Network Modelling and Connectivity in Functional Neuroimaging – Keeping It Real

Mark Woolrich
University of Oxford

Oxford centre for Human Brain Activity

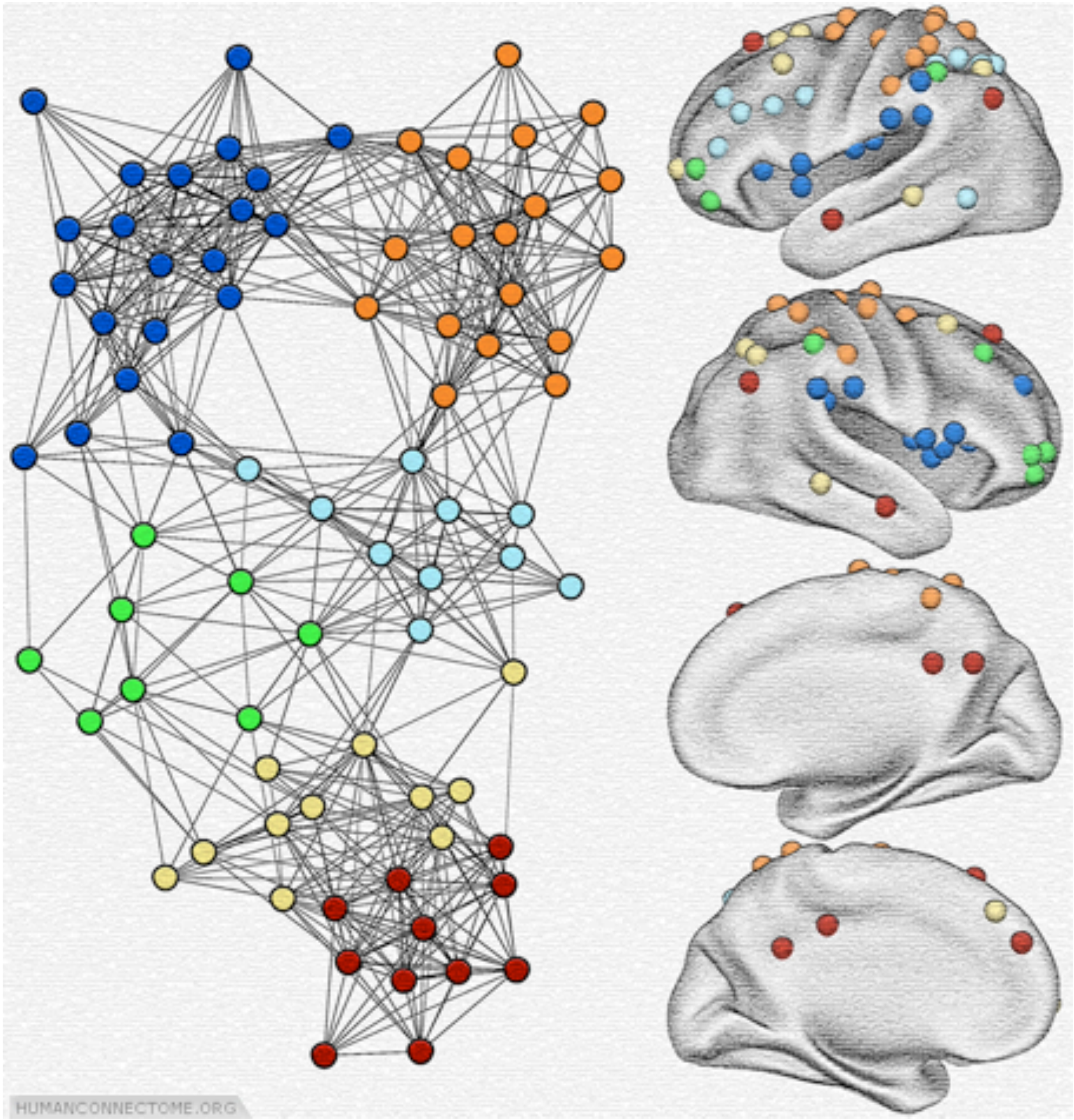
Centre for FMRI of the Brain

Overview

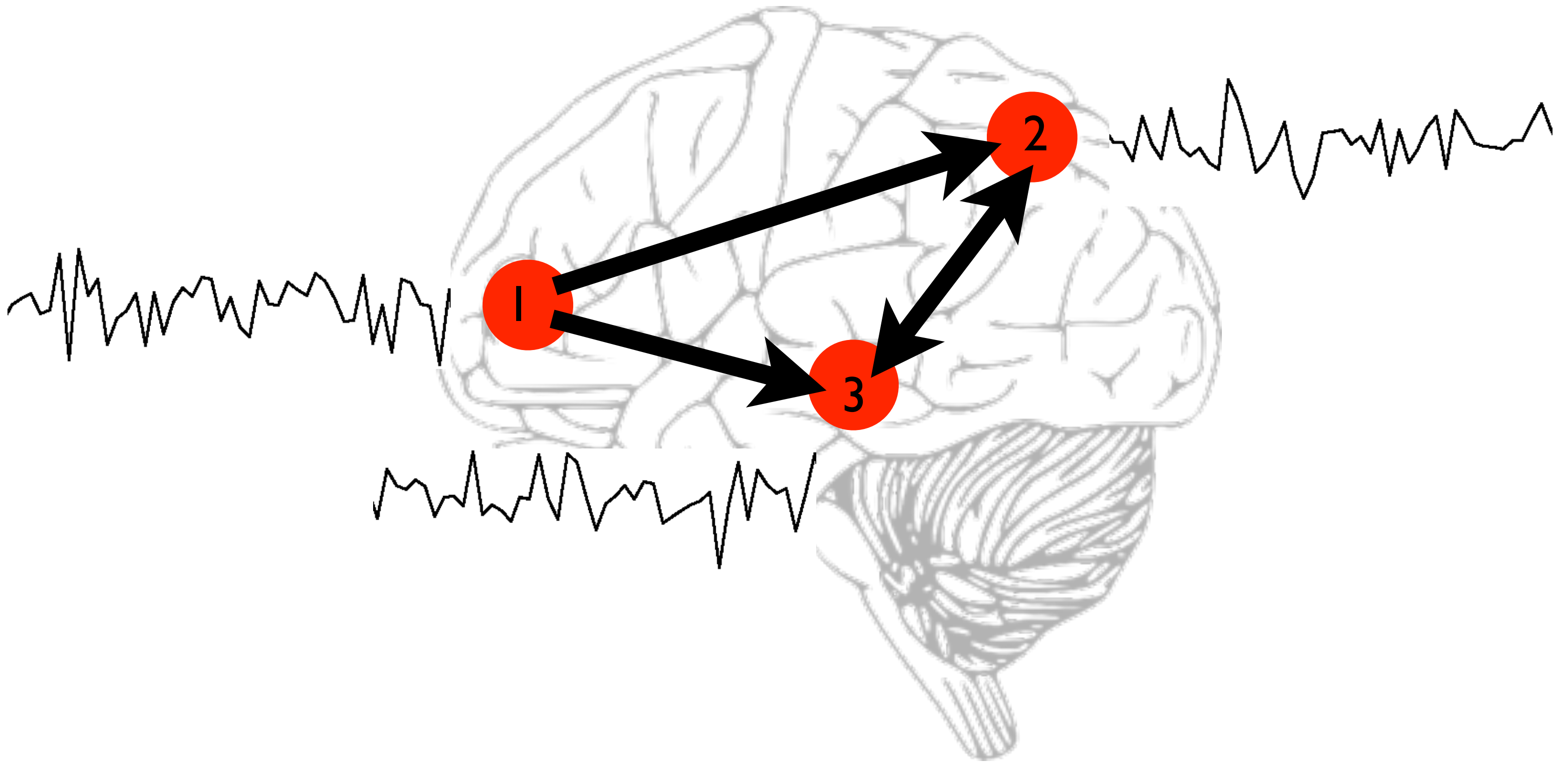
- Functional network analysis
  - Focus on functional connectivity in task and rest
- FMRI:
  - Task FMRI?
  - Direct vs indirect connections?
  - Missing Node problem?
  - Spurious FC changes?
- MEG
  - Zero lag correlations?
  - Signal leakage due to source reconstruction
- Time-varying FC
  - Spurious FC changes?

Functional Network Analysis

- The estimation of brain networks from task- and ***resting***-functional neuroimaging data (***FMRI***, M/EEG etc.)



How to do network analysis?



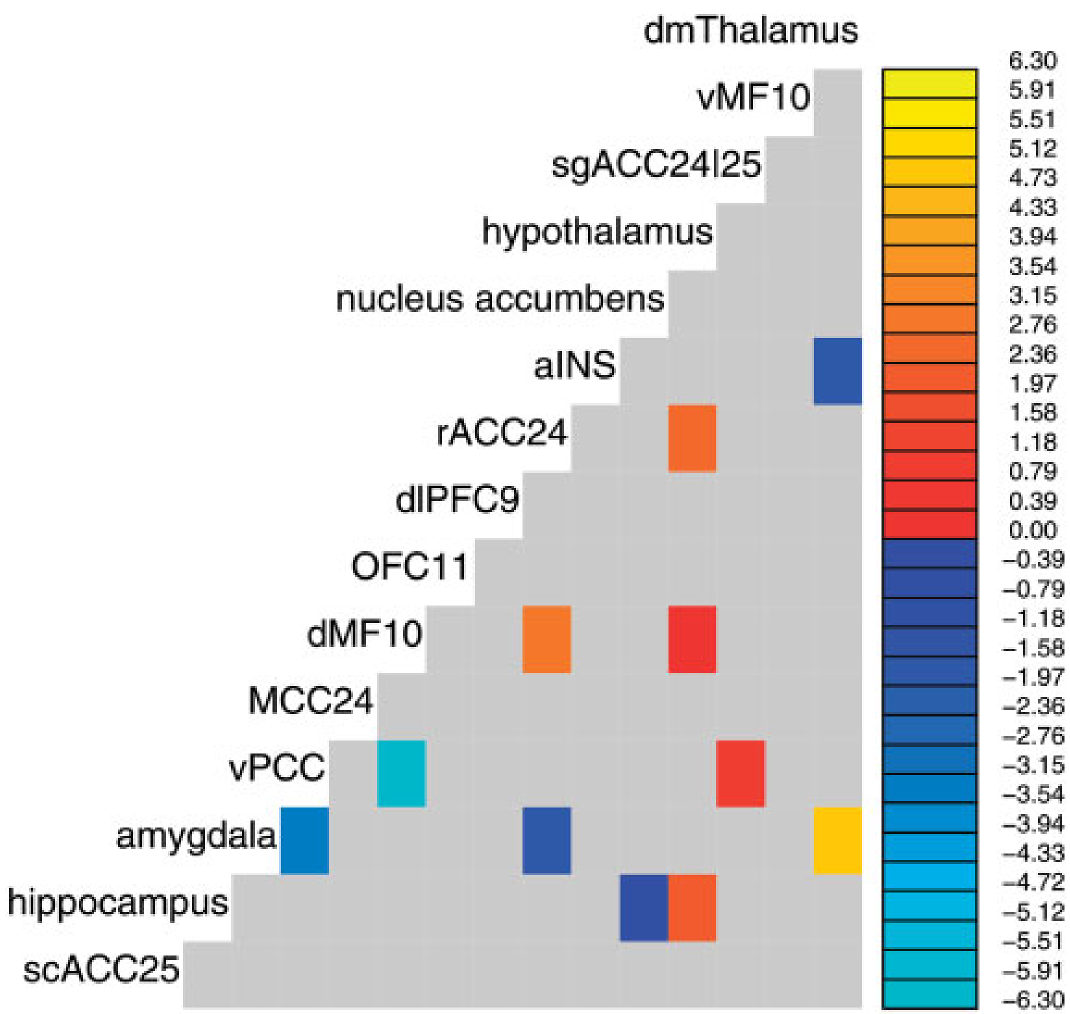
to

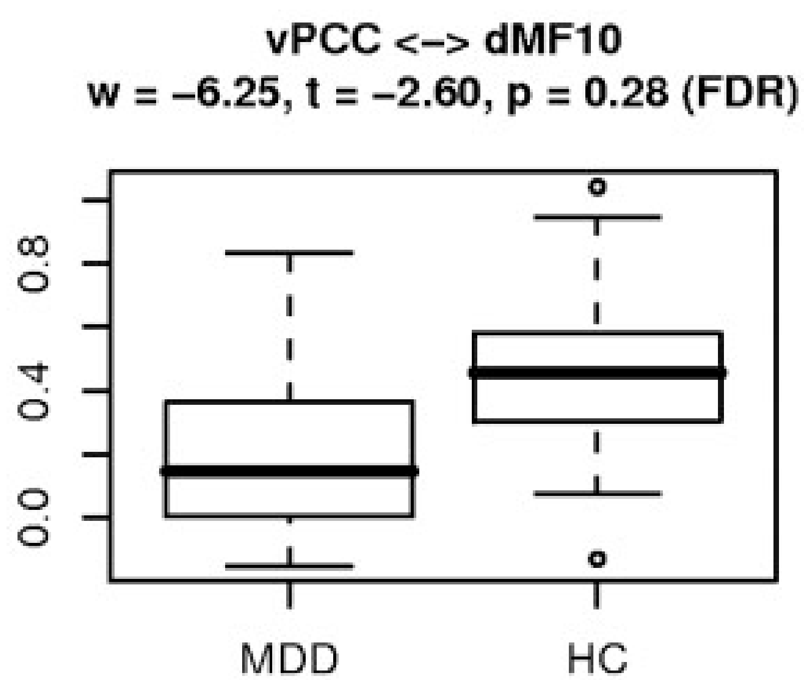
from	1	2	3
1	0	1	1
2	0	0	1
3	0	1	0

network matrix

- Define network “nodes” (spatial ROIs or coordinates)
- Identify a timeseries associated with each node
- Estimate the connections between the nodes (edges)
    - For example, correlate any pair of timeseries together

Applications of network analysis





- Edge strengths used as features
- Used to discriminate controls and subjects with a disease/disorder

Craddock et al., MRM (2009)

What are the main methods?

- Pairwise measures (***functional connectivity***): correlation, Mutual Information (MI), coherence

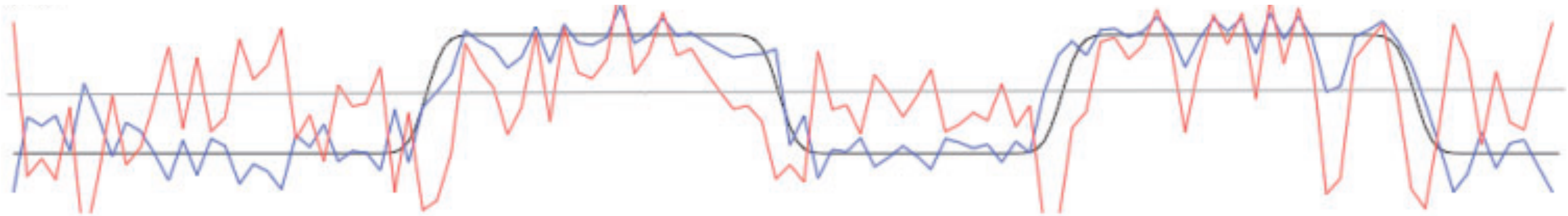
- Semi-global: partial correlation/regularised inverse covariance (ICOV)
    - Tries to distinguish direct from indirect connections

- Global model-based (***effective connectivity***):
    - Multivariate AR (Granger), Structural Causal Models (SEM, Bayes Nets e.g. GES [Ramsey, NI (2010)]), Dynamic Causal Models
        - In theory better at modelling "whole story"

Task Data

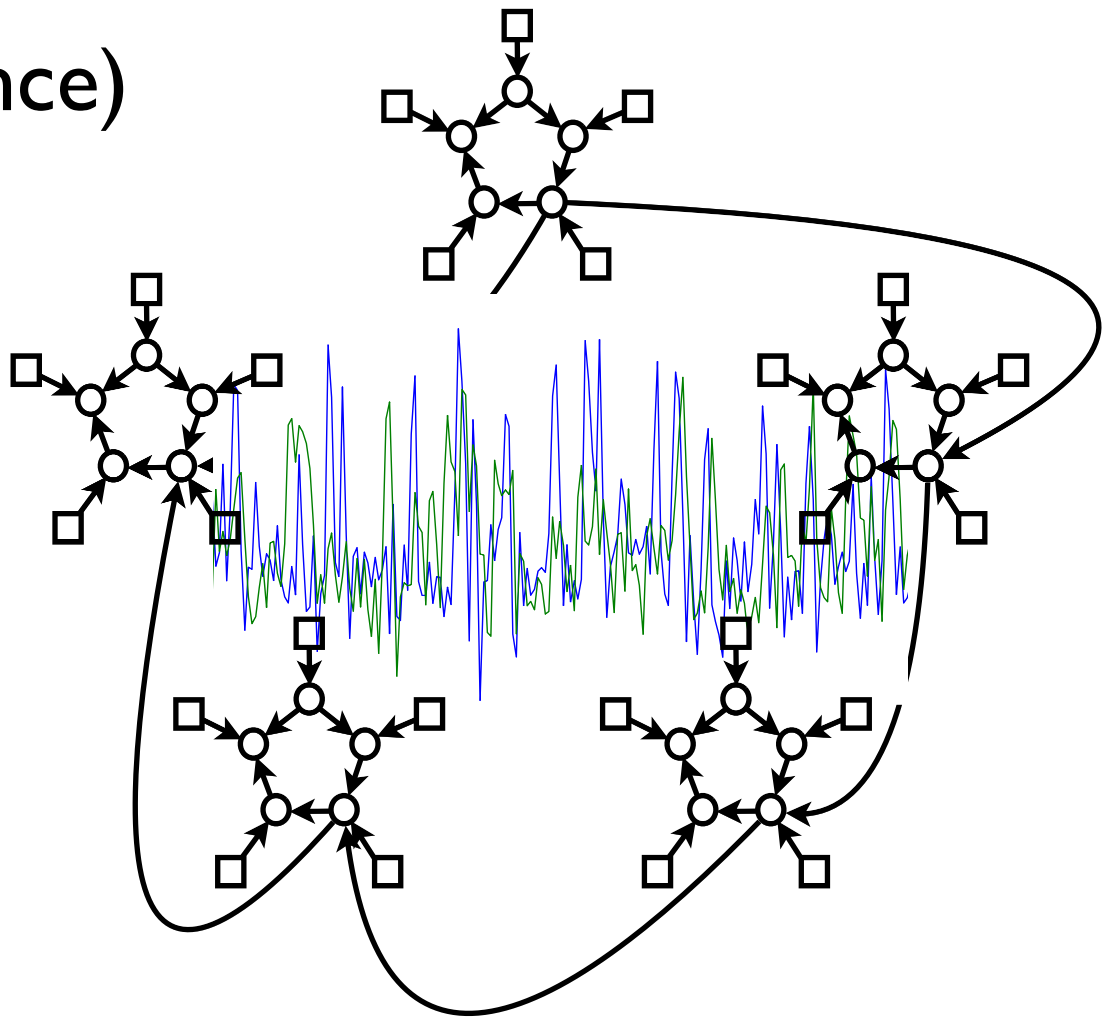
- In **resting** state data we can correlate across whole time series
- Problem: in **task** data, if two brain areas both respond to the task stimulus, then they will be correlated, even if there is no connectivity between them.
  - This can be thought of as a special case of the missing node problem, where the external stimulus input is the "missing node"
- Solution:
  - look at FC ***within*** task conditions only
  - or, if using correlation, use PPI analysis *(O'Reilly et al. Soc Cogn Affect Neurosci, 2012)*

PPI regressor (**red** line) is as an element-wise product of the HRF convolved task regressor (**black** line) and the seed ROI regressor (**blue** line).



What are the common pitfalls of FMRI network analysis?

- Ground-truth networks used to ***simulate*** BOLD timeseries
- Compare network modelling methods for estimating:
  - **direct** connections (edge presence)

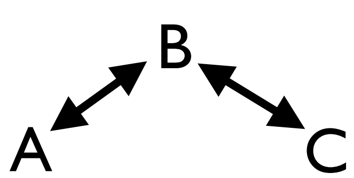


Smith et al. NeuroImage 2011

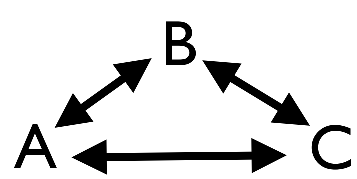
Indirect Connections

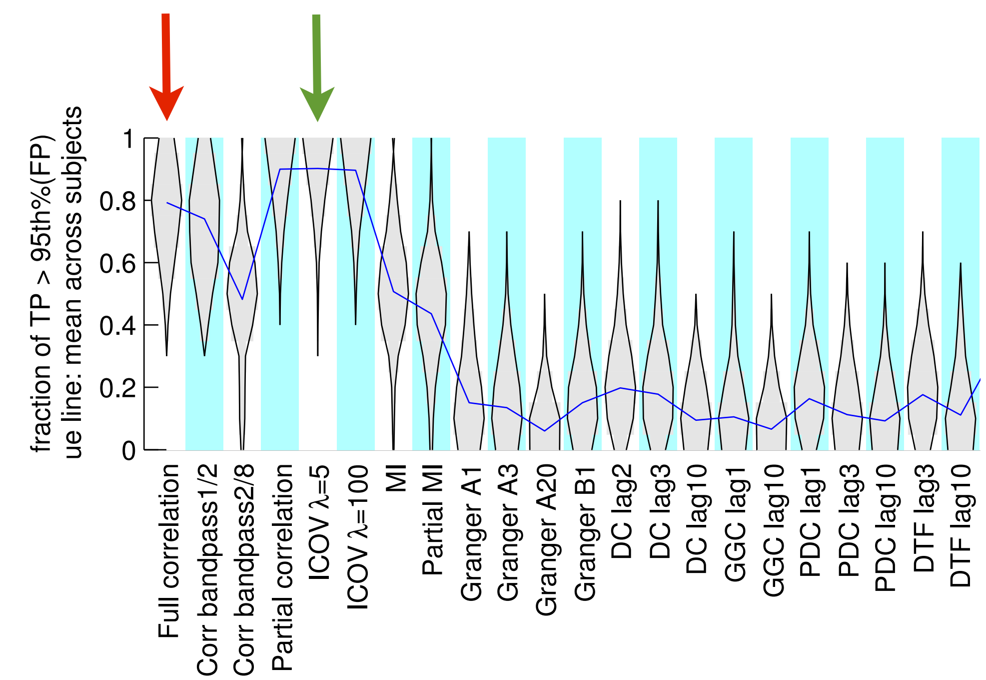
- Problem: raw correlations include indirect connections!

true network:



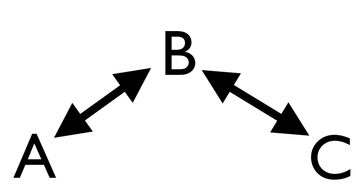
raw correlation inferred network





- Solution: look at partial correlation, e.g. regularised inverse covariance (ICOV) (or use an effective connectivity approach, e.g. DCM).

partial correlation inferred network

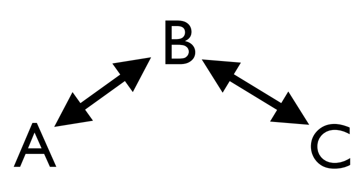


Smith et al. NeuroImage 2011

Missing Node Problem

- Problem: missing nodes means that partial correlation approaches will erroneously infer a direct connection, e.g.:

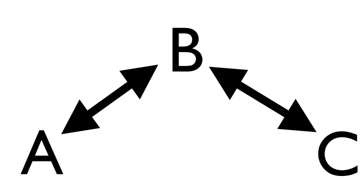
true network:



partial correlation network, inferred when
B is a missing node:

- Solution: Include **all** nodes

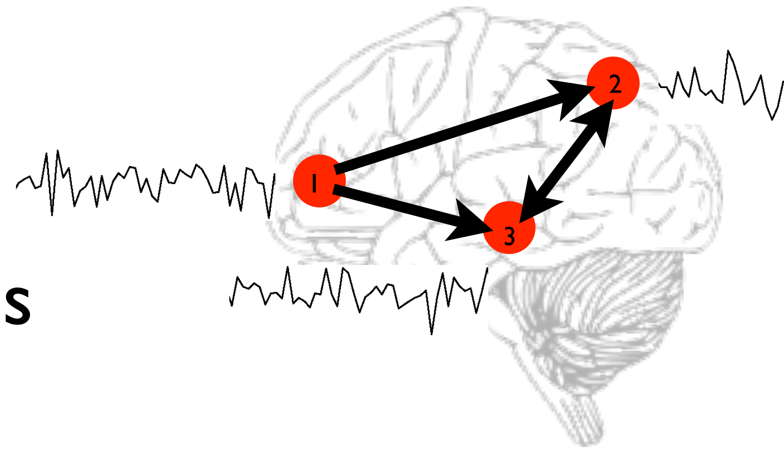
partial correlation network, inferred when
B is included:



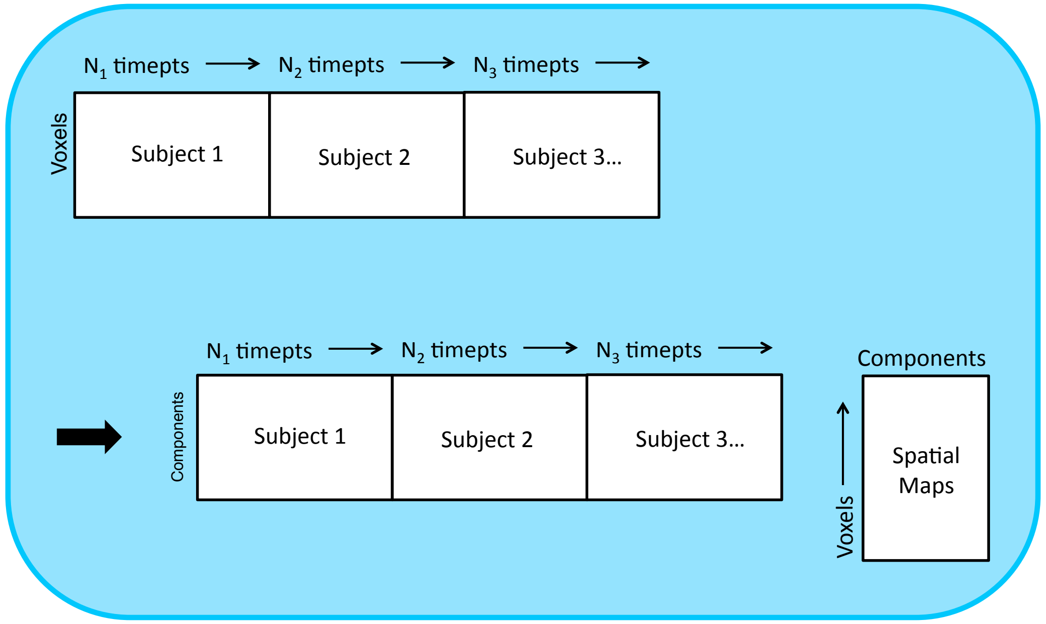
  - This is a ubiquitous issue, including for effective connectivity approaches such as DCM

ROI/Parcellation selection

- Problem: atlas-based parcellation causes erroneous connectivity inference
  - due to mixing of overlapping true ROI timeseries



- Solution: use data driven parcellations, e.g.:
  - Clustering of voxels with similar timecourses *Craddock, HBM (2011)*
  - Gradients in seed-based correlation maps *Cohen, NeuroImage (2009)*
  - Spatial ICA



Beckmann, Phil. Trans. R. Soc. (2005)

Smith et al. NeuroImage 2011

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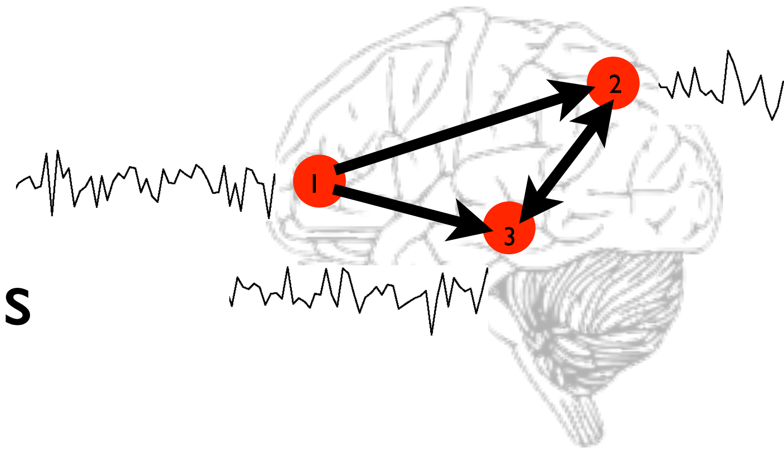

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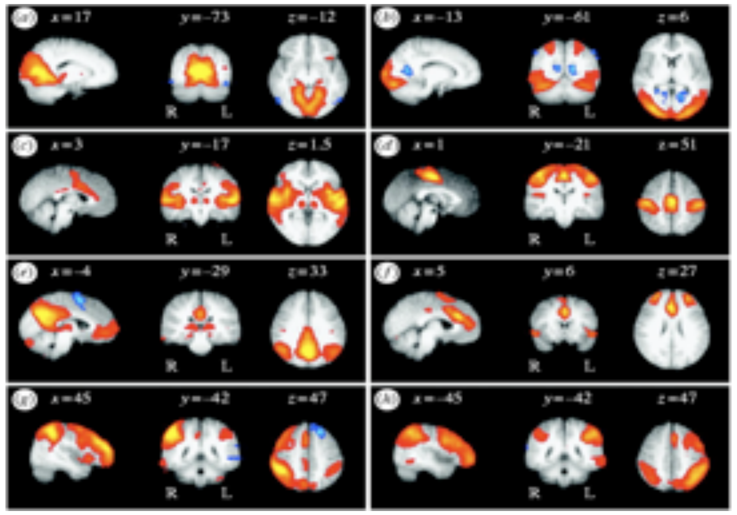
  - Gradients in seed-based correlation maps *Cohen, NeuroImage (2009)*
  - Spatial ICA (low-dimensional: ~25 comps)



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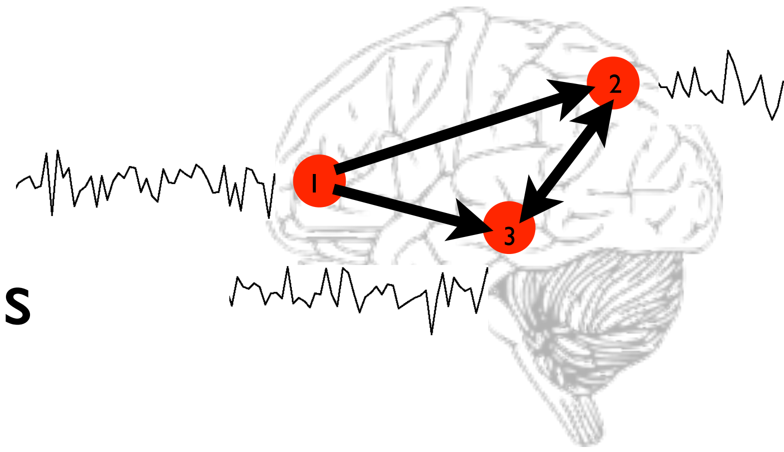
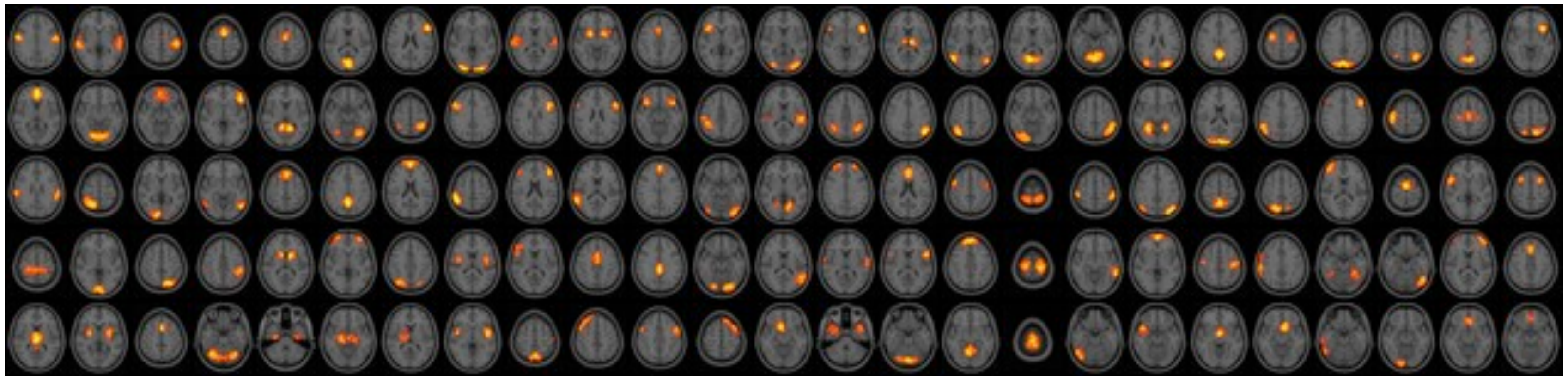


- Solution: use data driven parcellations, e.g.:
  - Clustering of voxels with similar timecourses *Craddock, HBM (2011)*
  - Gradients in seed-based correlation maps *Cohen, NeuroImage (2009)*
  - Spatial ICA (high-dimensional: ~125 comps)



Beckmann, Phil. Trans. R. Soc. (2005)

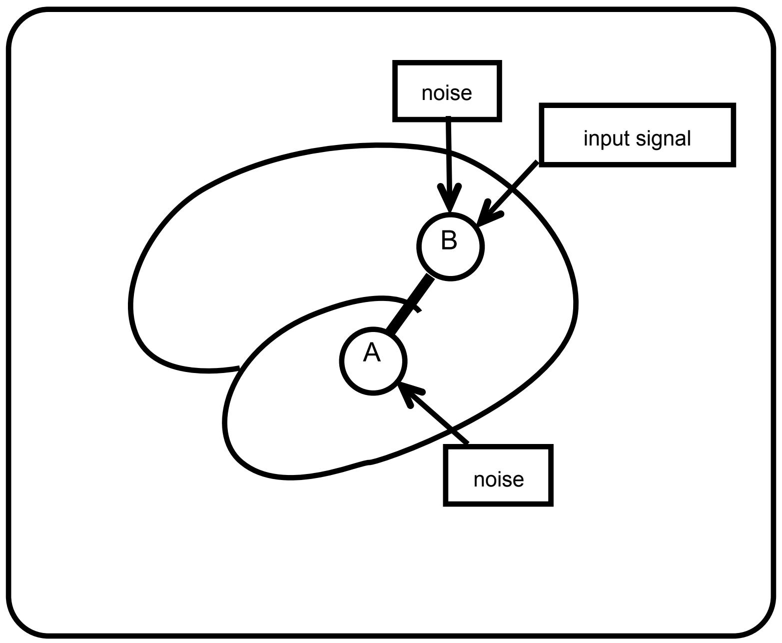
- Use these as a spatial basis set to get subject ROIs (c.f. dual regression)

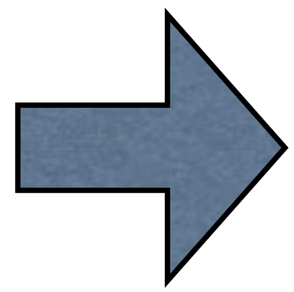
Filippini, PNAS (2009)

Smith et al. NeuroImage 2011

Changes in Functional Connectivity

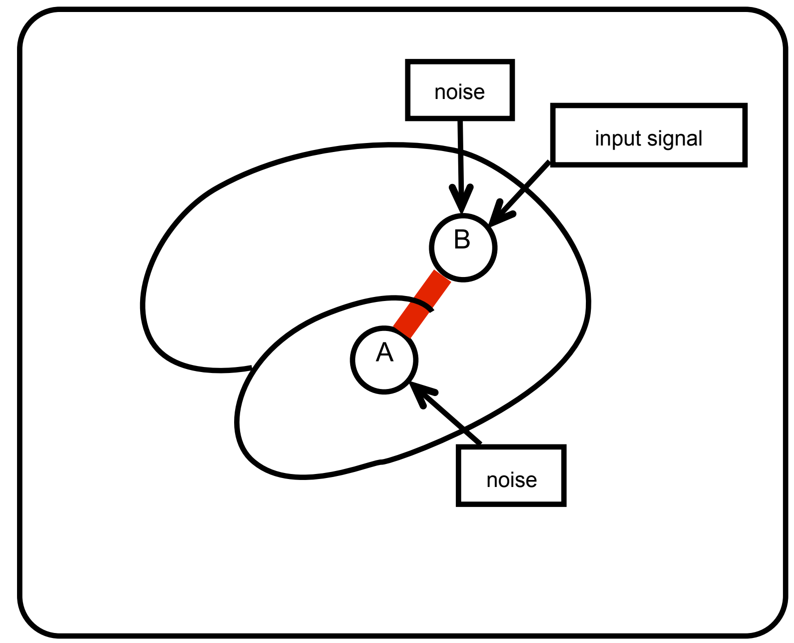
Controls





Change in
corr(A,B)

Patients

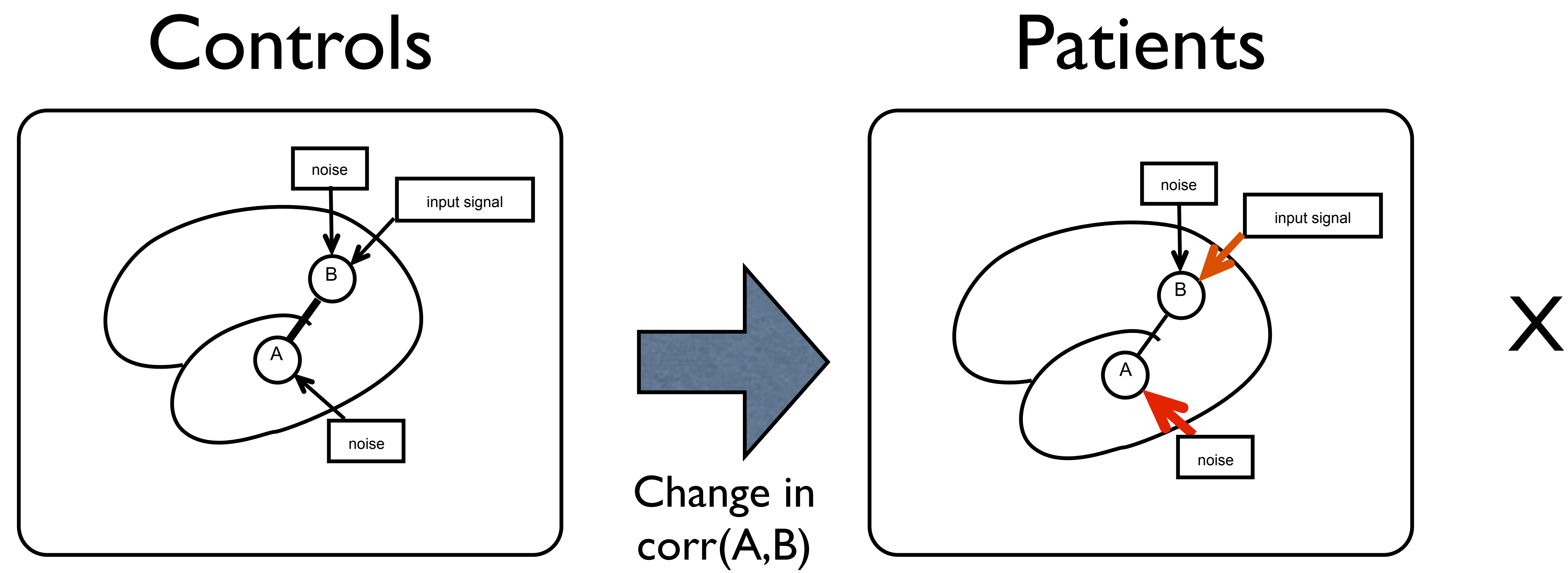


OK

- Changes in an edge correlation between two groups/conditions could be interpreted as a change in connectivity in that edge

Friston et al., Brain Connectivity (2011)

SNR Changes



- Problem: change in SNR can cause ***artefactual*** correlation change
  - SNR could change due to changes observation noise amplitude or change in endogenous activity (input signal).
- Solution:

1) Use Monte-Carlo simulations to get null (i.e. no connectivity change) distribution

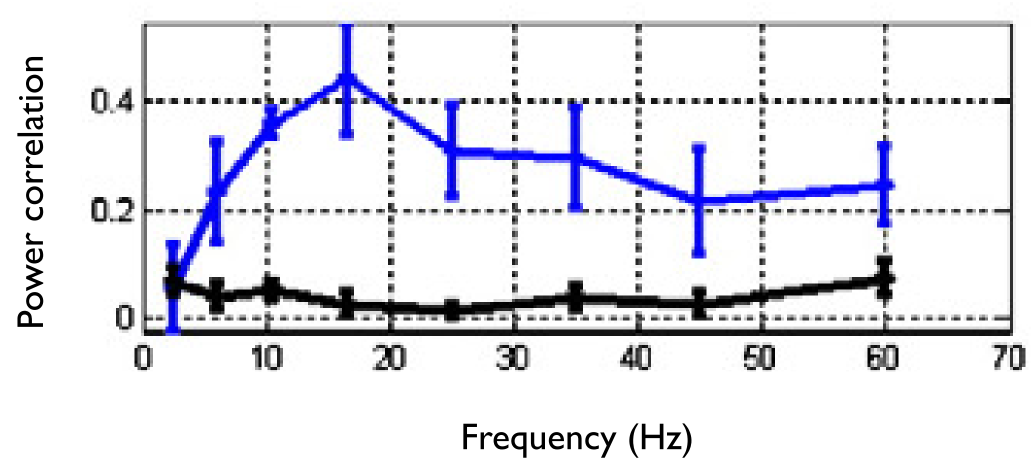
2) Use effective connectivity/generative model approaches

Friston et al., Brain Connectivity (2011)

What about using MEG?

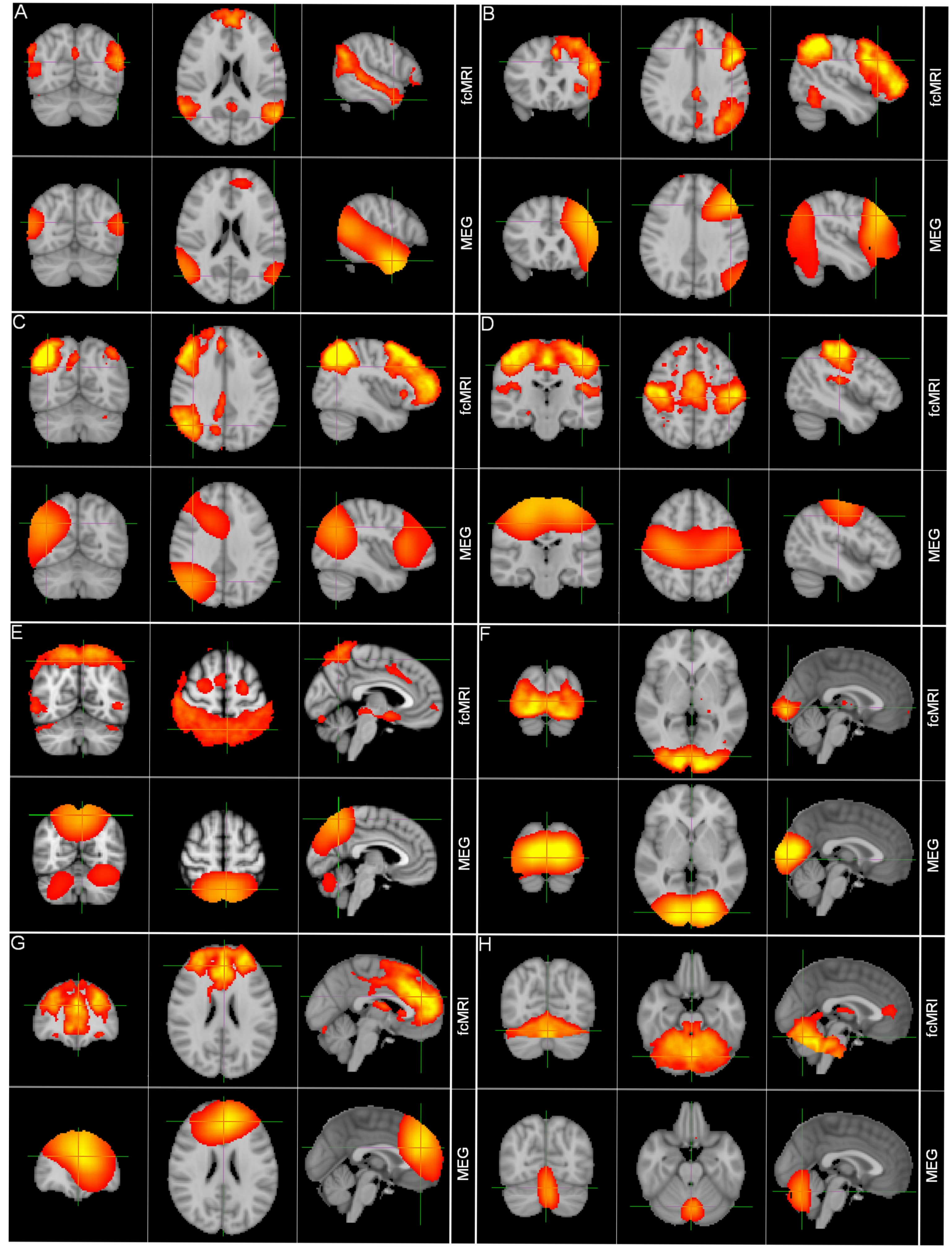
- High temporal resolution (~1000Hz) allows for richer exploration of dynamic neuronal interactions
- Problem: zero lag correlation no good
- Solution: use other FC measures: e.g. band-limited power (BLP) correlations

Resting state MEG data: BLP power correlations between left and right Motor Cortex



Brookes et al., Neuroimage (2011)

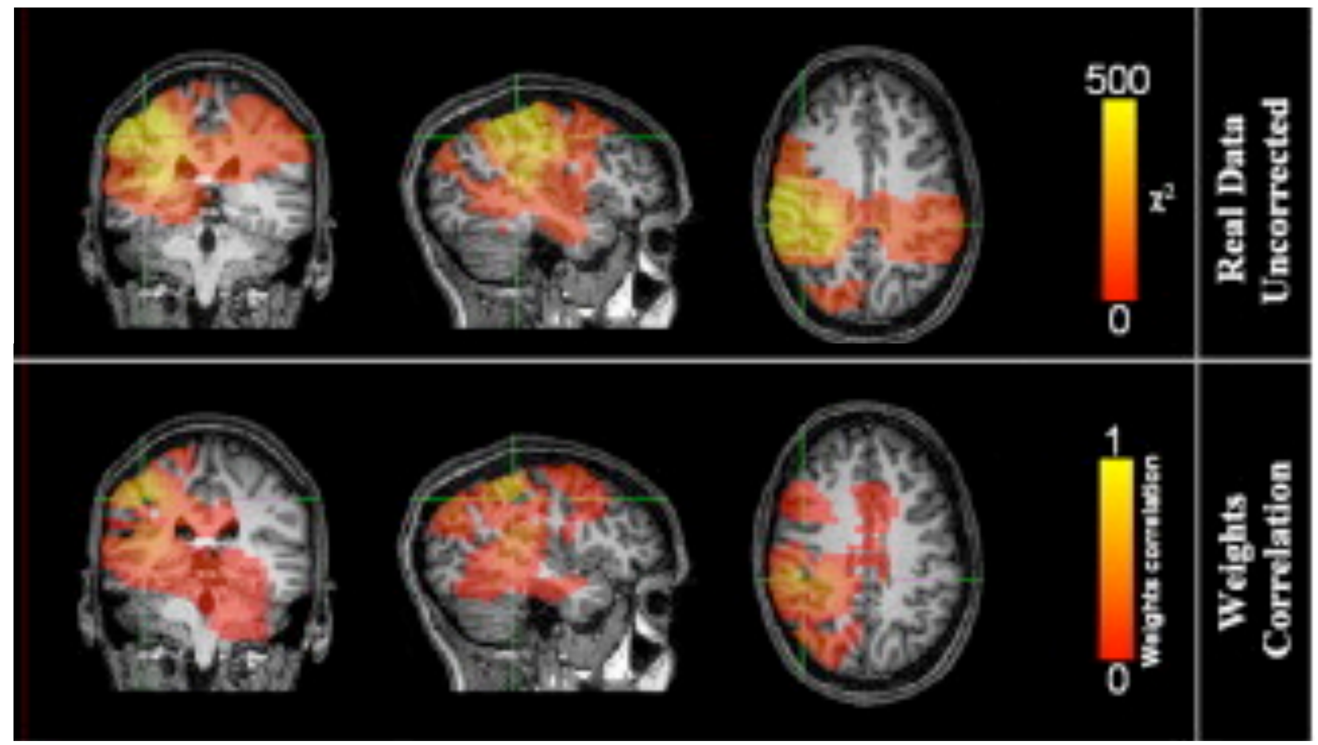
- RSNs found in MEG data (mainly beta band)
- Eyes open, 10 subjects
- ICA run on BLP timecourses
- Excellent correspondence with fMRI ICA Resting state Networks



Brookes et al., PNAS, 2011
Luckoo et al. NI 2012

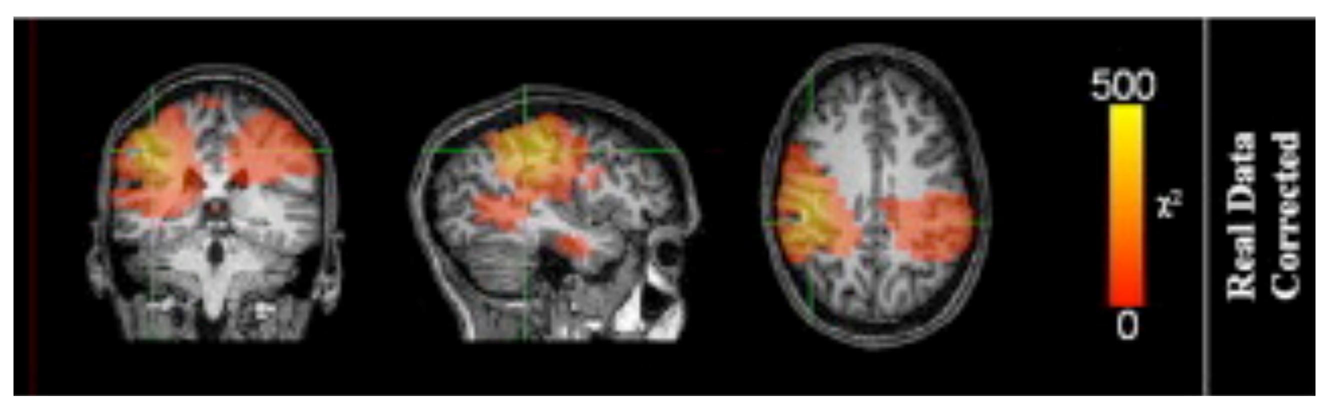
Signal Leakage

- Problem: source reconstruction (e.g. beamforming, minimum norm) introduces spurious seed-based correlations



* *weights* are the linear weightings applied to the sensors to map from sensor to brain space

- Solution: regress out zero lag correlations, and then compute BLP correlations



Brookes, Woolrich, Barnes. NI (2012)
Hipp et al. Nat Neuro (2012)

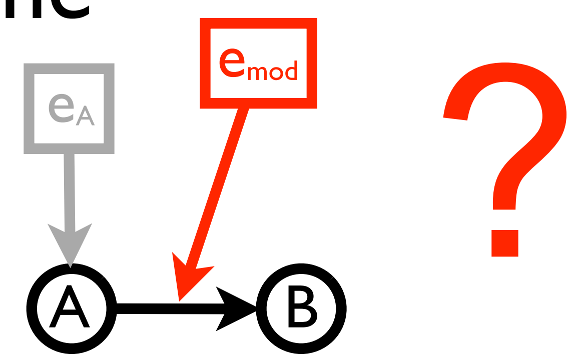
Functional Connectivity (correlation) is a *time-averaged* network measure

- Correlation-based resting-state network analysis assumes *stationarity* (correlations not changing over time)
- The correlation between two regions' timecourses is an *average* over the whole experiment duration
- However, if the "true underlying" connectivity is changing over time (e.g., has several distinct states), the time-averaged correlation is an oversimplification of the network structure *[Chang NeuroImage 2010]*

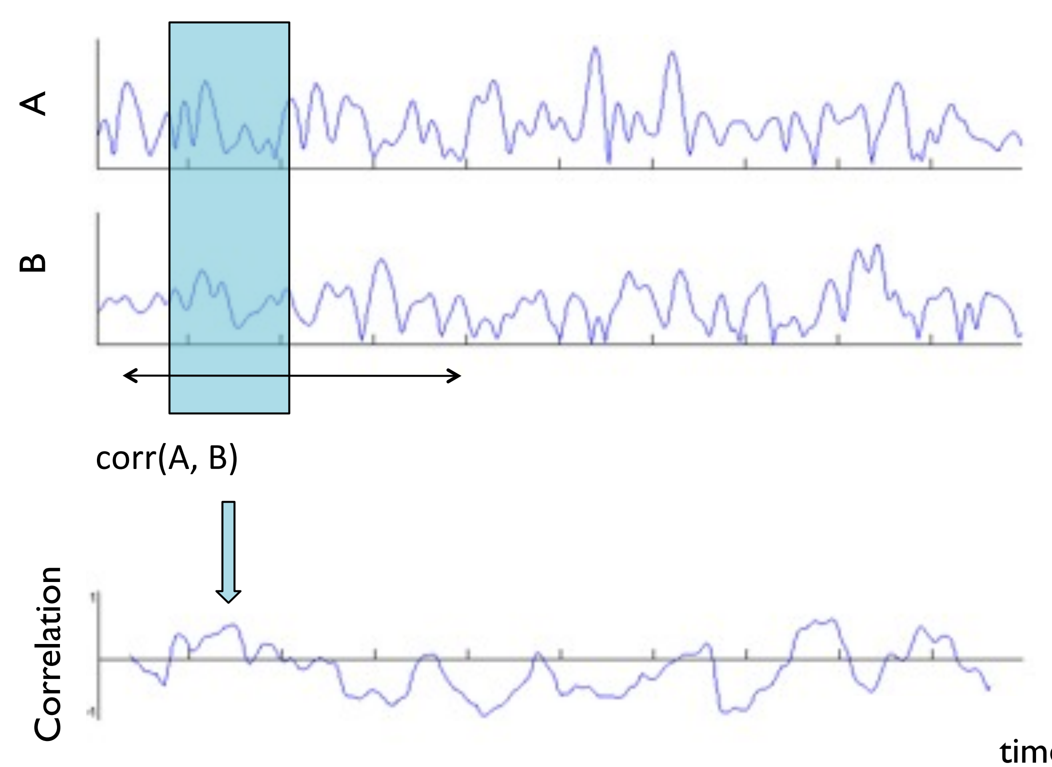
Temporal Nonstationarity

- Various things of interest might be *nonstationary*

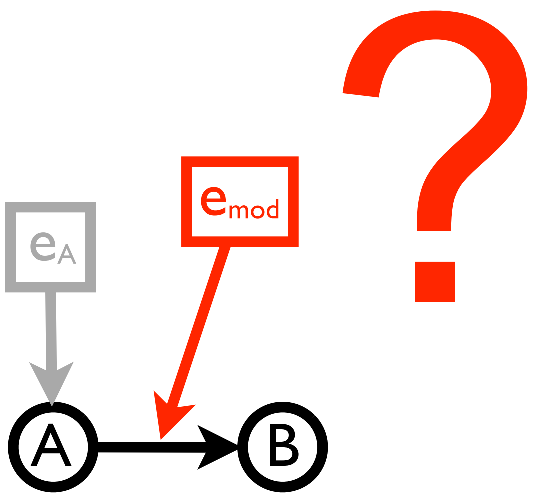
- Here we focus on the ***neuronal connectivity***, e.g. between A and B, changing over time

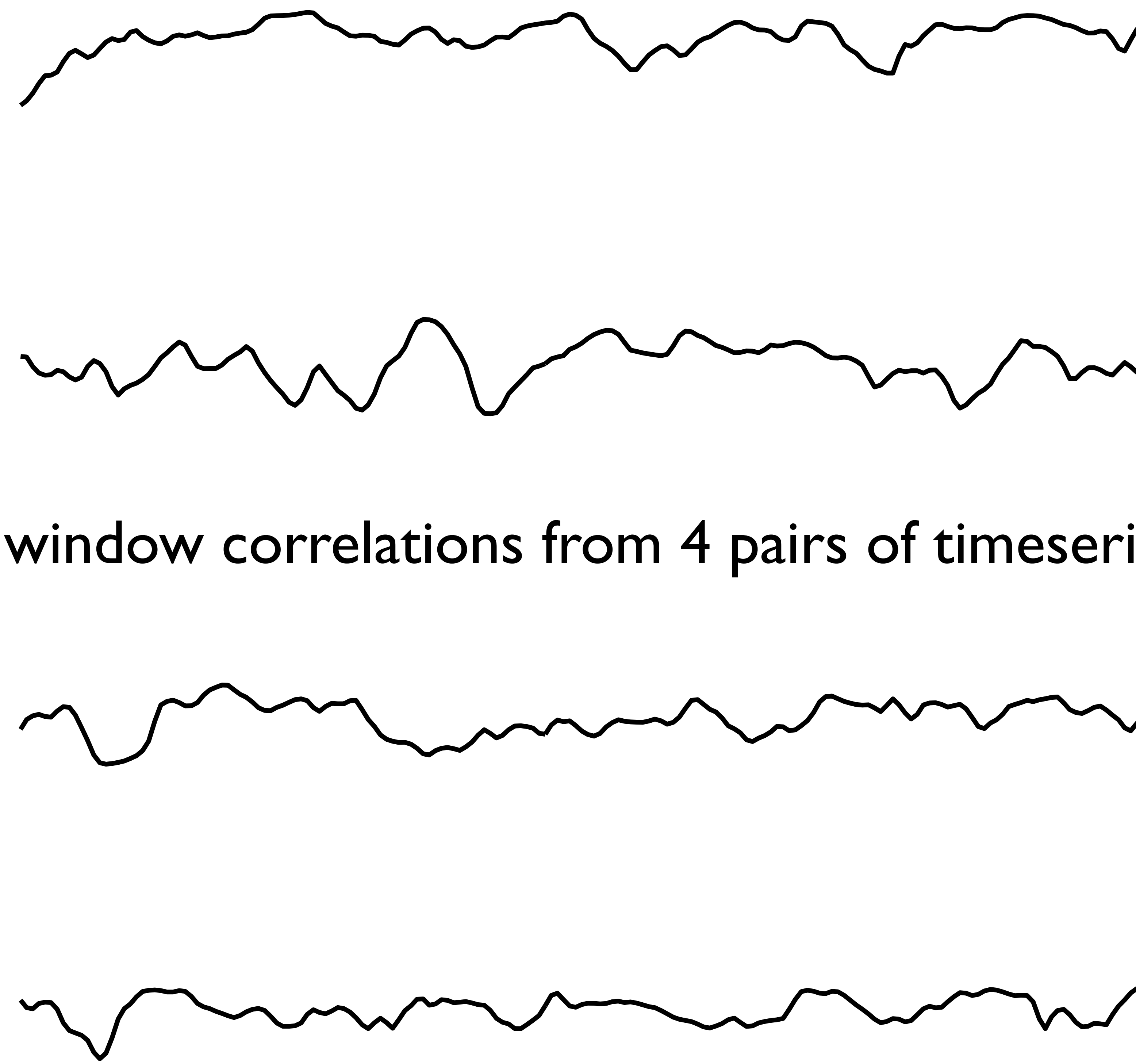


- Can we detect this using ***sliding window correlation*** approaches?
  [Chang NeuroImage 2010]



Sliding-window “nonstationarity” ?

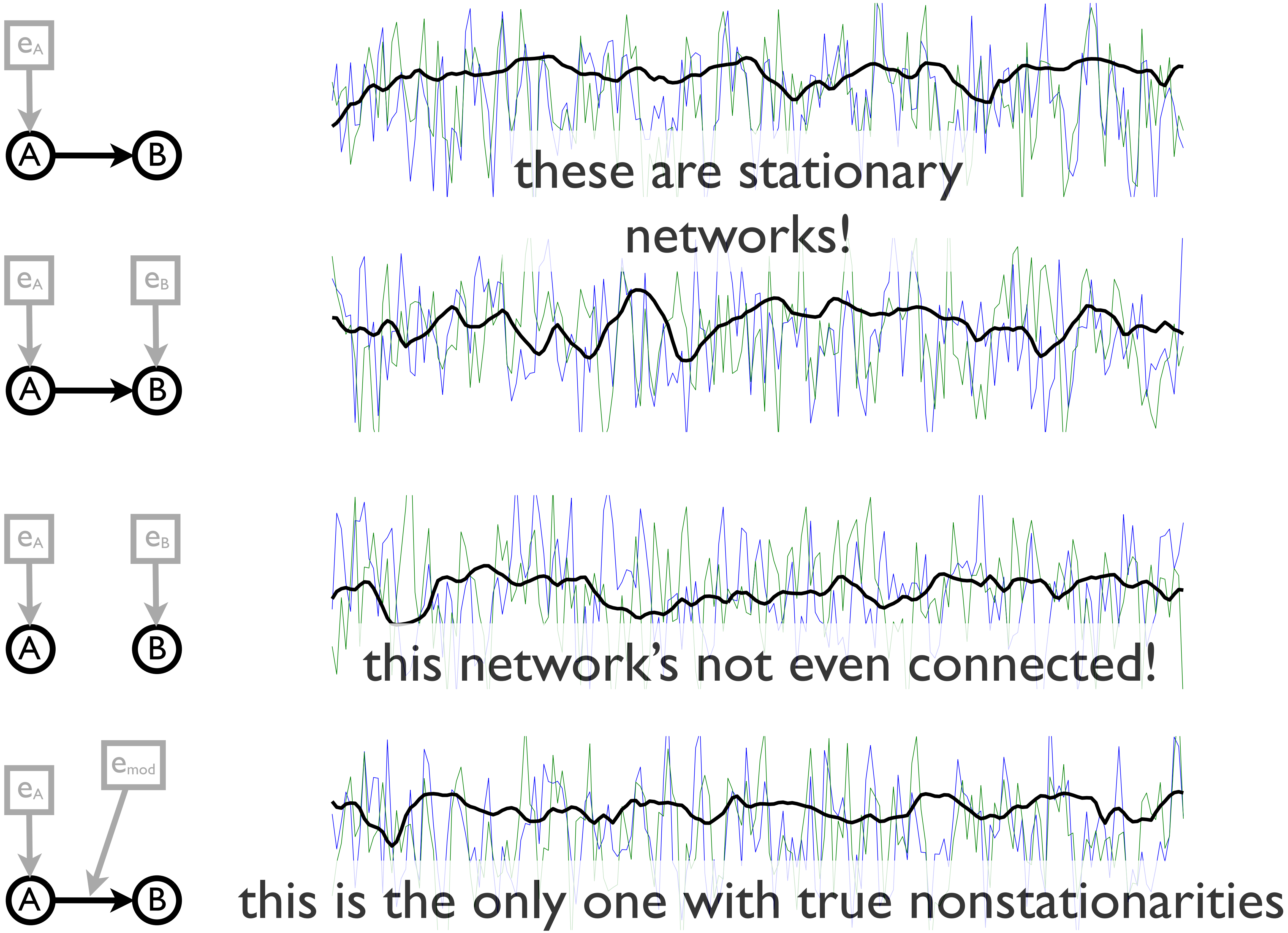




sliding window correlations from 4 pairs of timeseries

the y-axis is the same in all plots!

Sliding-window “nonstationarity” ?



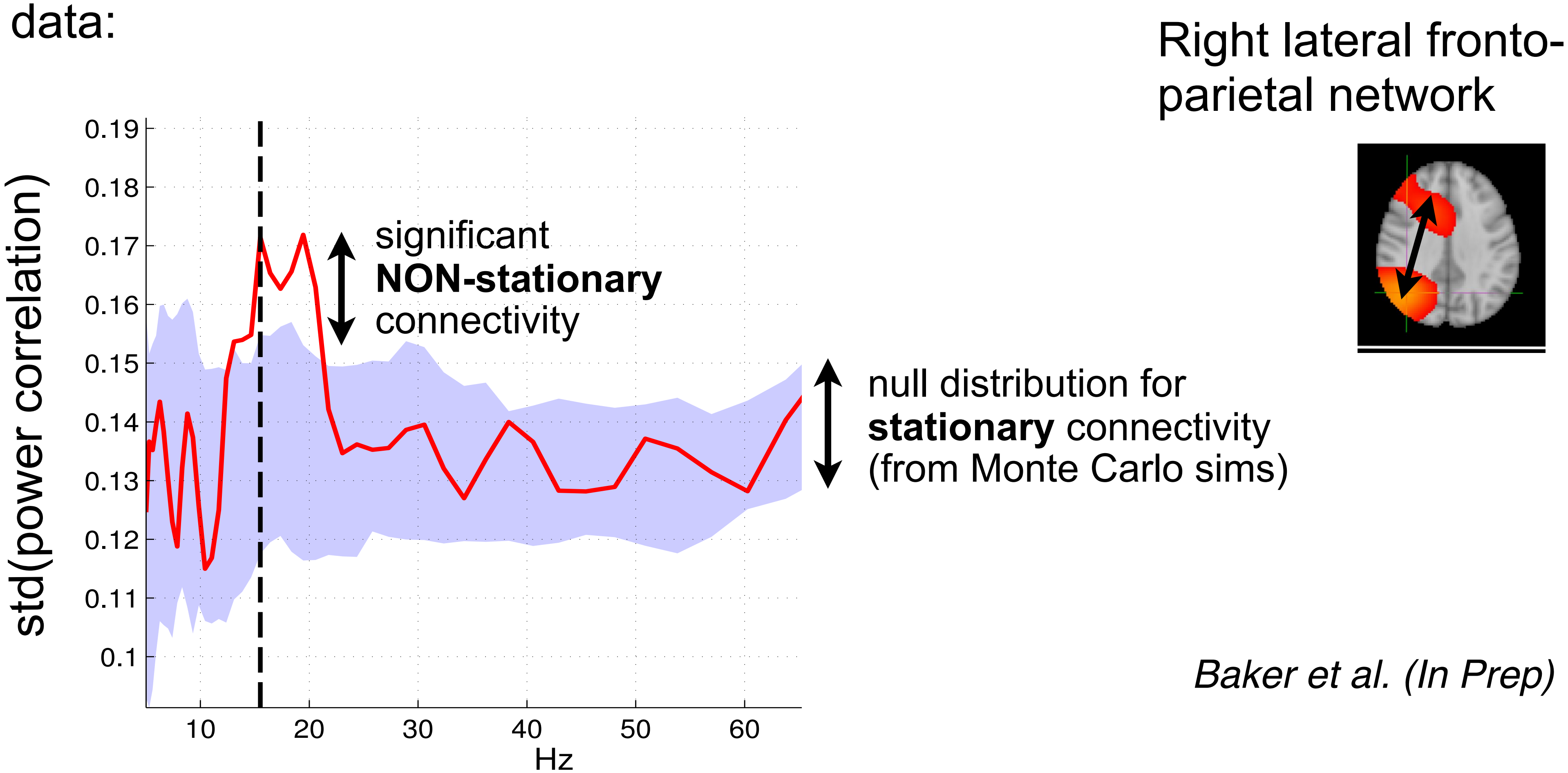
Sliding-window "nonstationarity" ?

- Problem: there will be apparent nonstationarity in connectivity when using techniques like sliding window correlations, even in a stationary network

- Solution:

  1) Use Monte-Carlo simulations to get null (no non-stationarity) distribution

Resting state MEG data:



Baker et al. (In Prep)

  2) Use effective connectivity/generative model approaches

Conclusions

- FMRI:
  - Task FMRI? - Model out common task stimuli
  - Direct vs indirect connections? - Use partial correlation to get direct conns
  - Missing Node problem? - Include all relevant nodes
  - Spurious FC changes? - Use Monte Carlo sims to get null (or use DCM)
- MEG
  - Zero lag correlations? - Use Band-Limited Power correlations
  - Signal leakage due to source reconstruction - Regress out zero lag corrs
- Time-varying FC
  - Spurious FC changes? - Use Monte Carlo sims to get null (or use DCM)

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