



Functional connectivity: can we find a common ground?

Natalia Bielczyk
Warsaw, November 18th 2017

Who am I?

causal inference and signal detection in neuroimaging (especially fMRI)

a talk at the Aspects of Neuroscience Conference, Saturday 25th November

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The screenshot shows the homepage of the Donders Institute. At the top, there are logos for Radboud University and Radboud UMC. The Donders Institute logo, featuring a stylized red 'd' icon, is prominently displayed. Below the logo, the text "Donders Institute for Brain, Cognition and Behaviour" is written. A search bar with a magnifying glass icon is located at the top right. To the right of the search bar, there are links for "Students • Staff • Alumni". A navigation menu below the header includes links for HOME, ABOUT, NEWS, AGENDA, RESEARCH, GRADUATE SCHOOL, SOCIETAL IMPACT, JOBS, PROEFPERSONEN, and DONDERS 200. The main content area features a large red silhouette of a human head profile on the left. Inside the head, various red icons represent different fields of study and research, such as a graduation cap, books, a DNA helix, and a brain scan. The text "About the Donders Institute" and "More >" is positioned next to the head silhouette. On the right side of the main content area, there is a sidebar with the heading "Directly to:" followed by a list of links:

- › Master's and PhD programme
- › Donders Tool-kit courses
- › For societal and business partners
- › For schools: hulp bij je profielwerkstuk
- › How to contact us

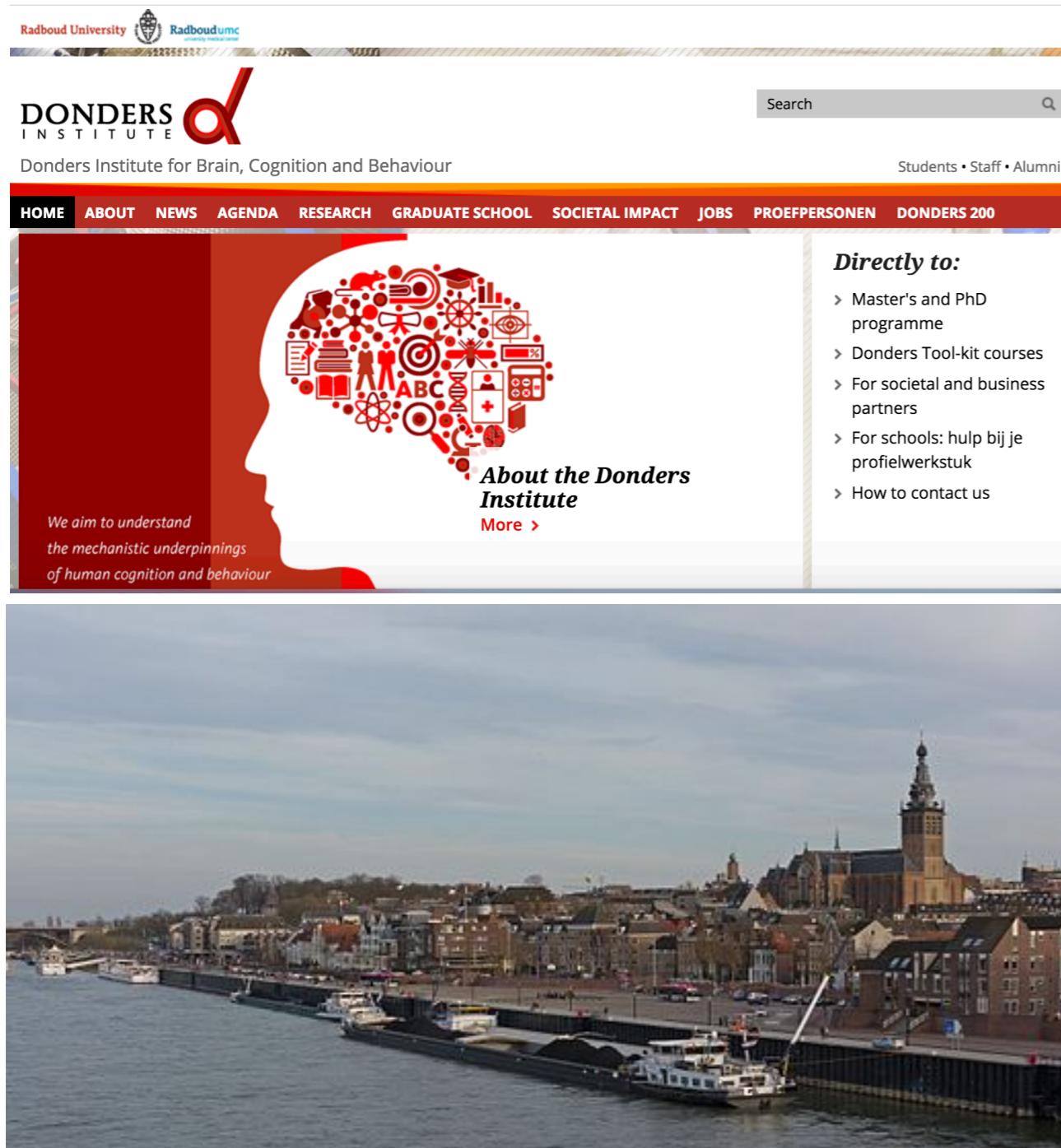


Nijmegen, the Netherlands

Who am I?

causal inference and signal detection in neuroimaging (especially fMRI)

a talk at the Aspects of Neuroscience Conference, Saturday 25th November



Nijmegen, the Netherlands



Must-knows before we start



Acknowledgments

The team who prepared the pipeline

Making-off



Natalia Bielczyk
Donders Institute
Nijmegen, the Netherlands



Małgorzata Wierzba
Nencki Institute of Experimental Biology
Warsaw, Poland



Florencia Garro
OTTA project
Cordoba, Argentina

Testing



Daniel Borek
Ghent University
Ghent, Belgium



Tools available during the project

- the project leader / your partner / our slack channel
- codes / datasets at the GitHub repository: **https://github.com/cryptofan/FunctionalConnectivity_AoNBrainhackWarsaw**
- an Overleaf project with the detailed description of methods and datasets: **<https://www.overleaf.com/11096911dptdwdbwrzdd>**

Plan of the presentation

- [0] what is functional connectivity?
 - [1] correlation vs causation
 - [2] Pearson's correlation vs partial correlation
 - [3] information-theoretical measures of functional connectivity
 - [4] time domain vs frequency domain
 - [5] static vs dynamic functional connectivity
 - [6] hierarchical models of functional connectivity
-
- [7]* higher order associations in the networks (multiple body interactions, graph theory)

Plan of the presentation

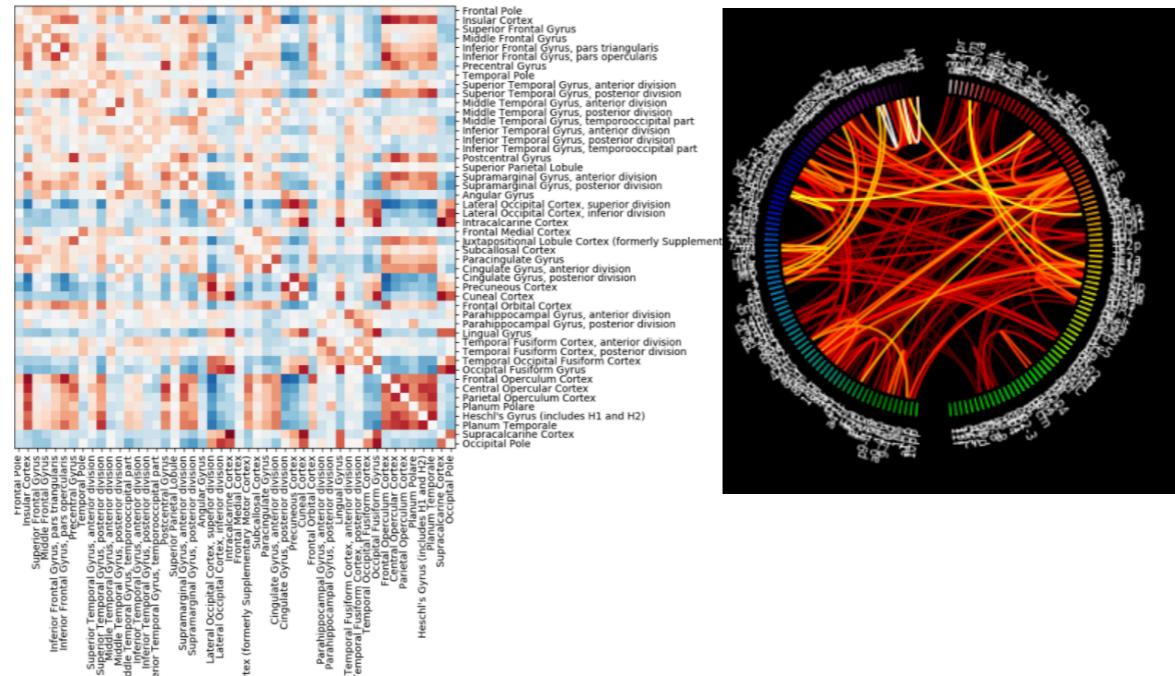
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- [7]* higher order associations in the networks (multiple body interactions, graph theory)

for most of these points, we will be using in-house written codes
rather than Python packages

Special functions at this project

[0] who is good in data visualization?

...and could implement some alternative visualizations of functional connectomes?



[1] who is good at scientific writing?

...and could write one-two paragraphs (with references) in the Overleaf project about:

- [a] Pearson's correlation (subsection 2.2.1)
 - [b] partial correlation (subsection 2.2.2)
 - [c] mutual information (subsection 2.2.3)
 - [d] coherence (subsection 2.3.1)
 - [e] dynamic functional connectivity (subsection 2.4.1)
 - [f] hierarchical models of functional connectivity (subsection 2.4.2)

[2] who is good at multitasking?

...and could be the slack communication liaison?



Datasets we will be working on in this project

- [1] Human Connectome Project fMRI datasets
- [2] MyConnectome Project multimodal datasets
- [3] open datasets on weather / stock exchange / social networks

...the list to be updated

You can add your own datasets!!
(please do so both on GitHub and in the Overleaf project)



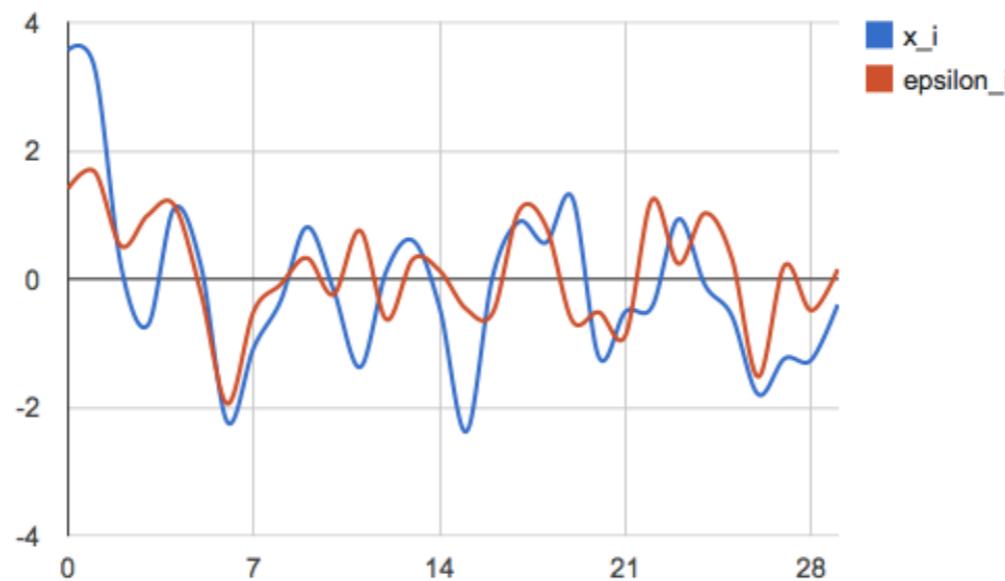
The background of the slide is a photograph of a long, straight asphalt road with yellow double lines. The road stretches from the foreground into the distance, where it meets a horizon line. The sky above is a vibrant blue, dotted with various sizes of white, fluffy clouds. In the far distance, there are low, rolling hills or mountains. The overall scene conveys a sense of journey, freedom, and possibility.

Let's get started!



But what is the functional connectivity, on the conceptual level?

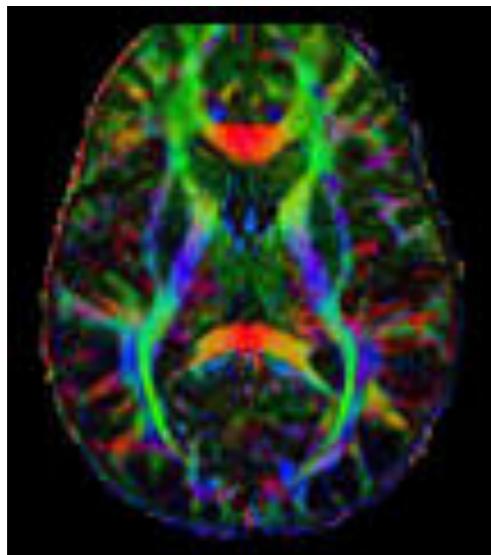
- functional connectivity = *association* between two variables
- assumption: if two variables correlate, they are a part of the same process



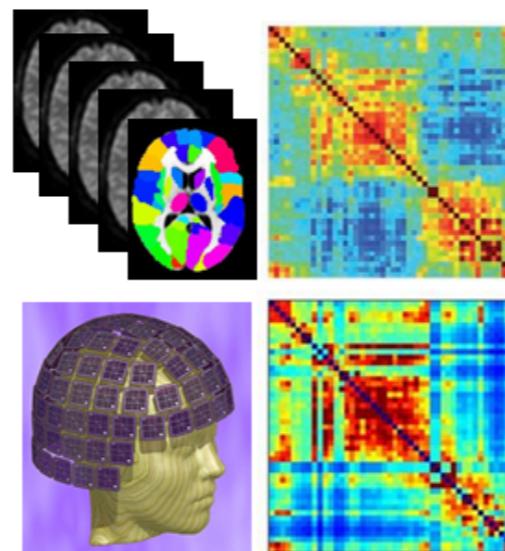
- there is no *official* definition of functional connectivity



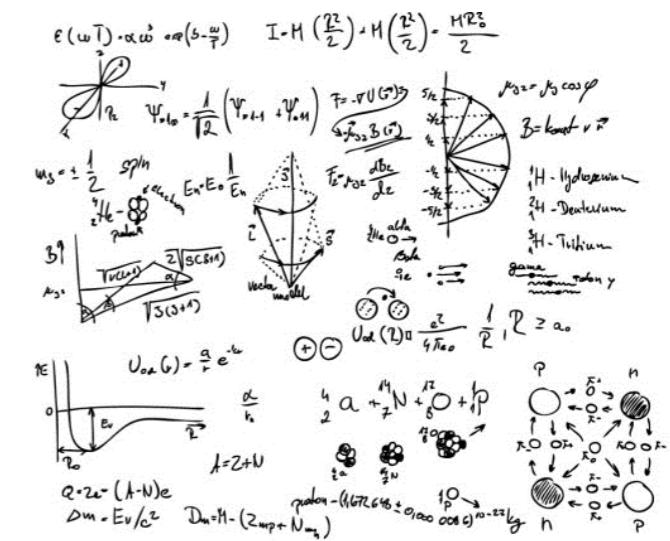
The concept of functional connectivity comes from brain research



anatomical connectivity



functional connectivity

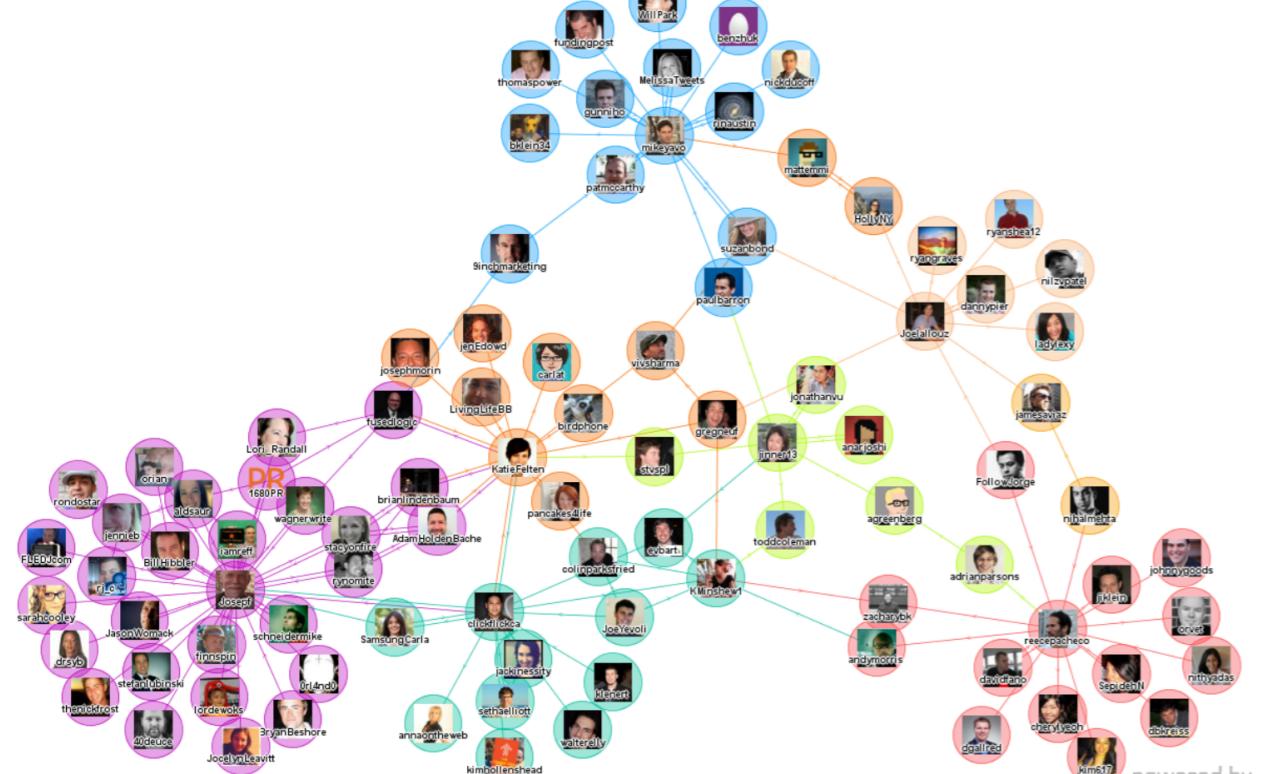


effective connectivity

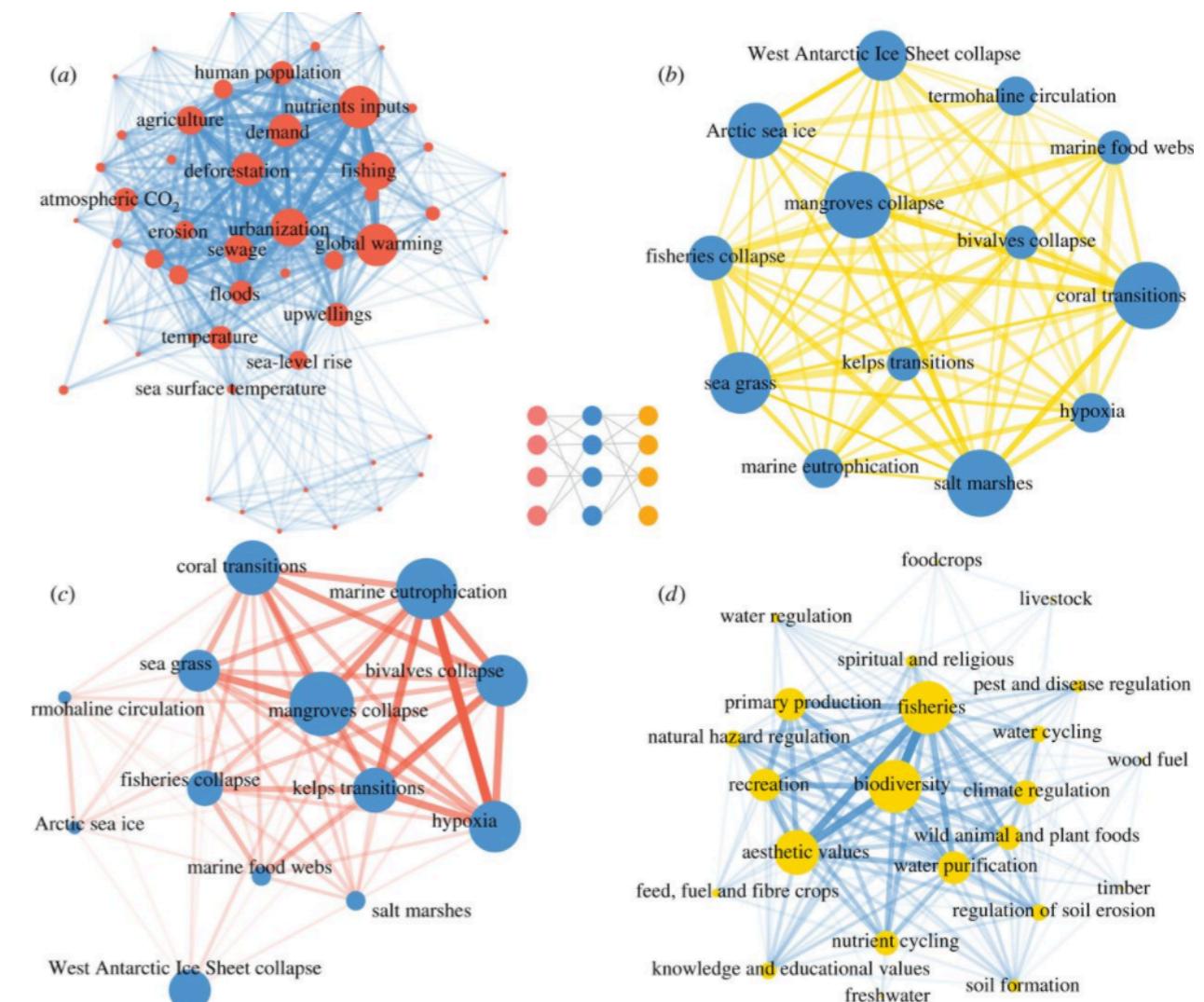


In what other areas of natural sciences can we define functional connectivity?

- in any area where we have networks of interacting nodes



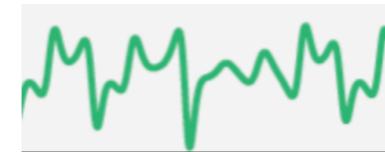
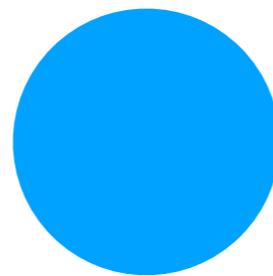
social networks



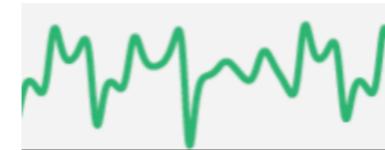
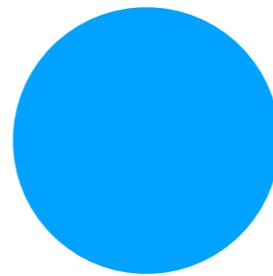
marine ecosystems
Rocha et al. (2014) Marine regime shifts: drivers and impacts
on ecosystems services. *Philosophical Transactions of the Royal Society B*



Correlation vs causation

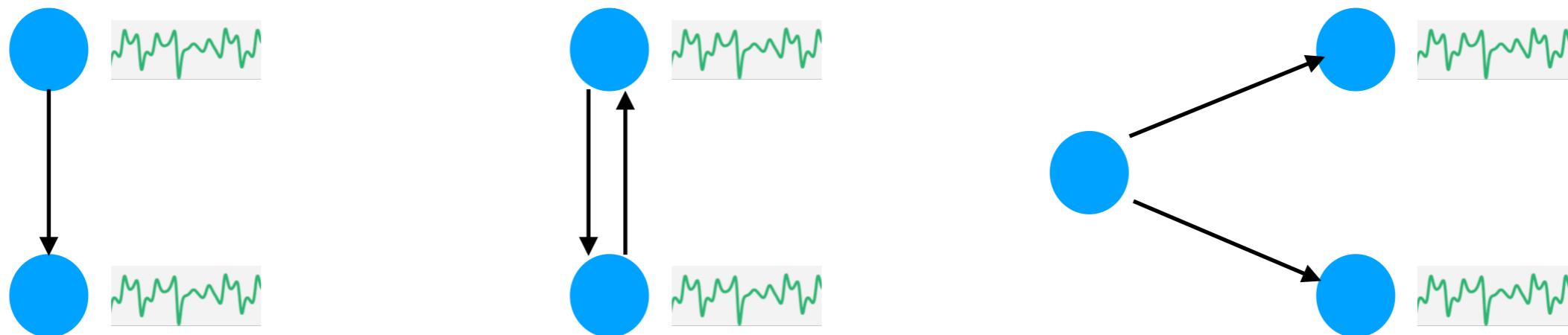


+

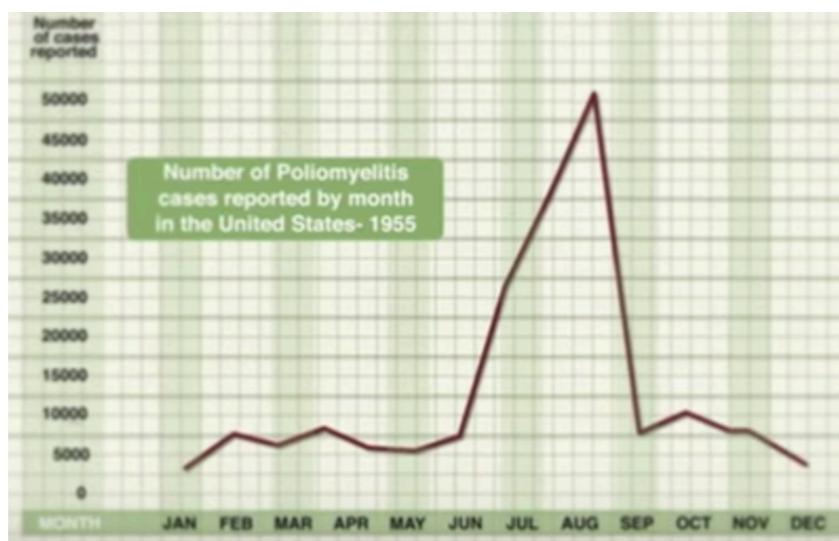




Correlation vs causation



example: polio epidemic in 1950-1960



source: Freakonomics movie

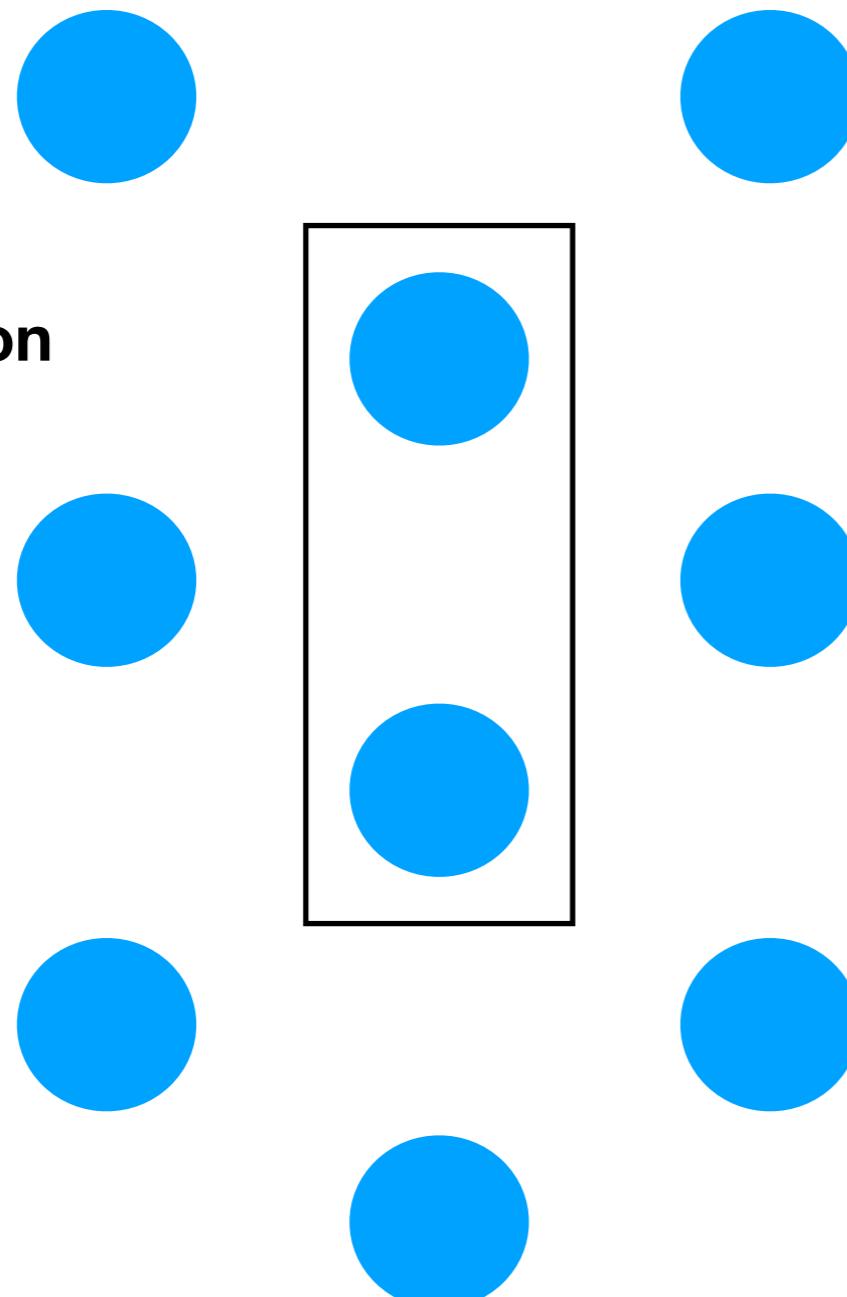


How to *operationalize* the functional connectivity?



Pearson's correlation vs partial correlation

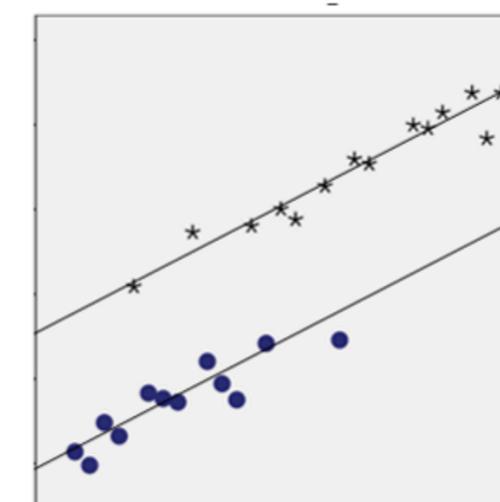
**picture with
linear interaction**



Pearson's correlation (Pearson's r)

a pairwise measure of association which treats the pair of nodes as an isolated system

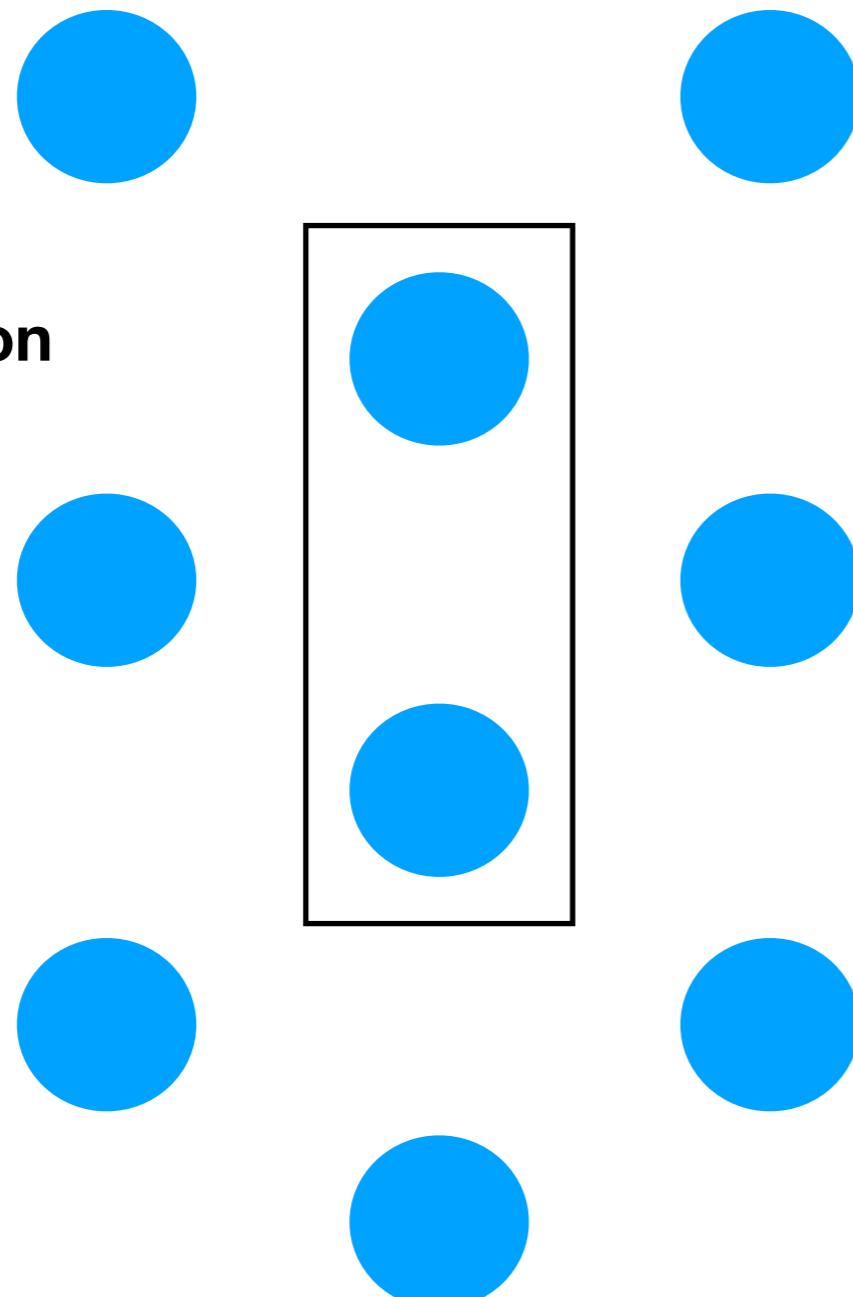
Pearson's r is parametric and assumes linear relationship between variables





Pearson's correlation vs partial correlation

**picture with
linear interaction**



[1] operationalization:
one standard way:

$$\rho_{X,Y} = \frac{\text{cov}(X, Y)}{\sigma_X \sigma_Y}$$

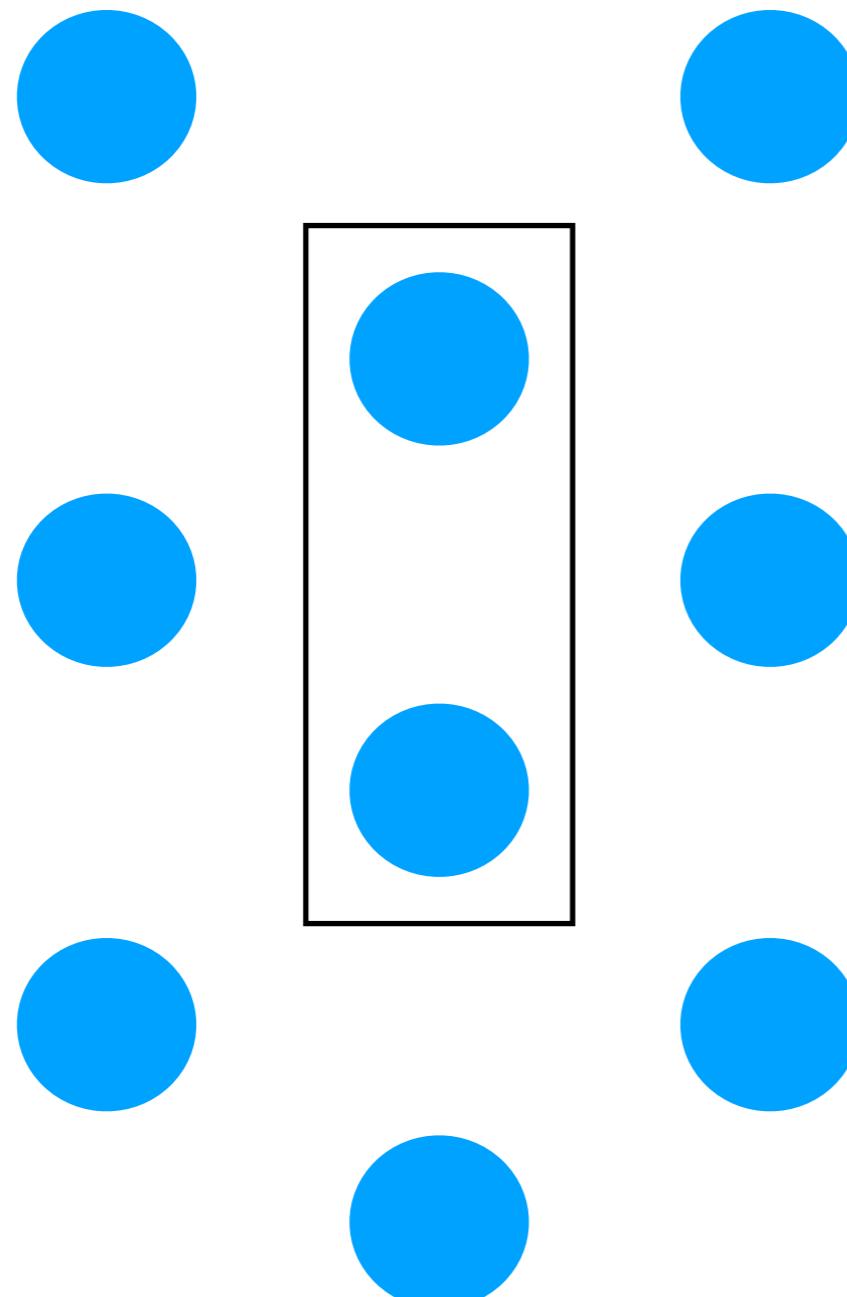
where

cov - covariance

σ - standard deviation



Pearson's correlation vs partial correlation



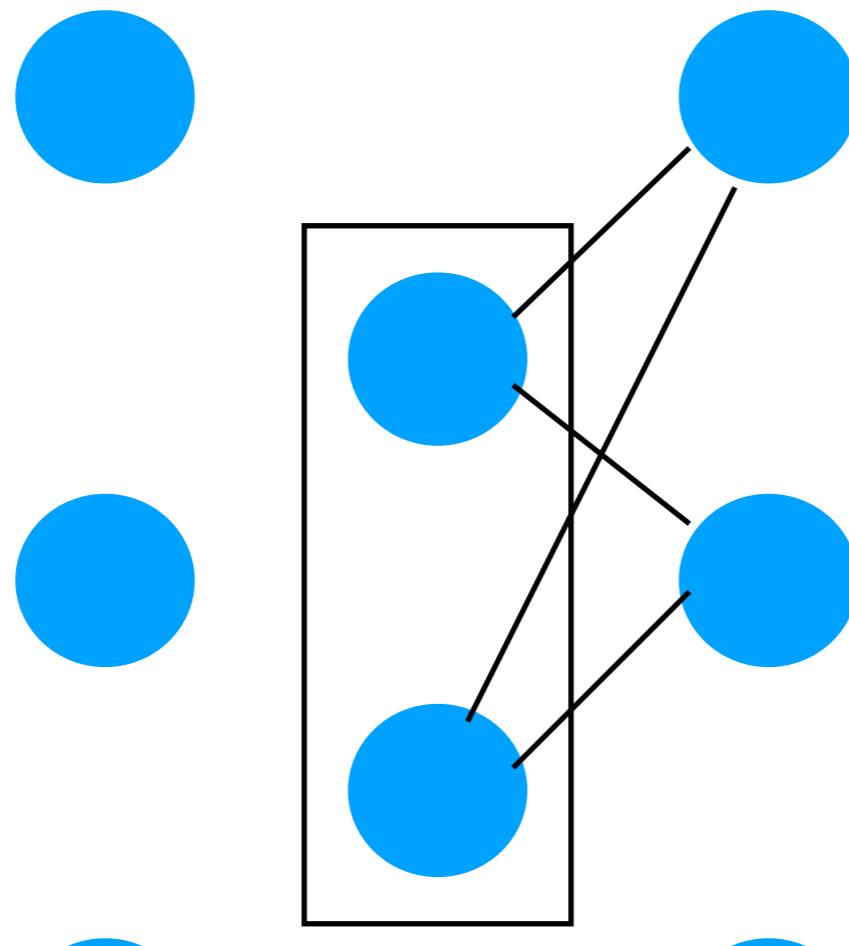
[2] building confidence intervals:
multiple ways:

[a] with use of t-statistic (MATLAB):
The p-value is computed by transforming the correlation to create a t statistic having $N-2$ degrees of freedom, where N is the number of rows of X .
The confidence bounds are based on an asymptotic normal distribution of $0.5 \cdot \log((1+R)/(1-R))$, with an approximate variance equal to $1/(N-3)$

[b] with use of Z-statistic:
Since the sampling distribution of Pearson's r is not normally distributed, Pearson's r is converted to Fisher's z' and the confidence interval is computed using Fisher's z' . The values of Fisher's z' in the confidence interval are then converted back to Pearson's r 's



Pearson's correlation vs partial correlation

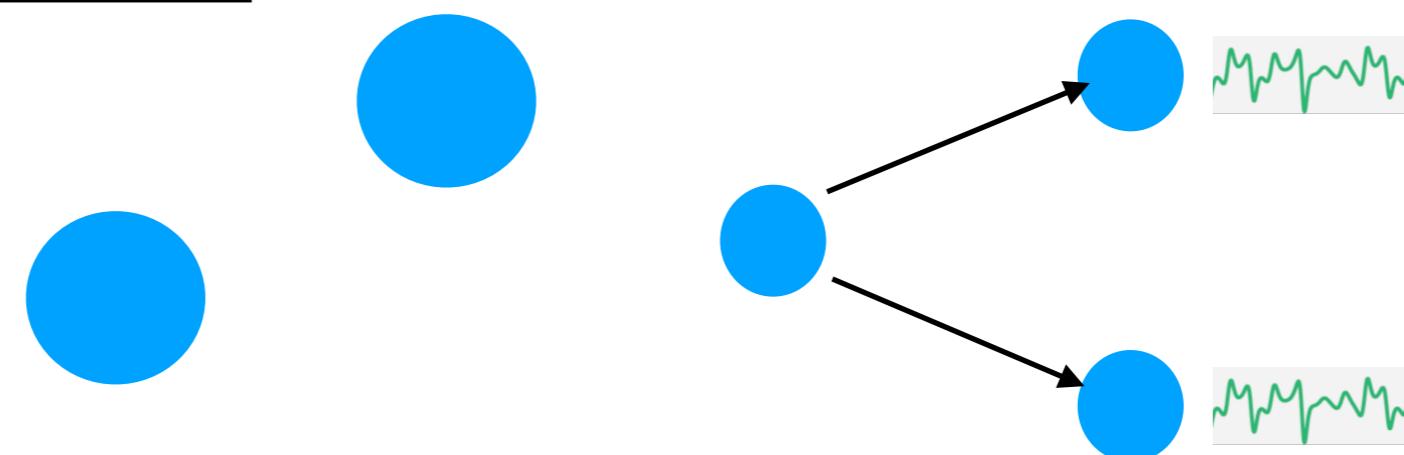


Partial correlation:

takes into account other nodes in the network

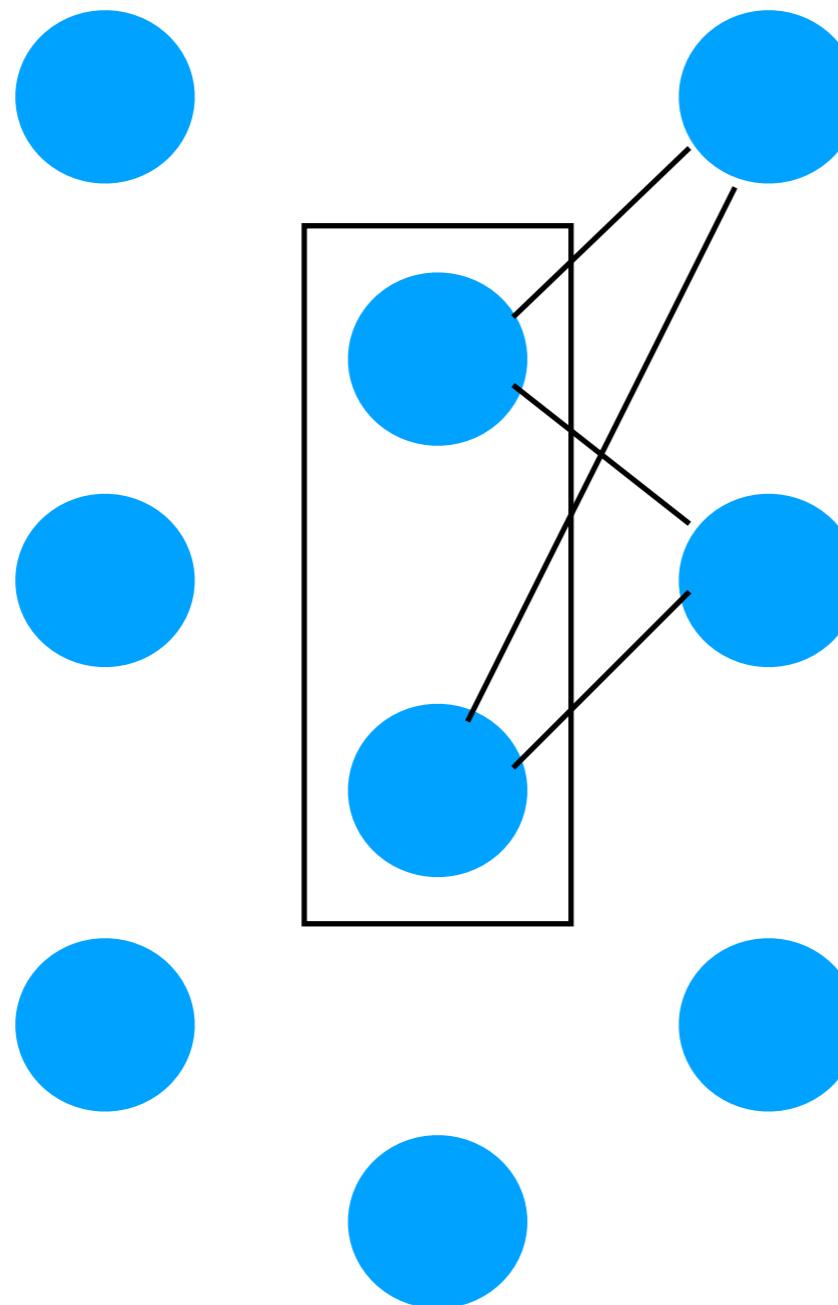
'first, regress the influence of other nodes in the network and isolate the two nodes, and then compute the Pearson's correlation between the two nodes'

many ways to compute partial correlation!





Pearson's correlation vs partial correlation



[1] Operationalization:

Partial correlation can be computed in multiple ways.

Two most popular algorithms:

[a] via Ordinary Least-Square Regression:

$$\mathbf{w}_X^* = \arg \min_{\mathbf{w}} \left\{ \sum_{i=1}^N (x_i - \langle \mathbf{w}, \mathbf{z}_i \rangle)^2 \right\}$$
$$\mathbf{w}_Y^* = \arg \min_{\mathbf{w}} \left\{ \sum_{i=1}^N (y_i - \langle \mathbf{w}, \mathbf{z}_i \rangle)^2 \right\}$$

The residuals are then:

$$e_{X,i} = x_i - \langle \mathbf{w}_X^*, \mathbf{z}_i \rangle$$

$$e_{Y,i} = y_i - \langle \mathbf{w}_Y^*, \mathbf{z}_i \rangle$$

+ Pearson's correlation on the residuals

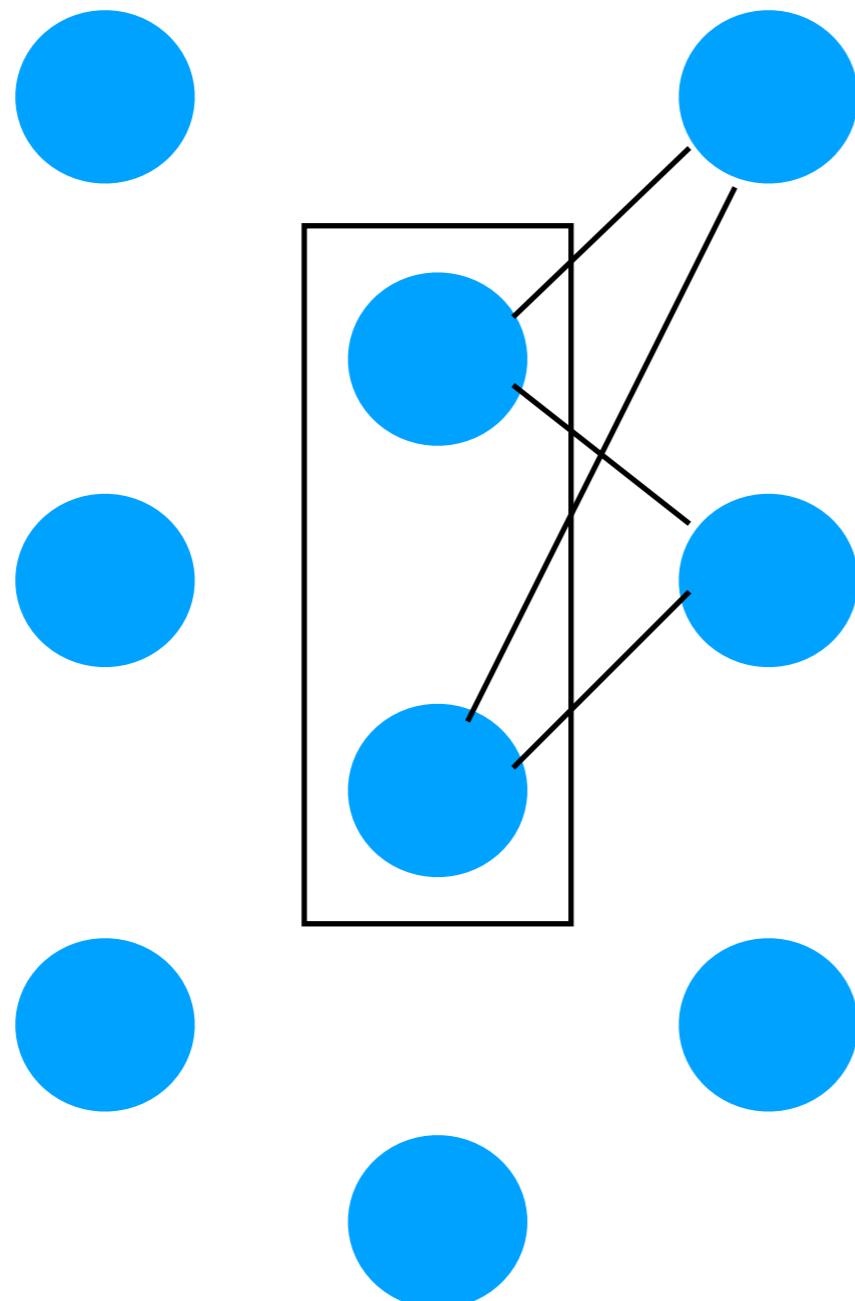
[b] an approximation through inverse covariance:

$$\rho_{ij.} = \frac{\mathbb{C}_{ij}^{-1}}{\sqrt{\mathbb{C}_{ii}^{-1} \mathbb{C}_{jj}^{-1}}}$$

(estimation recommended for large networks)



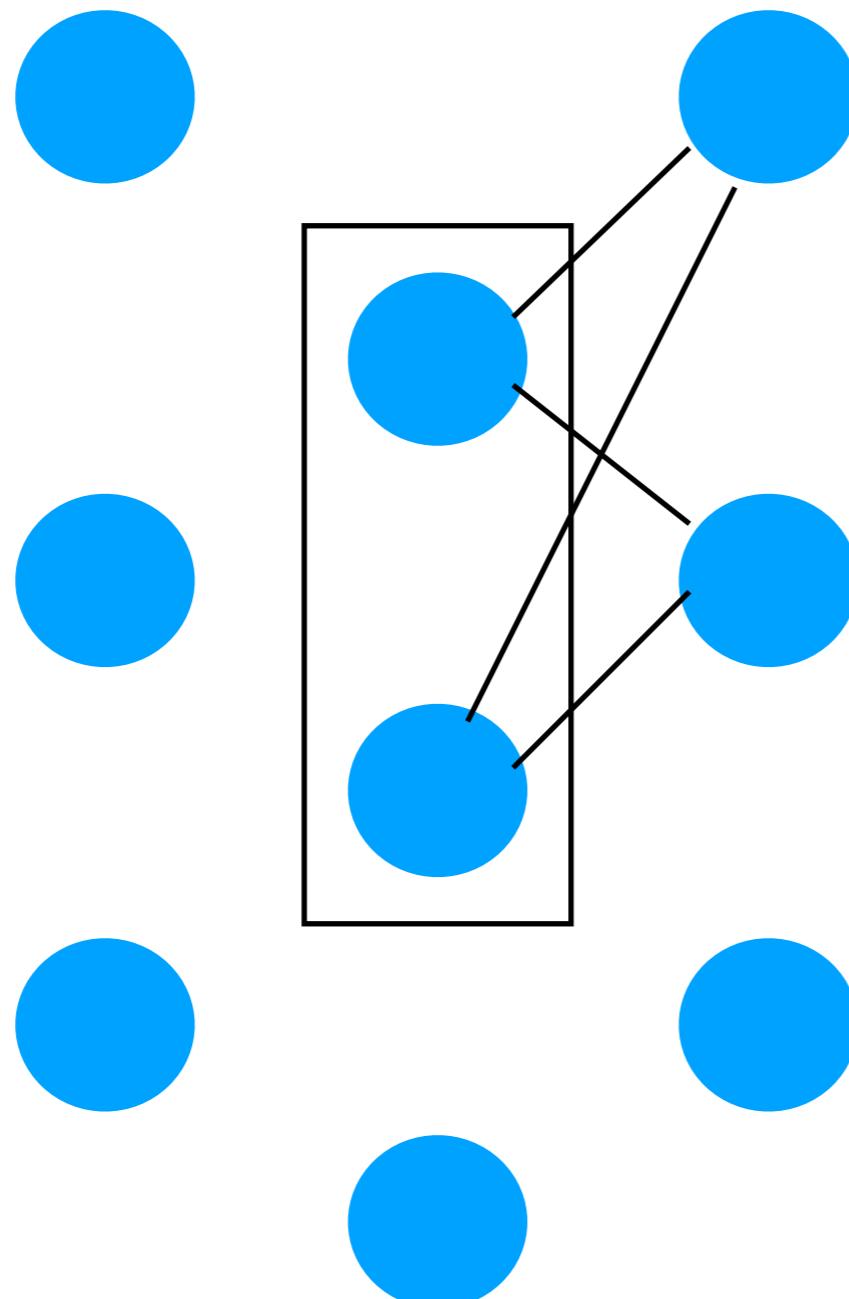
Pearson's correlation vs partial correlation



[2] building confidence intervals:
multiple ways (the same as in case of Pearson's r)



Pearson's correlation vs partial correlation



[2] building confidence intervals:
multiple ways (the same as in case of Pearson's r)

a control question: how do these two types of correlation - Pearson and partial - relate to each other?

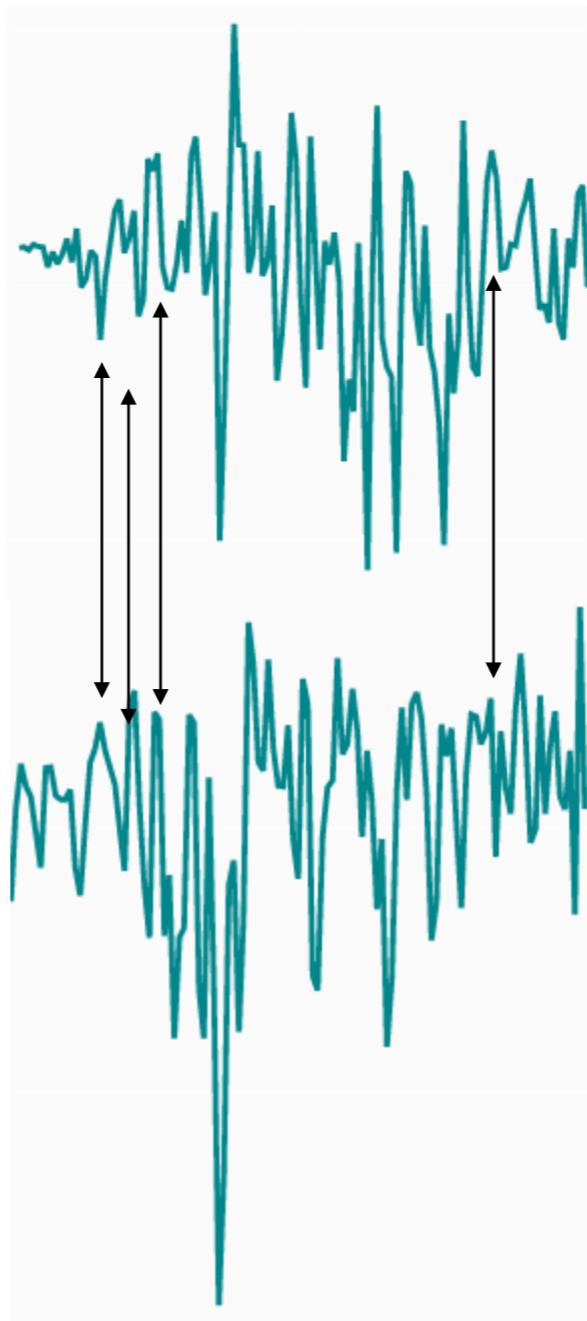
Which one of them requires more assumptions with respect to the data?



Other measures of association between two time series

(rarely encountered in brain research)

measures of the **distance** between two time series:

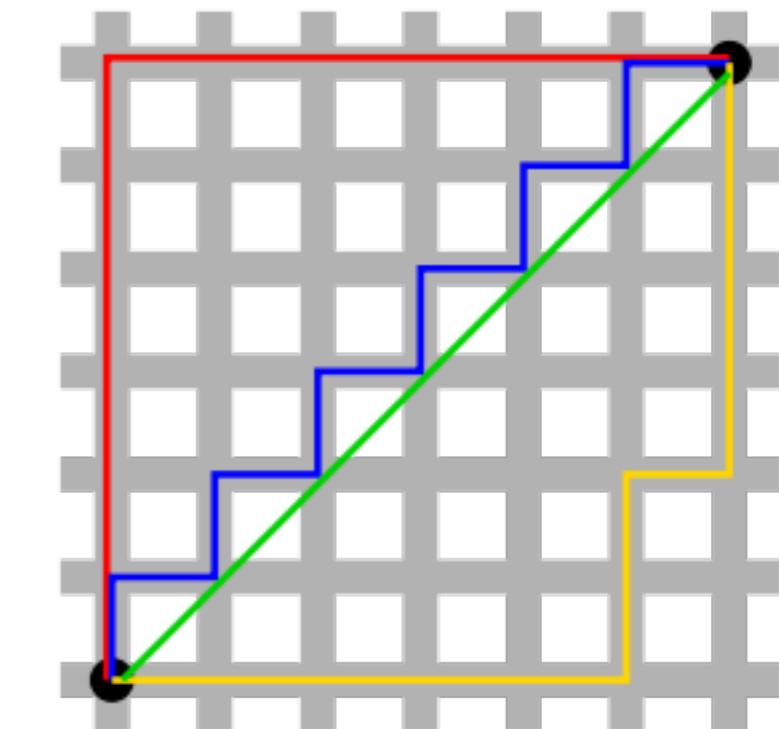
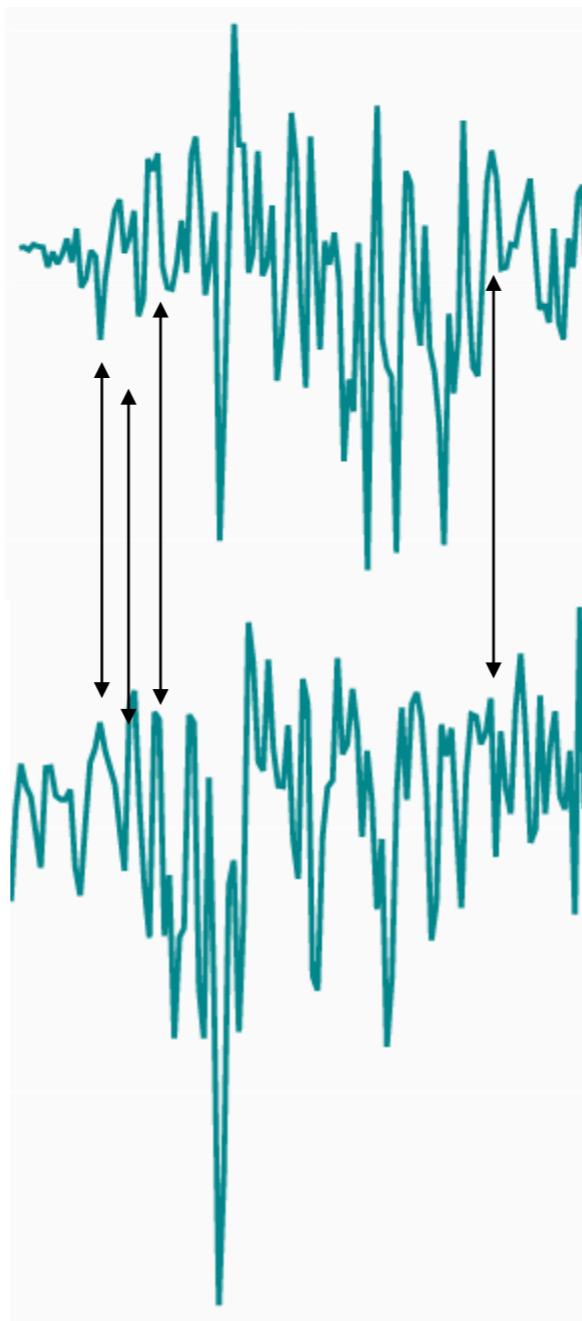




Other measures of association between two time series

(rarely encountered in brain research)

measures of the **distance** between two time series:



Euclidean vs Manhattan distance:
Manhattan distance
is the distance between two points
as the sum of the absolute differences
of their Cartesian coordinates



Information-theoretical measures of functional connectivity

Mutual information:

$$I(X; Y) = \sum_{x,y} P_{XY}(x, y) \log \frac{P_{XY}(x, y)}{P_X(x)P_Y(y)}$$

P_{xy} - joint probability for X and Y

P_x, P_y - marginals:

$$P_X(x) = \sum_y P_{XY}(x, y)$$

This definition works for discrete variables.



Facts about mutual information

The difference between correlation and mutual information

Pearson's correlation measures the *linear* relationship (Pearson's correlation) between two variables, X and Y.

Mutual information is more general and measures the reduction of uncertainty in Y after observing X. Therefore, MI can measure non-monotonic relationships and other more complicated relationships.

practical implementation of mutual information contains a free parameter (bin size)

not much done in the literature in terms of efficient ways of computing confidence intervals for mutual information



Most common traps in functional connectivity research

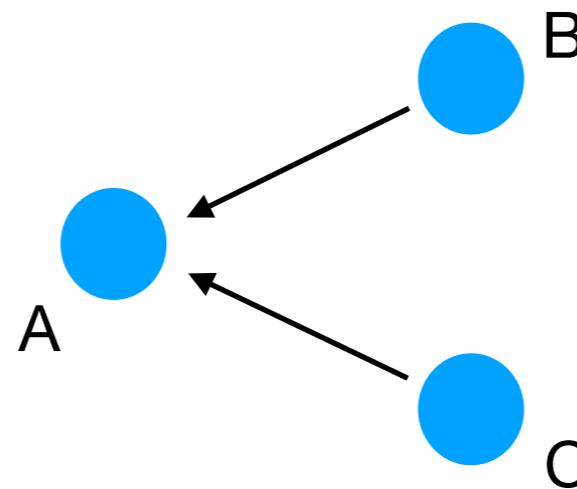
[1]

- Pearson's correlation can result in networks denser than the true underlying connectivity
- partial correlation can result in networks sparser than the true underlying connectivity

Conclusion: it is a good idea in general to compare compute both of them as the truth is somewhere in between

[2] the multiple comparisons problem —> true degree of freedom is unknown

[3] Berkson's paradox



happens when calculating partial correlation with use of Ordinary Least Squares regression
for two unrelated sources with a common sink

regressing time series A from B and C induces a *spurious negative correlation* between B and C



Assignment 1: in iPython notebook

[1_measures_of_functional_connectivity_basic.ipynb](#)

you have got an overview of the aforementioned methods for functional connectivity in the time domain.

Go through the codes, read the implementation of the four methods:

- Pearson's correlation
- partial correlation
- measures of similarity
- mutual information

(a) How do the outcome connectomes differ from each other?

Are the functional connectomes coming from Pearson and partial correlation similar to each other?

Discuss this topic with your partner.

(b) Load a dataset from another subject and compare the results between two subjects. Are methods differ in terms of cross-subject reproducibility?

(b) Create a new notebook 'Assignment1', choose datasets other than fMRI from the 'datasets' database, and create other functional connectomes in datasets coming from other disciplines: stock exchange datasets, climate data etc. How do these connectomes look like? Do you see any patterns?

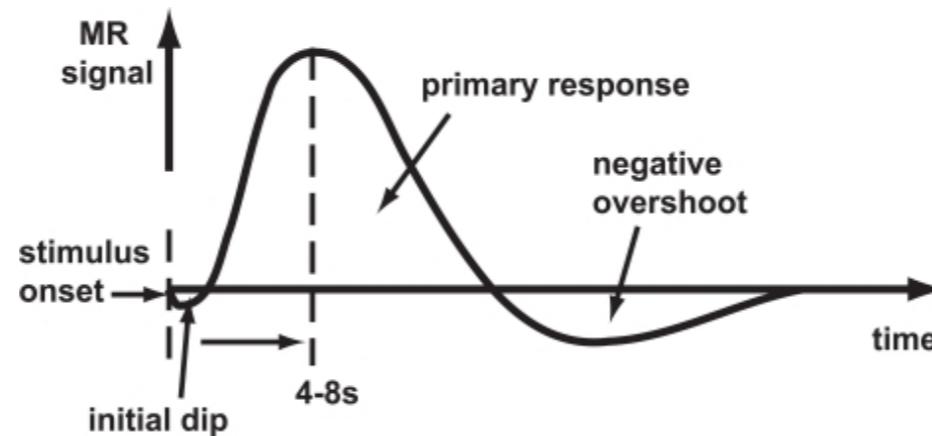
(d) Can you think of any other measures of functional connectivity in the time domain? (space for creativity) You can propose any function of the data you can think of. You can define it in a separate function, give it a name and

- test on a pair of random time series in order to check whether your measure is unbiased
- apply to fMRI datasets and compare to other, established measures of functional connectivity



General remark about building confidence intervals for functional connectivity measures

- building confidence intervals for correlation variables and mutual information through **t-test** or **F-test** contains an assumption that the samples are *independent*
- in many datasets this assumption is not true. E.g. in the fMRI data, samples are dependent: slow haemodynamics induces crosscorrelations between subsequent samples



Possible solutions:

[1] permutation testing

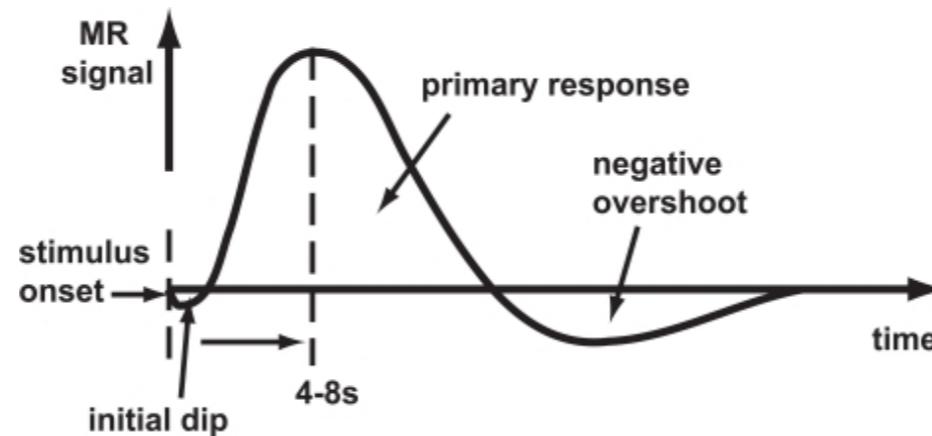
[2] through mixture modeling
(Bielczyk & Walocha et al, NeuroImage 2017)

General remark:
in datasets where samples are autocorrelated,
building confidence intervals on the second
level of analysis is advised



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General remark about building confidence intervals for functional connectivity measures

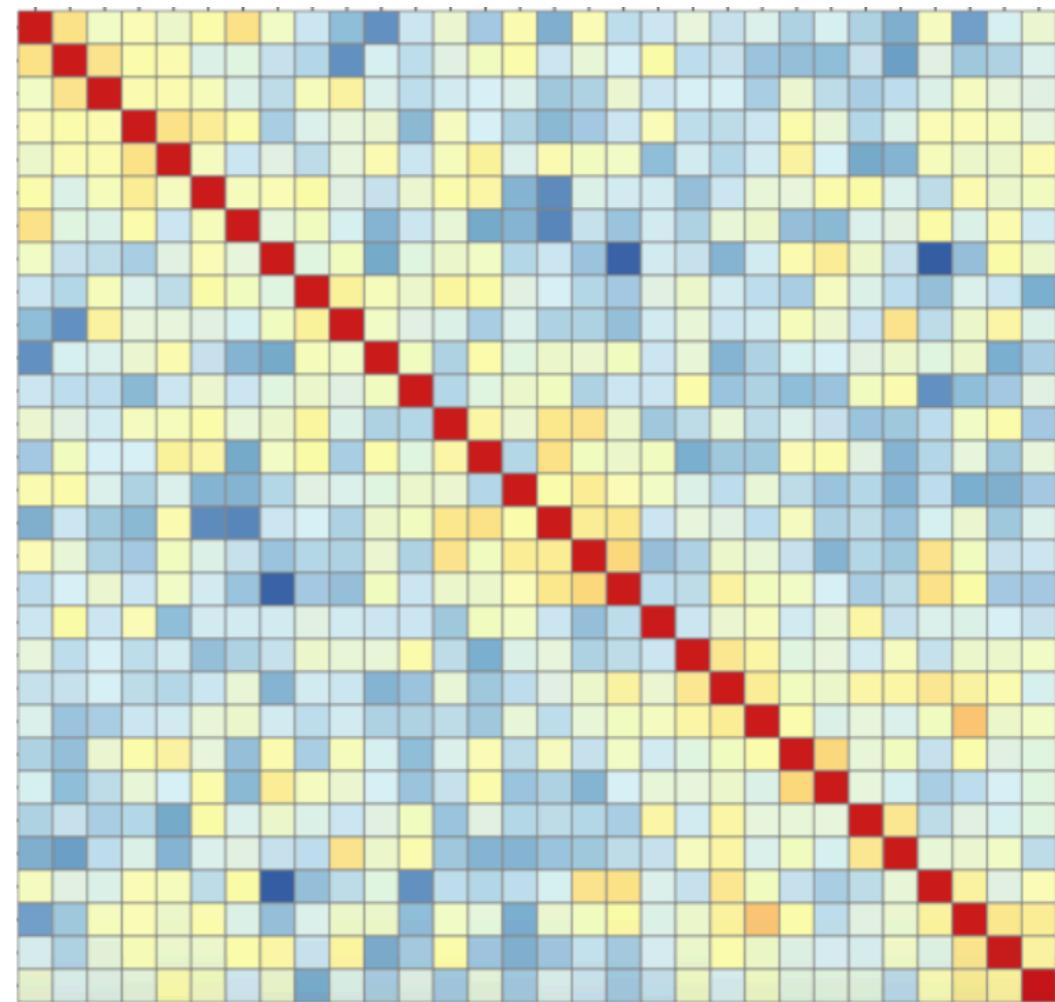
- how about the difference between two conditions?
- a number of subjects, task versus rest
- paired t-test can be a solution, as subjects are independent from each other, but the measurement is repeated per subject



General remarks about building confidence intervals for functional connectivity measures

FC matrices can be of any arbitrary size
—> testing for multiple comparisons
is necessary

- [1] Bonferroni correction
- [2] Benjamini-Hochberg correction





General remark about building confidence intervals for functional connectivity measures

- how about the difference between two conditions?
- a number of subjects, task versus rest
- paired t-test can be a solution, as subjects are independent from each other, but the measurement is repeated per subject

Assignment 2: in iPython notebook

[`3_measures_of_functional_connectivity_second_level_computation_significance_testing.ipynb`](#)

you have examples of significance testing in fMRI data with use of permutation testing (effect versus no effect, e.g. answering the question: which correlations in the resting state are significant?)

The task now is to answer another question: which differences between two conditions (e.g., between task and rest or, between resting state day 1 versus resting state day 2) are significant? Try to answer this question with use of the available fMRI second-level datasets, which you can find in the folder ‘output_second_level’

Note: when you are comparing task versus rest, choose the version derived from the resting state datasets of the same sample length as the task dataset (e.g. 558 sampels for the MOTOR task and 800 sampels for the WM task)



Time domain vs frequency domain

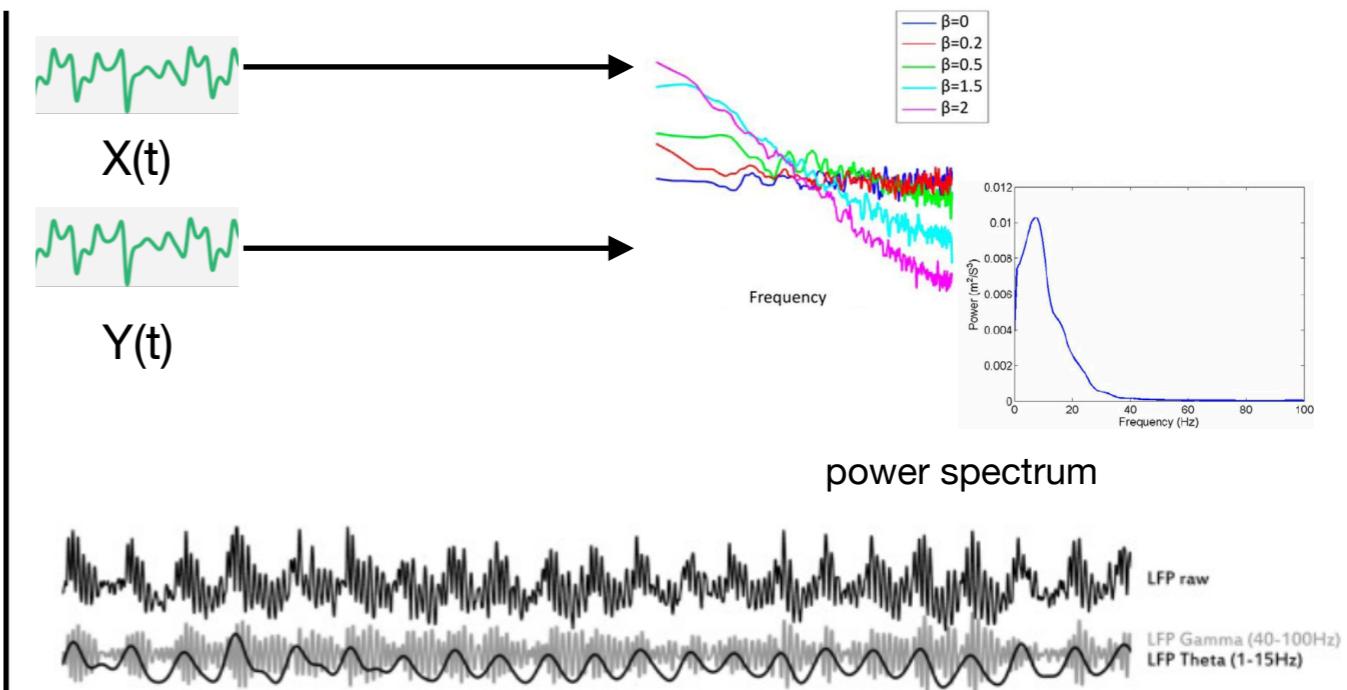
**poor time resolution
no oscillatory patterns**



Correlation

- > Pearson's correlation
- > partial correlation

time domain



Coherence

- > phase-phase coupling
- > phase-amplitude coupling
- > amplitude-amplitude coupling

frequency domain

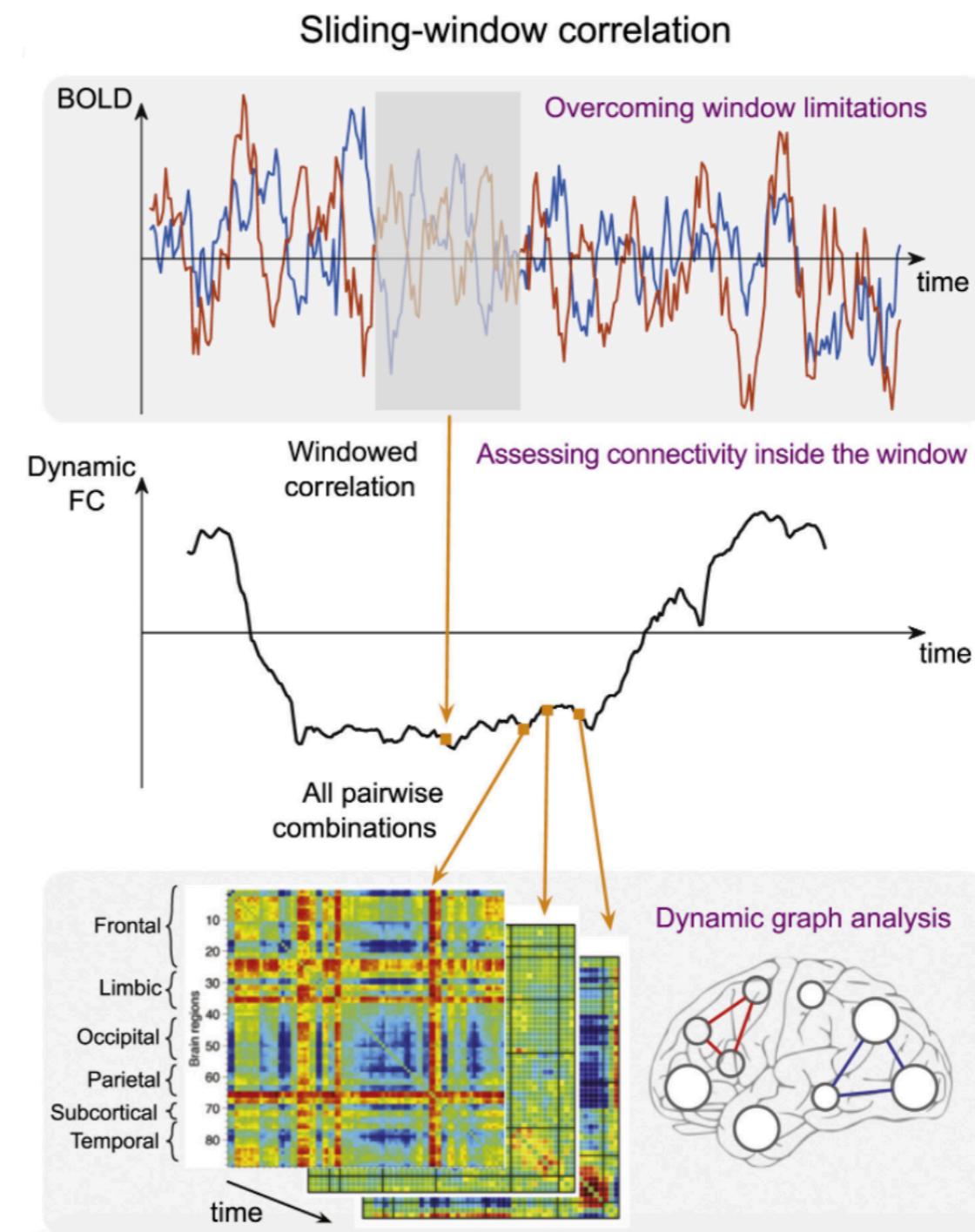


Static vs dynamic functional connectivity

analysis of the temporal patterns in functional connectivity with use of a *sliding window*
(Sakoḡlu et al, 2010)

“chronnectome”

used primarily in fMRI research,
see a review paper:

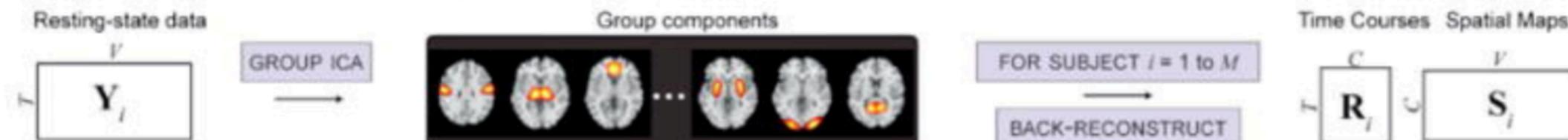




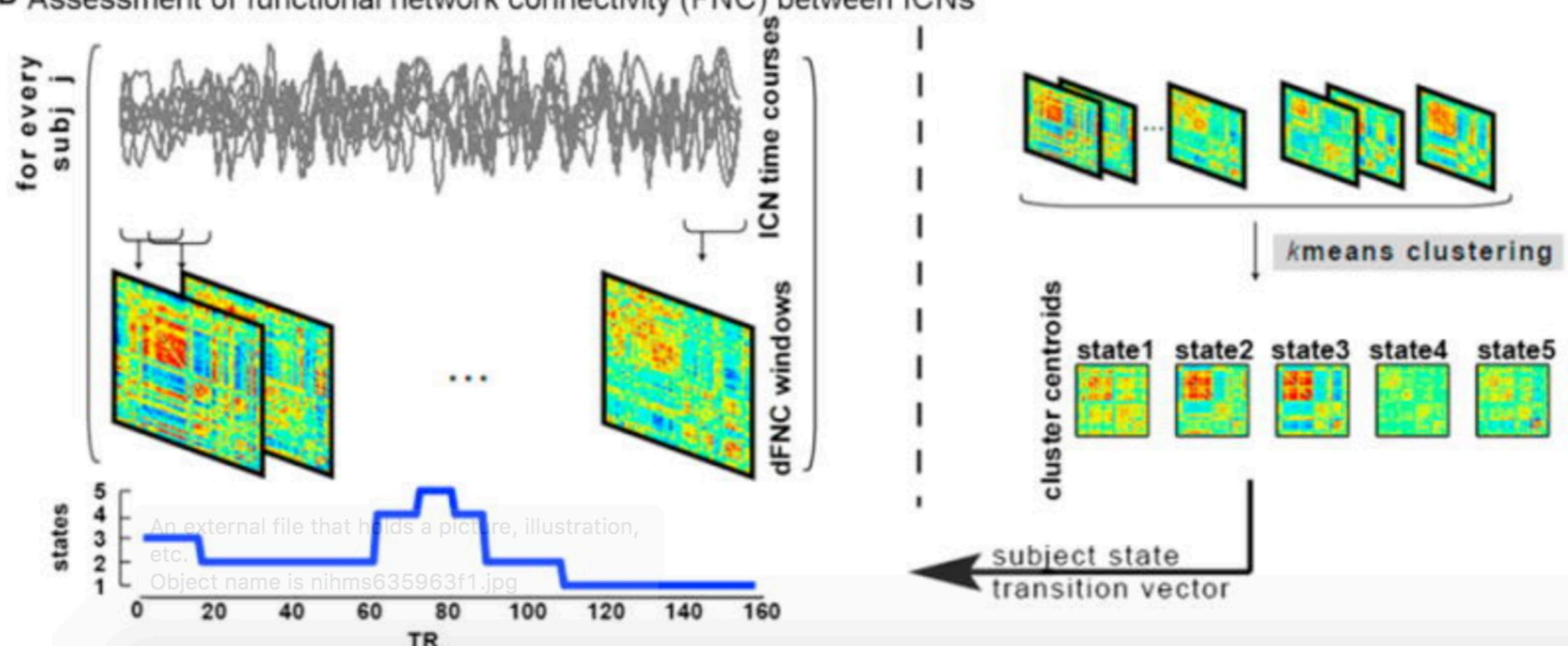
Static vs dynamic functional connectivity

A 'Chronnectome' idea:

A Identification of intrinsic connectivity networks (ICNs)



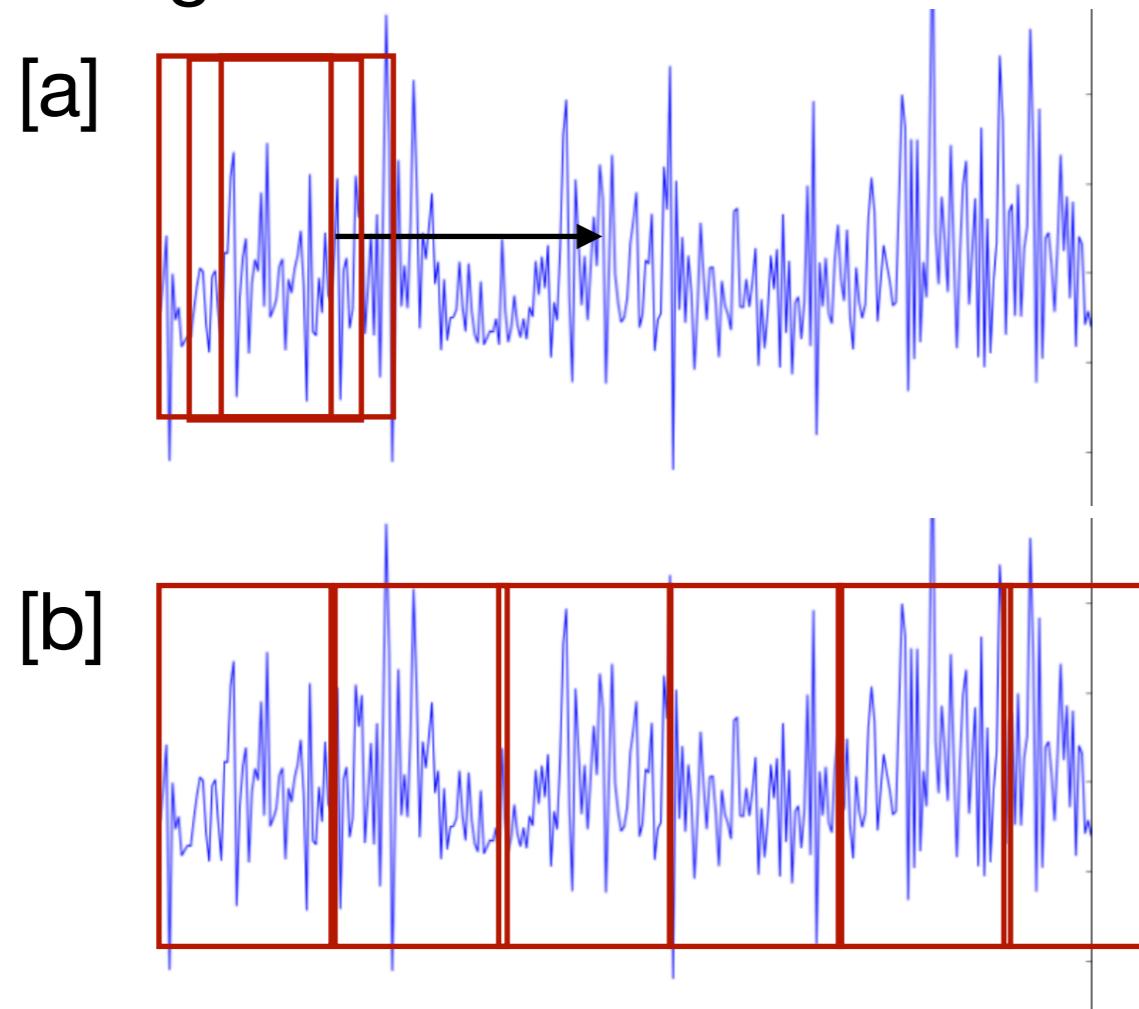
B Assessment of functional network connectivity (FNC) between ICNs





Two main ways of computing dynamic functional connectivity (dFC)

- [a] through sliding window (either rectangular or more fancy)
- [b] through series of windows



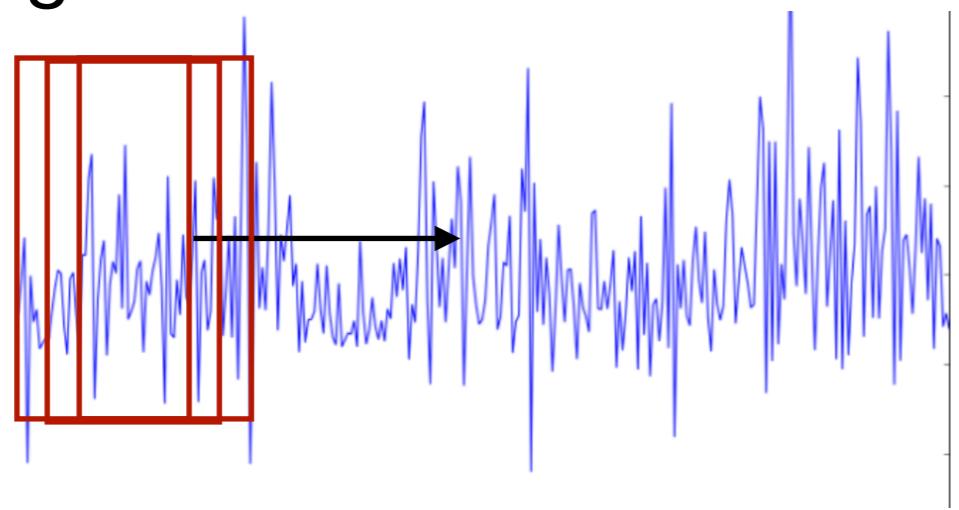


Two main ways of computing dynamic functional connectivity (dFC)

[a] through sliding window (either rectangular or more fancy)

[b] through series of windows

[a]



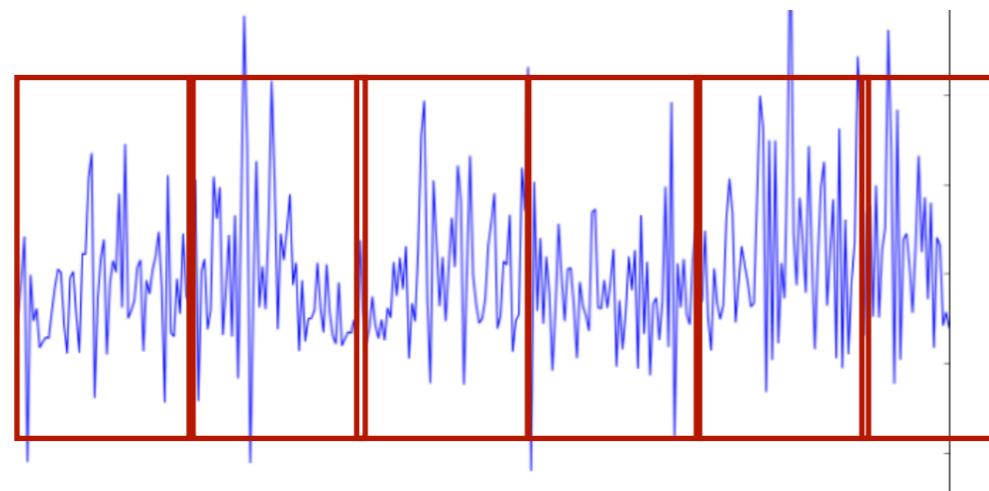
Pros:

dynamics is easier to catch

Cons:

windows are highly correlated

[b]



Pros:

FC within each window can be treated as an independent sample

Cons:

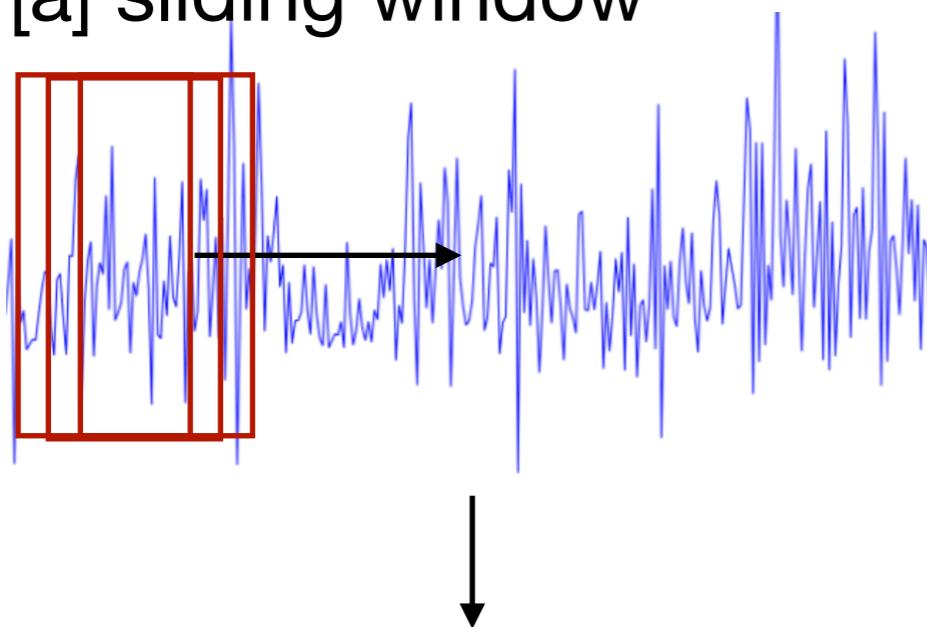
dynamics is very poor

Which method is better? —> Hindriks et al, NeuroImage 2016



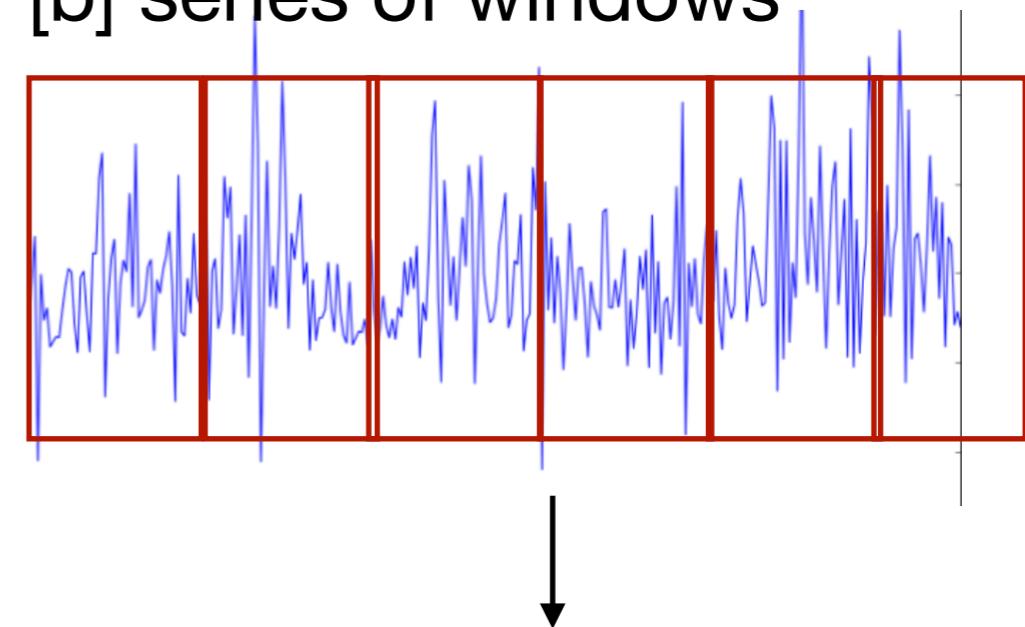
How to test significance in the dFC?

[a] sliding window



samples dependent
from each other

[b] series of windows



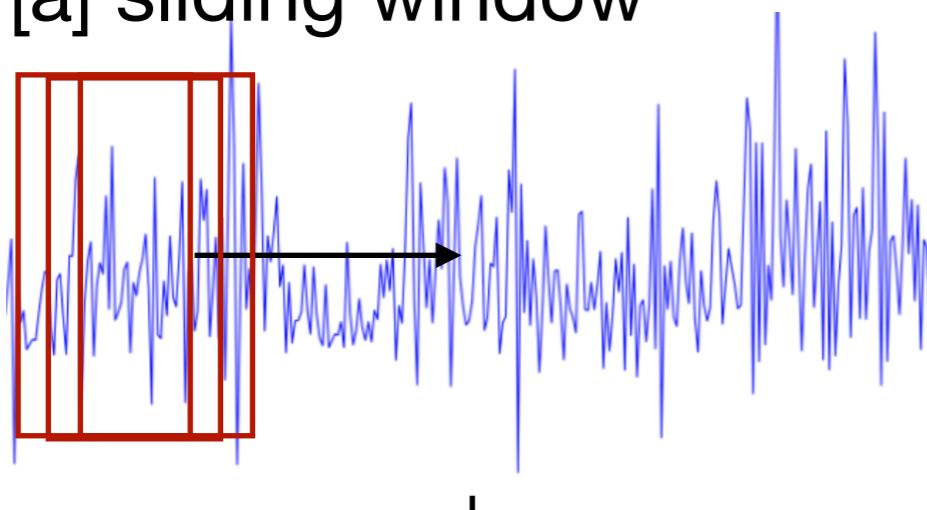
samples independent
from each other

Which method is better? —> Hindriks et al, NeuroImage 2016



How to test significance in the dFC?

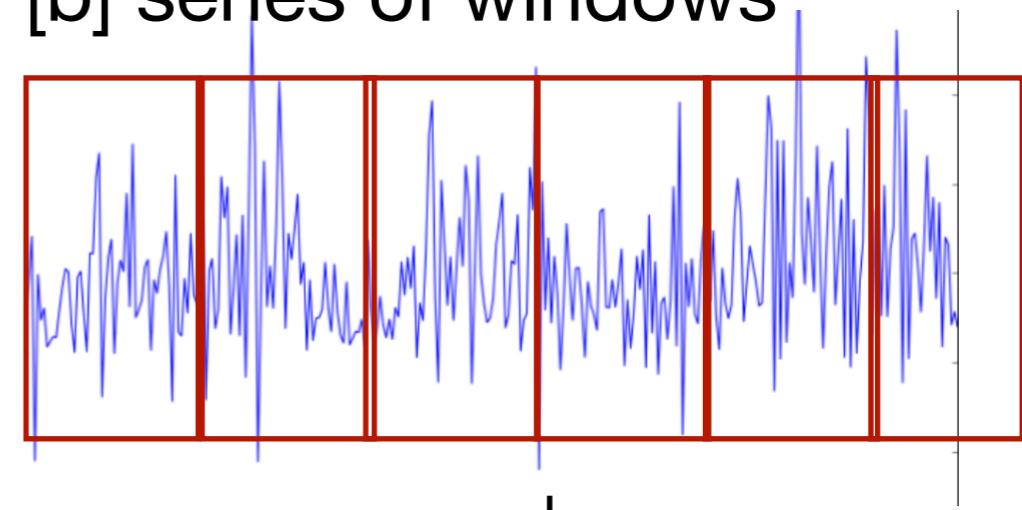
[a] sliding window



samples dependent
from each other

permutation testing

[b] series of windows



samples independent
from each other

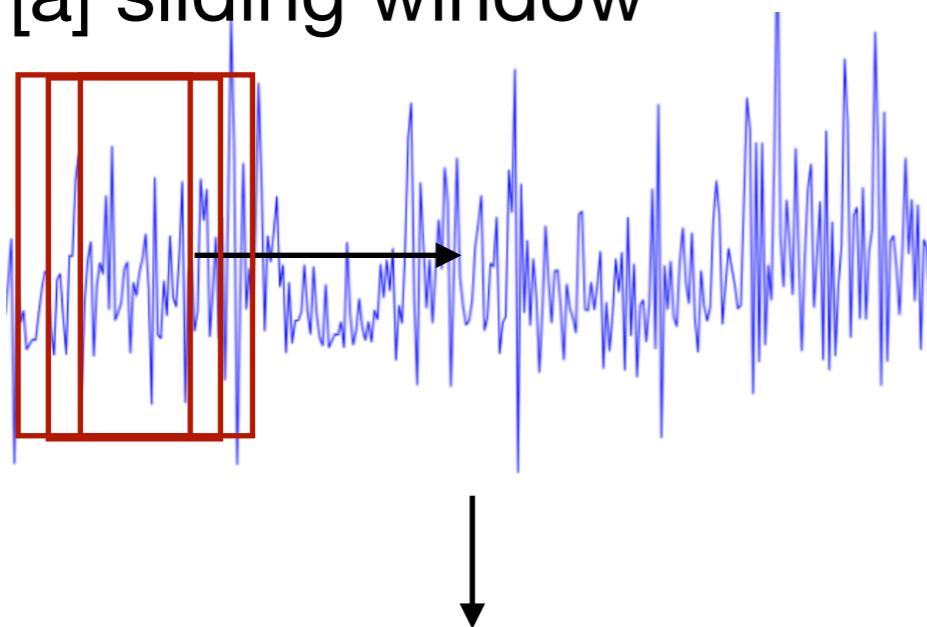
t-test

Which method is better? —> Hindriks et al, NeuroImage 2016

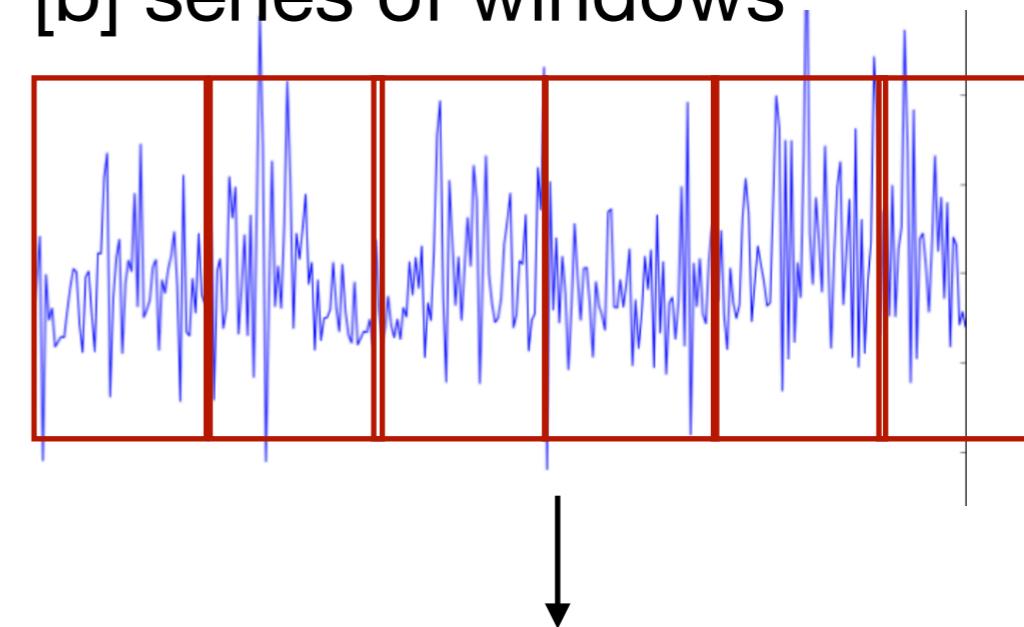


What do we get out of dFC?

[a] sliding window



[b] series of windows





How to visualize dFC in Python?

HoloViews

Stop plotting your data - annotate your data and let it visualize itself.

HoloViews is an [open-source](#) Python library designed to make data analysis and visualization seamless and simple. With HoloViews, you can usually express what you want to do in very few lines of code, letting you focus on what you are trying to explore and convey, not on the process of plotting.

For examples, check out the thumbnails below and the other items in the [Gallery](#) of demos and apps and the [Reference Gallery](#) that shows every HoloViews component. Be sure to look at the code, not just the pictures, to appreciate how easy it is to create such plots yourself!

The [Getting-Started](#) guide explains the basic concepts and how to start using HoloViews, and is the recommended way to understand how everything works.

The [User Guide](#) goes more deeply into key concepts from HoloViews, when you are ready for further study.

The [API](#) is the definitive guide to each HoloViews object, but the same information is available more conveniently via the `hv.help()` command and tab completion in the

Tweets by [@HoloViews](#)



New in GeoViews 1.4: Native GeoPandas support for easy choropleths and interactive colormapping thanks to [@BokehPlots](#)



Rafał Skolasiński

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View on Twitter



Assignment 3: in iPython notebook

4_dynamic_functional_connectivity.ipynb

you have a simple implementation of dFC. First, reimplement the dFC so that next to [a] the sliding window, you will also have version [b]. You can also experiment with the window types (rectangular versus smooth) Then, answer the following questions:

- [a] how does dFC depend on the window length?
- [b] which of the two types of dFC is more informative to you? why?
- [c] load the dataset from two different subjects, and check if the dFC dynamics looks similar
- [d] load the datasets other than fMRI and compute dFC on this data. Does the dynamics differ between datasets?

- [e] in iPython notebook



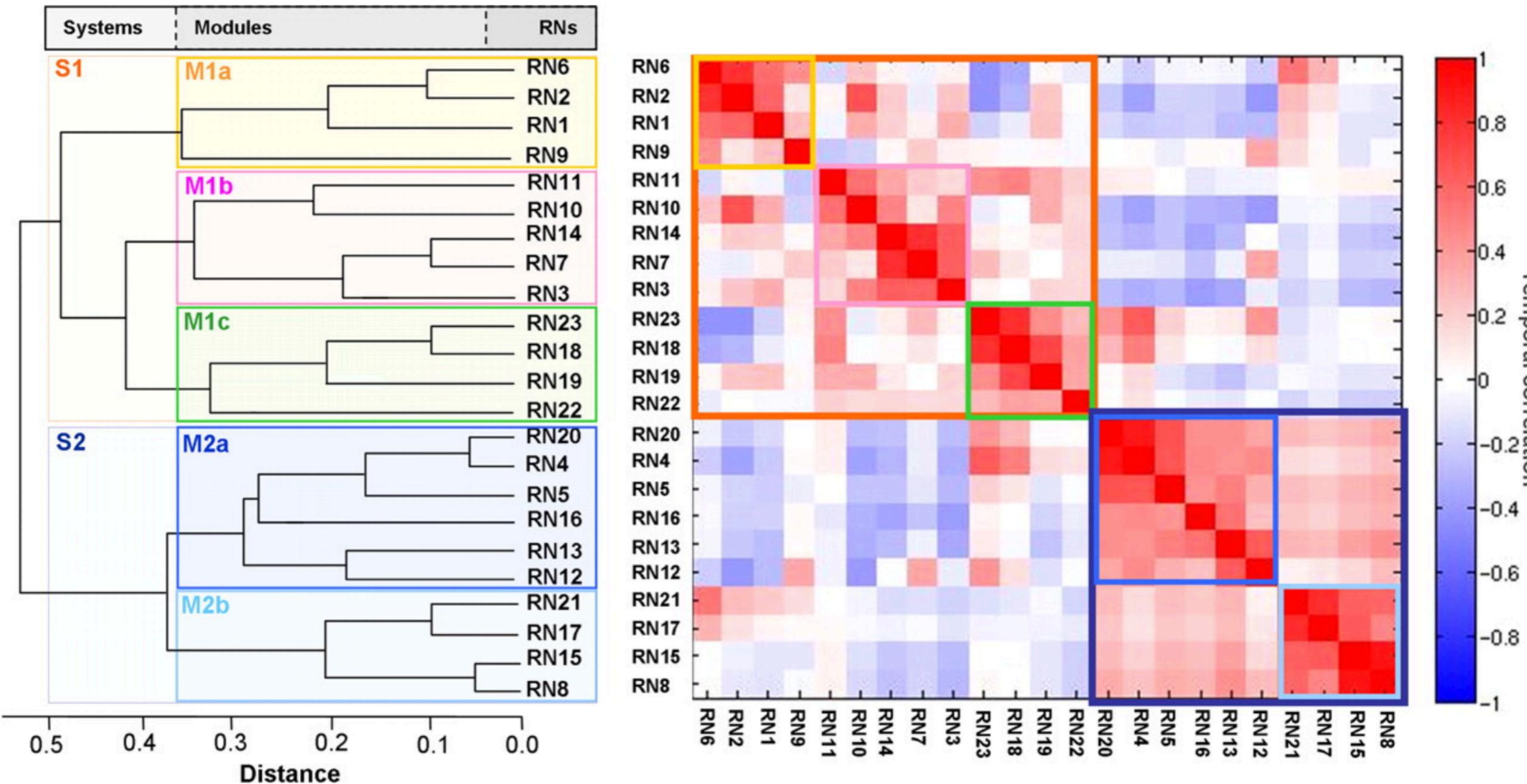
5_coherence.ipynb

you can find codes for computing a coherence between two time series (from EEG/MEG datasets etc.). Get familiar with these codes, and play around with the synthetic data in the notebook in order to figure out how the coherence works.

- [f]* how to operationalize dFC *dynamics*? would you rather go for the variance of dFC or for FFT analysis?
- [g]* reimplement dFC so that coherence is computed within each window (coherence instead of correlation). Compute dFC on exemplary EEG and fMRI datasets, and discuss the results with your partner.



Hierarchical models of functional connectivity





Hierarchical models of functional connectivity

the algorithm:



Assignment 4: in iPython notebook

[`6_hierarchical_models_of_functional_connectivity.ipynb`](#)

you will find codes for finding hierarchy in functional connectomes. Get familiar with this notebook, and answer the questions:

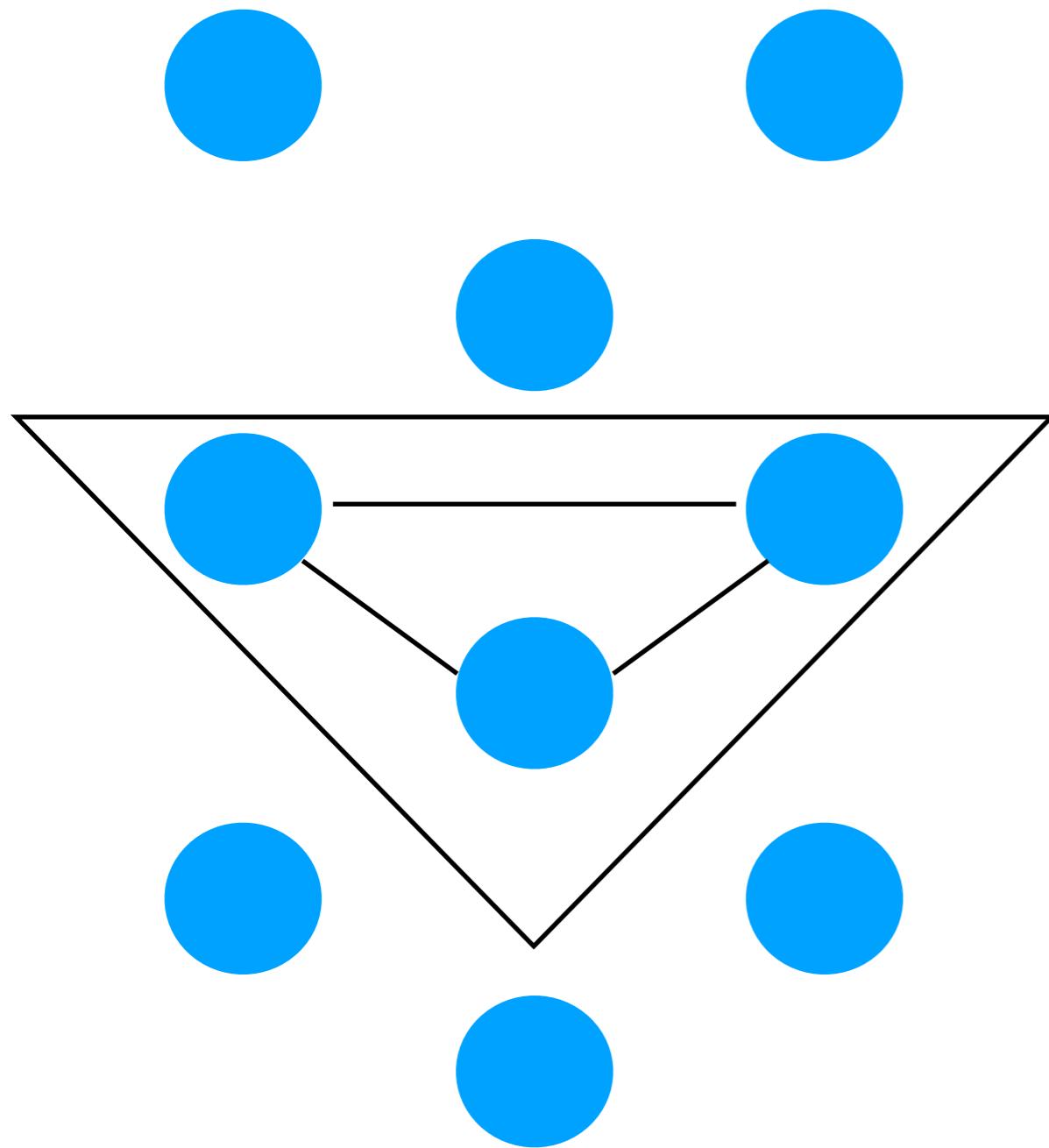
- [a] is the hierarchy reproducible between subjects?
- [b] how do the hierarchical models differ between different datasets?



***Other intriguing topics within the subject-matter
of functional connectivity**



Higher order statistics part 1: Multiple body interactions



Pearson's r for two nodes:

$$\frac{E\{(X - \mu_X)(Y - \mu_Y)\}}{\sqrt{\text{Var}(X)\text{Var}(Y)}}$$

Pearson's r for three nodes:

$$\frac{E\{(X - \mu_X)(Y - \mu_Y)(Z - \mu_Z)\}}{\sqrt{\text{Var}(X)\text{Var}(Y)\text{Var}(Z)}}$$

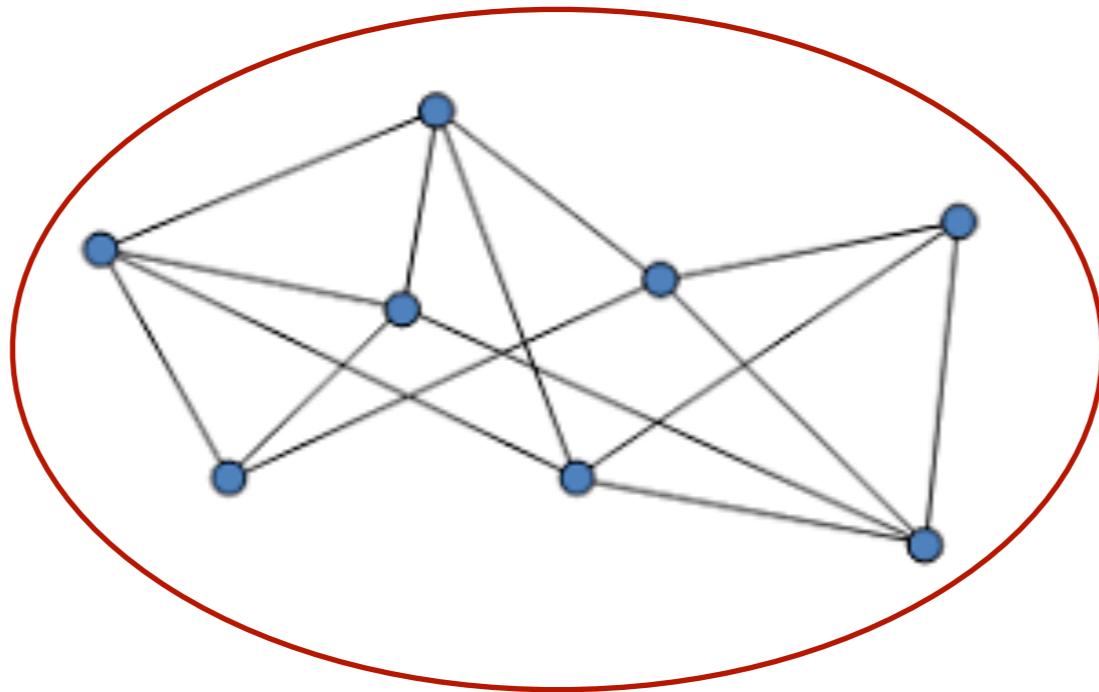
Assignment 5*:

Implement this statistic and launch the code on datasets of choice. What do you see?



Higher order statistics part 2: Graph theory

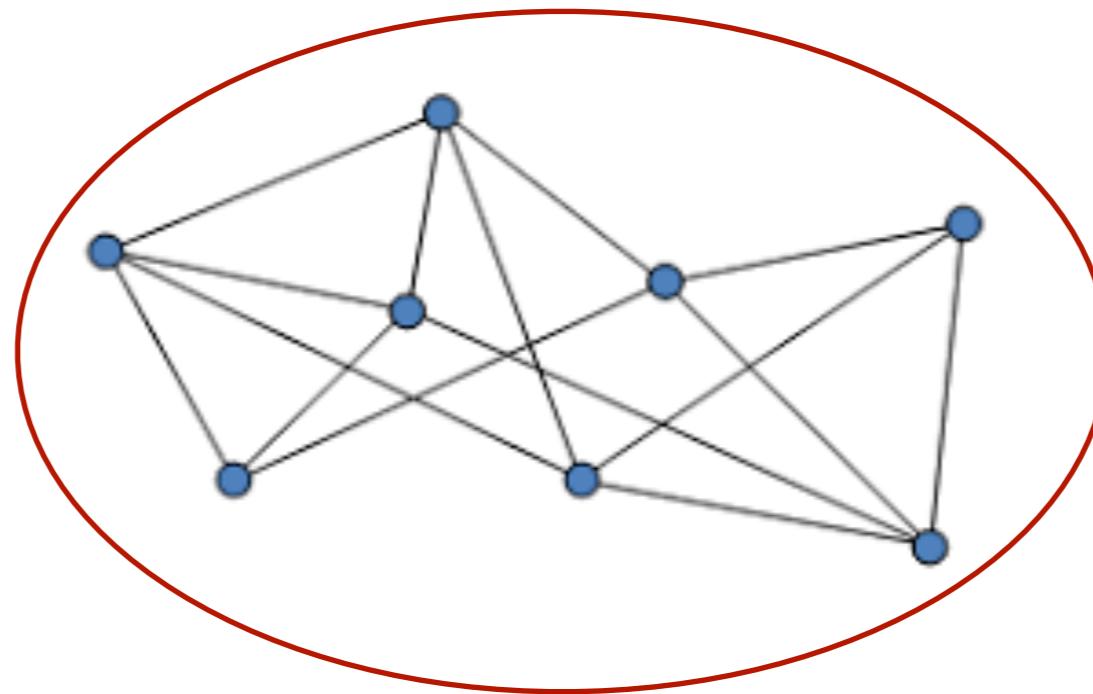
Why do we do graph theory?





Higher order statistics part 2: Graph theory

Why do we do graph theory?



decentralized measures of network functional structure

Pros:

no need for the correction for multiple comparisons

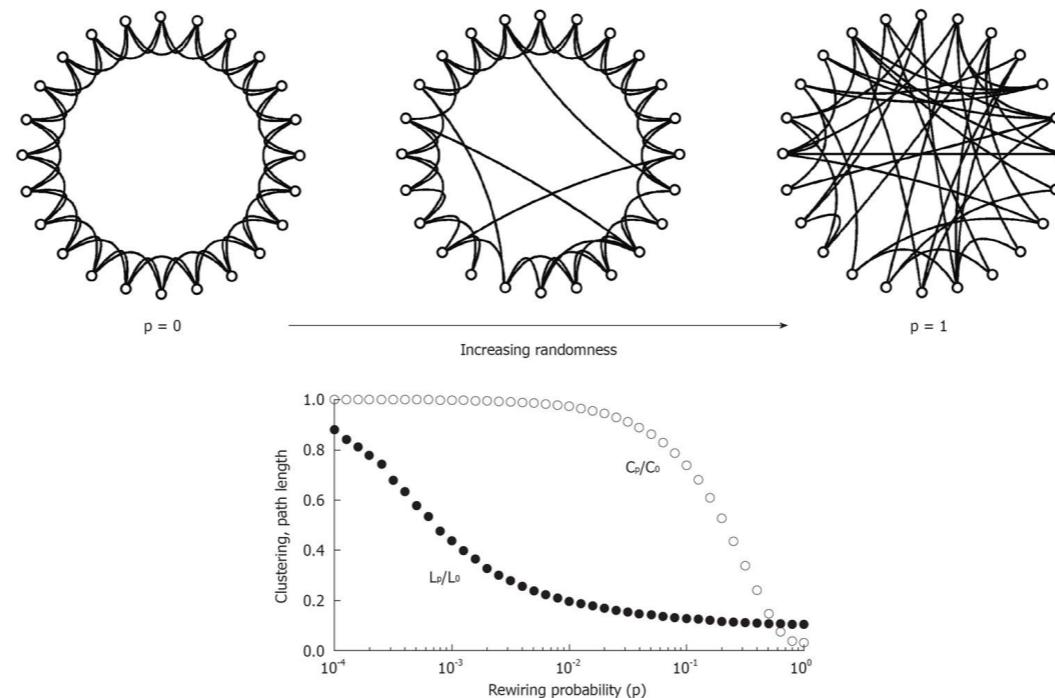
Cons:

decentralized!



Higher order statistics part 2: Graph theory

[1] Small worldness (a.k.a. global clustering coefficient): a measure of the degree to which nodes in a graph tend to cluster together



Watts and Strogatz, Nature 1998

$$C = \frac{3 \times \text{number of triangles}}{\text{number of connected triplets of vertices}} = \frac{\text{number of closed triplets}}{\text{number of connected triplets of vertices}}$$



Higher order statistics part 2: Graph theory

[2] Modularity



Higher order statistics part 2: Graph theory

[3] Degree distribution



Higher order statistics part 2: Graph theory

Assignment 6*: in iPython notebook

[7_graph_theory.ipynb](#)

you will find codes for computing few basic graph theoretical measures. Launch these codes on the datasets of choice and answer the questions:

- [a] what can I learn about the network functional structure from each one of these quantities?
- [b] which network features are data specific, and which of them are transferrable between datasets?



Food for thought: Functional connectivity research vs prediction studies

functional connectivity:

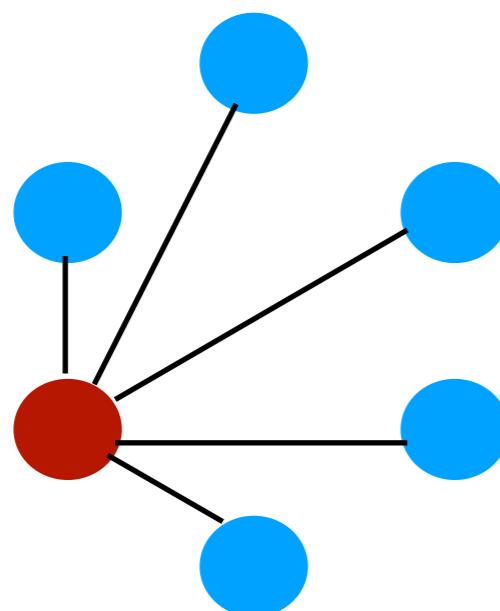
do the two variables correlate?

prediction study:

you can predict a value of one variable from a value of another variable
(usually because these two variables correlate)

Linear Discriminant Analysis finds coefficients a_i such that:

$$v = \sum a_i v_i$$



Conclusion: these two research problems are mathematically close to each other

A research question:

How about applying Linear Discriminant Analysis to do a functional connectivity research?
Can the activity in one node of the network be predicted from activity in other nodes in the network?



Thank you for your attention!