



# Brain networks: Why, what, how – and how not?

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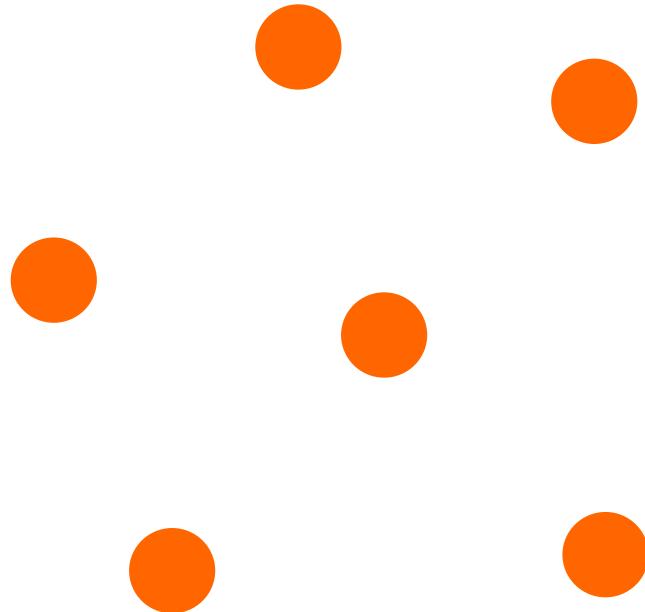
*25.5.2020*

Slides: <https://github.com/onerva-korhonen/presentations/blob/master/upsala-250520.pdf>

# Networks: what and why?

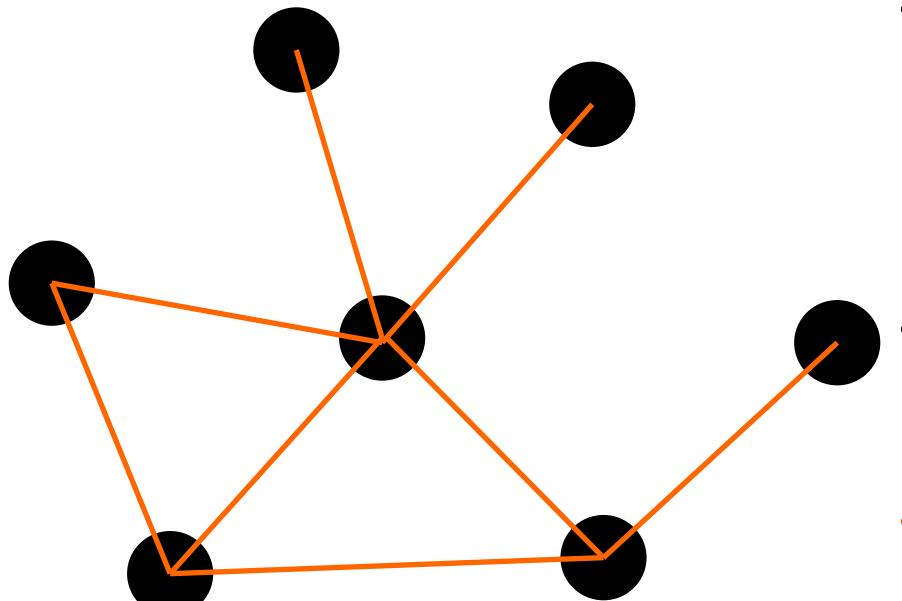
- **Network:** a model of connections and interactions
  - Internet, public transport, social networks

# Networks: what and why?



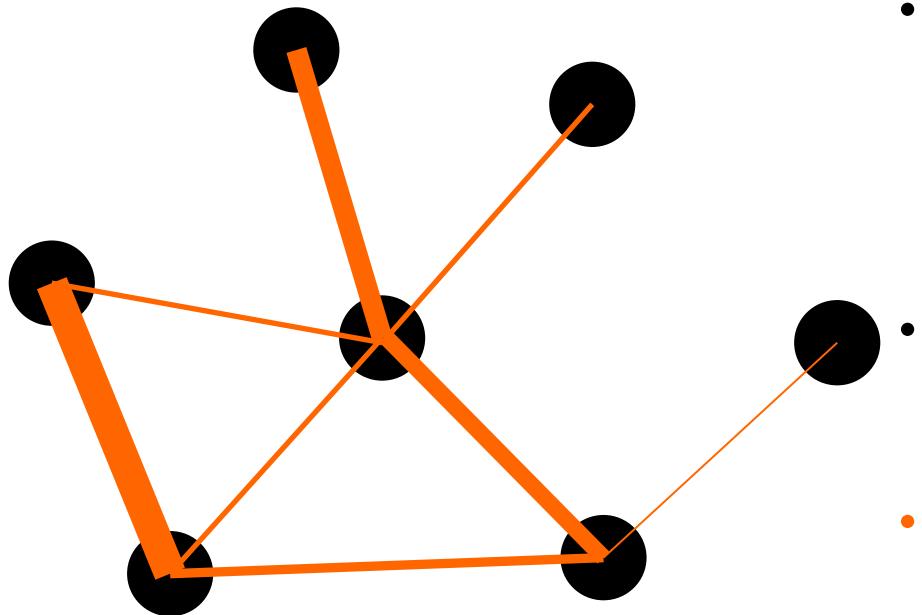
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- **Nodes:** network's basic elements
  - Web pages, stops, people

# Networks: what and why?



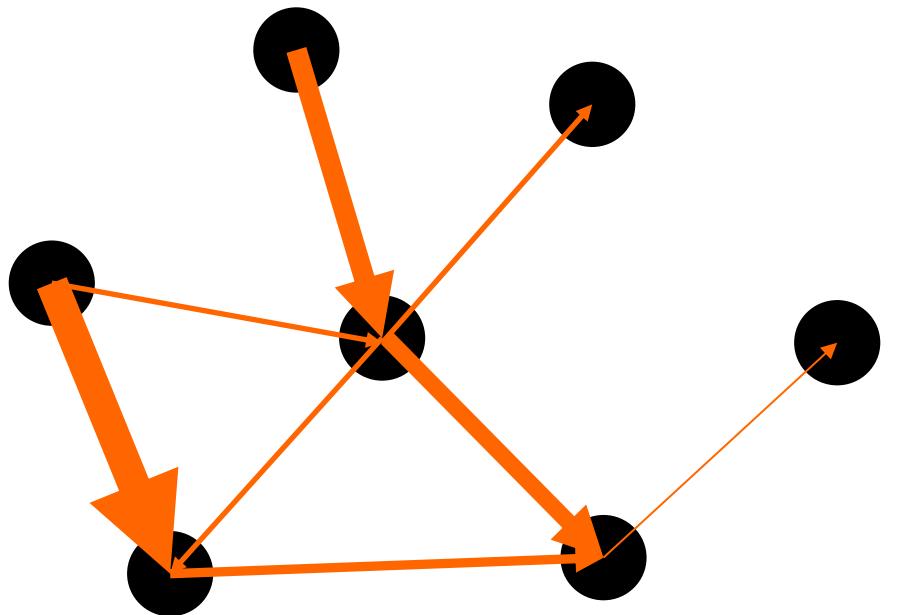
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# Networks: what and why?



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  - Weights?

# Networks: what and why?

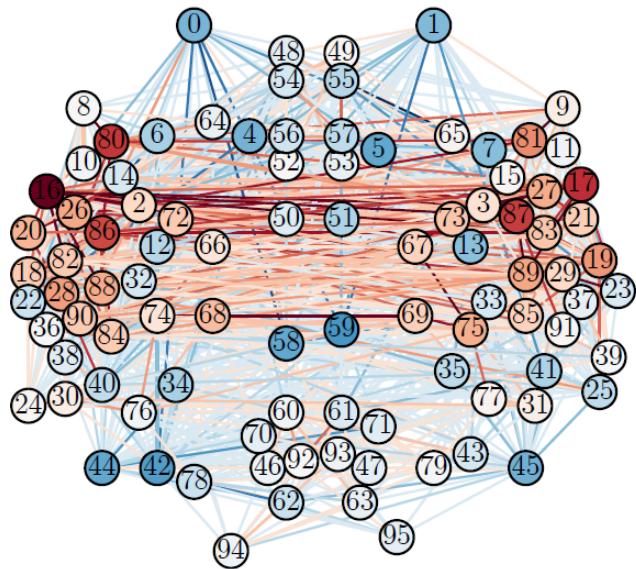


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- **Nodes:** network's basic elements
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- **Links:** connections between nodes
  - Web links, transport lines, social relationships
  - Weights?
  - Direction?

# **Brain networks: Why?**

# Why is the brain a network?

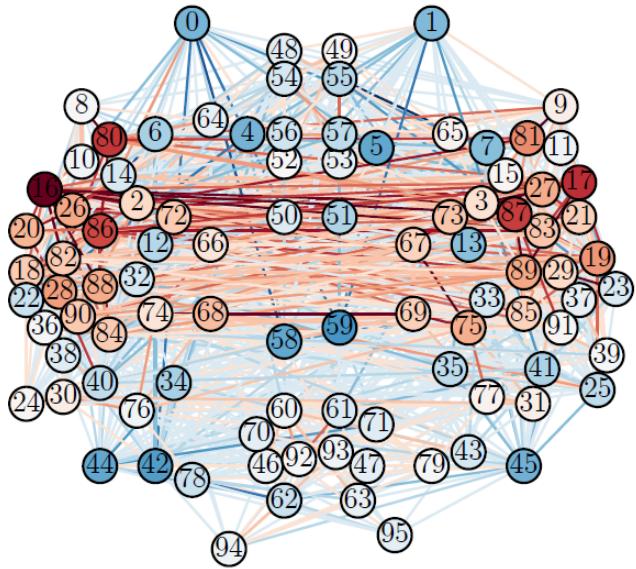
Fig: Alakörkkö et al. 2017,  
European Journal of Neuroscience



- Brain = a system of neurons
  - Separated neurons tend to reconnect

# Why is the brain a network?

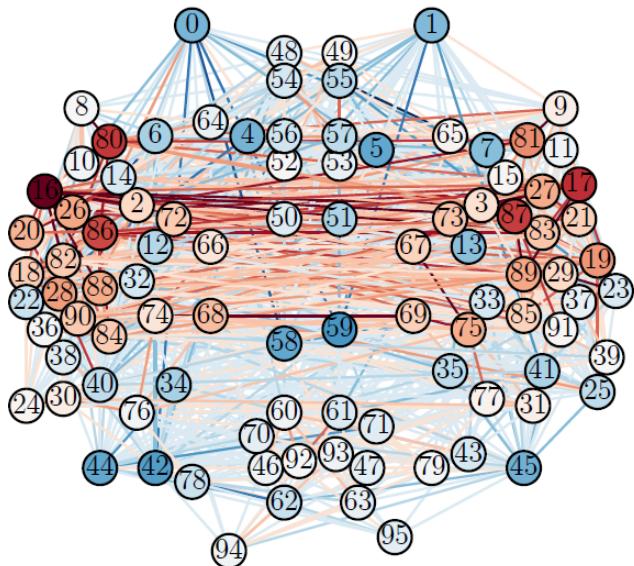
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- Brain = a system of neurons
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- Axon bundles connect brain areas

# Why is the brain a network?

Fig: Alakörkkö et al. 2017,  
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- Brain = a system of neurons
  - Separated neurons tend to reconnect
- Axon bundles connect brain areas
- Cognitive tasks require collaboration of brain areas

# **Brain networks: What?**

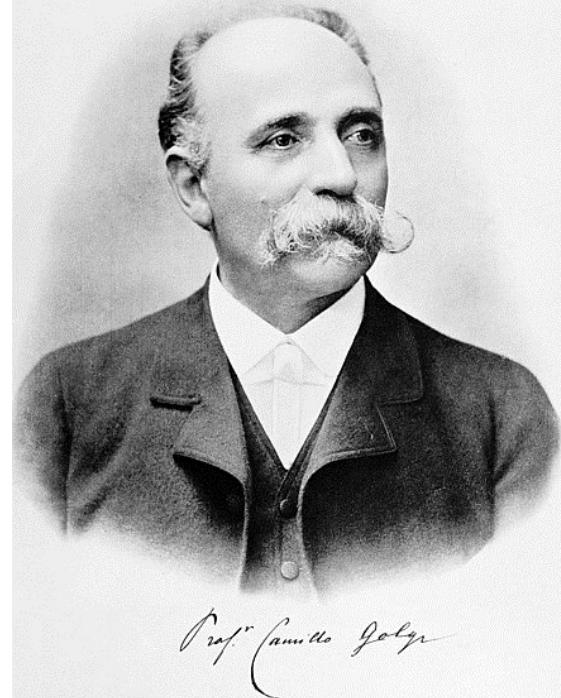
# Brain networks: some history

Fig: Wikipedia Commons, public domain



Joseph von Gerlach (1820-1896)

Fig: Wikipedia Commons, public domain



Camillo Golgi (1843-1926)

# Brain networks: some history



The *reticulum* theory:

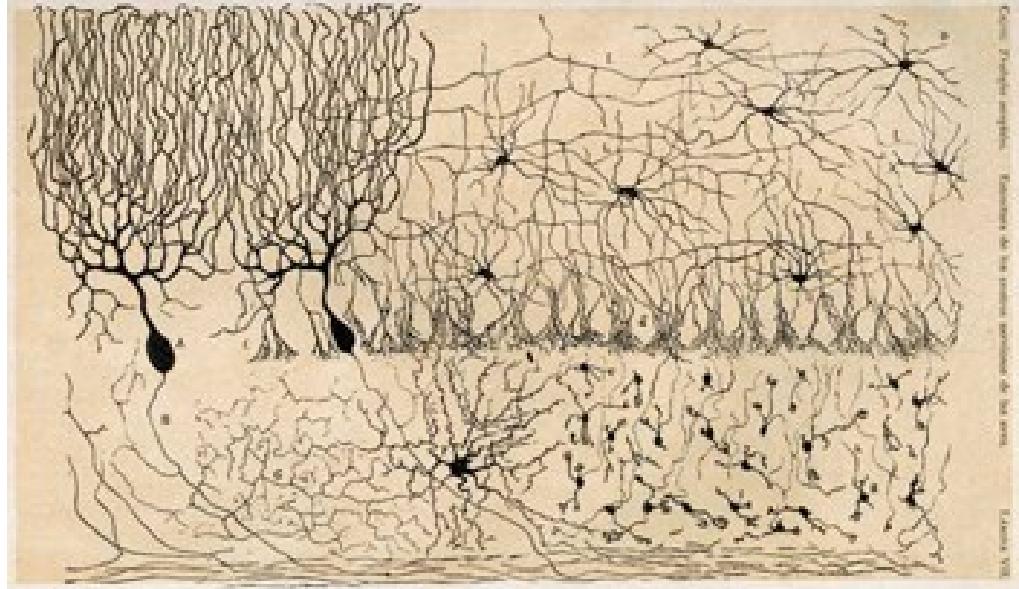
- The brain tissue = a continuous network, *reticulum*
- First attempts to map the nervous networks of animals
- Problem: no neurons = no nodes

# Brain networks: some history

Fig: Wikipedia Commons, public domain



Fig: Wikipedia Commons, public domain



Santiago Ramón y Cajal (1852-1934)

- The brain = a collection of neurons

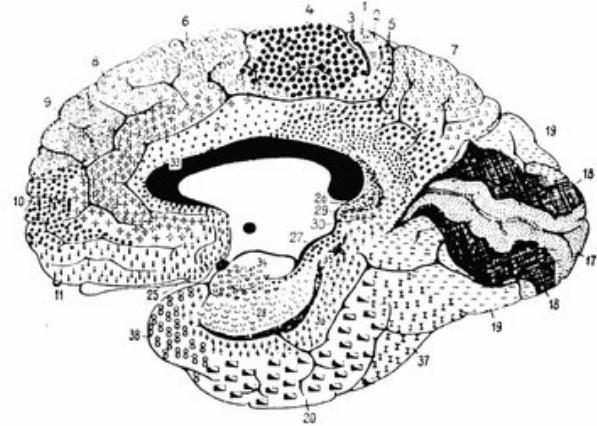
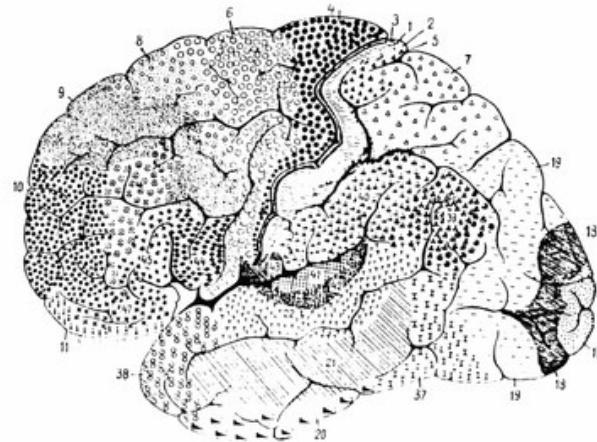
# Brain networks: some history



Korbinian Brodmann (1868-1918)

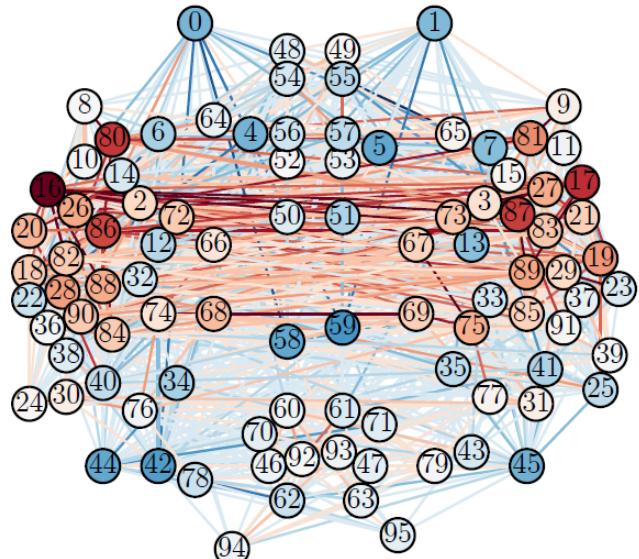
- Brain areas have different cells
- Different cells = different tasks

Fig: Wikipedia Commons, public domain



# Brain networks: some history

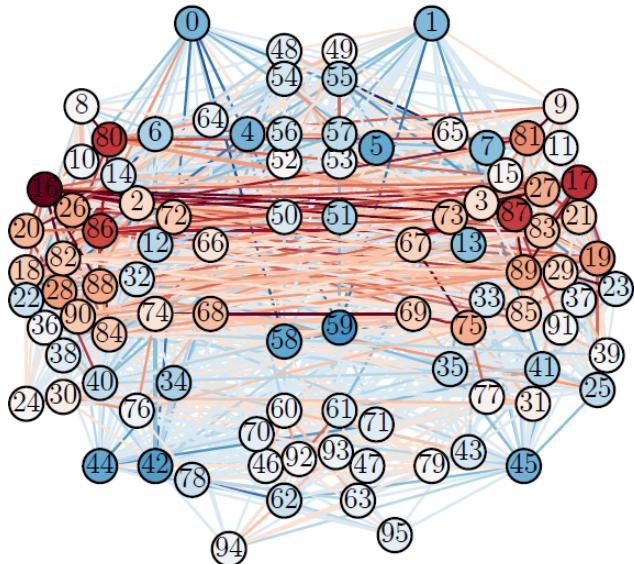
Renaissance of brain networks:



- The neural network of *C. elegans* (White et al. 1986)
- First neural networks of human in 1990s
- **Connectome, connectomics** = network of structural connections (Hagmann 2005, Sporns et al. 2005)
- **Network neuroscience** = neuroscience with network tools (Muldoon & Bassett 2016, Bassett & Sporns 2017)

# Network neuroscience

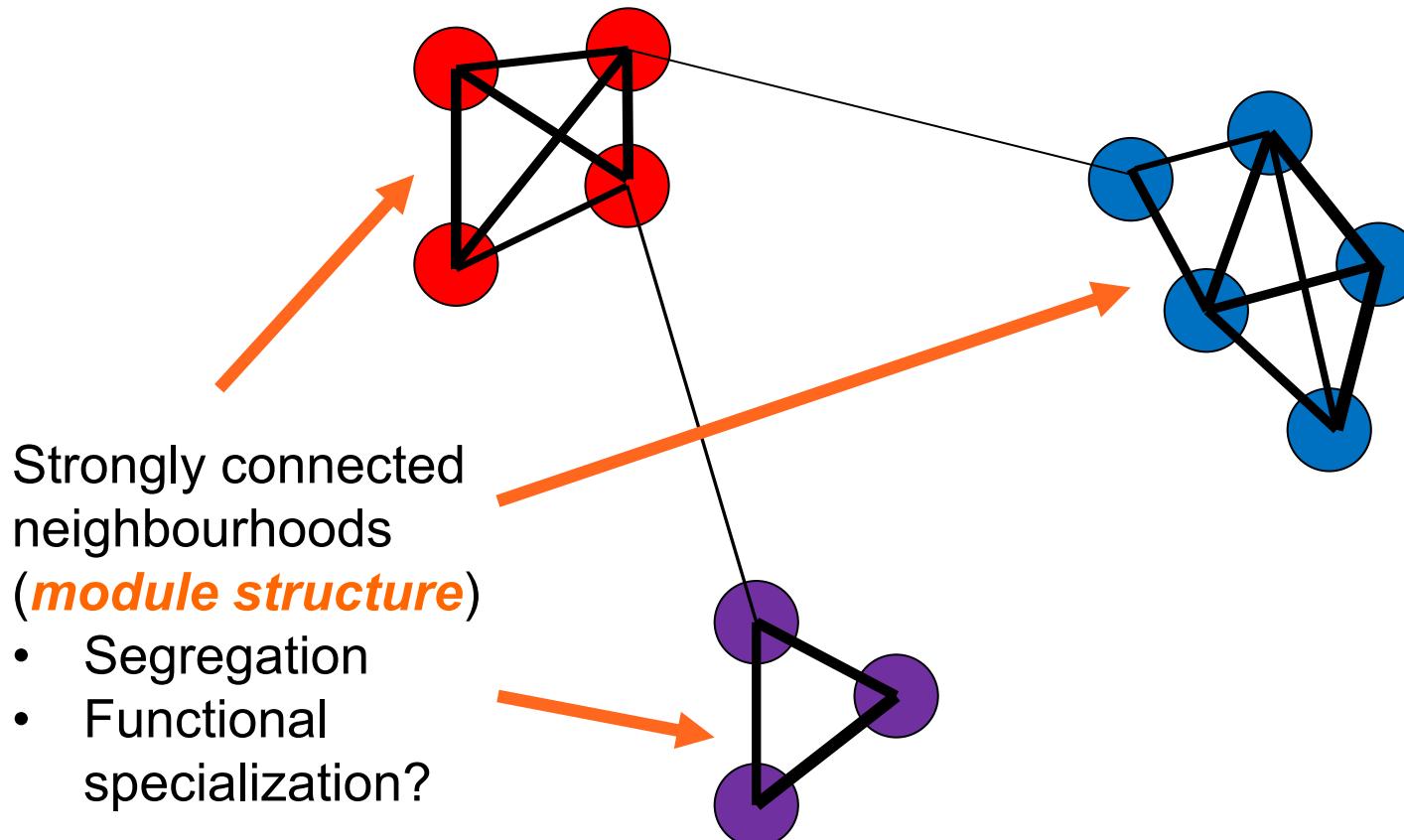
Fig: Alakörkkö et al. 2017,  
European Journal of Neuroscience



- Network neuroscience = applying network tools on the brain
- Two aims:
  1. Understand the healthy brain
  2. Find causes of diseases
- Broad scales:
  - Molecule – neuron – brain area – human
  - Milliseconds – years
- Different brain networks:
  - **Structural:** anatomic connections
  - **Functional:** temporal coactivation
  - **Effective:** causality

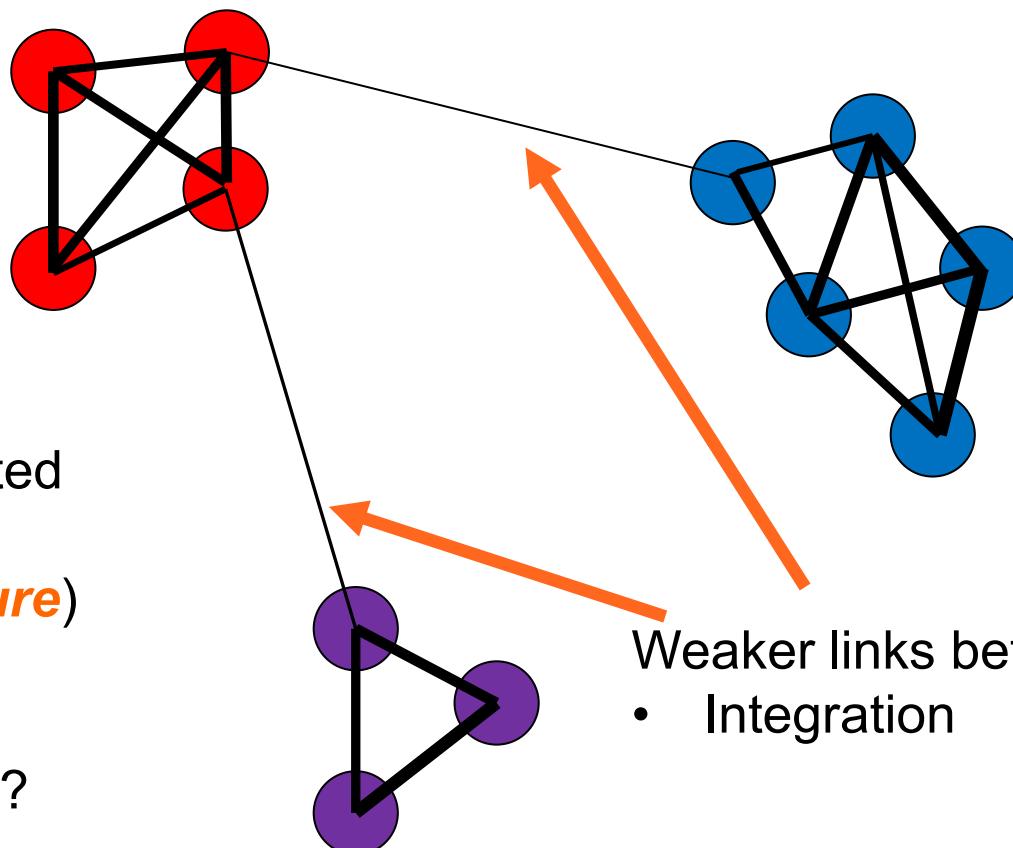
# What do brain networks look like?

Segregation-integration (Sporns 2013):



# What do brain networks look like?

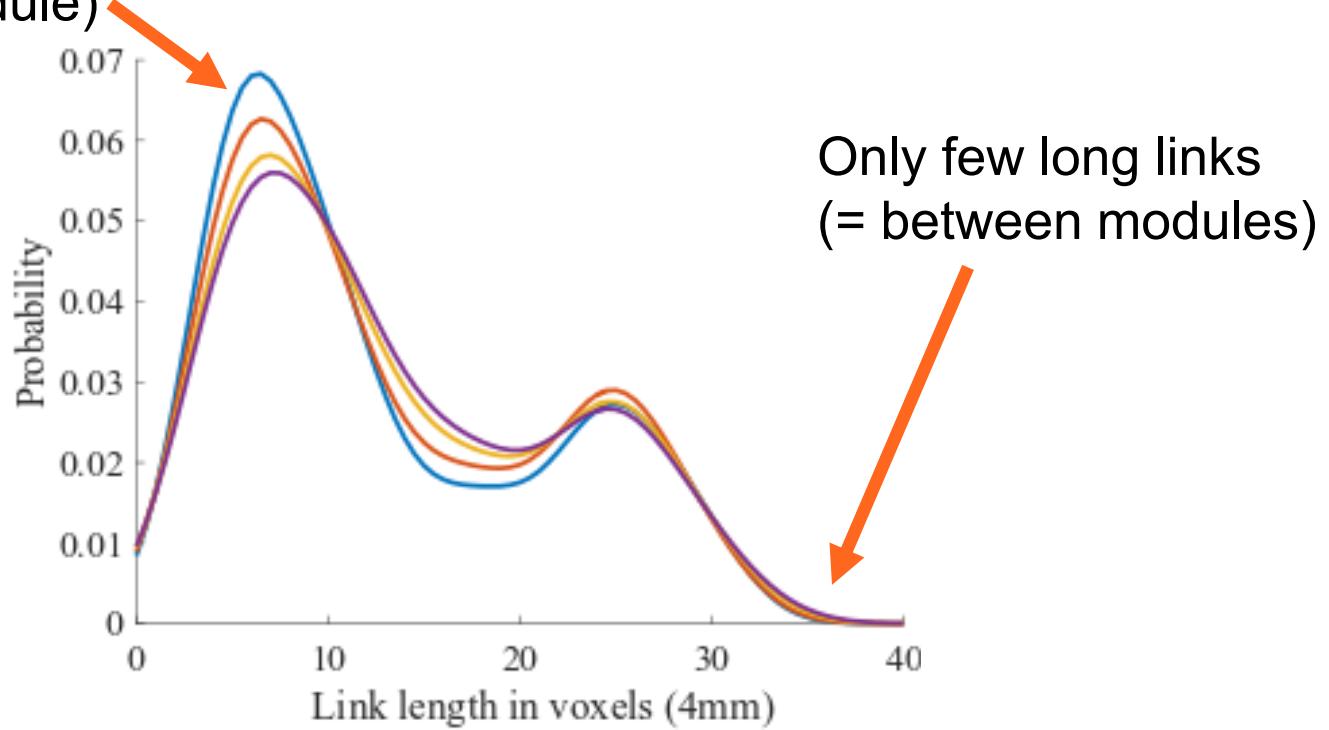
**Segregation-integration** (Sporns 2013):



# What do brain networks look like?

**Segregation-integration** (Sporns 2013):

Most network links are short (= inside module)



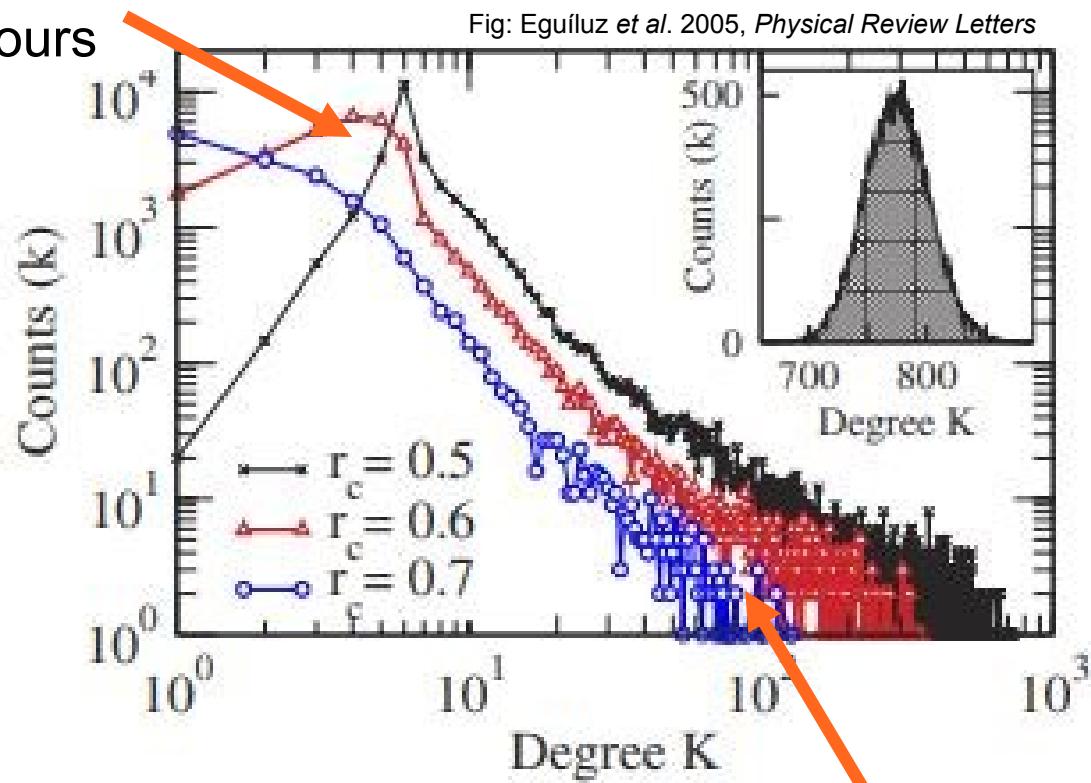
Only few long links  
 (= between modules)

Fig: Alakörkkö et al. 2017, *European Journal of Neuroscience*

# What do brain networks look like?

**Scale-freeness** (Eguíluz et al. 2005)

Most nodes have few neighbours



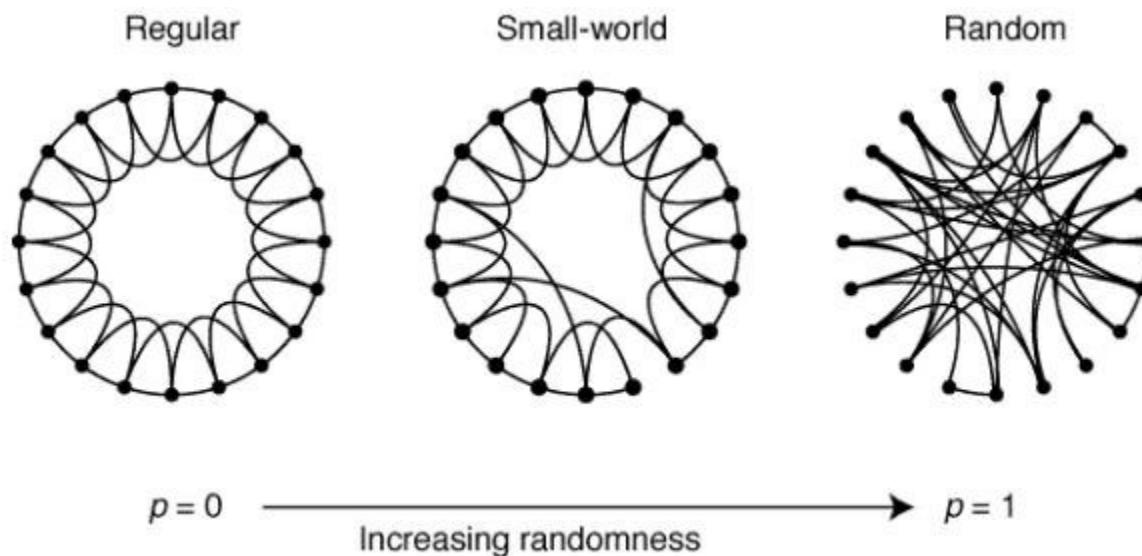
Some nodes (**hubs**) with lots of neighbours

- Hubs connect to each other (**rich-clubs**)

# What do brain networks look like?

**Small-worldness** (Watts & Strogatz 1998,  
Sporns & Zwi 2004)

Fig: Watts & Strogatz. 1998, *Nature*



Compared to random:

- High clustering
- Short paths

# What do brain networks look like?

**Small-worldness** (Watts & Strogatz 1998,  
Sporns & Zwi 2004)

Fig: Watts & Strogatz. 1998, *Nature*

Regular

Small-world

Random

But is the brain really a small world?  
(Papo et al. 2016)

- Data collection and preprocessing?
- Measuring small-worldness?
- Interpretation?

$p = 0$  —————→  $p = 1$   
Increasing randomness

Compared to random:

- High clustering
- Short paths

# What do brain networks look like?

Never the same!

Brain networks change:

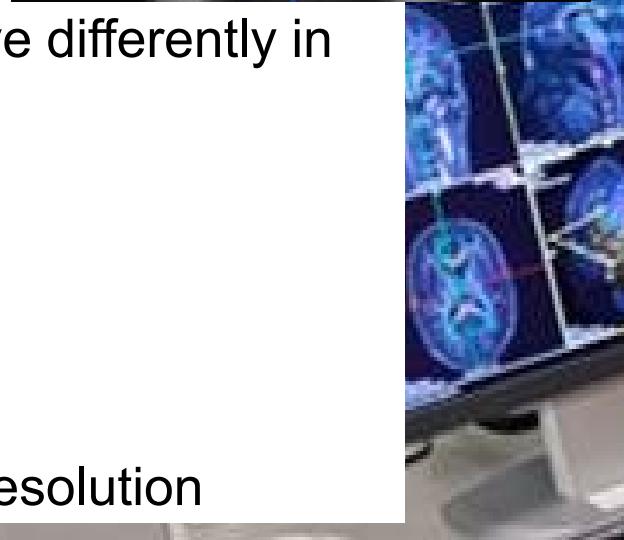
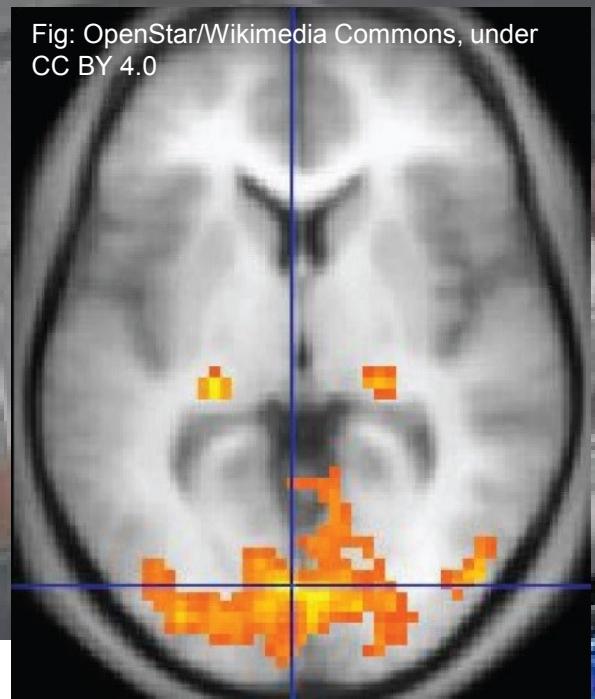
- Spontaneously over time
- Between cognitive tasks
- With age
- Between health and disease (e.g. Alzheimer's disease, Parkinson's disease, Autism Spectrum Disorders, epilepsy)

# **Brain networks: How?**

# Functional networks: fMRI



Fig: OpenStar/Wikimedia Commons, under CC BY 4.0



- Based on magnetic properties of haemoglobin
- Oxygen-rich and oxygen poor haemoglobin behave differently in (strong) magnetic field  
    => **oxygen-rich areas localized**
- Brain function requires oxygen  
    => **high oxygen level = high activity**
- Measurement unit = voxel
- High (~mm) spatial resolution, low (~s) temporal resolution

# Functional networks: EEG & MEG

Fig: Chris Hope/Wikimedia Commons, under CC BY 2.0

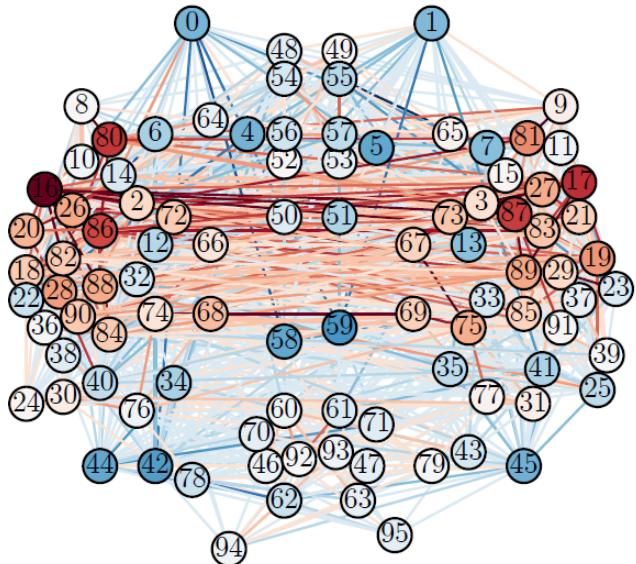


Fig: Wikimedia Commons, public domain



- Neurons interact electronically
- **EEG**: the electrical field of the brain
- **MEG**: the magnetic field of the brain
- Inverse model: time series of brain surface vertices
- Excellent (~ms) temporal resolution, lower spatial resolution

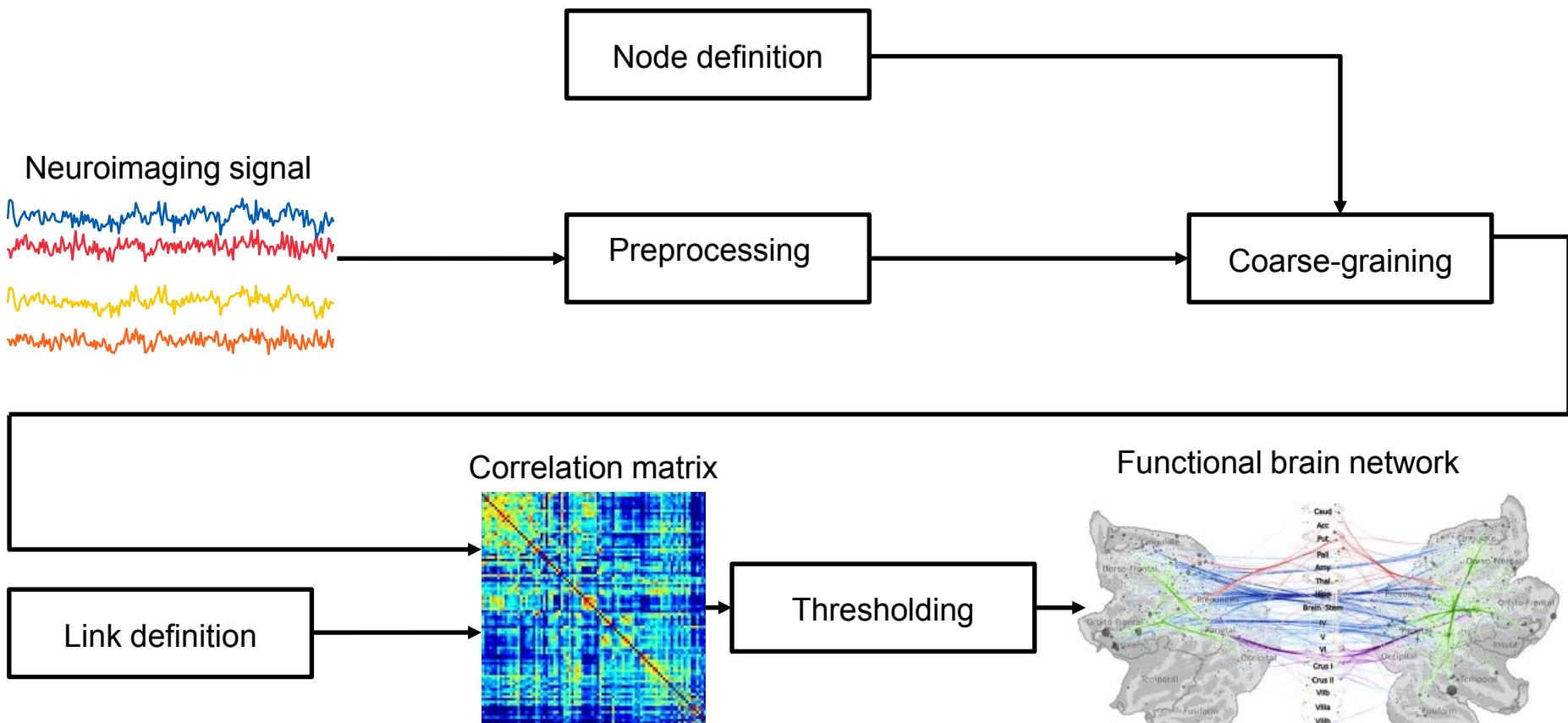
# Functional networks: how-to?



Weighted networks from time series: a simple recipe

1. Define nodes (each one with a time series)
2. Define links (measures of similarity between time series)
3. Define threshold and keep only super-threshold links

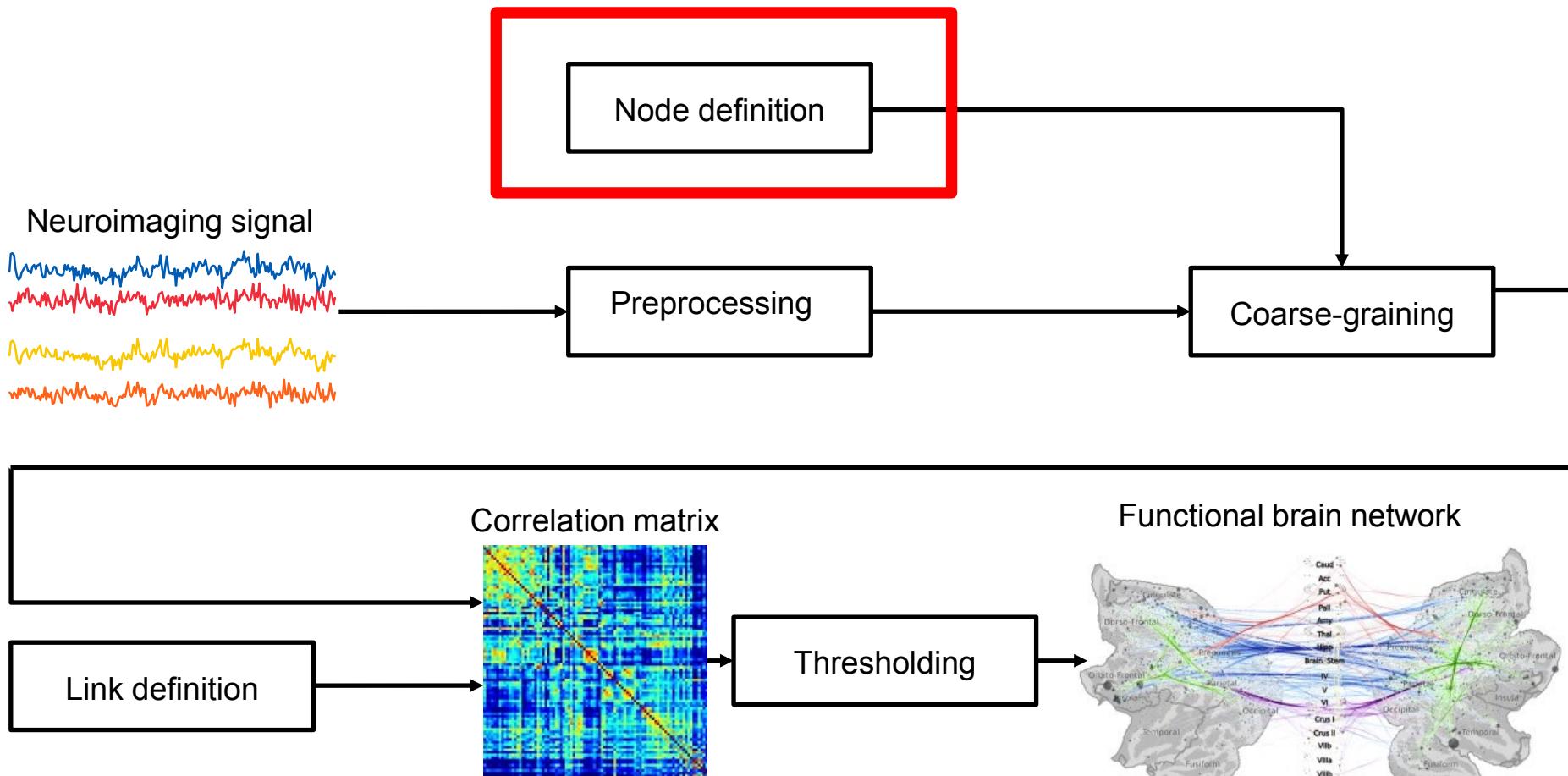
# Functional networks: how-to?



Network from Nummenmaa et al. 2014,  
*NeuroImage*, by permission

# **Brain networks: How not?**

# Functional networks: how-to?



Network from Nummenmaa et al. 2014,  
*NeuroImage*, by permission

# The problem of node definition

- No natural candidates above the neuronal scale
- Node selection affects network properties (e.g. Wang et al. 2009)
- Some commonly used nodes:
  - voxels/vertices
  - random clumps of voxels/vertices
  - Regions of Interest (***ROIs***): collections of voxels/vertices

# Voxels vs ROIs

## Voxels:

- fMRI imaging resolution
- noisy signals?
- ~10.000 nodes
- large computational load

## ROIs:

- collections of voxels
- defined by anatomy, function, connectivity, ...
- Homogeneous (= all voxels have same dynamics)?
- ROI time series to represent voxel dynamics:

$$X_I = \frac{1}{N_I} \sum_{i \in I} x_i$$

Violent?

# Consistency of Regions of Interest as nodes of fMRI functional brain networks

Korhonen, O., Saarimäki, H., Glerean, E., Sams, M., & Saramäki, J. 2017. *Network Neuroscience*

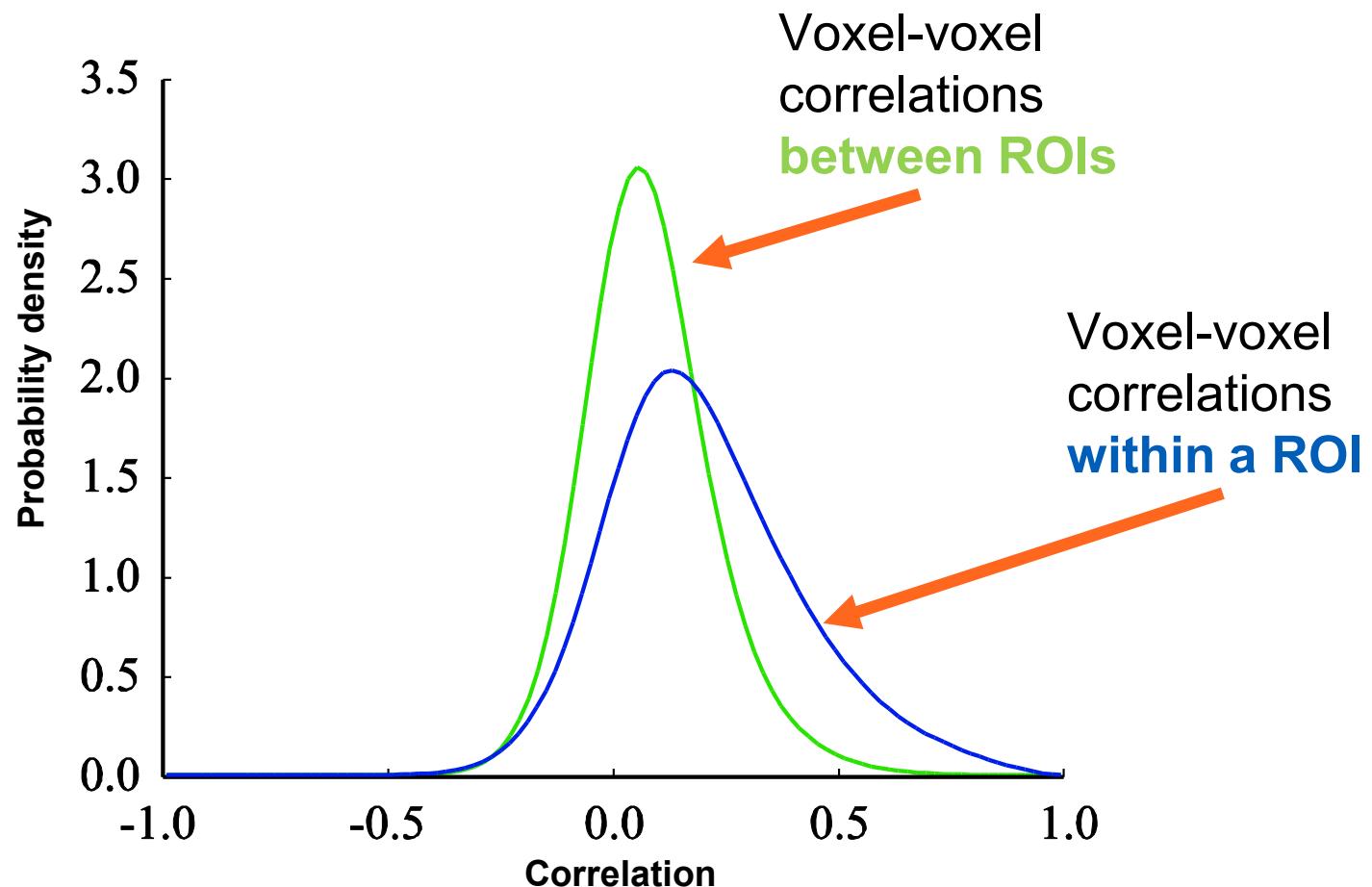
# Research questions

- What should nodes of brain networks depict?
  - ROIs or voxels?
  - Are ROIs functionally homogeneous?

# Methods

- Two sets of resting-state fMRI data:
  - 13 in-house subjects
  - 28 subjects from ABIDE I initiative
- 215 time points (~6 min)
- ROIs from three atlases:
  - HO: anatomical
  - AAL: anatomical
  - Brainnetome: connectivity-based
- Connectivity investigated at voxel and ROI levels

# How correlated are voxels of a ROI?



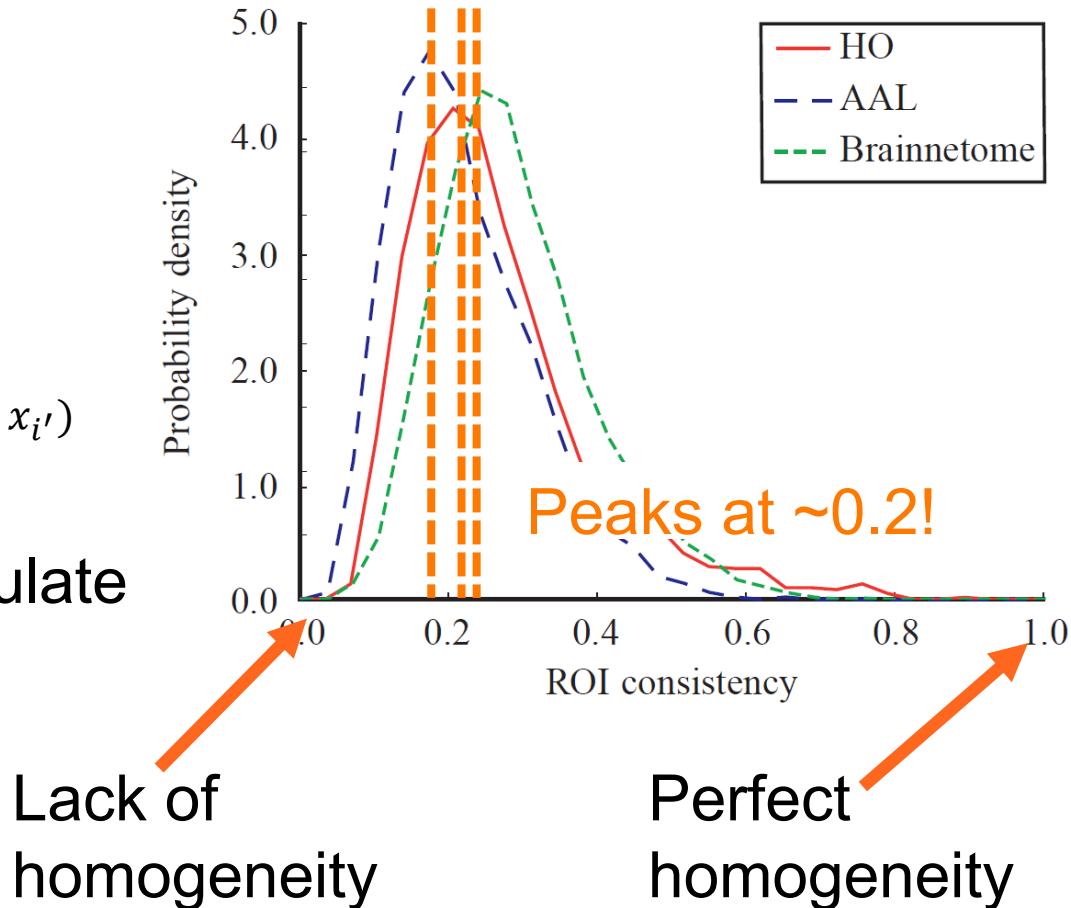
# How homogeneous are ROIs?

- **Spatial consistency**

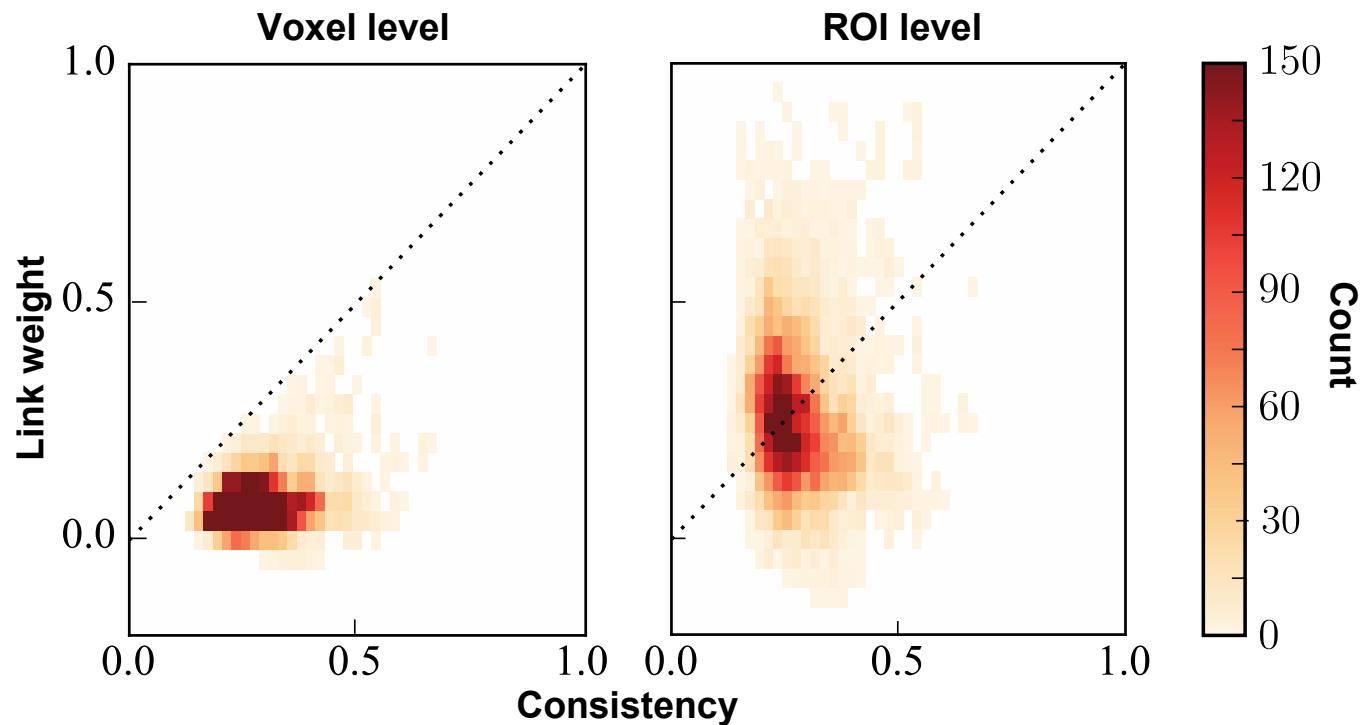
= measure of functional homogeneity:

$$\varphi_{spat}(I) = \frac{1}{N_I(N_I - 1)} \sum_{i,i' \in I} C(x_i, x_{i'})$$

- Straightforward to calculate
- Easy to interpret

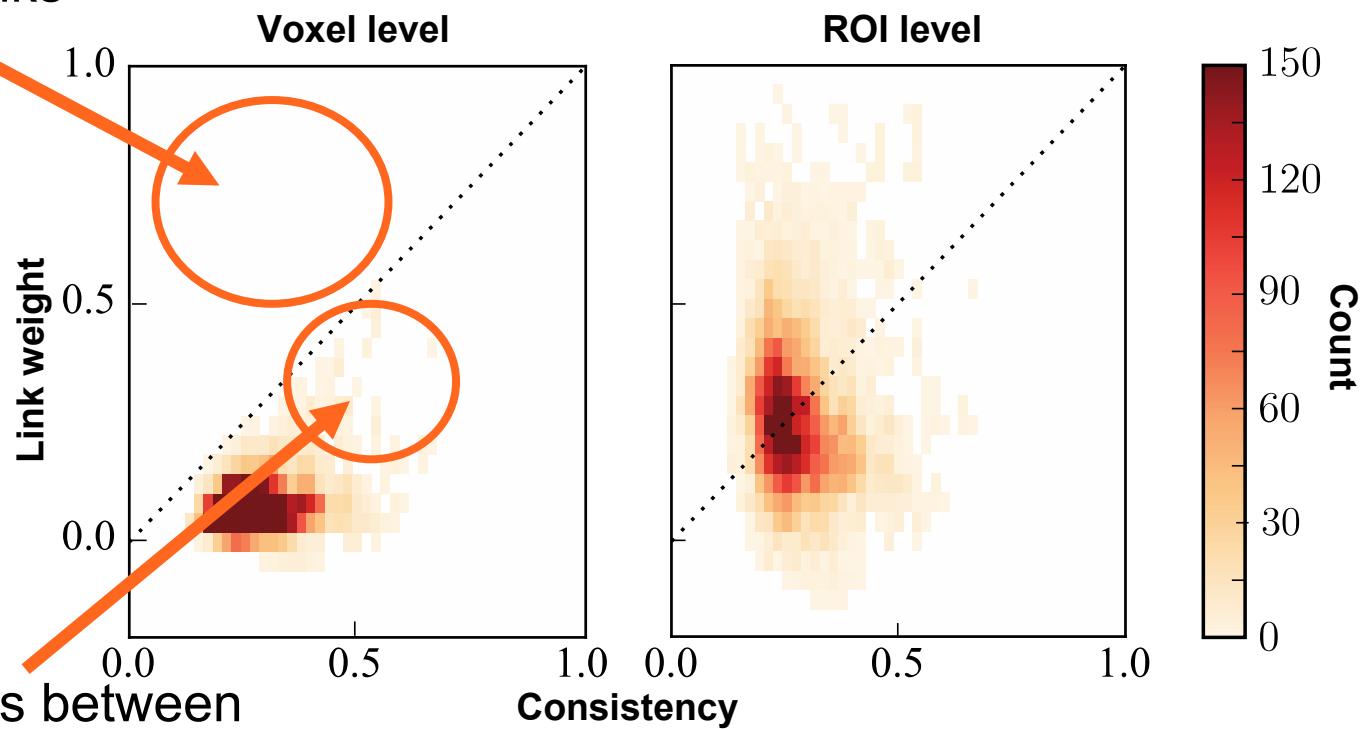


# Does consistency predict connectivity?



# Does consistency predict connectivity?

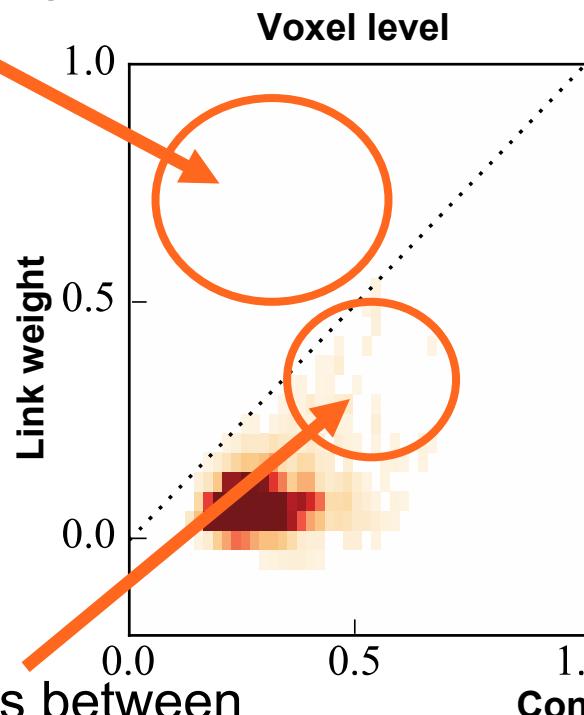
No links



Strong links between  
consistent ROIs

# Does consistency predict connectivity?

No links



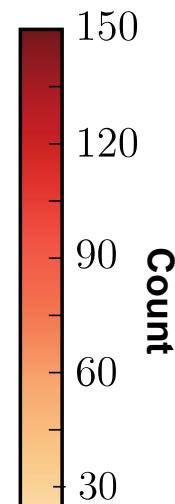
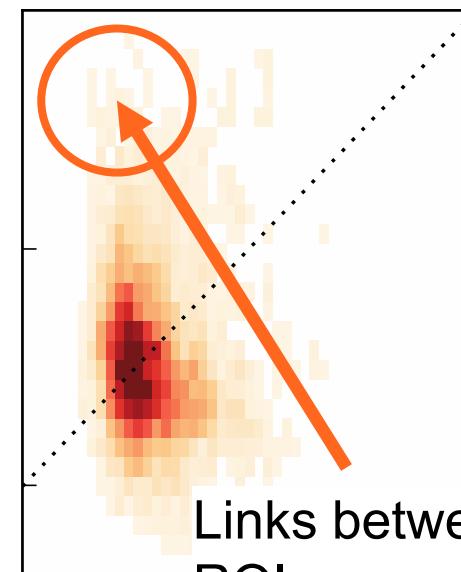
Voxel level

ROI level

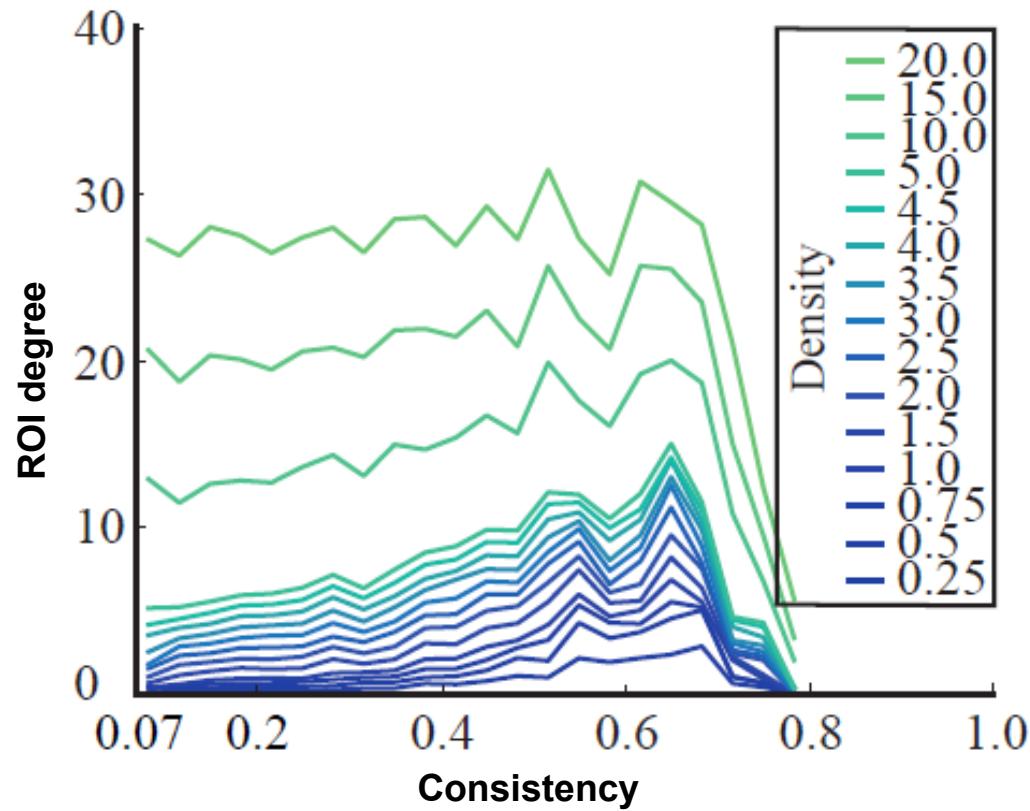
Links between non-consistent ROIs

- How to interpret?

Strong links between consistent ROIs



# Does consistency tell about ROI's functional role?



# Conclusions

- ROIs are not always functionally homogeneous
- Strong ROI-level correlations between low-consistency ROIs may be spurious
- Does a low spatial consistency tell about
  - a) A bad ROI definition
  - b) High noise level
  - c) Inactivity of the ROI?

# Regions of Interest as nodes of dynamic functional brain networks

Ryppö, E., Glerean, E., Brattico, E., Saramäki, J., & Korhonen, O. 2018, *Network Neuroscience*

# Research questions

- ROIs as nodes of dynamic brain networks?
- Temporal behaviour of spatial consistency?

# Methods

- Two sets of fMRI data:
  - Music listening (13 subjects)
  - Resting-state (28 subjects)
- ROIs:
  - Brainnetome
  - HO
  - AAL
- Time windows: 80 samples (160s), 50% overlap
- For each ROI, we build “closest neighborhoods” (35 strongest links of ROI)

# Measures

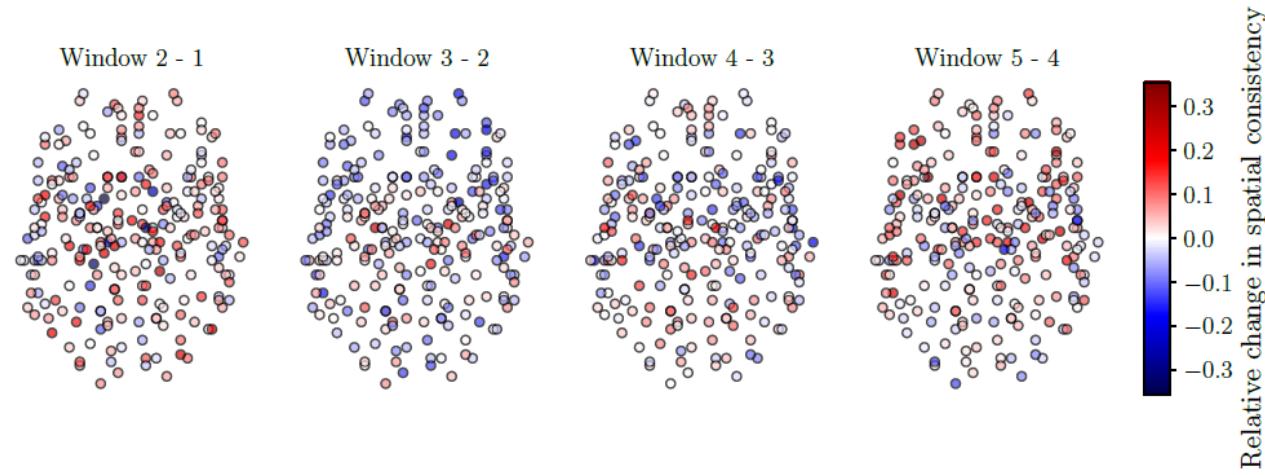
- Spatial consistency  $\varphi_{spat}$ : functional homogeneity of ROI
- Spatiotemporal consistency: time-dependence of  $\varphi_{spat}$

$$\varphi_{st}(I) = \frac{N_t(N_t - 1)}{2 \sum_{t < t'} \frac{|\varphi_{spat}(I, t) - \varphi_{spat}(I, t')|}{\varphi_{spat}(I, t)}}$$

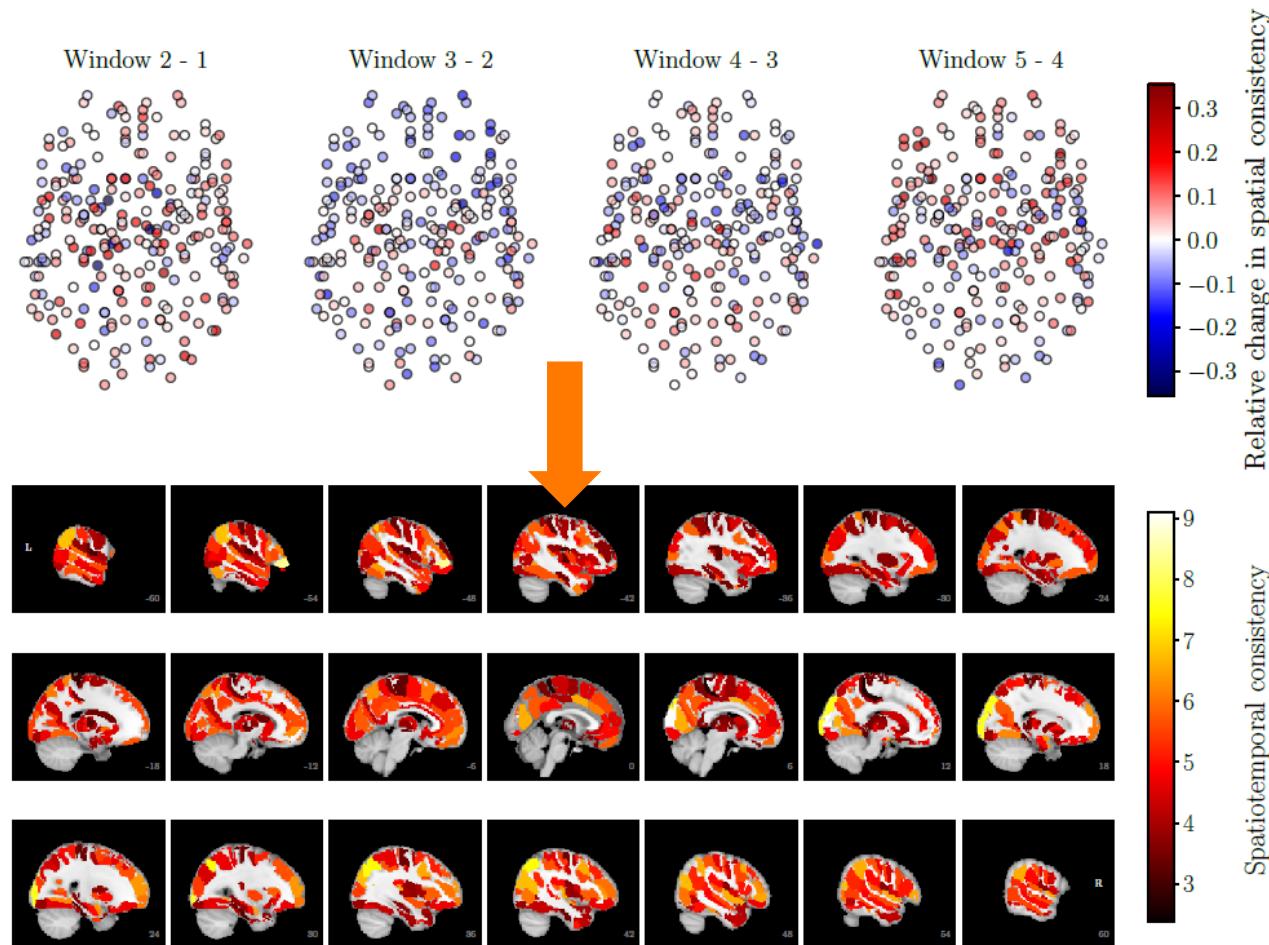
- Network turnover: changes in local network structure

$$\delta_{network}(I) = 1 - \mu_t^{Jaccard}(I)$$

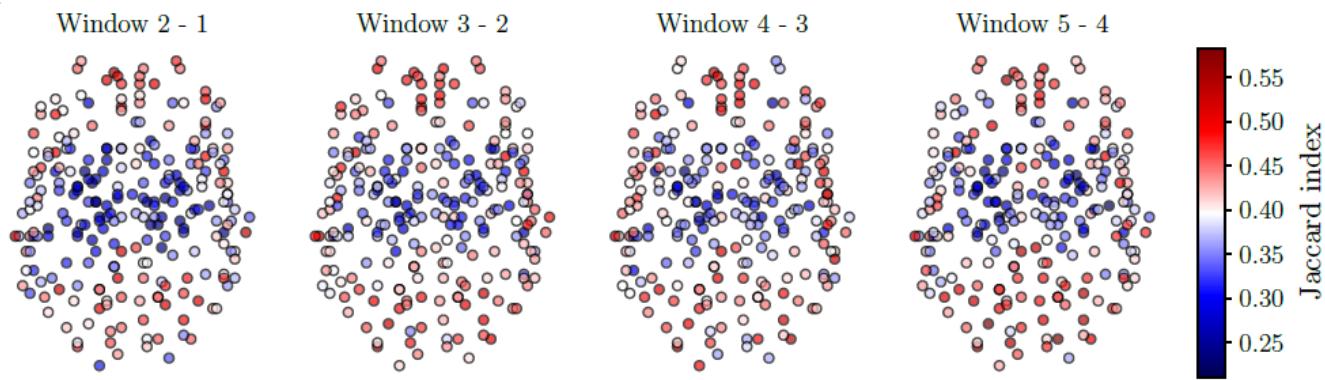
# Spatial consistency changes in time



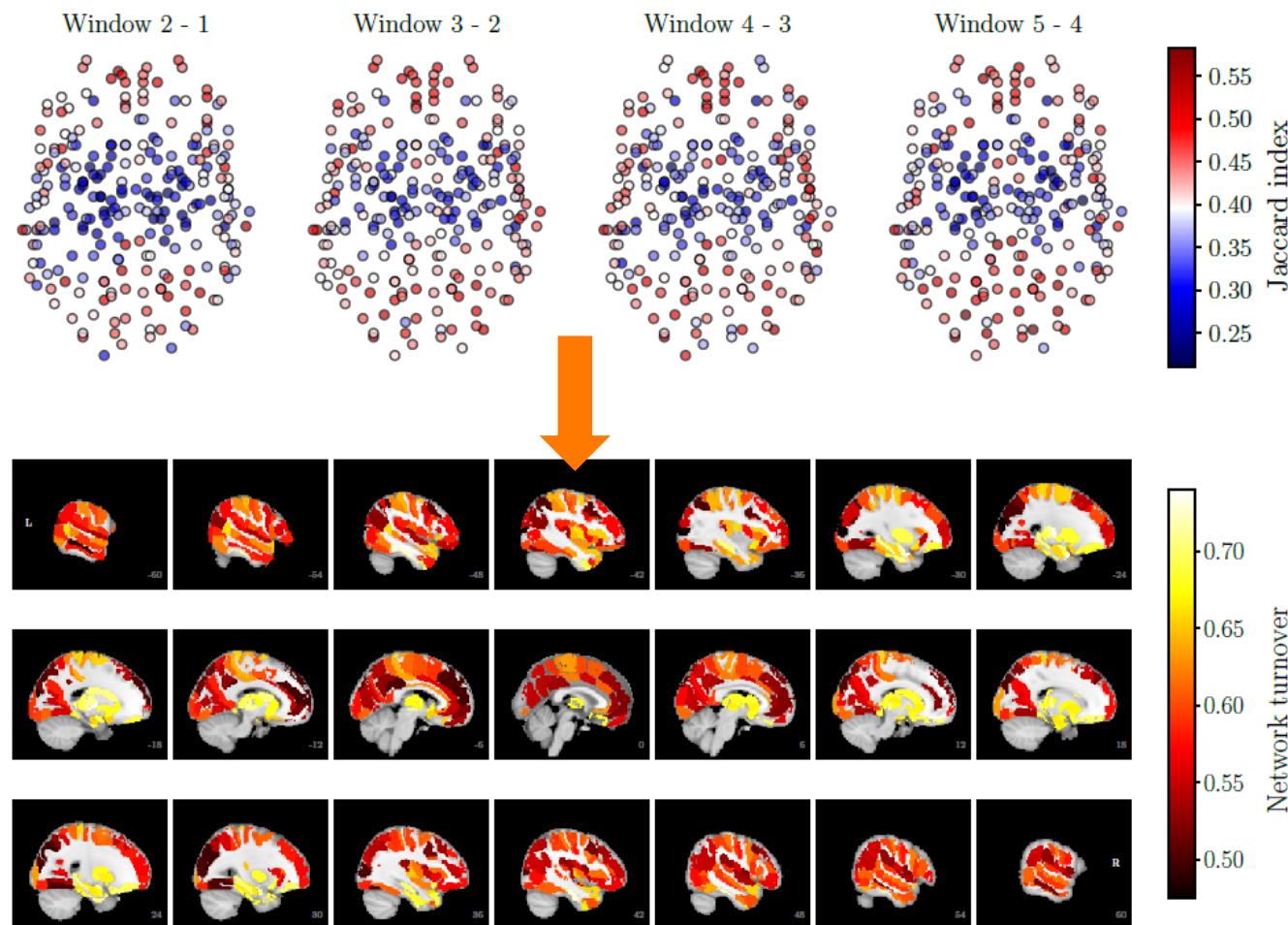
# Spatial consistency changes in time



# Turnover in network neighborhoods

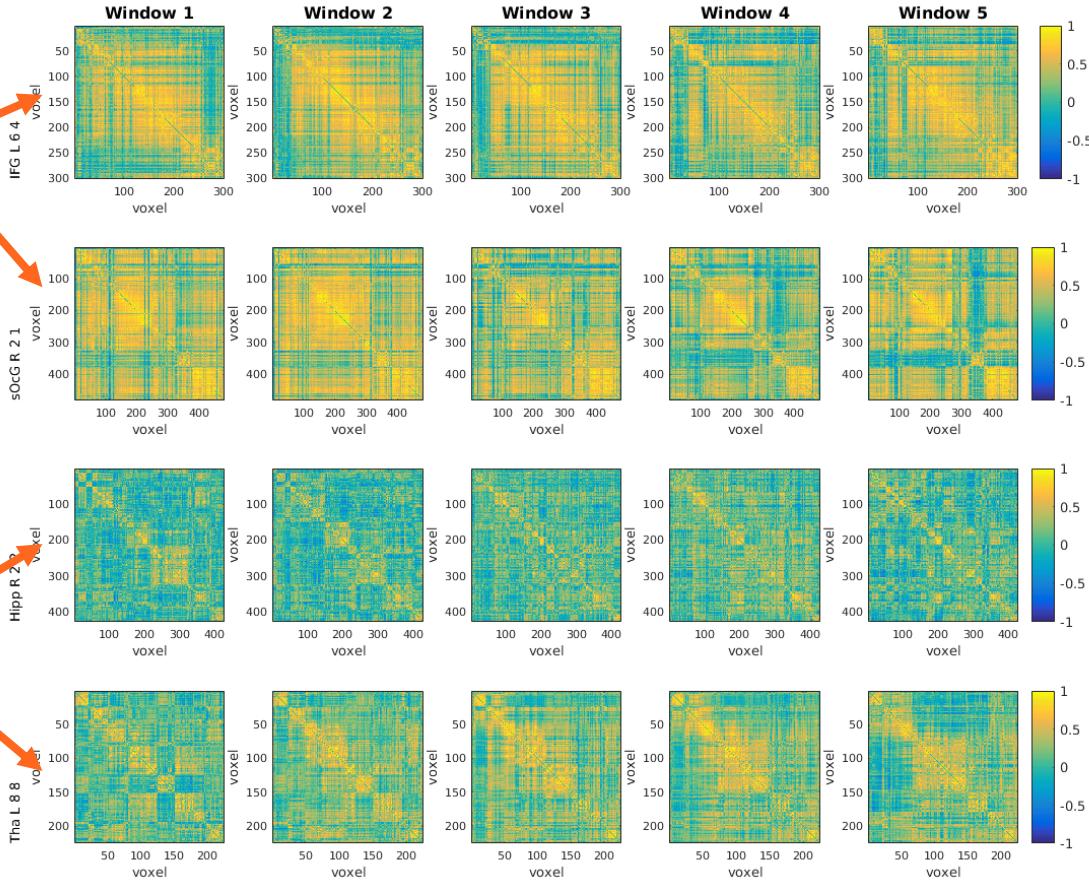


# Turnover in network neighborhoods



# ROIs have rich internal connectivity structure

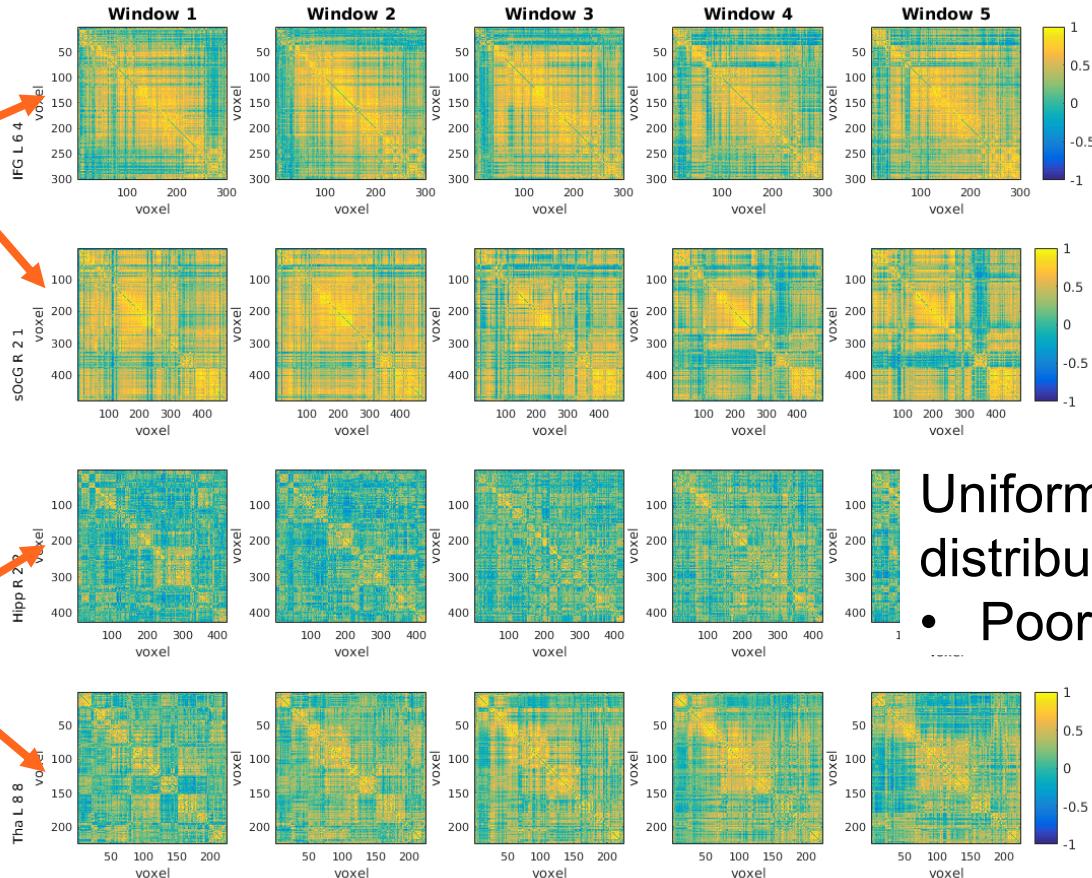
High spatial consistency



Low spatial consistency

# ROIs have rich internal connectivity structure

# High spatial consistency



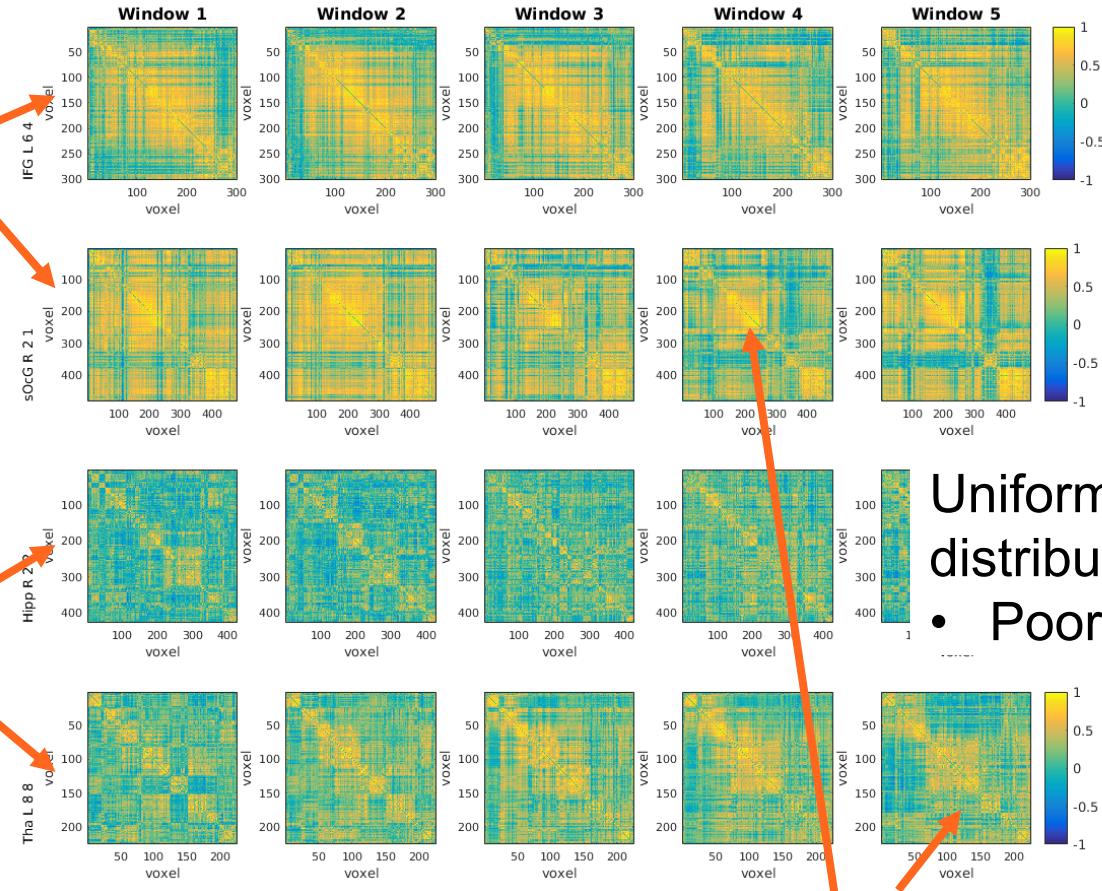
## Low spatial consistency

Uniform correlation distribution

- Poorly defined ROI?

# ROIs have rich internal connectivity structure

# High spatial consistency



## Low spatial consistency

Uniform correlation distribution

- Poorly defined ROI?

- Poorly defined ROI?

Intra-ROI modules

  - Network topology?

# Conclusions

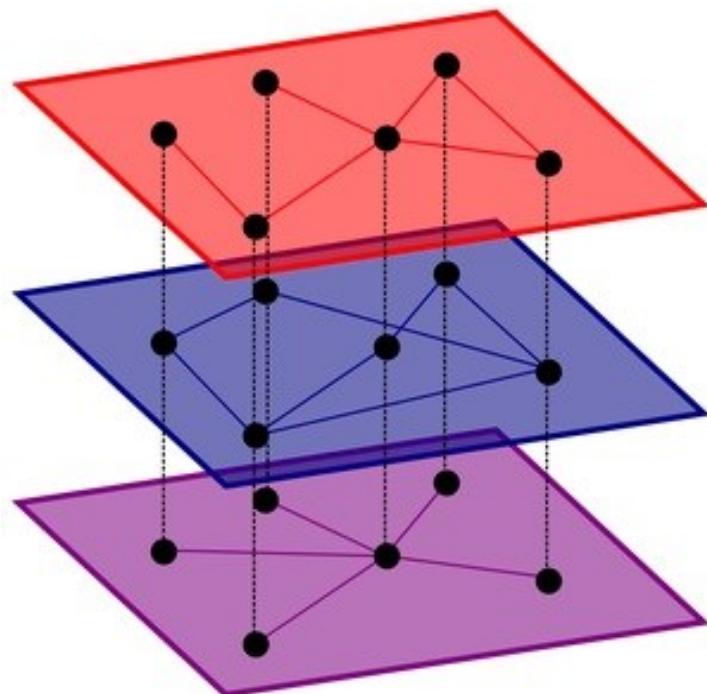
- Spatial consistency changes in time
  - Reflects activation?
- ROIs have time-dependent internal structure
  - Relates to network topology?
- Do brain networks have stable nodes?

# **On-going work: Multilayer brain networks with flexible nodes**

with Tarmo Nurmi, Maria Hakonen, Iiro Jääskeläinen &  
Mikko Kivelä

# Network model with flexible nodes

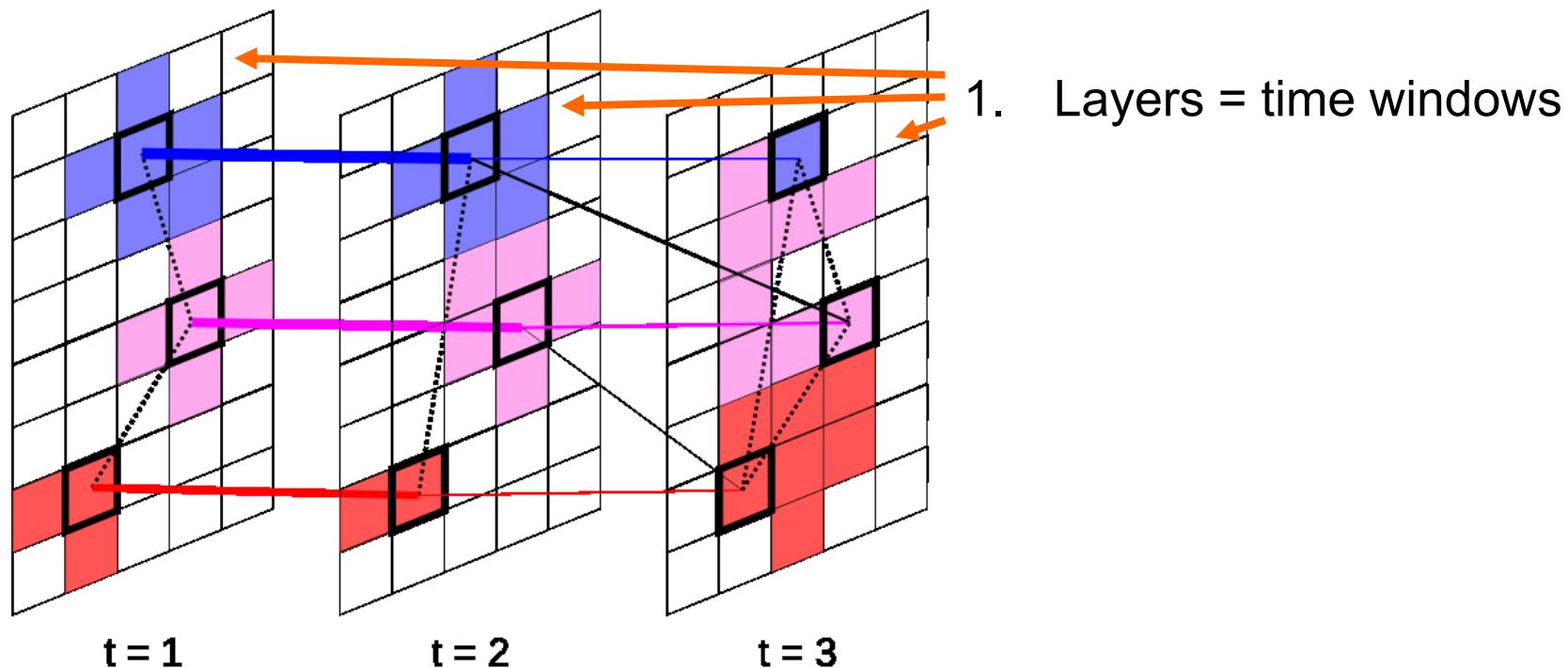
- Based on *multilayer networks* (e.g. Kivelä et al. 2014):



- Different connections in a single network
- Each connection type on its own layer
- Interpretation of inter-layer connections?
- Typical examples: social networks, transport, ...

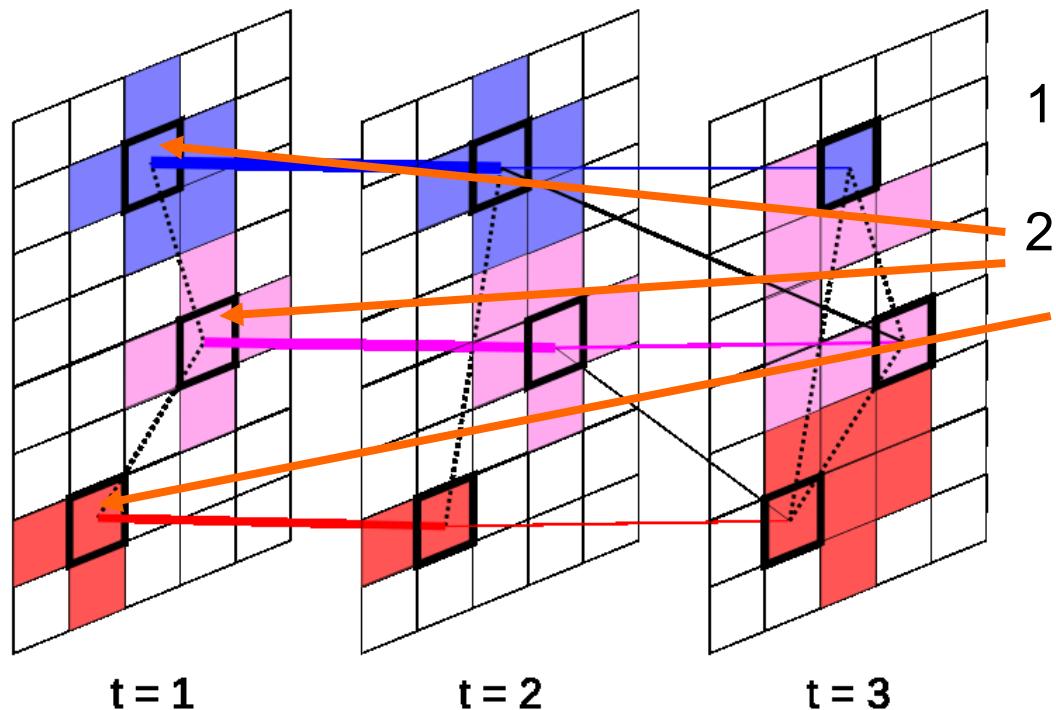
# Network model with flexible nodes

- Based on multilayer networks (= different connections in the same network)



# Network model with flexible nodes

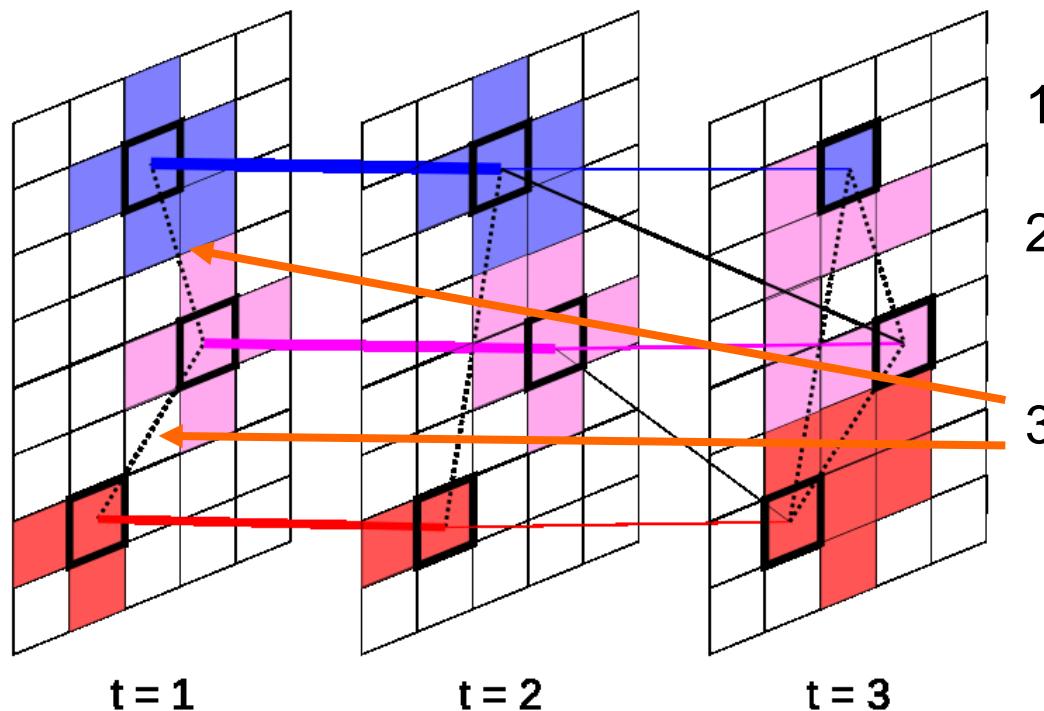
- Based on multilayer networks (= different connections in the same network)



1. Layers = time windows
2. ROIs optimized inside layers for maximal consistency

# Network model with flexible nodes

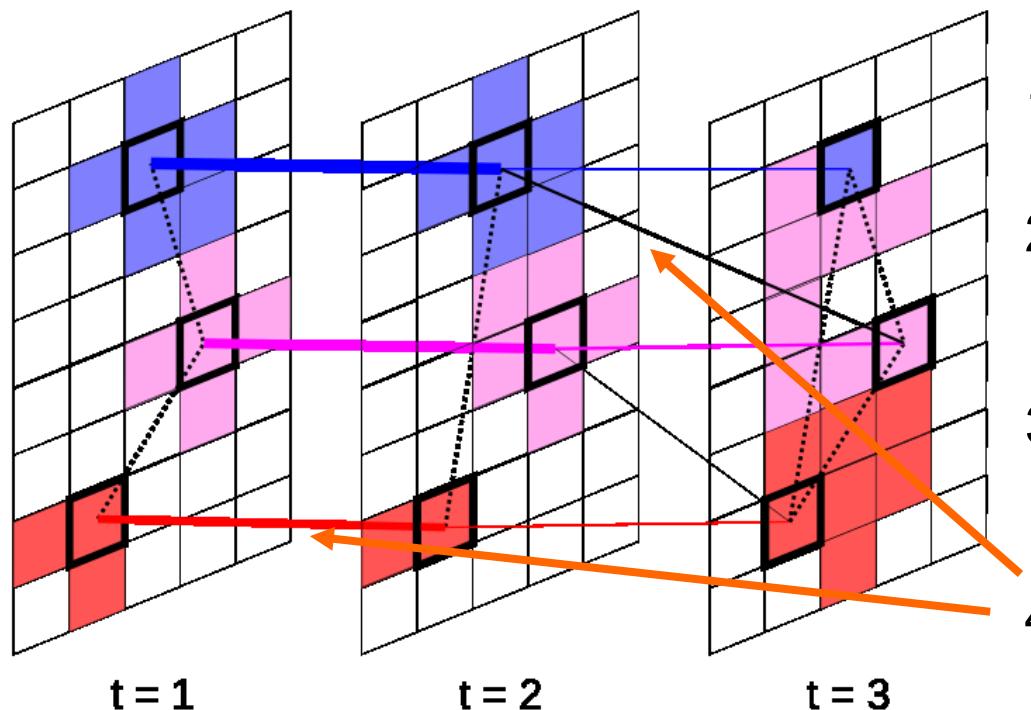
- Based on multilayer networks (= different connections in the same network)



1. Layers = time windows
2. ROIs optimized inside layers for maximal homogeneity
3. Interlayer links = Pearson correlation

# Network model with flexible nodes

- Based on multilayer networks (= different connections in the same network)



1. Layers = time windows
2. ROIs optimized inside layers for maximal homogeneity
3. Interlayer links = Pearson correlation
4. Intralayer links = spatial overlap

# General conclusions

- It's not trivial to construct a functional brain network
  - **Know your methods!**
- Currently used nodes are not functionally homogeneous
  - Data lost in averaging
  - Risk of spurious connectivity?
- Homogeneity changes in time
  - Changes relate to function?
- Low homogeneity isn't a technical flaw
  - ⇒ Can't be fixed by new static nodes
  - ⇒ **Flexible nodes needed!**

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**Thank you!**

**Questions, comments?**

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