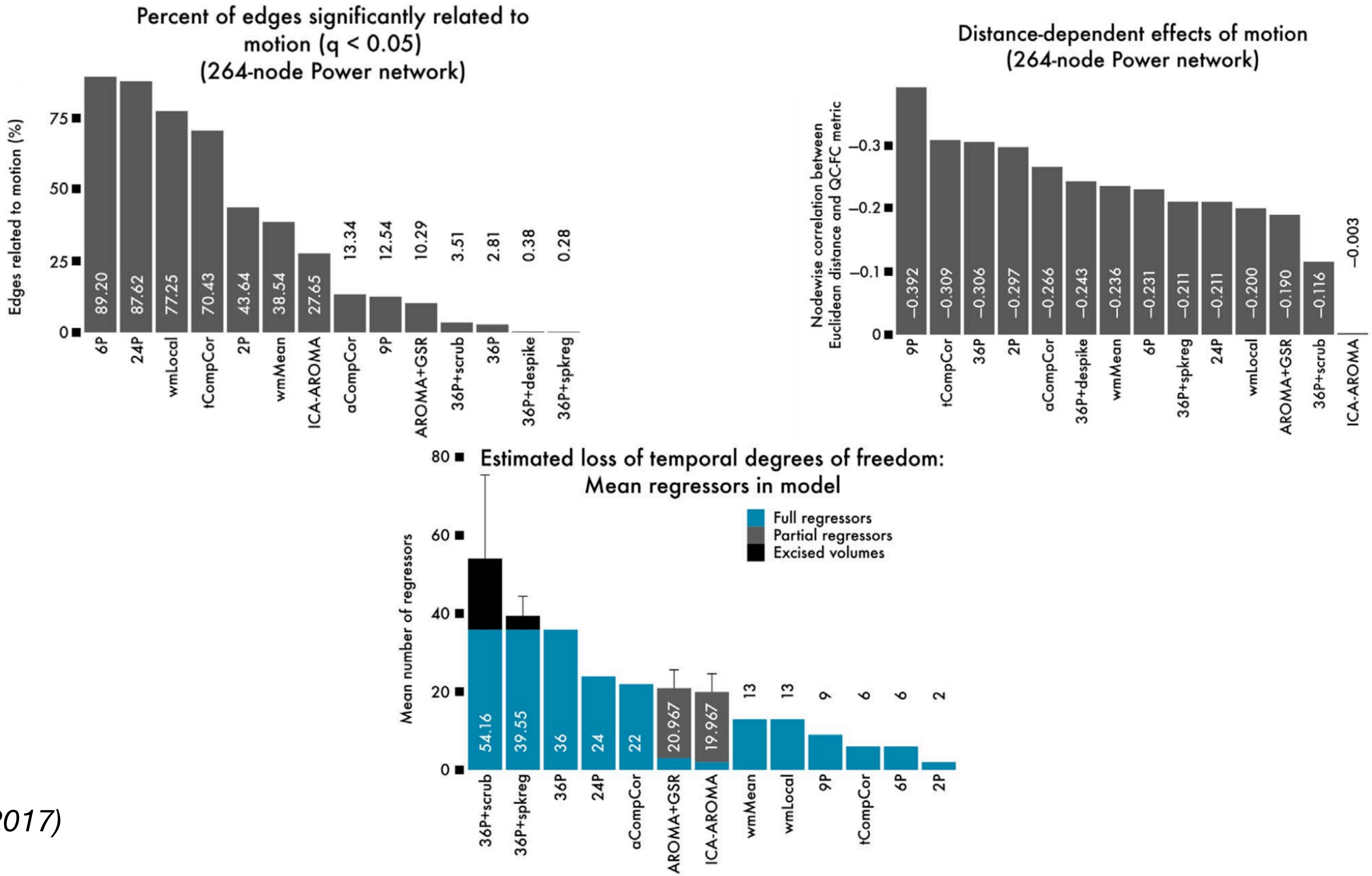
ICA-AROMA



FMRI data

DVARS

Clean-up comparison



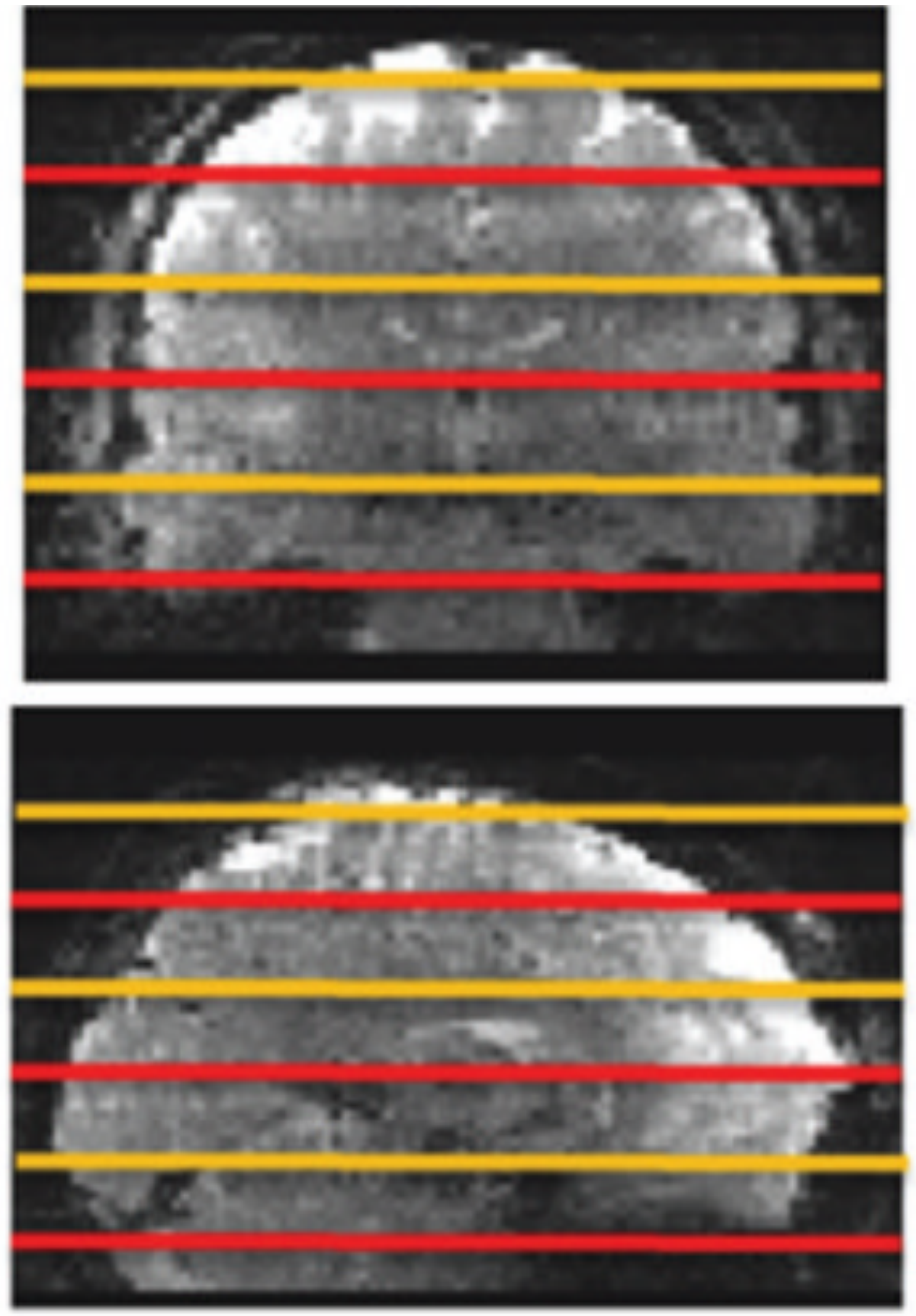
Ciric et al (2017)

Preprocessing advice

- Read up on the latest literature
- Nuisance regression is not enough
- Low-pass filtering is not enough & often not necessary when using other approaches
- Use ICA-based methods and/or volume censoring
- Use physiological noise regression when interested in brainstem or other vulnerable brain regions
- Don’t use global signal regression

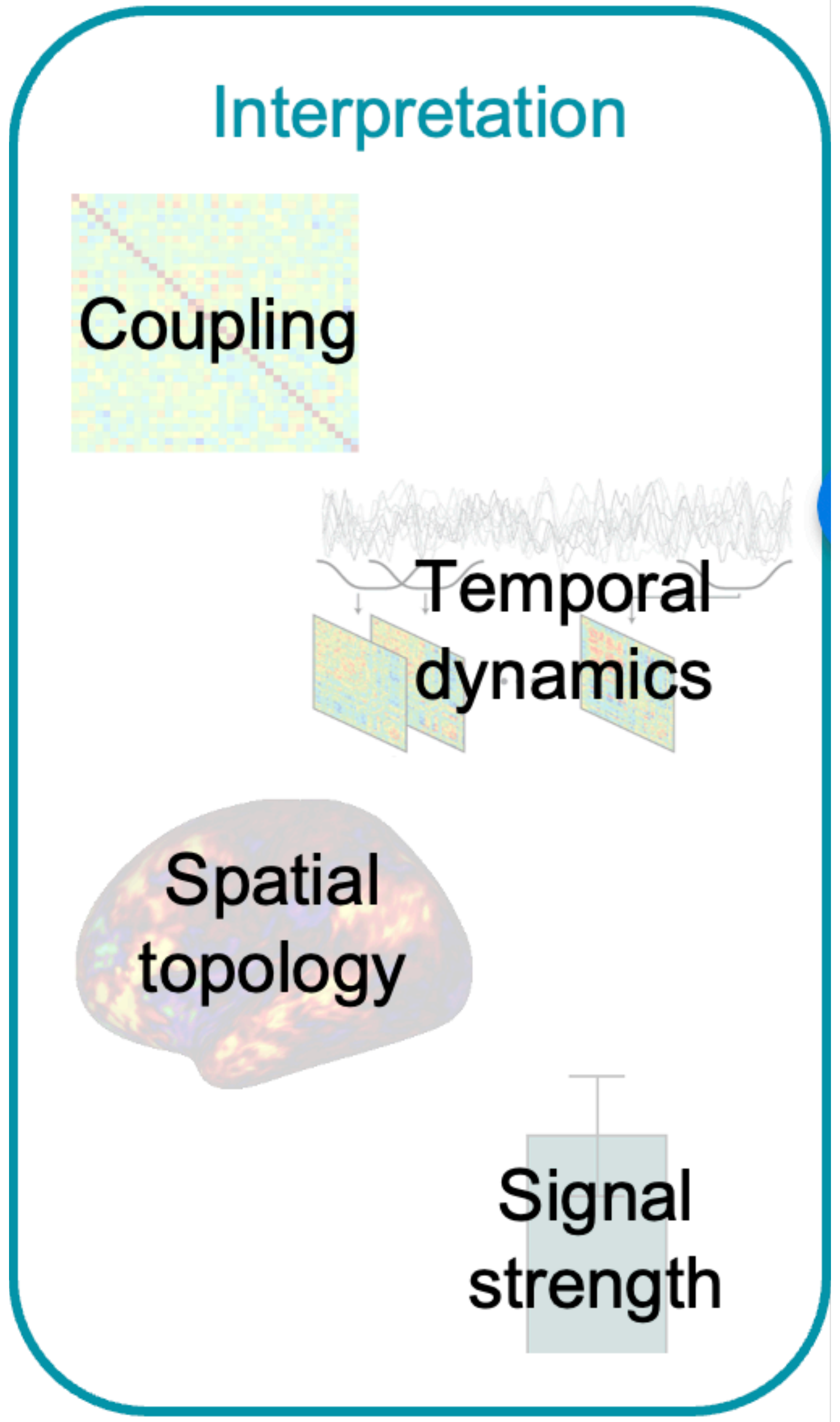
Data acquisition advice

- Just a guide, may vary depending on study aims!
- Whole brain coverage, voxelsize: 2 - 3 mm
- Scan duration:
  - 10-15 minutes per scan
  - Potentially multiple scans
- Repetition time: ideally close to 1 second (multiband/ multiplexed imaging)
- Paradigm: eyes open, fixation cross
- Auxiliary data: physiology, sleep



Analysis method advice

- Don't do the same thing that your lab always does without further consideration
- Do think about your study and hypotheses
  - Brain areas will inform spatial summary
  - Expected change will inform feature type
- Ok to test multiple dimensionalities (e.g., ICA) without looking at final statistical results
- Could be interesting to look at multiple brain representations, but only if it can be done robustly

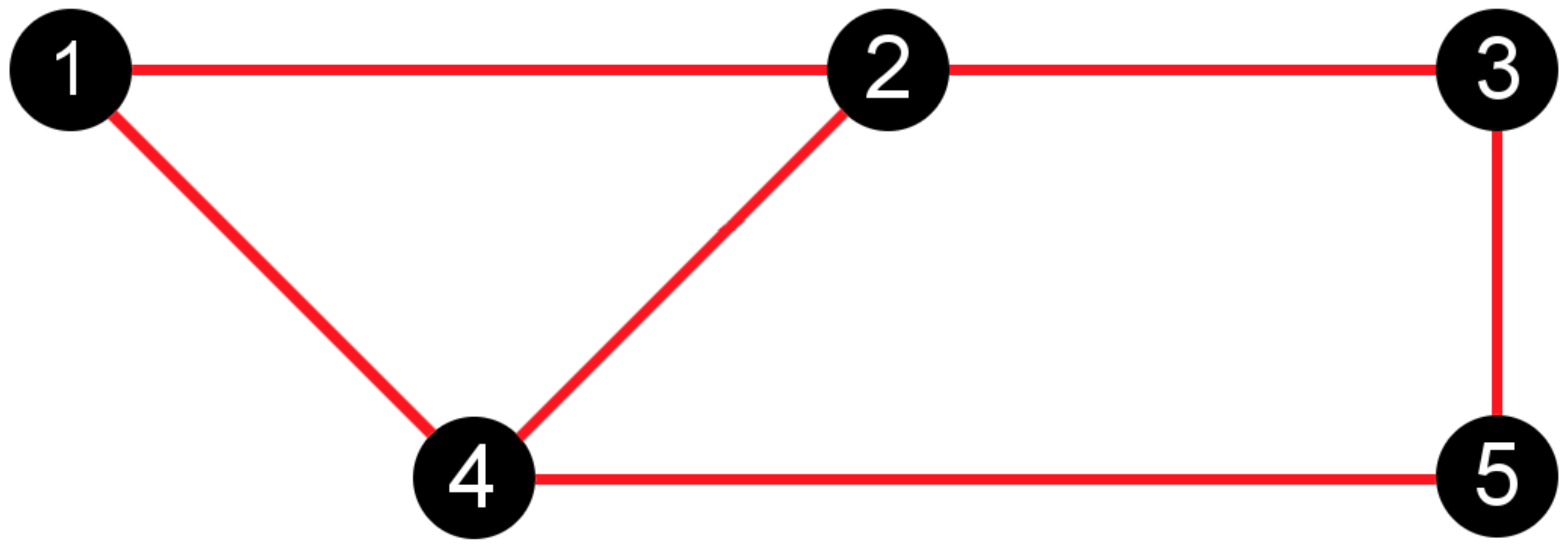


Time for a break!

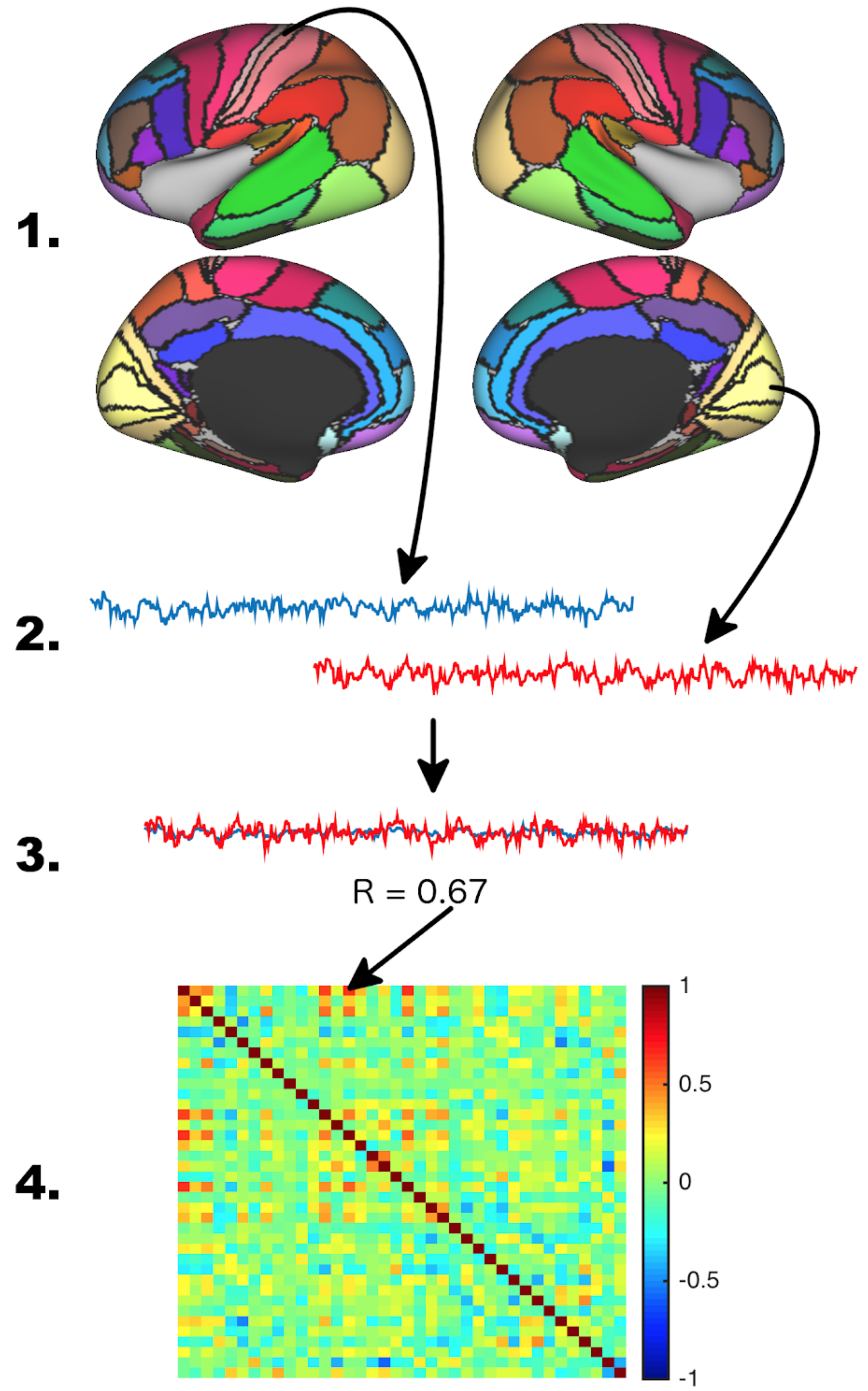
Network modelling analysis

Glossary

- Node = functional brain region
  - Contiguous nodes = interconnected ‘blobs’
  - Non-contiguous nodes = e.g. bilateral
- Parcellation = separation of all voxels into a set of nodes
  - Hard parcellation = binary regions
  - Soft parcellation = weighted regions
- Edge = connection between nodes
- Connectomics = mapping all connections between all brain regions



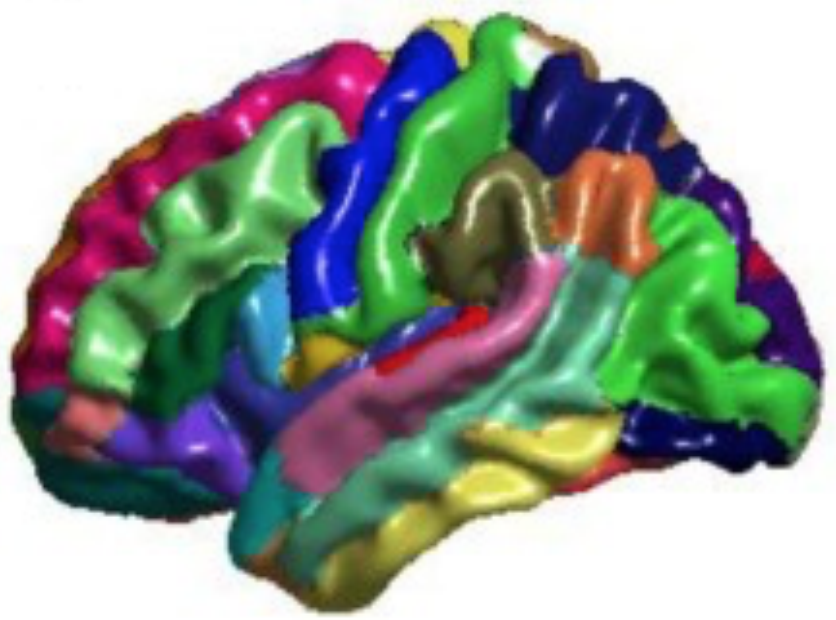
Analysis steps



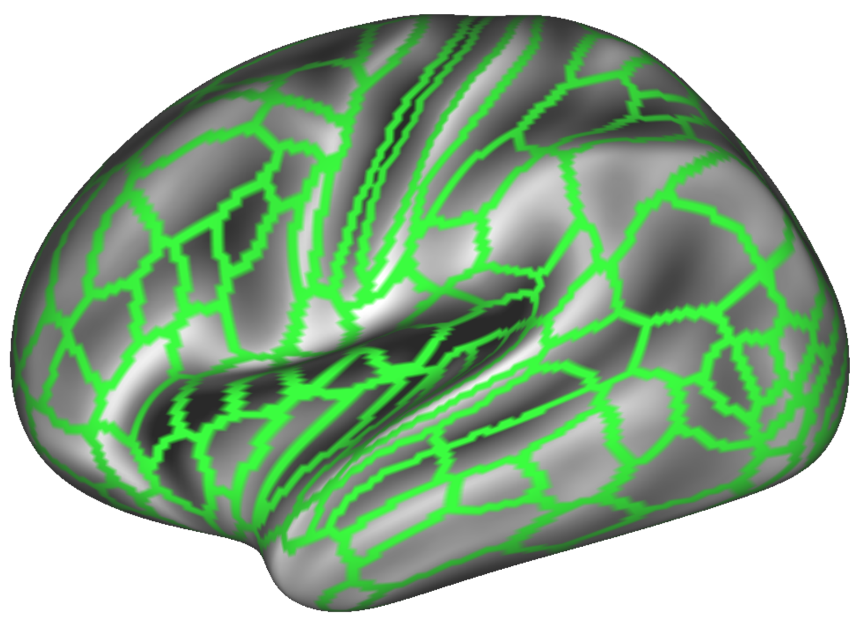
- Node definition
- Timeseries extraction
- Edge calculation
- Network matrix
- Group analysis

Node definition

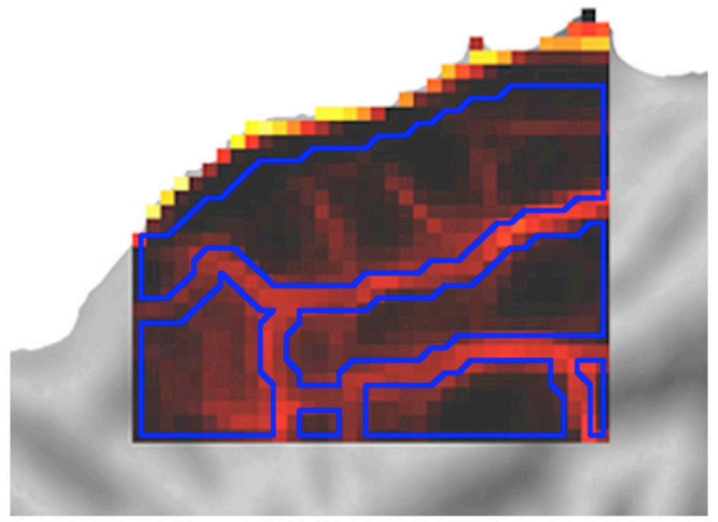
<u>Anatomical atlases</u>



<u>Functional atlases</u>



<u>Data-driven parcellation</u>

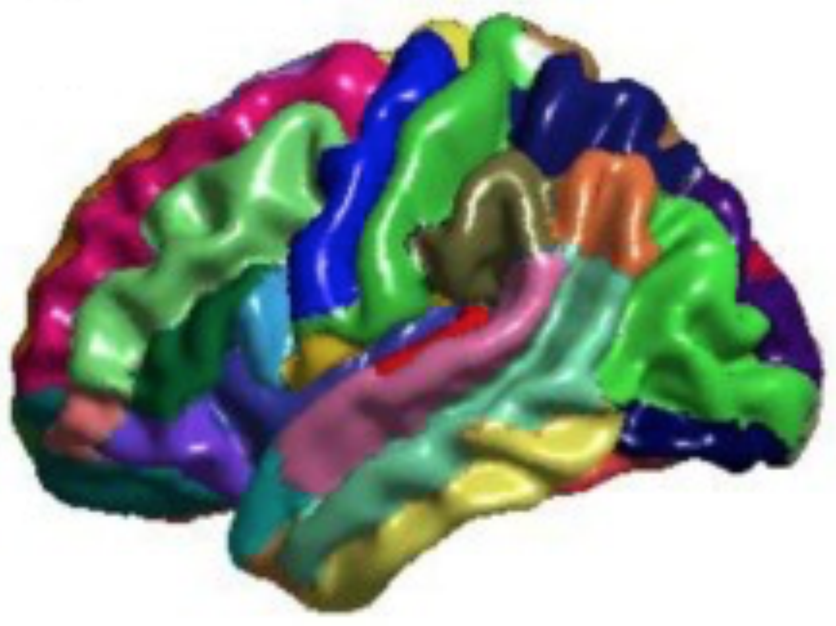


Tzourio-Mazoyer et al (2002), Yeo et al (2011), Glasser et al (2016), Cohen et al (2009)

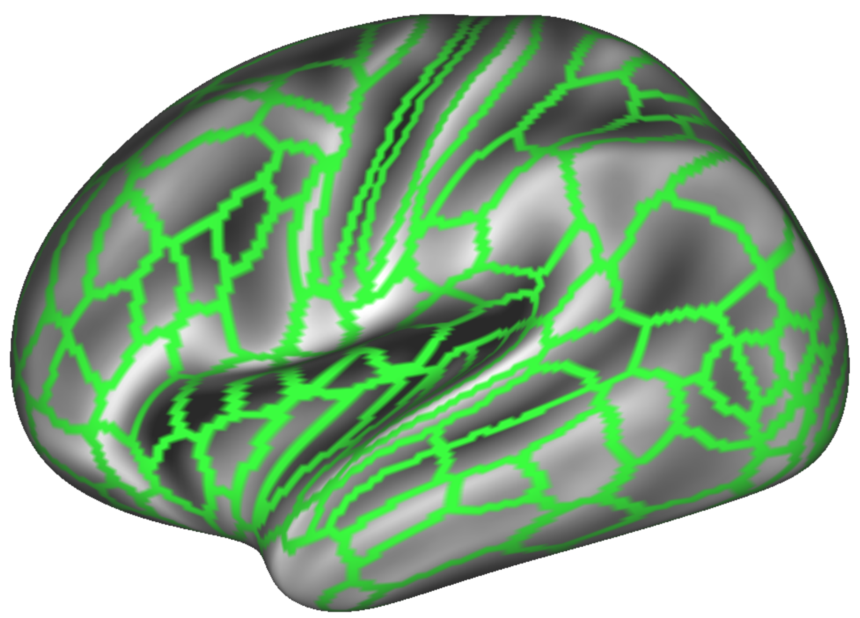
Node definition

<u>Anatomical atlases</u>

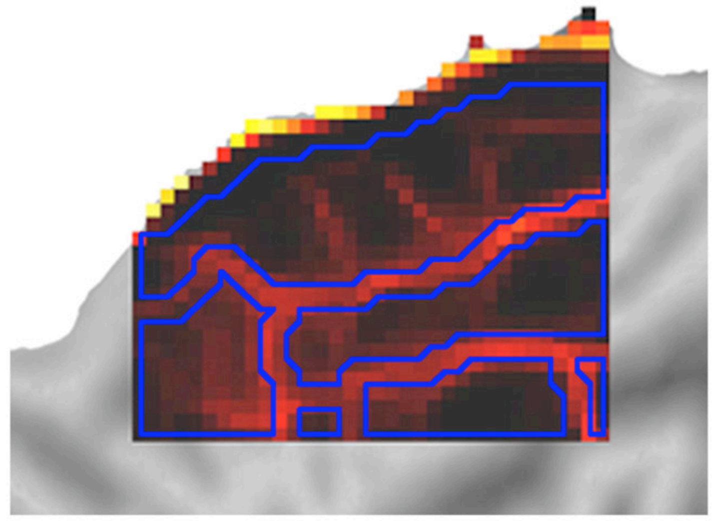
- Harvard-Oxford/ AAL
- Avoid if possible because typically based on small number of subjects and not a good estimation of functional boundaries



<u>Functional atlases</u>



<u>Data-driven parcellation</u>



Tzourio-Mazoyer et al (2002), Yeo et al (2011), Glasser et al (2016), Cohen et al (2009)

Node definition

Anatomical atlases

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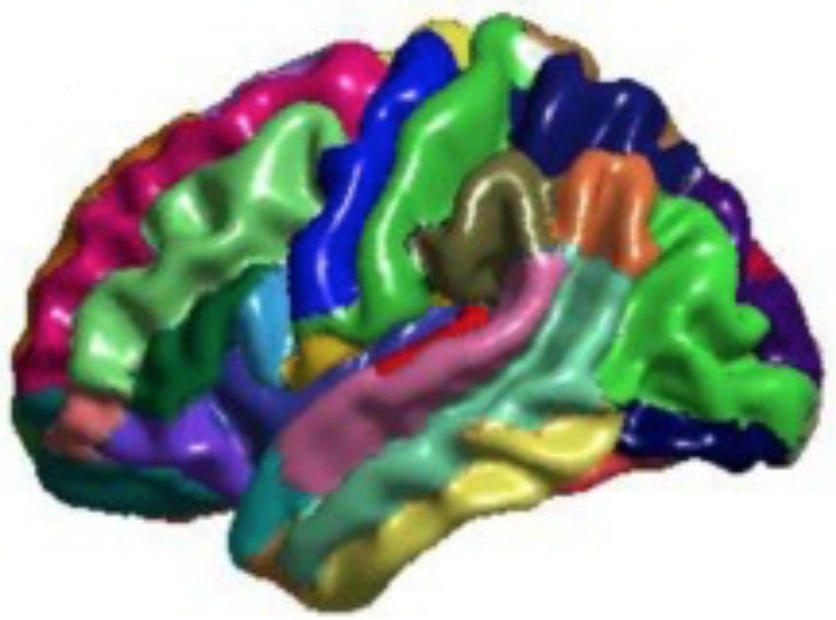
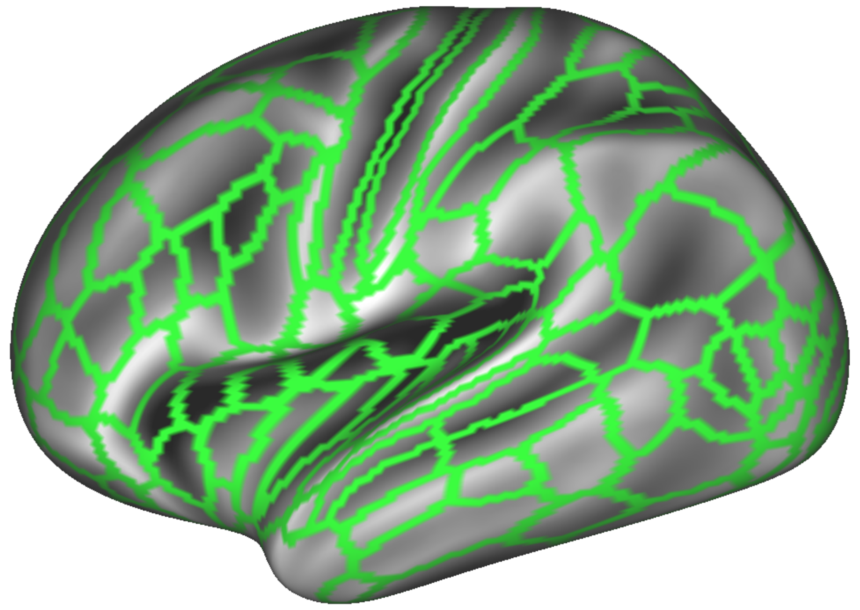
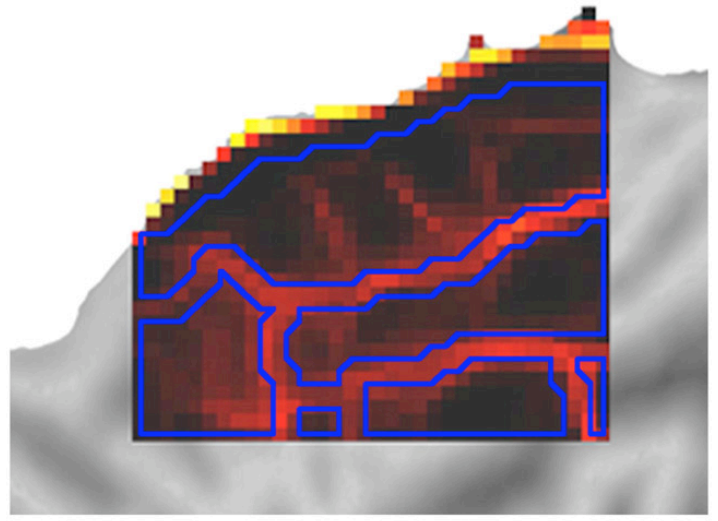


Functional atlases

- Yeo 2011/ Glasser 2016
- Many good functional atlases available, though few comparison studies
- How to map onto individuals is very important



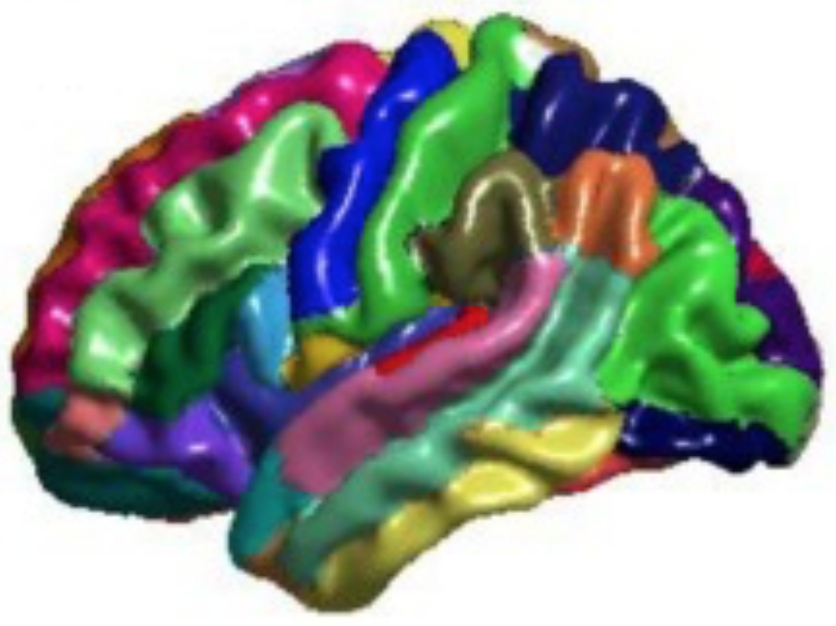
Data-driven parcellation

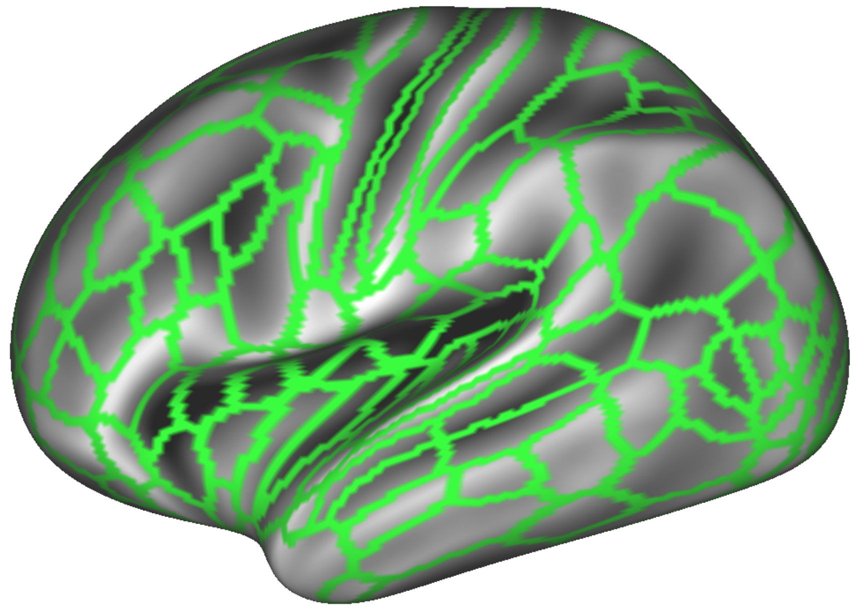


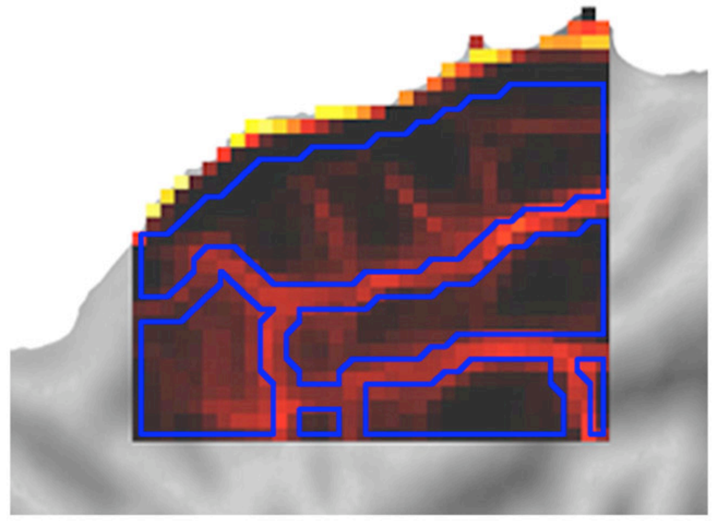
Tzourio-Mazoyer et al (2002), Yeo et al (2011), Glasser et al (2016), Cohen et al (2009)

Node definition

Anatomical atlases	Functional atlases	Data-driven parcellation
• Harvard-Oxford/ AAL • Avoid if possible because typically based on small number of subjects and not a good estimation of functional boundaries	• Yeo 2011/ Glasser 2016 • Many good functional atlases available, though few comparison studies • How to map onto individuals is very important	• ICA/ Clustering/ Gradients • Estimate parcellation from the same dataset used for further analyses • How to map group parcellation onto individuals very important

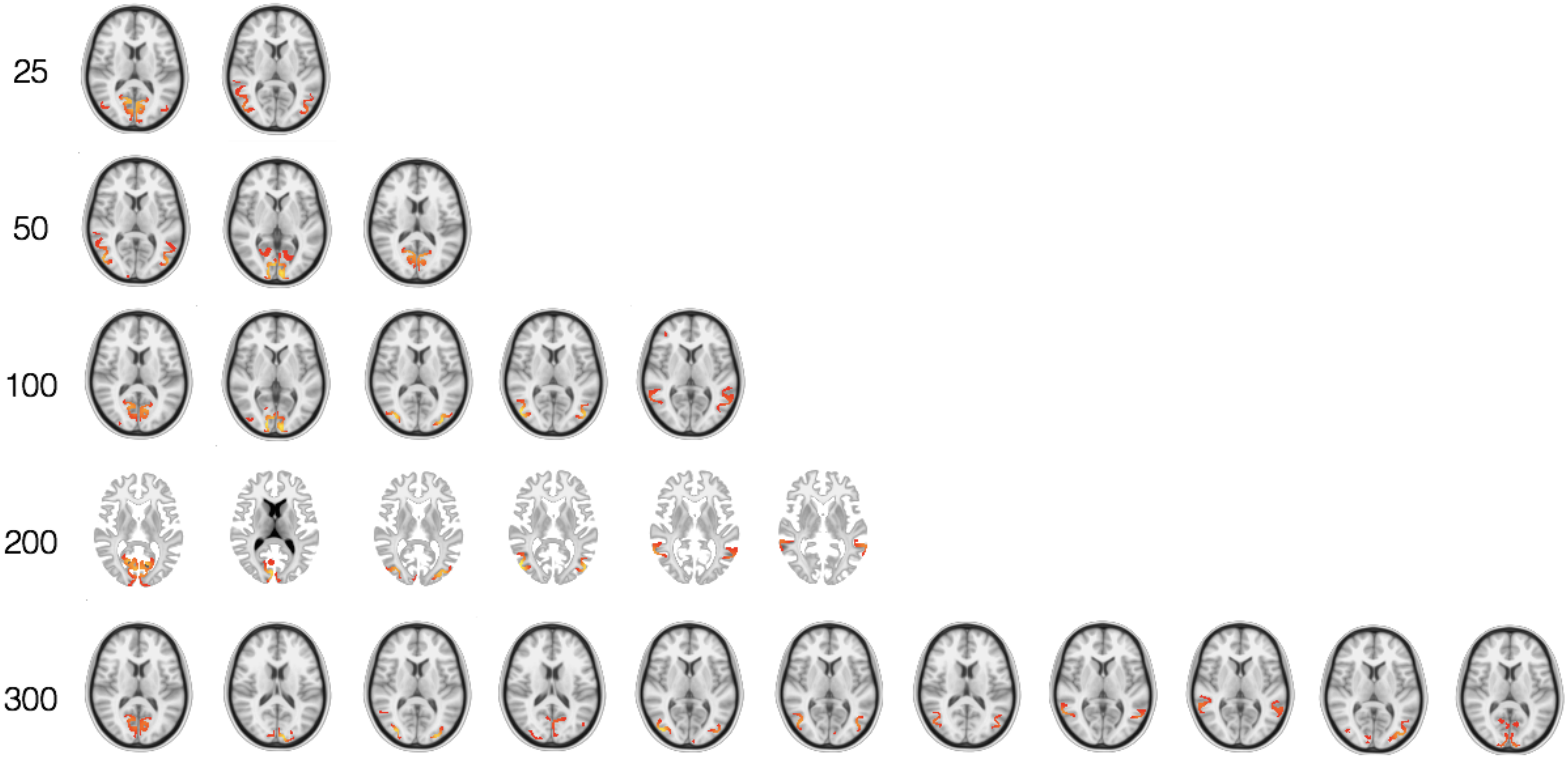






Tzourio-Mazoyer et al (2002), Yeo et al (2011), Glasser et al (2016), Cohen et al (2009)

ICA for parcellation



Timeseries extraction

Hard parcellation:

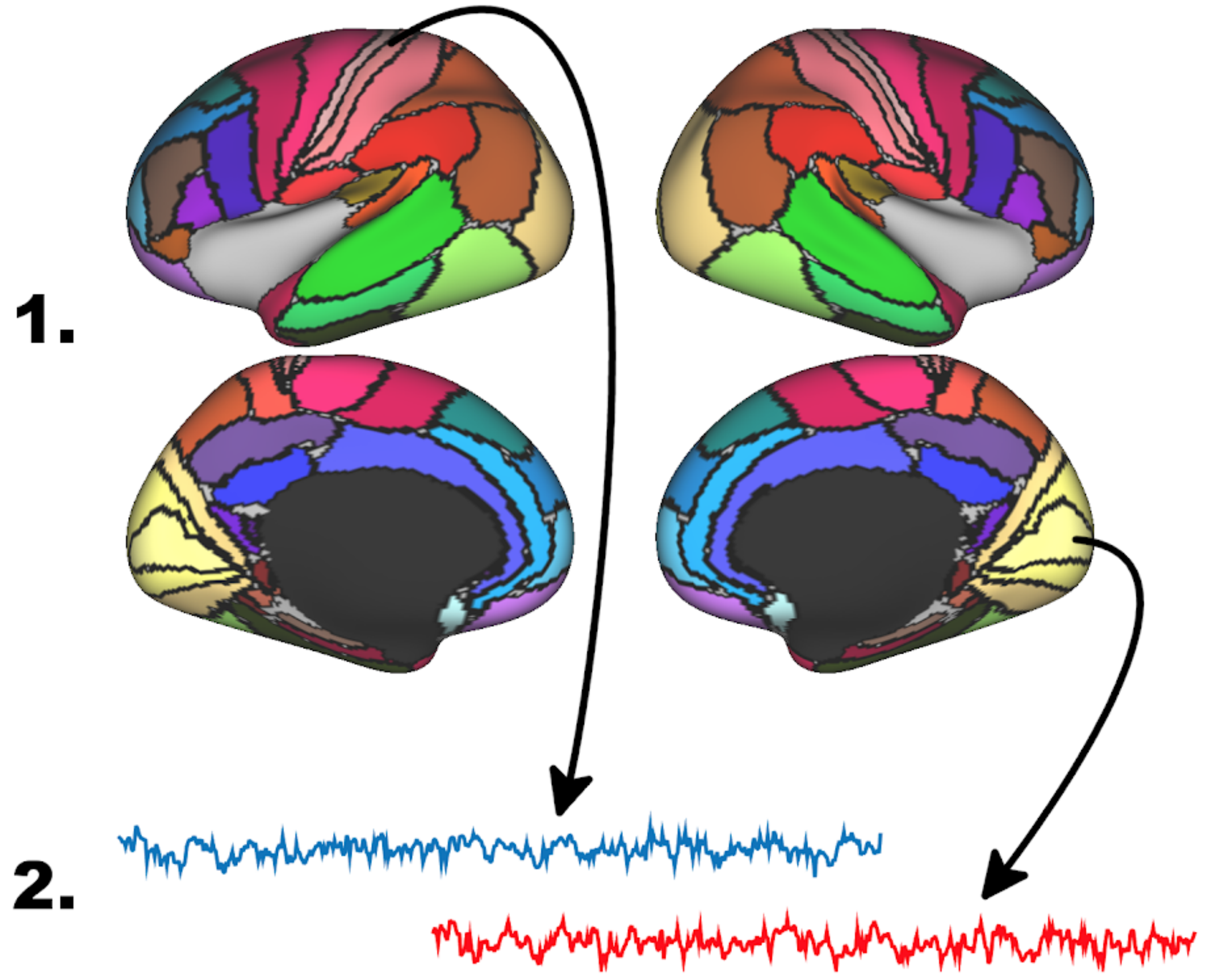
- Masking (mean timeseries)
- Eigen timeseries (PCA)
- Using multilayer classifier

ICA (soft parcellation):

- **Thresholded** dual regression/ back projection

Alternative:

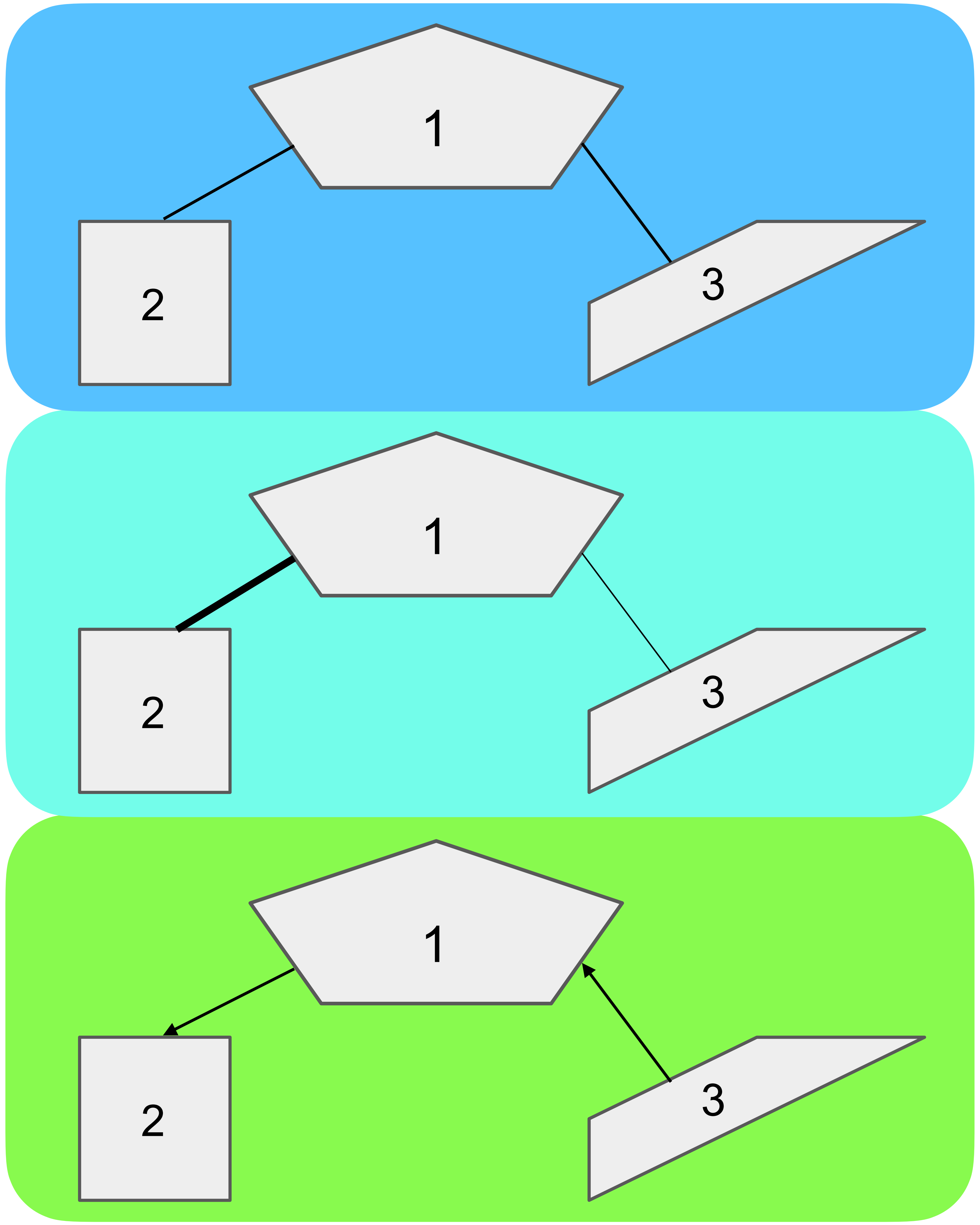
- Hierarchical estimation of group & subject
- e.g. PROFUMO



Hacker et al (2013) , Fillippini et al (2009), Calhoun et al (2001), Harrison et al (2015), Bijsterbosch et al (2019)

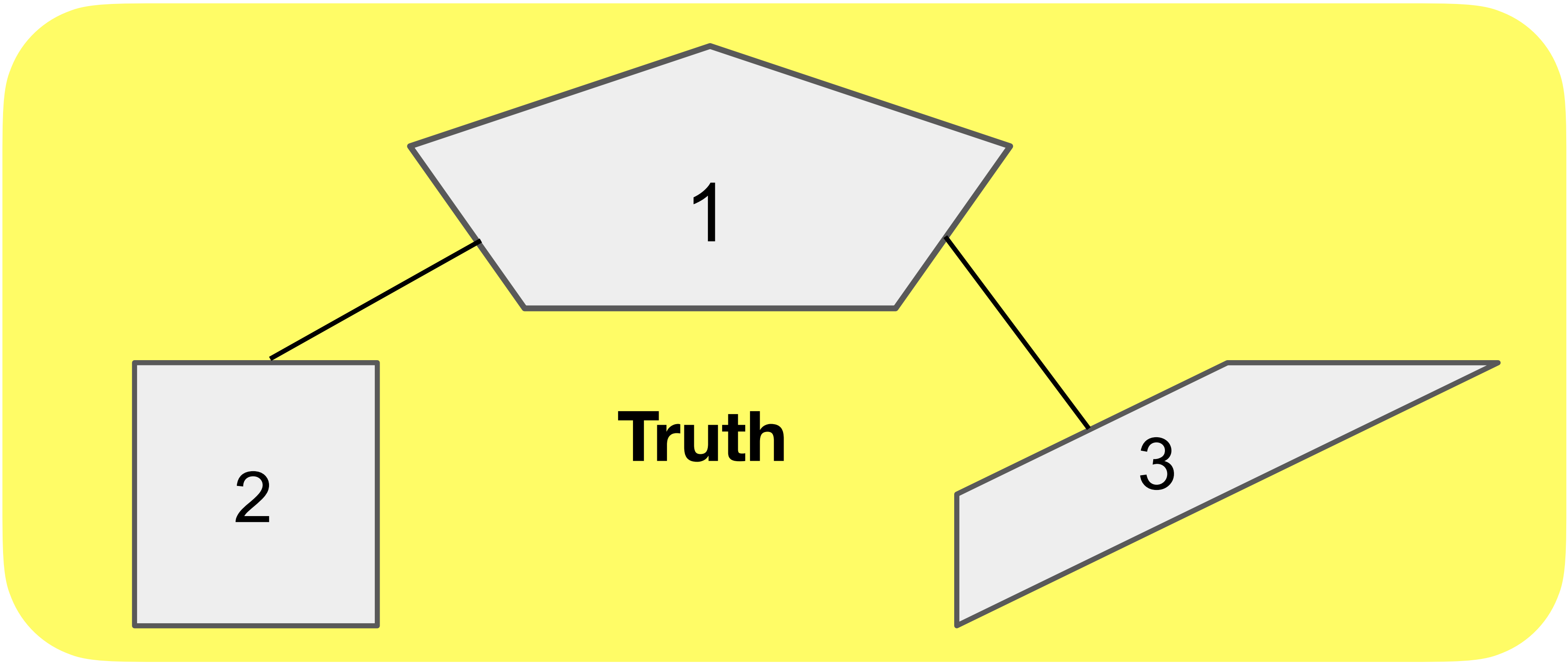
Edge calculation

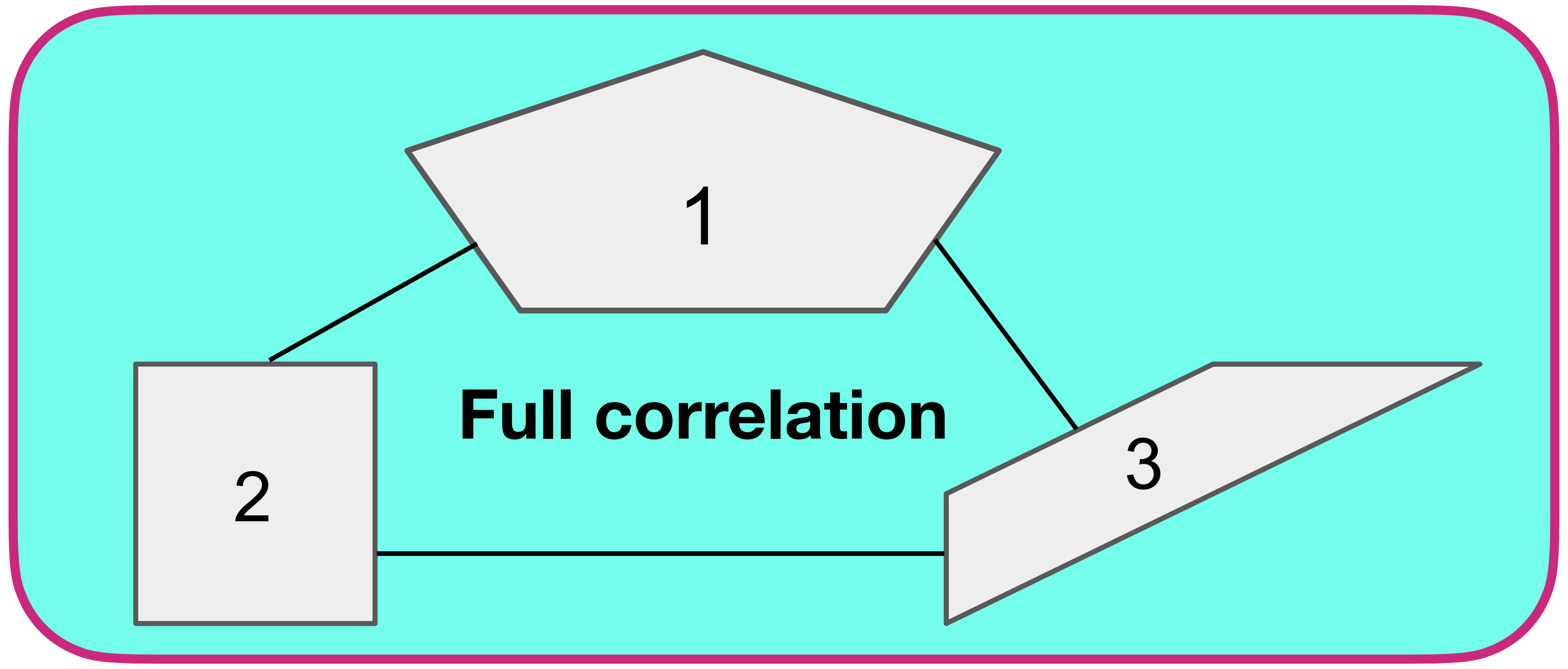
- Presence/ absence of edges
- Strength of edges
- Directionality of edges



Direct versus indirect connections

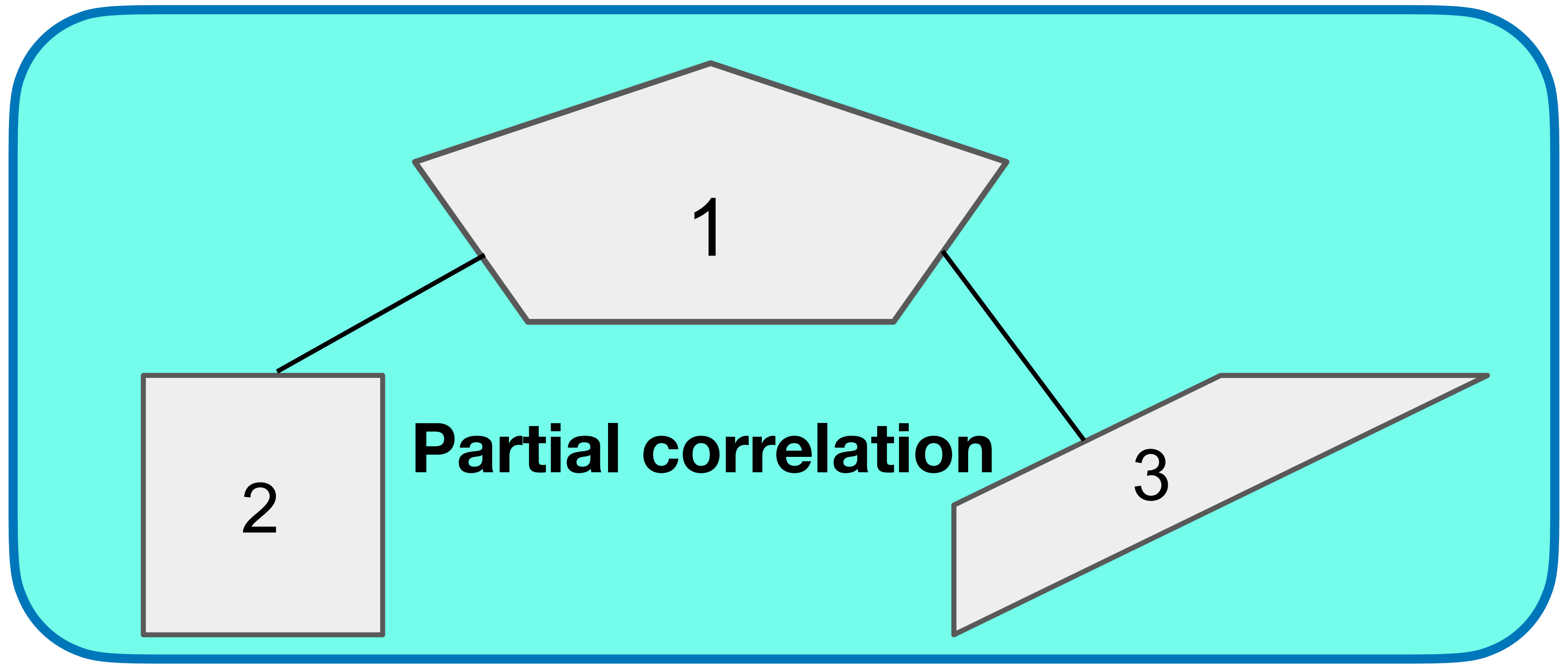
- Correlation between 2 and 3 will exist
- Therefore full correlation will incorrectly estimate connection 2-3
- 2-3 is an indirect connection

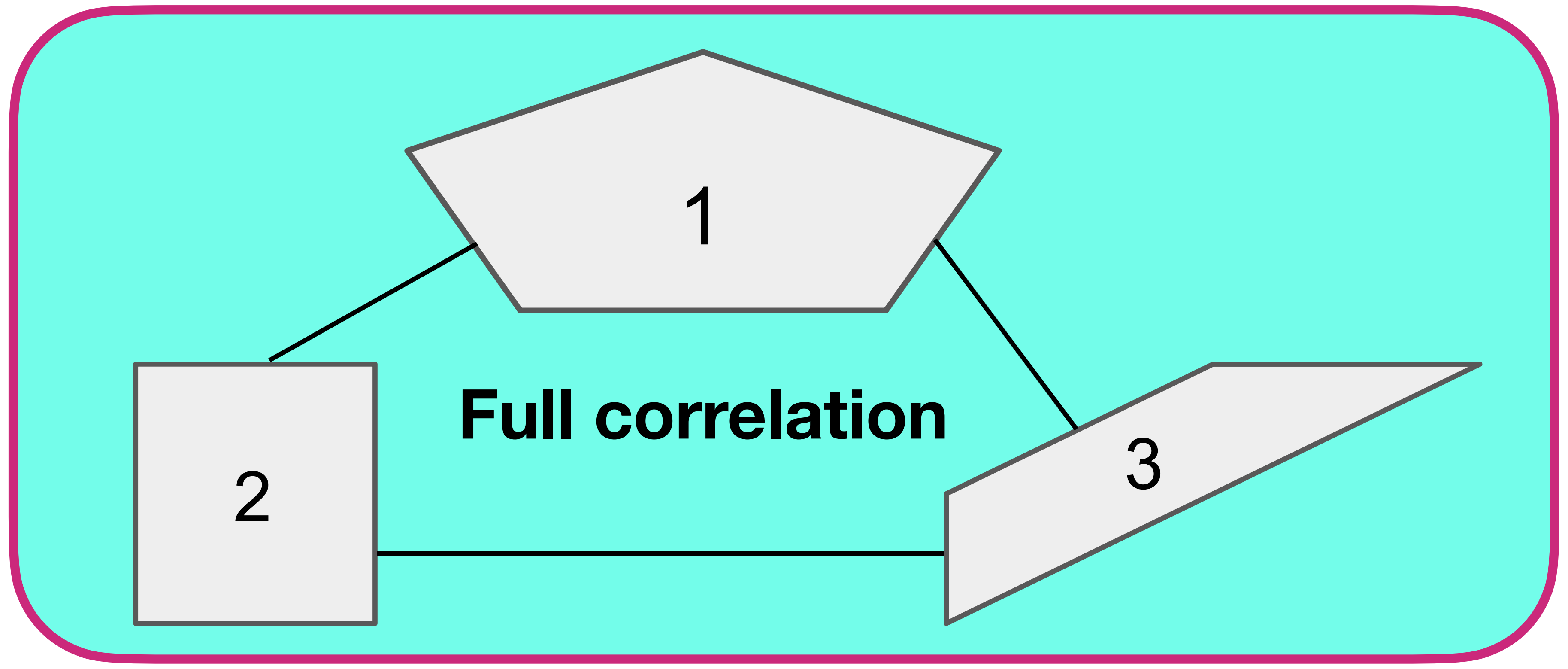




Partial correlation

- Before correlating 2 and 3, first regress 1 out of both (“orthogonalise wrt 1”)
    - If 2 and 3 are still correlated, a direct connection exists
- More generally, first regress all other nodes’ timecourses out of the pair in question
    - Equivalent to the inverse covariance matrix

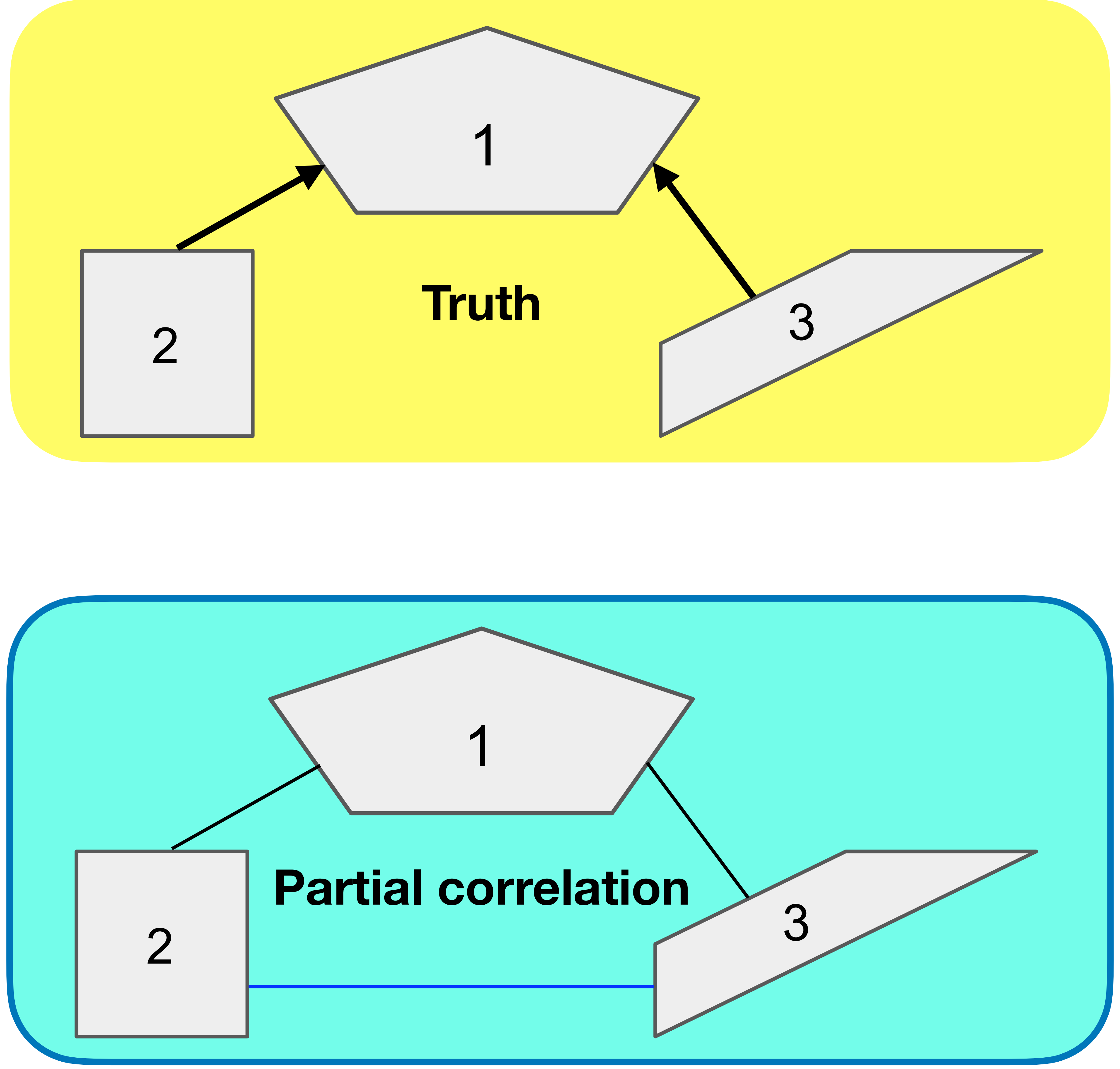




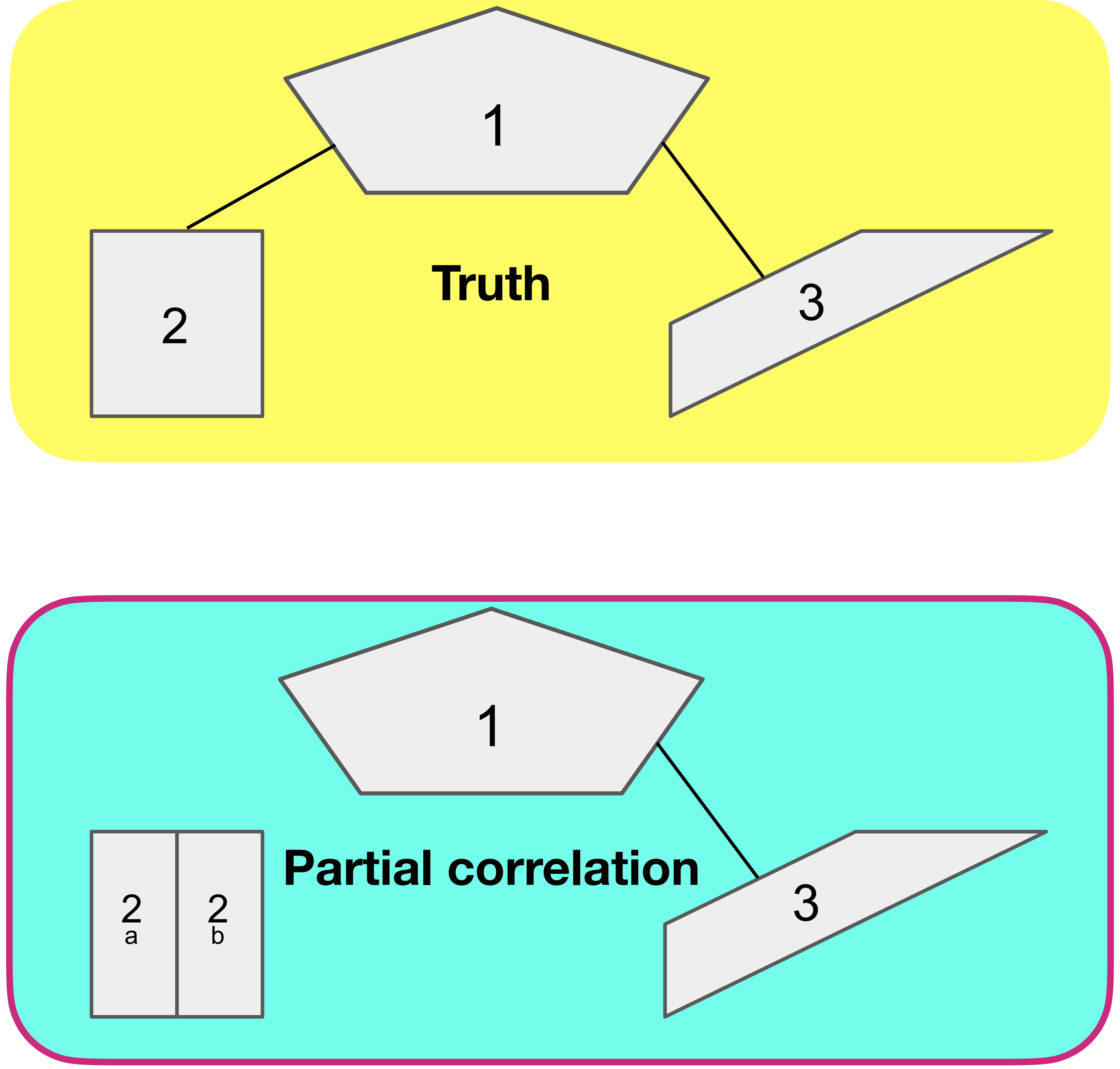
Regularisation

- Urgh! If you have 200 nodes and 100 timepoints, this is impossible!
- A problem of DoF - need large #timepoints - #nodes
- When inverting a “rank-deficient” matrix it is common to aid this with some mathematical conditioning, e.g. force it to be sparse (force low values that are poorly estimated to zero)
- Regularised partial correlation (such as ICOV, Ridge)
- But still important to maximise temporal degrees of freedom

Need to carefully define nodes



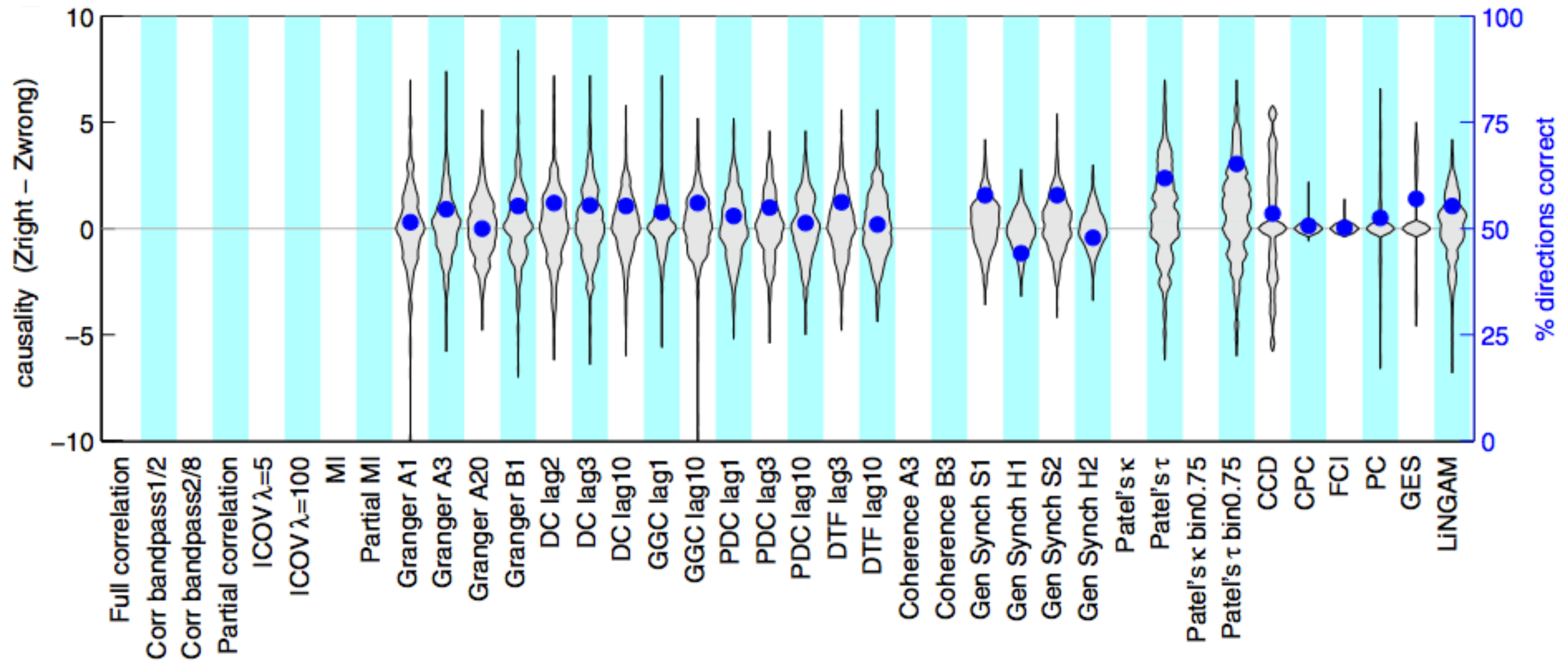
Berkson's paradox = false positive (2-3)



Over-splitting = false negative (1-2)

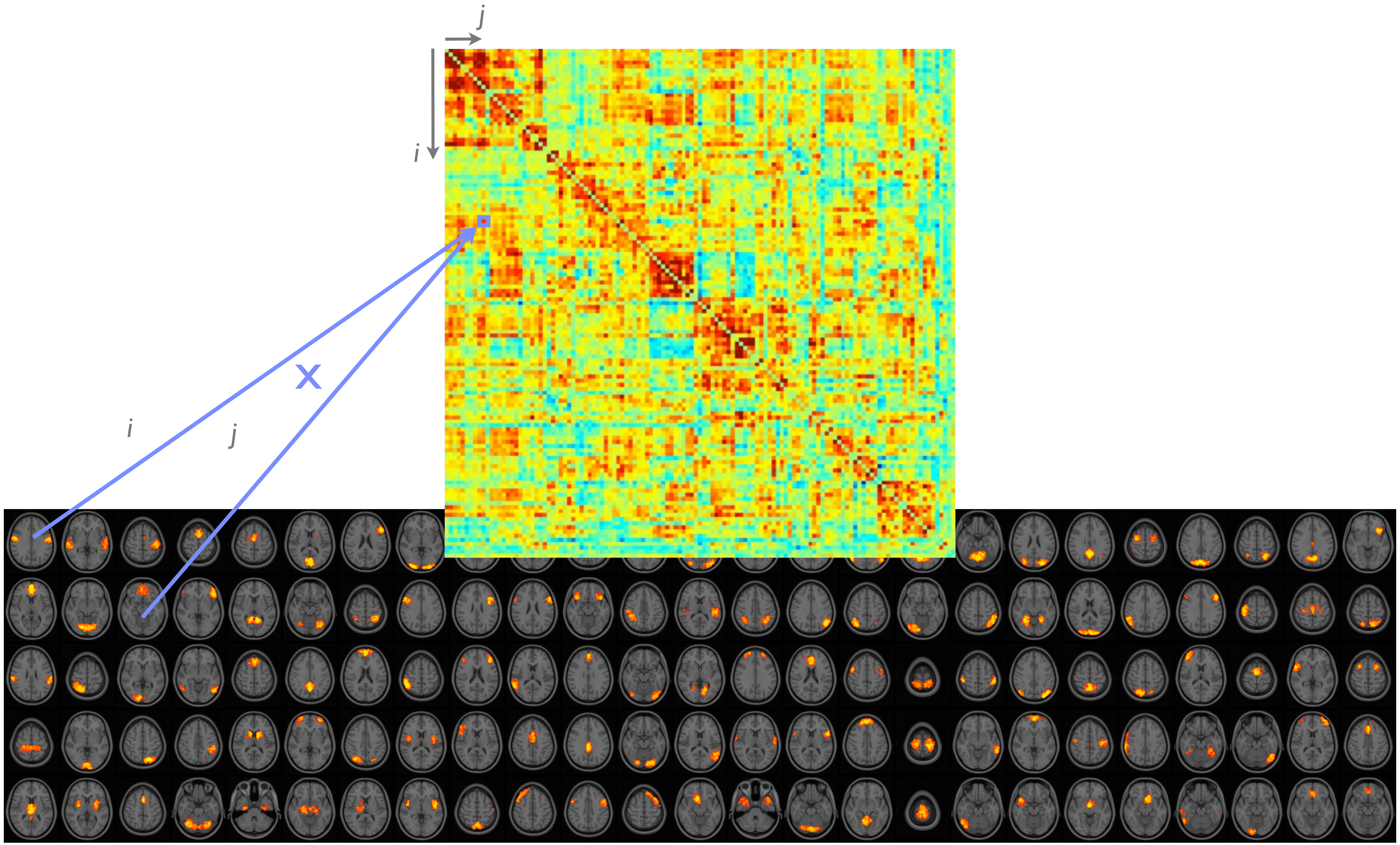
Directionality of edges

- Directionality is hard to estimate in BOLD data
- Don't use lag-based methods such as Granger causality
- Perhaps directionality is oversimplistic view of neural connectivity (particularly in resting-state)?

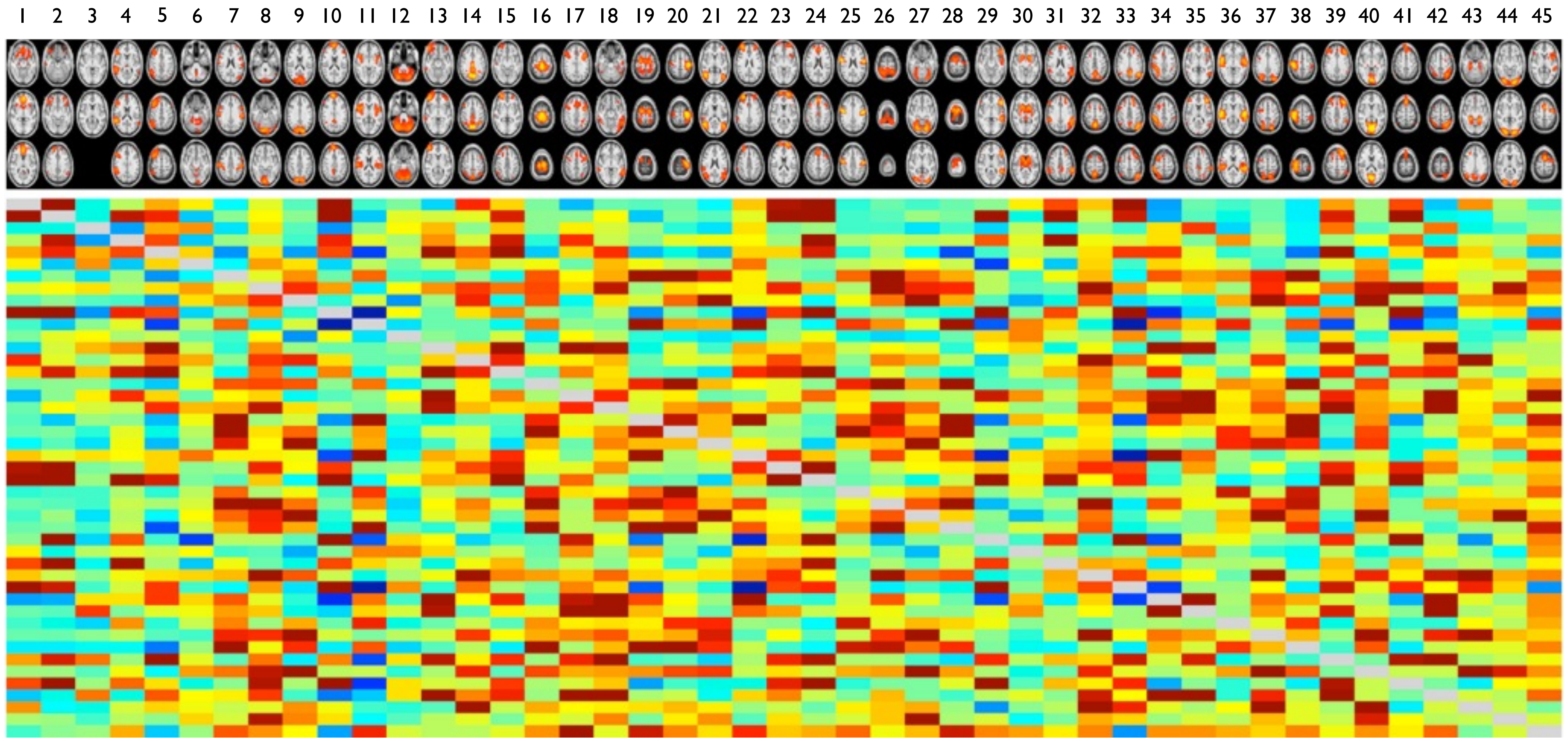


Smith et al (2011)

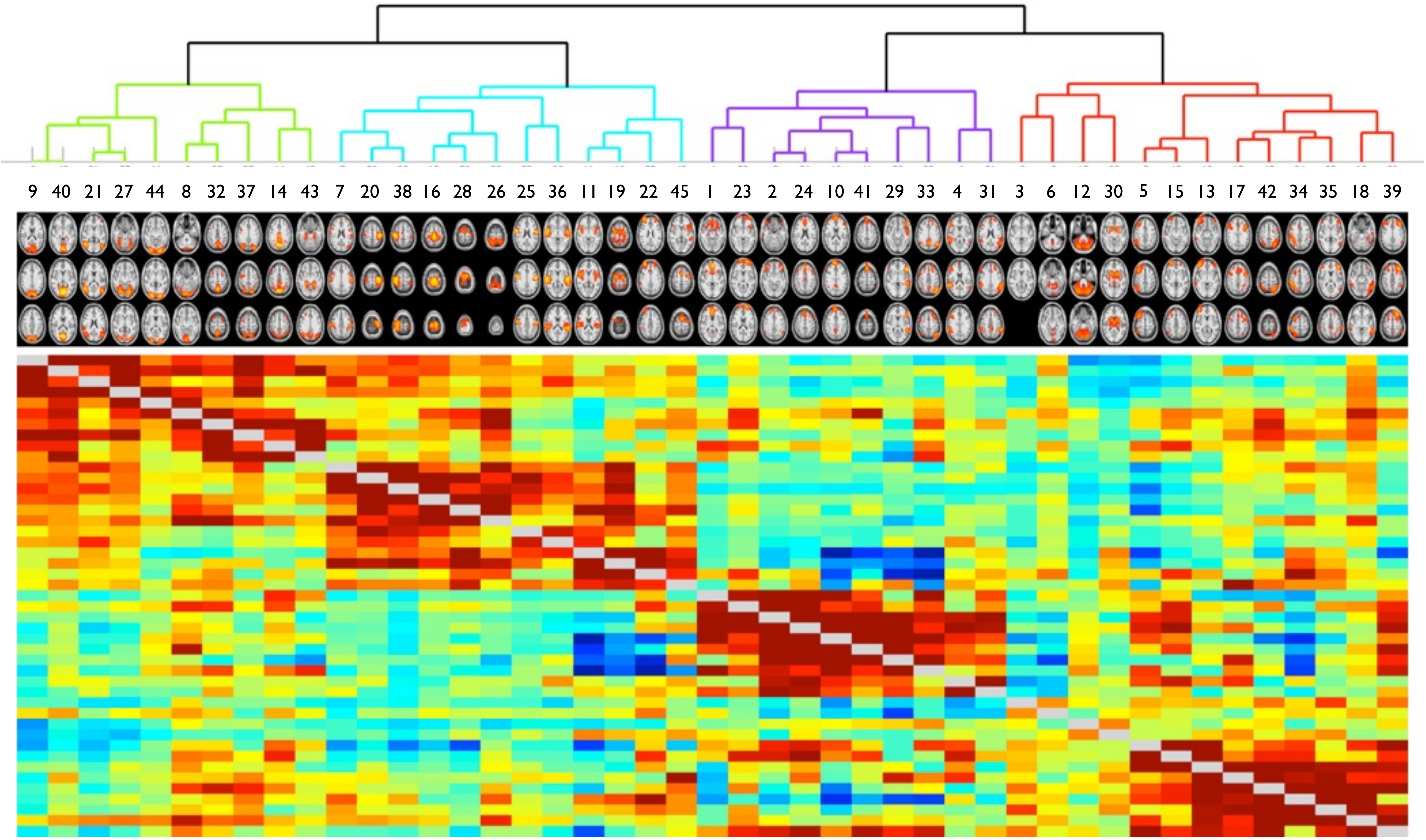
Building a network matrix



Network matrix

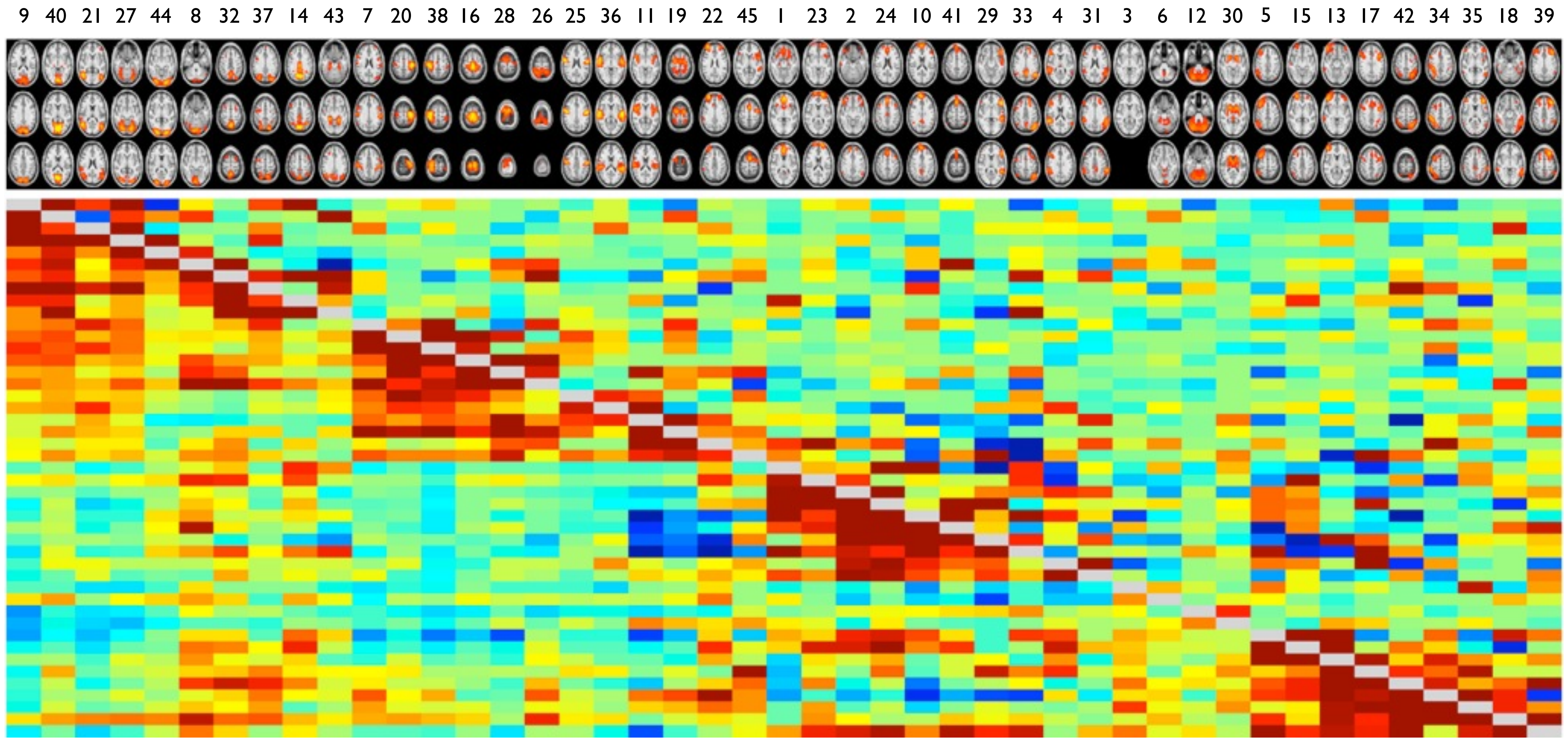


Hierarchical clustering



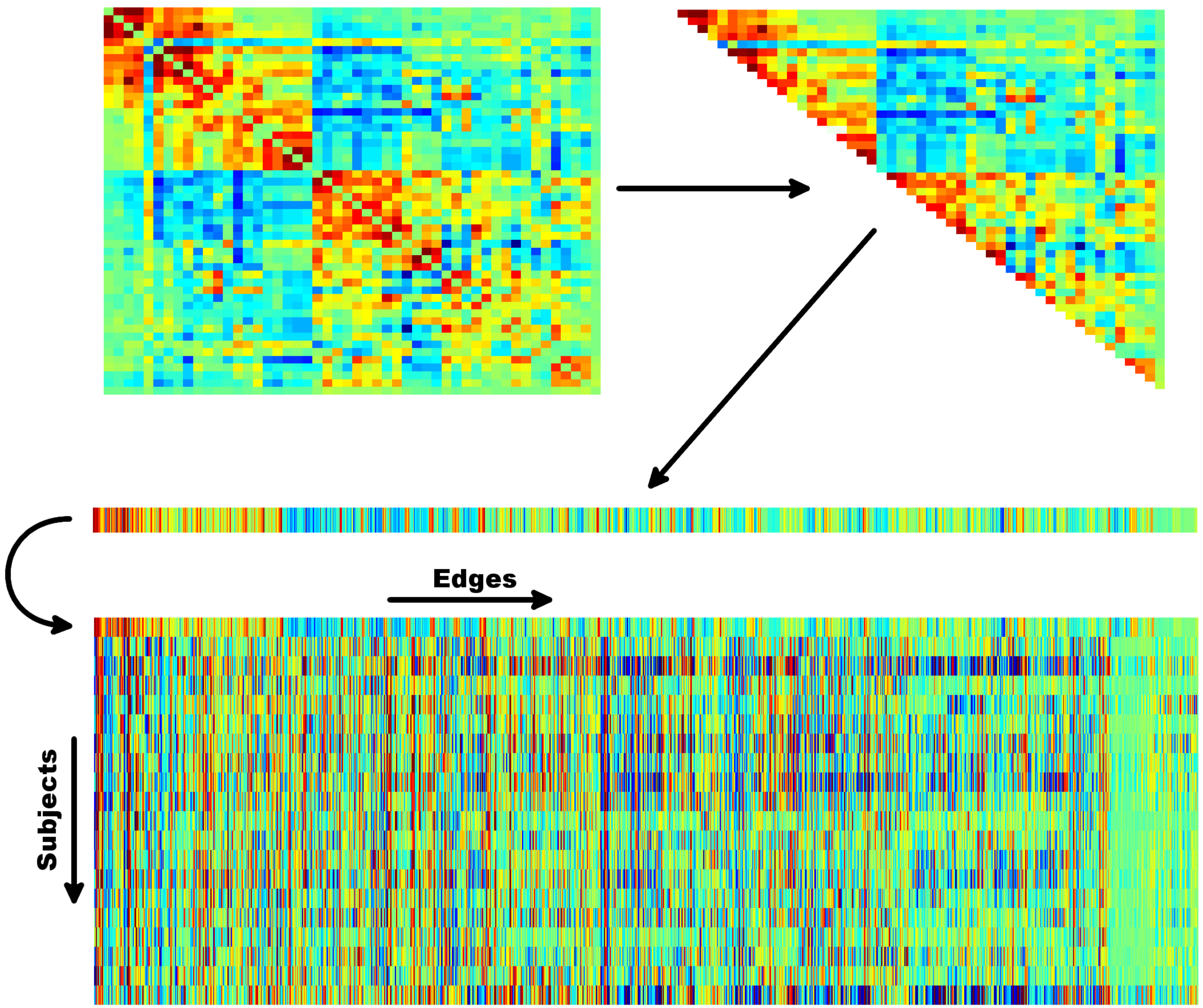
Partial correlation is sparser than full

Full correlation matrix



Partial correlation matrix

Group analysis

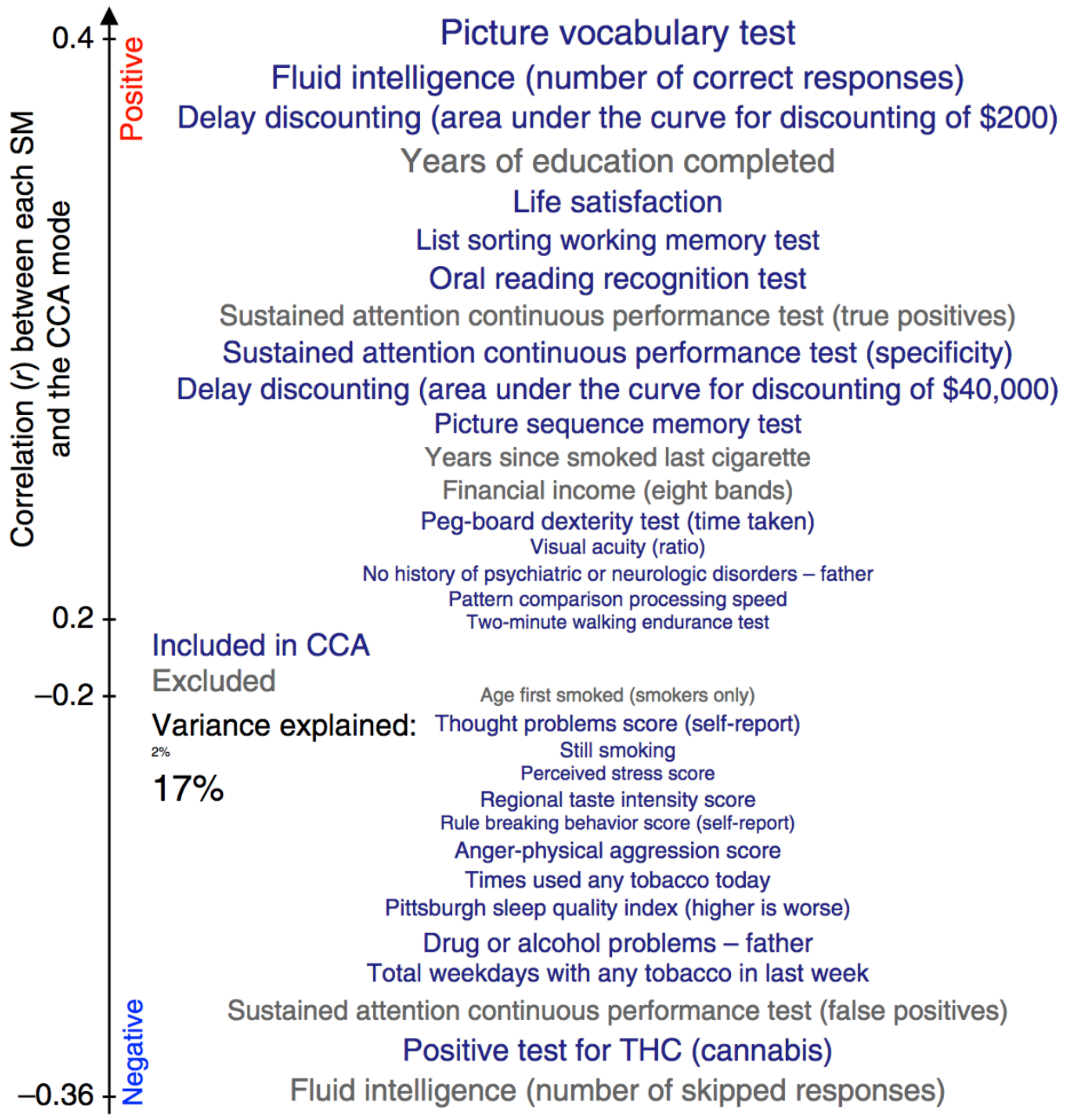


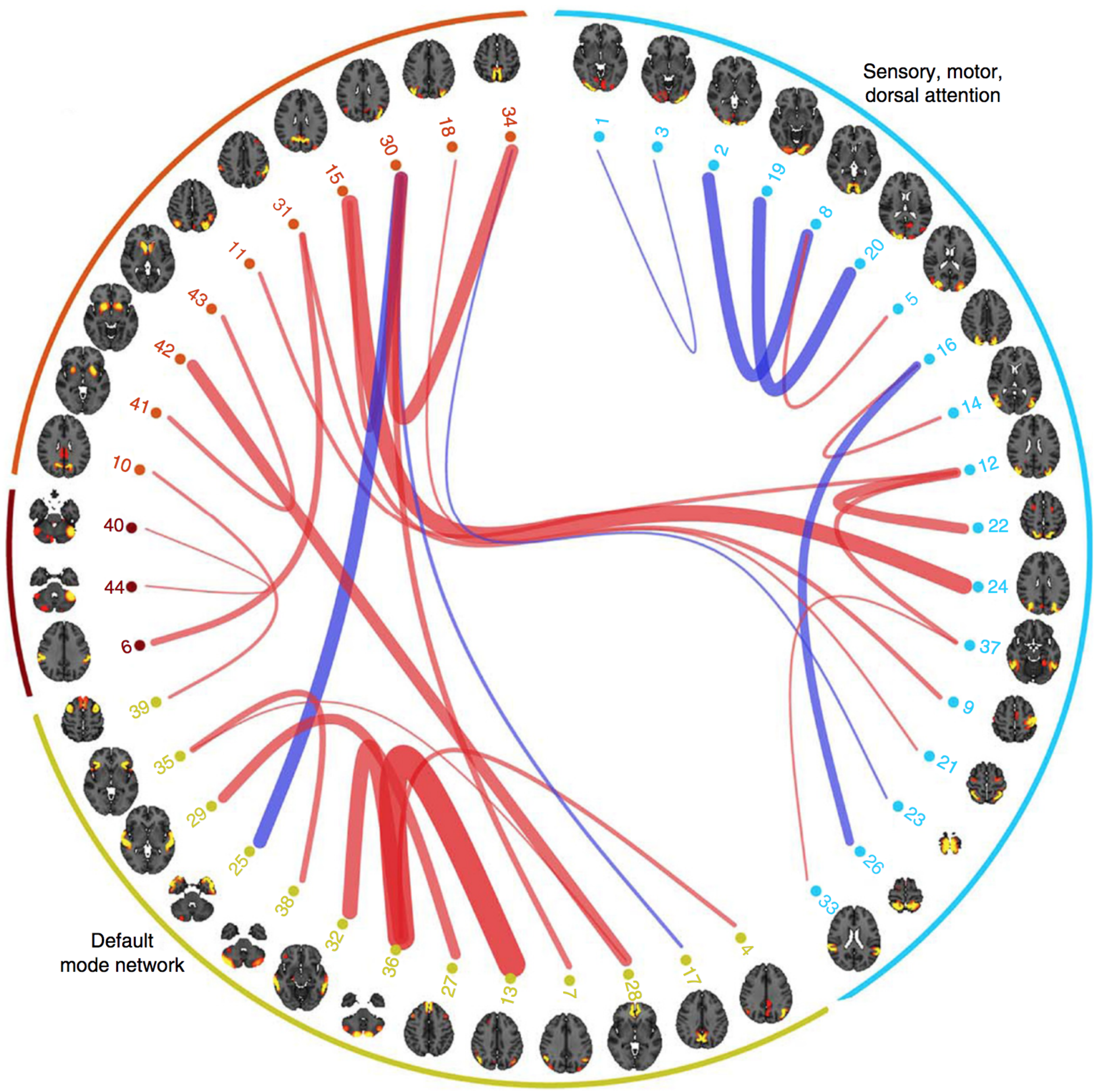
- Calculate network matrix for each subject
- Combine all network matrices into one
- Perform group-level comparisons:
    - Univariate tests for each edge (GLM)
    - Multivariate prediction methods (SVM)

FSLnets

- Currently uses Matlab or Octave
- Therefore this practical will be a bit different from other practicals
- More information and download here: https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLNets

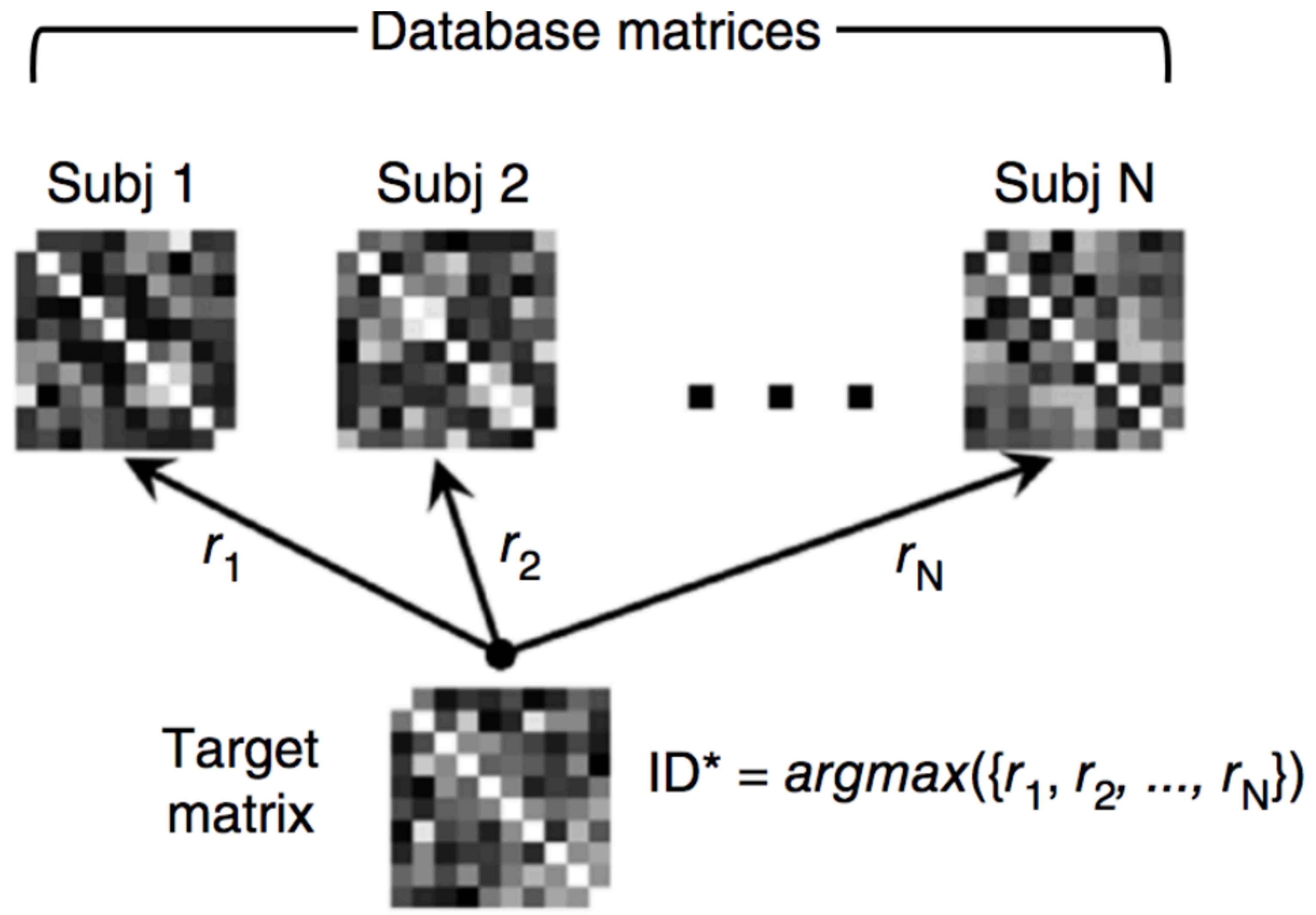
Example: positive-negative mode

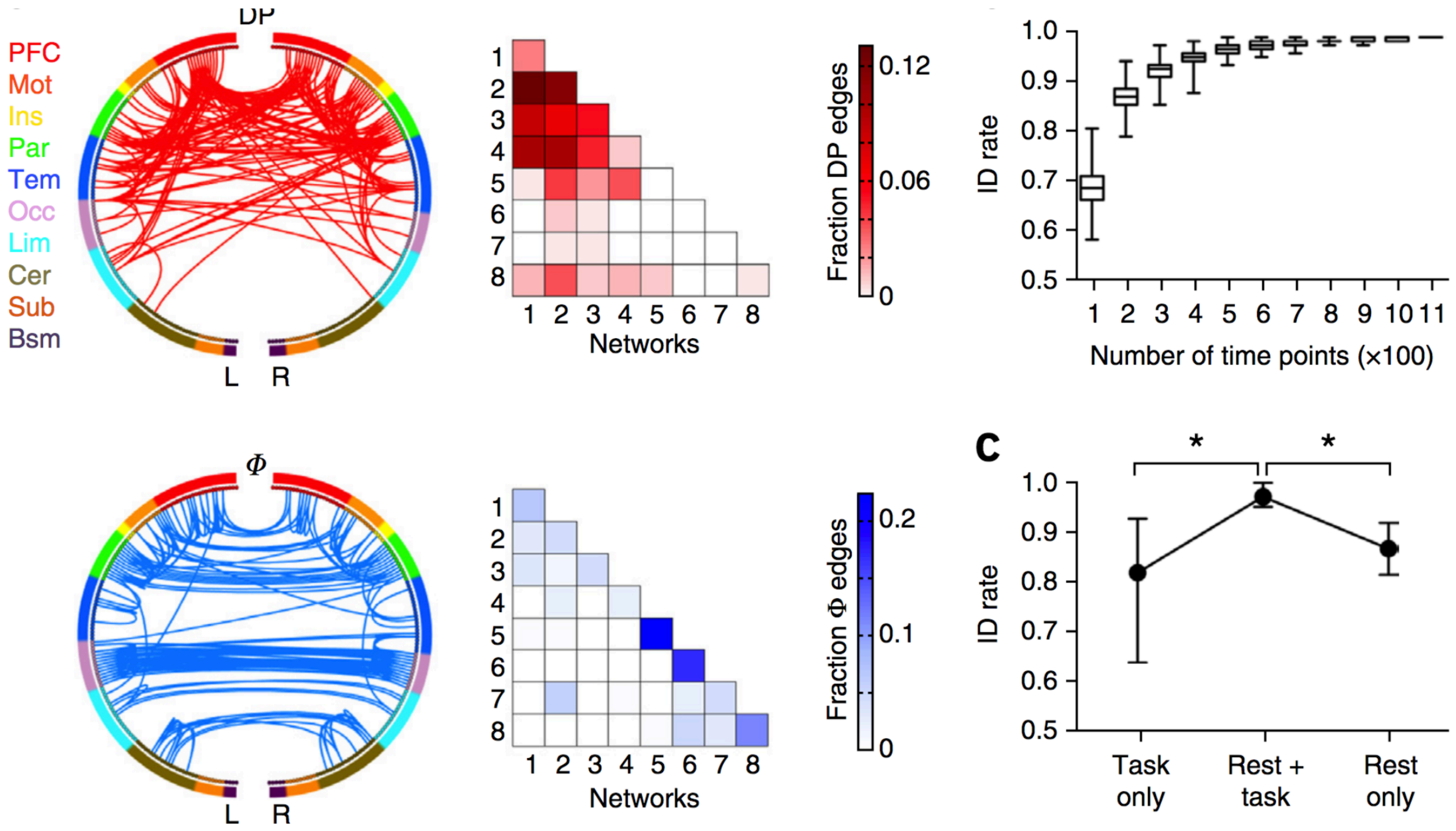




Smith et al (2015)

Example: connectivity fingerprint



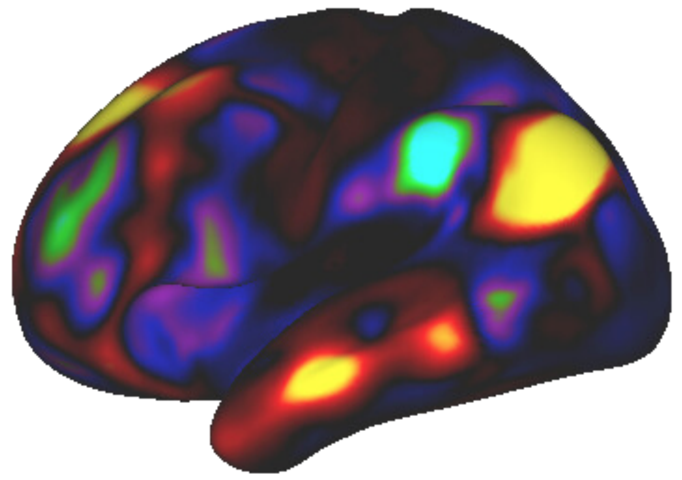


Finn et al (2015)

Comparison of methods

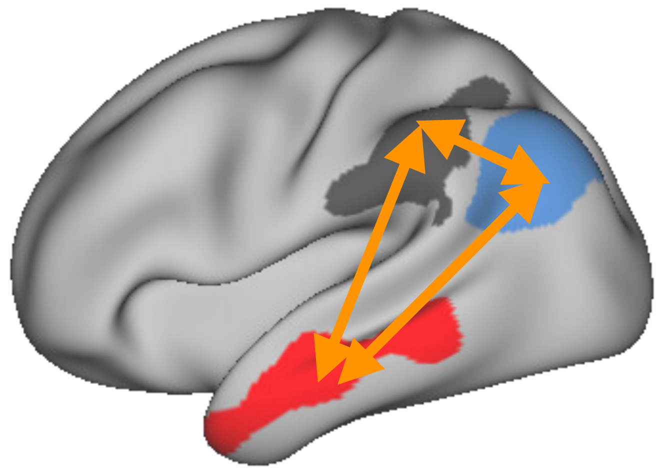
Overview of resting state methods

Voxel-based



- Seed-based correlation analysis
- Independent component analysis
- Amplitude of low frequency fluctuations
- Regional homogeneity

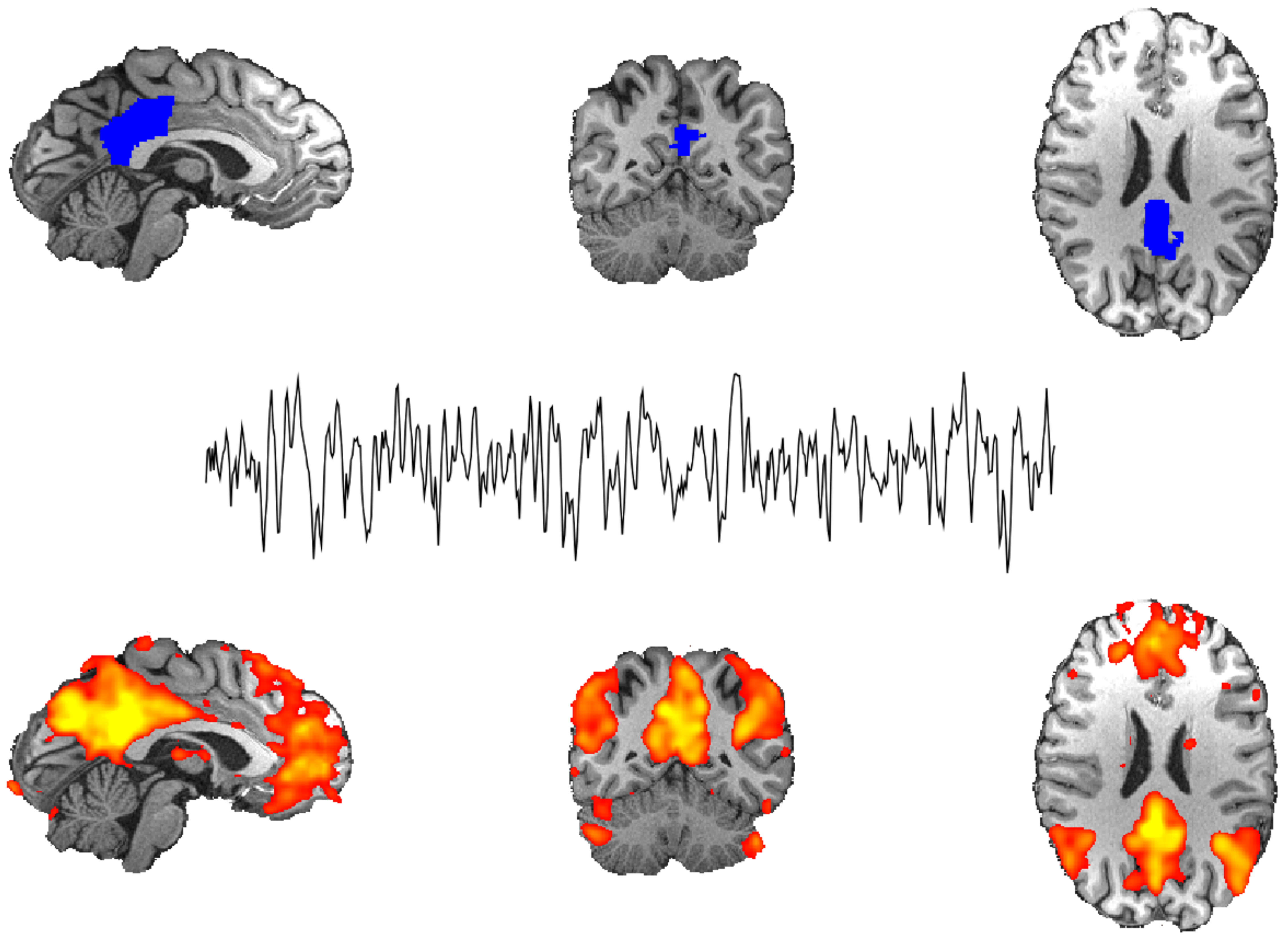
Node-based



- Network modelling analysis
- Graph theory analysis
- Dynamic causal modelling
- Non-stationary methods

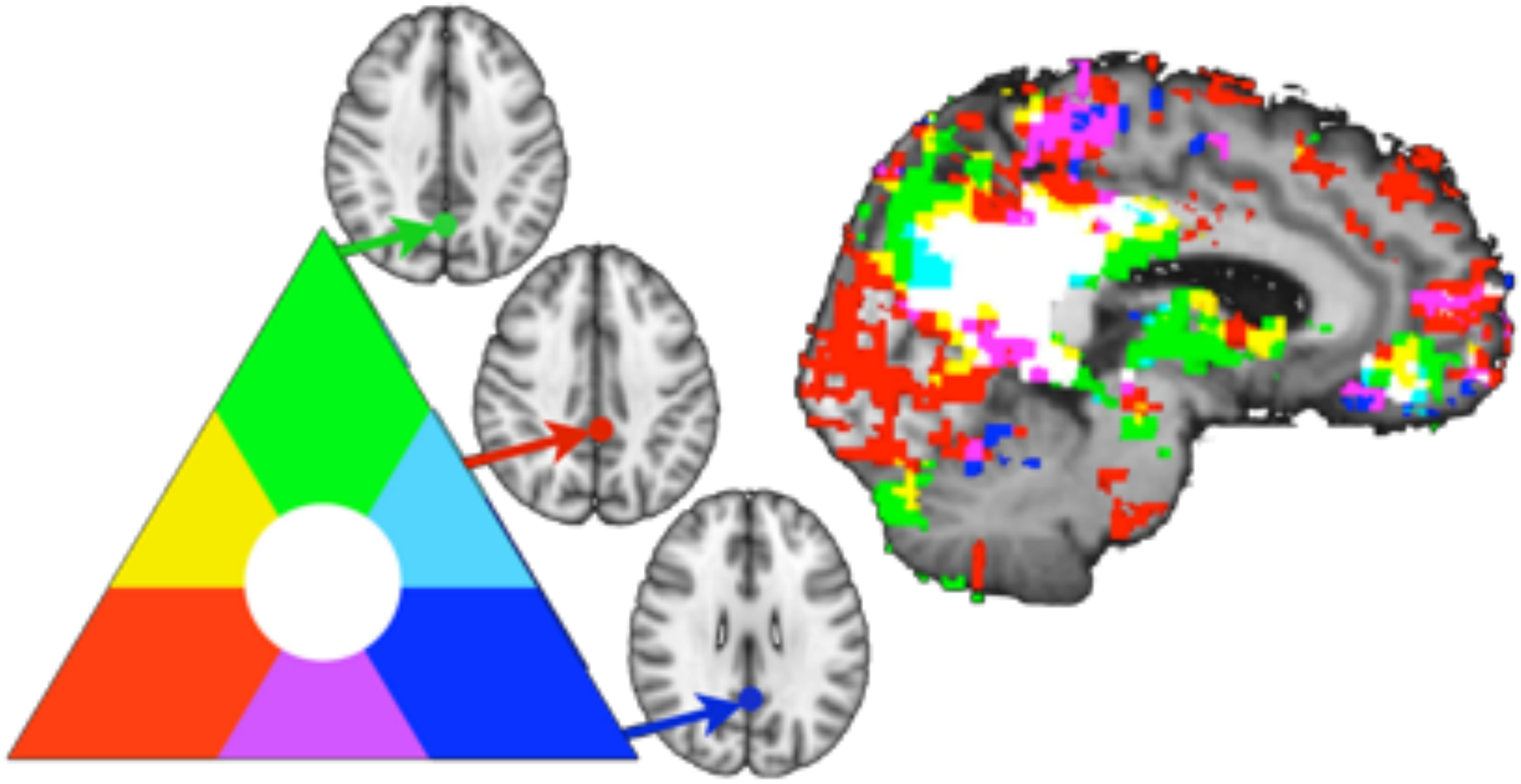
Seed-based correlation

- Easy to interpret
- No correspondence problem
- Seed-selection bias
- Only models seed-effect (ignoring complex structure & noise)



Seed-selection bias

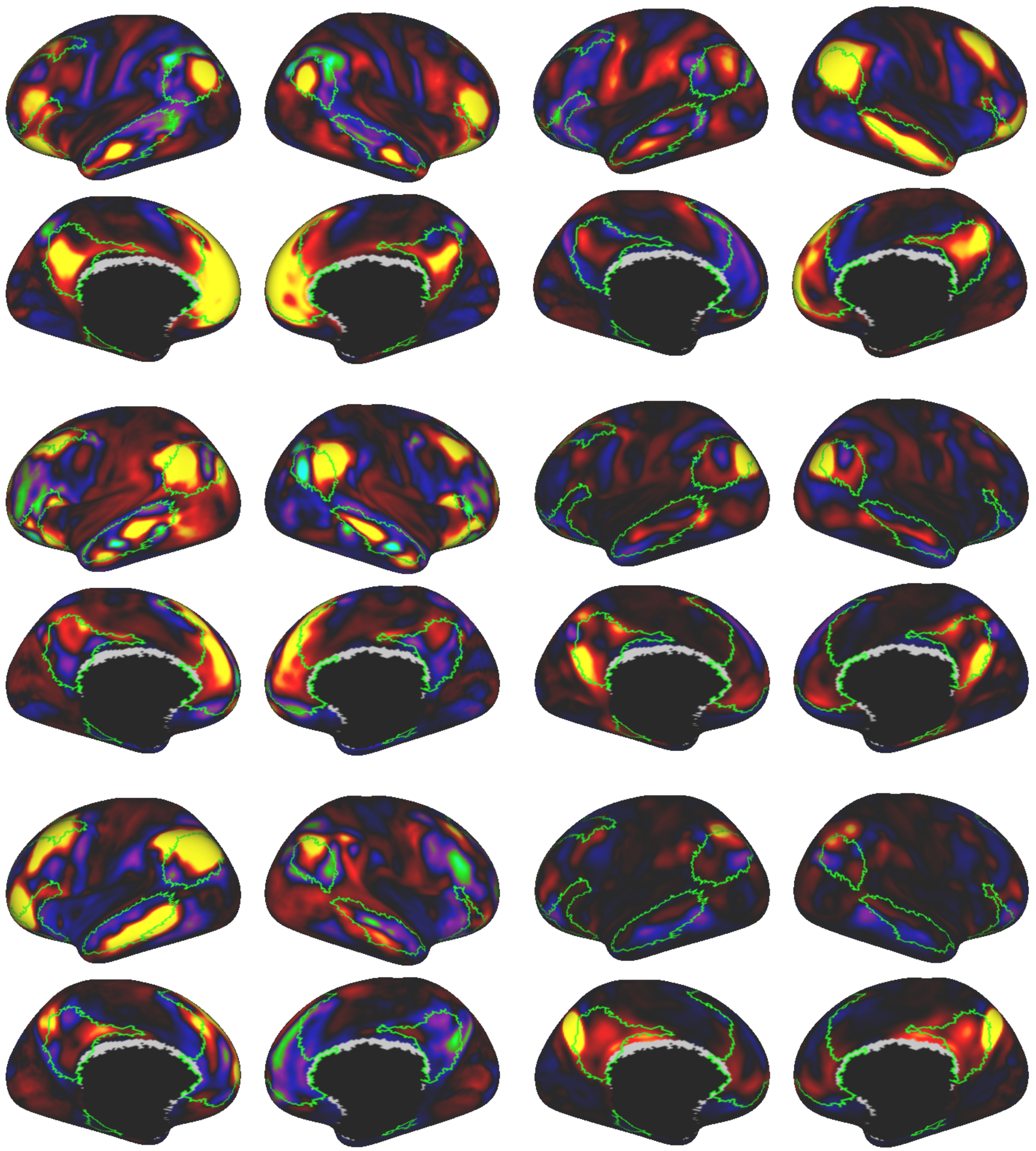
Seed-based correlation results are strongly influenced by small changes is seed location



Cole et al (2010)

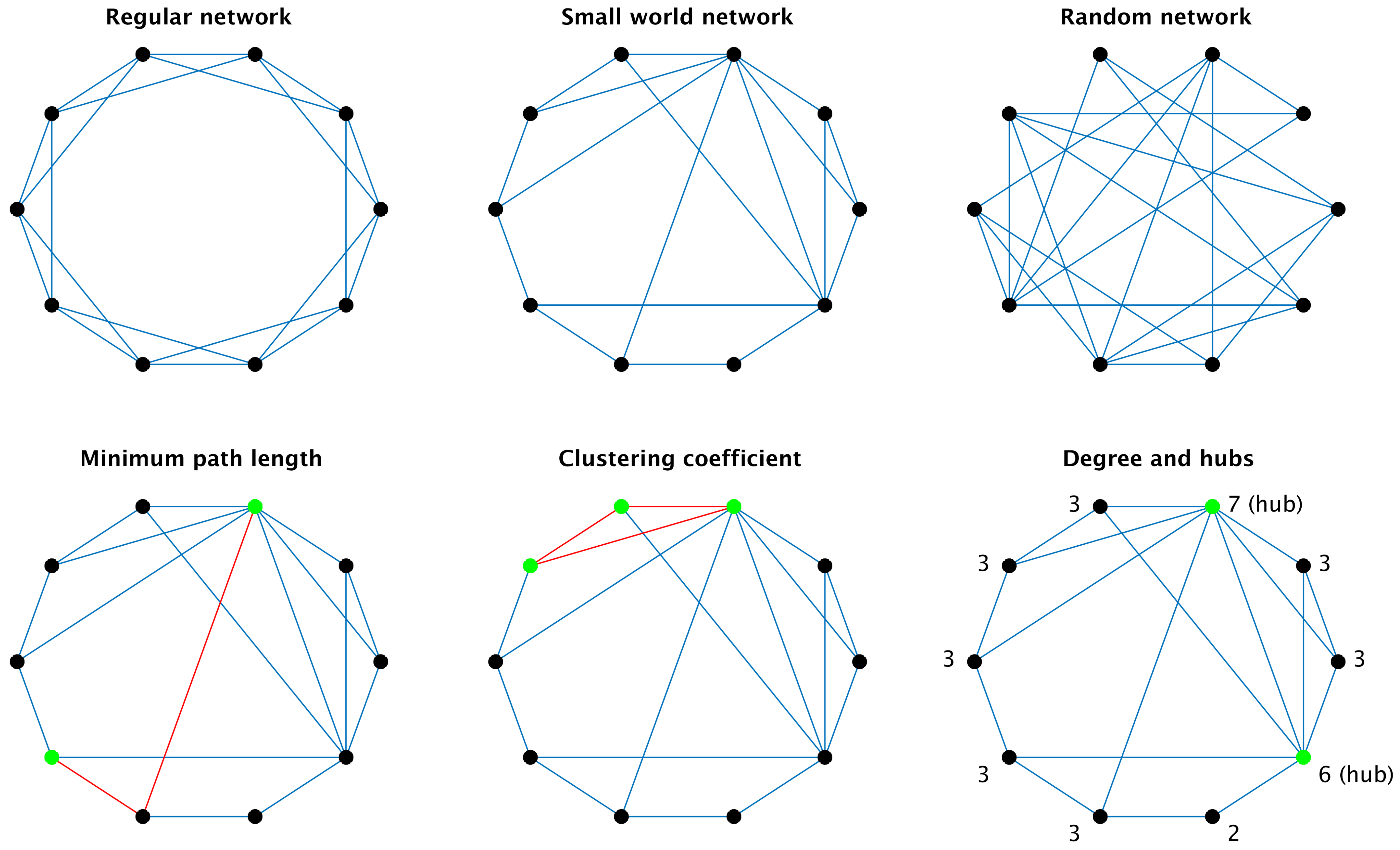
ICA

- Multivariate: decompose full dataset
- Test for shape & amplitude
- Can be hard to interpret
- No control over decomposition (may not get breakdown you want)



Graph theory

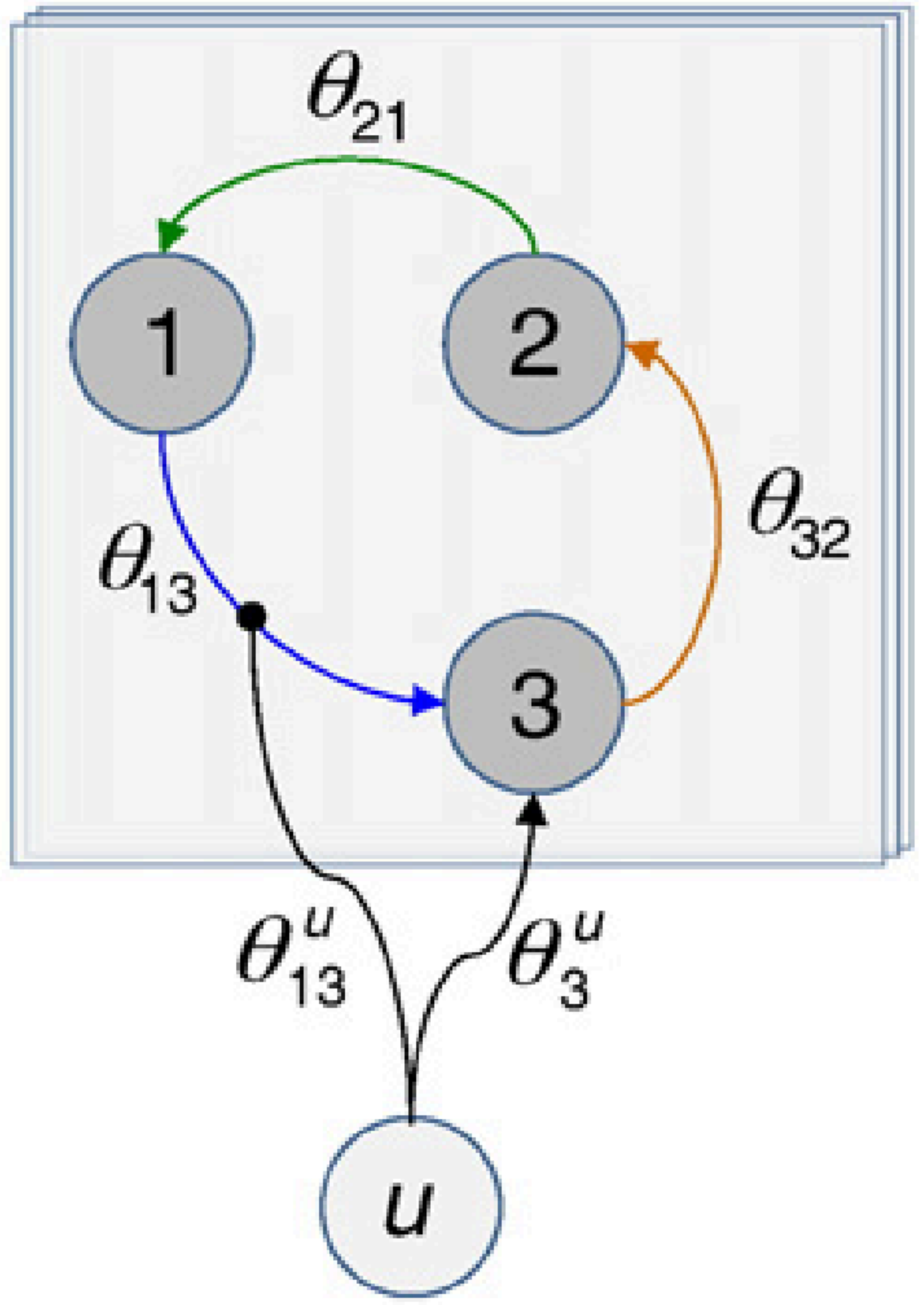
- Simple summary measures (derived from network matrix)
- Network matrix often binarised
- Difficult to meaningfully interpret (abstract and far removed from data)



Rubinov et al (2010)

Dynamic causal modelling

- Directional interpretation (effective connectivity)
- Biophysical model
- Assumes HRF homogeneity
- Limited model comparisons



Daunizeau et al (2011)

Overview of node-based methods

graph theory

clusters / hierarchies, network hubs,
network summary statistics (e.g. small-worldness, efficiency)

network modelling from FMRI data

functional connectivity
simpler, less meaningful,
network "discovery",
better conditioned,
can handle more nodes

full correlation

partial correlation

regularised partial correlation

Bayes nets

SEM

non-biological dynamic Bayes nets

biophysical neural-groups to FMRI-signal forward model, fit to data using Bayes (e.g. DCM)

effective connectivity
more complex, more meaningful,
pre-specify (constrain) network model,
harder to estimate,
can handle fewer nodes

closeness to (interaction with) real FMRI data

bottom-up neural network simulations

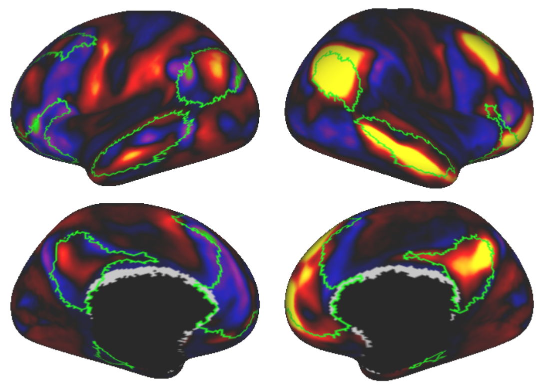
network of individual neurons simulated

network of groups of neurons simulated (e.g. neural mass model)

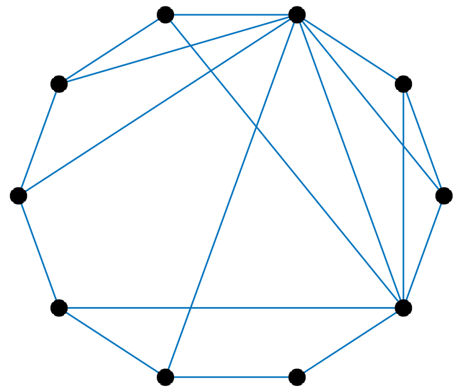
Which method to chose?

Interpretation

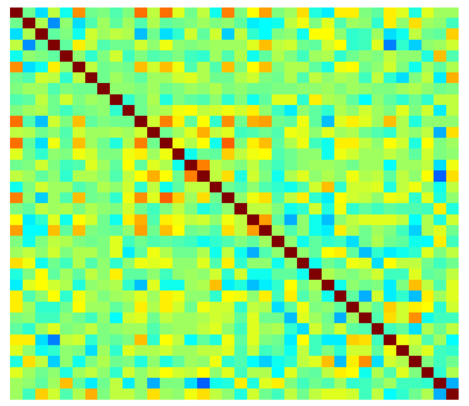
Relationship to RSNs → Dual regression



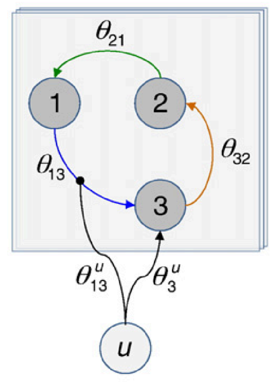
Summary values → Graph theory



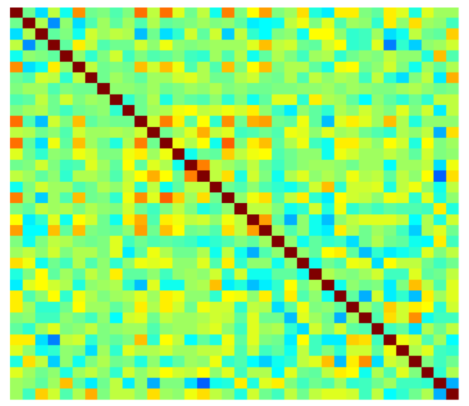
Connections in system → Network modelling



Biophysical system → DCM



Connectomics → Network modelling



That's all folks