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


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Slides: https://github.com/onerva-korhonen/presentations/blob/master/uppsala-250520.pdf

# Networks: what and why?

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

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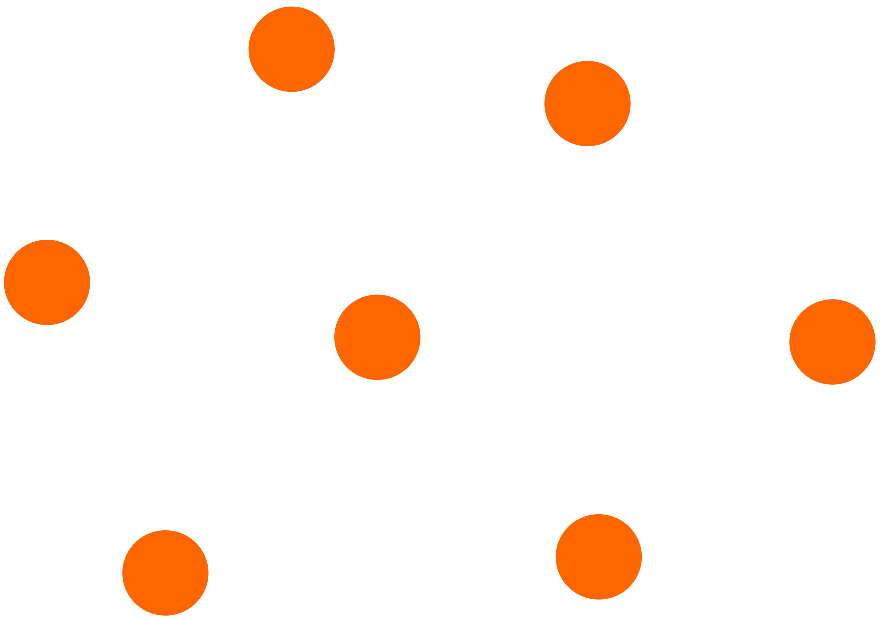

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- **Nodes:** network's basic elements
  - Web pages, stops, people

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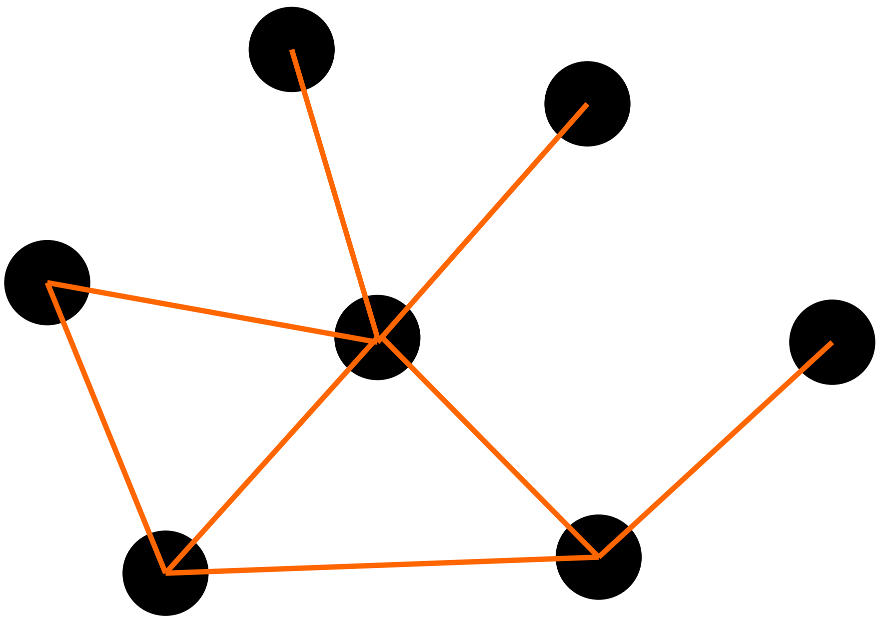

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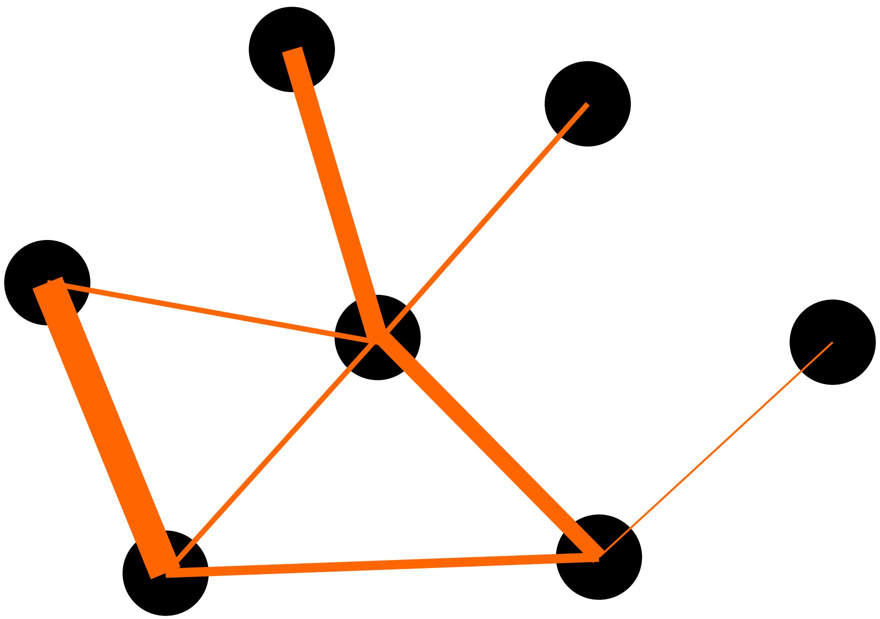

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  - Weights?

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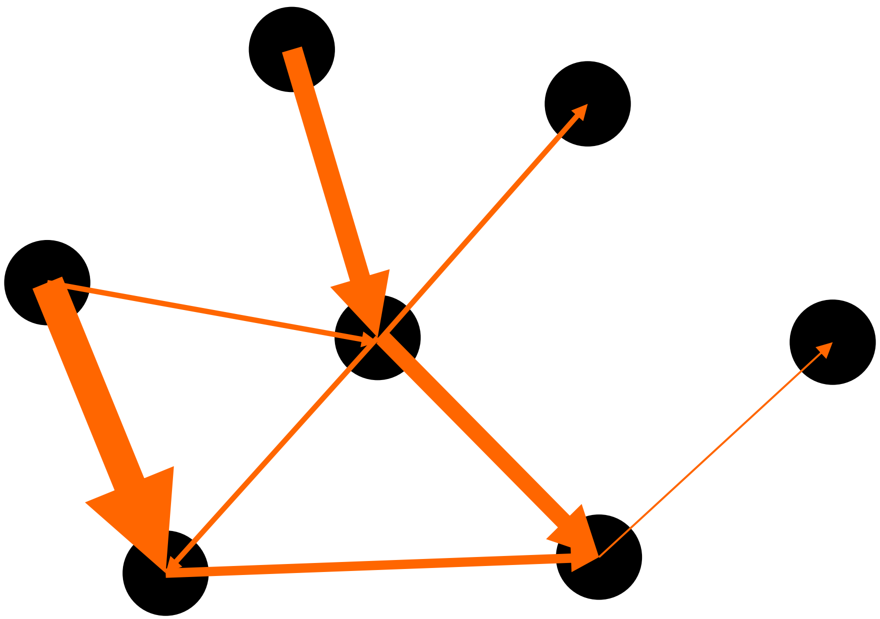

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  - Weights?
  - Direction?

# Brain networks: Why?

# Why is the brain a network?

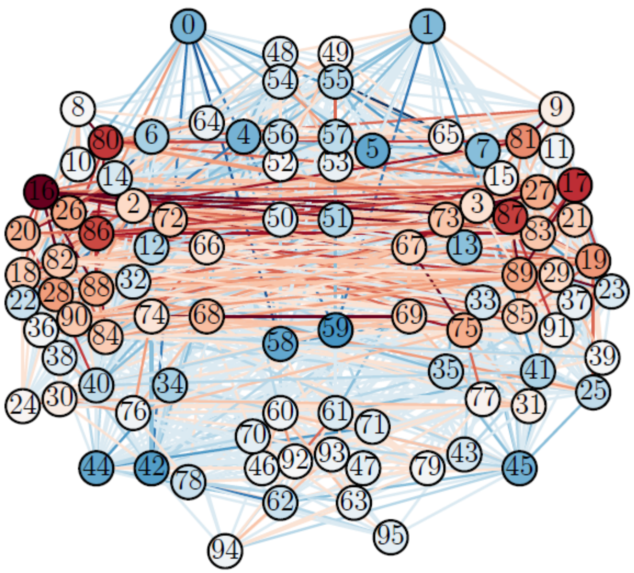


Fig: Alakörkkö *et al.* 2017, *European Journal of Neuroscience*

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

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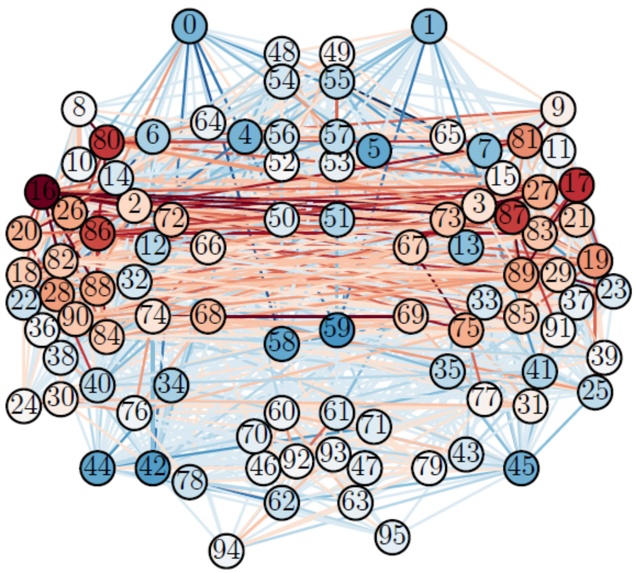

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# Why is the brain a network?

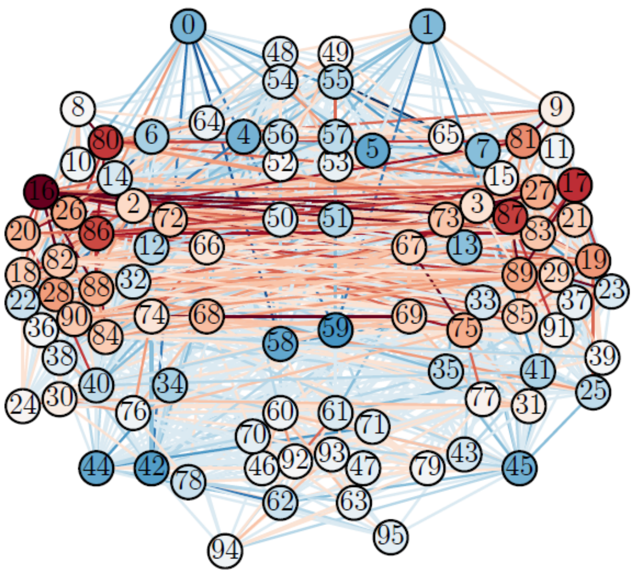


Fig: Alakörkkö *et al.* 2017,
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- Brain = a system of neurons
  - Separated neurons tend to reconnect
- Axon bundles connect brain areas
- Cognitive tasks require collaboration of brain areas

# Brain networks: What?

# Brain networks: some history

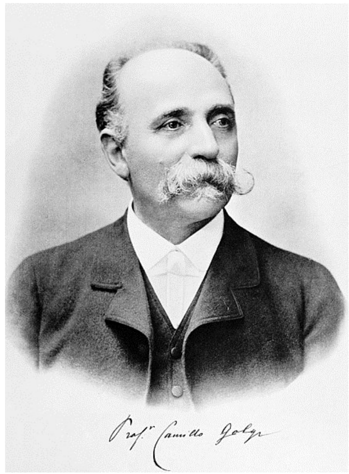
Fig: Wikipedia Commons, public domain

Joseph von Gerlach (1820-1896)

Fig: Wikipedia Commons, public domain

Camillo Golgi (1843-1926)

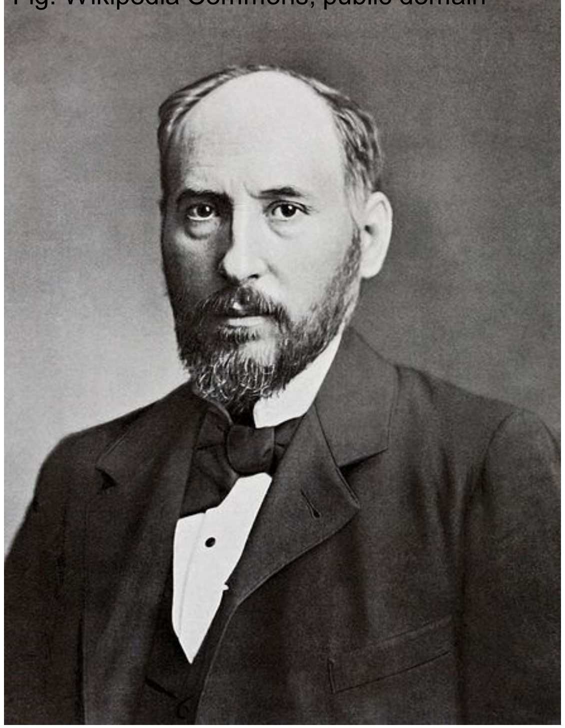
# Brain networks: some history




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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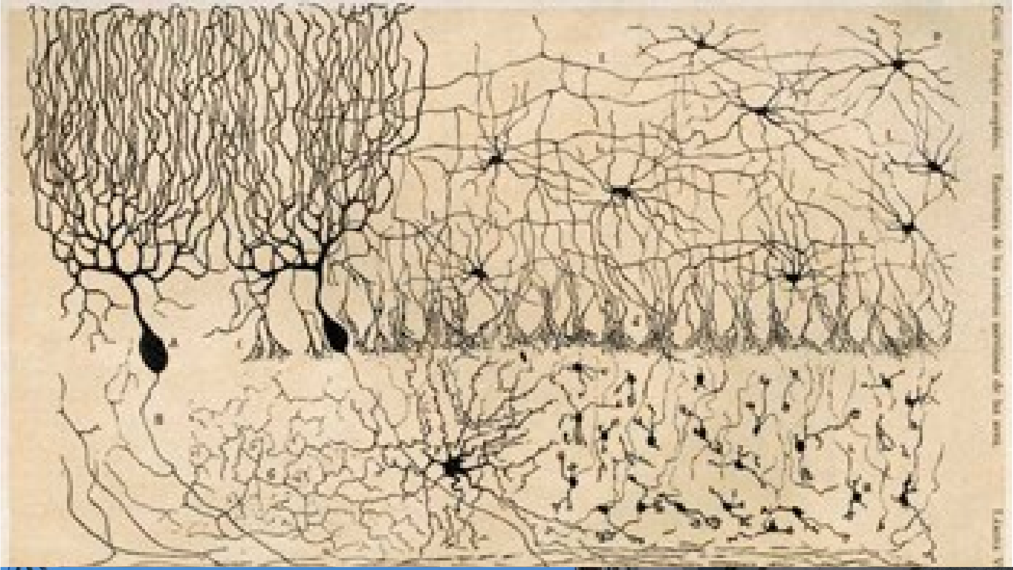
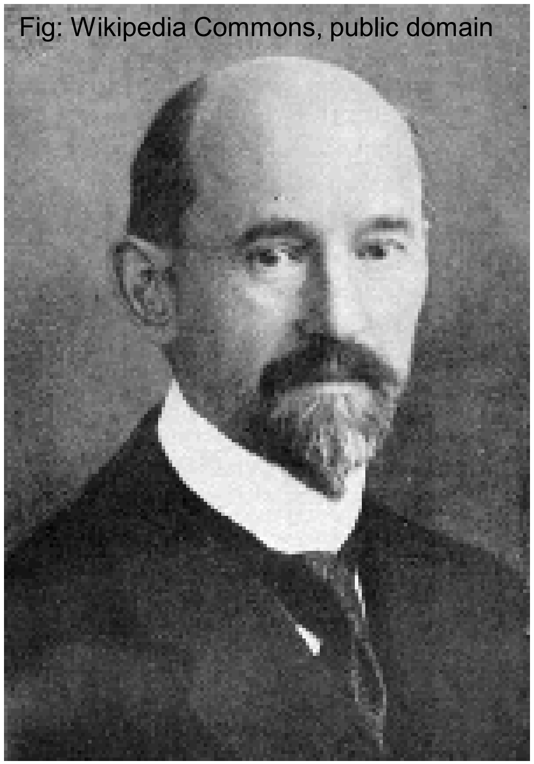


Fig: Wikipedia Commons, public domain

Photo: Milja Heikkinen

Santiago Ramón y Cajal (1852-1934)
- The brain = a collection of neurons

# Brain networks: some history



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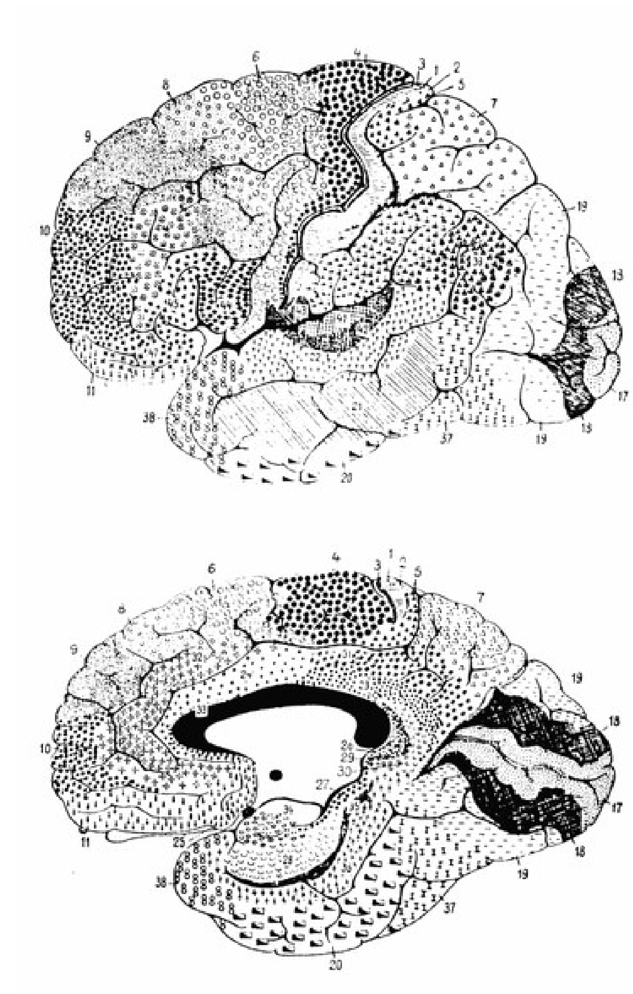


Fig: Wikipedia Commons, public domain

Korbinian Brodmann (1868-1918)

- Brain areas have different cells
- Different cells = different tasks
  => specialized brain areas

# Brain networks: some history

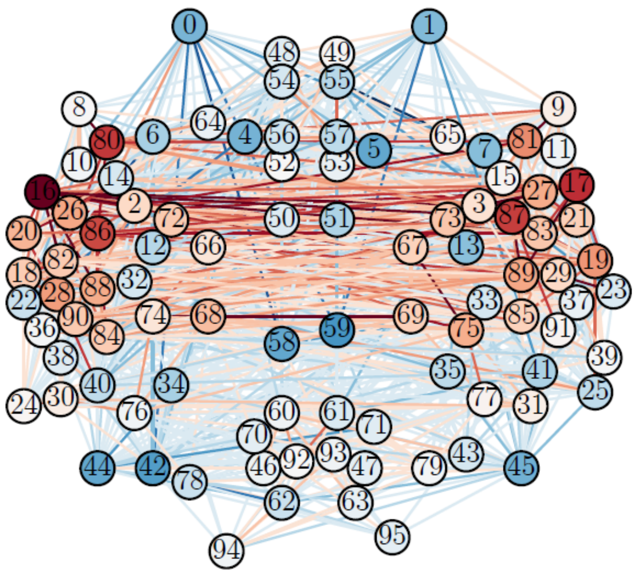


*Fig: Alakörkkö et al. 2017, European Journal of Neuroscience*

Renaissance of brain networks:

- The neural network of *C. elegans* (White et al. 1986)
- First mappings of human brain networks 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

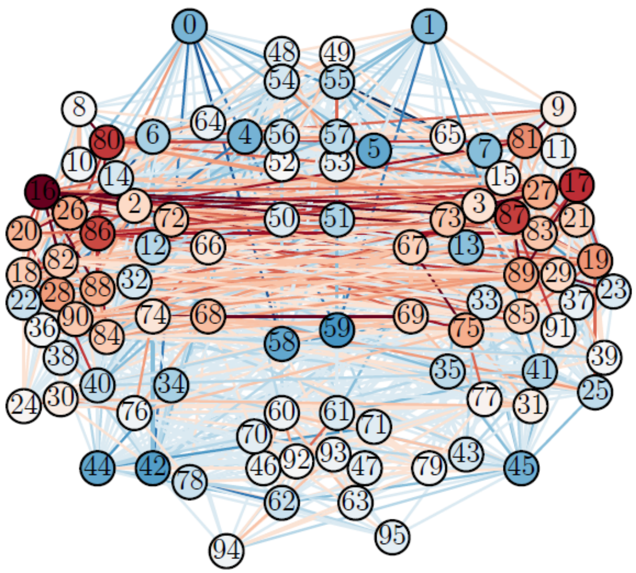
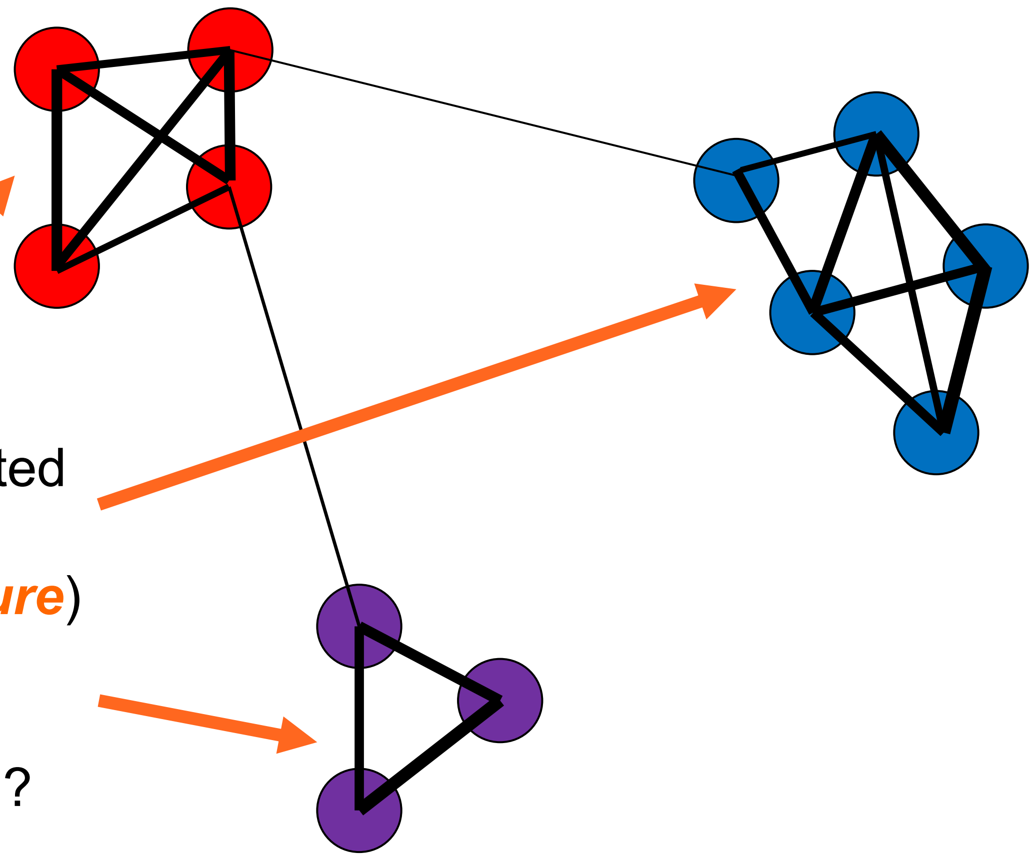


Fig: Alakörkkö *et al.* 2017, *European Journal of Neuroscience*

- 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):



Strongly connected neighbourhoods (***module structure***)

- Segregation
- Functional specialization?

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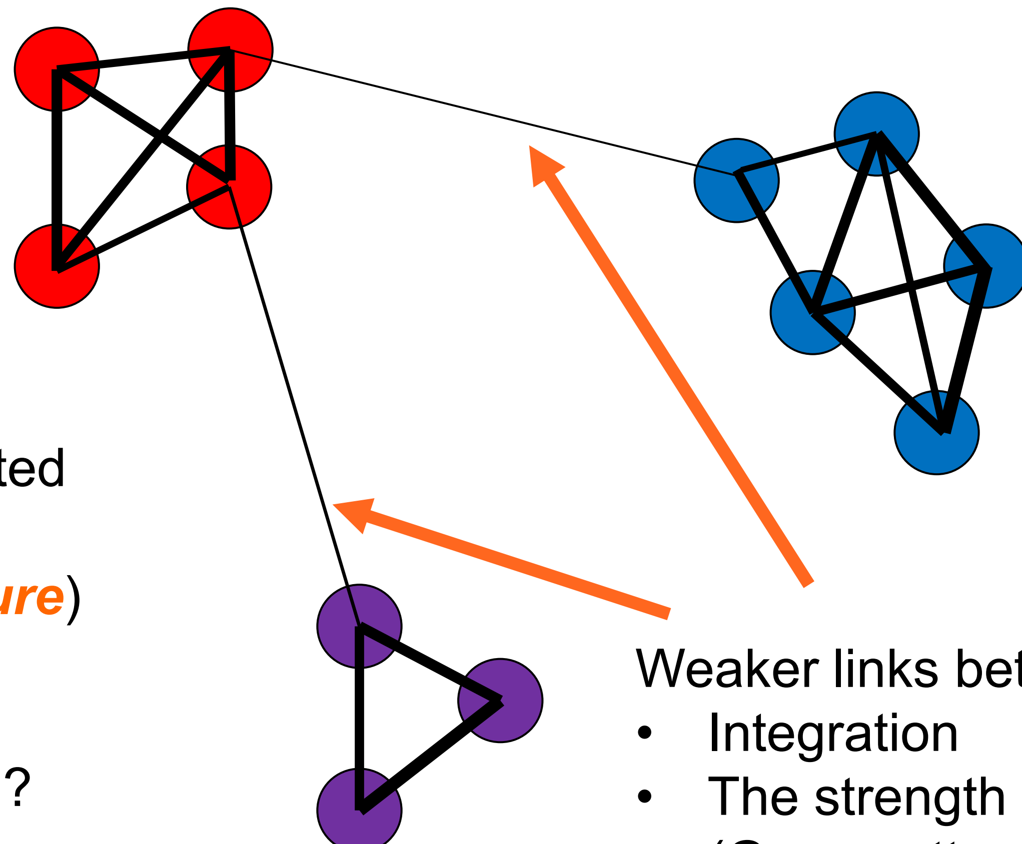


Strongly connected neighbourhoods (***module structure***)

- Segregation
- Functional specialization?

Weaker links between modules

- Integration
- The strength of weak ties (Granovetter 1973)

# What do brain networks look like?

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

Most network links are short (= inside module)

Only few long links (= between modules)

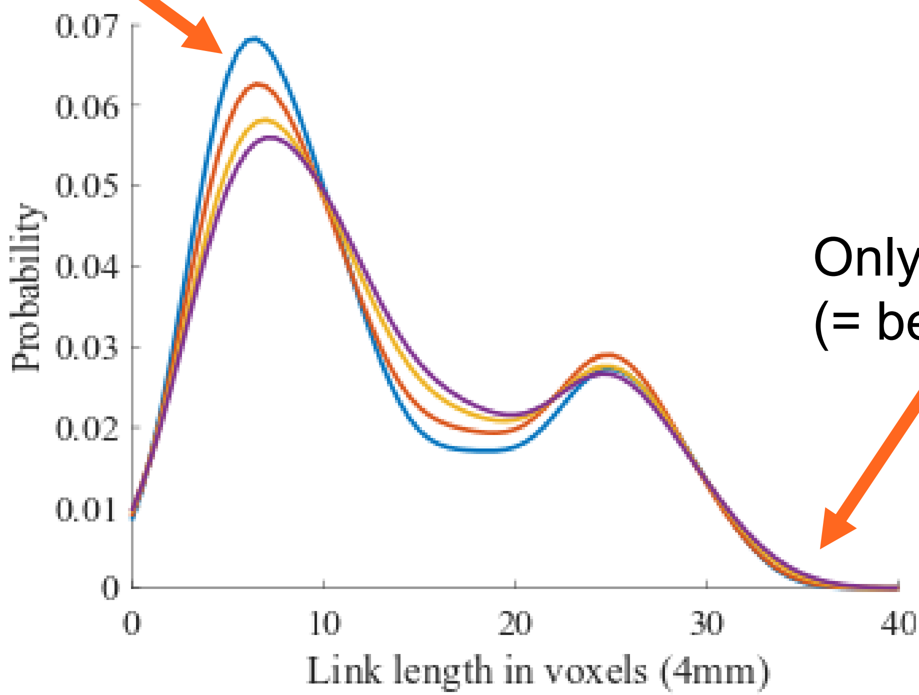


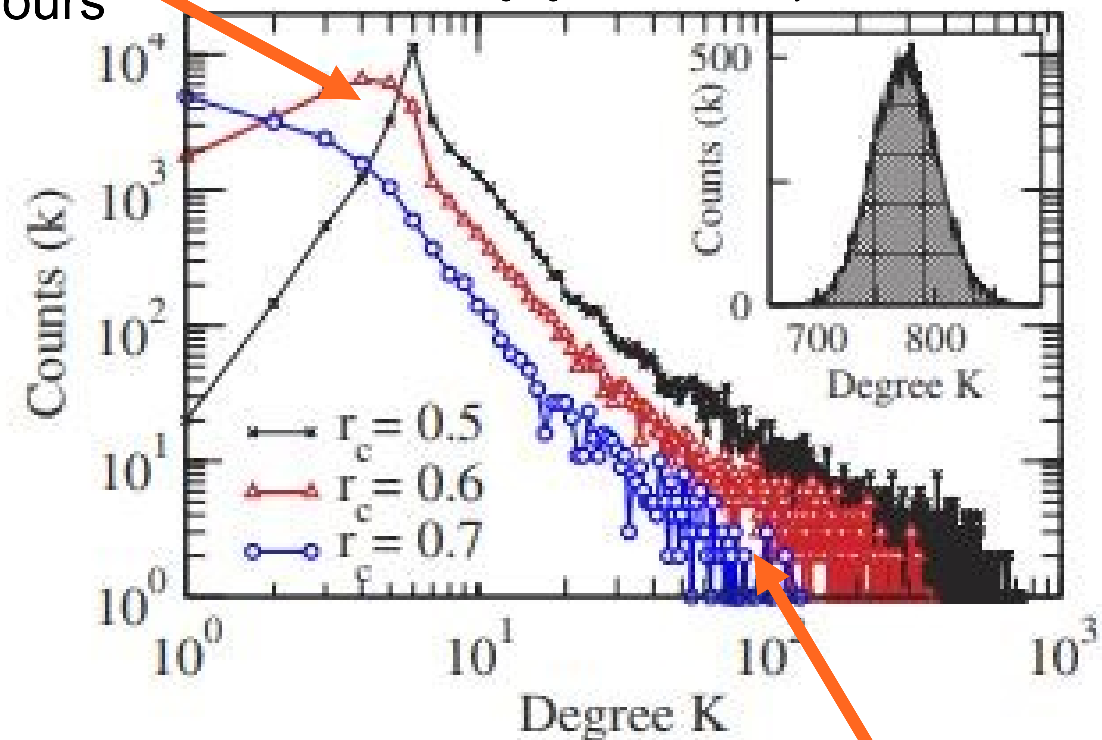

Fig: Alakörkkö *et al*. 2017, *European Journal of Neuroscience*

# What do brain networks look like?

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

Most nodes have few neighbours

Fig: Eguíluz *et al*. 2005, *Physical Review Letters*



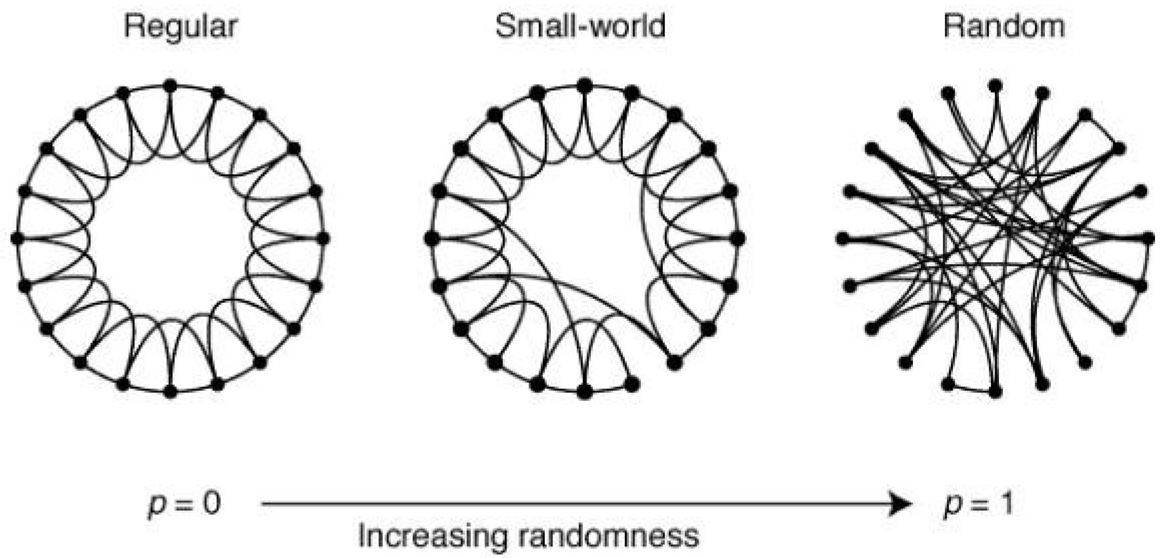

Some nodes (***hubs***) with lots of neighbours

- 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 (”friends of my friends are my friends”)
- Short paths

# What do brain networks look like?

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

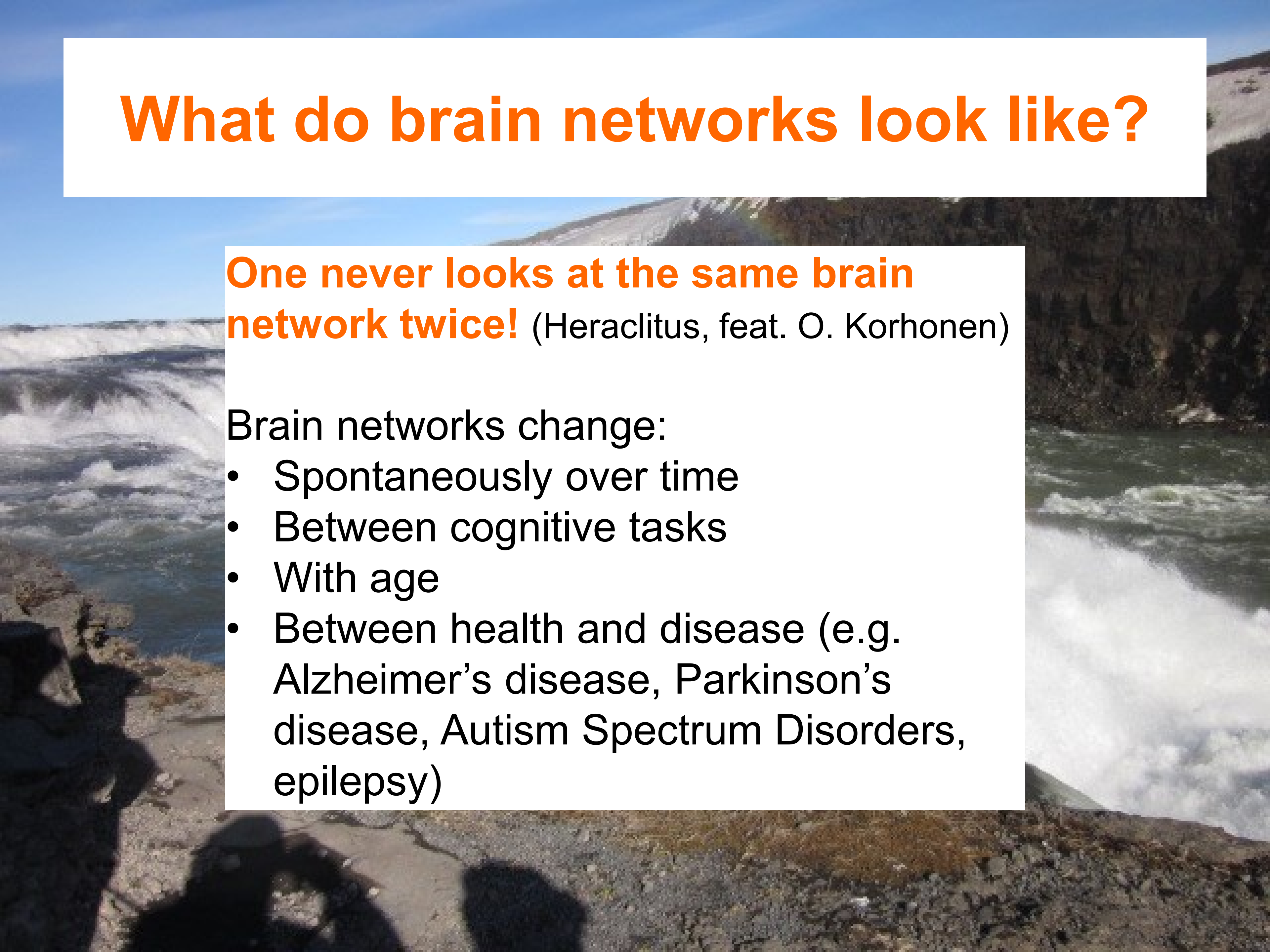
But is the brain really a small world? (Papo et al. 2016)

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

- A fundamental organization principle or a concequence of limited space?


Compared to random:

- High clustering (”friends of my friends are my friends”)
- Short paths



# What do brain networks look like?

**One never looks at the same brain network twice!** (Heraclitus, feat. O. Korhonen)

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: Aalto Magnetic Imaging (AMI Center), by permission

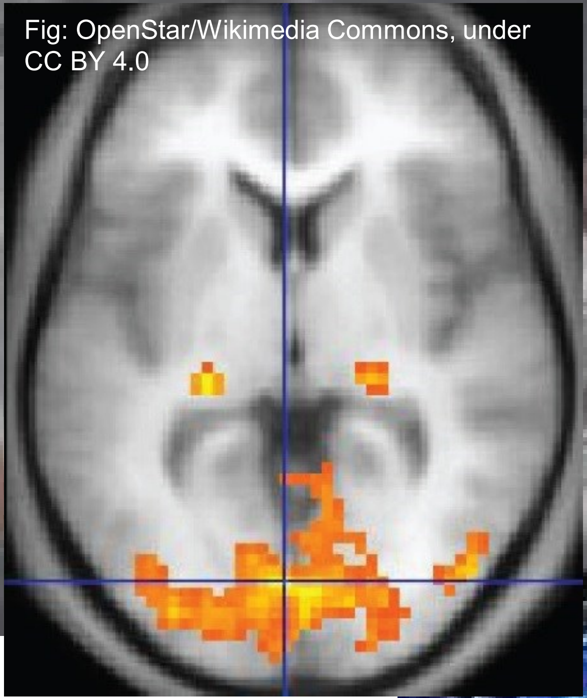


Fig: OpenStar/Wikimedia Commons, under CC BY 4.0

- 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

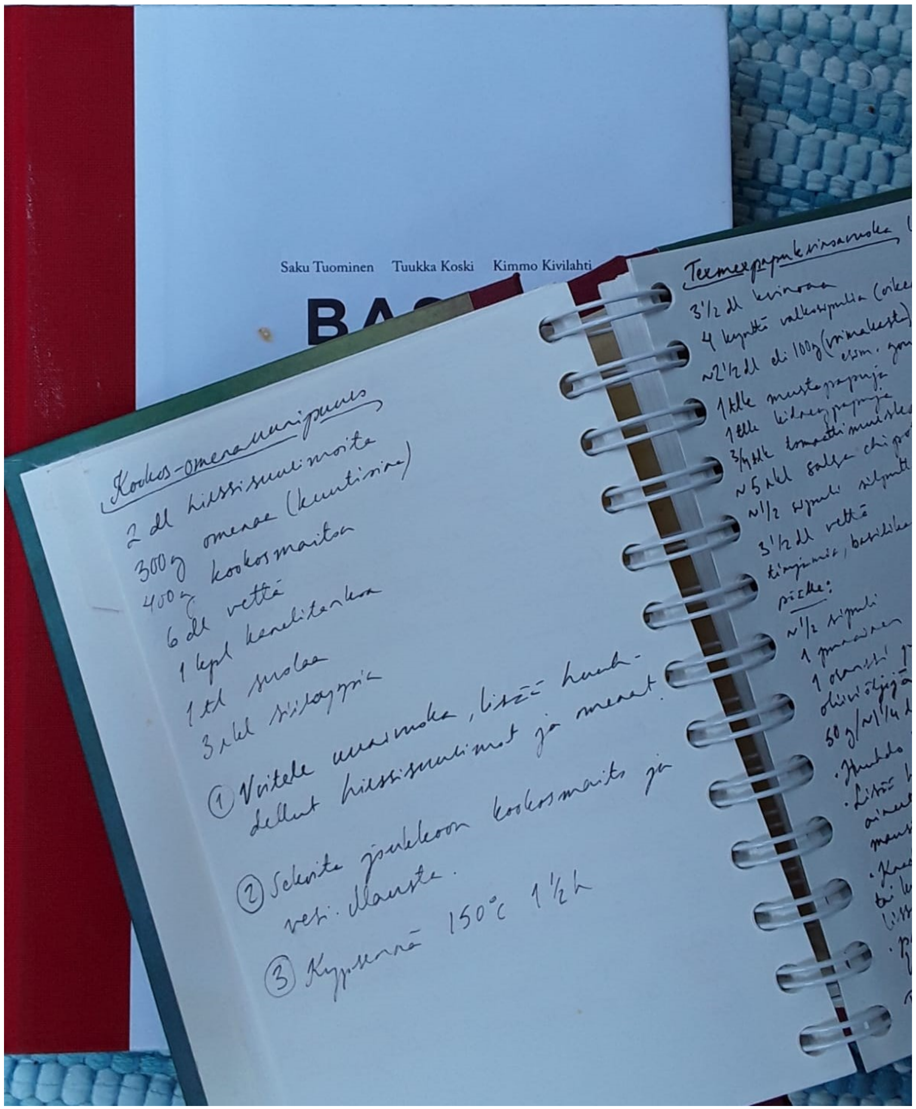

Fig: Chris Hope/Wikimedia Commons, under CC BY 2.0

- 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


Fig: Wikimedia Commons, public domain

- Excellent (~ms) temporal resolution, lower spatial resolution

# Functional networks: how-to?



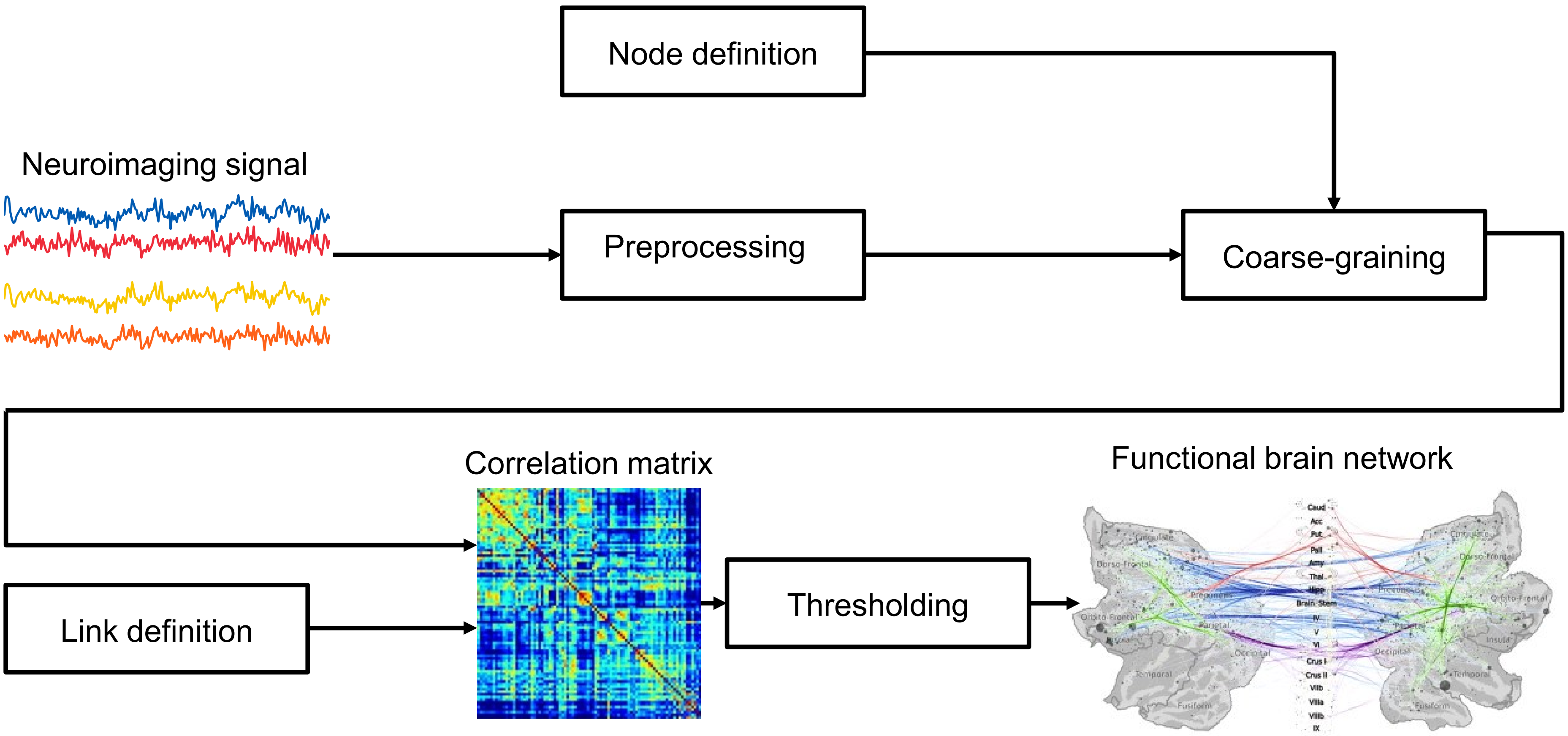

A simple recipe:
***weighted networks from time series***

1. Define nodes
   (each one with a time series)

2. Define link weights
   (measures of similarity between time series)

3. Define threshold,
   discard sub-threshold links

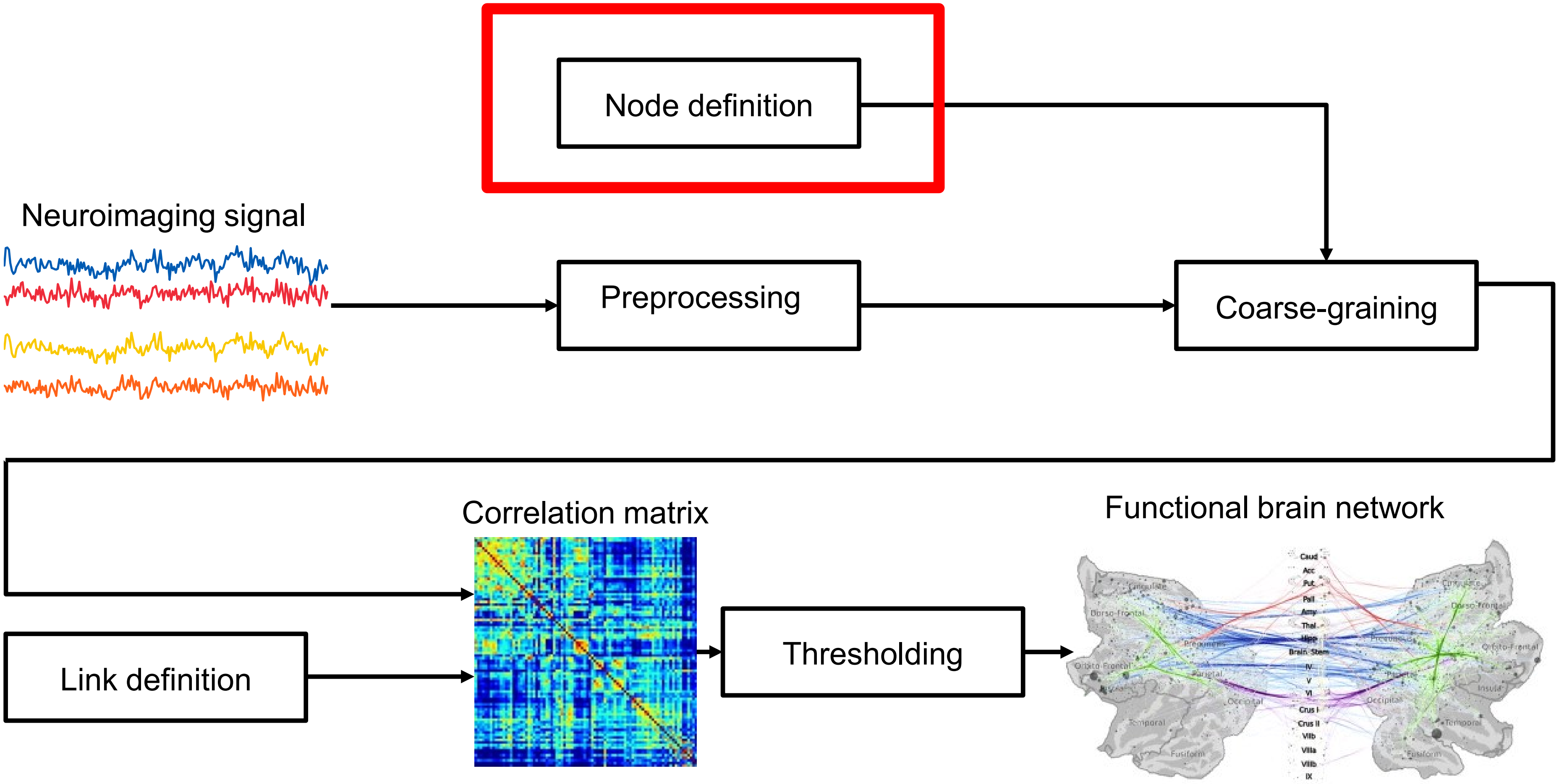
# Functional networks: how-to?




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

# Brain networks: How not?

# Functional networks: how-to?

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# 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:

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

**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*

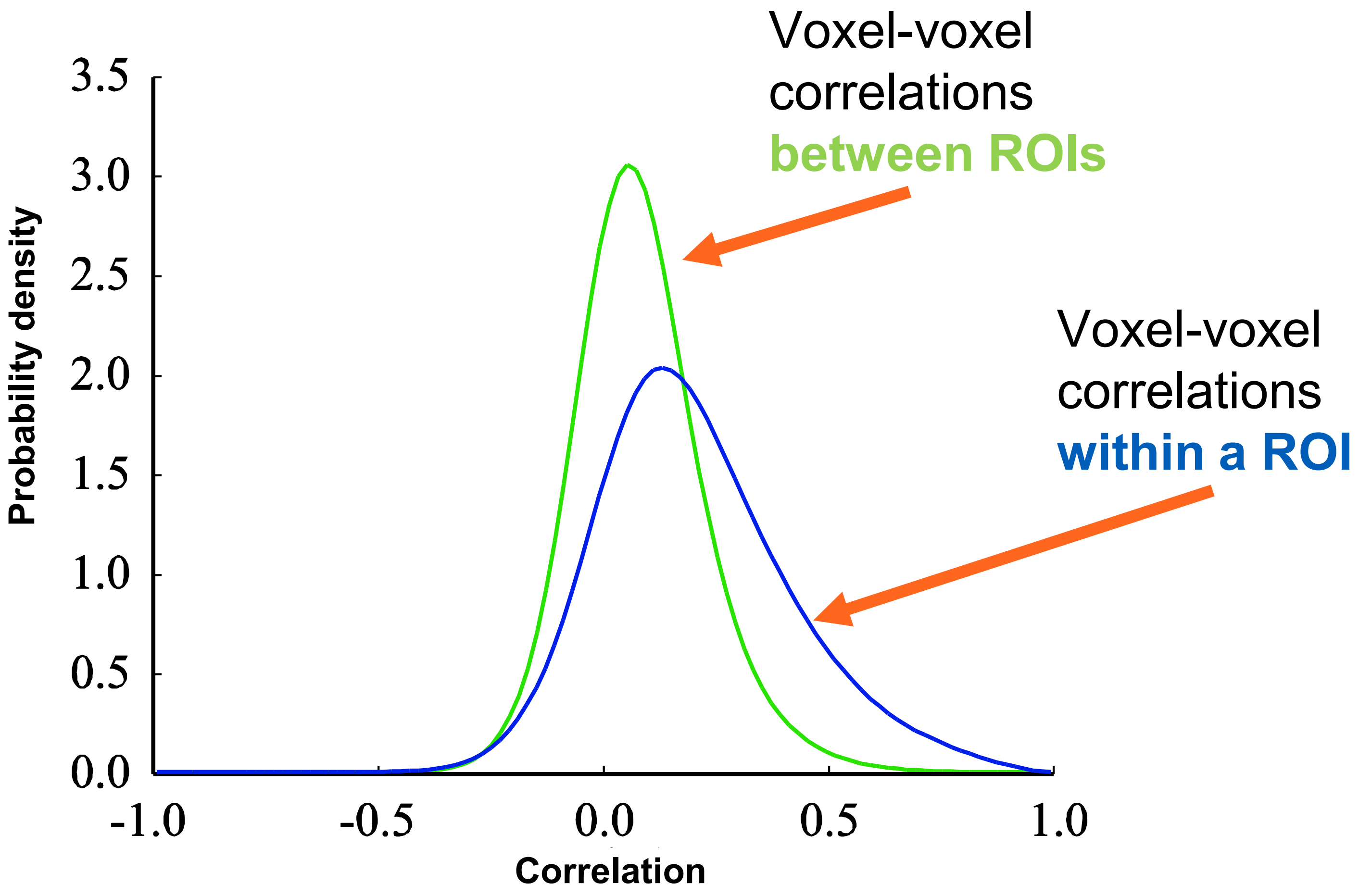
# Research questions

- 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?

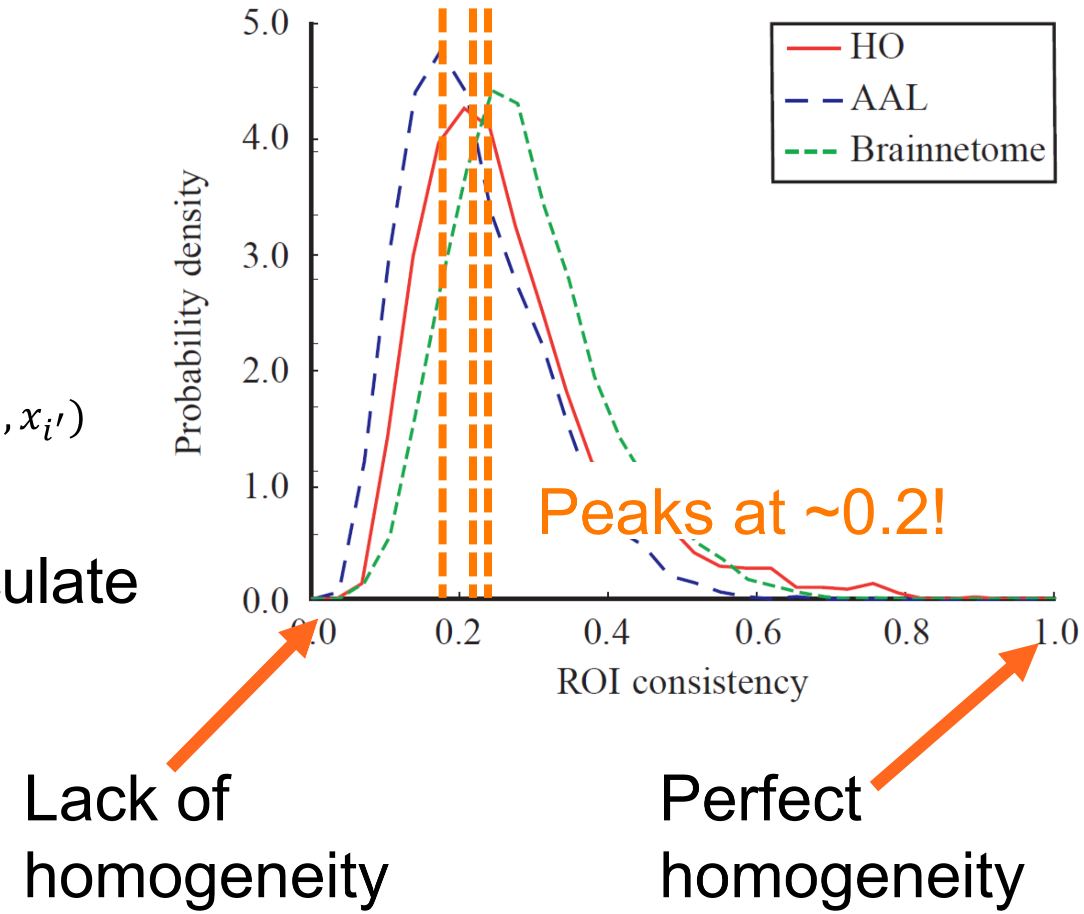


# How homogeneous are ROIs?

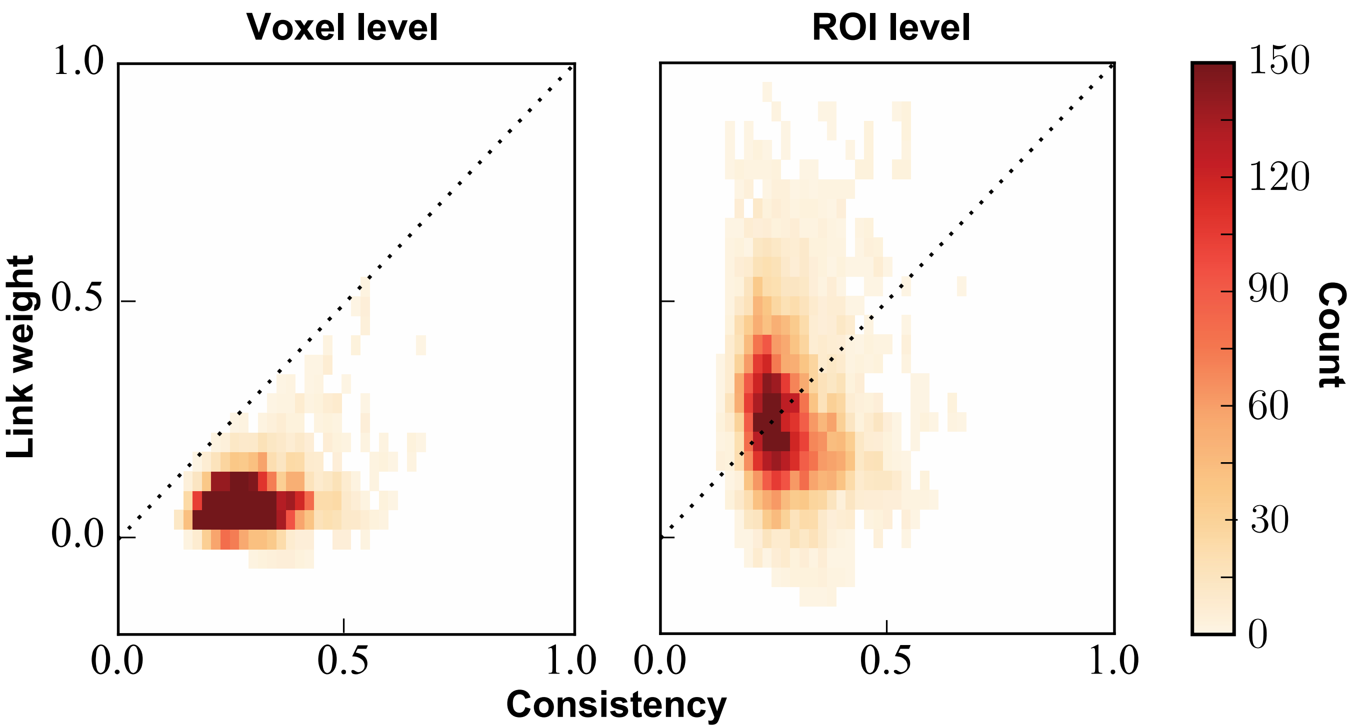
- **Spatial consistency**
= measure of functional homogeneity:

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

- Straightforward to calculate
- Easy to interpret

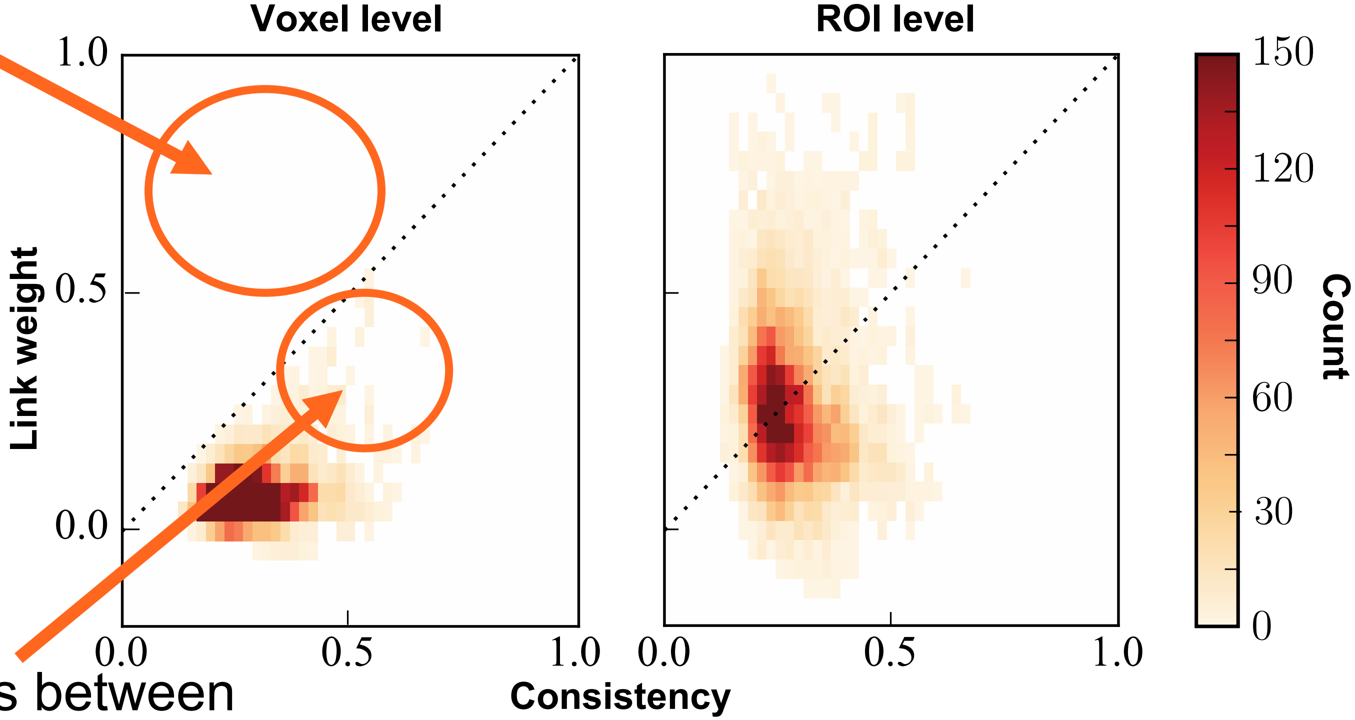


# Does consistency predict connectivity?



# Does consistency predict connectivity?

No links




Strong links between consistent ROIs

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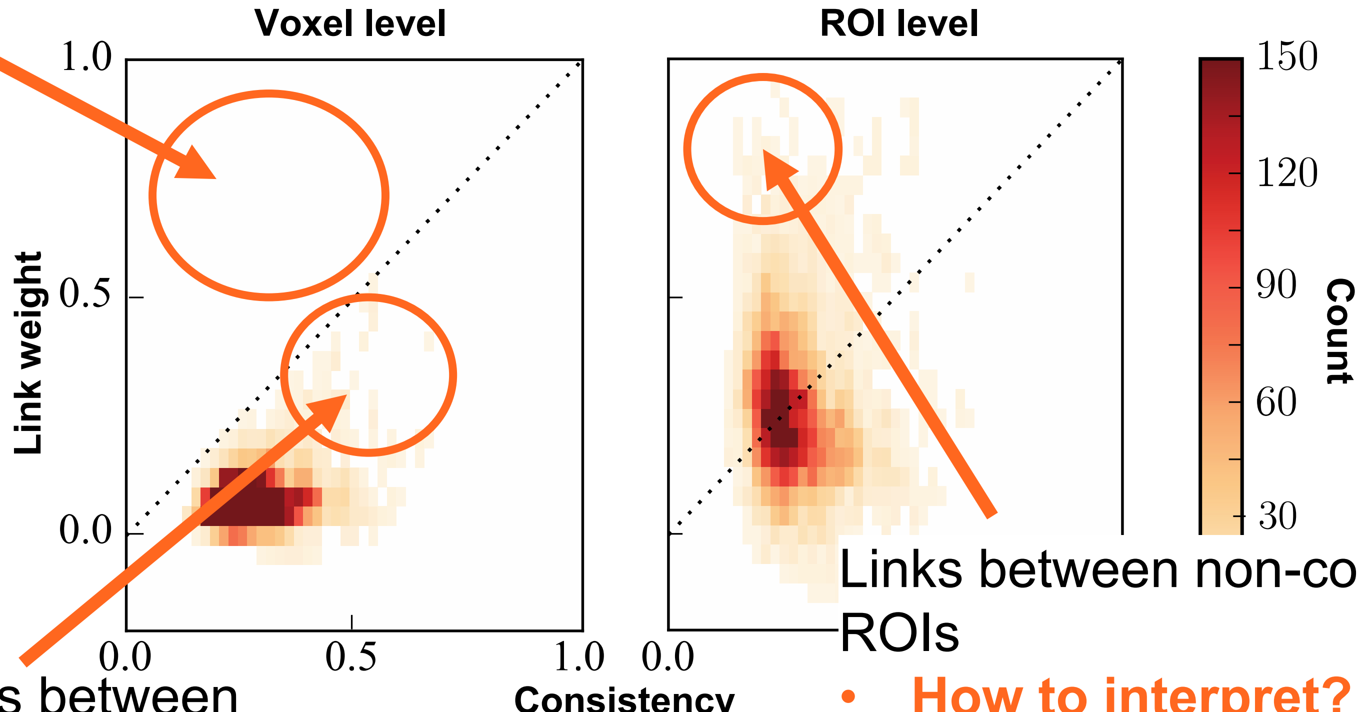
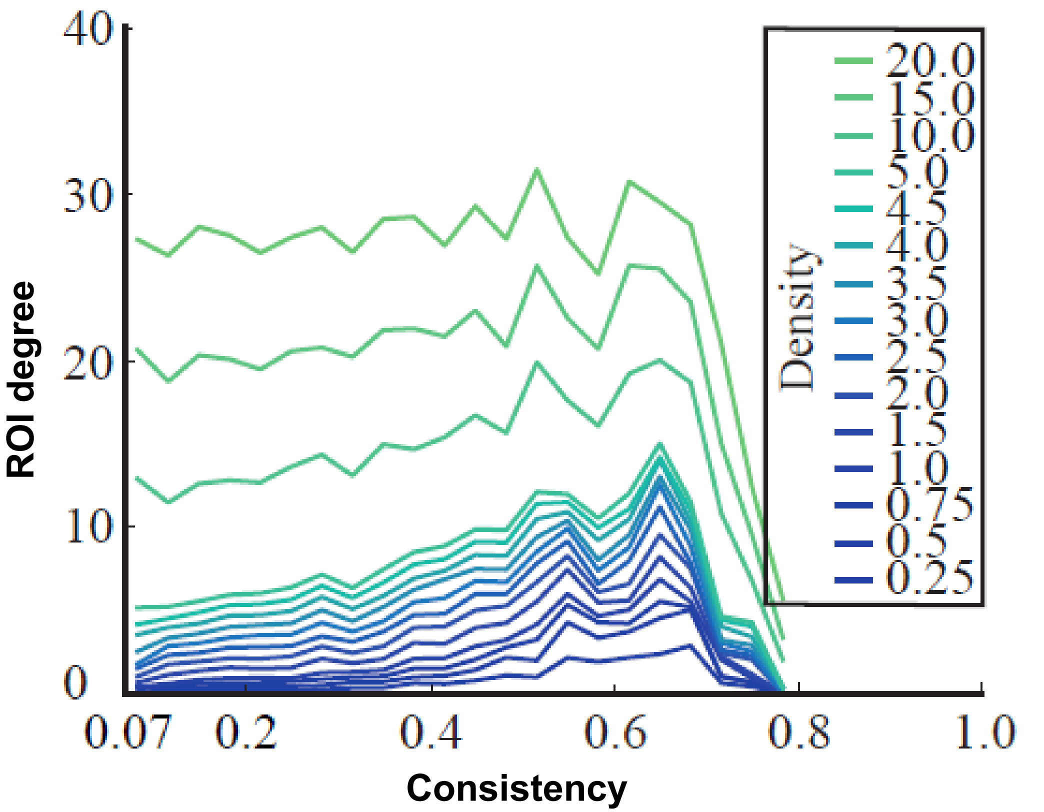



Links between non-consistent ROIs

- **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

Ryyppö. 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 listenig (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

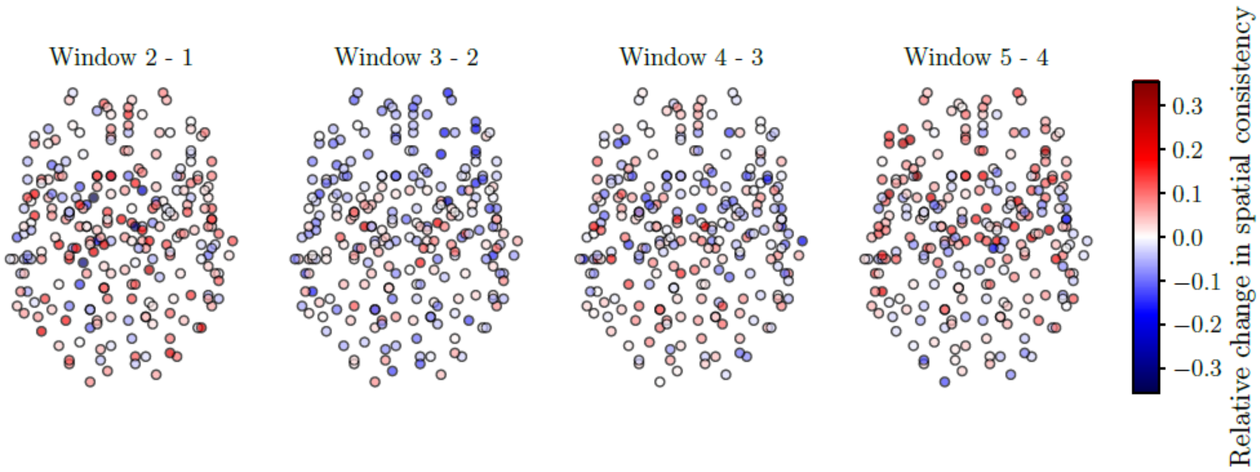
- Spatial consistency $\varphi_{spat}$: functional homogeneity of ROI
- Spatiotemporal consistency: time-dependence of $\varphi_{spat}$

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

- Network turnover: changes in local network structure

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

# Spatial consistency changes in time



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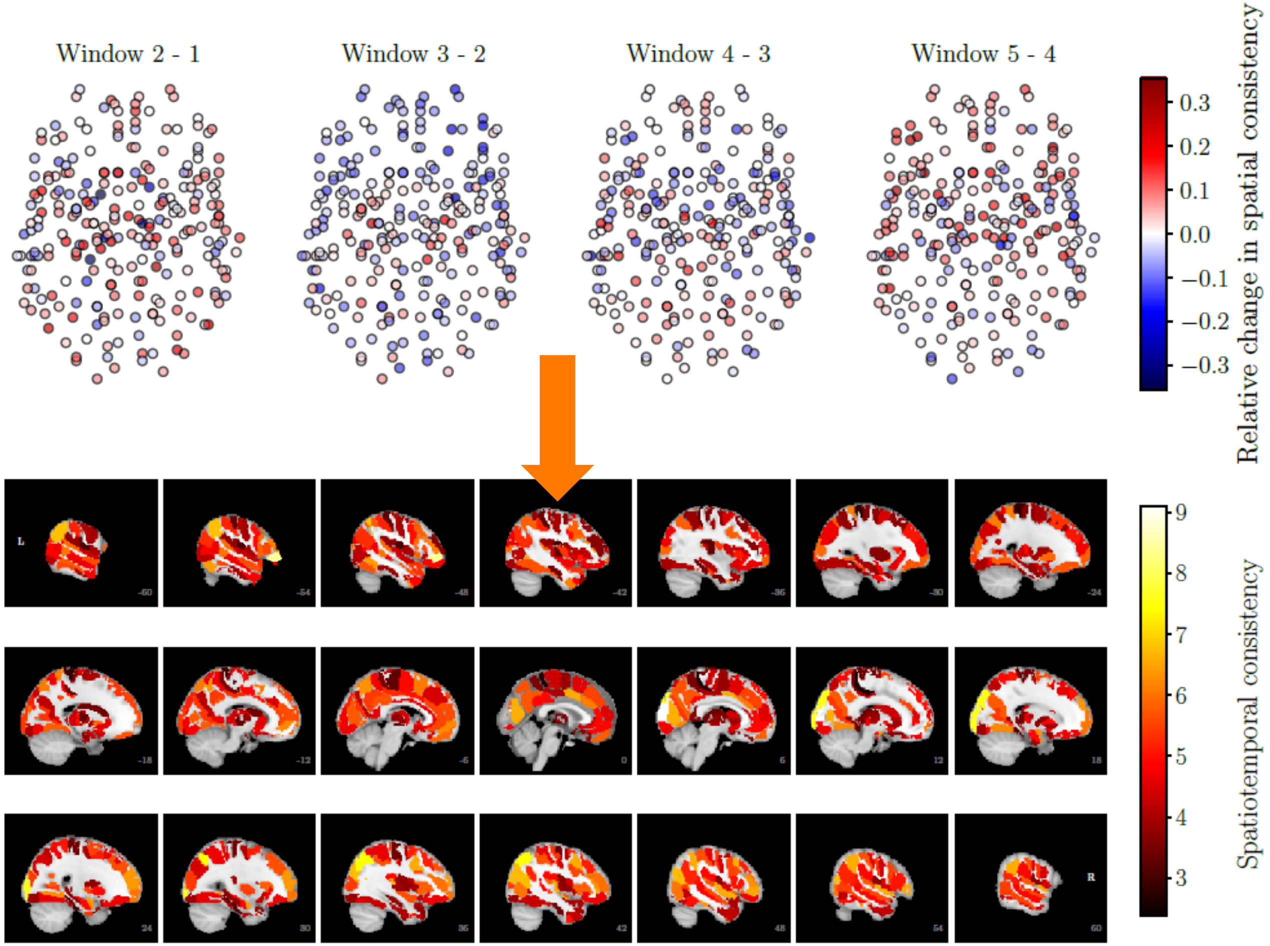
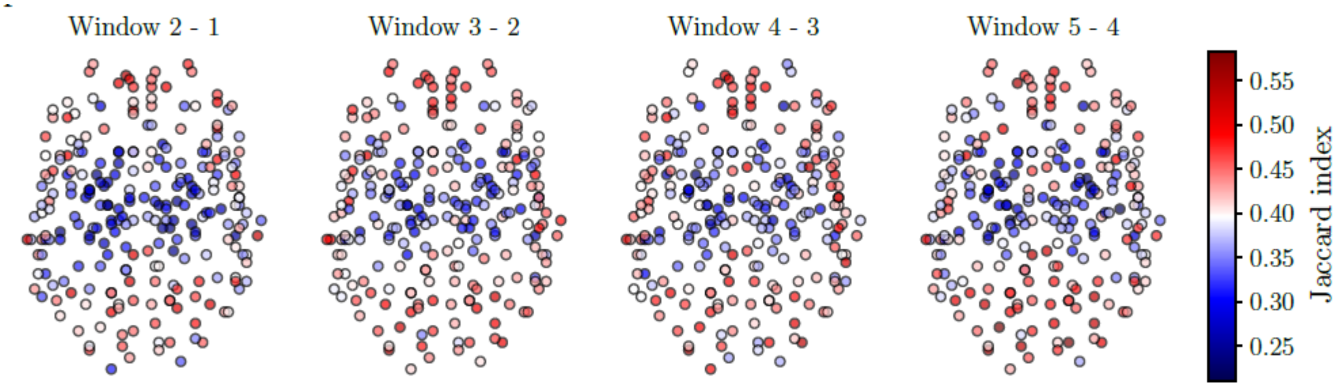


# Turnover in network neighborhoods



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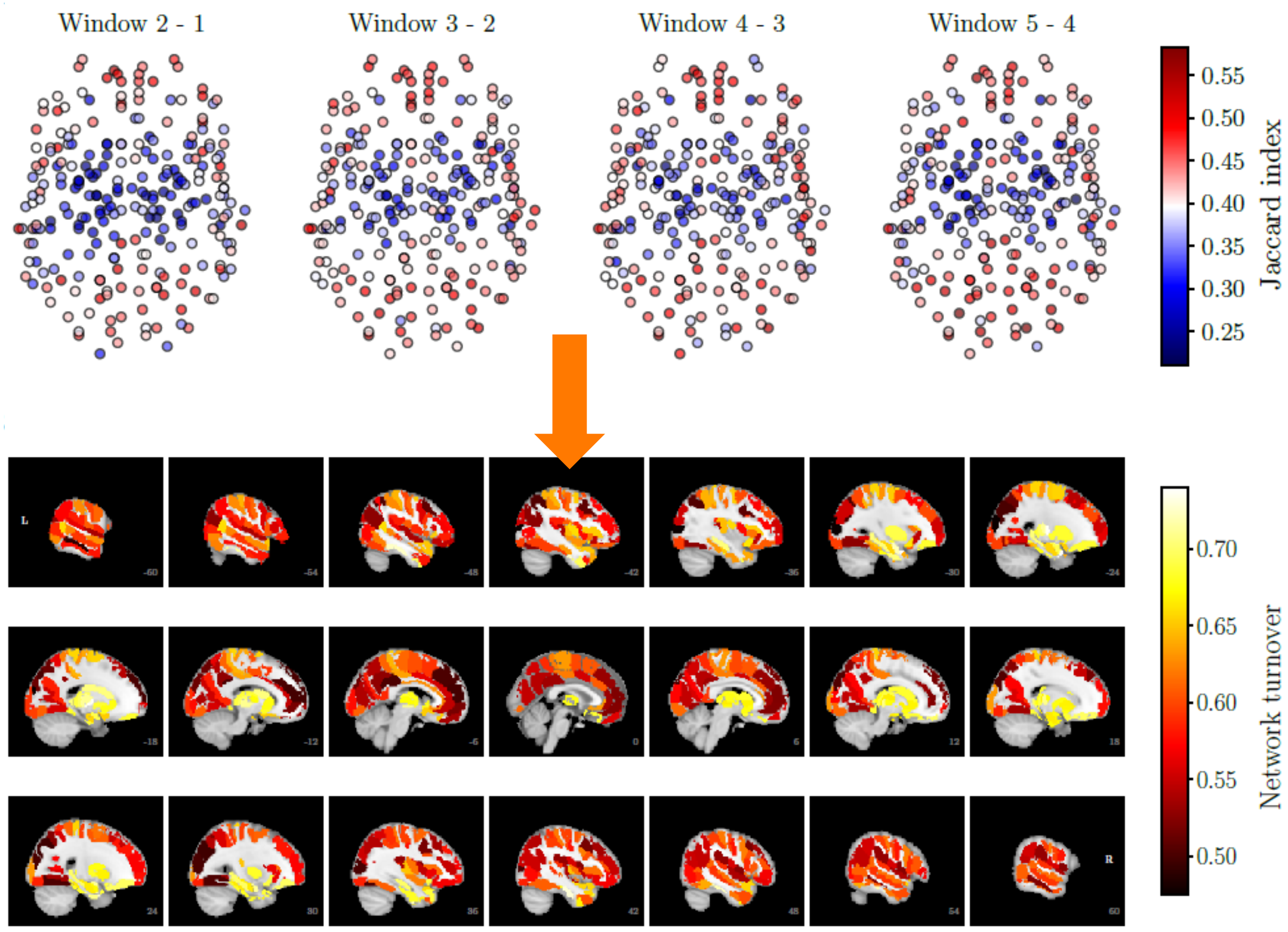
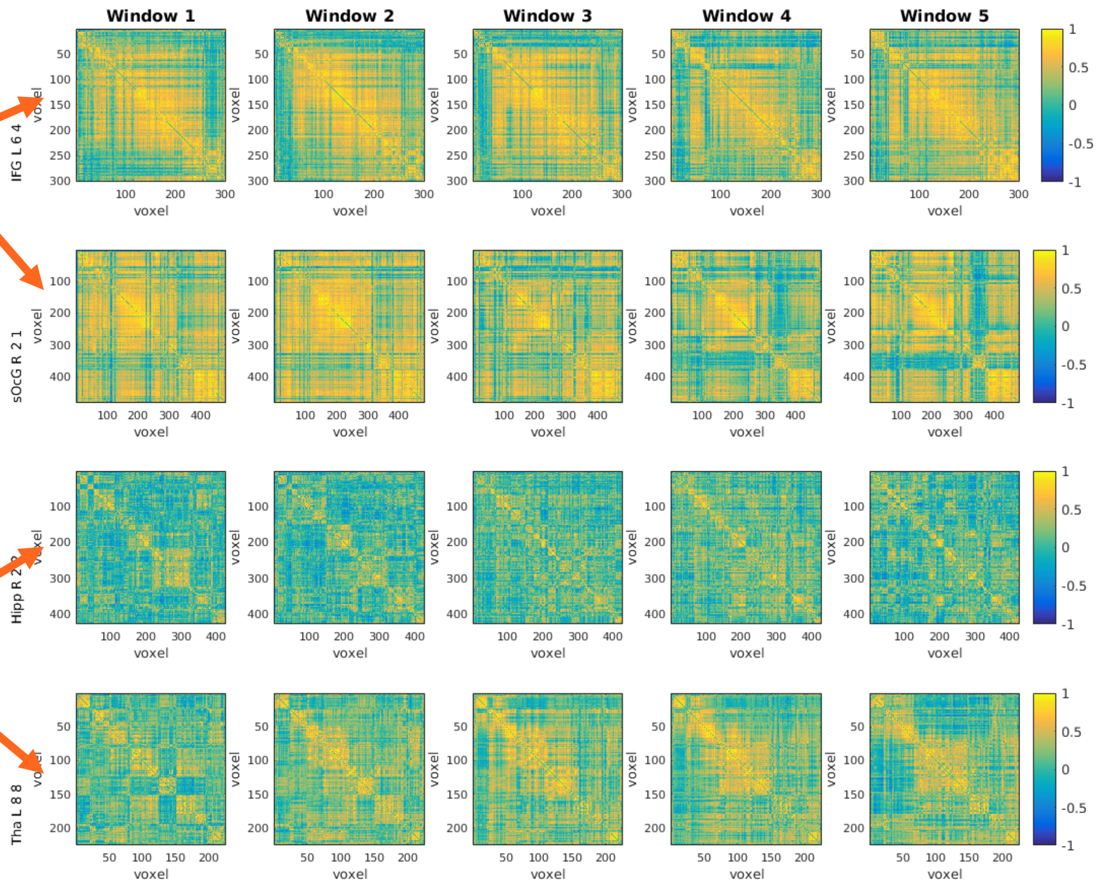


# ROIs have rich internal connectivity structure

High spatial consistency

Low spatial consistency



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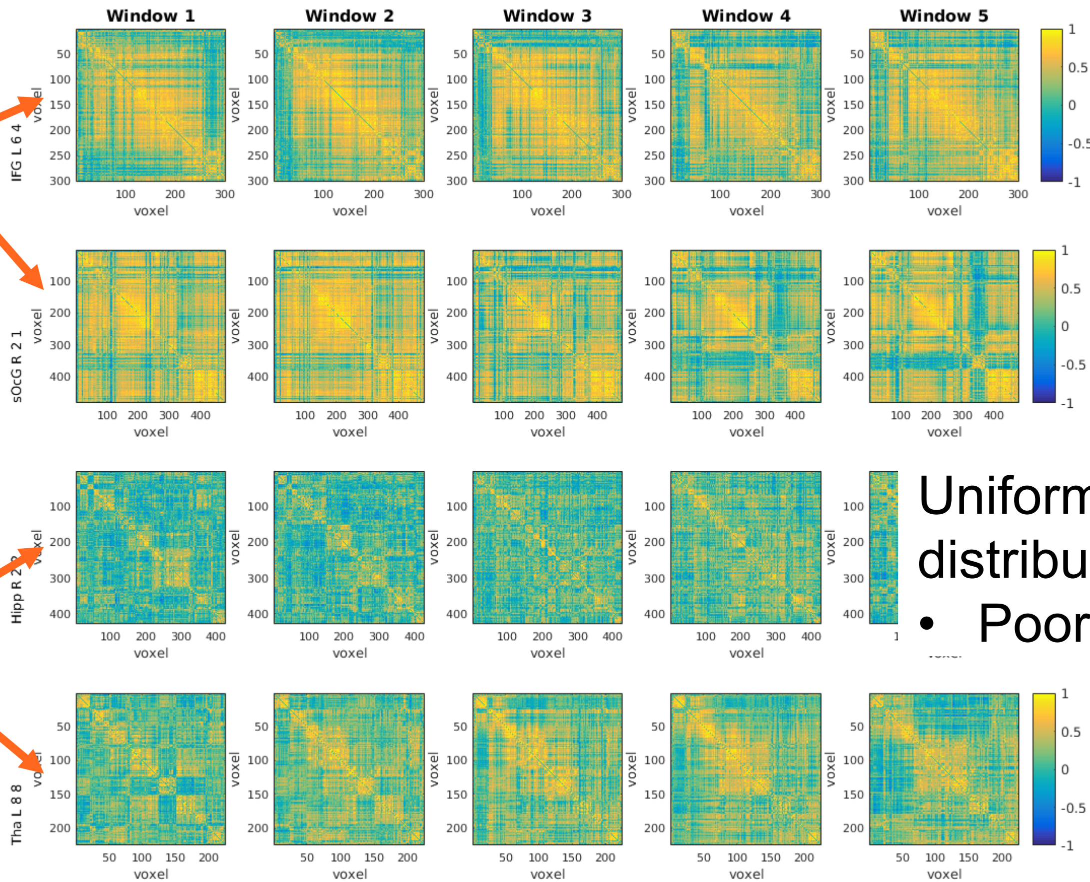


Uniform correlation distribution

- Poorly defined ROI?

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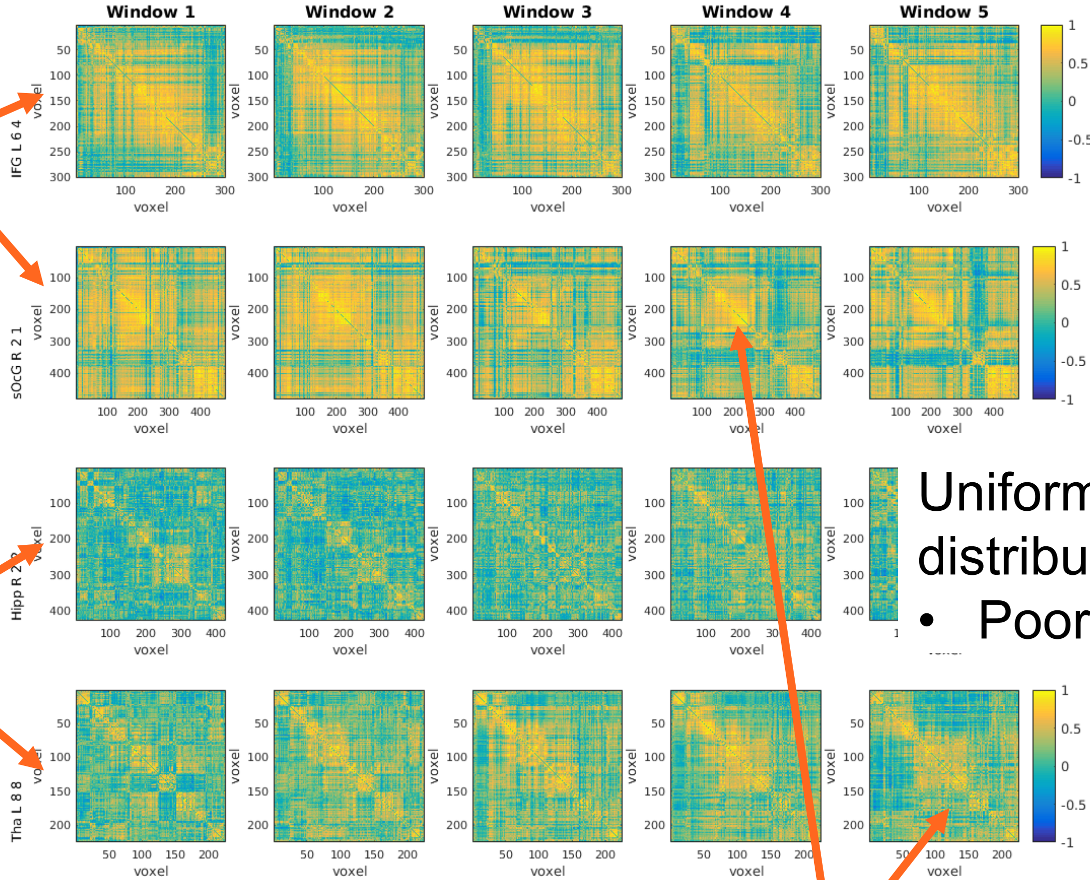



Uniform correlation distribution

- 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?

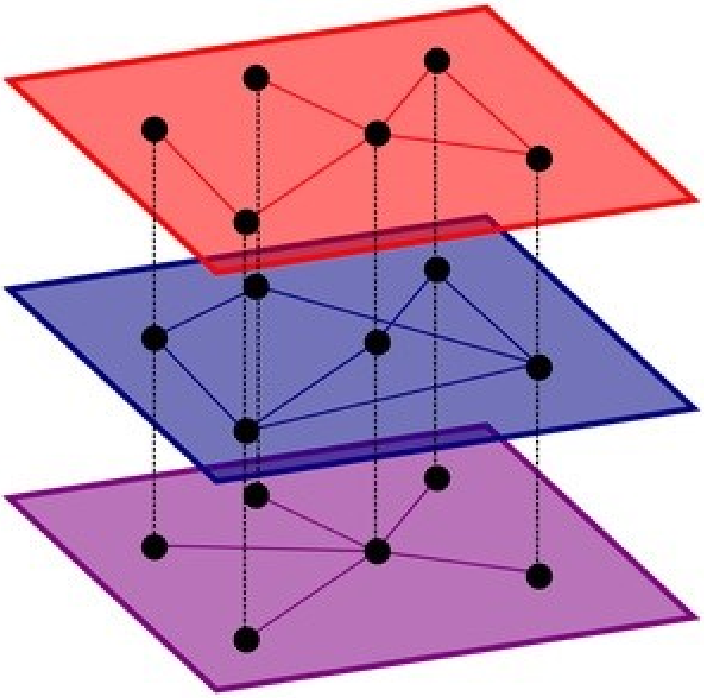
- Do brain networks have stable nodes?

# 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):

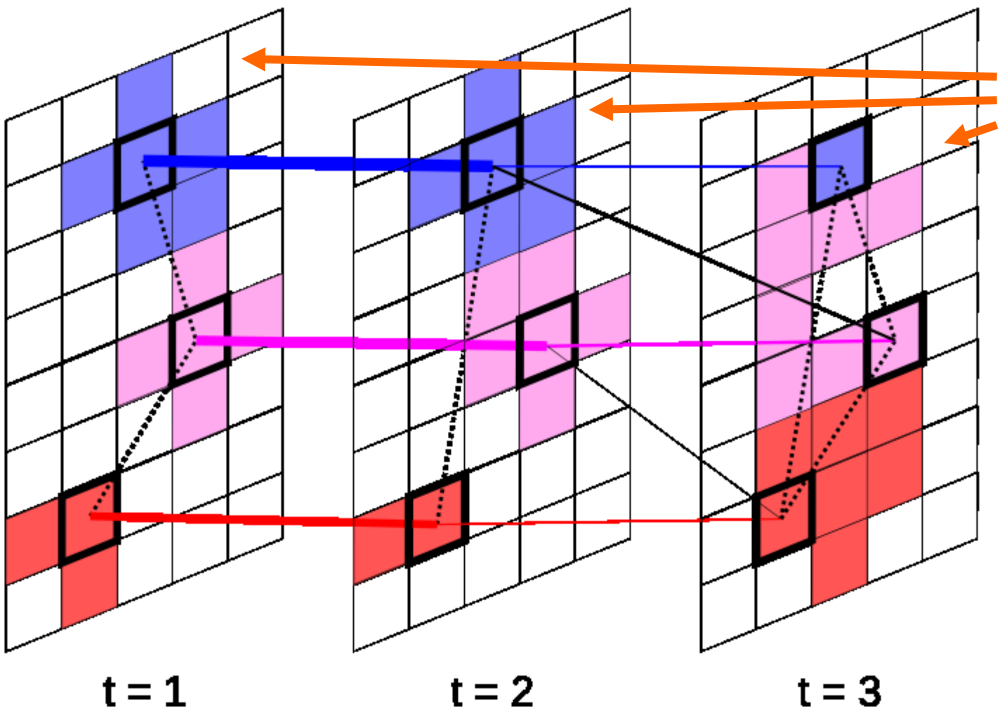


- Different connections in a single network
- Each connection type on its own layer
- Interpretation of inter-layer connections?

- Typical examples: social networks, transport, …

# Network model with flexible nodes

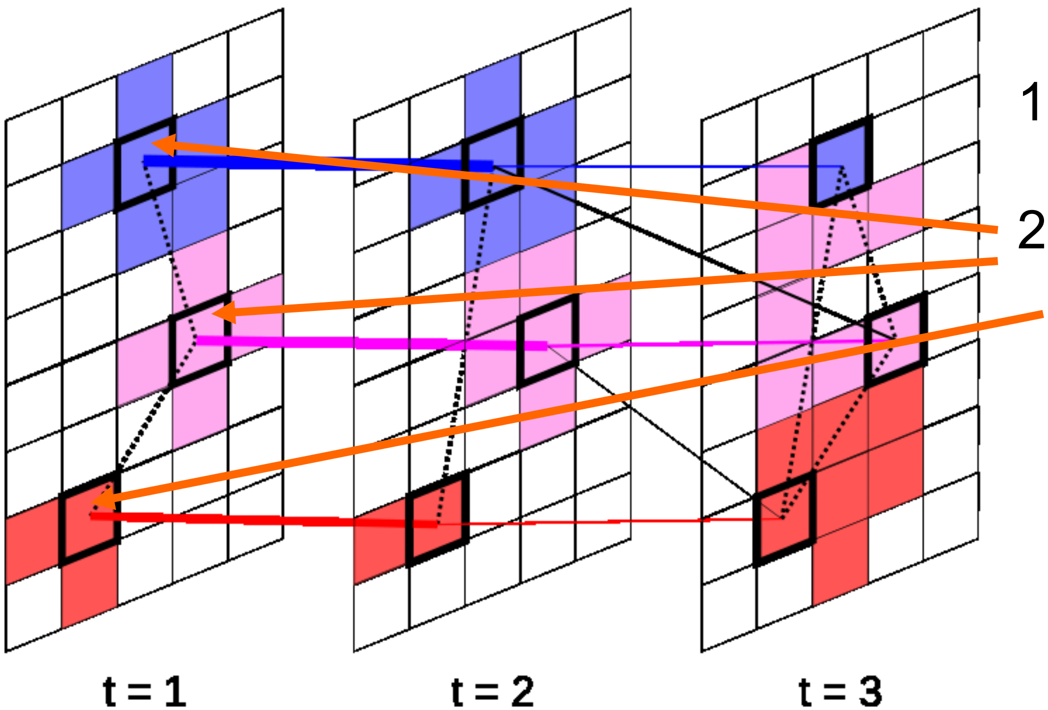
- Based on multilayer networks (= different connections in the same network)




1. Layers = time windows

# 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

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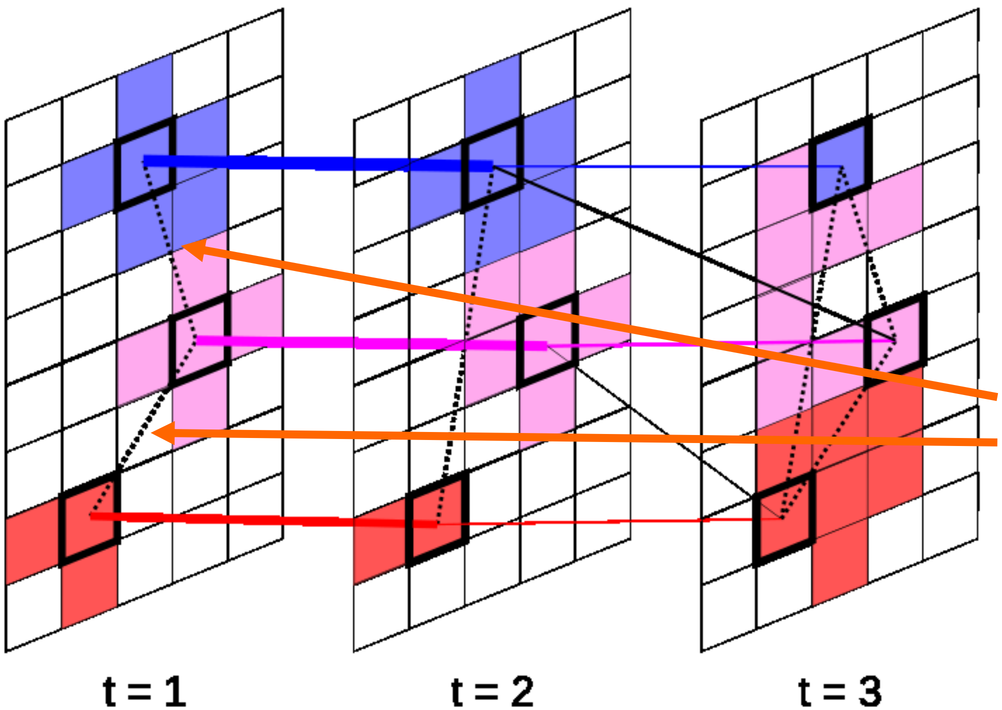
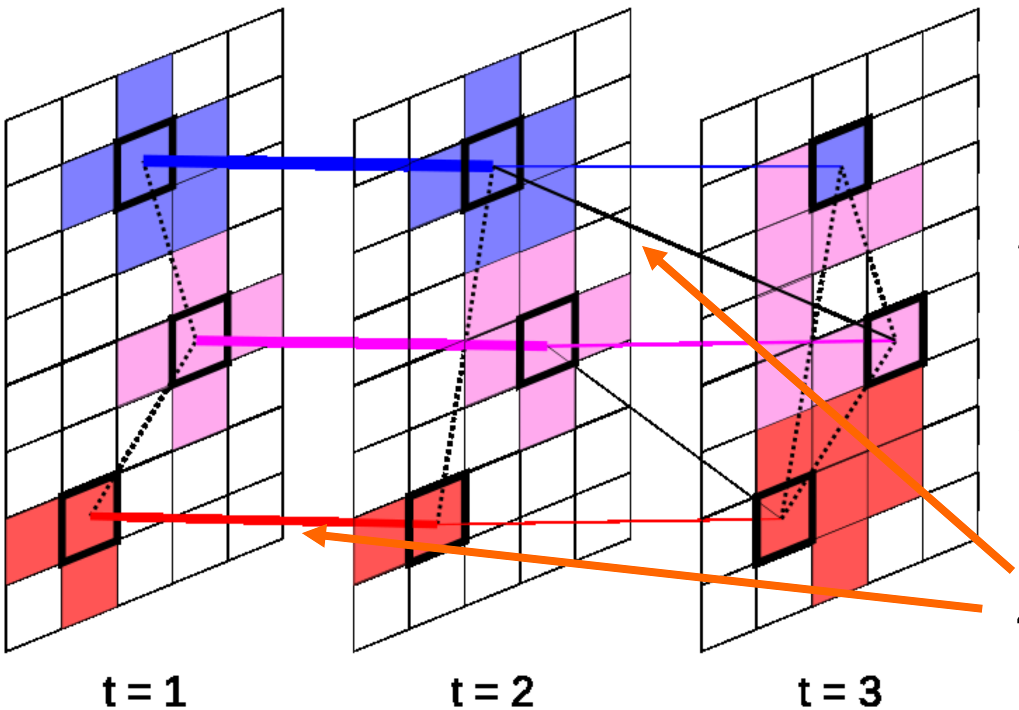



1. Layers = time windows
2. ROIs optimized inside layers for maximal homogeneity
3. Interlayer links = Pearson correlation

# 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

$\Rightarrow$ Can't be fixed by new static nodes

$\Rightarrow$ **Flexible nodes needed!**

# References

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# Thank you!

# Questions, comments?

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